EVIDENCE-BASED UROLOGY

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Edited by
Philipp Dahm
Roger Dmochowski

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Evidence-Based Urology

Second Edition

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EDITED BY

Philipp Dahm

Minneapolis VA Health Care System
and
Department of Urology
University of Minnesota
Minneapolis, Minnesota
MN, USA

Roger R. Dmochowski

Vanderbilt University
Medical Center
North Nashville, TN
USA

WILEY Blackwell

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Contents

Contributors

Kourosh Afshar, MD, MHSc, FRCSC
Division of Pediatric Urology
Department of Urologic Sciences
University of British Columbia
Vancouver, BC, Canada

Ashok Agarwal, PhD
Andrology Center
The Cleveland Clinic
Cleveland, OH, USA

Nima Almassi, MD
Glickman Urological and Kidney Institute
The Cleveland Clinic
Cleveland, OH, USA

Paholo G. Barboglio Romo, MD
Department of Urology
University of Michigan Medical Center
Ann Arbor, MI, USA

Daniel A. Barocas, MD, MPH, FACS
Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, TN, USA

Peter C. Black, MD, FACS, FRCSC
Vancouver Prostate Centre
Department of Urologic Sciences
University of British Columbia
Vancouver, BC, Canada

Samuel Borofsky, MD
Molecular Imaging Program
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

Caitlin Bowen, MRCP
School of Medicine
Cardiff University
Velindre Hospital
Velindre NHS Trust
Cardiff, UK

Luis H.P. Braga, MD, MSc, PhD
Department of Surgery (Urology), Pediatrics, and
Department of Health Research Methods, Evidence and Impact
McMaster University
Hamilton, ON, Canada

Rodney H. Breau, MD, MSc, FRCSC
Division of Urology
Department of Surgery
The Ottawa Hospital Research Institute
The Ottawa Hospital/University of Ottawa
Ottawa, ON, Canada

Elizabeth Timbrook Brown, MD, MPH
Department of Urology
Georgetown University School of Medicine
Washington, DC, USA

Jeanette Buckingham
John W. Scott Health Sciences Library
University of Alberta
Edmonton, AB, Canada

Benjamin K. Canales, MD, MPH
Department of Urology
University of Florida
Gainesville, FL, USA
North Florida/South Georgia VAMC
Gainesville, FL, USA

Steven E. Canfield, MD
Division of Urology
University of Texas Medical School at Houston
Houston, TX, USA

Culley C. Carson, MD
Department of Urology
University of North Carolina School of Medicine
Chapel Hill, NC, USA

Clint Cary, MD, MPH
Indiana University School of Medicine
Indianapolis, IN, USA

Sam S. Chang, MD
Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, TN, USA

Christopher R. Chapple, MD
Department of Urology
Royal Hallamshire Hospital
Sheffield, UK

Cyrus Chehroodi, MD
Division of Pediatric Urology
Department of Urologic Sciences
University of British Columbia
Vancouver, BC, Canada

Peter L. Choyke, MD
Molecular Imaging Program
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

David I. Chu, MD
Division of Urology
Children's Hospital of Philadelphia
Philadelphia, PA, USA

Paul Chung, MD
Department of Urology
University of Texas Southwestern Medical Center
Dallas, TX, USA

Roderick Clark, MD
Division of Urology
The University of Western Ontario
London, ON, Canada

J. Quentin Clemens, MD, FACS, MSCI
Division of Neurourology and Pelvic Reconstructive Surgery
University of Michigan Medical Center
Ann Arbor, MI, USA

Joshua A. Cohn, MD
Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, TN, USA

Bernadette Coles, MSc
University Library Service
Cardiff University
Cancer Research Wales Library
Velindre NHS Trust
Cardiff, UK

Michael S. Cookson, MD, MMHC
Department of Urology
University of Oklahoma College of Medicine
Oklahoma City, OK, USA

R. Matthew Coward, MD
Department of Urology
University of North Carolina School of Medicine
Chapel Hill, NC, USA

Jonathan C. Craig, MD
Centre for Kidney Research, The Children's
Hospital at Westmead
Westmead, NSW, Australia;
School of Public Health
University of Sydney
Sydney, NSW, Australia

Philipp Dahm, MD, MHSc, FACS
Minneapolis VA Medical Center, Urology Section
and Department of Urology
University of Minnesota
Minneapolis, MN, USA

Sia Daneshmand, MD
USC Institute of Urology
Keck School of Medicine
University of Southern California
Los Angeles, CA, USA

Shawn Dason, MD, FRCSC
Memorial Sloan Kettering Cancer Center
New York, NY, USA

Sumit Dave, MD
Division of Urology
The University of Western Ontario
London, ON, Canada

Fnu Deepinder, MD
Department of Endocrinology
Cedars Sinai Medical Center
Los Angeles, CA, USA

Justin M. Dersch, MD
Department of Urology
University of Florida
Gainesville, FL, USA
North Florida/South Georgia VAMC
Gainesville, FL, USA

Roger R. Dmochowski, MD, MMHC
Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, TN, USA

Michelle Echevarria, MD
Department of Radiation Oncology
Moffitt Cancer Center and Research Institute
University of South Florida
Tampa, FL, USA

Sean P. Elliott, MD, MS
Department of Urology
University of Minnesota
Minneapolis, MN, USA

Mir Sohail Fazeli, MD
Division of Pediatric Urology
Department of Urologic Sciences
University of British Columbia
Vancouver, BC, Canada

Robert A. Figlin, MD, FACP
Samuel Oschin Comprehensive Cancer Institute
Cedar Sinai Medical Center
Los Angeles, CA, USA

Arvin K. George, MD
Prostate Cancer Section, Urologic Oncology Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

Robert A. Goldfarb, MD
Chesapeake Urology Associates
Baltimore, MD, USA

Howard B. Goldman, MD, FACS
Glickman Urological and Kidney Institute
The Cleveland Clinic
Cleveland, OH, USA

Alex Gomelsky, MD
Department of Urology
Louisiana State University Health – Shreveport
Shreveport, LA, USA

Justin R. Gregg, MD
Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, TN, USA

Oliver W. Hakenberg, MD, PhD
Department of Urology
Rostock University
Rostock, Germany

Louise Harris, FRCR
Velindre Cancer Centre
Velindre NHS Trust
Cardiff, UK

Michael R. Harrison, MD
Division of Medical Oncology and Duke Cancer Institute
Department of Medicine
Duke University School of Medicine
Durham, NC, USA

Bryan J. Hill, MD
Department of Gynecology and Obstetrics
Division of Female Pelvic Medicine and Reconstructive Surgery
Loma Linda University
Loma Linda, CA, USA

Bryan Hinck, MD
Department of Urology
Glickman Urological and Kidney Institute
The Cleveland Clinic
Cleveland, OH, USA

John M. Hollingsworth, MD
Department of Urology
University of Michigan Medical Center
Ann Arbor, MI, USA

Cory Hugen, MD
School of Medicine
University of California
Irvine, CA, USA

Michael S. Humeniuk, MD
Division of Medical Oncology
Department of Medicine
Duke University School of Medicine
Durham, NC, USA

Ryan Hutchinson, MD
Department of Urology
University of Texas Southwestern Medical Center
Dallas, TX, USA

Ruiyang Jiang, MD
Division of Urologic Surgery
Duke University Medical Center
Durham, NC, USA

Peter A. Johnstone, MD
Department of Radiation Oncology
Moffitt Cancer Center and Research Institute
University of South Florida
Tampa, FL, USA

Jae Hung Jung, MD, PhD
Department of Urology
Yonsei University Wonju College of Medicine
Wonju, Republic of Korea;
Minneapolis VA Medical Center, Urology Section and
Department of Urology
University of Minnesota, Minneapolis, MN, USA

Alexander Karl, MD
Department of Urology
University Hospital Munich
Ludwig-Maximilians University
Munich, Germany

Melissa R. Kaufman, MD, PhD
Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, TN, USA

Tobias Klatte, MD
Department of Urology
Medical University of Vienna
Vienna General Hospital
Vienna, Austria

Laurence Klotz, MD, FRCSC, CM
Division of Urology
Sunnybrook Health Sciences Centre
University of Toronto
Toronto, ON, Canada

Christian Kollmannsberger, MD, FRCPC
Division of Medical Oncology
British Columbia Cancer Agency–Vancouver
Cancer Centre
University of British Columbia
Vancouver, BC, Canada

Badrinath R. Konety, MD, MBA
Department of Urology
University of Minnesota
Institute for Prostate and Urologic Cancers
Masonic Cancer Center
Minneapolis, MN, USA

Amy Krambeck, MD
Department of Urology
Mayo Clinic
Rochester, MN, USA

Alexander Kretschmer, MD
Department of Urology
University Hospital Munich
Ludwig-Maximilians University
Munich, Germany;
Department of Urological Sciences
University of British Columbia
Vancouver, BC, Canada

Satish Kumar, MD
School of Medicine
Cardiff University
Velindre Hospital
Velindre NHS Trust
Cardiff, UK

Luke T. Lavallée, MDCM, MSc, FRCSC
Division of Urology
Department of Surgery
The Ottawa Hospital Research Institute
The Ottawa Hospital/University of Ottawa
Ottawa, ON, Canada

Aaron H. Lay, MD
Department of Urology
Emory University School of Medicine
Atlanta, GA, USA

Derek J. Lomas, MD
Department of Urology
Mayo Clinic
Rochester, MN, USA

Yair Lotan, MD
Department of Urology
University of Texas Southwestern Medical Center
Dallas, TX, USA

Ilaria Lucca, MD
Department of Urology
Medical University of Vienna
Vienna General Hospital
Vienna, Austria;
Department of Urology
Centre Hospitalier Universitaire Vaudois
Lausanne, Switzerland

Giuseppe Magistro, MD
Department of Urology
Campus Grosshadern
Ludwig-Maximilians-Universität München
Munich, Germany

Altaf Mangera, MD
Department of Urology
Royal Hallamshire Hospital
Sheffield, UK

Malcolm Mason, MD
School of Medicine
Cardiff University
Velindre Hospital, Velindre NHS Trust
Cardiff, UK

Romain Mathieu, MD
Department of Urology
Rennes University Hospital
Rennes, France;
Department of Urology
Medical University of Vienna
Vienna General Hospital
Vienna, Austria

Justin T. Matulay, MD
Department of Urology
Columbia University Medical Center
New York, NY, USA

J. Abram McBride, MD
Department of Urology
University of North Carolina School of Medicine
Chapel Hill, NC, USA

James M. McKiernan, MD
Department of Urology
Columbia University Medical Center
New York, NY, USA

Megan A. McNamara, MD
Division of Medical Oncology
Department of Medicine
Duke University School of Medicine
Durham, NC, USA

Francesca V. Mertan, MD
Molecular Imaging Program
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

Vikram Narayan, MD
Department of Urology
University of Minnesota
Minneapolis, MN, USA

Ann Oldendorf, MD
University of Michigan Medical Center
Ann Arbor, MI, USA

Nadir I. Osman, MD
Department of Urology
Royal Hallamshire Hospital
Sheffield, UK

Brandon J. Otto, MD
Department of Urology
University of Florida
Gainesville, FL, USA
North Florida/South Georgia VAMC
Gainesville, FL, USA

Margaret S. Pearle, MD, PhD
Department of Urology
University of Texas Southwestern Medical Center
Dallas, TX, USA

David F. Penson, MD, MPH
Department of Urologic Surgery
Vanderbilt University Medical Center and VA Tennessee
Valley Healthcare System
Nashville, TN, USA

Nathan Perlis, MD, FRCSC
Division of Urology
Sunnybrook Health Sciences Centre
University of Toronto
Toronto, ON, Canada

Peter A. Pinto, MD
Prostate Cancer Section
Urologic Oncology Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

Frédérick Pouliot, MD, PhD, FRCSC
Centre de Recherche sur le Cancer
Université Laval
Ville de Québec, QB, Canada

Julio M. Pow-Sang, MD
Department of Genitourinary Oncology
Moffitt Cancer Center
Tampa, FL, USA

Glenn M. Preminger, MD
Comprehensive Kidney Stone Center
Division of Urologic Surgery
Duke University Medical Center
Durham, NC, USA

Sundhar Ramalingam, MD
Division of Medical Oncology
Department of Medicine
Duke University School of Medicine
Durham, NC, USA

Jay D. Raman, MD
Division of Urology
Penn State Health Milton S. Hershey Medical Center
Hershey, PA, USA

W. Stuart Reynolds, MD, MPH
Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, TN, USA

Michael C. Risk, MD, PhD
University of Minnesota and Minneapolis VA Medical Center
Minneapolis, MN, USA

Monique J. Roobol, MD
Erasmus University Medical Centre
Rotterdam, The Netherlands

Jonathan C. Routh, MD, MPH
Division of Urologic Surgery
Duke University Medical Center
Durham, NC, USA

Edmund S. Sabanegh, Jr., MD
Department of Urology
Cleveland Clinic Lerner College of Medicine
The Cleveland Clinic
Cleveland, OH, USA

Abhinav Sidana, MD
Prostate Cancer Section, Urologic Oncology Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

Yahir Santiago-Lastra, MD
University of Michigan Medical Center
Ann Arbor, MI, USA

Charles D. Scales, Jr., MD, MSHS
Duke Clinical Research Institute and Division of Urology
Department of Surgery
Duke University Medical Center
Durham, NC, USA

Shahrokh F. Shariat, MD
Department of Urology
Medical University of Vienna
Vienna General Hospital
Vienna, Austria;
Department of Urology
University of Texas Southwestern Medical Center at Dallas
Dallas, TX, USA;
Department of Urology
Weill Cornell Medical College
New York, NY, USA

Pranav Sharma, MD
Department of Urology
Texas Tech University Health Sciences Center
Lubbock, TX, USA

Phillip D. Stricker, MBBS
St. Vincent's Prostate Cancer Centre
Darlinghurst, NSW, Australia;
Garvan Institute of Medical Research
The Kinghorn Cancer Centre
Darlinghurst, NSW, Australia

Shahnaz Sultan, MD
Minneapolis VA Medical Center, Gastroenterology
Section and Department of Medicine
University of Minnesota
Minneapolis, MN, USA

Stacy T. Tanaka, MD, MS
Urologic Surgery and Pediatrics
Division of Pediatric Urology
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, TN, USA

Gregory E. Tasian, MD
Division of Urology
Children's Hospital of Philadelphia
Philadelphia, PA, USA

Timothy Y. Tseng, MD
Department of Urology
University of Texas Health Science Center at San Antonio
San Antonio, CA, USA

Baris Turkbey, MD, FSAR
Molecular Imaging Program
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

Przemyslaw W. Twardowski, MD
Department of Medical Oncology and Therapeutics Research
City of Hope National Medical Center
Duarte, CA, USA

Pim J. van Leeuwen, MD, PhD
St. Vincent's Prostate Cancer Centre
Darlinghurst, NSW, Australia;
Garvan Institute of Medical Research
The Kinghorn Cancer Centre
Darlinghurst, NSW, Australia

Philippe Violette, MD
Division of Urology
The University of Western Ontario
London, ON, Canada
Department of Surgery and Department of Health
Research Methods, Evidence and Impact
McMaster University
Hamilton, ON, Canada

Bryan B. Voelzke, MD, MS
Department of Urology
Harborview Medical Center
University of Washington School of Medicine
Seattle, WA, USA

Josip Vukina, MD
Department of Urology
University of North Carolina School of Medicine
Chapel Hill, NC, USA

Florian M.E. Wagenlehner, MD
Clinic for Urology, Pediatric Urology and Andrology
Justus-Liebig-Universität Giessen
Giessen, Germany

Matthew J. Watson, MD
Prostate Cancer Section, Urologic Oncology Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

Eric Webb, MD
Department of Genitourinary Oncology
Moffitt Cancer Center
Tampa, FL, USA

Angela C. Webster, MD
Centre for Kidney Research
The Children's Hospital at Westmead
Westmead, NSW, Australia;
Centre for Transplant and Renal Research
Westmead Hospital
Westmead, NSW, Australia;
School of Public Health
University of Sydney
Sydney, NSW, Australia

Hunter Wessells, MD, FACS
Department of Urology
University of Washington School of Medicine
Seattle, WA, USA

Gabrielle J. Williams, BSc (Hons), MPH, PhD
Centre for Kidney Research
The Children's Hospital at Westmead
Westmead, NSW, Australia;
School of Public Health
University of Sydney
Sydney, NSW, Australia

Kosj Yamoah, MD, PhD
Department of Radiation Oncology
Moffitt Cancer Center and Research Institute
University of South Florida
Tampa, FL, USA

Tian Zhang, MD
Division of Medical Oncology
Department of Medicine
Duke University School of Medicine
Durham, NC, USA

PART 1

Evidence-based methods

Philipp Dahm

1 CHAPTER 1

Searching for evidence

Jeanette Buckingham
John W. Scott Health Sciences Library, University of Alberta, Edmonton, AB, Canada

The shape of clinical literature

The mass of published literature now far exceeds our ability to cope with it as individuals; the evidence for practice is out there but in blinding volume and in a bewildering array of formats and platforms. Experienced clinicians in the past have tended to choose one or two principal sources of information, often old friends such as PubMed, a general journal such as *BMJ* or the *New England Journal of Medicine*, plus two or three journals in their specialty – say, *Urology*, *BJU International* or *European Urology* – and stick with them. This is no longer sufficient to allow a practitioner to keep up with new relevant and applicable clinical research. However, in a very positive turn of events over the past decade, the geometrically growing mass of published clinical research has brought with it the development of resources to summarize and synthesize this new knowledge and present it in methodologically sound and extremely accessible formats. Armed with these resources and a few relatively simple techniques, it is indeed possible to find evidence for practice quickly and efficiently.

The literature of evidence for practice follows a hierarchical structure based on the degree of processing and appraisal applied to the primary research literature [1] (see Box 1.1). Summaries and syntheses of the evidence, including practice guidelines, are at the top, followed by preappraised synopses, with primary studies at the base. Typically, the search for evidence for clinical practice starts at the top, in the summaries and syntheses, dropping down to synopses and systematic reviews. If a satisfactory result has not been found or if the searcher wishes for more recent evidence, primary research studies are the final resource. Unfortunately, the primary literature is massive: a simple PubMed search for prostate cancer at the time of this writing (November 2015) turned up over 131 000 references. Using Clinical Queries, as we recommend in PubMed to filter in the research literature, in this case for therapy studies, reduced the number to 3450 randomized controlled trials (RCTs) and 3271 systematic reviews. These very daunting numbers persuade clinicians of the value of starting at the top of the evidence pyramid for general questions. For more specific questions, search results will usually be less alarming.

Some "federated searches" are available that are structured to search simultaneously through all three categories of evidence and present the results according to evidence levels. TRIP (Turning Research Into Practice, https://www.tripdatabase.com) is one such search engine, freely accessible worldwide (registration is free and provides more unrestricted access to content than unregistered use).

The approach for finding evidence for practice is exactly the opposite of that for conducting a literature review at the beginning of a research project. In the case of the literature review, one conducts a thorough search of all appropriate bibliographic databases: MEDLINE (whether via PubMed or some other search interface), EMBASE, Web of Science, Scopus, Biosis Previews, plus resources such as the Cochrane Library, to ensure one has not missed an important controlled trial or systematic review, and databases listing clinical trials in progress, to ensure that all relevant studies have been found. If possible, one consults a research librarian to be sure that no stone has been left unturned.

However, to find evidence to apply to clinical problems, the search begins with synthesized resources, progresses through selected, preappraised resources, and moves into bibliographic databases of primary studies only if no satisfactory

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BOX 1.1 A hierarchy of resources.

1 Summaries, syntheses and guidelines
- **1.1** Point-of-care summaries (e.g. DynaMed, UpToDate)
- **1.2** Practice guidelines (e.g. NICE, International Guidelines Clearinghouse)
- **1.3** Evidence-based textbooks (e.g. *Campbell–Walsh Urology* and other textbooks available via Clinical Key, Access Medicine, and Books@Ovid)

2 Preappraised research
- **2.1** Synopses of systematic reviews (e.g. DARE [Database of Abstracts of Reviews of Effects], *ACP Journal Club*)
- **2.2** Systematic reviews (e.g. Cochrane Reviews)
- **2.3** Synopses of primary studies (e.g. *ACP Journal Club*, *Evidence-Based Medicine*, McMasterPLUS)

3 Primary studies
- **3.1** Filtered (e.g. Clinical Queries in MEDLINE/PubMed)
- **3.2** Unfiltered (e.g. PubMed, EMBASE, BIOSIS, Web of Science)

answer has been found in the first two resource classes. With a literature review, the search is exhaustive. With the search for clinical evidence, it is acceptable to stop when a good answer has been found.

Some of the resources described in this chapter are free; most are broadly available to those affiliated with medical societies or institutions or are available by individual subscription. New synthesized resources, point-of-care resources in particular, are continually emerging as established resources evolve. How does one choose among these resources? Availability and affordability are two obvious factors, but consider also how well a resource covers your discipline, how current the resource is, and how quickly it updates and includes new evidence, whether its inclusion practices are transparent and its authorship explicitly stated, whether the evidence is assessed for quality and citations are provided for all summaries and recommendations, and whether there are numerical estimates of effect provided within the summaries. Ease of use is vitally important. Some recent studies have compared point-of-care resources for currency, inclusion of new evidence, and ethical factors [2–4]. Consideration of all of these factors will assist clinicians to become enlightened consumers of complex information resources.

A case to consider

Mr. W, 63 years old and otherwise fit and healthy, has been referred to you with symptoms of benign prostatic hyperplasia (BPH) (frequency, nocturia, and slow flow). Digital rectal examination reveals an enlarged prostate gland, about 45 g, with no nodules. His postvoid is approximately 100 mL and he reports three documented urinary tract infections over the course of the last year. His serum creatinine and prostate-specific antigen (PSA) levels are normal.

He has been advised by his family physician that he may require surgery to resolve his condition. He is apprehensive about this and asks if there are medical interventions for the BPH that could be tried first. He has searched the web and has found information that saw palmetto may be an effective herbal remedy to improve his voiding symptoms.

What do you want? Asking a focused clinical question

The first two steps of the protocol of evidence-based practice (Assess, Ask, Acquire, Appraise, Apply) [5] involve *assessing* the situation – pulling out the salient features of a patient's presentation and history – and *asking* one or more questions that are both focused and answerable. Assessing the situation may require some background information about the condition itself – for example, "how does BPH promote voiding complaints?" Background information is most readily found in textbooks. Online textbooks are preferable to the heavy printed tomes of earlier years for reasons of accessibility and currency.

To find primary research evidence to apply to the patient at hand, however, a focused, answerable question must be crafted. Asking a focused clinical question is a mental discipline that will also pay off enormously in effective searching and in finding good evidence to apply to practice. Assigning a domain – therapy/prevention, diagnosis, prognosis, etiology/harm – is the essential first step in framing the question, because questions are asked differently, depending on the domain (Box 1.2). Often questions regarding a single case will fall into multiple domains. In this instance, separate focused questions for each relevant domain will result in clearer answers.

Once the domain has been established, the elements of the focused clinical question (PICOT) must be identified:

- *P* = Population. The patient's characteristics, including age, gender, and condition, plus other relevant clinical or medical history features.
- *I* = Intervention. What intervention are you considering using? In a diagnostic question, this becomes "what new test do I wish to try?" In a prognostic question, this equates to "prognostic factor," and in the harm/etiology domain, this becomes "exposure."
- *C* = Comparison. In the therapy domain, this might be the standard of care or a placebo, where this is appropriate; in diagnosis, the comparison is always the "gold standard" diagnostic test; in the case of a causation/etiology question, this obviously might be "no exposure"; and in prognosis, this might be the lack of the relevant prognostic factor.
- *O* = Outcome. For therapy, what changes are you seeking to accomplish in the patient's condition? Are they clinical changes, such as a reduction in the number of urinary tract infection (UTI) recurrences? Or are they surrogate, such as reduction in the size of the prostate? In diagnosis, how likely

BOX 1.2 The well-built clinical question (PICOT).

Therapy

Population (patient)

How would I describe a group of patients similar to mine? (condition, age, gender, setting, etc.)

Intervention (medication, procedure, etc.)

Which main/new intervention am I considering?

Comparison

What is the alternative to compare with the intervention? (placebo, standard of care, etc.)

Outcome

What might I accomplish, measure, improve, or affect?

Type of study

What study design would provide the best level of evidence for this question?

Diagnosis

Population (patient)

What are the characteristics of the patients? What is the condition that may be present?

Intervention (diagnostic test)

Which diagnostic test am I considering?

Comparison

What is the diagnostic gold standard (or reference standard if a gold standard is not feasible)?

Outcome

How likely is the test to predict/rule out this condition?

Type of study

What study design would provide the best level of evidence for this question?

Prognosis

Population (patient)

How would I describe a cohort of patients similar to mine (stage of condition, age, gender, etc.)?

Intervention (prognostic factor)

Which main prognostic factor am I considering?

Comparison (optional)

What is the comparison group, if any?

Outcome

What disease progression can be expected (mortality, morbidity, outcomes)?

Type of study

What study design would provide the best level of evidence for this question?

Harm/Causation/Etiology

Population (patient)

How would I describe a group of patients similar to mine?

Intervention (exposure, risk factor)

Which main exposure/risk factor am I considering?

Comparison

What is the main alternative to compare with the exposure (e.g. no exposure)?

Outcome

How is the incidence or prevalence of the condition in this group affected by this exposure?

Type of study

What study design would provide the best level of evidence for this question?

Table 1.1 A simplified hierarchy of evidence.

Therapy
Level 1. Systematic review of randomized controlled trials or n of 1 trials
Level 2. Individual randomized controlled trials or observational studies with dramatic effects
Level 3. Nonrandomized cohort or follow-up studies
Level 4. Case series, case-control, case studies, or retrospective studies
Level 5. Expert opinion, bench research, or mechanism-based reasoning
Diagnosis
Level 1. Systematic review of cross-sectional studies with consistently applied reference standard and blinding
Level 2. Individual cross-sectional studies with consistently applied reference standard and blinding
Level 3. Nonconsecutive studies or studies without consistently applied reference standards.
Level 4. Case–control studies or studies with poor reference standards
Level 5. Mechanism-based reasoning
Prognosis
Level 1. Systematic review of inception cohort studies
Level 2. Individual inception cohort studies
Level 3. Cohort study or control arm of a randomized controlled trial
Level 4. Case series or case–control studies, or poor quality cohort study
Harm
Level 1. Systematic review of randomized trials, or systematic review of case–control studies based in the population of cohort studies
Level 2. Individual randomized trials or individual case–control studies based in the population of cohort studies
Level 3. Nonrandomized trials or follow-up studies
Level 4. Case series, case–control studies or retrospective studies
Level 5. Mechanism-based reasoning

Source: Data from Oxford Centre for Evidence-Based Medicine, OCEBM Levels of Evidence Working Group [6].

is the new test, in comparison with the gold standard, to predict or rule out the presence of a condition? In a prognostic question – often the most important for the patient – what is the expected disease progression? And in the etiology domain, how closely is this risk factor associated with the condition?

- *T*=Type of study. What study design will generate the best level of evidence with which to answer this question? This will vary from domain to domain, and also depending upon the subject itself (see Table 1.1).

Although the pinnacle of research quality is usually considered to be the double-blinded RCT or systematic reviews of such studies, blinding and randomization are not feasible for many kinds of investigations, particularly in surgery. Similarly, strong observational studies, specifically prospective cohort studies, are most appropriate for the prognosis domain. RCTs cannot be carried out for studies of diagnostic tests, because all subjects must receive both the gold standard test and the investigational test. For etiological studies, although RCTs are perhaps the ideal way of testing adverse drug reactions, they are ethically inappropriate for potentially

harmful exposures, so case–control studies from a cohort group are perhaps the most appropriate. The Oxford Centre for Evidence-Based Medicine has a well-established table of levels of evidence appropriate for the various domains [6]. The key with study design is flexibility: the point is to find the best available evidence (as opposed to the best possible) that is relevant to the topic and applicable to the patient.

The points extracted into a PICOT structure may be framed into a question. In the case example, for instance, one question might be "In an otherwise healthy 63 year old with BPH (P), how effective is medical therapy (I), compared with surgery (C), in reducing lower urinary tract symptoms (O), as demonstrated in an randomized controlled trial or systematic review of randomized controlled trials (T)?"

Searching for clinical evidence: start with synthesized sources

First look for sources that have synthesized the best available evidence. The first mental question that must be asked is, "How common is this situation and how likely am I to find an answer derived from the best evidence?" The more common a condition is, the more likely it is that good summarized point-of-care resources and practice guidelines will be available (Box 1.1). The next step down would be pre-appraised sources, including systematic reviews (which arguably could also be considered synthesized sources), and synopses of both systematic reviews and good-quality individual clinical studies. Finally, if nothing that specifically addresses your question emerges from these two sources, delve into primary studies. The following sections provide examples of how to access a selection of these resources.

Point-of-care summaries

Point-of-care information resources have been available as long as medicine has been practiced, traditionally taking the form of handbooks and textbooks. The key is to look for references to find where their information came from, whether those sources were grounded in primary research, and, if so, whether that research is believable, important, and applicable to your patients.

Point-of-care resources available now are very different from the traditional handbooks. They are elaborately produced, explicitly linked to the evidence, and designed for rapid, easy use by clinicians. The best of them incorporate aspects of systematic reviews into their methodology, requiring critical appraisal of the primary research that they cite and discussion of the quality of evidence behind recommendations made.

Our example is DynaMed, an evidence-based, peer-reviewed point-of-care resource, with somewhat broad subject coverage, very rapid updating, and explicit links to the primary literature and practice guidelines supporting its statements and recommendations. DynaMed provides extensive coverage of causation and risk factors, complications and prognosis, in addition to presenting in an outline format approaches to history taking, physical examination, and diagnosis, prevention, and treatment. The coverage for urology appears to be very good. It is available by subscription worldwide and is also available to members of universities, teaching hospitals, and associations, such as the Canadian Medical Association. Further information is available at DynaMed's website, www.dynamed.com.

Let us see how DynaMed handles our question about medical management of BPH. A simple search for BPH produced the outline for a chapter on benign prostatic hyperplasia (Figure 1.1). This search was done in mid-November 2015: note the update of 2 November 2015, referring to a NICE practice guideline on lower urinary tract symptoms.

To begin to address our query regarding the effectiveness of medical treatment of BPH, we will look at the treatment outline. Note that there are recommendations in the outline that indicate simply the level of evidence but not the source. To find the actual evidence, we would click on the hotlink for the specific therapy—alpha-1 blockers, for example, or diet (Figure 1.2) – and find both a summary of the evidence and a link to the PubMed record for the relevant study or studies; this in turn provides a direct link to the original article.

Scrolling down past surgical interventions, we find "phytotherapies" (Figure 1.3).

To delve further into the evidence behind this summary statement in search of an answer for our patient's question, we click on the link for saw palmetto (Figure 1.4), and find information that is more in depth, leading to the studies that were the evidence behind their recommendations(Figure 1.5).

If we wish to pursue this to the actual study, the active link provides us access through PubMed (Figures 1.6 and 1.7).

Beyond evidence-based recommendations for the management of specific conditions, DynaMed also provides direct access to national and international practice guidelines and links for patient information (Figure 1.8).

Practice guidelines

Practice guidelines focus on patient management and summarize current standards of care. The best guidelines are based explicitly on the best available clinical evidence, indicating levels and grades of evidence supporting each recommendation and linking to the primary research on which the recommendation is based. The source and purpose of individual guidelines are important: are the guidelines produced by professional societies to promote optimum care or are they the product of healthcare providers such as health maintenance organizations (HMOs) or insurers, where the aim might be cost-effectiveness in disease management. The American Urological Association

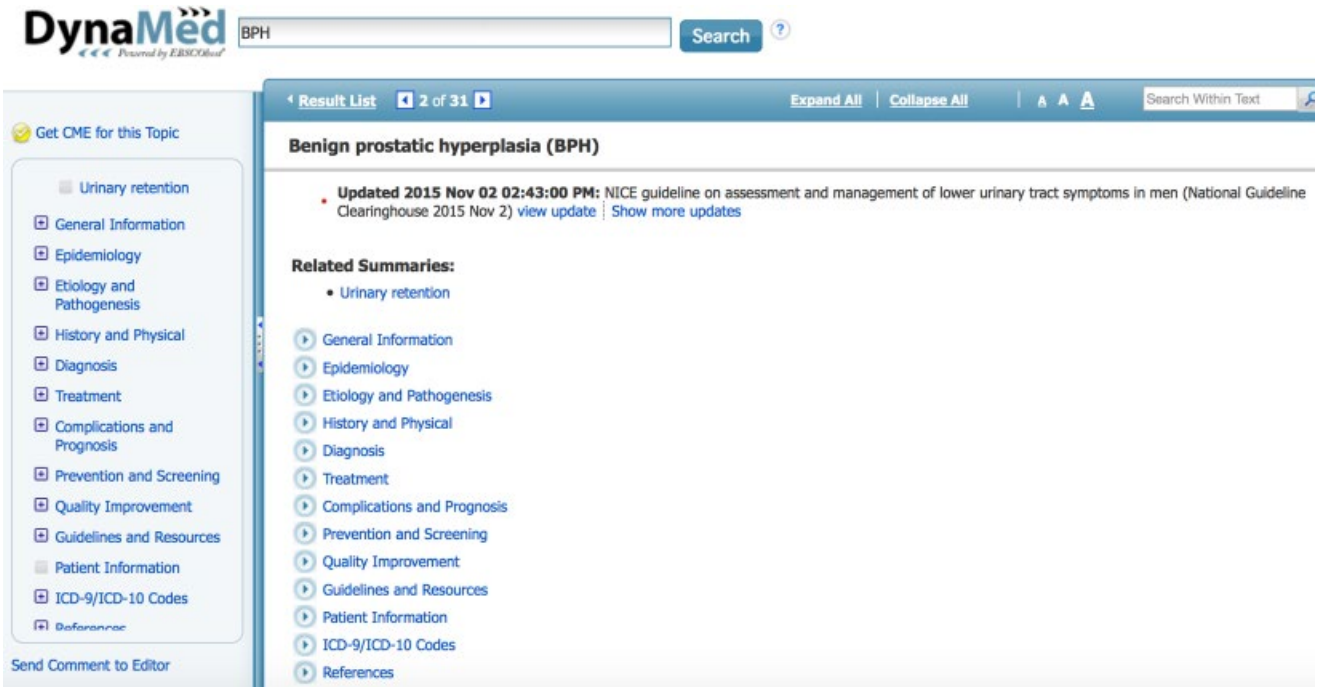


Figure 1.1 A screenshot from DynaMed on BPH showing the chapter outline.

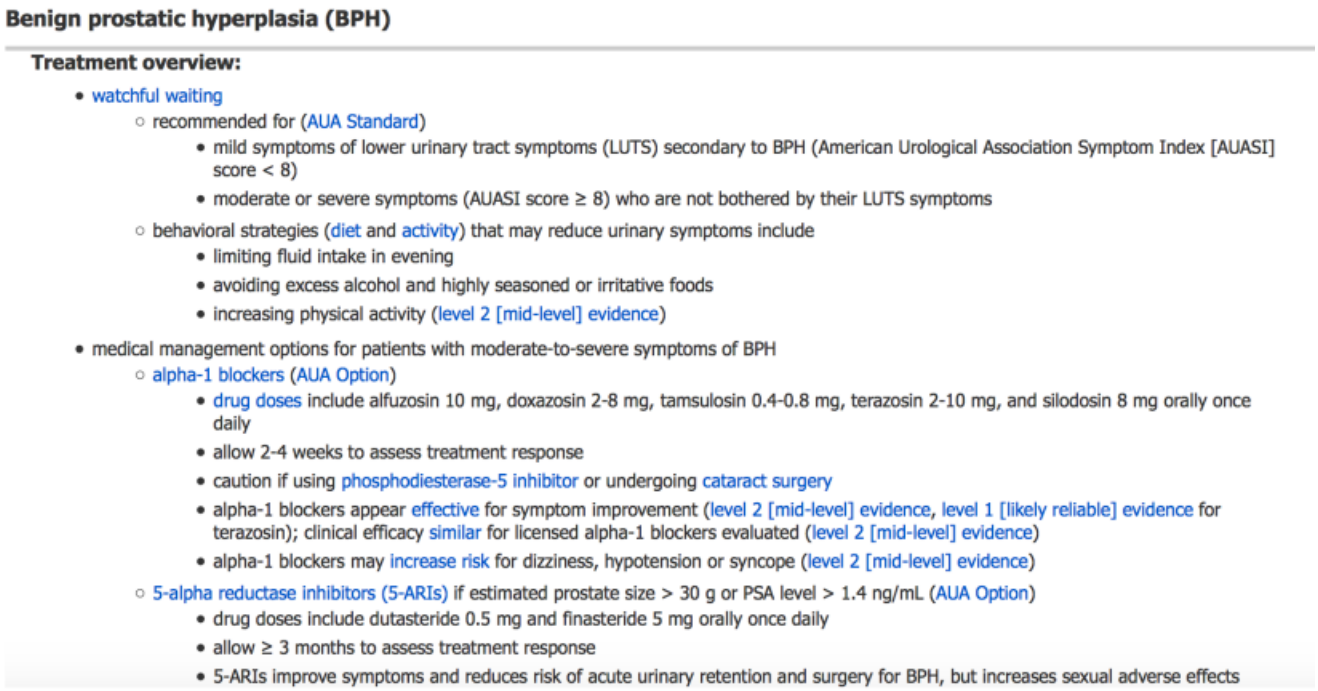


Figure 1.2 Screenshot from DynaMed on BPH on behavioral and medical therapy.

guidelines are available free of charge at the Association's website, www.auanet.org/guidelines. European Association of Urology guidelines are also available for members (or for a fee for nonmembers) from the association's website, www.uroweb.org.

National Guideline Clearinghouse (www.guideline.gov) is an excellent international source of practice guidelines, available free as an initiative of the Agency for Healthcare Research and Quality (AHRQ) in the United States. The National Guideline Clearinghouse has inclusion criteria:

- surgical options include
  - transurethral resection of the prostate (TURP) (AUA Option)
  - transurethral vaporization of the prostate (AUA Option)
  - transurethral incision of the prostate (TUIP) if estimated prostate size < 30 g (AUA Option)
  - laser therapies (AUA Option)
  - prostatectomy if estimated prostate size > 80 g (AUA Option)
- most transurethral surgical treatments appear to have similar efficacy for reducing LUTS due to BPH (level 2 [mid-level] evidence)

- prostatic urethral lift (UroLift) improves lower urinary tract symptoms in men with benign prostatic hypertrophy without increasing risk of erectile dysfunction (level 1 [likely reliable] evidence)
- minimally invasive therapies
  - treatment options for bothersome moderate or severe LUTS due to BPH include
    - transurethral needle ablation (TUNA) (AUA Option)
    - transurethral microwave thermotherapy (TUMT) (AUA Option)
  - National Institute for Health and Care Excellence (NICE) recommends AGAINST offering minimally invasive treatments
  - limited evidence to determine which minimally invasive intervention is most effective, but all appear less effective than TURP (level 2 [mid-level] evidence)
- phytotherapies, dietary supplements, and other nonconventional therapies not recommended for management of LUTS due to BPH (AUA Recommendation)
  - some specific saw palmetto extracts shown not to improve LUTS in men with BPH (level 1 [likely reliable] evidence), effect of saw palmetto (considering any formulation) on urinary symptoms appears inconsistent (level 2 [mid-level] evidence)
  - phytotherapies with possible efficacy include beta-sitosterols, Pygeum africanum (African plum), and Cernilton (rey grass extract) (level 2 [mid-level] evidence)

Figure 1.3 A screenshot from DynaMed on BPH showing on surgical treatment options.

Benign prostatic hyperplasia (BPH)

Herbal treatments:

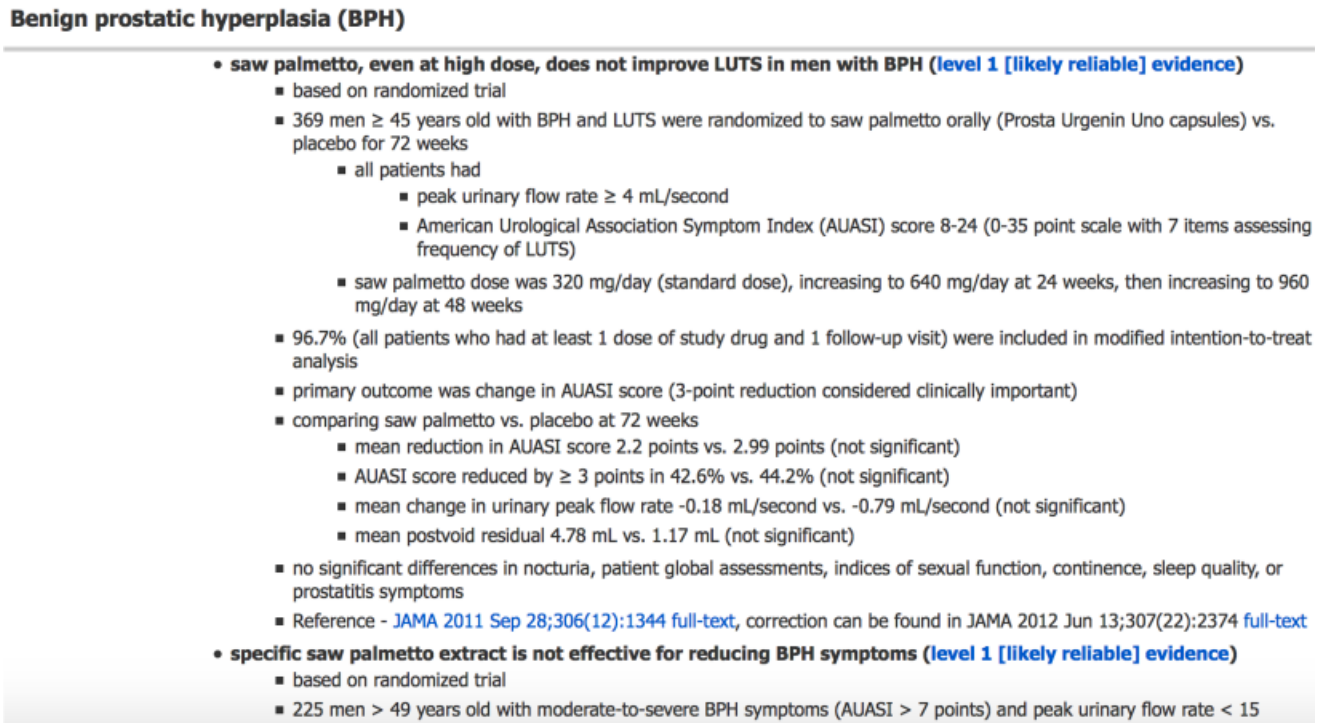
- no dietary supplement, combination phytotherapeutic agent, or other nonconventional therapy is recommended for management of LUTS secondary to BPH (AUA Recommendation)[1]
- National Institute for Health and Care Excellence (NICE) recommends against offering homeopathy or phytotherapy for treating LUTS in men[2]

Saw palmetto:

- available data do not suggest that saw palmetto has clinically meaningful effect on LUTS secondary to BPH (AUA Recommendation)[1]
- general information
  - also called saw palmetto berry, *Serenoa repens*, palmetto scrub, *Sabal serrulata*, *Sabalis serrulatae*, sago palm
  - medications with this ingredient include Permixon, PA109, Curbicin, Prostagalen, Prostaselect, Prostavigol, Strogen forte; based on purified lipid soluble extract of saw palmetto berry
  - mild adverse effects include headache, nausea, dizziness, 3.1% hypertension with Permixon in 1 study, diarrhea with high doses
  - no serious drug interactions, although studies generally excluded patients on diuretics, alpha blockers and anticoagulants
  - concerns
    - long-term effects on lipids and bone density unknown
    - many companies combine with other ingredients
    - trials done on commercial European products which may not be available in United States
  - Reference - Alternative Medicine Alert 1998 Jan;1(1):1
- mechanism of action unclear
  - active ingredient believed to be beta-sitosterol (Alternative Medicine Alert 1998 Jan;1(1):1)
  - saw palmetto is biochemically distinct from beta-sitosterol, saw palmetto (but not beta-sitosterol) may have alpha-1-adrenergic-blocking properties (ACP J Club 2000 May-Jun;132(3):94)

Figure 1.4 A screenshot from DynaMed on BPH with basic information on herbal treatments such as saw palmetto.

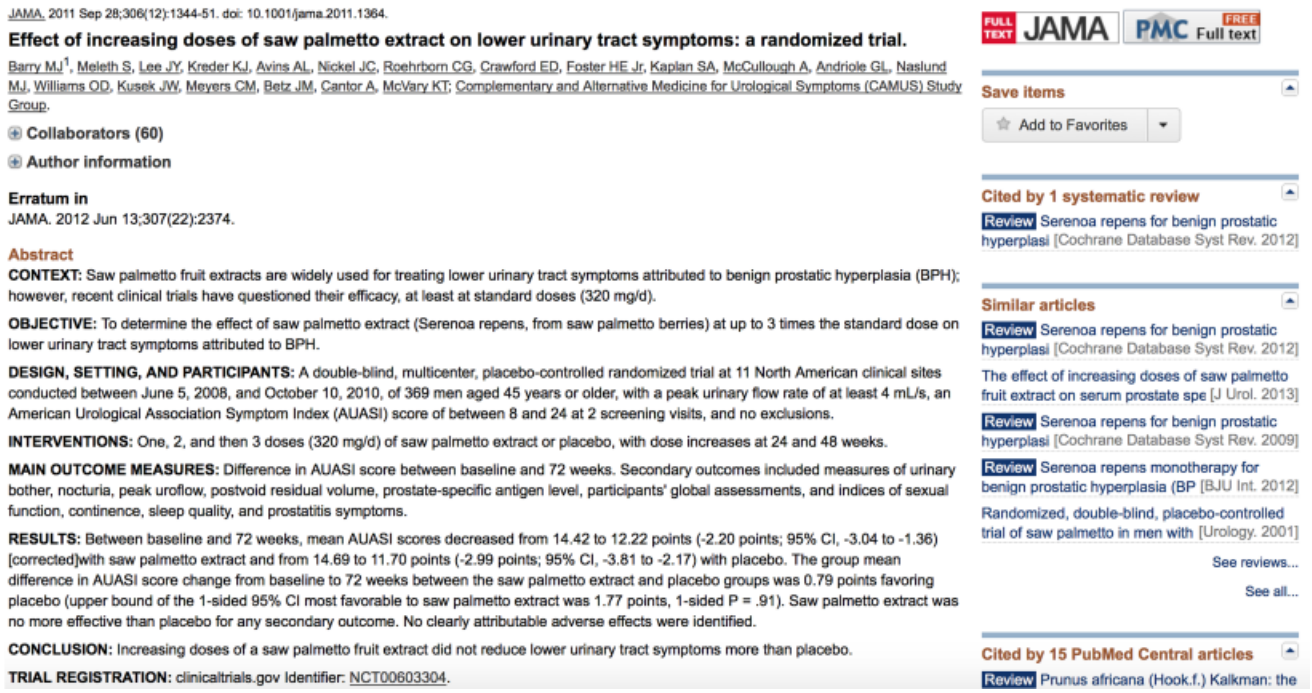
guidelines must have systematically developed recommendations or information that will assist health professionals in deciding on appropriate care, must be produced by public or private medical organizations, and must be supported by a systematic review of the literature. The full text of each guideline must also be available, and it must have been produced or revised within the past 5 years. One particular bonus in searching the National Guideline Clearinghouse is that multiple guidelines on similar topics may be compared at all points, from purpose to recommendations. For



Benign prostatic hyperplasia (BPH)

- **saw palmetto, even at high dose, does not improve LUTS in men with BPH (level 1 [likely reliable] evidence)**
  - based on randomized trial
  - 369 men ≥ 45 years old with BPH and LUTS were randomized to saw palmetto orally (Prosta Urgenin Uno capsules) vs. placebo for 72 weeks
    - all patients had
      - peak urinary flow rate ≥ 4 mL/second
      - American Urological Association Symptom Index (AUASI) score 8-24 (0-35 point scale with 7 items assessing frequency of LUTS)
    - saw palmetto dose was 320 mg/day (standard dose), increasing to 640 mg/day at 24 weeks, then increasing to 960 mg/day at 48 weeks
  - 96.7% (all patients who had at least 1 dose of study drug and 1 follow-up visit) were included in modified intention-to-treat analysis
  - primary outcome was change in AUASI score (3-point reduction considered clinically important)
  - comparing saw palmetto vs. placebo at 72 weeks
    - mean reduction in AUASI score 2.2 points vs. 2.99 points (not significant)
    - AUASI score reduced by ≥ 3 points in 42.6% vs. 44.2% (not significant)
    - mean change in urinary peak flow rate -0.18 mL/second vs. -0.79 mL/second (not significant)
    - mean postvoid residual 4.78 mL vs. 1.17 mL (not significant)
  - no significant differences in nocturia, patient global assessments, indices of sexual function, continence, sleep quality, or prostatitis symptoms
  - Reference - JAMA 2011 Sep 28;306(12):1344 full-text, correction can be found in JAMA 2012 Jun 13;307(22):2374 full-text
- **specific saw palmetto extract is not effective for reducing BPH symptoms (level 1 [likely reliable] evidence)**
  - based on randomized trial
  - 225 men > 49 years old with moderate-to-severe BPH symptoms (AUASI > 7 points) and peak urinary flow rate < 15

Figure 1.5 A screenshot from DynaMed on BPH detailing trial information on saw palmetto.



JAMA. 2011 Sep 28;306(12):1344-51. doi: 10.1001/jama.2011.1364.

Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: a randomized trial.

Barry MJ[1], Meleth S, Lee JY, Kreder KJ, Avins AL, Nickel JC, Roehrborn CG, Crawford ED, Foster HE Jr, Kaplan SA, McCullough A, Andriole GL, Naslund MJ, Williams OD, Kusek JW, Meyers CM, Betz JM, Cantor A, McVary KT; Complementary and Alternative Medicine for Urological Symptoms (CAMUS) Study Group.

Collaborators (60)

Author information

Erratum in
JAMA. 2012 Jun 13;307(22):2374.

Abstract

CONTEXT: Saw palmetto fruit extracts are widely used for treating lower urinary tract symptoms attributed to benign prostatic hyperplasia (BPH); however, recent clinical trials have questioned their efficacy, at least at standard doses (320 mg/d).

OBJECTIVE: To determine the effect of saw palmetto extract (Serenoa repens, from saw palmetto berries) at up to 3 times the standard dose on lower urinary tract symptoms attributed to BPH.

DESIGN, SETTING, AND PARTICIPANTS: A double-blind, multicenter, placebo-controlled randomized trial at 11 North American clinical sites conducted between June 5, 2008, and October 10, 2010, of 369 men aged 45 years or older, with a peak urinary flow rate of at least 4 mL/s, an American Urological Association Symptom Index (AUASI) score of between 8 and 24 at 2 screening visits, and no exclusions.

INTERVENTIONS: One, 2, and then 3 doses (320 mg/d) of saw palmetto extract or placebo, with dose increases at 24 and 48 weeks.

MAIN OUTCOME MEASURES: Difference in AUASI score between baseline and 72 weeks. Secondary outcomes included measures of urinary bother, nocturia, peak uroflow, postvoid residual volume, prostate-specific antigen level, participants' global assessments, and indices of sexual function, continence, sleep quality, and prostatitis symptoms.

RESULTS: Between baseline and 72 weeks, mean AUASI scores decreased from 14.42 to 12.22 points (-2.20 points; 95% CI, -3.04 to -1.36) [corrected]with saw palmetto extract and from 14.69 to 11.70 points (-2.99 points; 95% CI, -3.81 to -2.17) with placebo. The group mean difference in AUASI score change from baseline to 72 weeks between the saw palmetto extract and placebo groups was 0.79 points favoring placebo (upper bound of the 1-sided 95% CI most favorable to saw palmetto extract was 1.77 points, 1-sided P = .91). Saw palmetto extract was no more effective than placebo for any secondary outcome. No clearly attributable adverse effects were identified.

CONCLUSION: Increasing doses of a saw palmetto fruit extract did not reduce lower urinary tract symptoms more than placebo.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00603304.

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The effect of increasing doses of saw palmetto fruit extract on serum prostate spe [J Urol. 2013]

Review Serenoa repens for benign prostatic hyperplasi [Cochrane Database Syst Rev. 2009]

Review Serenoa repens monotherapy for benign prostatic hyperplasia (BP [BJU Int. 2012]

Randomized, double-blind, placebo-controlled trial of saw palmetto in men with [Urology. 2001]

See reviews...

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Cited by 15 PubMed Central articles

Review Prunus africana (Hook.f.) Kalkman: the

Figure 1.6 PubMed record.

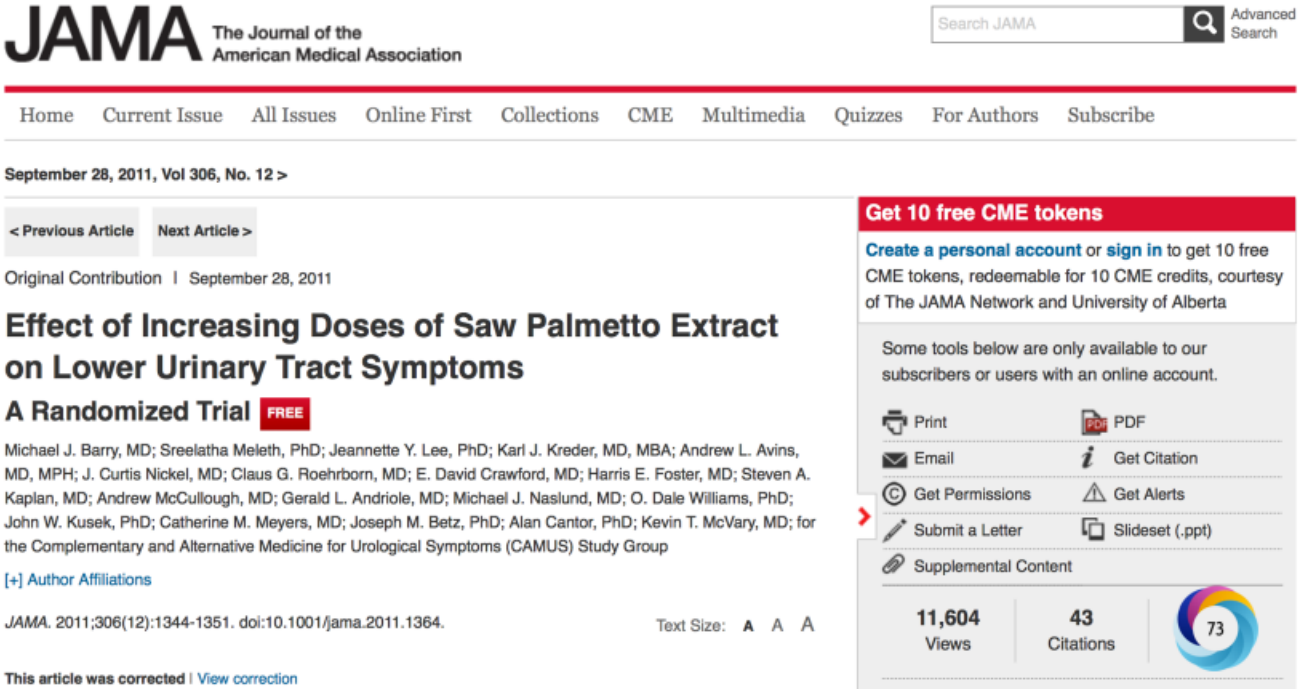

Figure 1.7 Online article on the *JAMA* website.

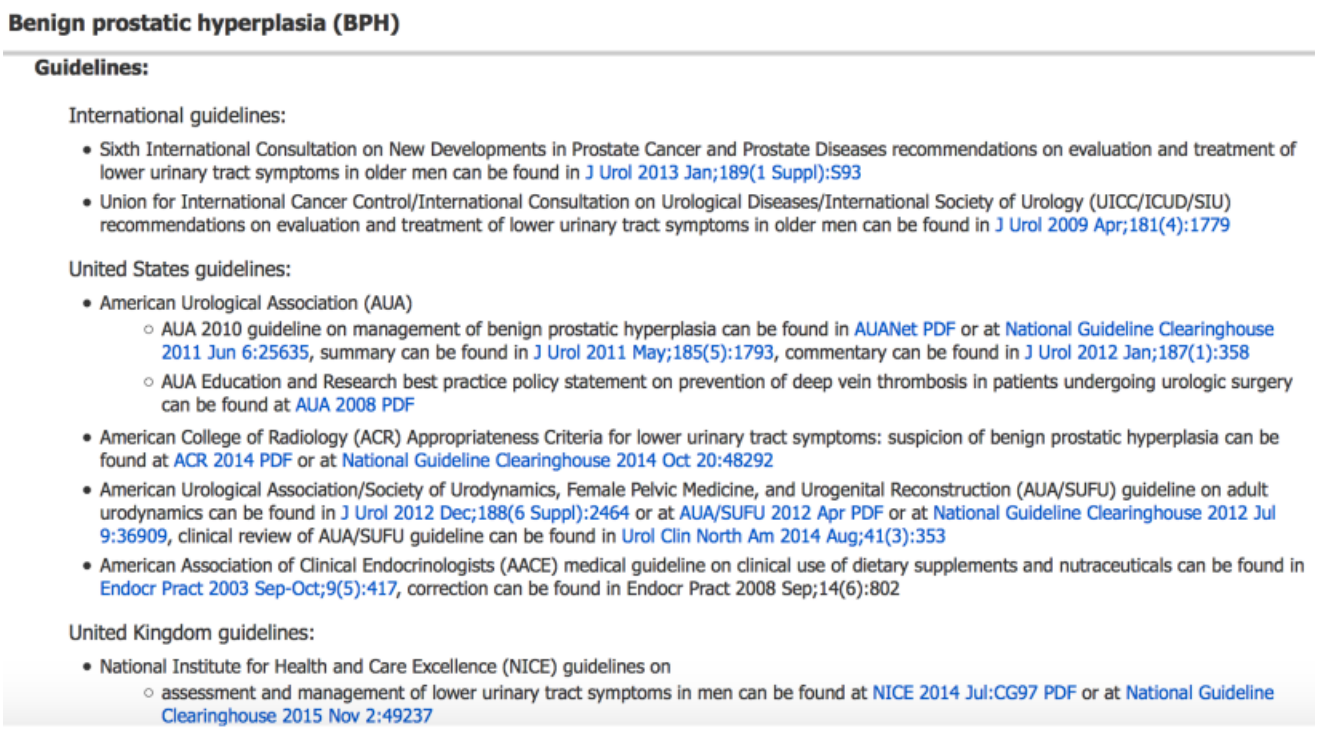

Figure 1.8 Practice guideline links on DynaMed.

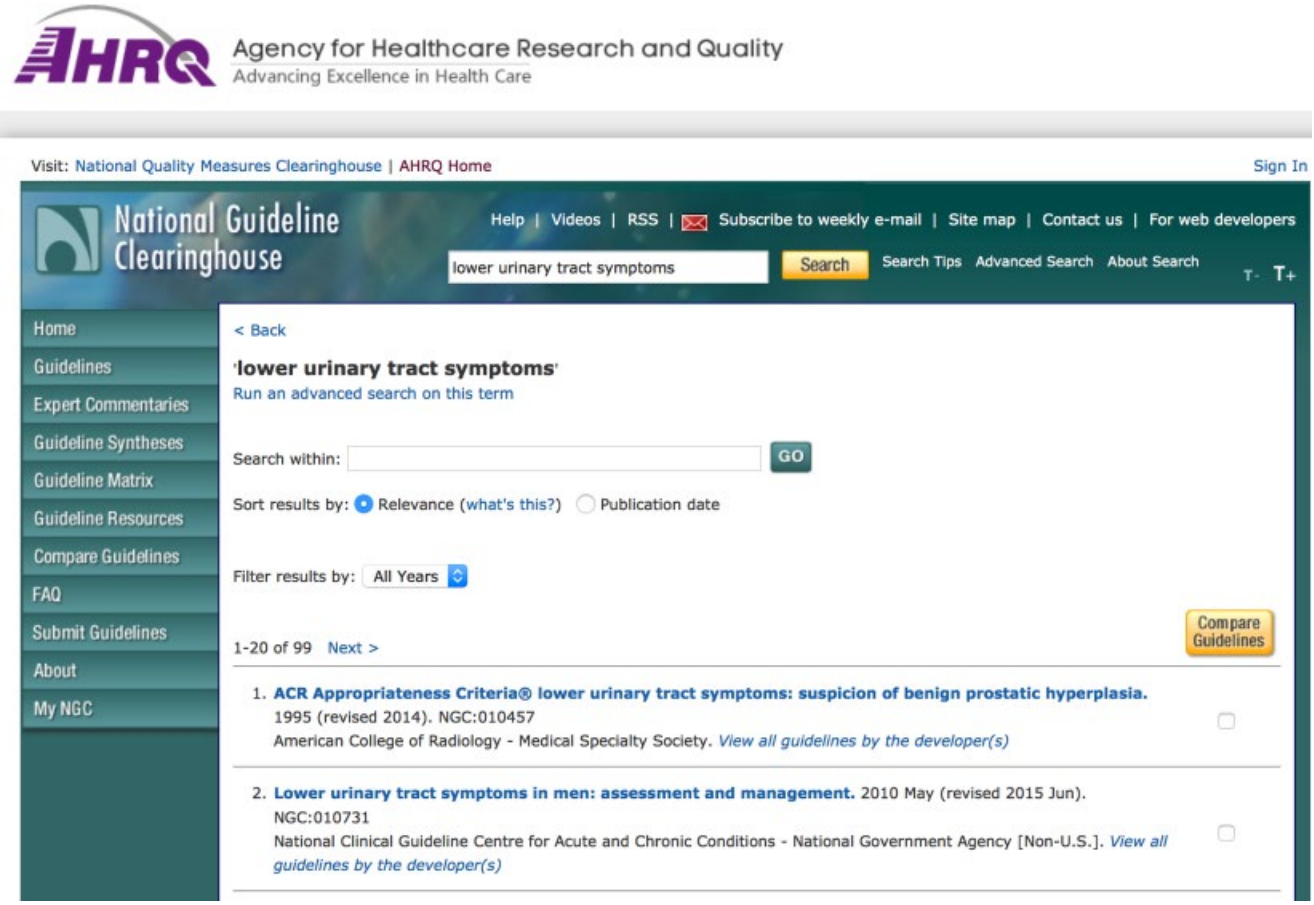

Figure 1.9 National Guideline Clearinghouse.

the question we are considering, a search on this website for "lower urinary tract symptoms" produced 99 relevant guidelines (Figure 1.9).

NICE (National Institute for Health and Care Excellence) provides practice guidelines and guidances (www.nice.org.uk/guidance). Under the broad topic of "urology" are several guidelines, including one on lower urinary tract symptoms in men, which would be highly useful in this case. NHS Clinical Knowledge Summaries are excellent practice guidelines and are available free of charge in the United Kingdom (http://cks.clarity.co.uk) and by subscription internationally (http://prodigy.clarity.co.uk).

TRIP – Turning Research Into Practice (www.tripdatabase.com) – is a federated search engine that presents a quick way of searching for guidelines, as well as searching other resources on a topic (Figure 1.10). A search for "lower urinary tract symptoms" on TRIP produced 446 North American, 363 British, 112 Australian/New Zealand, and 25 other practice guidelines, with functional links for access. Beyond providing an quick route to practice guidelines, TRIP searches evidence-based practice digests of important journal articles (e.g. *Evidence-Based Medicine*), searches for systematic reviews in both Cochrane and DARE, links to e-textbook articles, and searches PubMed applying simultaneously the quality filters for all four clinical query domains of Therapy, Diagnosis, Etiology, and Prognosis (this will be discussed later). Search results are organized hierarchically, according to evidence type.

Systematic reviews

In systematic reviews, primary research on a topic is thoroughly searched, selected through explicit inclusion criteria, and critically appraised to provide a reliable overview of a topic. Data from the included studies may be pooled (meta-analysis) to produce a statistical summary of the studies' findings.

Systematic reviews have existed since the 1970s in other disciplines but came into their own for medicine in the 1990s, with the advent of the Cochrane Collaboration. The purpose of the Cochrane Collaboration is to facilitate knowledge transfer from research to practice, and its influence on medical publishing has certainly achieved that [7]. Cochrane review groups collaborate to produce the highest standard of systematic reviews of clinical research. Among other review groups, there is a Cochrane Prostatic Diseases and Urologic

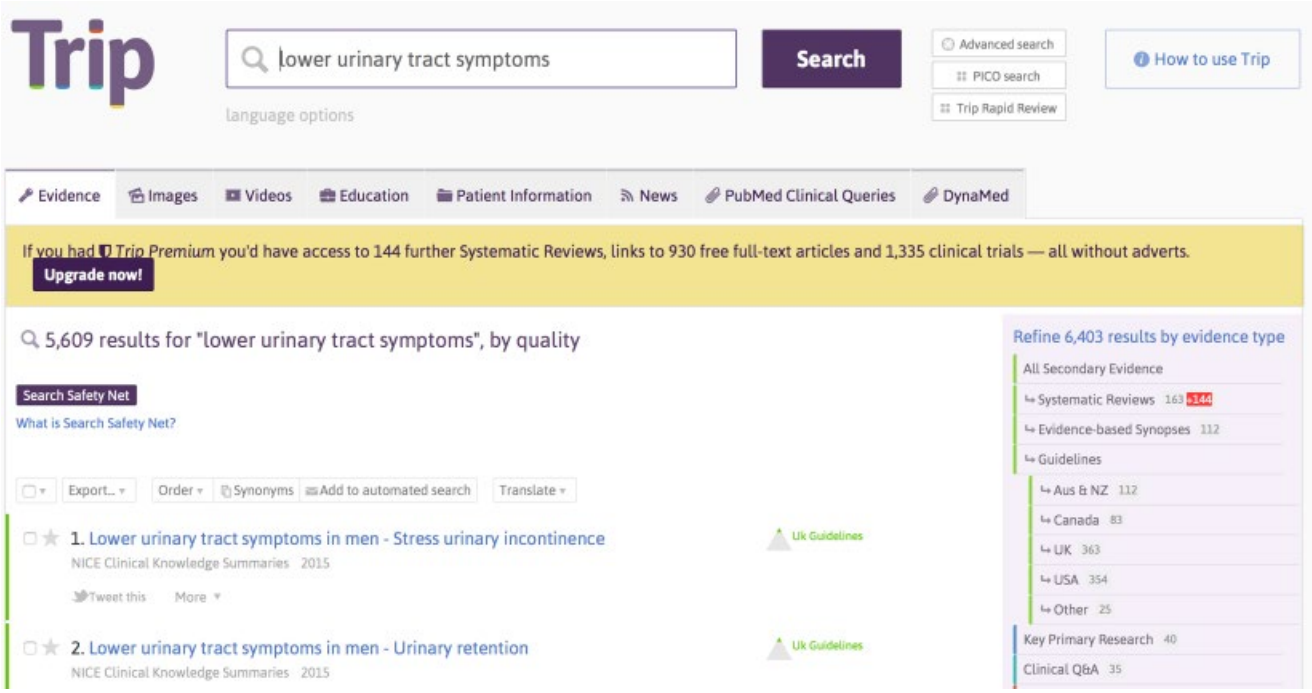

Figure 1.10 TRIP (Turning Research Into Practice) – a federated search engine.

Cancers Group, a Cochrane Renal Group, and also a Cochrane Incontinence Group, all of them producing a substantial volume of high-quality systematic reviews. Although Cochrane Reviews tend to be very long, quick clinically oriented information can be found either in the "plain language summary" or by going directly to the "forest plots," which provide graphic presentations of the data summaries (meta-analyses) contained in the review. (For a detailed description of Cochrane Reviews and the work of the Cochrane Collaboration, see www.cochrane.org.) Previously, review articles were much relied upon for clinical information but were a mixed and often subjective bag. Cochrane systematic reviews implied an elaborate methodological protocol and became the quality benchmark for evidence for practice and for published reviews.

The Cochrane Library, which includes the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE, an index with commentary of systematic reviews other than Cochrane Reviews), the Central Registry of Controlled Trials, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database, is an excellent source of evidence for urologists. In the example, a search for "lower urinary tract symptoms" in the Cochrane Library (Figure 1.11) turned up, among other references, a Cochrane Review assessing the effectiveness of saw palmetto (*Serenoa repens*) for BPH [8], providing an answer for one of the patient's questions in our case. On the broad topic of LUTS, the Cochrane Library also produced a substantial number of Cochrane Reviews, other published systematic reviews from DARE, clinical trials from Central, and useful studies from the Health Technology Assessment database and the NHS Economic Evaluations Database.

Textbooks and handbooks

Textbooks, particularly specialist textbooks such as *Campbell's Urology*, have been a mainstay of clinical information throughout the history of medicine. Over the past decade, however, most of the standard medical textbooks have become available in an electronic format, which changes continuously (as opposed to the large paper volumes that appear in new editions every few years). Most electronic textbooks and sets are searchable simply by keywords. Electronic textbooks usually are grouped into collections, such as Clinical Key (which includes *Campbell's Urology*), Access Medicine, and Books@Ovid. These sets are available through professional associations, universities, hospitals, or other administrative groups, and also through personal subscription.

NCBI Bookshelf (www.ncbi.nlm.nih.gov/sites/entrez?db=Books&itool=toolbar) (searchable) is available at no cost. E-Medicine is an excellent free textbook, triple peer reviewed and with good urology content (www.emedicine.com/urology/index.shtml); it is most easily searchable via TRIP.

The key with all textbooks is to ensure that they are evidence based, as demonstrated by footnotes and bibliographies. With electronic textbooks, usually the notes are linked

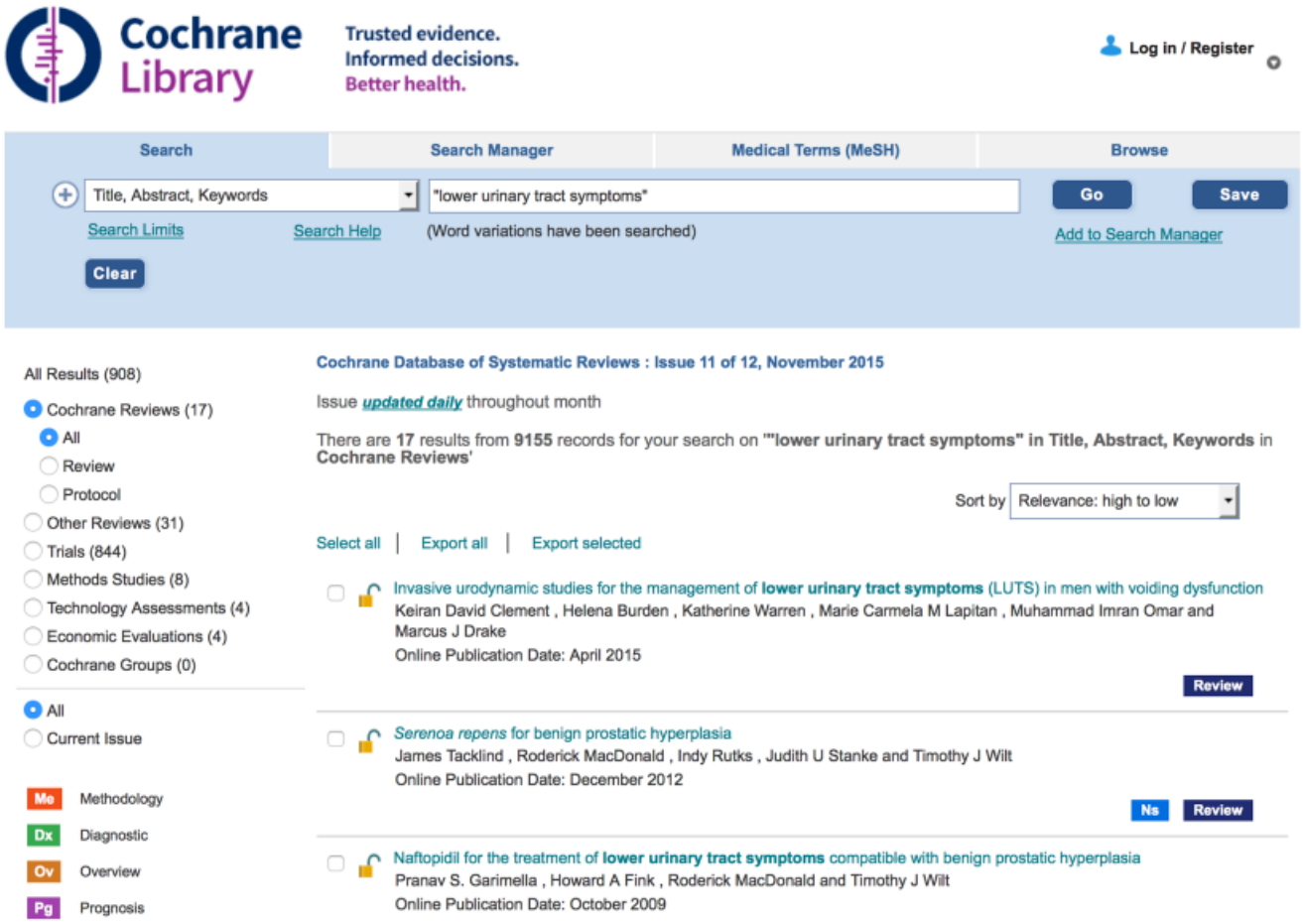

Figure 1.11 Cochrane Library.

to the references, which in turn are linked to the PubMed record, allowing the reader to track back to the evidence underlying a statement.

Searching for clinical evidence: try preappraised sources next

In response to the volume of published clinical research and the need to extract the best and most important studies to inform practitioners, *ACP Journal Club* (*ACP JC*) (http://www.acpjc.org) emerged in 1991; since 2005 it has continued as a section of *Annals of Internal Medicine*. *ACP JC* provides expanded structured abstracts of articles selected from core clinical journals by an editorial board, plus a thumbnail critical appraisal of the validity, importance, and applicability of the study, all usually in a single page. *Evidence-Based Medicine* (http://ebm.bmj.com) (now *BMJ Evidence-Based Medicine*) emerged shortly thereafter, based on *ACP JC* but expanding its subject coverage beyond internal medicine to include pediatrics, surgery, obstetrics, and other disciplines. Now both sources include ratings, applied by a panel of clinical experts, showing the relative importance and newsworthiness of each study, according to discipline. *Evidence-Based Medicine* can be searched by keyword and is also available via the federated search engine TRIP.

Evidence Updates from BMJ (http://plus.mcmaster.ca/EvidenceUpdates) (now *EvidenceAlerts*, http://plus.mcmaster.ca/EvidenceAlerts), a collaboration between *BMJ* and McMaster University's Health Information Research Unit, selects important articles from an array of 130 core journals, rates them for their importance, and provides expanded structured abstracts, but does not go the additional step of appraising the quality of the study. *Evidence Updates from BMJ* can be also searched by keyword.

The Cochrane Central Register of Controlled Trials (often known simply as "Central") is part of the Cochrane Library. It consists of studies included in Cochrane Reviews, plus other controlled studies on the same topic, selected by the review teams. Unlike the other resources, studies included in Central are not limited to a core of English-language clinical journals. No critical appraisal is provided; simple inclusion in Central achieves a preappraised status for these papers.

The advantage of preappraised sources is that they remove the "noise" of minor or duplicative studies, case reports, and commentary found in the larger databases by providing highly selective smaller databases. All link to the full-text original article, usually via PubMed, so the clinician can review the original study. All of these resources provided good studies relevant to the case under consideration, and all would be appropriate for urologists (although *ACP JC* would perhaps be more applicable to medical urological questions than to surgical questions).

Searching for clinical evidence: filtering unfiltered databases

Synthesized and preappraised sources may fail to answer questions in specialties such as urology or urological surgery. Point-of-care sources may carry a limited number of topics, usually only the most commonly seen; preappraised sources and systematic reviews are most frequently in the therapeutic domain or are RCTs or systematic reviews of RCTs, which are inappropriate for surgical, procedural, diagnostic, or prognostic questions. In these cases, the large bibliographic databases of primary research evidence are the final resource.

The most commonly used health sciences database in English-language medicine is MEDLINE. Produced since 1966 by the US National Library of Medicine in Bethesda, MD, MEDLINE is available through a wide variety of search engines, the best known of which is PubMed (www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed). Medline currently (2015) indexes about 5600 US and international biomedical and health sciences journals, and contains about 22 million references dating from 1950 to the present. MEDLINE's great strength lies in its system of subject headings, known as MeSH, including subheadings and limits that allow the knowledgeable searcher to conduct a very precise search. Tutorials are available online to provide more detailed instruction in searching PubMed than is possible here (www.nlm.nih.gov/bsd/disted/pubmed.html).

The Clinical Queries function in MEDLINE (Figure 1.12), also available on PubMed and other platforms, injects quality filters (search strategies based largely on study designs) into a search statement. The Clinical Queries search strategies were developed by the Health Information Research Unit at McMaster University; a detailed bibliography for the derivation and validation of their filters can be found at www.nlm.nih.gov/pubs/techbull/jf04/cq_info.html. The value added by searching with a quality filter is similar to that of preappraised sources: the removal of "noise" by extracting clinical trials from the vast sea of news, commentaries, case studies, and general articles. Care must be taken, however, with topics that do not lend themselves to RCTs, masking, or higher levels of study designs, because they will be lost when the quality filters for articles on therapy or prevention are applied. For such topics it is best to search MEDLINE without quality filters.

The PICOT question described at the beginning of this chapter provides an excellent way of crafting a sound search strategy. Starting with the population (P), then adding intervention (I) and outcome (O), and finally the study design, will enable the searcher to conduct a precise search and stay on target for answering the original question.

Other databases

Sometimes MEDLINE does not produce the desired information, possibly because it does not index all journals. Alternative databases that are useful for urology are EMBASE, Scopus, and Web of Science. EMBASE principally indexes clinical medical journals; frequently it indexes journals not caught by MEDLINE, in part because it is larger, indexing 8400 journals and holding about 28 million records. Like MEDLINE, EMBASE has a detailed subject heading thesaurus; recently, EMBASE has added MEDLINE subject headings (MeSH) to its indexing, so that it may be possible on a search platform that includes both (such as OVID) to carry a search strategy from MEDLINE to EMBASE.

Scopus and Web of Science are more general academic databases. They do not have controlled vocabularies, so topic searching must include as many synonyms as possible. Scopus indexes approximately 21 000 journals and contains about 57 million records, including book series and conference proceedings; moreover, Scopus searches international patents and the web, making it an excellent source of information about instruments, techniques, and guidelines. Web of Science covers more than 12 000 journals from 15 separate databases, dating from 1900. Articles listed in Scopus and Web of Science are not analyzed by indexers and, although this makes these indexes somewhat harder to search by subject than MEDLINE or EMBASE, it also means that newly published articles appear much more quickly. Of all the indexes, Scopus picks up new journals the fastest and provides possibly the best coverage of open-access electronic publications. A very thorough literature search, for a research project or grant proposal, would involve a detailed search of all four databases, and possibly others as well. Inevitably, there will be overlap among these databases, but there will also be previously unseen studies that you would not want to have missed.

Backing up your search: citation searching

Both Scopus and Web of Science allow citation searching – tracking studies that have cited other studies. Aside from its use as a quick way to determine the relative importance of an article as shown by the number of times it has been cited since publication, citation searching allows one to find newer studies on a similar topic For example, an article cited in the DynaMed chapter on Benign Prostatic Hyperplasia noted that increased physical activity reduced the risk of

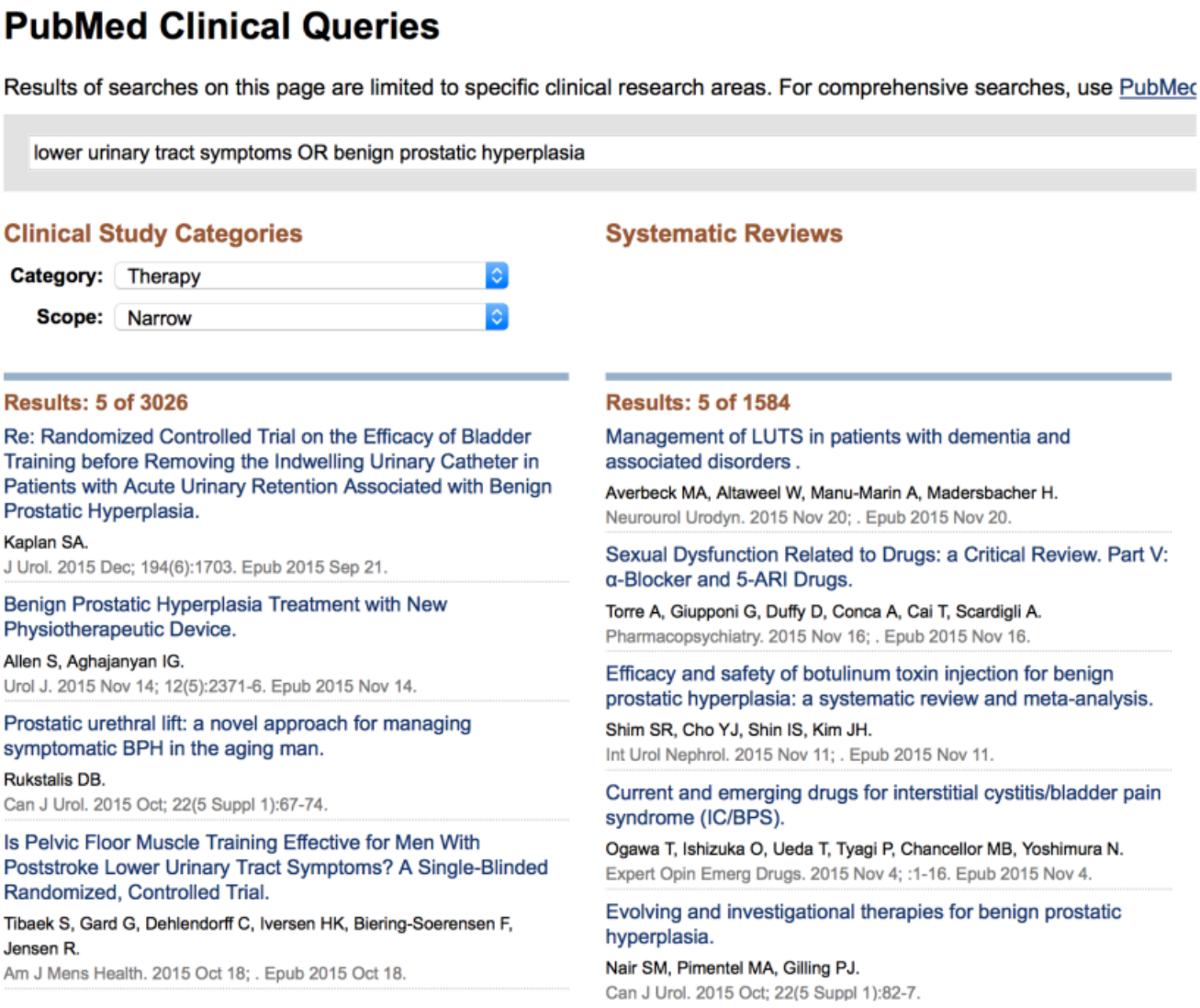

Figure 1.12 PubMed Clinical Queries search.

BPH in men between 40 and 75 years of age [9]. You would like to find a more recent article. A citation search showed that the article had been cited 87 times (as at November 2015), according to Web of Science, and 98 times according to Scopus. Reviewing the lists of citing articles turned up clinical trials, book chapters, and retrospective cohort studies published in the past 2 years. On obscure or interdisciplinary topics, when thesaurus terms and keywords fail to produce an effective or focused search, citation tracking can be a very powerful search method.

Evidence your patients can understand

In this information-rich era, your patients will be very interested in searching for information on their own condition. They may well come to their appointment armed with studies and information that they have found for themselves on the web, as they seek to participate in their own treatment (as the man in our case scenario has, with his query about saw palmetto).

A physician or the physician's clinic staff should be aware of reliable resources to which patients can be guided, should they express an interest. The Cochrane Collaboration is particularly interested in getting research information out to patients, and to that end now provides a "plain language summary" with each review; these are available free at www.cochrane.org/reviews. MedlinePlus (https://www.nlm.nih.gov/medlineplus) is a reliable source of sound patient information available free in a variety of formats, produced by the US National Library of Medicine for the National Institutes of Health (Figure 1.13). In the United Kingdom, NHS Choices (http://www.nhs.uk/pages/home.aspx)

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Health Topics Drugs & Supplements Videos & Tools Español

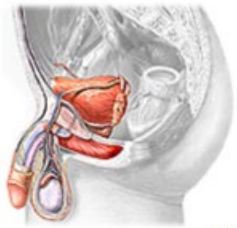
Home → Health Topics → Enlarged Prostate (BPH)

Enlarged Prostate (BPH)

Also called: benign prostatic hyperplasia

On this page

Basics	Learn More	See, Play and Learn
Summary	No links available	Videos
Start Here		
Diagnosis/Symptoms		
Prevention/Screening		
Treatments and Therapies		
Research	**Resources**	**For You**
Clinical Trials	Find an Expert	Patient Handouts
Journal Articles		



Get Enlarged Prostate (BPH) updates by email

Enter email address GO

MEDICAL ENCYCLOPEDIA

Summary

The prostate is a gland in men. It helps make semen, the fluid that contains sperm. The prostate surrounds the tube that carries urine out of the body. As men age, their prostate grows bigger. If it gets too large, it can cause problems. An enlarged prostate is also called benign prostatic hyperplasia (BPH). Most men will get BPH as they get older. Symptoms often start after age 50.

Figure 1.13 Patient information on MedlinePlus.

Home | About | Contact | Tools | Video | e-Referral Service | Communities | IPS Translate Log in or create an account

NHS choices Your health, your choices

Enter a search term

Health A-Z | Live Well | Care and support | Health news | Services near you

Benign prostate enlargement

Share: Save: Print: IP

Overview | Clinical trials

Benign prostate enlargement | Symptoms | Causes | Diagnosis | Treatment | Complications

Introduction

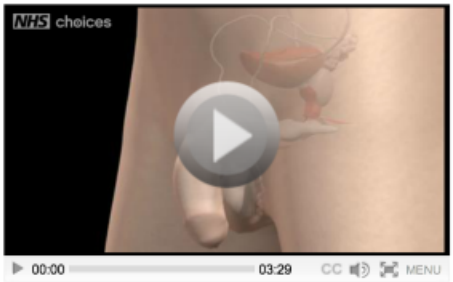
Benign prostate enlargement (BPE), also known as benign prostatic hyperplasia (BPH), is a condition that affects older men.

It's particularly common in men over 50 years of age and isn't usually a serious threat to health.

Prostate gland

The prostate is a small gland found only in men, located in the pelvis, between the penis and bladder. It's involved in the production of semen.

Prostate enlargement animation



Prostate enlargement or benign prostatic

Figure 1.14 Patient information about BPH on NHS Choices.

Figure 1.15 Patient information links about BPH on DynaMed.

offers a section called Health A–Z, which leads to an excellent section on Benign Prostatic Hyperplasia (Figure 1.14). DynaMed also provides a selection of patient handouts and links for further information (Figure 1.15).

Conclusion

Searching for evidence is actually relatively simple, thanks to new resources designed specifically for clinicians. It may be helpful to consult information specialists, such as experienced medical librarians or clinical informaticists, to advise on which of these resources might best fit your needs. Such professionals are themselves a resource, especially when you are stumped for evidence or are conducting an intensive literature search.

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2

CHAPTER 2

Clinical trials in urology

Charles D. Scales, Jr.[1] and David F. Penson[2]

[1] *Duke Clinical Research Institute and Division of Urology, Department of Surgery, Duke University Medical Center, Durham, NC, USA*

[2] *Department of Urologic Surgery, Vanderbilt University Medical Center and VA Tennessee Valley Healthcare System, Nashville, TN, USA*

Introduction

Evidence-based clinical practice has been defined as the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [1, 2]. Clinical decision-making should combine patient preferences and values with the best available evidence when making treatment choices for individual patients [3]. Inherent in this philosophy of practice is that a hierarchy of evidence exists – certain study types provide higher quality evidence than others. This chapter briefly outlines the hierarchy of evidence for questions of therapy and identifies the place of clinical trials within that hierarchy. Subsequently, the design and analytical elements of clinical trials that provide key safeguards against bias are explained, followed by an overview of key principles for applying the results of clinical trials in practice. Finally, the chapter concludes with an overview of pragmatic clinical trials, which will be increasingly applied to compare treatment alternatives in the practice of urology.

The hierarchy of evidence

A central tenet of evidence-based practice is that a hierarchy of evidence exists. Study designs are ordered in a hierarchy based on the risk of bias inherent in the study design. Among individual studies, the randomized controlled trial (RCT) provides the highest level of evidence, although ideally a meta-analysis of several RCTs will provide better estimates of treatment effects than a single RCT. Following the RCT in the hierarchy of evidence come observational cohort studies, which follow groups of patients through time. The key difference between cohort studies and RCTs is that patients are not randomly allocated to treatments in an observational cohort study. Cohort studies may be prospective – that is, patients are allocated into cohorts prior to the occurrence of the primary outcomes. Alternatively, cohort studies may be retrospective, when the primary outcome has already occurred. RCTs comprise approximately 10% of the urology literature and cohort studies approximately 45% [4]. cohort studies are case–control studies, case series or reports, and finally expert opinion.

The hierarchy of evidence exists because individual study designs are inherently prone to *bias*, that is, systematic deviation from the truth. As opposed to random error, bias has a magnitude and a specific direction. Bias may serve to over- or underestimate treatment effects, and therefore lead to erroneous conclusions about the value of therapeutic interventions. RCTs top the hierarchy of evidence because well-designed and executed RCTs contain the strongest methodological safeguards against bias. Study designs further down the hierarchy of evidence are subject to increasing potential for bias, and therefore constitute lower levels of evidence.

RCTs are unique in the hierarchy of evidence, as participants in the trial are not selected for specific interventions but instead are allocated randomly to a specific therapy or control. Effective randomization ideally balances both known and unknown confounders, and provides the greatest assurance that prognostic balance between study arms is achieved at the outset of the study. With appropriate methodological safeguards, RCTs have the potential to provide the highest level of evidence for questions of therapy. For this reason, informed consumers of the urology literature should understand how to interpret appropriately the results of a clinical trial [5]. RCTs form only a small proportion of published studies in the urology literature, likely due to several barriers to conducting surgical RCTs [4], including the lack of equipoise among surgeons and patients regarding interventions and lack of expertise among urologists with respect

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to clinical research methodology [6]. In addition, new techniques inherently involve a learning curve; technical proficiency is a requisite for unbiased conduct of an RCT.

One method for overcoming technical proficiency barriers is the expertise-based RCT [7], in which the patient is randomized to an intervention conducted by an expert. For example, in a hypothetical trial of robot-assisted laparoscopic prostatectomy versus open retropubic prostatectomy, in each arm the procedure would be performed by an expert in that specific treatment, recognizing that it is difficult to separate the surgeon from the scalpel when evaluating surgical interventions. Despite innovative methods to overcome barriers, it remains true that RCTs are not always feasible or ethical [8] and, for these reasons, physicians must also incorporate results from nonrandomized studies while maintaining awareness of the increased potential for bias in observational designs.

Observational designs, such as cohort and case–control studies, have certain advantages over RCTs, although with the significant limitation of greatly increased risk of bias. However, for certain questions, such as those of harm, observational designs may provide the only feasible means to examine rare adverse outcomes of an intervention. Cohort studies for harm may be most useful when randomization of the exposure is not possible, and may be more generalizable than RCTs [9]. Case–control studies can overcome long delays between exposure and outcome, and also the need to accrue enormous sample sizes to identify rare events [9]. In addition, for questions of prognosis, prospective cohort designs provide the highest level of evidence.

Clinical trial design elements: safeguarding against bias

Several elements of clinical trial design guard against the introduction of bias into the results of the treatment under evaluation. The objective of these design elements is to ensure that (on average) patients begin the trial with a similar prognosis and retain a similar prognosis (outside therapeutic effect) once the trial begins. The Consolidated Standards of Reporting Trials (CONSORT) statement provides a comprehensive list of reporting guidelines for clinical trials [10, 11]. Included in the CONSORT statement are several design elements that provide important safeguards against bias in trial results. These include randomization, concealment, blinding, equal treatment of groups, and complete follow-up.

Randomization refers to the method by which patients are allocated to treatment arms. As the term implies, patients should be placed in treatment arms in a random, that is, not predictable, fashion. The purpose of randomization is to balance both *known* and *unknown* prognostic factors between treatment arms [3]. For example, in a trial of active surveillance versus radical prostatectomy for prostate cancer, it would be important for Gleason grade (among other factors) to be balanced between the active surveillance and radical prostatectomy groups. It would also be important to balance potentially unknown prognostic factors, such as comorbid conditions, in such a trial, and randomization optimizes the balance of these conditions. It is important to realize that randomization is not always successful in balancing prognostic factors, particularly with smaller sample sizes. Therefore, when interpreting the results of any trial, the reader should examine the balance of patient characteristics (often presented in the first table in the report) between groups.

Equally important to maintaining an initial balance of prognostic factors is the concept of *concealment*. Concealment refers to the principle that study personnel should not be able to predict or control the assignment of the next patient to be enrolled in a trial [3]. This concept is important because it prevents the selection, either conscious or unconscious, of subjects for specific treatment arms. Remote randomization, where investigators call to a centralized center to ascertain the assignment of a study subject, is a method frequently used to ensure concealment of randomization. Other methods, such as placing study arm assignments in sealed envelopes, may not always ensure concealment. For example, in a study of open versus laparoscopic appendectomy, concealment by sealed envelope was compromised when surgery occurred overnight, potentially introducing bias to the trials results [3, 12]. Lack of concealment has empirically been associated with bias in study results [13–15]. Therefore, it is very important for the informed consumer of medical literature to be aware of whether randomization in a clinical trial was concealed, in order to ensure balance of prognostic factors in the study.

Once a trial is under way, maintaining the balance of prognostic factors achieved by randomization is critical. During the study, it is essential, to the extent feasible, that several groups remain *blinded* to the treatment assignment for each study subject. These groups include patients, caregivers, data collectors, outcome assessors, and data analysts [3]. In this context, the ubiquitous terms "double blind" and "single blind" may be difficult to interpret, and should be avoided [16]. Patients should be blinded in order to minimize the influence of well-known placebo effects [17, 18]. Caregivers, to the extent possible, should be blinded to the intervention to prevent differences in the delivery of the experimental or control treatment. In pharmacological trials, it is relatively straightforward to administer a placebo intervention that blinds both patients and caregivers. However, blinding of caregivers presents special challenges in surgical trials, as surgeons clearly would be aware of the patient's surgical intervention. This may be a potential source of bias, if a surgeon consciously or subconsciously favors one procedure over another [7]. One potential solution to this challenge is the concept introduced by Devereaux et al. [7] of "expertise-based" clinical trials, where a surgeon performs only one procedure, in which he/she has special skill or experience.

The comparison procedure would be performed by a different surgical expert. In this manner, potential bias from unblinded surgeons would be minimized.

Other groups within the study can almost always feasibly be blinded, even when caregivers or patients cannot, which provides additional methodological safeguards against bias. Perhaps most importantly, adjudicators of outcomes should be blinded to the treatment assignment, even if caregivers or patients cannot be feasibly blinded. Blinding of outcome adjudicators prevents differential interpretation of marginal results or variations in subject encouragement during performance tests, either of which could result in the introduction of bias [19]. For example, in a trial of laparoscopic versus open radical prostatectomy, assessors of continence and erectile function should ideally be blinded to the treatment arm, to avoid unconscious introduction of bias on the part of the surgeon. In a similar fashion, data collectors should also be blinded to the treatment assignment of subjects. Finally, analysts should be blinded to the study assignment in order to prevent introduction of bias in the analytical phase of the study.

In addition to blinding, two other design elements help maintain the balance of prognostic factors. First, subjects in each study arm should be treated equally, aside from the intervention of interest, throughout the duration of the trial. For example, if subjects undergoing an intervention receive closer or more frequent follow-up than the control subjects, the potential exists for introduction of bias into the results. Therefore, study procedures in each trial arm, apart from the intervention, should remain the same.Second, follow-up of subjects should be complete. As more patients are lost to follow-up (and especially not randomly lost), the risk of biased results increases. If differences in follow-up rates exist between treatment arms, the risk of bias becomes very high. Consider a hypothetical trial of medical versus surgical therapy for benign prostatic hyperplasia. If patients undergoing surgical intervention fail to return because their symptoms improve, then bias may be introduced to the surgical arm of the trial. Similarly, if subjects in the medical therapy arm do poorly and seek care elsewhere, this could also introduce bias into the results. An appropriate follow-up rate depends on a number of factors, but loss to follow-up of less than 20% is generally considered acceptable [5]. Similar treatment of study subjects and ensuring complete follow-up will minimize the introduction of bias during the conduct of the trial.

In summary, several key design elements help to minimize bias in the results of an RCT, including randomization, concealment, blinding, equal treatment, and complete follow-up. The informed consumer of the urology literature should look for these elements when assessing the validity of a clinical trial [5]. It is important to note that reporting of many of these trial elements in RCTs in the urology literature remains suboptimal [20], although lack of reporting of these key elements does not always imply absence of the design element during trial execution [21]. However, reporting remains the only assurance that the trial employed key safeguards against bias, hence complete reporting of trial design is encouraged by widely accepted standards [10, 11].

Clinical trial analysis elements: safeguarding against bias

In addition to design elements, adherence to certain analytical elements guards against biased or misleading results in RCTs. Several of these elements are identified in the CONSORT statement [10, 11] and include appropriate sample size calculations, conducting analyses according to the intention-to-treat principle, reporting effect size and precision for primary and secondary outcomes, and accounting for the effects of subgroup analyses and multiple testing when interpreting trial results. Notably, randomized trials in the urology literature are frequently deficient in the utilization or reporting of these key statistical elements [4, 22, 23]. Therefore, it is incumbent on the informed consumer of the urology literature to appraise reports of randomized trials critically, with a close eye on the use of key elements in the data analysis.

Perhaps the most important statistical element to consider when planning a randomized trial is the sample size necessary to detect a clinically meaningful difference in the primary outcome. Frequently referred to as a sample size or power calculation, this procedure takes into account the expected event rate in the trial arms, the expected variation in the event rate, and the minimum clinically relevant difference that the trial is expected to detect in order to arrive at the number of study subjects needed. Inadequate sample size (an underpowered study) can result in the appearance of no difference between groups, when in fact a clinically meaningful difference exists [24]. Underpowered clinical trials are scientifically unsound, are of questionable ethics, and may inhibit the study of clinically important questions [23, 24]. The reporting of sample size calculations in RCTs in the urology literature improved from 19% of studies in 1996 to 47% of studies in 2004 (odds ratio [OR] 2.36, 95% confidence interval [CI] 1.39–4.02, $p<0.001$) [22]. Despite this improvement, however, Breau et al. demonstrated that among urological randomized trials reporting no difference between treatment arms, fewer than one in three had sufficient power to detect a 25% difference in treatment effect [23]. Users of the urology literature should therefore devote particular attention to the reporting of sample size calculations, especially when the outcome of the trial demonstrates no statistically significant difference between groups.

Another particularly important analytical element in the reporting of RCTs is the intention-to-treat principle. Briefly, this means analyzing all patients in a clinical trial in the arm to which they were randomized, regardless of their

adherence to or completion of therapy [3]. The intention-to-treat principle helps to avoid systematic error introduced by nonrandom loss of subjects to treatment or follow-up [25]. Investigators will often report an analysis of only adherent subjects, frequently termed a *per protocol analysis*. However, results of per protocol analyses are often misleading [3]. For example, in an RCT of clofibrate, a lipid-lowering agent, the mortality rate among patients with less than 80% adherence to medication was 24.6%, compared with 15.0% among adherent patients ($p<0.001$) [26]. However, a similar risk difference in mortality (28.2% in patients with low adherence versus 15.1% in adherent patients) was noted in the placebo arm. Hence the high-adherence groups were prognostically different, which would potentially lead to an erroneous conclusion had the intention-to-treat principle not been followed.

In the urology literature, only about one-third of randomized trials published in 1996 and 2004 reported an intention-to-treat analysis [22]. Even when authors use the term "intention-to-treat analysis," reports may not be complete and the term may be incorrectly applied [27, 28]. Adherence to the intention-to-treat principle is empirically associated with overall methodological quality in clinical trials [27, 28]. Therefore, adherence to the intention-to-treat principle should be a point of emphasis for investigators and users of the urology literature.

Users of the urology literature are likely most interested in the results of clinical trials, that is, the effect of treatment with the intervention under study. Informative reporting of trial results includes a measure of contrast between the control and experimental arms, and also some measure of the precision of the observed treatment effect [29]. The difference in outcomes (e.g. death, symptom score) between the experimental and control groups is typically referred to as the *effect size*. Effect size is frequently expressed as a risk ratio or odds ratio for categorical outcomes or a difference between means for continuous outcomes. It is important to recognize, however, that the results of a single RCT represent a *point estimate* of a given treatment effect, and the true effect size for all patients with the target condition lies within a range of values, typically expressed as the *confidence interval*. For example, consider the results of an RCT of the long-term efficacy and safety of finasteride (PLESS trial) for the treatment of benign prostatic hyperplasia [30]. In this trial, the rate of urinary retention in the treatment arm was 7%, compared with 3% in the placebo arm, a relative risk reduction of 57%. The 95% CI for the relative risk reduction was 40–69%. One way to interpret the 95% CI is that if the trial were repeated 100 times, in 95 of those cases the treatment effect (relative risk reduction) would be between 40 and 69%. The reporting of effect size and precision is important for clinicians, as they provide both a measure of the expected treatment result and a plausible range of results with which to counsel patients. Therefore, effect size and precision should be considered one of the key statistical reporting elements for RCTs in the urology literature.

Another key statistical element to consider when interpreting trial results, particularly in trials where multiple endpoints or outcomes are reported, is the effect of multiple testing. Multiple testing typically involves comparing the control and experimental arms across several different clinical outcomes. Alternatively, conducting subgroup analyses (e.g. comparison within gender groups or within age groups) also constitutes multiple testing. This practice greatly increases the likelihood of false-positive results [29]. Analyses that are prespecified and account for the potential effects of multiple testing are more reliable than those inspired by the data [29]. It is frequently difficult to determine whether subgroup analyses are prespecified [31]. In addition, empirical evidence from comparison of trial protocols and reports suggests that selective reporting of outcomes is problematic in the medical literature [32]. Ideally, when subgroup analyses or multiple outcome analyses are conducted, corrections for the risk of false-positive findings should be employed (i.e. the Bonferroni correction). Uncorrected multiple testing is a significant problem in the urology literature: only 6% of RCTs reported in 2004 addressed the potential effects of multiple testing on results [22]. Therefore, users of the urology literature should be aware of the potential for misleading trial results when safeguards against the effects of multiple testing are lacking.

Applying clinical trial results

Once the results of a clinical trial are deemed valid, they must be applied in practice. Generalizability (external validity) refers to the extent to which the findings of a study may be extended to other settings [29]. Patients treated in actual practice frequently differ from those in a clinical trial, and a decision as to the applicability of trial results must be made by the clinician. Frequently, clinicians determine whether a compelling reason exists as to why the trial results should not apply to a given patient [33]. In addition, providers should assess whether patients can comply with the treatment, whether the intended intervention can be delivered adequately, and whether the benefits are worth the risks and costs [3]. These potential barriers to applicability of trial results frequently result in observable differences between the effect size of an intervention in a clinical trial (efficacy) and the effect of an intervention in practice (effectiveness). Therefore, clinicians must carefully weigh the risks, benefits, feasibility, and costs when applying the results of clinical trials to individual patients.

Pragmatic clinical trials

Emerging emphasis in healthcare and health policy focuses on studies to support clinical decision-making, leading to

a call for practical or *pragmatic clinical trials* [34]. Pragmatic clinical trials often focus on choosing from among two or more options for clinical care and are designed to be more reflective of real-world settings than "traditional" randomized clinical trials [35]. Tunis et al. [34] described four predominant features that characterize pragmatic clinical trials. First, these trials compare two or more clinically relevant alternatives for a specific disease state. Second, pragmatic trials include a diverse population of study subjects, in contrast to explanatory trials, where study populations tend to be homogeneous and exclude certain populations [34]. Third, heterogeneity in practice settings is encouraged, so as to approximate effectiveness of the treatment alternatives in a "real-world" setting. Finally, pragmatic trials tend to examine a broad range of clinical outcomes.

It remains important to consider that pragmatic trials are subject to the same risks of bias as traditional randomized trials. For this reason, Zwarenstein et al. [36] recommended specific extensions of the CONSORT criteria when pragmatic trials are reported. For example, the eligibility criteria should explicitly describe the extent to which subjects, clinicians, and sites reflect typical patients and care settings. Similarly, the outcomes and chosen length of follow-up should be pertinent to patients and those who care for them [36]. If blinding is not feasible for certain groups, this should be explained in detail.

With the advent of electronic health records, enthusiasm exists for the incorporation of existing clinical data into research activities, and specifically clinical trials, as one means to reduce the cost and administrative burden of traditional randomized clinical trials. For example, the Patient-Centered Outcomes Research Institute (PCORI) is currently sponsoring the ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-term Effectiveness) study (http://www.pcornet.org/aspirin). In this unique study comparing doses of 81 and 325 mg of aspirin for heart attack and stroke prevention, follow-up is planned entirely using elements of the electronic health record together with web-based questionnaires of subjects. Across nine networks, a common data model will be used to create a research network. Conceptually, these innovations may lead to reduced costs of clinical trials in the future.

Conclusion

Results of well-designed and executed RCTs provide the highest level of evidence for the practice of urology. Evidence suggests that the quality of reporting in urological RCTs is at times suboptimal [20, 22]. Therefore, the informed reader of the urology literature should be aware of the design and statistical elements that safeguard against bias and misleading results from trials. Ultimately, becoming an informed consumer of the urology literature should be the goal of every urologist aspiring to an evidence-based clinical practice.

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3

CHAPTER 3

Systematic reviews in urology

Philipp Dahm[1], Shahnaz Sultan[2], and Jae Hung Jung[3,1]

[1] *Minneapolis VA Medical Center, Urology Section and Department of Urology, University of Minnesota, Minneapolis, MN, USA*
[2] *Minneapolis VA Medical Center, Gastroenterology Section and Department of Medicine, University of Minnesota, Minneapolis, MN, USA*
[3] *Department of Urology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea*

Introduction

It is one of the fundamental paradigms of evidence-based medicine that decisions about diagnosis, treatment, and healthcare management for both individ ual patients and populations should be based on evidence [1]. Rarely are important questions in healthcare appropriately informed by consulting the result of a single empirical study. Historically, we credit Sir Archie Cochrane, a British physician who founded Cochrane and was knighted for his contributions to evidence-based medicine, with this realization [2]. Today, we recognize the ethical obligation to summarize the best available evidence for a given clinical question to guide clinical practice and research and also to avoid unnecessary trials if reliable knowledge already exists. Many national funding agencies such as those in the United Kingdom, Denmark, the Netherlands, and other countries and also leading medical journals such as *The Lancet* and *BMJ* require that clinical trials not only be registered but be preceded by a systematic review summarizing the known evidence and justifying the need for further trials [3]. An example from the urological literature that followed this model is the SUSPEND trial, which assessed the value of alpha-blockers and calcium channel blockers as medical expulsive therapy in patients with ureteral colics [4]. Despite the existence of several systematic reviews on this topic, including a Cochrane Review, the authors convincingly argued that there was continued uncertainty about the true effects of the two agents in this setting [5]. Meanwhile, numerous examples exist where cumulative meta-analyses have demonstrated that unbeknown to the medical community, sufficient evidence existed to forgo the need for additional trials and in fact to change medical practice. Instead, not only were precious resources wasted in the conduct of additional research but also, more importantly, a change in the standards of care was delayed [6,7]. Examples include the use of beta-blockers in patients who have suffered a myocardial infarction and the importance of placing children on their back to sleep to reduce the risk of sudden infant death syndrome [8,9]. In both cases, many lives could have been saved if the best evidence had been synthesized in a systematic review and meta-analysis. It has been argued that many healthcare challenges of our time should be tackled by first performing a rigorous systematic review to understand better what we already know about a given topic [10]. The logo of the Cochrane Collaboration is a representation of the systematic review and meta-analysis that demonstrated the value of prenatal corticosteroids in women expected to give birth to premature infants [11].

A systematic review is a study that uses a predefined, systematic, and transparent approach to identify, select, appraise, and summarize primary studies addressing a focused clinical question using methods to reduce the likelihood of bias. They should be distinguished from so-called narrative reviews where many or all of the steps are omitted (Table 3.1) [12]. Narrative reviews have a limited role in guiding evidence-based clinical practice. Given that questions of therapy and prevention make up approximately 70% of questions in which clinicians are interested, it is these types of questions that dominate systematic reviews and for which the methods have been best developed [13]. However, we are now increasingly seeing systematic reviews addressing questions of diagnostic test accuracy, prognosis, and others.

Cochrane is credited for its pioneering work in how to conduct a methodologically rigorous systematic review [2]. Details of these methods are summarized in the *Cochrane Handbook for Systematic Reviews of Interventions* [14]. In addition, Cochrane subsequently published methodological reporting

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Table 3.1 Differences between narrative reviews and systematic reviews.

	Narrative reviews	Systematic reviews
Review process		
Defining scope of question	Usually broad question	Specific question with PICO components (Population, Intervention, Comparator, and Outcome)
Defining methods	No protocol	Predefined protocol
Searching for studies	Usually not described	Comprehensive: transparent, reproducible search of diverse database
Screening and selecting studies	Mostly limited by reviewers	Based on predefined criteria
Assessing risk of bias	Usually not described	Explicit quality assessment (e.g. Cochrane Collaboration's tool for assessing risk of bias)
Data extraction	Simple description of study finding	Continuous or dichotomous statistical values
Data synthesis	Usually qualitative summary	Usually quantitative summary (e.g. meta-analysis)
Data quality	Usually not described	Formally grading quality of evidence by transparent approach (e.g. GRADE)
Interpreting results	Usually expert opinion	Evidence based
Advantages	Useful for obtaining broad overview of review question	Reliable and unbiased answer to a focused clinical question
Disadvantages	Prone to cumulative systematic biases	Sometimes time consuming May not be easy to combine studies

standards that every Cochrane Review needs to follow and that provide a template for authors of non-Cochrane Reviews to follow [15].

Systematic reviews are best understood through the steps that go into their development. In the following section, we discuss the steps that are integral to the conduct of the systematic review.

How to perform a systematic review

Formulating a focused clinical question

One of the distinguishing features of a systematic review that separates it from other narrative reviews is that it addresses a focused clinical question that "drives" the literature. The components of a focused clinical question are represented by the mnemonic PICOS, which stands for Population, Intervention, Comparison, Outcome, and Study design [16,17]. Focused clinical questions that are informed by systematic reviews relate to foreground questions that relate to the clinical management of individuals with a condition rather than understanding the prevalence or pathophysiology of the disease. How to develop a focused clinical question is the subject of a separate chapter in this book. Formulating a focused clinical question is at least as important for clinical practice guidelines and other documents that seek to provide clear and actionable guidance without a clearly defined question, there is unlikely to be a clear answer. This is the first step where many clinical practice guidelines fall short [18,19].

Whereas the outcomes defined in the PICO are not primarily used in the search, it is critical to predefine the most important outcomes for the systematic review. GRADE (Grading of Recommendations Assessment, Development and Evaluation Working Group) emphasizes the importance of identifying the most patient-important outcomes of actual relevance to decision-making and distinguishes these from secondary or surrogate outcomes [20]. For example, prostate cancer-specific survival is a directly patient-important outcome whereas biochemically disease-specific survival is not. The latter outcome is a surrogate outcome (biochemical recurrence is associated with the risk of dying from prostate cancer), but most prostate cancer patients who suffer biochemical recurrence experience a fairly extended period of time without adverse sequelae (apart from the anxiety of knowing that their cancer has returned). It is important to make that distinction. Another example is bone density as measured by a dual energy X-ray absorptiometry (DEXA) scan versus symptomatic fractures. Although information on the measured bone density points towards an estimated fracture risk over time, it is actual symptomatic fractures that matter to patients. The primary outcomes chosen in a systematic review should be directly patient important. Information from surrogate outcomes may be used, but they only inform indirectly the outcomes that we should care about.

It will become clear from the following sections that the conduct of a high-quality, comprehensive, and rigorous systematic review is labor intensive and may require a lot of time. Although we would welcome systematic reviews on every topic in the specialty of urology, this may not be feasible. It is therefore important to prioritize systematic review topics based on their likely newsworthiness and impact. Doing so is part of a routine process of each Cochrane group as it considers where to place its resources. Table 3.2 provides

examples of high-priority questions addressed by systematic reviews published by the Cochrane Library and also outside the Cochrane Library.

Developing a written, a priori protocol

It has become widely accepted that randomized controlled trials (RCTs) be registered prior to the initiation [21]. The registration document ideally represents a detailed protocol describing the purpose of the trial, its inclusion and exclusion criteria, its primary and secondary outcomes, assessment methods, and the analytical methods to be used. The realization of the importance of registering trials was derived from empirical evidence that many trials, especially those with negative findings, are never published, thereby contributing to publication bias, and second, even if reported, that there commonly were substantial differences between the planned analysis and reporting and what was actually undertaken. For example, specific issues have been the alteration of what was considered the primary outcome or the omission of an outcome altogether, potentially because study findings did not match what the investigators and sponsors had hoped to find. These are examples of selected reporting, which is an important domain for assessing the risk of bias in RCTs. While discrepancies between the planned and the actual execution and analysis of the trial may be justifiable, the reasons should be clearly delineated. The documentation of an a priori protocol helps to keep all involved parties honest.

The same rationale applies to systematic reviews. During the conduct of a systematic review, authors face a number of potentially critical decisions that may affect the results of their review. Specifically, inclusion and exclusion criteria need to be predefined to avoid bias. For example, in systematic reviews related to prostate-specific antigen (PSA)-based prostate cancer screening, determinations of which of the screening trials meet the minimal methodological standards to be included in the review have a profound impact on the results. If the only admissible study were to be the European Randomised Study of Screening for Prostate Cancer (ERSPC) study, the reported results will be different than when also including the (negative) Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening study, or some of the prior studies [22,23]. Although it may be difficult to determine right from wrong in this setting, it is incredibly helpful to see documented that the authors of a systematic review have thought about these issues beforehand. Similar issues relate to the choice of primary outcomes, which would be those endpoints that are of most direct patient importance and also the analytical approach chosen [24]. There is increasing recognition that all systematic reviews should be registered. This not only contributes to transparency but also avoids duplication of effort. Much has been written about the waste of critical healthcare resources when systematic review authors from different countries and different institutions duplicate each other's efforts [6,7]. Once registering a systematic review has become a widely expected standard, prospective systematic review authors will be able to research relevant databases to see what other systematic reviews are ongoing and then potentially partner with those author teams. To date, all Cochrane Reviews are automatically co-registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO), a dedicated systematic review database maintained at the University of York in the United Kingdom. High-quality medical journals including *BJU International* are requiring systematic review authors to document registration with PROSPERO in a prospective manner [21]. In the future, we would also hope that systematic review authors will place the raw data files of their analysis in a dedicated depository, which may serve as the basis for future systematic review authors and guideline developers planning to update a given review [25,26]. Such efforts would go a long way towards lessening the waste of limited healthcare research resources.

Comprehensive literature search

One of the hallmarks of a well-done systematic review is a comprehensive literature search [17]. Typically, this will entail the search of multiple electronic databases capturing both published and unpublished studies. These efforts should be supplemented as needed by a search of trial registries, databases of the so-called gray literature, and handsearching of abstract proceedings. Given the complexities of conducting a high-quality search, it is to be strongly encouraged that systematic review authors include an information specialist in their efforts. A separate chapter in this book provides additional detail about how to conduct a comprehensive literature search in the context of a systematic review.

Study screening applying predefined inclusion/exclusion criteria

The results of the comprehensive search are then typically uploaded to computer software either in spreadsheet format or a more dedicated systematic review program. Either way, it is typically two or more systematic review authors who independently screen the titles and abstracts that were retrieved by the search to determine eligibility. References that are clearly not relevant because they do not meet eligibility criteria with regard to the study design, do not address the intervention or comparison of interest, or do not report any of the outcomes that were predefined can be excluded at that stage. Studies that are likely to be included or for which a definite decision cannot be made will be included at that stage. In the following, full-text stage, the actual text of the full-text publication, typically as PDF documents retrieved and uploaded in the inclusion and exclusion criteria, will be applied once again by at least two independent investigators. Studies may be excluded because it becomes evident that they are not addressing the comparison or do not report on any of the outcomes that have been identified as relevant to the focused clinical question to be addressed.

Table 3.2 High priority questions addressed by systematic reviews in urology.

Ref.	Question	Participants	Interventions	Comparisons	Outcomes	Study design
Anderson [48]	Is conservative management efficacious for men with urinary incontinence after prostate surgery?	Adult men with urinary incontinence following prostatectomy	1 Pelvic floor muscle training 2 Electrical stimulation 3 Lifestyle adjustment 4 Extra-corporeal magnetic innervation 5 External penile compression devices	1 No treatment or sham therapy 2 Active treatment (described in interventions)	*Primary outcomes:* 1 Number of men reporting urinary incontinence 2 Quality of life 3 Number of men reporting adverse effects *Secondary outcomes:* 1 Participant-reported observations 2 Quantification of symptoms 3 Clinician-reported urinary outcome measures 4 Quality of life 5 Adverse effects 6 Health economics outcomes 7 Other outcomes	RCT
Boehm [49]	Are bacillus Calmette–Guérin strains efficacious for treatment of nonmuscle invasive bladder cancer?	Patients with CIS or Ta or T1 bladder cancer	Intravesical BCG (any strain)	1 TURBT alone 2 Intravesical chemotherapy 3 Intravesical BCG (either different strain or different dose) 4 Non-BCG biological 5 Combination of intravesical treatments	Tumor recurrence	RCT
Dahm [50]	Are newer medications effective for lower urinary tract symptoms attributed to benign prostatic hyperplasia?	Men aged ≥45 years with LUTS attributed to BPH	Newer alpha-blockers, antimuscarinics, a beta-3 adrenoceptor agonist, phosphodiesterase type 5 inhibitors, or combination therapy	Conventional medical treatment	1 Urological symptom scores 2 Quality of life 3 Disease progression 4 Treatment failure 5 Adverse events	1 RCT 2 Long-term observational study (duration ≥1 year)
Elshout [51]	Is early endoscopic realignment superior to suprapubic cystostomy and delayed urethroplasty for pelvic fracture-related posterior urethral injuries?	Men with traumatic urethral posterior distraction injuries	Early endoscopic realignment	Suprapubic cystostomy and delayed urethroplasty	1 Post-traumatic stricture rate 2 Urinary incontinence 3 Erectile dysfunction 4 Subsequent procedures	1 RCT 2 Nonrandomized comparative studies 3 Single-arm case series
Hollingsworth [52]	In patients diagnosed with a ureteral stone, how does medical expulsive therapy with an alpha-blocker compare with placebo with regard to patient-important outcomes?	Adult patients with ureteral stones of the upper, mid or lower ureter	Medical expulsive therapy with an alpha-blocker	Placebo or usual care	*Primary outcomes:* 1 Stone-free rates 2 Rates of secondary intervention 3 Adverse event rates (serious) *Secondary outcomes:* 4 Time to stone clearance 5 Adverse event rates (other than serious)	RCT

Ilic [53]	Does screening of prostate cancer improve mortality or quality of life without adverse events?	All men enrolled in studies of prostate cancer screening	Studies that used 1 Digital rectal examination 2 Prostate-specific antigen test 3 Transrectal ultrasound-guided biopsy	NA	*Primary outcomes:* 1 Prostate cancer-specific mortality 2 All-cause mortality *Secondary outcomes:* 1 Incident prostate cancers 2. Metastatic disease at follow-up 2 Quality of life 3 Harms of screening 4 Costs associated with screening programs	RCT
Kunath [54]	Is partial nephrectomy effective for the treatment of clinically localized renal carcinomas?	Participants with unilateral localized renal cell carcinoma	Partial nephrectomy	Radical nephrectomy	*Primary outcomes:* 1 Time-to-death of any cause 2 Serious adverse events *Secondary outcomes:* 1 Cancer-specific survival 2 Time-to-recurrence 3 Immediate postoperative adverse events 4 Long-term adverse events 5 Quality of life	RCT
Lardas [55]	Which primary treatment is effective in quality of life outcomes for clinically localized prostate cancer?	Men (≥18 years of age) diagnosed with clinically localized prostate cancer (T1–t2c), who had not undergone any previous treatment	1 Active surveillance 2 Radical prostatectomy 3 Radiotherapy 4 Brachytherapy	Active treatment (described in interventions)	Quality of life	1 RCT 2 Nonrandomized comparative studies

BCG, bacillus Calmette–Guérin; BPH, benign prostatic hyperplasia; CIS, carcinoma *in situ*; LUTS, lower urinary tract symptoms; NA, not available; RCT, randomized controlled trial; TURBT, transurethral resection of bladder tumor.

An issue to note is that in the absence of direct evidence, indirect evidence may be used to inform a clinical question with the implication that a broader scope of studies may need to be included [27]. For example, in a systematic review of the role of medical expulsive therapy in children with ureteral colics and in the absence of RCTs in this patient population, one may use evidence drawn from studies in adults as indirect evidence to inform this question. As discussed in a separate chapter, we would downgrade the quality of evidence according to GRADE for indirectness. This has implications for the application of the inclusion/exclusion criteria.

It is not uncommon for there to be some disagreement as to whether a given study should be included or excluded. Such discrepancies should be documented and are typically resolved by discussion and consensus. Systematic review authors are encouraged to measure and report the degree of interobserver agreement that was achieved [28]. If no consensus can be reached, a third independent investigator can be drawn in to make a final determination. The results of this process are ultimately documented in a PRISMA flow diagram (Figure 3.1) [29].

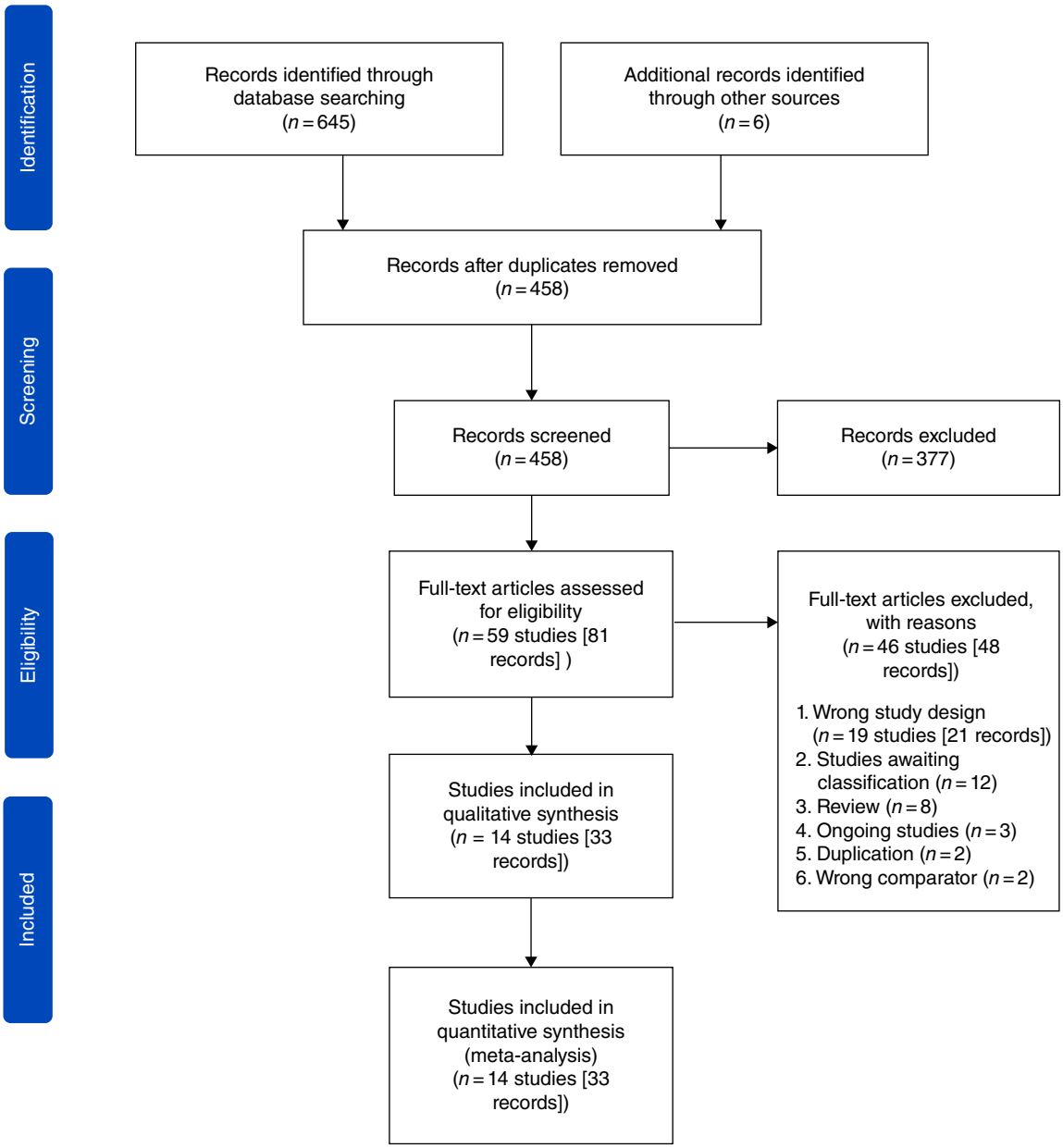

Figure 3.1 PRISMA flow diagram.

Data extraction

Once a group of studies has been determined that meets inclusion criteria, the data need to be abstracted. This includes basic items such as information on the study authors, the contact information of the corresponding author, the geographic origin of the study, the study funder, and any conflicts of interest reported by the authors. Further information relates to the study design (e.g. parallel group RCT), the details of the intervention (e.g. route of administration, dosing and timing of the medication), the details of the comparison, and the outcomes reported in a given trial. For this data abstraction, investigators should use electronic (or paper) data abstraction or dedicated systematic review software that allows formatting of data abstraction forms. Either way, it is most advisable to pilot test such a form to make sure it performs as intended and is well understood by the individuals who perform the data extraction.

The data abstraction process is one of the most laborious steps in the systematic review process. There are efforts to automate this process, but to date this step relies heavily on the human mind. High-quality systematic reviews perform data extraction in duplicate and then go through a similar process as during the screening of eligible studies to establish a final version of the data to be used in the data analysis stage.

Risk of bias assessment

Aside from determining if an intervention works or not and to what extent, it is at least equally important to qualify how confident we are in that estimate. The GRADE Working Group is widely credited with having developed a methodologically rigorous and transparent system rating the quality of evidence, which is the subject of a separate chapter in this book [20,30]. One of several domains that affect the quality of evidence (or certainty in the estimates of effect) is that of study limitations or risk of bias. This domain addresses to what extent methodological safeguards against bias have been appropriately addressed. The most widely known methodological safeguards against bias are those related to RCTs. They are most commonly assessed using the Cochrane risk of bias tool and include random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessors, attrition bias, and selective reporting bias. The judgment that the systematic review authors need to make, once again independently and in duplicate, is whether these methodological safeguards were appropriately implemented (low risk of bias), likely not appropriately implemented (high risk of bias), or whether it is unclear what happened (unclear risk of bias). Figure 3.2 provides an example of a risk of bias assessment.

For assessing observational studies, the Newcastle–Ottawa instrument is the most widely used, although a new Cochrane tool for nonrandomized trials has also been developed and is beginning to find some uptake, despite the complexity involved in applying it appropriately [31,32].

Assessing the risk of bias is a fundamental aspect of performing a systematic review. It is one of the contributions of the GRADE Working Group to have clarified that this assessment needs to occur on a per outcome basis [33]. Whereas an assessment as to whether random sequence generation and allocation concealment were performed appropriately or not "cuts across" all outcomes, it is important to make distinctions when it comes to performance, detection, and attrition bias.

Blinding of patients and personnel guards against performance that relates to bias and potential co-interventions that might affect the outcomes. Depending on the clinical question and the outcomes of interest, conceivable co-interventions may be relevant or not. For example, in the setting of terminal cancer in the absence of any interventions known to impact on overall survival, blinding of patients and personnel may not be important. However, it may be important to blind these two parties when it comes to the outcomes of quality of life.

Blinding of outcome assessors guards against detection bias. Once again, it is important to consider the extent to which a given outcome is potentially susceptible to detection bias. For example, for the outcome of overall survival, blinding is unlikely to be important given that the determination as to whether a patient has died (irrespective of cause) on a certain date can be objectively determined. Meanwhile, the determination that somebody has died of metastatic renal cell carcinoma, for example, requires some judgment with regard to the likely etiology. In the setting of a targeted therapy trial of metastatic renal cell carcinoma, it will therefore be important to blind the outcome assessors. Similarly, length of hospital stay and operating room time can be determined objectively with little risk of bias, making blinding of outcome assessors less important for these outcomes.

Lastly, attrition bias should be assessed on a per outcome basis. Attrition bias addresses the question of the extent to which all patients allocated to a given group were also analyzed in that particular group for a given outcome. In the setting of an RCT, loss of follow-up and crossover threaten the prognostic balance at baseline, which was achieved by randomization and allocation concealment. An example in which risk of attrition bias will vary by outcome within a trial is when a given outcome is assessed at different time points, for example, at 3 months and at 24 months. It is common that the proportion of patients who could be evaluated in 3 months is much higher than it is at the extended time point of 24 months. For example, the proportion of patients included at 3 months might be 97 and 98% for the two arms of a given trial, whereas it might only be 69 and 75% at 24 months. In such cases, there is the concern that this loss to follow-up is not a random event but may have

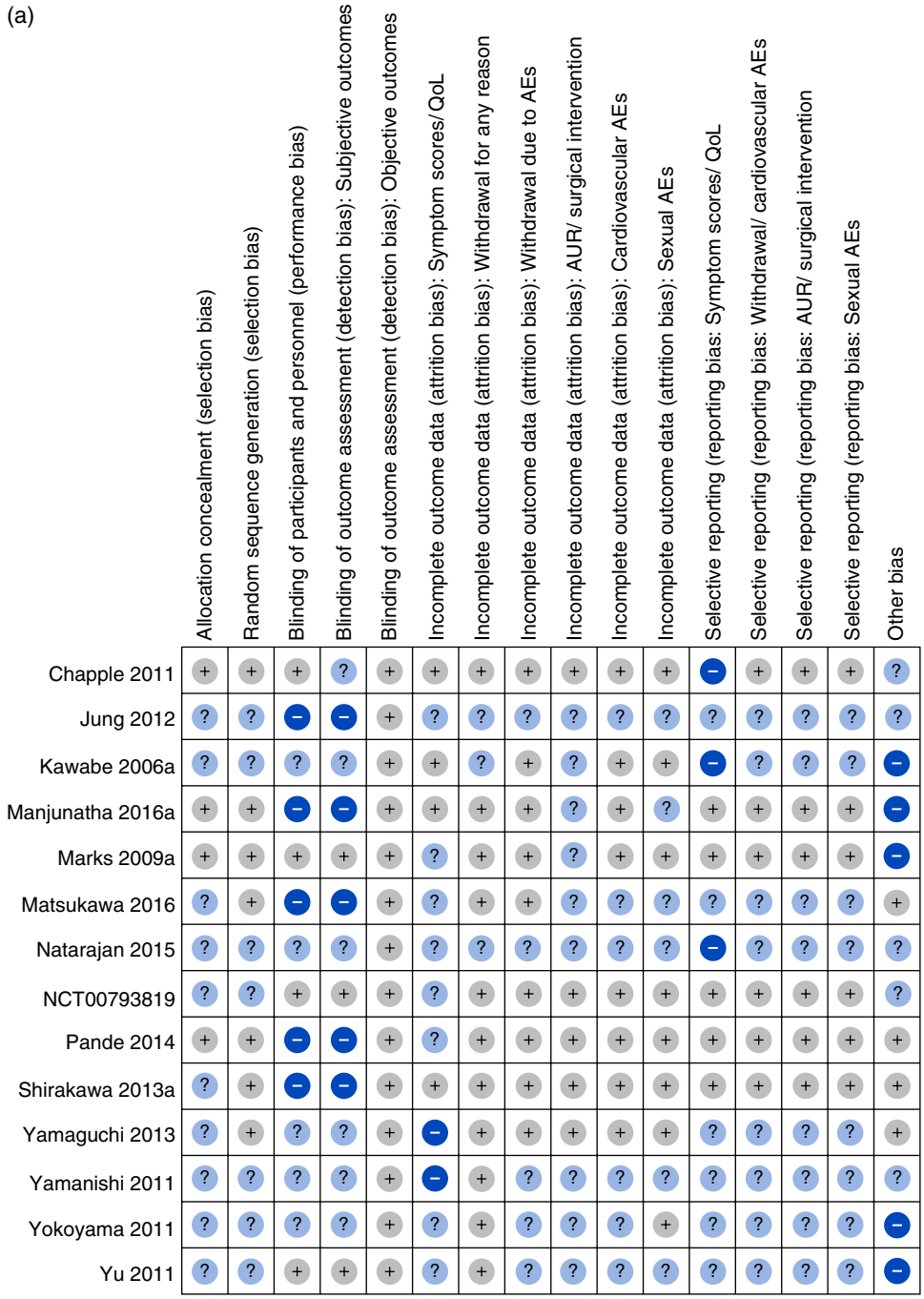

Figure 3.2 Risk of bias graph (a) and summary (b) for silodosin versus placebo.

affected a population with a different prognosis, thereby introducing bias.

In addition, studies of different methodological quality may contribute to a pooled effect size estimate from a systematic review and meta-analysis. However, not all studies may report all outcomes therefore, the overall risk of bias may differ by outcome.

Data analysis (including meta-analysis)

Data abstraction and risk of bias assessment are followed by the data analysis. Usually, there is an interest in a statistical pooling of the results to arrive at a common effect size estimate that characterizes the effect of an intervention. The effect size measures that are most commonly used are risk ratios for dichotomous outcomes, hazard ratios for timed

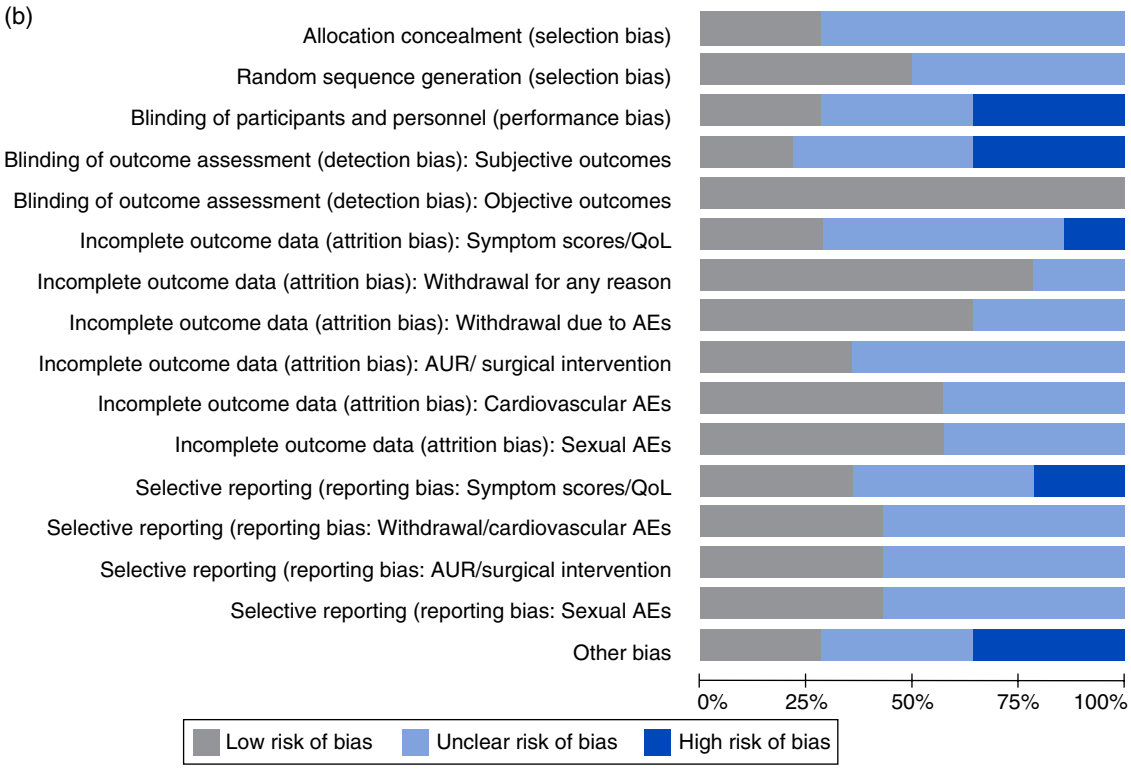

Figure 3.2 (Continued)

event outcomes and weighted mean differences or standardized mean differences for continuous outcomes. Statistical pooling or meta-analysis is only meaningful and/or feasible if the outcome of interest was measured similarly. In those cases, the results of studies should be reported individually and the overall results can be characterized narratively. It is important to realize that not every systematic review has to include a meta-analysis in that not all meta-analyses are based on a systematic review. This happens, for example, if a group of study investigators who have completed similar trials decide to combine the results of the trials in which they were involved. If they do not perform a search for other existing trials and include these in their meta-analysis, their effort is not a systematic review. However, it is systematic reviews that have a distinguished role in guiding evidence-based practice because they combine the totality of evidence addressing a given clinical question.

A number of statistical programs are available to perform meta-analyses. The most widely known and used is RevMan, which is available free of charge from Cochrane (http://community.cochrane.org/tools). Another free meta-analysis program is OpenMeta (www.cebm.brown.edu/openmeta/download.html). Comprehensive Meta-Analysis (https://www.meta-analysis.com) requires an annual licensing fee but is easy to use and provides excellent documentation. Lastly, STATA (https://www.stata.com) allows even the most sophisticated statistical analysis.

The classic representation of the results of a meta-analysis is a so-called forest plot (Figure 3.3). In a forest plot, each study's effect estimate and its corresponding confidence interval (CI) are represented by a rectangle and horizontal line, respectively. The size of the rectangle corresponds to the relative weight of the study in the meta-analysis, which is a function of the event rate and/or sample size. The pooled effect size estimate is represented by a diamond.

An important consideration when interpreting the results of a meta-analysis is the degree of observed heterogeneity or inconsistency, which describes the extent to which the individual study results differ. The most widely used (and most readily interpretable measure) is the I^2 statistic, which assumes values between 0 and 100% and characterizes the extent to which there is variability in outcomes that cannot be explained by chance alone. Thus, an I^2 of 0% does not mean there is no heterogeneity but that all the heterogeneity that exists can be explained by chance. Large degrees of heterogeneity, certainly settings when the I^2 is 80% or above, should be explored using secondary analyses as described in the following [34].

Secondary analysis

The two most commonly encountered secondary analysis types are subgroup analyses and sensitivity analyses. Subgroup analyses address the question of whether there is reason to believe that the observed effect size estimate

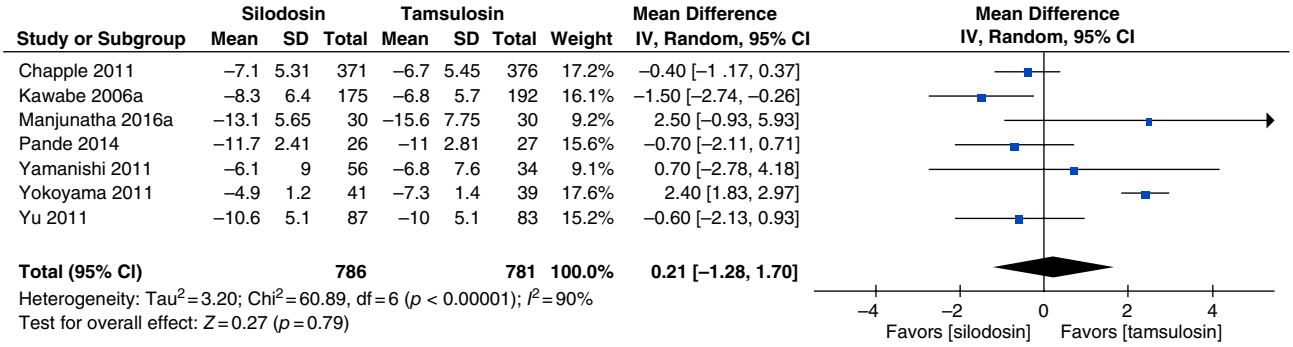

Figure 3.3 Forest plot of comparison: silodosin versus placebo.

is different by group, and justified by a good rationale, for example for different types of study participants (e.g. men versus women) or type of intervention (e.g. a 2.5 or 5 mg dose of a medication). Subgroup analyses should be defined a priori, few in number, and justified by a good rationale [35–37]. Otherwise, they can lead to spurious results, the likelihood of which increases with the number of subgroup analyses that are performed. When interpreting the results of a subgroup analysis, it is important to review the so-called test of interaction. This result should be statistically significant if a subgroup effect is to be assumed to be true.

Sensitivity analyses are a similar type of secondary analysis. In contrast to subgroup analyses, where there is interest in two or more groups and information as to how the results differ, sensitivity analyses explore the effect of modifying one or more variable on the overall outcome. For example, investigators of a systematic review and meta-analysis that includes both placebo-controlled and non-placebo-controlled studies, might be interested in removing the non-placebo-controlled trials to assess whether the overall results will change. Given that we would have less confidence in the non-placebo-controlled trials as less methodologically rigorous studies, there would be no interest in the results of those studies pooled by themselves.

Rating the quality of evidence using GRADE

An important aspect in every systematic review is to provide the reader with a sense of how trustworthy the results are. The confidence that we can place into a given result of a systematic review (and meta-analysis) is also referred to as the quality of evidence. Every effect size estimate should be qualified accordingly the associated quality of evidence is at least as important as the numerical value.

Historically, the quality of evidence was largely seen as a result of the study design. Based on this concept, it is still very common to hear people refer to "level I evidence" when indicating that there is at least one RCT to support a given finding. However, the quality of evidence rating that is based largely on study design falls short of appreciating a number of factors that affect our confidence in the estimate effect [13,38].

First, there are study limitations or risk of bias. An assessment of risk of bias makes a determination of the extent to which the methodological safeguards against bias that are available to investigators conducting an RCT have actually been put in place. These are the methods of random sequence generation and allocation concealment, which guard against selection bias, blinding of patient personnel to guard against performance bias, and blinding of the outcome assessors to blind against detection bias. In addition, there is attrition bias and selective reporting bias. It is one of the contributions of the GRADE Working Group to recognize that the impact of study limitations (and the quality of evidence) needs to be determined on a per outcome basis.

Other domains that GRADE defines as determinants of the quality of evidence are inconsistency, indirectness, imprecision, and publication bias [27,34,39,40]. Inconsistency refers to the degree that included studies included in a systematic review and meta-analysis suggests different results. Explanations for such differences may lie in clinical differences relating to the elements of the PICO (and thereby could relate to differences in the patient population, intervention, comparison, or the way the outcome is measured), methodological differences (such as the extent to which included studies were blinded), and chance variation. The degree to which chance variation may be responsible for the differences in the results can be assessed by statistical tests, for example the I^2 test, as mentioned earlier.

The domain of indirectness asks the question of to what extent the studies identified in the systematic review match the clinical question that is sought to be addressed. Once again, the differences may stem from the elements of the PICO. For example, in the case of a systematic review assessing the role of medical expulsive therapy in children with usual stones, the best available evidence may come from adult patients. However, such evidence would be labeled as indirect and investigators would likely choose to downgrade the quality of evidence, thereby indicating decreased confidence in the results, due to indirectness. Similarly, a surrogate outcome such as biochemical recurrence-free

survival may serve as indirect evidence to inform disease-specific survival in patients with prostate cancer.

Imprecision can be assessed in different ways, including the measure called the absolute information size. More readily, systematic review authors will stipulate a clinically important threshold such as a minimum important chemical difference for judgments about imprecision. For example, assuming that the minimum point difference for the International Prostate Symptom Score is 3, then a mean improvement of 3.4 (95% CI 3.1–3.7) would be identified as precise. However, a mean improvement of 3.4 (95% CI 1.8–5.2), in which the confidence interval crosses the threshold of a three-point improvement, would be labeled as imprecise.

Lastly, there is publication bias. It is a well-established phenomenon that so-called negative studies that fail to confirm the investigator's hypothesis, typically of effectiveness of a new agent or drug, are slow to be published and less likely to be published at all. If no dedicated effort is made to search for these studies, the result will be biased as the estimate of effect will be driven by positive studies and omit unpublished negative studies. Therefore, investigators need to perform a comprehensive search of studies irrespective of publication bias and irrespective of language. A dedicated effort should be made to search the so-called gray literature and to screen abstract proceedings. There are statistical tests to assess for publication bias, of which the funnel plot is the best known. However, these tests are not particularly sensitive and require a minimum of 10 studies [41].

Findings for these domains ultimately inform a quality of evidence for each comparison. GRADE distinguishes high-, moderate-, low-, and very low-quality evidence (Table 3.3).

Interpretation of the results

Ultimately, the results of a systematic review really speak for themselves but need to be interpreted in the context of

Table 3.3 Summary of findings table: silodosin versus placebo.

Silodosin compared with tamsulosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Reltive effect (95% CI)	Anticipated absolute effect	
				Risk with tamsulosin	Risk difference with silodosin
Urological symptom scores assessed with: IPSS Scale from: 1 to 35 follow-up: range 3 months to 12 months	1567 (7 RCTs)	⊕⊕◯◯ LOW[a,b]	–	The meam urologic symptom scores was – 15.60 to – 6.70	MD 0.21 higher (1.28 lower to 1.7 higher)
Quality of life assessed with: IPSS-QoL Scale from: 1 to 6 follow-up: range 3 months to 12 months	1567 (7 RCTs)	⊕⊕◯◯ LOW[a,b]	–	The mean QoL was – 3.60 to – 1.00	MD 0.1 lower (0.53 lower to 0.34 higher)
Treatment withdrawal due to any reason follow-up range 3 months to 12 months	1391 (7 RCTs)	⊕⊕◯◯ VERY LOW[a,b,c]	RR 0.90 (0.49 to 1.64)	Study population 124 per 1000	12 fewer per 1000 (63 fewer to 79 more)
Cardiovascular adverse events follow-up: mean 3 months	1599 (7 RCTs)	⊕⊕◯◯ LOW[a,c]	RR 0.72 (0.46 to 1.11)	Study population 73 per 1000	20 fewer per 1000 (39 fewer 8 more)
Sexual adverse events follow-up: range 1 months to 3 months	1590 (7 RCTs)	⊕⊕◯◯ LOW[a,c]	RR 6.15 (3.21 to 11.79)	Study population 31 per 1000	161 more per 1000 (69 more to 338 more)

CI, confidence interval; IPSS, International Prostate Symptom Score; MD, mean difference; QoL, quality of life; RCT, randomized controlled trial; RR, risk ratio.

Explanations

[a] Downgraded by one level in study limitation: unclear or high risk of bias for one or more domains among the included studies.

[b] Downgraded by one level in inconsistency: considerable heterogeneity among the included studies.

[c] Downgraded by one level in imprecision: confidence interval crosses assumed threshold of minimal clinically important difference.

clinical expertise. It is not uncommon to read systematic reviews that are technically well done, but lack any connection to clinical reality, for example, because the study authors had no particular familiarity with the field. Importantly, all results should be interpreted together with the quality of evidence rating. For example, if the quality of evidence rating is "very low," this indicates major uncertainty about the true effect size. Similarly, the results of any subgroup analysis should be interpreted with great caution. It is only those systematic reviews that have been conducted with great methodological rigor and in which the results have been interpreted with appropriate content expertise that deserve a special place in the hierarchy of evidence.

Using existing systematic reviews

The *JAMA* Users' Guide to the Medical Literature provides a well-established framework for critically appraising different types of studies, including systematic reviews. This framework is primarily aimed towards clinicians seeking to make decisions for individual patients. An eight-part Users' Guide series to the Urological Literature has also been published, translating the same concept into urology-relevant examples [42]. This includes an article about how to interpret a systematic review [43].

Meanwhile, for guideline developers and health policy makers who would like to assess whether a given systematic review is of good quality and likely to provide reliable results, there is a validated instrument called Assessment of Multiple Systematic Reviews (AMSTAR), which includes a total of 11 domains [44]. The AMSTAR criteria range from the existence of a priority protocol to the comprehensiveness of the literature search, the consideration of published and unpublished studies, and the disclosure of potential conflicts of interest both of the systematic review authors and those from the individual studies that inform the systematic review. Using this instrument, a recent systematic assessment of the quality of systematic reviews published in the urological literature suggests that despite an exponential increase in the number of systematic reviews published each year, quality has stagnated (Figure 3.4) [45]. This is a notable contrast to the quality of reporting of RCTs, which is found to have improved substantially over recent decades [46]

Although AMSTAR is an excellent and widely used tool that has been the basis of many methodological studies, it has shortcomings and is therefore in the process of being

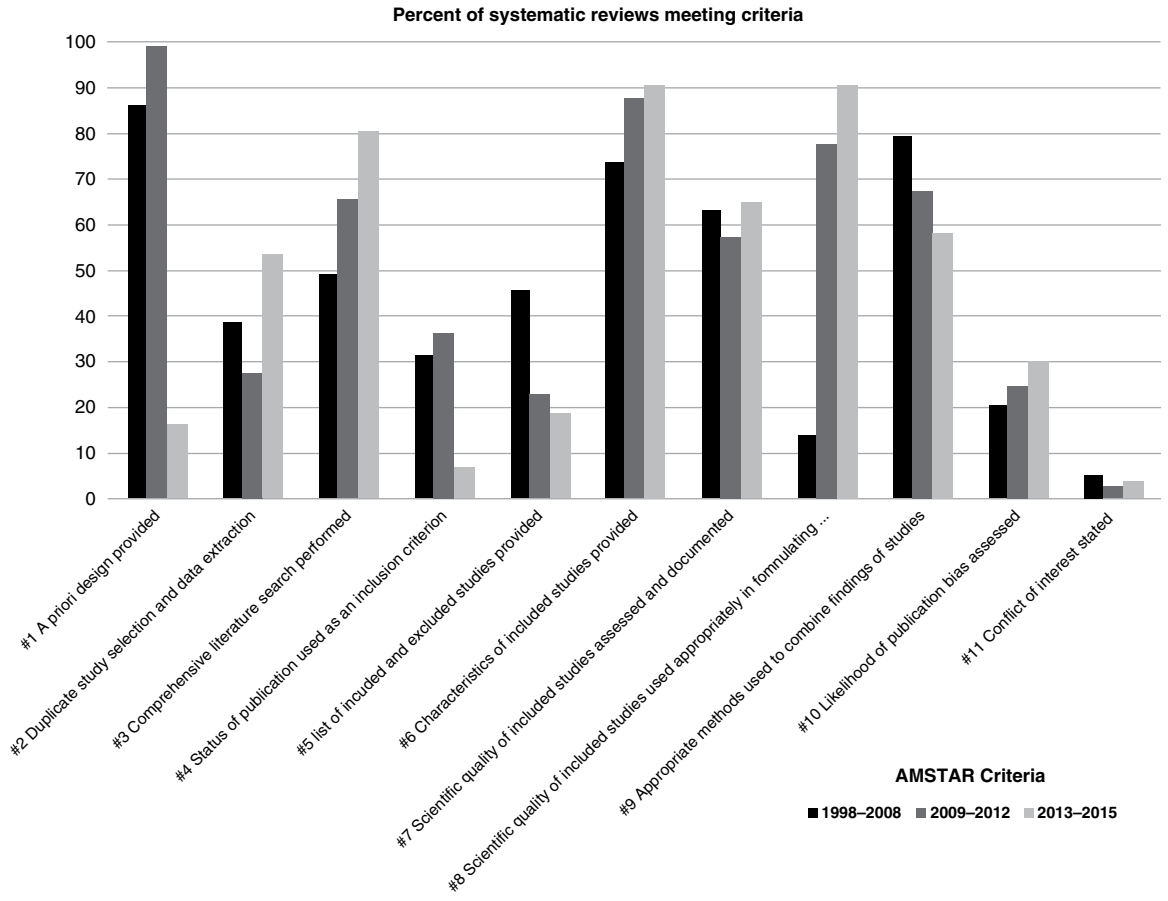

Figure 3.4 Systematic review meeting 11-point AMSTAR criteria (1998–2008, 2009–2012, and 2013–2015).

updated. A more recent edition is the ROBINS-I instrument, which assesses the risk of bias that may have impacted the execution of a systematic review [47]. Although it may prove to be a better tool, it is also harder to apply appropriately and has undergone less real-life testing.

Conclusion

Systematic reviews have a tremendous importance to the practice of evidence-based medicine in all clinical fields, including urology. As with many other types of studies, there is tremendous variability in quality. It is therefore important for clinicians to have an understanding of what determines the quality of a systematic review to identify those that are the most trustworthy. Readily identifiable markers include the availability of a written protocol, a comprehensive literature search not limited by publication status and language, completion of all important steps related to study screening, data extraction and risk of bias assessment in duplicate, use of an established framework such as GRADE for rating the quality of evidence on a per outcome basis, transparent disclosure of all conflicts of interest, and, lastly, judicious interpretation of all results, in particular the results of subgroup analysis.

Among urology journals, *BJU International* has made the most laudable effort of labeling the number of AMSTAR criteria that a published systematic review meets, thereby alerting the reader and raising awareness of this issue [21]. It is hoped that, through the concerted efforts of well-informed readers, editors, and review authors, it will be possible to raise the quality of systematic reviews published in the urological literature.

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4

CHAPTER 4

Rating the quality of evidence and making recommendations

Philipp Dahm[1] and Shahnaz Sultan[2]

[1] *Minneapolis VA Medical Center, Urology Section and Department of Urology, University of Minnesota, Minneapolis, MN, USA*

[2] *Minneapolis VA Medical Center, Gastroenterology Section and Department of Medicine, University of Minnesota, Minneapolis, MN, USA*

Introduction

Urologists require clinical expertise to integrate a patient's circumstances and values with the best available evidence to initiate decision-making related to the medical and surgical treatment of their patients. Using "best evidence" implies that a hierarchy of evidence exists and that clinicians are more confident about decisions based on evidence that offers greater protection against bias and random error [1].

Protection against bias and greater confidence in decisions arise from high-quality research evidence. We can consider quality of evidence as a continuum that reflects the confidence in estimates of the magnitude of effect of alternative patient management interventions on the outcomes of interest. However, gradations of this continuum are useful for communication with practicing clinicians, providing useful summaries of what is known for specific clinical questions to aid interpretation of clinical research.

Aiding interpretation becomes increasingly important considering that much of clinicians' practice is guided by recommendations from experts summarized in clinical practice guidelines and textbooks such as this second edition of *Evidence-Based Urology*. To integrate recommendations with their own clinical judgment, clinicians need to understand the basis for the clinical recommendations that experts offer them. A systematic approach to grading the quality of evidence and the resulting recommendations for clinicians thus represent an important step in providing evidence-based recommendations.

In this chapter, we describe the key features of "quality of evidence" and how the authors of individual chapters were asked to evaluate the available evidence and formulate their recommendations using a pragmatic approach that, out of necessity, falls short of the full development of evidence-based guidelines. The approach that most authors used was based on the work of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [2–6]. Over 100 international organizations, including the World Health Organization, the American College of Physicians, the American College of Chest Physicians, the American Thoracic Society, the European Respiratory Society, UpToDate® and the Cochrane Collaboration, are now using the GRADE system.

Question formulation and recommendations in this book

The editors of this book asked authors to ask clinical questions that are particularly relevant to urology practice using the framework of identifying the patient population(s), the intervention(s) examined (or exposure), alternative interventions (comparison), and the outcomes of interest [7]. Authors were further asked to identify relevant studies related to these questions or sets of questions. For example, in Chapter 30, the authors address the question of whether asymptomatic patients with metastatic kidney cancer benefit from a cytoreductive debulking radical nephrectomy with regard to overall survival.

The authors were further asked to base the answers to their questions on evaluations of the scientific literature, in particular focusing on recent, methodologically rigorous systematic reviews of randomized controlled trials (RCTs) [8]. If authors could not identify a recent and rigorous systematic review, they were asked to search for RCTs and summarize the findings of these studies to answer their clinical questions. Only if RCTs did not answer the specific question (or did not provide information on a particular outcome) were observational studies included. Thus, the search studies we suggested focused on relevant systematic reviews or

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meta-analyses (a pooled statistical summary of relevant studies) followed by searches for randomized trials and observational studies if systematic reviews did not exist or did not include sufficient information to answer the questions posed.

Evaluating the quality of evidence and making recommendations

All authors were asked to formulate specific, actionable recommendations that we view as the key deliverables of this book using consistent terminology followed by a brief explanation as needed. For strong recommendations, authors used the words "We recommend … (for or against a particular course of action)." For conditional (or weak) recommendations, they used "We suggest … (using or not using)" what they believed to be an optimal management approach. They then indicated the methodological quality of the supporting evidence, labeling it as high quality, moderate quality, or low or very low quality. In this updated version of *Evidence-Based Urology*, we have no longer used letters and numbers to designate the strengths of recommendations or the quality of evidence.

Strength of the recommendation

In determining the strength of recommendations, the GRADE system focuses on the degree of confidence in the balance between desirable effects of an intervention on the one hand and undesirable effects on the other (see Table 4.1). Desirable effects or benefits include favorable health outcomes, decreased burden of treatment, and decreased resource use (usually measured as costs). Undesirable effects or downsides include rare major adverse events, common minor side effects, greater burden of treatment, and more resource consumption. We define burdens as the demands of adhering to a recommendation that patients or caregivers (e.g. family) may dislike, such as taking medication and need for inconvenient laboratory monitoring, repeated imaging studies or office visits. If desirable effects of an intervention outweigh undesirable effects, we recommend that clinicians offer the intervention to typical patients. The balance between desirable and undesirable effects, and the uncertainty associated with that balance, will determine the strength of recommendations.

Table 4.2 describes the factors that GRADE relies on to determine the strength of recommendation. When chapter authors were confident that the desirable effects of adherence to a recommendation outweighed the undesirable effects or vice versa, they offered a strong recommendation. Such confidence usually requires evidence of high or moderate quality that provides precise estimates of both benefits and downsides, and their clear balance in favor of, or against, one of the management options. The authors offered a weak recommendation when low-quality evidence resulted in appreciable uncertainty about the magnitude of benefits and/or downsides or the benefits and downsides were finely balanced. We describe the factors that influence the quality of evidence in subsequent sections of this chapter. Other reasons for not being confident in the balance between desirable and undesirable effects include imprecise estimates of benefits or harms, uncertainty or variation in how different individuals value particular outcomes and thus their preferences regarding management alternatives, small benefits, or situations when benefits may not be worth the costs (including the costs of implementing the recommendation). Although the balance between desirable and undesirable effects, and thus the strength of a recommendation, is a continuum, the GRADE system classifies recommendations

Table 4.1 Grading recommendations.

Grade of recommendation	Balance of desirable versus undesirable effects	Methodological quality of supporting evidence
Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies
Strong recommendation, moderate-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise), or very strong evidence from observational studies
Strong recommendation, low- or very low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence
Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies
Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise), or very strong evidence from observational studies
Weak recommendation, low- or very low-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence

for or against an intervention into two categories: strong or weak. This is inevitably arbitrary. The GRADE Working Group believes that the simplicity and behavioral implications of this explicit grading outweigh the disadvantages.

Clinical decision-making in the setting of weak recommendations remains a challenge. In such settings, urologists should have more detailed conversations with their patients than for strong recommendations, to explore the individual patient's values, and to ensure that the ultimate decision is consistent with these. For highly motivated patients, decision aids that present patients with both benefits and downsides of therapy are likely to improve their understanding and reduce decision-making conflict, and may promote a decision most consistent with the patient's underlying values and preferences [9]. Thus, another way for clinicians to interpret strong recommendations is that they provide, for typical patients, a mandate for the clinician to provide a simple explanation of the intervention along with a suggestion that the patient will benefit from its use. Further elaboration will seldom be necessary. On the other hand, when clinicians face weak recommendations, they should more carefully consider the benefits, harms, and burdens in the context of the patient before them, and ensure that the treatment decision is consistent with the patient's values and preferences. These situations arise when appreciable numbers of patients, because of variability in values and preferences, will make different choices.

As benefits and risks become more finely balanced or more uncertain, decisions to administer an effective therapy also become more cost sensitive. Authors were not asked to explicitly include cost in the recommendations, but cost will bear on the implementation of many recommendations in clinical practice [10].

Table 4.2 Determinants of strength of recommendation.

Factors that influence the strength of a recommendation	Comments
Balance between desirable and undesirable effects	A strong recommendation is more likely as the difference between the desirable and undesirable consequences becomes larger. A weak recommendation is more likely as the net benefit becomes smaller and the certainty around that net benefit decreases
Quality of the evidence	A strong recommendation becomes more likely with higher quality of evidence
Values and preferences	A strong recommendation is more likely as the variability of or uncertainty about patient values and preferences decreases. A weak recommendation is more likely as the variability or uncertainty about patient values and preferences increases
Costs (resource allocation)	A weak recommendation is more likely as the incremental costs of an intervention (more resources consumed) increase

Interpreting strong and weak recommendations

Table 4.3 shows suggested ways to interpret strong and weak recommendations. For decisions in which it is clear that benefits far outweigh downsides, or downsides far outweigh benefits, almost all patients will make the same choice and guideline developers can offer a strong recommendation.

Another important factor that affects the strength of a recommendation is the importance of a given outcome. For example, recommendations involving outcomes of high patient importance, i.e. outcomes to which patients assign greater values and preferences, will usually lead to stronger recommendations than those involving outcomes of lesser importance to the patient. For example, prophylactic antibiotics have been shown to be effective in preventing recurrent urinary tract

Table 4.3 Implications of strong and weak recommendations.

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	The majority of individuals in this situation would want the suggested course of action, but many would not
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his or her values and preferences. Decision aids can help individuals to make decisions consistent with their values and preferences
For policy makers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and involvement of many stakeholders

infections (UTIs) in nonpregnant women. In fact, the number needed to treat (NNT), i.e. the number of women with recurrent UTIs who need to be exposed to prolonged antibiotics for one patient to gain a small but important reduction in the number of UTI recurrences, is only two patients [11]. In contrast, one might need to treat 100 patients with a history of myocardial infarction (MI) with agents such as aspirin (ASA), beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, or statins to extend one patient's life. Despite the much lower NNT to prevent one recurrent UTI, compared with preventing one MI, many women in that situation might choose to forego antibiotic prophylaxis, but take the agents that might prevent a future MI. This discrepancy may be explained by the differential value that patients assign to different outcomes. In consequence, the use of ASA would warrant a stronger recommendation.

Individualization of clinical decision-making in the context of weak recommendations remains a challenge. Although clinicians always should consider patients' preferences and values, when they face weak recommendations they should consider more detailed conversations with patients than for strong recommendations to ensure that the ultimate decision is consistent with the patient's values. For patients who are interested, a decision aid that presents patients with both benefits and downsides of therapy is likely to improve knowledge and decrease decision-making conflict, and may support a decision most consistent with patients' values and preferences [12, 13]. Because of time constraints and because decision aids are not universally available, clinicians cannot use decision aids with all patients, and for strong recommendations the use of decision aids is inefficient.

Other ways of interpreting strong and weak recommendations relate to performance or quality indicators. Strong recommendations are candidate performance indicators. For example, proposed quality indicators for prostate cancer such as those directed against the overuse of bone scans for the staging of low-risk patients or the use of adjuvant hormonal therapy in patients with high-risk disease undergoing external beam radiation are based on strong recommendations from existing guidelines [14]. For weak recommendations, performance could be measured by monitoring whether clinicians have discussed recommended actions with patients or their surrogates or carefully documented the evaluation of benefits and downsides in the patient's chart.

How methodological quality of the evidence contributes to the strength of recommendation

In the GRADE system, evidence of the highest quality comes from one or more well-designed and well-executed RCTs yielding consistent and directly applicable results. High-quality evidence can also come from well-performed observational studies yielding very large effects (defined as a relative risk reduction of at least 80%).

RCTs with important methodological limitations and well-performed observational studies yielding large effects constitute the moderate-quality category. Well-performed observational studies yielding modest effects and RCTs with very serious limitations will be rated as low-quality evidence. In the following, we describe the system of grading the methodological quality of evidence in more detail.

Factors that decrease the quality of evidence

Box 4.1 shows the limitations that may decrease the quality of evidence supporting a recommendation.

Limitation of methodology

Our confidence in recommendations decreases if studies suffer from major limitations that are likely to result in a biased assessment of the treatment effect. These methodological limitations include lack of blinding when subjective outcomes highly susceptible to bias are measured, failure to adhere to an intention-to-treat principle in the analysis of results, a large loss to follow-up, or stopping the study early because of observed benefit.

For example, a systematic review has compared the efficacy of long-term antibiotic use versus placebo/no treatment to prevent recurrent UTIs in children [15]. Based on three RCTs, antibiotics compared with placebo/no treatment reduced the risk of recurrent UTI (relative risk [RR] 0.36, 95% confidence interval [CI] 0.16–0.77; risk difference [RD] –46%, 95% CI –59 to –33%). However, the method of allocation concealment in the three trials was inadequate, unclear, and adequate, respectively. Allocation concealment protects randomization by preventing any individual involved in enrolling participants knowing or predicting the allocation sequence in advance, which might alter their behavior. In this example, lack of allocation concealment raises the question of whether the true treatment effect was overestimated. Therefore, guideline developers

BOX 4.1 Factors that may decrease the quality of evidence.

- Limitations in the design and implementation suggesting high likelihood of bias
- Inconsistency of results (including problems with subgroup analyses)
- Indirectness of evidence (indirect population, intervention, control, outcomes)
- Imprecision of results (wide confidence intervals)
- High probability of publication bias

would formulate a weaker recommendation than they may have otherwise have done if allocation concealment in these trials was found to be adequate.

Inconsistent results (unexplained heterogeneity of results)

If studies yield widely differing estimates of the treatment effect (heterogeneity or variability in results), investigators should look for explanations for that heterogeneity. For example, interventions may have larger relative effects in sicker populations or when given in larger doses. When heterogeneity exists but investigators fail to identify a plausible explanation, the quality of evidence decreases. For example, a meta-analysis of 26 studies in children investigating the utility of a urine dipstick test to rule out the presence of infection showed major heterogeneity of diagnostic accuracy across studies, which could not be fully explained by differences in age or by differences in the definition of the criterion standard [16, 17]. Many elements and differences in the process of urine collection and analysis, and in the selection of patients, may influence the presence of microorganisms that can be detected by the dipstick, and also the presence of substances that may give false results. The methodological quality of the studies might also be an important determinant of the reported accuracy and cause heterogeneity of the results. However, at present, the lack of an adequate explanation for the heterogeneity of the dipstick accuracy remains an ongoing debate. This unexplained heterogeneity could lead guideline panelists to make a weaker recommendation.

Indirectness of evidence

In this situation, the question being addressed in the recommendation is quite different from the available evidence with regard to the population, intervention, comparison, or outcome. Investigators may have undertaken studies in populations similar to but not identical with those under consideration for a recommendation. For example, an RCT has demonstrated that local treatment in the form of radical prostatectomy is effective in reducing the risk of prostate cancer-specific death in patients with localized prostate cancer (PCA) compared with watchful waiting [18, 19]. After a median period of 8 years, death rates from PCA were 8.6% versus 14%, which presents a relative risk reduction (RRR) of 40% (95% CI 8.2–61%) and an NNT of 18 (95% CI 10–101). The study was designed nearly 20 years ago, and in the meantime, prostate-specific antigen (PSA) screening and stage migration have changed the clinical picture of early prostate cancer. Also, watchful waiting has been replaced by active surveillance [20]. It is therefore unclear to what extent the results of this trial are applicable to today's patient population. This may raise concerns about indirectness of evidence to a guideline panel, which may lead to a downgrading of the level of evidence.

Imprecision

Imprecision exists if studies include few patients and few events and therefore have wide confidence intervals, because of resulting uncertainty in the outcomes. For instance, one small trial investigated men who had undergone radical prostatectomy catheterized with an antibiotic-impregnated catheter versus standard catheters and found a lower rate of asymptomatic bacteriuria in the antibiotic group at less than 1 week of catheterization (RR 0.36, 95% CI 0.18– 0.73). One of 56 men in the antibiotic-impregnated group had a symptomatic UTI compared with six of 68 who had standard catheters (RR 0.20, 95% CI 0.03–1.63) [21]. Although the results indicate a potentially large benefit, they are not statistically significant and are still compatible with an increase in risk when using impregnated catheters.

Publication bias

The quality of evidence can be reduced if investigators fail to report outcomes (typically those that may be harmful or for which no effect was observed) or studies (typically those that show no effect), or if other reasons lead to results being withheld. Unfortunately, it is often necessary to make guesses about the likelihood of reporting bias. A prototypical situation that should elicit suspicion of reporting bias is when published evidence includes a number of small trials, all of which were industry funded [22]. For example, 14 trials of flavanoids in patients with hemorrhoids have shown apparent large benefits, but enrolled a total of only 1432 patients [23]. The heavy involvement of sponsors in most of these trials raises questions of whether unpublished trials suggesting no benefit exist. A particular body of evidence can suffer from more than one of these limitations, and the greater the limitations, the lower is the quality of the evidence. One could imagine a situation in which several RCTs were available but all or virtually all of these limitations would be present, and in serious form; a very low quality of evidence would then result.

Factors that increase the quality of evidence

One of the strengths of the GRADE system is its recognition that observational studies can, in select cases, provide moderate or strong evidence [24]. Although well-performed observational studies usually yield low-quality evidence, there may be particular circumstances in which the developers of guidance documents may classify such evidence as moderate or even high quality (Box 4.2).

Magnitude of the effect size

On rare occasions when methodologically strong observational studies yield large or very large and consistent estimates of the magnitude of a treatment effect, we may be confident about the results. Although the observational

BOX 4.2 Factors that may increase the quality of evidence.

- Large magnitude of effect (direct evidence, RR >2 or RR <0.5 with no plausible confounders; very large with RR >5 or RR <0.2 and no threats to validity
- All plausible confounding would reduce a demonstrated effect
- Dose–response gradient

studies are likely to overestimate the true effect, a weak study design is unlikely to explain the entire benefit if the treatment effect is very large. Hence, despite reservations based on the observational study design, we are confident that the effect exists. Box 4.2 shows how the magnitude of the effect in these studies may move the assigned quality of evidence from low to moderate, or even to high. For example, the effectiveness of androgen ablation (e.g. orchidectomy or ketoconazole administration) in hormone-naive prostate cancer patients with impending spinal cord compression due to metastatic disease has never been evaluated in an RCT. However, treatment results in a large reduction in neurological symptoms and pain in most patients [25]. In this setting, conducting an RCT may be considered unethical, and existing observational studies provide strong enough evidence to support a strong recommendation.

Direction of bias

On occasion, all plausible biases from observational studies may be working to underestimate an apparent treatment effect. For example, if only sicker patients receive an experimental intervention or exposure, yet they still fare better, it is likely that the actual intervention or exposure effect is larger than the data suggest. This will be a rare circumstance and only a few good examples exist. A rigorous systematic review of observational studies including a total of 38 million patients compared private for-profit with private not-for-profit hospital care. The meta-analysis demonstrated higher death rates in the private for-profit hospitals [26]. The investigators postulated two likely sources of bias. The first was residual confounding with disease severity. It is likely that, if anything, patients in the not-for-profit hospitals were sicker than those in the for-profit hospitals. Hence, to the extent that residual confounding existed, it would bias results against the not-for-profit hospitals. The second likely bias was the possibility that higher numbers of patients with excellent private insurance coverage could lead to a hospital having more resources and a "spill-over" effect that would benefit those without such coverage. Since for-profit hospitals are likely to admit a larger proportion of such well-insured patients than not-for-profit hospitals, the bias is once again against the not-for-profit hospitals. Because the plausible biases would all diminish the demonstrated treatment effect, one might consider the evidence from these observational studies as moderate rather than low quality.

Dose–response gradient

The presence of a dose–response gradient may also increase our confidence in the findings of observational studies and thereby enhance the assigned quality of evidence. For example, our confidence in the results of observational studies that show an increased risk of bleeding in patients who have supratherapeutic anticoagulation levels is increased by the observation that there is a dose–response gradient between higher levels of the international normalized ratio (INR) and the increased risk of bleeding [24].

What to do when strength of evidence differs across outcomes?

In this book, authors provide a single rating of quality of evidence for every recommendation. Recommendations, however, depend on evidence regarding a variety of outcomes and it is possible that evidence quality may differ across those outcomes. For example, when RCT results are available, strength of evidence will often differ between efficacy and toxicity outcomes, usually between efficacy outcomes and cost, and almost always between efficacy outcomes and rare but serious adverse effects. The GRADE approach suggests explicit judgments about the importance of all outcomes by a guideline panel, including those that are considered harmful adverse events. This judgment requires assigning levels of importance to the outcomes. The GRADE approach asks the developers of guidance documents to decide whether outcomes are critical, important, or not important for a recommendation. For example, a meta-analysis has compared tacrolimus with ciclosporin as primary immunosuppression in renal transplant patients [27]. At 1 year, tacrolimus patients suffered less acute rejection (RR 0.69, 95% CI 0.60–0.79) and less steroid-resistant rejection (RR 0.49, 95% CI 0.37–0.64), but more insulin-requiring diabetes mellitus (RR 1.86, 95% CI 1.11–3.09), in addition to other side effects. In this scenario, the quality of evidence and strength of recommendation about the use of tacrolimus will depend on whether new-onset diabetes mellitus is judged as a critical adverse event or not.

Only critical outcomes influence the overall judgment about the quality of evidence and strength of a recommendation. Important outcomes can influence the strength (weak or strong) of a recommendation. For example, if harmful events are critical to decision-making, guideline developers should rate the overall quality of evidence based on the lowest quality evidence of any critical outcome, including that of harm. For example, there is evidence from a systematic review and meta-analysis that estrogens are

more effective in treating urinary incontinence in women compared with placebo [28]. Subjective impression of cure was higher among those treated with estrogen for all categories of incontinence (36/101, 36% versus 20/96, 21%; RR for cure 1.61, 95% CI 1.04–2.49). However, there was little evidence from the trials after estrogen treatment had finished and none about long-term effects.

Consideration of potential risk of endometrial and breast cancer after long-term use will impact on the strength of recommendation that guideline developers make, especially in women with an intact uterus. If one ignores toxicity, one might rate the quality of evidence as high. If, however, one considers the potential long-term risk of malignancy as crucial, the uncertainty about impact of treatment increases. If editors look for observational studies to estimate steroid toxicity, the quality of the evidence about toxicity is likely to be low and this may be the most appropriate rating for the overall quality of evidence. Alternatively, they may seek randomized trials of steroids in other conditions, and face limitations of directness. They may then conclude that the evidence regarding long-term toxicity, and the overall quality of the evidence, is moderate. On the other hand, if most outcomes are of higher quality than a few others, but across all outcomes there is an indication either that the benefits outweigh the risks and burdens, or vice versa, authors may decide to base the overall quality of evidence on those of the critical outcomes of higher quality and consider the other outcomes important but not critical. Therefore, guideline panels should consider whether toxicity endpoints are critical to the decision regarding the optimal management strategy. If they are, they should consider the strength of evidence regarding those endpoints, and make a final rating about strength of evidence accordingly. Outcomes that are neither critical nor important do not influence the overall quality of evidence or the strength of a recommendation.

Interpreting recommendations

Practicing urologists, third-party payers, institutional review committees, and the courts should not construe recommendations in this book as absolute. Generally, anything other than a strong recommendation indicates that the chapter authors acknowledge that other interpretations of the evidence, and other clinical policies, may be reasonable and appropriate. Even strong recommendations will not apply to all patients in all circumstances, and following these recommendations will at times not serve the best interests of patients with atypical values or preferences, or whose risks differ markedly from those of the usual patient.

Conclusion

The strength of any recommendation for practice depends on two factors: the trade-off between desirable factors and undesirable factors (risks, burdens, and cost) and our confidence in estimates of those effects. Additional factors include feasibility, equipoise, and acceptability to stakeholders. Clinicians must use their judgment when using the recommendations, considering both local and individual patient circumstances and patient values, to help patients make individual decisions.

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5

CHAPTER 5

Evidence-based clinical practice guidelines in urology

Steven E. Canfield
Division of Urology, University of Texas Medical School at Houston, Houston, TX, USA

Introduction

Guidelines are a complex and multilayered product, to say the least. Most guideline users, be they urologists or any other consumer, typically will not see that complexity. Ideally, a user of a guideline will find an easy to understand statement that helps to direct treatment decision-making. Most users consider a "good" guideline to be one that is easy to use, is easy to understand, and provides actual guidance. Clearly, these end products are highly desirable. The user takes for granted that the end product is a result of vigorous research, evidence-based methodology, and best reporting practice. In fact, to get to the final guidance statement, an exhaustive process needs to be followed. Much has been written on the best ways to organize that process [1–5], and here we review best practices in general and also evaluate how a few selected organizations that produce guidelines for urology go about the process.

The American Urological Association (AUA) produces a comprehensive set of guidelines and guideline-related products [6]. They follow a two-and-a-half year process that incorporates the following nine steps: topic selection, panel identification, research question definition, literature review, data extraction, analysis, and synthesis, evidence report review and guideline statement development, guideline writing, peer review, and guideline approval and publication. Following publication of the guideline, they pursue various methods of dissemination and education to encourage awareness and use of the guidelines. An additional step in the process is how the guideline then remains current. The AUA uses an "update literature review," process which itself involves four more steps: identify the panel, develop the TRD (topic refinement document), conduct the literature review, and develop the recommendation to revise or delay. Revisions to the guideline can be either limited or full, and allow the guideline to remain in circulation indefinitely. A guideline that has not been updated or revised for 10 years is retired.

The European Association of Urology (EAU) also has comprehensive guidelines in circulation that undergo yearly evaluation and updating [7]. Their process involves the development of guideline panel member-generated, topic-specific questions that specify inclusion and exclusion criteria using an iterative process to define standard patient, intervention, comparison, and outcome (PICO) parameters. These questions are then systematically reviewed according to Cochrane methodology [8]. and follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [9], with evidence products produced for panelists subsequently to generate final recommendation statements. Level of evidence and grading for each recommendation statement is also applied. For certain sections of the guidelines that do not conform to systematic review methodology, a traditional narrative review is utilized. Similarly to the AUA guidelines, each yearly update is published and disseminated through various educational and media strategies.

The National Comprehensive Cancer Network (NCCN) includes urological oncology guidelines that follow the organization's larger format [10]. Because the NCCN is specific to oncology topics, the guidelines are set and the overall process does not include the development of new guidelines, but provides a framework for their at least yearly update and review process. The components incorporated by the NCCN include: panel composition and roles, transparency and conflict of interest management, update and review process, levels of evidence and consensus for recommendations, and publication process. An interesting facet to the NCCN process is that they perform an overall annual review of each guideline every year, overseen by their Annual Institutional

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Review body, and also allow for even more frequent, interim panel meeting updates whenever they determine that new evidence has emerged that may influence the guideline. These interim updates may be initiated by current panel members or through invited open submission of review requests by outside parties, including industry, external clinicians, patient advocates, and payers.

A final example is the National Institute for Health and Care Excellence (NICE), which also produces guidelines covering urological topics [11]. NICE follows a multistep process for developing and updating their guidelines that includes topic selection, scope, guideline development, draft review, consideration of draft comments and revisions, sign off, publication, and updating. Each step involves various sectors of the UK health services and appropriate topic stakeholders. Evidence to support the guideline is reviewed by committees comprised of practitioners, professionals, care providers, commissioners, those who use services, and family members or care providers. These committees then follow a detailed process for recommendation statement development, including language, wording, and strength rating.

Guideline creation checklist

In 2014, a respected group of international guideline process development experts assessed the need for a comprehensive guideline creation list and resource portal [12]. Despite the abundance of guideline methodology publications and organization-specific handbooks available for guideline creation, they felt there was a need for a comprehensive "checklist" of items necessary for the start to finish guideline process (keeping in mind that the guideline process is never truly "finished"). The final checklist pulls from nine specific methodology groups and 18 separate organization handbooks, and distills everything down to 18 specific process steps. This review summarizes these process steps, with greater depth and explanation of certain key steps critical for urology guidelines.

Organization, budget, planning, and training

It may seem that only a new organization planning to create guidelines from scratch would need to consider this initial step. In reality, it is likely that every guideline in existence utilizes this step, arguably every year it continues to operate. Guideline development and maintenance can be a costly undertaking, and budget will often direct the scope of what is possible. Even a single question within a single guideline can generate high cost, depending on how the data search is accomplished, who is involved in the work, and how the information is disseminated. Organization and planning become critical, based on the budget and goals for each year. Urology guidelines, for example, often comprise over 20 different topics, each of which may include 20–40 separate subtopics [6, 7]. As new topics and new evidence evolve, decisions around new guidelines and strategies to update old guidelines must be made. Because guideline methodology can be complex, it is unlikely that a typical panel of topic experts within an organization will be competent in this aspect of the process. Training is therefore another integral component of the development process, and another aspect that can generate large expense.

Priority setting

Determining which guidelines need to be addressed in general, and each year, is best done in a well-organized fashion. Consideration should be made regarding what is most needed by the organization's consumers, and these stakeholders should ideally be involved in this process [13]. Currently available guidelines or systematic reviews should be considered, and potential overlap with other organization should be identified. Many guideline developers attempt to collaborate on mutual topics to save duplication of effort and expense and broaden overall utility and dissemination.

Guideline group membership

Although many groups will nominate topic panel members based on their established expertise in the field, the ideal group should also reflect the target audience for the guideline. Therefore, it may be appropriate for a panel to include a patient, a policy maker, and a healthcare system representative, for example. Consideration should also be made to include methodology expertise on the panel. The size, leadership, and responsibilities of the group can all be approached systematically.

Establishing a guideline group processes

Having a well-organized structure for the group will facilitate efficiency of process and flow, aid in conflict resolution, and set training goal expectations.

Identifying target audience and topic selection

Most established guidelines will have a clearly defined target audience, such as patients, physicians, healthcare systems, or policy makers. In urology, guidelines are for the most part directed at helping urologists make well-informed, evidence-based decisions for their patients. The target audience for a guideline is an essential component of what defines that guideline organization and its mission. Topic selection is driven based on the changing needs of the target audience.

Consumer and stakeholder involvement

Knowing the target audience can then identify appropriate stakeholders who may ideally participate in the guideline development process. Inclusion of external stakeholders can be a cumbersome and tricky endeavor, and a well-defined process and roles can greatly facilitate this component.

Conflict of interest considerations

Dealing with conflict of interest within guideline organizations and topic panels is another critically important step in the process. The majority of specialty organizations that create guidelines, such as in urology, will have guidelines targeted at physicians and panels largely composed of physician experts in the field. It is highly likely that many of these experts will have external ties to grant organizations, research, industry, and investments that could be in clear conflict with the guideline topic. It is preferable to have rules around these potential conflicts that are well defined ahead of time by the organization, to guide how these conflicts will be disclosed and dealt with impartially.

Question generation

At the start of all new inquiries and updates is the clinical question. A precisely structured process for generating questions, ranking them, and determining which will proceed with the process is essential. Some organizations may choose to use a template form to provide structure for the topic panelists who will generate the questions, for example. Questions in general and whenever possible will adhere to the PICO format, and outcomes will be systematically assessed, ranked, and agreed upon. Additional details such as subgroup and confounders can also be identified early during this phase [14].

Considering the importance of outcomes and interventions, values, preferences, and utilities

This step is best addressed during the creation of recommendations and their strength. Panelists will often be faced with uncertainty around the weight of some outcomes, particularly for complex patient values and preferences scenarios. Organizations have attempted to add structure and transparency to this step in the process by including rules and methods early on to understand these factors better when necessary.

Deciding what evidence to include and searching for evidence

This well-defined step within the systematic review process should be clearly explained by the organization, including instances where the process deviates, includes, or excludes certain types of evidence not routinely accepted [15]. For example, in the absence of randomized controlled trials, observational studies or even case series might be included in the search, and this decision should be explained and available. Similarly, for massive topics, the search may be limited in various ways to comply with budgets of expense and time. This decision should be discussed by the panel and explained to the consumer. The actual search for evidence is usually performed by experts trained in this methodology, such as library information scientists, who should provide the scope and search details such that they can be reproduced by others if desired.

Summarizing evidence and considering additional information

Each organization will need to determine how it will present the summary of evidence. This can be accomplished in many ways, including lengthy narrative review of the data and unique methods such as the "index patient" found in the AUA Guidelines [6]. Commonly accepted summary examples are the evidence tables, evidence profiles, and summary of findings tables promoted by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [16, 17]. Ideally, the information will be presented in a concise fashion that includes an assessment of evidence quality, accuracy, confidence, balance of benefits and harms, knowledge of patient values and preferences, resource utilization when appropriate, and estimation of effect size.

Judging quality, strength, and certainty of a body of evidence

Appraising the quality of the evidence should be performed by members familiar with standard methodology such as used by Cochrane and GRADE. Ideally, individual outcomes, in addition to the entire body of evidence, should be assessed for quality [18]. Judgments about the quality should also be documented so that readers can understand the thought process that went into these decisions, especially for evidence that may be interpreted as having higher or lower quality, strength, or certainty depending on these judgments.

Developing recommendations and determining their strength

The actual recommendation statement should be crafted according to a structured plan that allows for a systematic determination of the direction (i.e. for or against an intervention) and strength of the recommendation, and reveals the thought process around these determinations, such as the process promoted by the GRADE Working Group [19, 20]. The strength of the recommendation should, of course, be informed by the quality of the available evidence, but also by the magnitude of effect, the balance between benefit and harm, the known, unknown, or variability of values and preferences of patients, and resource utilization when appropriate. Provisions should be made for circumstances where evidence is lacking and, in such cases, how research recommendations will be handled (e.g. "further research on this topic is recommended"). All of these considerations should be summarized in a manner that allows a clear understanding of how the recommendation statement has then been formulated. The strength of recommendations should be directly linked to the supporting evidence summaries, and judgments used to decide the final strength

that incorporate all the factors listed (i.e. benefit to harm, patient values, etc.) should be explained. At times there will be disagreement in determining the strength among members of the guideline panel, and the method for resolving this should be predetermined and explained. The ultimate purpose of these steps is to make the strength rating transparent, so that users of the guideline can understand why the rating was applied, if they care to do so, and if they agree or disagree and therefore wish to incorporate the recommendation into their patient care.

Wording of recommendations and of considerations of implementation, feasibility, and equity

Proper wording of recommendations is critically important to ensure that all of the effort spent in assessing the evidence, weighing the strength, and crafting the statement is not lost because of confusing or unfocused language. Variability present in the wording of recommendations leads to confusing interpretations regarding the need to follow those recommendations, the strength they imply, and their meanings in general. An example of how wording can be confusing is demonstrated with words such as "can," "may," and "might," which do not directly help the reader to know how important it is to follow the stated recommendation. There is no exact wording that can accurately relay the author's implied meaning, which is why a standardized, simple, and limited vocabulary is best for recommendation statements, along with an explanation of the meaning of this vocabulary [21]. There is a direct link between the strength of recommendation levels used by a guideline and the wording that follows. The GRADE Working Group suggests using the words "strong" or "weak" along with either "for" or "against" for each recommendation, to keep the statements consistently interpretable [20]. Other organizations use similar systems or modifications. The AUA recognized that its former wording system, which utilized the terms "Standard," "Recommendation," and "Option" to classify its statements, was limited and possibly confusing. The organization now uses the terms "strong," "moderate," and "conditional" to classify the strength of its recommendations, which is a more direct modification of the two-word GRADE system (i.e. "strong" and "weak") [22]. The EAU, which did not have a well-structured wording system in place for many years, now uses "strong" and "weak" to guide the user. By conforming to a commonly accepted system in this manner, albeit with very minor variations, guidelines can more easily be compared, shared, and even merged across organizations. Words such as "may" and "might" are discouraged in these statements. It is equally important that the recommendation is actionable, and is not simply a statement of fact or another evidence summary [23]. A guideline "recommendation" statement that is not actionable does not actually provide any guidance. Finally, clear descriptions of who the statement is for (i.e. the population), what the intervention is, and specifics of circumstance, feasibility, and subgroups should be made [13]. Some organizations have even included visuals to guide readily the direction and strength of the statement, such as arrows up or down [19].

Reporting and peer review

Each guideline will have its own style and format for presenting the evidence, the summaries, and the actual recommendations. The format should be standardized and applied throughout the body of different guidelines offered by the organization. A well-organized guideline will also have set rules for authorship and for the work of actually writing the texts, with a planned internal and external peer review process.

Dissemination and implementation

After all the work put into developing and creating an evidence-based guideline product, it is critical to get it into the hands of the consumer and to have it used properly. Dissemination can occur in many ways and formats, which should all be part of the organization process of the guideline group. With rapidly changing media formats, this step in the process should also remain fluid and flexible to keep up with technology and consumer demand. Decisions around how the guideline will be translated into other languages, if appropriate, should be made. Implementation of guidelines is also one of the most difficult steps and can include efforts focused on education of the target audience, ensuring ease of access to the guideline through useful dissemination, and point-of-care embedding of the guideline into practice such as within electronic medical record systems [24].

Evaluation and use

Along with implementation challenges, it is exceedingly difficult to assess the actual impact of a guideline on clinical practice. Evaluation of a guideline can also include internal audits and feedback on the process from panel members, but most often implies the assessments directed at the impact that the guideline has on clinicians and patients. Tools for such evaluation can be built into the guideline in the form of outcome measures that conform to the recommendations. A promising area under development that may yield improved assessment of guideline impact is within the electronic medical record (EMR). Guideline organizations such as the AUA are partnering with major EMR providers to embed guidelines into the clinical chart to provide improvements in the areas of dissemination, implementation, and evaluation. Ideally, users of these EMR systems will be able to understand when recommendations should be implemented (in real time), decisions around the recommendations can be captured (i.e. implementation), and outcomes based on use of recommendations can be assessed.

Updating

The moment a guideline is completed and published it begins to become outdated. Different organizations will determine how they will address the challenge of keeping a guideline up to date, and who will be responsible for the components of the updates. Policies for various circumstances should exist, such as how to handle a new practice-changing single study, and how to decide if a topic should be updated or retired [4]. Most guidelines have a timetable for basic updates. For example, the EAU updates certain sections of their guidelines each year, and the AUA updates the entire guideline every few years at predetermined intervals.

Conclusions

The comprehensive process for guideline development, creation, dissemination, evaluation, and updating reviewed here includes every possible step thus far identified; however, each organization that produces guidelines will decide how best to incorporate any of these steps into their own process. Not all steps will be deemed necessary to each organization, although the urology guidelines used as examples in this review each include components of many. Equally as important as the steps themselves is the quality of enacting each step. The guideline consumer can use existing tools to compare different guidelines, which summarize these steps and provide a means of objective evaluation [25]. What is most helpful is that each organization provides a transparent and accessible explanation of its process to the consumer, who can then more easily determine how to weigh the findings. Recommendation statements may look the same or completely different between organizations. Understanding the steps taken to end up with the final statement may shed light on which organization's recommendations one might choose to follow, for example. On a broader scale, organizations that understand each other's process can evolve towards closer alignment, lead to endorsements across organizations, and even allow for combined guidelines when appropriate. The field of urology has many fine guidelines that can provide point-of-care assistance to providers and patients. Understanding differences in their creation process may help to differentiate when one urology guideline might be useful over another. Just as it is important to understand then critical appraisal process for individual research, users of guidelines should also be well aware of the complex process required for quality guideline creation.

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6

CHAPTER 6

Understanding concepts related to health economics in urology

Yair Lotan and Ryan Hutchinson
Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Introduction

National healthcare expenditures are rising both in terms of actual dollars and as a percentage of gross domestic product [1]. With an aging population, an increasing proportion of patients with coverage and a slowly recovering national economy, healthcare economics are an area of growing focus. Urologists often view cost as a secondary issue in the care of a patient; however, in light of increasing administrative oversight of care decisions, the impact of economics on the day-to-day practice of urology is increasing. Economic issues affect the clinical availability of new technologies, the development of medications by companies, the willingness of patients to take medications based on cost, and the personal income of providers. The central issue in economics involves choices between different options based on scarce resources. The current healthcare environment is one in which institutions and healthcare plans face limited budgets that need to be utilized in the most cost-efficient manner. Hence choices must be made regarding different treatments, diagnostics, and care models taking into consideration both efficacy and cost. Such cost-utility or cost-effectiveness analyses play an increasingly large role as the costs of new treatments and drugs increase and the margin of benefit decreases. There is a growing need to identify objectively the best use of resources in the presence of competing risks, benefits, and costs.

In order for urologists to optimize their care of patients, they need to understand the economic factors that affect their ability to practice medicine. In this chapter, we review the concepts that form the foundation of health economics and apply them from a urological perspective.

Economic parameters

There are several issues that are common to all economic analyses. These include the perspective of the analysis, outcomes using cost versus charge, and discounting. National regulatory bodies in the United States evaluate new therapies for safety and efficacy but they do not evaluate treatment cost or cost efficacy. These economic measures are of paramount importance to those on the financial side of healthcare, including insurers, hospital administrators, and consumers. Within the urological literature, cost parameters are of low prominence in most standard clinical research; however, they can heavily impact the outcome and validity of economic studies and also the treatments and care environments used to treat real-world patients.

The importance of perspective

Cost analyses can be constructed from different perspectives based on the factors included in the analysis. In order to determine which costs to include in an analysis, one needs to determine who incurs those costs. In the US healthcare system, there are three "payer" perspectives: society, hospital, and patient.

The perspective of the patient is the most subjective to evaluate as it depends on individual factors, including insurance, deductible level, and employment status. A patient with insurance or financial independence may be more likely to seek medical care rather than delay care until it is urgent. The level of drug benefits and co-pay may affect a patient's willingness to initiate medical management or

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remain compliant with medications, which are expensive relative to their ability to pay. Patients without insurance may delay their care or be less likely to purchase costly medications. In countries where medical care is freely available to all citizens, this issue may have less impact on individual patient decision-making or may be replaced with other constraints such as medication availability, care rationing, and systems-based efficacy decisions for drugs.

The hospital's perspective is usually the easiest to measure because most of the resources utilized can be itemized and accounted for. Hospital costs include the resources required to perform a procedure and immediate post-procedural care. Hospitals have costs, which are individualized to the patient, including the cost of the supplies used in surgery, medications, room and board, nursing, etc. There are also the general costs such as hospital administration and amortization of capital equipment. In evaluating the cost-effectiveness of surgical approaches, for example, the cost of capital equipment can play a significant role. A hospital may not receive additional payment for robotic prostatectomy but has to pay for the robot and its maintenance [2, 3]. Similarly, the outlays for a shock-wave lithotripter or ureteroscope are significantly different whereas treatment outcomes may be similar.

An important consideration when evaluating costs from the hospital's perspective is that budgets within hospitals are often divided by department. Some areas may be financially profitable whereas other areas may lose money for certain procedures. Hence the costs associated with obtaining new equipment or maintaining current equipment must be viewed in relation to the entire hospital rather than considering the impact on one budget, such as that of the operating room. A common example is minimally invasive procedures that result in decreased length of stay [3], but with higher operating room supply costs (e.g. laparoscopic procedures such as nephrectomy). Hospital administrations must therefore take a broader look at the financial implications of new technologies as they affect different cost centers under the same institutional banner.

The economic perspective of society is complex and involves both direct and indirect costs. As Medicare plays a large role in financing healthcare in the United States, a significant percentage of direct costs affect the overall national healthcare budget. Costs borne by private insurance companies are also passed on to employers and participants through higher premiums. Society is also influenced by opportunity costs, including loss of productivity that results during an illness, and also indirect opportunity costs, including loss of productivity for caregivers. These indirect costs can be difficult to measure but can represent a significant portion of cost from a societal perspective. Furthermore, there are quality of life issues, including long-term morbidities that can incur significant costs for the rest of a patient's life. For example, a patient with incontinence after prostatectomy will incur lifelong costs not immediately accounted for by his hospital and immediate postoperative care. Likewise, a patient who has renal insufficiency after nephrectomy may incur significant costs that are a direct outcome of kidney cancer but not accounted for by evaluating the cost of the nephrectomy from a hospital perspective.

Cost versus charge

Evaluating the literature regarding health economics can be confusing because of interchangeable use of the terms *cost* and *charge*. The charge for a service is set by the provider and incorporates the cost of an item, indirect costs, and anticipated profit margins. Discerning between analyses that use cost data as opposed to charge data is critical because there are significant differences in how these values are derived and their accuracy in reflecting true resource utilization. Many published evaluations use charge figures provided by the hospital system because they are easier to obtain [4]. The disadvantage of using charge data is that they do not reflect the true resource allocation or even true money changing hands. Moreover, there are several confounding factors involving use of charge data; for example, different departments in a hospital may use different cost-to-charge ratios such that the radiology department may charge two times cost for an X-ray but the pharmacy may charge four times cost for a medication. Another consideration is the fact that hospitals rarely get paid the actual amount that they charge owing to Medicare-set rates and insurance contracts. The reimbursement further varies per hospital and geographic location such that comparing costs is a more uniform means of evaluating differences between treatment or management options.

Even the use of costs can bring variability. The true cost of a procedure depends on utilization. For example, if one pays $1 million for a robot and performs robotic surgery 10 times per year, then that cost is distributed over those 10 patients. However, if one uses the robot 100 times per year then the cost is 10-fold lower per patient [3]. This is true for the use of any capital equipment such as computed tomography scanners, shock-wave lithotripters, and laboratory equipment. It is also true for hospital beds, since the costs of nursing and building the hospital are fixed, so the increased utilization of the facilities of the hospital, such as the emergency room or beds, will affect the per-unit cost of patient care.

There are also problems with the accurate assessment of the cost of capital equipment. Items such as a surgical robot, laparoscopic ultrasound, camera, and televisions are usually paid for from operating room capital budgets and amortized over many years. Depreciation costs and usage per case can then only be estimated. Conversely, costs of disposable equipment and medications can be established with more accuracy but are still influenced by the vendor contract, which varies based on the volume of purchase.

Although cost analyses result in a more accurate estimation of resource utilization than analyses using charge data, it is important to understand where the data upon which the cost analyses were based were obtained. Furthermore, when comparing cost within an institution or country, there is need to understand that the conclusions may not be accurate in other economic settings or with other cost assumptions [5].

Discounting

In some analyses, there is a time component such that outcomes occur in the future. This applies to many cancer-related analyses in which survival and progression outcomes occur at different time points from the initial treatment. In order to compare future costs with current costs, the concept of discounting needs to be utilized [6]. Discounting is necessary when the experience of the patient in the near term is valued more than future costs and health outcomes [7, 8]. It is necessary because people in general prefer benefits today rather than next year. For example, $1 today is worth more to an individual than the same $1 next year. Most cost analyses apply a yearly discounting rate of around 3% to future costs and future years of life [8, 9]. This discounting rate is based on historical annual inflation rates of 0–5% but is a distinct entity from inflation. In other words, the time preference for money exists even in the absence of inflation. Most cost analyses in urology involve comparison of costs associated with procedures or techniques. Discounting is very important for cost-effectiveness analyses evaluating screening or chemoprevention where the initial costs are high but benefits may take a long time to materialize [10, 11].

Costs in economic evaluation

In cost analyses, it is important to determine how to obtain the costs used in the analysis. The costs are determined by the resources used and the value of the resources. They are typically recorded on a per-patient basis. Although costs used to be categorized as direct and indirect, this led to confusion regarding categorization of indirect costs [12]. Classification of costs as health service related and non-healthcare related is utilized for better categorization.

Another important part of transparency in economic evaluation is the utilization of an explicitly stated reference case. This is not appropriate in all analyses but should be included in cost-based studies when feasible as it provides transparency to the assumptions and a reference point for generalizability of the findings. For example, a study that states that a therapy is the most cost-effective for kidney cancer is unlikely to have utility to a reader unless that therapy can actually be shown to be highly cost-effective in all patients with all stages and subtypes of disease, which is unlikely. A more effective and useful statement comes from a study with a clearly defined reference case, for example, "In patients with clinically localized T1 clear cell renal cell carcinoma eligible for surgery, this therapy was the most cost effective."

Health service costs

Health service costs include the direct costs of the treatment, general illness costs, trial costs, and future costs. Direct costs include any inpatient and outpatient costs associated with an illness or treatment. These include any cost associated with treatment, including room and board, any laboratory tests or imaging, medications use, the use of capital equipment, and overheads such as nursing.

General illness includes any related diseases that are diagnosed while being treated for the primary diagnosis. If someone diagnoses high blood pressure or skin cancer during prostate cancer screening, then there are additional costs incurred that would not have been included if the patient had not undergone screening. If these diagnoses are related to the primary diagnosis, then their costs should be included.

Trial costs are only relevant if a patient is involved in a clinical protocol and has additional tests or visits that are specific to the protocol. If tests performed are part of standard practice, then they are not added specifically to the trial arm, but if they are unique to a protocol, then they need to be accounted for.

Future costs include those that are specifically related to treatment [13]. Future costs may include cost of future treatment for diseases specifically related to the initial therapy or illnesses that are unrelated but occur because of added life-years which result from treatment. There is no consensus on the need to include all costs in every cost-effectiveness analysis, but some rationale should be used for including or excluding certain costs. In some instances, it makes sense to include costs such as morbidities related to treatment. In an analysis of quality of life-years saved after prostatectomy or prostate cancer screening, it is logical to include the loss of quality of life in patients who suffer from incontinence or impotence [11]. On the other hand, if a screening policy saves a patient from dying of prostate cancer early, it is not clear whether the cost of having pneumonia or a heart attack in the latter part of his life should be included in determining the cost-effectiveness of screening.

Non-health service costs

Non-health service costs are those not directly related to the treatment of a disease. This includes those costs incurred by social services provided to the patient and loss of productivity to society by either the patient or caregivers. There are also patient-related costs such as out-of-pocket expenses and travel [14]. These costs are difficult both to attribute and to quantify; therefore, they are often omitted from cost analyses of specific interventions but can be included in

more global analyses of the economic burden of diseases or management strategies.

Economic analyses

The purpose of economic analyses is to try to address a particular question. This is most useful when there is a discrepancy between economic aspects (i.e. cost) and effectiveness. Effectiveness is a critical issue in economic evaluations because of the fixed nature of resources. If there were unlimited resources then one would always choose the most effective treatment or approach to a problem. The crux of economic analyses is that there is a trade-off between cost and efficacy of an intervention.

Effectiveness is typically measured in terms of direct outcomes, such as survival, or as utilities. Utilities may reflect preferences of patients or society. Values are assigned to various health states on a scale ranging from 0 (dead) to 1 (perfect health). A common utility is quality of life, which can be measured using validated questionnaires. There are general health questionnaires such as the SF-36, which is composed of 36 items relating to eight dimensions of well-being: physical functioning, role limitation caused by physical health problems, bodily pain, general health perception, energy/fatigue, social functioning, role limitation caused by emotional problems, and emotional well-being [15]. These types of questionnaires are useful for evaluating chronic conditions such as nephrolithiasis [16, 17]. There are several validated questionnaires specific to urological practice. One of the most commonly used is the American Urological Association symptom index [18].

In studies evaluating outcomes that are affected by quality of life measures such as quality-adjusted life-years (QALYs) saved, these types of validated questionnaires are critical. For example, in determining the cost-effectiveness of chemoprevention or screening QALYs, the use of prostate-specific questionnaires is needed to determine the impact of treatments and age on related symptoms such as voiding [19], potency, and continence [11, 20, 21]. Validated questionnaires can be used to assign a utility value to living with certain conditions, including different states of cancer [22, 23]. Patients with cancer, even those who are "cured," have a lower quality of life than if they had never had to worry about cancer in the first place.

In order to perform a cost analysis, one needs to determine the cost of different approaches and the measured outcome of the different approaches. The cost-effectiveness ratio is the difference between costs (cost 1 minus cost 2) and the difference in outcome (effect 1 minus effect 2). The increase in cost between approaches is known as the incremental cost and the increase in outcome is the incremental utility, whether it is measured in survival, QALYs, or another metric. As noted above, if time is a factor, such as in Markov models, then both cost and effect need to be discounted.

There are several different types of economic analyses that vary by the type of information used and the question that is being asked. The simplest model is that of cost analysis or cost minimization, which seeks to evaluate total costs associated with different interventions and does not evaluate the efficacy of the interventions. This would be the case in determining the least expensive surgical approach for nephrectomy with the assumption that the oncological outcomes are identical [24]. On the other hand, if there is concern that the outcomes may be different qualitatively, then one should consider performing a cost-effectiveness (CE) analysis, assuming a difference in effect. Hence if, when comparing radical with partial nephrectomy, one wants to take into consideration a small difference in recurrence rates, then one would evaluate the difference in cost and difference in outcome. Although cost-minimization analyses are easier to conduct than cost-effectiveness studies, they can result in misleading conclusions when the underlying assumptions are not met. An example is that of delivery methods for external beam radiation in localized prostate cancer. Although hypofractionated methods of delivery (commonly called stereotactic body radiotherapy) offer lower costs [25] and appear oncologically equivalent to the more expensive methods of intensity-modulated radiation therapy and proton beam radiotherapy, these approaches may be associated with more severe late regional organ toxicity, undermining the assumption of treatment equivalency.

CE analyses assume a limited financial resource and attempt to find the most efficient way to spend a certain budget. These types of analyses are only necessary if there is both a difference in outcome and a difference in cost. If the cost is comparable, then the most effective outcome is preferred. If the outcome is equivalent, then the analysis is a cost-minimization analysis. CE analyses are primarily helpful when there are many variables and the outcome is not clearly obvious. For example, in the case of chemoprevention for prostate cancer, the primary endpoint of the Prostate Cancer Prevention Trial was a reduction in cancer prevalence [26]. However, a more important question is: does chemoprevention save lives and is it cost-effective? Since the cost per life-year saved was not part of the trial design, it can only be extrapolated using a CE analysis. In this study, finasteride resulted in a reduction of cancer but at a cost of providing medication to many subjects who never had cancer and treatment to patients who may not have an increase in survival. In order to determine the CE ratio, a Markov model estimating the survival advantage of finasteride (incremental life-years) and cost of chemoprevention (incremental cost) can be designed to determine the cost-effectiveness of chemoprevention [27]. One advantage of models is the ability to utilize sensitivity analyses, which can allow the evaluation of outcomes with varying assumptions. Hence if there is a variable cost, one can determine the CE ratio under different circumstances. Cost–utility analyses

are CE analyses that compare effects using different utilities such as QALYs. This requires the sometimes dubious task of assigning economic value to patient life-years. A famous precedent for this type of analysis is the coverage of dialysis to extend the life of end-stage renal patients, placing the value of a QALY at a minimum of $50 000 [28].

Additional utility in cost efficacy

When a device, test, or drug comes to market, it must pass through US regulatory bodies that evaluate for safety and efficacy. The regulatory approval process does not evaluate marginal utility or cost efficacy. These are concepts of primary concern to whether a product is actually used or how much benefit it ultimately confers. In order to be safe and effective, something must offer a tangible benefit to the receiver while doing so with a disease-specific acceptable risk. In instances where no other management option exists, this makes sense; if there is no therapy for a disease, the alternative is expectant management and a natural disease course. It becomes far more complicated when interventions are superimposed upon already complicated management algorithms.

Consider the example of Ki-67, a cell proliferation marker, as a prognostic aid in bladder cancer. Ki-67 does an excellent job of estimating post-cystectomy disease prognosis in isolation. However, when this information is added to what is already in practice, namely evaluation of tumor staging, nodal staging, and tumor factors such as lymphovascular invasion, the added prognostic information from Ki-67 evaluation is small [29]. From an additional utility perspective, this evaluation would be unlikely to be able to justify its cost, despite the fact that it provides good prognostication.

Taking the example one step further, even a test that does provide significant additional, independent prognostic information may have difficulty with cost-effectiveness. Molecular marker panels can add prognostic information above TNM staging about disease recurrence and survival after surgery for various genitourinary malignancies [30]. In the event that an effective secondary therapy exists, this information can have high utility, allowing patients who would otherwise have bad outcomes to be salvaged and sparing those patients with a low chance of recurrence unnecessary therapy. In the more common instance, where secondary therapies are palliative in nature and used based on the clinical picture, even an excellent prognostic test may provide limited additional value.

Much of the dramatic increases in the cost of healthcare in the United States have been due to indiscriminate incorporation of new tests and treatments without evaluation of the economic impact. Advances such as immunotherapy for prostate cancer are exciting but agents such as sipuleucel-T, with costs over $100 000 and providing a survival benefit of around 4 months, result in an incremental cost–utility ratio of around US$283 000 per QALY saved [31, 32]. There are many examples of the impact of treatment decisions on the cost of overall care. Although there have been no randomized trials supporting surgery versus radiation therapy as the optimal treatment of prostate cancer, several studies have evaluated the economic impact of the type of treatment chosen. Cooperberg et al. compared the cost-effectiveness of seven therapies (not including active surveillance) for low-risk prostate cancer [33]. They determined that the greatest QALY (11.3) was achieved with surgery (any approach), and intensity-modulated radiation therapy (IMRT) and brachytherapy (BT) provided similar QALY (10.8). This benefit in terms of QALY was also accompanied by a lower cost of surgical therapy ($19 901 for robotic-assisted laparoscopic prostatectomy) compared with radiation therapy ($25 067 for BT and $40 588 for IMRT). The utilization of proton therapy for prostate cancer has so far not demonstrated an advantage over IMRT but is a significantly more costly treatment. There is a considerable cost of setting up a proton center ($150–200 million) and also costs associated with travel and accommodation due to the limited availability of proton centers nationwide. One can expect that until there are reliable constraints on testing or treatment based on cost considerations, there will be a continued introduction of expensive tools without adequate evaluation of cost-effectiveness.

Conclusion

Financial considerations play a major role in healthcare decisions both directly and indirectly. As technologies and medications are introduced at a time of budgetary constraints on healthcare systems, there will be increased scrutiny into the likely benefit of these treatments. Cost analyses aid in this type of decision-making whether at the patient, hospital, or societal level. For urologists, it is important to understand the concepts that underlie such decision-making.

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7

CHAPTER 7

Quality improvement in urology

Nima Almassi and Howard B. Goldman
Glickman Urological and Kidney Institute, The Cleveland Clinic, Cleveland, OH, USA

Introduction

Although frequently discussed, *quality* remains an abstract concept with widely varied meaning. To the urologist, quality may be measured in functional terms such as continence rates following radical prostatectomy. To the nurse manager of an inpatient ward, quality may refer to achieving 100% compliance with hand hygiene protocols. Meanwhile, a patient may find quality in the empathy of his or her healthcare team. How we define and measure quality affects our ability to identify opportunities for quality improvement. Once such opportunities have been identified, a framework is needed within which to implement and evaluate quality improvement initiatives. While quality is important for the health of our patients and community, it is becoming increasingly important for healthcare providers and hospital systems as value-based purchasing is incorporated into healthcare reimbursements. In this environment, it is imperative that urologists understand quality and be able to spearhead quality improvement.

We begin this chapter with a brief introduction to the history of quality improvement in healthcare. Quality *domains* and *measures* are introduced, laying the necessary foundation to identify quality improvement opportunities. We conclude with a discussion of *frameworks* in which quality improvement can be effectively implemented, using examples relevant to the practicing urologist. Our goal is to provide the necessary tools for urologists, trainees, nurses, and hospital administrators to pursue quality improvement in urology.

Background

Despite high healthcare expenditures, the United States continues to lag behind many developed nations in health outcomes. The United States spends more than any other nation on health at an estimated $8508 per person in 2011, 50% more than the next highest nation [1]). This represents 17.7% of the US gross domestic product. Yet despite these expenditures, the United States trails behind other developed nations in several health indices, including life expectancy [1]. Several factors likely underlie this discrepancy, including unequal access to healthcare, racial and socioeconomic health disparities, and behavioral factors contributing to higher rates of obesity and homicide [1].

Stated simply, we are not achieving our full potential of healthcare *value*. *Value* is directly related to the quality of care and inversely related to cost. Strategies to improve healthcare value thus target quality improvement, cost reduction, or both. The priority with which this is being pursued on the national stage is highlighted by passage of The Patient Protection and Affordable Care Act of 2010, which seeks to broaden healthcare access, reduce cost, and maintain quality through value-based purchasing [2]. With enactment of this legislation, healthcare systems and practitioners must assume responsibility for quality improvement while working towards cost containment. In this environment, it is imperative for urologists to develop the necessary tools to implement quality improvement. The first step in the process is defining *quality*.

Defining quality

The definition of quality depends on an individual's perspective, priorities, and values. To a urological oncologist, quality includes cancer-specific survival following radical cystectomy. The operating room manager sees quality in achieving 100% on-time surgical starts. The patient may see quality as the professionalism with which he or she is cared for. Each individual's perspective includes different quality *domains*, which will be

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discussed later. It is only by incorporating each perspective that we form a comprehensive understanding of quality and can pursue quality improvement that is meaningful to each stakeholder.

In the setting of growing healthcare expenditures, the US Congress charged the National Academy of Sciences to "design a strategy for quality review and assurance in Medicare" (Omnibus Budget Reconciliation Act 1986). The Institute of Medicine (IOM), established to examine policy matters relating to public health [3], published a report "Medicare: A Strategy for Quality Assurance" in which *quality* was defined as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" [4]. In a subsequent report, "Crossing the Quality Chasm," the IOM outlined six domains of quality improvement [3]: safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity (Table 7.1).

1 *Safety*. Embodying the maxim "do no harm," this domain refers to providing care that avoids accidental injury or harm. A key strategy to fulfilling this aim is eliminating error. The IOM defines error as either "failure of a planned action to be completed as intended" or "use of a wrong plan to achieve an aim" [3]. Failure to administer perioperative antibiotics within 60 min of surgery is an example of the former, while treating male factor infertility with testosterone supplementation is an example of the latter. Surgical safety checklists have been designed to prevent error and have been demonstrated to promote safety by reducing operative morbidity [6].

2 *Effectiveness*. Effective care relies on high-quality evidence to guide the selection of the diagnostic and therapeutic interventions most likely to yield the desired outcome. Effective care minimizes underuse of effective interventions and overuse or inappropriate use of unnecessary interventions [7]. The low rate of urethroplasty in the management of urethral stricture disease likely represents underuse of the most effective therapy for this disease process [8]. Conversely, the use of bone scans to stage patients with asymptomatic low-risk prostate cancer represents inappropriate use of a diagnostic study with limited value in such patients [9]. Quality improvement measures designed to increase effectiveness include standardized care paths outlining appropriate, evidence-based diagnostic studies for common urological diseases.

3 *Patient-centeredness*. This aim focuses on the patient perspective, ensuring that the care provided incorporates the values, needs, and desires of an individual patient. The patient becomes an integral member of the treatment team and must be empowered to make informed decisions. In this vein, patients must understand their disease process, the diagnostic and treatment options available, and the risks and benefits of each option. This level of understanding lies at the core of informed consent, yet research suggests that a significant proportion of patients lack a basic understanding of the procedures to which they consent [10]. Furthermore, the recall rate following informed consent has been shown to be as low as 20–25% [11]. The ability to make an informed decision is limited in this setting. These findings represent an area of great need for quality improvement.

4 *Timeliness*. The timeliness with which care is administered is of the utmost importance to patients and practitioners alike. Minimizing delays in diagnosis and treatment improves outcomes across a wide breadth of diseases, including muscle-invasive urothelial carcinoma, where delay in time to cystectomy is associated with reduced disease-specific and overall survival [12]. Highlighting the importance of timeliness as a quality domain, several groups have used Lean Management and Six Sigma – frameworks for quality improvement discussed later in this chapter – to reduce clinic wait times and improve operating room efficiency [13].

5 *Efficiency*. Efficient care is that which is delivered effectively while minimizing cost and resource use. Strategies to

Table 7.1 The six quality domains.

Domain	Description	Examples in urology
1 Safety	"Do no harm"	Avoiding PDE5 inhibitors for erectile dysfunction in patients taking nitrates owing to the risk of severe hypotension
2 Effectiveness	Using high-quality evidence to guide diagnostic and treatment plans	Instituting perioperative fluid restriction during radical cystectomy to reduce post-operative morbidity [5]
3 Patient-centeredness	Tailoring care to the patient's values, beliefs, and goals	Eliciting and incorporating the patient's values into the treatment plan
4 Timeliness	Administering care in a timely manner by minimizing delays in diagnosis and treatment	Reducing clinic and operating room wait times to optimize time to treatment
5 Efficiency	Avoiding waste and minimizing cost	Standardizing cystoscopy suite work flow to accommodate more patients per day, optimizing efficiency of personnel and resource utilization
6 Equity	Providing high-quality healthcare to all individuals	Focusing on racial and gender disparities in outcomes among bladder cancer patients

PDE5, phosphodiesterase 5.

optimize efficiency seek to reduce waste, such as avoiding overuse of unnecessary diagnostic studies, or to reduce cost, as has been demonstrated by minimizing robotic instrument use during robotic prostatectomy [14]. Efforts to reduce length of stay and reduce readmissions similarly promote efficiency.

6 *Equity*. Equity refers to providing high-quality healthcare to all individuals. Seen at a population level, this means eliminating health disparities among different subgroups of the population. At the individual level, equity refers to maintaining the same quality of care regardless of an individual's race, religion, gender, sexual orientation, or socioeconomic status [3]. Racial and gender disparities exist among bladder cancer patients, with women having a higher risk of death within 1 year of diagnosis than men [15] and black men having a lower 5-year survival than white men [16]. These inequities may result from differences in disease biology, access to healthcare, or the quality of care administered, and must be understood to target inequity properly with effective quality improvement initiatives.

When conceptualized within the framework of these six domains, it becomes easier to identify opportunities for quality improvement in the clinical setting. *Quality measures* can then be used to quantitatively measure quality, allowing us not only to identify areas for improvement but also to measure the impact of quality improvement initiatives.

Quality measures

A *quality measure* provides an assessment of the care delivered by providing a measure of a specifically defined parameter that can then be compared with the *standard* or desired achievable result for that given parameter [2]. *Quality measures* assess parameters of either the process of care delivery or the outcomes obtained [17]. A useful quality measure should be quantifiable and easily measured, allowing assessment of a system's or process's baseline characteristics and facilitating evaluation of the impact of quality improvement initiatives.

Multiple types of quality measures have been described and are summarized in Table 7.2. A *structure measure* provides an assessment of the environment in which care is delivered, including the physical space, equipment, resources, and institutional organization. An example of a structure measure is the surgical volume of radical cystectomy performed at an institution. Structure measures are cleared defined and easily measured; however, the relationship between structure measures and outcomes is not always well defined [18].

A *process measure* assesses the actions that make up healthcare delivery and include the process of diagnosis, treatment, and preventive care [2]. Process measures are often designed to answer the question, "what percentage of patients have received the standard of care?" Process measures are developed based on a known relationship between a process and a given outcome. An example of a process measures is the percentage of surgical patients receiving appropriate DVT chemoprophylaxis following pelvic surgery.

Table 7.2 Quality measures.

Quality measure	Description	Examples in urology
Structure measure	Assesses the institution and environment in which care is delivered	The number of urologists board-certified in female pelvic medicine and reconstructive surgery at a given institution
Process measure	Assesses the manner in which care is delivered	The rate of appropriate postoperative VTE prophylaxis
Outcome measure	Assesses the outcomes obtained from the care provided	Continence and potency rates 1 year following radical prostatectomy

VTE, venous thromboembolism.

Outcome measures reflect the health results obtained from the care provided and typically reflect the rate of a specific outcome. These rates are then compared either with benchmark data for the outcome of interest, or with a predefined desired, achievable result [17]. Outcome measures include 30-day postoperative morbidity and mortality rates following partial nephrectomy, 5-year cancer-specific survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive bladder cancer, and patient satisfaction with orthotopic neobladder urinary diversion. Unlike process measures that can often be quickly measured in a short period of time, outcome measures may take longer to assess owing to the relative infrequency of the measured outcome [18].

To understand better the role of quality measures in quality improvement, consider the following scenario. On a hospital's monthly quality review, the inpatient urology ward is noted to have a 4% rate of surgical site infections among patients undergoing major pelvic surgery. This *outcome measure*, when compared with benchmark data from other institutions, is found to be higher than the accepted standard of 1%. Understanding the relationship between administering perioperative antibiotics within 60 min of surgery and reducing surgical site infections [19], the Chief Quality Officer decides to study the rate of appropriate perioperative antibiotic dosing over the preceding 3 months. This *process measure* evaluates the institution's compliance with an evidence-based clinical standard. This investigation reveals poor compliance, with a 56% rate of appropriate perioperative antibiotic administration, suggesting a potential cause of the ward's high surgical site infection rate. Before describing how the institution tackled this problem, we must first develop a framework for quality improvement.

Frameworks for quality improvement

Quality improvement is best pursued using a systematic approach or framework. Many frameworks have been described and adapted to the healthcare setting. In this section, we discuss two such frameworks: Lean Management and Six Sigma.

Lean Management

Lean Management, also referred to as the Toyota Production System, was developed by the Toyota Motor Corporation to optimize workflow and efficiency [20]. The focus of Lean Management is optimizing process efficiency. To do so, a process is broken down into its component steps, each of which is defined as either "value added" or "non-value added," depending on whether that step contributes value to the process's underlying goal. Non-value-added steps are considered wasteful and should be eliminated to yield a more efficient process [21].

Within this framework, the patient is seen as the "customer" and processes are defined by whether they provide value to the patient or support a process that provides value to the patient. Each process is mapped to create a *value stream*, accounting for each step in the process, determining whether it adds value to the process, and determining the amount of time each step requires. Non-value-added steps are eliminated to create a smooth flow from one value-added step to the next. The process is continually evaluated to optimize the efficiency.

Although originally developed in manufacturing, Lean Management has been successfully implemented in the healthcare setting, the most prominent examples of which include Virginia Mason Medical Center and ThedaCare, Inc. [21]. Using Lean Management, these health systems increased efficiency of endoscopy suite use, reduced total cost of inpatient care, and raised patient satisfaction [22]. Within the Urological literature, Lean methodology has been used to reduce patient wait times and increase physician-patient face-to-face time in clinic, increasing the proportion of value-added time spent in clinic [20]. Implementing Lean management requires a culture in which all members of the healthcare team are trained to identify non-value added steps *and* empowered to enact change.

Six Sigma

Like Lean Management, Six Sigma was initially developed in the corporate sector, in this case at Motorola. Sigma is a measure of the variability of a given process, and in the corporate sector a company's performance can be reported in terms of its "sigma level." The Six Sigma standard allows 3.4 errors for every one million opportunities, reflecting the high-quality standard that Six Sigma seeks to create [23]. The goal is minimizing error and reducing variability using a five-step process referred to as DMAIC – Define, Measure, Analyze, Improve, Control [23]. When a problem or error is identified, one must:

1 *Define* the process involved and develop a hypothesis as to the cause of the error.
2 Develop a *measure* for the root cause of the problem.
3 *Analyze* the root cause.
4 *Improve* the process, by modifying or eliminating the root cause.
5 *Control* the process to prevent recurrence.

We will now apply Six Sigma methodology to our earlier example of surgical site infections. The institution identified the problem as the high rate of surgical site infections following major pelvic surgery. Understanding the role of appropriate perioperative antibiotic prophylaxis administration in preventing surgical site infections, the quality team first *defined* the process of perioperative antibiotic administration. The process *measure* selected was the percentage of patients undergoing major pelvic surgery receiving perioperative antibiotic prophylaxis within 60 min of surgery and was found to be 56%. *Analysis* of the perioperative antibiotic administration process required mapping the process, including all steps from scheduling a patient for surgery, through patient preparation in the preoperative area, to arrival in the operating room and surgical incision [24]. Critical inputs were identified, including completing the antibiotic order form, obtaining antibiotics from the pharmacy, and antibiotic administration. Variability in timing of antibiotic administration, for example by administering antibiotics in the preoperative unit, and failure to account for antibiotic administration during the surgical huddle were identified as additional contributing factors.

Based on this analysis, *improvement* measures were implemented, including educating operative personnel, standardizing the antibiotic order form, standardizing the timing of antibiotic administration in the operating room, and including antibiotic administration on the preoperative checklist reviewed during the surgical timeout. After this quality improvement initiative had been implemented, data were collected and the rate of appropriate perioperative antibiotic administration within 60 min of surgery was found to have increased from 56% to 92%. Having quantitatively demonstrated improvement, the quality team standardized these reforms within the operative pathway. Periodic audits were then scheduled to ensure compliance, representing the *control* to maintain the outcomes obtained.

Conclusions

Quality improvement is a continual process to improve the process of healthcare delivery and the health outcomes obtained. Not only does quality improvement translate into greater patient satisfaction and improved outcomes, it will also yield greater reimbursement, as value-based purchasing and pay-for performance become the standard. It is imperative

for our patients, and the sustainability of our healthcare system, that practicing urologists be empowered to champion quality improvement.

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PART 2

General urology and stone disease

Charles D. Scales, Jr.

8

CHAPTER 8

Antibiotic prophylaxis in urological surgery

Roderick Clark[1] and Philippe Violette[1,2,3]

[1] *Division of Urology, The University of Western Ontario, London, ON, Canada*

[2] *Department of Surgery, McMaster University, Hamilton, ON, Canada*

[3] *Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada*

Introduction

Antimicrobial prophylaxis is defined as the periprocedural systemic administration of an antimicrobial agent intended to reduce the risk of surgical site infection as well as secondary systemic infections [1]. Infections in the perioperative setting are associated with significant patient morbidity and mortality and reductions in patient quality of life and carry significant cost. Although patient safety remains paramount, we must also recognize that we live in an era of increasing microbial resistance that requires vigilance in antimicrobial stewardship. In this chapter, we systematically review the evidence for or against the use of prophylactic antibiotics in four commonly performed urological procedures.

Clinical question 1

In patients undergoing ureteroscopy for ureteral stones, does antibiotic prophylaxis decrease the incidence of infectious complications when compared with no prophylaxis?

Literature search

We conducted a systematic literature search in PubMed (1966–2016) using the Mesh search terms "antibiotic prophylaxis" and "ureteroscopy." The search was limited to randomized controlled trials (RCTs) and systematic reviews with a human population. For completeness, we included the studies identified in the previous iteration of this chapter and used a snowballing technique from the identified literature (Figure 8.1)

The evidence

Four RCTs [2–5] and one systematic review were identified in our literature review. A study by Fourcade et al. [2] randomized 120 patients undergoing ureteroscopy for ureteral stones to cefotaxime 1 g IV versus placebo. Interpretation of this study was made difficult by the inclusion of a subset of patients undergoing percutaneous nephrolithotripsy that were not reported separately. A second, more recent study by Knopf et al. [5] randomized 113 patients to 250 mg of levofloxacin versus placebo. Aghamir et al. [3] randomized 114 participants who were blinded to either 1 g cefazolin or placebo 60 min before ureteroscopy. They examined several outcomes, including positive blood culture, urine culture, pyuria, and postoperative bacteremia. Hsieh et al. [4] double blindly randomized 206 individuals to 1 g cefazolin, 1 g ceftiraxone, 500 mg cevofloxacin, or no placebo who underwent ureterorenoscopy lithotripsy for ureteric stone. These trials were evaluated for risk of bias (Table 8.1) and study results were compared (Table 8.2).

A recent meta-analysis was performed by Lo et al., which was assessed using the AMSTAR tool for the systematic evaluation of meta-analyses [6] independently by each author (R.C. and P.V.). This study was scored at 6/11, indicating that it is of moderate quality [7]. Given that there were differences of judgment between Lo et al. and the authors of this chapter regarding risk of bias assessment and data extraction for meta-analysis, we elected to repeat the analysis (see Figures 8.2–8.5).

The available evidence suggests that there was a statistically significant benefit for the use of antibiotics in reducing positive urine culture (Figure 8.3), which was reduced from 11% (22/203) to 3% (10/301) and pyuria (Figure 8.4). These reflect relative risks (RR) of 0.26 (95% confidence interval [CI] 0.11, 0.58) and RR 0.42 (0.25, 0.69), respectively. Of note, data were not available for more clinically important outcomes such as urosepsis and were not able to demonstrate a significant reduction in fever with antibiotic prophylaxis.

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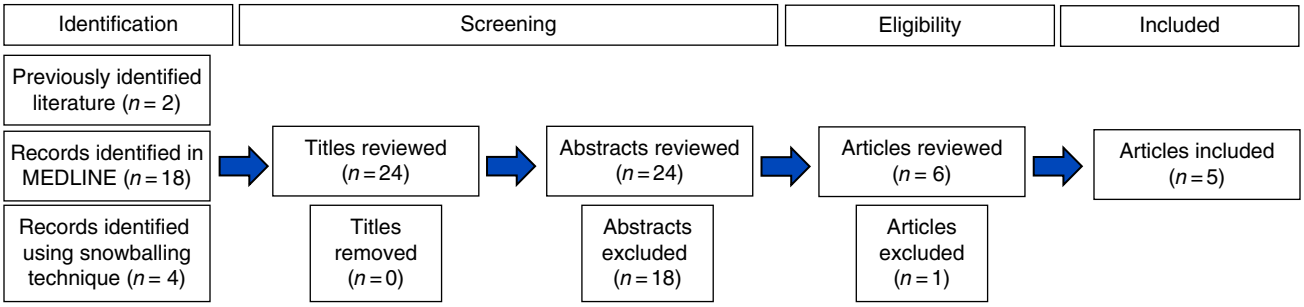

Figure 8.1 PRISMA flow diagram: article selection on antibiotic prophylaxis for the prevention of infectious complications in patients undergoing ureteroscopy for ureteral stones.

Harms of intervention were also considered in a very limited way grouped into "associated side effects," which were reported across studies (Figure 8.5). The strength of evidence and balance of desirable and undesirable outcomes (Table 8.3) provide the basis of our clinical recommendation.

Clinical implications

We suggest the use of prophylactic antibiotics in patients with negative preoperative urinary cultures undergoing uncomplicated ureteroscopy for stone disease (conditional recommendation based on low-quality evidence). This recommendation is based on indirect evidence on the positive impact of prophylactic antibiotics on patient-important outcomes and few treatment-related harms, with a resulting favorable benefit-to-risk ratio.

Clinical question 2

In patients undergoing shock-wave lithotripsy for the treatment of renal and ureteral calculi, does antibiotic prophylaxis decrease the incidence of infectious complications when compared with no prophylaxis?

Literature search

We conducted a systematic literature search in PubMed (1966–2016) using the search terms "antibiotic prophylaxis," "antimicrobial prophylaxis," and "extracorporeal shock-wave lithotripsy." The search was limited to RCTs and systematic reviews in a human population. A summary of our selective process is presented in Figure 8.6.

The evidence

The literature review identified of 10 RCTs addressing this clinical question [8–18]. All studies had methodological limitations (Table 8.4) and also low event rates, which led to downgrading to low- or very low-quality evidence for all relevant outcomes. This evidence has previously been summarized by two meta-analysis. The first was conducted in 1997 by Pearle et al. and a second in 2012 by Lu et al. These were evaluated by the AMSTAR criteria and were assigned scores of 1 and 6, indicating poor and moderate quality [6,7], respectively. Each meta-analysis included different studies and the respective selection criteria were not clear. The later study by Lu et al. included nine studies with 1364 individuals within their analysis. They found that antibiotic prophylaxis as compared with placebo did not result in lower rates of fever, the incidence of positive urine culture, or the incidence of symptomatic urinary tract infection (UTI) [19]. Given that there were differences of judgment between Lu et al. and the authors of this chapter regarding selection criteria and risk of bias assessment, we elected to repeat the analysis (see Figures 8.7–8.9). A summary of the characteristics for RCTs evaluating antibiotic use with SWL is given in Table 8.5.

The available evidence suggests that there were no significant benefits in the use of antibiotics in reducing occurrence of sepsis, fever, or positive urine cultures (Figures 8.7–8.9). Of note, the harms of intervention were not reported and the overall quality of reporting was very limited across RCTs. The strength of evidence and balance of desirable and undesirable outcomes are summarized in Table 8.6 and provide the basis of our clinical recommendation.

Clinical implications

We suggest against the use of prophylactic antibiotics to prevent infectious complications in patients with negative preoperative urinary cultures undergoing SWL for stone disease (conditional recommendation against based on low-quality evidence). The use of prophylactic antibiotics was not associated with a statistically significant reduction of sepsis, fever, or positive urine cultures. Harms of prophylaxis use seem to be few and considerable variations in trial results and intervention characteristics limit the ability to identify clearly the benefits and harms of therapy.

Clinical question 3

In patients undergoing transrectal biopsy of the prostate, does antibiotic prophylaxis decrease the incidence of infectious complications compared with no prophylaxis?

Table 8.1 Risk of bias summary: judgments about each risk of bias item for included studies.

Study ID	Random sequence generation (selection bias	Allocation concealment	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aghamir (2011) [3]	?	?	?	+	+	+	?
Fourcade (1990) [2]	?	?	+	+	+	–	?
Hsieh (2014) [4]	?	?	+	+	+	+	?
Knopf (2003) [5]	?	–	–	+	–	–	?

Table 8.2 Summary of study characteristics for RCTs that evaluate antibiotic prophylaxis during ureteroscopy.

Study ID	Inclusion criteria	Exclusion criteria	Population	Exposure	Outcome	Complications	Observed effect
Fourcade (1990) [2]	Individuals undergoing endoscopic extraction (PCNL + URS) of an upper urinary tract stone within a single year (year not specified)	<18 or >60 years of age	120 (treatment $n=60$, control $n=60$)	Cefotaxime 1 g perioperatively vs. placebo	Postoperative bacteriuria, other infection, or fever	2 individuals with mild skin rash in treatment arm	Incidence of postoperative bacteriuria between postoperative days 1–3 greater in placebo group ($p=0.014$)
Knopf (2003) [5]	Individuals undergoing ureteroscopic stone removal between January and December 2000	Clinical or laboratory signs of infection (T >38.0, WBC >15 000/μL), antibiotics within 1 week, allergy to quinolones, cerebral cramp, tendinitis, pregnancy, lack of informed consent	113 (treatment $n=57$, control $n=56$)	Levofloxacin 250 mg PO 60 min preoperatively vs. placebo	Bacteriuria, symptomatic UTI, or inflammatory complications	No complications associated with levofloxacin recorded	Higher rate of postoperative significant bacteriuria in placebo group ($p=0.026$)
Aghamir (2011) [3]	Individuals undergoing unilateral transurethral ureterolithotripsy between January 2005 and December 2007	Positive preoperative urine cultures, bacteriuria, history of type 2 diabetes or malignancy, and those requiring endocarditis prophylaxis	114 (treatment $n=57$, placebo $n=57$)	Cefazolin 1 g IV60 min preoperatively vs. placebo	Postoperative + blood culture + urine culture, pyuria, or bacteriuria	Not reported	Significantly higher rate of bacteriuria ($p<0.001$) and pyuria ($p<0.003$) in treatment arm compared with control
Hsieh (2014) [4]	Individuals undergoing ureterorenoscopic lithotripsy between 2009 and 2012	Preoperative pyuria, + leukocyte esterase, nitrite, or bacteriuria, allergy to quinolone or cephalosporine, antibiotic or infection 4 weeks before procedure, and immunocompromise	206 (treatment $n=155$, placebo $n=51$)	Levofloxacin 500 mg PO 1–2 h preoperatively or ceftriaxone or levofloxac 1 g in 60 min preoperatively vs. placebo	Postoperative bacteriuria, pyuria, febrile UTI	Not reported	Lower rates of pyuria in treatment arms ($p=0.04$)

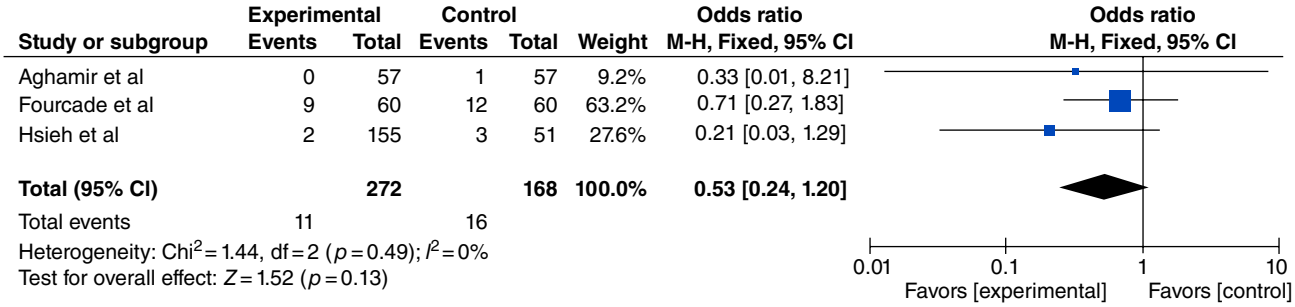

Figure 8.2 Forest plot of comparisons: antibiotics prophylaxis versus no antibiotics for prevention of *fever* post-ureteroscopy.

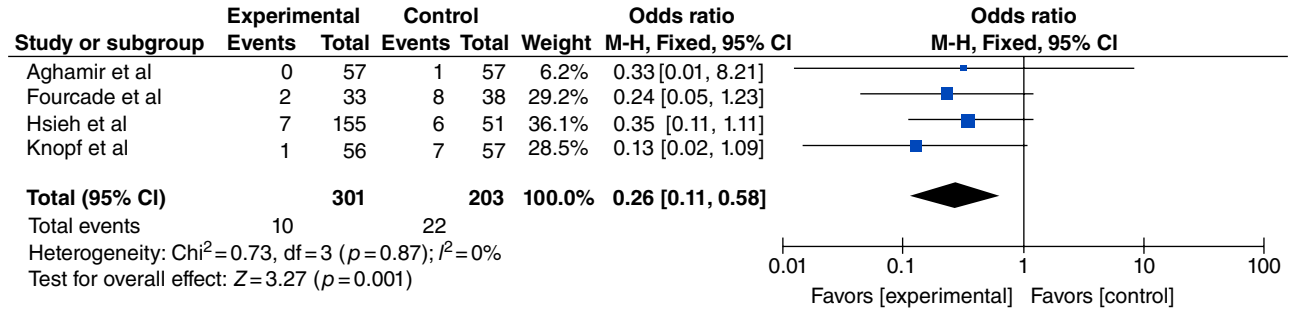

Figure 8.3 Forest plot of comparisons: antibiotics prophylaxis versus no antibiotics for prevention of *positive urine culture* post-ureteroscopy.

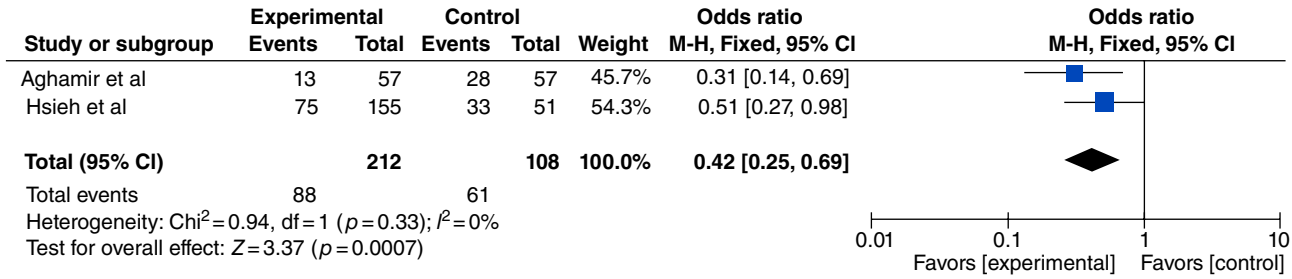

Figure 8.4 Forest plot of comparisons: antibiotics prophylaxis versus no antibiotics for prevention of *pyuria* post-ureteroscopy.

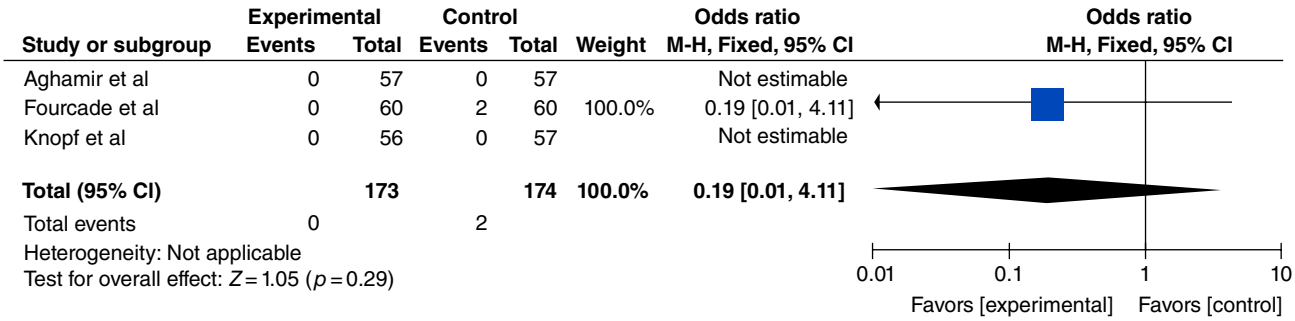

Figure 8.5 Forest plot of comparisons: antibiotics prophylaxis versus no antibiotics *associated side effects* (skin rash *n* = 2) post-ureteroscopy.

Table 8.3 Summary of findings table for the use of antibiotics among patients undergoing ureteroscopy.

Should patients undergoing ureteroscopy receive prophylactic antibiotics?

Patient or population: ureteroscopy
Setting: Hospital
Intervention: Antibiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Comments
	Risk with placebo	Risk with antibiotics				
Incidence of fever assessed with: follow-up assessment follow up: range 6 days to 84 days	95 per 1000	**50 per 1000** (23 to 114)	**RR 0.53** (0.24 to 1.20)	440 (3 RCTs)	⊕⊕◯◯ LOW[a,b,c]	
Incidence of bacturia assessed with: post operative urine culture follow-up: 1 days	129 per 1000	**35 per 1000** (17 to 70)	**RR 0.27** (0.13 to 0.54)	553 (4 RCTs)	⊕⊕⊕◯ MODERATE[a,b]	
Incidence of pyuria assessed with: post operative urinalysis follow-up: 1 days	565 per 1000	**237 per 1000** (141 to 390)	**RR 0.42** (0.25 to 0.69)	320 (2 RCTs)	⊕⊕⊕◯ MODERATE[a,b]	
Side effect	0 per 1000	**0 per 1000** (0 to 0)	RR 0.19 (0,01 to 4.11)	347 (3 RCTs)	⊕◯◯◯ VERY LOW[a,d]	

*The risk in the intervention group (and its 95% confidence Interval) Is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval: RR: risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[a]No double-blind objective outcomes, allocation concealment or intention to treat.
No explanation was provided.
[c]many differences in term of follow-up between studies.
[d]no clear definition of side effects provided.

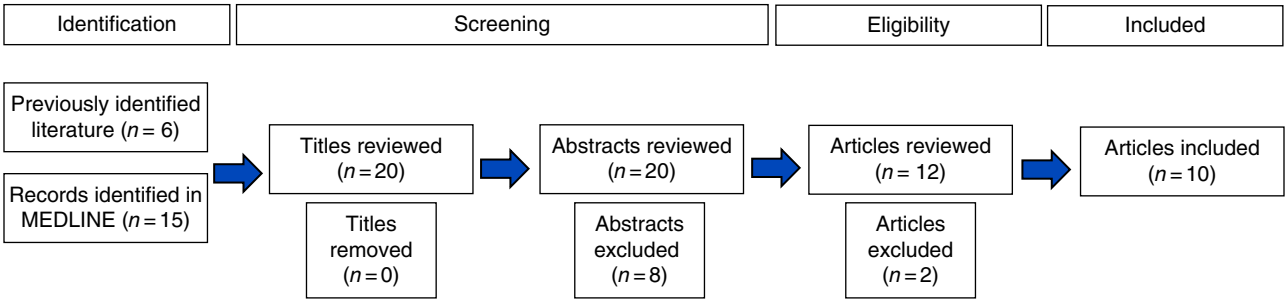

Figure 8.6 PRISMA flow diagram: article selection on antibiotic prophylaxis for the prevention of infectious complications in patients undergoing ESWL.

Literature search

We conducted a systematic literature search in PubMed (1966–2016) using the mesh terms "antibiotic prophylaxis," "prostate," and "biopsy." The search was limited to RCTs and systematic reviews with a human population. A summary of our selective process is presented in Figure 8.10.

The evidence

Nine eligible RCTs were identified in our literature review (Figure 8.10) [20–28] and one recent Cochrane Review [29] of this body of evidence. These trials were evaluated for risk of bias (Table 8.7) and study results were compared (Table 8.8).

Fortunately, a high-quality Cochrane Review was performed by Zani et al. [29], which included nine trials and found significant improvements in all outcomes (bacteriuria, bacteremia, fever, UTI, and hospitalization) for antibiotics versus placebo. They also examined several secondary exposures and found that longer course (3-day) versus short course (1-day) antibiotic treatment was significantly better for bacteria, multiple doses of antibiotics versus single dose resulted in fewer bacteria, and that there was no difference in outcomes when comparing delivery modes (oral versus intravenous versus intramuscular). We evaluated this systematic review using the AMSTAR tool [6] and found that it had a score of 10/11, corresponding to a high-quality review [7]. These results are presented in a summary of findings table (Table 8.9).

Clinical implications

We recommend the use of prophylactic antibiotics in patients undergoing prostate biopsy (strong recommendation based on moderate-quality evidence). There is convincing aggregate evidence that antibiotic prophylaxis helps prevent bacteriuria, bacteremia, fever, UTI, and hospitalization. Although poorly reported in these studies, other studies on the adverse effects of the short-term courses of antibiotics used for antibiotic prophylaxis in this setting would suggest that these are rare and mild in severity.

Clinical question 4

In patients undergoing transurethral resection of the prostate, does antibiotic prophylaxis decrease the incidence of infectious complications compared with no prophylaxis?

Literature search

We conducted a systematic literature search in PubMed (1966–2016) using the search terms "antibiotic prophylaxis," "antimicrobial prophylaxis," "transurethral resection" and "prostate." An updated literature review was performed using the MsSH term "transurethral resection of the prostate," as this term was introduced in 2000.The search was limited to RCTs and systematic reviews with a human population. A summary of our selective process is presented in Figure 8.11.

The evidence

We identified a total of 39 relevant RCTs [30–66] and one systematic review. Six studies addressed the incidence of septic episodes, 17 studies that of procedure-related fever and 39 studies that of positive urine cultures following transurethral resection of the prostate (TURP). The quality of evidence for these outcomes was low, very low, and moderate, respectively (Table 8.10).

Prophylactic antibiotics were associated with an approximately 50% relative risk reduction (RR 0.51, 95% CI 0.27–0.96) for septic episode and a 2% absolute risk reduction (number needed to treat [NNT] = 50). The rate of febrile episodes was 0.64 (95% CI 0.55–0.75). Lastly, the rate of positive urine cultures was approximately one-third (RR 0.37, 95% CI 0.32–0.41) in the antibiotic-treated group compared with the control group, with an absolute risk reduction of 21.0% (NNT = 5). None of these studies reported data on adverse events.

We have omitted a risk of bias table in this section for brevity and also as the evidence was found to have serious or very serious limitations. This is reflected in the assessment of overall quality of evidence in this section's summary of findings table (Table 8.10).

Table 8.4 Risk of bias summary for positive urine culture across included studies.

Study ID	Random sequence generation (selection bias)	Allocation concealment	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bierkens (1997) [8]	–	?	–	+	–	–	?
Claes (1989) [9]	?	?	–	+	–	–	?
Dejter (1989) [14]	?	?	+	+	–	–	?
Gattegno (1988) [10]	+	–	–	+	?	–	?
Ghazimoghaddam (2011) [15]	?	?	–	+	?	–	?
Herrlinger (1987) [16]	?	–	–	+	?	+	?
Ilker (1995) [11]	?	?	–	+	–	–	?
Mosli (1993) [18]	?	?	?	+	?	–	?
Pettersson (1989) [13]	–	–	–	+	?	–	?
Rigatti (1989) [17]	?	–	–	+	?	–	?

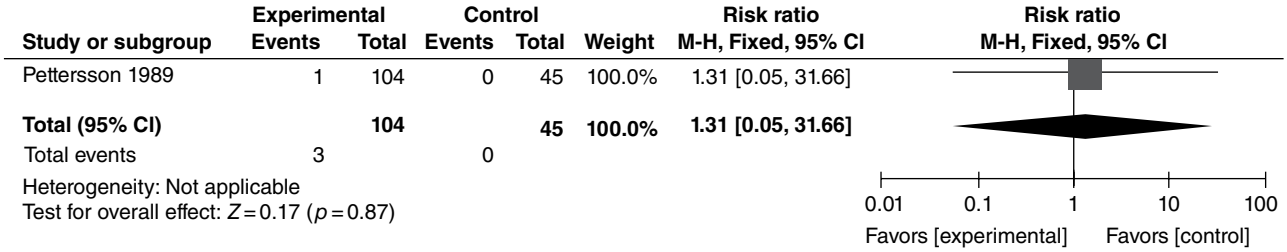

Figure 8.7 Forest plot comparing antibiotic prophylaxis versus no antibiotic prophylaxis for the prevention of *sepsis* in patients undergoing shock-wave lithotripsy.

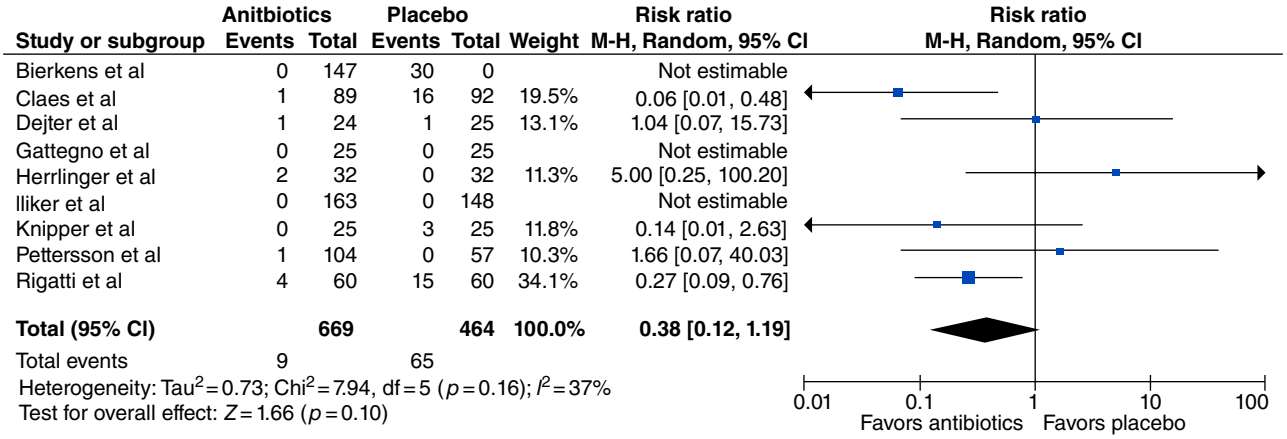

Figure 8.8 Forest plot comparing antibiotic prophylaxis versus no antibiotic prophylaxis for the prevention of *fever* in patients undergoing shock-wave lithotripsy.

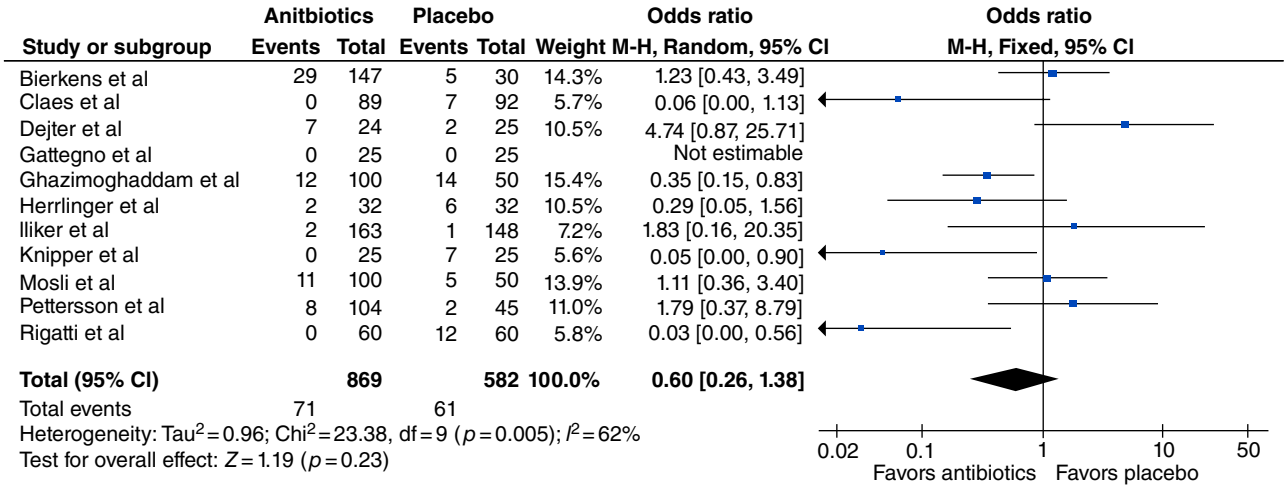

Figure 8.9 Forest plot comparing antibiotic prophylaxis versus no antibiotic prophylaxis to prevent *positive urine cultures* in patients undergoing shock-wave lithotripsy.

Table 8.5 Summary of characteristics for RCT evaluating antibiotic use with shock-wave lithotripsy (SWL).

Study ID	Inclusion criteria	Exclusion criteria	Population	Exposure	Outcome	Complications	Observed effect
Bierkens (1997) [8]	>17 years, planned for SWL	Positive preoperative urine culture	*n* = 174 patients at 2 weeks, one center (147 in treatment groups, 30 control), 181 at 6 weeks (144 in treatment groups, 37 in placebo)	One dose of ciprofloxacin preoperatively vs. ciprofloxacin preoperatively and 1 week postoperatively vs. cefuroxime preoperatively vs. cefuroxime preoperatively followed by 1 week postoperatively vs. placebo	Positive urine culture, micturation complaints at 2 and 6 weeks	Pruritis in 2 patients who were excluded after randomization	Non-significant
Claes (1989) [9]	Planned for SWL	Staghorn, known UTI, double J, anticipation adjuvant endoscopy	*n* = 194 patients from a single center (97 treatment, 97 control)	One dose clavulin 30 min before SWL vs. no treatment	Fever, urinary frequency and nocturia, leukocyturia and positive urine culture at 1 day postoperatively	None reported	Non-significant
Dejter (1989) [14]	Planned for SWL	Not reported	*n* = 49 patients from a single center (24 treatment, 25 control)	Norfloxacin q 12 h for 48 h preoperatively vs. placebo	Positive urine culture at 1 and 10 days postoperatively	None reported	Non-significant
Gattegno (1988) [10]	Planned for SWL	Positive urine culture within 7 days, use of antibiotic within 7 days	*n* = 50 patients from a single center (25 treatment, 25 control)	One dose cetriaxone vs. placebo	Fever within first day, positive blood culture 1 and 5 h post-procedure, urine culture at 1 and 7 days	None reported	Non-significant
Ghazimoghaddam (2011) [15]	Planned for SWL	Positive urine culture, sign of infection recurrent stone procedure, no antibiotic for 1 week	*n* = 150 patients from a single center (100 treatment and 50 control)	One dose timoxazole vs. 1 dose nitrofurantoin vs. no treatment	Positive urine culture 2 weeks postoperatively, pyuria and hematuria 2 weeks postoperatively	None reported	Non-significant
Herrlinger (1987) [16]	Planned for SWL	Positive preoperative urine culture	*n* = 64 patients from a single center (32 treatment and 32 control)	One dose azlocillin vs. no treatment	Positive urine culture 1 day after SWL, pyuria, systemic infection, fever	None reported	Non-significant
Ilker (1995) [11]	Planned for SWL	Positive urine culture, require stent, partial or full staghorn	*n* = 360 patients from a single center (163 treatment and 148 control, 32 excluded after randomization)	One dose ofloxacin vs. no treatment	Positive urine culture, urine analysis for pyuria 1 day after SWL, fever, chills, urinary symptoms within 4 weeks post-SWL	None reported	Non-significant

Mosli (1993) [18]	Planned for SWL	Positive urine culture, history of allergy to treatment drug, antibiotic within 10 days of treatment, recent instrumentation, severe renal insufficiency	*n*=150 patients from a single center (100 treatment and 50 control)	One dose amoxicillin clavulinate vs. gentamicin vs. saline	Positive urine culture at 1 day and 1 week post-SWL, temperature >38.5 °C	None reported	Possible small increase in positive urine culture in treatment group (reporting unclear)
Pettersson (1989) [13]	Planned for SWL	Sign of infection, struvite stone, positive urine culture	*n*=149 patients from a single center (57+47 in the treatment groups and 45 controls) (Randomization procedure was dependent on patient's birth date)	Septra (trimethoprim+sulfamethoxazole) or mecillinam vs. methenamine hippurate vs. no treatment	Positive urine culture 2 weeks post-SWL, fever, sepsis, or UTI up to 4 weeks post-SWL	None reported	Non-significant
Rigatti (1989) [17]	Planned SWL, stone <2 cm, no planned endoscopic manipulation, patient in "good general condition"	Positive urine culture, infection at another site, allergy to treatment drug, severe hepatic dysfunction, granulocytopenia, steroid use, other antibiotic within 5 days of SWL	*n*=120 patients from a single center (60 treatment and 60 control)	Azetronam q 8 h×3 prior to SWL vs. no treatment	Subjective scoring of urinary symptoms, >38.5 °Cat 1, 8, 24, and 48 h post-SWL, positive urine culture	None reported	Non-significant

Table 8.6 Summary of findings table for the use of antibiotics among patients undergoing SWL*.

Outcomes	No. of participants (studies) Follow-up	Quality of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with placebo	Risk difference with abx
Sepsis (sepsis) assessed with: clinical history at follow-up (1 day to 1 north)	149 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	**RR 1.31** (0.05 to 31.66)	0 per 1000	**0 fewer per 1000** (0 fewer to 0 fewer)
Fever assessed with: clinical history within 1 month	1133 (9 RCTs)	⊕◯◯◯ VERY LOW[b,d,e]	**RR 0.38** **(0.12** to 1.19)	140 per 1000	**87 fewer per 1000** (123 fewer to 27 more)
Positive urine culture assessed with: urine culture at 1-14 days	1451 (11 RCTs)	⊕⊕◯◯ LOW[b,d]	**RR 0.6 0** (0.26 to 1.38)	105 per 1000	**42 fewer per 1000** (73 fewer to 40 more)
Side effect from antibiotic - not reported		–		–	–

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.
Low quality: Our confidence in tine effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[a]Single trial, description of randomization was unclear and seemed to depend on patient's birthday, allocation was not concealed, data assessors and analyst were not blind to allocation, attrition for this outcome is also not reported.
[b]Description of Randomization was inadequate to conclude that it was conducted appropriately in most cases. Allocation concealment was not done in half and poorly reported in remaining trials. Outome assessors were not blinded. The majority of trials did not blind patients, seemed to report selectively and frequently violated the intent-to-treat principle. Loss to follow-up, when reported revealed a high risk of bias given the low incidence of dichotomous outcomes.
[c]Sample size is very small for the outcome specified. Incidence of sepsis are very rare with SWL and confidence intervals for this estimate are very wide.
[d]Very wide confidence intervals with point estimates that vary in magnitude and direction.
[e]Sample size is small for event rate reported.

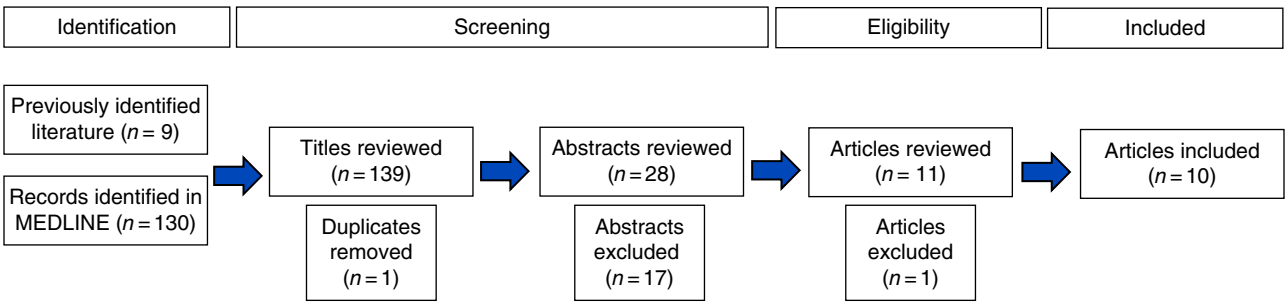

Figure 8.10 PRISMA flow diagram: article selection on antibiotic prophylaxis for the prevention of infectious complications in patients undergoing prostate biopsy.

A meta-analysis has been completed on this subject. The identified article was of moderate methodological quality as assessed by the AMSTAR guidelines (AMSTAR grade: 5/11) [6]. Yang et al. [28] identified 12 articles involving 1987 patients and found that prophylactic antibiotics significant reduced the incidence of bacteriuria and middle degree fever, but did not significantly reduce the incidence of bacteremia. These results are in contrast to our own meta-analysis, and likely

Table 8.7 Risk of bias summary.

Study ID	Allocation concealment	Blinding of participants and personnel (performance bias)	Blinding of outcomes assessment (detections bias)	Incomplete outcomes data (attrition bias)	Selective reporting (reporting bias)	Free of other bias	Random sequence generation (selection bias)	Ref.
Aron (2000)	?	+	+	+	+	+	+	[20]
Brown (1981)	?	–	?	+	+	?	?	[21]
Crawford (1932)	+	+	+	+	+	+	+	[22]
Isen (1999)	?	?	?	+	+	?	?	[23]
Kapoor (1998)	?	+	+	+	+	+	+	[24]
Melekos (1990)	?	–	?	+	+	+	?	[25]
Ruebush (1979)	?	+	+	+	+	+	?	[26]
Tekdogan (2006)	?	–		+	+	+	?	[27]
Yang (2009)	?	+	+	+	+	+	+	[28]

Table 8.8 Summary of study results.

Study ID	Inclusion criteria	Exclusion criteria	Population	Exposure	Outcome	Complications	Observed significant effect
Aron (2000) [20]	Individuals with clinical suspicion of prostate cancer between 55 and 85 years of age undergoing transrectal prostate biopsy between 1996 and 1998	No patients excluded after randomization	231 patients randomized to one of three groups (control $n=75$, treatment 1 $n=79$, and treatment 2 $n=77$)	**Control**: placebo tablet twice per day for 3 days **Treatment 1**: ciprofloxacin 500 mg and tinidazole 600 mg once and placebo b.i.d. for 5 doses. **Treatment 2**: ciprofloxacin 500 mg and tinidazole 600 mg b.i.d. for 3 days	Bacteremia, fever, UTI, and infectious complications	Multiple endpoints collected	No significant difference between groups in noninfective complications, but the incidence of UTI was higher in the control group ($p=0.003$)
Brown (1981) [21]	Individuals undergoing transrectal prostate biopsy	Use of antibiotics or urological manipulation 24 h before biopsy, positive blood or urine culture, marked debility, valvular heart disease, valvular prosthesis	40 patients randomized to one of four groups	**Control:** saline clean enema **Treatment 1:** gentamicin 80 mg IV single dose **Treatment 2:** povidone-iodine enema **Treatment 3:** gentamicin + enema	Bacteriuria, bacteremia, fever	None collected	No statistical controls
Crawford (1982) [22]	Individuals undergoing transrectal prostate biopsy	Individuals with UTIs, prosthetic devices, rheumatic valvular heart disease, allergy to penicillin, or use of antibiotics 14 days before biopsy	48 males randomized to two groups	**Control**: placebo with enema **Treatment**: carbenicillin 2 tablets q 6 h for 1 day	Bacturia, bacteremia, fever	Multiple endpoints collected	No statistical controls
Isen (1999) [23]	Individuals undergoing transrectal prostate biopsy	Individuals with artificial heart valve, indwelling catheter, diabetes, steroid use, prostatitis, ATB use 72 h before	110 males randomized to three groups	**Control**: placebo with enema **Treatment 1:** ofloxacin 400 mg orally single dose **Treatment 2:** trimethoprim/sulfonamide methoxazole 160/800 mg orally single dose	Bacturia, hospitalization	None collected	Both of these antibiotic regimens produced a statistically significant reduction in urinary infection ($p<0.02$, $p<0.05$)
Kapoor (1998) [24]	Individuals undergoing transrectal prostate biopsy	Individuals with hypersensitivity to ciprofloxacin, valvular heart disease, significant gastrointestinal disease, epilepsy, bacteriuria, urological manipulation, indwelling catheter, antibiotic use in past 7 days, or granulocyte count $<1000/mm^3$	537 males randomized to two groups	**Control**: placebo with enema **Treatment: c**iprofloxacin 500 mg PO single dose	Bacteriuria, bacteremia, fever, UTI, sepsis, hospitalization, adverse events	Multiple endpoints	More placebo-treated patients had bacteriuria after the procedure ($p=0.009$)

Melekos (1990) [25]	Individuals undergoing transrectal prostate biopsy	Individuals with general disability, heart disease, UTI, use of antibiotics in last 24 h, or recent urological manipulation	81 males randomize to three groups	**Control**: placebo with enema **Treatment 1**: piperacillin 2 g IV single dose **Treatment 2:** piperacillin 2 g IV single dose + enema	Bacteriuria, bacteremia, fever	None collected	No statistical controls
Ruebush (1979) [26]	Individuals undergoing transrectal prostate biopsy	Individuals with valvular heart disease, intravascular prosthesis, fever, or use of antibiotics 7 days before biopsy	79 males randomized to two groups	**Control:** placebo with no enema **Treatment:** trimethoprim/ sulfonamide metoxazole 40/200 mg orally 2 tablets q 12 h for 7 days	Bacteriuria, bacteremia, fever	None	Trimethoprim/ sulfamethoxazole did not reduce the frequency of fever or bacteremia but did produce a significant reduction in bacteriuria (p <0.05)
Tekdogan (2006) [27]	Individuals undergoing transrectal prostate biopsy	Previous prostatic biopsy or surgery, diabetes, elevated WBC, neurogenic bladder, valvular heart disease, UTI, catheterization in previous 7 days, any active antibiotic, immunosuppressant, or anticoagulant use	159 males randomized to four groups	**Control:** no treatment **Treatment 1**: ciprofloxacin 1000 mg/day for 4 days **Treatment 2**: rifampicin enema **Treatment 3:** antibiotics + enema	Bacteriuria, bacteremia, fever	None	Unknown – unable to retrieve article
Yang (2009) [28]	Individuals undergoing transrectal prostate biopsy	Coagulopathy, active infection, severe cardiac disease	192 males randomized to three groups	**Control:** placebo with enema **Treatment 1:** single dose ciprofloxacin 500 mg PO + metronidazole 400 mg PO **Treatment 2:** ciprofloxacin 500 mg PO q 12 h + metronidazole 400 mg PO q 12 h for 3 days	Bacteriuria, bacteremia, fever	Rectal bleeding, hematuria, pain	There was no significant difference among the three groups in noninfective complications, but the incidence of infective complications in the placebo group was significantly higher than in the treatment arms (p<0.01). There was no significant difference among treatment arms in infective complications (p>0.05)

Table 8.9 Summary of findings table for the use of antibiotics among patients undergoing transrectal biopsy of the prostate.

Should patients undergoing transrectal prostate biopsy receive prophylactic antibiotics?

Outcomes	No. of participants (studies) Follow-up	Quality of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with placebo	Risk difference with antibiotics
Sepsis	48 (1 RCT)	⊕⊕⊕◯ MODERATE[1]	**RR 0.36** (0.04 to 3.24)	120 per 1000	**77 fewer per 1000** (115 fewer to 265
Hospitalization	68 (2 RCTs)	⊕⊕⊕◯ MODERATE[1]	**RR 0.13** (0.03 to 0.55)	130 per 1000	**113 fewer per 1000** (127 fewer to 59 fewer)
Incidence of bacteremia assessed with: blood culture	494 (5 RCTs)	⊕⊕⊕◯ MODERATE[1]	**RR 0.67** (0.49 to 0.92)	190 per 1000	**63 fewer per 1000** (97 fewer to 15 fewer)
Incidence of bacturia assessed with: urinalysis	870 (7 RCTs)	⊕⊕⊕◯ MODERATE[1]	**RR 0.25** (0.15 to 0.42)	148 per 1000	**111 fewer per 1000** (126 fewer to 86 fewer)
Incidence of fever assessed with: patient report	820 (7 RCTs)	⊕⊕⊕◯ MODERATE[1]	**RR 0.39** (0.23 to 0.64)	40 per 1000	**25 fewer per 1000** (31 fewer to 14 fewer)
Incidence of urinary tract infection assessed with: urine culture	1086 (3 RCTs)	⊕⊕⊕◯ MODERATE[1]	**RR 0.37** (0.22 to 0.62)	33 per 1000	**56 fewer per 1000** (69 fewer to 34 fewer)
Adverse outcome assessed with: patient reported nausea, abdominal cramps, pruritis, and/or diarrhea	127 (2 RCTs)	⊕◯◯◯ LOW[1]	**RR 1.62** (0.23 to 11.56)	16 per 1000	**10 more per 1000** (12 fewer to 170

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.

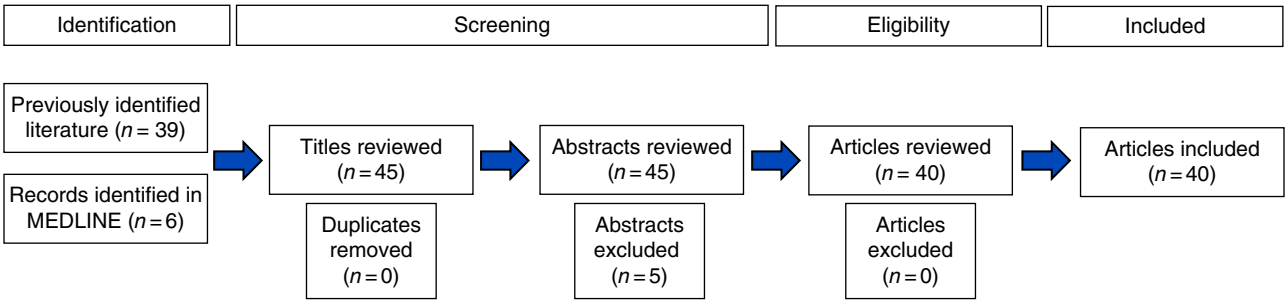

Figure 8.11 PRISMA flow diagram: article selection on antibiotic prophylaxis for the prevention of infectious complications in patients undergoing transurethral resection of the prostate.

reflect the paucity of data that were included in this updated meta-analysis. The results of our meta-analysis are presented in a summary of findings table (Table 8.10). Forest plots are presented in Figures 8.12–8.14.

Clinical implications

We suggest the use of prophylactic antibiotics in patients undergoing TURP (conditional recommendation based on low-quality evidence). This recommendation considers

Table 8.10 Summary of findings table for patients undergoing transurethral resection of the prostate.

Should patients undergoing transurethral resection of the prostate receive antibiotic prophylaxis?

Patient or population: TURP
Setting:
Intervention: antibiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with antibiotics				
Sepsis	34 per 1000	**17 per 1000** (9 to 33)	**RR 0.51** (0.27 to 0.96)	1666 (6 RCTs)	⨁⨁◯◯ LOW	
Fever	221 per 1000	**141 per 1000** (122 to 166)	**RR 0.64** (0.55 to 0.75)	2754 (17 RCTs)	⨁◯◯◯ VERY LOW	
Positive urine culture	337 per 1000	**125 per 1000** (108 to 138)	**RR 0.37** (0.32 to 0.41)	5165 (39 RCTs)	⨁⨁⨁◯ MODERATE	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

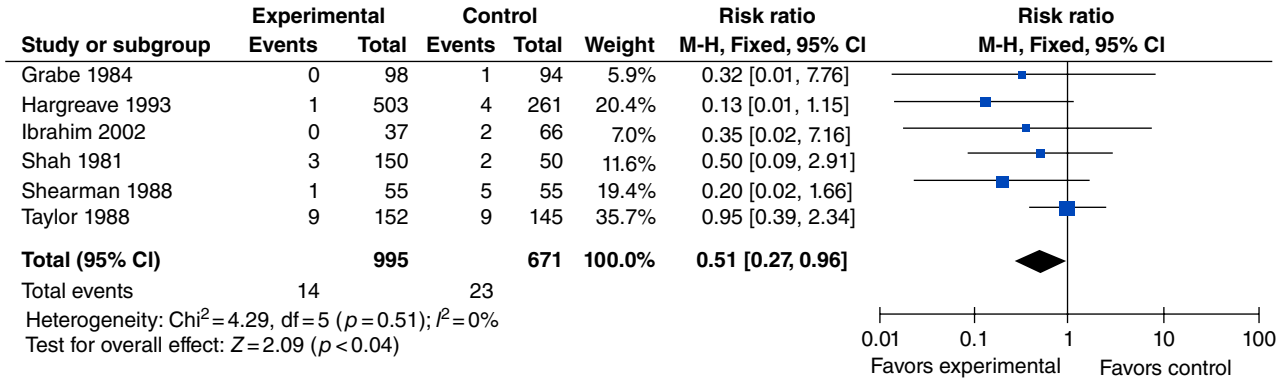

Figure 8.12 Forest plot comparing antibiotic prophylaxis versus no antibiotic prophylaxis for the prevention of *sepsis* in patients undergoing TURP.

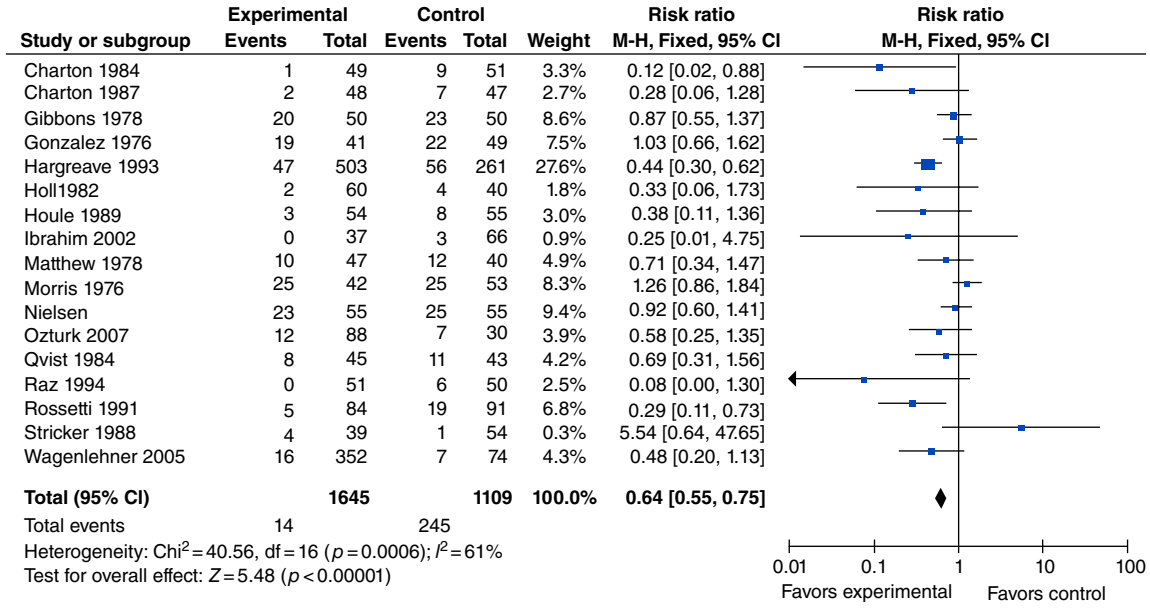

Figure 8.13 Forest plot comparing antibiotic prophylaxis versus no antibiotic prophylaxis for the prevention of *fever* in patients undergoing TURP.

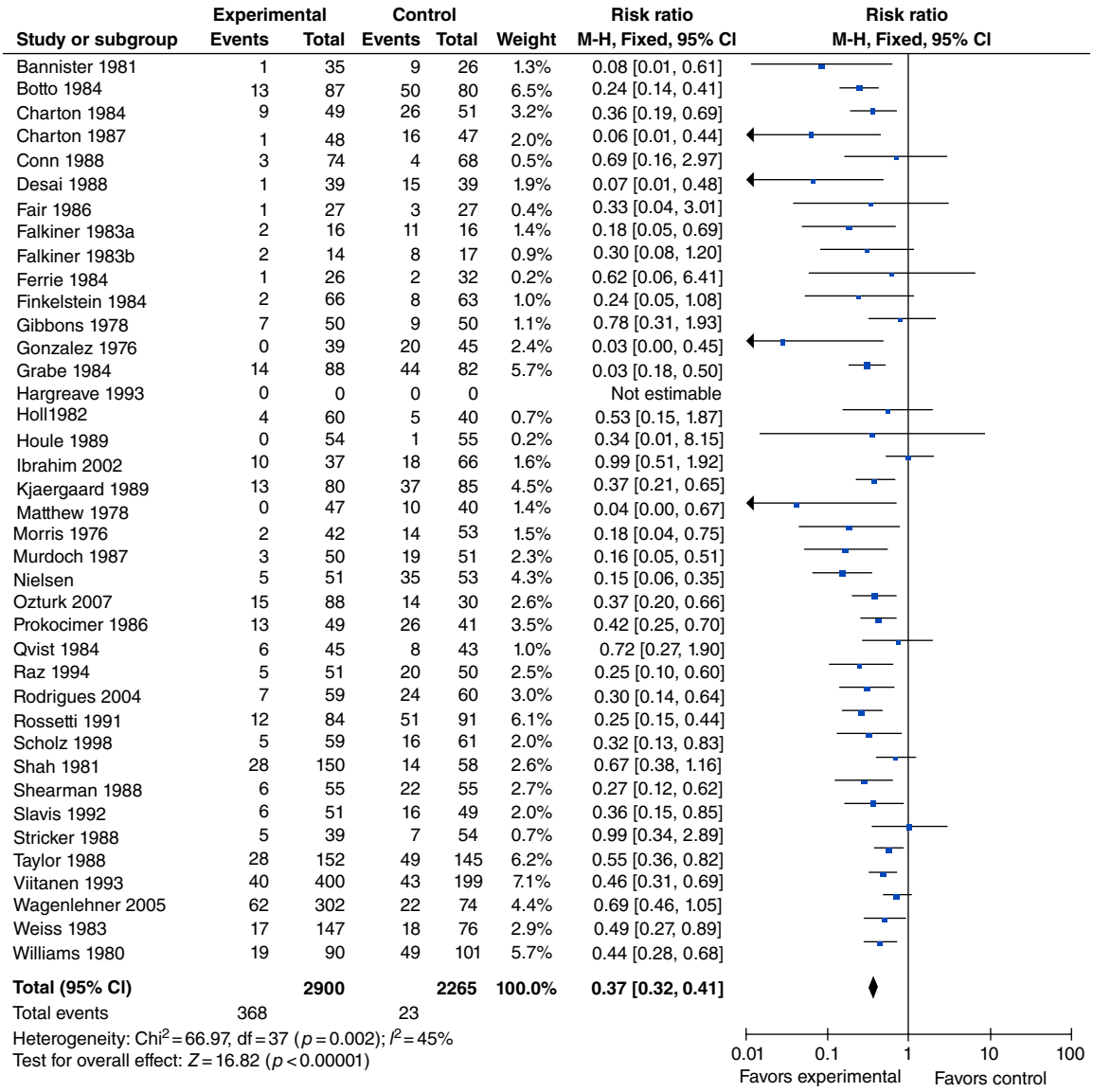

Figure 8.14 Forest plot comparing antibiotic prophylaxis versus no antibiotic prophylaxis to prevent *positive urine cultures* in patients undergoing TURP.

the consistent benefit of prophylactic antibiotics across critical and important outcomes, and also the fact that the adverse events associated with these agents are relatively uncommon and mild, and the associated costs of antibiotic prophylaxis are relatively low.

Future considerations

Many areas of antibiotic prophylaxis research would benefit from high-quality RCTs and systematic reviews of higher methodological rigor. Guidelines should adopt a transparent method to consider the quality of the evidence base for each clinical question using judgment and clinical understanding to integrate this evidence into meaningful clinical guidance.

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9

CHAPTER 9

Venous thromboembolism (VTE) prophylaxis

Vikram Narayan and Philipp Dahm

Minneapolis VA Health Care System, Urology Section and Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA

Introduction

Venous thromboembolism (VTE) is a major source of mortality and morbidity in patients undergoing major surgery. There are an estimated 350 000–650 000 cases of VTE annually, with >200 000 deaths per year (including in nonsurgical patients) [1]. Patients undergoing surgery for cancer are at a 5–7-fold increased risk for VTE, and it represents the most common cause of death within 30 days following major oncological surgery [2]. This remains a significant source of preventable hospital-related morbidity and mortality.

A retrospective study that queried the National Surgical Quality Improvement Program (ACS-NSQIP) database identified 27 455 patients who underwent surgery for urological malignancy (radical nephrectomy, partial nephrectomy, nephroureterectomy, radical prostatectomy, or radical cystectomy) between 2005 and 2012. The incidence of overall 30-day VTE, post-discharge VTE, and post-VTE death was calculated for each procedure. A total of 391 VTE events were identified and, across all procedures, 248 (63.4%) occurred after discharge. The overall VTE rate was the highest among patients undergoing radical cystectomy. These patients also had the longest length of hospital stay among the surgeries included in the analysis [3].

In general, about 50% of major bleeds occur between surgery and postoperative day 1 and approximately 90% occur within the first four postoperative days. In comparison, VTE risk is similar during the first four postsurgical weeks (Figure 9.1) [4].

There remains considerable variability in physician practice patterns with respect to the use of pharmacological thromboprophylaxis. This is due to the historical lack of high-quality evidence and, until recently, the paucity of urology-specific guidelines.

In order to make a judgment about the balance of likely benefits to harms of providing VTE prophylaxis, the baseline risks of VTE and major bleeding events need to be known; these represent the most patient-important or critical outcome for decision-making. The risk of thrombosis and bleeding in urological surgery (ROTBUS) study performed a systematic review and meta-analysis to help answer this question on a per procedure basis [5]. Recognizing that the risk of VTE may also vary to a large extent based on patient characteristics, they developed and applied a basic risk stratification system: patients at low risk had no risk factors, those at medium risk were ≥75 years of age, had a body mass index (BMI) ≥35 kg/m^2, or had a family history of VTE in a first-degree relative, and those at high risk had either a prior VTE or any combination of two other risk factors (Table 9.1).

It should be noted that many of the risk estimates found by the ROTBUS study should be interpreted within the context of patient selection factors that may have played a role. Most of the data are based on observational studies and risk estimates varied between open, robot-assisted, and laparoscopic approaches depending on patient factors that may have led a surgeon to preselect one operation over another for a given patient. As a result, there is likely selection bias in the risk estimates as patients who are at higher VTE risk may have been counseled on undergoing one type of operation over another.

In considering the likely trade-off between a reduced rate of symptomatic VTE versus increased rate of major bleeding requiring reoperation, we follow the lead of the EAU guidelines, which suggested that one episode of major bleeding requiring reoperation is twice as important as a symptomatic VTE event. Although there is no direct evidence for this 2 : 1 ratio from the urological literature, there is indirect evidence in its support. It therefore serves as the basis of the recommendations that follow.

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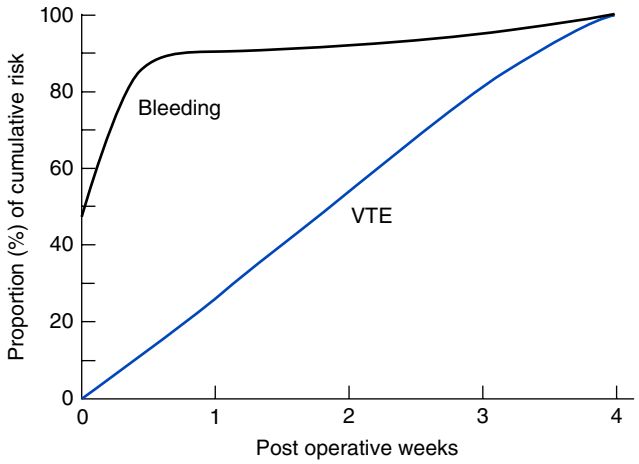

Figure 9.1 Time course of risk for post operative bleeding compared to DVT on immediate spot operative period.

Table 9.1 Risk stratification for venous thromboembolism (VTE) estimates as modeled by Tikkinen et al. [4].

Risk	Risk factor
Low risk	No risk factors
Medium risk	Age ≥75 years
	Body mass index ≥35 kg/m^2
	VTE in first-degree relative (parent, full sibling, child)
High risk	Prior VTE
	Any combination of two or more risk factors

The timing of prophylaxis varied between studies. In our opinion, pharmacological thromboprophylaxis should be started the morning after surgery, with an optimal duration of approximately 4 weeks postsurgery. Considerable variations in practice patterns remain among urologists owing to uncertainties in duration, timing, and difficulties in generalizing guidelines to individual patients. In summary, however, VTE pharmacoprophylaxis should be initiated if the risk of bleeding is less than the patient's individual risk of developing a symptomatic VTE event within 30 days of surgery.

Literature search

We performed a search of the National Library of Medicine database through PubMed on 23 August 2017 using the Medical subject headings including the "urological procedures" term family combined with the "thrombosis" term family and also the "urological procedures" term family combined with the "bleeding" term family. We then used the systematic review filter located under the clinical queries filter to identify relevant systematic reviews. The central resources informing this chapter were two systematic reviews by the ROTBUS working group and the recent EAU guidelines on VTE prophylaxis that provided the framework for moving from evidence to recommendations.

Clinical question 1

Do patients undergoing radical cystectomy require pharmacological VTE prophylaxis?

The evidence

Based on English-language studies that enrolled a minimum of 50 adult patients undergoing cystectomy, the ROTBUS study identified nine studies including 3036 patients who underwent open radical cystectomy, and five studies including 1320 patients who underwent robot-assisted radical cystectomy. Based on this study, the estimated risk for VTE for patients undergoing open radical cystectomy for low-, intermediate-, and high-risk patients was estimated as 2.9, 5.8, and 11.6%, respectively. The quality of evidence was rated as moderate for all three risk strata. The risk of major bleeding requiring reoperation was estimated as 0.3% based on low-quality evidence.

The corresponding risks for patients undergoing robotic-assisted radical cystectomy were rated lower at 2.6, 5.2, and 10.3%, respectively (low-quality evidence throughout), with an identical risk of major bleeding requiring reoperation of 0.3% (low-quality evidence). Based on other systematic reviews, the VTE reduction associated with pharmacological anticoagulants was estimated as 50%. The increase in relative risk of major bleeding was also estimated as 50%.

Clinical implications

In patients undergoing radical cystectomy (and urinary diversion) using an open surgical approach, we recommend 4 weeks of pharmacological prophylaxis (strong recommendation based on moderate-quality evidence). This recommendation is based on a net benefit of at least 10 per 1000 patients (trading off two symptomatic VTE events for one event of major bleeding requiring reoperation), as summarized in Table 9.2.

In patients undergoing radical cystectomy (and urinary diversion) using a robotic-assisted laparoscopic surgical approach, we suggest 4 weeks of pharmacological prophylaxis (conditional recommendation based on low-quality evidence).). This recommendation is based on a net benefit of at least 9 per 1000 patients (trading off two symptomatic VTE events for one event of major bleeding requiring reoperation), as summarized in Table 9.3, but we are less confident in this net benefit compared with the open cystectomy setting.

Clinical question 2

Do patients undergoing radical prostatectomy require VTE prophylaxis?

Table 9.2 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing open cystectomy. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(9 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 0.50 (0.45 to** 0.55)	**Low** 29 per 1000	**14 fewer per 1000** (16 fewer to 13 fewer)
				Moderate 58 per 1000	**29 fewer per 1000** (32 fewer to 26 fewer)
				High 116 per 1000	**58 fewer per 1000** (64 fewer to 52 fewer)
Major bleeding requiring reoperation	(9 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 1.50** (1.45 to 1.55)	**Moderate** 3 per 1000	**2 more per 1000** (1 more to 2 more)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence confidence interval; RR, risk risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a]This number describes the number of observational studies that informed the control event rate.

Table 9.3 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing robotic-assisted radical cystectomy. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(5 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 0.50** (0.45 to 0.55)	**Low** 26 per 1000	**13 fewer per 1000** (14 fewer to 12 fewer)
				Moderate 52 per 1000	**26 fewer per 1000** (29 fewer to 23 fewer)
				High 103 per 1000	**52 fewer per 1000** (57 fewer to 46 fewer)
Major bleeding requiring reoperation	(3 RCTs)[a]	⨁⨁◯◯ LOW	**RR 1.50** (1.45 to 1.55)	**Moderate** 3 per 1000	**2 more per 1000** (1 more to 2 more)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
Explanation
[a]This number describes the number of observational studies that informed the control event rate.

Table 9.4 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing open prostatectomy without PLND. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(5 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 0.50** (0.45 to 0.55)	**Low** 10 per 1000	**5 fewer per 1000** (6 fewer to 5 fewer)
				Moderate 20 per 1000	**10 fewer per 1000** (11 fewer to 9 fewer)
				High 39 per 1000	**20 fewer per 1000** (21 fewer to 18 fewer)
Major bleeding requiring reoperation	(3 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 1.50** (1.45 to 1.55)	**Moderate** 1 per 1000	**1 more per 1000** (0 fewer to 1 more)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a]This number describes the number of observational studies that informed the control event rate.

The evidence

For radical prostatectomy, the ROTBUS study found variations in the estimated baseline risk of VTE depending on whether the procedure was performed with or without a pelvic lymph node dissection. The incidence of VTE for robot-assisted laparoscopic prostatectomy (RALP) varied between 0.2 and 0.9% at 4 weeks if no pelvic lymph node dissection (PLND) was performed (compared with a 0.4% bleeding risk); laparoscopic radical prostatectomy without lymph node dissection conferred a 0.4–1.5% VTE risk at 4 weeks (0.7% bleeding risk), and open radical prostatectomy without lymph node dissection was found to have a VTE risk between 1.0 and 3.9% (0.1% bleeding risk) [6]. The highest risk of VTE at 4 weeks was identified in patients who underwent an open radical prostatectomy with extended pelvic lymph node dissection (3.9–15.7%, depending on risk group), compared with a bleeding risk in those patients of only 0.2%. The open radical prostatectomy/extended PLND estimates were based on five studies involving 4001 patients, with the certainty of risk estimates judged to be moderate.

In summary, the ROTBUS systematic review found that the risk of VTE at 4 weeks was highest after open prostatectomy (1.0–15.7%), followed by laparoscopic prostatectomy (0.4–6.0%), and finally RALP (which had the lowest VTE risk, 0.2–3.7%). The risk of bleeding requiring reoperation was highest after laparoscopic prostatectomy, followed by robot-assisted and open prostatectomy [6].

The VTE risk reduction associated with pharmacological anticoagulants was again assumed to be 50%; the increase in relative risk of major bleeding was also estimated as 50%.

Clinical implications

In patients undergoing open radical prostatectomy without PLND, we suggest pharmacological prophylaxis in low-risk patients (conditional recommendation based on moderate-quality evidence) for an estimated net benefit of 3 per 1000 (Table 9.4). We recommend pharmacological prophylaxis in medium- and high-risk patients (strong recommendation based on moderate-quality evidence) for an estimated net benefit of at least 8 per 1000.

In patients undergoing open prostatectomy with standard or extended PLND, we recommend pharmacological prophylaxis in moderate- and high-risk patients (strong recommendation based on moderate-quality evidence) for an estimated net benefit of at least 18 per 1000 (Tables 9.5 and 9.6). We also recommend pharmacological prophylaxis in low-risk

Table 9.5 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing open prostatectomy with standard PLND. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(5 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 0.50** (0.45 to 0.55)	**Low** 20 per 1000	**10 fewer per 1000** (11 fewer to 9 fewer)
				Moderate 39 per 1000	**20 fewer per 1000** (21 fewer to 18 fewer)
				High 79 per 1000	**40 fewer per 1000** (43 fewer to 36 fewer)
Major bleeding requiring reoperation	(3 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 1.50** (1.45 to 1.55)	**Moderate** 2 per 1000	**1 more per 1000** (1 more to 1 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a]This number describes the number of observational studies that informed the control event rate.

Table 9.6 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing open prostatectomy with extended PLND. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(5 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 0.50** (0.45 to 0.55)	**Low** 39 per 1000	**20 fewer per 1000** (21 fewer to 18 fewer)
				Moderate 79 per 1000	**40 fewer per 1000** (43 fewer to 36 fewer)
				High 157 per 1000	**79 fewer per 1000** (86 fewer to 71 fewer)
Major bleeding	(3 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 1.50** (1.45 to 1.55)	**Moderate** 2 per 1000	**1 more per 1000** (1 more to 1 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a]This number describes the number of observational studies that informed the control event rate.

Table 9.7 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing RALP without PLND. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(7 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 0.50** (0.45 to 0.55)	**Low** 2 per 1000	1 **fewer per 1000** (1 fewer to 1 fewer)
				Moderate 5 per 1000	**3 fewer per 1000** (3 fewer to 2 fewer)
				High 9 per 1000	**5 fewer per 1000** (5 fewer to 4 fewer)
Major bleeding requiring reoperation	(6 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 1.50** (1.45 to 1.55)	**Moderate** 4 per 1000	**2 more per 1000** (2 more to 2 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a]This number describes the number of observational studies that informed the control event rate.

patients undergoing open prostatectomy with extended PLND (strong recommendation based on moderate-quality evidence) for an estimated net benefit of 18 per 1000. We suggest pharmacological VTE prophylaxis in low-risk patients undergoing open prostatectomy with standard PLND (conditional recommendation based on moderate-quality evidence) for an estimated net benefit of 9 per 1000.

In patients undergoing RALP without PLND (Table 9.7) we recommend against pharmacological VTE prophylaxis in low-risk patients (strong recommendation against based on moderate-quality evidence) and suggest against pharmacological VTE prophylaxis in moderate- and high-risk patients (conditional recommendation against based on moderate-quality evidence).

Similarly, in patients undergoing RALP with standard PLND (Table 9.8), we recommend against pharmacological VTE prophylaxis in low-risk patients (strong recommendation against based on moderate-quality evidence) and suggest against pharmacological VTE prophylaxis in moderate-risk patients (conditional recommendation against based on moderate-quality evidence). In patients at high risk for VTE, we suggest pharmacological VTE prophylaxis (conditional recommendation based on moderate-quality evidence) for an estimated net benefit of 7 per 1000.

In patients undergoing RALP with extended PLND (Table 9.9), we suggest against pharmacological VTE prophylaxis in low-risk patients (conditional recommendation against based on moderate-quality evidence) but suggest for pharmacological VTE prophylaxis in moderate-risk patients (conditional recommendation based on moderate-quality evidence). In patients at high risk for VTE, we recommend pharmacological VTE prophylaxis (strong recommendation based on moderate-quality evidence) for an estimated net benefit of 21 per 1000.

Clinical question 3

Do patients undergoing surgery for kidney cancer require pharmacological VTE prophylaxis?

The evidence

For patients undergoing surgery for kidney cancer, the ROTBUS systematic review looked at partial nephrectomy (open, laparoscopic, and robot-assisted) and also radical nephrectomy (open and laparoscopic) [6].

Table 9.8 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing RALP with standard PLND. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(7 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 0.50** (0.45 to 0.55)	**Low** 5 per 1000	**3 fewer per 1000** (3 fewer to 2 fewer)
				Moderate 9 per 1000	**5 fewer per 1000** (5 fewer to 4 fewer)
				High 19 per 1000	**10 fewer per 1000** (10 fewer to 9 fewer)
Major bleeding requiring reoperation	(6 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 1.50** (1.45 to 1.55)	**Moderate** 6 per 1000	**3 more per 1000** (3 more to 3 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a]This number describes the number of observational studies that informed the control event rate.

Table 9.9 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing RALP with extended PLND. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(7 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 0.50** (0.45 to 0.55)	**Low** 9 per 1000	**5 fewer per 1000** (5 fewer to 4 fewer)
				Moderate 19 per 1000	**10 fewer per 1000** (10 fewer to 9 fewer)
				High 37 per 1000	**19 fewer per 1000** (20 fewer to 17 fewer)
Major bleeding requiring reoperation	(6 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 1.50** (1.45 to 1.55)	**Moderate** 8 per 1000	**4 more per 1000** (4 more to 4 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a]This number describes the number of observational studies that informed the control event rate.

Those undergoing a laparoscopic partial nephrectomy were at highest risk for bleeding at 4 weeks requiring reoperation, with a risk estimate of 1.7%. This was compared with VTE risks between 1.1 and 4.2% depending on risk group. The certainty of these estimates was judged to be low. The estimates were based on seven studies involving 2848 patients. Radical nephrectomy with thrombectomy was associated with the highest VTE risks at 4 weeks, estimated to be between 2.9 and 11.6% depending on risk group (bleeding risk 2.0%); however, these estimates were judged to be of very low certainty and were based on data from three studies involving 298 patients [6]. Open and robot-assisted partial nephrectomy had similar VTE risks (between 1.0 and 3.9%) with bleeding risks of 0.1 and 0.5%, respectively. Patients who underwent an open radical nephrectomy had VTE risk estimates at 4 weeks between 1.1 and 4.4% (low certainty of estimates), with a bleeding risk of 0.05% (very low certainty of estimate).

The VTE risk reduction associated with pharmacological anticoagulants was again assumed to be 50%; the increase in relative risk of major bleeding was also estimated as 50%.

Clinical implications

For patients undergoing open radical nephrectomy (Table 9.10), we suggest pharmacological VTE prophylaxis for all patients (conditional recommendation based on very low-quality evidence) for an estimated net benefit of 9 per 1000 or greater.

For patients undergoing open partial nephrectomy (Table 9.11), we suggest pharmacological VTE prophylaxis for all patients (conditional recommendation based on very low-quality evidence) for an estimated net benefit of at least 3 per 1000.

For patients undergoing laparoscopic radical nephrectomy (Table 9.12), we suggest against pharmacological VTE prophylaxis in low- and medium-risk patients (conditional recommendation against based on very low-quality evidence). In high-risk patients, we suggest pharmacological VTE prophylaxis (conditional recommendation based on very low-quality evidence) for an estimated net benefit of at least 7 per 1000.

For patients undergoing robotic-assisted partial nephrectomy (Table 9.13), we suggest against pharmacological VTE prophylaxis in low-risk patients (conditional recommendation against based on moderate-quality evidence) given an

Table 9.10 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing open radical nephrectomy. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(3 studies)[a]	⨁◯◯◯ VERY LOW	**RR 0.50** (0.45 to 0.55)	**Low** 11 per 1000	**6 fewer per 1000** (6 fewer to 5 fewer)
				Moderate 22 per 1000	**11 fewer per 1000** (12 fewer to 10 fewer)
				High 44 per 1000	**22 fewer per 1000** (24 fewer to 20 fewer)
Major bleeding requiring reoperation	(2 studies)[a]	⨁◯◯◯ VERY LOW	**RR 1.50** (1.45 to 1.55)	**Moderate** 1 per 1000	**0 fewer per 1000** (0 fewer to 0 fewer)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; RR, risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanation

[a]This number describes the number of observational studies that informed the control event rate.

Table 9.11 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing open partial nephrectomy. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(6 studies)[a]	⨁◯◯◯ VERY LOW	**RR 0.50** (0.45 to 0.55)	**Low** 10 per 1000	**5 fewer per 1000** (6 fewer to 5 fewer)
				Moderate 20 per 1000	**10 fewer per 1000** (11 fewer to 9 fewer)
				High 39 per 1000	**20 fewer per 1000** (21 fewer to 18 fewer)
Major bleeding requiring reoperation	(2 studies)[a]	⨁◯◯◯ VERY LOW	**RR 1.50** (1.45 to 1.55)	**Moderate** 1 per 1000	**1 more per 1000** (0 fewer to 1 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a]This number describes the number of observational studies that informed the control event rate.

Table 9.12 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing laparoscopic radical nephrectomy. Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(3 studies)[a]	⨁◯◯◯ VERY LOW	**RR 0.50** (0.45 to 0.55)	**Low** 7 per 1000	3 fewer per 1000 (4 fewer to 3 fewer)
				Moderate 13 per 1000	7 fewer per 1000 (7 fewer to 6 fewer)
				High 26 per 1000	13 fewer per 1000 (14 fewer to 12 fewer)
Major bleeding requiring reoperation	(2 studies)[a]	⨁◯◯◯ VERY LOW	**RR 1.50** (1.45 to 1.55)	**Moderate** 5 per 1000	3 more per 1000 (2 more to 3 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a] This number describes the number of observational studies that informed the control event rate.

Table 9.13 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing robotic-assisted laparoscopic partial nephrectomy.
Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(2 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 0.50** (0.45 to 0.55)	**Low** 10 per 1000	**5 fewer per 1000** (6 fewer to 5 fewer)
				Moderate 19 per 1000	**10 fewer per 1000** (10 fewer to 9 fewer)
				High 39 per 1000	**20 fewer per 1000** (21 fewer to 18 fewer)
Major bleeding requiring reoperation	(2 studies)[a]	⨁⨁⨁◯ MODERATE	**RR 1.50** (1.45 to 1.55)	**Moderate** 5 per 1000	**3 more per 1000** (2 more to 3 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a] This number describes the number of observational studies that informed the control event rate.

estimated net harm of 1 per 1000. In moderate-risk patients, we suggest pharmacological VTE prophylaxis (conditional recommendation based on moderate-quality evidence) for an estimated net benefit of 4 per 1000 and in high-risk patients we recommend pharmacological VTE prophylaxis (strong recommendation based on high-quality evidence) for an estimated net benefit of 14 per 1000.

Clinical question 4

Do patients undergoing transurethral procedures require VTE prophylaxis?

The evidence

For noncancer procedures such as transurethral resection of the prostate, the risk of VTE would be expected to be different. The ROTBUS study also separately looked at noncancer procedures common in urology, including transurethral procedures (transurethral resection of the prostate [TURP], laser-TURP, and transurethral vaporization in saline) [7]. Risk stratifications for patients (low, medium, or high risk) were identical with those outlined previously (Table 9.1). Between 2002 and 2011, eight studies involving 13 644 patients were identified, with four studies reporting thromboprophylaxis use.

At 4 weeks, the baseline risk estimates were for patients at low risk 0.2%, medium risk 0.4%, and high risk 0.8%. The confidence of these estimates based on GRADE was deemed to be low. The risk of bleeding requiring reoperation at 4 weeks was estimated to be 0.2%, with a confidence of the estimate deemed to be very low. Limitations to the data that led to the low and very low judgments of the confidence of the risk estimates included the fact that many of the studies did not provide information on the precise length of follow-up and type of thromboprophylaxis use [7]. Overall, the evidence in noncancer urological surgery, including transurethral surgery, is of low or very low quality, including for common procedures such as TURP. As a result, clear generalizable guidance cannot be given regarding the use of thromboprophylaxis in these patients and the decision should be individualized based on patient risk factors. The risk of VTE does not clearly outweigh the risk of bleeding in these patients based on the low-quality evidence currently available.

Table 9.14 Pharmacological prophylaxis compared with no pharmacological prophylaxis in patients undergoing TURP.
Bibliography: Based on EAU Guidelines on Thromboprophylaxis in Urological Surgery (2017).

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no pharmacological prophylaxis	Risk difference with pharmacological prophylaxis
Symptomatic VTE	(4 studies)[a]	⨁◯◯◯ VERY LOW	**RR 0.50** (0.45 to 0.55)	**Low** 2 per 1000	**1 fewer per 1000** (1 fewer to 1 fewer)
				Moderate 4 per 1000	**2 fewer per 1000** (2 fewer to 2 fewer)
				High 8 per 1000	**4 fewer per 1000** (4 fewer to 4 fewer)
Major bleeding requiring reoperation	(4 studies)[a]	⨁◯◯◯ VERY LOW	**RR 1.50** (1.45 to 1.55)	**Moderate** 2 per 1000	**1 more per 1000** (1 more to 1 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; RR, risk ratio.
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanation
[a]This number describes the number of observational studies that informed the control event rate.

The VTE risk reduction associated with pharmacological anticoagulants was again assumed to be 50%; the increase in relative risk of major bleeding was also estimated as 50%.

Clinical implications

We suggest against pharmacological prophylaxis in patients undergoing transurethral surgery such as TURP (Table 9.14), irrespective of VTE risk category (conditional recommendation against based on very-low quality evidence).

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10 CHAPTER 10
Operative safety

Elizabeth Timbrook Brown[1], Bryan J. Hill[2], and Roger R. Dmochowski[3]

[1] *Department of Urology, Georgetown University School of Medicine, Washington, DC, USA*

[2] *Department of Gynecology and Obstetrics, Division of Female Pelvic Medicine and Reconstructive Surgery, Loma Linda University, Loma Linda, CA, USA*

[3] *Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA*

Background

Patient safety in the operating room is paramount – wrong site surgery, incorrect medication administration, retained surgical instruments (RSI), poor compliance with deep vein thrombosis (DVT), or antibiotic prophylaxis, and myriad errors can compound already precarious surgical procedure risks. Current literature suggests that 3–16% of all patients undergoing a major surgery will have a serious complication – half of which are preventable [1, 2]. In fact, teamwork and communication failures are a leading cause of adverse events in healthcare facilities, and the operating room is no exception [3]. As such, there have been several multidisciplinary interventions over the past decade to improve patient outcomes, including global initiatives to enhance surgical safety. Organizations such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and the World Health Organization (WHO) have proposed recommendations and mandates to make surgical safety an international priority. Most notably, safety checklists such as those used in aviation to prevent errors and minimize risks have been created, implemented, and mandated throughout surgical facilities.

JCAHO initiated a surgical checklist to create an expectation of effective communication and safe practices during the three perioperative periods: prior to anesthesia administration, prior to skin incision, and prior to the patient leaving the operating room. These implementations are part of the Universal Protocol (UP) for Preventing Wrong Site, Wrong Procedure, Wrong Person Surgery, effective 1 July 2004, which requires a preoperative verification process, marking the operative site, and a surgical "time-out" immediately prior to the procedure start [4]. The UP is based on a consensus of experts from relevant clinical specialties and is endorsed by more than 40 professional medical associations, including the American Urological Association (AUA) [4]. The use of the UP is now ubiquitous throughout healthcare centers and, as such, Centers for Medicare and Medicaid Services (CMS) is currently implementing a new quality reporting program for ambulatory care centers to introduce a structural measure on the use of a safe surgery checklist [5].

Distraction in the operating room can also have a detrimental effect on patient safety by causing an attention lapse from the primary task at hand. Studies in aviation reveal a significant correlation between cockpit distractions and omitting task sequences, with distraction often cited in aviation accident reports as a causative factor [6]. In addition to aviation, other industries such as nuclear power and offshore oil production have repeatedly emphasized the need for formalized training in teamwork and the ability to have free communication to reduce errors [7]. Translational studies in healthcare have shown that such training improves the culture of safety and attitudes across a range of surgical specialties [4]. In recent years, there has also been increasing research on unintentional patient harm due to surgical team communication failures in a disruptive operative environment.

Furthermore, with an increasing focus on patient safety, there has been a recent paradigm shift in medical education. Historically, medical students and residents performed procedures for the first time during their training on living patients. However, as technology rapidly advances, procedure simulation opportunities have become more readily available. As a result, the former adage of "see one, do one, teach one" has now changed to "see one, simulate many, and then do one" [8]. Traditionally, some procedures may have been taught on cadavers, but now trainees have the opportunity to learn either on an interactive manikin or with an electronic simulator such as for a laparoscopic, endoscopic, or robotic procedures. Trainees can now practice many procedures, ranging from airway intubation to a robotic-assisted laparoscopic prostatectomy, without ever jeopardizing patient care. With the advent of minimally invasive

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technology, surgical simulation has allowed resident physicians to train in a more controlled environment. Surgical simulation can be integrated into many, if not all, surgical specialties and can certainly increase physician confidence and decrease physician anxiety, and may potentially improve patient safety. Nevertheless, there is ongoing research to determine whether these simulated skills translate into improved patient outcomes.

Clinical question 1

In a patient undergoing surgery, how does the use of a preoperative checklist affect outcomes?

Literature search

Evidence for the following clinical recommendations was obtained using three separate methods to ensure completeness. First, PubMed/MEDLINE searches were conducted, including all forms of published, English-language studies using the keywords "preoperative checklist," "patient safety," "surgical checklist," and "checklist and operating room." The references for these studies were in turn examined for further relevant studies that may have been omitted in the search. Next, texts considered authoritative in the field were reviewed with specific attention to the studies used to form those resources' clinical recommendations. This also included searches at meta-analyses clearing houses. Finally, active practitioners and researchers within the field were queried about recent evidence used for their own clinical decision-making. The sum of information found through all of these means was reviewed and the following clinical recommendations are made based on this evidence.

The evidence

Globally, the WHO also recommended the use of a Safe Surgery Checklist in 2007 (Table 10.1), which has now been adapted and implemented in many nations worldwide [9]. At that time, the Safe Surgery Saves Lives study group created a 19-item checklist, which was designed to be concise, simple, and user friendly, while also targeting critical actions, which, if forgotten, could be life threatening to the patient.

Table 10.1 World Health Organization Surgical Safety Checklist [9].

Before induction of anesthesia	Before skin incision	Before patient leaves operating room
Sign in	*Time-out*	*Sign out*
Patient has confirmed: • Identity • Site • Procedure • Consent	Confirm all team members have introduced themselves by name and role	Nurse verbally confirms with the team: • Name of the procedure recorded • Instrument, needle, and sponge counts are correct (or N/A) • How the specimen is labeled • Whether there are any equipment problems to be addressed
Site marked or N/A	Surgeon, anesthesia professional, and nurse verbally confirm: • Patient • Site • Procedure	Surgeon, anesthesia professional, and nurse review the key concerns for recovery and management of this patient
Anesthesia safety check completed Pulse oximeter on patient and functioning	**Anticipated critical events** *Anesthesia team reviews:* • Are there any patient-specific concerns? *Nursing team reviews:* • Has sterility (including indicator results) been confirmed? • Are there equipment issues or any concerns?	
Does patient have a: Known allergy? • Yes • No Difficult airway/aspiration risk? • No • Yes, and equipment available Risk of >500 mL blood loss? • No • Yes, and adequate IV access and fluids planned	Has antibiotic prophylaxis been given within the last 60 min? • Yes • N/A Is essential imaging displayed? • Yes • N/A	

N/A, not applicable.

This checklist was implemented and trialed at eight hospitals in eight different cities worldwide: Toronto, Canada; New Delhi, India; Amman, Jordan; Auckland, New Zealand; Manila, Philippines; Ifakara, Tanzania; London, England; and Seattle, WA, USA. This was designed to be a prospective, nonrandomized study with a pre- and post-intervention interrupted time series. Data were collected prior to the initiation of the surgical checklist on clinical processes and outcomes for 3733 consecutively enrolled patients undergoing noncardiac surgery. After the introduction of the surgical checklist, similar data were collected on 3955 patients. The primary outcome of the study was the complication rate, including death, during hospitalization within the first 30 days after the operation. Prior to initiation of the checklist, the death rate was 1.5%, compared with 0.8% after implementation of the surgical checklist ($p=0.003$). Similarly, inpatient complications declined from 11.0% at baseline to 7.0% after introduction of the checklist ($p<0.001$). These differences did not change when adjusted for case mix variables [10]. Hence the reduction in the complication and death rates suggests that a checklist program can improve the safety of surgical patients in diverse clinical and economic environments.

In fact, a study by Katz et al. recently reported that a preoperative checklist for inflatable penile prosthesis (IPP) may reduce the risk of postoperative infection.The study identified a baseline risk of IPP infection at their institution of 2.9%; however, the hospital had a rise in infection rates to 54.5%. With this, an external infection control team was brought in and found no infection control issues within the hospital. At that point, a mandatory checklist for perioperative practices was implemented and included a documented preoperative negative urine culture, a serum hemoglobin A1c ≤10% within the month of surgery for diabetic patients, an abdominal and perineal 2% chlorhexidine scrub for two nights prior to surgery, intravenous vancomycin or cefazolin and gentimicin administration within 1 h of incision, hair removal from the surgical area with clippers, a 10 min preoperative chlorhexidine scrub of the surgical area, a 5 min surgeon hand scrub and double gloving, and the implantable device could only be handled by the surgeon (Table 10.2) [11]. As such, this is an uncontrolled, pre- and post-intervention study design. There were 131 patients included in the study (68 prior to the infection rate escalation, 11 during the infection rise, and 52 after the implementation of the checklist). After initiation of the perioperative IPP checklist, infection rates dropped to 0% (0/52 patients), $p<0.001$. The multivariate analysis did not demonstrate any obvious differences between patients, suggesting an overall benefit for the IPP specific preoperative checklist.

Certainly there is a need for further research regarding checklist use for individual procedures; however, the majority of checklists used in surgery today involve a presurgical checklist to ensure compliance with national perioperative guidelines. A retrospective, observational study by the Veterans Health Administration (VHA) assessed the specific impact on overall compliance with regulatory standards for preoperative DVT and antibiotic prophylaxis before and after the initiation of a surgical checklist. Patient records from 74 VHA facilities were reviewed (mean number of charts reviewed per facility for DVT and antibiotic prophylaxis: 78 ± 12 and 60 ± 6, respectively). Compared with before the initiation of a preoperative checklist, antibiotic and DVT prophylaxis rates improved significantly (from 92.1 ± 1.5 to 97.0 ± 0.1%, $p=0.01$, and from 85.1 ± 4.6 to 95.7 ± 0.8%, $p=0.05$, respectively), showing that implementation of a standardized checklist can improve compliance [12]. As with many of these studies, compliance represents a surrogate for patient outcomes, suggesting that improved adherence improves patient care and subsequently patient outcomes.

Despite these recommendations and outcomes, there is still resistance among healthcare providers to initiate a surgical checklist. Many studies have cited that culture change is the most difficult obstacle in the implementation of new regulatory procedures for the operating room [1–3, 13]. As a result, a study by Porter et al. proposed an "attestation"-type format for the preprocedural pause (PPP) (also known as the preoperative checklist or "time-out"). The study evaluated the effects of a new interactive time-out, which required members of the operating room team to introduce themselves as well as jointly complete a scripted portion of the time-out preprocedural checklist. This included verbal participation by the circulating nurse, scrub technician, surgeon, and anesthesia provider. Prior to implementation of the "attestation" format, a surgeon-led time-out completed only 54% of the items on the checklist, compared with 97% after the intervention, $p<0.0001$. Only 44% of team members introduced themselves prior to the intervention, whereas 94% did so afterwards, $p<0.0001$. Hence completion of all components of the time-out was better after the

Table 10.2 Example of an IPP preoperative checklist [11].

Preoperative measures:
- Urine culture result within 1 month prior to surgery date
- HbA_{1c} level within 2 months of surgery date: value 9% or less for diabetic patients
- 2% chlorhexidine whole-body and groin wash for two nights preceding surgery

Intraoperative measures:
- Guideline-based IV antibiotics administered within 1 h prior to incision
- Double glove technique for all scrubbed personnel
- Prosthesis is to be handled only by surgeons
- 5 min chlorhexidine hand scrub for all scrubbed personnel
- 10 min chlorhexidine genital scrub for patient followed by ChloraPrep
- Antibiotic irrigation solution
- Multilayered surgical closure and running skin closure
- Minimize turnover of personnel and no room traffic after skin incision has been made until wound is dressed

team-based time-out was introduced, suggesting a correlation with improved patient safety and teamwork in the operating room [13].

Healthcare providers who continue to resist the use of checklists often cite operating room start delays as a reason for their persistent opposition. As a result, Weld et al. evaluated operating room efficiency and patient safety in a prospective study applying crew resource management strategies that have been previously used in aviation.The Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS) project implemented pre- and postoperative briefings to encourage situational awareness and communication for all members of the healthcare team. The TeamSTEPPS training first included didactic-based modules on the four core competencies: leadership, situation monitoring, mutual support, and communication. With TeamSTEPPS, a preoperative briefing was conducted in the operating room 30 min prior to the planned start time for that day, which included all pertinent aspects for each case scheduled. The attending and resident urologists, anesthesia team members, circulating nurse, and surgical technician were present for the briefing. There was also a postoperative briefing with all team members during patient arousal. Results from 1481 urological cases with the TeamSTEPPS model were compared with 1513 urological cases that were performed at the institution prior to TeamSTEPPS. The mean case time with TeamSTEPPS was 12.7 min less ($p<0.001$), with the on-time first start rate improving by 21% ($p<0.001$). Patient safety issues declined overall from 16 to 6% ($p<0.001$) within 6 months and remained stable with the initiation of TeamSTEPPS [14]. These results show that implementation of checklists can actually improve operating room efficiency and yet still improve patient safety.

The aforementioned study interventions, intended outcomes, and actual results are summarized in Table 10.3.

Clinical implications

We recommend that urologists routinely apply the Universal Protocol and preprocedural "time-out," which includes a preoperative surgical checklist (strong recommendation based on low-quality evidence).

This recommendation is based on indirect evidence that these interventions improve perioperative processes and ultimately positively impact patient outcomes. This recommendation assumes that patients place a very high value on reducing even rare, but potentially catastrophic, adverse intraoperative events, and places a low value on the required resource utilization required for implementation.

Clinical question 2

Does a controlled operative environment that minimizes surgeon stress and distraction improve patient safety?

Literature search

Evidence for the following clinical recommendations was obtained using three separate methods to ensure completeness. First, PubMed/MEDLINE searches were conducted, including all forms of published, English-language studies using the keywords "distraction," "safety," "performance," and "operating room." The references for these studies were in turn examined for further relevant studies that may have been omitted in the search. Next, texts considered authoritative in the field were reviewed, with specific attention to the studies used to form those resources' clinical recommendations. This also included searches at meta-analyses clearing houses. Finally, active practitioners and researchers within the field were queried about recent evidence used for their own clinical decision-making. The sum of information found through all of these means was reviewed and the following clinical recommendations are made based on this evidence.

Table 10.3 Intended and actual outcomes of a preoperative checklist.

Study	Intervention (int.)	Intended outcome	Actual effect	Pre-int. (%)	Post-int. (%)	*p* Value
WHO [9]	Safe surgery checklist	Decrease complication rate and death (postoperative 30-day period)	Death rateInpatient complication rate	1.51 1.0	0.8 7.0	$p=0.003$ $p<0.001$
Katz et al. [11]	IPP preoperative checklist	Decrease perioperative IPP infection	Perioperative infection rate	52	0	$p<0.001$
Paul et al. [12]	Preoperative surgical checklist	Improve preoperative DVT and antibiotic prophylaxis compliance	DVT compliance rate Antibiotic prophylaxis compliance rate	92.1±1.5 85.1±4.6	97.0±0.1 95.7±0.8	$p=0.01$ $p=0.05$
Porter et al. [13]	Attestation format for the PPP	Improve compliance for all components of the PPP	Compliance rate	54	97	$p<0.0001$
Weld et al. [14]	TeamSTEPPS	Encourage situational awareness and communication for all healthcare members	Prevalence of patient safety issues	16	6	$p<0.001$

The evidence

In a randomized controlled trial (RCT) by Persoon et al., physician distraction was evaluated by asking 86 third-year medical students to complete simulated endourological tasks. The subjects were all shown an instructional video and then asked to perform surveillance cystoscopy or an endoscopic task. The students were randomized to a control group and an intervention group, in which a distraction was administered during the simulation. Both groups then completed follow-up questionnaires. In the intervention group, the distraction was a clinical question regarding a previous case presentation during the presimulation instructional video. Primary outcomes were the number of traumatic injuries caused by the cystoscope or endoscopic instruments, task completion time, and the number of bladder lesions identified. Mean completion time for the intervention group was 25 min and that for the control group was 18 min. The mean number of missed bladder lesions and traumatic injuries were also higher in the intervention group than the control group (0.2 vs. 0.0, $p<0.05$, and 26 vs. 14, $p<0.001$, respectively) [15].

While distraction may increase errors by novice surgeons, the same effect may not be observed with more experienced surgeons. A case–control study by Hsu et al. sought to determine if the degree of surgical experience influenced surgical performance in the presence of operating room distractors. A total of 31 novice surgeons (medical students and residents in postgraduate years [PGYs] 1 and 2) were compared with nine experienced surgeons (PGYs 4–5, clinical fellows, and attending physicians) while undergoing a peg transfer task as part of the Fundamentals of Laparoscopic Surgery (FLS) training. A baseline FLS peg transfer task was collected from each subject. Then, during the second part of the study, the FLS peg transfer task was repeated and distractors were given to each group in the form of simple math questions. The subject was asked to complete as many math questions as possible during 1 min while continuing the peg transfer task. The results indicated that, compared with baseline, experienced surgeons who were exposed to the dual-task performance had no difference in peg transfer score ($p=0.48$), the number of questions completed in 1 min ($p=0.32$), the number of correct answers ($p=0.06$), or the percentage of correct answers ($p=0.60$). However, the novice group demonstrated a decrease in the number of questions attempted ($p=0.001$) and the number of correct answers per minute ($p=0.02$) compared with baseline. Thus, intraoperative distractions can certainly be detrimental, but the effect may be mitigated in experienced surgeons [16].

A similar study by Suh et al. exposed 15 resident participants to three distractions during a robotic-assisted laparoscopic knot-tying simulation. These distractions included answering math questions, listening to noise and acknowledging a change in the auditory heart rate from 60 to 120 beats per minute, and listening to noise containing a stable heart rate. Objective measurements were obtained from electromyography (EMG) recordings on the forearm and kinematics of the surgical instrument tips. A standardized assessment was also performed using the National Aeronautics and Space Administration Task Load Index and Fundamentals of Laparoscopic Surgery score. Significant distraction effect was found for EMG measurements ($p<0.03$) and for all kinematic measures of the instrument tips ($p<0.05$) [17].

Clinical implications

We recommend the implementation of a controlled operative environment to improve patient safety in the operating room (strong recommendation based on low-quality evidence).

This recommendation is based on indirect evidence that distraction increases stress, reduces performance, and ultimately impacts patient outcomes negatively. This recommendation assumes that patients place a very high value on reducing even rare, but potentially catastrophic, adverse intraoperative events, and places a low value on the required resource utilization required for implementation.

Clinical question 3

Does the use of laparoscopic and endoscopic simulators, compared with traditional patient-based education models, improve patient outcomes?

Literature search

Evidence for the following clinical recommendations was obtained using three separate methods to ensure completeness. First, PubMed/MEDLINE searches were conducted, including all forms of published, English-language studies using the keywords "simulation," "safety," "improvement," and "operating room." The references for these studies were in turn examined for further relevant studies that may have been omitted in the search. Next, texts considered authoritative in the field were reviewed, with specific attention to the studies used to form those resources' clinical recommendations. This also included searches at meta-analyses clearing houses. Finally, active practitioners and researchers within the field were queried about recent evidence used in their own clinical decision-making. The sum of information found through all of these means was reviewed and the following clinical recommendations are made based on this evidence.

The evidence

A recent systematic review of the simulation literature by Dawe et al. aimed to determine if skills acquired during simulation-based training were able to be extrapolated to the patient care setting. Of the 255 articles reviewed, only 28 articles (27 RCTs) assessed surgical skills *in vivo* after simulation. The representative studies were from a variety of surgical subspecialities: general surgery (11), gastroenterology (6), otolaryngology (4), obstetrics/gynecology (3), and urology (2) (Table 10.4). There were 23 studies that demonstrated improvement in the operating room after simulated surgery, while five found no difference in measured parameters

Table 10.4 Comparison of 27 randomized controlled trials evaluating the effect of simulation on simulated and patient-based outcomes.

Investigators	Assessment procedure	Study population	Results
Laparoscopy			
Simulation versus no simulation			
Ahlberg et al. (2007) Sweden [22]	Cholecystectomy	Surgical residents	IG made fewer errors during exposure, clipping, tissue division, and dissection compared with CG ($p<0.04$)
Hogle et al. (2009) USA [23]	Cholecystectomy	Surgical residents	No significant difference between IG and CG in depth perception, bimanual dexterity, efficiency, tissue handling, autonomy
Cosman et al. (2007) Australia [24]	Cholecystectomy	Basic surgical trainees	IG had better bimanual coordination ($p=0.05$), fewer errors ($p=0.05$), and higher global score ($p=0.04$) than CG
Sroka et al. (2010) Canada [25]	Cholecystectomy	General surgery residents	IG had higher total GOALS score than CG ($p<0.001$). No significant difference found in depth perception, efficiency, and autonomy ($p>0.05$)
Banks et al. (2007) USA [26]	Bilateral tubal ligation	Ob/Gyn residents	IG scored higher than CG in pass–fail grade ($p=0.003$), task-specific checklist ($p=0.002$), and OSATS ($p=0.003$).
Gala et al. (2013) USA [27]	Bilateral tubal ligation	Ob/Gyn residents	IG had higher progression score on OSATS compared with CG ($p=0.03$)
Larsen et al. (2009) Denmark [28]	Salpingectomy	Ob/Gyn residents	IG completed procedure in half of time and had higher objective assessment score of laparoscopic salpingectomy compared with CG ($p<0.001$)
Van Sickle et al. (2008) USA [29]	Nissen fundoplication	Surgical residents	IG completed task with fewer errors ($p<0.01$), fewer excess needle manipulations ($p<0.05$), and in less time ($p<0.003$) than CG
Simulation training versus patient-based training			
Zendejas et al. (2011) USA [30]	Inguinal hernia repair	Surgical residents	IG showed decreased operative time ($p<0.001$), improved trainee performance, and decreased intra-/postoperative complications and overnight stays after laparoscopic inguinal hernia repair compared with CG ($p<0.05$)
Franzeck et al. (2012) Switzerland [31]	Camera navigation	Medical students	No significant difference was found in any parameter: horizon alignment, organ visualization, completion time, correct scope rotation handling between IG and CG ($p>0.05$)
Simulation with patient-based residency training compared with patient based-based residency training			
Palter and Grantcharov (2012) Canada [32]	Right hemicolectomy	General surgery residents	Higher level of technical proficiency attained in IG compared with CG using OSATS score ($p=0.030$)
Palter et al. (2013) Canada [33]	Cholecystectomy	General surgery residents	IG had higher OSATS during first four laparoscopic cholecystectomies compared with CG ($p<0.05$), achieving no statistical difference by the fifth subsequent procedure ($p=0.065$)
Endoscopy			
Simulation training versus no simulation training			
Kallstrom et al. (2010) Sweden [34]	Transurethral resection of prostate	Urology residents	IC had longer operating time than CG ($p=0.025$). No significant difference was found between groups for all other parameters
Schout et al. (2010) The Netherlands [35]	Flexible cystourethroscopy	Surgical interns	IG scored higher than CG in respect of tissue, time and motion, handling endoscope, flow of procedure, and knowledge of procedure. IG scored higher on global rating than CG ($p<0.01$)
Park et al. (2007) Canada [36]	Colonoscopy	General surgery and internal medicine residents	Global rating performance were higher in IG compared with CG ($p=0.04$)
Sedlack (2007) USA [37]	Esophagogastro-duodenoscopy	Fellows in gasteroenterology	CG had higher scores in recognizing patient discomfort compared with IG ($p=0.015$), with no significant difference between groups in other scores
Shirai et al. (2008) Japan [38]	Esophagogastro-duodenoscopy	Medicine residents	IG scored higher than CG for passing orogastric junction ($p<0.01$), passing through pyloric ring ($p<0.05$), examination of duodenal bulb ($p<0.05$), and viewing fornix ($p<0.05$). Less assistance by supervisor required for IG group ($p=0.002$)
Ferlitsch et al. (2010) Austria [39]	Esophagogastro-duodenoscopy	Medicine residents	IG completed examination in less time ($p=0.012$), had better technical accuracy ($p<0.02$) than CG for first 10 endoscopic examinations in patients which persisted by the 51st to 60th examination ($p<0.003$). No difference in diagnostic accuracy between groups was found

Table 10.4 (Continued)

Investigators	Assessment procedure	Study population	Results
Fried et al. (2012) USA [40]	Sinus surgery	Otolaryngology residents	IG had faster mucosal injection time ($p=0.003$) and dissection time ($p<0.001$), fewer injection errors ($p=0.048$), greater surgical confidence (p 0.009), and higher level of dexterity ($p=0.011$) than CG
Ossowski et al. (2008) USA [41]	Flexible laryngoscopy	Medical students	No significant difference found between groups
Deutschmann et al. (2013) Canada [42]	Transnasal fiber-optic flexible laryngoscopy	Residents and medical students of otolaryngology	No statistically significant differences in qualitative or quantitative evaluation found between groups
Simulation training versus patient based training versus simulation plus patient-based training.			
Ende et al. (2012) Germany [43]	Esophagogastro-duodenoscopy	Medicine and surgery residents	Simulator plus patient-based training group had less time to intubate the esophagus than all other groups ($p=0.02$). Skills score was better for simulator plus patient-based training group than simulator group alone ($p<0.05$)
Haycock et al. (2010) UK [44]	Colonoscopy	Novice colonoscopists	No significant difference between simulation vs. patient-based groups in case completion, maximum tip position, time taken, straight insertion depth, and global score
Other procedures			
Simulation training versus no simulation training			
Bagai et al. (2012) Canada [45]	Cardiac catheterization	Cardiology trainees	IG had greater change in technical performance score from baseline to 1 week compared with CG ($p=0.04$)
Hseino et al. (2012) Ireland [46]	Superficial femoral artery angioplasty	General surgery residents	IG had higher score than CG on 12-item global rating scale ($p=0.003$) and procedure-specific checklist ($p=0.001$)
Howells et al. (2008) UK [47]	Knee arthroscopy	Junior orthopedic surgeons	IG had higher proportion of satisfactory scores on OSATS rating scale ($p=0.001$) and on OCAP checklist ($p=0.007$) compared with CG
Palter et al. (2011) Canada [48]	Abdominal fascia wall closure while listening to script	General surgery and Ob/Gyn residents	IG had higher cognitive skills ($p=0.03$) and OSATS score ($p=0.04$) compared with CG

Source: Adapted from Dawe et al. [49].
IG, intervention group; CG, control group; GOALS, Global Operative Assessment of Laparoscopic Skills; OSATS, Objective Structured Assessment of Technical Skills; OCAP, Orthopedic Competence Assessment Project; Ob/Gyn, obstetrics and gynecology.

among participants who were simulation-trained compared with those without.

Specifically within urology, a study by Källström et al. demonstrated improvement in the use of a resectoscope for a transurethral resection of the prostate (TURP) after undergoing a simulated TURP procedure. This improvement was observed when compared with baseline assessment (having no simulation). When participants with simulated TURP training were compared with participants with *in vivo* TURP training, there was no statistical difference between the groups [18]. Another study, by Schout et al., aimed to determine if participants trained in simulated flexible cystourethroscopy performed better than participants trained with the patient-based approach. The primary endpoint was the measurement of skills during a flexible cystourethroscopy case using a validated five-point scale. The results showed that the simulation group outperformed the patient-based group [19]. Overall, the review by Dawe et al. concluded that skills appear to be transferable from the simulation laboratory to the operating room and that, owing to the diversity of specialties and procedures studied, it is likely that these results may be generalizable.

Moreover, there may also be a benefit in using simulation as a means of reinforcement to improve long-term retention of knowledge and surgical skills. Madani et al. conducted a 1-year follow-up on an initial RCT of participants randomized to either a goal-directed simulation group or an unstructured control group for electrosurgery. Compared with baseline, the simulation group showed immediate improved knowledge assessment scores compared with control groups (89 vs. 83%, $p<0.05$). The 1-year follow-up assessment found that the simulation group retained higher scores than the control group (70 vs. 60%). A degradation in knowledge was found in both groups, suggesting the importance of skill reinforcement sessions [20].

While simulation may be used to teach an initial procedure or reinforce previously learned surgical skills, it may also be

used to mimic a stressful event for training purposes. For example, a study by Zattoni et al. simulated 20 emergencies during a robotic-assisted laparoscopic prostatectomy (RALP) requiring conversion to laparotomy. During the simulation, the most commonly occurring errors were robot replacement errors (70%) and spatial conflict and loss of sterility (50%), with communication errors, lack of leadership, and accidental fall of the surgical devices occurring <50%. As a result, procedure modifications were created to improve leadership, clearly define roles, and improve the overall knowledge base and surgical room organization. When the simulation was subsequently repeated, there was a 55% decrease in the time needed to convert to laparotomy compared with the initial simulation. Furthermore, after the simulation, the conversion was performed without errors. Although this study was limited to a small population and a single institution, it suggests a benefit for the simulation of critical events in the operating room [21].

Clinical implications

We suggest the routine implementation of surgical simulation to improve tactile and visual–spatial skills ultimately to improve outcomes in novice urological surgeons (conditional recommendation based on low-quality evidence).

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11 CHAPTER 11

Prophylaxis and treatment of urinary tract infections in adults

Gabrielle J. Williams[1,2], Angela C. Webster[1,2,3], and Jonathan C. Craig[1,2]

[1] *Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, Australia*

[2] *School of Public Health, University of Sydney, Sydney, NSW, Australia*

[3] *Centre for Transplant and Renal Research, Westmead Hospital, Westmead, NSW, Australia*

Introduction

Urinary tract infection (UTI) is the presence of a number of bacteria in the urine, typically defined as a threshold of $>10^8$ colony-forming units/L, accompanied by symptoms. The type of symptoms experienced can indicate whether the infection is limited to the bladder (cystitis) or involves the kidneys (pyelonephritis). Cystitis often involves symptoms such as dysuria, urgency, and frequency, and may include signs such as cloudy urine, hematuria, and pyuria. Symptoms of pyelonephritis include flank pain or back pain, fever, chills with shaking, feeling generally unwell, plus symptoms of cystitis. High amounts of bacteria can also be measured in people with no symptoms of illness (asymptomatic bacteriuria) but are screened as part of routine care, for example in pregnancy.

Treatment of cystitis and pyelonephritis is usually antibiotic therapy using various types of antibiotic for varying durations. This is largely effective in eradicating the bacteria and improving symptoms. Whether or not to treat asymptomatic bacteriuria depends on the clinical setting and the preferences of patient and clinician. Complimentary medicines such as cranberry products and probiotics are also used in the setting of UTI management and prevention.

Urinary tract infections (UTIs) are common; each year around 7% of children [1], 0.05% of men [2], and 10% of women [3] experience a UTI. Peak prevalence occurs in sexually active women aged 18–24 years [4]. The risk of recurrence of a UTI varies across age group; in children 12–20% [5, 6] and 21–44% in adult women [7]. Certainty around prevalence and recurrence rates in the elderly is more difficult to estimate because differentiating true symptomatic UTI from asymptomatic bacteriuria in the elderly is more difficult [8].

Management of UTI is a well-studied field and this chapter aims to bring together the latest, good-quality evidence around five clinical care decisions for adults experiencing a UTI. Systematic reviews and randomized controlled trials (RCTs) provide the highest level of evidence for treatment interventions and this chapter is limited to these types of studies.

Management options

Antibiotic treatment

Prescription of antibiotics for preventing and treating UTIs is the most commonly used strategy. Additionally, manipulation of comedications prescribed for comorbidity may be beneficial, as sedatives, narcotic analgesics, and anticholinergic drugs may contribute to urinary retention and so exacerbate symptoms and interfere with treatment of UTIs. The use of alpha-adrenergic blocking agents in appropriately screened men over 50 years old may also prove advantageous in reducing urinary retention caused by lower urinary tract symptoms.

Complimentary medicines

Cranberries have been used widely for the prevention and treatment of UTIs for several decades. Constituted of 90% water, cranberries also contain malic acid, citric acid, quinic acid, fructose, and glucose. Although controversial, it is proposed that fructose and proacanthocyanidins inhibit adherence of type 1 and α-galactose-specific fimbriated *Escherichia coli* to the uroepithelial cell lining of the bladder. Urinary acidification with vitamin C is also proposed, but a lack of evidence for its ability to alter urinary pH significantly and also concerns regarding the risk of calcium oxalate stone formation have limited its widespread use.

The concept of artificially boosting normal bacterial flora, using probiotics, to prevent the spread of pathogens has

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been considered and used by sections of the community. Observational studies often show a benefit in this treatment, but more rigorous evidence from RCTs is less definitive. In recent years, oral and vaginal estrogens have been considered for the prevention of repeat infections. This was based on the knowledge that estrogen receptors are present in the vagina, urethra, the trigone of the bladder, and pelvic floor musculature and the prevalence and recurrence risk of UTI in postmenopausal women. Observational studies and randomized trials of this treatment are being published. Additional complimentary treatments such as Chinese herbal medicines, vitamin D and various immunostimulants have also been explored for their efficacy in preventing repeat UTIs.

Clinical question 1

For people with a history of UTI, do cranberry products prevent the recurrence of UTI?

Literature search

The Cochrane Library, Cochrane Central Register of Controlled Trials, and MEDLINE were searched from 2008 (the year of the previous update) to June 2015. Terms included beverage, fruit, cranberry, phytotherapy, *Vaccinium macrocarpon*, *Vaccinium oxycoccus*, *Vaccinium vitisidaea*, urinary tract infection, bacteriuria, pyuria, UTI, cystitis, recurrence, reinfection, prophylaxis, and prevention.

The evidence

Three systematic reviews and six RCTs were identified and summarized (Table 11.1 [9–20]). The Jepson systematic review included 24 trials, the Wang review included 13 trials and the Beerepoot review included two trials. All trials in the Wang and Beerepoot reviews were included in the Jepson review. The six RCTs, published after the Jepson review, included two trials in elderly people, three trials in women, and one trial in adults with recurrent UTI.

The most complete evidence for cranberry products is the 2012 Jepson systematic review, which includes 24 trials

Table 11.1 Summary of the characteristics of the studies to address the question, "For people with a history of UTI, do cranberry products prevent the recurrence of UTI?"

Study ID	Study participants	Interventions	Description
Systematic reviews			
Beerepoot 2013 [9]	Women with recurrent UTI	Cranberry juice or tablets vs. placebo or no treatment	2 randomised trials (250 participants) (Both trials in Jepson and Wang reviews)
Jepson 2012 [10]	Women, elderly people, and children with recurrent UTI, pregnant women, cancer patients, and people with neuropathic bladder or spinal injury	Cranberry juice and/or capsules vs. placebo, no treatment, water, methenamine hippurate, antibiotics, or *Lactobacillus*	24 randomized trials (4473 participants). Data from 13 were synthesized in meta-analysis Duration, 6 weeks to 1 year; 12 trials used 6 months
Wang 2012 [11]	Women, elderly people, children with recurrent UTI, pregnant women, and people with neuropathic bladder	Cranberry juice or tablets vs. placebo, no treatment, or water	13 randomised trials (1616 participants) (All in Jepson review)
Randomized controlled trials			
Caljouw 2014 [12]	Elderly people with high risk of UTI	Cranberry capsule vs. placebo	458 people on cranberry capsule, 470 on placebo, 12 months of treatment
Dotis 2014 [13]	Children with recurrent UTI	Cranberry capsule vs. no treatment	38 on cranberry 38 not treated, 3 months of treatment
Fromentin 2014 [14]	Women with recurrent UTI	Cranberry powder vs. placebo	83 on cranberry, 93 on placebo, 6 months of treatment
Gautam 2014 [15]	People with recurrent UTI	Cranberry extract vs. placebo	36 on cranberry, 36 on placebo, 3 months of treatment
Afshar 2012 [16]	Children with recurrent UTI	Cranberry juice vs. placebo	20 children on cranberry juice, 20 on placebo, 12 months of treatment
Bianco 2012 [17] (+ Maddden 2015 [18])	Elderly women with recurrent UTI	Cranberry capsules, 1, 2, or 3 per day, vs. placebo	60 patients on cranberry, 20 on placebo, 1 month of treatment
Stapleton 2012 [19]	Women with recurrent UTI	Cranberry juice, 118 mL (4 oz) or 237 mL (8 oz), vs. placebo	63 given 4 oz juice, 62 given 8 oz juice, 31 on 4 oz placebo juice, and 30 on 8 oz placebo juice, 6 months of treatment
Vidlar 2011 [20]	Women with recurrent UTI	Cranberry powder vs. placebo	86 women taking cranberry, 79 on placebo, 6 months of treatment

Table 11.2 Summary of evidence of effects of cranberry products to prevent UTI in adults.

Study ID	Outcomes relevant to clinical question	Results
Systematic reviews		
Beerepoot 2013 [9]	UTI	Cranberries decreased UTI recurrence (RR 0.53, 95% CI 0.33 to 0.83)
Jepson 2012 [10]	Symptomatic UTI, adverse effects	Across all groups, no difference in frequency of symptomatic UTI (RR 0.86, 95% CI 0.71 to 1.04). No difference in women with recurrent UTIs (RR 0.74, 95% CI 0.42 to 1.31), older people (RR 0.75, 95% CI 0.39 to 1.44), pregnant women (RR 1.04, 95% CI 0.97 to 1.17), children with recurrent UTI (RR 0.48, 95% CI 0.19 to 1.22), cancer patients (RR 1.15 95% CI 0.75 to 1.77), or people with neuropathic bladder or spinal injury (RR 0.95, 95% CI: 0.75 to 1.20) Adverse effects were not well reported, but generally few and similarly distributed across the treatment groups
Wang 2012 [11]	UTI	Benefit in taking cranberry product to prevent UTI; RR 0.62 (95% CI 0.49 to 0.80)
Trials		
Caljouw 2014 [12]	UTI, hospitalization, mortality	Hazard ratio for cranberry tablets compared with placebo was 0.74 (95% CI 0.57–0.97). Hospitalization and mortality rates were equally distributed across the treatment groups
Dotis 2014 [13]	UTI, adverse events	Children on cranberry tablets had a lower percentage of UTIs than controls (18.4 vs. 63.2%). No adverse effects were experienced
Fromentin 2014 [14]	UTI, adverse events	The proportion of women experiencing at least one UTI was significantly lower in the cranberry group compared with placebo, 10.8 vs. 25.8%. No adverse events were experienced
Gautam 2014 [15]	UTI, adverse events	Recurrent UTI occurred less frequently in the cranberry group compared with the placebo group, 33.33 vs. 88.89%
Afshar 2012 [16]	UTI	65% reduction in the risk of UTI for children taking cranberry juice with active ingredient
Bianco 2012 [17] (+ Madden 2015 [18])	UTI	Older women taking cranberry juice had 58% lower odds of having bacteriuria and pyuria than controls
Stapleton 2012 [19]	UTI, adverse effects	Adjusted hazard ratio for UTI was 0.68 (95% CI 0.33 to 1.39). Minor adverse events occurred in 24.2% of those taking cranberry product and 12.5% in the placebo group
Vidlar 2011 [20]	UTI, adverse effects	50% absolute reduction in UTI recurrence rate for those taking cranberry powder. No adverse effects occurred

involving 4473 participants (Table 11.2). Thirteen studies evaluated only cranberry juice or concentrate, 10 studies used cranberry tablets, and one study evaluated both. The meta-analysis showed that cranberry products did not reduce the occurrence of symptomatic UTI when compared with placebo (risk ratio [RR] 0.86, 95% confidence interval [CI] 0.71 to 1.04). This finding remained true for the separate groups of women with recurrent UTI (RR 0.74, 95% CI 0.42 to 1.30), older people (RR 0.75, 95% CI 0.39 to 1.44), pregnant women (RR 1.04, 95% CI 0.97 to 1.17), children with recurrent UTI (RR 0.48, 95% CI 0.19 to 1.22), cancer patients (RR 1.15, 95% CI 0.75 to 1.77), and people with neuropathic bladder or spinal injury (RR 0.95, 95% CI 0.75 to 1.20). There was no significant difference between gastrointestinal adverse effects from cranberry product compared with those of placebo/no treatment (RR 0.83, 95% CI 0.31 to 2.27). A feature of many of the included trials was the high rate of treatment cessation by those assigned to cranberry juice and the poor reporting of the quantity of active ingredient in the juice and tablet products.

All trials in the Beerepoot and Wang reviews were included in the Jepson review and as such do not provide additional evidence.

Six RCTs in adults have been published after the systematic reviews. Five of the six trials reported a reduction in frequency of repeat urinary tract infections with cranberry products, although this was limited to only high risk long term care facility participants in the most robustly designed trial (Caljouw). Only three studies reported adverse events, with none occurring in two trials and minor gastrointestinal effects in one trial with 24.2% of cranberry treated participants affected compared with 12.5% in the placebo group.

Th quality of evidence

The 24 RCTs evaluated in the Jepson systematic review [10] were of variable quality, 14/24 described randomization adequately, 15/24 detailed allocation concealment, 17/24 had blinded participants and clinicians but only 11 had blinded outcomes assessors (Table 11.3). Nine trials showed evidence of incomplete reporting, mostly from loss to follow-up, and 14 showed or had possible other biases evident. These design issues limit the quality of the summarized evidence, meaning that there is considerable uncertainty in the findings.

The six RCTs published after the systematic review were variable in quality. Three were reported only as abstracts, so contained little methodological detail. Small study size

Table 11.3 GRADE profile of included studies addressing the question of whether cranberry products reduce the frequency of UTI recurrence in adults.

Study ID	Quality of included trials	Consistency	Directness	Precision	Other	Overall
Systematic reviews						
Beerepoot 2013 [9]	2/2 had adequate allocation concealment. 1 scored 3 on Jadad score and the other 5 (high)	I^2 = 0%, no heterogeneity	Direct comparisons with placebo and no treatment	Meta-analysis for efficacy		Limitations to evidence Does not provide good evidence to support a strong recommendation
Jepson 2012 [10]	14/24 trials described the randomization process 15/24 had adequate allocation concealment 17/24 used blinding	I^2 = 55%, moderate heterogeneity	Direct comparisons with placebo/no treatment, antibiotics, and probiotics	Meta-analysis for efficacy within population groups,for different comparators, for adverse effects and dose effects	High dropout rate for juice, uncertainty over effective dose	Reasonable evidence Does not support strong recommendation for efficacy of cranberry treatment
Wang 2012 [11]	4/14 trials described the randomization process 2/14 reported allocation concealment 14/14 used blinding	I^2 = 43%, moderate degree of heterogeneity	Direct comparisons with placebo/no treatment	Meta-analysis for efficacy within population groups, by age > or < 18 years), juice alone or juice/tablet, and by dose	10/14 were considered at high risk of bias from selective reporting	Limitations to evidence Does not support efficacy of cranberry treatment
Trials						
Caljouw 2014 [12]	Computer-generated randomization sequence Adequate allocation concealment Participants, clinicians, and outcome assessors blind	–	Direct comparisons between cranberry and placebo tablets	928 patients, 194 UTI events. Confidence intervals reported	14 participants had incomplete follow-up due to study cessation	Results are valid (no difference for low-risk participants, may reduce symptoms in high-risk participants but not of a strictly defined UTI)
Dotis 2014 [13]	Randomization process, not stated Allocation concealment, not stated Blinding, not reported	–	Direct comparison between cranberry and no treatment	76 children, 31 children had a UTI. No confidence intervals reported	Published as abstract only	Uncertain validity
Fromentin 2014 [14]	Randomization, not stated Allocation concealment, not stated Participants and clinicians blinded, uncertain blinding of outcome assessors	–	Direct comparison between cranberry product and placebo	179 patients, 33 people had a UTI. No confidence intervals	Published as abstract only	Uncertain validity
Gautam 2014 [15]	Randomization, not stated Allocation concealment, not stated Blinding; not stated	–	Direct comparison between cranberry product and placebo	Few details reported, not able to determine	Published as abstract only	Uncertain validity

Afshar 2012 [16]	Randomization, computer generated Allocation concealment was adequate Participants, clinicians, and outcome assessors blind	–	Direct comparison between cranberry juice with proanthocyanidin and juice without proanthocyanidin	40 children, 13 children had a UTI event	12/40 children did not complete the study	Does not provide good evidence to support a strong recommendation
Bianco 2012 [17] (+ Madden 2015 [18])	Randomization, not stated Allocation concealment, not stated Participants blinded	–	Direct comparison of 2 cranberry tablets, 1 tablet and placebo	80 patients,298 cultures, 141 events. No confidence intervals reported	Outcome is inflated by using culture as the unit of analysis rather than the patient	Does not provide good evidence to support a strong recommendation
Stapleton 2012 [19]	Computer-generated randomization Adequate allocation concealment Participants, clinicians, and outcome assessors blind	–	Direct comparisons between 2 volumes of cranberry juice and placebo	176 patients, 50 women had UTIs		Results are valid (no difference between cranberry and placebo)
Vidlar 2011 [20]	Randomisation, not stated Allocation concealment, not stated Blinding, uncertain	–	Direct comparison of cranberry powder and placebo	165 patients, 32 events. Wide confidence intervals reported	Published as abstract only. States more outcomes than were reported	Does not provide good evidence to support a strong recommendation

and limitations to reported trial design make five of these trials of uncertain validity. Only the Caljouw trial was well designed and reported. Trial results in the Jepson systematic review were moderately variable with an I^2 measure of 55%. Findings from subsequent trials were reasonably consistent in that most measured a benefit to cranberry treatment. However, the size of the effect was measured in different ways, for example, the proportion of people experiencing a UTI, hazard ratio, odds ratio, and absolute rate reduction, and this made it difficult to compare the size of the treatment benefit across different studies. Confidence intervals were provided for all analyses in the Jepson review and all crossed 1, the point of no effect, demonstrating that cranberry products provide no real benefit in preventing UTI. Only two of the six subsequent trials reported a confidence interval, demonstrating poor reporting and suggesting low-quality evidence.

Clinical implications

We suggest against the use of cranberry products to reduce the risk of subsequent UTI in susceptible people (conditional recommendation based on low-quality evidence).

Clinical question 2

For people with a history of UTI, do prophylactic antibiotics reduce the frequency of subsequent infection?

Literature search

The Cochrane Library, Cochrane Central Register of Controlled Trials, and MEDLINE were searched from 2008 (the year of the previous update) to June 2015. Terms included urinary tract infection, bacteriuria, pyuria, UTI, cystitis, recurrence, reinfection, prophylaxis, prevention, anti-infective agents, antibiotics, and 28 specified antibiotic names, and excluded any with child in the title.

The evidence

The study characteristics are summarized in Table 11.4 [21–24]. A systematic review by Schneeberger [21] of antibiotic treatment with nitrofurantoin compared with surveillance, in pregnant women, was identified, but it included only a single trial of 200 women. Three additional RCTs that were published after the Schneeberger review were identified. The Constantini trial included 152 women with recurrent UTI, the Nachum trial included 226 postpartum women who had experienced UTIs during their pregnancies, and the Zhong trial included 81 postmenopausal women with recurrent UTI. The Constantini trial compared fosfomycin and prulifloxacin, the Nachum trial compared continuation of prophylactic antibiotics for 6 weeks after birth to cessation of antibiotics at delivery, and the Zhong trial compared continuous antibiotic use with patient-initiated single-dose antibiotic treatment.

The Schneeberger systematic review of prophylaxis in pregnant women showed no difference in the risk of recurrent pyelonephritis (RR 0.89, 95% CI 0.31 to 2.53), or in recurrent UTI before birth, (RR 0.30, 95% CI 0.06 to 1.38), preterm birth (RR 1.18, 95% CI 0.42 to 3.35) or asymptomatic bacteriuria (RR 0.55, 95% CI 0.34 to 0.89) with antibiotic prophylaxis compared with surveillance (Table 11.5). Adverse events were not reported.

The two RCTs also showed no difference between the two antibiotic regimens (Costantini trial), no benefit in continuation of prophylaxis after birth (Nachum trial), and both intermittent and continuous antibiotics were similarly effective in reducing the number of repeat infections in postmenopausal women (Zhong trial). No difference in adverse

Table 11.4 Summary of the characteristics of the studies to address the question "For people with a history of UTI, do prophylactic antibiotics reduce the frequency of subsequent infection?"

Study ID	Study participants	Interventions	Description
Systematic reviews			
Schneeberger 2012 [21]	Pregnant women	Nitrofurantoin vs. surveillance	One trial involving 200 women Duration of treatment was the remainder of pregnancy
Randomized controlled trials			
Costantini 2014 [22]	Women with recurrent UTI	Prulifloxacin vs. fosfomycin	76 on prulifloxacin, 76 on fosfomycin 3 months of treatment
Nachum 2015 [23]	Postpartum women who experienced recurrent UTI during pregnancy	Prophylactic antibiotics continued for 6 weeks after birth vs. prophylactic antibiotics ceased at delivery	110 women continued antibiotics for 6 weeks after giving birth, 116 ceased antibiotics after giving birth
Zhong 2011 [24]	Postmenopausal women with recurrent UTI	Continuous low dose vs. patient-initiated single dose	41 women assigned to intermittent dose, 42 assigned to continuous dose for 12 months

Table 11.5 Summary of evidence of effects of prophylactic antibiotics for preventing repeat UTI.

Study ID	Outcomes relevant to clinical question	Results
Systematic review		
Schneeberger 2012 [21]	Recurrent pyelonephritis, recurrent UTI before birth, premature birth, asymptomatic bacteriuria	No difference in recurrent pyelonephritis (RR 0.89, 95% CI 0.31 to 2.53), recurrent UTI before birth (RR 0.30, 95% CI 0.06 to 1.38), preterm birth (RR 1.18, 95% CI 0.42 to 3.35), asymptomatic bacteriuria (RR 0.55, 95% CI 0.34 to 0.89)
Randomized controlled trials		
Costantini 2014 [22]	UTI, disease-free duration, quality of life	No significant differences in UTI were found between the prulifloxacin and fosfomycin groups. No difference in disease-free duration was seen between the two therapy groups. Mean scores for quality of life were similar across the treatment groups (5.51 in prulifloxacin group and 5.59 in fosfomycin group)
Nachum 2015 [23]	Recurrent UTI, pyelonephritis, adverse events	No statistical difference in recurrence of UTI was seen between women given prophylactic antibiotics and those not treated (22 vs. 40%). One untreated woman was hospitalized for pyelonephritis. Two treated patients stopped the antibiotics due to abdominal pain and vulvovaginal candidiasis
Zhong 2011 [24]	UTI episodes/year, adverse effects	No statistical difference in recurrence of UTI in the continuous vs. intermittent dose groups. Adverse effects in the intermittent group were less frequent than in the continuous treatment group

events (diarrhea, gastric pain, nausea, vomiting, and vaginitis) was seen in the Costantini trial. Two of 54 women taking antibiotics ceased treatment due to abdominal pain and vulvovaginal candidiasis in the Nachum trial. Adverse events were significantly lower in the single dose compared with the continuous treatment groups in the Zhong trial (63.6 versus 92.5%)

The quality of evidence

The single trial in the Schneeberger review was poorly reported, with considerable post-randomization loss to follow-up (33/200; 16.5%), making this evidence uncertain (Table 11.6). The other three trials were variable in the quality of their reported methods, resulting in uncertain validity. Each of the four trials included in this section addressed different questions but were consistent in finding no differences between specific treatment options. The 95% confidence intervals were reported in the Schneeberger review and were wide, showing imprecision. None of the other three trials reported a confidence interval around the primary outcome.

Clinical implications

We are unable to recommend for or against prophylactic antibiotics to prevent recurrent UTI in pregnant women (insufficient evidence). We do not recommend any specific antibiotic treatment over another for women with a history of recurrence or postmenopausal women (insufficient evidence)

Clinical question 3

For people with a history of UTI, are nonantibiotic therapies effective in reducing the frequency of subsequent infections?

Literature search

The Cochrane Library, Cochrane Central Register of Controlled Trials, and MEDLINE were searched from 2008 (the year of the previous update) to June 2015. Terms included urinary tract infection, bacteriuria, pyuria, UTI, cystitis, recurrence, reinfection, prophylaxis, prevention, and antiinfective agents.

The evidence

Four systematic reviews of nonantibiotic treatments to prevent repeat UTI in susceptible people were identified (Table 11.7 [9, 25–38]). Chinese herbal medicines were evaluated in a systematic review of seven trials by Flower [25]. Treatment periods ranged from 3 weeks to 4 months and follow-up ranged from 3 to 6 months. The Beerepoot systematic review included trials of oral immunostimulant OM-89 (four trials), vaginal vaccine Solco-Urovac (three trials), oral/vaginal estrogens (four trials), cranberries (two trials), acupuncture (two trials), *Lactobacilli* (two trials), and *Armoraciae rusticanae radix* and *Tropaeoli majoris herba* (one trial). Treatment durations ranged from 3 weeks to12 months.

Table 11.6 GRADE profile of included studies addressing the question of whether prophylactic antibiotics reduce the frequency of subsequent UTI in adults.

Study ID	Quality of included trials	Consistency	Directness	Precision	Other	Overall
Systematic review						
Schneeberger 2012 [21]	Randomization using random number table Allocation concealment was unclear No blinding was used (Single trial only)	Not appropriate (single study)	Direct comparison of antibiotic (nitrofurantoin) with no treatment	167 patients, 13 UTI events. 95% CI 0.31 to 2.53	18/200 lost to follow-up	Does not provide good evidence to support a strong recommendation
Trials						
Costantini 2014 [22]	Computer-generated randomization sequence Adequate allocation concealment No blinding	–	Direct comparison between prulifloxicin and fosfomycin	152 patients, number of patients experiencing a UTI was not reported	28/152 lost to follow up	Does not provide good evidence to support a strong recommendation
Nachum 2015 [23]	Randomization, not stated Allocation concealment, not stated Blinding, not stated	–	Direct comparison between prophylactic antibiotics and no treatment	226 randomized, 97 patients completed, 29 patients had a UTI. Confidence intervals not reported	Published as abstract only. 129 lost to follow-up	Uncertain validity
Zhong 2011 [24]	Random numbers table for randomization Allocation concealment uncertain Blinding; not reported	–	Direct comparison between continuous and intermittent doses of antibiotic	68 women completed the study, 59 UTIs in the intermittent group, 52 UTIs in the continuous group	15/81 dropped out and not analyzed	Uncertain validity

Table 11.7 Summary of the characteristics of the studies to answer the question, "For people with a history of UTI, are nonantibiotic therapies effective in reducing the frequency of subsequent infections?"

Study ID	Study participants	Interventions	Description
Systematic reviews			
Flower 2015 [25]	Adult women	Chinese herbal medicine vs. conventional antibiotic treatments (3) Chinese herbal medicine plus antibiotics vs. antibiotics alone (2) Two different Chinese herbal medicine regimens (2)	7 RCTs involving 542 women Treatment duration 3 weeks to 4 months, follow-up 3 to 6 months
Beerepoot 2013 [9]	Women (13 studies) Men and women (3 studies)	Oral immunostimulant OM-89 (4 trials) Vaginal vaccine Solco-Urovac (3 trials) Oral/vaginal estrogens (4 trials) Cranberries (2 trials) Acupuncture (2 trials) Lactobacilli (2 trials) *Armoraciae rusticanae radix* and *Tropaeoli majoris herba* (horseradish and nasturtium) (1 trial)	17 trials with data for 2165 patients
Lee 2012 [26]	Heterogeneous groups at risk of UTI	Methenamine hippurate vs. placebo, dose comparisons, vs. antibiotics, with cranberry	13 studies, 2032 participants Treatment duration 7 days to 1 year
Perrotta 2008 [27]	Postmenopausal women with recurrent UTI	Oral/vaginal oestrogen vs. placebo or antibiotics	9 studies in 3345 women Treatment duration 12 weeks to 4 years
Randomized controlled trials			
Minardi 2015 [28]	Women with recurrent UTI and dysfunctional voiding	Uroflowmetry biofeedback (group 1) vs. α_1-AR antagonists (group 2) vs. uroflowmetry biofeedback combined with α_1-AR antagonists (group 3) vs. no treatment (group 4)	128 women, 35 treated with uroflowmetry, 38 α_1-AR antagonists, 37 uroflowmetry biofeedback combined with α_1-AR antagonists and 18 in the no treatment group, 12 months follow-up
Kochiashvili 2014 [29]	Adults with recurrent UTI	Solco-Urovac vs. no treatment	50 (32 men, 18 women) given Solco-Urovac, 65 no treatment
Kranjčec 2014 [30] (+ Altarac 2014 [31])	Women with recurrent UTI	D-Mannose powder daily for 6 months vs. 50 mg of nitrofurantoin once per day vs. no treatment	103 on D-mannose, 103 on nitrofuratoin, 102 on no treatment
Porru 2014 [32]	Women with recurrent UTI	Oral D-mannose vs. trimethoprim/sulfamethoxazole	60 patients, cross-over design
Pouwels 2013 [33]	Adults with persistent proteinuria	Pravastatin alone, fosinopril alone, pravastatin and fosinopril, or placebo	655 participants, 169 on placebo, 158 on pravastatin, 160 on fosinopril, 168 on both pravastatin and fosinopril. 4 years follow-up
Stepanova 2013 [34]	Women with recurrent UTI	Ciprofloxacin vs. oral lactobacilli	85 women, 12 months follow-up
Damiano 2011 [35]	Women with recurrent UTI	Hyaluronic acid and chondroitin sulfate vs. placebo	28 on hyaluronic acid/chondroitin sulfate, 29 on placebo
Krcméry 2010 [36]	Women with recurrent UTI	Urovaxom vs. Luivac then 12 months of fluoroquinolones or no treatment	85 on Urovaxom, 84 on Luivac
Skerk 2010 [37]	Women with recurrent UTI	Acidosalus® probiotic vs. no treatment	56 received probiotic for 3 months, 61 received no treatment
Czaja 2007 [38]	Premenopausal women with recurrent UTI	*Lactobacillus crispatus* vaginal suppository vs. placebo suppository	15 received *Lacotobacillus*, 15 received placebo suppositories

The Lee systematic review included 13 trials that evaluated methenamine hippurate against placebo, antibiotics, and cranberry products and also dose comparisons. Duration of treatment was reported in 11 of 13 trials and ranged from 7 days to 1 year.

The Perrotta systematic review included nine trials of oral or vaginal estrogen compared with placebo or no treatment in postmenopausal women with recurrent UTI. One trial did not report treatment duration and in the remaining eight trials the duration of treatment ranged from 12 weeks to 4 years. The four trials of estrogen included in the Beerepoot systematic review were included in the Perrotta systematic review.

Nine additional RCTs of nonantibiotic products for prevention of UTI were identified. Treatments studied included uroflowmetry biofeedback, alpha-1 adrenergic antagonists, immunoactive agents such as Solco-Urovac, D-mannose, statins, and probiotics using *Lactobacillus* products.

The Flower systematic review showed a greater efficacy in treating acute UTI with Chinese herbal medicines than antibiotics and reduced recurrent UTI rates (RR 0.28, 95% CI 0.09 to 0.82). Two trials combining antibiotics and Chinese herbal medicines showed greater efficacy in treating the UTI and lower frequency of repeat UTI 6 months after treatment cessation (Table 11.8) Two of seven trials reported there were no adverse effects.

Results from the Beerepoot systematic review showed that the oral immunostimulant OM-89 decreased the rate of UTI recurrence (RR 0.61, 95% CI 0.48 to 0.78), as did the vaginal vaccine Solco-Urovac (RR 0.81, 95% CI 0.68 to 0.96). Probiotic *Lactobacillus* did not reduce repeat UTI. Trials of immunostimulant showed comparable rates of adverse effects (headache, gastrointestinal complaints, allergic reaction) across the groups. Some 27.8% of women experienced vaginal irritation in the trials of vaginal vaccine.

The Lee systematic review of trials of methenamine hippurate showed that there may be a benefit in patients without renal tract abnormalities (symptomatic UTI: RR 0.24, 95% CI 0.07 to 0.89). All trials reported low rates of adverse events.

The Perrotta review of estrogens showed that vaginal estrogen reduced UTI recurrence (RR 0.25, 95% CI 0.13 to 0.50 in one trial and RR 0.64, 95% CI 0.47 to 0.86 in the other) but oral estrogens did not (RR 1.08, 95% CI 0.88 to 1.33). Adverse events for vaginal estrogens were breast tenderness, vaginal bleeding or spotting, nonphysiological discharge, vaginal irritation, burning, and itching. Results from the other individual trials were highly variable (Table 11.8).

The quality of evidence

All seven trials included in the Flower systematic review were suboptimal in design (Table 11.9). All seven reported an adequate randomization process but other design features were less robust. Trials summarized in the Beerepoot review were of variable quality, with poor reporting of methodology. The Lee systematic review included poorly reported trials with few well-designed trials. The Perrotta review reported that one of nine trials detailed adequate allocation concealment. Randomization was not stated in the review and eight of nine trials reporting the use of blinding.

Of the nine randomized trials identified, all failed to report allocation concealment. Only two trials stated blinding and loss to follow-up. Methodological issues across all trials led to uncertainty in the validity of each trial's findings. The four systematic reviews showed a benefit to active treatment, but most included trials were poorly designed. Two of the nine trials involved probiotic treatment and found different effects. Two trials analyzed D-mannose treatment and both reported a possible benefit. The remaining trials examined different interventions. Each systematic review provided confidence intervals around point estimates and these varied from small (0.48–0.78) to very wide (1.1–33). Precision was unclear across many of the trials since not all point estimates had confidence intervals. Sample sizes were generally low and event rates variable.

Clinical implications

We suggest that oral estrogen therapy, oral immunostimulants, vaginal vaccine, probiotics, D-mannose, and uroflowmetry treatments should not be used to prevent repeat UTI (conditional recommendation against based on very low-quality evidence). We are unable to make a recommendation for or against vaginal estrogen therapy, methenamine hippurate, and Chinese herbal medicines, which may reduce the risk of repeat infection and appear to have few adverse effects.

Clinical question 4

For people with UTI, which antibiotic is most effective for treating the infection?

Literature search

The Cochrane Library, Cochrane Central Register of Controlled Trials, and MEDLINE were searched from 2008 (the year of the previous update) to June 2015. Terms included urinary tract infection, bacteriuria, pyuria, UTI, cystitis, anti-infective agent, trimethoprim, sulfamethoxazole, cotrimoxazole, ciprofloxacin, ofloxacin, nitrofurantoin, and norfloxacin.

The evidence

Four systematic reviews and five randomized trials were identified (Table 11.10 [39–47]). The Vasquez systematic review included 10 trials of treatment for symptomatic UTI in pregnant women looking at antibiotic type and

Table 11.8 Summary of evidence of effects of non-antibiotic therapies for prevention of UTI in adults.

Study ID	Outcomes relevant to clinical question	Results
Systematic reviews		
Flower 2015 [25]	UTI, adverse effects, quality of life	Three studies involving 282 women that looked at Chinese herbal medicines vs. antibiotics suggested that Chinese herbal medicines had a higher rate of effectiveness for acute UTI (RR 1.21, 95% CI 1.11 to 33) and reduced recurrent UTI rates (RR 0.28, 95% CI 0.09 to 0.82). Two studies involving 120 women that compared Chinese herbal medicines plus antibiotics vs. antibiotics alone found the combined intervention had a higher rate of effectiveness for acute UTI (RR 1.24, 95% CI 1.04 to 1.47) and resulted in lower rates of recurrent infection 6 months after the study (RR 0.53, 95% CI 0.35 to 0.80)
Beerepoot 2013 [9]	Recurrent UTI, adverse effects	Oral immunostimulant OM-89 decreased the rate of UTI recurrence (RR 0.61, 95% CI 0.48 to 0.78). vaginal vaccine Solco-Urovac slightly reduced UTI recurrence (RR 0.81, 95% CI 0.68 to 0.96), Vaginal estrogens showed a trend towards preventing UTI recurrence (RR 0.42, 95% CI 0.16 to 1.10) but vaginal irritation occurred in 6–20% of women. Oral estrogens and lactobacilli prophylaxis did not decrease the rate of UTI recurrence
Lee 2012 [26]	Symptomatic UTI	Methenamine hippurate may have some benefit in patients without renal tract abnormalities (symptomatic UTI: RR 0.24, 95% CI 0.07 to 0.89). For short-term treatment duration (1 week or less) there was a significant reduction in symptomatic UTI in those without renal tract abnormalities (RR 0.14, 95% CI 0.05 to 0.38). The rate of adverse events was low
Perrotta 2008 [27]	Recurrent UTI	Oral estrogens did not reduce UTI compared with placebo (4 studies, 2798 women: RR 1.08, 95% CI 0.88 to 1.33). Vaginal estrogens vs. placebo reduced the number of women with UTIs in two small studies using different application methods. The RR was 0.25 (95% CI 0.13 to 0.50) in one and 0.64 (95% CI 0.47 to 0.86) in the other
Randomized controlled trials		
Minardi 2015 [28]	Urodynamic studies, repeat UTI	The prevalence of UTI decreased significantly in all active treatment groups after treatment (7/27, 7/30, 6/28) compared with no treatment (17/18) and this decrease remained stable during the follow-up
Kochiashvili 2014 [29]	Symptom relief repeat UTI	4/50 in the Solco-Urovac group experienced a UTI and 15/57 in the untreated group had a repeat infection during the 6 months of follow-up
Kranjčec 2014 [30] (+ Altarec 2014 [31])	Recurrent UTI, adverse effects	15/103 women on D-mannose powder had a UTI, 21/103 women taking nitrofurantoin and 62/102 women on no treatment had a UTI during 6 months of follow-up. D-Mannose patients had a lower risk of side effects compared with nitrofurantoin (RR 0.276)
Porru 2014 [32]	Time to UTI recurrence, bladder pain, urinary urgency	Mean time to UTI recurrence was 52.7 days with antibiotic treatment and 200 days on oral D-mannose. Bladder pain and urgency scores decreased during D-mannose treatment
Pouwels 2013 [33]	Number of UTIs, occurrence of first UTI antibiotic prescription, second UTI prescription	Pravastatin was associated with a reduced total number of UTI antibiotic prescriptions (RR 0.43, 95% CI 0.21 to 0.88)and occurrence of a second UTI antibiotic prescription (HR 0.25, 95% CI 0.08 to 0.77). Fosinopril was associated with an increased occurrence of first UTI antibiotic prescription (HR 1.82, 95% CI 1.16 to 2.88)
Stepanova 2013 [34]	Recurrent UTI	Mean number of UTI recurrences after 12 months of treatment with ciprofloxacin was 1.8 and after lactobacilli treatment 2.7. Median time to first UTI was 8.2 monmths in the ciprofloxacin group and 3.8 monmths in the lactobacilli group
Damiano 2011 [35]	Recurrent UTI, quality of life, adverse effects	15/28 women on hyaluronic acid and chondroitin sulfate treatment had at least one UTI over the 12 months while 29/29 in the placebo group experienced at least one UTI. Quality of life scores for pelvic pain and urgency/frequency were significantly improved. No adverse effects were experienced
Krcméry 2010 [36]	Recurrent UTI	Decreased rate of recurrences over 12 months, 3.6 down to 0.48 UTIs/year Urovaxom, 3.6 to 0.41 UTIs/year Luivac. 36/85 had a UTI on Urovaxom, 33/84 had a UTI on Luivac
Skerk 2010 [37]	Recurrent UTI	Fewer women taking probiotics experienced a UTI, 3/56 (5.4%), compared with women not taking probiotics, 11/56 (18.3%)
Czaja 2007 [38]	Recurrent UTI	4/9 taking *Lactobacillus* and 1/10 on placebo experienced cystitis at 6 months

Table 11.9 GRADE profile of included studies addressing whether there is effective nonantibiotic treatment to prevent subsequent UTI in adults.

Study ID	Quality of included trials	Consistency	Directness	Precision	Other	Overall
Systematic review						
Flower 2015 [25]	Randomization, 7/7 trials adequate randomization processes Allocation conealment, 7/7 did not report details Blinding, 6/7 trials did not blind participants and none reported blinding of outcome assessors	I^2 was 0% for 4 of 5 analyses and 80% for the outcomes of UTI recurrence	Direct comparisons between Chinese herbal medicines and antibiotic treatment	542 women, 95% CIs reported for each analysis		Limitations to evidence, studies are poorly reported
Beerepoot 2013 [9]	5/15 trials rated as adequate allocation concealment. 2 trials rated 5 on Jadad score (high), 4 trials rated 4, 6 trials rated 3, 2 trials rated 3 and 1 trial rated 1 Blinding, not reported	I^2 ranged from 0 to 85.3%	Direct comparisons with placebo/no treatment	Meta-analysis for efficacy of each different intervention. 95% CIs provided		Limitations to evidence. Does not provide good evidence to support a strong recommendation
Lee 2012 [26]	3/13 trials had adequate randomization 2/13 trials reported as adequate allocation concealment 1/13 used blinding for participants, clinicians, and outcome assessors, 5/13 used blinding for participants	I^2 for the primary meta-analysis was 72%.	Direct comparisons between treatment options and placebo	Most point estimates of the multiple meta-analyses favored the intervention but 95% CIs crossed 1, no effect. Estimates in people with renal tract abnormalities favored controls but with large CIs		Limitations to evidence. Does not provide good evidence to support a strong recommendation
Perrotta 2008 [27]	Randomization method was not detailed 1/9 trials reported adequate allocation concealment 8/9 trials used blinding	I^2 for the primary and several subgroup analyses was 0% and 99% for vaginal oestrogens vs. antibiotics	Direct comparisons for all analyses, 6/9 with placebo, 1/9 with no treatment, and 2/9 compared with antibiotics	Point estimates were variable and all 95%CIs crossed 1		Limitations to evidence. Does not provide good evidence to support a strong recommendation
Trials						
Kochiashvili 2014 [29]	Randomization method, not stated Allocation concealment, not stated Not blinded	–	Direct comparisons	115 patients, 52 had a UTI		Uncertain validity
Kranjčec 2014 [30] (+ Altarac 2014 [31])	Randomization by dice thrown Allocation concealment using sealed envelopes Blinding, not stated	–	Direct comparisons	308 patients, 98 had a UTI. CIs reported		Uncertain validity
Porru 2014 [32]	Randomization method, not stated Allocation concealment, not stated Blinding, not stated	–	Direct comparisons	60 patients, 55 had a UTI. No CIs reported		Uncertain validity

Pouwels 2013 [33]	Randomization, not stated Allocation concealment, not stated Blinding, double blinded	–	Direct comparisons	655 patients analyzed, 189 scripts for UTI antibiotics in 112 participants were identified		Uncertain validity
Stepanova 2013 [34]	Randomization, not stated Allocation concealment, not stated Blinding, not blinded, open label	–	Direct comparison	85 patients, 12 had a UTI		Uncertain validity
Damiano 2011 [35]	Randomization method, computer-generated list Allocation concealment, adequate Double blinded	–	Direct comparisons	57 patients, 44 had a UTI. CIs reported	3/30 lost to follow-up	Uncertain validity
Krcméry 2010 [36]	Randomization method, not stated Allocation concealment, not stated Blinding, unclear	–	Direct comparisons	169 patients, 69 patients had a UTI. CIs reported		Uncertain validity
Skerk 2010 [37]	Randomization method, not stated Allocation concealment, not stated Blinding, not blinded, open label	–	Direct comparisons	117 patients, 14 had a UTI		Uncertain validity
Czaja 2007 [38]	Randomization method, not stated Allocation concealment, nt stated Double blinded	–	Direct comparisons	30 patients, UTI events not reported	Focus is tolerability not efficacy	Uncertain validity

Table 11.10 Summary of the characteristics of the studies addressing the question, "For people with UTI, which antibiotic is most effective for treating the infection?"

Study ID	Study participants	Interventions	Description
Systematic reviews			
Vasquez 2011 [39]	Pregnant women	Various antibiotic types, IV and oral comparisons, and duration of treatment comparisons	10 studies, 1125 pregnant women
Guinto 2010 [40]	Pregnant women (asymptomatic bacteriuria)	Single dose fosfomycin Trometamol vs. 5-day course of twice-daily cefuroxime (1) Pivmecillinam vs. ampicillin (1) Cephalexin vs. pivmecillinam/pivampicillin (1) Nitrofurantoin, 1 day vs. 7 days (1) Cycloserine vs. sulfadimidine (1)	5 studies, 1140 women
Zalmanovici-Trestioreanu 2010 [41]	Adult women with uncomplicated UTI	Nalidixic acid vs. a beta-lactam (1) Fluoroquinolone vs. a beta-lactam (5) Nitrofurantoin vs. TMP-SMX (4) TMP-SMX vs. a beta-lactam (5) Fluoroquinolones vs. TMP-SMX (8) Nitrofurantoin vs. a beta-lactam (2)	21 studies, 6016 participants
Rafalsky 2006 [42]	Women ≥16 years old with uncomplicated acute cystitis	Different quinolones compared	11 trials, 7535 women
Randomized controlled trials			
Monsen 2013 [43]	Adult women with UTI	Pivmecillinam (3 different regimens) vs. placebo	855 on pivmecillinam, 288 on placebo
Akarsu 2010 [44]	Pregnant women, asymptomatic and symptomatic for UTI	Single dose of 3 g fosfomycin trometamol and 7 days of 675 mg amoxicillin–clavulanic acid	22 asymptomatic and 20 symptomatic women, given single-dose fosfomycin
Bleidorn 2010 [45]	Adult women with uncomplicated UTI	Ibroprofen 3× 400 mg daily for 3 days vs. ciprofloxacin 2× 250 mg daily for 3 days	36 on ibroprofen, 33 on ciprofloxacin
Ceran 2010 [46]	Adult women with uncomplicated UTI	Single-dose fosfomycin vs. 5-day ciprofloxacin	77 allocated to fosfomycin, 65 to ciprofloxacin
Estebanez 2009 [47]	Pregnant women with asymptomatic UTI	Single dose of 3 g of fosfomycin vs. 7 days of amoxicillin clavulanate	53 women allocated to fosfomycin, 56 given amoxicillin clavulanate

duration. The Guinto review included five trials involving 1140 pregnant women with asymptomatic bacteriuria. The Zalmanovici-Trestioreanu systematic review included 21 trials of treatment for symptomatic UTI in nonpregnant women. The Rafalsky review included 11 studies looking at different quinolones for treating cystitis in nonpregnant women. A single trial was common to both the Zalmonovici-Trestioreanu and Rafalsky reviews.

Additional trials published after the systematic reviews included pregnant women (two trials, Akarsu and Estebanez,151 women) and adult women with UTI (three trials Monsen, Bleidorn, and Ceran, 1354 women). All comparisons of different antibiotic treatments were confounded by differences in treatment dose or duration.

The Vasquez systematic review reported a single significant difference; a lower cure rate for cephradine compared with cefuroxime (Table 11.11). The review states that adverse events were reported in few women. Few significant differences in efficacy were seen between the various antibiotics used in the trials included in the Guinto and Zalmanovicic-Trestioreanu systematic reviews. No difference between various quinolones was identified in the Rafalsky review. One trial in the Guinto systematic review reported a significant difference in frequency of vomiting in patients taking pivmecillinam compared with ampicillin. The Zalmanovicic-Trestioreanu review reported that rashes were more frequent in patients treated with trimethoprim–sulfamethoxazole than with nitrofurantoin or fluoroquinolones and in patients treated with beta-lactam drugs compared with fluoroquinolones. Nine trials reported adverse events in the Raflasky review but no pooled results were possible.

The three trials comparing two antibiotic treatments (the Akarsu, Ceran, and Estebanez trials) reported similar efficacy for the different antibiotic options. The two trials comparing an antibiotic with placebo (the Monsen trial) or ibuprofen pain relief (the Bleidorn trial) reported superiority of antibiotic treatment. The Akarsu trial reported no adverse events, In the Estebanez trial, nausea, vomiting, and diarrhea were more frequent in the amoxicillin clavulate-treated group compared with the fosfomycin-treated group. In the Ceran

Table 11.11 Summary of evidence for which antibiotic is most effective in treating UTI in adults.

Study ID	Outcomes relevant to clinical question	Results
Systematic reviews		
Vasquez 2011 [39]	UTI "cure," recurrence of UTI, preterm delivery, admission to neonatal ICU, need to change antibiotic, prolonged pyrexia	1 trial of cephradine vs. cefuroxime showed lower cure rates for cephradine (RR 0.75, 95% CI 0.57 to 0.99) and more frequent recurrences. No other comparisons between different antibiotics showed significant difference. No significant differences in preterm delivery, neonatal ICU admission, need to change antibiotics, and incidence of prolonged pyrexia were seen
Guinto 2010 [40]	Persistent or recurrent infection	One trial reported an advantage with a longer course of nitrofurantoin, a second trial reported better tolerability with ampicillin compared with pivmecillinam. For the remaining findings, there was no significant difference demonstrated between groups treated with different antibiotics
Zalmanovici-Trestioreanu 2010 [41]	Cure of UTI symptoms, bacteriological cure, adverse effects, bacterial resistance	Trimethoprim–sulfamethoxazole was as effective as fluoroquinolones in achieving short-term (RR 1.00, 95% CI 0.97 to 1.03) and long-term (RR 0.99, 95% CI 0.94 to 1.05) symptomatic cure. Beta-lactam drugs were as effective as trimethoprim–sulphamethoxazole for short-term (RR 0.95, 95% CI 0.81 to 1.12) and long-term (RR 1.06, 95% CI 0.93 to 1.21) symptomatic cure. Short-term cure for nitrofurantoin was similar to that of trimethoprim–sulfamethoxazole (RR 0.99, 95% CI 0.95 to 1.04) as was long-term symptomatic cure (RR 1.01, 95% CI 0.94 to 1.09) Fluoroquinolones were more effective than beta-lactams (RR 1.22, 95% CI 1.13 to 1.31) for short-term bacteriological cure. Rashes were more frequent in people taking trimethoprim–sulfamethoxazole compared with nitrofurantoin or fluoroquinolones, and also more common in people taking beta-lactam drugs compared with those taking fluroquinolones
Rafalsky 2006 [42]	Clinical cure, bacteriological cure, adverse effects	No significant differences between clinical or bacteriological cure by the different quinolones were identified. Adverse effects varied in frequency and type across different quinolones
Randomized controlled trials		
Monsen 2013 [43]	Clinical and bacteriological cure	Pivmecillinam was superior to placebo in reducing symptoms at 8–10 days, but similar at 35–49 days follow-up
Akarsu 2010 [44]	Bacteriological cure, symptomatic cure, adverse effects	Clinical symptom resolution and bacteriological cure were similarly successful for both a single dose of fosfomycin and 7 days of amoxicillin–clavulanic acid. No serious adverse effects were apparent in either group
Bleidorn 2010 [45]	Symptom free at day 4, need for further antibiotics, adverse effects	21/36 patients on ibruprofen and 17/33 patients given ciprofloxacin were symptom free on day 4. 12/36 patients on ibruprofen and 6/33 taking ciprofloxacin required further antibiotic treatment due to ongoing or worsening symptoms. No difference in adverse effects was seen between the two groups
Ceran 2010 [46]	Clinical cure, antibiotic sensitivity, bacteriological cure	Clinical cure was similar in the two groups, occurring in 64/77 people on fosfomycin and 53/65 people taking ciprofloxacin; bacterial eradication was similarly effective in the two groups (64/77 on fosfomycin and 61/65 on ciprofloxacin). Antibiotic sensitivity was lower for ciprofloxacin; 131 of 142 bacterial isolates were sensitive to fosfomycin compared with 85 of 142 isolates for ciprofloxacin
Estebanez 2009 [47]	Bacteriological cure, recurrence of positive culture, adverse effects. Compliance	Bacteriological cure was similar, over 80%, for the amoxicillin clauvulanate and fosfomycin groups (RR 1.195, 95% CI 0.451 to 3.165). The number of repeat infectons was higher in the amoxicillin clauvulanate group, 8/56 vs. 1/53

trial, gastrointestinal symptoms occurred in three patients in the fosfomycin group and two patients in the ciprofloxacin group. The Monsen trials of antibiotic versus placebo did not report adverse effects. The Bleidorn trial reported similar, nonserious adverse effects across the ibruprofen and antibiotic groups

The quality of evidence

Many of the individual trials within the four systematic reviews were well designed and reported; however few trials used similar treatments, which made synthesis impossible (Table 11.12). Three of the five trials, were of uncertain validity due to poor reporting of methods. Two trials (the

Table 11.12 GRADE profile of included studies addressing the question of which antibiotic is most effective in treating urinary tract infection in adults.

Study ID	Quality of included trials	Consistency	Directness	Precision	Other	Overall
Systematic reviews						
Vasquez 2011 [39]	7/10 reported adequate randomization 5/10 were considered adequate for allocation concealment 1/10 trials reported blinding	I^2 reported for pooled analyses, highly variable	Direct comparisons	95% CIs reported for all analyses	Many comparisons involved a single trial	Insufficient data to recommend any specific drug regimen
Guinto 2010 [40]	1/5 had adequate randomization 2/5 stated allocation concealment 2/5 used blinding	I^2 not reported, no pooled analyses	Direct comparisons	No meta-analysis. Confidence intervals for single trial results	Few studies, all different treatments	Does not provide good evidence to support a strong recommendation
Zalmanovici-Trestioreanu 2010 [41]	9/21 reported their randomization method 4/21 detailed allocation concealment 8/21 trials stated double blinding, 4/21 reported single blind	I^2 measured, variable across the many analyses	Direct comparisons	95% CIs reported for all analyses	Few studies for each comparison	Reasonable evidence to support no difference between different antibiotics
Rafalsky 2006 [42]	7/11 trials reported randomization processes 10/11 reported allocation concealment 10/11 reported double blinding, 1/11 reported also blinding outcome assessors	I^2 not reported, no pooled analyses	Direct comparisons	No meta-analysis. Confidence intervals for single trial results	11 trials, all different treatments	Individual trials are valid but synthesis was not possible. Evidence does not support a strong recommendation
Trials						
Monsen 2013 [43]	Randomization, not stated Allocation concealment, not stated Double blind	–	Direct comparison	1143 patients anlayzed. No CIs reported	195/1143 dropped out and excluded from analyses	Uncertain validity
Akarsu 2010 [44]	Randomization, not stated Allocation concealment, not stated Blinding, not stated	–	Direct comparisons	84 patients, no CIs		Uncertain validity
Bleidorn 2010 [45]	Randomization, adequate Allocation concealment, adequate Double blinded	–	Direct comparison	79 patients, CI for symptom score	11 post-randomization exclusions, data not shown	Reasonable evidence to support no difference between ibroprofen and ciprofloxacin
Ceran 2010 [46]	Randomization, alternating patients Allocation concealment, opaque envelopes Single blind	–	Direct comparison	142 patients evaluated. No CIs reported	118 excluded post-randomization,	Uncertain validity
Estebanez 2009 [47]	Randomization, adequate Allocation concealment, adequate No blinding	–	Direct comparison	109 patients, CIs reported	22/131 randomized were not analyzed	Reasonable evidence to support no difference between different antibiotic regimens

Table 11.13 Summary of the characteristics of the studies to address the question, "For people with UTI, what duration of antibiotic therapy is optimal?"

Study ID	Study participants	Interventions*	Description
Systematic reviews			
Widmer 2011 [48]	Pregnant women with asymptomatic bacteriuria	Single-dose treatment compared with 4- to 7-day treatments	13 studies involving 1622 women
Lutters 2008 [49]	Elderly women	Sulfamethoxazole single dose vs. 6 days Fosfomycin trometamol single dose vs. norfloxacin for 7 days Single dose various AB vs. 7–10 days Ciprofloxacin single dose vs. 3 days Pefloxacin single dose vs. 10 days norfloxacin Pefloxacin single dose vs. 3 days lomefloxacin, Lomefloxacin 3 days vs. norfloxacin Fosfomycin trometamol single dose vs. pipemidic acid 5 days Trimethoprim single dose vs. 5 days Isepamicin single dose vs. ofloxacin for 3 days Norfloxacin for 3 days vs. 7 days Ofloxacin 3 days vs. cefalexin 7 days Temafloxacin 3 days vs. ciprofloxacin for 7 days Trimethoprim 3 days vs. 5 days Ciprofloxacin 3 days vs. 7 days	15 studies involving 1644 elderly women
Trial			
Usta 2011 [50]	Pregnant women with symptomatic UTI	Single-dose fosfomycin trometamol or 5-day courses of amoxicillin clavulanate or cefuroxime axetil	90 women, 30 on fosfomycin trometamol, 30 on amoxicillin clavulanate, 30 on cefuroxime axetil

Estebanez and Bleidorn trials) included details of methodology and are likely to provide valid results. Findings across the reviews and individual trials were relatively consistent in showing little difference in microbiological cure and adverse effects between different antibiotic regimens. The precision across the reviews and trials varied.

Clinical implications

We recommend that empiric antibiotic choice be based upon knowledge of local resistance patterns, adverse events, and economic considerations (clinical principle).

Clinical question 5

For people with UTI, what duration of antibiotic therapy is optimal?

Literature search

The Cochrane Library, Cochrane Central Register of Controlled Trials, and MEDLINE were searched from 2008 (the year of the previous update) to June 2015. Terms included urinary tract infection, bacteriuria, pyuria, UTI, cystitis, anti-infective agent, trimethoprim, sulfamethoxazole, cotrimoxazole, ciprofloxacin, ofloxacin, nitrofurantoin, norfloxacin, and 3 day.

The evidence

Two systematic reviews were identified (Table 11.13 [46–48]). The Widmer review included 13 trials of single dose compared with 4–7 days' treatment in 1622 pregnant women with asymptomatic bacteriuria. The Lutters review included 15 trials in 1644 elderly women with symptomatic UTI, with trials comparing single dose with 3 days', single dose with 5–10 days', and 3 days with 6–10 days' treatment. One subsequent trial was identified (the Usta trial), comparing single-dose fosfomycin trometamol with 5 days' treatment with amoxicillin clavulanate or cefuroxime axetil in pregnant women with symptomatic UTI (Table 11.14).

Results

The Widmer systematic review in pregnant women showed no difference in bacteriological cure and recurrence rate between the single and 4–7-day treatment groups (RR 1.33, 95% CI 0.88 to 2.01) and single-dose treatment was associated with fewer adverse effects (RR 0.70, 95% CI 0.56 to 0.88). The Lutters review reported that there was a significant benefit in short-course (RR single vs. short 2.01, 95% CI 1.05 to 3.84) and long-course (RR 1.93, 95% CI 1.01 to 3.70) treatments compared with single-dose treatment for the outcome of persistent UTI over the short term (<2 weeks), but this did not remain over the long term. There were no significant differences in

Table 11.14 Summary of evidence of what duration of antibiotic treatment is most effective for treating UTI in adults.

Study ID	Outcomes relevant to clinical question	Results
Systematic reviews		
Widmer 2011 [48]	Bacteriological cure, recurrent bacteriuria, pyelonephritis, preterm birth, adverse effects	Bacteriological cure and recurrence rate were not statistically different between the single and longer dose groups. Single-dose treatment was associated with fewer adverse effects (RR 0.77, 95% CI 0.61 to 0.97) in trials comparing the same antibiotic
Lutters 2008 [49]	Persistent UTI, clinical cure, reinfection, patient satisfaction, adverse effects	There was a significant difference for persistent UTI between single-dose and short-course treatment (RR 2.01, 95% CI 1.05 to 3.84) and single- vs. long-course treatment (RR 1.93, 95% CI 1.01 to 3.70), in the short-term(<2weeks post-treatment) but not at long-term follow-up or on clinical outcomes
Trial		
Usta 2011 [50]	Bacteriological eradication	Single dose of fosfomycin trometamol was as effective for UTI as the 5-day course of treatment with amoxicillin clavulanate or cefuroxime axetil. Numbers with sterile urine at 2 weeks: 23/28 fosfomycin, 22/27 amoxycillin, 26/29 cefuroxime groups. No significant difference in adverse effects across the three groups

Table 11.15 GRADE profile of included studies addressing the question of what duration of antibiotic treatment is most effective for treating urinary tract infection in adults.

Study ID	Quality of included trials	Consistency	Directness	Precision	Other	Overall
Systematic reviews						
Widmer 2011 [48]	6/13 reported randomization process 4/13 detailed allocation concealment 2/13 trials reported blinding	I^2 values were reported and variable across analyses	All comparisons were direct	95% CIs were reported, variable across analyses		Reasonable evidence to support similar efficacy for single vs. longer course antibiotic treatment
Lutters 2008 [49]	6/15 described randomization 5/15 reported adequate allocation concealment 4/15 reported double blinding, 2/15 stated single blind	I^2 values were reported and variable across analyses	All comparisons were direct	95%CIs were reported, variable across analyses		Reasonable evidence to support a 3–6-day course of antibiotics
Trial						
Usta 2011 [50]	Randomization, computer generated Allocation concealment, adequate Blinding, not stated	–	Direct comparison across groups	No CIs reported	6 post-randomization exclusions from analysis	Uncertain validity

the rate of adverse drug reactions (RR 0.80, 95% CI 0.45 to 1.41). Findings from the Usta trial showed little difference in bacteriological eradication across the three treatment options and no differences in adverse events (Table 11.14).

The quality of evidence

Trials within the two reviews were of low quality, with major deficiencies in reporting important methodological issues such as randomization and allocation concealment (Table 11.15). The individual Usta trial reported adequate randomization and allocation concealment methods but did not use blinding and excluded six patients who were lost to follow-up from the analysis. Design limitations led to uncertainty around the validity of these findings. Trials were reasonably consistent within the reviews and heterogeneity was measured. Confidence intervals were reported and tended to be variable across the different analyses, demonstrating imprecision in estimates of effect.

Clinical implications

In elderly women, we recommend that antibiotics be given for 3–10 days for treatment of UTI (strong recommendation based on moderate-quality evidence).

In pregnant women, we recommend single-dose antibiotics (strong recommendation based on moderate-quality evidence).

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12 CHAPTER 12
Medical management of stone disease

Timothy Y. Tseng[1] and Glenn M. Preminger[2]

[1] *Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, CA, USA*

[2] *Comprehensive Kidney Stone Center, Division of Urologic Surgery, Duke University Medical Center, Durham, NC, USA*

Introduction

Although the management of renal and ureteral calculi is frequently thought to revolve around surgical removal techniques, increasing emphasis has been placed on medical management in both the acute and chronic settings. This chapter highlights issues in the medical management of ureteral calculi in the acute setting and the prevention of stone recurrences with medical management strategies in the long term.

Ureteral muscle spasm is thought to be one factor contributing to the impaction of ureteral stones. The physiology of ureteral smooth muscle is well studied. Numerous investigations have demonstrated that both alpha-adrenergic receptors and calcium channel antagonist binding sites exist in ureteral smooth muscle [1]. Inhibition of alpha-adrenergic receptors results in a decrease in basal tone, ureteral contractions, and ureteral peristalsis [2]. Inhibition of the voltage-dependent smooth muscle calcium channel results in a blunted rise in intracellular calcium ion concentrations during activation, leading to decreased electrical and contractile activity [3]. Because of their relatively low side-effect profile, these drugs have been explored as a means to treat the ureteral spasm component of stone impaction.

Multiple meta-analyses have demonstrated clinically important increases in spontaneous ureteral stone passage with the use of alpha-blockers and calcium channel blockers [4]. Recently, however, a well-designed randomized controlled trial (RCT) was published and demonstrated no differences in outcomes with alpha-blockers and calcium channel blockers [5]. Many of the primary studies have also utilized corticosteroids concurrently in an effort to decrease ureteral edema and to enhance ureteral stone expulsion. In the first half of this chapter, the recent evidence supporting such medical expulsive therapy (MET) is reviewed.

Medical management strategies for the prevention of recurrent stone disease have been investigated for several decades. Several medications, including thiazide diuretics, allopurinol, potassium citrate, acetohydroxamic acid, phosphate, and magnesium, have been evaluated in RCTs. Thiazide diuretics stimulate resorption of calcium with concomitant excretion of sodium in the distal nephron, thereby reducing urinary calcium concentration. As an inhibitor of xanthine oxidase, allopurinol, and more recently febuxostat, decrease the conversion of xanthine and hypoxanthine to uric acid, which results in a decrease in urinary uric acid concentration. Alkali therapy with potassium citrate increases urinary pH, which improves urinary saturation of calcium oxalate and uric acid. Additionally, alkali therapy results in an increase in urinary citrate, which is a known inhibitor of calcium stone formation. Acetohydroxamic acid is a urease inhibitor and is thought to inhibit stone formation due to chronic urea-splitting organisms [6]. A lack of proven efficacy of phosphate and magnesium treatments has led to a lack of use of these two medications in the current era and they are not reviewed [7]. The current evidence supporting preventive medical therapy for recurrent stone disease is reviewed in the second half of the chapter.

Clinical question 1

What is the effect of alpha-adrenergic antagonist therapy on expulsion of ureteral stones?

Literature search

A search of the PubMed electronic database using the terms "drug therapy" and "nephrolithiasis or urinary calculi" limited to the "clinical trial, randomized controlled trial, or comparative study" publication types found 36 unique randomized trials dealing with the use of an alpha-blocker

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for MET of ureteral stones. Similar searches of CINAHL and the Cochrane Central Register of Controlled Trials did not identify any additional published randomized studies. Randomized trials without a true nonintervention control group were excluded.

The evidence

Of the 36 randomized trials that used an alpha-adrenergic antagonist for MET of stones, 30 utilized a tamsulosin arm, six used a doxazosin arm, three used a terazosin arm, three used an alfuzosin arm, and two utilized a naftopidil arm (Table 12.1). Most of the trials examined patients with distal ureteral stones that ranged in size up to 18 mm who had not been previously treated with shock-wave lithotripsy. Two trials examined patients with proximal ureteral stones. Three trials examined patients with stones at any location in the ureter. Follow-up was performed between 7 days and 6 weeks. In all but one trial, the alpha-blocker was used as the initial treatment. The exception was one trial that studied the use of the alpha-blocker after previously failed MET.

Spontaneous stone passage rates for alpha-adrenergic antagonists as initial therapy in individual trials ranged from a low of 35% to a high of 100%, with the overall stone passage rate being 79%. Spontaneous stone passage rates for controls in these studies ranged from a low of 4% to a high of 90%, with the overall stone passage rate being 59%. The relative risk (RR) of stone passage for initial treatment with an alpha-adrenergic antagonist ranged from 0.95 to 13.5 with an overall RR of 1.35 (95% confidence interval [CI] 1.29–1.41) (all relative risk calculations were performed using RevMan 5.3, available at http://tech.cochrane.org/revman). Two-thirds of individual trials demonstrated a statistically significant improvement in stone expulsion rates with an alpha-adrenergic antagonist. The mean/median time to stone passage ranged from 1 to 16.5 days versus 3 to 24.5 days for controls. Among the 18 trials that examined analgesic usage or pain episodes, only 11 demonstrated a statistically significant decrease in pain measurements with an alpha-adrenergic antagonist.

Despite the overall evidence pointing towards a significant benefit for MET using alpha-adrenergic antagonists, the largest trial to date, by Pickard et al. [5], demonstrated no improvement in stone passage, time to stone passage, or days of pain medication use. This trial included over 1000 patients and appears to have been well designed. However, unlike most of the much smaller trials that examined only distal ureteral stones, this trial examined ureteral stones at any location. The Pickard trial also used lack of intervention in lieu of imaging confirmation of stone passage.

Clinical implications

We suggest that patients presenting with single, noncomplicated ureteral stones be treated with a trial of MET using an alpha-adrenergic antagonist (conditional recommendation based on low-quality evidence). This recommendation places a high value on patients' desire to avoid surgical intervention and further assumes that MET is well tolerated and relatively cheap. MET with an alpha-adrenergic antagonist may be most useful in patients with larger or proximal/mid ureteral stones that are less likely to pass spontaneously.

Clinical question 2

What is the effect of calcium channel antagonist therapy on expulsion of ureteral stones?

Literature search

The same PubMed search as used in the previous question found seven unique RCTs dealing with the use of a calcium channel antagonist for MET of ureteral stones. Searches of CINAHL and the Cochrane Central Register of Controlled Trials did not identify any additional published randomized studies.

The evidence

All seven RCTs using calcium channel antagonists as initial MET used nifedipine. Three trials utilized nifedipine in conjunction with other medications including glucocorticoids, antibiotics, and acetaminophen (Table 12.2). Three studies were performed with a tamsulosin arm also. Most trials examined patients with distal ureteral stones that ranged in size up to 18 mm. One study did not specify the size of the stones and one did not specify location in the ureter. None of the studies included patients who had undergone previous shock-wave lithotripsy or prior MET. Follow-up was between 28 and 45 days.

Spontaneous stone passage rates for nifedipine ranged from 77 to 89%, with the overall stone passage rate being 80%. Spontaneous stone passage rates for controls in these studies ranged from 35 to 80%, with the overall stone passage rate being 68%. The RR for stone passage with nifedipine versus controls ranged from 1.00 to 2.24, with an overall RR of 1.16 (95% CI 1.09–1.24). Mean time to stone passage was sometimes shorter for nifedipine arms (5.0–16.2 days) compared with controls (5.0–20.0 days). Porpiglia et al. [44] and Balci et al. [40] found a statistically decreased analgesic requirement with nifedipine. Additionally, Cooper et al. found a statistically significant decrease in the number of workdays lost with nifedipine [43]. The largest trial, by Pickard et al., however, demonstrated no statistically significant improvement in stone passage, time to stone passage, or days of pain medication [5].

Although relatively well tolerated, nifedipine usage was associated with adverse reactions resulting in discontinuation of treatment in a small number of patients. Nifedipine usage was also associated with an up to 21% incidence of minor side effects including headache, palpitations, asthenia, and stomach ache [44].

Table 12.1 Effect of alpha-adrenergic antagonists on ureteral stone passage.

Study ID	Methods[a]	Intervention	Participants	Outcomes	Results	Notes
Červenàkov [8]	RCT Distal ureteral stones 1–10 mm FU: 7-day inpatient monitoring	NSAIDs and benzodiazepines ± tamsulosin	Tamsulosin – 51 pts Control – 53 pts	Spontaneous stone passage	RR stone passage 1.28 (95% CI 1.00–1.65)	All inpatient 2 control pts excluded due to pyelonephritis
Dellabella [9]	Randomized trial Distal ureteral stones 3.8–13 mm, colic lasting ≤1 day FU: 28 days	NSAIDs and glucocorticoid ± tamsulosin or FGTMB	Tamsulosin – 30 pts FGTMB – 30 pts	Spontaneous stone passage Time to stone passage Diclofenac usage	RR stone passage tamsulosin vs. FGTMB 1.42 (95% CI 1.12–1.80) Mean time to expulsion 66 h (tamsulosin), 111 h (FGTMB), $p=0.020$ Mean diclofenac injections 0.1 (tamsulosin), 2.8 (FGTMB), $p<0.001$	Single blind
Porpiglia [10]	RCT Distal ureteral stones 3–10 mm FU: 4 weeks	NSAIDs and glucocorticoid ± nifedipine or tamsulosin	Tamsulosin – 28 pts Nifedipine – 30 pts Control – 28 pts	Spontaneous stone passage Time to stone passage Diclofenac usage	RR stone passage vs. control 2.00 (95% CI 1.27–3.15) (tamsulosin), 1.87 (95% CI 1.17–2.97) (nifedipine) Mean time to expulsion 7.9 days (tamsulosin), 9.3 days (nifedipine), 12 days (control) Mean diclofenac usage 26 mg (tamsulosin), 19.5 mg (nifedipine), 105 mg (control)	1 pt each in nifedipine and tamsulosin groups discontinued treatment due to side effects
Kupeli [11]	RCT Distal ureteral stones <5 mm FU: 15 days	NSAIDs ± tamsulosin	Tamsulosin – 15 pts Control – 15 pts	Spontaneous stone passage	RR stone passage 2.67 (95% CI 0.87–8.15)	Small sample sizes Differences in stone passage rates not statistically significant
Resim [12]	RCT Distal ureteral stones 5–13 mm FU: 6 weeks	NSAIDs ± tamsulosin	Tamsulosin – 30 pts Control – 30 pts	Spontaneous stone passage No. of colic episodes Severity of colic episodes using visual analog scale	RR stone passage 1.18 (95% CI 0.91–1.53) Mean no. of colic episodes 2.0 (tamsulosin), 2.6 (control), $p=0.038$ Severity of colic episodes by visual analog scale 5.7 (tamsulosin), 8.3 (control), $p<0.001$	Differences in stone passage rates not statistically significant
Autorino [13]	RCT Distal ureteral stones 3–10 mm FU: 14 days	NSAIDs ± tamsulosin	Tamsulosin – 32 pts Control – 32 pts	Spontaneous stone passage Time to stone passage Need for additional analgesics Need for hospitalization	RR stone passage 1.47 (95% CI 1.08–2.02) Mean time to stone passage 4.8 days (tamsulosin), 7.4 days (control), $p=0.005$ Need for additional analgesics 9% (tamsulosin), 31% (control), $p=0.003$ Need for hospitalization 9% (tamsulosin), 21% (control), $p=0.01$	

(*continued overleaf*)

Table 12.1 (Continued)

Study ID	Methods[a]	Intervention	Participants	Outcomes	Results	Notes
Yilmaz [14]	RCT Distal ureteral stones ≤10 mm FU: 1 month	NSAIDs ± tamsulosin, terazosin, or doxazosin	Tamsulosin – 29 pts Terazosin – 28 pts Doxazosin – 29 pts Control – 28 pts	Spontaneous stone passage Time to stone passage No. of pain episodes Analgesic use	RR stone passage vs. control 1.48 (95% CI 1.00–2.19) (tamsulosin), 1.47 (95% CI 0.99–2.18) (terazosin), 1.42 (95% CI 0.95–2.12) (doxazosin), 1.45 (95% CI 1.01–2.09) (combined) Mean time to stone passage 6.3 days (tamsulosin), 5.8 days (terazosin), 5.9 days (doxazosin), 10.5 days (control) No. of pain episodes 1.7 (tamsulosin), 1.6 (terazosin), 1.7 (doxazosin), 2.4 (control) Mean analgesic usage 129 mg (tamsulosin), 118 mg (terazosin), 119 mg (doxazosin), 182 mg (control)	Differences in stone passage rates not statistically significant for individual alpha-blockers
Dellabella [15]	Randomized trial Distal ureteral stones 4–18 mm, colic lasting ≤1 day FU: 28 days	NSAIDs ± tamsulosin, nifedipine, or phloroglucinol	Tamsulosin – 70 pts Nifedipine – 70 pts Phloroglucinol – 70 pts	Spontaneous stone passage Time to stone passage Diclofenac usage Need for hospitalization No. of workdays lost	RR stone passage vs. phloroglucinol 1.51 (95% CI 1.26–1.81) (tamsulosin), 1.20 (95% CI 0.97– 1.49) (nifedipine) Median time to stone passage 72 h (tamsulosin), 120 h (nifedipine), 120 h (phloroglucinol), $p<0.001$ Median no. of PRN diclofenac vials used 0 (tamsulosin), 1 (nifedipine), 2 (phloroglucinol), $p<0.001$ Need for urgent hospitalization 0% (tamsulosin), 4% (nifedipine), 16% (phloroglucinol), $p=0.001$ Need for delayed hospitalization 1.4% (tamsulosin), 16% (nifedipine), 19% (phloroglucinol), $p=0.004$ Median workdays lost 2 (tamsulosin), 3 (nifedipine), 5 (phloroglucinol), $p<0.001$	
De Sio [16]	RCT Distal ureteral stones ≤10 mm FU: 2 weeks	NSAIDs ± tamsulosin	Tamsulosin – 50 pts Control – 46 pts	Spontaneous stone passage Time to stone passage Analgesic usage Need for hospitalization Adverse reactions	RR stone passage 1.53 (95% CI 1.18–1.99) Mean time to stone passage 4.4 days (tamsulosin), 7.5 days (control), $p=0.005$ Analgesic use 10% (tamsulosin), 37% (control), $p=0.003$ Need for hospitalization 10% (tamsulosin), 28% (control), $p=0.01$ Adverse reactions 6% (tamsulosin), 4% (control), $p=0.05$	Analgesic use not defined No adverse reactions resulted in discontinuation of treatment regimen

Erturhan [17]	RCT Distal ureteral stones 4–10 mm FU: 3 weeks	NSAIDs ± tamsulosin ± tolterodine	Tamsulosin – 30 pts Tamsulosin and tolterodine – 30 pts Tolterodine – 30 pts Control – 30 pts	Spontaneous stone passage Time to stone passage Analgesic use Need for hospitalization	RR stone passage tamsulosin vs. control 1.83 (95% CI 1.12–2.99) RR stone passage tamsulosin + tolterodine vs. control 1.75 (95% CI 1.06–2.88) Mean time to stone passage 6.4 days (tamsulosin), 7.5 days (tamsulosin + tolterodine), 11.4 days (tolterodine), 12.2 days (control) Mean daily analgesic use 40 mg (tamsulosin), 55 mg (tamsulosin + tolterodine), 120 mg (tolterodine), 155 mg (control) Hospitalization 3% (tamsulosin), 0% (tamsulosin + tolterodine), 7% (tolterodine), 7% (control)	Addition of tolterodine does not confer an advantage over tamsulosin alone 4 pts did not complete the study due to severe colic, obstruction, and fever
Liatsikos [18]	RCT Distal ureteral stones ≤5 mm and 6–10 mm, colic <1 day FU: 4 weeks	± Doxazosin	Doxazosin, ≤5 mm – 20 pts Doxazosin, 6–10 mm – 22 pts Control, ≤5 mm – 15 pts Control, 6–10 mm – 16 pts	Spontaneous stone passage Time to stone passage	RR stone passage, stones ≤5 mm, 1.42 (95% CI 0.90–2.23) RR stone passage, stones 6–10 mm, 1.66 (95% CI 0.90–3.06) RR stone passage, overall, 1.52 (95% CI 1.05–2.22) Mean time to stone passage 7.6 days (doxazosin, ≤5 mm), 7.1 days (doxazosin, 6–10 mm), 8.8 days (control, ≤5 mm), 12.1 days (control, 6–10 mm)	Small sample sizes Unblinded Randomization based on date of presentation with increased allocation to intervention arms Relative risk of stone passage not statistically significant in original subset analysis
Pedro [19]	RCT Distal ureteral stones <8 mm FU: 4 weeks	± Alfuzosin	Alfuzosin – 34 pts Placebo – 35 pts	Spontaneous stone passage Time to stone passage Need for opioid analgesics	RR stone passage 0.95 (95% CI 0.73–1.25) Mean time to stone passage 5.2 days (alfuzosin), 8.5 days (placebo), $p=0.003$ Morphine equivalents consumed 7.6 (alfuzosin), 8.4 (placebo), $p=0.83$	Differences in stone passage rates and opioid usage not statistically significant 7 pts did not complete study
Wang [20]	RCT Distal ureteral stones <10 mm FU: 2 weeks	NSAIDs ± tamsulosin or terazosin	Tamsulosin – 32 pts Terazosin – 32 pts Control – 31 pts	Spontaneous stone passage Time to stone passage No. of colic episodes	RR stone passage vs. control 1.48 (95% CI 1.03–2.12) (tamsulosin), 1.42 (95% CI 0.99–2.06) (terazosin), 1.45 (95% CI 1.03–2.05) (combined) Mean time to stone passage 6.3 days (tamsulosin), 6.3 days (terazosin), 10.1 days (control), $p<0.001$ No. of colic episodes 1.97 (tamsulosin), 1.84 (terazosin), 2.16 (control), $p>0.05$	Differences in stone passage rates not statistically significant for terazosin

(*continued overleaf*)

Table 12.1 (Continued)

Study ID	Methods[a]	Intervention	Participants	Outcomes	Results	Notes
Lojanapiwat [21]	RCT Distal ureteral stones 4–10 mm FU: 28 days	Diclofenac ± tamsulosin 0.2 mg/day or tamsulosin 0.4 mg/day	Tamsulosin, 0.2 mg – 25 pts Tamsulosin, 0.4 mg – 25 pts Control – 25 pts	Spontaneous stone passage Time to stone passage	RR stone passage 10.00 (95% CI 1.38–72.39) (tamsulosin 0.2 mg/day) RR stone passage 17.00 (95% CI 2.45–118.19) (tamsulosin 0.4 mg/day) RR stone passage 13.50 (95% CI 1.95–93.69) Mean time to stone passage 9.3 days (tamsulosin 0.2 mg/day), 10.8 days (tamsulosin 0.4 mg/day), 23.0 days (control), $p<0.001$	Stone passage rates and time to stone passage statistically improved with both tamsulosin 0.2 and 0.4 mg/day
Agrawal [22]	RCT Distal ureteral stones <10 mm FU: 4 weeks	Diclofenac ± tamsulosin or alfuzosin	Tamsulosin – 34 pts Alfuzosin – 34 pts Control – 34 pts	Spontaneous stone passage Time to stone passage Diclofenac usage	RR stone passage 2.33 (95% CI 1.44–3.77) (tamsulosin), 2.00 (1.21–3.31) (alfuzosin), 2.17 (95% CI 1.35–3.48) (combined) Mean time to stone passage 12.3 days (tamsulosin), 14.5 days (alfuzosin), 24.5 days (control), $p<0.05$ for comparisons to control, $p=0.25$ between tamsulosin and alfuzosin Diclofenac injections 0.88 (tamsulosin), 1 (alfuzosin), 6.2 (control), *p*-value not provided	Stone passage rates and time to stone passage statistically improved with tamsulosin and alfuzosin
Sun [23]	RCT Distal ureteral stones mean size 5.5–5.7 mm FU: 14 days	± Naftopidil	Naftopidil – 30 pts Control – 30 pts	Spontaneous stone passage Time to stone passage	RR stone passage 3.38 (95% CI 1.84–6.18) Median time to stone passage 7 days (naftopidil), 6 days (control), $p=0.52$	Time to stone passage not statistically different
Porpiglia [24]	RCT Distal ureteral stones >5 mm Failed one 10-day cycle tamsulosin MET FU: 10 days	NSAIDs and glucocorticoid ± tamsulosin	Tamsulosin – 46 pts Control – 45 pts	Spontaneous stone passage No. of colic episodes Diclofenac usage	RR stone passage 1.65 (95% CI 1.18–2.29) Mean no. of colic episodes 1.4 (tamsulosin), 1.0 (control), $p>0.05$ Mean diclofenac usage 123 mg (tamsulosin), 127 mg (control), $p>0.05$	First cycle of tamsulosin shorter than that used in other trials No statistical benefit to second cycle tamsulosin in colic episodes and diclofenac usage Earlier report from earlier subset of pts showed no statistical difference in stone passage rates
Ferre [25]	RCT Distal ureteral stones mean size 3.5–3.8 mm FU: 14 days	Ibuprofen, oxycodone ± tamsulosin	Tamsulosin – 38 pts Control – 39 pts	Spontaneous stone passage Time to stone passage	RR stone passage 1.15 (95% CI 0.84–1.59) Median time to stone passage 1 day (tamsulosin), 3 days (control), $p=0.337$	Stone passage and time to stone passage not statistically different Number of colicky stone pain episodes and opioid usage not statistically different at any time point

Hermanns [26]	RCT, double-blind, placebo controlled Distal ureteral stones ≤7 mm FU: 3 weeks	± Tamsulosin	Tamsulosin – 45 pts Placebo – 45 pts	Spontaneous stone passage Time to stone passage	RR stone passage 0.97 (95% CI 0.84–1.14) Median time to stone passage 7 days (tamsulosin), 10 days (placebo), $p=0.36$	Stone passage and time to stone passage not statistically different
Aydogdu [27]	RCT Distal ureteral stones <10 mm in children 2–14 years old FU: Mean 19 days	Ibuprofen ± doxazosin	Doxazosin – 19 pts Control – 19 pts	Spontaneous stone passage Time to stone passage	RR stone passage 1.14 (95% CI 0.82–1.59) Mean time to stone passage 5.9 days (doxazosin), 6.1 days (placebo), $p>0.05$	Stone passage and time to stone passage not statistically different
Yencilek [28]	RCT Proximal ureteral stones ≤10 mm FU: 4 weeks	± Tamsulosin	Tamsulosin – 42 pts Control – 50 pts	Spontaneous stone passage Time to stone passage No. of colic episodes	RR stone passage 1.19 (95% CI 0.66–2.14) Time to stone passage 8.4 days (tamsulosin), 11.6 days (control), $p=0.015$	Stone passage rate not statistically different overall Stone passage rate statistically improved for stones <5 mm Distal relocation statistically improved for stones 5–10 mm
Zehri [29]	RCT Distal ureteral stones 4–7 mm FU: 28 days	± Doxazosin	Doxazosin – 33 pts Control – 32 pts	Spontaneous stone passage Time to stone passage Diclofenac usage	RR stone passage 1.86 (95% CI 1.13–3.07) Mean time to stone passage 168 h (doxazosin), 300 h (control), $p<0.005$ Diclofenac tablets 7.45 (doxazosin), 16 (control), $p<0.001$	Unblinded Randomization by alternating consecutive patients
Al-Ansari [30]	RCT, double-blind, placebo controlled Distal ureteral stones ≤10 mm FU: 4 weeks	± Tamsulosin	Tamsulosin – 50 pts Control – 46 pts	Spontaneous stone passage Time to stone passage No. of pain episodes	RR stone passage 1.35 (95% CI 1.03–1.76) Mean time to stone passage 6.4 days (tamsulosin), 9.9 days (control), $p=0.001$ Pain episodes 1.6 (tamsulosin), 2.3 (control), $p=0.02$	
Kaneko [31]	RCT Ureteral stones at any location ≤10 mm FU: 4 weeks	± Tamsulosin	Tamsulosin – 31 pts Control – 34 pts	Spontaneous stone passage Time to stone passage Diclofenac usage	RR stone passage 1.55 (95% CI 1.05–2.28) Mean time to stone passage 14 days (tamsulosin), 17 days (control), $p=0.6$ Diclofenac doses 0.5 (tamsulosin), 0.47 (control), $p=0.91$	Time to stone passage and diclofenac usage not statistically different

(*continued overleaf*)

Table 12.1 (Continued)

Study ID	Methods[a]	Intervention	Participants	Outcomes	Results	Notes
Abdel-Meguid [32]	RCT, double-blind, placebo controlled Distal ureteral stones 4–10 mm FU: 4 weeks	± Tamsulosin	Tamsulosin – 75 pts Placebo – 75 pts	Spontaneous stone passage Time to stone passage	RR stone passage 1.45 (95% CI 1.16–1.82) Median time to stone passage, stones ≤6 mm, 9 days (tamsulosin), 17 days (placebo) Median time to stone passage, stones 7–10 mm, 15 days (tamsulosin), 20 days (placebo)	
Vincendeau [33]	RCT, double-blind, placebo controlled Distal ureteral stones 2–7 mm FU: 6 weeks	Ketoprofen, phloroglucinol ± tamsulosin	Tamsulosin – 66 pts Placebo – 63 pts	Weekly stone passage rates Spontaneous stone passage rate	RR stone passage at 6 weeks 1.06 (95% CI 0.85–1.31) Weekly stone passage rates $p > 0.05$ at each week	Neither overall stone passage rate nor weekly stone passage rate were statistically different
Chau [34]	RCT Ureteral stones at any location 5–10 mm FU: 5 weeks	Dologesic ± alfuzosin	Alfuzosin – 33 pts Control – 34 pts	Spontaneous stone passage Dologesic usage	RR stone passage 1.64 (95% CI 1.13–2.38) Dologesic tablet usage 17 (alfuzosin), 16 (control), $p = 0.867$	
Zhou [35]	RCT Distal ureteral stones 5–9 mm FU: 2 weeks	± Naftopidil or tamsulosin	Naftopidil – 43 pts Tamsulosin – 45 pts Control – 43 pts	Spontaneous stone passage Time to stone passage Pain episodes	RR stone passage 2.38 (95% CI 1.46–3.89) (naftopidil), 2.72 (95% CI 1.69–4.37) Mean time to stone passage 7.6 days (naftopidil), 7.7 days (tamsulosin), 9.4 days (control), $p \leq 0.001$ for comparisons with control Pain episodes 1.3 (naftopidil), 1.2 (tamsulosin), 2.1 (control), $p = 0.002$ comparing all arms	Statistically improved stone passage rates for both naftopidil and tamsulosin Naftopidil and tamsulosin not statistically different
Mokhless [36]	RCT Distal ureteral stones <12 mm in children 2–15 years old FU: 4 weeks	± Tamsulosin	Tamsulosin – 33 pts Placebo – 28 pts	Stone-free status Time to stone passage Pain episodes	RR stone free 1.37 (95% CI 1.01–1.85) Mean time to stone passage 8.2 days (tamsulosin), 14.5 days (placebo), $p < 0.001$ Mean pain episodes 1.4 (tamsulosin), 2.2 (placebo), $p < 0.02$	
Kirac [37]	RCT Distal ureteral stones <10 mm FU: 4 weeks	± Tamsulosin	Tamsulosin – 42 pts Control – 39 pts	Stone-free status Time to stone passage	RR stone free 1.22 (95% CI 0.81–1.84) Mean time to stone passage 15.1 days (tamsulosin), 15.3 days (control)	Differences in stone passage rates not statistically significant Statistical significance not provided for tamsulosin vs. control time to stone passage

Erturhan [38]	RCT Distal ureteral stones in children 3–15 years old FU: 3 weeks	NSAIDs ± doxazosin	Doxazosin – 24 pts Control – 21 pts	Spontaneous stone passage Time to stone passage	RR stone passage 2.48 (95% CI 1.29–5.11) Median time to stone passage 6 days (doxazosin), 8 days (control), $p=0.001$	No difference identified in daily colic episodes seen but reported as statistically favoring doxazosin
Lee [39]	RCT Proximal ureteral stones ≤6 mm FU: 4 weeks	± Tamsulosin	Tamsulosin – 54 pts Control – 54 pts	Spontaneous stone passage Time to stone passage	RR stone passage 1.60 (95% CI 1.15–2.22) Mean time to stone passage 14.3 days (tamsulosin), 19.6 days (control), $p<0.05$	Secondary outcome of oral analgesic usage not statistically different
Balci [40]	RCT Distal ureteral stones FU: 4 weeks	± Tamsulosin or nifedipine	Tamsulosin – 25 pts Nifedipine – 25 pts Control – 25 pts	Spontaneous stone passage Time to stone passage Diclofenac usage	RR stone passage vs. control 2.11 (95% CI 1.20–3.72) (tamsulosin), 1.78 (95% CI 0.98–3.24) (nifedipine) Mean time to stone passage 9.0 days (tamsulosin), 9.1 days (nifedipine), 10.3 days (control), $p<0.001$ for comparisons with control Mean diclofenac usage 544 mg (tamsulosin), 602 mg (nifedipine), 1408 mg (control), $p<0.001$ for comparisons with control	Stone passage rate increase statistically significant for tamsulosin only
Alizadeh [41]	RCT Distal ureteral stones 3–6 mm FU: 4 weeks	± Tamsulosin	Tamsulosin – 50 pts Control – 46 pts	Spontaneous stone passage Time to stone passage Indomethacin doses	RR stone passage 1.26 (95% CI 0.98–1.61) Mean time to stone passage 3.7 days (tamsulosin), 4.7 days (control), $p<0.05$ Indomethacin doses 1.5 (tamsulosin), 2.3 (control), $p<0.05$	Stone passage rate differences not statistically significant Time to passage was statistically shorter for tamsulosin
Ahmad [42]	RCT Distal ureteral stones 4–8 mm FU: 4 weeks	± Tamsulosin	Tamsulosin – 49 pts Placebo – 48 pts	Spontaneous stone passage	RR stone passage 1.58 (95% CI 1.19–2.10)	Time to stone expulsion was also statistically shorter for tamsulosin
Pickard [5]	RCT, double-blind, placebo controlled Ureteral stones <10 mm at any location FU: 4 weeks	± Tamsulosin or nifedipine	Tamsulosin – 378 pts Nifedipine – 379 pts Placebo – 379 pts	Spontaneous stone passage defined as absence of need for intervention at 4 weeks Time to stone passage Days of pain medication use	RR stone passage 1.02 (95% CI 0.95–1.09) (tamsulosin), 1.00 (95% CI 0.93–1.08) Mean time to stone passage 16.5 days (tamsulosin), 16.2 days (nifedipine), 15.9 days (placebo), $p>0.05$ Days of pain medication use 11.6 days (tamsulosin), 10.7 days (nifedipine), 10.5 days (placebo), $p>0.05$	Stone passage not confirmed by imaging Stones at all locations in the ureter were included

FGTMB, fluoroglucine trimetossibenzene; FU, follow-up; MET, medical expulsive therapy; NSAID, nonsteroidal anti-inflammatory drug; pts, patients; RCT, randomized controlled trial; RR, relative risk.

[a] Actual ranges for stone size are given where available

Table 12.2 Effect of calcium channel antagonists on ureteral stone passage.

Study ID	Methods[a]	Intervention	Participants	Outcomes	Results	Notes
Borghi [46]	RCT Ureteral stones ≤15 mm FU: 45 days	± Nifedipine and methylprednisolone	Intervention – 43 pts Placebo – 43 pts	Spontaneous stone passage Time to stone passage	RR stone passage 1.42 (95% CI 1.04–1.93) (intention-to-treat) Mean time to stone passage 11.2 days (intervention), 16.4 days (placebo), $p=0.036$ Diclofenac usage in both groups was similar Decrease in systolic blood pressure (–20 mmHg), decrease in diastolic blood pressure (–8 mmHg), and increase in heart rate (+8 bpm) with nifedipine statistically significant	4 pts in intervention arm did not complete study due to adverse reactions 2 pts with adverse reactions, 2 pts with bacteriuria, and 2 pts lost to follow-up in placebo arm did not complete the study Multiple drugs given in intervention arm
Cooper [43]	RCT Private practice urology patients Ureteral stones 2–6 mm FU: 6 weeks	NSAIDs ± nifedipine, prednisone, trimethoprim-sulfamethoxazole, and acetaminophen	Intervention – 35 pts Control – 35 pts	Spontaneous stone passage Time to stone passage Workdays lost	RR stone passage 1.63 (95% CI 1.18–2.26) Mean time to stone passage 12.6 days (intervention), 11.2 days (control) Mean workdays lost 1.8 days (intervention), 5.0 days (control), $p=0.024$	No IRB approval 6 patients did not complete study Analysis was not intention-to-treat Multiple drugs given in intervention arm Time to stone passage shorter in control group
Porpiglia [44]	RCT Distal ureteral stones ≤10 mm FU: 4 weeks	± Glucocorticoid and nifedipine	Intervention – 48 pts Control – 48 pts	Spontaneous stone passage Time to stone passage Diclofenac usage	RR stone passage 2.24 (95% CI 1.49–3.36) Mean time to stone passage 7 days (intervention), 20 days (control), $p<0.05$ Mean diclofenac usage 15 mg (intervention), 105 mg (control), $p<0.05$	2 pts in intervention arm discontinued therapy due to adverse reactions 10 pts in intervention arm had minor side effects Multiple drugs given in intervention arm
Porpiglia [10]	RCT Distal ureteral stones 3–10 mm FU: 4 weeks	NSAIDs and glucocorticoid ± nifedipine or tamsulosin	Tamsulosin – 28 pts Nifedipine – 30 pts Control – 28 pts	Spontaneous stone passage Time to stone passage Diclofenac usage	RR stone passage vs. control 2.00 (95% CI 1.27–3.15) (tamsulosin), 1.87 (95% CI 1.17–2.97) (nifedipine) Mean time to expulsion 7.9 days (tamsulosin), 9.3 days (nifedipine), 12 days (control) Mean diclofenac usage 26 mg (tamsulosin), 19.5 mg (nifedipine), 105 mg (control)	1 pt each in nifedipine and tamsulosin groups discontinued treatment due to side effects Tamsulosin superior to nifedipine in time to stone passage

Dellabella [15]	Randomized trial Distal ureteral stones 4–18 mm, colic lasting ≤1 day FU: 28 days	NSAIDs ± tamsulosin, nifedipine, or phloroglucinol	Tamsulosin – 70 pts Nifedipine – 70 pts Phloroglucinol – 70 pts	Spontaneous stone passage Time to stone passage No. of PRN diclofenac vials used Need for hospitalization No. of workdays lost	RR stone passage vs. phloroglucinol 1.51 (95% CI 1.26– 1.81) (tamsulosin), 1.20 (95% CI 0.97–1.49) (nifedipine) Median time to stone passage 72 h (tamsulosin), 120 h (nifedipine), 120 h (phloroglucinol), $p<0.001$ Median no. of PRN diclofenac vials used 0 (tamsulosin), 1 (nifedipine), 2 (phloroglucinol), $p<0.001$ Need for urgent hospitalization 0% (tamsulosin), 4% (nifedipine), 16% (phloroglucinol), $p=0.001$ Need for delayed hospitalization 1.4% (tamsulosin), 16% (nifedipine), 19% (phloroglucinol), $p=0.004$ Median workdays lost 2 (tamsulosin), 3 (nifedipine), 5 (phloroglucinol), $p<0.001$	No control group Difference in stone passage rate with nifedipine not statistically significant Tamsulosin superior to nifedipine in all outcomes
Balci [40]	RCT Distal ureteral stones FU: 4 weeks	± Tamsulosin or nifedipine	Tamsulosin – 25 pts Nifedipine – 25 pts Control – 25 pts	Spontaneous stone passage Time to stone passage Diclofenac usage	RR stone passage vs. control 2.11 (95% CI 1.20–3.72) (tamsulosin), 1.78 (95% CI 0.98–3.24) (nifedipine) Mean time to stone passage 9.0 days (tamsulosin), 9.1 days (nifedipine), 10.3 days (control), $p<0.001$ for comparisons with control Mean diclofenac usage 544 mg (tamsulosin), 602 mg (nifedipine), 1,408 mg (control), $p<0.001$ for comparisons with control	Stone passage rate increase statistically significant for tamsulosin only
Pickard [5]	RCT, double-blind, placebo controlled Ureteral stones <10 mm at any location FU: 4 weeks	± Tamsulosin or nifedipine	Tamsulosin – 378 pts Nifedipine – 379 pts Placebo – 379 pts	Spontaneous stone passage defined as absence of need for intervention at 4 weeks Time to stone passage Days of pain medication use	RR stone passage 1.02 (95% CI 0.95–1.09) (tamsulosin), 1.00 (95% CI 0.93–1.08) Mean time to stone passage 16.5 days (tamsulosin), 16.2 days (nifedipine), 15.9 days (placebo), $p>0.05$ Days of pain medication use 11.6 days (tamsulosin), 10.7 days (nifedipine), 10.5 days (placebo), $p>0.05$	Stone passage not confirmed by imaging Stones at all locations in the ureter were included

[a] Actual ranges for stone size are given where available.

Clinical implications

For patients with single noncomplicated ureteral stones who are unable to tolerate or receive an alpha-adrenergic antagonist, we suggest a trial of MET using a calcium channel antagonist (conditional recommendation based on low-quality evidence). This recommendation is based on direct and indirect evidence that alpha-adrenergic antagonists are more effective in promoting stone passage and may have a more favorable side-effect profile, thereby making them the first choice of MET. This recommendation once again places a high value on the avoidance of urological intervention.

Clinical question 3

What is the effect of corticosteroid therapy on expulsion of ureteral stones?

Literature search

The PubMed literature search as used previously yielded one RCT that specifically studied the use of a corticosteroid in MET for distal ureteral stones. Searches of CINAHL and the Cochrane Central Register of Controlled Trials did not identify any additional published randomized studies.

The evidence

Dellabella et al. [45] studied the use of deflazacort in conjunction with tamsulosin for MET of distal ureteral stones (Table 12.3). This trial examined patients with distal ureteral stones that were ≤15 mm in size with follow-up of 45 days. The stone passage rate was 97% with tamsulosin and deflazacort and 90% with tamsulosin alone with an RR of stone passage of 1.07 (95% CI 0.94–1.23). Only median time to stone passage was significantly different at 3 days with deflazacort and 5 days without deflazacort, $p=0.036$. Need for hospitalization, analgesic usage, and workdays lost were not significantly different between treatment arms. Two out of 30 patients (7%) receiving deflazacort developed dyspepsia as a side effect.

Clinical implications

We suggest against corticosteroids in the setting of MET of ureteral stones (conditional recommendation against based on very low-quality evidence). This recommendation is based on the lack of evidence to support its benefit in improving stone passage as well as the risk of increased adverse event rates.

Clinical question 4

What is the effect of medical therapy on expulsion of renal and ureteral stones after shock-wave lithotripsy (SWL)?

Literature search

A PubMed literature search combining the terms "shock wave lithotripsy" and "alpha-adrenergic antagonist or calcium channel blocker or medical expulsive therapy" identified 11 RCTs that studied the use of a calcium channel

Table 12.3 Effect of corticosteroids on ureteral stone passage.

Study ID	Methods[a]	Intervention	Participants	Outcomes	Results	Notes
Dellabella [45]	RCT Distal ureteral stones ≥4 mm, colic lasting ≤1 day FU: 28 days	Tamsulosin 28 days± deflazacort 10 days	Deflazacort – 30 pts Control – 30 pts	Spontaneous stone passage Time to stone passage Need for hospitalization Analgesic usage Workdays lost Side-effect prevalence	RR stone passage 1.07 (95% CI 0.94–1.23) Median time to stone passage 72 h (deflazacort), 120 h (control), $p=0.036$ Need for urgent hospitalization 0% for both arms Need for delayed hospitalization 3.3% (deflazacort), 10% (control), $p=0.612$ Analgesic usage, 0 vials in each arm, $p=0.625$ Workdays lost, 2 days in each arm, $p=0.994$ Side-effect prevalence 6.7% dyspepsia (deflazacort), 0% (control), $p=0.492$	Need for delayed hospitalization for tamsulosin alone significantly greater than in Dellabella et al. [39] No significant differences except for time to stone passage

[a] Actual ranges for stone size are given where available.

antagonist or an alpha-adrenergic antagonist as adjunctive MET after SWL. Searches of CINAHL and the Cochrane Central Register of Controlled Trials did not identify any additional published randomized studies. Multiple studies utilized *ad libitum* shock-wave lithotripsy sessions to achieve their outcomes in conjunction with MET and were excluded from this review.

The evidence

Of the 11 RCTs using MET as an adjunct to SWL, eight studies utilized tamsulosin, one utilized alfuzosin, one utilized nifedipine, and one utilized both tamsulosin and nifedipine (Table 12.4). Most trials examined MET in conjunction with primary SWL. One trial, by Resim et al., included only patients who had developed steinstrasse after SWL [47]. Stone location varied from the renal collecting system to the distal ureter and stone size varied from 4 to 30 mm. Follow-up was performed between 15 days and 12 weeks.

The primary measure of success in these studies was variously defined as stone-free status, residual fragments <3 mm in size or asymptomatic residual fragments <3 mm in size. It should be noted, however, that "success" in these trials did not equal "stone free." Using these definitions, successful stone clearance rates for adjunctive MET ranged from 37 to 91%, with an overall stone clearance rate of 74%. Successful stone clearance rates for controls ranged from 30 to 88%, with an overall stone clearance rate of 60%. The RR for successful stone clearance with adjunctive MET ranged from 0.95 to 2.13 with an overall RR of 1.25 (95% CI 1.15–1.36). In seven trials, the differences in clearance rates were not statistically significant. Differences in mean/median time to successful stone clearance were not statistically significant in the studies that reported such information. Among the five trials that examined analgesic usage, all but one demonstrated a statistically significant decrease in analgesic consumption with adjunctive MET.

Clinical implications

We suggest that urologists use MET in the form of alpha-blockers (preferred) or calcium channel blockers following SWL (conditional recommendation based on low-quality evidence). This recommendation once against places a high value on the avoidance of secondary urological interventions and assumes a favorable side-effect profile of these agents in this setting.

Clinical question 5

What is the effect of MET on stone passage after ureteroscopy?

Literature search

A PubMed literature search combining the terms "ureteroscopy" and "alpha-adrenergic antagonist or calcium channel blocker or medical expulsive therapy" identified one RCT that studied the use of tamsulosin as adjunctive MET after ureteroscopy with laser lithotripsy. Searches of CINAHL and the Cochrane Central Register of Controlled Trials did not identify any additional published randomized studies.

The evidence

John and Razdan studied the use of tamsulosin after ureteroscopy with laser lithotripsy for ureteral and renal stones 1–2 cm in size [57] (Table 12.5). Follow-up was 4 weeks. The stone-free rate was 80% with tamsulosin and 66% without tamsulosin with an RR of stone passage of 1.22 (95% CI 0.92–1.66). The percentage of patients with colic episodes was 5.4% with tamsulosin and 22.2% for controls, $p<0.01$.

Clinical implications

We suggest MET as an adjunct to stone fragmentation after ureteroscopy (conditional recommendation based on very low-quality evidence). Further study will be required to determine more accurately and definitively the benefits of MET in this setting.

Clinical question 6

What is the effect of thiazide and nonthiazide diuretic therapy on recurrence of urinary calculi?

Literature search

A PubMed literature search combining the terms "nephrolithiasis, urolithiasis, urinary calculi, or kidney calculi" with the terms "random" or the "randomized controlled trial" publication type identified six RCTs that studied the effect of a thiazide diuretic or the nonthiazide diuretic indapamide on the recurrence of urinary calculi. Indapamide is included in the thiazide diuretic group because of its similar mechanism of action. A search of the Cochrane Central Register of Controlled Trials identified one additional published randomized controlled trial [58]. A search of CINAHL did not identify any additional published or unpublished randomized studies.

The evidence

Of the seven trials studying thiazide and nonthiazide diuretic treatment for medical prophylaxis of stone disease, two used hydrochlorothiazide, two used bendroflumethiazide, and one study each used trichloromethiazide, chlorthalidone, and indapamide (Table 12.6). Only three studies limited their study populations to calcium stone formers and only two studies limited their study population to those patients with documented hypercalciuria. Two studies limited the study population to patients who were stone free at the start of the study [58, 59]. The remainder utilized radiographic imaging to document pre-existing stones. Primary outcomes involved "stone events" that were variously defined to include spontaneous passage of stones, radiographic evidence of new stones, and/or growth

Table 12.4 Effect of medical expulsive therapy on stone passage after shock-wave lithotripsy.

Study ID	Methods[a]	Intervention	Participants	Outcomes	Results	Notes
Porpiglia [48]	RCT Solitary ureteral stones in any location Mean size 11.6 mm (intervention), 10.1 mm (control) FU: 45 days	SWL and NSAIDs ± nifedipine and glucocorticoid	Nifedipine – 40 pts Control – 40 pts	Success defined as residual fragments <3 mm in size Percentage of pts with colic episodes Diclofenac usage	RR success 1.50 (95% CI 1.05–2.15) Percentage of pts with colic episodes 37.5% (nifedipine), 42.5% (control) Mean diclofenac usage 38 mg (nifedipine), 86 mg (control), $p=0.020$	4 pts in nifedipine group experienced side effects including asthenia and headache but did not discontinue therapy
Kupeli [11]	RCT Solitary distal ureteral stones 6–15 mm FU: 15 days	SWL and NSAIDs ± tamsulosin	Tamsulosin – 24 pts Control – 24 pts	Stone-free status	RR stone-free 2.13 (95% CI 1.14–3.96)	
Gravina [49]	RCT Solitary renal stones 4–20 mm FU: 12 weeks	SWL, glucocorticoid, and NSAIDs ± tamsulosin	Tamsulosin – 65 pts Control – 65 pts	Success defined as asymptomatic residual fragments <3 mm in size Percentage of pts with colic episodes Diclofenac usage	RR success 1.31 (95% CI 1.03–1.66) Percentage of pts with colic episodes 26.1% (tamsulosin), 76.9% (control), $p<0.001$ Mean diclofenac usage 375 mg (tamsulosin), 675 mg (control), $p<0.001$	Differences in stone-free status not statistically significant at 4 and 8 weeks FU Differences in stone-free status not statistically significant in subset of pts with stones ≤10 mm in size
Resim [47]	RCT SWL-induced distal ureteral steinstrasse from stones originally 10–30 mm in diameter Pts without severe pain or hydronephrosis FU: 6 weeks	NSAIDs ± tamsulosin	Tamsulosin – 32 pts Control – 35 pts	Resolution of steinstrasse Time to resolution of steinstrasse No. of colic episodes Pain scores Side-effect profile	RR resolution of steinstrasse 1.05 (95% CI 0.77–1.43) Median time to resolution of steinstrasse 9 days (tamsulosin), 10 days (control), $p>0.05$ Median no. of colic episodes 0 (tamsulosin), 1 (control), $p<0.01$ Median visual analog pain score 4 (tamsulosin), 6 (control), $p<0.001$ Percentage of pts without side effects 60% (tamsulosin), 57% (control)	Sample population limited to nonobese pts not taking psychiatric medications or antihistamines Differences in steinstrasse resolution not statistically significant Differences in colic episodes may not be clinically significant
Bhagat [50]	RCT, placebo controlled, double-blind Renal stones 6–24 mm or ureteral stones 6–15 mm FU: 1 month	SWL, narcotics, and NSAIDs ± tamsulosin	Tamsulosin – 30 pts Placebo – 30 pts	Success defined as asymptomatic residual stone fragments <3 mm in size No. of analgesic doses given	RR success 1.22 (95% CI 0.98–1.52) Mean no. of analgesic doses 1 (tamsulosin), 2 (placebo), $p=0.3$	1 pt in each group discontinued therapy Differences not statistically significant with intention-to-treat analysis Time to clearance in the 18 pts who developed steinstrasse was longer with tamsulosin

Gravas [51]	RCT Distal ureteral stones 6–13 mm FU: 4 weeks	SWL and NSAIDs ± tamsulosin	Tamsulosin – 31 pts Control – 31 pts	Success defined as asymptomatic residual stone fragments <3 mm in size Time to success Diclofenac usage	RR success 1.11 (95% CI 0.75–1.65) Median time to success 13.0 days (tamsulosin), 13.2 days (control), $p > 0.05$ Mean diclofenac usage 57 mg (tamsulosin), 119 mg (control), $p = 0.02$	Randomization based on hospital record number Study enrolled fewer pts than required by their preset sample size calculation Unblinded Differences not statistically significant
Kobayashi [52]	RCT, placebo controlled Ureteral stones >4 mm Mean stone size 10.65 mm (tamsulosin), 10.45 mm (intervention), 9.85 mm (control) FU: 28 days	SWL ± tamsulosin, placebo	Tamsulosin – 38 pts Placebo – 34 pts	Success defined as residual fragments <3 mm in size Time to success	RR success 0.95 (95% CI 0.79–1.15) Mean time to stone passage 15.7 days (tamsulosin), 35.5 days (placebo), $p = 0.042$	Blinding not reported Success difference not statistically significant
Falahatkar [53]	RCT, placebo controlled Renal and ureteral stones 4–20 mm FU: 12 weeks	SWL ± tamsulosin, placebo	Tamsulosin – 70 pts Placebo – 71pts	Stone clearance not otherwise defined	RR stone clearance 1.18 (95% CI 0.93–1.50)	Blinding not reported Difference not statistically significant
Pirzada [54]	RCT Renal stones 0.5–1.5 cm FU: 1 month	SWL and diclofenac ± alfuzosin	Alfuzosin – 30 pts Control – 30 pts	Spontaneous stone passage not otherwise defined Diclofenac usage	RR stone passage 1.64 (95% CI 1.07–2.53) Mean diclofenac usage 485 mg (alfuzosin), 768 mg (control), $p = 0.002$	Blinding not reported Differences statistically significant
Vicentini [55]	RCT, placebo controlled Non-lower pole renal stones 5–20 mm that changed radiographically after SWL FU: 1 month	SWL ± tamsulosin, nifedipine, placebo	Tamsulosin – 45 pts Nifedipine – 45pts Placebo – 46 pts	Success defined as residual fragments ≤4 mm in size Time to success	RR success tamsulosin 1.68 (95% CI 1.00–2.83), nifedipine 1.24 (95% CI 0.70–2.21) Mean time to success 15.3 days (tamsulosin), 15.9 days (nifedipine), 16.7 days (placebo), $p > 0.05$	Differences not statistically significant except for subgroup analysis of stones 10–20 mm with tamsulosin Nifedipine 28.5% headache and dizziness
Georgiev [56]	RCT Renal and ureteral stones <5 mm after SWL FU: 12 weeks	SWL and prednisolone, antibiotic, and diclofenac ± tamsulosin	Tamsulosin – 99 pts Control – 87 pts	Success defined as residual fragments ≤3 mm in size	RR success 1.22 (95% CI 1.06–1.40)	Differences statistically significant

[a] Actual ranges for stone size are given where available.

Table 12.5 Effect of medical expulsive therapy on stone passage after ureteroscopy.

Study ID	Methods[a]	Intervention	Participants	Outcomes	Results	Notes
John [57]	RCT Ureteral and renal stones 1–2 cm treated with ureteroscopy and laser lithotripsy Mean size 1.3 cm (tamsulosin), 1.2 cm (control) FU: 4 weeks	Tylenol with codeine ± tamsulosin	Tamsulosin – 40 pts Control – 38 pts	Stone-free status Percentage of pts with colic episodes	RR stone-free 1.22 (95% CI 0.92–1.60) Percentage of pts with colic episodes 5.4% (tamsulosin), 22.2% (control), $p<0.01$	Stone-free rates not statistically different

[a] Actual ranges for stone size are given where available.

of pre-existing stones. Many of the studies were of poor quality. Most suffered from small sample sizes, many had exceedingly high attrition rates, and several were reported prior to completion of enrollment or used incomplete datasets. Additionally, randomization methodology was sparsely reported and, in at least one study, resulted in the intervention arm having a significantly more favorable baseline stone formation rate. The majority of studies, however, were placebo controlled.

The stone event rate ranged from 0.05 to 0.24 stones per patient per year for thiazide and indapamide therapy versus 0.11 to 0.58 stones per patient per year for controls. In only three of the eight studies where such data were provided were the differences in stone event rates reported as being statistically significant. Remission rates for thiazide and indapamide therapy, where calculable, ranged from 76 to 100%, with an overall remission rate of 83%. Remission rates for controls ranged from 52 to 83%, with an overall remission rate of 73%. The RR of remission with treatment ranged from 0.95 to 17.31 with an overall RR of 2.76 (95% CI 1.62–4.70). In the study by Ettinger et al., up to 21% of chlorthalidone patients discontinued therapy due to side effects that included fatigue, impotence, and light-headedness [60].

Clinical implications

We suggest that urologists prescribe thiazides and nonthiazide diuretics for secondary prevention of renal stones in appropriately selected hypercalciuric patients (conditional recommendation based on very low-quality evidence). This recommendation places a high value on the avoidance of future stones and a relatively low value on the issue of long-term compliance and resource utilization.

Clinical question 7

What is the effect of xanthine oxidase inhibitor therapy on recurrence of urinary calculi?

Literature search

The PubMed literature search used previously yielded three RCTs that studied the use of xanthine oxidase inhibitors for prevention of recurrent stone disease. Searches of CINAHL and the Cochrane Central Register of Controlled Trials did not identify any additional published randomized studies.

The evidence

Two RCTs utilizing allopurinol for medical prophylaxis of stone disease and one RCT utilizing febuxostat and allopurinol were identified (Table 12.7). Two of the three trials selected for hyperuricosuric patients [58, 65]. One trial assessed the effect of allopurinol in conjunction with indapamide [59]. Stone events were variously defined to include spontaneous passage of stones, radiographic evidence of new stones, and/or growth of pre-existing stones. Most studies suffered from small sample sizes. The stone event rate in trials comparing allopurinol to no treatment ranged from 0.12 to 0.28 stone events per patient per year versus 0.26 to 0.28 stone events per patient per year for controls. The remission rates, where calculable, for allopurinol treatment ranged from 69 to 88%, with an overall remission rate of 78%. The remission rates for controls ranged from 42 to 57%, with an overall remission rate of 48%. The RR of remission with allopurinol treatment ranged from 3.08 to 5.76, with an overall RR of 3.89 (95% CI 1.66–9.07). The study by Goldfarb et al. included only patients with known stones and demonstrated significant reductions in 24 urine uric acid excretion but found no significant change in stone size or number, but may have been limited by the short follow-up time [65]. There did not appear to be a significant benefit to the addition of allopurinol to a regimen of indapamide in hypercalciuric patients [59]. Up to 15% of patients taking allopurinol had adverse reactions, including gastrointestinal discomfort, rash, and fatigue, leading to discontinuation of therapy.

Table 12.6 Effect of thiazide and nonthiazide diuretic therapy on urinary calculi formation.

Study ID	Methods	Intervention	Participants	Outcomes	Results	Notes
Brocks [61]	RCT, placebo controlled, double-blind Any pt with radiographic history of ≥2 upper urinary tract stones FU: planned 4 years, actual mean FU 1.6 years	Bendroflumethiazide (BFMZ)	BMFZ – 33 pts Placebo – 29 pts	Newly formed stones per pt per year Remission rate	Stones per pt per year 0.09 (BFMZ), 0.11 (placebo) Remission rate 84.8% (BFMZ), 82.8% (placebo) RR remission 1.17 (95% CI 0.30–4.52)	Randomization resulted in intervention group having significantly fewer stones per pt per year prior to treatment Study reported prior to completion of the study period Not selected for pts with hypercalciuria Differences in remission rate not statistically significant
Scholz [62]	RCT, placebo controlled Pts with "metabolically active calcium stone formation" FU: 12 months	Hydrochlorothiazide (HCTZ)	HCTZ – 25 pts Control – 26 pts	Spontaneous passage of newly formed stones Remission rate	Stones per pt per year 0.24 (HCTZ), 0.23 (placebo) Remission rate 76.0% (HCTZ), 76.9% (placebo) RR remission 0.95 (95% CI 0.26–3.47)	Method of assessing outcome not stated Not selected for pts with hypercalciuria 2 pts in intervention group and 1 pt in placebo group discontinued therapy due to side effects Differences in remission rate not statistically significant
Laerum [63]	RCT, placebo controlled, double-blind Any pt with history of ≥2 urinary tract stones with most recent one radiographically documented FU: 3 years	HCTZ	HCTZ – 25 pts Placebo – 25 pts	Spontaneously passed and newly formed radiographically identified stones per pt per year Remission rate	Passed and newly formed stones per pt per year 0.21 (HCTZ), 0.32 (placebo) Remission rate 78.3% (HCTZ), 52.0% (placebo), $p=0.05$ RR remission 3.32 (95% CI 0.94–11.76)	2 pts in intervention group lost to follow-up Not selected for pts with hypercalciuria Differences in remission rates not statistically significant
Mortensen [58]	RCT, placebo controlled, double-blind Stone-free pts with radiographic history of ≥1 stone FU: 2 years	BFMZ and potassium	BFMZ – 12 pts Placebo – 10 pts	Remission rate	Remission rate 100% (BFMZ), 60% (placebo) RR remission 17.3 (95% CI 0.80–373.45)	Study enrolled fewer than 50% of planned enrollment 15% of pts lost to follow-up Not selected for pts with hypercalciuria Differences in remission rates not statistically significant

(*continued overleaf*)

Table 12.6 (Continued)

Study ID	Methods	Intervention	Participants	Outcomes	Results	Notes
Ettinger [60]	RCT, placebo controlled, double-blind Pts with active recurrent stone disease FU: 3 years	Low-dose chlorthalidone, high-dose chlorthalidone or placebo	Low-dose chlorthalidone – 19 pts High-dose chlorthalidone – 23 pts Placebo – 31 pts	Stone events (defined as growth of previous calculi, appearance of new calculi, or passage of calculi) per pt per year Remission rate	Stone events per pt per year 0.07 (low-dose chlorthalidone), 0.05 (high-dose chlorthalidone), 0.22 (placebo) Remission rate 84.2% (low-dose chlorthalidone), 87.0% (high-dose chlorthalidone), 85.7% (chlorthalidone overall), 54.8% (placebo) RR remission 4.94 (95% CI 1.62–15.10)	Randomization based on hospital record number 38% of intervention pts did not complete the study (18% lost interest, 21% developed side effects including fatigue, impotence, and light-headedness) 16% of placebo pts did not complete the study Not selected for pts with hypercalciuria
Ohkawa [64]	RCT Calcium stone formers with idiopathic hypercalciuria FU: actual mean FU 2 years	Trichlormethiazide (TMZ)	TMZ – 82 pts Control – 93 pts	Spontaneously passed and newly formed radiographically identified stones per pt per year Remission rate defined as total relapse-free pt-years per total pt-years	Passed and newly formed stones per pt per year 0.13 (TMZ), 0.31 (placebo), $p<0.05$ Remission rate 91.7% (TMZ), 85.9% (placebo), $p>0.05$ RR remission cannot be calculated from these data	17% of pts did not complete the study 2 pts in intervention group discontinued therapy because of side effects Differences in relapse-free rates not statistically significant
Borghi [59]	RCT Stone-free recurrent calcium stone formers with idiopathic hypercalciuria FU: 3 years	± Indapamide ± allopurinol	Indapamide – 25 pts Indapamide + allopurinol – 25 pts	Spontaneous passage and newly formed radiographically identified stones per pt per year Remission rate	Passed and newly formed stones per pt per year 0.06 (indapamide), 0.04 (indapamide + allopurinol), 0.28 (control), $p<0.01$ Remission rate 84.2% (indapamide), 87.5% (indapamide + allopurinol), 57.2% (control) RR remission vs. control 4.13 (95% CI 1.09–15.59) (indapamide), 5.76 (95% CI 1.36–24.36) (indapamide + allopurinol)	44% of control pts, 24% of indapamide pts, and 4% of indapamide + allopurinol pts did not complete the study

Table 12.7 Effect of xanthine oxidase inhibitor therapy on urinary calculi formation.

Study ID	Methods	Intervention	Participants	Outcomes	Results	Notes
Ettinger [68]	RCT, placebo controlled, double-blind Hyperuricosuric, normocalciuric pts with ≥2 calcium oxalate stones in the prior 5 years with 1 stone in the prior 2 years FU: 2 years	± Allopurinol	Allopurinol – 29 pts Placebo – 31 pts	Stone events (defined as growth of previous calculi, appearance of new calculi, or passage of calculi) per pt per year Remission rate	Stone events per pt per year 0.12 (allopurinol), 0.26 (placebo), $p<0.05$ Remission rate 69.0% (allopurinol), 41.9% (placebo) RR remission 3.08 (95% CI 1.06–8.90)	15% of enrolled intervention pts discontinued therapy within the first 6 months due to gastrointestinal discomfort, rash, or fatigue and were not included in the results 10% of intervention pts did not complete the study 6% of placebo pts did not complete the study
Borghi [59]	RCT Stone-free recurrent calcium stone formers with idiopathic hypercalciuria FU: 3 years	± Indapamide ± allopurinol	Indapamide – 25 pts Indapamide + allopurinol – 25 pts	Spontaneous passage and newly formed radiographically identified stones per pt per year Remission rate	Passed and newly formed stones per pt per year 0.06 (indapamide), 0.04 (indapamide + allopurinol), 0.28 (control), $p<0.01$ Remission rate 84.2% (indapamide), 87.5% (indapamide + allopurinol), 57.2% (control) RR remission vs. control 4.13 (95% CI 1.09–15.59) (indapamide), 5.76 (95% CI 1.36–24.36) (indapamide + allopurinol) RR remission indapamide + allopurinol vs. indapamide 1.40 (95% CI 0.28–7.00)	44% of control pts, 24% of indapamide pts, and 4% of indapamide + allopurinol pts did not complete the study Not selected for hyperuricosuria Differences in remission rates not statistically significant between indapamide + allopurinol and indapamide alone arms
Goldfarb [65]	RCT, placebo controlled, double-blind Hyperuricosuric calcium stone formers with stone ≥3 mm FU: 6 months	± Febuxostat, ± allopurinol	Febuxostat – 33 pts Allopurinol – 33 pts Placebo – 33 pts	24 h urine uric acid excretion Change in stone size Change in stone number	24 h urine uric acid excretion 59% decrease (febuxostat), 36% decrease (allopurinol), 13% decrease (placebo), $p<0.001$ and $p=0.008$ vs. placebo, respectively, $p=0.003$ febuxostat vs. allopurinol Mean stone size 6.5% decrease (febuxostat), 0.6% increase (allopurinol), 3.2% increase (placebo) Mean stone number 0.1% decrease (febuxostat), 0.3% increase (allopurinol), 0.1% increase (placebo)	Differences in 24 h urine uric acid excretion statistically significant No significant differences in stone size or number

Comment

We suggest that urologists prescribe xanthine oxidase inhibitors in hyperuricosuric patients (conditional recommendation based on very low-quality evidence). This recommendation places a high value on the avoidance of future stone and a relatively low value on the issue of long-term compliance and resource utilization. The evidence is insufficient to make a recommendation in non-hyperuricosuric patients in whom this is a reasonable option.

Clinical question 8

What is the effect of alkali citrate therapy on recurrence of urinary calculi?

Literature search

The PubMed literature search used previously yielded three RCTs that studied the use of alkali therapy for the prevention of recurrent stone disease. Searches of CINAHL and the Cochrane Central Register of Controlled Trials did not identify any additional published or unpublished randomized studies.

The evidence

Of the three placebo-controlled RCTs utilizing alkali citrate therapy for medical prophylaxis of stone disease, one trial used potassium citrate, one used sodium–potassium citrate (Na-K-Cit), and one used potassium–magnesium citrate (K-Mg-Cit) (Table 12.8). All three studies suffered from a high rate of patient noncompliance. In the only trial that selected for hypocitraturic patients, Barcelo et al. measured radiographically identified new stone formation events and found that potassium citrate therapy resulted in a stone event rate of 0.1 stones per patient per year compared with 1.1 stones per patient per year for placebo [66]. Hofbauer et al. did not define their stone event outcome and found no difference in stone formation rates between Na-K-Cit and placebo (0.9 and 0.7 stones per patient per year, respectively) [67]. The remission rates for alkali citrate therapy ranged from 31 to 88%, with an overall remission rate of 60%. The remission rates for placebo patients ranged from 20 to 36%, with an overall remission rate of 29%. The RR of remission with alkali citrate therapy ranged from 1.21 to 12.44, with an overall RR of 4.83 (95% CI 2.13–10.92). Minor adverse reactions, primarily gastrointestinal, occurred in up to 42% of patients. Significant gastrointestinal adverse reactions resulting in discontinuation of therapy occurred in up to 16% of patients.

Clinical implications

We recommend that urologists prescribe alkali therapy for the secondary prevention of calcium stone disease (strong recommendation based on low-quality evidence). This recommendation places a high value on the avoidance of future stone disease and a relatively low value on the issue of long-term compliance and resource utilization. Potassium citrate and potassium–magnesium citrate appear to be the preferred agents.

Clinical question 9

What is the effect of acetohydroxamic acid (AHA) therapy on the course of struvite stone disease?

Literature search

The PubMed literature search used previously yielded three RCTs that studied the use of AHA for prevention of recurrent stone disease. Searches of CINAHL and the Cochrane Central Register of Controlled Trials did not identify any additional published or unpublished randomized studies.

The evidence

All patients in each of the three placebo-controlled RCTs that used AHA for the treatment and/or prevention of struvite stone disease had chronic urinary tract infections (UTIs) due to urea-splitting organisms (Table 12.9). The primary outcome in each trial was the variably defined growth of stones and ranged from 0 to 42% for AHA groups versus 37 to 60% for placebo groups. In two of these trials, these differences were statistically significant [70, 71]. In these two trials, the RR of stone growth with AHA treatment were 0.04 and 0.23, with an overall RR of 0.18 (95% CI 0.08–0.44). The third trial, which was limited to patients with spinal cord injuries in a Veterans' Affairs hospital setting, suffered from an extremely high dropout rate of 49% [72]. However, this study illustrates the relatively high rate of toxicity associated with AHA, with up to 20% of patients discontinuing therapy due to severe or recurrent gastrointestinal, neurological, or hematological adverse reactions.

Clinical implications

We suggest that urologists prescribe AHA in patients with recurrent, treatment-refractory struvite stones (conditional recommendation based on very low-quality evidence). This recommendation places a high value on the avoidance of further urological intervention and a relatively low value on the avoidance of treatment-related adverse events specific to AHA.

Table 12.8 Effect of alkali therapy on urinary calculi formation.

Study ID	Methods	Intervention	Participants	Outcomes	Results	Notes
Barcelo [66]	RCT, placebo controlled Idiopathic hypocitraturic active calcium stone formers with ≥2 stones in previous 2 years FU: 3 years	Potassium citrate	Potassium citrate – 18 pts Placebo – 20 pts	Newly formed radiographically identified stones per pt per year Growth of stones ≥100% increase in stone size Remission rate	Stones per pt per year 0.1 (potassium citrate), 1.1 (placebo), $p<0.001$ Growth of stones 16.7% (potassium citrate), 20.0% (placebo) Remission rate 72.2% (potassium citrate), 20% (placebo) RR remission 10.40 (95% CI 2.31–46.83)	28% of pts excluded due to noncompliance 17% of potassium citrate pts reported minor GI adverse reactions 4% of potassium citrate and 2% of placebo pts discontinued therapy due to GI intolerance
Hofbauer [67]	RCT, placebo controlled Recurrent idiopathic calcium stone formers ≥1 stone per year in previous 3 years FU: 3 years	Sodium–potassium citrate (Na-K-Cit)	Na-K-Cit – 22 pts Placebo – 16 pts	Stones per pt per year Remission rate	Stones per pt per year 0.9 (Na-K-Cit), 0.7 (placebo), $p=0.65$ Remission rate 31% (Na-K-Cit), 27% (placebo) RR remission 1.21 (95% CI 0.29–3.47)	Stone events not defined 16% of pts excluded due to noncompliance 16% of Na-K-Cit pts discontinued therapy due to GI intolerance Differences in remission rates not statistically significant Not selected for pts with hypocitraturia
Ettinger [69]	RCT, placebo controlled Recurrent idiopathic calcium stone formers FU: 37 months	Potassium–magnesium citrate (K-Mg-Cit)	K-Mg-Cit – 16 pts Placebo – 25 pts	Remission rate	Remission rate 87.9% (K-Mg-Cit), 36.4% (placebo) RR remission 12.44 (95% CI 2.29–67.56)	16% of K-Mg-Cit pts discontinued therapy due to GI intolerance 42% of K-Mg-Cit pts and 40% of placebo pts reported minor GI adverse reactions Not selected for pts with hypocitraturia

Table 12.9 Effect of acetohydroxamic acid (AHA) therapy on urinary calculi formation.

Study ID	Methods	Intervention	Participants	Outcomes	Results	Notes
Williams [71]	RCT, placebo controlled Stone analysis-confirmed struvite stone formers or staghorn calculi pts with persistent urea-splitting organism UTI FU: mean 15.8 months (AHA), 19.6 months (placebo)	Suppressive antibiotics ± AHA	AHA – 20 pts Placebo – 19 pts	Doubling of two-dimensional stone area or formation of new stones No. of surgical interventions for obstruction or infection Adverse reactions	Doubling of stone area 0% (AHA), 37% (placebo), $p=0.008$ RR doubling of stone area 0.04 (95% CI 0.00–0.77) No. of surgical interventions 0% (AHA), 11% (placebo), p not significant Adverse reactions 45% (AHA), 5% (placebo), $p=0.008$	Adverse reactions included tremulousness, deep venous thrombosis, and intolerable headache
Griffith [72]	RCT, placebo controlled, double-blind Spinal cord injury patients with chronic urea-splitting organism UTI FU: planned 2 years, actual not stated	AHA	AHA – 121 pts Control – 89 pts	Freedom from stone growth Doubling of stone area or increase in stone size to ≥100 mm^2	Freedom from stone growth at 1 year 67% (AHA), 40% (placebo), $p=0.017$ Freedom from stone growth at 2 years 58% (AHA), 40% (placebo), p not significant Doubling of stone area at 1 year 17% (AHA), 33% (placebo) Doubling of stone area at 2 years 4% (AHA), 31% (placebo)	49% of pts did not complete the study 20% of AHA pts did not complete the study due to severe or recurrent adverse reactions including gastrointestinal, neurological, and hematological side effects 1-year analysis includes only 85 pts, 2-year analysis includes only 59 pts
Griffith [70]	RCT, placebo controlled, double-blind Struvite stone formers with urea-splitting organism UTI FU: mean 18 months	AHA	AHA – 45 pts Placebo – 49 pts	Stone area growth ≥25%	Stone area growth 17% (AHA), 46% (placebo), $p<0.005$ RR stone area growth 0.23 (95% CI 0.09–0.63)	4% of AHA pts discontinued treatment due to toxic reactions including hemolytic anemia and phlebitis

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13 CHAPTER 13

Surgical management of renal stone disease

Justin M. Dersch, Brandon J. Otto, and Benjamin K. Canales
Department of Urology, University of Florida, Gainesville, FL, and North Florida/South Georgia VAMC, Gainesville, FL, USA

Background

Minimally invasive surgical techniques, including extracorporeal shock-wave lithotripsy (SWL), ureteroscopy (URS), and percutaneous nephrolithotomy (PCNL), have supplanted open surgery for the management of nearly all renal calculi. Over the last 15 years, advances in flexible ureteroscope design and miniaturized accessories have enhanced intracorporeal kidney stone surgical outcomes (URS, PCNL), and the use of adjuvant medications and therapies has improved the success rates of SWL. Worldwide, SWL remains the mainstay stone treatment (40–50%) and PCNL, for larger stones, remains the least utilized (5–10%) [1, 2]. URS has been shown in contemporary studies to have an upward trend in utilization over other modalities (30–40% worldwide), particularly in the United States and Canada and among younger urologists [3]. This chapter reviews the available surgical evidence for renal stone surgery by stratifying outcomes for lower pole stones and for asymptomatic calyceal stones. In addition to randomized controlled trials (RCTs) in these areas, studies involving SWL delivery and adjuvant therapies following stone treatment are also reviewed.

Clinical question 1

Should patients with symptomatic small (<10 mm) and medium-sized (10–20 mm) lower pole (LP) kidney stones undergo PCNL, URS, or SWL?

Literature search

Relevant studies were retrieved from electronic databases including the Cochrane Central Register of Controlled Trials (The Cochrane Library), MEDLINE 1996–current, and EMBASE 1980–current. Reference lists were also made from urology and nephrology textbooks, review articles, and relevant studies and also electronic communications seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies. Search terms included all forms and abbreviations of "PCNL," "SWL," "URS," "lithotripsy," "lower pole," and nephrolithiasis.

The evidence

The gravity-dependent nature of the renal lower pole and its anatomy, including infundibular length, width, and infundibulopelvic angle, is thought to reduce spontaneous passage of stone fragments following lithotripsy. Five prospective randomized clinical trials have evaluated SWL, URS, and PCNL as treatment modalities for small and medium-sized kidney stones in the lower pole (Table 13.1). One trial compared PCNL with SWL and four trials compared URS with SWL [4]. In general, the early multicenter studies demonstrated a lack of standardization in SWL treatment, including variations in number of shocks and power settings used. Similarly, ureteral stent placement during the procedure was not standardized. The more recent single-center studies have more thoroughly standardized their SWL cohorts. Additionally, many of these studies excluded patients with unfavorable factors for SWL success, such as a steep infundibular-pelvic angle. These exclusions, which are appropriate in a trial setting, could potentially overestimate the true stone-free rate (SFR) for SWL of small LP stones.

In 2001, Albala et al. compared SWL with PCNL in a prospective multicenter randomized trial of 128 patients with LP stones measuring <3 cm [5]. In the "Lower Pole I" study, the KUB (kidney–ureter–bladder X-ray) SFR was considerably higher for PCNL (95%) than SWL (37%, $p<0.001$).

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Table 13.1 Surgical outcomes for lower pole kidney stones.

Study ID	Methods	Intervention	Participants	Outcomes	Results	Notes
Albala, 2001 [5]	Randomized, multicenter FU: 3 months annually for 3 years	SWL (settings and no. of shocks variable) PCNL (lithotripters variable)	Symptomatic LP calculi ≤3.0 cm SWL: $n=68$ PCNL: $n=60$	SFR LP anatomy Complication rates QOL (SF-36)	Overall SFR: SWL 37% PCNL 95% ($p<0.001$) SFR not influenced by LP anatomy No difference in rates of complications ($p=0.087$) or QOL metric ($p=0.7$)	Failures were treatments other than assigned treatment Stenting at surgeon discretion Tomography follow-up imaging
Pearle, 2005 [6]	Randomized, multicenter FU: 2–6 weeks, 3 months	SWL (settings and no. of shocks variable) URS (scopes, stent, access sheaths variable)	Symptomatic LP stone <1 cm SWL: $n=32$ URS: $n=35$	SFR QOL (RAND 36 Health Survey) Secondary procedures	SFR not statistically significantly different ($p=0.92$) QOL: SWL favored over URS (significant in all categories) Secondary treatments not significantly different	60% of patients' stones manually removed by URS Stent placement variable Noncontrast CT follow-up imaging
Sener, 2014 [7]	Randomized, single-center FU: 1 week, 3 months	SWL (2500–3000 shocks at 14–17 kV) URS (same scopes and access sheaths, stent only for complications)	Symptomatic LP stone <1 cm SWL: $n=70$ URS: $n=70$	SFR Complication rates	Overall SFR: SWL 91.5% URS 100% ($p<0.05$) SWL group had a mean of 2.7 sessions, 6 patients required URS No difference in rates of complications	Excluded patients with steep (<30°) infundibulopelvic angle KUB and US for follow-up imaging No difference in SFR at 1 week (49% SWL vs. 52% URS)
Singh, 2014 [8]	Randomized, single-institution FU: 3 and 4 weeks	SWL (settings per a step protocol, minimum of 3500 shocks) URS (same scopes, access sheaths, routine stenting)	Symptomatic LP stone 1–2 cm SWL: $n=35$ URS: $n=35$	SFR Retreatment rate Auxiliary procedure rate Complication rates Patient-reported outcomes	Overall SFR: SWL 49% URS 83% ($p=0.005$) Retreatment (65 vs. 6%, $p=0.0001$) and auxiliary procedures (45 vs. 8%, $p=0.0009$) higher for SWL Patient satisfaction higher in URS group ($p=0.026$) Pain, voiding symptoms, and return to work significantly better in SWL group No difference in rates of complications	Trend towards larger stone size in SWL group (16.45 vs. 15.05 mm, $p=0.054$) BMI >29 excluded ESWL repeated up to 2 times prior to auxiliary procedures KUB and US for follow-up imaging Patient-reported outcomes used nonvalidated investigator-made questionnaires
Kumar, 2015 [9]	Randomized, single-center FU: 2 weeks and 3 months	SWL (100 shocks/min, up to 3000 shocks) URS (same scopes, access sheaths, stents for "large" stone burden)	Symptomatic LP stone ≤2 cm SWL: $n=97$ URS: $n=98$	SFR with subgroup analysis (≤1 and 1–2 cm) Modified Efficiency Quotient (EQ) Retreatment rate Auxiliary procedure rate	Overall SFR not different ($p=0.34$) Modified EQ higher for URS (83 vs. 46%, $p=0.01$) for 1–2 cm stones Retreatment rate higher with SWL (61.1 vs. 10.1%, $p<0.001$) Auxiliary procedure and complication rates were not different	Excluded patients >60 years old, unfavorable LP anatomy, and serum Cr >1.5 Local anesthesia and diclofenac only for SWL KUB and US for follow-up imaging

FU, follow-up.

These effects were also seen with stones <1 cm, with SFR for PCNL 100% and for SWL 63%. In fact, this is the only size range where SWL demonstrated SFR >50%. Quality of life assessments and complication rates were similar for both modalities.

When considering URS versus SWL for the treatment of symptomatic LP stones, four studies have now been published. The first, by Pearle et al. in 2005, compared SWL with URS in a prospective multicenter randomized trial of 67 patients with LP stones measuring <1 cm [6]. The "Lower Pole II" study found no difference in computed tomography (CT) SFR at 3 months between SWL and URS (35 vs. 50%, $p=0.92$). This remained true for URS patients who had residual stone fragments manually extracted or left in place to pass spontaneously. In addition, there was no difference in the need for secondary procedures between URS and SWL cohorts. Operative time, hospital stay, and quality of life (QOL) measures significantly favored patients treated with SWL.

In 2014, Sener et al. reported a prospective single-center randomized trial comparing SWL with URS in 140 patients with LP stones measuring <1 cm [7]. They showed an improved KUB/US (ultrasound) SFR at 3 months with URS (100%) versus SWL (91.5%, $p<0.05$). For URS, the procedure was terminated after stone fragments were <3 mm and stents were not routinely left. The SWL group had a mean of 2.7 sessions and 8.6% had URS for symptomatic fragments >3 mm. There was no difference in complication rates.

Also in 2014, Singh et al. described results from a prospective single-center randomized trial comparing SWL with URS in 70 patients with 1–2 cm symptomatic LP stones [8]. They showed an improved KUB/US SFT at 4 weeks with URS (83%) versus SWL (49%, $p=0.005$). There was a trend towards larger stones in the SWL group (16.45 vs. 15.05 mm, $p=0.054$). Retreatment (65 vs. 6%, $p=0.0001$) and auxiliary procedure rates (45 vs. 8%, $p=0.0009$) were higher for the ESWL group. Using nonvalidated self-made questionnaires to evaluate patient-reported outcomes, the authors found patient satisfaction to be higher in the URS group; however, pain, voiding symptoms, and return to work were significantly better in the SWL group.

Most recently, in 2015, Kumar et al. reported results from a prospective single-center randomized trial comparing SWL with URS in 195 patients with symptomatic LP stones <2 cm [9]. At 3 months, the overall KUB/US SFR was not different between the two groups. This finding persisted on subgroup analysis of stones <1 and 1–2 cm. The authors found an improved modified efficiency quotient (incorporates retreatment rates) with URS for 1–2 cm LP stones (83 vs. 46%, $p=0.01$). The retreatment rate was higher for SWL (61.1 vs. 10.1%, $p<0.001$). There was no difference in both auxiliary procedures and complication rates between the two groups.

Clinical implications

We suggest the use of either URS or SWL over PCNL for the treatment of symptomatic small (<10 mm) LP stones (conditional recommendation based on moderate-quality evidence). Multiple studies have shown either no difference or a slight benefit to URS compared with SWL with regard to SFR. URS has a lower retreatment rate, however QOL metrics favor SWL. These tradeoffs need to be discussed with the patient; patients who are risk averse may favor SWL whereas those who seek to minimize the probability of requiring retreatment may prefer URS.

We suggest the use of either PCNL or URS over SWL for the treatment of symptomatic medium-sized (10–20 mm) LP stones (conditional recommendation based on moderate-quality evidence). A preponderance of evidence has shown improved SFR with either PCNL or URS compared with SWL without any increase in complication rates. Kumar et al. did not show a benefit in SFR, but did show an improvement in the modified efficiency quotient for URS compared with SWL secondary to an increased retreatment rate associated with SWL [9]. No randomized studies between PCNL and URS have been published to date.

Clinical question 2

Should patients undergoing SWL for renal stones receive adjuvant medical expulsive therapy?

Literature search

Relevant studies were retrieved from electronic databases including the Cochrane Central Register of Controlled Trials (The Cochrane Library), MEDLINE 1996–current, and EMBASE 1980–current. Reference lists were also made from urology and nephrology textbooks, review articles, and relevant studies and also electronic communications seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies. Search terms included all forms and abbreviations of "percussion, diuresis, and inversion (PDI)," "PCNL," SWL," "URS," "lithotripsy," "nephrolithiasis," "medical," "therapy," and "*niruri*."

The evidence

Evidence that ureteral stone clearance may be enhanced with medication has been increasing for several years, and indeed multiple RCTs comparing SFR of SWL with or without tamsulosin in the setting of ureteral stones have now been performed. Here we examine the evidence for tamsulosin and other alpha-blockers and also dietary supplements (*Phyllanthus niruru*) or mechanical assistance in increasing SFR following SWL for renal rather than ureteral stones (Table 13.2).

Six studies have prospectively looked at the role of adjuvant alpha-blocker therapy following SWL for renal stones.

Table 13.2 Adjuvant therapies following SWL.

Study ID	Methods	Intervention	Participants	Outcomes	Results	Notes
Gravina, 2005 [10]	RCT, single-center, no blinding FU: 3 months	Standard therapy: SWL followed by 1 mg methylprednisolone b.i.d. × 15 days, 75 mg diclofenac i.m. prn, 15 mg lansoprazole daily, drink ≥2 L water daily Standard therapy + tamsulosin	Renal stones 4–20 mm Std: *n* = 65 Tam: *n* = 65	KUB, RUS, IVP SFR Adverse events Analgesic use	KUB SFR: Tam 79% compared with standard therapy 60% (p = 0.0037) Stones >10 mm had higher clearance rates	Decreased episodes of pain and diclofenac use Significant improvement in first (p = 0.015, Tam) and last follow-up visits
Naja, 2008 [11]	RCT, single-center, no blinding FU: ≤3 months	Tamsulosin + SWL SWL alone	Single, radiopaque renal stone 6–15 mm Tam: *n* = 51 SWL: *n* = 65	KUB SFR Rapidity of clearance	KUB SFR at 3 months: Tam 94% vs. SWL alone 85% (p = 0.14) Higher success rate at 3 weeks in Tam arm	Power calculation performed Up to 4 SWL performed No blinding
Bhagat, 2007 [12]	RCT, single-center, double-blinded FU: 1 month	Tamsulosin + SWL Placebo + SWL	Renal and ureteral stones 6–24 mm Tam: *n* = 29 SWL: *n* = 29	KUB SFR Adverse events Median dose analgesics	KUB SFR: Tam 97% compared with placebo 79% (p = 0.04) Stones >10 mm had higher clearance rates	No differences noted in mean analgesic dose Unable to separate renal from ureteral stones in results
Hussein, 2010 [13]	RCT, single-center, single-blinded FU: 3 months	Tamsulosin + SWL SWL alone	Single, radiopaque <25 mm pelvic, <15 mm upper or mid-pole, <10 mm lower pole stones Tam: *n* = 67 SWL: *n* = 69	KUB, RUS SFR, or asymptomatic <3 mm residual Rapidity of clearance Analgesic use	Success at 3 months: Tam73% vs. SWL alone 55% (p = 0.008) Time to clearance at 1 month : Tam 46% vs. SWL alone 31% (p = 0.02) Decrease in patients with colic, total episodes of colic, and total analgesia used (p = 0.003, 0.001, and 0.002, respectively)	Convenience sample No patients with mid-pole stones Time to clearance significant in pelvic and upper pole stones, with trend towards significance for lower pole
Vicentini, 2011 [14]	RCT, single-center, double-blinded FU: 1 month	Tamsulosin + SWL Nifedipine + SWL Placebo + SWL	Radiopaque non-lower pole renal stone Tam: *n* = 38 Nif: *n* = 35 SWL: *n* = 38	KUB, RUS SFR, or asymptomatic ≤4 mm residual Adverse events Rapidity of clearance Analgesic use	Success: Tam 60.5% vs. Nif 48.6% vs. SWL 36.8% (p = 0.118) Stones 10–20 mm Success: Tam 61.9% vs. Nif 60% vs. SWL 26.1% (p = 0.024)	Power calculation performed Nifedipine as safe and effective as tamsulosin
Zaytoun, 2012 [15]	RTC, single-center FU: 3 months	Phloroglucinol + SWL Tamsulosin + phloroglucinol + SWL Doxazosin + phloroglucinol + SWL	Solitary radiopaque <20 mm pelvic, middle calyceal, or upper renal stone Phlo: *n* = 50 Tam: *n* = 50 Dox: *n* = 50	KUB SFR or asymptomatic ≤3 mm residual Rapidity of clearance Adverse events Analgesic use	SFR: Phlo 84% vs. Tam 92% vs. Dox 90% (p = 0.23–0.73) Expulsion rate (weeks): Phlo 7.3 vs. Tam 5.3 vs. Dox 6.8 (p = 0.002–0.026 favoring Tam) Diclofenac use: Phlo 546 mg vs. Tam 312 mg vs. Dox 410 mg (p = <0.001–0.028 favoring Tam)	No blinding Variable SWL sessions (1–4) No difference in SFR but more rapid expulsion and less analgesic use, with tamsulosin better than doxazosin better than placebo

Micali, 2006 [16]	RCT, single-center FU: 1, 2, 3, 6 months (KUB/US)	Uriston (*P. niruri*) + SWL SWL alone	Any size calcium oxalate renal calculi Uriston: $n=78$ Control: $n=72$	KUB SFR and KUB fragments ≤3 mm Retreatment rate	No KUB SFR (94 vs. 83%, $p=0.48$) or small fragment (89 vs. 76%, $p=0.08$) differences LP KUB SFR higher in Uriston (94%) compared with no Uriston (71%, $p<0.001$) KUB SFR higher with stones <10 mm (97 vs. 85%, $p=0.02$) No difference in retreatment rate (40 vs. 43%, $p=0.2$)	Stents placed for stones >2.0 cm Variable SWL sessions (1–3) Dornier S lithotripter 3000 shocks/session Uriston group had faster stone clearance rates at 1 month (54 vs. 19%, $p=0.02$) and 2 month FU (69 vs. 35%, $p=0.03$)
Pace, 2001 [17]	RCT, single-center, single-blinded FU: 3 months	Mechanical percussion, diuresis, and inversion (PDI) + SWL SWL alone	Residual lower pole fragments <4 mm; 3 or more months after SWL PDI: $n=35$ ESWL: $n=34$	KUB SFR Adverse effects of intervention Prognostic factors affecting outcome	KUB SFR: PDI 40% compared with SWL alone 3% ($p<0.001$) No adverse effects in either group Stone area, location, and infundibular width were independent predictors of outcome	Observation group offered cross-over if persistent stones after 1 month Blinded radiologist- determined SFR Intervention effect at randomization and cross-over was identical
Chiong, 2005 [18]	RCT, single-blinded FU: 1, 3 months	Mechanical percussion, inversion, diuresis (PDI) + SWL SWL alone	Radiopaque lower pole calculi ≤2 cm that fragmented during SWL to ≤4 mm PDI: $n=59$ ESWL: $n=49$	KUB SFR Adverse effects of intervention Prognostic factors affecting outcome	KUB SFR: PDI 63% compared with SWL alone 35% ($p=0.006$) One patient found PDI painful until resolution of an SWL hematoma	Blinded radiologist- determined SFR 16% PDI received 5 or more sessions Variable SWL sessions (1–4)

Gravina et al. reported the first evidence for adjunctive tamsulosin following SWL for kidney stones [10]. Their group studied 130 patients who were randomized to standard therapy or standard therapy plus tamsulosin for a total of 12 weeks or until another intervention occurred. They reported higher KUB SFR (79 vs. 60%, $p=0.0037$) and less pain and analgesic use in the tamsulosin group compared with controls. Subgroup analysis showed that subjects with larger diameter renal stones (>10 mm) benefited most from therapy (81 vs. 55%, $p=0.009$) compared with stones ≤10 mm (75 vs. 68%, $p>0.05$). Incidence of repeat SWL or ureteroscopy (31% total) was less in the tamsulosin group but not statistically significant ($p>0.05$). Naja et al. [11] reported a very similar study design to that of Gravina et al. [10]. They randomized 116 patients with a single radiopaque renal stone measuring 6–15 mm with SWL only or SWL with tamsulosin. Patients had SWL done every 3 weeks for up to 12 weeks or until radiographic success. Success rates after the first, second, and third SWL sessions initially increased more in the tamsulosin arm (53, 78, 94%) than in controls (31, 52, 75%; $p=0.016$, 0.004, 0.005, respectively), representing more rapid clearance of stone fragments, but SFR at 3 months was not statistically different between study groups ($p=0.14$). Naja et al. concluded that adjunctive tamsulosin decreases time to clearance but did not affect long-term SFR. In addition to earlier clearance of fragments, subjects on tamsulosin required fewer SWL sessions (1.4 vs. 10.4%), had less pain, and developed fewer episodes of steinstrasse than controls.

In 2007, Bhagat et al. reported higher KUB SFR after randomizing 58 patients with both ureteral and renal stones to tamsulosin (96.6%) or placebo (79.3%) after SWL, although analgesic administration between the groups was similar [12]. Subgroup analysis revealed that patients with stones >10 mm had significantly higher SFR (93.3 vs. 58.3%, $p=0.03$) compared with stones ≤10 mm (100 vs. 94.1%, $p=0.35$). Methods for analgesic dosing in the study were unclear, and location of stone clearance was not evaluated. In 2010, Hussein reported on a single-center randomized trial comparing tamsulosin after single SWL session with SWL alone in 136 patients with renal stones. They found that the addition of tamsulosin resulted in increased KUB and RUS (renal ultrasound) SFR (73 vs. 55%; $p=0.008$) and earlier time to clearance (46 vs. 31%; $p=0.02$), and also a decrease in the number of patients reporting colic (13.4 vs. 30.4%; $p=0.003$). [13]. Only patients were blinded to group assignment, subjects were not randomized to placebo, and reporting of pain episodes was subjective. More recently, Vicentini et al. examined the effect of tamsulosin versus nifedipine versus placebo after SWL for non-LP renal stones in a single-center double-blind RCT of 111 patients [14]. There was no difference in overall treatment success between the three study arms (60.5, 48.6, 36.8%; $p=0.118$). Subgroup analysis of the 69 patients with stones 10–20 mm demonstrated results supporting those found by Bhagat et al., finding tamsulosin and nifedipine superior to placebo at 1 month of follow-up only for stones 10–20 mm (61.9, 60, 26.1%; $p=0.024$). Vicentini et al. therefore suggested that nifedipine may be as effective as tamsulosin as adjunctive treatment following SWL. Most recently, Zaytoun et al. found no difference in SFR at 3 months after ESWL between tamsulosin or doxazosin in addition to standard therapy with 80 mg phloroglucinol three times daily versus standard therapy alone (92 vs. 90 vs. 84%; $p=0.73$) in 150 patients undergoing SWL for solitary pelvic, middle or upper pole stones measuring <2 cm [15]. However, analysis of secondary endpoints did show decreased weeks to expulsion (5.3 vs. 6.8 vs. 7.3 weeks; $p=0.002$ and 0.026) and decreased milligrams of analgesic used (312, 410, 546 mg; $p<0.001$ and $p=0.028$) in both treatment groups, with tamsulosin more effective than doxazosin.

One study has prospectively looked at the role of adjuvant *P. niruri* following SWL for renal stones. In 2006, Micali et al. hypothesized that the plant *P. niruri* would improve SFR after SWL in patients with calcium oxalate stones [16]. *P. niruri* belongs to the Euphorbiaceae family and has been shown to reduce urinary calcium by inhibiting calcium oxalate crystal adhesion and growth. A total of 150 patients with calcium oxalate renal calculi of any size were randomized to receive either *P. niruri* extract Uriston® or no medical therapy following SWL. There was no difference in overall SFR ($p=0.48$). Subgroup analysis of the 56 patients who had stones in the LP showed that the 32 patients taking Uriston had SFR of 93.7% compared with 70.8% ($p=0.001$) in patients receiving no oral therapy. Similarly, patients in the Uriston arm achieved significantly higher SFR when the stones were ≤10 mm ($p=0.02$). No significant difference was seen in retreatment rates between groups.

Two studies have prospectively evaluated the role of adjuvant mechanical therapy following SWL for renal stones. In 1990, Brownlee et al. first introduced the concept that residual stone debris in dependent portions of the kidney could be manipulated by changing body position [19]. Pace et al. reported the first single-center prospective randomized trial comparing adjuvant weekly mechanical percussion, diuresis, and inversion (PDI) following SWL with SWL alone in 69 patients with residual LP fragments <4 mm at 3 or more months following SWL [17]. All patients were followed with an imaging study (X-ray and tomography or CT) read by a radiologist blinded to the treatment groups in order to determine stone-free status. At 3 months, the SFR for the treatment group and observation group were 40 and 3%, respectively ($p<0.001$). Patients undergoing observation who had residual stones at 4 weeks were offered cross-over into the treatment arm, and these patients also experienced improvement in SFR. Chiong et al. corroborated their findings

by demonstrating significantly higher SFR in patients undergoing PDI with small, post-SWL residual LP stones [18].

Clinical implications

We recommend the use of tamsulosin as adjunctive therapy following SWL for renal stones to increase SFR (strong recommendation based on moderate-quality evidence). This recommendation assumes that patients place a high value on optimizing stone clearance and avoiding secondary procedures and place a low value of the burden of taking MET, and its (minor) side effects and (relatively low) costs.

We suggest nifedipine or doxazosin as an alternative adjunctive therapy to tamsulosin following SWL (conditional recommendation based on low-quality evidence)

We suggest against the use of Uriston following SWL to improve SFR for LP calcium oxalate stones (conditional recommendation based on low-quality evidence).

For motivated patients, we further suggest the use of PDI to improve SFR following SWL (conditional recommendation based on low-quality evidence). For the average patient, diuresis carries the least physical burden and has a very low risk profile and cost. However, its efficacy to improve SFR as a single modality has not been studied after SWL.

Clinical question 3

For patients with small asymptomatic renal calyceal stones, what is more beneficial – stone intervention or stone observation?

Literature Search

Relevant studies were retrieved from electronic databases including the Cochrane Central Register of Controlled Trials (The Cochrane Library), MEDLINE 1996–current, and EMBASE 1980–current. Reference lists were also made from urology and nephrology textbooks, review articles, and relevant studies and also electronic communications seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies. Search terms included all forms and abbreviations of "SWL," "lithotripsy," "nephrolithiasis," "calyceal, and "kidney stone."

The evidence

Three prospective trials randomized asymptomatic patients with renal calyceal stones to observation versus intervention (Table 13.3). One trial compared observation with SWL, a second trial compared observation with PCNL or SWL, and a third trial compared observation with SWL or URS. Keeley et al. compared a multicenter randomized trial of prophylactic SWL with observation in 128 patients with asymptomatic renal stones measuring <1.5 cm [20]. Patients were treated with repeated SWL if residual fragments (≤5 mm) were present on KUB or until three treatment sessions were completed. At a median follow-up of 2.2 years, there was no difference in SFR for the SWL group (28%) compared with observation alone (16%, $p=0.06$). The SWL group had an overall decrease in stone burden defined as an improvement on KUB compared with patients under observation ($p=0.026$). The requirement for additional procedures, QOL measures, and renal function tests were not significantly different between the groups, but 49 additional procedures were required in 20 patients in the observation group. Of these procedures, 10 were considered invasive (ureteroscopy or stenting). In contrast, only nine additional procedures in three patients were required in the SWL group, none of which were invasive.

Yuruk et al. randomized 94 patients with asymptomatic LP stones to PCNL, SWL, or observation at a single center [21]. Mean stone size was between 139 and 153 mm^2 for the three groups. The observation arm was followed for a mean of 19.3 months. They found higher noncontrast CT SFR with PCNL (100%) and SWL (61.3%) compared with observation (3.1%, $p<0.001$) at 12 months. In the observation group, seven patients (18.7%) required intervention during follow-up. Intervention occurred at a median time of 22.5 months. In addition, the authors looked at renal scarring with dimercaptosuccinic acid (DMSA) scans at 6 and 12 weeks and found a trend towards increased scarring with SWL (16.1%) compared with PCNL (3%) and observation (0%, $p=0.05$).

Sener et al. randomized 150 patients with asymptomatic small (<10 mm) LP stones to SWL, URS, or observation at a single center [22]. The observation arm was followed for a mean of 21 months. They found higher noncontrast CT SFR with URS (92 and 92%) and SWL (92 and 100%) versus observation (2 and 10%, $p<0.001$ and $p<0.001$) at 3 months and the end of the study, respectively. The auxiliary procedure rate was no higher in the observation group (12%) versus the URS (8%) and SWL (6%) group ($p=0.555$); 88% of patients in the observation group did not require intervention over the course of the study. After 2 years, the mean stone size was 8.1 mm from 8 mm. Complication rates were no different between the URS (14% total, 6% major) and SWL (6% total, 2% major) groups ($p=0.318$).

Comment

We suggest that patients with small asymptomatic renal calyceal stones are managed observantly (conditional recommendation based on very low-quality evidence). This recommendation places a high value on avoiding potentially unnecessary surgical interventions.

Clinical question 4

For patients with renal stones undergoing SWL, does slower shock-wave delivery (90 or 60 shocks/min) as opposed to the traditional delivery rate (120 shocks/min) provide a better stone-free rate?

Table 13.3 Outcomes of intervention versus observation for small, asymptomatic calyceal stones.

Study ID	Methods	Intervention	Participants	Outcomes	Results	Notes
Keeley, 2001 [20]	RCT, multicenter FU: 3, 26 months	SWL: Retreatment until fragments ≤5 mm (no more than three sessions) Observation group	Asymptomatic patients, combined renal stone burden of ≤1.5 cm Obs: 115 pts SWL: 113 pts	SFR (stone free) Need for additional treatment/ procedures	Similar KUB SFR ($p=0.29$) with improved stone burden in SWL pts ($p=0.026$) Large residual fragments improved with SWL ($p=0.001$) No significant differences in need for additional treatment	Two centers with different lithotripters 88% of pts completed 1-year FU Invasive intervention: 10 pts in observation group (8.6%) No patients in SWL group No difference in symptoms, QOL, or renal function tests
Yuruk, 2010 [21]	RCT, single-center FU: 3 and 12 months Mean FU: 19.3 months	Observation SWL: no anesthesia, power increase from 14 to 24 kV, 3000 shocks, repeat up to 3 times PCNL: 30 F sheath, combined pneumatic and ultrasonic lithotripter, 14 F PCN	Asymptomatic patients, LP stones <1.5 cm Obs: $n=32$ SWL: $n=31$ PCNL: $n=31$	SFR Auxiliary procedure rate Renal scarring	SFR: 12 months: PCNL 100%, SWL 61%, Obs 3.1% ($p<0.001$) 18.7% of Obs group required intervention at median of 22.5 months DMSA: Scarring: PCNL 3%, SWL 16.1%, Obs 0% ($p=0.05$)	Noncontrast CT for follow-up 67.8% of SWL patients had >1 session DMSA scan at 6 weeks and 12 months
Sener, 2015 [22]	RCT, single-center FU: Obs: q3 months, for 24 months SWL/URS: 1 week, 3 months	Observation SWL: 2500–3000 shocks at 14–17 kV, up to 3 courses URS: same scopes and access sheaths, stent only for complications	Asymptomatic patients, LP stones <1 cm Obs: $n=50$ SWL: $n=50$ URS: $n=50$	SFR Retreatment rate Auxiliary measures Complication rates	3 month SFR: URS 92%, SWL 92%, Obs 2% ($p<0.001$) End of study SFR: URS 92%, SWL 100%, Obs 10% ($p<0.001$) No difference in secondary measures: URS 8%, SWL 6%, Obs 12% ($p<0.001$)	Noncontrast CT for follow-up at 3 and 12 months for SWL/URS group, every 6 months in observation group Mean number of ESWL sessions: 1.5

Literature search

Relevant studies were retrieved from electronic databases including the Cochrane Central Register of Controlled Trials (The Cochrane Library), MEDLINE 1996–current, and EMBASE 1980–current. Reference lists were also made from urology and nephrology textbooks, review articles, and relevant studies. Search terms included all forms and abbreviations of "SWL," "lithotripsy," "nephrolithiasis," "rate," and "kidney stone."

The evidence

Five RCTs have been performed examining the effect of shock-wave rates from 60 to 120 shocks/min on the outcome of SWL for renal stones (Table 13.4). A meta-analysis of the first four of these RCTs demonstrated that patients who were treated at 60 shocks/min experienced a 10.2% (95% confidence interval [CI] 3.7–16.8) increase in the likelihood of a successful treatment outcome ($p=0.002$) over those who had 120 shocks/min [23]. However, only one of these studies mentions blinding the outcome assessor to group assignment. The studies were heterogeneous in definition of treatment success, inclusion criteria, lithotripsy device, anesthetic protocol, and imaging modality used for demonstration of successful treatment. Additionally, the most recent study varied not only in the shock rate but also the total number of shocks delivered between the two study arms.

Madbouly et al. prospectively randomized 156 patients with a single renal or ureteral stone measuring <30 mm to 60 or 120 shocks/min and found that a slow shock-wave rate improved the SFR at 3 months (99 vs. 90%, $p=0.034$) [24]. This study also demonstrated that delivery of 60 rather than 120 shocks/min could achieve successful stone clearance using fewer total shocks ($p=0.004$), although the treatment time was longer ($p<0.001$). Of the 156 study patients, 114 (73.1%) were male and 94 (60.3%) had renal stones as opposed to ureteral stones. Although the total number of SWL treatments required to achieve SFR was statistically different between treatment and control groups in univariate analysis, it was not significant in multivariate analysis. A slower shock-wave delivery rate, however, was found to lower SFR significantly in multivariate analysis.

Pace et al. randomized 218 previously untreated patients with ≥5 mm renal stones to 120 or 60 shocks/min groups [25]. Success was defined as stone free or clinically asymptomatic fragments <5 mm, and achieved by 61 and 75% of patients in the 120 and 60 shocks/min groups, respectively ($p=0.027$). A slower shock rate was even more strongly favored in patients with renal stones >10 mm, with a success rate of 71 vs. 32% ($p=0.002$) and stone-free rates of 60 vs. 28% ($p=0.015$), suggesting that patients with larger stones receive a greater benefit from a reduction in shock delivery rate. Slower delivery was also associated with less need for repeat SWL ($p=0.018$) and demonstrated a trend towards fewer complications ($p=0.079$). As previously reported by Madbouly et al., Pace et al. reported fewer total shocks (2423 vs. 2906; $p<0.001$) with a longer treatment time (40.6 vs. 24.2 min; $p<0.001$).

Yilmaz et al. prospectively randomized 170 patients with single renal stones <20 mm to 120, 90, or 60 shocks/min groups and evaluated the outcome of the single SWL session after 10 days, using KUB and RUS to determine treatment success [26]. Both 90 and 60 shocks/min were superior to 120 shocks/min in producing clinical success ($p=0.032$ and 0.015, respectively) and decreased analgesia use ($p=0.003$ and 0.001, respectively). The slower shock-rate groups also required a longer SWL session, significant even when comparing 90 to 60 shocks/min ($p=0.009$). However, the total energy delivered during SWL was not significantly different between the three treatment groups.

Davenport et al. randomized 100 patients with single renal stones to SWL at 120 or 60 shocks/min, evaluating SFR by KUB 3 months after treatment [27]. There were no significant differences between the 120 and 60 shocks/min groups in stone size ($p=0.32$), which varied from 6 to 364 mm^2, analgesia use ($p=0.82$), complications (10 vs. 8%; $p=0.68$), or clinically successful treatment (61 vs. 59%; $p=0.87$). The researchers suggested that the effect of reduced shock-wave delivery rate may be dependent on the lithotripsy device used.

Mazzuchi et al. compared the stone-free rate and the rate of clinically asymptomatic fragments <3 mm in 128 patients with single untreated renal stones 4–22 mm in size with a mean of 8.5 mm who were randomized to receive either 3000 shocks at a rate of 60 per minute or 4000 shocks at a rate of 90 per minute [28]. SFR overall was 53.1 and 54.8%, respectively ($p=0.603$), and was not statistically significant when stratified by stone size or location. Likewise, complications did not differ significantly between the two groups.

Comment

We suggest that urologists use a slower rate of 60–90 shocks/min when performing SWL for renal stones (conditional recommendation based on low-quality evidence). This recommendation assumes that patients place a high value on optimizing stone clearance rates. Additionally, there may not be a difference in patient-important outcomes between 60 and 90 shocks/min, with 90 shocks/min providing the increased SFR of a slower shock rate without substantially increasing the length and therefore the resource utilization of the procedure. Future studies may examine SFR, patient perception, and resource utilization differences between 60 and 90 shocks/min treatment regimens.

Table 13.4 Outcomes for SWL at varying delivery rates.

Study ID	Methods	Intervention	Participants	Outcomes	Results	Notes
Madbouly, 2005 [24]	RCT, single-center FU: 3 month KUB (100%)	SWL at 60 shocks/min SWL at 120 shocks/min	Single <30 mm radiopaque renal or ureteral stone 60 Hz: $n=76$ 120 Hz: $n=80$	Success: <2 mm fragments or stone free	Success rate 99 vs. 90% ($p=0.034$)	Ureteral stones 40% Electromagnetic lithotripter and general/regional anesthesia Mean stone length 13 mm
Pace, 2005 [25]	RCT, single-center FU: 2 weeks and 3 month KUB (95%), CT (3%), or IVP (2%)	SWL at 60 shocks/min SWL at 120 shocks/min	Single ≥5 mm radiopaque kidney stone 60 Hz: $n=110$ 120 Hz: $n=108$	Success: <5 mm residual Stone-free rate Complications Retreatment	Success rate 75 vs. 61% ($p=0.027$) Stone-free rate 60 vs. 44% ($p=0.065$) Complications 11 vs. 19% ($p=0.079$) Retreatment rate 18 vs. 32% ($p=0.018$)	Electrohydraulic lithotripter and sedation Mean stone size 80 mm^2
Yilmaz, 2005 [26]	RCT, single-center FU: 10 days with KUB and RUS (100%)	SWL at 60 shocks/min SWL at 90 shocks/min SWL at 120 shocks/min	Single <20 mm radiopaque kidney stone 60 Hz: $n=56$ 90 Hz: $n=57$ 120 Hz: $n=57$	Success: <3 mm residual Sedation requirement Stone location and mineral composition	Higher success rates with 60 (89%, $p=0.015$) and 90 (88%, $p=0.032$) compared with 120 shocks/min (73%) More sedation used with 120 (41%) vs. 90 (16%, $p=0.018$) and 60 shocks/min (14%, $p<0.01$) No differences for location nor composition	Electrohydraulic lithotripter and local±-sedation Mean stone size 13 mm
Davenport, 2006 [27]	RCT, multicenter FU: 3 months with KUB (100%)	SWL at 60 shocks/min SWL at 120 shocks/min	Single uncomplicated radiopaque kidney stone 60 Hz: $n=49$ 120 Hz: $n=51$	Success: <4 mm residual	Success rate 61 vs. 59% ($p=0.87$) Stone-free rate 60 vs. 44% ($p=0.065$) Complications 11 vs. 19% ($p=0.079$) Retreatment rate 18 vs. 32% ($p=0.018$)	Electromagnetic lithotripter and sedation 49% retreatment rate Mean stone size 60 mm^2
Mazzucchi, 2010 [28]	RCT, single-center FU: 3 months with KUB and RUS (100%)	SWL 3000 shocks at 60 shocks/min SWL 4000 shocks at 90 shocks/min	Single untreated uncomplicated radiopaque kidney stone 60 Hz: $n=103$ 90 Hz: $n=115$	Success: stone free Complications	Success rate 53 vs. 55 ($p=0.603$) Complications 2.3 vs. 3.3%	Ureteral stones 27% Electromagnetic lithotripter and sedation 72% stone <10 mm, 28% stone >10 mm

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14 CHAPTER 14

Surgical management of ureteral stone disease

Aaron H. Lay[1], Jay D. Raman[2], and Margaret S. Pearle[3]

[1] *Department of Urology, Emory University School of Medicine, Atlanta GA, USA*

[2] *Division of Urology, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA*

[3] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA*

Background

In the United States, nephrolithiasis occurs with an estimated overall prevalence of 8.8%, and there is evidence that stone disease is on the rise [1]. However, many stones in the kidney go undetected because they cause no symptoms or obstruction. Conversely, ureteral stones rarely remain silent, and they have greater potential for causing pain and obstruction. As such, ureteral stones that fail to pass spontaneously require surgical intervention. Although the introduction of medical expulsive therapy (MET) (the use of pharmacological agents to promote spontaneous stone passage) has changed the natural history of ureteral stone disease [2], not all ureteral stones respond to MET. Furthermore, a recent large-scale randomized trial found that MET was *not* effective in reducing the need for surgical intervention in patients managed expectantly [3].

Indications for surgical intervention to remove ureteral calculi include stones that are unlikely or fail to pass spontaneously with or without MET, cause unremitting pain regardless of the likelihood of spontaneous passage, are associated with persistent, high-grade obstruction, or occur in patients with an anatomically or functionally solitary kidney. Surgical intervention is also indicated in those with renal insufficiency or in patients for whom occupation or circumstances mandate prompt resolution (e.g. pilots, frequent travelers).

Once the decision has been made to intervene surgically for a patient with a ureteral stone, treatment options include shock-wave lithotripsy, ureteroscopy, percutaneous antegrade ureteroscopy, and open or laparoscopic ureterolithotomy. Although special circumstances may favor percutaneous antegrade ureteroscopy or ureterolithotomy (large, impacted stones, stones in patients with urinary diversions, or stones that fail less invasive approaches), the two most widely practiced treatment modalities for ureteral stones are shock-wave lithotripsy (SWL) and ureteroscopy (URS). Both are associated with high success rates and low morbidity. However, the optimal treatment for ureteral stones remains controversial because of passionate advocates on both sides of the controversy. Proponents of SWL cite the noninvasiveness, high patient satisfaction, and ease of treatment, whereas URS advocates favor the short operative times, high success rates, and short time interval to become stone free. This chapter weighs the evidence in favor of SWL or URS for the treatment of ureteral stones, and also explores some of the nuances of each treatment that have evidence-based support.

The optimal treatment modality for ureteral calculi depends on the size, location, and composition of the stone, and also the availability of equipment and the expertise of the practitioner. For example, cystine stones respond poorly to SWL; consequently, URS is the preferred treatment for cystine ureteral calculi [4]. Likewise, proximal ureteral stones in a male patient may be difficult to access with a semi-rigid ureteroscope; therefore, practitioners without access to a flexible ureteroscope might not choose URS for the treatment of a proximal ureteral calculus in a male patient. Extenuating circumstances aside, however, the optimal treatment modality for noncystine, non-uric acid stones in patients with normal ureteral anatomy who are otherwise appropriate candidates for either treatment modality will be considered. Of note, however, stone size and location are important variables that affect treatment outcomes for both URS and SWL.

Placement of a ureteral stent following ureteroscopy for the treatment of renal/ureteral calculi is common practice for most urologists [5]. There are some clear indications for stent

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placement following URS, including ureteral injury, dilation of stricture, presence of an anatomically or functionally solitary renal unit, renal insufficiency, or treatment of a large stone burden [6]. However, the need for ureteral stent placement after routine, uncomplicated ureteroscopy is controversial. Because ureteral stents are associated with lower urinary tract symptoms and flank pain, require an office procedure for removal, and may be complicated by stent migration, breakage, encrustation, obstruction, and urinary tract infection/sepsis, identification of patients who can be safely left unstented is desirable.

Clinical question 1

What is the optimal surgical management for proximal, middle, and distal ureteral calculi (SWL versus URS)?

Literature search

A search of the MEDLINE database was performed using the terms "ureteral calculi," "shock-wave lithotripsy," "ureteroscopy," and "randomized, controlled trials (RCTs)." The search was limited to the English-language literature published between 1948 and 2015 and focused primarily on RCTs comparing SWL and URS.

The evidence

There is extensive literature reporting outcomes of single-institution series of both SWL and URS for the treatment of patients with ureteral calculi, and also retrospective series comparing the two treatment modalities. Most importantly, there are seven RCTs that directly compared SWL and URS, five of which were focused exclusively on patients with distal ureteral calculi and two that addressed only patients with proximal ureteral calculi (Table 14.1).

Lee et al. randomized 42 patients with large (>15 mm) proximal ureteral calculi to SWL ($n=22$) or URS ($n=20$) [7]. Single-procedure stone-free rates for both SWL and URS were poor, at 32 and 35%, respectively. Complication rates were higher in the URS group (70%) than in the SWL group (9%). Among the URS complications were five ureteral perforations and one ureteral stricture, perhaps as a result of using a semi-rigid ureteroscope in the proximal ureter. Hospital stay (1.8 vs. 4.7 days), visual analog pain scores (1.86 vs. 4.35), and patient satisfaction scores (4.12 vs. 3.86) all favored SWL over URS, although only length of stay reached statistical significance. Of note, the degree of hydronephrosis correlated negatively with SWL success ($p=0.005$). The authors concluded that in the absence of hydronephrosis, both SWL and URS were reasonable

Table 14.1 Randomized controlled trials of URS versus SWL for ureteral calculi.

Study ID	Location (size)	FU	Lithotripter	Patients	Stone-free rate	*p*-Value
Hendrikx [9]	Extended-mid and distal (5–11 mm)	12 weeks	Dornier HM4	69 SWL	51% (35/69) Ext-mid 51% (20/39) Distal 50% (15/30)	–
				87 URS	91% (79/87) Ext-mid 81% (26/32) Distal 96% (50/52)	
Peschel [10]	Distal (40 > 5 mm; 40 < 5 mm)	43 days	Dornier MFL 5000	40 SWL	85% (17/20) <5 mm 95% (19/20) >5 mm	–
				40 URS	100% (20/20) <5 mm 100% (20/20) >5 mm	
Pearle [11]	Distal (<15 mm)	3 months	Dornier HM3	32 SWL 32 URS	100% (32/32) 100% (32/32)	NS
Zeng [12]	Distal (6–21 mm)	28 days	HB-ESWL-V	210 SWL 180 URS	78% (164/210) RTx 12% 93% (168/180) RTx 2%	<0.05
Lee [7]	Proximal (≥15 mm)	N/A	Siemens Lithostar 2	22 SWL 20 URS	32% (14/22) single Tx 35% (7/20) single Tx	–
Verze [13]	Distal (5–15 mm)	3 months	Modulith SLX	137 SWL	95.7% (66/69) ≤1 cm 89.7% (61/68) >1 cm	–
				136 URS	95.5% (63/66) ≤1 cm 94.3% (66/70) >1 cm	
Salem [8]	Proximal (5–20 mm)	3 months	Dornier HM3	100 SWL	80% (46/58) <1 cm 60% (25/42) ≥1 cm	NS
				100 URS	100% (52/52) <1 cm 88% (44/48) ≥1 cm	

FU, follow-up; N/A, not applicable; NS, not significant; RTx, retreatment rate; Tx, treatment.

therapies for large proximal ureteral stones. However, with the use of current small, flexible ureteroscopes, it is possible that the outcomes would be substantially different, since ureteral perforation, inaccessible stone, and retrograde stone migration accounted for the majority of URS failures. Such factors are now routinely overcome with the use of a flexible ureteroscope.

Salem also randomized 200 patients with proximal ureteral stones to SWL or URS and stratified stone-free rates according to stone size (<1 vs. ≥1 cm) [8]. In both size categories, stone-free rates were higher for URS than SWL, although the differences were not statistically significant in either size range (100 vs. 80%, respectively, for stones <1 cm and 88 vs. 66%, respectively, for stones ≥1 cm).

Hendrikx et al. randomized patients with extended-middle and distal ureteral calculi to SWL ($n=69$) or URS ($n=87$) [9]. Overall, URS was associated with higher stone-free and lower retreatment rates than SWL (91 and 9%, respectively, for URS vs. 51 and 45%, respectively, for SWL). This relationship also held true when outcomes were stratified by stone location: stone-free rates for URS and SWL were 81 vs. 51% for extended-middle ureteral calculi and 96 vs. 50% for distal ureteral calculi. On the other hand, complication rates and hospital length of stay favored SWL (4.3% and 2.2 days, respectively, for SWL vs. 25.2% and 4.4 days, respectively, for URS). When stratified by stone size <11 and ≥11 mm, stone-free rates were more disparate for SWL (58% for stones <11 mm and 17% for stones ≥11 mm) than URS (92% for stones <11 and 75% for stones ≥11 mm). Consequently, although stone-free and retreatment rates strongly favored URS, the lower complication rate and shorter length of stay perhaps make SWL a reasonable alternative for smaller stones.

Patients with distal ureteral stones have been the most extensively studied, with four RCTs comparing SWL and URS. Peschel et al. randomized 80 patients with distal ureteral stones that failed to pass to SWL ($n=40$) or URS ($n=40$) [10]. Although stone-free rates were high in both groups (90% for SWL vs. 100% for URS), the authors recommended URS over SWL for distal ureteral calculi because the time to become stone free was shorter in the URS group (1.8 days) than the SWL group (10 days).

Zeng et al. also favored URS for the treatment of distal ureteral calculi based on their RCT comparing 180 patients treated with URS with 210 patients treated with SWL [12]. The stone-free rate was higher for URS than SWL (93 vs. 78%, $p<0.05$), and the retreatment rate was fivefold higher for SWL than URS (11.9 vs. 2.2%, $p<0.05$).

In contrast, Pearle et al., in a multicenter study, randomized 64 patients with distal ureteral calculi to URS or SWL using an HM3 lithotripter ($n=32$ for each group) [11]. Stone-free rates were 100% in both groups, but secondary outcomes, including operating time ($p<0.05$), outpatient procedure rate, and patient satisfaction, favored SWL. As such, although SWL was more costly than URS at their institution, the authors recommended HM3 SWL over ureteroscopy since it was equally efficacious, more efficient, and less morbid.

Verze et al. randomized patients with solitary radiopaque distal ureteral calculi between 5 and 15 mm to SWL ($n=137$) or URS ($n=136$) [13]. No significant difference in overall stone-free rates was found between SWL and URS (92.7 vs. 94.9%). Subgroup analysis stratifying outcomes according to stone size showed no difference in stone-free rates between SWL and URS for stones >1 cm in size (89.7 vs. 94.3%), but did reveal higher retreatment (80.3 for SWL vs. 10.6% for URS, $p<0.05$) and complication rates (27.9% for SWL vs. 14.3% for URS, $p<0.05$) for SWL over URS. For stones ≤1 cm, there was no statistically significant difference in stone-free or retreatment rates between the two modalities, although complication rates were higher for URS than SWL (24.4 vs. 7.3%). As such, the authors recommended SWL for ≤1 cm and URS for >1 cm distal ureteral calculi.

Park et al. compared patient-reported outcomes in a group of 160 patients with single, 4–15 mm distal ureteral calculi randomized to SWL or URS using a self-administered nonvalidated questionnaire evaluating overall satisfaction in four domains (pain, hematuria, voiding symptoms, and time to return to routine activity) and also willingness to undergo the procedure again [14]. Despite a significantly higher stone-free rate for URS compared with up to three-session SWL (100 vs. 93.5%, $p=0.023$), patient satisfaction and willingness to undergo the procedure again were comparable between the two groups.

Aboumarzouk et al. performed a meta-analysis using stone-free rate, retreatment rate, need for auxiliary procedures, efficiency quotient, length of stay, complication rate, and patient satisfaction as endpoints [15]. Their analysis revealed a lower stone-free rate (relative risk [RR] 0.84, 95% confidence interval [CI] 0.73–0.96, $p=0.011$) and higher retreatment rate (RR 6.18, 95% CI 3.68–10.38, $p<0.00001$) in the SWL arm compared with the URS arm. However, SWL-treated patients had a lower complication rate (RR 0.54, 95% CI 0.33–0.88, $p=0.01$), less need for auxiliary treatment (RR 0.43, 95% CI 0.25–0.74, $p=0.003$), and shorter hospital stay (RR −2.55 days, 95% CI −3.24 to −1.86 days, $p<0.00001$). The authors concluded that URS is associated with a higher stone-free rate, but at a cost of a higher complication rate and a longer hospital stay. It should be noted, however, that combining the treatment arms of these studies may be problematic because of the heterogeneity of patient groups (e.g. stone location differed among the studies, one study included only patients with >15 mm stones, lithotripters were different in each study). Consequently, these conclusions should be interpreted with caution.

The American Urological Association (AUA)/European Association of Urology (EAU) 2007 Guideline for the Management of Ureteral Calculi also performed a comprehensive meta-analysis comparing SWL and URS based on

Table 14.2 Stone-free rates for SWL and URS of ureteral calculi from the AUA/EAU 2007 Guideline for the Management of Ureteral Calculi [16].

Stone location/size	Stone-free rate (primary Tx), median (%) (95% CI)	
	URS	SWL
Distal ureter	74 (73–75)	94 (93–95)
<10 mm	86 (81–90)	97 (96–98)
>10 mm	74 (57–87)	93 (88–96)
Middle ureter	73 (66–79)	86 (81–89)
<10 mm	84 (65–95)	91 (81–96)
>10 mm	76 (36–97)	78 (61–90)
Proximal ureter	82 (79–85)	81 (77–85)
<10 mm	90 (85–93)	80 (73–85)
>10 mm	68 (55–79)	79 (71–87)

Tx, treatment.

a review of 348 articles published between 1996 and 2006, 244 of which contained extractable data suitable for this purpose [16]. Despite the lack of a large number of RCTs, this analysis is less susceptible to the inherent biases associated with smaller series and provided the best available evidence to guide surgical treatment decisions for ureteral calculi up to 2007.

Overall, median stone-free rates for SWL and URS were 82 vs. 81% for proximal ureteral calculi, 73 vs. 86% for middle ureteral calculi, and 74 vs. 94% for distal ureteral calculi (Table 14.2). The more distal the stone, the greater was the disparity in outcomes between the two treatment modalities, in favor of URS. When stratified by stone size (≤10 and >10 mm), SWL stone-free rates were consistently higher for smaller than larger stones: 90 and 68%, 84 and 76%, and 86 and 74% for proximal, middle and distal ureteral calculi, respectively. URS stone-free rates showed a less stringent size dependence than SWL: 80 and 79% for proximal ureteral stones, 91 and 78% for middle ureteral stones, and 97 and 93% for distal ureteral stones ≤10 and >10 mm, respectively. Notably, the sample size for middle ureteral stones, particularly when stratified by stone size, was small, only 1607 overall for SWL and 1024 for URS. The number of patients treated with SWL for ≤10 mm stones was only 44 and for those with >10 mm stones only 15. Likewise, only 80 and 73 patients comprised the ≤10 and >10 mm URS groups, respectively. Consequently, the stratified data for middle ureteral calculi may not be as reliable as the overall outcome data.

Taking into account the total number of procedures per patient associated with treatment of the target stone, including the primary procedure (and retreatments), secondary procedures to remove stones and auxiliary, non-stone removal procedures, the number is not remarkably different between SWL and URS (1.62 vs. 1.45 for proximal ureteral stones, 1.52 vs. 1.2 for middle ureteral stones, and 1.37 vs. 1.4 for distal ureteral stones). However, the number of primary procedures (the intended treatment modality) was fewer for URS than SWL at all ureteral locations, indicating higher retreatment rates for SWL. Complication rates were low with both treatment modalities and largely involved infection and obstruction with SWL and infection and ureteral injury/stricture with URS.

Clinical implication

We suggest that patients with noncystine ureteral stones undergo URS and laser stone fragmentation (conditional recommendation based on low-quality evidence). This recommendation assumes that patients place a high value on achieving high stone-free rates and limiting the number of retreatments and place a relatively low value on the avoidance of treatment-related complications.

Clinical question 2

Is post-procedure stenting mandatory after ureteroscopy?

Literature search

A search of the MEDLINE database was performed using the terms "ureteral calculi," "ureteroscopy," "ureteral stent," and "randomized, controlled trials." The search was limited to the English-language literature published between 1948 and 2015.

The evidence

Over the last 15 years, there have been numerous RCTs that compared clinical outcomes and quality of life measures with or without ureteral stent placement after uncomplicated ureteroscopy (Table 14.3) [17–30]. Uniformly, no differences in complication rates or stone-free rates have been identified between the stented and unstented groups in these individual trials. However, stent placement was associated with significant lower urinary tract symptoms that affected quality of life in the immediate postoperative period.

Two fairly recent meta-analyses identified RCTs comparing stented and unstented ureteroscopy and both concluded that routine stent placement does not improve outcomes after URS [31, 32]. Tang et al. identified 14 RCTs comparing stented with unstented URS [32]. Among these trials, none reported differences in stone-free rates between the two groups. Although there was a trend towards reduced unplanned medical visits and rehospitalization in the stented group (RR 0.60, 95% CI 0.33–1.11, $p=0.11$), the difference did not reach statistical significance. The incidence of dysuria (RR 1.91, 95% CI 1.18–3.08, $p=0.008$), hematuria (RR 2.26, 95% CI 1.20–4.24, $p=0.01$), and frequency (RR 2.23, 95% CI 1.48–3.36, $p=0.0001$) were higher in the stented than the unstented group. Finally, no significant differences were found between groups with respect to postoperative

Table 14.3 Randomized, prospective trials comparing stent versus no stent after ureteroscopy.

Study ID	No. of patients	Stone location (size)	URS intervention	FU	Outcomes	Comments
Borboroglu [18]	113 total 53 stent 60 no stent	Distal (mean 6.6 mm)	6.0–9.5 Fr ureteroscope (~50% 9.5 Fr), Ho:YAG or EHL 6 Fr stent × 3–10 days	48 h, 1 week, 4 weeks	Stented with more OP, FP, BP, USx, and NU	4 nonstented readmitted and 2 required stent, 6 unstented withdrawn due to intraoperative ureteral trauma
Denstedt [30]	58 29 stent 29 no stent	Variable (mean 9 mm)	6.9–7.5 Fr Ho:YAG or EHL stent × 1 week	1, 6, and 12 weeks	SFR 100% in both at 1 week. Stented with more FP, BP, USx	No difference in USx or pain at any other time points, 1 patient in each group readmitted
Netto [26]	295 133 stent 162 no stent	Variable (2–50 mm)	7.5 Fr ultrasonic lithotripter stent × 2–3 days	3 months	No difference in SFR, OP, complications. Stented with longer OR	Cost higher for stent cases
Chen [19]	60 30 stent 30 no stent	Variable (mean 6.2 mm)	6.0 Fr ureteroscope, EHL 7 Fr stent × 3 days	3 and 7 days	No difference in SFR, OP, AU. 83% stented vs. 13% nonstented with USx or BP	–
Cheung [20]	58 29 stent 29 no stent	Variable (mean 9.7 mm)	6.5–7.0 Fr ureteroscope, Ho:YAG 6 Fr stent × 2 weeks	1 and 3 days	No difference in SFR, OR. Stented with more OP, USx, H	No difference in % of unplanned medical visits (17% nonstented vs. 21% stented)
Srivastava [25]	48 26 stent 22 no stent	Distal (mean 7.6 mm)	8.5 Fr ureteroscope, SL 6 Fr stent × 3 weeks	3 weeks	No difference in SFR, OR, AU. Stented with more FP, USx	–
Damiano [21]	104 52 stent 52 no stent	Variable (mean 10.5 mm)	8.9 Fr ureteroscope, SL 4.8 or 6 Fr stent × 2 weeks	3, 7, and 15 days	No difference in SFR, OR, USx, H. Nonstented with less pain on day 3, but not 7 or 10	22.8% (11/52) nonstented required readmission with 6 ureteral stents placed
Jeong [24]	45 23 stent 22 no stent	Variable (mean 5.3 mm stent, 7.1 mm no stent)	8.5 Fr ureteroscope, EHL 7 Fr stent × 7 days	7 and 28 days	No difference in OR, HOSP, FP, USx. Presence of H only difference between groups	–
Grossi [22]	56 28 stent 28 no stent	Variable (mean 9.2 mm)	8.5 Fr ureteroscope, ballistic lithotripsy 6 Fr stent × 3–10 days	3 and 7 days	No difference in SFR, OP, complications	1 nonstented required stenting POD 1
Ibrahim [23]	220 110 stent 110 no stent	Distal (mean 13 mm)	7.5–10.5 Fr ureteroscope, Ho:YAG or SL 6 Fr stent × 2 weeks	48 h and 1 week	No difference in SFR, HOSP, H, complications. Stented group with more USx	–
Cevik [17]	60 total 30 stent 30 no stent	Variable (mean 8.3 mm)	8 Fr semirigid ureteroscope, pneumatic lithotripsy 4.8 Fr multilength stent × 3 weeks	5 days and 3 weeks	No difference in SFR. Nonstented group had higher narcotic usage until POD 5	Patients had impacted stones

(*continued overleaf*)

Table 14.3 (Continued)

Study ID	No. of patients	Stone location (size)	URS intervention	FU	Outcomes	Comments
Xu [27]	110 total 55 stent 55 no stent	Variable (mean 11.3 mm)	7 Fr semirigid ureteroscope, Ho:YAG 4.8 Fr stent × 3 weeks	48 h, 1 and 4 weeks	No difference in SFR. Stent group had longer OR time and higher incidence of H	–
Wang [28]	228 total 90 control (no stent, no edema) 71 stent (edema, polypoid change) 67 no stent (edema, polypoid change)	Variable (mean 10.1 mm)	7 Fr semi--rigid ureteroscope, pneumatic lithotripsy 7 Fr stent × 1 week	POD1, 6 weeks, 12 weeks	No difference in SFR. FP, dysuria, frequency higher in stent group on POD 1. Higher rate of fever and flank pain in nonstented group	Stents can be safely omitted if ureteral mucosa smooth after URS
Başeskioğlu [29]	286 total 144 stent 142 no stent	Variable (mean 12.2 mm)	9.8 Fr rigid ureteroscope after balloon dilation of ureteral orifice, Ho:YAG or pneumatic lithotripsy	2 weeks and 3 months	No difference in SFR. Higher rates of dysuria and urgency in stent group	Stents can be safely omitted in cases of balloon dilation of ureteral orifice

AU, analgesic use; BP, bladder/suprapubic pain; EHL, electrohydraulic lithotripsy; FP, flank pain; FU, follow-up; H, hematuria; HOSP, hospital stay; Ho:YAG, holmium–YAG laser; OP, overall pain; OR, operative time; POD, post-operative day; SFR, stone-free rate; SL, Swiss Lithocloast; USx, urinary symptoms.

analgesia requirement, urinary tract infections, postoperative fever, and occurrence of ureteral stricture.

Shen et al. also performed a meta-analysis of 16 RCTs comprising 1573 patients evaluating the necessity and adverse effects of routine ureteral stent placement after ureteroscopic lithotripsy for ureteral stones [31]. The mean operative time was shorter (RR −3.44 min, 95% CI −6.00 to −0.87) and lower urinary tract symptoms were less prevalent (dysuria [RR 0.45, 95% CI 0.28–0.72], frequency and urgency [RR 0.61, 95% CI 0.50–0.74], and hematuria [RR 0.54, 95% 0.33–0.87]) among the unstented compared with the stented group. On the other hand, no significant differences between the groups were found with regard to fever, urinary tract infections, analgesic need, unplanned readmission rates, and late postoperative complications.

Finally, Hollenbeck et al. performed a multivariable logistic regression analysis of 219 ureteroscopic procedures for stones with no stent left in place in order to identify factors predictive of postoperative morbidity [33]. Taking into account patient, operative, and stone characteristics, they found that bilateral stentless procedures, history of recent/recurrent infections, and history of stones were independently associated with postoperative complications in patients undergoing stentless URS.

Clinical implications

We recommend against routine stenting following uncomplicated ureteroscopy (conditional recommendation against based on very low-quality evidence).

Clinical question 3

Is there an advantage to placement of a ureteral stent in conjunction with SWL of ureteral calculi?

Literature search

A search of the MEDLINE database was performed using the terms "ureteral calculi," "shock-wave lithotripsy," "*in situ* shock-wave lithotripsy," "stent bypass," "push-back," "push-bang," "ureteral stent," and "randomized, controlled trials." The search was limited to the English-language literature published between 1948 and 2015.

The evidence

Although many clinical series have demonstrated favorable stone-free rates with *in situ* SWL at all locations in the ureter, RCTs directly comparing stent bypass/push-back with *in situ* SWL are limited primarily to patients with proximal ureteral calculi. Among eight randomized trials comparing stent bypass/manipulation with *in situ* SWL for patients with proximal ureteral calculi, none showed a significant or substantial difference in stone-free rates between groups (Table 14.4) [34–41]. However, one trial found that stented patients were less likely to return to the hospital or require an emergency room visit than *in situ*-treated (unstented) patients. Chandhoke et al. randomized 97 patients undergoing SWL for 10–20 mm renal or <20 mm proximal ureteral calculi with no stent, 4.7 Fr stent, or 7 Fr stent [40]. Although outcomes were not stratified by stone location (renal or ureteral) and ureteral calculi comprised only 33–40% of stones in each group, the authors found no difference in stone-free rates (85, 80, and 77%, respectively) or retreatment rates between the three groups. However, patients in the unstented group required rehospitalization more frequently than patients in the stented groups (22 vs. 7%, respectively), Likewise, the need for an emergency room visit was significantly lower in the 4.7 Fr stent group than in the unstented group (5 vs. 19%, respectively). Stented patients did, however, experience more lower urinary tract symptoms (urgency, frequency, nocturia) than the unstented patients. Of note, the mean stone size in the three groups was fairly large (13.3, 11.3, and 12.7 mm, respectively), which could account for the more frequent need for medical attention postoperatively in the unstented patients.

In an RCT comparing stent bypass with *in situ* SWL, Ghoneim et al. randomized 60 patients with impacted solitary ≤2 cm proximal ureteral calculi to undergo 6 Fr stent placement 1 week before or no stent at the time of SWL [34]. No significant differences between groups were found with regard to stone-free rates (90 vs. 87%, respectively, $p=0.35$) or number of SWL sessions (2.0 vs. 1.9, respectively, $p=0.44$). However, patients with ureteral stents experienced more frequent side effects attributable to the stent, including dysuria, frequency, pyuria, and suprapubic pain.

In 1997, the AUA/EAU Ureteral Stone Clinical Guidelines Panel reviewed the available literature for outcomes on SWL of proximal ureteral stones and found no significant difference in stone-free rates among patients treated with *in situ*, stent bypass, or push-back: 82, 82, and 88%, respectively [42]. Likewise, stone-free rates for *in situ* and stent bypass SWL for distal ureteral calculi were comparable (86% for each group). Patient numbers for push-back SWL for distal ureteral calculi were too small to be meaningful.

A 2011 systematic review and meta-analysis of the available literature on SWL outcomes of upper urinary calculi (renal and proximal ureteral) with and without ureteral stents found no significant difference in SFR between the two groups (RR 0.97, 95% CI 0.91–1.03, $p=0.27$) [43]. However, the incidence of lower urinary tract symptoms was higher in the stented group than the unstented group (RR 4.10, 95% CI 2.21–7.61, $p<0.00001$).

No RCTs have directly compared stent bypass with *in situ* SWL for patients with middle and distal ureteral calculi. Visualization of middle ureteral calculi is often obscured by the pelvic bone, thereby necessitating the use of intravenous contrast or placement of a ureteral stent or catheter to

Table 14.4 Randomized, clinical trials comparing stent manipulation (bypass or push-back) with no stent (*in situ*) for SWL treatment of proximal ureteral calculi.

Study ID	Lithotripter	*In situ*				Stent bypass or push-back			
		No. of pts	Stone free (%)	Auxiliary procedure (%)	Retreatment (%)	No. of pts	Stone free (%)	Auxiliary procedure (%)	Retreatment (%)
Hendrikx[a] [35]	Lithostar	23	91	–	–	24	83	–	–
Danuser [36]	Dornier HM3	48	96	2	2	48[b]	94	0	0
Albala [37]	Lithostar	19	74	11	0	18	89	11	0
	Dornier HM3	10	80	10	0	15	67	13	20
Chang [38]	Lithostar	26	77	8.5	33.3	51[c]	61	2.8	35
Kumar [39]	Lithostar Plus	35	80	–	0	35	88.5	–	0
Chandhoke[d] [40]	Dornier HM3	31	84	–	–	60[e]	78.5	–	–
El-Assmy [41]	Dornier MFL 5000	93	91	8	21.5	93	85	15	20
Ghoneim [34]	Dornier Doli S	30	86.7	–	66.7	30	90	–	76.7

[a] Series included 8 patients in the *in situ* group and 6 patients in the manipulated group with middle ureteral stones; only 9 of 24 patients in the push-back group underwent successful push-back of the stone into the kidney and the remaining stones were treated *in situ*. Of the 9 stones treated with push-back, 100% were stone free. Of the 15 failing push-back and treated *in situ*, 73% were stone free.

[b] All patients except four had stone pushed back into kidney. Of the remaining four, three were treated with stent bypass and one was treated with catheter just distal to stone.

[c] Includes 27 patients treated with stent bypass and 24 patients treated with placement of a catheter below the stone with continuous manipulation.

[d] Series includes patients with renal calculi. Patients with ureteral calculi comprised 33–40% of patients in the three groups.

[e] Includes 30 patients each with 4.7 Fr stent and 7 Fr stent. All patients in this group underwent SWL with stent bypass.

facilitate targeting of the stone. Nonetheless, retrospective, single-institution series have reported satisfactory success rates with *in situ* SWL in patients with middle and distal ureteral calculi [44, 45]. Indeed, in a large series of over 18 000 patients treated with SWL for ureteral calculi, Mobley et al. found no difference in stone-free, retreatment, or auxiliary procedure rates between *in situ* and stent bypass SWL [45]. Stone-free rates in this series for *in situ* versus stent bypass treatment of patients with ≤20 mm ureteral calculi were 86 vs. 82% for proximal, 83 vs. 84% for middle, and 84 vs. 78% for distal ureteral calculi.

Clinical implications

For patients with proximal ureteral stones, we recommend against ureteral stent placement in conjunction with *in situ* SWL (strong recommendation based on low-quality evidence).

For patients with middle and distal ureteral stones, we advise against ureteral stent placement in conjunction with *in situ* SWL (conditional recommendation based on very low-quality evidence). This recommendation is based on lack of evidence to suggest superior outcomes in stented patients but evidence of increased risk of adverse events and increased resource utilization.

Clinical question 4

Does medical expulsive therapy improve stone-free rates following SWL?

Literature search

A search of the MEDLINE database was performed using the terms "ureteral calculi," "shock-wave lithotripsy," "medical expulsive therapy," "alpha-blocker," "calcium channel blocker," "tamsulosin," "nifedipine," and "randomized, controlled trials." The search was limited to the English-language literature published between 1948 and 2015.

The evidence

Based on the success of alpha-adrenergic receptor antagonists and calcium channel blockers in promoting spontaneous stone passage, medical expulsive therapy has been used as an adjunct to SWL to promote clearance of fragments from the ureter. To date, eight published RCTs have evaluated tamsulosin ($n=4$), nifedepine ($n=2$), doxazosin ($n=1$), alfuzosin ($n=1$), or both tamsulosin and nifedipine ($n=1$) in conjunction with SWL of ureteral calculi (Table 14.5) [46–53]. In all but two of these studies [47, 52], a statistically significant improvement in stone clearance rates was observed with the initiation of adjuvant MET. Although Cho et al. found no significant difference in stone clearance rates between patients treated with alfuzosin and a no-treatment control group, they did find that alfuzosin was associated with a shorter time to become stone free (9.5 vs. 18.6 days, respectively, $p=0.005$) [52]. Gravas et al. also found no improvement in stone-free rates with tamsulosin, although patients in the treatment arm required less supplemental diclofenac for pain than those in the control arm [47].

Table 14.5 Prospective trials of adjunctive tamsulosin or nifedipine for SWL of ureteral calculi.

Study ID/design	No. of pts	Location, size (mm)	Therapy regimen	Additional therapy	FU	Stone clearance rates	Comments
Tamsulosin							
Kupeli [48], R/C	78	Distal ureter (1–15 mm)	TAM 0.4 mg daily × 15 days (n=39) CON (n=39)	Diclofenac	15 days	TAM 64.1% CON 28.2%	Best stone clearance for stones >5 mm
Gravas [47], R/C	61	Distal ureter (6–13 mm)	TAM 0.4 mg daily × 30 days (n=30) CON (n=31)	Diclofenac	1–4 weeks	TAM 66.7% CON 58.1%	No difference in stone clearance rates, but TAM group required less diclofenac
Bhagat [46], R/C/DB	60	Renal (6–24 mm) All ureter (6–15 mm)	TAM 0.4 mg daily × 30 days (n=30) Placebo (n=30)	Proxyvon	1 month	TAM 96.6% CON 79.3%	Includes renal stones (67%) in each arm. Best clearance rates for stones >10 mm
Singh [51], R/C	119	Distal ureter (4–12 mm)	TAM 0.4 mg daily × 30 days (n=60) Placebo (n=59)	None	4 weeks	4–7 mm: TAM 93% CON 90% 8–12 mm: TAM 80% CON 52%	Statistically significant difference in stone clearance for stones 8–12 mm size
Alfuzosin							
Cho [52], R/C	84	All ureter (5–10 mm)	Alfuzosin 10 mg daily × 42 days (n=41) CON (n=43)	Loxoprofen	42 days	Alfuzosin 95% CON 93%	Statistically significant shorter time to stone free for alfuzosin (9.5 vs. 18.6 days, p=0.005)
Doxazosin							
Ateş [53], R/C	79	Proximal ureter (≥5 mm)	Doxazosin 4 mg daily × 14 days (n=35) CON (n=44)	None	14 days	Doxazosin 91.3% CON 79.5%	Doxazosin group also less likely to need additional treatments and less steinstrasse.
Nifedipine							
Porpiglia [50], R/C	80	All ureter (mean 10.5 mm)	NIF 30 mg daily × 10 days (n=40) CON (n=40)	Deflazacort	45 days	NIF 75% CON 50%	NIF group required less deflazacort (37.5 vs. 86.25 mg)
Tamsulosin and nifedipine							
Micali [49], C	113	Upper/mid ureter Distal ureter (6–14 mm)	NIF 30 mg daily × 14 days (n=35) CON (n=29) TAM 0.4 mg daily × 14 days (n=28) CON (n=21)	Ketoprofene	1 and 2 months	NIF 85.7% CON 51.7% TAM 82.1% CON 57.1%	SWL/endoscopy retreatment rate: NIF 14.3% TAM 17.8% CON 46%

C, controlled; CON, control; DB, double-blind; FU, follow-up; NIF, nifedipine; PC, placebo controlled; R, randomized; TAM, tamsulosin.

One study selectively compared ketoprofene and nifedipine with ketoprofene alone in conjunction with SWL for proximal/middle ureteral calculi and ketoprofene and tamsulosin with ketoprofene alone for patients with distal ureteral calculi [48]. Both MET regimens were associated with higher stone-free rates than their respective control arms (86 vs. 51% for the nifedipine and control arms, respectively, $p=0.005$; and 82 vs. 58% for the tamsulosin and control arms, respectively, $p=0.05$).

In a related trial, Resim et al. randomized patients with steinstrasse occurring after SWL for renal calculi to either tamsulosin and tanoxicam or tanoxicam alone [54]. Although the rate of resolution of steinstrasse was slightly higher in the tamsulosin group than the control group (75 vs. 66%), the difference was not statistically significant. However, tamsulosin was associated with fewer episodes of renal colic and lower visual analog pain scores than the control group.

Clinical implications

We recommend adjuvant MET, either nifedipine or tamsulosin, to facilitate clearance of fragments after SWL of ureteral calculi and perhaps in reducing pain medication requirements (strong recommendation based on moderate-quality evidence).

However, it should be recognized that the individual RCTs vary in the drug regimens used (both dose and duration), the study population (patients with only distal ureteral stones or all ureteral stones), and the use of other potentially active drugs in both the control and treatment arms (nonsteroidal anti-inflammatory drugs or corticosteroids), thereby making comparison between trials problematic. Indeed, variations in the stone-free rates in the control arms of these trials may in part be accounted for by the use of no treatment in some trials and potentially active agents in other trials (e.g. corticosteroids). Finally, data on retreatment rates and interval to stone passage were only sporadically reported and therefore no meaningful conclusions can be derived regarding these endpoints. These limitations notwithstanding, the use of adjuvant MET in conjunction with SWL is strongly recommended.

Clinical question 5

Does slowing the rate of shock-wave (SW) delivery improve stone-free rates for SWL of ureteral calculi?

Literature search

A search of the MEDLINE database was performed using the terms "ureteral calculi," "shock-wave lithotripsy," "shock-wave rate," and "randomized, controlled trials." The search was limited to the English-language literature published between 1948 and 2015. Owing to the paucity of data on shock-wave rate for ureteral calculi, we supplemented our search with data obtained from published abstracts from the American Urological Association (AUA) and World Congress of Endourology annual meetings from 2005 to 2015.

The evidence

Historically, lithotripters were gated with the QRS complex of the electrocardiogram so as to avoid inducing cardiac arrhythmias. As a result, SW rates rarely exceeded 60–80 SW/min. With the introduction of second- and third-generation lithotripters, nongated SWL became common and treatment times were shortened.

More recent *in vitro* and animal studies, however, have shown superior stone fragmentation when the SW rate is reduced to 30–60 SW/min [55–57]. Clinical trials have validated these experimental findings and confirmed superior stone-free rates for patients with renal calculi treated with SWL at 60 vs. 120 SW/min [58]. In a meta-analysis of four RCTs comprising 589 patients treated with SWL for renal calculi at slow versus fast SW rates, Semins et al. found that patients treated at slow SW rate (60 SW/min) had a 10% higher likelihood of becoming stone free than those treated at fast SW rate (120 SW/min) (95% CI 3.4–16.8, $p=0.0002$) [58].

Two RCTs specifically addressed SW rate for SWL of ureteral calculi [59, 60]. Honey et al. randomized 157 patients with ≥5 mm proximal ureteral calculi to 60 or 120 SW/min [59]. They found that slow SW delivery was associated with a higher SFR (68 vs. 51%, $p=0.03$), reduced auxiliary procedure rate (31 vs. 47%, $p=0.03$), and a lower cumulative number of shock waves (2667 vs. 2938, $p<0.001$), although at a cost of longer operative duration (44 vs. 24.5 min, $p<0.001$) compared with patients treated at 120 SW/min.

In contrast, Nguyen et al. randomized 254 patients with ureteral stones to SWL treatment at 60 or 90 SW/min and found that a faster SW delivery rate was associated with a *higher* SFR than a slower SW rate (91 vs. 80%, respectively, $p=0.01$) [60]. However, no significant differences were found between the two groups with regard to treatment time, complications, or need for secondary treatments.

Clinical implications

We suggest that urologists use slow delivery rates (60–90 SW/min) for the SWL treatment of ureteral stones (conditional recommendation based on very low-quality evidence). This recommendation assumes that patients place a high value on stone-free rates and a relatively low value on the duration of the procedure.

Clinical question 6

Is there an advantage to stone fragmentation with active retrieval over complete fragmentation during laser lithotripsy for ureteral stones?

Literature search

A search of the MEDLINE database was performed using the terms "ureteral calculi," "ureteroscopy," "holmium laser", "dusting", "basketing", and "randomized, controlled trials." The search was limited to the English-language literature published between 1948 and 2015.

The evidence

Stone fragmentation during ureteroscopy is most commonly accomplished with the holmium:YAG laser [61, 62]. Strategies for stone removal generally include complete stone fragmentation to allow for spontaneous passage of fragments or limited stone fragmentation into pieces just small enough to be actively retrieved through the ureter or access sheath. The technique of complete stone fragmentation has subsequently been optimized by adjusting laser settings to maximize stone vaporization and formation of stone "dust" (laser energy 0.2 J and frequency 40 Hz) [63].

Only one RCT has compared active fragment retrieval with complete stone fragmentation for ureteroscopic management of ureteral calculi [64]. Schatloff et al. randomized 60 patients undergoing ureteroscopy and laser lithotripsy for ureteral calculi to active fragment retrieval versus complete stone fragmentation. Of note, laser settings and the size of the fiber were identical in the two groups (0.8–1 J per pulse and 8–10 Hz with a 365 µm fiber), although a "painting" technique was used to fragment the stones completely into <2 mm pieces), compared with traditional limited fragmentation into pieces just large enough to pull through the ureter. Although the stone-free rate was higher in the group undergoing active fragment retrieval compared with those undergoing complete fragmentation (100 vs. 87%), the difference was not statistically significant, and hospitalization rates were comparable between the two groups (10 vs. 0%, respectively, $p=0.24$). However, unplanned emergency department visits were 10-fold more frequent in the complete fragmentation group than the active retrieval group (30 vs. 3%, respectively, $p=0.01$).

A recent multicenter prospective, non-randomized trial by the Endourology Disease Group for Excellence (EDGE) Research Consortium addressed this question in renal calculi and found a higher stone-free rate according to 3-month ultrasound and plain abdominal radiograph results in a group of 82 patients undergoing ureteroscopy with stone basketing than in a group of 68 patients undergoing ureteroscopy with complete stone fragmentation ("dusting") (74.3 vs. 58.2%, respectively, p=0.04 on univariate analysis) [65]. However, multivariate analysis demonstrated no difference between groups. However, outcomes may not be appropriately extrapolated to ureteral stones since fragments are more likely to pass from the ureter than the kidney.

Clinical implications

At present, there is insufficient evidence to make a recommendation supporting one endoscopic lithotripsy technique over another (no recommendation can be made).

Clinical question 7

Does medical expulsive therapy improve stone-free rates after ureteroscopic lithotripsy of ureteral stones?

Literature search

A search of the MEDLINE database was performed using the terms "ureteral calculi," "ureteroscopy," "laser lithotripsy", "medical expulsive therapy," "alpha-blocker," "calcium channel blocker," "tamsulosin," "nifedipine," and "randomized, controlled trials." The search was limited to the English-language literature published between 1948 and 2015.

The evidence

Only a single RCT has addressed the effectiveness of MET in promoting the clearance of stone fragments after ureteroscopic lithotripsy. John and Razdan randomized 78 patients undergoing ureteroscopy for 1–2 cm renal or ureteral calculi to receive either 0.4 mg of tamsulosin along with Tylenol #3 as needed for pain or as-needed Tylenol #3 (Tylenol with codeine) alone [66]. The mean stone size was comparable between the two groups (1.3 cm in the study group and 1.2 cm in the control group). Of note, less than half of the patients in the study group were treated for ureteral stones (34/78) and, unfortunately, stratified outcomes were not provided for renal versus ureteral calculi. Nonetheless, stone-free rates were higher (86.5 vs. 69.4%, respectively, $p<0.01$) and episodes of renal colic were less frequent (5.4 vs. 22.2%, respectively, $p<0.01$) in the tamsulosin group compared with the control group.

Clinical implications

We suggest against MET after URS (conditional recommendation against based on low-quality evidence) given the absence of direct evidence to support its effectiveness and this setting in conjunction with the potential for albeit mostly mild drug-related side effects and associated costs.

Although evidence in support of MET for improving stone clearance and reducing pain episodes after URS is promising, it is insufficient to recommend the routine use of MET after URS for ureteral calculi. Further studies, limited to patients with ureteral calculi, will be necessary to validate the findings of John and Razdan.

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PART 3

Pediatric urology

Luis H.P. Braga

15 CHAPTER 15
Prenatal hydronephrosis

Shawn Dason[1] and Luis H.P. Braga[2]

[1] *Memorial Sloan Kettering Cancer Center, New York, NY, USA*

[2] *Department of Surgery (Urology), Pediatrics, and Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada*

Introduction

Prenatal hydronephrosis (HN) refers to fetal dilation of the renal collecting system [1]. Prenatal HN is usually identified on routine prenatal ultrasonography (US). Two grading systems are widely used to describe prenatal HN – the semi-quantitative Society for Fetal Urology (SFU) grading system (Table 15.1) and the measurement of antero-posterior diameter (APD) of the renal pelvis in the transverse plane on US [2]. The prevalence of prenatal HN is a function of the specified threshold APD value and ranges from 0.37 to 5.5% [3]. For the purpose of this chapter, Society for Fetal Urology (SFU) grades 1 and 2 and/or APD between 4 and 14.9 mm on postnatal US were considered low-grade HN. SFU grades 3 and 4 HN and/or an APD of 15 mm or more were considered high-grade HN.

The most common etiologies of prenatal HN include physiological HN, ureteropelvic junction obstruction (UPJO), vesicoureteric reflux (VUR), and primary nonrefluxing megaureter [3]. Many additional obstructive and nonobstructive abnormalities will present with HN, including prune belly syndrome, posterior urethral valves (PUV), ureteroceles, and ectopic ureters.

Patients with prenatal HN may go on to develop complications related to their underlying pathology, including urinary tract infections (UTIs), urolithiasis, hypertension, renal scarring, and chronic kidney disease. The identification of prenatal HN is intended to prevent these complications by prompting early workup and management.

Literature search

This review involved a search of 4 databases (MEDLINE, Embase, CINAHL, CENTRAL) in quadruplicate. When possible, the search used MeSH terms and the search strategy was devised with the assistance of a medical information specialist. Gray literature was searched with the PapersFirst and ProcedingsFirst databases along with a manual search of *Dialogues in Pediatric Urology*. The reference lists of retrieved review articles were also searched to identify additional relevant primary studies. Lastly, a content expert review of the final lists of included studies was conducted. Studies published between 1990 and 2010 were included from a previous systematic review conducted by the senior author [1]. Using the same methodology as in the previous systematic review, this search was conducted again to include studies published up to 2015.

Study inclusion criteria were as follows: (1) primary diagnosis of prenatal HN; (2) all subjects aged <2 years; (3) intervention arms include continuous antibiotic prophylaxis (CAP), no treatment, or both; (4) reported rate of UTI; (5) reported number of patients who underwent a voiding cystourethrogram (VCUG); (6) HN grade according to SFU classification and/or anteroposterior diameter (APD) of renal pelvis. Exclusion criteria were case reports, case series with fewer than subjects, and review articles. No language restrictions were imposed.

Included studies are displayed in Table 15.2. Studies in which the authors provided sufficient information to answer the questions of this review (e.g. UTI rate stratified by grade of hydronephrosis, CAP status, and presence of VUR) were included in the relevant meta-analyses. A random effects DerSimonian–Laird model was used for meta-analysis to estimate the pooled weighted proportion or odds ratio relevant to each question. Additional methodological information and a quality appraisal of the retrieved literature are available in the text of this previous systematic review [1].

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Table 15.1 Society for Fetal Urology (SFU) grading system for hydronephrosis [3].

Grade	Definition
1	Urine in renal pelvis barely splits renal sinus
2	Urine fills intrarenal pelvis or urine fills an extrarenal pelvis with dilation of major calyces
3	SFU grade 2 and minor calyces uniformly dilated and parenchyma preserved
4	SFU grade 3 and parenchyma thinned

Clinical question 1

Do patients with high-grade hydronephrosis have higher UTI rates than those with low-grade hydronephrosis?

The evidence

UTI rates for patients with low-grade HN were reported for 2254 patients in 11 observational studies (Figure 15.1a). The pooled UTI rate for patients with low-grade HN was 7.0% (95% confidence interval [CI] 4.6–9.8%). UTI rates for patients with high-grade HN were reported for 987 patients in 11 observational studies (Figure 15.1b). The pooled UTI rate for patients with high-grade HN was 22.3% (95% CI 15.3–30.2%).

Clinical implications

Patient populations with higher UTI rates will benefit from more intensive investigation, follow-up, and parental counseling. Additionally, interventions (e.g. antibiotics) found to have an impact on UTI rates are more relevant in patient populations with higher UTI rates. There is low-quality evidence that children with high-grade HN are more likely to develop UTIs than children with low-grade HN (Table 15.3). Further research will impact our confidence in the estimate of the difference in UTI rates between high- and low-grade HN.

Clinical question 2

Should continuous antibiotic prophylaxis (CAP) be used in prenatal hydronephrosis?

The evidence

The UTI rate for patients receiving CAP was reported in 12 studies including 1552 patients. The pooled UTI rate for patients receiving CAP was 11.3% (95% CI 6.6–17.2%). The UTI rate for patients not receiving CAP was reported in 13 studies including 2828 patients. The pooled UTI rate for patients not receiving CAP was 12.1% (95% CI 5.2–21.4%). When looking only at studies that reported UTI rates for both patients receiving CAP and not receiving CAP, the odds ratio for developing a UTI for patients receiving CAP versus no CAP was 1.14 (95% CI 0.53–2.47, $p=0.73$) (Figure 15.2).

In efforts to limit a confounding variable, Braga et al. have previously published an individual patient data meta-analysis regarding the effect of CAP status on UTI rate stratified by high-grade versus low-grade HN [1]. Patients with low-grade HN had a similar UTI rate regardless of CAP status (2.2% [95% CI 1.3–4.0%] for infants receiving CAP vs. 2.8% [95% CI 2.1%–3.7%] for infants not receiving CAP; $n=2181$ patients). Patients with high-grade HN had a significantly lower UTI rate when receiving CAP (14.6% [95% CI 9.3–22.0%] vs. 28.9% [95% CI 24.6–33.6%], $p<0.01$; $n=507$ patients). The estimated number needed to treat for CAP to prevent a UTI in infants with high-grade HN was 7.

When interpreting these recommendations, it is important to understand that confounding factors such as grade of HN, etiology of HN, gender, presence of VUR, and circumcision status undoubtedly affected the selection of patients for CAP in these observational studies. As a result, analysis of UTI rates based on CAP status will be subject to bias. Additionally, prenatal HN studies generally focused on UTI rates. Although this is a clinically relevant outcome with significant short-term morbidity, other relevant outcomes, such as renal scarring, hypertension, renal failure, and operation rates, are generally unavailable.

Continuous antibiotic prophylaxis has few documented adverse effects. In a recent large randomized trial that included 302 children treated with trimethoprim–sulfamethoxazole CAP for VUR [31], the main adverse effect observed was resistance to the study drug in 63% of *Escherichia coli* breakthrough infections in the prophylaxis group versus 19% of controls. The authors observed no significant difference between CAP patients and controls in rates of fever, otitis media, diarrhea, pharyngitis, or viral infection. Although common short-term adverse effects may be inferred from this study, the long-term and/or rare consequences of CAP use are uncertain. The additional consideration with respect to CAP use relates to the cost of the medication.

The senior author is currently conducting a randomized controlled trial to investigate the effect of CAP on UTI rate in patients with prenatal HN [32]. Inclusion criteria for this trial are (1) isolated hydronephrosis or hydroureteronephrosis, (2) age between 1 and 7 months, and (3) confirmation of SFU grade III/IV hydronephrosis by postnatal renal bladder ultrasound. Infants must have a VCUG prior to consideration for this study and those with VUR are excluded. Patients with an allergy to trimethoprim, those who require chronic antibiotics for another reason, and those with urogenital issues including a solitary kidney, posterior urethral valves, renal insufficiency, duplication anomalies, and neuropathic bladder are excluded. Patients are randomized to receive CAP with trimethoprim (2 mg/kg daily) orally or a placebo for 12 months or until the first febrile UTI. The primary

Table 15.2 Characteristics of included studies.

Study ID	Year	Country	Study type	*n*	Girls	Boys	Boys, circumcised	SFU I–II patients *n* (%)	SFU III–IV patients *n* (%)	CAP *n* (%)	VUR *n* (%)	UTI *n* (%)
Dacher [4]	1992	USA	Prospective	413	3	10	3	NS	NS	NS	47 (11%)	13 (3.1%)
Blachar [5]	1994	Israel	Prospective	99	NS	NS	NS	101[a]	15[a]	NS	14 (14.1%)	7 (7.1%)
Misra [6]	1999	UK	Prospective	42	17	25	NS	22[a]	18[a]	12 (28.6%)	5 (11.9%)	NS
Herndon [7]	1999	USA	Retrospective	71	15	56	37	NS	NS	NS	71 (100%)	18 (25.4%)
Yerkes [8]	1999	USA	Prospective	60	17	43	NS	60 (100%)		NS	6 (10%)	NS
Farhat [9]	2000	Canada	Retrospective	31	7	24	NS	31[a]	9[a]	31 (100%)	31 (100%)	8 (25.8%)
McIlroy [10]	2000	New Zealand	Retrospective	69	37	32	NS	NS	NS	NS	69 (100%)	8 (11.6%)
Brophy [11]	2002	USA	Retrospective	234	60	174	NS	141 (60.3%)	80 (34.2%)	97 (41.5%)	40 (17.1%)	10 (4.3%)
McLellan [12]	2002	USA	Retrospective	54	18	36	NS	NS	NS	54 (100%)	0	0
Shukla [13]	2005	USA	Retrospective	40	8	32	NS	NS	NS	12 (30.0%)	0	2
Wollenberg [14]	2005	Switzerland	Retrospective	78	NS	NS	NS	42 (53.8%)	36 (46.2%)	41 (52.6%)	9 (11.5%)	15 (19.2%)
Mears [15]	2007	UK	Prospective	55	16	39	NS	NS	NS	NS	8 (14.5%)	NS
Song [16]	2007	South Korea	Retrospective	105	23	82	0	0	105 (100%)	0	0	38 (36.2%)
Coelho [17]	2008	Brazil	Prospective	192	52	140	0	139 (72.4%)	53 (27.6%)	119 (62.0%)	16 (8.3%)	27 (14.1%)
de Kort [18]	2008	Netherlands	Retrospective	125	26	99	NS	106 (84.8%)	19 (15.2%)	125 (100%)	11 (8.8%)	9 (7.2%)
Lee [19]	2008	South Korea	Retrospective	430	79	351	0	255 (59.3%)	175 (40.7%)	0	0	83 (19.3%)
Lidefelt [20]	2008	Sweden	Retrospective	103	NS	NS	NS	NS	NS	50 (48.5%)	9 (8.7%)	9 (8.7%)
Estrada [21]	2009	USA	Retrospective	1514	NS	NS	NS	1514 (100%)		322 (21.3%)	322 (21.3%)	21 (1.4%)
Mamì [22]	2009	Italy	Prospective	223	NS	NS	NS	223 (100%)		0	4 (1.8%)	8 (3.6%)
Roth [23]	2009	USA	Retrospective	92	20	72	NS	0	92 (100%)	0	0	4 (4.3%)
Yavascan [24]	2010	Turkey	Prospective	246	63	183	NS	NS	NS	246 (100%)	32 (13.0%)	NS
Szymanski [25]	2012	Canada	Retrospective	206	53	153	51	148	58	53	17	14
Zareba [26]	2014	Canada	Retrospective	376	99	277	76	248	128	227	79	50
Herz [27]	2014	USA	Retrospective	405	169	236	197	194	211	378	84	134
Sencan [28]	2014	USA	Retrospective	760	225	608	480	760	0	369	13	23
Duzenli [29]	2010	Turkey	Prospective	136	27	109	NS	87	49	58 (43%)	19 (13.9%)	23 (17%)
Braga [30]	2015	Canada	Prospective	334	73	261	95	142	192	96	57	65

NS, not stated.

[a] In renal units. Some studies did not report results otherwise.

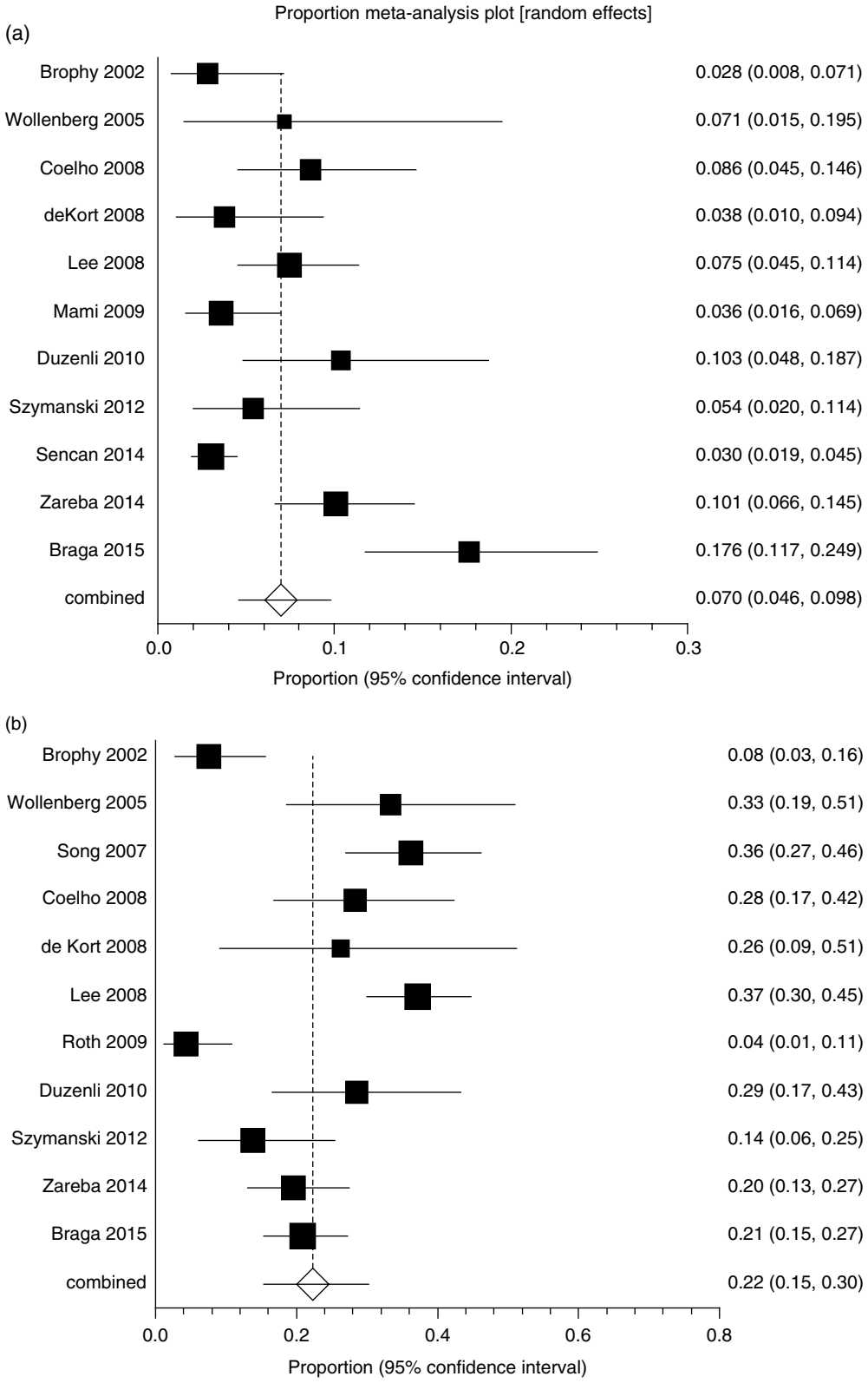

Figure 15.1 UTI rate by grade of hydronephrosis. (a) Pooled UTI rates in infants with low-grade hydronephrosis; (b) pooled UTI rates in infants with high-grade hydronephrosis.

Table 15.3 Summary of findings table for patients with hydronephrosis.

Do patients with high-grade hydronephrosis have higher UTI rates than those with low-grade hydronephrosis?

Patlent or population UTI rates
Setting: Prenatal hydronephrosis
Intervention: high-grade hydronephrosis
Comparison: low-grade hydronephrosis

Outcome No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)*			Quality	What happens
		Without highgrade hydronephrosis	With highgrade hydronephrosis	Difference		
UTI Rate No. of participants: 3208(13 observational studies)	**Rate ratlo 3.97** (3.20 to 4.90)	**Low** 5.0%	**20 per 100 (16** to **25)**	**15 more per 100** (11 more to 20 more)	⊕⊕◯◯ LOW[a,b,c]	Based on low-quality evidence, we make a strong recommendation that high-grade HN is associated with a higher UTI rate in patients with prenatal HN.
		Moderate 10.0%	**40 per 100** (32 to 49)	**30 more per 100** (22 more to 39 more)		
		High 15.0%	**60 per 100** (48 to 74)	**45 more per 100** (33 more to 59 more)		

*The risk in the Intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval.
GRADE Working Group grades of evidence.
High quality: We are very confident: that the true effect: lies close to that of the estimabe of the effect.
Moderate quality: We are moderabely confident in the effect estimate: The true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[a] Downgraded due to serious risk of bias.
[b] Downgraded due to indirectness of evidence.
[c] Downgraded as publication bias was strongly suspected.

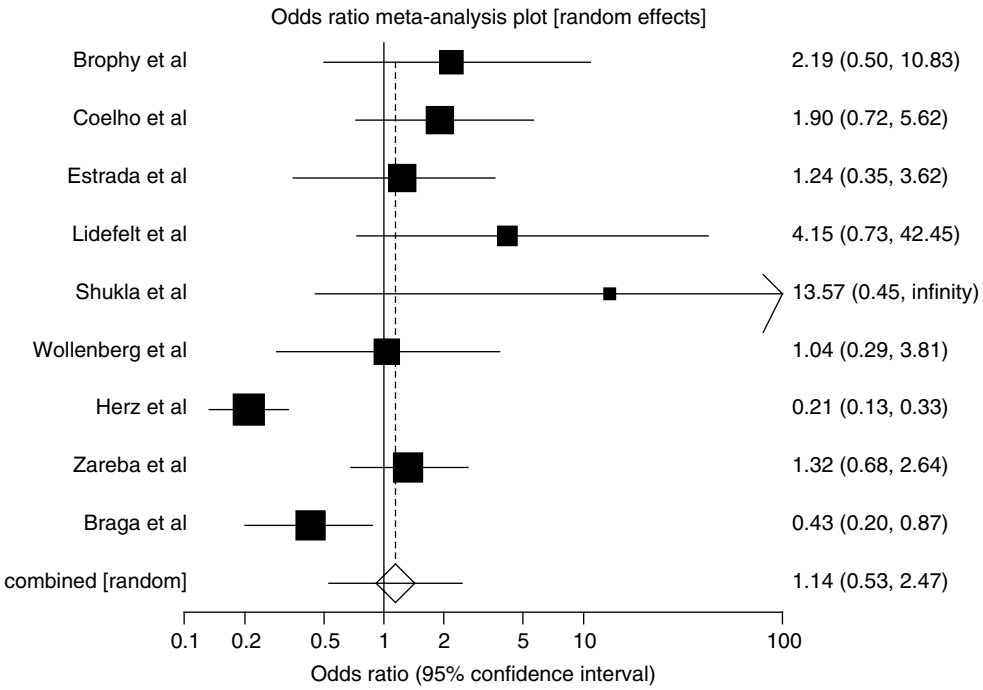

Figure 15.2 Pooled odds ratio of UTI rates in patients based on continuous antibiotic prophylaxis (CAP) status when looking only at studies including both CAP and no CAP groups.

outcome is the development of febrile UTIs during the study period. A pilot study suggesting feasibility of this trial has been published [32], and upcoming results of this trial are anticipated to guide the use of CAP in patients with high-grade prenatal HN.

Clinical implications

We recommend against the routine use of CAP in all patients with prenatal HN (strong recommendation based on very low-quality evidence) (Table 15.4). Although the cost and morbidity of CAP are low, CAP does not seem to be effective at reducing UTI rates for all patients with prenatal HN in the included observational studies (Table 15.1).

We suggest against the use of CAP in children in low-grade HN (conditional recommendation against based on very low-quality evidence). This recommendation is based on findings that the incidence of UTIs in this patient group is relatively low and the impact of CAP in this particular patient subset is uncertain. This recommendation does not apply to patients with additional risk factors for UTI (e.g. VUR) for whom we have insufficient data upon which to make recommendations.

We suggest the use of CAP in children in high-grade HN (conditional recommendation based on very low-quality evidence).This recommendation is based on the judgment that benefits of CAP outweigh the associated patient burden and costs.

Clinical question 3

Do all patients with prenatal hydronephrosis need a voiding cystourethrogram (VCUG)?

The evidence

We focused our literature search on whether the presence of VUR had an impact on UTI rates. A total of 10 studies including 705 patients with VUR demonstrated a pooled UTI rate of 26.0% (95% CI 12.1–43.0%) (Figure 15.3a). A total of 10 studies including 2823 patients without VUR demonstrated a pooled UTI rate of 10.2% (95% CI 4.5% – 17.8%) (Figure 15.3b). Stratification by grade of VUR or CAP status was not possible owing to limitations in the data available.

Clinical implications

We suggest against a VCUG in all children with prenatal HN (conditional recommendation based on very low-quality evidence) (Table 15.5). This recommendation is based on the assessment that the benefits of establishing or ruling out a diagnosis of VUR does not outweigh the burden of additional testing, the risk of a UTI from the VCUG, the radiation exposure, and the associated costs. The rate of VUR is estimated to be 16% in patients with prenatal ££HN and is effectively diagnosed with a VCUG [33].

Instead, we suggest the selective use of VCUG testing in the following situations where findings may alter patient

Table 15.4 Summary of findings table for CAP use in patients with prenatal hydronephrosis.

Should continuous antibiotic prophylaxis (CAP) be used in prenatal hydronephrosis?

Patlent or population Prenatal Hydronephrosis
Setting: Prenatal hydronephrosis
Intervention: Continuous Antibiotic Prophylaxis
Comparison: No Antibiotic Prophlaxis

Outcome No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)*			Quality	What happens
		Without continuous antibiotic prophylaxis	With continuous antibiotic prophylaxis	Difference		
UTI Rate (CAP vs no CAP No. of participants: 1180 cases 1812 controls (9 observational studies)	**OR 1.14** (0.53 to 2.47)	**Low** 10.0%	**11 per 100** (16 to 25)	**1 more per 100** (4 fewer to 12 more)	⊕○○○ VERY LOW[a,b,c,d]	
		Moderate 20.0%	**22 per 100** (12 to 38)	**2 more per 100** (8 fewer to 18 more)		Based on very low-quality evidence, we make a strong recommendation that CAP should not be routinely used for all patients with prenatnl HN.
		High 30.0%	**33 per 100** (19 to 51)	**3 more per 100** (11 fewer to 21 more)		
UTI Rate–low-grade hydronephrosis (CAP vs no CAP) No. of participants: 459 cases 1722 controls (6 observational studies)	**OR 0.76** (0.34 to 1.53)	7.0%	**5 per 100** (2 to 10)		⊕○○○ VERY LOW[b,c,d,e,f]	
				2 fewer per 100 (5 fewer to 3 more)		Based on very low-quality evidence, we also make a weak recommendation that CAP should not be routinely used in patients with low-grade HN.
UTI Rate – high – grade hydronephrosis (CAP vs no CAP) No. of participants: 123 cases 384 controls (6 observational studies)	**OR 0.42** (0.23 to 0.74)	22.0%	**11 per 100** (6 to 17)		⊕○○○ VERY LOW[c,d,e,f]	
				11 fewer per 100 (16 fewer to 5 fewer)		Based on very low-quality evidence, we make a weak recommendation that CAP be used for patients with high grade HN.

*The risk in the Intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; OR, odds ration.
GRADE Working Group grades of evidence.
High quality: We are very confident: that the true effect: lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[a]Downgraded due to serious risk of bias.
[b]Downgraded due to inconsistent results.
[c]Downgraded due to imprecision of oubcome measure.
[d]Downgraded as publication bias is suspected.
[e]Downgraded due to very serious risk of bias.
[f]Downgraded due to indirectness of outcome.

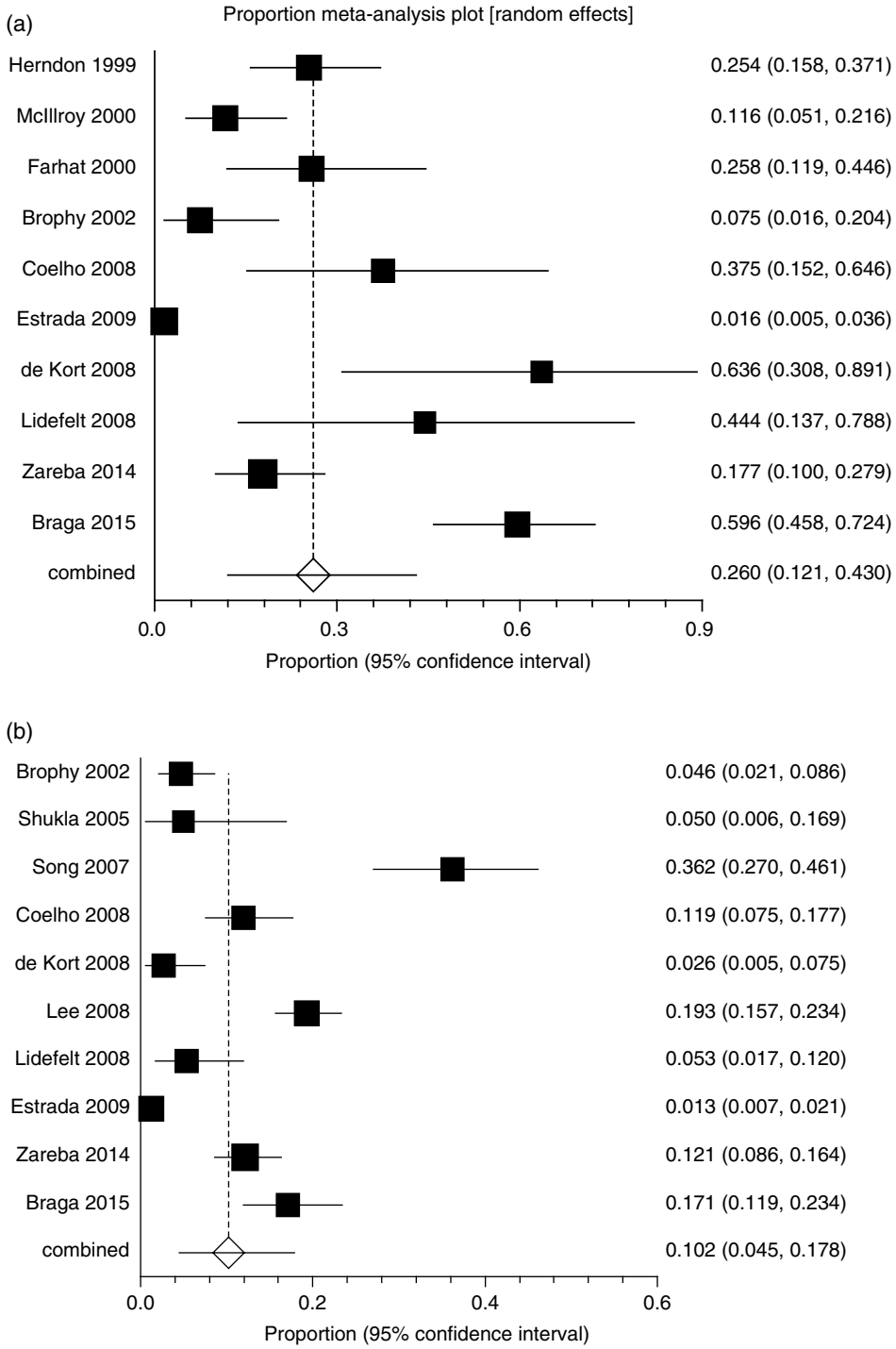

Figure 15.3 UTI rate based on the presence of vesicoureteric reflux (VUR). (a) Pooled UTI rate in patients with VUR; (b) pooled UTI rate in patients without VUR.

Table 15.5 Summary of findings table for VUR use in patients with prenatal hydronephrosis.

Does vesicoureteric reflux (VUR) increase the rate of UTI in patients with prenatal hydronphrosis?		
Patient or population: Antenatal Hydronephrosis **Setting:** **Intervention:** VLR **Comparison:** no VUR		
Outcome No. of participants (studies)	**Impact***	**Quality**
UTI Rate (VUR vs no VUR) No.of participants: 3526 (10 observational studies)	Based on low-quality evidence, we make a weak recommendation that not all patients with prenatal HN require a VCUG. UTI rate with VUR: 26.0% (95%.CI 12.1%-43.0%) UTI rate without VUR: 10.2% (95% CI 4.5%-17.8%).	⊕◯◯◯ VERY LOW[a,b,c,d,e]

*The risk in the Intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval.
GRADE Working Group grades of evidence.
High quality: We are very confident: that the true effect: lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
[a]Downgraded due to very serious risk of bias.
[b]Downgraded due to inconsistent results.
[c]Downgraded due to inconsistent results.
[d]Downgraded due to imprecision of outcome measure.
[e]Downgraded as publication bias is suspected.

management (conditional recommendation based on very low-quality evidence):

- diagnosis of certain non-VUR conditions, such as posterior urethral valves;
- patients who would be placed on CAP if a diagnosis of VUR were made;
- patients on CAP who continue to have breakthrough UTIs and may be candidates for VUR correction;
- prior to intervention for patients with prenatal HN arising from a non-VUR etiology, where the diagnosis of VUR would alter management.

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16 CHAPTER 16
Cryptorchidism

David I. Chu and Gregory E. Tasian
Division of Urology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Introduction

Cryptorchidism is the absence of one or both testicles in the dependent scrotum. It is the most common congenital genitourinary condition among male infants, with an estimated 3% prevalence in full-term boys, and up to 30% prevalence among boys born prematurely. Some cryptorchid testes may undergo spontaneous descent within the first 6 months after birth [1, 2]. Cryptorchidism is associated with increased risks of testicular cancer and decreased fertility potential.

Management of cryptorchid testicles includes hormonal therapy and surgical intervention, which have been covered in recently published professional guidelines and systematic reviews. In this chapter, we provide an updated systematic review of the literature on the success rates of hormonal therapy and surgical intervention, the optimal timing of surgery with respect to fertility and cancer risk, and the diagnostic accuracy of preoperative imaging for nonpalpable undescended testes.

Clinical question 1

Should intranasal luteinizing hormone-release hormone (LHRH) be given to prepubertal boys with cryptorchidism to bring the undescended testicle into the scrotum?

Literature search

We conducted a systematic literature search in PubMed from January 1980 to June 2015 using the search terms "hormonal therapy," "hormone therapy," "testicular descent," "undescended testicle," and "cryptorchidism," limiting our search to English-language clinical trials, systematic reviews, meta-analyses, and observational studies among children from birth to 18 years old.

The evidence

Six systematic reviews were found [3–8], with three national guidelines [9–11]. These were reviewed and cross-referenced for additional articles. A total of 56 articles were found, among which 14 were randomized controlled trials with comparison arms. Of these 14, nine were placebo-controlled and the remaining five compared different hormonal therapy regimens. Of the nine placebo-controlled trials, seven compared intranasal luteinizing hormone-release hormone (LHRH) alone against placebo. One trial compared busrelin, an LHRH analogue, against placebo, although both arms received human chorionic gonadotropin (hCG). The last placebo-controlled trial compared hCG against LHRH and placebo. Since the most robust evidence centered around LHRH, the busrelin and hCG results were excluded from our analysis. Outcome definitions of full testicular descent varied among the eight trials comparing LHRH versus placebo. As our outcome was testicular descent to the scrotum specifically and not just any form of descent, data synthesized from the individual papers did not always agree with the authors' conclusions of success. All eight studies examined prepubertal boys up to age 12 years. A meta-analysis was conducted with a pooled risk ratio estimate of 2.91 (95% confidence interval [CI] 1.32–6.40; I^2=43%; Figure 16.1) for testicular descent of LHRH compared with placebo.

Five trials found better short-term success with LHRH compared with placebo [12–16], whereas the remaining three trials did not observe a clinically significant difference between the arms [17–19]. The overall quality of these trials was very low (Table 16.1). All studies administered 4 weeks of LHRH, although the doses varied. Only four of the eight studies tested for statistical significance in the rates of success between arms. Of note, the five trials that favored LHRH over placebo all had follow-up at 4 weeks after initiation of

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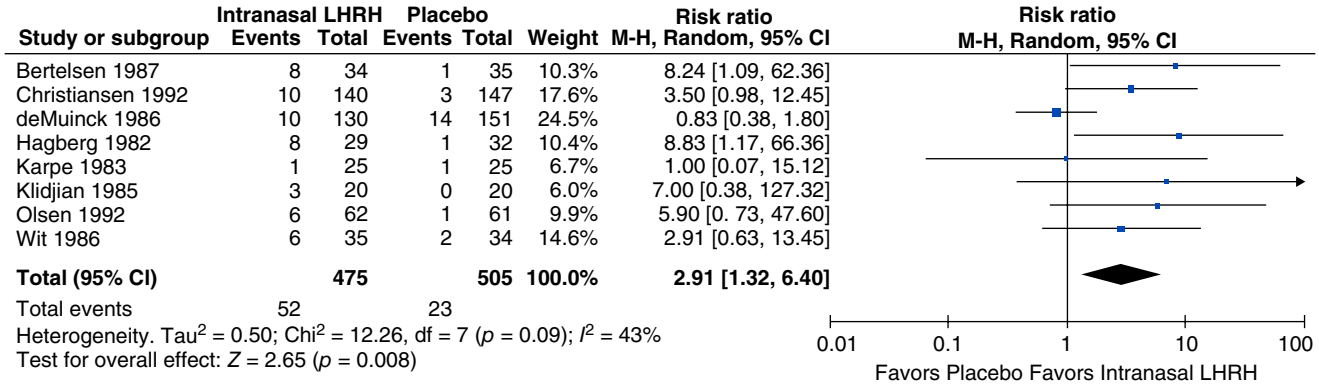

Figure 16.1 Forest plot of results for eight randomized placebo-controlled trials comparing intranasal LHRH against placebo on testicular descent.

therapy, whereas the three trials that found no difference had a longer follow-up of 2–6 months. Using our definition of successful testicular descent into the scrotum, Hagberg and Westphal [12] found a 52% success rate with intranasal LHRH compared with 3% with placebo. Klidjian et al. [13] noted that 41% of testes descended in the LHRH arm compared with 12% in the placebo arm. Bertelsen et al. [16] found that 24% of testicles descended with LHRH compared with 3% of those treated with placebo. Christianson et al. [14] showed in 257 boys that LHRH caused testicular descent in 27% of testes compared with 11% with placebo. Olsen et al. [15] found a 27% success rate in 97 testicles treated with LHRH compared with 14% in 90 testicles treated with placebo.

On the other hand, at a follow-up of 6 months, Karpe et al. [17] found that 8% of testicles treated with LHRH descended to the scrotum compared with 4% of those treated with placebo. deMuinck Keizer-Schrama et al. [18] performed a trial with 252 boys and noted a 9% descent rate with LHRH compared with 8% with placebo at 2 months' follow-up. Wit et al. [19] demonstrated a 9% success rate with LHRH compared with 6% with placebo at 2 months' follow-up.

For the important outcome of adverse effects of hormonal therapy, of the eight trials analyzed, five reported side effects [12, 14, 15, 17, 19]. Most of the reported hormonal adverse effects were behavioral changes or local nasal irritation, with no major signs of virilization such as increase in penile length. One study did note that nearly one-quarter of the patients in the treatment group showed aggressive behavior compared with none in the placebo group [19]. The results reported were too inconsistent and inconclusive to be summarized.

Clinical implications

We suggest that prepubertal boys under the age of 12 years with cryptorchidism not be treated with intranasal LHRH (conditional recommendation against based on very low-quality evidence). This recommendation is based on evidence that treatment with LHRH is not better than placebo in the longer term and that the potential harms of treatment outweigh the benefits. At best, hormonal therapy with intranasal LHRH conferred 50% success within 4 weeks of initiation of therapy and appeared to be most effective for testicles distal to the external ring. However, in those randomized controlled trials with longer follow-up, no difference in success was found. Adverse behavioral changes were also not uncommon with hormonal therapy.

Clinical question 2

In boys who undergo surgical correction for their cryptorchidism, how do success rates compare for open versus laparoscopic approaches for primary orchiopexy, one-stage Fowler–Stephens orchiopexy, and two-stage Fowler–Stephens orchiopexy?

Literature search

We conducted a systematic literature search in PubMed from January 1980 to June 2015 using the search terms "orchiopexy," "orchidopexy," "Fowler–Stephens," "laparoscopic orchiopexy," "laparoscopic orchidopexy," "undescended testicle," and "cryptorchidism," limiting our search to English-language clinical trials, systematic reviews, meta-analyses, and observational studies among children from birth to 18 years old.

The evidence

Six systematic reviews [3, 4, 20–23] and three national guidelines [9–11] were found. These were reviewed and cross-referenced for additional articles. A total of 31 original studies were reviewed. These consisted of six randomized trials [24–29], two prospective cohort studies [30, 31], two high-quality retrospective cohort studies [32, 33], and the rest retrospective low-quality studies.

We stratified outcomes by surgical indication. Primary orchiopexy, whether for inguinal or intra-abdominal testes, was categorized into open versus laparoscopic. We then restricted our analysis only to studies of intra-abdominal

Table 16.1 GRADE evidence profile for clinical question 1: Should intranasal LHRH be given versus placebo to boys with cryptorchidism to bring the undescended testicle into the scrotum?

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hormonal therapy**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Testicular descent												
8	Randomized trials	Serious[a]	Serious[b]	Serious[c]	Serious[d]	None	47/418 (11.2%)	22/447 (4.9%)	**RR 2.91** (1.32 to 6.40)	**94 more per 1000** (from 16 more to 266 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI, confidence interval; RR, risk ratio.

[a] Most studies have inadequate description of randomization, allocation concealment, and placebo; most are double-blinded; poor mention of intention-to-treat (ITT) analysis; no power calculations; heterogeneous loss to follow-up.

[b] Heterogeneity of dosing, duration of treatment, and definitions of success.

[c] Short follow-up (only 4 weeks).

[d] Small number of events, commonly underpowered studies.

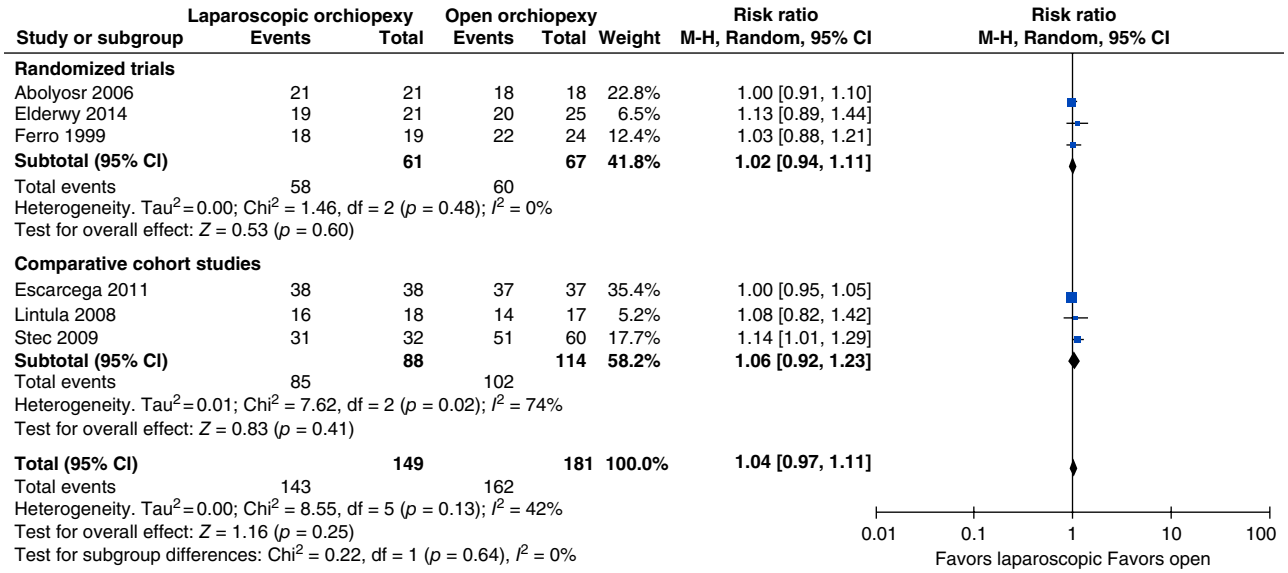

Figure 16.2 Forest plots of results for three randomized trials and three comparative cohort studies comparing primary laparoscopic against primary open orchiopexy on surgical success.

testes. High intra-abdominal testes, which require division of the testicular vessels (Fowler–Stephens technique), were separated into one-stage versus two-stage orchiopexy, with comparison of open and laparoscopic approaches.

Our results for primary orchiopexy included 25 studies – six randomized trials [24–29], two prospective cohort studies [30, 31], and the remainder retrospective studies [32–48]. Of the six randomized trials, three compared primary open versus laparoscopic orchiopexy [24, 25, 29], one compared scrotal orchiopexy versus scrotal pouch neck closure [26], one compared external oblique fascia incision versus fascia sparing [28], and one compared inguinal versus scrotal approaches [27]. Of the three trials – two of abdominal or nonpalpable testes and one of peeping testes – comparing primary laparoscopic versus primary open orchiopexy, a meta-analysis was conducted of surgical success with a pooled risk ratio estimate of 1.02 (95% CI 0.94–1.11; $I^2 = 0\%$; Figure 16.2; Table 16.2). Of the prospective cohort and retrospective studies, only three directly compared primary laparoscopic versus primary open orchiopexy [30, 32, 42], with a pooled risk ratio estimate of 1.06 (95% CI 0.92–1.23; $I^2 = 74\%$; Figure 16.2; Table 16.2). The remaining studies did not directly compare primary open against primary laparoscopic orchiopexy but gave success rates for one or the other. Cumulatively across all 25 studies, primary open orchiopexy resulted in a success rate of 96.1% in 1042/1084 testicles. Primary laparoscopic orchiopexy resulted in a success rate of 97.5% in 1036/1063 testicles. Restriction of data only to intra-abdominal testicles showed a success rate of 89% in 194/218 testicles with primary open orchiopexy, compared with a success rate of 97% in 808/833 testicles with primary laparoscopic orchiopexy.

Our results for two-stage Fowler–Stephens orchiopexy included 17 studies – one randomized trial [25], one prospective cohort study [31], and the remainder retrospective studies [37, 38, 44, 47–54]. Only three of these studies directly compared open versus laparoscopic two-stage Fowler–Stephens orchiopexy [30, 37, 41]. The randomized trial found 16/19 success in the open two-stage group and 20/22 success in the laparoscopic two-stage group, giving a risk ratio of 0.93 (95% CI 0.73–1.17; not shown). Two small retrospective cohort studies found a pooled risk ratio estimate of 0.93 (95% CI 0.69–1.24; $I^2 = 0\%$; not shown). The remaining studies did not directly compare open against laparoscopic two-stage Fowler–Stephens orchiopexy but gave success rates for one or the other. Cumulatively, success rates of 85.7 and 91.9% were found in 24/28 and 331/360 testicles for open and laparoscopic two-stage Fowler–Stephens orchiopexy, respectively.

Our results for one-stage Fowler–Stephens orchiopexy included 12 studies – all small retrospective cohort studies [32, 34–36, 38, 39, 43, 44, 47, 49, 50, 52]. Only one study directly compared open versus laparoscopic one-stage Fowler–Stephens orchiopexy [32], with success in 62.5% (5/8 testicles) laparoscopic and 63.2% (12/19) open one-stage Fowler–Stephens orchiopexies. No randomized trials have been performed that directly compared open versus laparoscopic one-stage Fowler–Stephens orchiopexy. Cumulative success rates of 66.7% (12/18) and 82.8% (135/163) were found for open and laparoscopic one-stage Fowler–Stephens orchiopexies, respectively.

Table 16.2 GRADE evidence profile for clinical question 2: Should open or laparoscopic primary orchiopexy be performed?

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Laparoscopic orchiopexy**	**Open orchiopexy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Surgical success in primary open versus laparoscopic orchiopexy												
3	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	Publication bias strongly suspected[b]	55/58 (94.8%)	63/70 (90.0%)	**RR 1.02** (0.94 to 1.11)	**18 more per 1000** (from 54 fewer to 99 more)	⨁⨁◯◯ LOW	IMPORTANT
Surgical success in primary open versus laparoscopic orchiopexy												
3	Observational studies	Serious[a]	Serious[c]	Not serious	Serious[d]	Publication bias strongly suspected[b]	85/88 (96.6%)	102/114 (89.5%)	**RR 1.06** (0.92 to 1.23)	**54 more per 1000** (from 72 fewer to 206 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI, confidence interval; OR, odds ratio.

[a] Small studies; variable follow-up.

[b] Publication bias suspected based on funnel plot.

[c] Variable populations; large I^2 (74%).

[d] Small sample sizes.

Clinical implications

We suggest that boys with cryptorchidism, depending on whether the orchiopexy is primary, two-stage Fowler–Stephens, or one-stage Fowler–Stephens, be treated with either open or laparoscopic orchiopexy (conditional recommendation against one being better than the other based on low- or very low-quality evidence). This recommendation is based on evidence that treatment with a laparoscopic approach is not significantly more or less successful than an open approach for primary or two-stage Fowler–Stephens orchiopexy. For one-stage Fowler–Stephens orchiopexy, high-quality evidence is lacking.

Clinical question 3

In boys with cryptorchidism, what is the optimal age cut-off to perform surgical orchiopexy?

Literature search

We conducted a systematic literature search in PubMed from January 1980 to June 2015 using the search terms "fertility," "testicular cancer," "testis cancer," "puberty," "timing," "orchiopexy," "orchidopexy," "undescended testicle," and "cryptorchidism," limiting our search to English-language clinical trials, systematic reviews, meta-analyses, and observational studies among children from birth to 18 years old.

The evidence

For the outcome of fertility, two systematic reviews [6, 55] and three national guidelines [9–11] were found. These were reviewed and cross-referenced for additional studies. A total of 24 studies were reviewed. Of these, eight studies were included – one randomized trial [56], one prospective cohort study [57], and six high-quality retrospective cohort studies [58–63].

Outcome measures of fertility potential differed across studies. Kollin et al. [56] and Kim et al. [61] used testicular catch-up growth as their primary outcome measure. Feyles et al. [58] and Canavese et al. [62] assessed total sperm count and motility on semen analyses. Kogan et al. [60], Park et al. [57], and Tasian et al. [63] analyzed testicular histology from biopsies and compared germ cell counts, seminiferous tubular diameters, and other indices of fertility. Lee et al. [59] looked at paternity rates. Owing to the heterogeneity of the definitions of fertility potential, we could not perform a meta-analysis.

Regardless of the outcome measure, results were consistently in favor of earlier orchiopexy. Although Lee et al. [59] examined the truest measure of fertility, paternity, they only stratified age into <7 and >7 years of age, with no difference found. Using testicular catch-up growth as a surrogate marker of fertility, Kollin et al. [56] found better catch-up growth with surgery at 9 months of age rather than 3 years of age. The study by Kim et al. [61] concurred with greatest catch-up growth in their youngest age group, <2 years old, compared with older age groups. All other studies found improved markers of fertility when orchiopexy was performed at <12 months of age. Both Feyles et al. [58] and Canavese et al. [62] found improved total sperm counts and sperm motility in young boys who underwent prior orchiopexy when they were <1 year old compared with young boys who underwent surgery between ages 1 and 2 years. Testicular histology results from Kogan et al. [60] noted the greatest seminiferous tubular diameter on biopsy in boys who underwent orchiopexy between ages 2 and 11 months compared with older boys. Tasian et al. [63] noted increasing odds of germ cell and Leydig cell loss with increasing age, with a quadrupling of odds of germ cell loss in boys who underwent orchiopexy between ages 13 and24 months compared with those who underwent surgery between ages 0 and 12 months. Park et al. [57] noted significantly better histological fertility indices in boys who underwent surgical repair before 1 year of age compared with older age groups.

For the outcome of testicular cancer risk, two systematic reviews [55, 64] and three national guidelines [9–11] were found. These were reviewed and cross-referenced for additional studies. In total, no randomized trials had been published, but four case–cohort studies [65–68] and three retrospective cohort studies [69–71] were included (Table 16.3).

One of the systematic reviews performed a concomitant meta-analysis [64] of five of the studies [65, 67, 68, 70, 71] included in our analysis. The pooled estimate of effect was an odds ratio (OR) of 3.4 (95% CI 0.7–17.7) for testicular cancer risk in patients who either did not undergo orchiopexy until age 10–11 years or never underwent surgery, compared with those who underwent orchiopexy before age 10–11 years. However, the meta-analysis did not include measures of heterogeneity. The authors of the other systematic review [55] suggested that a meta-analysis was inappropriate given the heterogeneity of the studies. In our analysis, data from all seven original studies had a pooled OR estimate of 0.26 (95% CI 0.09–0.70; $I^2 = 68\%$; Figure 16.3). Subgroup analysis of cohort versus case–control studies showed that most of the heterogeneity arose from the cohort studies.

Individually, with the exception of Swerdlow et al.'s cohort study [71], which showed a lack of association between testicular cancer risk and age of orchiopexy, the remaining individual studies found positive associations between increasing age of orchiopexy and risk of testicular cancer. The cut-off ages in the positive studies varied but centered generally around the age of male puberty (10–13 years). Strader et al. [65] found that orchiopexy at ≤10 years of age reduced (OR 2.6, 95% CI 0.8–9.7) the increased risk of testicular cancer compared with surgery at age 11–13 years (OR 5.6, 95% CI 1.7–18.1) or ≥14 years (OR 19.6, 95% CI 3.7–104.7), with baseline being no cryptorchidism. Petterson et al. [69] found a similar result with a relative risk (RR) of 5.4 (95%

Table 16.3 GRADE evidence profile for clinical question 3: In boys with cryptorchidism, what is the optimal age cut-off to perform surgical orchiopexy, specifically to reduce risk of testicular cancer?

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prepubertal orchiopexy**	**Postpubertal or no orchiopexy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Case–control studies												
4	Observational studies	Serious[a]	Not serious	Not serious	Serious[b]	Publication bias strongly suspected very strong association[c]	31/45 (68.9%)	63/89 (70.8%)	**OR 0.15** (0.06 to 0.41)	**441 fewer per 1000** (from 210 fewer to 581 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Cohort studies												
3	Observational studies	Serious[d]	Serious[e]	Not serious	Not serious	None	45/17718 (0.3%)	26/3640 (0.7%)	Not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CI, confidence interval; OR, odds ratio.

[a] Possibility of bias in finding appropriate controls.

[b] Small numbers of cases and controls.

[c] Via funnel plot.

[d] Selection bias, lack of power calculation, loss to follow-up.

[e] Two found positive results, one negative.

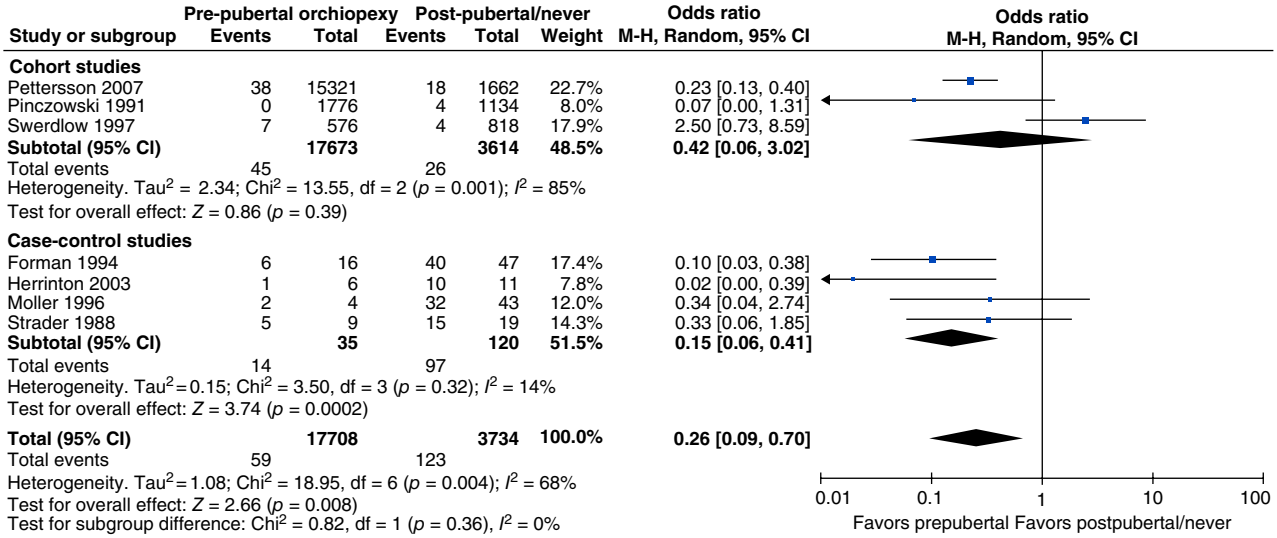

Figure 16.3 Forest plots of results for three cohort and four case–control studies comparing testicular malignancy risk by age of orchiopexy.

CI 3.20–8.53) if orchiopexy was performed at ≥13 years of age compared with an RR of 2.23 (95% CI 1.58–3.06) if orchiopexy was performed at <13 years of age. Forman et al. [66] found a significantly increased testicular cancer risk in patients undergoing orchiopexy at age 10–14 years (OR 7.67, 95% CI 2.30–25.53) than before age 10 years. Herrinton et al. [67] showed the same for patients who underwent surgery after age 11 years (RR 32, 95% CI 4–250) than before. Moller et al. [68] demonstrated a stepwise increase in risk, with OR 1.1 (95% CI 0.2–8.2) for repairs performed before age 10 years, OR 2.9 (95%CI 1.2–7.1) at age 10–14 years, and OR 3.5 (95%CI 0.9–13.8) at age ≥15 years.

Clinical implications

We recommend that boys with cryptorchidism should undergo orchiopexy before the age of 2 years rather than at a later age (strong recommendation based on very low-quality evidence). This recommendation assumes that the surgical procedure is relatively safe at this age and that patients' parents have a strong preference for optimizing their sons' future chance of fertility and reducing their cancer risk, despite the underlying uncertainty about the effectiveness of earlier versus later orchipexy.

Clinical question 4

In boys with nonpalpable cryptorchidism, how accurate is preoperative ultrasound or magnetic resonance imaging (MRI) versus surgical exploration in localizing the undescended testes?

Literature search

We conducted a systematic literature search in PubMed from January 1980 to June 2015 using the search terms "ultrasound," "magnetic resonance imaging," "MRI," "diagnostic accuracy," "sensitivity," "specificity," "undescended testicle," and "cryptorchidism," limiting our search to English-language clinical trials, systematic reviews, meta-analyses, and observational studies among children from birth to 18 years old.

The evidence

Three meta-analyses – one of just ultrasound [72], one of just MRI [73], and one of both [3] – and three national guidelines [9–11] were found. These were reviewed and cross-referenced for additional articles. No randomized trials were found. A total of 19 observational studies were reviewed regarding use of ultrasound, seven of which were prospective and the remainder retrospective. Eight observational studies were reviewed regarding use of conventional MRI, of which seven were prospective and one retrospective. Because of the low quality and heterogeneity of the few additional more recent studies not included in the meta-analyses, we only analyzed the results of the three high-quality meta-analyses.

The two meta-analyses [3, 72] on the diagnostic accuracy of ultrasound for nonpalpable cryptorchidism found that the accuracy depended on the true location of the undescended testis as determined at the time of surgery. Tasian et al. [72] noted that in the 12 studies that assessed the diagnostic performance of ultrasound in localizing nonpalpable testes, ultrasound detected 97% of viable inguinoscrotal testes versus 38% of intra-abdominal testes. Overall sensitivity and specificity were 45% (95% CI 29–61%) and 78% (95% CI 43–94%), respectively. The corresponding LR+ and LR– were 1.48 (95% CI 0.54–4.03) and 0.79 (95% CI 0.46–1.35), respectively. Notably, the confidence intervals for both LR+ and LR– cross the value 1 and are therefore not helpful as a diagnostic tool. Sensitivity and specificity were 44% (95% CI 22–68%) and 93% (95% CI 34–100%), respectively, for

nonpalpable intra-abdominal testes, compared with 52% (95% CI 27–75) and 88% (95% CI 33–99), respectively, for nonpalpable inguinoscrotal testes. Using a pretest probability of 55% that a nonpalpable testis was intra-abdominal, Tasian et al. [72] calculated that the post-test (posterior) probability of an intra-abdominal testis was 49% if the ultrasound was negative and 64% if the ultrasound was positive. Penson et al. [3] similarly found that results were better with ultrasound for nonpalpable inguinoscrotal testes with an overall accuracy rate of 92% (97% in the study by Tasian et al. [72]) compared with 33% (38% in the study by Tasian et al. [72]) for nonpalpable intra-abdominal testes. Likelihood ratios were not utilized. Sensitivity and specificity were not pooled, but ranged from 15 to 80% and from 67 to 100%, respectively, using surgical exploration as the reference standard.

The two meta-analyses [3, 73] on the diagnostic accuracy of conventional MRI for nonpalpable cryptorchidism were by the same group of authors. They likewise found that the accuracy varied by testicular position. Krishnaswami et al. [73] performed a meta-analysis of eight studies that used conventional MRI and demonstrated an overall accuracy of 42–88%, with higher accuracy in correctly diagnosing nonpalpable inguinoscrotal than nonpalpable intra-abdominal testes. Sensitivities for overall, inguinoscrotal, and intra-abdominal nonpalpable testes were 62, 86, and 55%, respectively, using surgery as the reference standard. Specificities for overall, inguinoscrotal, and intra-abdominal nonpalpable testes were 100%. Using the pooled estimates of overall sensitivity (62%) and specificity (100%), LR– for MRI can be estimated to be 0.38. Assuming a pretest probability of 55% that a nonpalpable testis is intra-abdominal, a negative MRI gives a post-test probability of 32%. Penson et al. [3], in comparing MRI against ultrasound, showed a much better accuracy with MRI for nonpalpable intra-abdominal testes (71 vs. 34%), although slightly inferior accuracy with MRI for nonpalpable inguino-scrotal testes (83 vs. 92%).

Clinical implications

We recommend against the use of ultrasound or MRI as an adjunctive diagnostic test in boys with nonpalpable cryptorchidism (strong recommendation based on high-quality evidence). Both imaging modalities lack diagnostic accuracy to rule out effectively the presence of a nonpalpable testes to forego the need for intra-abdominal exploration.

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17 CHAPTER 17
Vesicoureteral reflux disease

Ruiyang Jiang and Jonathan C. Routh
Division of Urologic Surgery, Duke University Medical Center, Durham, NC, USA

Introduction

Primary vesicoureteral reflux (VUR) is a common condition that is present in 1–10% of all children in the United States [1]. In the setting of a febrile urinary tract infection (UTI), VUR has been reported to be present in one-third of children [2]. In affected children, VUR is associated with an increased risk of recurrent pyelonephritis and, hence, is also associated with an increased risk of renal scarring [2, 3]. Typical interventions for children with VUR include antireflux surgery (whether endoscopic, laparoscopic, or open) and continuous antibiotic prophylaxis (CAP). The purpose of CAP is to keep the urine "sterile" so that the risk of retrograde renal infection will be reduced. Since a significant proportion of VUR will spontaneously resolve over time [4, 5], many authors recommend a conservative approach: using CAP as the initial option in children with VUR and reserving surgical intervention for those in whom CAP is ineffective at preventing UTI.

However, significant controversy and treatment-related variability exist regarding VUR treatment [6]. In particular, the effectiveness of CAP at reducing infections in children has been called into question [7]. Randomized controlled trials (RCTs) investigating the effect of CAP on UTI prevention in VUR demonstrated conflicting results [8–15]. Further clouding this picture is the fact that, as noted in a Cochrane review, many of these RCTs had significant design or reporting flaws that limit their impact [16]. However, with the recent publication of the NIH-sponsored RIVUR trial [12], it is unclear whether the accumulated data on CAP have shifted enough to affect treatment recommendations.

Clinical question 1

Should children with VUR who develop a febrile UTI undergo a dimercaptosuccinic acid (DMSA) renal scan to assess for renal scarring?

Literature search

We searched MEDLINE, EMBASE, the Cochrane Controlled Trials Register, Google Scholar, and ClinicalTrials.gov electronic databases for trials and systematic reviews published between January 2010 and May 2016 in any language. We used the search terms "renal scarring," "kidney scarring," "renal fibrosis," "febrile UTI," "pyelonephritis," "vesico-ureteral reflux," and "vesico-ureteric reflux." Reference lists of included studies were manually screened for any additional studies. We also manually searched for unpublished abstracts presented at relevant scientific meetings.

The evidence

One systematic review and two meta-analyses were identified. A review by Shaikh et al. [17] included 33 articles (n=4891 children, age <18 years). For inclusion criteria, patients must have a first episode of UTI defined by positive urine culture along with a DMSA scan in either the acute (<15 days) or latent phase (>5 months). Fever was included in 17 of the 33 articles. The overall prevalence of renal scarring as evidenced on latent DMSA scan was 18%. Renal scarring was 2.6 times (95% confidence interval [CI] 1.7–3.9) higher among children with VUR than among children without VUR (41 vs. 17%; p<0.001). Furthermore, children with VUR grade 3–5 had a 2.1 times (95% CI 1.4–3.2) higher

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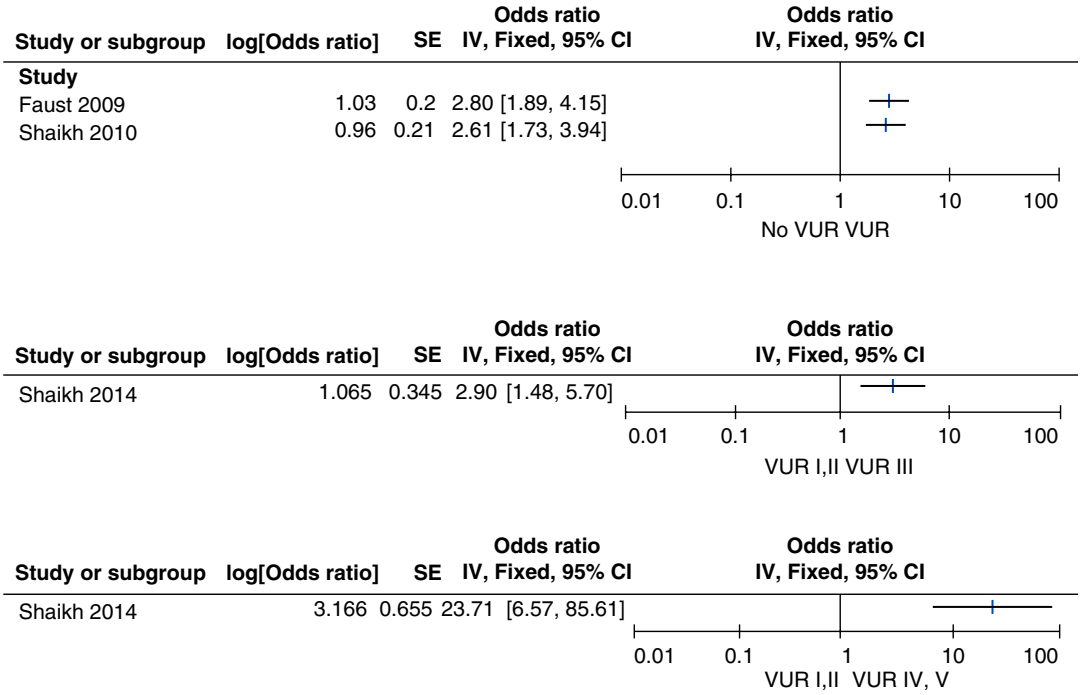

Figure 17.1 Forest plot of risk of renal scarring in children with VUR versus without VUR. Shaikh et al. [19] also compared risk of scarring with degree of VUR.

risk of developing renal scarring than children with VUR grade 1–2 (53 vs. 25%; $p<0.001$) [17].

A meta-analysis by Faust et al. [18] included 23 articles ($n=2106$ children, mean age 38 months). For inclusion criteria, patients must have a first episode of acute pyelonephritis (APN) defined by fever and/or positive urine culture and areas of photopenia on DMSA and a follow-up DMSA scan that confirmed scarring. The overall rate of renal scarring was 41.6%, and children with VUR had an increased risk of scarring than children without VUR (odds ratio [OR] 2.8, 95% CI 1.9–4.2). In addition, an interesting observation was that the overall rate of renal scarring varied by geographic region, with Asia having the highest rate at 49% and Oceania having the lowest at 26.5%. The United States had the second highest rate behind Asia at 48% [18].

A second, more recent meta-analysis by Shaikh et al. [19] included nine articles ($n=1280$ children, age <18 years). For inclusion criteria, subjects must have a positive urine culture along with DMSA scan to confirm renal scarring. Fever to 39 °C was present in 48% of the children. Renal scarring was seen in 15.5% of the patients, and 50.3% of the patients with renal scarring had VUR. The proportion of renal scarring increased from 11.1% in children without VUR to 68.6% in children with VUR grade 4 or 5. Using a multivariate model, it was found that children with VUR grade 1–2 did not have any increased risk of renal scarring. Children with VUR grade 3 were 2.9 times (95% CI 1.48–5.70, $p<0.01$) more likely to develop renal scarring than children without VUR. For VUR grade 4 and 5, children were 23.7 times (95% CI 6.5–85.6, $p<0.01$) more likely to develop renal scarring compared with children without VUR. However, only 4.1% of the children had VUR grade 4–5 (Figure 17.1) [19].

In summary, children with VUR have an increased risk of renal scarring after a febrile UTI. The risk for renal scarring correlates with the degree of reflux.

Clinical implications

We suggest against the use of a DMSA scan in patients with VUR grade 1–2 (conditional recommendation based on low-quality evidence). This recommendation is based on the judgment that the burden of testing on the patients, the risk of false-positive findings, and the required resource utilization do not outweigh the burden of finding a small number of patients with renal scarring.

We suggest the use of a DMSA scan in patients with VUR grade 4–5 (conditional recommendation based on low-quality evidence) in whom the risk of renal scarring is much higher and the benefits outweigh the burden and potential harms.

Clinical question 2

Should patients with VUR be placed on antibiotic prophylaxis?

Literature search

We searched MEDLINE, EMBASE, the Cochrane Controlled Trials Register, Google Scholar, and ClinicalTrials.gov electronic databases for trials and systematic reviews published between January 2010 and May 2016 in any language. We used the search terms "vesicoureteral reflux," "vesicoureteric reflux," "vesico-ureteral reflux," and "vesico-ureteric reflux." Reference lists of included studies were manually screened for any additional studies. We also manually searched for unpublished abstracts presented at relevant scientific meetings.

The evidence

One meta-analysis was identified; Wang et al. [20] included eight RCTs ($n=1594$ children, age <18 years). All of the patients were diagnosed with VUR after a UTI. Follow-up ranged from 1 to 3 years. Two of the eight RCTs were deemed at low risk of bias. The overall rate of renal scarring in the control and antibiotic prophylactic group was 5.9 and 3.9%, respectively. There was no significant decrease in renal scarring in the antibiotic group compared with the control group (OR 0.74; 95% CI 0.27–2.04) (Figure 17.2, Table 17.1) [20].

In the same meta-analysis by Wang et al. [20], CAP significantly decreased the risk of febrile or symptomatic UTI in children with VUR (pooled OR 0.63; 95% CI 0.42–0.96, $p=0.03$). When stratified by the susceptibility of each study to bias, those studies at lower risk of bias showed an even more significant protective effect from CAP (pooled OR 0.51; 95% CI 0.35–0.73, $p=0.0003$). There was no statistically significant impact of CAP on febrile or symptomatic UTI in studies at higher risk of bias (p=0.34). Bivariate meta-regression models revealed no significant association between the likelihood of febrile or symptomatic UTI and duration of follow-up ($p=0.5$), gender ($p=0.1$), placebo (vs. no treatment, $p=0.5$), and study year ($p=0.1$) (Figure 17.3, Table 17.1) [20].

However, in the same meta-analysis, the rate of antibiotic resistance in the treatment and control groups was 76 vs. 24%. The risk for developing resistant bacteria was significantly higher in the treatment group than control group (pooled OR 8.75; 95% CI 3.52–21.73, $p<0.0001$). This remained significant after stratifying between studies based on risk of bias (Figure 17.4, Table 17.1) [20].

In summary, CAP did not significantly impact the rate of new renal scarring or reported treatment-related adverse events. Compared with no treatment or placebo, CAP did significantly reduce the risk of febrile and symptomatic UTI in children with VUR. The protective effect of CAP was more prominent in studies deemed to be at low risk of bias. However, children with VUR who are treated with CAP are at increased risk for developing antibiotic-resistant bacterial colonization and/or infection. Given this tradeoff of potential harms versus benefits, it is important to select carefully patients who are most likely to benefit from CAP.

Clinical implications

We suggest antibiotic prophylaxis in children with VUR and a history of febrile or symptomatic UTI (conditional recommendation based on high-quality evidence). This recommendation assumes that family/patients place a relatively high value on the avoidance of symptomatic febrile UTIs and are willing to accept the possibility of bacterial resistance. We do not suggest CAP for the purpose of preventing new renal scarring. We similarly do not suggest the routine use of CAP in patients without a history of febrile or symptomatic UTI, particularly in those patients with grade 1–2 VUR (conditional recommendation with moderate-quality evidence).

Clinical question 3

In children with VUR, how does surgery (ureteral reimplant or endoscopic injection) plus antibiotics compare with antibiotics alone?

Literature search

We searched MEDLINE, EMBASE, the Cochrane Controlled Trials Register, Google Scholar, and ClinicalTrials.gov electronic databases for trials and systematic reviews published between January 2010 and May 2016 in any language. We used the search terms "ureteral reimplant," "deflux," "renal scarring," "kidney scarring," "renal fibrosis," "febrile UTI," "pyelonephritis," "vesico-ureteral reflux," and "vesico-ureteric reflux." Reference lists of included studies were manually screened for any additional studies. We also manually searched for unpublished abstracts presented at relevant scientific meetings.

The evidence

One Cochrane review was found that evaluated the benefits and harms of different treatment options for VUR [16].

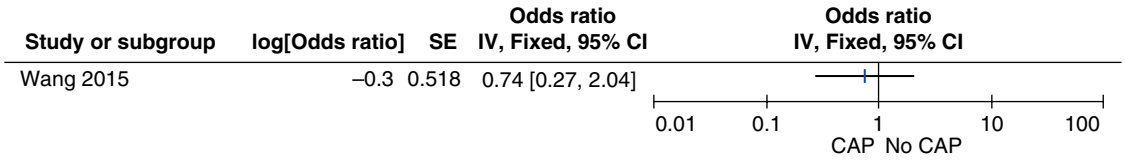

Figure 17.2 Forest plot of CAP did not impact risk of renal scarring.

Table 17.1 GRADE evidence table for clinical questions 1 and 2.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CAP**	**No CAP**	**Relative (95% CI)**	**Absolute (95% CI)**		
Renal scarring												
8	Randomized trials	Serious[a]	Not serious[b]	Serious[b]	Not serious	None	25/639 (3.9%)	33/562 (5.9%)	**OR 0.74** (0.27 to 2.04)	**15 fewer per 1000** (from 42 fewer to 54 more)	⨁⨁◯◯ LOW	IMPORTANT
Symptomatic and febrile UTI												
8	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None	117/804 (14.6%)		**OR 0.63** (0.42 to 0.96)	**70 fewer per 1000** (from 7 fewer to 116 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Drug-resistant bacteria												
8	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	70/92 (76.1%)	36/147 (24.5%)	**OR 8.75** (3.52 to 21.73)	**495 more per 1000** (from 288 more to 631 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI, confidence interval; OR, odds ratio.

[a] Only two of the eight studies included placebo that was similar to the active antibiotic.

[b] Renal scarring due to indirectness.

[c] As little as 7 fewer per 1000.

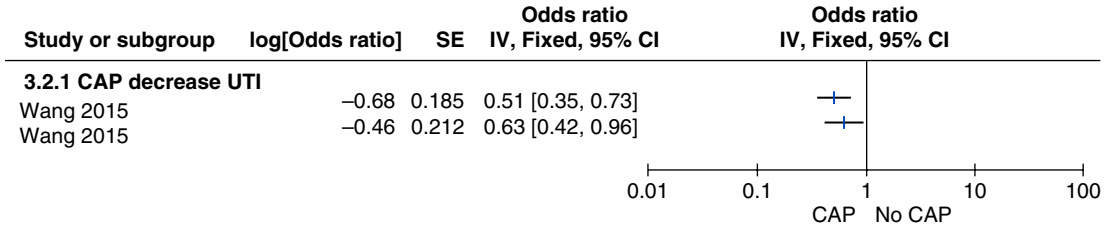

Figure 17.3 Forest plot of CAP decreased risk of symptomatic and febrile UTI.

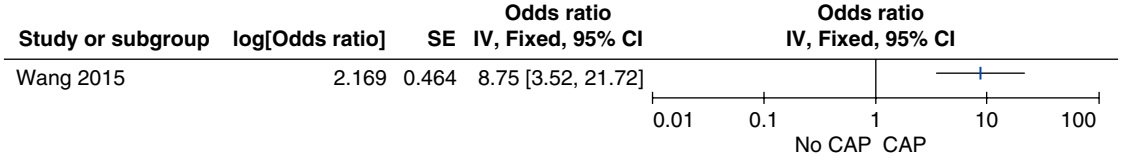

Figure 17.4 Forest plot of risk on developing antibiotic-resistant bacteria in children on CAP.

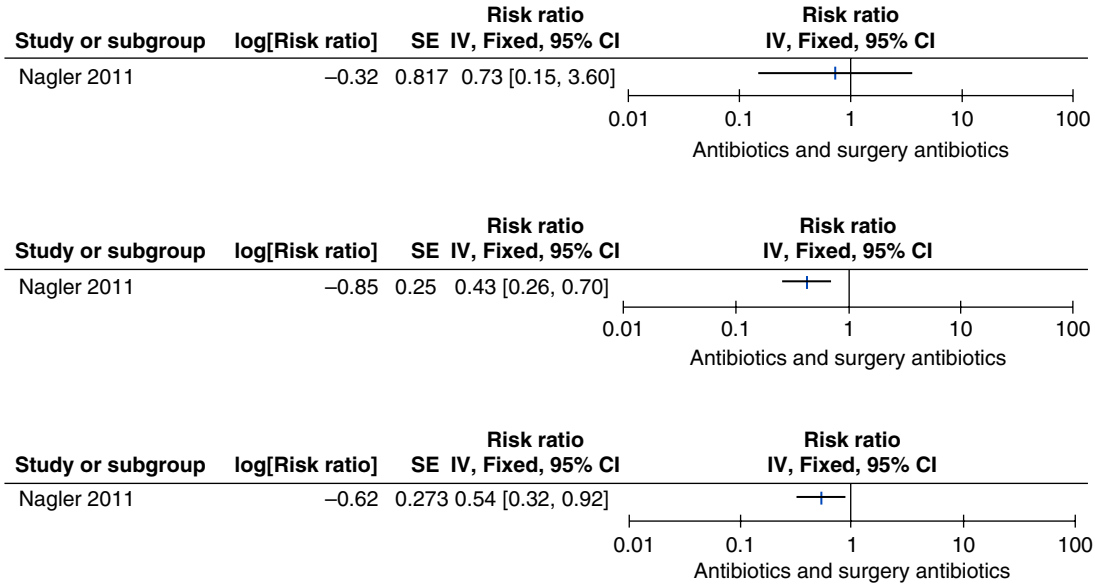

Figure 17.5 Forest plot of impact of surgery plus antibiotics on reducing febrile UTI at 2-, 5-, and 10-year follow-up.

In this review, 22 RCTs were included ($n = 2324$ children, age <18 years). To evaluate whether surgery had any impact on symptomatic and febrile UTI, combined data from three RCTs were included. At 2-year follow up, there was no significant difference in the frequency of febrile (RR 0.73; 95% CI 0.15–3.6) or symptomatic UTI (RR 0.88; 95% CI 0.26–3.01) between patients treated with surgery plus antibiotics versus antibiotics alone. However, at 5-ye4ar follow up, the frequency of febrile UTI in children who had undergone surgery (8–10%) was significantly lower than in those who only received antibiotics (22%) (RR 0.43; 95% CI 0.27–0.7). Similarly, this significant decrease in the frequency of febrile UTI holds true for patients who were followed for 10 years (RR 0.54; 95% CI 0.32–0.92). There was no significant difference in the number of symptomatic UTIs at any time period (Figure 17.5, Table 17.2) [16].

In summary, surgery plus antibiotics over antibiotics alone decreased the risk of febrile UTI in children with VUR but did not have any significant impact on the development of symptomatic UTI.

Clinical implications

In parents of children who place a relatively high value on avoiding the potential risks of surgery and place a relatively low value on avoiding the burden and risks of CAP, we suggest CAP use for avoidance of febrile or symptomatic UTI (recommendation based on high-quality evidence). In contrast, for parents of children who place a relatively low value

Table 17.2 GRADE evidence profile for clinical question 3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotics**	**Surgery + antibiotics**	**Relative (95% CI)**	**Absolute (95% CI)**		
Surgery (reimplant or deflux) plus antibiotics vs. antibiotics alone												
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	48/218 (22.0%)	20/211 (9.5%)	**RR 0.43** (0.27 to 0.70)	**54 fewer per 1000** (from 28 fewer to 69 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

CI, confidence interval; RR, risk ratio.

on avoiding the potential risks of surgery and place a relatively high value on avoiding the burden and risks of CAP, we suggest CAP use for avoidance of febrile UTI (recommendation based on high-quality evidence). Given the inherent challenges of surgical decision-making in children, this decision should be made in the context of a discussion between family and urologist after weighing the risks/benefits of surgery and the patient's current renal function (conditional recommendation based on low-quality evidence).

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18 CHAPTER 18
Circumcision

Roderick Clark and Sumit Dave
Division of Urology, The University of Western Ontario, London, ON, Canada

Introduction

Male circumcision (MC) is the oldest planned operative procedure in the history of human civilization, but there continues to be a lack of consensus and strong opposing views on the benefits of this procedure. The discussion centers on whether a relatively minor surgical procedure, with minimal risk of complications and consented to by parents when performed in the neonatal period, should be adopted universally as a public health measure.

The American Academy of Pediatrics (AAP) guideline of 2012 on MC reversed its prior stand stating that the "health benefits of newborn male circumcision outweigh the risks" and therefore justified access to the procedure if the parents so choose [1]. This recommendation was primarily based on the significant protective estimates provided by three well-conducted African randomized controlled trials (RCTs) demonstrating benefits of MC against human immunodeficiency virus (HIV) and sexually transmitted infections (STIs) in adult males. Following suit, the US Centers for Disease Control and Prevention (CDC) released a draft recommendation for providers on counseling parents and adults on the positive effects of MC against HIV, STIs, and other health outcomes [2]. The primary issue of contention relating to these recommendations is the external validity of trials in Sub-Saharan Africa guiding recommendations in a significantly different population in North America and other developed countries. Guidelines have to be specific to the population to which they are applicable and this chapter answers questions as applicable to the USA and Canada.

Neonatal MC rates are declining across several countries, reflecting changing demographic patterns and parental beliefs. In 2009, the Public Health Agency of Canada reported an overall Canadian circumcision rate of 31.9% for 2006–2007 [2]. A CDC report showed decreasing trends in US newborn MC rates from 60% (1999–2000) to 55% (2008–2010) [3]. In the UK between 1997 and 2004, MC rates declined from 2.6/1000 boys/year to 2.1/1000 boys/year [4]. However, a more recent study from the USA using the Nationwide Inpatient Sample noted an increasing trend of neonatal MC from 48% (1988–1991) to 61% (1997–2000) [5].

Data on MC complication rates are fraught with possible underreporting, especially when factoring in long-term complications such as meatal stenosis. The rate of complications associated with neonatal MC is variable and reports suggest that it is between 2 and 6/1000 [6]. The rate of overall complication for children is estimated to be around 1.6% within contemporary literature [7].The three RCTs on MC for prevention of HIV in Africa showed complication rates in adults in a trial setting between 1.7 and 3.8% [8–11].

A review of the literature on MC suggests strong personal biases and lack of high-quality evidence in some areas to provide reliable recommendations. Several factors, which require consideration, include generalizability of positive effects to our population, the concern regarding the true complication rate of routine MC accurately, the resource burden of advocating universal MC against other proven interventions, ethical issues relating to a surgical procedure performed with parental consent for future benefits and the costs of training and implementation of universal neonatal MC. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology allows us to assess objectively the current evidence supporting or refuting MC for three key questions addressed in this chapter. This chapter is directed towards health policy makers, medical practitioners, parents and their children, and adult males to allow them to make an informed decision about the benefits of MC. Some of the factors mentioned, such as complication

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rates for MC, healthcare costs and a cost–benefit analysis comparing MC with other health interventions, are not addressed in this chapter.

Methods

The methods reported in this chapter follow those developed by the GRADE Working Group as outlined in their series [12]. We have formulated three focused clinical questions that directed literature reviews within each area. We allowed the state of the literature in each clinical area to dictate the types of studies that were included within each review. For each area, we identified a high-quality systematic review or meta-analysis, and updated their search results from their search time to 2016, so that we could focus our review on the most up-to-date literature while still representing the previous literature concisely.

Study information was abstracted by the two authors (R.C. and S.D.) and entered into relevant evidence profile (EP) tables. The quality of evidence informing each clinical question was rated on an outcome-specific basis as high, moderate, low according to GRADE guidelines [13]. Dimensions of evidence quality considered for trials were study limitations, inconsistency, indirectness, imprecision, and publication bias. These steps were performed independently by the authors and disagreements were resolved by discussion. The information from these EP tables were input into GRADEPRO [14] and used to generate formal evidence profile tables in standard format as presented.

In order to identify relevant articles for inclusion for each clinical question, we performed an initial broad systematic literature review to assess the benefits and drawbacks of MC. Systematic literature searches were conducted in MEDLINE including Pre-MEDLINE, EMBASE, BIOSIS Previews®, Web of Science® – with Conference Proceedings – and the Cochrane Central Register of Controlled Trials electronic bibliographic databases, and were restricted to either adult or pediatric studies (</>18 years of age) published between 1 January 2002 and March 2016. All searches were restricted to studies published in the English language only. Search queries were developed using combinations of subject headings and free-text terms such as circumcision, circumcision male, uncircumcised, male sexual dysfunction, sexual dysfunction physiological, sexual dysfunctions psychological, erectile dysfunction, sexual problems, sexual arousal disorder, ejaculation dysfunction, sexuality, prostatic neoplasms, prostate cancer, prostate tumor, penile neoplasms, penile cancer, urinary tract infections, phimosis, HIV infections, HIV, human immunodeficiency virus, HPV infections, and STIs. For all searches, editorials, news, and letters were excluded. The bibliographies of all relevant retrieved articles and reviews were also examined to identify further relevant articles. A total of 2674 records were identified and, after removing duplicate records and excluding nonrelevant studies, 230 studies were identified for detailed study and included in this analysis. This search and review of relevant articles allowed us to identify our sentinel systematic reviews or meta-analyses (MAs) for each clinical question and guided us in our subsequent identification of relevant literature.

Table 18.1 Arguments in favor of and against MC for the prevention of UTI, HIV, and human papillomavirus (HPV) infection.

Benefits	Risks
Decreased population-level burden of HIV and STIs	Risk of complications of MC is possibly underestimated
A relatively minor surgical procedure leading to possible benefits over a lifetime	Cost of universal MC in a universal healthcare system (training and implementation)
Significant benefits of MC in HIV prevention well documented in other populations	NNT estimates in populations with low prevalence of HIV/HPV/UTI are likely to be high
Other benefits such as reduced STI risk and reduced risk of penile cancer of MC	Countermeasures of prevention can be more beneficial, easier to implement, more cost-effective, and more acceptable

NNT, number needed to treat.

The eventual recommendation using the GRADE system was reached by consensus between the two authors and weighed the available quality and strength of evidence against generalizability of the evidence to a different socioeconomic environment in a developed country such as Canada or the USA, variation in the epidemiology and modes of disease transmission, and alternative strategies available for disease prevention. Table 18.1 lists the arguments considered in making our recommendations for and against MC for our three clinical questions.

Clinical question 1

Does newborn male circumcision decrease the risk of urinary tract infections during childhood?

Epidemiology

A decreased risk of urinary tract infection (UTI) is believed to be one of the primary benefits of neonatal MC. Circumcision can theoretically prevent UTIs, by reducing periurethral bacterial colonization secondary to reduced adherence of bacteria to keratinized surfaces, and by removing the growth-promoting moist preputial environment [6, 15, 16]. The role of neonatal MC in preventing UTIs should be studied separately in males with normal urinary tracts and those with urological conditions predisposing them to UTI, such as prenatal hydronephrosis (ureteropelvic junction obstruction [UPJO], ureterovesical junction obstruction [UVJO]), vesicoureteric reflux (VUR), and posterior urethral valves. This is because the

underlying rate of UTIs is significantly higher in these infants compared with normal male infants.

In boys without predisposing urological conditions, the estimated incidence of UTI in the first 10 years of life varies between 1 and 2% [17, 18]. In an MA of 18 studies, Shaikh et al. estimated that among febrile infants (males and females 0–24 months), the prevalence of UTI was 7% (95% confidence interval [CI] 5.5–8.4%) [19]. Males under 3 months of age had the highest prevalence of UTI (8.7%, 95% CI 5.4–11.9).

Literature search

For this clinical question, we classified our available evidence into two important subgroups for which relevant studies were identified:

1 circumcision for prevention of UTI in infant boys with normal urinary tracts, and

2 circumcision for prevention of UTIs in infant boys with urinary tract anomalies.

During our literature review, we identified a recent systematic review (SR) by Morris [20] and replicated their search strategy to identify relevant contemporary articles. We used the search terms highlighted in Table 18.2. The article selection process is highlighted in Figures 18.1 and 18.2 for our populations of interest.

The evidence

Boys with normal urinary tracts

For our literature search on MC benefits for the prevention of UTI in infant boys with normal urinary tracts, we identified two SRs, one randomized control trial (RCT), and one significant and well-conducted observational study.

Singh-Grewal et al. performed an MA of 12 published studies (one RCT, four cohort, seven case–control) on 402 908 children [21]. Assuming a 1% risk of UTI, the authors calculated a number needed to treat (NNT) of 111 to prevent one UTI. This equation changes in the favor of an MC in those with recurrent UTI (assuming a UTI risk of

Table 18.2 Search strategy for circumcision and prevention of UTI in boys with normal urinary tracts[a].

No.	Search items	Hits
#1	"Circumcision, Male"[Mesh] OR circumcised OR uncircumcised	4947
#2	"Urinary Tract Infections"[Mesh] OR UTI OR bacteriuria	43743
#3	#1 AND #2	230
#4	#1 AND #2 ("2011/09/09"[Date - Publication] : "3000"[Date - Publication])	45

[a] Search strategy derived from the Morris 2013 reference [20] and updated to the present from the time of their search.

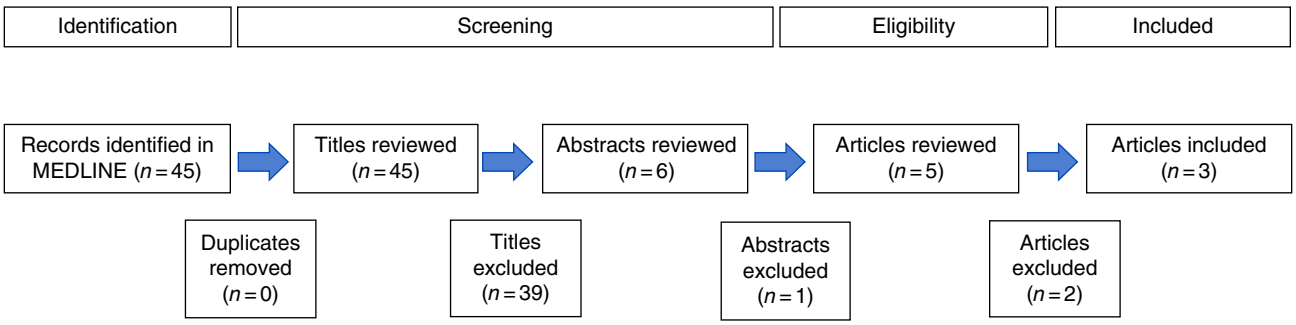

Figure 18.1 PRISMA flow diagram: article selection on circumcision for prevention of development of UTI in boys with normal urinary tracts.

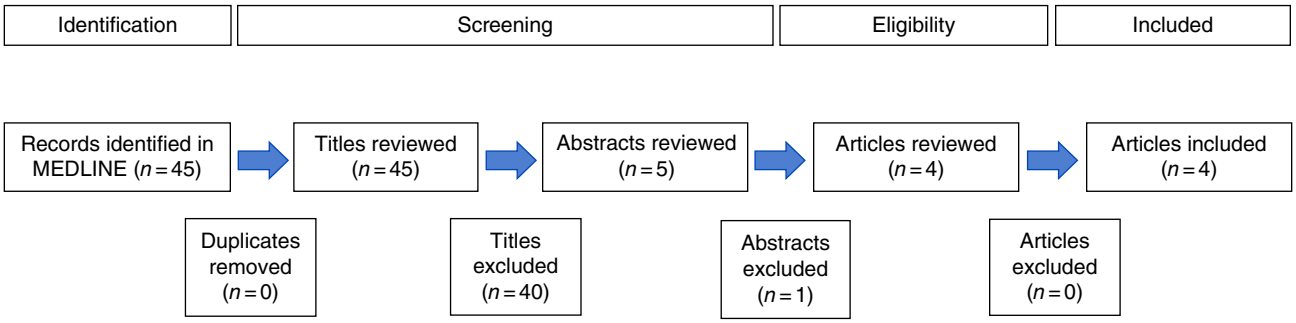

Figure 18.2 PRISMA flow diagram: article selection on circumcision for prevention of development of UTI in boys with urinary tract abnormalities.

10%, the NNT is 11) and boys with urological abnormalities such as obstruction or reflux (assuming a UTI risk with VUR being 30%, the NNT is 4) [21]. The other SR, conducted by Morris and Wiswell, calculated the *lifetime* risk of a UTI to be 32% in uncircumcised males compared with 9% in circumcised males [20]. The authors calculated an NNT of 4.2 (95% confidence interval [CI] 2.2–27) for preventing one UTI over a *lifetime*. Simforoosh et al. performed a prospective cohort study of 4000 boys that demonstrated an increased absolute risk difference of 2% of UTI in uncircumcised compared with circumcised boys [22]. Unfortunately, this study had several serious limitations, including no clear definition of UTI and significant loss to follow-up in the non-circumcised group. Shaikh et al. also performed an SR but addressed this question in a different manner [23]. In infants presenting with fever, the likelihood of having a UTI was 2.8 times more likely in male infants who were uncircumcised than those who underwent an MC (95% CI 1.9–4.3).

An evidence profile table was completed on the two relevant MA studies and confirmed by both authors (Table 18.3).

Boys with urinary tract abnormalities

For our literature search on MC and prevention of UTI in infant boys with urinary tract anomalies, we identified five observational studies for review, each addressing this issue for a different diagnosis but focusing on VUR or obstruction.

1 Vesicoureteric reflux (VUR): In a prospective cohort study, Alsaywid et al. noted a lower but nonsignificant incidence of new defects on dimercaptosuccinic acid (DMSA) renal scans in circumcised males with grade IV–V VUR compared with uncircumcised boys (5.25 versus 10.2%) [24]. Circumcision was more effective than antibiotic prophylaxis alone or antireflux surgery in preventing breakthrough UTI (odds ratio [OR] 0.9).

2 Posterior urethral valves (PUV): A single study specifically looking at boys with PUV was conducted by Mukherjee et al. in a retrospective cross-sectional study that demonstrated that MC in boys with PUV significantly reduces the incidence of UTI beyond infancy by 83% [25]. This study had serious methodological limitations and, despite these limitations, the NNT to prevent one UTI in boys with PUV was 1, suggesting a need for discussion with parents with infants newly diagnosed with PUV.

3 Prenatal hydronephrosis: Braga et al. conducted a prospective cohort study on 334 patients with antenatal hydronephrosis secondary to ureteropelvic or ureterovesical junction obstruction and/or VUR and evaluated seven potential risk factors for febrile UTI, including MC status [26]. A voiding cystourethrogram was not performed for all patients, possibly raising a risk of misclassification. Antibiotic prophylaxis was prescribed according to physician discretion. The hazard ratio (HR) for febrile UTI in uncircumcised males (HR 3.2) was lower than other more prominent risk factors such as lack of antibiotic prophylaxis (HR 5.2), hydroureteronephrosis (HR 10.9), or VUR (HR 20.8). Excluding patients with VUR, lack of circumcision was associated with a higher risk of febrile UTI (HR 3.6, 95% CI 1.1–14.8).

An evidence profile table was completed on these studies and confirmed by both authors (Table 18.4).

Clinical implications

In infants without urinary tract abnormalities, we suggest against neonatal MC (conditional recommendation against based on low-quality evidence). This recommendation weighs the benefits of MC for UTI prevention against potential complications of a neonatal MC and, given the relatively large NNT defined to prevent one UTI, does not recommend universal neonatal MC for UTI prevention. Parental views are relevant on this topic as neonatal MC does decrease the risk of UTI in normal infants, although this effect is limited and minimal considering the overall risk of UTIs in this population.

In infants with urinary tract abnormalities, such as high-grade VUR, PUV, and ureteropelvic or ureterovesical junction obstruction, we suggest neonatal MC to reduce UTI risk (conditional recommendation based on low-quality evidence). This recommendation is based on a higher baseline risk for these children developing UTIs and the likelihood of compromised renal function or decreased renal reserve in these patients.

Clinical question 2

Does adult male circumcision decrease the incidence of HIV infection in heterosexual circumcised males, circumcised men who have sex with men, and the female partners of heterosexual circumcised males infected with human immunodeficiency virus?

Epidemiology

Globally, there are approximately 35 million people living with HIV/AIDS (0.8% of all adults aged 15–49 years), and 1.5 million individuals died of AIDS-related illnesses in 2013 [27]. Nearly one in 20 individuals in Sub-Saharan Africa have HIV, accounting for approximately 70% of the total global HIV population [27]. In 2012, the US CDC estimated that there were 1.2 million Americans infected with HIV in the USA, of whom 12.8% were undiagnosed [28]. Each year there are approximately 50 000 new HIV infections among adults and adolescents [29]. Of the 47 165 new cases diagnosed in the USA in 2013, approximately 30 000 (65%) were via male-to-male sexual contact and 11 918 (25%) were via heterosexual contact [29].

Literature search

For our search, we identified three important subgroups for analysis:

1 circumcision for prevention of HIV infection in heterosexual males;

Table 18.3 GRADE evidence profile: newborn circumcision for the prevention of UTI in children with normal urinary tracts.

Quality assessment	Summary of findings									
Study (Design)	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**No. of patients**			**Absolute risk**		
						Uncircumcised	**Circumcised**	**Relative risk (95% CI)**	**Control risk[a]**	**Risk difference**	**Quality**
UTI in males with normal urinary tracts											
Singh-Grewal (Meta-analyses)	Mainly observational studies, 1 RCT. Variable outcome measurement, recall bias possible	Minimal inconsistency	Some indirectness	Likely	None	109 194	293 714	OR 0.13 (0.08–0.20)	1.3%	0.009 (NNT = 111)	MODERATE
Morris (Meta-analyses)	Mainly observational studies, 1 RCT	Minimal inconsistency	Some indirectness	Likely	None	111 065	296 837	**0–1 years** RR 0.10 (0.13-0.07) **1–16 years** RR 0.15 (0.03–0.07) **Lifetime risk** RR 0.27 (0.91–0.08)	**0–1 years** RR 0.79 (1.42-0.47) **1–16 years** RR 0.37 (0.58–0.24) **Lifetime risk** RR 0.03 (0.06–0.02)	**Circumcised–uncircumcised** **0–1 years** 0.9 **1–16 years** 0.44 **Lifetime risk** 0.04	MODERATE
	Variable outcome measurement, recall bias. *Included studies on children with abnormal urinary tracts*										

GRADE, Grading of Recommendations Assessment Development and Evaluation; RCT, randomized control trial; CI, confidence interval; RR: risk ratio; UTI, urinary tract infection.
[a]The control rate is based on the median control group risk across studies.

Table 18.4 GRADE evidence profile: newborn circumcision for the prevention of UTI in children with normal urinary tracts.

Quality assessment	Summary of findings									
Study (Design)	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**No. of patients**		**Relative risk (95% CI)**	**Absolute risk**		**Quality**
						Uncircumcised	**Circumcised**		**Control risk[a]**	**Risk difference**	
UTI in males with urinary tract abnormalities											
Kose (Prospective cohort)	Serious limitations included all diagnoses, normal urinary tracts, comparison between UTI rates pre- and post-circumcision	None	Some indirectness	Likely	None	23	111	N/A	UTI frequency: 0.25/year	UTI frequency difference: 2.77/year	LOW
Braga (Prospective cohort) Prenatal hydronephrosis	Some limitations (multiple diagnoses, lack of uniform management protocol)	None	None	None	None	166	95	Adjusted HR 3.2 (1.2–8.5)	5.2%	UTI rate difference-16%	MODERATE
Gucuk (RCT) VUR	Serious limitations	Some	Serious indirectness	Serious imprecision	None	46	45	Not available	0	0.13%	LOW
Mukherjee (Retrospective cross-sectional)	Very serious limitations	Likely	Serious indirectness	Likely	None	Not direct comparison	Not direct comparison	5.5	N/A	N/A	LOW

GRADE, Grading of Recommendations Assessment Development and Evaluation; RCT, randomized control trial; CI, confidence interval; HR: hazard ratio; UTI, urinary tract infection. N/A, not applicable.
[a] The control rate is based on the median control group risk across studies.

2 circumcision for prevention of HIV in men who have sex with men (MSM);
3 circumcision for prevention of HIV transmission from HIV-positive men to their female partners.

To identify relevant articles on circumcision and HIV prevention in heterosexual men, we used the Cochrane Systematic Review and meta-analysis by Siegfried et al. [30]. We replicated their search strategy to identify relevant contemporary articles published from the upper time limit of their search to the present. We used the search terms highlighted in Table 18.5. The article selection process is highlighted in Figure 18.3.

To identify relevant articles on circumcision for the prevention of HIV in men who have sex with men, we identified the Cochrane Systematic Review and meta-analysis by Wiysonge et al. [31]. We replicated their search strategy to identify relevant contemporary articles published from the upper limit of their search to the present. We used the search terms highlighted in Table 18.6. The article selection process is highlighted in Figure 18.4.

To identify relevant articles on circumcision for prevention of HIV transmission from HIV-positive men to their female partners, we identified the systematic review and meta-analysis by Weiss et al. [32]. We replicated their search strategy to identify relevant contemporary articles published from the upper limit of their search to the present. We used the search terms highlighted in Table 18.7. The article selection process is highlighted in Figure 18.5.

The evidence

HIV prevention in heterosexual males

The literature search on circumcision for prevention of HIV infection in heterosexual males, identified seven systematic review articles. These articles were divided into three groups: (1) reviews of RCTs, (2) reviews of observational studies, and (3) reviews of both observational and RCT studies. Results were consistent across these trials, so we considered systematic reviews of RCTs only.

Two reviews of RCTs were identified, by Siegfried et al. [30] and Mills et al. [33]. These studies were published after

Table 18.5 Search strategy for circumcision and prevention of HIV infection in heterosexual men[a].

No.	Search items	Hits
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR HIV[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR HIV infect*[tw] OR human immunodeficiency virus[tw] OR human immune deficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome [tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral" [MESH:NoExp]	339 553
#2	Search randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])	997 776
#3	Search MALE CIRCUMCISION OR MALE CIRCUMCISIONS OR CIRCUMCISION OR CIRCUMCIS* OR UNCIRCUMCIS*	7 114
#4	Search # 1 AND #2 AND #3	536
#5	Search # 1 AND #2 AND #3 AND ("2007/01/01"[Date - Publication] : "3000"[Date - Publication]) Sort by: PublicationDate	324

[a] Search strategy derived from the Siegfried (2009) reference [30] and updated to the present from the time of their search.

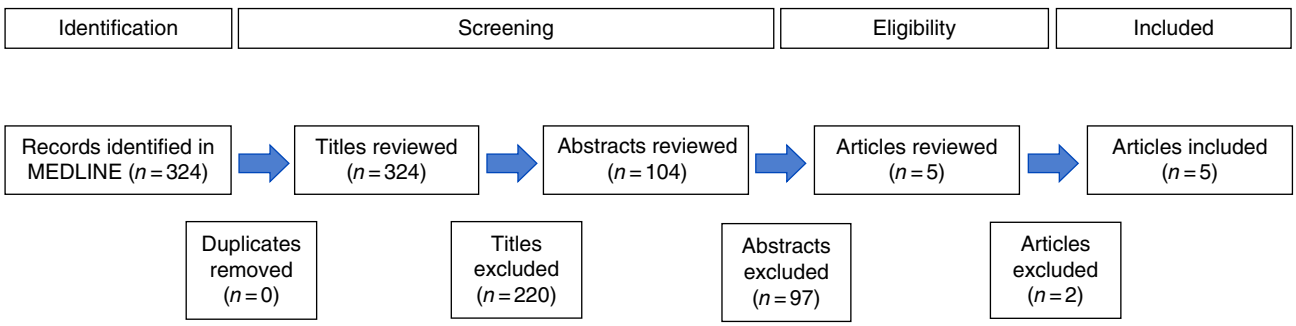

Figure 18.3 PRISMA flow diagram: article selection on circumcision for prevention of acquisition of HIV among heterosexual men.

Table 18.6 Search strategy for circumcision and prevention of HIV infection in men who have sex with men[a].

No.	Search items	Hits
#1	Search (HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw]OR acquired immuno-deficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]) Sort by:PublicationDate	344 170
#2	Search circumcision, male[mh] OR circumcis*[tiab] OR uncircumcis*[tiab] Sort by:PublicationDate	6 454
#3	Search homosexuality, male[mh] OR bisexual*[tiab] OR gay*[tiab] OR transgender[tiab] OR MSM[tiab] OR homosexual*[tiab] Sort by: PublicationDate	29 540
#4	Search #1 AND #2 AND #3	115
#5	Search #1 AND #2 AND #3 AND ("2011/03/17"[Date - Publication] : "3000"[Date - Publication]) Sort by: PublicationDate	46

[a] Search strategy derived from the Wiysonge (2011) reference [31] and updated to the present from the time of their search.

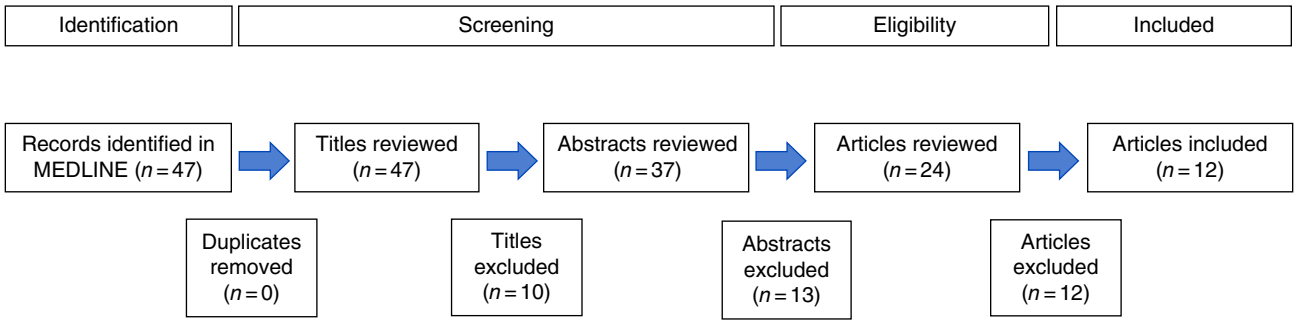

Figure 18.4 PRISMA flow diagram: article selection on circumcision for prevention of acquisition of HIV among men who have sex with men.

Table 18.7 Search strategy for circumcision and prevention of HIV infection in serodiscordant female partners of HIV-positive men[a].

No.	Search items	Hits
#1	("HIV seropositivity/epidemiology"[MeSH] or "HIV seropositivity/etiology"[MeSH] or "HIV seropositivity/prevention and control"[MeSH] or "HIV seropositivity/transmission"[MeSH] or "HIV infections/epidemiology"[MeSH] or "HIV infections/etiology"[MeSH] or "HIV infections/prevention and control"[MeSH] or "HIV infections/transmission"[MeSH] or HIV[MeSH] or hiv[text word]) and ("epidemiologic studies"[MeSH] or seroepidemiologic studies"[MeSH] or "risk factors"[MeSH] or "odds ratio"[MeSH] or "prevalence"[MeSH] or "incidence"[MeSH] or "risk" [MeSH] or "cross sectional studies"[MeSH] or "epidemiologic methods"[MeSH] or prevalence[text word] or incidence[text word]) and (journal article[pt] or letter[pt]) and "humans"[MeSH] and "female"[MeSH] and ("circumcision, male"[MeSH] or circumcision[text word])	1453
#2	Search #1 AND ("2009/08/08"[Date - Publication] : "3000"[Date - Publication]) Sort by: PublicationDate	811

[a] Search strategy derived from the Weiss (2009) reference [32] and updated to the present from the time of their search.

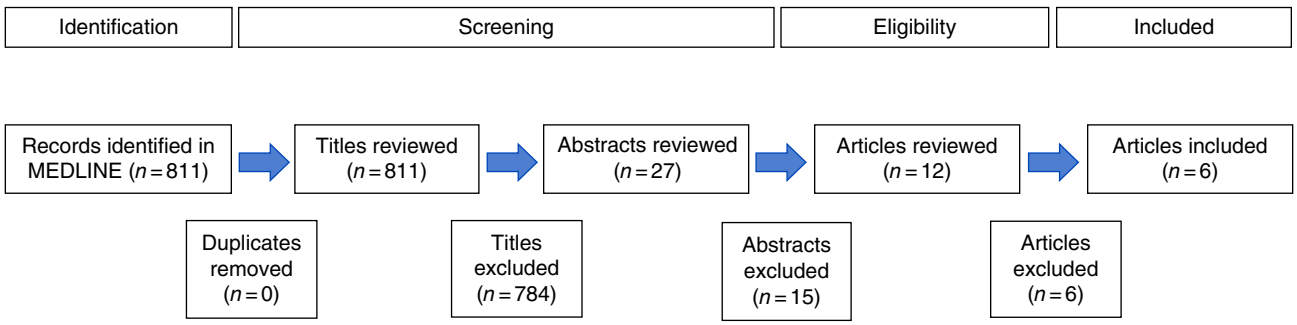

Figure 18.5 PRISMA flow diagram: article selection for circumcision and prevention of HIV infection in serodiscordant female partners of HIV-positive men.

the completion of three seminal RCTs on circumcision for HIV prevention in Africa [8–10]. These trials were organized after multiple observational trials had demonstrated conflicting evidence on this issue. Both concluded that circumcision was effective in reducing the acquisition of HIV among heterosexual men and was associated with minimal risk of adverse events. The authors of the Cochrane Review on this subject went so far as to declare that "research on the effectiveness of male circumcision for preventing HIV acquisition in heterosexual men is complete" [30].

A summary of findings table was completed on these studies and confirmed by both authors (Table 18.8).

HIV prevention in men who have sex with men

For the literature search on circumcision for the prevention of HIV infection in men who have sex with men, we identified one systematic review and 11 observational studies.

Wiysonge et al. performed a systematic review of the studies published to date and concluded that there was insufficient evidence to support circumcision for the prevention of HIV acquisition in MSM overall, but in a subgroup analysis in MSM who mainly or exclusively performed the penetrative role during sex, there was a decrease in HIV risk (3465 participants; OR 0.27, 95% CI 0.17–0.44) [31]. They advocated further exploration of this hypothesis and we updated their search terms as outlined.

Our search yielded 11 observational studies and no further meta-analyses or RCTs. We prepared a meta-analysis and forest plot of these studies, which showed a significant benefit of circumcision in MSM males (OR 0.71, 95% CI 0.61–20.82) and minimal heterogeneity ($I^2 = 4\%$) (Figure 18.6).

It must be acknowledged that this finding is based on observational studies, which did have a certain degree of inconsistency and variation in their quality. Table 18.9

Table 18.8 Summary of findings table: circumcision for prevention of HIV acquisition in heterosexual men.

Should circumcision be used in adult men for the prevention of acquisition of human immunodeficiency virus?

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no circumcision	Risk difference with circumcision
HIV acquisition	10 904 (3 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.44** (0.33 to 0.60)	25 per 1000	**1.4 fewer per 1000** (17 fewer to 10 fewer)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; RR, risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

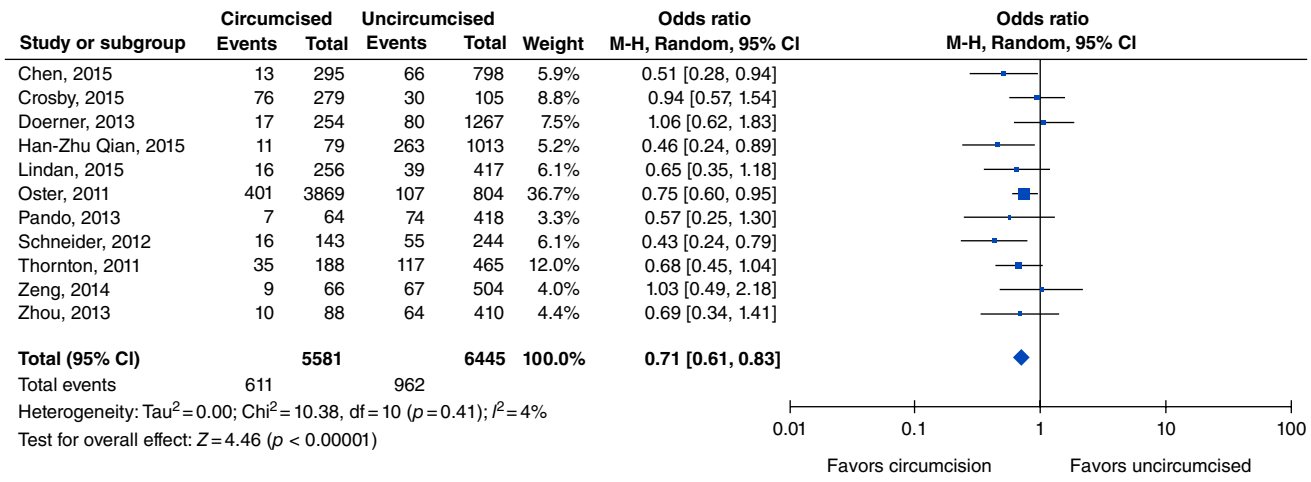

Figure 18.6 Meta-analysis of selected observational studies for prevention of HIV acquisition in men who have sex with men.

Table 18.9 Study limitations of observational trials in prevention of acquisition of HIV in men who have sex with men.

Study (Design)	Appropriate eligibility criteria	Appropriate measurement	Control of confounding	Appropriate follow-up
Chen, 2015 (Cross-sectional)	MSM attending gay saunas in Taiwan	Nonvalidated questionnaire, HIV status confirmed via DNA sequencing and phylogenetic analysis	Minimal: Multivariate logistic regression analysis	Single time point
Crosby, 2015 (Cross-sectional)	Black MSM enrolled in an RCT in the USA	Nonvalidated questionnaire, HIV status via clinic records or OraSure	None: Chi-squared test	Single time point
Doerner, 2013 (Cross-sectional)	British MSM recruited through websites, sexual health clinics, bars, clubs, and other venues	Nonvalidated questionnaire, HIV self-report	Minimal: Multivariate model not specified	Single time point
Qian, 2015 (Cross-sectional)	MSM recruited through gay-friendly community-based organizations in Beijing	Nonvalidated questionnaire and HIV self-report or Western blot HIV test if HIV reported negative	Minimal: Multivariate logistic regression analysis	Single time point
Lindan, 2015 (Cross-sectional)	Ugandan motorcycle taxi drivers recruited via respondent-driven sampling	Nonvalidated questionnaire and HIV status confirmed via parallel testing algorithm using Vironostika or Murex combination	Minimal: Multivariate logistic regression analysis	Single time point
Oster, 2011 (Cross-sectional)	Data derived from the 2008 US National HIV Behavioral Surveillance System performed with MSM	Nonvalidated questionnaire and self-reported HIV status	Minimal: Multivariate logistic regression analysis	Single time point
Pando, 2013 (Cross-sectional)	MSM in Buenos Aires, Argentina, recruited through respondent-driven sampling	Nonvalidated questionnaire and blood sample taken for confirmation of HIV status	None: *t*-test, Fisher's exact test, and Mann–Whitney test	Single time point
Schneider, 2012 (Cross-sectional)	Indian MSM recruited at drop-in centres	Nonvalidated questionnaire and three sequential ELISA tests for HIV	Minimal: Multivariate logistic regression analysis	Single time point
Thorton, 2011 (Cross-sectional)	British MSM visiting central London gyms	Non-validated questionnaire and self-reported HIV status	Minimal: Multivariate logistic regression analysis	Single time point
Zeng, 2014 (Cross-sectional)	Chinese MSM recruited from stratified snowball sampling	Nonvalidated questionnaire and rapid serological testing for HIV	Minimal: Multivariate logistic regression analysis	Single time point
Zhou, 2013 (Cross-sectional)	Chinese MSM recruited from respondent-driven sampling	Nonvalidated questionnaire and serological testing for HIV	Minimal: Multivariate model not specified	Single time point

compiles the potential study limitations for included observational trials. An evidence profile table was completed on these studies and confirmed by both authors (Table 18.10).

HIV prevention in female partners of men infected with HIV

For the literature search on circumcision for the prevention of HIV transmission from HIV-positive men to their female partners, we identified five systematic reviews and six observational studies.

The sentinel systematic review (on one RCT and six longitudinal analyses) was published by Weiss et al. in 2009 [32] and concluded that there was little evidence that male circumcision directly reduces the risk of HIV in women and that a further RCT in this area would be "logically unfeasible," hence more effort should be focused on adjuvant measures to prevent HIV acquisition in women who engage in sex with HIV-positive men. Several other meta-analyses were published in this area, including those which directly sought to quantify the per-sex act probability of HIV transmission [34–36] and one systematic review of couples-based HIV prevention strategies [37].

Since the Weiss review, further observational studies have been conducted in this area. Several studies specifically examined the risk of HIV transmission in serodiscordant couples [38–40]. Given the significant variations in reported outcomes from these studies, we could not prepare a forest plot for analysis. We have compiled a table of study limitations for these observational trials (Table 18.11). Data from these observational studies were not included in our summary of finding table as it was unlikely to affect the findings significantly.

An evidence profile table was completed on these studies and confirmed by both authors (Table 18.12).

Table 18.10 GRADE evidence profile: circumcision for HIV acquisition prevention in men who have sex with men.

Quality assessment	Summary of findings								
No. of studies (Design)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	No. of patients		Risk estimates	Quality
						Uncircumcised	Circumcised		
1 Meta-analysis (Observational)	None	Serious	Serious indirectness	No serious imprecision	No serious risk	Total population: 65 784		OR: 0.86 (0.70, 1.06) I^2: 53%	HIGH
11 Observational	Very serious	None	Serious indirectness	No serious imprecision	No serious risk	6 445	5 581	OR: 0.71 (0.61, 0.83) I^2: 4%	LOW

GRADE: Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio; I^2, test for heterogeneity.

Table 18.11 Study limitations of observational trials in prevention of acquisition of HIV in female serodiscordant partners of HIV-positive men.

Study (Design)	Appropriate eligibility criteria	Appropriate measurement	Control of confounding	Appropriate follow-up
Baeten, 2010 (Cohort study)	African serodiscordant couples (male partner HIV positive) enrolled in a multicenter RCT	HIV status confirmed by dual rapid HIV test and confirmed with Western blot	None: Cox proportional hazards regression modeling	2-year follow-up with testing every 3 months
Hughes, 2012 (Cohort study)	Data analyzed from the Partners in Prevention HSV/HPV Transmission study in Africa	HIV status tested by HIV-1 rapid test with positive results confirmed with Western blot	None: Maximum likelihood method to estimate the parameters of model of probability of HIV transmission	2-year follow-up with testing every 3 months
Kaiser, 2011 (Cross-sectional)	Data from the 2007 KAIS, a nationally representative population-based sero-survey in Kenya	Serodiscordant couples	Minimal: Multivariable logistic regression model	Single time point

HSV, herpes simplex virus; HIV, human immunodeficiency virus; KAIS, Kenya AIDS Indicator Survey.

Clinical implications

We are unable to make a recommendation with regard to circumcision for heterosexual men in high-income developed countries (no recommendation can be made owing to lack of sufficiently direct evidence).

Although high-quality evidence suggests substantial protection for heterosexual men against HIV infection in Sub-Saharan Africa, these benefits cannot be generalized for heterosexual men in high-income developed countries with adequate confidence, and there is no current local evidence of similar quality to support this evidence for our population. In the era of highly effective and available antiretroviral therapy, widely available condoms, and comprehensive sexual education in schools, MC cannot replace other preventive measures and should be an adjunct to these measures to prevent HIV infection within our population.

We suggest circumcision to reduce the risk of HIV transmission in homosexual men who assume the insertive sexual role (conditional recommendation based on low-quality evidence).

We recommend against circumcision of HIV-infected men to prevent viral transmission to their HIV-negative female partners (strong recommendation based on low-quality evidence).

Clinical question 3

Does adult male circumcision decrease the risk of HPV infection in males?

Epidemiology

Human papillomavirus (HPV) is the most common STI, with most sexually active individuals estimated to contract it at some point in their life [41]. The most common and "high-risk" (HR) HPV genotypes are 16 and 18 [42]. HPV infection with HR-HPV genotypes is associated with cervical cancer,

Table 18.12 GRADE evidence profile: circumcision for HIV acquisition prevention in the female partners of HIV-positive men.

Quality assessment						Effect				
No. of studies (design)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No. of patients[a]**		**Relative risk (95% CI)**	**Absolute risk (95% CI)**	**Quality**
						Uncircumcised	**Circumcised**			
7 Meta-analyses (1 RCT + 6 cohort studies)	Serious	Serious	Very serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	17/92 (18.5%)	8/67 (11.9%)	RR: 0.80 (0.51, 1.36) (p-heterogeneity = 0.05)	24 fever per 1000 (from 23 more to 55 fewer)	⊕◯◯◯ VERY LOW

GRADE: Grading of Recommendations Assessment, Development and Evaluation, RCT: randomized control trial., RR, relative risk.
[a]Number of participants is only from RCT.

genital warts, and anal cancers. Epidemiology of HPV should consider three separate measures of disease burden: HPV prevalence, incidence, and clearance rates. Moreover, given spontaneous HPV clearance, studies on prevalence and incidence have to account for clearance over time and also report clearly the sampling sites assessed. Coinfection with other STIs, including HIV, impacts acquisition and clearance of HPV [43].The contribution of these issues results in significant heterogeneity between studies and complicates pooled analyses.

Literature search

To identify relevant articles on circumcision and HPV prevention in men, we identified a systematic review and meta-analysis by Albero et al. [44]. We replicated their search strategy to identify relevant contemporary articles published after their search to the present. We used the search terms highlighted in Table 18.13. The article selection process is highlighted in Figure 18.7.

The evidence

For the literature search on MC for the prevention of HPV acquisition, we identified two SRs, five RCTs, and five observational studies.

The sentinel article, by Albero et al. [44], examined 21 studies, and found significantly reduced odds of genital HPV prevalence associated with circumcision. This MA failed to demonstrate a benefit of MC against acquisition of HPV or increased clearance of HPV [44]. A second MA of 23 studies was published in 2011 by Larke et al. [45], which demonstrated that circumcised men were less likely to have prevalent genital HPV infection than uncircumcised men. In subgroup analyses, Larke et al. showed that the effect of circumcision on HPV prevalence was dependent on penile location (weaker effect away from the glans). MC had a weak influence on HPV incidence and did not alter HPV clearance [45]. Both of these analyses demonstrated significant variation in anatomical sites used for HPV sampling.

Five studies utilizing data from the African RCTs on HIV were identified. Potential methodological limitations of these studies are presented in Table 18.14. Significant heterogeneity was found in these studies, therefore a meta-analysis was not attempted. Senkomago et al. found that MC decreased the acquisition of HR-HPV and increased the clearance of both HPV-16 and HPV-18 strains [46]. Tarnaud et al. demonstrated that the prevalence and mean number of infecting LR-HPV (low-risk HPV) genotypes were decreased among circumcised men [47]. Tobian et al. showed a reduction in HR-HPV prevalence detected on the penile coronal sulcus and penile shaft in those who had been circumcised [48]. Tobian et al. also demonstrated that HR-HPV clearance was increased by circumcision in individuals who were HIV negative. They further demonstrated that HIV infection increased HR-HPV acquisition and decreased HR-HPV clearance [49]. Finally, Wilson et al. showed a significant reduction in viral load among circumcised individuals for HR-HPV-16 for individuals who acquired HPV during the course of the study and were not infected at baseline [50]. Given the significant variation in outcomes of interest, differences in sites sampled, varying effects seen for different serotypes, and variable results depending on HIV status, further research is required to allow for meaningful subgroup meta-analyses.

Five observational studies were identified through our literature search in this area. Methodological limitations

Table 18.13 Search strategy for circumcision and prevention of HPV[a].

No.	Search items	Hits
#1	((("Papillomaviridae"[Mesh]) OR "Condylomata Acuminata"[Mesh]) OR "Genital Diseases, Male"[Mesh])	330 316
#2	"Circumcision, Male"[Mesh]	4 363
#3	SEARCH #1 AND #2	1 271
#4	SEARCH #1 AND #2 ("2010/09/31"[Date - Publication] : "3000"[Date - Publication])	265

[a] Search strategy derived from the Albero (2012) reference [44] and updated to the present from the time of their search.

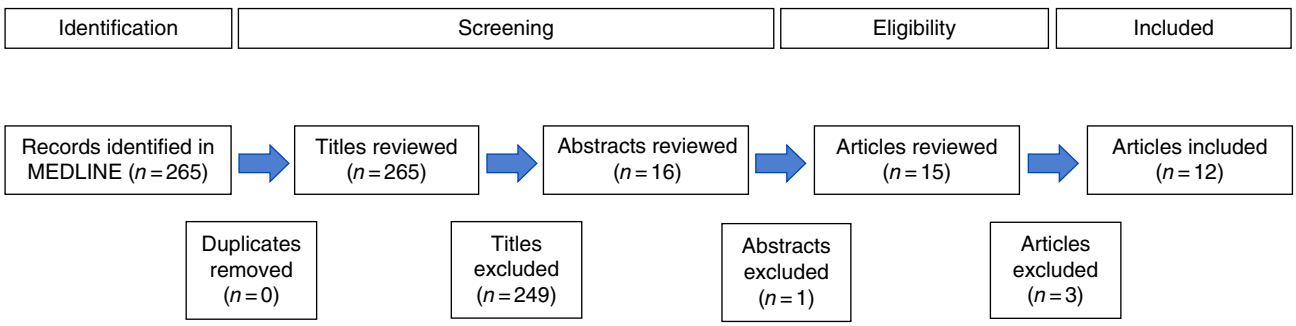

Figure 18.7 PRISMA flow diagram: article selection on circumcision for prevention of acquisition of HIV infection.

Table 18.14 Study limitations of observational trials in prevention of human papillomavirus.

Study (Design)	Allocation concealment	Blinding	Accounting for patients and outcome events	Selective outcome reporting	Other/comments
Senkomago, 2014 (RCT)	Non	None	Baseline and 24-month follow-up. Subgroup analysis of acquisition and persistence of HPV	Swab specimens from glans and shaft of the penis tested with PCR to detect HPV-16 and/or HPV-18 at baseline and 24 months	RCT stopped early for benefit
Tarnaud, 2011 (RCT)	None	None	Cross-sectional subgroup analysis at 21-month follow-up	Urethral swabs for 23 low-risk HPV genotypes	RCT stopped early for benefit
Tobain, 2011 (RCT)	None	None	Cross-sectional subgroup analysis at 12-month follow-up	Penile and coronal swabs for high-risk HPV genotypes	RCT stopped early for benefit
Tobain, 2012 (RCT)	None	None	Testing for HPV was performed at baseline and 6, 12, and 24 month time intervals	Penile swabs from coronal sulcus and glans tested for high-risk HPV strains	RCT stopped early for benefit
Wilson, 2013 (RCT)	None	None	Testing for HPV was performed at baseline and 6, 12, and 24 month time intervals	Penile swabs from coronal sulcus and glans tested for high-risk HPV strains	RCT stopped early for benefit

Table 18.15 Study limitations of observational trials in prevention of acquisition of HPV.

Study (Design)	Appropriate eligibility criteria	Appropriate measurement	Control of confounding	Appropriate follow-up
Albero, 2013 (Cross-sectional)	Men aged 18–70 years from Brazil, Mexico, and USA	Three samples taken from penile coronal sulcus/glans, penile shaft, and scrotum	Minimal. Poisson regression modeling	Testing at baseline
Albero, 2014 (Cohort study)	Men aged 18–70 years from Brazil, Mexico, and USA	Three samples taken from penile coronal sulcus/glans, penile shaft, and scrotum	Minimal. Survival analysis	Testing at baseline and 6-month intervals to 4 years
Canadas, 2013 (Cross-sectional)	HIV-infected men with no HPV-related conditions at baseline	Urethral swab for high-risk HPV testing.	Minimal. Multivariable regression modeling	Testing at baseline
VanBuskirk, 2011 (Cohort study)	US university student males	Shaft/scrotal, glans, and urine samples for 37 HPV genotypes	Minimal. Cox proportional hazards modeling	Baseline and annual testing
Poynten, 2012 (Cohort study)	MSM from Sydney, Australia	HPV-16 testing	Minimal. Multivariable modeling	Baseline and annual testing

of these studies are presented in Table 18.15. Albero et al. performed a cross-sectional analysis of a cohort study, and found that MC was not associated with decreased prevalence of HR-HPV strains, but did decrease the prevalence of LR-HPV genotypes [51]. In addition, in the same cohort, MC was not associated with increased HPV clearance [52]. Canadas et al. examined a cohort of HIV-positive men and did not demonstrate a difference in HPV prevalence by circumcision status for HIV-infected heterosexual men and MSM [53]. Poynten et al. found a decreased in HPV incidence but not a prevalence associated with circumcision status [54]. Finally, VanBuskirk et al. showed no difference in the likelihood of HPV infection in MSM who are circumcised [55]. Again, we did not meta-analyze these studies as there were significant variations in both target outcomes and anatomical HPV testing sites.

An evidence profile table was completed on these studies and confirmed by both authors (Table 18.16).

Clinical implications

We recommend against MC to prevent new HPV infection (strong recommendation based on low-quality evidence). This recommendation is based on the lack of strong and consistent evidence to support its effectiveness and also the increasing availability and use of other preventive measures such as effective vaccination to prevent HPV infection.

Table 18.16 GRADE evidence profile: circumcision for HPV.

Quality assessment	Summary of findings							
No. of studies (Design)	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**No. of patients**	**Risk estimates**	**Quality**
						Uncircumcised Circumcised		
2 Meta-analyses	None	Serious	No serious indirectness	No serious imprecision	No serious risk	Albero: uncirc, 6336: circ, 8046	Albero: genital HPV prevalence. OR: 0.57 (0.42, 0.77)	MODERATE
						Larke: total population, 8742	Larke: genital HPV prevalence. OR: 0.57 (0.45, 0.71). I^2, 50.5%	
5 RCTs	Serious	Serious	No serious indirectness	No serious imprecision	No serious risk	Senkomago: uncirc, 1140; circ,1159	Senkomago: acquisition (1). OR: 0.32 (0.20, 0.49). HPV-16 clearance. OR: 0.36 (0.18-0.72). HPV-18 clearance. OR: 0.34 (0.13-0.86)	LOW
						Tarnaud: uncirc, 863; circ, 890	Tarnaud: LR-HPV prevalence. aPRR: 0.54 ($p<0.001$)	
						Tobain: uncirc, 228; circ; 231	Tobain: HR-HPV prevalence coronal sulcus. aPRR: 0.57 (0.39, 0.84)	
						Tobain: uncirc, 316; circ, 175	Tobain: HR-HPV clearance in HIV– men.ajdRR: 0.70 (0.55, 0.89)	
						Wilson: uncirc, 425; circ, 460	Wilson: lower viral load newly acquired HPV. PRR: 0.61 (0.43, 0.86)	
5 Observational	Very serious	Serious	No serious indirectness	No serious imprecision	No serious risk	Albero: 4072 men	Albero: HR-HPV. PRR: 0.95 (0.87, 1.03). LR-HPV. PRR: 0.85 (0.76, 0.95)	LOW
						Albero: 4033 men	Albero: HPV clearance. aHR: 0.95 (0.88, 1.02)	
						Canada: 706 HIV-positive men	Canadas: HPV prevalence. OR: 1.0 (0.6, 1.6)	
						Poynten: HIV+, 245; HIV–, 1427	Poynten: HPV seroincidence. HR: 0.47 (0.28–0.98) HPV seroprevalence. HR: 0.98 (0.60, 1.61)	
						VanBuskirk: 477 men aged 18–20 years	VanBuskirk: acquisition. HR: 0.9 (0.7, 1.2)	

GRADE, Grading of Recommendations Assessment, Development and Evaluation. RCT, randomized control trial; OR, odds ratio; I^2, test for heterogeneity; LR-HPV, low-risk human papillomavirus; PRR, prevalence rate ratio; aPRR, adjusted prevalence risk ratio; HR-HPV, high-risk human papillomavirus; adjRR, adjusted rate ratio; HR, hazard ratio; aHR, adjusted hazard ratio.

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19 CHAPTER 19
Nocturnal enuresis

Stacy T. Tanaka
Urologic Surgery and Pediatrics, Division of Pediatric Urology, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA

Introduction

Bedwetting (nocturnal enuresis), defined as urinary incontinence during sleeping periods, is highly prevalent throughout childhood. A combination of nocturnal polyuria, nocturnal detrusor overactivity, and a high sleep arousal threshold are factors in pathogenesis [1]. Although many children outgrow enuresis without any intervention, symptoms can persist into adolescence and adulthood [2]. Recent research suggests that children who wet the bed have significantly lower self-esteem than children who stay dry at night [3–5].

The term for enuresis without any additional lower urinary tract symptoms is monosymptomatic nocturnal enuresis. The International Children's Continence Society (ICCS) has published a standardization document with treatment recommendations for monosymptomatic nocturnal enuresis [6]. Primary recommended treatment therapies include general bladder advice, enuresis alarm, and/or desmopressin. The authors acknowledge that evidence-based medicine in this field is limited. Additionally, because enuresis is also often accompanied by nonurological comorbidities, including sleep-disordered breathing [7, 8] and attention deficit hyperactivity disorder [9], nonurological therapies can also influence enuresis. In this chapter, we systematically review the evidence for different therapies for monosymptomatic enuresis and provide practical guidance.

Methods

The methods follow those developed by the GRADE working group [10]. Four focused clinical questions were developed. Comprehensive literature searches were performed for high-quality systematic reviews and individual randomized controlled trials. Observational studies were not included. Outcome variables were rated as critical, important, or not important depending on the relevance to clinical decision-making. Achieving 14 consecutive dry nights was considered a critical outcome. An increase in the number of dry nights during treatment was considered an important outcome. Side effects from treatment and compliance with treatment were considered important but not critical to clinical decision-making. The quality of evidence for each clinical question was rated as high, moderate, low, or very low for each outcome according to GRADE. Quality of evidence was assessed by considering the following limitations: study limitations, inconsistency of results, indirectness of evidence, imprecision, and publication bias. Recommendations for or against a given intervention were formulated based on the quality of evidence for the defined outcomes.

Clinical question 1

In children with monosymptomatic nocturnal enuresis, do behavioral therapies compared with no treatment increase the number of dry nights?

Literature search

A systematic literature search in PubMed (1966–2015) was conducted using the search terms "enuresis," "behavioral/behavioral," and "urotherapy." The search was limited to randomized controlled trials and systematic reviews in English with a human population.

The evidence

One of the treatment mainstays of monosymptomatic enuresis is behavioral therapy. Current recommended general bladder advice includes regular voiding, good voiding posture, and treatment of constipation if present [6].

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Over the past decades, multiple studies have investigated the effects of behavioral therapy on nocturnal enuresis. One eligible systematic review published in 2013 [11] and one subsequent eligible randomized controlled trial [12] were identified.

Caldwell et al. [11] performed a systematic review published in the Cochrane Library to determine the effects of behavioral intervention on nocturnal enuresis in children. They identified 16 eligible randomized controlled trials from 1970 to 2009. Studies included patients with monosymptomatic and nonmonosymptomatic enuresis. Behavioral interventions were diverse and included reward systems, lifting or waking children at night to urinate, delaying urination to increase bladder capacity, and fluid restriction. The diverse behavioral treatments compared with control could not be combined for meta-analysis. The critical outcome of 14 dry nights favored behavioral treatment over no active treatment. For example, reward was associated with a risk ratio (RR) of 0.84 (95% confidence interval [CI] 0.73–0.95) and lifting was associated with RR 0.79 (95% CI 0.68–0.92). The important outcome of decreased number of wet nights favored behavioral treatment over no active treatment.

An additional randomized controlled trial by Cederblad et al. [12] specifically evaluated the effect of regular voiding and good voiding posture for 1 month prior to alarm therapy compared with immediate alarm therapy. Children with nonmonosymptomatic enuresis were included. None of the children had daytime urinary incontinence; however, a subset had daytime urinary urgency. The critical outcome of 14 dry nights was not assessed. The important outcome of decreased number of wet nights was assessed. General bladder advice did not decrease the number of wet nights compared with pretreatment values or improve response to alarm therapy.

We rated the quality of evidence as low due to study limitations (unclear allocation concealment, lack of blinding) and inconsistency. Although no adverse effects were reported for behavioral intervention, dropout rates were often high.

Clinical implications

In patients with monosymptomatic nocturnal enuresis, we suggest behavioral interventions over no intervention (conditional recommendation based on low-quality evidence) as an acceptable first-line management approach. This recommendation is based on the judgment that in the absence of any serious adverse events, the benefits of behavioral interventions outweigh the harms.

Clinical question 2

In children with monosymptomatic nocturnal enuresis, does alarm therapy compared with no treatment increase the number of dry nights?

Literature search

A systematic literature search in PubMed (1966–2015) was conducted using the search terms "enuresis" and "alarm." The search was limited to randomized controlled trials and systematic reviews in English with a human population.

The evidence

The ICCS recommends the enuresis alarm as one of the mainstays of primary therapy for monosymptomatic enuresis [6]. Wetting triggers an alarm, which may be a bell or buzzer, to wake the child. The parent or caregiver should attend to the child to ensure that the child awakens to the alarm. Over the search period, multiple studies have investigated the effects of alarm interventions on nocturnal enuresis. One eligible systematic review published in 2005 [13] comparing alarm to control was identified. There were no subsequent randomized controlled trials that compared alarm intervention with no treatment.

Glazener et al. [13] performed a systematic review published in the Cochrane Library to determine the effects on alarm interventions on nocturnal enuresis in children. They identified 17 eligible randomized controlled trials from 1965 to 2002 that compared an alarm intervention with a no-treatment control. The majority of the studies used a buzzer/bell-type alarm. Two studies used an electric shock device. Studies included patients with monosymptomatic and nonmonosymptomatic enuresis. Most of the children were recruited from enuresis clinics and may represent a more motivated group than the general population. In the 14 studies that assessed the critical outcome of 14 dry nights, alarm intervention was better than no treatment (RR 0.39, 95% CI 0.33–0.45). The important outcome of decreased number of wet nights also favored alarm intervention over no active treatment. In the four studies which reported standard deviations, the mean difference in number of wet nights per week was –3.34 (95% CI –4.14 to –2.55] in the alarm group compared with the control group.

Although the results from the studies were very consistent, we rated the quality of evidence as moderate owing to study limitations (unclear allocation concealment, lack of blinding). For the buzzer/bell-type alarms, adverse events were minimal, including alarm malfunction or disturbance to the family. In sharp contrast, the alarms that delivered electric shocks frightened children and caused burns.

Clinical implications

In patients with monosymptomatic nocturnal enuresis, we suggest alarm intervention with bell/buzzer-type alarms over no treatment as a first-line therapy option (conditional recommendation based on moderate-quality evidence). This recommendation is based on moderate evidence quality and minimal adverse events.

Clinical question 3

In children with monosymptomatic nocturnal enuresis, does desmopressin therapy compared with no treatment increase the number of dry nights?

Literature search

A systematic literature search in PubMed (1966–2015) was conducted using the search terms "enuresis," "DDAVP," and "desmopressin." The search was limited to randomized controlled trials and systematic reviews in English with a human population.

The evidence

The ICCS recommends desmopressin as one of the mainstays of primary therapy for monosymptomatic enuresis [6]. Desmopressin is the synthetic form of the neurohypophysial hormone vasopressin, also known as antiduretic hormone. Desmopressin regulates the body's retention of water by increasing water absorption in the kidneys. One eligible systematic review published in 2002 [14] and one subsequent eligible randomized controlled trial [15] were identified.

Glazener and Evans [14] performed a systematic review published in the Cochrane Library to determine the effects of desmopressin versus no active treatment on nocturnal enuresis in children. They identified 29 eligible randomized controlled trials from 1970 to 2001. Desmopressin doses varied among the studies; however, the trials were consistent. Desmopressin is available in both tablet and nasal spray forms. The trials included both intranasal and oral formulations. Of the 29 trials identified, only seven included the oral formulation. Adverse effects reported included anorexia, bad taste, headache, nasal discomfort, nosebleeds, rash/dermatitis, edema, sight disturbance, vomiting, and other minor problems. The US Food and Drug Administration no longer recommends the intranasal formulation for the treatment of nocturnal enuresis because of severe hyponatremia and seizures [16]. Studies included patients with monosymptomatic and nonmonosymptomatic enuresis.

In the 10 studies that assessed the critical outcome of 14 dry nights, the most common dosages of desmopressin were 20 and 40 μg. At 20 μg, desmopressin was better than no treatment (RR 0.84, 95% CI 0.78–0.91). At 40 μg, desmopressin was better than no treatment (RR 0.81, 95% CI 0.74–0.89). The important outcome of decreased number of wet nights also favored desmopressin over no active treatment. In the 17 studies that reported standard deviations, the mean difference in number of wet nights per week was –1.34 (95% CI –1.57 to –1.11) at 20 μg compared with control. At 40 μg, the mean difference in number of wet nights per week was –1.33 (95% CI –1.67 to –0.99) compared with control. An additional randomized controlled trial by Ferrara et al. [15] included treatment arms with placebo and oral desmopressin. The oral desmopressin arm had more children achieving 14 dry nights and had a decreased number of wet nights per week compared with the placebo arm.

The results from the studies were consistent despite varying doses and different medication formulations. We rated the quality of evidence as moderate owing to study limitations (unclear allocation concealment, lack of blinding). Reported adverse effects were minimal. However, the intranasal formulation of desmopressin is no longer recommended for treatment of enuresis because of risk of hyponatremia and seizures.

Clinical implications

In patients with monosymptomatic nocturnal enuresis, we suggest oral desmopressin over no treatment as a first-line therapy option (conditional recommendation based on moderate evidence quality). Although serious adverse effects are uncommon, patients and families need to be warned about water intoxication with risk of hyponatremia and seizures.

Clinical question 4

In children who fail treatment with desmopressin and/or bed alarm, does additional pharmacotherapy increase the number of dry nights?

Literature search

A systematic literature search in PubMed (1966–2015) was conducted using the search terms "enuresis," "pharmacotherapy," and "drug." The search was limited to randomized controlled trials and systematic reviews in English with a human population. Studies of interest compared: (1) enuresis alarm versus enuresis alarm + drug and (2) drug alone versus combination drug therapy.

The evidence

Desmopressin and bed alarm are first-line treatment options for nocturnal enuresis. Desmopressin reduces the number of wet nights per week, although the effect is often not maintained when the medication is stopped [14]. Bed alarms are also an effective treatment for bedwetting, with more children remaining dry once treatment is stopped [13]. Some children will fail treatment with desmopressin and/or bed alarm. The literature search yielded two systematic reviews [13, 17] and two additional randomized controlled studies [18, 19] relevant to additional pharmacotherapy for therapy-resistant nocturnal enuresis.

Glazener et al. [13] performed a Cochrane systematic review of alarm therapies for nocturnal enuresis in 2005. Five studies compared bed alarm with bed alarm + desmopressin [20–24]. Data from individual studies were conflicting. The critical outcome of 14 dry nights did not favor combination

treatment with alarm + desmopressin over alarm alone (RR 1.32, 95% CI 0.80–2.16). The important outcome of decreased number of wet nights did not favor combination treatment with alarm + desmopressin over alarm alone, with a mean difference of –0.10 (95% CI –1.55 to 1.35).

We rated the quality of evidence as low owing to study limitations, which included unclear allocation concealment and lack of blinding. Results from individual studies were inconsistent. Three of the five studies did not exclude subjects with daytime urinary incontinence. Studies included varying doses of both oral and intranasal formulations of desmopressin. Reported adverse effects included nose bleed and headache. Adverse effects were often not reported.

Two studies [25, 26] compared bed alarm with bed alarm + tricyclic. The important outcome of decreased number of wet nights favored bed alarm + imipramine over bed alarm alone [26], but effect size could not be calculated. The critical outcome of 14 dry nights did not favor combination treatment with alarm + nortriptyline over alarm alone (RR 0.81, 95% CI 0.61–1.06) [25]. We rated the quality of evidence as low owing to study limitations, which included unclear allocation concealment. Study results were inconsistent. The two studies used different tricyclic medications and reported different outcomes. Both studies did not exclude subjects with daytime urinary incontinence. Reported adverse effects included being frightened by alarm, dry mouth, and difficulty sleeping

An additional randomized controlled trial [19] compared bed alarm with alarm + oxybutynin. The critical outcome of 14 dry nights did not favor combination treatment with alarm and oxybutynin over alarm alone in this one study (RR 0.96, 95% CI 0.56–1.65). Daytime urinary incontinence was not specifically excluded. We rated the quality of evidence as low owing to lack of allocation concealment and blinding.

Desphande et al. [17] performed a Cochrane systematic review of drug therapies for nocturnal enuresis. They evaluated combination therapy with oxybutynin + imipramine compared with imipramine alone [27, 28]. The critical outcome of 14 dry nights favored combination treatment with oxybutynin + imipramine over imipramine alone (RR 0.68, 95% CI 0.50–0.95). The important outcome of decreased number of wet nights favored combination treatment with oxybutynin + imipramine over imipramine alone, with mean difference of –2.1 (95% CI –2.99 to –1.21). We rated the quality of evidence as moderate owing to study limitations of one of the trials related to unclear allocation concealment, blinding, and incomplete outcome data. However, the study results were consistent. Both studies were limited to monosymptomatic enuresis subjects. Adverse effects of combination therapy with oxybutynin + imipramine included dry mouth and nausea.

The authors of the review also evaluated combination therapy with anticholinergic + desmopressin compared with desmopressin alone [29, 30]. A more recent randomized controlled trial by Montaldo et al. [18] was not included in this review. Based on Lee et al. [30], the critical outcome of 14 dry nights did not favor combination treatment with oxybutynin + desmopressin (RR 0.91, 95% CI 0.63–1.31). Based on Austin et al. [29], the critical outcome of 14 dry nights did not favor combination treatment with tolterodine + desmopressin (RR 0.89, 95% CI 0.70–1.13). Based on Montaldo et al. [18], the important outcome of decreased number of wet nights seemed to favor combination treatment with oxybutynin + desmopressin over desmopressin alone; however, the effect size could not be calculated. We rated the quality of evidence as low owing to study limitations related to unclear allocation concealment, blinding, and incomplete outcome data. The study results were inconsistent. Not all studies specifically excluded daytime urinary incontinence. Adverse effects included headache.

Clinical implications

In children who have tolerated imipramine well but who are not dry at night, we suggest a combination of oxybutynin + imipramine (conditional recommendation based on moderate-quality evidence). Reported adverse effects of this combination treatment were infrequent. However, the population who have failed imipramine monotherapy is expected to be small. Tricyclic medications are not recommended as first-line therapy for nocturnal enuresis by the ICCS because of potential cardiotoxicity [6].

In patients with monosymptomatic nocturnal enuresis, we suggest combination therapy of alarm + desmopressin versus alarm alone; alarm + imipramine versus alarm alone; alarm + oxybutynin versus alarm alone; or anticholinergic + desmopressin versus desmopressin alone (conditional recommendation based on low-quality evidence). Results from trials were inconsistent. This recommendation is further based on the judgment that in the absence of any serious adverse events, the potential benefits of combination therapy outweigh the harms.

Clinical question 5

In children who use desmopressin and/or enuresis alarm, do additional nonpharmacological treatments increase the number of dry nights?

Literature search

A systematic literature search in PubMed (1966–2015) was conducted using the search terms “enuresis,” “miscellaneous,” and “complementary,” The search was limited to randomized controlled trials and systematic reviews in English with a human population.

The evidence

In patients who are not completely dry at night following first-line treatment with desmopressin and/or bed alarm,

some families may want to know if any additional nonpharmacological treatments may be helpful. The literature search yielded two systematic reviews [13, 31] and one additional randomized controlled trial [32] relevant to this clinical question.

Glazener et al. [13] performed a Cochrane systematic review of alarm therapies for nocturnal enuresis. Sixteen studies compared bed alarm with bed alarm + additional behavioral interventions. Behavioral interventions used in adjunct to bed alarm included retention control training, overlearning, dry bed training, and reward system. The critical outcome of 14 dry nights seemed to favor alarm alone compared with alarm + retentional control training (RR 0.39, 95% CI 0.20–0.77). Additional behavioral intervention was not more effective than alarm alone for overlearning (RR 1.22, 95% CI 0.0.62–2.42), dry bed training (RR 1.21, 95% CI 0.82–1.81), or reward for dry bed (RR 1.81, 95% CI 0.73–4.46). The review identified some success with duration of response with dry bed training and overlearning, but this particular outcome, although clinically important, is not a focus of this chapter. We rated the quality of evidence as low owing to study limitations related to unclear allocation concealment, blinding, and incomplete outcome data. The study results were inconsistent. Not all studies specifically excluded daytime urinary incontinence. No adverse effects were reported.

Huang et al. [31] performed a systematic Cochrane review of complementary and miscellaneous treatments for nocturnal enuresis. A total of 24 randomized controlled trials were identified that investigated treatment for nocturnal enuresis with hypnosis, psychotherapy/counseling, acupuncture, chiropractic therapy, diet, faradization, and medicinal herbs. Data from studies could not be combined for meta-analysis because of statistical and clinical heterogeneity. An additional more recent randomized controlled trial investigated combination therapy with desmopressin and acupuncture [32]. The critical outcome of 14 dry nights was not assessed. The important outcome of decreased number of wet nights favored treatment with hypnosis, psychotherapy, acupuncture, chiropractic therapy, and medicinal herbs in some single small trials, often with questionable methodological rigor.

We rated the quality of evidence as very low owing to suboptimal methodological quality in the majority of studies. Not all studies specifically excluded daytime urinary incontinence or organic causes for urinary incontinence. Adverse effects included headache, stiff neck, and spine pain with chiropractic treatment, and poor appetite and dry mouth with medicinal herbs.

Clinical implications

In patients with monosymptomatic nocturnal enuresis who have failed alarm therapy, we suggest that alarm may be supplemented by some forms of behavioral training such as overlearning, dry bed training, or reward systems (conditional recommendation based on low-quality evidence). This recommendation is based on the judgment that in the absence of any serious adverse events, the potential benefits of combination therapy outweigh the harms.

We suggest against additional complementary treatments including acupuncture and medicinal herbs (conditional recommendation against based on very low-quality evidence). This recommendation is based on the judgment that with the reported adverse effects in the absence of clear treatment benefit, the potential harms outweigh the benefit.

Clinical question 6

In children with concomitant sleep or psychiatric disorders, do nonurological treatments increase the number of dry nights?

Literature search

A systematic literature search in PubMed (1966–2015) was conducted using the search terms "enuresis," "sleep disordered breathing," "apnea," and "attention deficit". The search was limited to randomized controlled trials and systematic reviews in English with a human population.

The evidence

Although nocturnal enuresis has been strongly associated with attention deficit hyperactivity disorder (ADHD) and sleep-disordered breathing, how treatment of these comorbidities affects nocturnal enuresis is not well defined. High-quality evidence is limited in these populations. One systematic review [33] of nonrandomized clinical trials on the effect of rapid palatal expansion on enuresis was identified. No randomized controlled trials or systematic reviews were identified for the effect of tonsillectomy on enuresis. Two randomized controlled medication trials in children with ADHD were identified [34, 35].

Poorsatta-Bejeh Mir et al. [33] performed a systematic review to evaluate the efficacy of rapid palatal expansion to treat nocturnal enuresis. Rapid palatal expansion increases maxillary width with an orthodontic device. The critical outcome of 14 dry nights was not assessed; however, the important outcome of decreased number of wet nights was assessed. The quality of evidence is very low. Of the six studies included, none were randomized and only one had a control group. Data from the control group are not available. The quality of the evidence is severely limited by both indirectness (with results compared at different post-procedural time points) and imprecision.

Nocturnal enuresis treatment with ADHD medication has been studied in randomized, double-blind, placebo-controlled trials for nortriptyline [34] and atomoxetine [35]. Ghanizadeh and Haghighat [34]. compared the effects

of methylphenidate + nortriptyline with methylphenidate + placebo in children with both ADHD and monosymptomatic enuresis. No subjects were undergoing concurrent treatment for enuresis such as desmopressin or bed alarm. The critical outcome of 14 dry nights did not significantly favor methylphenidate + nortriptyline treatment (RR 3.56, 95% CI –2.26 to 9.13). The most common adverse effects in the nortriptyline group were decrease of appetite, drowsiness, and headache. Sumner et al. [35] compared the effects of atomoxetine with placebo in children with nocturnal enuresis in an industry-supported study. Of the subjects, 27/87 had nonmonosymptomatic enuresis and 60/87 did not have an ADHD diagnosis. The critical outcome of 14 dry nights was not assessed. The important outcome of decreased number of wet nights was higher in the atomoxetine group but the effect size could not be estimated. We rated the quality of evidence as low owing to study limitations related to randomization allocation concealment. Daytime urinary incontinence or organic causes for urinary incontinence were not specifically excluded. Adverse effects included decrease of appetite, drowsiness, and headache for nortriptyline + methylphenidate, and headache, nausea/vomiting, decreased appetite, gastroenteritis, increased heart rate, insomnia, pyrexia, abdominal pain, and diarrhea for atomoxetine.

Clinical implications

We suggest that the subset of enuretic patients with concomitant ADHD and sleep-disordered breathing be evaluated for additional nonurological treatment (conditional recommendation based on low-quality evidence). We do not recommend these treatments without a confirmed diagnosis of ADHD or sleep-disordered breathing. This recommendation is based on the judgment that with the reported adverse effects in the absence of clear treatment benefit, the potential harms outweigh the benefit.

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20 CHAPTER 20

Management of neurogenic bladder in children with spina bifida

Kourosh Afshar, Mir Sohail Fazeli, and Cyrus Chehroodi
Division of Pediatric Urology, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada

Introduction

Spina bifida or myelodysplasia is the most common cause of neurogenic bladder in children [1]. The incidence has been reported to be between 0.3 and 1 in 1000 live births [2]. The clinical consequences of spina bifida vary widely. Multisystem involvement is common, affecting the central nervous, musculoskeletal, genitourinary, and gastrointestinal systems. The quality of life of many of the affected children is significantly lowered.

Urologists are an essential part of multidisciplinary teams that provide care to this complex group of patients with neurogenic bladder. With a better understanding of the pathophysiology of neurogenic bladder and the addition of clean intermittent catheterization (CIC), anticholinergic drugs, and improved surgical techniques to our armamentarium, urinary-related morbidity and mortality have been dramatically reduced in these children. The main urological goals are to preserve renal function, keep the child infection free, and treat or manage urinary incontinence, with the aim of improving the quality of life. There are many controversial areas in the urological care of this challenging group of patients.

In this chapter, we systematically review the evidence related to some of the most important aspects of the management of the urinary tract.

Clinical question 1

In children with neurogenic bladder due to spina bifida, does the use of antibiotic prophylaxis reduce the likelihood of urinary tract infection (UTI)?

Literature search

We conducted a systematic search, developed by a medical librarian, in PubMed, MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and Web of Science databases for search terms and subheadings such as: "spinal dysraphism," "meningomyelocele," "urinary catheter," "intermittent catheterization," "urinary tract infection," and "bacteriuria." We also manually searched the bibliography of all included studies for additional potential studies to be included in the review. Study inclusion criteria and quality were assessed by two reviewers. Any disagreement was resolved by discussion with the senior author. The search was limited to randomized controlled trials (RCTs) and the human population.

The evidence

Seventeen citations were identified, of which two studies met the inclusion criteria. Owing to fundamental differences in interventions, outcome assessment, and reporting, we were not able to perform a meta-analysis. The results are reported individually.

The study by Johnson et al. [3] included children with neurogenic bladder and spina bifida followed in a multidisciplinary clinic. All subjects were on intermittent catheterization. This was a randomized, controlled cross-over study comparing low-dose nitrofurantoin with placebo. A total of 66 patients were recruited and received 12 weeks of treatment with placebo or antibiotics, then crossed over to the other arm. Outcomes of interest included asymptomatic bacteriuria and symptomatic UTI. Each patient provided six biweekly urine specimens for each arm. The two outcomes were not reported separately. Only the proportions of positive urine specimens for each patient were compared. The mean proportion of positive urine culture in each patient was 19 and 39% in the prophylaxis versus the placebo group ($p < 0.0003$).

The study by Zegers et al. [4] included 176 patients with spina bifida who were on CIC and low-dose prophylactic antibiotics.

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These patients were randomized to either stop or continue on prophylaxis. The participants had biweekly urinary dipstick and cultures during the 18 months of follow-up. The incidences of asymptomatic bacteriuria and febrile and nonfebrile UTIs were compared in the two groups. The authors reported a twofold higher incidence of febrile UTI in the discontinuation group, but this was not statistically significant. The relative risk (RR) for both nonfebrile UTI and asymptomatic bacteriuria was significantly higher in the discontinuation group (RR = 1.44, $p = 0.003$ and RR = 1.25, $p = 0.002$, respectively). Nevertheless, the absolute effect size for reduction of nonfebrile UTI was very small (1.8–1.5 UTIs per year). The number needed to harm was estimated as 2.2.

The risk of bias for these studies is summarized in Figure 20.1. The study by Johnson et al. [3] is at high risk for multiple biases, mainly due to unclear methods of randomization and blinding. The study by Zegers et al. [4] was of better quality but still at high risk for performance. The evidence is summarized in Table 20.1.

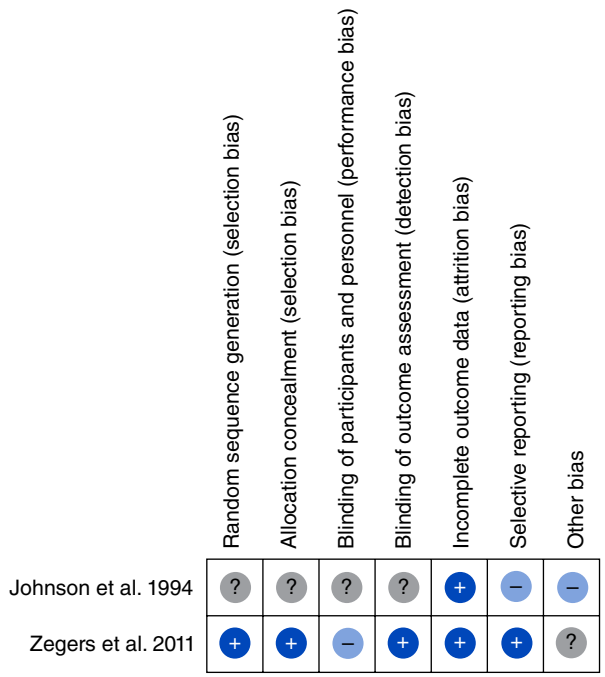

Figure 20.1 Risk of bias assessment.

Clinical implications

We suggest against routine prophylactic antibiotics in children with spina bifida who are on CIC (conditional based on

Table 20.1 Antibiotic prophylaxis compared with placebo or no treatment for the prevention of urinary infection in children with spina bifida and neurogenic bladder.

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with placebo or no treatment	Risk difference with antibiotic prophylaxis
Proportion of positive urine culture Scale: from 0 to 100 follow-up: mean 12 weeks	112 (1 RCT)	⨁⨁⨁◯ MODERATE[a,b]	–	The mean proportion of positive urine culture was **39**%	Mean **20% lower** (29.8 lower to 11.6 lower)
Proportion of cases with febrile UTI follow-up: mean 18 months	176 (1 RCT)	⨁⨁◯◯ LOW[b,c,d]	**RR 0.50** (0.09 to 2.66)	45 per 1000	**23 fewer per 1000** (41 fewer to 75 more)
Proportion of cases with afebrile UTI	176 (1 RCT)	⨁⨁⨁◯ MODERATE[b,c]	**RR 0.48** (0.26 to 0.87)	61 per 100	**32 fewer per 100** (45 fewer to 8 fewer)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; RR, risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Unclear method of randomization and concealment, unknown blinding of participants and investigators, only a composite outcome of positive urine culture is reported, no information about symptomatic UTI provided.

[b]Not applicable.

[c]High risk for performance bias because of nonblinding of participants and investigators.

[d]Low number of events resulting in wide 95% CI.

low-quality evidence). This recommendation is based on the fact that although the probability of asymptomatic bacteriuria is decreased by prophylactic antibiotics, this intervention does not reduce the clinically important outcomes such as febrile UTIs.

Clinical question 2

In children with neurogenic bladder due to spina bifida who are on CIC, do sterile, single-use catheters decrease the likelihood of UTI compared with multiple-use catheters?

Literature search

We conducted a systematic literature search in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and Web of Science (for search terms and subheading such as "spinal dysraphism," "meningomyelocele," "urinary catheter," "intermittent catheterization," "urinary tract infection," "bacteriuria," and "patient satisfaction"). Study inclusion criteria and quality were assessed by two reviewers. Any disagreement was resolved by discussion with the senior author. The search was limited to RCTs and the human population.

The evidence

After reviewing 33 citations and abstracts, three studies were included in the meta-analysis and evidence profile.

Two studies ($n=679$) addressed the incidence of bacteriuria and could not show a significant difference between single-use and multiple-use catheters [5, 6] (Figure 20.2).

Two studies ($n=113$) that reported the incidence of symptomatic UTI also could not show a statistically significant difference between two types of catheter [6, 7] (Figure 20.3).

Only the study by Kiddoo et al. [7] reported on patient satisfaction with different types of catheter, which showed more satisfaction with multiple-use catheters; however, this did not reach statistical significance (RR = 0.83, 95% confidence interval [CI] 0.67–1.03). The main reason for dissatisfaction was difficulty in handling single-use prelubricated catheters.

The evidence is of low to moderate quality, mainly due to methodological issues. The studies had limitations with regard to the method of randomization, allocation concealment, blinding, intention-to-treat analysis, and funding and were downgraded to low- and moderate-quality evidence (Figure 20.4). However, one should note in this type of study that blinding of participants and/or investigators to the interventions may not be possible (Table 20.2).

Clinical implications

We suggest against the use of single-use over multiple-use catheters in children with spina bifida managed by CIC (conditional recommendation based on low-quality evidence). This recommendation is based on a lack of evidence to support any significant reduction in the rates of UTI, likely higher costs, and possibly lower satisfaction due to more difficult handling.

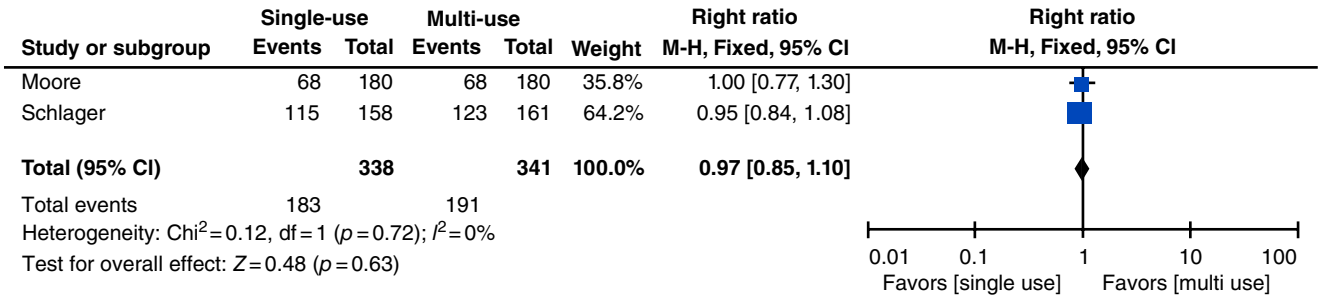

Figure 20.2 Effect of type of catheter on incidence of bacteriuria.

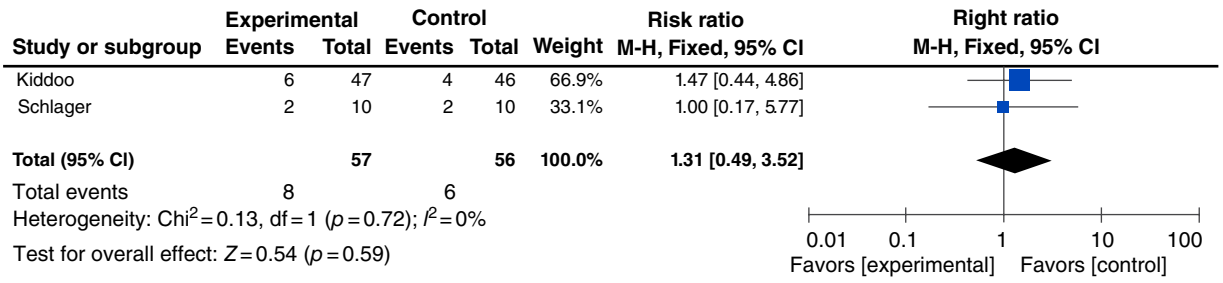

Figure 20.3 Effect of type of catheter on incidence of symptomatic UTI.

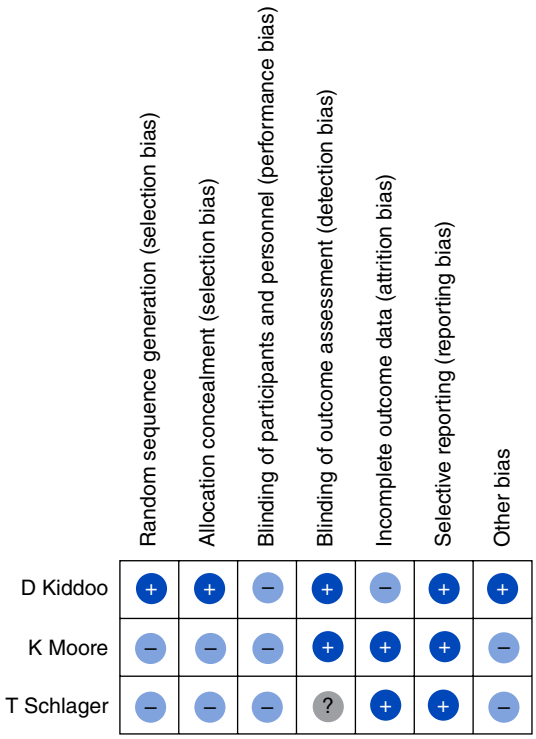

Figure 20.4 Risk of bias assessment.

Clinical question 3

Is electrostimulation (ES) therapy effective in the treatment of urinary incontinence in children with neurogenic bladder due to spina bifida?

Literature search

We conducted a systematic literature search in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Web of Science, CINAHL, EBM reviews and Google Scholar (for search terms and subheading such as "spinal dysraphism," "meningomyelocele," "electrostimulation," and "neuromodulation"). Two reviewers assessed study inclusion criteria and quality. Any disagreement was resolved by discussion with the senior author. The search was limited to RCTs and the human population.

The evidence

Five studies were selected for full text review and eventually four studies were included in the systematic review.

Two studies [8, 9] were similar enough to be pooled in a meta-analysis. A total of 60 children with neurogenic bladder due to spina bifida who were on intermittent catheterization and not responding to standard management were included. They were randomized to transcutaneous electrostimulation

Table 20.2 Single- versus multiple-use catheter in the management of children with spina bifida and neurogenic bladder.

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with multiple-use catheter	Risk difference with single-use catheter
Bacteriuria follow-up: range 32–48 weeks	679 (2 RCTs)	⨁⨁◯◯ LOW[a]	**RR 0.97** (0.85 to 1.10)	56 per 100	**2 fewer per 100** (8 fewer to 6 more)
UTI follow-up: range 32–48 weeks	113 (2 RCTs)	⨁⨁◯◯ LOW[b]	**RR 1.31** (0.49 to 3.52)	11 per 100	**3 more per 100** (5 fewer to 27 more)
Overall satisfaction with catheter assessed with: survey follow-up: 48 weeks	93 (1 RCT)	⨁⨁⨁◯ MODERATE[c,d]	**RR 0.83** (0.67 to 1.03)	87 per 100	**15 fewer per 100** (29 fewer to 3 more)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; RR, risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Method of randomization and allocation concealment is not mentioned for one study, one study is quasi-randomized, lack of blinding in participants and investigators due to type of intervention, funding bias.

[b]Method of randomization and allocation concealment not mentioned for one study, one study is quasi-randomized, lack of blinding in both studies for participants and investigators due to type of intervention, no mention of ITT analysis in one study, one study with funding bias.

[c]Lack of blinding in participants and investigators, no ITT analysis.

[d]Not applicable.

or sham treatment. Clinical and urodynamics (UDS) outcome variables included night-time enuresis, mean bladder capacity (MBC), mean detrusor compliance (MDC), and mean maximal detrusor pressure. Overall, a small but statistically significant effect favoring ES was shown in reduction of night-time enuresis (mean difference of –1.12 nights/week [95% CI –2.26 to 0.02, $p = 0.05$]) (Figure 20.5). None of the UDS parameters were significantly different in the two groups (Figures 20.6, 20.7, and 20.8).

The study by Kajbafzadeh et al. [8] did not show a statistically significant benefit for ES in reducing urinary frequency (mean difference 0.4 times/week, 95% CI –1.51 to 2.31) or gaining continence (RR = 2.37, 95% CI 0.63–8.93). However, significant reductions in post-voiding residue (PVR) (mean difference –42.70 mL, 95% CI –78.66 to –6.74) and number of patients with detrusor sphincter dyssynergia (RR = 0.47, 95% CI 0.27–0.82) were described.

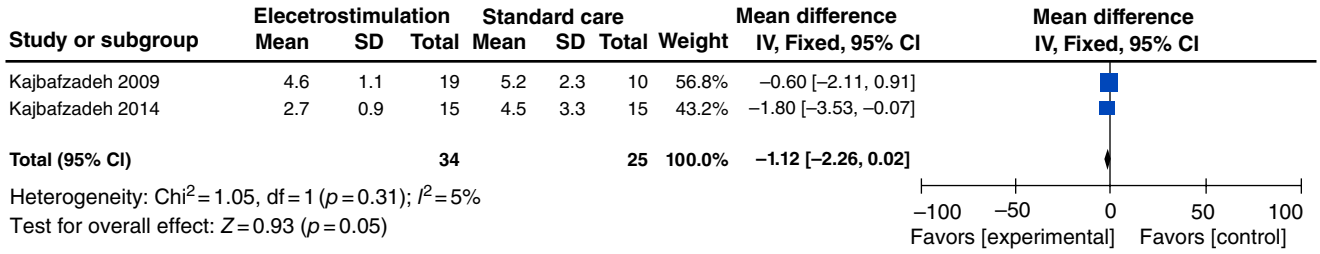

Figure 20.5 Effect of electrostimulation on nocturnal enuresis (nights per week).

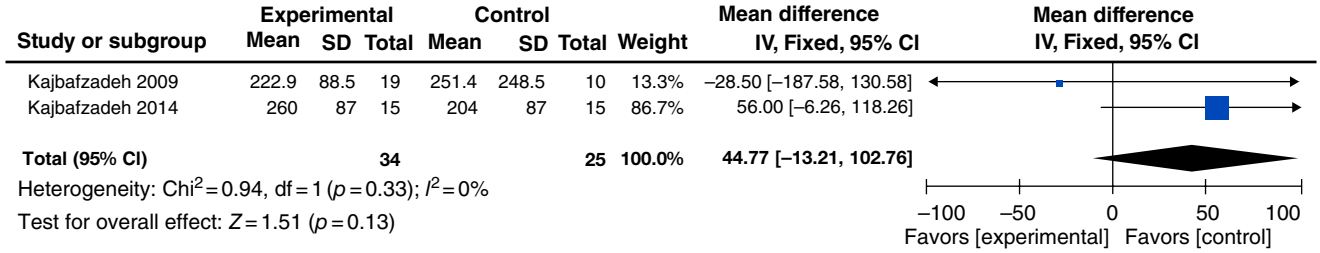

Figure 20.6 Effect of electrostimulation on mean bladder capacity.

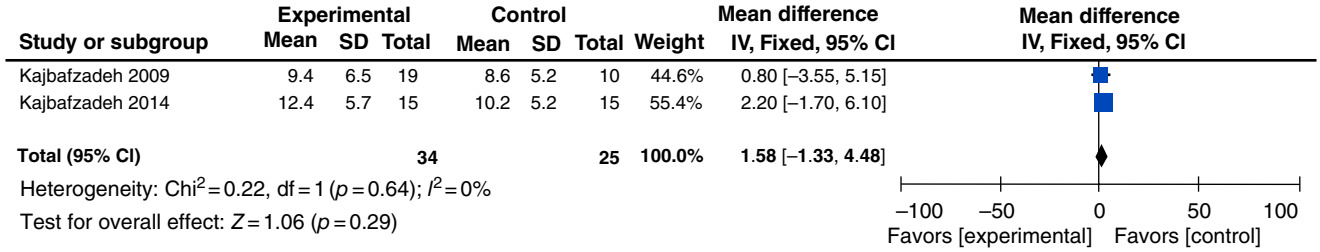

Figure 20.7 Effect of electrostimulation on mean detrusor compliance.

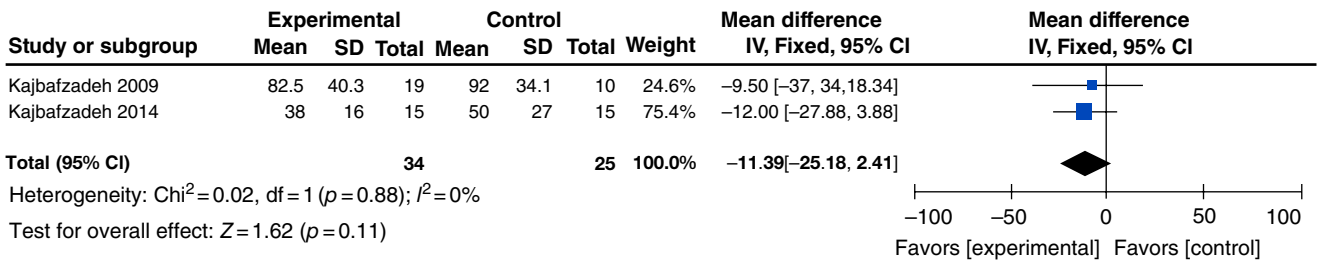

Figure 20.8 Effect of electrostimulation on mean maximal detrusor pressure.

In a later study, Kajbafzadeh et al. [9] showed a significant reduction in frequency of pad change (mean difference 1.1, 95% CI 2.8–0.02 times/day fewer) and daily incontinence score (mean difference –0.7, 95% CI –1.25 to 0.15) in the ES group. A significant increase in detrusor leak point pressure (DLPP) (mean difference 18.6 cmH_2O, 95% CI 4.82–32.38) for the ES therapy groups was also reported.

The study by Kamal and Khalaf [10] reported the amount of urine loss (weight) and did not show any benefit for ES therapy (mean difference –4 g, 95% CI –10.3 to 2.39)

The study by Boone et al. [11] also failed to show any significant differences for the presence of active detrusor contractions (RR = 1.01, 95% CI 0.41–2.48) or bladder capacity (mean difference –2.70 mL, 95% CI –71.87 to 66.47). It also failed to show any difference in subjective functional outcomes such as a change in the degree of incontinence. We were unable to pool this study with others owing to different methodology and the way in which the outcomes were reported.

All included studies had serious methodological limitations due to biases (mostly due to the method of randomization, allocation concealment, blinding, no intention-to-treat analysis), and imprecise results (Figure 20.9). However, blinding of investigators in the included clinical trials would have been difficult owing to the nature of the intervention.

It also should be noted that not all statistically significant changes can be assumed to be clinically important (Table 20.3). For example, a one night per week decrease in enuresis may not have any meaningful quality of life benefit that can justify the cost and burden of ES. Using outcome variables such as the number of pad changes is very subjective and dependent on the patient preference. The urinary incontinence score used in some studies has not been validated for responsiveness. In addition, it is not clear how much change in incontinence score is associated with improvement in quality of life. Changes in UDS parameters are either non-significant or inconsistent. In one study [8], changes in PVR and detrusor sphincter dyssynergia (DSD) were reported in spite of no alteration in the continence rate. This draws into

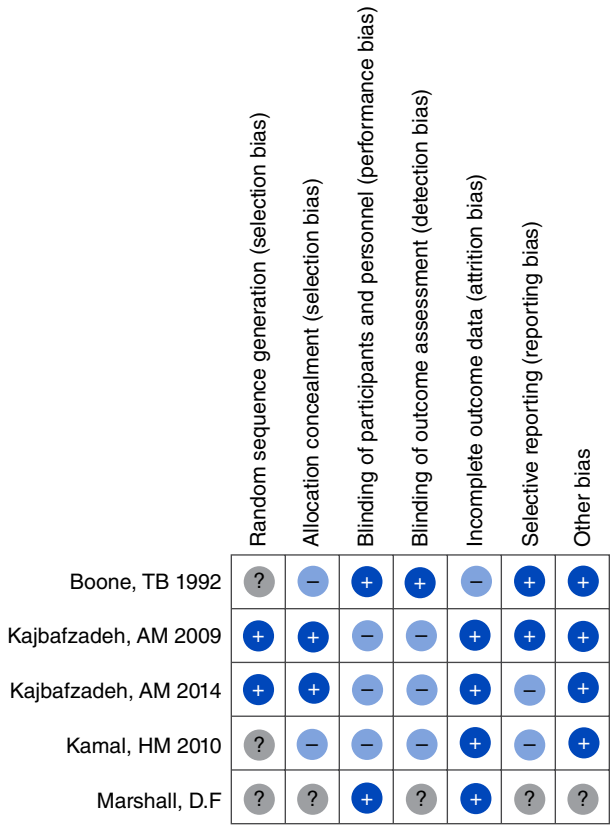

Figure 20.9 Risk of bias assessment summary.

Table 20.3 Electrostimulation in the management of children with spina bifida and neurogenic bladder.

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with standard management	Risk difference with electrostimulation
Enuresis follow-up: range 6–36 months4	59 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	–	The mean enuresis ranged from **4.5 to 5.2** nights/week	MD **1.12 nights/week lower** (2.26 lower to 0.02 higher)
Continence follow-up: range 6–36 months	29 (1 RCT)	⨁⨁◯◯ LOW [a,b,c]	**RR 2.37** (0.63 to 8.93)	20 per 100	**27 more per 100** (7 fewer to 159 more)
MMDP assessed with: UDS follow-up: range 6–36 months	59 (2 RCTs)	⨁⨁◯◯ LOW[a,c]	–	The mean MMDP ranged from **50 to 92 cmH_2O**	MD **11.39 cmH_2O lower** (25.18 lower to 2.41 higher)
MBC assessed with: UDS follow-up: range 6–36 months	59 (2 RCTs)	⨁⨁◯◯ LOW[a,c]	–	The mean MBC ranged from **204 to 251.4 mL**	MD **44.77 mL higher** (13.21 lower to 102.74 higher)
MDC assessed with: UDS follow-up: range 6–36 months	59 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	–	The mean MDC ranged from **8.6–10.2 mL/cmH_2O**	MD **1.58 mL/cmH_2O higher** (1.33 lower to 4.48 higher)
DSD assessed with: UDS follow up: range 6 months to 36 months	29 (1 RCT)	⨁⨁◯◯ LOW[a,b,c]	**RR 0.47** (0.27 to 0.82)	90 per 100	**48 fewer per 100** (66 fewer to 16 fewer)

Table 20.3 (Continued)

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with standard management	Risk difference with electrostimulation
Detrusor leak point pressure assessed with: UDS follow up: mean 6 months	30 (1 RCT)	⨁⨁◯◯ LOW [a,b,c]	–	The mean detrusor leak point pressure was **37 cmH_2O**	MD **18.6 cmH_2O higher** (4.82 higher to 32.38 higher)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; MD, mean difference; RR, risk ratio: RCT, randomized controlled trial.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] No blinding of investigators due to nature of intervention, no mention of blinding for assessors.

[b] Not applicable.

[c] Wide CI.

question the clinical importance of these findings. Although an increase in DLPP may be associated with reduced urinary leakage, its potential detrimental effect on the upper tract cannot be overlooked. In addition, different types of ES (cutaneous versus transurethral) used in the studies prohibited combining the trials in a meta-analysis.

Clinical implications

We suggest against treating children with neurogenic bladder due to spina bifida with ES (conditional recommendation against based on low-quality evidence). This recommendation is based on the lack of evidence to demonstrate a clinically meaningful impact on patient-important outcomes. Based on the available evidence, possible benefits do not outweigh the associated potential harms and costs.

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21 CHAPTER 21
Wilms tumor

Ruiyang Jiang and Jonathan C. Routh
Division of Urologic Surgery, Duke University Medical Center, Durham, NC, USA

Introduction

Wilms tumor (WT) is the most common solid renal malignancy in children. The incidence of WT is 7.1 cases per 1 million children younger than 15 years. Each year in the United States, there are approximately 500 cases of WT identified. About 5–10% of individuals with WT have bilateral tumors, and bilateral involvement is more likely in patients with genetic predisposition syndromes [1, 2].

A multidisciplinary approach is the mainstay of WT management. Treatment for children with WT differs between North America and Europe. Initial radical nephrectomy (RN) followed by chemotherapy and/or radiation is utilized in the United States for patients with unilateral WT, whereas in Europe, preoperative chemotherapy before definitive resection is used. Regardless of the treatment protocol, the overall survival is currently in excess of 90% [3].

An ongoing area of controversy in WT treatment is the utilization of nephron-sparing surgery (NSS) in patients with unilateral disease. This is in large part due to the lack of high-quality data regarding long-term renal function, hence the potential benefit may not outweigh the risk for decreased survival. Recent systematic reviews have found no significant differences in oncological outcomes between NSS and RN [4, 5]. However, at present, NSS is recommended only for patients with bilateral WT, solitary kidney, or horseshoe kidney, or in patients who have predisposition syndromes. A second area of current investigation is the role of computed tomography (CT) scan in detecting metastatic lung lesions. Traditionally, metastatic lung disease in WT is evaluated by chest X-ray (CXR). Hence it is unclear whether patients with small lung lesions detectable only on CT require more intensive therapy. Finally, treatment-related toxicity continues to be an area of increasing concern, and there is a growing interest in the study of long-term renal function in WT survivors [6–10].

Clinical question 1

In patients with Wilms tumor, how does nephron-sparing surgery (NSS) compare with radical nephrectomy (RN)?

Literature search

We searched MEDLINE, EMBASE, the Cochrane Controlled Trials Register, Google Scholar, and ClinicalTrials.gov electronic databases for trials and systematic reviews published between January 2010 and May 2016 in any language. We used the search terms "Wilms tumor," "radical nephrectomy," "partial nephrectomy," and "nephron-sparing surgery." Reference lists of included studies were screened manually for any additional studies. We also searched manually for unpublished abstracts presented at relevant scientific meetings.

The evidence

Two systematic reviews were identified. A review by Cost et al. included 19 articles ($n=82$) on patients treated with NSS for nonsyndromic unilateral WT [4]. For inclusion criteria, studies must have available data on disease stage, disease recurrence, location of recurrence, overall survival, and time-to-event. A comparison group was formed from a cohort of patients managed with RN for nonsyndromic unilateral WT at the Children's Medical Center of Dallas. In the NSS group, there were nine recurrences (three systemic, three local, three combined) and four deaths. In the RN group, there were 20 recurrences (14 systemic, four local, two combined) and six deaths. The authors found no statistically significant difference between the two groups in terms

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of median recurrence-free survival (RFS) (83.1% RN vs. 89.1% RSS, $p=0.21$) or overall survival (95% RN vs. 95.1% RSS, $p=0.92$). There was no significant increase in oncological risk for RFS (hazard ratio [HR] = 0.95, 95% confidence interval [CI] 0.39–2.34) or overall survival (HR = 0.45, 95% CI 0.17–4.39) (Figure 21.1; Table 21.1) [4].

A second, more recent review by Vanden Berg et al. included 66 articles ($n=1632$ children age <18 years) [5]. Bilateral WTs were present in 29% of patients. The authors did not perform direct comparisons of outcomes owing to the highly variable data among studies, but a descriptive analysis was made. The mean tumor rupture rate was 13% in RN and 7% in NSS. Tumor recurrences were 12% in RN and 11% in NSS; 8% of the patients who underwent RN developed ESRD whereas 3% of patients with NSS had end-stage renal disease (ESRD). The overall survival was 85% for the patients who underwent RN and 88% for those with NSS. The authors concluded that most contemporary studies reported similar long-term outcomes between RN and NSS [5].

In summary, the long-term surgical outcome appears to be similar between RN and NSS in both unilateral and bilateral WT.

Clinical implications

We suggest against nephron-sparing surgery in patients with unilateral WT (conditional recommendation based on very low-quality evidence). This recommendation is based on the lack of evidence for superiority, concerns over increased short-term complications, and limited experience by surgeons with this approach given the low incidence of the condition.

Clinical question 2

In patients with syndromic and bilateral WT, how does nephron-sparing surgery (NSS) compare with radical nephrectomy (RN)?

Literature search

We searched MEDLINE, EMBASE, the Cochrane Controlled Trials Register, Google Scholar, and ClinicalTrials.gov electronic databases for trials and systematic reviews published between January 2010 and May 2016 in any language. We used the search terms "Wilms tumor" and "renal function." Reference lists of included studies were screened manually for any additional studies. We also searched manually for unpublished abstracts presented at relevant scientific meetings.

The evidence

One systematic review was identified, Romao and Lorenzo, who evaluated the long-term renal function in three distinct WT groups: unilateral nonsyndromic WT, syndromic WT, and bilateral WT [10]. For unilateral nonsyndromic WT, data from the National Wilms Tumor Study Group (NWTSG) were extracted. The NWTSG study followed 8000 patients from 1969 to 2002. They found that the incidence of ESRD at 20 years of follow-up was 0.7%. For WT patients with predisposition syndromes, data from Breslow et al. [11] were extracted. In the Breslow study, the cumulative incidence of ESRD for Denys–Drash syndrome and WAGR syndrome was 12/17 patients (74%; 95% CI 45–89%) and 11/37 patients (36%; 95% CI 18–55%), respectively [11]. For bilateral nonsyndromic WT, data from the National Wilms Tumor Study 4 (NWTS-4) were extracted. A total of 23 (12%) out of the 188 patients with bilateral disease followed from 1986 to 1994 developed ESRD [10].

In summary, whereas the incidence of ESRD is low for patients after surgical resection of unilateral nonsyndromic WT, it is high for patients with syndromic and bilateral WT.

Clinical implications

In patients with syndromic and bilateral WT, we recommend NSS (strong recommendation based on low-level evidence).

Following surgery, we recommend that patients receive routine renal function monitoring (strong recommendation based on low-level evidence)

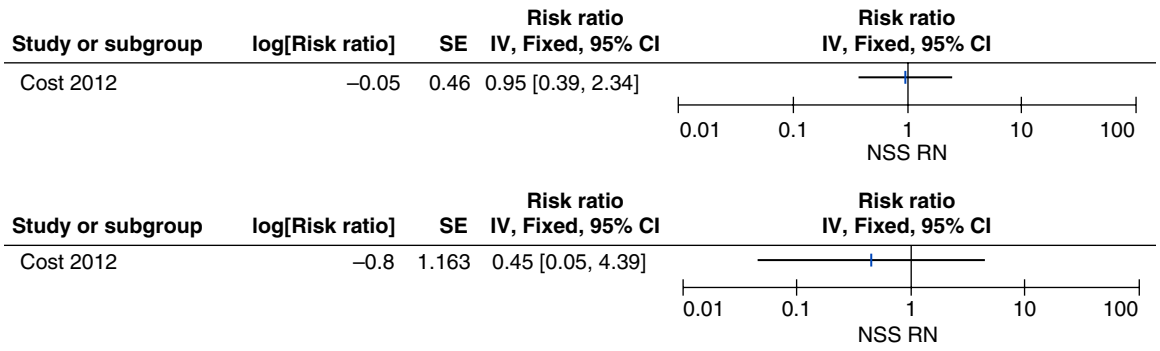

Figure 21.1 RFS and OS between NSS and RN.

Table 21.1 RFS and OS for nephron-sparing surgery and radical nephrectomy.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NSS**	**RN**	**Relative (95% CI)**	**Absolute (95% CI)**		
RFS												
19	Observational studies	Serious[a]	Not serious[a]	Not serious	Not serious[b]	All plausible residual confounding would reduce the demonstrated effect[c]	100/121 (82.6%)	73/82 (89.0%)	**RR 0.95** (0.39 to 2.34)	**45 fewer per 1000** (from 543 fewer to 1000 more)	⨁⨁◯◯ LOW	IMPORTANT
OS												
19	Observational studies	Serious[a]	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect[c]	114/121 (94.2%)	77/82 (93.9%)	**RR 0.45** (0.17 to 4.39)	**516 fewer per 1000** (from 779 fewer to 1000 more)	⨁⨁◯◯ LOW	IMPORTANT

CI, confidence interval; RR, risk ratio.

[a] Different reporting outcomes for recurrences.

[b] 45 fewer per 1000.

[c] No explanation was provided.

Clinical question 3

In patients with CT-only pulmonary lesions (negative CXR), how does three-drug therapy (vincristine, dactinomycin, and doxorubicin) compare with two-drug therapy (vincristine and dactinomycin)?

Literature search

We searched MEDLINE, EMBASE, the Cochrane Controlled Trials Register, Google Scholar, and ClinicalTrials.gov electronic databases for trials and systematic reviews published between January 2010 and May 2016 in any language. We used the search terms "Wilms tumor," "CT-only lesion," and "negative CXR." Reference lists of included studies were screened manually for any additional studies. We also searched manually for unpublished abstracts presented at relevant scientific meetings.

The evidence

One retrospective analysis and one randomized controlled trial (RCT) were identified. The retrospective analysis by Owens et al. included 141 children who had normal CXR in addition to chest CT at initial diagnosis [12]. A total of 31 of the 141 children had a positive CT scan. Eight of the 31 patients in the CT-positive group subsequently developed relapse and four of the relapses were in the lung. The risk of pulmonary relapse in the children with stage I tumors were significantly greater in the CT-positive group (3/7, 43%) than in the CT-negative group (5/48, 10%, $p=0.02$). Three-year pulmonary-free survival for the CT negative group was 89.5% (95% CI 77.5–95%) and for the CT-positive group 57% (95% CI 25.1–84.2%) [12].

The RCT by Grundy et al. extracted data from National Wilms Tumor Studies NWTS-4 and -5. The Grundy study included 186 patients with CT-only lesions and evaluated whether additional chemotherapy or lung radiation in patients with CT-only lesions improved event-free survival (EFS) and overall survival (OS). A total of 37 patients received two-drug therapy (vincristine and dactinomycin) and 145 received three-drug therapy (vincristine, dactinomycin, and doxorubicin). The EFS at 2 years was 59.8% (95% CI 41.6–73.9%) and 84.2% (95% CI: 77–89.3%) for two and three-drug therapy, respectively ($p=0.004$). The EFS at 5 years was 56% (95% CI 37.7–70.9%) and 79.7% (95% CI 71.3–85.9%) for two- and three-drug therapy, respectively ($p=0.004$). The OS at 2 years was 91.3% (95% CI 75.5–97.1%) and 94% (95% CI 88.2–97%) for two- and three-drug therapy, respectively ($p=0.91$). The OS at 5 years was 86% (95% CI 65.2–94.8%) and 87% (95% CI 78.6–92.3%) for two- and three-drug therapy, respectively ($p=0.91$). There was no statistically significant difference between the lung radiation group and the nonradiation group for EFS or OS at 2 and 5 years ($p=0.11$ and 0.73, respectively) [13]

In summary, CT scanning is able to identify a group of stage I patients who are at increased risk for pulmonary relapse. In addition, patients with CT-only lung lesions have improved EFS but not OS from addition of doxorubicin. However, patients with CT-only lesion do not appear to benefit from pulmonary radiation.

Clinical implications

In patients with CT-only pulmonary lesions, we suggest the addition of doxorubicin to vincristine and dactinomycin (conditional recommendation based on low-level evidence).

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PART 4

Prostate cancer

Julio M. Pow-Sang

22

CHAPTER 22

Early detection and screening for prostate cancer

Pim J. van Leeuwen[1,2], Monique J. Roobol[3], and Phillip D. Stricker[1,2]

[1] *St. Vincent's Prostate Cancer Centre, Darlinghurst, NSW, Australia*

[2] *Garvan Institute of Medical Research, The Kinghorn Cancer Centre, Darlinghurst, NSW, Australia*

[3] *Erasmus University Medical Centre, Rotterdam, The Netherlands*

Background

Population-based screening for prostate cancer is a complex issue, with experts and guidelines providing conflicting results [1–3]. The concept of screening is to identify a disease at a stage in its natural history where treatment can be applied in order to prevent death or suffering. For prostate cancer, this is challenging because the variable natural history of the disease differs markedly from slow-growing indolent tumors and highly aggressive and potentially fatal forms. The main tool in screening for prostate cancer, prostate-specific antigen (PSA), was first described in 1979. It is a human protein secreted by prostate epithelial cells and is perhaps more a specific organ marker than a tumor marker, since prostatitis, benign prostate hyperplasia (BPH), and other conditions can also increase PSA. PSA has a large intra-individual day-to-day variation and is influenced by bodyweight [4]. Partly because PSA is not a cancer-specific measurement, no clear threshold level exists for PSA sensitivity and specificity [5]. In Table 22.1, the continuum of prostate cancer risk for different PSA ranges is presented [5, 6]. As shown, sensitivity decreases with increasing PSA level, while specificity increases.

Population-based screening programs aim to reduce disease-specific mortality and morbidity. In addition to these outcomes is a requirement that the benefits of the program outweigh the costs and adverse effects of early detection. Possible disadvantages of screening are overdetection with resultant overtreatment, increased costs, side effects, and complications. The criteria for an effective population-based screening program are well established and have been formally documented in the World Health Organization's screening guidelines [7]. In this chapter, we systematically review the evidence on population-based prostate cancer screening using PSA as a primary screening test.

Clinical question 1

In asymptomatic men, does population-based screening decrease the prostate cancer-specific mortality, all-cause mortality, and the cumulative incidence of metastatic prostate cancer while increasing the overall quality of life?

Literature search

We conducted a systematic search in PubMed–MEDLINE using the terms "prostate cancer," "prostate-specific antigen, "PSA," "mass screening," "prostatic neoplasms," "prostate metastasis," "mortality," and "quality of life." The search was limited to English-language randomized control trials (RCTs) and systematic reviews with meta-analyses published between January 2000 and December 2014.

The evidence

Data on prostate-specific mortality have been presented from five RCTs [8–12]. All RCTs across outcomes had important methodological limitations with regard to randomization, intention-to-screen analysis, contamination (screening in the control arm), compliance with the screening protocol, and completeness of follow-up. Details of the RCTs are presented in Tables 22.2 and 22.3. The two largest RCTs are the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial. The ERSPC was conducted in eight European countries and randomized men aged 55–69 years to PSA screening (72 952 men) every 4 years (in Sweden every 2 years) and control (89 435 men). The PLCO trial randomized 76 685 men aged 55–74 years to annual PSA testing for 6 years and digital rectal examination (DRE) for 4 years, with men with suspicious results referred to their usual source of care. The ERSPC trial reported that PSA screening is associated with a 21% relative

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Table 22.1 The continuum of prostate cancer risk for different PSA ranges, presented for the ERSPC and the Prostate Cancer Prevention Trial (PCPT).

Study	Methods	Intervention	Participants	Outcomes	Results						Notes
Thompson et al. [5]	RCT	To estimate the ROC curve for PSA, PCPT	*n*=5587	Sensitivity and specificity of PCa detection for all PSA ranges in relation to Gleason grade	PSA (ng/mL)	Prostate cancer, any grade			Prostate cancer, Gleason grade ≥8			*n*=1225 (21.9%) were diagnosed with prostate cancer
						Sen. (%)	Spec. (%)	LR	Sen. (%)	Spec. (%)	LR	
					1.1	83.4	38.9	1.4	94.7	35.9	1.5	
					2.1	52.6	72.5	1.9	86.0	65.9	2.5	
					2.6	40.5	81.1	2.1	78.9	75.1	3.2	
					3.1	32.2	86.7	2.4	68.4	81.0	3.6	
					4.1	20.5	93.8	3.3	50.9	89.1	4.7	
					6.1	4.6	98.5	3.1	26.3	97.5	10.5	
					10.1	0.9	99.7	3.0	5.3	99.5	10.6	
Schröder et al. [6]	RCT	Cancer detection rate for different PSA ranges in the ERSPC, Rotterdam section	*n*=9779	Distribution of PSA and PCa in men aged 55–74 years biopsied (2267 men) for PSA ≥4.0, DRE, and TRUS	PSA (ng/mL)	Total biopsies (%)	Cancer (*n*)	Total cancer (%)	PPV	Biopsy (*n*) per cancer		
					0.0–0.9	36.4	4	0.8	2.2	45.8		
					1.0–1.9	31.2	45	9.5	8.8	11.4		
					2.0–2.9	12.3	30	6.3	13.6	7.4		
					3.0–3.9	7.2	44	9.3	25.3	3.9		
					4.0–9.9	10.9	241	51.0	24.5	4.1		
					≥10.0	2.1	109	23.0	56.5	1.8		

DRE, digital rectal examination; ERSPC, European Randomized Study of Screening for Prostate Cancer; LR, likelihood ratio; PCa, prostate cancer; PCPT, Prostate Cancer Prevention Trial; PPV, positive predictive value; PSA, prostate-specific antigen; ROC, receiver operating characteristic; RCT, randomized controlled trial; Sen., sensitivity; Spec., specificity; TRUS, transrectal ultrasound.

Table 22.2 Characteristics of RCTs evaluating PSA screening for prostate cancer.

Study	No. randomized		Age range (years)	Screening test	Screening interval	Randomization	Contamination	Intention-to-screen analysis	Median follow-up (years)
	Screening	Control							
ERSPC [12]	72 890	89 353	50–69	PSA+DRE	2- or 4-year	Good	20%	Yes	11
Nörrkoping study [9]	1 494	7 532	50–69	DRE/ PSA+DRE	3-year	Inadequate	No data	Yes	15
PLCO study [11]	38 343	38 350	55–74	PSA+DRE	Annual	Good	40–52%	Yes	11
Quebec study [10]	31 133	15 353	45–80	PSA+DRE	Annual	Good	No data	No	11
Stockholm study [8]	2 400	24 202	50–70	PSA+DRE	Screened once	Inadequate	No data	Yes	13

DRE, digital rectal examination; PSA, prostate-specific antigen; RCT, randomized controlled trial.

Table 22.3 Outcomes of RCTs evaluating PSA screening for prostate cancer.

Study	RR (95% CI)			Quality of life (life-years gained)
	Prostate cancer mortality	All-cause mortality	Prostate cancer metastasis	
ERSPC [12]	0.79 (0.69–0.91)	1.00 (0.98–1.02)	0.70 (0.60–0.82)	+73
Nörrkoping study [9]	1.16 (0.78–1.73)	NR	NR	NR
PLCO study [11]	1.09 (0.87–1.36)	0.96 (0.93–1.10)	NR	NR
Quebec study [10]	1.01 (0.76–1.34)	NR	NR	NR
Stockholm study [8]	1.10 (0.83–1.46)	0.98 (0.92–1.05)	NR	NR

CI, confidence interval; NR, not reported; prostate cancer metastasis, cumulative incidence of prostate cancer metastasis; RR, relative risk.

reduction (RR 0.79; 95% CI 0.69–0.91) in the death rate from prostate cancer at 13 years' follow-up [12]. Subgroup analysis age indicated only a significant decrease in prostate cancer mortality for men aged 65–69 years (RR 0.69; 95% CI 0.55–0.87). After adjustment for nonparticipation, a 27% relative reduction (RR 0.71; 95% CI 0.61–0.88) was observed. The ERSPC documented that 27 additional men needed to receive a diagnosis through screening for every one fewer prostate cancer death after 13 years. In contrast, the PLCO trial reported no prostate cancer-specific mortality benefit from combined screening with PSA testing and DRE at 12 years' follow-up (RR 1.09; 95% CI 0.87–1.36) [11]. There was no demonstrable effect of PSA screening on all-cause mortality in the PLCO and ERSPC trials (Table 22.3) [11, 12]. After 12 years of follow-up, the ERSPC showed a 30% significant difference (RR 0.70; 95% CI 0.60–0.82) in the cumulative incidence of metastatic prostate cancer between the screening (0.67%) and control population (0.86%) [13]. No data on cumulative incidence of metastatic disease was reported by the PLCO [11, 14].

Since the PLCO and ERSPC trials provide contradictory outcomes, at least a few differences in the study designs should be mentioned. First, the results of the PLCO trial are likely more influenced by contamination. In the PLCO trial, the level of contamination is well established, i.e. the rate of PSA testing was 40–52% and the rate of screening by DRE ranged from 41 to 46% in the control group [14]. In the ERSPC trial, the level of contamination by PSA testing in the control group was estimated to be in the order of 20–31% [15]. Another explanation for the contradictory results is the difference in the compliance with the screening protocol. In the PLCO trial, the average rate of compliance with biopsy recommendations was 40% and in the ERSPC trial it was 85.8% (range, 65.4–90.3) [14, 15].

Despite these fundamental differences, with one or more substantial methodological limitation in all RCTs, systematic reviews with meta-analyses have been carried out combining the outcomes of the ERSPC and PLCO trials, along with the outcomes with smaller population-based screening RCTs [16–19]. Consequently, these meta-analyses have been heavily criticized for their limitations by including trials with methodological shortcomings, differences in contamination, and duration of follow-up [20]. Table 22.4 provides the characteristics of the reviews and a summary of the prostate cancer and all-cause mortality risk estimates of the meta-analyses [16–19]. None of the reviews found a statistically significant reduction in prostate cancer mortality or all-cause mortality in the screened population compared with the control group. Two reviews determined the effect of length of follow-up on prostate cancer mortality. Lee et al. found no effect on prostate cancer mortality, whereas in the review by Lumen et al. a statistically significant relative

Table 22.4 Characteristics and outcomes from systematic reviews.

Study	Year	Review type	Time period	No. of studies included	RR (95% CI)		
					Prostate cancer mortality	All-cause mortality	Prostate cancer metastasis
Djulbegovic et al. [17]	2010	SR-MA	2005–2010	6	0.88 (0.71–1.09)	0.99 (0.97–1.02)	NR
Ilic et al. [16]	2013	SR-MA	Up to 2012	5	1.00 (0.86–1.17)	1.00 (0.96–1.03)	NR
Lee et al. [18]	2013	SR-MA	Since 2009	5	0.93 (0.81–1.07)	0.99 (0.98–1.01)	NR
Lumen et al. [19]	2011	SR-MA	Up to 2011	7	0.88 (0.72–1.06)	0.90 (0.75–1.08)	NR

CI, confidence interval; MA, meta-analysis; NR, not reported; prostate cancer metastasis, cumulative incidence prostate cancer metastasis; RR, relative risk; SR, systematic review.

Table 22.5 GRADE evidence profile for clinical question 1.

	No. of studies	Design	Limitations	Inconsistency	Imprecision	Other considerations	Quality
Prostate cancer mortality	9	RCT + SR	Serious	Serious	No	None	Moderate
All-cause mortality	7	RCT + SR	Serious	No	Serious	–[a]	Moderate
Prostate cancer metastases	1	RCT	No	No	No	None	Low
Quality of life	1	RCT	Serious	No	No	None	Low

SR, systematic review.

[a] All RCTs for prostate cancer screening were not powered to show a difference in all-cause mortality, neither were the systematic reviews.

reduction in prostate cancer was found when trials with less than 8 years' follow-up were excluded (RR 0.76; 95% CI 0.58–0.98) [18, 19]. Two reviews assessed the effects of the estimated overall risk of study bias in the RCTs on prostate cancer mortality and made an adjustment [16, 18]. Each RCT included in the systematic review was assessed for their risk of bias. Although in both studies the relative risk reduction increased in favor of the screening population, the difference in relative risk did not reach statistical significance. However, the three smaller RCTs [8–10] were assessed as posing a "high" risk of bias, whereas, surprisingly, the ERSPC and PLCO trials were both assessed as posing a "low" risk of bias, although the differences in terms of contamination and compliance are significant. Finally, data on the cumulative incidence of prostate cancer metastases data are lacking for adequate meta-analysis [16]. The resulting GRADE evidence profile is summarized in Table 22.5.

The main adverse effects of population-based screening are the risks related to false-positive results for the PSA test, the limited positive predictive value of PSA, prostate biopsy (e.g. bleeding, pain, urosepsis, short-term anxiety), overdiagnosis, and overtreatment. Overdiagnosis within the ERSPC was estimated to be 50% [21]. In a comprehensive overview by Loeb et al. [22], the estimated overdiagnosis by PSA-based screening ranged from 30 to 67%, depending on the method of assessment, resulting in a high risk of overtreatment with unavoidable side effects, which is a major adverse consequence of prostate cancer screening. Only the ERSPC trial provided data on the effects of screening on participants' quality-adjusted life. They used a simulation model based on their own data to project lifetime numbers of cancer diagnoses, treatments, deaths, and quality-adjusted life-years gained with population-based screening [23]. Annual screening between ages 55 and 69 years would result in a favorable balance of benefits (73 life-years gained), but with a 23% smaller gain in quality-adjusted life-years (56 years) due to the harms of, in particular, overdiagnosis and overtreatment [23]. Systematic reviews or meta-analyses on the effect of prostate cancer screening on the quality-adjusted life-years balance are not reported.

Clinical implications

We suggest against routine, population-based screening as an approach to reduce prostate cancer-specific mortality or overall mortality (weak recommendation against based on moderate-quality evidence). This recommendation is based the existing results from the systematic reviews and meta-analyses based on the evidence from the RCTs.

Prostate cancer mortality reductions differ by RCT, country, and screening program, with none of the meta-analyses demonstrating a statistically significant effect on the prostate cancer mortality. Nevertheless, the largest RCT for prostate cancer screening (ERSPC), with the highest quality of evidence, showed a statistically significant relative reduction in the prostate cancer mortality. Population-based prostate cancer screening has no effect on the all-cause mortality, although none of the RCTs were designed to show an effect on the overall mortality. Based on the data from the ERSPC

trial, prostate cancer screening decreases the cumulative risk of prostate cancer metastases. Based on the data from the ERSPC trial, annual population-based screening between ages 55 and 69 years would result in a favorable balance of quality of life.

Finally, population-based estimates of screening are difficult to translate to the individual. Prostate cancer screening has been shown to have effects on the prostate cancer-specific mortality, with individuals benefiting from early detection, although it always comes with a risk of overdiagnosis and overtreatment and impaired effects on quality of life. Therefore, at the individual level, some patients can benefit from early detection. For these patients, shared decision-making should be recommended with men well informed about the individual benefits and harms associated with screening and with individual patients' values and preferences as key factors for decision-making.

Clinical question 2

In asymptomatic men, does PSA screening result in prostate cancer detection at an earlier stage?

Literature search

We conducted a systematic search in PubMed–MEDLINE using the terms "prostate cancer" and "stage" with other relevant keywords "mass screening," "early detection," and "incidence." The search was limited to English-language RCTs and systematic reviews with meta-analyses published between January 2000 and December 2014.

The evidence

Seven trials (three RCTs and four systematic reviews; Table 22.6) met eligibility criteria and were included in the evidence profile (Table 22.7) [9, 11, 12, 14–19]. A statistically significantly higher detection rate for prostate cancers was reported for the screening group compared with the control group among all studies. A significant stage shift to a greater detection of stage 1 or localized prostate cancer stage was reported by six of the seven studies (Table 22.7). In the ERSPC trial, after comparing the intervention arm with the control arm, a statistically significant migration to more favorable stages (localized prostate cancer) was observed in the screening arm (RR 1.84; 95% CI 1.77–1.91), while a statistically significant reduction in the number of men with metastatic disease at diagnoses was shown (RR 0.50; 95% CI 0.41–0.62) [12, 13]. In the Ilic et al. review, the detection of localized prostate cancer, defined as T1, T2, N0, M0, was significantly increased in the screening group (RR 1.79; 95% CI 1.19–2.70), while the detection of advanced prostate cancer, defined as clinical stage T3, T4, N1, or M1, was significantly reduced in the screening group (RR 0.80; 95% CI 0.73–0.87) [16].

Clinical implications

We suggest population-based prostate screening to detect prostate cancer at an earlier disease stage, which may afford earlier, more effective treatment (weak recommendation for based on high-quality evidence). This recommendation is based on a substantial body of evidence that population-based prostate cancer screening causes a stage distribution to an earlier stage and helps to detect prostate cancer at an earlier stage. The distribution to a more favorable stage at diagnosis, however, is also associated with an increase in prostate cancer incidence, the risk of overtreatment, and potential adverse downstream effects.

Clinical question 3

In asymptomatic men undergoing PSA testing, has DRE additional value over PSA in the early detection of prostate cancer.

Literature search

We searched PubMed–MEDLINE using the terms "digital rectal examination" with other relevant keywords "prostate cancer," "screening," early detection," "PSA," "sensitivity," and "specificity." The search was limited to English-language clinical trials, randomized control trials, and systematic reviews with meta-analyses published between January 1995 and December 2014.

Table 22.6 Summary screening for prostate cancer on prostate cancer detection.

Study	RR (95% CI)		
	Prostate cancer detection	Localized prostate cancer	Advanced prostate cancer
ERSPC [12]	1.57 (1.51–1.62)	1.84 (1.77–1.91)	0.50 (0.41–0.62)
Nörrkoping study [9]	1.47 (1.11–1.86)	3.10 (2.17–4.43)	0.88 (0.62–1.24)
PLCO [11]	1.12 (1.07–1.17)	1.13 (1.08–1.18)	0.88 (0.71–1.09)
Djulbegovic et al. [17]	1.46 (1.21–1.77)	1.95 (1.22–3.13)	0.94 (0.85–1.04)
Ilic et al. [16]	1.30 (1.02–1.65)	1.79 (1.19–2.70)	0.80 (0.73–0.87)
Lee et al. [18]	1.13 (1.13–1.85)	1.67 (0.95–2.94)	0.94 (0.85–1.04)
Lumen et al. [19]	1.55 (1.17–2.06)	1.81 (1.15–2.86)	0.63 (0.38–1.05)

Table 22.7 Positive predictive value for prostate cancer detection, DRE for different PSA ranges.

Study	Method	Intervention	Participants	Outcomes	Results
Schröder et al. [27]	RCT	The usefulness of DRE as a stand-alone screening test and in conjunction with measured PSA ERSPC, Rotterdam section	*n*=10 523	The PPV and sensitivity of DRE	PSA: 0.0–0.9 PPV: 4% PSA: 1.0–1.9 PPV: 10% PSA: 2.0–2.9 PPV: 11% PSA: 3.0–3.9 PPV: 33% PSA: 4.0–9.9 PPV: 45% PSA: ≥10.0 PPV: 83%
Crawford et al. [26]	CT	Methods of prostate cancer early detection, PPV of PSA	*n*=31 953	Detection rates of prostate cancer relative to PSA range and findings on DRE	PSA: 0.0–4.0 PPV: 15% PSA: 4.1–9.9 PPV: 34% PSA: ≥10.0 PPV: 72%
Yamamoto et al. [25]	CT	Investigate the usefulness of DRE for prostate cancer diagnosis in subjects with PSA levels of ≤4.0 ng/mL	*n*=90	Detection rates of prostate cancer relative to PSA range and findings on DRE	PSA: 0.0–0.9 PPV: 4% PSA: 1.0–1.9 PPV: 0% PSA: 2.0–2.9 PPV: 19% PSA: 3.0–4.0 PPV: 44%
Bozeman et al. [28]	CT	Men with abnormal DRE findings and a PSA level <4.0 ng/mL who underwent prostate biopsy	*n*=986	PPV of DRE for PSA <4.0 ng/mL	PSA: 0.0–0.9 PPV: 2% PSA: 1.0–1.9 PPV: 6% PSA: 2.0–2.9 PPV: 13% PSA: 3.0–3.9 PPV: 21%
Andriole et al. [30]	RCT	Diagnostic evaluation of DRE as initial screening test	*n*=34 115	Detection rates of prostate cancer relative to PSA range and findings on DRE	PSA: 0.0–4.0 PPV: 17% PSA: 4.1–7.0 PPV: 47% PSA: ≥10.0 PPV: 90%
Okotie et al. [31]	CT	Examine clinical and pathological features of men with prostate cancer detected by DRE alone, PSA level ≤4.0 ng/mL	*n*=36000	Cancer detection PSA level ≤4.0 ng/mL with suspicious DRE in relation to Gleason score	303 men were diagnosed with prostate cancer by DRE alone 60 (20%) were non-organ confined and 56 (20%) had a Gleason score ≥7
Gosselaar et al. [29]	RCT	Two populations, PSA 2.0–3.9 ng/mL, were studied. Group 1 was biopsied if DRE was suspicious. In group 2, all men were offered biopsy, regardless of DRE result. ERSPC, Rotterdam section	Group 1, *n*=1877 Group 2, *n*=801	Cancer detection rates and tumor characteristics	Group 1: abnormal DRE prompted biopsy in 253 (13.5%) men, (236 (93.3%) actually biopsied). 49 prostate cancers detected, CDR 49/1877=2.6% Group 2: 120 cancers in 666 (83.1%) men actually biopsied, CDR=120/801=15.0%. Of all prostate cancers, 46.9% in group 1 and 15.0% in group 2 had biopsy Gleason score ≥7

CT, clinical trial; CDR, cancer detection rate; DRE, digital rectal examination; PPV, positive predictive value; PSA, prostate-specific antigen; RCT, randomized controlled trial.

The evidence

Although DRE is still widely used for the diagnosis of prostate cancer, its central role is superseded by the widespread application of serum PSA. DRE is possible owing to the anatomical position of the prostate in the pelvis, with easy access for palpation using a finger placed per rectum. In screening and early detection programs for prostate cancer, the value of DRE remains controversial because it is not standardized and varies widely among physicians [24]. Table 22.7 provides an overview of the positive predictive value (PPV) for DRE in different PSA ranges [25–31]. DRE has a low sensitivity and predictive value in men with low PSA levels where it should be most useful. At serum PSA levels below 3.0 ng/mL, 289 rectal examinations are required to find one case of clinically significant disease, and 96 rectal examinations are needed to diagnose prostate cancer of any size, grade, or stage [32]. Although an abnormal DRE should no longer be an independent indicator for biopsy in low PSA ranges, Okotie et al. found that a substantial proportion of cancers detected by DRE alone at PSA levels <4.0 ng/mL have clinically aggressive features; nearly 20% had a Gleason score ≥7 [31]. Furthermore, Gosselaar et al. pointed out that potentially aggressive cancers (Gleason score ≥7) are more prevalent among men who have an abnormal DRE compared with normal DRE at PSA levels ≥3.0 ng/mL [29]. Okotie et al. suggested that omission of DRE from screening protocols might

compromise treatment outcomes because many of the cancers detected by DRE alone are potentially curable but may have worse outcomes by the time PSA also reaches a higher level [31]. However, Okotie et al. conducted a univariate analysis for suspected DRE only and not a multivariate analysis with consideration of PSA. Consequently, the additional value of DRE over PSA would be small, since Thompson et al. showed that 15% of men with PSA ≤4.0 ng/mL had cancer on biopsy [33].

Clinical implications

We recommend against DRE as a primary screening tool for prostate cancer (strong recommendation based on moderate-quality evidence). This recommendation considers the much better performance characteristics of increasing levels of serum PSA in detecting prostate cancer. Suspect DRE in patients with a PSA level <2 ng/mL has a PPV of 2–10% and in patients with a PSA level <4 ng/mL a PPV of 2–21%. Therefore, DRE is not recommended as a primary screening tool since it may result in an unfavorable number of biopsies to detect one cancer in low PSA ranges.

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23 CHAPTER 23

Molecular markers for prostate cancer

Pranav Sharma[1], Eric Webb[2], and Julio M. Pow-Sang[2]

[1] *Department of Urology, Texas Tech University Health, Sciences Center, Lubbock, TX, USA*

[2] *Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL, USA*

Introduction

Although prostate-specific antigen (PSA) and its derived components (i.e. age-adjusted PSA, percent free PSA, PSA doubling time, PSA velocity, PSA density) may provide useful diagnostic and prognostic information with regard to prostate cancer (PCa) [1], a more personalized approach is needed to define better men at higher risk of developing this disease, differentiate indolent from aggressive disease, and improve risk stratification after treatment by predicting the likelihood of disease recurrence and/or progression. Since no reliable screening tool exists that can consistently differentiate indolent versus potentially life-threatening disease, an individualized, patient-centered approach may improve diagnostic and prognostic criteria for PCa and minimize the risk of unnecessary treatment and any associated impairment in quality of life [2].

Improvements in technology aimed at the genetic analysis of tumor tissue (based on either prostate biopsy specimens or radical prostatectomy [RP] specimens) have led to the discovery of an abundance of new genomic molecular markers that may be utilized in the prediction of PCa incidence, outcomes, and response to therapy [3]. The characterization of genetic mutations in tumor tissue through advanced genomic technologies, such as microarray analyses and next-generation sequencing, can subsequently create personalized roadmaps to guide clinical decision-making due to a better understanding of a patient's risk of PCa development and disease aggressiveness [4].

Background

PCa screening is still controversial since early detection can lead to the overdiagnosis and overtreatment of clinically insignificant disease, with long-term effects on patient quality of life with no added benefit in survival [5, 6]. The most common current screening test for PCa is a measurement of the serum concentration of PSA and digital rectal examination (DRE). There is currently, however, no single cut-off value for PSA that can accurately distinguish patients with PCa from those without [7]. Additionally, there has been considerable uncertainty about using PSA velocity or other PSA kinetics for decisions about prostate biopsy for diagnosis, since changes are related to cancer growth rates only partially owing to both malignant and nonmalignant processes contributing to PSA fluctuations [8]. Data from the REDUCE and the PCPT trial also clearly indicate that changes in PSA are unable to predict the risk of a repeat positive biopsy after initially negative findings and would lead to many additional biopsies per year without a corresponding increase in the number of high-grade cancers [9, 10]. Since current screening cannot consistently differentiate indolent from potentially life-threatening disease or identify adverse pathological features, molecular markers may serve as a useful adjunct or alternative diagnostic tool in PCa detection.

We present four clinical questions regarding the use of prostate biomarkers in current practice. A summary of the evidence behind the use of various molecular markers for each relevant question is given in Table 23.1.

Clinical question 1

In men with borderline elevation of PSA and no previous prostate biopsy, do molecular markers decrease the rate of unnecessary biopsies and improve the detection of clinically significant prostate cancer?

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Table 23.1 Evidence for molecular markers in prostate cancer.

Clinical question	Distribution of studies				
	Systematic review	Meta-analysis	Internal validation	External validation	Other
In men with borderline elevation of PSA and no previous prostate biopsy, do molecular markers decrease the rate of unnecessary biopsies and improve the detection of clinically significant prostate cancer?	PCA3: 5 PHI: 3	4K: 1 PCA3: 5	PCA3: 6 PHI: 3 4K: 7	PCA3: 1 PHI: 1	PHI vs. 4K: 1 PHI vs. PCA3: 6 4K vs. PCA3: 1 PCA (prospective): 1 PCA3: 4
In men with negative prostate biopsies and elevating PSA, do molecular markers assist in determining whether to forgo re-biopsy?	PCA3: 1 PHI: 1	PCA3: 2	PCA3: 4 ConfirmDx: 4	4K: 1	PHI vs. PCA3: 1 PCA3: 3 ConfirmMDX (cost–benefit study): 1
In men with newly diagnosed, localized prostate cancer, do molecular markers improve risk stratification?	2	Prolaris: 1	Oncotype Dx: 3 Prolaris: 4 4K: 1	None	None
In men post-radical prostatectomy with positive surgical margins, do molecular markers help determine if to forgo adjuvant radiation therapy and rather proceed with close observation?	2		Decipher: 8 Prolaris: 1	None	None

4K, 4-kallikrein.

Table 23.2 PCA3 meta-analysis.

Ref.	No. of studies	No. of patients	Summary	Quality
Yong et al. 2014	24	8275	Cutoff for PCA3: 35 Pooled Sn: 59%; Sp: 72% LR+ 2.388; LR– 0.51 AUC=0.74 Diagnostic OR=4.89	QUADA score: moderate
Hu et al. 2014	16	6130	Cutoff for PCA3: 35 Pooled Sn: 57%; Sp: 71% LR+ 2.12; LR– 0.55 AUC=0.71 Diagnostic OR=3.93	QUADAS score: moderate

AUC, area under the curve; LR, likelihood ratio; Sn, sensitivity; Sp, specificity.

Literature search

We performed a PubMed search using the terms "prostate biomarkers" or "prostate molecular markers" and other relevant keywords (prostate cancer, diagnosis, prognosis, clinically significant, cohort studies, trials). We limited the searches to English-language articles published between January 1995 and June 2015. Non-English-language studies were excluded, because their quality was difficult to evaluate.

The evidence

There are data to suggest that expression of a noncoding RNA in the urine and prostatic fluid, called prostate cancer antigen 3 (PCA3), can increase the probability of a positive repeat prostate biopsy in men with one or two prior negative biopsies [11]. A summary of the meta-analysis available for PCA3 is shown in Table 23.2. PCA3 is specific to PCa cells, shown to be highly overexpressed in 95% of PCa cases compared with benign prostatic tissue [12]. A PCA3 score of >35 in the urine correlates with an average sensitivity and specificity of 60% and 70%, respectively, for the diagnosis of PCa [13]. Lower cut-off scores have been used (>20) with higher sensitivities but lower specificities. A summary of PCA3 effectiveness in PCa detection using various cut-off points is given in Table 23.3. PCA3, therefore, may play a complementary role to PSA alone in PCa screening for PCa detection. This has also been validated in prospective, multicenter clinical studies [14]. Head-to-head studies of PCA3 versus traditional screening tools have additionally shown superior outcomes compared with PSA alone (Table 23.4).

Table 23.3 PCA3 effectiveness in prostate cancer detection.

Study	No. of patients	Mean PSA	Sn (%)	Sp (%)	PPV	NPV	Diagnostic OR
PCA3 > 20							
Pepe+Aragona et al. 2013	100	7.9	92.9	16.7	30.2	85.7	2.8
Wu et al. 2012	103	11	67	64	52	78	3.45
Pepe et al. 2012	118	8.5	90.6	27.9	31.9	88.9	3.74
Bollito et al. 2012	509	6.7	88.2	44.3	40.7	89.6	5.73
Barbera et al. 2012	177	9.5	91.7	25.6	31.5	89.5	3.78
Auprich et al. 2012	127	16	85	25.3	38	77.8	1.32
Pepe+Aragona et al. 2011	74	8.9	92.6	21.6	43.1	88.9	5.3
Remzi et al. 2010	463	7.2	73.4	50.7	36.3	83.3	2.85
Aubin et al. 2010	1072	ND	70.5	56.9	26.1	89.9	3.16
Haese et al. 2008	463	7.0	73.4	50.7	36.3	83.3	2.85
PCA3 > 35							
Pepe+Aragona et al. 2013	100	7.9	78.6	23.6	28.6	73.9	–
Goode et al. 2013	167	4.8	42	71	15.7	90.5	–
Wu et al. 2012	103	11	38	77	50	66	–
Pepe et al. 2012	118	8.5	71.9	41.8	31.5	80	–
Bollito et al. 2012	509	6.7	75.2	69.8	52	86.7	–
Barbera et al. 2012	177	9.5	73	41.8	35	80.6	–
Auprich et al. 2012	127	16	75	57.8	48.5	81.4	–
Pepe+Aragona et al. 2011	74	8.9	70.4	43.5	42.2	71.5	–
Remzi et al. 2010	463	7.2	46.9	71.9	38.9	77.9	–
Aubin et al. 2010	1072	ND	48.4	78.6	32.6	87.6	–
Haese et al. 2008	463	7.0	47	72	39	78	–

NPV, negative predictive value; PPV, positive predictive value; OR, odds ratio.

Table 23.4 PCA3 versus PSA studies.

Study	No. of patients	% Initial Bx	AUC PCA3	AUC PSA	Difference
Adam et al. 2011	105	82	0.71	0.84	–0.14
Nyberg et al. 2010	62	55	0.74	0.80	–0.05
Aubin et al. 2010	1072	0	0.64	0.61	0.03
Roobol et al. 2010	721	71	0.64	0.58	0.05
Ankerst et al. 2008	215	74	0.66	0.60	0.06
Rigau et al. 2010	336	–	0.72	0.65	0.06
Hessels et al. 2010	336	–	0.72	0.65	0.07
Wu et al. 2012	103	0	0.64	0.57	0.07
Ouyang et al. 2009	92	–	0.67	0.59	0.08
Bollito et al. 2012	1246	59	0.68	0.59	0.09
Mearini et al. 2009	96	–	0.81	0.70	0.12
Ochiai et al. 2011	105	81	0.85	0.72	0.13
Ploussard et al. 2010	301	0	0.69	0.55	0.14
Auprich et al. 2011	127	0	0.70	0.57	0.14
Cao et al. 2011	131	–	0.74	0.57	0.17
De la Taille et al. 2011	516	100	0.76	0.58	0.18
Perdona et al. 2011	218	61	0.83	0.64	0.19
Schilling et al. 2010	32	56	0.81	0.61	0.20
Goode et al. 2012	456	63	0.73	0.51	0.22
Deras et al. 2008	557	50	0.69	0.55	0.14
Chun et al. 2009	809	29	0.68	0.53	0.15
Marks et al. 2007	226	0	0.68	0.52	0.16
Haese et al. 2008	463	0	0.66	0.60	0.06

Bx, biopsy.

In addition to predicting PCa diagnosis, PCA3 has been shown to correlate with PCa tumor volume and extracapsular extension in RP specimens and disease aggressiveness [15]. The median and mean PCA3 scores have been shown to be significantly lower in men with biopsy Gleason score <7 vs. ≥7, with clinical stage T1c vs. T2a–T2c and T3a cancers, with ≤33 vs. >33% positive biopsy cores and with "biopsy indolent" vs. "biopsy significant" PCa based on the Epstein criteria [16].

As a component of free PSA, [–2]proPSA is more specific for PCa than either total or free PSA alone [17, 18]. The Beckman Coulter Prostate Health Index (PHI) combines total, free, and [–2]proPSA into a single score, which has been shown to improve PCa detection [19]. A summary of PHI effectiveness in PCa detection is given in Tables 23.5 and 23.6. Catalona et al. evaluated the PHI in a prospective, multi-institutional trial of 892 men with a PSA between 2 and 10 ng/mL and a negative DRE [20]. The predictive ability of PHI to diagnose PCa exceeded that of serum PSA alone, free PSA, percent free PSA, or p2PSA (the primary form in PCa tissue) [20]. PHI also performed better than percent free PSA in its ability to discriminate PCa with a Gleason score (GS) of >4 + 3 = 7 versus lower grade PCa or benign histology [20]. These results have similarly been reproduced in other cohort studies where PHI improved prostate cancer detection at initial biopsy in a total PSA range of 2–10 ng/mL [21]. Loeb et al. also externally validated the PHI in a multicenter prospective trial of 658 men aged >50 years with a PSA of 4–10 ng/mL and normal DRE who underwent prostate biopsy [22]. Based on Epstein criteria, the PHI was able to detect clinically significant disease with more accuracy than percent free PSA, [–2]proPSA, or PSA alone, implicating its use in reducing unnecessary prostate biopsies and the overdiagnosis of indolent disease [22]. A summary of PHI effectiveness in PCa prognosis is given in Table 23.7.

PHI has shown improved PCa detection rates compared with %p2PSA (Table 23.8). Additionally, in a head-to-head comparison of PHI and urinary PCA3 for predicting PCa at initial or repeat biopsy, PHI was more accurate than PCA3 for predicting PCa in the initial biopsy setting and in the repeat biopsy setting, although no statistically significant difference was observed [23]. Although both PHI and PCA3 provided a significant increase in the sensitivity and specificity for PCa detection compared with all other markers examined, PCA3

Table 23.5 PHI effectiveness in prostate cancer detection.

Study	Design	No. of patients	Sn (%)	Sp (%)	PPV	NPV
Ferro et al. 2013	Single center, prospective	300	74	70	58	83
Guazzoni et al. 2011	Single center, prospective	268	43	90	74	70
Jansen et al. 2010	Retrospective	Site 1: 405	35	90	81	52
		Site 2: 351	31	90	75	57
Lazzeri et al. 2013	Multicenter, prospective	646	63	62	54	71
Le et al. 2010	Single center, prospective	63	88	65	64	89
Loeb et al. 2013	Multicenter, prospective	706	90	30	57	74
Ng et al. 2013	Single center, retrospective	230	90	50	15	98

Table 23.6 PHI effectiveness in prostate cancer detection 2.

Study	Design	No. of patients	PHI AUC	PSA AUC	% free PSA AUC
Catalona et al. 2011	Multicenter, prospective	892	0.703	0.525	0.648
Guazzoni et al. 2011	Prospective	268	0.76	0.53	0.58
Houlgatte et al. 2011	Retrospective	452	0.73	0.56	0.59
Jansen et al. 2010	Retrospective	Site 1: 405	0.716	0.585	0.675
		Site 2: 351	0.695	0.534	0.576
Le et al. 2010	Prospective	63	0.77	0.50	0.68
Sokoll et al. 2010	Multicenter, prospective	429	0.76	0.58	0.66
Stephan et al. 2009	Retrospective	475	0.78	0.56	0.77
Sokoll et al. 2009	Multicenter, retrospective	89	0.73	0.52	0.53
Lazzeri et al. 2013	Multicenter, retrospective	158	0.733	0.549	0.60
Lughezzani et al. 2012	Prospective	729	0.70	0.51	0.62
Lughezzani et al. 2013	Multicenter, prospective	833	0.68	0.51	0.64
Ng et al. 2013	Retrospective	230	0.781	0.547	0.654

Table 23.7 PHI effectiveness in prostate cancer prognosis.

Study	No. of patients	Results
Lazzeri et al. 2012	222	At PHI of 28.8, 52% of Bx could be avoided
Lazzeri et al. 2013	646	At PHI of 27.6, 15.5% of Bx could be avoided
Stephan et al. 2013	1362	The proportion of aggressive PCa increased with rising PHI
Ito et al. 2013	239	Sensitivity at 95%, unnecessary Bx avoided in 28%
Ng et al. 2013	230	Sensitivity at 90%, unnecessary Bx avoided in 45.2%
Lughezzani et al. 2012	729	PHI increased AUC from 0.73 to 0.80

Table 23.8 PHI vs. % p2PSA studies.

Variable	No. of studies	Sn (%)	Sp (%)	Diagnostic OR	AUC
PHI	5	90	17	3.06	0.67
% p2PSA	4	96	9	3.77	0.54

did not increase the accuracy of predicting PCa when PHI was assessed [23]. A summary of PCA3 versus PHI studies is given in Table 23.9.

Another promising serum-based molecular marker is the kallikrein panel, which consists of total PSA, free PSA, intact PSA, and human kallikrein-related peptidase 2 (KLK2) [24]. A 4-kallikrein panel was able to predict PCa in men who had a recent screening history and provided independent confirmation that multiple kallikrein forms contribute important diagnostic information for men with elevated PSA [25]. A summary of the kallikrein panel effectiveness in PCa detection is given in Tables 23.10 and 23.11. This prostate 4-kallikrein panel was shown by Vickers et al. to improve the predictive accuracy of PCa detection over PSA alone with a reduction in the biopsy rate by 362 for every 1000 men with an elevated PSA [26]. Similar results have been seen in externally validated populations in France, Sweden, and the Netherlands with an improvement in the detection of high-grade cancers [27–29]. On comparing the 4-kallikrein panel with the PHI, both similarly improved discrimination when predicting both PCa and high-grade PCa, reducing the number of unnecessary biopsies compared with PSA alone [30]. A summary of kallikrein panel comparative studies is shown in Table 23.12. The 4-kallikrein panel has also been

Table 23.9 PCA3 vs. PHI studies.

Study	Design	No. of patients	AUC PCA3	AUC PHI	Results
Ferro et al. 2012	Prospective	251	0.71	0.77	No difference; PCA3 able to detect HGPIN
Perdona et al. 2011	Prospective	290	0.66	0.71	No difference; AUC increased to 0.77 in combination
Ferro et al. 2013	Prospective	300	0.71	0.77	No difference; AS patients had low PHI and PCA3
Seisen et al. 2015	Prospective	138	Overall PCa: 0.71 Significant PCa: 0.55	Overall PCa: 0.65 Significant PCa: 0.80	PHI better at predicting significant PCa (Epstein criteria)
Scattoni et al. 2013	Prospective	Initial Bx=116 Repeat Bx=95	Overall PCa: 0.57 Significant PCa: 0.63	Overall PCa: 0.69 Significant PCa: 0.72	No difference; PHI improved predictive accuracy whereas PCA3 did not

AS, active surveillance; HGPIN, high-grade prostatic intraepithelial neoplasia.

Table 23.10 Kallikrein panel effectiveness in prostate cancer detection.

Study	Design	AUC difference vs. laboratory model (overall PCa)	AUC difference vs. laboratory model (significant PCa)	AUC difference vs. clinical model (overall PCa)	AUC difference vs. clinical model (significant PCa)
4 K panel vs. base models					
Vickers et al. 2008	RCT (n=740)	0.15	0.11	0.05	0.04
Vickers et al. 2010	RCT (n=2914)	0.13	0.05	0.08	0.03
Vickers et al. 2010	RCT (n=1501)	0.16	0.12	0.13	0.09
Vickers et al. 2010	RCT (n=1241)	0.11	0.16	0.08	0.11
Gupta et al. 2010	RCT (n=925)	–	–	0.10	0.11
Benchikh et al. 2010	RCT (n=262)	–	–	0.15	0.10
Vickers et al. 2011	CCS (n=792)	0.10	–	–	–

CCS, case–control study.

Table 23.11 Kallikrein panel effectiveness in prostate cancer detection 2.

Study	No. of false negatives vs. laboratory base	% reduction of biopsy vs. laboratory base	No. of false negative base vs. clinical model	% reduction of biopsy vs. clinical base
Vickers et al. 2008	4	57.3	1	59.9
Vicker et al. 2010	12	48.7	12	51.3
Vickers et al. 2010	4	29.8	4	36.2
Vickers et al. 2010	1	35.7	1	41.3
Gupta et al. 2010	–	–	3	81.7
Benchikh et al. 2010	–	–	12	49.2
Vickers et al. 2011	–	42.1	–	–

Table 23.12 Comparative 4-kallikrein studies.

Study	No. of patients	Design	AUC 4K	AUC PCA3/PHI	Results
4 K vs. PCA3					
Vedder et al. 2014	708	Bx performed if: PSA>3 or PCA3>10 (22% previous Bx)	Total population: 0.56 With elevated PSA: 0.78	*AUC PCA3* Total population: 0.65 With elevated PSA: 0.62	$p=0.05$ $p=0.01$
4 K vs. PHI					
Nordstrom et al. 2014	531	Cohort with PSA of 3–15	Total population: 0.69 High-grade PCa: 0.718	*AUC PHI* Total population: 0.704 With elevated PSA: 0.711	Both improved PCa detection

shown to enhance the prediction of lethal PCa associated with metastasis compared with PSA alone, providing an additional use as a screening tool for men with elevated PSA [31]. In patients with elevated PSA (>3 ng/mL), low percent free PSA, or suspicious DRE, the 4-kallikrein panel of kallikrein markers improved discrimination over age and PSA alone for high-grade cancer (GS >7), reducing the number of biopsies by 236 per 1000 to detect 195 of 208 high-grade cancers [29]. These results have been further confirmed in large prospective trials [32]. The above studies also provided proof of principle that predictions based on levels of 4-kallikrein markers in blood distinguish between pathologically insignificant and aggressive disease after RP with good accuracy. In the future, clinical use of the model could potentially reduce rates of immediate unnecessary active treatment.

Clinical implications

In men at risk for prostate cancer due to borderline elevation of PSA and no previous prostate biopsy, we suggest the use of molecular markers for improved risk stratification to guide clinical decision-making (conditional recommendation based on low-quality evidence). Although there is no direct, high-quality evidence that ties the use of these markers to improved outcomes when compared with individuals managed without use of these markers, there is indirect evidence in support of their value in this setting. At this time, there is insufficient evidence to recommend one molecular marker over another, the evidence may favor the 4-kallikrein panel of markers over PHI and over PCA3.

Clinical question 2

In men with prior negative prostate biopsies and rising PSA, do molecular markers assist in determining whether to forego re-biopsy?

Literature search

We performed a PubMed search using the terms "prostate biomarkers" or "prostate molecular markers" and other relevant keywords (prostate cancer, diagnosis, prognosis, clinically significant, negative biopsy, cohort studies, trials). We limited the searches to English-language articles published between January 1995 and June 2015. Non-English-language studies were excluded, because their quality was difficult to evaluate.

The evidence

DNA hypermethylation of CpG islands in the promoter regions of cancer-associated genes is another novel molecular marker in the early detection of PCa [33]. Since DNA hypermethylation of genes occurs early during carcinogenesis, it is ideally suited for PCa screening. Three of these methylation genes include glutathione *S*-transferase P (GSTP1), which is involved in DNA detoxification

[33], adenomatous polyposis coli (APC), which is involved in cell apoptosis, migration, and adhesions [34], and ras association domain-containing protein 1 (RSSF1), which is involved in cell cycle regulation [35]. GSTP1 is the most widely reported hypermethylated gene in PCa [36]. A meta-analysis concluded that GSTP1 methylation occurs in up to 90% of PCa cases whereas it is seen in only 5% of noncancerous controls [37]. Due to the concept of the epigenetic field effect in prostate oncogenesis, investigators have evaluated whether biopsy samples taken with negative pathology findings may produce a positive molecular result [38]. Genetic alterations, therefore, may occur in histopathologically nonmalignant tissue that is contiguous with early-stage cancer [39].

In the Methylation Analysis To Locate Occult Cancer (MATLOC) study, Stewart et al. determined the amount of methylation of GSTP1, APC, and RASSF1 to detect PCa in initially histopathologically negative prostate biopsy samples from men who subsequently underwent repeat biopsy [40]. This epigenetic assay resulted in a negative predictive value (NPV) of 90% (compared with 70% for histopathology alone), and it was an independent predictor of PCa detection up to 30 months before repeat biopsy [40]. In the follow-up DOCUMENT study, this epigenetic test was externally validated in 350 subjects with an initially negative prostate biopsy across five urological centers in the United States [41]. It resulted in an NPV of 88% and again was an independent predictor of PCa detection on multivariate analysis after correcting for age, PSA, DRE, histopathological characteristics on first biopsy, and race [41]. Negative findings of this assay, therefore, could be used to decrease concern about unsampled cancer and avoid unnecessary repeat prostate biopsies. A summary of the effectiveness of this epigenetic test (commercially available as ConfirmMDx [MDxHealth, Irvine, CA, USA]) to predict negative prostate biopsies is given in Table 23.13. The impact of this epigenetic test on repeat biopsy rates was recently surveyed at five centers and, among 138 patients with a negative assay, only six patients (4%) underwent repeat biopsy, decreasing the number of unnecessary procedures [42].

Clinical implications

In men with prior negative prostate biopsies and a rising PSA, we suggest the use of hypermethylation markers to risk stratify men and guide decision-making about repeat transrectal ultrasound-guided (TRUS) biopsies (conditional recommendation based on very low-quality evidence). Although there is no direct, high-quality evidence that ties the use of these markers to improved outcomes when compared with individuals managed without the use of these markers, there is indirect evidence in support of their value in this setting.

Clinical question 3

In men with newly diagnosed, localized prostate cancer, do molecular markers improve oncological outcomes?

Literature search

We performed a PubMed search using the terms "prostate biomarkers" or "prostate molecular markers" and other relevant keywords (localized prostate cancer, prognosis, clinically significant, high-risk, cohort studies, trials). We limited the searches to English-language articles published between January 1995 and June 2015. Non-English-language studies were excluded, because their quality was difficult to evaluate.

The evidence

Multiple genetic markers are often necessary to provide sufficient prognostic information for clinical decision-making versus any single genetic abnormality alone. Panels evaluating the differential expression of multiple genes are ideally created using knowledge of well-known carcinogenic pathways in PCa [43]. There is a risk of chance associations due to the large number of genetic mutations associated with prostate malignancy, but blinded marker analysis and external validation are essential before any clinical application to patients can be considered [44]. Additionally, the biomarkers in the panel have to provide additional independent predictive ability above and beyond standard clinical and pathological characteristics [45]. It is important to note that there are virtually no comparative studies evaluating any expression panels head-to-head in the same patient group. There is also a lack of prospective studies analyzing the effectiveness of these marker panels.

Klein et al. identified 17 genes through polymerase chain reaction (PCR) based on a collection of 441 RP specimens from low- and intermediate-risk patients [46]. These genes represented multiple biological pathways in PCa out of a candidate 732 genes. Upon further analysis, 288 genes predicted clinical recurrence and tumor multifocality, and 198

Table 23.13 Confirm MDx effectiveness in predicting negative prostate biopsies.

Study	No. of patients	Design	Sn (%)	Sp (%)	NPV	Results
Partin et al. 2014	320	Multicenter validation CCS	62	64	88	OR: 2.69
Stewart et al. 2012	498	Retrospective cohort	68	64	90	OR: 3.17

genes were predictive of disease aggressiveness after adjustments for PSA, GS, and clinical stage [46]. The utility of the 17-gene expression panel was further confirmed in 167 pre-RP prostate biopsy specimens to create a multi-gene, expression-based signature called the Genomic Prostate Score (GPS) [46]. This algorithm was subsequently internally validated in 395 prostate needle biopsies from contemporary patients who were candidates for active surveillance to determine its ability to predict clinical recurrence, PCa-related death, and adverse pathological features at the time of RP [46]. In this validation study, GPS predicted high-grade (Gleason >4+3) and high-stage (pT3 or higher) disease on RP specimens after controlling for established clinical and pathological factors (age, PSA, clinical stage, biopsy GS) [46]. This predictive ability remained after inclusion of a clinical risk model (i.e. Cancer of the Prostate Risk Assessment post-Surgical [CAPRA-S]) [46]. A summary of the GPS (commercially available as the Oncotype DX test [Genomic Health, Redwood City, CA, USA]) effectiveness in PCa prognosis is given in Table 23.14.

This test was subsequently externally validated by Cullen et al. in 431 prostate biopsies from men with very low-, low-, or intermediate-risk PCa based on National Comprehensive Cancer Network (NCCN) guidelines [47]. GPSs were correlated with biochemical recurrence (BCR), adverse RP pathology (primary Gleason pattern 4 or any pattern 5, pT3 disease), and metastatic recurrence [47]. GPS did not vary across race, and it was an independent predictor of BCR, time to metastases, and adverse pathology after adjusting for the NCCN risk group [47]. This 17-marker genetic panel performed on a patient's original prostate needle biopsy tissue, therefore, may predict PCa aggressiveness and help men make decisions regarding immediate active treatment versus surveillance.

Clinical implications

In men with newly diagnosed, localized prostate cancer, we suggest the use of molecular markers to improve risk stratification and improve outcomes (conditional recommendation based on very low-quality evidence). Although there is no direct, high-quality evidence that directly ties the use of these markers to improved outcomes when compared with individuals managed without the use of these markers, this recommendation is based on the indirect evidence that improved risk stratification will better guide treatment, which should lead to better outcomes.

Clinical question 4

In men post-radical prostatectomy with positive surgical margins, does the use of molecular markers improve outcomes?

Literature search

We performed a PubMed search using the terms "prostate biomarkers" or "prostate molecular markers" and other relevant keywords (radical prostatectomy, prognosis, surgical margins, cohort studies, trials). We limited the searches to English-language articles published between January 1995 and June 2015. Non-English-language studies were excluded, because their quality was difficult to evaluate.

The evidence

A group of genetic markers have also been created to predict PCa prognosis and risk of disease recurrence and/or progression after surgical treatment based on RP specimens. Cuzick et al. identified a 46-gene expression model using 31 cell-cycle progression (CCP) genes and 15 housekeeping genes via quantitative PCR on RNA extracted from PCa tumor samples from the RP specimens [43]. This CCP score was subsequently evaluated retrospectively in a cohort of patients after RP and transurethral resection of the prostate (TURP) managed conservatively [43]. The primary endpoint was BCR in the RP group and overall survival (OS) in the TURP group [43]. The CCP score was an independent predictor of BCR for RP patients, and it was also strongly associated with time to death from PCa for TURP patients [43]. The

Table 23.14 Oncotype DX genetic panel effectiveness in prostate cancer prognosis.

Study	Design	Endpoint	Mean follow-up (years)	Results
Klein et al. 2014	Prospective, retrospective evaluation: 1 RP (n=441) 2 Bx (n=167) 3 Validation (n=395)	MFS (1); Adverse RP pathology (2, 3)	5.2	GPS score predictive of adverse RP pathology (high-grade: OR=2.3; high stage: OR=1.9)
Cullen et al. 2014	Prospective, retrospective evaluation (n=431)	Adverse RP pathology, BCR	5.2	GPS score predictive of BCR (HR=2.9), metastasis (HR=3.8), adverse pathology (OR=3.3)

BCR, biochemical recurrence; HR, hazard ratio; MFS, metastasis-free survival.

Table 23.15 Prolaris genetic panel effectiveness in prostate cancer prognosis.

Study	Design	Endpoint	Mean follow-up (years)	Results
Cuzick + Swanson et al. 2011	Retrospective, observational (n=366 [RP]; n=337 [TURP])	BCR, DSS	9.4	CCP score predictive for BCR (in RP pts) (HR=1.74) or PCa mortality (TURP) (HR=2.82)
Cooperberg + Simko et al. 2013	Prospective, retrospective evaluation (n=413 and 353, respectively)	BCR	7.1	CCP score predictive of BCR (HR=2.1); combined CAPRA-S and CCP scores were more predictive than each individually
Bishoff et al. 2014	Retrospective observational cohort: 1 (n=283) 2 (n=176) 3 (n=123)	BCR, MFS	5.1 (1) 7.3 (2) 11.0 (3)	CCP score predictive of BCR (HR=1.6) and MFS (HR=5.35)
Cuzick + Berney et al. 2012	Retrospective observational cohort (n=349)	DSS	11.8	CCP score predictive of DSS (HR=2.02)
Freeland et al. 2013	n=141 (s/p XRT)	BCR, DSS	4.8	CCP score predictive of BCR (HR=2.55)
Cuzick, Stone et al. 2015	Retrospective observational cohort (n=585)	DSM	9.52	CCP score predictive of DSM (HR=1.76)

DSM, disease-specific mortality; DSS, disease-specific survival.

CCP score was also found to be a stronger prognostic factor than any other measured variable, including PSA, tumor stage, and Gleason score [43]. A summary of the effectiveness of the CCP score (commercially available as the Prolaris test [Myriad Genetics, Salt Lake City, UT, USA]) in PCa prognosis is shown in Table 23.15.

This genetic panel and the CCP score were subsequently externally validated using biopsy and TURP specimens in 349 patients managed conservatively with the primary endpoint being PCa-specific mortality [48]. The CCP score was again independently associated with PCa-related death after adjusting for known risk factors [48]. This test has also been externally validated in RP studies. Cooperberg et al. analyzed 413 men who underwent RP and determined whether the CCP score analyzed on RP tissue could predict BCR defined as two consecutive PSA levels >0.2 ng/mL [49]. The CCP score was also assessed as an independent prognostic factor beyond standard postoperative risk assessment instruments such as the CAPRA-S score [50], which uses pathological data from RP to predict PCa recurrence and mortality and has been externally validated in over 2500 men across multiple institutions [51]. CCP score was independently predictive of BCR after RP after adjusting for the CAPRA-S score [50]. CCP score also was able to sub-stratify patients with low clinical risk, defined by a CAPRA-S score <2 [50]. Combining the CCP score and CAPRA-S score improved the concordance index for both the overall cohort and the low-risk subset, suggesting that the combined score outperformed both individual scores in clinical decision-making as a predictor of disease aggressiveness [50].

Bishoff et al. also evaluated the CCP score as a predictor of BCR and metastatic disease based on pre-RP biopsy tissue in 582 men treated with RP for clinical localized PCa [52]. CCP score was the strongest predictor of BCR, and it was also the strongest predictor of metastatic disease after adjusting for other clinical variables [52]. Freedland et al. tested the prognostic utility of this genetic panel to predict BCR using pretreatment diagnostic prostate biopsy specimens in 141 PCa patients treated with external beam radiation therapy (EBRT) as their primary curative therapy [53]. BCR was defined using the Phoenix definition, and half of the cohort was African American [53]. The BCR rate was 13% (n=19), and the CCP score significantly predicted BCR after accounting for GS, PSA, percent positive cores, and use of androgen deprivation therapy.The CCP score also was associated with PCa-specific mortality at 10 years [53].

Alternatively, other genetic panels have been developed to serve a similar purpose. Erho et al. presented a case–control study that analyzed a 22-gene expression signature in men with early clinical metastasis after a postoperative rising PSA to predict survival after RP [54]. This 22-gene panel was based on the primary tumor in the RP specimen, and it was the only significant prognostic factor for early metastasis and PCa-specific death. It also had a good correlation with disease-specific survival (DSS) on internal validation analysis [54]. Patients with higher genomic classifier (GC) scores experienced earlier death from PCa and reduced OS, suggesting its use as an identifier of aggressive prostatic malignancy after treatment. A summary of the effectiveness of the GC score (commercially available as the Decipher test [GenomeDX Biosciences, Vancouver, BC, Canada]) in PCa prognosis is given in Table 23.16.

This 22-gene panel has been externally validated in multiple studies. Cooperberg et al. compared the CAPRA-S score

Table 23.16 Decipher genetic panel effectiveness in prostate cancer prognosis.

Study	Design	Endpoint	Mean follow-up (years)	Results
Erho et al. 2013	CCS (n=639)	Metastatic PFS	16.9	AUC=0.75 for prediction of metastasis (improved over PSA and GS)
Cooperberg et al. 2015	CCS (n=185) (high-risk pts)	CSM	6.4	CAPRA-S and GC scores predict PCa mortality; combined low scores predict low CSM even after adjuvant therapy adjustment
Ross et al. 2015	CCS (n=85)	MFS	–	GC score more predictive than clinical nomograms of MFS (AUC=0.82 vs. GS=0.62 vs. PSADT=0.69)
Karnes et al. 2013	Case cohort, prospective (n=219) (high-risk RP pts)	MFS	6.7	GC AUC=0.79 vs. GS=0.64 vs. ECE=0.65; GC able to stratify lower risk Gleason 7+8 PCa
Den et al. 2014	CCS (n=139) (Radiation pts post-RP)	BCR, MFS	7.4	GC score predictive of BCR and MFS; added value when GC combined with clinical model (AUC=0.78/0.80 vs. AUC=0.70/0.70, respectively)
Klein et al. 2014	Case cohort, prospective (n=169) (high-risk RP pts)	MFS	7.8	GC score most predictive of rapid metastasis (OR 1.48); GC score concordance=0.77 vs. Stephenson model=0.75 vs. CAPRA-S=0.72
Ross et al. 2015	Case cohort, prospective (n=260) (intermediate- and high-risk RP pts)	MFS	10	GC score prognostic of MFS (HR 1.26); risk of metastasis for low/high GC scores=12 and 47%

CSM, cancer-specific mortality; GC, genomic classifier; PSADT, PSA doubling time.

and the GC score as a predictor of PCa-specific mortality in 185 men at high risk for recurrence (PSA >20, GS >8, stage pT3b) after RP [55]. In this population, 25 patients experienced PCa-associated death [55]. The GC score had a higher concordance with CSS and OS than the CAPRA-S score, and it reclassified many men stratified to high-risk based on the CAPRA-S score >6 [55]. Both high CAPRA-S and GC scores were independently predictive of PCa-specific mortality, with a cumulative incidence of PCa-related death of 45% at 10 years [55]. This suggests that integration of genomic and clinical risk factors may permit better identification of post-RP patients at high risk for death who should be considered for more aggressive secondary therapies, such as adjuvant radiation therapy (XRT), and other clinical trials.

Karnes et al. also evaluated 219 men at high risk of recurrence (PSA >20, GS >8, stage pT3b) with the GC score based on the genomic information from the primary tumor in the RP specimen [56]. The ability of the GC score to predict 5-year metastasis after RP exceeded that of any other clinical models. The GC score was also the predominant predictor of metastasis 5 years after RP with a cumulative incidence of 2.4, 6.0, and 22.5% in patients with low, intermediate, and high scores, respectively.

In another study, 85 clinically high-risk RP patients who developed BCR after surgery were analyzed using the GC score as a predictor of metastatic disease progression [57]. The GC score was superior at predicting metastasis after BCR compared with Gleason score, PSA doubling time, and time to BCR. It was the only variable associated with metastatic progression, and it performed superiorly to models based solely on clinicopathological features (i.e. CAPRA-S).

Finally, studies have also evaluated the utility of the GC score to predict which men would benefit from adjuvant XRT therapy and to forecast outcomes after postoperative XRT following RP. Den et al. calculated GC scores from the primary RP tumor specimens of 188 patients with pT3 or margin-positive PCa after RP who received post-RP XRT [58]. The primary endpoint was clinical metastasis, and the prognostic accuracy of the GC score was compared with other routine clinical and pathological features [58]. The GC score and pre-RP PSA were both independent predictors of metastasis with a cumulative incidence at 5 years of 0%, 9%, and 29% for low, average, and high GC scores [58]. For patients with low GC scores, there was no difference in the cumulative incidence of metastasis comparing patients who received adjuvant vs. salvage XRT, but for patients with high GC scores, the cumulative incidence of metastasis at 5 years was significantly lower in patients who received adjuvant vs. salvage XRT (6% vs. 23%) [58]. These findings suggest that patients with high GC scores may benefit from adjuvant XRT while patients with low GC scores are best treated with salvage XRT.

This same group also reported on the ability of the GC score to predict BCR and distant metastasis in men receiving

XRT after RP [59]. The authors evaluated 139 PCa patients with pT3 or positive margins after RP who received postoperative XRT (both adjuvant and salvage) and found that the addition of the GC score improved the ability of a clinical model (i.e. Stephenson model) as a predictor of BCR and distant metastasis [59]. Higher GC scores were independent predictors of BCR and distant metastasis with a cumulative incidence of 21, 48, and 81% for BCR and 0, 12, and 17% for distant metastasis for low, intermediate, and high GC scores, respectively. The GC score, therefore, may be predictive of oncological outcomes after post-RP XRT and improve clinical decision-making in high-risk cases.

Clinical implications

In men post-radical prostatectomy with positive surgical margins, we suggest the use of molecular markers to risk stratify patients and identify those who are most likely to benefit from adjuvant treatment and thereby improve outcomes (conditional recommendation based on very low-quality evidence). This recommendation assumes that patients place a relatively high value on improving oncological outcomes and a relative low value on the avoidance of treatment-related adverse effects.

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24 CHAPTER 24

Imaging of the prostate

Matthew J. Watson[1], Francesca V. Mertan[2], Samuel Borofsky[2], Arvin K. George[1], Abhinav Sidana[1], Peter L. Choyke[2], Peter A. Pinto[1]*, and Baris Turkbey[2]*

[1] *Prostate Cancer Section, Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*

[2] *Molecular Imaging Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*

Introduction

Recent advances in imaging technology have contributed to an evolving paradigm shift in the diagnostic algorithm of prostate cancer (PCa). The growing body of evidence in multiparametric prostate magnetic resonance imaging (mpMRI) and novel molecular imaging techniques have better defined its indications, resulting in tangible changes in clinical practice. In this chapter, we review the latest evidence as it pertains to important clinical questions in the diagnosis and staging of PCa.

Methods

We formulated four clinical questions and performed systematic literature reviews to identify pertinent studies. From the body of relevant literature, we further narrowed our scope through the application of our stated inclusion and exclusion criteria. Where applicable, study information was extracted and entered into RevMan by a single reviewer who assessed dimensions of evidence quality, in particular risk of bias. These study characteristics were then used as a guide to refine our analysis. Where possible, quantitative analysis was performed. Recommendations were made based on the aggregate study evidence based on the quality of the evidence, inferences of patient preferences, and cost–benefit analysis of the intervention.

Clinical question 1

In patients with abnormal digital rectal examinations and/or with elevated serum prostate-specific antigen (PSA) levels, does magnetic resonance imaging (MRI) fusion-guided prostate biopsy or standard (extended sextant) transrectal ultrasound (TRUS) biopsy identify more clinically significant PCa?

Literature Search

We conducted a systematic literature search in PubMed (1990–2015) using search terms "prostate tumor," "biopsy," "magnetic resonance imaging," "MRI," "TRUS," and "predictive value." The search was limited to articles in English.

The evidence

Twenty-five studies [1–25] were identified comparing MRI fusion-guided biopsy with standard TRUS biopsy for the identification of clinically significant lesions. There is currently no accepted definition of clinically significant disease [26], so all studies [1–13] that provided a clear definition of clinically significant prostate were included in our analysis. We included both prospective and retrospective studies, which reported on a total of 2700 participants. Owing to the multiple variables that influence lesion identification and sampling (i.e. navigational system for biopsy, MRI magnet strength, endorectal coil use, operator experience), we did not stratify outcomes based on these variables. Importantly, five of the studies did not blind the operator to the location of the lesions at the time of TRUS biopsy [2, 4, 5, 9, 11]. Ten of the 13 studies found that MRI fusion-guided biopsies outperformed standard TRUS biopsy for the identification of clinically significant PCa. Our comparative analysis of the 13 studies corresponded to a relative risk (RR) of 1.15 (95% confidence interval [CI] 1.06–1.32) of identifying clinically significant PCa on MRI fusion-guided biopsies compared with standard TRUS biopsy (Figure 24.1). Interestingly, our analysis showed considerable heterogeneity, as evidenced by

* Sharing senior authorship.

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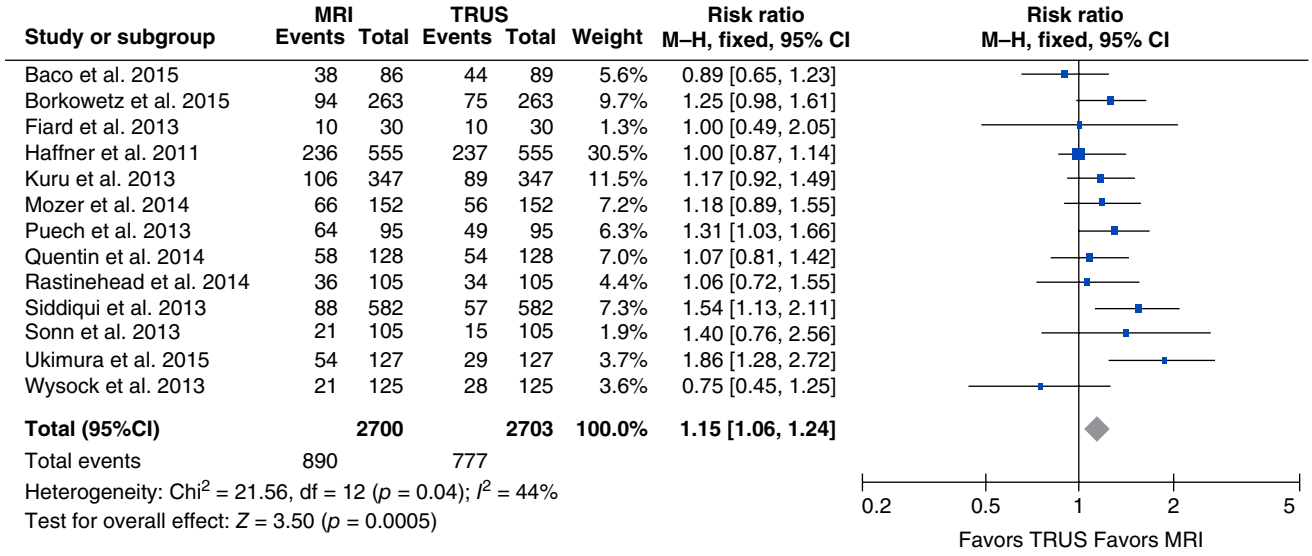

Figure 24.1 Comparative analysis of risk ratio of identifying clinically significant prostate cancer for MRI-guided versus TRUS-guided biopsy procedures in studies with overall patient population.

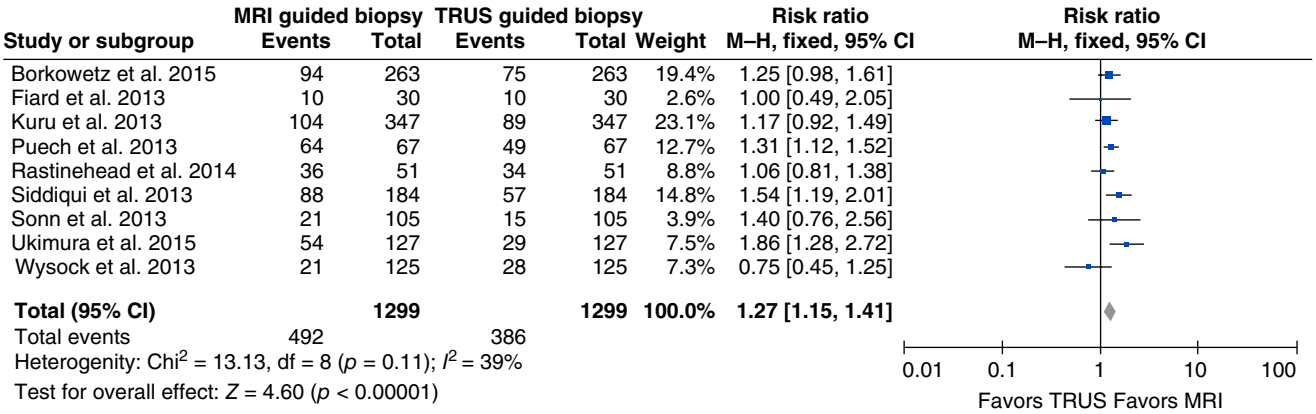

Figure 24.2 Comparative analysis of risk ratio of identifying clinically significant prostate cancer for MRI-guided versus TRUS-guided biopsy procedures in studies with non-biopsy-naive patient population.

the forest plot I^2 value of 63%. Our findings differ from a meta-analysis performed by Moore et al. [27], which found that MRI fusion-guided biopsy and standard TRUS biopsy detected equal numbers of clinically significant PCa.

Removing studies that sampled only biopsy-naive patients, that is, analyzing only studies that selected for patients who had undergone one or more prior negative standard TRUS biopsies, the RR increased to 1.27 (95% CI 1.15–1.41) with decreased heterogeneity (Figure 24.2). In contrast, when analysis was performed on studies that included biopsy-naive patients alone, the RR decreased to 1.04 (95% CI 0.86–1.25) and no between-study heterogeneity was detected (Figure 24.3). This difference in the RR values between the two groups may be secondary to standard TRUS biopsy having the greatest yield on the first biopsy and rates of detection declining drastically thereafter, whereas fusion biopsy allows for sampling outside the traditional biopsy template [28, 29].

Clinical implications

In patients at increased risk for prostate cancer (abnormal digital rectal examination [DRE], elevated PSA), we recommend MRI-guided fusion biopsy over standard (sextant) biopsy (strong recommendation based on moderate-quality evidence). This recommendation takes into consideration aggregate analyses, where MRI fusion-guided biopsy was found to be superior to standard TRUS biopsy despite differences in patient biopsy history and differences in MRI-targeted biopsy parameters.

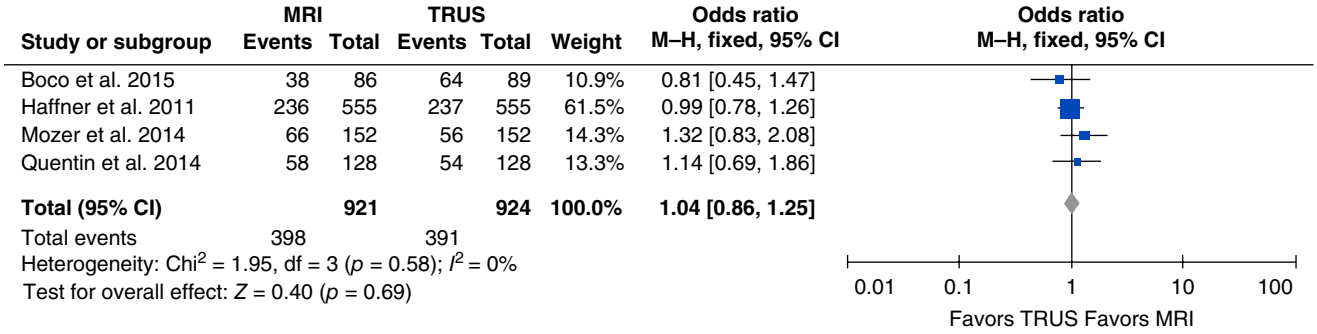

Figure 24.3 Comparative analysis of risk ratio of identifying clinically significant prostate cancer for MRI-guided versus TRUS-guided biopsy procedures in studies with biopsy-naive patient population.

Clinical question 2

In patients with low-risk PCa, how do mpMRI-based nomograms compare with classical clinical pathology-based nomograms for predicting active surveillance eligibility?

Literature search

We conducted a systematic literature search in PubMed (1990–2015) using the search terms "prostate," "prostate cancer," "prostate carcinoma," "nomogram," "predictive model," "selection," "eligibility," "active surveillance," "AS," "multiparametric magnetic resonance imaging," "multiparametric MRI," and "mpMRI." Prospective and retrospective studies were included. The search was limited to studies whose predictive criteria were validated against post-radical prostatectomy whole-mount histopathology findings. Importantly, validation of a nomogram's predictive accuracy using whole-mount pathology is necessary because at present whole-specimen histopathological analysis is the only method available for measuring the true cancer burden. Additional inclusion criteria were that the area under the curve (AUC) values of the receiver operator characteristic curve were explicitly stated and studies were written in English. Studies assessing the use of PCA3 as a parameter in the nomogram were excluded as this is not routinely performed. Furthermore, we also excluded one study that permitted only one positive core at biopsy [30] as we felt that this was a rare occurrence and not clinically useful.

The evidence

No prospective studies were identified. Seven retrospective studies were identified (Table 24.1) that met our inclusion criteria [31–37]. We chose to include an eighth retrospective study, which did not meet our inclusion criteria of nomogram validation through whole-mount pathology [38]. Although this study did not fully meet our inclusion criteria, it was the only published nomogram identified that exclusively utilized an mpMRI-based criterion, which is important for the purposes of this chapter. A measure of a nomogram's predictive accuracy is the AUC. The AUC value is the probability that in a randomly selected patient, the patient with indolent disease will be assigned a higher risk of insignificant cancer than the patient without it. AUC values can range from 0.5 (no discrimination) and 1.0 (perfect discrimination). AUC values in the selected studies ranged from 0.686 to 0.933 [37].

Since there is no accepted definition of clinically insignificant disease, studies have attempted to validate the AUC findings originally reported in each clinical pathological nomogram study utilizing various definitions of insignificant disease found on whole-mount pathology [37, 39, 40]. The predictive value of the models was diminished by these validating studies in patients with a high probability of indolent disease. For example, using the indolent disease criteria of pathological stage 2 (pT2), Gleason score ≤3+4=7, the Chun nomogram had an AUC of 0.587, and when the stringent Epstein criteria were applied, the AUC decreased to only 0.563 [39].

Shukla-Dave et al. created a nomogram that used a combination of clinical pathological and mpMRI criteria in the predictive model. Initially, the predictive model reported a high AUC of 0.854; however, a second study performed by the same group revealed a decreased predictive utility of 0.738 [36]. Furthermore, magnetic resonance spectroscopic imaging (MRSI), the parameter of which the model relied heavily upon, has been shown to be the least helpful in subsequent mpMRI studies relating imaging to pathology [41]. Finally, the National Cancer Institute (NCI) nomogram, which uses only mpMRI criteria, generated an AUC of 0.71. This nomogram was developed with biopsy pathology as an endpoint, which is a method that has not yet been validated. Although the reported negative predictive value (NPV) of mpMRI for clinically significant lesions varies dramatically [42], more recent studies have shown it to be approximately 80% [43, 44]. Other studies have shown that mpMRI misses 9% of high-grade cancers [45]. Using mpMRI biopsy histopathology as an endpoint may introduce an intrinsic positive bias when evaluating the nomogram's predictive accuracy because this endpoint does not account for those high-grade lesions that are missed.

Table 24.1 Characteristics of studies comparing mpMRI-based nomograms with classical clinical pathology-based nomograms for predicting active surveillance eligibility.

Study	Population model derived from	Nomogram parameters	Reported AUC of receiver operator characteristic curve
Kattan et al. (2003)	1986–2000 *n*=409 Exclusion criteria: PSA >20, biopsy GG 4/5, positive cores >50%, MCCL >20 mm or benign tissue in all cores <40 mm 80/409 had insignificant disease at RP as defined by ≤pT2c, no GG 4/5, TV≤0.5 mL	Kattan Full Model: cT, PSA, GS, cumulative cancer core length/ cumulative noncancer core length, US TV	0.79
Shukla-Dave et al. (2007)	2000–2004 *n*=220 Inclusion criteria: ≤cT2a, PSA <20, biopsy GS 6 90/220 had insignificant cancer at RP as defined by ≤pT2, TV≤0.5 mL, no poorly differentiated elements	MRI/MRSI: cT, %BC+, MRI lesion score	0.854
Steyerberg et al. (2007)	1994–2004 *n*=247 Inclusion criteria: ≤cT2a, PSA ≤20, ≤GG 3, ≤50% positive cores, ≤20 mm MCCL and >40 mm benign tissue in all cores 121/247 had insignificant cancer at RP as defined by ≤pT2, GS≤6, TV≤1.3 mL	Steyerberg nomogram: biopsy GS (includes 2+2, 2+3), PSA, cumulative cancer core length cancer/cumulative noncancer core length, US TV	0.79
Chun et al. (2008)	1992–2003 *n*=1132 Inclusion criteria: ≤cT2a, PSA <10, biopsy GS 6 65/1132 had insignificant cancer at RP as defined by ≤pT2c, GS ≤6, RP	Chun nomogram: PSA, biopsy GS, cumulative cancer length, %BC+	0.904
O'Brien et al. (2011)	1998–2009 *n*=2525 Inclusion criteria: ≤pT2c, no GG 4/ 5, TV<0.5 mL 152/2525 had insignificant cancer at RP as defined by ≤pT2c, <50% GG 4/5, TV ≤0.5 mL, organ confined, no GG 4/5 at RP	O'Brien nomogram: PSAD, MCCL, %BC+, % BC GG 4/5, cumulative cancer length <6 mm, prostate volume, age	0.933
Shukla-Dave et al. (2012)	2005–2009 *n*=181 Inclusion criteria: ≤cT2a, PSA <10, GG ≤3 (GS ≤6) 49/181 had insignificant disease at RP as defined by ≤pT2c, GG <4, TV ≤0.5 mL	Medium MRI/MRSI: cT, PSA, %BC+, MRI prostate volume, MRI/MRSI score	0.738
Stamatakis et al. (2013)	2007–2012 *n*=85 males Inclusion criteria: ≤cT1c, PSAD <0.15, biopsy GS ≤6, ≤2 positive biopsy cores, ≤50% BC+ 60/85 had insignificant cancer at MRI-targeted fusion biopsy as defined by ≤cT1c, PSAD <0.15, biopsy GS ≤6, ≤2 positive biopsy cores, ≤50% BC+ No whole-mount histopathology	mpMRI nomogram: number of lesions, lesion density, and highest MRI suspicion	0.71
Truong et al. (2013)	2005–2011 *n*=1956 males Inclusion criteria: ≤cT2a, PSA <10, biopsy GS ≤6 1759/1956 (calculated) had low-risk disease at RP as defined by GS <7	Badger nomogram: PSAD using US volume, obesity, number of positive cores, and maximum core involvement	0.686

%BC+, percent biopsy core positive; AS, active surveillance; cT, clinical stage; GG, Gleason grade; GS, Gleason score; MCCL, maximum cancer core length; MRI, magnetic resonance imaging; MRSI, magnetic resonance spectroscopic imaging; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; pT, pathological stage; RP, radical prostatectomy; TV, tumor volume; US, ultrasound.

Clinical implications

We suggest against mpMRI-based nomograms for determining active surveillance eligibility in patients with low-risk PCa (conditional recommendation against, based on low-quality evidence). However, the lack of standardization in current studies investigating both types of nomograms due to the heterogeneous definitions of clinically insignificant disease prevents a truly meaningful interstudy analysis. Although mpMRI-based nomograms purportedly have similar predictive values to the clinical pathological nomograms, a study that develops a nomogram based solely on MRI parameters that has been validated by whole-mount pathological analysis needs to be generated to assess predictive values most accurately. Finally, the burden of proof is on the mpMRI-based nomograms to outperform clinicopathological-based nomograms, as the nomograms currently based on clinicopathological covariates are more user friendly and less resource intense.

Clinical question 3

In post-radical prostatectomy (RP) patients with biochemical recurrence, does MRI compared with positron emission tomography (PET)/computed tomography (CT) improve the detection of PCa local recurrence?

Literature search

We conducted a systematic literature search in PubMed (1999–2015) using "PET/CT," "MRI," "PET/MRI," "post-radical prostatectomy biochemical recurrence," "local recurrence," "11C-choline," 11C-acetate," "18F-choline," "18F-FDG," "PSMA PET/CT," "18F-FACBC," "68Ga-PSMA," and "prostate" as search terms. The search was limited by studies that evaluated the detection of PCa recurrence using MRI and/or PET/CT in patients post-RP. The search was limited to articles in English.

The evidence

Fourteen studies were included that met our eligibility criteria. Three studies were identified that made direct comparisons between PET/CT and MRI. Additionally, three systematic reviews and eight independent studies discussing sensitivities and specificities of MRI and PET/CT were included [46–53]. All data are summarized in Table 24.2.

A retrospective study by Kitajima et al. compared [^{11}C]choline PET/CT with pelvic mpMRI using an endorectal coil (ERC) in 115 post-RP patients with suspected recurrence. A total of 61 patients had local recurrence and 36.1% of patients with local recurrence (LR) were correctly diagnosed with MRI alone. However, only 1.6% of patients were correctly diagnosed using PET/CT alone. This study concluded that mpMRI with ERC is better at detecting local recurrence in post-RP patients with suspected local recurrence than [^{11}C]choline PET/CT [54].

A study by Panebianco et al. compared proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) and dynamic contrast-enhanced (DCE) MRI with [^{18}F]choline PET/CT in the detection of local PCa recurrence in post-RP patients. A total of 84 patients were included in the study and divided into two groups according to suspicious lesion sizes (group A did not undergo TRUS-fusion biopsy as group B did). The ^{1}H-MRSI and DCE-MRI group B showed a sensitivity of 94%, a specificity of 100%, and a positive predictive value (PPV) of 100%. PET/CT showed a sensitivity of 92% and a specificity of 33% with a PPV of 98% in determining local prostate recurrence for the same group. The study concluded that the diagnostic accuracy of MRSI-DCE MRI was higher than that of PET/CT in identifying local PCa recurrence, but limited in patients with low PSA levels (0.2–2 ng/mL). The accuracy of MR was 94% and that of PET/CT was 91% [55]. Both group A and B results are included in Table 24.2.

Vees et al. conducted a study of 20 patients comparing [^{18}F]choline and/or [^{11}C]acetate PET/CT with MRI for the detection of residual or progressive subclinical disease at low PSA levels (<1 ng/mL) after RP. Twenty-two PET/CT studies were conducted with 11 patients in each group (two patients had imaging with both tracers). Vees et al. found that the sensitivity of both [^{18}F]choline and [^{11}C]acetate PET/CT was less than the ERC MRI sensitivity (45.5 and 54.5%, respectively, vs. 89%). They concluded that ERC MRI presents greater utility than both [^{18}F]choline and [^{11}C]acetate PET/CT, but also stated that these studies cannot yet recommend PET/CT as the standard in diagnosing early relapse of BCR post-RP [56, 57].

Two systematic reviews found mpMRI to be more sensitive to local recurrence than PET/CT modalities [58, 59]. A study by Zaorsky et al. found that both mpMRI and small-molecule PET tracers had potential to detect local prostatic disease recurrence, although the sensitivity range of both modalities varied widely (mpMRI sensitivities 56–92%, PET tracers sensitivities 30–98%) [58]. A study by Beresford et al. found, based on sensitivity, that MRI outperformed [^{11}C]choline PET by about 10% (MRI 95% sensitivity based on TRUS biopsy as gold standard, 71% sensitivity for DCE MRI) in detecting local recurrence visibility. [^{18}F]Ccholine PET sensitivities ranged from 20 to 80% and CT sensitivities from 14 to 36% in biochemical recurrence, still falling short of MRI sensitivities [59].

Evangelista et al. surveyed the available clinical and diagnostic modalities to detect recurrent PCa early. They concluded that mpMRI is best at diagnosing small local recurrent cancer in PSA ranges from 0.2 to 1 ng/mL. In the included studies, a pooled sensitivity range of 25–100% for detection of local recurrence on T2W MRI after RP was reported. Pooled detection rates for radiolabeled PET/CT for PSA levels <1 ng/mL ranged from 9.9 to 31.3%. Detection rates for [^{18}F]FACBC and [^{68}Ga]PSMA for low PSA levels ranged from 40 to 80%, although these numbers are limited since no direct comparisons with histology or biopsy were performed [57].

Table 24.2 Characteristics of studies comparing positron emission tomography (PET)/computed tomography (CT) in patients post-prostatectomy with biochemical recurrence.

Study	Study type	No. of patients	Direct correlation between MRI and PET/CT?	PET/CT	MRI sensitivity (%)	MRI specificity (%)	MRI accuracy (%)	MRI detection rate (%)	PET/CT sensitivity (%)	PET/CT specificity (%)	PET/CT accuracy (%)	PET/CT detection rate (%)	Recommendation	Limitations
Kitajima et al. (2013)	Retrospective	115	Yes	[^{11}C]Choline	36.1				1.6				MRI	
Panebianco et al. (2011)	Retrospective	84	Yes	[^{18}F]Choline	92–94	75–100	89–94		62–92	33–50	60–91		MRI	
Vees et al. (2007)	Retrospective	20	Yes	[^{11}C]Acetate and [^{18}F] choline	82–89				455–54.5				MRI	MRI used in only 18/20 patients
Zaorsky et al. (2014)	Review		No	Multiple	56–92	75–97			30–98	33–100			MRI	
Beresford et al. (2014)	Review		No	[^{11}C]Choline and [^{18}F] choline	71–95	94–100			20–91	50–90			MRI	
Evangelista et al. (2015)	Review		No	Multiple	25–100	52–100	54–74					99–31.3 ([^{18}F] FACBC and [^{68}Ga] PSMA=40–80)	MRI	
Eiber et al. (2015)		248	No	[^{68}Ga]PSMA ligand								579–96.8 (0.5<PSA ≥2)	PET/CT	Only 87 patients with LR: 18 (PET/CT+)/87 total)
Hofer et al. (1999)		20	No	[^{18}F]FDG									[^{18}F]FDG not useful to determine LR after RP	Only 7 patients with recurrence post-RP
Reske et al. (2008)	Retrospective	49	No	[^{11}C]Choline					0.73	0.88			PET/CT	PET/CT missed 10/33 local recurrences
Rinnab et al. (2009)	Retrospective	41	No	[^{11}C]Choline					67–89	0–67			PET/CT	Sensitivity and specificity differ according to PSA value
Giovacchini et al. (2010)	Retrospective	161	No	[^{11}C]Choline					0.58				Pathological stage, age, elevated PSA levels, and history of BCF are independent predictive factors of positive [^{11}C] choline PET findings	55/161 had local recurrence and only 32 of the 55 were found with their tracer; 3 different PET scanners used
Cirillo et al. (2008)	Retrospective	72	No		0.841	0.893	0.861						DCE MRI	Only looked at MRI; all values reported with DCE contrast
Afshar-Oromieh et al. (2014)	Retrospective	20	No	[^{68}Ga]PSMA ligand									MRI/PET	Only 16 out of 20 patients were post-RP; decision based on visual assessment of MRI/PET images being easier than PET/CT
Beer et al. (2011)	Review		No	Multiple									MR/PET	

Clinical implications

In post-prostatectomy patients with suspected local recurrence, we suggest MRI over PET/CT (conditional recommendation based on low-quality evidence). This conclusion was reached on aggregate analysis of a modest number of studies reporting on small patient samples producing low-quality evidence. Moreover, it reflects a wide variety of PET agents. Studies comparing MRI with PET/CT, although limited, are promising and raise the possibility of combining PET and MRI. Additionally, promising new PET agents may prove superior to current methods.

Clinical Question 4

In high-risk patients with PCa, does sodium fluoride (NaF) PET/CT as compared with conventional nuclear medicine bone scintigraphy improve the detection of skeletal metastases?

Literature search

A systematic literature search was performed in PubMed (2000–2015) using the search terms "18F NaF," "18F-fluoride," "PET/CT," "scintigraphy," "bone scan," "bone metastases," "skeletal metastases," and "prostate." The search was limited to studies in which both NaF PET/CT and conventional nuclear medicine bone scintigraphy, with or without single photon emission computed tomography (SPECT), were performed. The search was limited to articles in English.

The evidence

Six studies met eligibility criteria. Even-Sapir et al. prospectively evaluated 44 patients with high-risk PCa who underwent NaF PET/CT and bone scintigraphy on the same day [60]. Diagnoses of metastases were based on definite PET/CT findings, biopsy, and imaging follow-up. NaF PET/CT significantly outperformed planar bone scintigraphy and bone scintigraphy with SPECT. The reported sensitivity and specificity of NaF PET/CT were found to be 100% (Table 24.3).

Although subsequent studies have not replicated the optimal results of this modality, they have shown a benefit of NaF PET/CT compared with conventional nuclear medicine studies [60]. Withofs et al. prospectively evaluated 10 patients with PCa by comparing NaF PET/CT with bone scintigraphy, using CT and MRI as the gold reference for PCa, depending on the site of the body where the lesion was detected. NaF PET/CT was found to have a higher accuracy than conventional bone scintigraphy (96 vs. 80%) [61]. Iagaru et al. prospectively evaluated 18 patients with PCa, and found NaF PET/CT to have improved sensitivity compared with conventional bone scintigraphy (100 vs. 87.5%), with similar specificity of the two modalities [62]. Damle et al. prospectively evaluated 49 patients with PCa, reporting an accuracy of 89.8% for NaF PET/CT compared with 77.5% for bone scan [63].

Poulsen et al. examined 50 consecutive patients with PCa using conventional bone scintigraphy, NaF PET/CT, [^{18}F]choline PET/CT, and whole-body MRI to evaluate for spine metastases. Whole-body MRI was used as the gold standard to determine whether the lesion was benign or malignant. A total of 363 metastatic lesions were found on MRI. NaF PET/CT showed the optimal sensitivity (93.1%) in the detection of these metastatic lesions, followed by [^{18}F]fluoromethylcholine (FCH) PET/CT (84.7%) and conventional bone scintigraphy (50.8%). However, NaF PET/CT was the least specific modality, with a specificity of 54%, compared with 82.2% for conventional bone scintigraphy and 91.1% for FCH PET/CT [64].

Recent studies have also begun to evaluate the potential of performing PET/CT with simultaneous imaging of [^{18}F]NaF and [^{18}F]fluorodeoxyglucose (FDG) decay. Minamimoto et al. prospectively evaluated 15 men with PCa with this technique following routine nuclear medicine bone scintigraphy. Whole-body MRI scans were also obtained. It was found that the combined [^{18}F]NaF and [^{18}F]FDG PET/CT method demonstrated 100% sensitivity and 60% specificity for the detection of osteoblastic skeletal lesions, compared with 81.3 and 100%, respectively, for bone scintigraphy and 65.4 and 40%, respectively, for whole-body MRI [65].

Clinical implications

In patients with high-risk prostate cancer who are at increased risk for bone metastases, we suggest NaF PET/CT imaging

Table 24.3 Characteristics of studies comparing sodium fluoride (NaF) PET/CT with conventional nuclear medicine bone scintigraphy in patients with high-risk prostate cancer.

Study	PET/CT positive	Patients with PCa metastases	Bone scan positive	Patients with metastasis
Even-Sapir et al. (2006)	23	23	13	23
Withofs et al. (2011)	9	9	6	9
Iagaru et al. (2012)	100%	100%	87.5%	100%
Damle et al. (2013)	32	32	31	32
Poulsen et al. (2014) (lesion based)	338 (lesions)	363 (lesions)	185 (lesions)	363 (lesions)
Minamimoto et al. (2015)	100% per lesion sensitivity	100%	81.3% per lesion sensitivity	100%

over nuclear medicine bone scintigraphy (conditional recommendation based on very low-quality evidence). This recommendation assumes that patients place a relatively high value on identifying bone metastases early to inform therapeutic management and a relatively low value on the avoidance of the discomfort and potential side effects of histological conformation, to confirm positive findings. With the high sensitivity in the detection of osseous metastases, the use of NaF PET/CT is best utilized following the initial diagnosis of PCa, in order to perform patient staging. However, histological confirmation would be necessary to confirm the presence of true osseous metastases in lesions with uptake on PET/CT, due to the high rate of false positives with this modality. This is of particular importance in patients with one or a few NaF avid osseous lesions on PET/CT, as the presence of metastatic disease would significantly alter patient management.

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25

CHAPTER 25

Active surveillance for localized prostate cancer

Nathan Perlis and Laurence Klotz

Division of Urology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

Introduction

Men have been known to have indolent prostate cancer ever since the 1950s when 10% of men having a transurethral resection of the prostate (TURP) were found to have small-volume, low-grade prostate cancer despite having no clinical evidence of malignancy. Interestingly, there was a prevailing and uncontroversial consensus that prostate cancer diagnosed in this manner did not warrant treatment [1]. By the 1980s, with the rising use of prostate-specific antigen (PSA) testing in well-funded healthcare systems, the incidence of micro-focal low-grade disease increased dramatically in North America and Europe. However, despite the historical consensus regarding conservative management of T1a disease, the majority of patients diagnosed with low-risk prostate cancer by PSA and biopsy in the United States were treated with definitive radiation or surgery.

Active surveillance is an alternative approach to definitive radiation or surgery for low-risk localized prostate cancer in select men. Its use is based on several assumptions [2]. Indolent prostate cancer has identifiable clinical and pathological parameters that distinguish it from cancer with metastatic potential. Additionally, all curative interventions for prostate cancer carry potential for significant morbidity and cost. For those patients on active surveillance who are reclassified into a higher risk category, definitive treatment can still be offered without significantly decreasing the chance of cure. Finally, health-related quality of life is better on active surveillance than following surgery or radiation, despite anxiety regarding living with prostate cancer and repeated blood tests and biopsies.

There is growing evidence that many men have asymptomatic, indolent prostate cancer that does not necessitate immediate intervention, may never require any treatment, and often goes undiagnosed for a lifetime. First, men dying without being diagnosed with prostate cancer have a high incidence of occult prostate cancer on autopsy series. These tumors have been identified in 30% of men aged under 40 years and 70–80% in those over 60 years of age. Evidence suggests that the prevalence of occult prostate cancer may be decreasing since the introduction of pervasive PSA screening for prostate cancer [3]. Extrapolations based on the frequency of serum abnormal PSA in men 50–70 years old and the rate of positive biopsies in that population group suggest that there are over 500 000 undiagnosed cases of prostate cancer in this subset [4]. Finally, a high incidence of occult prostate cancer was observed in the Prostate Cancer Prevention Trial, where men underwent routine prostate biopsy at the completion of the trial [5]. Impressively, for those men receiving placebo who had a normal digital rectal examination and PSA test, 15% had occult prostate cancer.

In the last 15 years, evidence regarding the indolent nature of low-grade disease and favorable outcomes with expectant management has shifted the treatment paradigm back to a more conservative approach. The increasing implementation of active surveillance protocols may also be a response to the 2012 US Preventive Services Task Force's criticism that PSA screening leads to overtreatment and excessive morbidity. Uptake of active surveillance is evidenced by the fact that the proportion of patients with low-risk disease managed conservatively increased from about 10% in 2000 to 35% in 2010 [6, 7].

Clinical question 1

In patients with indolent, localized prostate cancer, how does conservative management compare with local treatment with curative intent?

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Literature search

We performed a literature search in PubMed using the search terms "active surveillance" and "prostate cancer."

The evidence

Observational studies reviewing the experience of active surveillance cohorts consistently demonstrate low rates of progression to metastatic disease or death from prostate cancer. In addition, the majority of patients do not require definitive therapy within the time frame of these studies [8–13].

An observational prospective study in Toronto followed 993 men treated with active surveillance since 1995 [8]. As of 2013, with 6.4-year median follow-up from first biopsy, 149 deaths were reported, 15 (1.5%) of which were attributed to prostate cancer. A further 13 patients (1.3%) developed metastatic disease, but either were alive or had died of other competing illnesses. The cause-specific survival rates were 98 and 94% at 10 and 15 years, respectively. The rates of remaining on active surveillance and avoiding any radical treatment were 76, 64, and 55% at 5, 10, and 15 years, respectively.

A total of 469 out of 968 patients with screen-detected prostate cancer in the randomized Göteborg population-based prostate cancer screening trial were treated with active surveillance [10]. The failure-free, treatment-free, and overall survival rates were 86, 45, and 81%, respectively, at 10 years.

In the ongoing, worldwide PRIAS study, patients with low-risk prostate cancer are being managed with active surveillance according to a specified protocol [9]. In a 2013 report, 2494 patients were enrolled and with a median of 1.6 years of follow-up, the results are consistent with those seen in other observational series.

Death from prostate cancer is rare in active surveillance cohorts. However, to rule out with certainty that being on active surveillance increases the risk of prostate cancer mortality requires a median follow-up time that has not yet been reached. The most mature surveillance cohort has a median follow-up of 8 years and ranges from 2 to 18 years, with an actuarial prostate cancer mortality of 5% at 15 years [8]. Cardiovascular disease is the most common cause of death in active surveillance groups. In the Toronto cohort at 9 years' follow-up, men were 10 times more likely to die from causes other than prostate cancer.

There is concern that there will be a steep rise in prostate cancer mortality during late follow-up. This is extrapolated from the Swedish study reporting a threefold rate of prostate cancer-related mortality at 15 years' follow-up for patients on watchful waiting [14]. For the 70 patients in the Toronto experience who have been followed for 14 years, only 1.5% have had late disease progression. This does not represent a sharp increase in mortality at long follow-up. It will still be 5 years before median follow-up times of 15 years are reached in several active surveillance cohorts.

Attempts to perform prospective randomized trials comparing active surveillance with radical intervention (surgery or radiation) in low-risk prostate cancer were carried out by the NCIC, the intergroup mechanism (CTEP) in the United States, and the United Kingdom beginning in 2004 (the START trial). These trials have been challenging to perform; for example, the START trial was to enroll 2100 patients, with prostate cancer mortality as the primary outcome measure. Unfortunately, failure to accrue sufficiently led to closure after 4 years and 240 registered patients.

The Prostate Testing for Cancer and Treatment (ProtecT) trial is being run in the United Kingdom (NCT00632983). This trial is designed to assign patients randomly to active surveillance, radical prostatectomy, or definitive radiation therapy [15]. Patients treated with active surveillance have their PSA tested every 3 months for 1 year and every 6 months thereafter. Further monitoring and testing are performed when indicated, the findings of which can alter the therapeutic course. The primary outcome of the trial is survival time from initial presentation. Enrollment started in June 2001, and 1643 patients had been randomized by 2009, which aligns with the statistical design of the trial. By 2016, the median 10-year follow-up was reached and the primary endpoint of prostate cancer mortality is being analyzed.

Clinical implications

We recommend that patients with indolent, low-grade prostate cancer be managed conservatively (string recommendation based on moderate-quality evidence). This recommendation is based on a body of evidence from both randomized controlled trials and large observational studies that disease-specific survival is not impaired, but treatment-related harms are averted.

Clinical question 2

In patients with Gleason score 6 (3+3) undergoing active surveillance, what is the risk of metastatic disease?

Literature search

We performed a literature search in PubMed using the search terms "active surveillance" and "prostate cancer."

The evidence

Prostate tumors are heterogeneous and their biology and behavior cover a spectrum from indolent to aggressive. Occasionally, small cancers that lack telomerase, VEGF, or other biological mechanisms that confer cellular immortality may even spontaneously involute and disappear [16]. In radical prostatectomy-confirmed Gleason 6 tumors, where there is a verified absence of occult higher grade cancer in the prostate, several large clinical series have reported no cases of metastatic disease [17].

However, occult higher grade cancer is present in approximately 25–40% of men with biopsy-confirmed Gleason 6 disease [18, 19]. This fact is a natural limitation when assessing whether patients are ideal candidates for active surveillance because the diagnostic entry criteria are based on needle biopsy. It is possible that occult, higher grade cancer present at the time of diagnosis is responsible for disease progression in the small group of patients who proceed to develop metastases. The long-term mortality for patients with biopsy-confirmed Gleason 6 disease managed without active intervention is about 25% [20]. The occult high-grade cancers are likely responsible for the majority of the prostate cancer deaths reported in conservative management series. Early identification of these more aggressive cancers would likely improve outcomes.

The true natural history of Gleason 6 disease may be garnered by examining the outcomes of patients following surgical pathological grading after radical prostatectomy. A total of 12 000 men with surgically confirmed Gleason 6 tumors were followed in a multicenter study of 24 000 post-radical prostatectomy patients [17]. Disease-specific mortality at median follow-up of 20 years was 0.2%. Of the 4000 men treated at the Memorial Sloan Kettering Cancer Center (MSKCC) in the study, only one died of prostate cancer. A pathological review of this patient suggested misclassification because it revealed Gleason 4+3 disease in the primary (Scott Eggener, personal communication). Another study of 14 000 men with surgically confirmed Gleason 6 disease identified 22 patients with lymph node metastases; analysis of these cases found that all 22 were misclassified, and that in fact the primary tumor was higher grade. On re-evaluating the cohort, the rate of node positive disease for the 14 000 patients without any Gleason 4 or 5 disease was zero [21].

An alternative explanation for the absence of metastasis following surgery for Gleason 6 cancer is that the intervention is completely successful and alters the natural history of the cancer so that it does not metastasize. However, higher grade prostate cancer commonly metastasizes to bone, lymph nodes, and soft tissue. If Gleason 6 cancer could metastasize, one would expect occasional Gleason 6 cancers to micrometastasize prior to surgery or recur locally with subsequent metastasis. This has rarely, if ever, been observed. Despite knowledge that several tumors without metastatic potential are appropriately classified as cancer (e.g. basal cell carcinoma of the skin), some suggest changing the designation for micro-focal Gleason 6 to "indolent lesions of epithelial origin" (IDLE tumors) [22].

Can Gleason 6 tumors progress to higher grade tumors? A case report with longitudinal genetic sequencing described a patient managed carefully for 15 years on surveillance for Gleason 6 disease, including 12 sets of biopsies. Gleason 6 or normal tissue was seen on pathology for the first 11 biopsies. In the fifteenth year following diagnosis, he was re-biopsied for a sharp PSA rise and diagnosed with Gleason 9 and 10 cancer with metastases. Interestingly, PTEN, ERG, P53, and Ki-67 expression switched from uniformly normal in the first 12 samples to abnormal in the last biopsy. This case highlights that the activation of genetic switches resulting in histological grade progression can occur in patients with previously diagnosed low-grade cancer. However, it is impossible to know whether these changes occurred in Gleason 6 cancer cell or previously normal cells. Fortunately, these kinds of cases are rare in clinical practice [23].

If we accept that Gleason 6 cancer does not metastasize, would any amount of Gleason 6 cancer be managed identically, or should high-volume Gleason 6 cancer be treated differently? Based on several large cohorts, it seems that higher volume Gleason 6 cancer predicts an increased risk of occult higher grade cancer [24–26]. In one study, a total Gleason 6 biopsy length of >8 mm predicted for a significantly increased risk of high-grade disease [27]. Therefore, high-volume Gleason 6 tumors require close scrutiny to exclude as carefully as possible the presence of higher grade disease.

Clinical implications

We recommend ruling out the presence of Gleason 4 disease (strong recommendation based on moderate-quality evidence). This is based on the observation that that Gleason 3 disease does not appear to have metastatic potential.

Clinical question 3

What patient and tumor factors are important for appropriate entry into active surveillance, monitoring during active surveillance, and considering when to abort active surveillance?

Literature search

We performed a literature search in PubMed using the search terms "active surveillance" and "prostate cancer."

The evidence

The published active surveillance literature includes 23 prospective studies. The 14 largest studies with extended follow-up encompass approximately 5000 men and are summarized in Table 25.1 [8–10, 28–39].

The studies contain varying eligibility criteria. While each was conceived to identify patients with favorable prognoses, and thus good candidates for active surveillance, the clinical criteria applied at different sites and in different studies vary [2]. They each include early clinical stage, low serum prostate specific antigen (PSA), and Gleason score consistent with well- or moderately differentiated tumors. Beyond these three core components, many incorporate number and percentage of positive cores, extent of tumor involvement within a biopsy core, PSA density, and kinetics. PSA density has been recognized by many groups

Table 25.1 Outcomes of active surveillance in large prospective series.

Study	*n*	Median follow-up (months)	% treated overall; % treatment free	Overall/disease-specific survival (%)	% BCR post deferred treatment
Klotz et al. (2015) [8, 28] University of Toronto	993	92	30; 72 at 5 years	79/97 at 10 years	25 (6 overall)
Bul et al. (2013) [9] Multicenter, Europe	2500	47	32; 43 at 10 years	77/100 at 10 years	20
Dall'Era et al. (2008) [29] UCSF	328	43	24; 67 at 5 years	100/100 at 5 years	NR
Kakehi et al. (2008) [30] Multicenter, Japan	118	36	51; 49 at 3 years	NR	NR
Tosoian et al. (2011) [31] Johns Hopkins, USA	407	NR	36; NR	NR	NR; 50 "incurable" based on RP pathology
Roemeling et al. (2007) [32] Rotterdam Netherlands	273	41	29; 71 at 5 years	89/100 at 5 years	NR (31 of 13 RP positive margins)
Soloway et al. (2010) [33] Miami, USA	99	35	8; 85 at 5 years	NR	NR
Patel et al. (2004) [34] Memorial Sloan Kettering, USA	88	35	35; 58 at 5 years	NR	NR
Barayan et al. (2014) [35] McGill, Canada	155	65	20	NR	NR
Rubio-Briones et al. (2014) [36] Spain	232	36	27	93 at 5 years/99.5	
Godtman et al. (2013) [10] Sweden	439		63	81/99.8	14
Thomsen et al. (2013) [37] Denmark	167	40	35/60 at 5 years		
Selvadurai et al. (2013) [38] UK	471	67	30	98/99.7	12
Eggener et al. (2013) [39] USA	262	29	15; 25 at 5 years	NR	5

NR, not reported.

as a biomarker for higher risk disease [40]. A PSA density of <0.15 is an indicator of a more benign phenotype and low-volume disease.

Although not universally accepted, several sites recommend repeat prostate biopsy before committing to active surveillance in order to identify patients in whom initial biopsies may have missed higher risk features [39]. In most patients, delaying this biopsy for 6 months to 1 year may not have an impact on long-term outcome, even if higher grade disease is eventually identified.

Eligibility criteria heterogeneity reflects a different risk tolerance between investigators. For those centers with more inclusive criteria, particularly the Toronto, Rotterdam, and UCSF series, the potential advantages of surveillance outweigh what is believed to be a small increased risk of metastasis occurring while being surveilled. In contrast, other centers only include very low-risk patients by National Comprehensive Cancer Network (NCCN) guidelines (1–2 cores positive, <50% of core involvement, and PSA density <0.15). Several decision analyses suggest that it would require a substantial increase in prostate cancer mortality under surveillance compared with radical intervention before surveillance would lose the net benefit for low- and intermediate-risk groups [40]. However, this conclusion is limited by the uncertainty inherent in these models.

Surveillance strategies also differ depending on the study center. Although the key parameters available for monitoring include PSA, digital rectal examination, and repeat prostate biopsy, no group has defined the appropriate criteria to trigger active intervention or testing intervals. The probability that higher grade disease will be diagnosed on biopsy during active surveillance is 8–28% [34, 41]. This usually represents a higher grade component of the original tumor that was not originally sampled rather than evolution to higher grade disease.

In the Toronto cohort, which is large and has contains mature follow-up, PSA was measured at 3-month intervals to monitor the PSA doubling time [28]. A doubling time threshold of less than 3 years was used as a criterion for intervention. Repeat prostate biopsy was carried out at 1 year to exclude higher grade cancer that was possibly missed on the original biopsy or that developed as a consequence

of tumor progression. In subsequent years, biopsies were repeated every 4–5 years, looking for evidence of biological progression to Gleason 4+3 or higher.

A rapid PSA elevation is sensitive for aggressive disease as all of the five men who died of metastatic prostate cancer while on active surveillance in Toronto had a PSA doubling time of less than 2 years [42]. However, the lack of specificity limits the application of doubling time appropriately in trials. In a study of PSA kinetics in a large surveillance group, PSA triggered unnecessary biopsies (doubling time <3 years, or PSA velocity >2 ng/year) in 50% of stable, untreated patients, none of whom went on to progress, require treatment, or die of prostate cancer [43].

Race is a consideration in designing inclusion and surveillance strategies. The potential increased risk with active surveillance may be inferred by examining the outcomes of African American men versus men of other races who undergo radical prostatectomy for very low-risk prostate cancer [44]. In this study, men had clinical stage T1c disease, biopsy Gleason score ≤6, less than three positive biopsy cores, no more than 50% involvement in any core, PSA ≤10 ng/mL, and a PSA density ≤0.15 ng/mL/cm^3. The African American men had significantly higher Gleason score upgrading (33 versus 13%) and more positive surgical margins (19 versus 6%). Race maintained statistical significance on multivariable analysis. Despite this knowledge, the majority of black men who choose active surveillance are able to avoid overtreatment. Japanese men younger than 60 years old have lower rates of histological cancer than Caucasian men [45]. Therefore, low-grade prostate cancer diagnosis in young Asian men is less common, and the risk of overdiagnosis may be less. Ethnicity is only one of many factors that should be taken into consideration in the selection of active surveillance or active treatment. Many black men with low-grade prostate cancer have little or no probability of death from prostate cancer in their lifetime, and active surveillance can be an appealing option for those who have been appropriately risk stratified.

Reasons for discontinuation of active surveillance are multifactorial. These were studied in a series of 1729 men in a Swedish database [46]. At 5 years, 36% of the men had come off the active surveillance protocol. Discontinuation was secondary to PSA progression, biopsy progression, or personal preference in 52, 24, and 20% of cases, respectively.

In a series of 470 men in an active surveillance program at Johns Hopkins University, disease progression was assessed with annual biopsies. [47] Overall, 51 patients (11%) underwent radical prostatectomy. Interestingly, three-quarters of progression occurred between 1 and 2 years from diagnosis. Such quick progression leads one to believe that undersampling of more aggressive tumor was the cause of progression rather than progression of indolent tumor.

Clinical implications

We suggest that active surveillance protocols utilize PSA metrics and routine repeat biopsies and consider race, age, and comorbidity (conditional recommendation based on low-quality evidence). There is no specific standard approach and none have been tested in randomized trials.

Clinical question 4

Can multiparametric magnetic resonance imaging (MRI) be used to refine patient selection into and out of active surveillance programs?

Literature search

We performed a literature search in PubMed using the search terms "active surveillance," "prostate cancer," "magnetic resonance imaging," and "MRI."

The evidence

A major development in the field of active surveillance is the increasing use of multiparametric MRI (mpMRI). The large active surveillance groups have not employed mpMRI until recently, hence the published active surveillance literature does not yet reflect the impact of mpMRI. The capability to identify large, high-grade cancers by imaging is compelling. Some groups are routinely using mpMRI for men who are surveillance candidates, with fusion biopsy of a target when present. Others use mpMRI selectively, either in patients with grade or volume increase on biopsy and surveillance is still desired, or in those with PSA kinetics suggesting more aggressive disease (usually defined as a PSA doubling time of <3 years). If an mpMRI target is suspicious for high-grade disease (e.g. PIRADS 4 or 5), a targeted biopsy should be performed or, alternatively, if the lesion is large and unequivocal, intervention should be considered.

mpMRI can assist in two main areas of active surveillance protocols, both of which carry major benefits: reassurance that no higher risk cancer is present in those with negative MRIs and, in the subset with positive mpMRIs, earlier identification and treatment of clinically significant disease. With respect to keeping appropriate patients in active surveillance, the key metric is the negative predictive value (NPV) of mpMRI. At the MSKCC, the NPV for mpMRI for a group of 300 active surveillance candidates is reported as 97% [48]. The performance of mpMRI in the Toronto cohort confirmed that a nonsuspicious mpMRI was highly correlated with the absence of clinically significant lesions with an NPV of mpMRI for Gleason 7 or greater cancer of 100% [49]. On comparing mpMRI-targeted biopsy and traditional transrectal ultrasound-guided (TRUS) biopsy, the former was 6.3 times more likely to yield Gleason 7 (25% of 141 versus 4% of 874, p <0.001). A contemporary report from Johns Hopkins University confirmed that a nonsuspicious MRI was highly correlated with a lack of pathologically significant lesions in an active surveillance population [50].

If these results of single-center cohorts are validated, negative mpMRI could impart sufficient confidence in the absence of clinically significant pathology to replace biopsies in men with elevated or rising PSA. This would decrease the number of men undergoing biopsies and facilitate earlier diagnosis of clinically significant disease. One limitation, however, is that accurate mpMRI interpretation is demanding, requires a particular skillset, and is not yet widely prevalent.

mpMRI may also be useful as a supplemental way to optimize patient selection for entry into active surveillance. A prospective study imaged 60 consecutive patients who had been selected for active surveillance based on standard criteria and, in addition to typical criteria used for intervention, suggested treating any mpMRI lesion >1 cm [51]. mpMRI results from study entry were correlated with pathology from the confirmatory biopsy. For the 13 patients with lesions >1 cm on their mpMRI (22%), 10 were reclassified at biopsy as having higher grade disease. Lesions <1 cm on mpMRI were found among 24 patients (40%), of whom only six were reclassified as being at increased risk. NPV was also demonstrated for the 22 patients with normal mpMRI, of whom only two were reclassified on repeat biopsy.

It is likely that the uptake of mpMRI will help identify accurately those patients harboring higher grade, usually anterior, cancers earlier, resulting in a shift of the intervention curve to the left. This should result in improved outcome for those patients with an occult higher grade cancer not detected by the TRUS biopsy.

Clinical implication

We suggest including mpMRI in active surveillance protocols to improve patient selection and identify those with progression (conditional recommendation, very low-quality evidence). Evidence to support mpMRI is still in its infancy.

Conclusions

Active surveillance is an effective response to the widely recognized problem of overtreatment for PSA screen-detected prostate cancer. Among the approximately 5000 patients included in Phase II cohort studies of active surveillance, very low rates of prostate cancer metastasis and death are reported. A randomized Phase III trial comparing surveillance with radical intervention was initiated in 2007, but closed prematurely owing to challenging accrual. Some uncertainty remains about the outcome for patients on active surveillance after >15 years of follow-up. The current minimum standard is a confirmatory biopsy targeting the anterior prostate within 6–12 months. PSA should be monitored at 6-month intervals and subsequent biopsies taken every 3–5 years until the patient is no longer a candidate for definitive therapy. The active surveillance methodology continues to evolve, and incorporating improved imaging is likely to improve individual risk characterization and outcomes with fewer biopsies. A reassessment of PSA screening based on these improved metrics may lead to a reconsideration of the value of early detection.

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26 CHAPTER 26

Surgical management of prostate cancer

Daniel A. Barocas[1] and Michael S. Cookson[2]

[1] *Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA*

[2] *Department of Urology, University of Oklahoma College of Medicine, Oklahoma City, OK, USA*

Background

Prostate cancer remains the most commonly diagnosed solid tumor among men in the United States, with an estimated annual incidence of 220 800 cases and 27 540 deaths in 2015 [1]. Prostate cancer represents and enormous public health challenge, in part because of the difficulty in distinguishing between nonaggressive disease that can be safely observed and more aggressive disease that warrants treatment. This difficulty, combined with the high prevalence of indolent prostate cancer in aging men, confounds issues surrounding prostate cancer screening and early detection.

In addition, once prostate cancer has been detected, the optimal management for localized prostate cancer remains controversial [2]. The complexity is particularly acute in high-risk and/or locally advanced prostate cancer, which has a high lethality and in which single-modality therapy is often inadequate to control the cancer. The aim of this chapter is to present the data that guide clinicians on four important questions that arise with respect to the surgical management of clinically localized and locally advanced prostate cancer.

Management controversies

One of the most controversial issues in the management of a patient with a newly diagnosed, clinically localized prostate cancer is whether or not any treatment should be recommended and, if treatment is advised, which of the available treatments is best for a particular patient. Specifically, with respect to surgery, it is debated whether or not radical prostatectomy (RP) offers a survival advantage over expectant management strategies, watchful waiting (WW), or active surveillance (AS).

At the root of this controversy are observational studies of the natural history of prostate cancer, which demonstrate that prostate cancer often manifests late in life and has a protracted clinical course [3]. The result is that up to 70% of men with prostate cancer and up to 90% of men with low-risk prostate cancer ultimately die of an unrelated cause. Another way of looking at it is that, on average, one in five or six men will be diagnosed with prostate cancer, but only one in 35 will potentially die of it. These data often fuel the debate and are even more controversial when treatment-related side effects are factored into the decision-making. Despite these sobering statistics, the fact remains that the majority of American men opt for initial treatment, and surgery is the most common form of treatment chosen, although there may have been some increase in the use of AS for low-risk disease in recent years [4–7]. Therefore, in this chapter, we focus on the available data to inform the comparative effectiveness of surgery versus observation for localized prostate cancer.

Following the review of the data on *whether to treat*, we address the equally challenging clinical dilemma of *how best to treat* men with localized disease who are at high risk for recurrence and mortality. Specifically, we explore the strategies designed to reduce the risk of disease recurrence and disease-specific mortality among men undergoing RP who are at high risk for recurrence and mortality with surgery alone. We present the available data on the use of neoadjuvant and adjuvant chemotherapy and hormonal therapy, and also adjuvant radiation therapy.

Clinical question 1

In considering management for clinically localized prostate cancer, is there a benefit to surgical intervention compared with observation (watchful waiting or active surveillance, WW/AS)?

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Literature search

We performed a search of PubMed for any English-language studies published up to June 2015 pertaining to this topic. We restricted our search to clinical trials. We included the following search terms in the queries: "watchful waiting" or "observation" or "surveillance" and "radical prostatectomy" and "prostate cancer."

The evidence

Randomized controlled trials (RCTs)

There are four completed RCTs that compare survival outcomes in men with clinically localized prostate cancer who were randomized to surgery or WW/AS, one of which included a radiation therapy (RT) arm [8–10]. These are presented in Table 26.1. In a high-quality randomized trial from the Scandinavian Prostate Cancer Group, Bill-Axelson et al. demonstrated advantages for RP over WW in a mixed population of clinically detected, localized prostate cancer patients [11]. The study randomized 695 Scandinavian men, with clinical stage T1 or T2 disease, well differentiated or moderately differentiated according to World Health Organization (WHO) criteria, with a negative bone scan and prostate-specific antigen (PSA) <50. Whereas the earlier report with 5-year outcomes data had failed to demonstrate an overall survival advantage for surgery, the 10-year outcome data, and subsequent analyses, did reveal such an advantage [9, 11]. By a median follow-up of 23.2 years, the absolute reduction in risk was 12.7% (56.1 vs. 68.9%) and the corresponding relative risk (RR) of overall mortality in patients randomized to surgery was 0.71 (95% confidence interval [CI] 0.59–0.86, $p<0.001$). RP also proved to have advantages over WW in reducing the risk of distant metastases, 26.1 vs. 38.3% (RR 0.57, 95% CI 0.44–0.75, $p<0.001$), and disease-specific mortality, 17.7 vs. 28.7% (RR 0.56, 95% CI 0.41–0.77, $p=0.001$). Prespecified subgroup analyses found that men <65 years of age had superior outcomes in terms of overall mortality, disease-specific mortality, and risk of metastases with surgery compared with WW. Men 65 years and older saw a reduction in metastases with surgery, but not in overall mortality and disease-specific mortality. Surgery was advantageous for all three outcomes in men with intermediate-risk disease. Those with low-risk disease had superior overall mortality and freedom from metastases, but not disease-specific mortality. Benefits of surgery in the high-risk group were limited to reduced risk of hormone therapy (59.3 vs. 88.1%, $p<0.001$).

This is an important landmark study because it is the first reliable evidence of a survival advantage for men with localized prostate cancer who undergo surgical treatment rather than WW. However, its applicability to the contemporary clinical presentation has been called into question. The population studied by the Scandinavian Prostate Cancer Group had clinically detected cancers (76% were palpable) that ranged from low- to high-risk disease. By contrast, the cohort studies of conservative management in Europe and North America enroll men with screening-detected, low-risk, low-volume prostate cancer, with characteristics suggestive of indolent disease [12, 13].

Moreover, the trend in conservative management of low-risk clinically localized prostate cancer is toward AS and away from WW [7]. In AS, the aim is to spare the patient the morbidity of treatment until or unless signs of progression are detected in a fairly rigorous surveillance protocol. At that point, treatment with curative intent is initiated. By contrast, the aim of WW is to intervene with systemic palliative therapy if symptoms of advanced disease arise. Thus, although the Scandinavian study demonstrates a survival advantage for surgery over WW in a mixed population of men with prostate cancer, it remains unclear whether surgery offers advantages over AS in a screening-detected population of low-risk prostate cancer patients.

A similarly designed trial was conducted within the Veterans' Administration hospitals in the USA, known as the PIVOT trial [10]. The original accrual goal of 2000 men was not met, as 731 men were accrued over an 8-year period. At a median of 10.0 years of follow-up, there was no difference between treatment groups in all-cause mortality or prostate cancer mortality, but men who underwent surgery had a lower risk of bone metastases compared with those on WW (4.7 vs. 10.6%, hazard ratio [HR] 0.40, 95% CI 0.22–0.70, $p<0.001$). In planned subgroup analyses, patients with a PSA >10 who underwent surgery had a lower risk of all-cause mortality (HR 0.67, 95% CI 0.48–0.94), as did those with intermediate-risk disease (HR 0.69, 95% CI 0.49–0.98). Prostate cancer-specific mortality seemed to favor high-risk patients who underwent RP (HR 0.40, 95% CI 0.16–1.00). Erectile dysfunction and urinary incontinence were more common among those treated with surgery.

The PIVOT trial has been criticized heavily for several reasons. First, although a 10-year life expectancy was an enrollment criterion, nearly half of patients had died by the close of the study (median follow-up 10.0 years.) Therefore, some argue that the study shows that surgery may not be beneficial in men with a 10-year life expectancy, but may not be informative for men with a life expectancy of >10 years, the group in which guidelines recommend considering surgery [14]. Second, the study fell far short of its accrual goal, suggesting that it may have been underpowered to detect important differences in outcome between groups.

Another RCT comparing RP with WW was performed by the Veterans Administration Cooperative Urological Research Group (VACURG) and was reported by Iversen et al. [8]. This was a very small study, involving only 142 patients, 66 of whom had palpable disease. After 23 years of follow-up, there was no significant difference in overall survival between groups. Not surprisingly, age and grade were strongly predictive of overall mortality. As the authors pointed out, it is difficult to draw conclusions with regard

to the efficacy of surgery compared with WW in light of the "lack of statistical power and methodological flaws."

The most recently published randomized trial is the ProtecT trial, which accrued 1643 men, who were randomized to active monitoring (AM) (545 men), RP (553), or external beam radiation therapy (EBRT) (545 men) [15]. After 10 years of follow-up, the authors found no difference in prostate cancer mortality or all-cause mortality among groups. However, the incidence of clinical progression was significantly higher in the AM group compared with the RP and EBRT groups (22.9 vs. 8.9 and 9.0 per 1000 person-years, respectively, $p<0.001$), and the same was true for the incidence of metastatic disease ($p=0.004$; see Table 26.1). There were significant differences between treatments in urinary, sexual, and bowel side effects of treatment [16]. Although the magnitude of difference needed to achieve clinical significance was not defined in the study, RP was associated with statistically significantly worse sexual and urinary incontinence scores compared with EBRT and AM. There was no difference among groups in urinary bother subscore or urinary obstructive/irritative subscale scores, and nocturia twice or more per night was better with RP than EBRT and AM. Bowel function scores were better for RP and AM than EBRT for each of the reported scales and individual items. Overall quality of life, anxiety, and depression scores were similar across groups.

This trial is critically important because it demonstrates the feasibility of randomizing men to different treatments, which has otherwise been difficult to achieve. The investigators succeeded in accruing, randomizing, and following

Table 26.1 Randomized controlled trials comparing surgery with observation (watchful waiting or active surveillance, WW/AS) for the management of clinically localized prostate cancer.

Study	Enrollment period	Criteria	Intervention	Results
Wilt et al. [10]	1994–2002	cT1 or T2 PSA <50 ng/mL At least 10-year life expectancy[a]	WW ($n=367$) RP ($n=364$)	*At 10.0-year median follow-up* RP vs. WW: disease-specific mortality 5.8 vs. 8.4% (HR 0.63, 95% CI 0.36–1.09, $p=0.09$) RP vs. WW: overall mortality 47.0 vs. 49.9% (HR 0.88, 95% CI 0.71–1.08, $p=0.22$) Benefit for RP suggested in planned subgroup analyses among men with PSA >10 ($p=0.04$) and intermediate- or high-risk tumors ($p=0.07$)
Bill-Axelson et al. [9]	1989–1999	cT1 or T2 PSA <50 ng/mL	WW ($n=348$) RP ($n=347$)	*At 23.2-year median follow-up* RP vs. WW: disease-specific mortality 17.7 vs. 28.7% (RR 0.56, 95% CI 0.41–0.77, $p=0.001$) RP vs. WW: overall mortality 56.1 vs. 68.9% (RR 0.71, 95% CI 0.59–0.86, $p<0.001$) RP vs. WW: distant metastases 26.1 vs. 38.3% (RR 0.57, 95% CI 0.44–0.75, $p<0.001$) Benefit greatest in men <65 years old at diagnosis and intermediate-risk disease. Significantly lower risk of metastases in patients aged 65+ years ($p=0.04$), and lower risk of metastases ($p=0.006$) and overall mortality ($p=0.002$) among those with low-risk disease
Iversen et al. [8]	1967–1975	VACURG stage I or II	Oral placebo ($n=68$) RP + oral placebo ($n=74$)	*At 23-year median follow-up* RP vs. WW: median overall survival 10.6 vs. 8.0 years ($p=$NS). Gleason grade 7–10 vs. ≤4 (RR 5.2, $p<0.001$)
Hamdy et al. [15]	1999–2009	Localized prostate cancer[b] PSA 3.0 to <20 ng/mL At least 10-year life expectancy	AM ($n=545$) RP ($n=553$) EBRT ($n=545$)	*At 10-year follow up* Prostate cancer deaths per 1000 person-years: AM 1.5; RP 0.9; EBRT 0.7 ($p=0.48$) Metastases per 1000 person-years: AM 6.3; RP 2.4; EBRT 3.0, $p=0.004$

NS, not significant; PSA, prostate-specific antigen; RP, radical prostatectomy; AM, active monitoring; EBRT, external beam radiotherapy; RR, relative risk; VACURG, Veterans Administration Cooperative Urological Research Group; WW, watchful waiting.

[a] Although the study required a 10-year life expectancy, nearly 50% of men were dead at 10-year follow-up, and the accrual fell far short of the original goal of 2000 men, casting some doubt on the generalizability of the results.

[b] 77% of men had Gleason 6 prostate cancer and 76% had T1c disease, indicating that this was largely a low-risk cohort.

these patients, and in measuring salient oncological and patient-reported outcomes over a long follow-up period. The study demonstrates that treatment prevents adverse oncological outcomes compared with AM. It also shows that, up to 10 years, prostate cancer mortality is uncommon regardless of treatment group, AM, RP, or EBRT, and neither prostate cancer mortality nor all-cause mortality differs between groups. However, the study can be criticized for several shortcomings. First, the population was largely low risk – the study may not be sufficiently powered to compare management options in intermediate- and high-risk disease, and the data were not presented in a way that answers the question of which treatment is best for men most likely to experience progression. Second, the treatments administered in the study may not reflect the current management options. About 87% of RP patients in ProtecT had open surgery, compared with over 80% having robotic surgery in the USA in recent years [17–19]. EBRT patients in ProtecT underwent 3D conformal radiotherapy with androgen deprivation therapy (ADT) regardless of risk stratum, whereas intensity-modulated radiation therapy with selective use of ADT is the current standard in the USA [20–22]. Patients of all risk strata were randomized to AM (whereas contemporary guidelines recommend observation only for patients with low-risk disease or a life expectancy <10 years), and the AM protocol did not include routine repeat biopsies [23, 24]. Finally, the study included 99% white European men, making it difficult to apply to more diverse populations.

Population-based observational studies

There are a number of population-based observational studies that demonstrate a survival advantage for surgery over conservative management of prostate cancer (Table 26.2) [25–32]. One of these studies failed to demonstrate an advantage of active treatments over conservative management [25]. The authors hypothesized that their appropriate use of an intention-to-treat analysis (whereby patients who had aborted prostatectomies after the discovery of positive lymph nodes were grouped with patients who had completed prostatectomies) evened the playing field for comparisons with other treatments in which lymph nodes are evaluated only by clinical means. This point is valid, as using a treatment-received approach would tend to enrich the prostatectomy group with lower risk men and those with advanced disease would end up in the observation group. However, other studies, such as that by Wong et al. [27], demonstrate a survival advantage for surgery in a lower risk population, with a low likelihood of aborted prostatectomy due to positive nodes.

Although observational studies are subject to bias by indication, making it difficult to attribute observed differences to treatment group reliably, these population-based observational studies suggest that there is a disease-specific survival advantage for patients undergoing surgery for treatment of clinically localized prostate cancer compared with men managed conservatively. Several of the studies actually demonstrate an overall survival advantage for patients managed surgically.

Other studies

Several groups have undertaken meta-analyses of this topic [2, 33, 34]. One from the Agency for Healthcare Research and Quality drew heavily on an earlier effort by the American Urological Association, and was updated more recently. These meta-analyses point out the paucity of high-quality evidence on which to base treatment decisions among the various management options.

There are numerous case series that describe single- or multi-institution experiences and pooled analyses looking at either surgery or observation [35–44]. Although each option can be shown to have excellent long-term disease-specific survival in appropriately selected patients, these studies are not particularly useful in comparing the two management strategies. For the most part, these studies are considered low-grade evidence.

There are two nonrandomized, retrospective case–control series comparing immediate surgery with delayed surgery [45, 46]. In one, a group of 38 men who were enrolled in an AS protocol at Johns Hopkins University went on to have delayed surgery at a median of 26.5 months after diagnosis [45]. Their pathological outcomes were compared with those of 150 patients with matched baseline clinical characteristics. Each group had a similar likelihood of adverse pathological findings. The other study of this type looked at 865 men with low-risk prostate cancer and examined the impact of the time between biopsy and surgery on the risk of biochemical progression [46]. The authors found no difference in the likelihood of biochemical progression between patients who delayed surgery for between 90 and 180 days compared with those who had surgery in less than 90 days (multivariable adjusted RR 1.10, 95% CI 0.70–1.71). However, they did find a significant trend when they included patients who delayed surgery for more than 180 days (multivariable adjusted RR 2.73, 95% CI 1.51–4.94, $p = 0.002$).

Recognizing that survival outcomes for localized prostate cancer are similar over a long period of time for different management strategies, and quality of life is a more salient outcome in many cases, some investigators have used patient-reported functional outcomes as endpoints for comparative effectiveness [47–49]. However, not all of these prospective studies include a sufficient number of observation patients to permit meaningful comparisons. The CEASAR study is a prospective, population-based observational cohort study, which is unique in that it is designed to compare the effectiveness of surgery, radiation, and AS for localized prostate cancer, with the primary outcomes being patient-reported sexual, urinary, and bowel function. That study accrued in 2011–2012; and 1- and 3-year outcomes are expected shortly, and 5-year data collection is also planned [49].

Table 26.2 Population-based observational studies comparing watchful waiting with surgery for the management of clinically localized prostate cancer.

Study	Enrollment	Criteria	Intervention	Results
Lu-Yao and Yao [25]	1983–1992 SEER database	Clinically localized disease. Age 50–79 years	RP (n=24 257, 40.5%) RT (n=15 721, 26.3%) Conservative management (n=19,898, 33.2%)	10-year cancer-specific survival by intention-to-treat analysis: RP 83% (81–84) RT 76% (74–78) Conservative treatment 82% (81–84)
Aus et al. [26]	1987–1999 National Cancer Registry of Sweden	Nonmetastatic disease (T1–T3, NO-NX, MO) Grade 1–3. PSA missing or <50 ng/mL. Age ≤75 years	WW (n=764, 36.4%) RP (n=546, 26.0%) RT (n=289, 13.8%) ADT or other palliative treatment (n=488, 23.3%) Other (n=11, 0.5%)	Active treatment vs. WW after 15 years' follow-up: Higher disease-specific survival for RP vs. WW (HR 0.40, 95% CI 0.27–0.59, p<0.00001). No clear benefit for RT vs. WW (HR 1.01, 95% CI 0.72–1.41, p=0.98)
Wong et al. [27]	1991–1999 SEER database	cT1 or T2. Gleason grade 2–7. Age 65–80 years	WW (n=12 608) Active treatment, either RT or RP (n=32 022)	Active treatment vs. WW after 12 years of follow-up: Lower risk of death from prostate cancer (HR 0.67, 95% CI 0.58–0.77). Lower risk of death from any cause (23.8 vs. 37.0%, p<0.001) Higher 5-year overall survival: 88% (87–89) vs. 78% (77–79) Higher 10-year overall survival: 66% (64–66) vs. 51% (49–52) Hazard ratio for death RP vs. WW: 0.50 (0.47–0.53) Hazard ratio for death RT vs. WW: 0.81 (0.78–0.85)
Liu et al. [28]	1992 SEER database	Local/regional disease. Age 65–74 years. Comorbidity score ≤1	RP (n=2567, 43.9%) RP+RT (n=302, 5.2%) RT (n=2006, 34.3%) WW (n=970, 16.6%)	Overall survival in months, adjusted HR for death: RP 127.8 mo; 0.31 (0.25–0.37) RP+RT 120.0 mo; 0.38 (0.28–0.52) RT 112.5 mo; 0.68 (0.56–0.81) WW 101.2 mo; 1.00 (reference) Disease-specific survival in months, adjusted HR: RP 139.7 mo; 0.17 (0.10–0.28) RP+RT 135.2 mo; 0.23 (0.13–0.48) RT 134.6 mo; 0.56 (0.37–0.85) WW 129.6 mo; 1.00 (reference)
Hadley et al. [29]	1995–2003 SEER-Medicare	Tumor stage T1 or T2. Age 66–74 years	n=14 302	On traditional multivariable modeling, overall survival (HR 1.47 [1.35–1.59]) and disease-specific survival (HR 1.59 [1.27–2.00]) favor RP compared with conservative management. Propensity score adjustment yielded similar result. Instrumental variable analysis – differences not significant
Rice et al. [30]	1989–2009 Veterans Administration	D'Amico low risk. Age ≥70 years	RP (n=194, 25%) RT (n=252, 33%) WW (n=324, 42%; 110 [34%] later underwent treatment)	Overall mortality, WW without secondary treatment HR 1.94 (1.19–3.17)
Albertsen et al. [31]	1990–1992 Connecticut Tumor Registry	Localized disease. PSA <50. Age 75 years or younger	RP (n=1618) RT (n=702) WW (n=114)	At median follow-up of 13.3 years, disease-specific mortality in WW was 3.4 (1.9–5.9) times higher than in RP
Abdollah et al. [32]	1992–2005 SEER-Medicare	Tumor state T1 or T2. Age ≥65 years	RP (n=22 244, 49.8%) WW (n=22 450, 50.2%)	Cancer-specific mortality favors RP (HR 0.48 [0.38–0.59]) in propensity score-matched analysis

HR, hazard ratio; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; SEER, Surveillance Epidemiology and End Results; WW, watchful waiting.

In summary, the best available evidence regarding comparative effectiveness of RP versus WW for localized prostate cancer comes from one high-quality RCT, two underpowered RCTs, and a number of large population-based observational studies. Thus, by GRADE criteria, the evidence is of moderate grade [50]. In aggregate, the data show that patients treated with surgery have a small but measurable advantage in terms of local control, prevention of distant metastases, disease-specific survival, and overall survival. The difference in survival advantage also appears to be most pronounced among younger patients in whom follow-up for a decade or more may be required before differences become apparent. Patients with intermediate-risk disease and/or PSA >10 are most likely to benefit. The disease control and survival advantages may come at the cost of surgical morbidity, which must be factored into treatment decisions [51]. Both the Scandinavian and PIVOT RCTs showed that patients undergoing surgery experienced increased rates of erectile dysfunction and incontinence but, in SPCG4, the overall sense of well-being and subjective quality of life were comparable to those of patients on WW at a median of 4 years [52].

Although RP appears to confer a survival advantage over WW according to one RCT and several population-based observational studies, the data are inconclusive and cannot be uniformly applied. Many factors, including patient age, comorbidity, risk category, patient preferences, and expected morbidity of treatment, impact the decision of how to manage clinically localized prostate cancer [53].

Clinical implications

In patients with clinically localized, intermediate- or high-risk prostate cancer and an estimated life expectancy of >10 years, we suggest radical prostatectomy over watchful waiting (conditional recommendation based on moderate-quality evidence). This recommendation assumes that most patients place a high value on the opportunity for cure and the avoidance of prostate cancer-specific morbidity and mortality, and are willing to accept the risk of treatment-related side effects for the opportunity for cure.

In patients with clinically localized, low- or very low-risk prostate cancer and an estimated life expectancy of >10 years, we suggest active surveillance over immediate radical prostatectomy (conditional recommendation for based on low-quality evidence). This recommendation is based on the assessment that most patients with this disease stage may derive only a small absolute survival benefit from radical surgery and that this benefit, in most instances, is outweighed by treatment-related harms.

However, these men must be informed that the best available evidence does show a measurable survival advantage in favor of RP compared with WW, at least in some patient subgroups. This recommendation is substantiated by only one high-quality RCT and several large population-based observational studies.

Future research

In terms of available studies, there is a paucity of high-quality data in the literature to allow for direct comparisons among different treatment modalities for patients with clinically localized prostate cancer. In part, this is due to the failure of several randomized trials (such as SPIRIT) to accrue [54]. The Cochrane Group reviewed the available data in 2010, and concluded that the existing trials were insufficient to guide the decision among treatment options [55].

Although surgery appears to provide some advantages over observation in oncological outcomes in randomized trials, the greatest challenge may lie in individualizing therapy. Given the relatively low likelihood of dying from prostate cancer, it is clear that some men are best served by observation. To this end, we need research aimed at determining appropriate criteria for observation (perhaps based on age, comorbidities, prostate cancer characteristics, patient preferences and new biomarkers), appropriate trigger points for initiating therapy, and development of decision aids to help patients and providers align treatment with patient goals and preferences.

Clinical question 2

Does the use of neoadjuvant androgen deprivation therapy (ADT) prior to radical prostatectomy improve outcomes over radical prostatectomy alone?

Literature search

Evidence was obtained by performing a systematic literature search using PubMed for any English-language studies pertaining to this topic, published up to June 2015. A search of studies pertaining to RP was limited to those articles categorized as a clinical trial, meta-analysis or randomized controlled trial. The search was performed with the terms "neoadjuvant," "androgen deprivation," "hormone therapy," "hormonal therapy," "RP," and "prostate cancer" combined.

The evidence

There are seven RCTs comparing neoadjuvant ADT prior to RP with RP alone (Table 26.3) [56–62]. There are also three RCTs comparing short-term versus longer-term neoadjuvant ADT prior to RP [63–65]. One of these studies had a surgery-only arm and was included in the surgery-alone versus neoadjuvant ADT plus surgery analysis of margin status [64]. In addition, there is a comprehensive review and meta-analysis of the use of neoadjuvant ADT published by the Cochrane Group [66].

Impact on pathological parameters

Most studies demonstrate superior pathological parameters in patients undergoing neoadjuvant ADT. Three out of four studies that evaluated the frequency of organ-confined disease at final pathology found that organ-confined rates were higher in patients who received neoadjuvant ADT and

Table 26.3 Randomized clinical trials of neoadjuvant androgen deprivation therapy prior to radical prostatectomy.

Study	Inclusion criteria	No. of patients	Intervention	Median follow-up	Outcome measures and conclusions
Aus et al. [56]	T1b–3a, NX[a], M0 Age <75 years Life expectancy ≥10 years	126 entered 111 evaluable	RP alone (n=55) Neo-ADT[b]+RP (n=56)	82 months	No difference in overall survival: 86.4 vs. 83.6%, p=0.513 No difference in PSA progression-free survival: 51.5% for RP vs. 49.8% for ADT, p=0.588 Lower positive margin rate in ADT group: 23.6 vs. 45.5%, p=0.016
Dalkin et al. [57]	T1c, T2A, T2B PSA >4.0 ng/mL Life expectancy >10 years	61 entered 56 evaluable	RP alone (n=28) Neo-ADT[c]+RP (n=28)		No difference in likelihood of organ-confined disease No difference in positive margin rate
Klotz et al. [58]	T1 or T2 PSA <50 ng/mL Negative bone scan	213 entered	RP alone (n=101) Neo-ADT[d]+RP (n=112)	69 months	No difference in overall survival: 93.9% for RP vs. 88.4% for ADT+RP, p=NS No difference in PSA progression-free survival: 68.2% for RP vs. 60.2% for ADT, p=0.73 Lower positive margin rate in ADT group: 27.7 vs. 64.8%, p=0.001 Higher rate of organ-confined pathology: 41.6 vs. 19.8%, p=0.0017
Labrie et al. [59]	Life expectancy >10 years "Localized" prostate cancer including SV and BN invasion and ECE	161 entered	RP alone (n=71) Neo-ADT[e]+RP (n=90)		Lower positive margin rate in ADT group: 7.8 vs. 33.8%, p<0.001 Higher rate of organ-confined disease in ADT group: 77.7 vs. 49.3% Net staging change: 21.1% downstaged in ADT group vs. 33.8% upstaged in control group
Prezioso et al. [60]	T1a–T2b Life expectancy >5 years WHO performance status ≤2	183 entered 167 evaluable	RP alone (n=81) Neo-ADT[f]+RP (n=86)		Lower rate of upstaging in ADT group: 67 vs. 93%, p=0.001 Lower positive margin rate in ADT group: 39 vs. 60%, p=0.01 Lower rate of positive lymph nodes in ADT group: 3 vs. 11%, p not given
Schulman et al. [61]	T2–T3, N0 PSA <100 ng/mL	487 entered 402 eligible 398 evaluable	RP only (n=210) Neo-ADT[g]+RP (n=192)	4 years	Higher rate of downstaging in ADT group: 15 vs. 7%, p<0.01 Lower positive margin rate in ADT group: p<0.01 for cT2; p=0.01 for cT3 No difference in PSA progression-free survival: 33% for RP vs. 26% for ADT, p=0.18 No difference in overall survival: 95% for RP vs. 93% for ADT+RP, p=NS
Soloway et al. [62]	T2bNXM0 Age <75 years PSA <50 ng/mL Normal bone scan	303 entered 282 eligible 275 evaluable	RP only (n=138) Neo-ADT[h]+RP (n=137)	5 years	No difference in seminal vesicle invasion: 15 vs. 22%, p=NS No difference in lymph node invasion: 6 vs. 6%, p=NS Lower positive margin rate in ADT group: 18 vs. 48%, p<0.001 No difference in PSA progression-free survival: 67.6% for RP vs. 64.8% for ADT, p=0.663

NS, not significant; Neo-ADT, neoadjuvant androgen deprivation therapy; PSA, prostate-specific antigen; RP, radical prostatectomy.

[a] Patients were excluded if found to have positive lymph nodes in frozen sections.

[b] Triptorelin depot 3.75 mg intramuscular, monthly for 3 months, with cyproterone acetate 1 week before and 2 weeks after the first triptorelin injection to prevent flare phenomenon.

[c] Goserelin acetate 3.6 mg subcutaneous, monthly for 3 months.

[d] Cyproterone acetate 100 mg by mouth, 3 times daily for 3 months.

[e] Flutamide plus a luteinizing hormone-releasing hormone (LHRH) agonist for 3 months.

[f] Leuprolide acetate 3.75 mg intramuscular, monthly for 3 months, with cyproterone acetate 1 week before and 2 weeks after the first leuprolide injection

[g] Goserelin 3.6 mg subcutaneous, monthly for 3 months, and flutamide 250 mg orally, three times per day for 3 months.

[h] Leuprolide acetate 7.5 mg intramuscular, monthly for 3 months, and flutamide 250 mg orally, three times per day for 3 months.

this was significant in the Cochrane Group's meta-analysis (overall OR 2.30, 95% CI 1.72–3.08, $p<0.00001$) [57–59, 61, 66]. Similarly, both studies that evaluated pathological downstaging found a higher rate of downstaging in patients who underwent neoadjuvant ADT (overall OR 2.42, 95% CI 1.50–3.90, $p=0.000$) [59, 61, 66].

Seven out of eight studies showed superior positive margin rates in patients undergoing neoadjuvant ADT (overall OR 0.34, 95% CI 0.27–0.42, $p<0.00001$) [56–61, 64, 66]. There were mixed results in the two studies that looked at seminal vesicle invasion rates [58, 62]. There were also mixed results in the five studies that looked at lymph node involvement, but the overall effect favored the neoadjuvant ADT group on the meta-analysis (overall OR 0.63, 95% CI 0.42–0.93, $p=0.02$) [57, 58, 60–62, 66]. A meta-analysis of the three studies that compared short-term with long-term neoadjuvant ADT showed superior surgical margin rates (overall OR 0.56, 95% CI 0.39–0.80, $p=0.002$ for case analysis) and higher rates of organ-confined disease (OR 1.41, 95% CI 1.05–1.89, $p=0.02$) with longer duration of therapy [63–65].

Cancer control outcomes

Three studies compared overall survival in patients undergoing neoadjuvant ADT prior to RP versus those receiving immediate RP [56, 58, 61]. None showed a statistically significant survival advantage for either group and this was confirmed on the meta-analysis (pooled OR 1.11, 95% CI 0.67–1.85, $p=0.69$) [59, 66]. Four studies compared disease-free survival as measured by detectable PSA [56, 58, 61, 62]. None demonstrated a statistically significant difference between groups. However, in one study, the investigators performed a subgroup analysis that demonstrated a small but significant advantage for cT2 patients who underwent neoadjuvant ADT (recurrence rate at 4 years 3 vs. 11%, $p=0.03$) [61]. Another study showed that men with a baseline PSA >20 ng/mL had a measurable benefit in terms of biochemical recurrence-free survival (30.5 vs. 18.8%, $p=0.015$) [58]. Despite the results of these small subset analyses, the meta-analysis showed no benefit to neoadjuvant ADT with regard to 5-year disease-free survival (pooled OR 1.24, 95% CI 0.97–1.57, $p=0.13$) [66].

In summary, although neoadjuvant ADT prior to RP leads to improved pathological outcomes, a benefit in terms of biochemical recurrence-free survival or overall survival has not been demonstrated. The data supporting superior pathological outcomes in patients undergoing neoadjuvant ADT are consistent and of high grade. The cancer control outcome data are of moderate grade, owing to inconsistency, fewer studies, and, potentially, insufficient follow-up to demonstrate overall survival differences. Additionally, most of these studies were designed to demonstrate pathological outcomes and were underpowered to demonstrate differences in either disease-free or overall survival. In summary, the data show that neoadjuvant ADT prior to RP yields superior pathological outcomes, particularly with respect to improved margin status. However, these findings did not translate into a biochemical recurrence-free or overall survival benefit.

Clinical implications

We recommend against neoadjuvant ADT prior to RP (strong recommendation based on moderate-quality evidence). This recommendation is based on a large body of evidence that indicates that although pathological outcomes are improved, this does not translate into improved disease-specific survival and is also associated with added risk of adverse events.

Future research

Might there be settings in which neoadjuvant ADT would be appropriate? The evidence for the ability of neoadjuvant ADT to result in pathological downstaging, higher rates of organ-confined disease, and lower rates of positive surgical margins suggest that neoadjuvant ADT may have a role in patients with bulkier tumors. However, this concept remains to be tested.

Several additional questions about the use of neoadjuvant ADT remain to be fully explored. First, why is there a discrepancy between the superior pathological findings and the absence of a cancer outcome or survival benefit? Some have suggested that it is due to alterations in the histological appearance of the prostate and prostate cancer induced by the androgen deprivation [67, 68]. Better methods of pathological evaluation may prove revealing.

Second, might there be synergistic effects between neoadjuvant ADT and systemic chemotherapy that would lead to a net survival benefit?

Third, can we demonstrate a survival benefit or improvement in biochemical disease-free rates by improving the trial design, power of the study, or length of follow-up in these types of studies? In the study with the longest follow-up (about 7 years) by Aus et al. [56], 84.4% of patients who had RP alone were still alive and 82.6% of patients who had neoadjuvant ADT were still alive at the time of last evaluation. However, given the relatively small numbers and other limitations cited, it is unlikely that any definitive improvement will be ascertained from the aforementioned studies.

Clinical question 3

Does neoadjuvant systemic chemotherapy prior to radical prostatectomy improve outcomes over radical prostatectomy alone?

Literature search

Evidence was obtained by performing a systematic literature search using PubMed. The search was performed with the terms "neoadjuvant," "chemotherapy," and "prostate cancer" combined with the clinical query filter function to limit the search to the English language. A search limit

was also utilized to search for those articles pertaining to RP and categorized as a clinical trial, meta-analysis, or randomized controlled trial. Studies published up to June 2015 were included.

The evidence

There are no adequately powered RCTs that have been completed evaluating the use of neoadjuvant chemotherapy combined with RP compared with RP alone. However, there have been several promising clinical trials evaluating the efficacy of several neoadjuvant chemotherapy regimens prior to RP (Table 26.4).

In one of the larger trials, Van Poppel et al. randomized 130 patients with clinical T2b and T3 disease to either 560 mg of estramustine daily for 6 weeks prior to RP, or RP alone [69]. Although the positive surgical margin rates decreased in the neoadjuvant group, this benefit did not extend to patients with clinical T3 tumors.

Pettaway et al. performed a Phase II study in which 33 patients with high-risk disease characterized as being clinical stage T1–2, Gleason score ≥8, or T2b–T2c, Gleason score of 7 and serum PSA >10 ng/mL or clinical stage T3 received 12 weeks of ketoconazole and doxorubicin alternating with vinblastine, estramustine, and androgen ablation followed by prostatectomy [70]. On pathological evaluation, 33% of the patients had organ-confined disease, 63% had negative lymph nodes, and 17% had positive surgical margins. Serum PSA was undetectable postoperatively in all patients. At a median follow-up of 13 months, 61% of patients showed no biochemical evidence of disease. However, the primary goal of achieving a 20% rate for pT0 status was not achieved in this study [70].

Konety et al. performed a Phase II study of 36 patients with locally advanced (stage T3 or greater) and/or high-risk tumors (Gleason score 8–10 and/or serum PSA >20 ng/mL) who received four cycles of paclitaxel, carboplatin, and estramustine followed by RP [71]. The positive surgical margin rate was 22%. The clinical stage was reduced in 39% of patients. At a median follow-up of 29 months, 45% remained free from biochemical recurrence. The clinical stage was reduced in 39% of patients [71].

Clark et al. reported a Phase II trial of 18 patients with high-risk disease (clinical stage T2b/c or T3, PSA level ≥15 ng/mL, and/or Gleason score ≥8) who received neoadjuvant estramustine and etoposide before RP [72]. Only 16 of the patients actually underwent RP. Organ-confined disease was observed in 31% and disease was confined to the prostatectomy specimen in 56% of patients. Half of the patients achieved an undetectable PSA after neoadjuvant therapy and prior to RP. All patients had an undetectable PSA postoperatively and, at a median follow-up of 14 months after RP, 78% had no biochemical evidence of disease [72].

Since the approval of the use of docetaxel in castration-resistant prostate cancer (CRPC), trials have been performed demonstrating its safety in a neoadjuvant setting [82, 83]. Dreicer et al. performed a Phase II trial consisting of 29 men with high-risk disease (clinical stage T2b–T3, PSA >15 ng/mL, and/or Gleason score ≥8) who received six doses of docetaxel 40 mg/m^2 administered intravenously weekly for

Table 26.4 Clinical trials using neoadjuvant chemotherapy ± ADT.

Trial	No. of patients	Therapy	Duration of therapy	Positive surgical margins (%)	Positive lymph node metastasis (%)	Biochemical disease-free survival	
						%	Follow-up
Van Poppel et al. [69]	130	RP vs. estramustine/RP	6 wks	N/A	N/A	84 bNED	9 mo (mean)
Pettaway et al. [70]	33	Ketoconazole/doxorubicin/vinblastine/ADT/RP	12 wks	17	37	61 bNED	13 mo (median)
Konety et al. [71]	36	Paclitaxel/carboplatin/estramustine/RP	4 cycles	22	6	45 bNED	29 mo (median)
Clark et al. [72]	18	Estramustine/etoposide/RP	3 cycles	13	13	78 bNED	14 mo (median)
Dreicer et al. [73]	29	Docetaxel/RP	6 wks	4	14	71 bNED	23 mo (median)
Febbo et al. [74]	19	Docetaxel/RP	6 mo	N/A	0	44 bNED	26.5 mo (median)
Hussain et al. [75]	21	Docetaxel/estramustine/RP	3–6 cycles	30	10	71 bNED	13 mo (median)
Prayer-Galetti et al. [76]	22	ADT/docetaxel/estramustine/RP	3 mo	26	21	42 bNED	53 mo (median)
Chi et al. [77]	72	ADT/docetaxel/RP	6 mo	27	6	70 bNED	42 mo (median)
Sella et al. [78]	22	ADT/docetaxel/estramustine	3 mo	27	18	54 bNED	23 mo (median)
Mellado et al. [79]	57	ADT/docetaxel	3 mo	35	4	65 bNED	35 mo (median)
Womble et al. [80]	22	Ketoconazole/docetaxel	3 mo	42	1.4	36.4 bNED	18 mo (median)
Narita et al. [81]	18	ADT/docetaxel/estramustine	6 wks	0	22	77 bNED	18 mo (median)

ADT, androgen deprivation therapy; bNED, no biochemical evidence of disease; N/A, not assessed; RP, radical prostatectomy; mo, months; wks, weeks.

6 weeks followed by RP [73]. On pathological review, only 11% had organ-confined disease, 89% had extracapsular extension, 14% had lymph node metastasis, and there were no pathological complete responders to docetaxel. Although 79% of patients experienced some reduction in PSA level post-chemotherapy, 24% of patients had more than a 50% reduction in PSA level in response to docetaxel alone. Postoperatively, 71% of the subjects were free from biochemical recurrence at 23 months follow-up.

Febbo et al. performed a trial utilizing neoadjuvant docetaxel prior to RP in 19 patients with high-risk PCA (clinical stage T3, PSA ≥20 ng/mL, and/or Gleason score 4+3=7 or greater) [74]. The patients received weekly docetaxel (36 mg/m^2) for 6 months, followed by RP. A reduction of at least 25 and 50% of tumor volume was seen in 68 and 21% of patients as measured by endorectal MRI, respectively. Sixteen of the 19 patients completed the chemotherapy regimen and underwent RP. On pathological evaluation, 38% had organ-confined disease, 62% had extracapsular extension, and none had lymph node metastasis. As with all the other neoadjuvant chemotherapy trials, there were no pathological complete responders. At a median follow-up of 26.5 months, seven out of 16 (44%) patients remained free of biochemical recurrence [74].

Hussain et al. combined the use of estramustine, which alters androgen metabolism, with docetaxel in 21 patients with high-risk PCA (clinical stage T2b or greater, PSA ≥15 ng/mL, and/or Gleason score ≥8) [75]. The chemotherapy regimen consisted of docetaxel (70 mg/m^2) and estramustine (280 mg three times daily) for 3–6 courses. Ten patients underwent RP, with negative surgical margins in seven patients (70%). At a median follow-up of 13 months, 71% of patients remained free of biochemical recurrence [75].

Several additional Phase II trials have been executed, using various combinations of chemotherapy and androgen deprivation therapy [76–81, 84]. In large part, these more recent Phase II studies confirm the safety of this approach, without demonstrating a clear oncological benefit.

The success of docetaxel in CRPC, along with the results of the aforementioned Phase II neoadjuvant studies, led to the development of Phase III trials by the Cancer and Leukemia Group B (CALGB 90203), and by the French Group for the Study of Geniturinary Tumors (GETUG-12) [85, 86]. CALGB 90203 randomized patients with clinical T1–T3aNXM0 PCA to either RP alone or a chemohormonal therapy regimen consisting of leuprolide acetate or goserelin for 18–24 weeks and also six cycles of docetaxel followed by RP [86]. The entry criteria also stipulated that the patients have high-risk disease with either a Gleason score of 8–10 or a probability of biochemical progression-free survival at 5 years after surgery less than 60% by Kattan nomogram prediction [87]. The goal of the trial is to enroll 750 patients, with the primary outcome being the 3-year biochemical progression-free survival rate. Enrollment was completed in October 2016 and initial results are expected in 2018.

The GETUG-12 study randomized patients to 3 years of goserelin versus goserelin plus four cycles of docetaxel and estramustine. Staging pelvic lymphadenectomy was done before randomization, and patients with negative nodes could undergo radiation or surgery, while those with positive nodes could undergo radiation or no local treatment. A total of 413 patients were randomized and followed for a median of 8.8 years. Overall, 358 (87%) had radiation, 25 (6%) had RP, and the remainder had no local treatment. Relapse-free survival was superior in the ADT plus chemotherapy group (HR 0.71, 95% CI 0.54–0.94, $p=0.017$). Overall survival was similar between groups (83% at median 8.8 years for each). Although this is a high-quality randomized trial, it contains too few men treated with prostatectomy to be informative regarding the role of neoadjuvant therapy prior to surgery.

In summary, the use of neoadjuvant chemotherapy alone or in combination with ADT prior to RP is associated with a decrease in both serum PSA levels and positive surgical margins. However, none of the agents studied to date have resulted in a pathological complete response. We await the results of ongoing and future RCTs to evaluate the efficacy of neoadjuvant chemotherapy alone or combination with ADT prior to RP to assess the true impact on overall survival.

Clinical implications

We recommend against neoadjuvant chemotherapy alone or in combination with ADT prior to RP (strong recommendation against based on low-quality evidence). This recommendation is based on the lack of evidence that any currently available regimen improves patient-important outcomes such as disease-specific survival. Given their inherent risk of adverse events (and costs), the potential harms clearly outweigh the benefits.

Future research

The true benefits of neoadjuvant chemotherapy remain to be fully explored. There is also a theoretical advantage of combining neoadjuvant ADT with systemic chemotherapy to exploit the synergistic effects of the combination therapy on tumor burden. The CALGB 90203 trial, comparing neoadjuvant ADT plus docetaxel and estramustine prior to RP with ADT plus RP alone in high-risk, clinically localized prostate cancer, may be informative in this regard [86]. Future studies may also focus on the role of novel hormonal agents, newer chemotherapies, and immunotherapy in the neoadjuvant setting.

Clinical question 4

In men with pathological T3 disease or pathological T2 disease with positive margins after RP, does adjuvant radiation therapy improve clinical outcomes?

Literature search

Evidence was obtained by performing a systematic literature search using PubMed. The search was performed with the terms "adjuvant," "radiation therapy," and "prostate cancer" combined with the clinical query filter function to limit the search to the English language. A search limit was also utilized to search for those articles categorized as a clinical trial, meta-analysis, or randomized controlled trial. Studies published up to June 2015 were included.

The evidence

Several RCTs have been performed comparing RP followed by immediate adjuvant radiation therapy with RP alone in men with pathological T3 disease or pathological T2 disease with positive margins (Table 26.5) [88–93]. In addition, Morgan et al. performed a meta-analysis of EORTC 22911 and SWOG 8794 trials [94].

EORTC 22911, reported by Bolla et al., was a multi-institutional RCT designed to compare RP followed by immediate adjuvant radiation ($n=502$) with RP alone ($n=503$) for patients with positive surgical margins or pT3 prostate cancer [88]. Immediate postoperative radiotherapy consisted of 60 Gy conventional radiation delivered over 6 weeks. Radiotherapy was instituted within 16 weeks of surgery irrespective of PSA level and only after patients had recovered from surgery and were without major voiding complaints. Patients were eligible for the trial if they were ≤75 years of age and had pN0M0 tumors with one or more high-risk pathological risk factor including extracapsular extension, positive surgical margins, or seminal vesicle invasion. The primary endpoint was biochemical progression-free survival. After a median follow-up of 5 years, the patients in the irradiated group had a significantly improved freedom from biochemical progression compared with RP alone (HR 0.48, 98% CI 0.37–0.62, $p<0.0001$). Clinical progression-free survival was also significantly improved ($p=0.0009$). Ten-year results were similar [89]. Patients with positive surgical margins benefited the most from postoperative radiotherapy, while the benefits were attenuated among patients over 70 years of age. Grade 2 or 3 late toxicities were more frequent in the irradiated group ($p=0.0005$), and severe toxicities (≥grade 3) were rare in either group and not significantly different. The authors concluded that immediate postoperative radiotherapy might improve clinical progression-free survival in those younger than 70 years and those with positive surgical margins [95].

SWOG 8794 was an RCT designed to determine if adjuvant radiotherapy after RP improves metastasis-free survival in patients with stage pT3N0M0 PCA [90, 91]. After undergoing RP, 214 patients were randomized to receive 60–64 Gy of external beam radiotherapy in 30–32 fractions to the prostatic fossa and another 211 patients to receive observation. Of those men randomized to observation, 70 (33%) ultimately crossed over to receive salvage radiation. Radiotherapy was administered within 18 weeks of surgery, and an undetectable PSA level was not required at enrollment. Patients were eligible for the trial if they had pN0M0 tumors with one or more high-risk pathological risk factor including extracapsular extension, positive surgical margins, or seminal vesicle invasion. Patients were excluded from randomization for total urinary incontinence, rectal injury, persistent urinary extravasation, or pelvic infection. The primary endpoint of the study was metastasis-free survival defined as time to first occurrence of metastatic disease or death due to any cause. An interim analysis of the trial with a median follow-up of 10.6 years demonstrated no statistical difference in metastasis-free survival or overall survival [90]. However, there was a significant improvement

Table 26.5 Randomized trials comparing adjuvant radiation with observation after RP for advanced pathological features.

Trial	Inclusion criteria	No. randomized	Time to initiation of adjuvant RT (weeks)	Median follow-up (years)	Primary endpoint	Outcomes
EORTC 22911 [88, 89, 95]	EPE, SVI, and/or PSM; age ≤75 years	1005	<16	10.6	BPFS	Improved BPFS (HR 0.49, 98% CI 0.41–0.59, $p<0.0001$)
SWOG 8794 [90, 91, 96]	EPE, SVI, and/or PSM; SWOG PS 0–2	431	<18	12.7	MFS	Improved MFS (HR 0.71, 95% CI 0.54–0.94, $p=0.016$) Improved OS (HR 0.72, 95% CI 0.55–0.96, $p=0.023$)
German Cancer Society ARO 96-02 and AUO AP 09/95 [92, 93]	EPE or SVI with or without PSM; undetectable PSA after RP	307	8–12	9.4	BPFS	Improved BPFS (HR 0.51, 95% CI 0.37–0.70, $p<0.0001$)

ADT, androgen deprivation therapy; BPFS, biochemical progression-free survival; EORTC, European Organization for the Research and Treatment of Cancer; EPE, extraprostatic extension; MFS, metastasis-free survival; NR, not reported; PS, performance status; PSM, positive surgical margin; RT, radiotherapy; SVI, seminal vesicle invasion; SWOG, Southwest Oncology Group.

in PSA relapse with adjuvant radiotherapy with a median biochemical recurrence-free interval of 10.3 years versus 3.1 years for observation (HR 0.43, 95% CI 0.31–0.58, $p<0.001$). Disease recurrence was also significantly reduced with radiotherapy with a median recurrence-free survival of 13.8 years versus 9.9 years for observation (HR 0.62, 95% CI 0.46–0.82, $p=0.001$). Additionally, adjuvant radiation was found to reduce the risk of initiation of hormonal treatment (HR 0.45, 95% CI 0.29–0.68, $p<0.001$). An update of this study confirmed that adjuvant radiotherapy was associated with significant improvement in metastasis-free survival (HR 0.71, 95% CI 0.54–0.94, $p=0.016$) and overall survival (HR 0.72, 95% CI 0.55–0.96, $p=0.023$) at a median follow-up of about 12.5 years [91]. More rectal complications, urethral strictures, and total urinary incontinence were encountered in patients who received adjuvant radiation. Similarly to EORTC 22911, a subset analysis demonstrated that patients who had positive surgical margins benefited the most from adjuvant radiation therapy [96].

The multi-institutional German Cancer Society ARO 96-02/AUO AP 09/95 trial randomized 307 patients with pT3–4N0M0 PCA with or without positive surgical margins after RP to observation or 60 Gy of adjuvant radiotherapy given in 30 fractions [92, 93]. Similarly to SWOG 8794, patients in EORTC 22911 were eligible for enrollment irrespective of postoperative PSA level. However, patients in the German Cancer Society trial were only eligible for randomization if they achieved an undetectable PSA postoperatively. The primary endpoint of the study was biochemical progression-free survival. At a median follow-up of 9.4 years, the HR for biochemical progression-free survival in the adjuvant radiation arm was 0.51 (95% CI 0.37–0.70, $p<0.0001$). Ten-year Kaplan–Meier estimates for PFS were 35 vs. 56% ($p<0.0001$). There were too few events to compare treatment groups with respect to distant metastases or survival. Toxicities were reported only in the adjuvant radiotherapy arm in this trial. The authors reported three grade 2 genitourinary adverse events (2%), two grade 2 gastrointestinal events (1%), and one grade 3 genitourinary event (3%). Overall, 21.9% of adjuvant radiation patients reported an adverse event (grade 1 or higher) in the bladder or rectum, compared with 3.7% in the non-treatment arm ($p<0.00001$).

In summary, adjuvant radiotherapy after RP given to men with pT3N0M0 PCA significantly reduces the risk of PSA recurrence, metastasis, and need for hormonal therapy, and results in an improvement in overall survival compared with observation alone.

Clinical implications

In patients with pT2 prostate cancer with positive surgical margins and patients with pT3 prostate cancer irrespective of margin status, we suggest adjuvant radiotherapy (conditional recommendation for based on moderate-quality evidence). This recommendation assumes that these patients place a high value on an opportunity for secondary cure and a relatively lower value on the avoidance of radiation-related side effects.

Future research

Although the available trials have addressed the question of whether patients with pT3 PCA with or without positive margins after RP benefit from immediate adjuvant radiotherapy compared with observation, perhaps the more relevant question to clinical practice is the timing of the administration of the radiotherapy, either when PSA is undetectable (adjuvant radiotherapy) or when it becomes detectable or surpasses a certain threshold (salvage radiotherapy). At issue is the observation that not all men with these pathological findings are destined for recurrence. Some retrospective studies have estimated the risk of recurrence at approximately 40% within 4 years, with factors such as pathological Gleason score and margin status distinguishing between those at high risk for recurrence and those at lower risk [97]. The limited recurrence rates, the lack of uniform evidence regarding an overall survival benefit, and the known genitourinary and gastrointestinal toxicities of adjuvant and salvage radiotherapy provide the incentive for initial observation despite the evidence supporting adjuvant radiotherapy. Indeed, despite relatively strong recommendations from the AUA and ASTRO [34, 98]. utilization remains <20% of eligible cases, up only slightly from 13.5% before 2009 to 15.8% after the publication of the SWOG trial [99].

Recognizing the inherent limitations of subgroup analyses, for the subset of patients in the SWOG 8794 trial who were initially observed and then received salvage radiation at the time of PSA failure, metastasis-free survival was inferior to that of those who received radiotherapy when PSA was still undetectable [91]. Radiotherapy and Androgen Deprivation in Combination after Local Surgery (RADICALS) is a Phase III trial currently accruing patients that is designed to address the optimal timing of the administration of postoperative radiation and to determine the optimal duration of hormonal therapy with adjuvant radiation to the prostate bed after RP. This trial randomizes patients with high-risk features such as pT3, positive margins, Gleason score >6 or PSA >10 ng/mL to either adjuvant radiation or salvage radiation at the time of biochemical failure (defined as two consecutive rises in PSA and PSA >0.1 ng/mL or three consecutive rises in PSA) radiotherapy. A second randomization attempts to determine the optimal duration of hormonal therapy with adjuvant radiotherapy by randomizing patients to radiotherapy alone, radiotherapy plus 6 months of androgen deprivation therapy, or radiotherapy plus 2 years of androgen deprivation therapy. The RADICALS trial aims to recruit more than 4000 patients, so widespread support from urologists, medical oncologists, and radiation oncologists will be

required for successful completion of this trial to answer these important clinical questions [100]. There are two additional trials, RAVES (NCT00860652) in New Zealand and Australia and GETUG-17 (NCT00667069) in France, that also seek to define the optimal timing of postsurgical radiotherapy [101]. In addition to these trials, there are other biomarker studies intended to risk stratify patients with respect to the likelihood of benefit from adjuvant radiotherapy [102].

Clinical question 5

In men with locally advanced prostate cancer, does adjuvant systemic therapy after RP improve clinical outcomes?

Literature search

Evidence was obtained by performing a systematic literature search using PubMed. The search was performed with the terms "adjuvant," "androgen deprivation," "chemotherapy," and "locally advanced prostate cancer" combined with the clinical query filter function to limit the search to the English language. A search limit was also utilized to search for those articles categorized as a clinical trial, meta-analysis, or randomized controlled trial. Studies published before June 2015 were included.

The evidence

There are three RCTs and a report of pooled results for three RCTs evaluating the use of adjuvant hormonal therapy after RP in men with locally advanced disease (Table 26.6) [103–107]. Messing et al. aimed to determine whether immediate androgen deprivation therapy (ADT) extends survival in men with node-positive PCA [103, 105]. In the study, 98 node-positive men who were status post-RP were randomized to immediate ADT (3.6 mg goserelin subcutaneously every 28 days or bilateral orchidectomy, by choice of the patient) or to observation with ADT to be given upon detection of distant metastasis or symptomatic recurrences. The primary endpoint was progression-free survival, the secondary endpoint being overall and disease-specific survival. With a median follow-up of 11.9 years, men who received immediate ADT had improved overall survival (HR 1.84, 95% CI 1.01–3.35, $p=0.04$), prostate cancer-specific survival (HR 4.09, 95% CI 1.76– 9.49, $p=0.0004$), and progression-free survival (HR 3.42, 95% CI 1.96–5.98, $p<0.0001$).

In the RCT by Wirth et al., 309 men with locally advanced, lymph node-negative PCA (defined as pT3–4N0M0) were randomized to receive either flutamide 250 mg three times daily or no adjuvant treatment [106]. The primary endpoints of the study were recurrence-free survival and overall survival. Recurrence was defined as a PSA value >5 ng/mL, two values >2 ng/mL more than 3 months apart, three values >1 ng/mL more than 3 months apart, or any clinical recurrence. With a median follow-up of 6.1 years, patients who received flutamide had a better recurrence-free survival (HR 0.51, 95% CI 0.32–0.81, $p=0.0041$). However, there was no difference in overall survival (HR 10.4, 95% CI 0.53–2.02, $p=0.92$). Although there was a significant improvement in recurrence-free survival, this advantage was not without significant side effects, as 43% of the patients in the flutamide arm withdrew from the trial because of toxicities such as nausea, vomiting, and hepatotoxicity [106].

The largest of the adjuvant hormonal therapy trials was the Early Prostate Cancer Program [107, 108]. This was an international, randomized, double-blinded, placebo-controlled study designed for a combined analysis. The three component trials randomized a total of 8113 men with clinically or pathologically localized (T1–2, N0/X) or locally advanced (T3–4, any N, or any T, N+) PCA with negative bone scans for metastatic disease to either bicalutamide 150 mg oral daily or placebo following standard care (WW, RP, or radiotherapy). Here, we focus on the 1719 patients from any of the study sites with locally advanced disease who were treated with surgery. At the 7.4-year median follow-up, there was an improvement in progression-free survival for the patients who received bicalutamide compared with placebo (HR 0.75, 95% CI 0.61–0.91, $p=0.004$) [108], but this difference was not significant at further follow-up at 9.7 years [107] (Table 26.6), and there was no difference in OS at either time point]. Patients who received adjuvant bicalutamide reported that the most common side effects of treatment were breast pain (73.6%) and gynecomastia (68.8%), which were mild to moderate in >90% of cases, but caused 16.8% of patients to withdraw from treatment. Other infrequent side effects included impotence (9.3%), decreased libido (3.6%), hot flushes (9.2%), and abnormal liver function tests (3.1%) [109].

Taken together, these studies demonstrate a significant benefit to adjuvant hormone therapy compared with delayed treatment in the node-positive patient in a single, small trial [103, 105]. There appears to be no difference in OS in the node-negative patient, or in a mixed population, and the results on PFS are mixed in this population [107, 108].

The Southwest Oncology Group (SWOG) 9921 trial was designed to compare ADT (bicalutamide 50 mg daily plus goserelin acetate 10.8 mg subcutaneously every 12 weeks for 2 years total) with ADT plus chemotherapy (mitoxantrone 12 mg/m^2 every 21 days for six cycles with prednisone 5 mg twice daily for six cycles) in patients with locally advanced disease, defined as Gleason score ≥8, pT3b–T4 or N1 disease, Gleason score 7 with positive surgical margin, preoperative PSA level ≥15 ng/mL or PSA level >10 ng/mL with Gleason score ≥8 [110]. A total of 983 patients were enrolled in the trial, which was short of the goal of 1360 patients. However, owing to three reported cases of acute myelogenous leukemia (AML) in the mitoxantrone treatment arm consisting of 487 patients (0.6%), the trial was closed to further accrual in January 2007. The prevalence of AML in this cohort (0.6%)

Table 26.6 Randomized trials comparing immediate androgen deprivation after RP with observation.

Trial	Inclusion criteria	No. randomized	Treatment arms	Median follow-up (years)	Primary endpoint	Outcomes
Messing et al. [105] ECOG 3886	≤cT2 disease who had RP+BPLND with nodal disease; negative BS+CXR; no hormonal treatment before randomization	98	3.6 mg goserelin subcutaneously every 28 days or bilateral orchidectomy vs. observation	11.9	PFS	Improved: OS (HR 1.84, 95% CI 1.01–3.35, $p=0.04$), PCSS (HR 4.09, 95% CI 1.76–9.49, $p=0.0004$), PFS (HR 3.42, 95% CI 1.96–5.98, $p<0.0001$)
Wirth et al. [106]	Age ≤75years; stage pT3–4N0M0	309	Flutamide 250 mg oral t.i.d. vs. observation	6.1	PFS, OS	Improved PFS (HR 0.51, 95% CI 0.32–0.81, $p=0.0041$). No difference in OS (HR 10.4, 95% CI 0.53–2.02, $p=0.92$)
Iversen et al. [107, 108] Early Prostate Cancer Programme	Locally advanced (T3–4, any N, or any T, N+); negative BS	1719	Bicalutamide 150 mg oral daily vs. placebo	9.7	PFS, OS	No improvement in PFS (HR 0.85, 95% CI 0.71–1.01, $p=0.065$) or OS (HR 1.03, 95% CI 0.84–1.26, $p=0.817$)

BPLND, bilateral pelvic lymph node dissection; BS, bone scan; CXR, chest X-ray; OS, overall survival; PCA, prostate cancer; PCSS, prostate cancer-specific survival; PFS, progression-free survival; RP, radical prostatectomy; t.i.d., three times daily.

was similar to that in subjects with breast cancer treated with mitoxantrone. The authors published the ADT-alone arm early upon recommendation of the data safety monitoring board because mortality outcomes in that arm were far fewer than anticipated. The OS at 5 years was 95.4% (95% CI 93.0–97.8%), and freedom from recurrence was 92.7% (89.8–95.6%). The low mortality prompted the investigators to reassess the potential for a positive trial, although there is still a plan to follow these patients in an effort to detect a difference between treatment arms [110, 111]. A similar single-arm series, including 173 pT3a/b N0–1 tumors, all with positive surgical margins, showed high prostate cancer-specific survival (88.7% at 5 years) among patients treated with continuous ADT [112]. Again, the high survival rate in patients treated with adjuvant ADT made it difficult for the investigators to detect differences between luteinizing hormone-releasing hormone (LHRH) therapy and maximal androgen deprivation.

There are three Phase III trials evaluating the use of adjuvant chemotherapy with or without ADT after RP, including the SWOG 9921 trial already described. TAX 3501 is a Phase III trial of adjuvant chemotherapy in men who have undergone RP. Participants were defined as high risk if they had a 5-year freedom from disease progression of ≤60% according to nomogram predictions. Men were randomly assigned to one of the following three treatment groups: observation, leuprorelide acetate for 18 months, or leuprorelin acetate plus docetaxel 75 mg/m^2 every 3 weeks for six cycles. In a second round of randomization, patients in the observation who showed evidence of disease progression were randomly assigned to receive 18 months of either ADT or ADT plus docetaxel. Target accrual was 1696 men and the primary endpoint is progression-free survival [113]. In fact, the study randomized 228 patients. At a median follow-up of 3.4 years, there were no differences identified in PSA progression, bone metastases, or death, although the study was underpowered to detect such differences.

The Veterans Affairs Cooperative Studies Program (CSP) recently opened the Veterans Affairs CSP 553 trial (NCT00132301), called Chemotherapy After Prostatectomy for High-Risk Prostate Carcinoma [114]. This trial is designed to compare prospectively early adjuvant chemotherapy after RP using docetaxel 75 mg/m^2 every 3 weeks plus prednisone 5 mg twice daily for a total of six cycles with observation alone for patients who are potentially cured by RP but who are at high risk for relapse (defined as a >50% risk for biochemical relapse at 5 years after RP). This Phase III study was started in June 2006 and has randomized 298 patients who had clinically localized (cT1–T2) PCA and were subsequently found to have poor prognostic features after RP and pelvic lymph node dissection including stage pT3b–T4 tumors, stage pT3a tumors with Gleason score ≥7, stage pT2 tumors with Gleason score 8–10 and positive surgical margins, or preoperative PSA >20 ng/mL. The primary endpoint of the trial is progression-free survival. Secondary outcomes include metastasis-free survival, cancer-specific survival, overall survival, quality of life and toxicity, and the interval to the initiation of ADT. The CSP 553 trial is the only study to date to evaluate the efficacy of chemotherapy alone, sparing patients the toxicities associated with ADT. The initial data collection was expected to be completed in October 2015 [114].

In addition to the published trials in this area, there are several published Phase II and observational design studies that evaluate safety and efficacy of chemotherapy after surgery [115, 116]. In addition, there is some interest in the use of novel therapies, such as abiraterone, enzalutamide, immunotherapy, and targeted therapies, and also combinations of these agents with or without traditional chemotherapy in the adjuvant setting. The most exciting among these is the STAMPEDE trial (NCT00268476), which has several arms that compare various interventions with standard of care, defined as ADT with or without RT for high-risk, localized, node-negative prostate cancer after RP. Recently added arms include standard of care plus abiraterone, and standard of care plus abiraterone and enzalutamide [117]. The docetaxel versus ADT arm was presented in abstract form at the American Society of Clinical Oncology meeting in 2015 [118]. The investigators demonstrated a 10-month survival benefit for the addition of docetaxel, although the population was quite mixed, including 61% with metastatic disease and 14% with positive lymph nodes, and many who received adjuvant radiation therapy. The subgroup with M0 disease did not appear to benefit, but the final publication may be more revealing.

In summary, in the setting of high-risk pathological features at the time of prostatectomy, local therapy may be insufficient to provide long-term disease control. A multimodal approach including systemic therapy may be necessary for successful clinical outcomes, although the available data are fairly limited. Enrollment of patients into prospective clinical trials is paramount in determining the effectiveness of these chemotherapeutic regimens. As more therapies prove effective in the metastatic setting, combinations of treatments and sequencing in the adjuvant setting will be important areas of study.

Currently, the data support the use of adjuvant hormone therapy in the setting of node-positive disease, although this is based on only one small randomized trial. The available trials in lymph node negative patients with locally advanced disease indicate that although there may be a benefit in terms of progression, no long-term survival benefit has been demonstrated. Furthermore, it must be acknowledged that hormone therapy is associated with significant toxicities, including loss of libido, hot flushes, metabolic and cognitive changes, changes in bone mineral density, gynecomastia, and breast pain. Currently, there is no evidence that adjuvant chemotherapy for locally advanced or lymph node-positive

disease provides a benefit in patients with locally advanced or nodal disease following radical prostatectomy and, again, chemotherapy is associated with significant side effects.

Clinical implications

We suggest adjuvant hormone therapy in patients having undergone radical prostatectomy with node-positive disease (conditional recommendation based on low-quality evidence). This recommendation assumes that patients place a higher value on improving cancer-related outcomes and a lower value on the avoidance of treatment-related side effects.

We suggest against the use of adjuvant hormone therapy in patients having undergone radical prostatectomy with node-negative disease (conditional recommendation against based on low-quality evidence). This recommendation is based on the lack of evidence to support a benefit in the setting of likely significant adverse events.

We further recommend against the use of adjuvant chemotherapy in patients with locally advanced disease or positive lymph nodes after radical prostatectomy, in the absence of distant metastases (strong recommendation based on low-quality evidence). This recommendation is based on the lack of evidence to support a benefit in the setting of very likely considerable adverse events.

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27

CHAPTER 27

Radiation therapy for clinically localized prostate cancer

Michelle Echevarria, Peter A. Johnstone, and Kosj Yamoah

Department of Radiation Oncology, Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, FL, USA

Background

Clinically localized prostate cancer is the predominant stage at diagnosis for men in the United States, largely due to early detection. As a result, disease progression often takes a relatively indolent clinical course, with some patients outliving their prostate cancer and succumbing to other diseases. Therefore, the decision-making process for determining whether to pursue active surveillance, watchful waiting, definitive treatment, or alternative management options is complicated by the balance between life expectancy, comorbidities, clinical benefits, and the side effects of treatment. Furthermore, treatment recommendations for men with clinically localized prostate cancer have become increasingly difficult owing to the availability of various treatment options, none of which have been compared head-to-head in a large randomized trial. The current guidelines for patients with organ-confined prostate cancer include definitive modalities such as radical prostatectomy (RP) and radiation therapy (RT). Although there has been no randomized trial comparing surgery versus RT in the management of organ-confined prostate cancer, either modality of treatment is thought to provide equivalent disease-free control. Table 27.1 summarizes the National Comprehensive Cancer Network (NCCN) risk classification for organ-confined prostate cancer and lists the general recommendations for patients who are treated with radiation therapy.

The focus of this chapter is to present available evidence on several aspects of radiation treatment for men with organ-confined prostate cancer. The topics included address the different techniques and outcomes with external beam radiotherapy (EBRT), including photon and proton therapy, the use of neoadjuvant and concurrent androgen-deprivation therapy, and postprostatectomy radiation therapy.

Clinical question 1

In a patient with localized prostate cancer selecting definitive external beam radiation, what is the optimal dose regimen?

Literature search

A literature search using PubMed and MEDLINE was performed. Search terms were "prostate cancer," "dose escalation," "intensity modulated radiation therapy," "randomized control trial," "phase III trials," "three dimensional conformal radiation therapy," and "brachytherapy boost."

The evidence

EBRT is one of the main modalities available for definitive treatment of prostate cancer. With the concern that conventional dose levels of EBRT were suboptimal in controlling disease in a substantial proportion of men with localized prostate cancer, several randomized dose-escalation trials have been successfully conducted to address this issue. Furthermore, the development of modern radiation delivery technology such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) allows for dose escalation with decreased risk for gastrointestinal (GI) and genitourinary (GU) toxicity. Based on evidence from randomized prospective trials that have shown improved biochemical control with higher radiation doses (Table 27.2), the NCCN guidelines recommend delivering doses of 75.6–79.2 Gy in low-risk patients and doses of 81.0 Gy in intermediate- and high-risk patients.

A Phase III dose-escalation trial from the M.D. Anderson Hospital assessed the benefit of higher doses compared with conventional doses in the treatment of localized prostate cancer. A total of 301 patients with T1–T3 prostate cancer were randomized to receive EBRT to a dose of 70 Gy versus EBRT

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Table 27.1 NCCN risk classification.

	NCCN risk classification				
	Very low	**Low**	**Intermediate**	**High**	**Very high**
PSA	<10 ng/mL and <0.15 ng/mL/g	<10 ng/mL	10–20 ng/mL	>20 ng/mL	Any
Gleason score	2–6 in 1–2 cores	2–6 in ≥3 cores	and/or 7	8–10	Any
Stage	T1c	T1c–T2a	T2b–T2c	T3a	T3b–T4
Radiation treatment	Active surveillance	Definitive RT (EBRT or brachytherapy)	High-dose RT ± short-term ADT	High-dose RT + long-term ADT	High-dose RT + long-term ADT

ADT, androgen deprivation therapy; EBRT, external beam radiation therapy; PSA, prostate-specific antigen; RT, radiotherapy;.

to a dose of 78 Gy using three-dimensional conformal radiation therapy (3D-CRT) [1]. Of these 301 patients, 21% were low risk, 47% were intermediate risk, and 32% were categorized as high risk. With a median follow-up of 8.7 years, a significant improvement in the 8-year freedom from failure rate was observed in the dose-escalation arm compared with the conventional dose arm (78 vs. 59%, $p=0.004$). In a subgroup analysis of patients stratified by prostate-specific antigen (PSA) level, patients with PSA >10 ng/mL treated with 78 Gy obtained the greatest benefit in freedom from biochemical failure (78 vs. 39%, $p<0.001$). Dose escalation was also associated with a significantly decreased rate of clinical failure compared with the conventional dose of 70 Gy (7 vs. 15%, $p=0.014$). Although initial data did not demonstrate a difference in distant failure rates, long-term follow-up results showed a statistically significant reduction in the rate of distant failures in patients with PSA >10 ng/mL treated with 78 Gy versus those treated with 70 Gy. Patients with PSA >10 ng/mL in the dose-escalation arm had a distant failure rate of 2% versus a 15% failure rate ($p=0.016$) in patients with PSA >10 ng/mL treated in the conventional dose arm [2]. Regardless of PSA level, rates of overall survival were not statistically different between the two arms. The 10-year grade 2 (26 vs. 13%) and grade 3 (7 vs. 1%) GI toxicity was increased in the dose-escalation arm compared with the conventional dose arm, but no statistically significant differences in the rates of GU toxicity were observed.

The PROG 95-09 study by Zietman et al. also showed improved long-term control rates in patients with localized prostate cancer treated with higher doses [3]. A total of 393 patients with T1–T2 prostate cancer, with PSA <15 ng/mL and a Gleason score <7 were enrolled in the study. All of the patients received EBRT to a dose of 50.4 Gy using photons and then were randomized to receive a proton boost to a total dose of 70.2 or 79.2 Gy. The 10-year biochemical failure rate was significantly improved in the high radiation dose arm versus the conventional dose arm (16.7 vs. 32.3%, $p<0.0001$), which translated into a 10-year biochemical progression-free survival (PFS) of 83% for the dose-escalation arm versus 68% for the conventional dose arm ($p=0.0001$). Although a trend in improvement of biochemical PFS was present in both low- and intermediate-risk patients, it was of marginal significance in the intermediate-risk subgroup. When stratified by risk group, the 10-year biochemical failure rate in the low-risk group was 28.2% in the 70.2 Gy arm versus 7.1% in the 79.2 Gy arm ($p<0.0001$), whereas in the intermediate-risk group the biochemical failure rate was 42.1 vs. 30.4% ($p=0.06$). There were no statistically significant differences in overall survival among the two arms (78 vs. 83%, $p=0.41$). In terms of toxicity, no differences in the rates of grade 3 toxicity among the two treatment arms were observed. The result of this trial demonstrated that men with localized prostate cancer do benefit from treatment with dose-escalated RT without a significant increase in grade 3 toxicity.

The UK Medical Research Council carried out the RT01 trial, in which 843 patients with T1b–T3a prostate cancer with PSA <50 ng/mL were randomized to a dose of 64 Gy or were dose escalated to 74 Gy. All patients in the study received neoadjuvant antiandrogen therapy for 3–6 months prior to undergoing radiation treatment [4]. At 5 years, PFS favored the dose-escalated arm at 71 vs. 60% for the conventional dose arm ($p=0.0007$). When stratified by risk, a significant benefit was observed across all groups. In the recently updated data, with a median follow-up of 10 years, a significant improvement in the biochemical PFS was still present in the dose-escalated group (55 vs. 43%, $p=0.0003$) [5]. Consistent with the previously discussed trials, the improvement in biochemical control did not translate into an overall survival benefit (71% in both arms, $p=0.96$). Although patients in both arms of this study received antiandrogen therapy, biochemical control was still improved in the dose-escalated arm, suggesting that dose escalation is beneficial irrespective of hormone treatment.

A Dutch multicenter trial by Peeters et al. randomized 664 T1b–T4 prostate cancer patients to either 68 or 78 Gy. The 5-year freedom from failure (FFF) was significantly better in the dose-escalation arm compared with the lower dose arm (64 vs. 54%, $p=0.02$) [6]. In the updated analysis, with a median follow-up of 7 years, the FFF rate was still

Table 27.2 RCT Phase III dose escalation trials for localized prostate cancer.

Study	Trial design	Intervention	Eligibility	No. of patients	Outcomes	Results	Toxicity	Notes	Grade
MDACC (Kuban et al. 2008)	RCTMedian f/u 8.7 years	EBRT dose: 70 vs. 78 Gy	Stage T1b–T3 patients, stratified by PSA	301	FFF	8-year biochemical clinical FFF: 78% (78 Gy) vs. 59% (70 Gy), $p=0.004$ If PSA >10: 78 vs. 39%, $p<0.001$ Clinical failure: 7% (78 Gy) vs. 15% (70 Gy), $p=0.014$ No difference in OS	No significant increase in GU toxicity Significant increase in grade 2 (26 vs. 13%, $p=0.013$) and 3 (7 vs. 1%, $p=0.018$) GI toxicity	21% were low risk, 47% intermediate risk, 32% high risk Statistically significant improvement in FFF seen in low- and high-risk groups but not intermediate	High
Dutch CKVO 96–10 (Al-Mamgani et al. 2008)	RCT Median f/u 70 months	EBRT dose: 68 vs. 78 Gy	Stage T1b–T4, with PSA <60	664	FFF, OS	7-year FFF: 45% (78 Gy) vs. 56% (68 Gy), $p=0.03$ Significant benefit in intermediate- and high-risk patients, but not in low-risk patients No difference in OS: 75% in both arms	Higher rates of rectal bleeding with higher doses (3 vs. 8%, $p=0.01$) Higher rates of fecal incontinence (7 vs. 13%, $p=0.02$)	Hormonal therapy was permitted 22% of patients received ADT	High
PROG 95-09 (Zietman et al. 2010)	RCT Median f/u 8.9 years	EBRT dose: 70.2 vs. 79.2 Gy	Stage T1b–T2b, PSA <15 ng/mL	393	BF, OS	10-year ASTRO BF rates: 32.4% (70.2 Gy) vs. 16.7% (79.2 Gy), $p<0.0001$ Dose escalation benefited low-risk patients: ASTRO BF rates 28.2 vs. 7.1% ($p<0.0001$) ASTRO BF not statistically significant for intermediate-risk patients: 42.1 vs. 30.4% ($p=0.06$) No difference in OS (78% vs. 83%, $p=0.41$)	2% grade ≥3 GU toxicity in the high-dose arm vs. 3% in the 70.2 Gy arm, $p=0.0745$ 1% grade ≥3 GI toxicity in the high-dose arm vs. 0% in the 70.2 Gy arm, $p=0.0895$	No ADT Median PSA 6.3 After 50.4 Gy a proton boost was given to complete the dose	High
GETUG (Beckendorf 2011)	RCT f/u 61 months	EBRT dose: 70 vs. 80 Gy	Stage T1–T3aN0M0 Initial PSA <50 ng/mL	306	BRR	5-year BRR: 39% (70 Gy) vs. 28% (80 Gy) ($p=.036$) Subgroup analysis: better biochemical outcome in the higher dose group for patients with PSA >15 ng/mL	-RTOG scale: Grade 2 or≥rectal toxicity rate was 14% (70 Gy) vs. 19.5% (80 Gy) ($p=.22$) -Grade 2 or≥urinary toxicity was 10% (70 Gy) and 17.5% (80 Gy) ($p=.046$)	No ADT was allowed All patients received 46 Gy to prostate and seminal vesicles followed by a boost (24 or 34 Gy) only to the prostate	High
MRC RT01 (Dearnley et al. 2014)	RCTMedian f/u 10 years	EBRT dose: 64 vs. 74 Gy	Stage T1b–3a, PSA <50 Neoadjuvant ADT 3–6 months	843	bPFS, OS	5-year bPFS: 60% (64 Gy) vs. 71% (74 Gy), $p=0.0007$ 10-year bPFS: 43% (64 Gy) vs. 55% (74 Gy), $p=0.0003$ Benefit in all risk groups No difference in OS (71% in each group, $p=0.96$)	-Grade 2≥GI toxicity was significant: 33% (74 Gy) vs. 24% (64 Gy), $p=0.005$ -Grade 2≥GU toxicity was not significant: 11% (74 Gy) vs. 8% (64 Gy), $p=0.14$	Local control, freedom from salvage ADT, DMFS favored high-dose arm but not statistically different	High

ADT, androgen deprivation therapy; BF, biochemical failure; bPFS, biochemical progression-free survival; BRR, biochemical relapse rate; DMFS, distant metastasis-free survival; EBRT, external beam radiation therapy; FFF, freedom from failure; f/u, follow-up; GU, genitourinary; GI, gastrointestinal; OS, overall survival; PCSS, prostate cancer-specific survival; PFS, progression-free survival; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; PSM, positive surgical margin; RCT, randomized controlled trial; RT, radiation therapy.

significantly improved in the 78 Gy arm versus the 68 Gy arm (45 vs. 56%, $p=0.03$) [7]. Subgroup analysis showed that the greatest benefit was seen in the intermediate- and high-risk groups, whereas this benefit was not statistically significant in the low-risk group. Again, both arms had similar overall survival rates (75% in both arms). Although there were no differences in GU toxicity, the dose-escalation arm had higher rates of ≥ grade 2 or higher GI toxicity.

The French multicenter GETUG trial randomized 306 intermediate-risk patients to either 70 or 80 Gy [8]. Patients initially received 46 Gy to the prostate and seminal vesicles and then were randomized to a prostate-only boost of 24 or 34 Gy. With a median follow-up of 61 months, the 5-year biochemical relapse rate was 23.5% in the dose-escalation arm versus 32% in the 70 Gy arm ($p=0.09$). When patients were stratified by PSA level, those with PSA >15 ng/mL had better biochemical control when treated at higher doses. Using the Radiation Therapy Oncology Group (RTOG) toxicity scale, the rates of rectal toxicity and urinary toxicity were not found to be significantly different between the two arms.

In the RTOG 9406 trial, Michalski et al. reported the outcomes of a Phase I/II multi-institutional dose-escalation study for patients with localized prostate cancer [9]. A total of 1051 patients were registered on five sequential dose levels (68.4, 73.8, 79.2, 74, and 78 Gy). With a median follow-up time between 9.2 and 11.8 years, the 5-year biochemical failure rates based on risk group were 68, 73, 67, 84, and 80% (low-risk patients), 70, 62, 70, 74, and 69% (intermediate-risk patients), and 42, 62, 68, 54, and 67% (high-risk patients) for levels I–V, respectively. Reported long-term toxicity outcomes revealed that 79.2 Gy given in 1.8 Gy fractions was much better tolerated and had significantly less grade ≥2 toxicity than with 78 Gy given in 2 Gy fractions [10].

Although many prospective trials have shown that dose escalation provides a local control benefit, the optimal dose fractionation is still uncertain. Radiation therapy for prostate cancer given at a dose of 1.8–2.0 Gy per fraction may extend treatment up to 9 weeks. In view of this prolonged treatment time with conventional fractionation, several studies have evaluated the efficacy of hypofractionation. Per NCCN guidelines, moderately hypofractionated IMRT regimens of 2.4–4 Gy per fraction over 4–6 weeks can be considered for the treatment of prostate cancer. Kupelian et al. analyzed local control rates in 770 patients treated with 70 Gy in 2.5 Gy fractions over the course of 5 weeks [11]. Long-term results showed that both efficacy and toxicity with hypofractionation were comparable to those with the conventional fractionation regimen. Other noninferiority randomized studies have shown similar rates of local control among the two different fractionation schemes. Extreme hypofractionation IMRT and stereotactic body radiation therapy (SBRT) dosing schedules (6.5 Gy per fraction or greater) have recently emerged as potential dosing regimens for treatment of prostate cancer. Although data from Phase I and II trials of extreme hypofractionation and SBRT look promising [12], there is still not enough evidence in the form of randomized trials to recommend the widespread use of these particular dosing schemes.

In addition to EBRT, dose escalation can also be achieved in combination with a brachytherapy boost. By positioning the radiation source inside the prostate, brachytherapy allows for a homogeneous dose distribution to the tumor while still maintaining a minimal dose to surrounding tissues. In view of this premise, it is theorized that EBRT in combination with a high dose rate brachytherapy (HDR-BT) boost is able to provide improved local tumor control without additional morbidity. An HDR- BT boost is normally completed in one to four fractions to a total dose of 12–30 Gy. This allows the total treatment time to be reduced from 7–9 weeks with monotherapy EBRT to about 3–4 weeks when EBRT and HDR-BT are combined. Multiple studies have shown similar if not improved local control rates with HDR-BT boost compared with single-modality EBRT [1, 3, 4, 7, 13]. A prospective randomized study by Hoskin et al., which enrolled 220 patients, showed a benefit in local control in patients treated in the HDR-BT boost arm compared with those treated in the EBRT-alone arm [14]. With a median follow-up of 7.1 years, the HDR-BT boost arm showed a 31% reduction in risk recurrence that was particularly significant in intermediate- and high-risk patients. Recently, preliminary results from the ASCENDE trial were released in abstract form [15]. This randomized multicenter trial compared dose-escalated EBRT with EBRT in combination with a low dose rate brachytherapy (LDR-BT) boost. With 398 patients enrolled, the 9-year Kaplan–Meier relapse-free survival estimate was significantly improved in patients treated with the LDR-BT boost (63 vs. 83%, $p=0.002$). Although some studies have shown improved outcomes with a brachytherapy boost, more multi-institutional studies are needed to elucidate if toxicity and quality of life outcomes are comparable.

Clinical implications

In patients with clinically localized low-risk prostate cancer, we recommend doses of 75.6–79.2 Gy and in patients with intermediate- and high-risk prostate cancer doses of up to 81 Gy, as these doses have been shown in Phase III trials to be associated with improved biochemical control (strong recommendation based on high-quality evidence).

We suggest against the use of more than moderate hypofractionation (beyond 4 Gy per session) owing to a lack of sufficient data to support equivalent oncological efficacy and toxicity profile (conditional recommendation against based on low-quality evidence).

Clinical question 2

In a patient with localized prostate cancer, is there a benefit with proton beam radiation therapy over photon radiation?

Literature search

A literature search using PubMed and MEDLINE was performed. Search term combinations were "prostate cancer," "protons," intensity modulated radiation therapy," "photons," and "3D conformal radiation therapy."

The evidence

Although proton beam radiation therapy has been used for decades in the treatment of various cancers, it has only recently become an emerging treatment option for localized prostate cancer. It is postulated that the dose distribution property of protons results in a decreased dose to the bladder and rectum, leading to less GI and GU toxicity and thereby allowing for possible dose escalation [16]. Currently, photon-based IMRT is the standard method of radiation delivery for prostate cancer. IMRT, compared with the previous standard of 3D-CRT, limits the dose to surrounding organs by using multiple-shaped beams, leading to improved conformity. In light of dosimetric advances in dose conformity, IMRT has become and has been accepted as the standard for treatment of prostate cancer. The toxicity and efficacy of protons should therefore be compared with those of photon-based IMRT, specifically in the prospective setting.

The rectum, bladder, and neurovascular bundles are critical tissues neighboring the prostate. These can be involved in treatment-related side effects, which can lead to significant acute and long-term morbidity. Studies have found that the volume of the bladder and rectum receiving high doses of radiation is associated with a higher rate of long-term toxicity [17, 18]. In view of the potential long-term morbidity, therapeutic options with fewer side effects are of increasing interest. Currently there are no prospective trials that compare the toxicity outcomes of photon-based IMRT with that of protons. There have been retrospective comparative studies that have looked at toxicity rates between the two modalities. A retrospective study comparing early toxicity in 27 647 prostate cancer patients treated with IMRT versus proton radiotherapy found no statistically significant differences in toxicity 12 months after treatment [19]. Prospectively collected quality of life data for patients treated with protons reported by the Massachusetts General Hospital found significant increases from baseline in incontinence, sexual dysfunction, and bowel dysfunction, with the extent of change from baseline being most significant for sexual dysfunction [20]. A prospective study of patient-reported quality of life outcomes showed no significant differences in sexual, bowel, and urinary scores in patients treated with IMRT versus proton radiotherapy [21]. Sheets et al. published data on one of the largest retrospective analyses using the SEER–MEDICARE linked database in which morbidity and disease control outcomes were compared in prostate cancer patients treated with IMRT versus those treated with protons [22]. The authors looked at the rates of erectile dysfunction, hip fractures, GI and GU morbidity, and the use of additional cancer therapy. On comparing the two cohorts, it was found that there were no significant differences in the rates of sexual dysfunction or GU morbidity. In contrast, on comparing the rates of GI morbidity, patients who were treated with protons were found to have higher rates of GI morbidity, with an absolute risk of 12.2 vs. 17.8 per 100 person-years. For multiple reasons, there can be significant movement of the prostate between treatments, which may explain the higher rates of GI toxicity in patients treated with protons. Because protons exhibit greater susceptibility than IMRT to organ motion, higher doses may inadvertently be delivered to the rectum, leading to a higher rate of GI morbidity. In addition to reporting morbidity outcomes, the rates of additional cancer therapy and thus disease control outcomes were also compared between the two modalities. The study reported no significant differences in the rates of additional cancer therapy among the patients who were treated with IMRT versus those treated with protons. Although this information implies that there is no difference in cure rates between IMRT and protons, further prospective trials are needed to answer clearly the question of efficacy between the two modalities.

In addition to radiation-induced acute side effects, the small but real risk of secondary malignancies from radiation is of concern to physicians and patients. Although the whole-body dose of radiation is less with protons than with IMRT, the lowest total body dose of radiation is actually seen in brachytherapy. In light of the fact that a greater volume of normal tissue receives more radiation with IMRT, it has been postulated that there may be a lower risk of secondary malignancies with protons than with IMRT. With an estimated secondary malignancy risk of 1.75% at 10 years with IMRT, the real question lies in whether or not this small risk translates into a true impact in the older patient population who develop prostate cancer. After radiation treatment, there is on average a latency period of about 10–20 years for the development of secondary cancers; therefore, although this risk is clearly of concern in young patients who are expected to live for many decades, the impact in the older population may be negligible [23]. Long-term data and randomized studies are still needed to elucidate further whether or not there is a real benefit in terms of secondary malignancy risk reduction for prostate cancer patients treated with proton therapy.

In addition to efficacy and morbidity, the costs associated with proton treatment are enormous and have been an area of controversy in healthcare spending. In an era, where "cost-effective" medicine is becoming more dominant, it is important to think about the high costs of proton therapy relative to IMRT when making treatment recommendations. A recent analysis comparing the cost-effectiveness of proton therapy versus IMRT showed that proton radiation treatment was in fact not cost-effective. The analysis used a Markov model to determine the incremental cost

per quality-adjusted life-year. Under the assumption that a higher dose of radiation treatment with protons would result in no toxicity and in a higher rate of biochemical disease-free survival, it was determined that proton radiation treatment in comparison with IMRT was not cost-effective for the treatment of intermediate-risk prostate cancer patients [24].

Currently, there are no prospective randomized trials available comparing the efficacy and morbidity of IMRT with those of proton therapy for the treatment of localized prostate cancer. There are many questions surrounding the true benefit of proton therapy for prostate cancer. There is an ongoing prospective randomized trial that is currently accruing patients with low- and intermediate-risk prostate cancer that hopes to answer these questions. This Phase III randomized trial will compare the efficacy of proton treatment versus IMRT, the side effects, the quality of life, and the cost-effectiveness of the two modalities.

Clinical implications

In patients with clinically localized prostate cancer, we recommend against proton beam therapy (strong recommendation based on low-quality evidence). This recommendation is based on the lack of data to suggest superior outcomes of proton beam therapy and also places a high value on the judicious allocation of resources. Undoubtedly, information from future comparative prospective studies is needed to support the widespread use of protons for the treatment of prostate cancer.

Clinical question 3

In a patient with newly diagnosed localized, high-risk prostate cancer, is hormonal therapy indicated as an adjunct to definitive radiation therapy?

Literature search

A literature search using PubMed and MEDLINE was performed. Search terms were "prostate cancer," "androgen deprivation therapy," "androgen suppression therapy," "high risk prostate cancer," "radiation therapy," "randomized controlled trial," and "hormonal therapy."

The evidence

Radiation therapy has been well established as a treatment option for men with localized prostate cancer. Although multiple studies have proven the efficacy of radiation therapy for prostate cancer, long-term outcomes have shown that patients with high-risk disease treated with external beam radiation therapy (EBRT) still carry a significant risk of recurrence, and therefore warrant additional treatment. In view of this increased risk with single-modality treatment, various randomized trials have evaluated the benefit of adding androgen deprivation therapy (ADT) to EBRT (Table 27.3). Evidence from those studies has shown that ADT in combination with radiation therapy leads to a decrease in local failure and distant metastasis, which subsequently translated into an improvement in overall survival.

The RTOG 8610 was one of the first Phase III randomized controlled trials to evaluate the benefit of RT in combination with ADT [25]. A total of 456 men with bulky tumors (cT2–T4) were randomized to either treatment with EBRT alone or treatment with EBRT in combination with ADT. All patients received RT to a total dose of 65–70 Gy, and the patients who were randomized to the ADT group received goserelin and flutamide 2 months prior to RT and during RT. With a median follow-up of 11.9 years for the combination arm and 13.2 years for the RT-alone arm, there was a significant improvement in 10-year disease-specific mortality (DSM), distant metastasis (DM) rate, and disease-free survival (DFS) in patients treated with both EBRT and ADT. Patients in the combination arm had a 10-year DSM of 23% compared with 36% ($p = 0.01$) in patients treated with EBRT alone. The DM rate was improved with the addition of ADT to EBRT at 35% compared with 47% ($p = 0.006$) in the EBRT-alone arm. DFS was reported at 11% for the EBRT + ADT arm versus 3% ($p < 0.0001$) for the single-modality arm. Although not statistically significant, overall survival was favored in the combination arm. Not only did this study show a benefit of ADT in high-risk prostate cancer, but it also revealed that even after 10 years of follow-up there was no significant increase in fatal cardiac events.

The European Organization of Research and Treatment of Cancer EORTC 22863 trial was also among the first studies to show a survival advantage with the combination of RT and ADT for the treatment of prostate cancer [26]. In contrast to the RTOG 8610 trial, the EORTC 22863 trial randomized patients to either EBRT alone or EBRT in combination with 36 months of ADT as opposed to 4 months. A total of 415 patients with T1–T2 WHO grade 3 or T3–T4 N0–N1 were enrolled. After a median follow-up of 9.1 years, the results showed that ADT significantly improved 10-year overall survival, prostate cancer mortality, and disease-free survival. The 10-year prostate cancer-specific mortality was improved from 30.4% in the EBRT-alone arm to 10.3% in the EBRT + ADT arm ($p = 0.0001$). This improvement in prostate cancer-specific mortality translated into a significant survival benefit, with a 40% risk of death reduction with the addition of ADT to EBRT. For patients in the EBRT-alone arm, 10-year overall survival was reported at 39.8% versus 58.1% for those patients in the combination treatment arm ($p = 0.0004$). Additionally, there was no increased risk in cardiovascular mortality with the addition of ADT to EBRT.

Like the RTOG 8610 trial, the RTOG 9408 trial also evaluated the benefit of short-course ADT in high-risk patients [27]. This trial randomized 1979 patients with T1b–T2b disease and PSA <20 to either EBRT alone (66 Gy) or EBRT in combination with 4 months of ADT. As in the RTOG 8610 trial, patients began ADT 2 months prior to RT. After a median follow-up of 9.1 years, a significant improvement in all of the endpoints was observed. The addition of ADT significantly improved the

Table 27.3 Effect of ADT with EBRT in localized prostate cancer.

Study	Trial design	Intervention	No. of patients	Eligibility	Outcomes	Results	Toxicity	Notes	Grade
RTOG 8610 (Roach et al. 2008)	RCT Median f/u 11.9 years (ADT + EBRT) and 13.2 years (EBRT alone)	EBRT alone (66–70 Gy) vs. EBRT (66–70 Gy) + ADT (4 months)	456	Bulky tumors (T2–T4) with or without pelvic nodal involvement	DSM, DM, BF, OS	10-year DSM: 23% (EBRT alone) vs. 36% (EBRT + ADT), $p = 0.01$ 10-year DM: 35 vs. 47%, $p = 0.006$ BF: 65 vs. 80%, $p < 0.0001$ 10-year OS: 43 vs. 34%, $p = 0.12$	No difference in the risk of cardiac events Fatal cardiac events: 12.5% (EBRT alone) vs. 9.1% (ABRT + ADT), $p = 0.32$	Patients in the EBRT + ADT arm received goserelin and flutamide 2 months before and 2 months during EBRT !0-year local progression rate was not significantly improved with addition of ADT to EBRT ($p = 0.18$)	High
RTOG 9202 (Horwitz et al. 2008)	RCT Median f/u 11.3 years	EBRT + ADT (4 months) vs. EBRT (24 months)	1554	T2c–T4, PSA <150	DFS, DSS, LP, DM, OS	10-year DFS: 13.2 vs. 22.5%, $p < 0.0001$ 10-year DSS: 83.9 vs. 88.7% ($p = 0.042$) 10-year LP: 22.2 vs. 12.3%, $p < 0.0001$ 10-year DM: 22.8 vs. 14.8%, $p < 0.0001$ 10-year OS: 51.6 vs. 53.9%, $p = 0.36$	No difference in CV mortality among arms	All patients received goserelin + flutamide for 2 months before and 2 months during XRT Subgroup analysis: Gleason 8–10 patients had a survival advantage with long-term ADT	High
Canada (Crook et al. 2009)	RCT Median f/u 6.6 years	EBRT (66 Gy) + ADT (3 months) vs. EBRT (66 Gy) + ADT (8 months)	378	T1c–T4	DFS, FFF, OS,	5-year DFS for high-risk patients: 71% (8 months) vs. 42% (3 months), $p = 0.01$ 5-year FFF: 72 vs. 75, $p = 0.18$ 5-year OS: 81 vs. 79%, $p = 0.7$	Not reported	No concurrent use of ADT with RT Flutamide + goserelin was given for either 3 months or 8 months prior to EBRT start	High
EORTC 22863 (Bolla et al. 2010)	RCT Median f/u 9.1 years	EBRT alone (70 Gy) vs. EBRT (70 Gy) + ADT (36 months)	415	T1–2 WHO grade 3 (GS 8–10) or T3–4 any grade, N0–1, M0	CaP mortality, DFS, OS	10-year CaP mortality: 30.4% (EBRT alone) vs. 10.3% (EBRT A DT), $p < 0.0001$ 10-year DFS: 22.7% (EBRT alone) vs. 47.7% (EBRT + ADT), $p < 0.0001$ 10-year OS: 39.8% (EBRT alone) vs. 58.1% (EBRT + ADT), $p = 0.0004$	No significant difference in CV mortality Two fractures in the EBRT + ADT group	92% of the patients had T3–T4 disease. Patients in the EBRT + ADT arm received goserelin monthly starting on first day of RT	High
TROG 96.01 (Denham et al. 2011)	RCT Median f/u 10.6 years	EBRT alone (66 Gy) vs. EBRT + ADT (3 months) vs. EBRT + ADT (6 months)	802	T2b–T4N0	CaP mortality, all-cause mortality	6-month arm only: decrease in distant progression (HR 0.49, $p = 0.001$), CaP mortality (HR 0.49, $p = 0.0008$), and all-cause mortality (HR 0.63, $p = 0.0008$)	No increase in morbidity with ADT	3-month ADT: goserelin + flutamide began 2 months prior to EBRT 6-month ADT: goserelin + flutamide starting 5 months prior to RT 3-month ADT had no effect on CaP mortality or all-cause mortality	High

ADT, androgen deprivation therapy; BF, biochemical failure; bPFS, biochemical progression-free survival; CaP mortality, prostate cancer-specific mortality; CSS, cause-specific survival; DM, distant metastasis; EBRT, external beam radiation therapy; ECE, extracapsular extension; FFF, freedom from failure; f/u, follow-up; GU, genitourinary; GI, gastrointestinal; HR, hazard ratio; LRR, locoregional recurrence; MetFS, metastasis-free survival; OS, overall survival; PCSS, prostate cancer-specific survival; PFS, progression-free survival; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; PSM, positive surgical margin; RCT, randomized controlled trial; RT, radiation therapy; SVI, seminal vesicle involvement; XRT, X-ray therapy.

rate of positive findings on repeat prostate biopsy at 2 years, the distant metastasis rate, and the rate of biochemical failure. In contrast to RTOG 8610, this trial showed a significant improvement in the 10-year rate of overall survival, with an overall survival of 62% in the combination treatment arm versus 57% in the EBRT-alone arm ($p=0.03$).

The Trans-Transman Radiation Oncology Group 96.01 trial studied the benefit of ADT at two different time frames [28]. This trial randomized 802 intermediate- and high-risk patients to either RT alone (66 Gy), RT in combination with 3 months of ADT, or RT in combination with 6 months of ADT. With long-term follow-up of 10.6 years, the addition of ADT was associated with a decrease in the rate of PSA progression and local progression. Although both time frames showed a significant benefit, there was a greater improvement in the 6-month arm compared with the 3-month arm. Furthermore, in addition to local control, the 6-month arm was also associated with an improvement in distant progression (20.6 vs. 10.9%, $p=0.001$) and all-cause mortality (42.5 vs. 29.2%, $p=0.0008$). In addition to showing the benefit of ADT in combination with RT for the treatment of prostate cancer, this trial also showed that a longer term use of ADT at 6 months had a greater impact on local control, prostate cancer-specific mortality, and overall survival without an additional increase in morbidity.

After multiple randomized trials proved that ADT in combination with RT resulted in improved local control and better overall survival, the focus shifted to determining the optimal duration and timing of ADT. Various trials have sought to answer this question and determine whether long-term androgen suppression would further benefit patients without substantial toxicity. The Canadian Urologic Oncology Group randomized 378 patients to either neoadjuvant ADT for 3 months followed by EBRT or neoadjuvant ADT for 8 months followed by EBRT [29]. After a median follow-up of 6.6 years, Crook et al. observed a significant improvement in the 5-year disease-free survival (71 vs. 42%, $p=0.01$) in high-risk patients who received 8 months of neoadjuvant ADT compared with those who received 3 months of ADT. The RTOG 92-02 trial also analyzed the outcomes of patients who received short-term versus long-term ADT [30]. This trial randomized 1554 patients with locally advanced prostate cancer to either EBRT and 4 months of ADT or EBRT and 2 years of ADT. All patients received 2 months of ADT prior to EBRT and 2 months of ADT concurrently with EBRT. The long-term ADT arm significantly improved local progression (22.2 vs. 12.3%, $p<0.0001$), disease-free survival (13.2 vs. 22.5%, $p<0.0001$), distant metastasis (22.8 vs. 14.8%, $p<0.0001$), and disease-specific survival (83.9 vs. 88.7%, $p=0.0042$). Although initial data did not show a significant improvement in overall survival, a subset analysis of patients with a Gleason of 8–10 revealed a statistically significant survival benefit with long-term ADT. The EORTC 22961 trial was also a Phase III randomized trial that compared short-term ADT with long-term ADT in men with locally advanced prostate cancer [31]. A total of 1113 men were enrolled and all patients received EBRT plus 6 months of ADT. Patients were then randomized to either no further treatment or continuation of ADT for 2.5 years. Patients who received 3 years of ADT had an improvement in 5-year overall survival (81 vs. 85%) and also 5-year cause-specific mortality (3.2 vs. 4.7%). In addition to the benefit in survival with long-term ADT, this study also showed comparable quality of life outcomes and no differences in fatal cardiac events.

As mentioned, previously various trials have shown improved outcomes in local control and overall survival with combined modality treatment in patients with high-risk prostate cancer. Although the benefit of high-dose RT has also been well established and is now standard of care, many ADT trials were performed in the pre-dose-escalation era, and therefore most patients in these dual-modality trials received conventional RT doses of less than 70 Gy in combination with ADT. In light of better local control with higher RT doses, the benefit of long-term ADT came into question. In order to determine the optimum duration of ADT in combination with high-dose RT, a multicenter Phase III randomized trial was conducted by the Spanish Cooperative Group [32]. This trial randomized 178 patients with T1c–T3bN0M0 disease with intermediate- and high-risk factors to either 4 months of ADT in combination with high-dose RT (76–82 Gy) or an additional 24 months of ADT after that initial treatment. With a median follow-up of 63 months, this study showed an improvement in the 5-year biochemical disease-free survival among patients in the long-term ADT arm, which subsequently translated into better outcomes for overall survival. Patients stratified to the long-term ADT arm had a 5-year biochemical disease-free survival of 90% versus 81% in patients in the short-term ADT arm ($p=0.01$). The 5-year metastasis-free survival and overall survival were 94 and 95%, respectively, for the long-term ADT arm compared with 83 and 86%, respectively, for the short-term ADT arm ($p=0.01$, $p=0.009$). There was no observed statistical difference in grade 3 rectal and urinary toxicity between the two arms. The results of this trial confirmed the benefit of long-term ADT even with higher doses of RT.

In patients undergoing combined treatment, ADT is usually started 2 months prior to EBRT. Part of this premise is based on previous laboratory studies in mice that showed an improved radiation response with androgen ablation [33]. Investigators also observed that the sequence of androgen ablation and radiation therapy was influential in dose response. Orchiectomy before radiation therapy resulted in better local tumor control at lower radiation doses. Furthermore, most prospective trials that have shown the benefit of combination ADT and EBRT for treatment of prostate cancer have started ADT in the neoadjuvant setting. In view of this information, patients are usually started on ADT 2 months prior to EBRT and are then continued on ADT concurrently with EBRT.

Clinical implications

In patients with clinically localized high-risk prostate cancer undergoing EBRT, we recommend concomitant treatment with ADT (strong recommendation based on high-quality evidence). Optimal duration of treatment has also been evaluated in the prospective setting. Trials have shown a survival advantage to long-term ADT compared with a short course of ADT and therefore in high-risk patients we recommend at least 24 months of ADT (strong recommendation based on high-quality evidence).

Clinical question 3

In a patient with positive surgical margins, extra-prostatic extension, and/or seminal vesicle involvement after radical prostatectomy, is there a benefit for adjuvant radiation therapy over salvage radiation therapy?

Literature search

A literature search using PubMed and MEDLINE was performed. Search term combinations were "prostate cancer," "adjuvant radiation therapy," "salvage radiation therapy," positive surgical margins," "radiation therapy," "randomized controlled trial," and "prostatectomy."

The evidence

Radical prostatectomy is a treatment option for clinically localized prostate cancer that offers excellent local control and survival for organ-confined disease. Despite high cure rates with prostatectomy, patients with certain adverse features may have a high risk of biochemical progression and disease recurrence. Studies have shown that patients with positive surgical margins, extra-prostatic extension (EPE), seminal vesicle involvement (SVI), and positive lymph nodes tend to have poor biochemical control rates at 10 years. In a multi-institutional study reported by Karakiewicz et al., positive surgical margins resulted in a 53.1% 5-year biochemical control rate whereas for patients with negative margins it was 83.8% [34]. For men with extra-prostatic disease treated with radical prostatectomy, local failure and biochemical progression after 5 years can range between 20 and 70% [35]. In view of this high risk of local recurrence in men with adverse pathological features, the role of adjuvant radiation after radical prostatectomy has been explored. Three randomized prospective studies (EORTC, SWOG, ARO) have reported a significant improvement in biochemical recurrence-free survival in patients with extra-prostatic involvement and/or positive surgical margins who have received adjuvant radiation therapy (RT) after radical prostatectomy (Table 27.4).

The EORTC 22911 trial by Bolla et al. randomized 1005 patients 75 years old and younger with either pT3N0 disease and/or positive surgical margins to either observation or adjuvant RT to a dose of 60 Gy in 30 fractions [36]. Radiation treatment was given within 16 weeks of radical prostatectomy and the median follow-up was 10.6 years. Adjuvant RT resulted in a significant reduction in locoregional relapse at 10.6 years, with 7.3% of the patients in the radiation treatment arm having locoregional relapse versus 16.6% of the patients in the observation arm ($p<0.0001$). There was also a significant improvement in the 10-year biochemical progression-free survival (bPFS) in the RT arm compared with the observation arm (61 vs. 41%, $p<0.0001$). No benefit in terms of overall survival, distant metastasis, or prostate cancer-specific mortality was observed. Toxicity was reasonable in the adjuvant RT arm, with grade 3 diarrhea (5.3%) and urinary frequency (3.3%) being the most common side effects. No additional risk of urinary incontinence in the adjuvant RT arm versus the observation arm was found.

The SWOG 8794 trial enrolled 425 patients with pT3N0 disease and/or positive surgical margins. Patients were randomized to observations versus adjuvant RT within 16 weeks of radical prostatectomy to a total dose of 60–64 Gy [37]. At 10-year follow-up there was a significant decrease in locoregional recurrence in the adjuvant RT arm compared with the observation arm (8 vs. 22%) and an improvement in 10-year biochemical failure-free survival (36 vs. 12%). In contrast to the EORTC trial, the SWOG trial also found a statistically significant improvement in overall survival and in metastatic recurrence-free survival. Based on Kaplan–Meier curves, the 10-year estimated metastasis-free survival was 71% in the adjuvant RT arm versus 61% in the observation arm ($p=0.016$). The 10-year estimated overall survival was 74% in the adjuvant RT versus 61% in the observation arm ($p=0.023$). This improvement in overall survival translated into a prolongation in median survival from 13.3 to 15.2 years. It is uncertain why an improvement in overall survival was seen in the SWOG trial but not in the EORTC trial. It is possible that the difference in median age between the two trials could account for this inconsistency. The patients in the observation arm of SWOG trial were on average older and had higher rates of Gleason 8 and 10 prostate cancer in comparison with the EORTC study. Another explanation may be that salvage treatment was more extensive in the EORTC trial. As in the EORTC trial, there were reasonably low levels of toxicity in the adjuvant RT arm versus the observation arm.

The ARO study from the German Cancer Society randomized 388 men with pT3N0 disease and/or positive surgical margins to either radical prostatectomy alone or to postoperative RT to 60 Gy in 30 fractions within 12 weeks after surgery [38]. In contrast to the previously mentioned trials, all the patients in this study had an undetectable PSA after radical prostatectomy. Adjuvant RT resulted in a significant improvement in 5-year biochemical PFS (72 vs. 54%, $p=0.015$). In a recent update, 10-year PFS was still significantly improved at 56% for the adjuvant RT arm versus

Table 27.4 Effect of adjuvant radiation therapy in patients with adverse features in localized prostate cancer.

Study	Trial design	Intervention	Eligibility	No. of patients	Outcomes	Results	Toxicity	Notes	Grade
SWOG 8794 (Thompson et al. 2009)	RCT Median f/u 12.6 years	Postoperative RT (60–64 Gy) vs. observation	pT2–T3N0 s/p RP with ECE, PSM, or SVI	431	MetFS, OS	10-year OS: 74% (RT) vs. 66% (obs.), $p=0.023$ 10-year Met FS: 71% (RT) vs. 61% (obs.), $p=0.016$	No difference in erectile dysfunction QOL study: increased bowel dysfunction and urinary frequency in the RT group No difference in bowel dysfunction after 2 years	All subgroups benefited from XRT. MetFS was inferior in RT patients with detectable PSA vs. those with undetectable PSA	High
EORTC 22911 (Bolla et al. 2012)	RCT Median f/u 10.6 years	Postoperative RT (60 Gy) vs. observation	pT2–T3N0 s/p RP with ECE, PSM, or SVI	1005	bPFS, LRR, OS, DM,	10-year bPFS: 61% (RT) vs. 41% (obs.), $p<0.0001$ 10=year LRR: 7.3% (RT) vs. 16.6% (obs.), $p<0.0001$ No difference in OS (94–96%, $p=0.202$) No difference in DM (10.1 vs. 11%, $p=0.94$)	No grade 4 toxicity Late grade 3 toxicity: 5.3% (RT) vs. 2.5% (obs.), $p=0.052$ Grade 2 GU toxicity: 21.3% (RT) vs. 13.% (obs.), $p=0.003$ Grade 2 GI toxicity was similar (2.5 vs. 1.9%, $p=0.47$) RT was interrupted owing to toxicity in 3.1%	Margin status was the strongest predictor of prolonged bDFS	High
German ARO 96-02 (Wiegel et al. 2014)	RCT Median f/u 9.3 years	Postoperative RT (60 Gy) vs. observation	pT2–T3N0 SVI, ECE, or PSM	385	PFS	5-year PFS: 54% (RT) vs. 72% (obs.), $p=0.0015$ 10-year PFS: 56% (RT) vs. 35% (obs.), $p<0.0001$	No grade 4 toxicity One case of grade 3 late toxicity Grade 2 GI toxicity in RT arm: 2% Grade 2 GU toxicity in RT arm: 1.4%	All patients had undetectable PSA at randomization. No difference in OS or MetFS Subgroup analysis: patients with positive margins have the greatest benefit	High

bPFS, biochemical progression-free survival; bDFS, biochemical disease-free survival; DM, distant metastasis; ECE, extracapsular extension; f/u, follow-up; GI, gastrointestinal; GU, genitourinary; LRR, locoregional recurrence; MetFS, metastasis-free survival; obs., observation; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; PSM, positive surgical margin; QOL, quality of life; RCT, randomized clinical trial; RT, radiation therapy; SVI, seminal vesicle involvement.

Table 27.5 Effect of salvage RT in patients with prostate cancer recurrence after radical prostatectomy.

Study	Trial design	Intervention	Eligibility	No. of patients	Outcomes	Results	Notes	Grade
Stephenson et al. 2007	Retrospective multi-institutional study Median f/u 53 months	All patients were treated with salvage RT (median 64. 8 Gy) 14% received ADT	PSA ≥0.2 and a subsequent higher value or single PSA ≥0.5 after RP	1540	bPFS	6-year bPFS: 32% (59% reached a PSA nadir of ≤0.1 ng/mL) 6-year PFS based on pre-RT PSA: 48% for PSA <0.50, 40% for PSA 0.51–1.00, 28% for PSA 1.01–1.5, 18% for PSA >1.5 41% 6-year bPFS for GS 8–10 or PSADT <10 months (if initiated with pre-RT PSA ≤0.5)	Predictors of unfavorable outcome: higher pre-RT PSA, GS 8–10, PSADT <10 months, negative margins, ADT, and positive lymph nodes Median pre-RT PSA 1.1, median doubling time 6.9 months	Low
Trock et al., 2008	Retrospective study Median f/u 6 years	Observation vs. RT (66.5 Gy) 12% received ADT	T1–2 with PSA >0.2	635	PCSS	10-year PCSS: 62% (obs.), 86% (RT), and 82% (RT + ADT), $p < 0.001$	Salvage RT was associated with a threefold increase in PCSS (HR 0.32, $p < 0.001$) Multivariate analysis: salvage RT reduced risk of death by >65% ($p < 0.001$) Main predictor of improved PCSS was PSADT <6 months No survival advantage in salvage RT after 2 years	Low
Cotter et al. 2011	Retrospective study - Median f/u 11.3 years	Observation vs. RT (66 Gy) 16% received ADT	T1c–T3 Two consecutive rising PSA of at least 0.2 ng/mL	519	All-cause mortality	Salvage RT decreased risk of all-cause mortality in men with a PSADT of ≥6 months (AHR, 0.52; $p = 0.003$) and men with a PSA DT of <6 months (AHR, 0.53; $p = 0.02$)	59% had positive surgical margins Salvage RT decreases the risk of mortality regardless of PSA doubling time	Low

ADT, androgen deprivation therapy; bPFS, biochemical progression-free survival; CSS, cause-specific survival; DM, distant metastasis; ECE, extracapsular extension; f/u, follow-up; GI, gastrointestinal; GU, genitourinary; LRR, locoregional recurrence; MetFS, metastasis-free survival; OS, overall survival; PCSS, prostate cancer-specific survival; PFS, progression-free survival; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; PSM, positive surgical margin; RCT, randomized clinical trial; RT, radiation therapy; RP, radical prostatectomy; SVI, seminal vesicle involvement.

35% for the observation arm ($p<0.0001$) [39]. Postoperative RT was also well tolerated, with minimal acute and late GI and GU toxicity. There was 3% of acute grade 3 bladder toxicity and no grade 3 acute rectal toxicity. There was no grade 4 toxicity reported and only one case of grade 3 late toxicity.

Whereas adjuvant RT refers to the administration of postprostatectomy radiation in patients with adverse features before evidence of recurrence, salvage RT is defined as the treatment with radiation of patients with biochemical recurrence after surgery [40]. Although there are no randomized prospective trials available, various retrospective studies have shown an improvement in survival in patients who received salvage RT after radical prostatectomy (Table 27.5). A multi-institutional retrospective study by Stephenson et al. analyzed the outcomes of 1540 patients who received salvage RT after recurrence [40]. The 6-year PFS was 32% and, of those men with PSA levels ≤0.50 ng/mL treated with salvage RT, 48% were disease free at 6 years. This study determined that salvage RT offers long-term disease control in nearly half of the patients with biochemical recurrence. An association between the PSA level and disease progression was also seen.

Those patients who were treated with salvage RT at lower PSA levels had the most favorable outcomes and derived the greatest long-term benefit from RT. It was therefore concluded that in order to obtain durable disease control, it is important to initiate salvage RT at low PSA levels when disease burden is low. Two other retrospective studies have also evaluated the potential benefit of salvage RT. A retrospective series from the Johns Hopkins Hospital evaluated 635 men with biochemical recurrence after prostatectomy [41]. Patients underwent either observation, salvage RT, or salvage RT plus hormone therapy. Salvage RT was found to improve cause-specific survival regardless of hormone therapy (85 vs. 62%). The second retrospective study comparing observation with salvage RT was reported by Cotter et al [42]. Salvage RT was associated with a significant decreased risk in mortality independent of the PSA doubling time.

Although there is a clear group of men who benefit from RT after prostatectomy, it is still unclear if early salvage RT yields the same disease-free survival benefit as adjuvant RT. At present there are no prospective data available comparing the efficacy of adjuvant RT in locally advanced prostate cancer with that of salvage RT after biochemical recurrence. Currently there are two randomized trials that intend to answer this question and therefore establish the best timing for postoperative RT. The RADICALS and RAVES trials are Phase III trials comparing the benefit of early salvage RT with that of adjuvant RT. In these two trials, patients will be randomized to either radiation treatment immediately after surgery or to radiation treatment after biochemical failure.

Clinical implications

In patients having undergone radical prostatectomy with high-risk pathological features such as extraprostatic extension, seminal vesicle involvement, or positive surgical margins, we recommend adjuvant RT within 18 weeks of prostatectomy (strong recommendation based on high-quality evidence).

In the setting of biochemical recurrence after prostatectomy, we suggest starting salvage RT at the earliest sign of biochemical recurrence (conditional recommendation based on low-quality evidence).

The use of individualized genomic biomarker information from patients as a predictive test for risk of disease recurrence has become a very attractive tool for the treatment decision for additional radiation postprostatectomy for patients who will derive the most benefit. One such tool is a validated genomic classifier test (Decipher), which may be a predictive marker that can help determine which patients will benefit from adjuvant versus salvage RT [43]. Further prospective validation studies are required to ascertain the generalizability of these genomic tests for widespread use in the clinical setting.

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28

CHAPTER 28

Management of metastatic prostate cancer

Michael S. Humeniuk[1], Tian Zhang[1], Megan A. McNamara[1], Sundhar Ramalingam[1], and Michael R. Harrison[1,2]

[1] *Division of Medical Oncology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA*

[2] *Duke Cancer Institute, Duke University School of Medicine, Durham, NC, USA*

Introduction

Prostate cancer is a clinically and biologically heterogeneous disease with a wide variation of outcomes based on its initial presentation and subsequent response to treatments. For instance, patients presenting with low-risk disease (stage Ic–IIa; Gleason 6 cancer) have a risk of death from prostate cancer of <1% at 15 years with no treatment [1], while those presenting with metastatic disease (stage IV) have a median life expectancy of <5 years [2, 3]. For patients with recurrent or metastatic disease, androgen deprivation therapy is still the standard of care. Yet within this population there is also an incredible range of outcomes driven by the development of castration-resistant prostate cancer (CRPC). It is this poor-risk disease state (those patients presenting with metastatic hormone-naive or sensitive disease and those developing metastatic CRPC (mCRPC), which is the topic of this chapter, for it is here that the greatest progress has been made in improving overall survival over the last 6 years. The clinical context of these disease states and the treatments they require frame the clinical questions presented here (see Figure 28.1). Understanding the management complexities of this population, from symptom palliation to treatment sequence to metastatic subgroups, are the goals of this chapter.

Clinical question 1

In patients with hormone-sensitive prostate cancer, how does up-front chemotherapy in conjunction with systemic androgen deprivation therapy (ADT) compare with systemic ADT alone?

Background

The majority of patients with prostate cancer present with localized disease, confined to the prostate and regional lymph nodes [4]. A proportion of these patients will develop recurrent prostate cancer after definitive local therapy (i.e. prostatectomy or pelvic radiation), which manifests as rising prostate-specific antigen (PSA) and eventually metastatic disease, despite androgen deprivation therapy (ADT) and castrate levels of testosterone (typically defined as testosterone <50 ng/dL). This disease state is termed mCRPC [5–8]. In contrast, a separate group of prostate cancer patients will either present with metastatic disease at diagnosis or will develop metastases after definitive local therapy but before attaining castrate levels of testosterone. By definition, these patients have metastatic prostate cancer in the absence of any hormonal therapy, a condition called metastatic hormone-sensitive prostate cancer (mHSPC).

Docetaxel (75 mg/m^2 every 21 days in combination with prednisone for up to 10 cycles) was first approved for the treatment of mCRPC in 2004, based on results of the TAX 327 study. This Phase III randomized controlled trial demonstrated a survival benefit of about 2.5 months in mCRPC patients treated with docetaxel, prednisone, and ADT, compared with mitoxantrone, prednisone, and ADT, the standard of care at the time (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.62–0.94; $p=0.009$) [9]. Since then, docetaxel has remained a mainstay of mCRPC treatment, and several new mCRPC therapies have also emerged [10–14]. However, until recently, the management of mHSPC has been limited to ADT alone, with additional therapies initiated once the patient becomes castration resistant.

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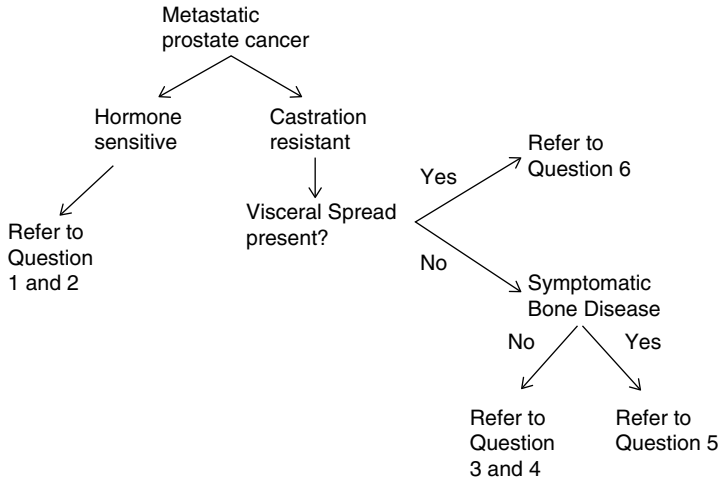

Figure 28.1 Metastatic prostate cancer treatment overview.

Based on the rationale that docetaxel improves overall survival in mCRPC and therefore might eliminate nascent castration-resistant clones if given earlier in the disease course, and also the theory that earlier docetaxel might permit treatment of men who would be unfit for chemotherapy later, three large Phase III randomized clinical trials have investigated the role of docetaxel in addition to ADT for the treatment of mHSPC. The evidence and clinical implications of these studies are reviewed here.

Literature search

We conducted a systematic literature search in PubMed using the search terms "metastatic," AND "castration sensitive," AND "hormone sensitive," AND "prostate cancer," AND "docetaxel." The search was limited to randomized controlled trials in English with a human population up to 1 March 2016.

The evidence

Three eligible randomized controlled trials (GETUG-AFU 15 [15], CHAARTED [3], and STAMPEDE [16]) were identified in our literature search.

GETUG-AFU 15 was the first randomized Phase III trial investigating the addition of docetaxel to ADT for the treatment of mHSPC to be completed and published. In this trial, 385 patients with mHSPC (either newly diagnosed or metastatic after treatment of local disease) were randomized 1 : 1 to either ADT alone ($n=193$) or ADT plus docetaxel 75 mg/m^2 every 21 days (without prednisone) for up to nine cycles ($n=192$). Of the patients in the ADT plus docetaxel group, 67% had metastatic disease at the time of diagnosis, with a median initial PSA of 26.7 ng/mL, compared with 75% with metastatic disease at diagnosis and a median PSA of 25.8 ng/mL in the ADT-alone group. After a median follow-up of 50 months, the trial failed to meet its primary endpoint and did not demonstrate a statistically significant improvement in overall survival (OS) with the addition of docetaxel chemotherapy to ADT (ADT plus docetaxel median OS 58.9 months, ADT alone median OS 54.2 months; HR 1.01, 95% CI 0.75–1.36; $p=0.955$). Furthermore, four treatment-related deaths were observed in the docetaxel plus ADT arm, attributed to febrile neutropenia, neutropenia with infection, multi-organ failure, and pulmonary embolism. The independent data monitoring committee subsequently recommended the addition of granulocyte colony-stimulating factor (5 μg/kg/day subcutaneously on days 5–10 of each docetaxel cycle). After this amendment, the rates of neutropenia and febrile neutropenia improved, and no additional treatment-related deaths were observed [15].

About 16 months after the publication of GETUG-AFU 15, the results of the CHAARTED trial were presented at a national conference in 2014 and then ultimately published a year later. In the CHAARTED trial, 790 men with mHSPC (either newly diagnosed or metastatic after treatment of local disease) with measurable disease on imaging were randomized 1 : 1 to either ADT alone ($n=393$) or ADT plus docetaxel 75 mg/m^2 every 21 days (without prednisone) for up to six cycles ($n=397$). Notably, this trial was initially designed to enroll only patients with high-volume metastatic disease, defined as the presence of either any visceral metastases or a minimum of four bone metastases, with at least one located outside the axial skeleton. The protocol was later amended to include also patients with low-volume metastatic disease, but the final trial population remained enriched for high-volume metastatic disease, with 64% of patients in the ADT-alone group and 67% in the ADT plus docetaxel group meeting this criterion [3].

Importantly, although the CHAARTED trial was initially designed to investigate docetaxel in patients with high-volume mHSPC, it was powered to detect a survival benefit in the overall population. After a median follow-up of 29 months, the trial met this primary endpoint,

demonstrating a statistically significant improvement in median overall survival of 13.6 months with the addition of docetaxel to ADT, compared with ADT alone (ADT plus docetaxel median OS 57.6 months, ADT-alone median OS 44.0 months; HR 0.63, 95% CI 0.48–0.82; $p = 0.0006$). Pre-specified subgroup analyses of overall survival by extent of metastatic disease showed that the magnitude of the survival benefit was even more substantial in patients with high-volume metastatic disease, reaching a median OS of 17 months in this group (ADT plus docetaxel median OS 49.2 months, ADT-alone median OS 32.2 months; HR 0.60, 95% CI 0.45–0.81; $p = 0.0006$). Among patients with low-volume metastatic disease, sufficient deaths had not yet occurred in either treatment arm to detect a difference in survival, owing to the more indolent nature and longer natural history of this disease state. The combination of early docetaxel and ADT was better tolerated in the CHAARTED trial than it was in the GETUG-AFU 15 study, with the most common grade 3–4 toxicities observed in the CHAARTED trial being neutropenia (12%), febrile neutropenia (6.2%), fatigue (4%), neutropenia with infection (2.3%), and one sudden death at home due to unknown cause, which was felt possibly to be related to docetaxel [3].

Finally, the STAMPEDE trial represents the third Phase III randomized controlled trial investigating the addition of docetaxel to ADT for the treatment of mHSPC [16]. The STAMPEDE trial is the largest randomized controlled trial ever conducted in prostate cancer. It employed a unique multi-arm, multi-stage design, which allowed several agents or combinations of agents to be assessed simultaneously against a single control group. STAMPEDE enrolled four different prostate cancer patient populations: (1) new mHSPC with at least one documented radiographic metastasis (referred to as M1); (2) biochemical (i.e. PSA) recurrence alone after local therapy with no measurable metastatic disease, (3) node-positive disease in addition to local disease without any metastases; and (4) high-risk localized prostate cancer. In the trial, 1776 men with mHSPC were randomized to either ADT alone ($n = 1184$) or ADT plus docetaxel 75 mg/m^2 every 21 days and prednisone 10 mg daily for up to six cycles ($n = 592$). Of patients in the total STAMPEDE trial population, 61% had metastatic disease, and the median PSA was 65 ng/mL. After a median follow-up of 42 months, the trial met its primary endpoint and demonstrated a statistically significant improvement in median overall survival of 10 months in the overall trial population with the addition of docetaxel to ADT, compared with ADT alone (ADT plus docetaxel median OS 77 months, ADT-alone median OS 67 months; HR 0.76, 95% CI 0.63–0.91; $p = 0.003$). However as already noted, the overall trial population included only one arm, of four, with M disease. Therefore, a *post hoc* subgroup analysis was carried out, comparing those with M1 disease with the other three arms without any measurable disease including both those known to be localized and those with PSA recurrence only (these three arms are collectively referred to as M0). The subgroup analysis showed that patients with M1 disease had a significant benefit with the addition of docetaxel (HR 0.76 95% CI 0.62–0.92) whereas those with M0 disease had no benefit to the addition of docetaxel (HR 0.95, 95% CI 0.62–1.47). In general, the toxicity observed in STAMPEDE was comparable to what was reported in CHAARTED. Finally, a recently published meta-analysis including all three of these randomized controlled trials revealed statistically significant clinical benefit to combination treatment with docetaxel in this disease setting [17].

Clinical implications

We recommend that patients with newly diagnosed, hormone-naive metastatic prostate cancer and high-volume disease burden be treated with six cycles of docetaxel 75 mg/m^2 without prednisone in combination with continuous ADT per the CHAARTED trial (strong recommendation for based on high-quality evidence).

In patents with low-volume disease, we recommend the same therapeutic approach (strong recommendation for based on moderate-quality evidence) based on seeing a smaller, less significant survival benefit with CHAARTED in low-volume disease but still seeing benefit overall in the STAMPEDE population.

Clinical question 2

In patients with hormone-sensitive prostate cancer, how does up-front abiraterone (AA) plus prednisone in conjunction with systemic ADT compare with ADT alone?

Background

As will be discussed in detail later in the chapter (Question 4), abiraterone acetate is a selective, irreversible inhibitor of cytochrome P17 (17a-hydroxylase/C17,20 lyase) that inhibits androgen synthesis. AA was studied in two Phase III trials (COU-AA-302, COU-AA-301) and approved based on improved outcomes versus prednisone alone, including improved survival, in men with metastatic castration-resistant prostate cancer (mCRPC), both pre- and post-docetaxel chemotherapy [18, 19]. Based on the rationale that AA improves survival in mCRPC and therefore more potent androgen blockade may have activity earlier in the disease course, two large randomized phase III clinical trials investigated the role of AA plus prednisone in addition to ADT for the treatment of mHSPC. The evidence and clinical implications of these studies are reviewed here.

Literature search

We conducted a systematic literature search in PubMed using the search terms "metastatic," AND "castration-sensitive," AND "prostate cancer," AND "abiraterone." We also searched for "metastatic," AND "hormone therapy,"

AND "prostate cancer," AND "abiraterone." The search was limited to randomized controlled trials in English with a human population up to 30 April 2018.

The evidence

Two eligible randomized controlled trials (LATITUDE and STAMPEDE) were identified in our literature search [20, 21]. These two trials were reported at a national meeting in 2017 and published simultaneously in the *New England Journal of Medicine*.

LATITUDE randomized 1199 men with mHSPC to AA at 1000 mg daily plus prednisone 5 mg daily plus ADT or dual placebos plus ADT. The co-primary endpoints were overall survival and radiographic progression-free survival. Median follow-up was 30.4 months. At the planned interim analysis, AA plus prednisone demonstrated improved median overall survival versus placebo (not reached vs. 34.7 months; HR 0.62, 95%CI 0.51–0.76; $p<0.001$). Median radiographic progression-free survival was also improved with AA plus prednisone compared with placebo (33.0 vs. 14.8 months; HR 0.47, 95% CI 0.39-0.55; $p<0.001$), as were time until pain progression, next subsequent therapy for prostate cancer, initiation of chemotherapy, and PSA progression (all $p<0.001$). In addition, median time to next symptomatic skeletal event was also delayed in the AA plus prednisone arm compared with placebo (HR 0.70, 95% CI 0.54–0.92; $p<0.009$). Grade 3 or 4 adverse events occurred in 63% of the AA plus prednisone group compared with 48% of the placebo group, resulting in treatment discontinuation in 12% and 10%, respectively. Grade 3 mineralocorticoid-related adverse events, such as hypertension (20 vs. 10%) and hypokalemia (10 vs. 1%), were more frequent in the AA plus prednisone group compared with placebo [22].

STAMPEDE randomized 1917 men with newly diagnosed and metastatic, node- positive, or high-risk locally advanced prostate cancer starting long-term ADT to ADT alone or AA (1000 mg daily) and prednisone (5 mg). Of note, the group with newly diagnosed metastatic disease comprised 941 patients (49%) and the group with previously treated metastatic disease comprised 61 patients (3.2%), for a total of 1002 mHSPC patients (52%). 20% had node-positive or node-indeterminate non-metastatic disease, and 28% had node-negative, non-metastatic disease. The primary outcome was overall survival, with the intermediate primary outcome of failure-free survival. Median follow-up was 40 months. The 3-year survival rate in the overall study population was 83% in the combination group compared with 76% in the ADT-alone group (HR 0.62, 95% CI 0.52–0.76; $p<0.001$). The hazard ratio was 0.61 in those with metastatic disease. The 3-year failure-free survival rate in the overall study population was 75% in the combination group compared with 45% in the ADT-alone group (HR 0.29, 95% CI 0.25–0.34; $p<0.001$). The hazard ratio was 0.31 in those with metastatic disease. The rate of grade 3 or higher adverse events was 74% in the combination group and 33% in the ADT-alone group. Adverse events were in line with those seen in LATITUDE and in the mCRPC trials.

Clinical implications

We recommend that patients with newly diagnosed, hormone-naïve metastatic prostate cancer, regardless of disease burden, be treated with AA 1000 mg daily plus prednisone 5 mg daily until progression of disease (strong recommendation for based on high-quality evidence). There is currently no direct evidence to suggest whether patients with mHSPC should be preferentially treated with AA plus prednisone alone, docetaxel alone, or both. One meta-analysis comprising data from five phase III trials involving AA or docetaxel in mHSPC subgroups, while limited by the indirect comparison of results and lack of patient-level data, concluded that AA plus.

Clinical question 3

In patients with mCRPC without visceral or symptomatic bone metastases, is there a benefit in overall survival when using cytotoxic chemotherapy?

Background

Clinical responses in metastatic prostate cancer to androgen deprivation therapy are common, but not durable. Eventually, virtually all patients' cancers began to progress while on hormonal therapy to CRPC, defined as disease progression by a rising PSA levels and/or progression on imaging studies in men with a sustained serum testosterone of less than 50 ng/dL [23]. Unfortunately such a disease state is terminal within a few years in many cases.

Chemotherapy for mCRPC was largely ineffective in terms of both overall survival and symptom palliation until 1996, when mitoxantrone (M), in combination with prednisone (P), was approved by the US Food and Drug Administration (FDA) for the treatment of mCRPC. Three randomized controlled trials indicated that M, with either P or hydrocortisone, was superior to corticosteroids alone in both frequency and duration of pain palliation for patients mCRPC [24–26]. Unfortunately the clinical benefit of M/P related only to progression-free survival and did not confer any overall survival benefit.

In an effort to improve upon these results, newer chemotherapeutics were tested in this disease setting. One of the chemotherapy drugs that showed promise in Phase II trials was the taxane docetaxel (D). Taxanes are chemotherapies that stabilize microtubules and prevent cell division. Docetaxel was tested as a single agent [9] or in combination with estramustine (E), which had been approved by the FDA in 1979. Docetaxel, alone or in combination, improved PSA response and duration compared with historical

results with MP in Phase II trials, and thus led to two major randomized Phase III trials in mCRPC: one with D/P and the other with D/P/E versus the same comparator control arm of M/P. These trials were the first to show a survival benefit for chemotherapy in mCRPC, and were reported in 2004 [9, 27]. This led to FDA approval of docetaxel and prednisone for metastatic CRPC that same year. The evidence from these trials and clinical implications is reviewed in the following.

Literature search

We conducted a systematic literature search in PubMed using the search terms "metastatic" AND "castration resistant" AND "hormone refractory" AND "prostate cancer" AND "chemotherapy" AND "phase III." The search was limited to randomized controlled trials and systematic reviews in English up to 1 March 2016.

The evidence

In 2004, the results of two randomized Phase III trials in mCRPC, TAX 327 and SWOG 9916, were published in the same issue of the *New England Journal of Medicine* [9, 27]. TAX 327 was an international trial of mCRPC patients randomized to one of three treatment arms. The control arm was the then standard of care M 12 mg/m^2 IV every 3 weeks for 10 cycles. The two experimental arms were (1) D 75 mg/m^2 every 3 weeks for 10 cycles with daily P and (2) D 30 mg/m^2 weekly for 5 of 6 weeks for five cycles. Both of the experimental arms, therefore, were designed to deliver an equal dose density of D of 150 mg/m^2 per 6 weeks for a total of 30 weeks. All three arms had identical P dosing of 5 mg twice daily. The results of TAX 327 showed a statistically significant overall survival advantage for D with P every 3 weeks versus M/P, but not for the weekly D with P regimen.

SWOG 9916 was a US cooperative group trial of mCRPC patients who were randomized to D 75 mg/m^2 every 3 weeks with daily P 10 mg and E, versus the control arm of M 12 mg/m^2 every 3 weeks plus P 10 mg daily. The results again showed a statistically significant overall survival advantage for the docetaxel regimen over the mitoxantrone regimen (HR 0.80, $p=0.02$). However, on comparing the trials, the addition of E to D/P in SWOG 9916 revealed a higher rate of cardiovascular events (15%) than was seen in TAX 327 with D/P. Although DP was associated with a number of low-grade toxicities, serious adverse events were rare (<10%), with the most common one being febrile neutropenia at 4% [9]. Therefore, D/P (without E) was approved by the FDA for treatment of metastatic "hormone-refractory" prostate cancer in late 2004.

Since 2004, there have been numerous Phase III trials trying to improve upon the D/P regimen, including bevacizumab [28], aflibercept [29], lenalidomide [30], GVAX [31], high-dose calcitriol [32], zibotentan [33], and dasatinib [34]. None of these agents in combination with D or D/P demonstrated any survival benefit versus D/P alone. In addition, the question of whether P adds any benefit to D alone has never been directly answered. Low-dose P was shown to have palliative benefit and also instances of PSA responses [35], hence P (or hydrocortisone) was used as the control arm in the original Phase III M trials. Since P was standard of care and did not interfere with M, M had to be added to P instead of being directly compared with P. Therefore, since M/P was the new standard of care, M/P had to be the control arm for the Phase III trials in mCRPC and P had to be combined with D, since D and M were both cytotoxic chemotherapies being compared with each other.

Although the true benefit of P is unclear, there are many clues to its single-agent benefit. One clue is that in the post-2004 trials in which P was omitted from the experimental arm, such as GVAX/D versus D/P [31] and high-dose calcitriol/D versus D/P [32], the control arm of D/P showed superior survival to the experimental arms without P. Other clues are that looking at the three mitoxantrone trials, P was a monotherapy in the control arm and did confer PSA and pain responses. Hence the combination of D and P is still the standard first-line chemotherapy choice for mCRPC.

For metastatic castration-refractory prostate cancer patients in the post-docetaxel space, multiple options are available and include abiraterone, enzalutamide, radium-223, and sipuleucel-T. However, as this section is addressing cytotoxic chemotherapies only, these options will not be discussed and instead addressed in later questions. Unfortunately, only one cytotoxic chemotherapy has demonstrated a survival advantage in mCRPC following docetaxel chemotherapy. In a large Phase III international randomized trial, TROPIC, 755 men with mCRPC were randomized to either cabazitaxel (C) 25 mg/m^2 plus prednisone (C/P) or mitoxantrone 12 mg/m^2 plus prednisone (M/P) [11]. Both regimens were given every 3 weeks. The primary statistical endpoint was overall survival. The results demonstrated that C/P had a median survival of 15.1 months, whereas M/P had a survival of 12.7 months(HR 0.70, 95% CI 0.59–0.83; $p<0.0001$). The adverse effect profile revealed that the most common side effects in the cabazitaxel arm were diarrhea (47%), fatigue (37%), nausea (34%), asthenia (20%), and back pain (16%). The predominant grade 3 or higher adverse events were neutropenia (82%), with febrile neutropenia in 8% and diarrhea in 6% of patients. These serious adverse events were observed more frequently compared with the mitoxantrone arm. Related to this, there was a higher rate of death due to drug toxicity: 4.9% in the C/P arm and 1.9% in the M/P arm. As a result of these data for C/P, it garnered approval in 2010 as progression after docetaxel.

Apart from D/P and C/P, no other chemotherapeutic agents have shown a definitive survival benefit for men with mCRPC in large Phase III randomized controlled trials; however, there are very promising results in a Phase II single-arm trial for using a combination of gemcitabine

and oxaliplatin [36]. In the trial, 33 men who had failed docetaxel were given this combination and achieved a 55% PSA response rate and 82% radiological response rate. An open question regarding D is the efficacy compared with C. A trial has been conducted (FIRSTANA) that compares D/P with two different doses of C/P (NCT 01308567) The trial has completed accrual, but final data analysis is pending. If C/P has a survival benefit versus D/P, or a significantly better toxicity profile, C/P could supplant D/P as the first-line chemotherapy choice for mCRPC but with the down-side of removing docetaxel as an option since it has limited to no activity in a post-cabazitaxel setting. Another potential option that is being investigated is to add carboplatin to cabazitaxel, and this was tested in a randomized Phase II trial [37]. Preliminary results showed that addition of carboplatin led to improved PFS and overall response rates. At is was underpowered, overall survival was not assessed.

All of the therapies described here were studied in metastatic adenocarcinoma of the prostate. Although most prostate cancer has a histology of adenocarcinoma, there are other subtypes. One such subtype is small-cell carcinoma of the prostate, and it is important to mention here briefly as it is not driven by androgen signaling and therefore does not respond to abiraterone and enzalutamide. It does, however, appear to respond to chemotherapy. No Phase III trials have been conducted to show benefit definitively, but many Phase II single-arm trials and also retrospective cohorts have shown response rates of >50% to platinum-based chemotherapy similar to regimens used for small-cell lung cancer [38–40]. A further discussion of small-cell carcinoma of the prostate is presented in clinical question 5.

Clinical implications

We recommend that patients with mCRPC who either have symptomatic disease or have progressed on secondary hormonal agents (i.e. abiraterone, enzalutamide) be treated with docetaxel/prednisone (strong recommendation for based on high-quality evidence).

In patients who have progressed during or following docetaxel chemotherapy and have a good performance status, we recommend treatment with cabazitaxel/prednisone (strong recommendation for based on high-quality evidence).

We suggest that patients who have progressed on these regimens consider being treated with gemcitabine/oxaliplatin based on a single-arm Phase II trial (conditional recommendation for based on moderate-quality evidence)

Clinical question 4

In patients with mCRPC, how do newer advanced hormonal agents targeting the androgen-signaling pathway (i.e. abiraterone, enzalutamide) compare with regard to patient survival?

Background

MCRPC develops when prostate cancer progresses despite castrate levels of testosterone (<50 ng/dL). This condition is aggressive and was lethal for approximately 27 540 men in 2015 [4]. Prostate cancer metastasizes most commonly to the bone and regional pelvic lymph nodes, less commonly to the liver and lungs. Until 2010, clinicians were limited in treatment options, with only docetaxel being approved for mCRPC.

Fortunately, further understanding of the biological underpinnings of mCRPC led to the paramount development of new treatment options for mCRPC. In 2004, upregulation of the androgen receptor (AR) was found in androgen-independent prostate cancer xenografts in the Sawyers laboratory [41]. Counter to previous thought that mCRPC relied on non-AR-related mechanisms, resistance to castration was found to include persistent AR activation through amplification, mutation, alterations in transcription factors, and c-terminal splice variants [42–46]. Additionally, higher androgen levels were found in clinical samples of prostate cancer, thus showing that prostate cancer can synthesize testosterone and signal through AR via autocrine and paracrine mechanisms to survive castration [47, 48]. Hence AR continues to have an important role as a fundamental mechanism of resistance to androgen deprivation therapy [49].

Therefore, two novel agents that inhibit prostate cancer growth through the AR axis were developed: abiraterone acetate, a selective, irreversible inhibitor of cytochrome P17 (17α-hydroxylase/C17,20-lyase) that inhibits androgen synthesis, and enzalutamide, a second-generation AR antagonist. Phase III randomized clinical trials have been performed with each of these agents and the evidence and clinical implications of these studies are reviewed in the following.

Literature search

We conducted a systematic literature search in PubMed using the search terms “metastatic,” AND “castration resistant,” AND “CRPC,” AND “prostate cancer,” AND [“abiraterone acetate,” OR “enzalutamide”]. We limited the search to randomized controlled trials and systematic reviews in English with a human population up to 1 March 2016.

The evidence

Abiraterone acetate (AA) has been studied in two Phase III clinical trials, one in mCRPC patients prior to chemotherapy (the COU-AA-302 trial) and the other in mCRPC patients after chemotherapy (the COU-AA-301 trial) [10]. In the post-chemotherapy study, 1195 patients with mCRPC were randomized in a 2 : 1 ratio to 5 mg of prednisone twice daily with either 1000 mg of AA (797 patients) or placebo (398 patients), with the primary endpoint of OS [10]. The study found that AA and prednisone improved the median OS by 3.9 months(14.8 vs. 10.9 months; HR 0.65, 95% CI, 0.54–0.77; $p<0.001$) [10]. AA also improved the objective

response rate based on RECIST criteria (14.0% in AA group vs. 2.8% in placebo group, $p<0.001$), PSA response rate (29.1% in AA group vs. 5.5% in placebo group, $p<0.001$), and time to PSA progression (10.2 months in AA group vs. 6.6 months in placebo group; HR 0.58, 95% CI 0.46–0.73; $p<0.001$) [10]. Furthermore, AA improved radiographic PFS (5.6 months for AA group vs. 3.6 months for placebo group, $p<0.001$) [10]. Patients treated with AA were more likely to develop adverse events associated with increased mineralocorticoid levels such as edema, hypokalemia, and hypertension (55 vs. 43%, $p<0.001$), but they did not develop significantly more cardiac events, including tachycardia and atrial fibrillation.

In patients who were less symptomatic, prior to chemotherapy, the Phase III randomized controlled trial COU-AA-302 randomized 1088 patients to prednisone 5 mg twice daily with either AA 1000 mg daily or placebo [50]. Co-primary endpoints were radiographic PFS and OS. The final analysis showed that AA plus prednisone improved OS by 4.4 months beyond prednisone alone (34.7 vs. 30.3 months; HR 0.81, 95% CI 0.70–0.93; $p=0.0033$) [51]. AA also increased time to opioid use for painful metastases by about 10 months (33.4 months for AA group vs. 23.4 months for placebo group; HR 0.72, 95% CI 0.61–0.85; $p<0.0001$) [51]. Common adverse events for patients treated with AA included edema (30% grade 1–2, 1% grade 3), hypokalemia (16% grade 1–2, 2% grade 3), hypertension (19% grade 1–2, 5% grade 3), and cardiac disorders (15% grade 1–2, 6% grade 3, and 1% grade 4). Cardiac-related deaths were similar on-study, 4 (<1%) in the AA group and 3 (<1%) in the placebo group [51].

AA was thus found to be an effective oral treatment for mCRPC both before and after chemotherapy.

Similarly to the development of AA, enzalutamide was also studied in two Phase III trials, one in patients with mCRPC after chemotherapy (AFFIRM study) and the other in patients with chemotherapy-naive mCRPC (PREVAIL study). Enzalutamide was initially found to select potently for AR and bind in the ligand binding domain [52], thereby inhibiting the ability of AR to translocate to the nucleus and to bind DNA. AFFIRM randomized 1199 men with mCRPC in a 2 : 1 ratio to enzalutamide 160 mg daily or placebo; the study's primary endpoint was OS [12]. At the planned interim analysis, enzalutamide was found to improve median OS by 4.8 months (18.4 vs. 13.6 months; HR 0.63, 95% CI 0.53–0.75; $p<0.001$) [12]. Additionally, enzalutamide was superior to placebo upon analyzing all secondary endpoints, including a ≥50% reduction in PSA (54 vs. 2%, $p<0.001$), soft-tissue response rate (29 versus 4%, $p<0.001$), quality-of-life response rate (43 vs. 18%, $p<0.001$), time to PSA progression (8.3 vs. 3.0 months; HR 0.25, 95% CI 0.20–0.30; $p<0.001$), radiographic PFS (8.3 vs. 2.9 months; HR 0.40, 95% CI 0.35–0.47; $p<0.001$), and the time to the first skeletal-related event (16.7 vs. 13.3 months; HR 0.69, 95% CI 0.57–0.84; $p<0.001$) [12]. The most common adverse events in the AFFIRM study were fatigue, diarrhea, and hot flashes. Of the 800 patients treated with enzalutamide, five (<1%) developed seizures, several of whom had either brain metastases or concomitant medications that lowered the patient's seizure threshold.

Subsequently, the PREVAIL study examined enzalutamide in patients with asymptomatic mCRPC who were chemotherapy naive. The PREVAIL study randomized 1717 patients to enzalutamide 160 mg daily or placebo, and co-primary endpoints were radiographic PFS and OS [53]. At the time of the interim analysis, enzalutamide improved radiographic PFS by 81% (HR 0.19, 95% CI 0.15–0.23; $p<0.001$) and OS by 29% (HR 0.71, 95% CI 0.60–0.84; $p<0.001$) [48]. Enzalutamide also improved the rate of >50% PSA decline (78 vs. 3%, $p<0.001$), had higher rates of complete radiographic response (20 vs. 1%, $p<0.001$), and lengthened the median time to PSA progression (11.2 vs. 2.8 months; HR 0.17, 95% CI 0.15–0.20; $p<0.001$) [53]. Quality of life was also improved in patients treated with enzalutamide using both the FACT-P and EQ-5D questionnaires [54]. Patients tolerated enzalutamide well, without a significant difference in grade 3 adverse events (43 vs. 37%) [53]. The most common enzalutamide-associated adverse events were back pain, fatigue, and constipation. There was a difference in grade 3 or higher hypertension, with 59 (7%) of men treated with enzalutamide versus 19 (2%) of men treated with placebo. Atrial fibrillation occurred in 16 men (2%) treated with enzalutamide compared with 12 men (1%) treated with placebo [53]. Only one patient (0.1%) in each treatment group developed seizure during the course of the study [53]. Enzalutamide was therefore established as an effective oral treatment for men with chemotherapy-naive mCRPC, significantly delaying disease progression and improving OS.

Enzalutamide's seizure toxicity likely stems from its partial antagonism of the GABAa receptor in the brain, which may increase in patients who have brain metastases, prior strokes, prior seizure disorders, or concurrent medications that lower the seizure threshold [55]. An ongoing Phase IV trial (UPWARD) will evaluate the risk of seizure in men with mCRPC and predisposing conditions at higher seizure risk (NCT01977651).

The optimal sequence between the AA and enzalutamide oral treatments has not been studied in any prospective randomized studies. Most retrospective studies have shown cross-resistance to the second hormonal agent in the sequence, with short median PFS of around 3–4 months [56–60]. The largest retrospective study to date examined patients treated with enzalutamide after AA and found that the median ezalutamide duration was 3.2 months [61]. Only 22/137 (18%) patients achieved a ≥50% PSA response [61]. Mechanisms of resistance are many and outside the scope of this review.

Clinical implications

We recommend that patients with mCRPC either before cytotoxic chemotherapy or refractory to chemotherapy be treated with abiraterone acetate or enzalutamide (strong recommendation for based on high-quality evidence). Since neither agent has been tried against the other, one cannot be definitively recommended over the other.

However, as enzalutamide does not need prednisone whereas abiraterone acetate does, we suggest that patients with various comorbidities such as diabetes or heart failure use enzalutamide over AA (conditional recommendation for based on moderate-quality evidence).

At failure of either therapy, we suggest that the other be used in minimally symptomatic patients as they are not mutually exclusive therapies and are generally well tolerated (conditional recommendation for based on moderate-quality evidence). The caveat to sequencing either behind the other is that the second therapy is not nearly as effective as if it were used first.

Although Phase III data suggest that treatment with abiraterone and prednisone, or enzalutamide, can improve the survival of patients who are either chemotherapy naive or previously treated, most patients are being treated with these agents prior to D/P chemotherapy. The reasons for this sequence of care are multifactorial but include the ease of administration (oral versus intravenous), the perceived lower toxicity profile of the oral hormonal agents compared with D/P chemotherapy, and the duration of response. However, there are no Phase III studies evaluating the sequence of D/P chemotherapy and abiraterone prednisone or enzalutamide and therefore no definitive recommendations can be made on their sequencing.

Clinical question 5

In patients with clinically significant symptomatic bone-only metastatic CRPC, how does radium-223 compare with placebo?

Background

Approximately one-third of patients with mCRPC will present with some degree of symptomatic disease and over half of patients develop clinically significant complications during their course. Many of these complications occur within or associated with osseous metastasis. Over 80% of patients with mCRPC develop bone metastases and a significant proportion of them present or develop a "bone-dominant" clinical picture that has a different prognosis to that for patients without bone metastases [62].

Literature search

We conducted a systematic literature search in PubMed using the search terms "radium 223" OR "abiraterone" OR "enzalutamide" OR "docetaxel" OR "cabazitaxel" AND "prostate cancer." Only Phase III clinical trials for FDA-approved survival-prolonging medications (abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223, sipuleucel-T) for symptomatic mCRPC were considered up to 1 March 2016.

The evidence

More than 80% of patients with mCRPC will have radiographic evidence of bone metastases [9, 62, 63]. Other sites of disease are much less common, such as lung (46%), liver (25%), pleura (21%), and adrenal glands (13%) [63]. Retrospective analysis of patients treated with docetaxel for bone-only mCRPC showed that patients with visceral metastases such as liver or lung disease had a median OS of 10 and 14.4 months, respectively; patients with bone-only disease had the next worse prognosis, with a median OS of 19 months, compared with 26.7 months for patients with node-only disease [62]. The importance of bone metastasis in mCRPC is further evidenced by the fact that at least two factors linked to bone involvement, opioid medication usage and anemia, are known to be prognostic factors for survival [64]. Bone metastases are also important clinically as they contribute to significant morbidity such as pathological fractures, spinal cord compression, pain, anemia, and decreased quality of life.

Few prospective randomized controlled trials have focused on symptomatic, bone-dominant clinical phenotypes for management; however, one such study was the Phase III ALSYMPCA trial. In this study, 921 patients with progressive mCRPC were randomly assigned 2 : 1 to receive either injections of the radiopharmaceutical alpha-emitter radium-223 every 4 weeks for six cycles or placebo. For eligibility, the men had to have mCRPC with no known visceral metastases or malignant lymphadenopathy that was larger than 3 cm in short-axis diameter. Prior docetaxel usage was not an exclusion factor. At interim analysis, radium-223 improved the primary endpoint of overall survival (14 vs. 11.2 months; HR 0.70, 95% CI 0.55–0.88; two-sided $p = 0.002$) [13]. Furthermore, patients in the radium-223 arm had a longer median time to first symptomatic skeletal event (15.6 vs. 9.8 months; HR 0.66, 95% CI 0.52–0.83; $p < 0.001$), median time to increase in total alkaline phosphatase level (7.4 vs. 3.8 months; HR 0.17, 95% CI 0.13–0.22; $p < 0.001$), and median time to increase in PSA (3.6 vs. 3.4 months; HR 0.64, 95% CI 0.54–0.77; $p < 0.001$). There was a small percentage of cytopenias, including only 3 and 6% grade 3 and 4 neutropenia and thrombocytopenia, respectively, with radium-223. Grade 3 or 4 anemia was similar at 12% in both the radium-223 and placebo arms. Gastrointestinal toxicities such as constipation, diarrhea, nausea, and vomiting were the most common non-hematological side effects of radium-223, with grade 3 or 4 toxicities occurring in 2% of patients or fewer.

Owing to the morbidity and mortality of pathological fractures, the prevention of skeletal-related events (SREs),

often defined as the development of pathological fractures, cord compression, or need for palliative bone-directed radiation, is an important clinical outcome of study in patients with mCRPC. Bone antiresorptive agents such as the osteoclast inhibitor zoledronic acid, and the monoclonal antibody to the receptor activator of NF-κB ligand (RANK-L) denosumab, are part of standard treatment for bone metastases in cancer therapy in general. Denosumab resulted in an improvement of 3.6 months in time to first SRE over zoledronic acid (20.7 vs. 17.1 months; HR 0.82, 95% CI 0.71–0.95; $p=0.0002$ for non-inferiority and $p=0.008$ for superiority) in a randomized Phase III study of patients with mCRPC, and therefore should be a standard of care for all patients [65]. Denosumab may also have added benefits when used concurrently with radium-223, based on a subgroup analysis of ALSYMPCA patients treated with antiresorptive agents combined with radium-223 that showed a trend towards better survival than in patients not on antiresorptive agents [13]. Among other treatments for mCRPC, Phase III studies of docetaxel and cabazitaxel failed to look at the incidence of skeletal-related events (SREs) as an endpoint, and so the proven benefit of radium-223 in delaying the time to SREs, which was a secondary endpoint of ALSYMPCA, should be especially recognized [13, 66]. Evidence from Phase III studies of the next-generation potent androgen suppression agents abiraterone and enzalutamide have also shown a benefit with respect to SREs [53, 54, 67, 68].

With respect to pain palliation, Phase III studies of life-prolonging medications for mCRPC, including docetaxel [9], abiraterone [50], and enzalutamide [54], have shown benefit, but none of these studies looked specifically at patients with bone-only metastases. Cabazitaxel (C) with prednisone demonstrated a survival benefit after the use of docetaxel when compared with mitoxantrone in the Phase III TROPIC study, but C/P did not show a significant improvement in pain progression score in this trial [11]. ALSYMPCA did not specifically look at pain palliation as an endpoint, but Phase I and II studies of radium-223 suggest that pain improvement occurs in more than half of treated patients [69, 70]. For patients with symptomatic bone metastases, radium-223 should be considered a reasonable therapy for pain palliation.

Finally, radium-223 is a fairly tolerable drug for patients. Previous radiopharmaceuticals including the beta-emitters samarium-153 and strontium-89 have been studied in randomized controlled trials, and have a benefit in the palliation of pain, but these drugs also result in significant hematological toxicity without definitive survival benefits [71–74]. Samarium-153 and strontium-89 emit beta-particles and generally have weaker biological effects and larger emitting radius. In contrast, radium-223 is an alpha-emitter and has higher potency with a shorter distance of effect, a characteristic often cited as an explanation for the improved efficacy and toxicity profile of radium-223 [75]. Overall, with caveats of cross-trial comparisons, radium-223 appears to have a much better toxicity profile compared with cytotoxic chemotherapies, which have higher rates of myelosuppression and gastrointestinal effects [9, 11]. Even after the administration of docetaxel, toxicity with radium-223 has been shown to be minimal. For instance, among patients who received docetaxel prior to radium-223 in ALSYMPCA, there was an 11% rate of grade 3–4 anemia and a <5% incidence of other notable grade 3–4 toxicities such as neutropenia, thrombocytopenia, constipation, diarrhea, and nausea and vomiting [76, 77].

Clinical implications

We recommend that patients with clinically significant symptomatic bone-only metastatic CRPC be treated with radium-223 (strong recommendation for based on high-quality evidence).

In routine practice, many patients receive potent androgen suppression with either abiraterone or enzalutamide as first-line treatment for symptomatic mCRPC followed by D/P chemotherapy. The results of ALSYMPCA provide strong evidence that radium-223 can be used before (for chemotherapy-ineligible patients) or after chemotherapy in mCRPC, and that radium-223 should be recognized for not only its benefits on overall survival, but also its association with preventing SREs, palliating pain, and low toxicity. For patients with more widespread symptomatic metastases, including lymph nodes and soft tissue, chemotherapy regimens, primarily D/P or C/P, should be considered standard of care. Multidisciplinary care with stereotactic radiosurgery, palliative low-dose external beam radiation therapy, or even surgery should be offered in the context of these systemic options when appropriate. Neuropathic pain syndromes can be challenging in this disease setting and, as such, palliative care consultation and collaboration are encouraged in particularly difficult symptomatic cases.

Clinical question 6

What are the prognosis and management for patients with mCRPC to the viscera such as the lung and liver?

Background

Prostate cancer is typically a bone-tropic disease, with bone metastases dominating the clinical metastatic presentation, and with lymph node metastases being additionally a common site of disease. Visceral spread is reported to occur in 10–20% of men with mCRPC, but may be increasingly recognized over time as disease progresses, and at autopsy is particularly common [78], and is observed in over 50% of men with lethal disease. Clinical experience has demonstrated the prognostic importance of the pattern of spread in men with mCRPC, with declining prognosis from nonmetastatic CRPC to lymph node-only mCRPC, bone mCRPC with and without nodal disease, lung metastases, and finally liver

metastases. Prognosis in these subgroups depends on prior therapies and multiple other prognostic characteristics (pain, hemoglobin, type of progression, alkaline phosphatase, LDH, etc.), but this pattern of spread is independently associated with overall survival. For example, the median survival of men with node only mCRPC was 27 months in a meta-analysis of men treated with docetaxel, whereas median survival was 20 months in men with bone metastases and 14 months in men with visceral patterns of spread. Patients with lung metastases had intermediate prognoses, with a median survival of 17 months, compared with men with liver metastases, where survival was shortest at 12 months [79].

Before 2004, with the discovery of docetaxel's survival benefit, there were no proven therapies to improve survival in mCRPC and visceral spread therefore remained as a negative prognosticator only. Since then, other new therapies have come out and visceral spread is now used to help decide future therapy, and several systemic agents are now typically offered to men with mCRPC who lack visceral spread (radium-223 and sipuleucel-T).

Literature search

We conducted a systematic literature search in PubMed limited to randomized controlled trials using the search terms "prostate cancer" AND ["abiraterone" OR "enzalutamide" OR "docetaxel" OR "cabazitaxel" OR "radium-223" OR "sipuleucel-T"] up to 1 March 2016, as these are all of the therapies known to prolong survival in metastatic prostate cancer. We then analyzed the search results and narrowed them to include only those trials that allowed visceral metastases.

The evidence

The literature review demonstrated that there were only five trials using four drugs that allowed patients with visceral metastases to be included: TAX 327, which evaluated docetaxel versus mitoxantrone in men with mCRPC [9]; COU-AA-301, which used abiraterone acetate versus placebo in men with mCRPC failing docetaxel [10]; AFFIRM, which used enzalutamide versus placebo in men with mCRPC failing docetaxel [12]; PREVAIL, which evaluated enzalutamide versus placebo in men with mCRPC who had not yet had docetaxel [53]; and TROPIC, which evaluated cabizitaxel versus mitoxantrone in men with mCRPC after failing docetaxel [11]. Both radium-223 and sipuleucel-T are not approved for use in men with visceral spread. A meta-analysis of docetaxel-based clinical trials has also been presented evaluating the prognostic importance of visceral spread in men with mCRPC [79].

As mentioned, the TAX 327 trial used D/P chemotherapy versus the standard of care at the time, M/P, which had no proven survival benefit but did have proven better symptom palliation. The results showed that docetaxel given every 3 weeks had an OS of 18.9 versus 16.5 months ($p=0.009$). Updated results of the trial confirmed that every 3-week docetaxel was beneficial to OS, but subgroup analysis showed that the visceral subgroup had an overall survival HR that crossed unity whereas the no visceral disease subgroup had an HR that did not cross unity. It also stated that the median OS of visceral disease was 13.1 versus 18.9 months in those without visceral spread [80]. A *post hoc* analysis of the TAX 327 trial looked at the patients receiving D/P and subdivided them into those with lymph node-only disease, bone-only disease (with and without nodes), and visceral spread [81]. This analysis demonstrated that men with visceral disease had a much worse outcome, with a median survival of 14.5 months compared with 19.5 months with bone-only and 35 months with node-only disease. A further analysis used both D/P- and M/P-treated patients and subclassified the visceral spread into lung only versus liver with and without other sites [62]. The study showed that men with liver metastases had a median OS of 10 months compared with lung only at 14.4 months, bone only at 19 months and node only at 26.7 months (see Figure 28.2). Interestingly, men with combined bone and node disease had a median OS of 15.7 months, which enhances the idea that spread to any soft tissue site in the presence of bone metastases has a poorer prognosis. These data have been confirmed in a larger meta-analysis as described earlier, which demonstrated clinically and statistically significant differences in OS based on these patterns of spread [79]. In this meta-analysis, lung metastases were associated with a 30% relative increase in the hazard of death over time compared with bone metastases, whereas liver metastases were associated with a further 40% increase in the risk of death compared with lung metastases (both $p<0.001$). These data clearly indicate the prognostic

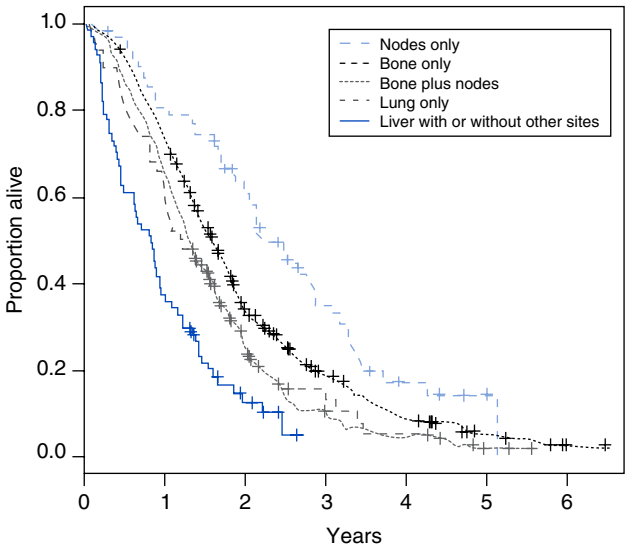

Figure 28.2 Kaplan–Meier plot for overall survival for all patients, based on patterns of metastatic spread. Source: Pond et al. 2014 [62]. Reproduced with permission from Elsevier.

importance of patterns of spread, which should be considered in the design of clinical trials of novel agents.

The data presented thus far about visceral spread concerned its relationship with D/P chemotherapy. Abiraterone acetate inhibits androgen biosynthesis and has a proven survival benefit in both chemotherapy-naive and post-docetaxel men with mCRPC. The COU-AA-301 trial randomized patients to abiraterone acetate versus placebo in men who had already failed docetaxel and demonstrated a significant improvement in OS of 14.8 months with abiraterone compared with 10.9 months [10]. *Post hoc* subgroup analyses within that study showed a significant benefit of using a HR for OS in patients with both visceral (HR 0.70) and nonvisceral disease (HR 0.62). In addition, radiographic PFS was delayed by abiraterone in men with visceral metastases (HR 0.60) and men without visceral metastases (HR 0.68), each statistically significant. Although PFS and OS were shorter in men with visceral spread, and radiographic PFS was only 5–6 months, these data indicate that hormonal therapy is still beneficial even in the presence of visceral spread, particularly lung metastases. A subsequent subgroup analysis showed that HR for OS in men with visceral spread was no longer significant at 0.79 (95% CI 0.60–1.05) [82]. It also showed that the median OS for men with lung metastases was 13.9 months versus 7.3 months in men with liver spread. Interestingly, men with lung metastases had improved radiographic PFS at 5.6 months compared with 2.8 months with placebo, but men with liver metastases did not seem to have an improvement in radiographic PFS (2.8 months in each group). This confirms the earlier observations about the importance of the site of metastasis and indicates the need for more effective therapies in these men. A subsequent study using abiraterone before having failed docetaxel did not include men with visceral spread, hence the activity of this agent is unknown in this pre-chemotherapy setting.

Enzalutamide is a second-generation AR antagonist that reduces AR nuclear localization and DNA binding, and has a proven survival benefit in men with mCRPC in the chemotherapy-naive and post-docetaxel settings. The AFFIRM trial randomized men to enzalutamide versus placebo after having failed docetaxel and showed a significant improvement in OS at 18.4 months versus 13.6 months [12]. Subgroup analysis in that trial showed a significant benefit for men without visceral disease, but in men with visceral disease the HR crossed unity and therefore did not meet statistical significance (HR 0.78, 95% CI 0.56–1.09). Although there were numerical improvements in survival in subsets of men defined by lung metastases (OS 10.4 → 16.5 months) or liver metastases (OS 5.7 → 9.0 months), the number of men with these patterns of spread was small and the power to demonstrate statistical significance was reduced [83]. In contrast, the PREVAIL trial randomized men to enzalutamide versus placebo before having tried docetaxel and showed a reduced risk of death not only in the overall study but also in patients with visceral disease [53]. For example, in the 98 men with chemotherapy-naive visceral-metastatic mCRPC in PREVAIL, the HR for OS was 0.82 (95% CI 0.55–1.23). Enzalutamide delayed radiographic PFS in these men with visceral spread, but with HR 0.28 (95% CI 0.16–0.49), which was statistically significant. Although the OS results did not meet statistical significance, these data suggest that enzalutamide has activity in men with visceral disease and can delay progression and death in these patients [84]. However, only controlled studies comparing either abiraterone or enzalutamide with chemotherapy in these subsets defined by visceral spread can define the optimal approach to these patients. Based on these data, however, current NCCN guidelines recommend either abiraterone, enzalutamide, or D/P as effective options for these men with mCRPC and visceral spread.

Finally, cabazitaxel (C), which is a taxane that acts similarly to D but has activity in D-resistant tumors, was compared with M/P in the TROPIC Phase III trial in men with mCRPC who had failed docetaxel-based chemotherapy. The results showed that the median OS was significantly improved at 15.1 versus 12.7 months [11]. The trial included visceral disease but no subgroup analysis was commented upon. However, a recent prognostic model [85] identified visceral spread as adversely prognostic in this second-line setting, and C/P remained significantly associated with improved survival despite this visceral pattern of spread. Thus, although visceral spread is adversely prognostic in this post-chemotherapy setting, second-line chemotherapy with C/P is still beneficial in these men.

Currently, one of the emerging approaches to treating men with mCRPC concerns drugs that modify the innate immune system of the patient to help fight the cancer. Sipuleucel-T, a form of immunotherapy, has not been evaluated in these men, and appears to have greater activity in earlier disease settings. Ipilimumab is a human monoclonal antibody that blocks negative feedback on T cells by blocking the cytotoxic T-lymphocyte antigen 4. In essence, it helps block the check on the immune system that would normally stop T cells from recognizing something as "self" and not foreign. Overall, this allows T cells to target tumor cells that had been otherwise ignored by the immune system. Ipilimumab has shown great effect in metastatic melanoma and was tested in men with mCRPC. The trial gave bone-directed radiation to all enrolled patients and then randomized them to either ipilimumab or placebo [86]. The radiation was given to try to create a release of neoantigens from the tumor so that when the immune system was altered by the ipilimumab, it might be more effective in its antitumor effects. Unfortunately, since the trial did not find an overall survival benefit, it is not currently approved. Subgroup analyses showed a significant benefit for patients with bone-only disease but absolutely no benefit for patients with visceral disease. Given this unusual response pattern, further study is ongoing with this drug and

other immunotherapies in combination trials and with other immune checkpoint approaches. However, these data suggest that novel approaches are needed for men with mCRPC and visceral spread, given their aggressive phenotype and poor outcomes.

Most patients with mCRPC have adenocarcinoma as the underlying histology. The more important clinical implication of visceral disease is that it may be a sign that the patient no longer has prostatic adenocarcinoma but instead has transformed into a more aggressive histology with neuroendocrine features including small-cell prostate cancer. Patients with this variant are castration resistant under 6 months, have bulky adenopathy, or have visceral-only disease, or express serum biomarkers of neuroendocrine prostate cancer (NEPC) such as chromogranin or neuron-specific enolase [40]. Emerging data suggest that men with NEPC have genomically complex tumors and harbor loss of RB1, have p53 mutations, and have activations of the PI3K/AKT pathways and amplifications of MYCN and Aurora kinase A, among many other molecular lesions [87, 88]. The distinction should be made from adenocarcinoma, because these men are much less likely to respond to the conventional therapies listed and instead should be treated with platinum-containing therapy commonly in the form of cisplatin and etoposide [89]. These patients should be worked up with a biopsy of a visceral metastatic site to confirm the diagnosis and in most cases be referred to centers of excellence where clinical trials might be available. In addition, biopsies should be assessed for phenotypic changes, including neuroendocrine transformation, and also for mutational profiling to identify potential targets for systemic therapy or clinical trial participation [90]. For example, in a recent survey of men with mCRPC, potentially actionable targets for therapy were identified in many of these men, particularly with respect to DNA repair pathways, that may be amenable to DNA-damaging agents such as platinum or PARP inhibitors.

Finally, there are emerging data that indicate that the NEPC phenotype may be increasing over time following treatment with potent AR pathway inhibitors such as abiraterone or enzalutamide. For example, the SU2C West Coast Team surveyed 124 evaluable metastatic biopsies of men with mCRPC, most of whom received prior abiraterone/enzalutamide therapy, and found that small-cell carcinoma was identified in 13% of men, 26% of men had mixed small-cell/adenocarcinoma, and only 35% had typical adenocarcinoma histology. A novel histological variant representing an intermediate phenotype was also present in 26% of cases [91]. Cases with small-cell or intermediate histologies had a clearly worse survival, indicating an aggressive phenotype. These data are in contrast to the SU2C East Coast Team survey results of men with mCRPC, in which fewer than half were abiraterone/enzalutamide naive, had a predominant adenocarcinoma histology (96.4%), and small-cell carcinoma or hybrid tumors were relatively uncommon (<4%) [90]. Although it is not possible at present to compare across these different studies given the differences in tissue processing and patient characteristics, these data suggest enrichment for NEPC-like phenotypes following potent AR blockade.

Clinical implications

In patients with mCRPC with visceral disease, we suggest that enzalutamide be used first over docetaxel (conditional recommendation for based on high-quality evidence). This recommendation recognizes the absence of head-to-head trials but is based on the fact that enzalutamide is taken orally and is usually better tolerated than docetaxel.

We recommend against the use of sipuleucel-T in this setting (strong recommendation against based on moderate-quality evidence). This recommendation is based on the lack of direct evidence on the role of this agent in this group of patients and also compelling evidence of effectiveness for other agents.

We also suggest that men with mCRPC with visceral metastases who may be transforming to a more aggressive phenotype that may be linked to NEPC-like transformation undergo directed metastatic biopsies and testing, as treatment of NEPC/small-cell prostate cancer is different from that of the more common adenocarcinoma (conditional recommendation for based on moderate-quality evidence).

Metastatic prostate cancer summary

Metastatic prostate cancer represents a clinically heterogeneous disease, which can be complicated to manage. Numerous treatment options, including novel hormonal agents, systemic chemotherapy, an immunotherapy, and a radiopharmaceutical, have demonstrated clinical benefit in patients with metastatic prostate cancer. A summary of approved drugs for use in mCRPC with visceral disease is given in Table 28.1. Management decisions and therapy selections in this population are often influenced by hormone status, location of metastases, and presence or absence of symptoms, as described, in addition to patient factors, such as performance status, comorbidities, and preference.

In the future, novel immunotherapies and also molecularly targeted and disease-specific treatments will likely emerge. Ongoing Phase III trials will shape the management landscape for these new agents, but so also will Phase IV and prospective observational cohort studies. Indeed, data will likely emerge faster and with greater clinical context in registries and we will need to look to these data sets to inform our best practices. In the end, understanding and maximizing the survival and quality of life of patients are the goal for most and this should be achieved with a collaborative and interactive relationship between specialties including urology, medical oncology, and radiation oncology.

Table 28.1 Summary of approved drugs for use in mCRPC with visceral disease.

Drug	Study name	Drug indication in trial	Control used in study	Median OS in drug arm (months)	Median OS in control arm (months)	HR for median OS benefit in visceral disease	Does HR cross unity?
Docetaxel	TAX 327	First-line mCRPC	Mitoxantrone	18.9	16.5	0.87	Yes
Abiraterone acetate	COU-AA-301	Men failing docetaxel	Placebo	14.8	10.9	0.79	Yes
Enzalutamide	AFFIRM	Men failing docetaxel	Placebo	18.4	13.6	0.78	Yes
Enzalutamide	PREVAIL	Men without prior docetaxel usage	Placebo	Not reached[a]	31	0.52 (0–3 bone lesions) 1.13 (≥4 bone lesions)	Yes in both cases
Cabazitaxel	TROPIC	Men failing docetaxel	Mitoxantrone	15.1	12.7	Not reported	Not reported

[a] Trial was halted early due to interim analysis showing statistically significant relative improvement in the co-primary endpoints of radiographic progression-free survival and overall survival.

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PART 5

Kidney and bladder cancer

Rodney H. Breau

29 CHAPTER 29

Treatment of superficial bladder cancer

Alexander Kretschmer[1,2], Alexander Karl[1], and Badrinath R. Konety[3]

[1] *Department of Urology, University Hospital Munich, Ludwig-Maximilians University, Munich, Germany*

[2] *Department of Urological Sciences, University of British Columbia, Vancouver, BC, Canada*

[3] *Department of Urology, University of Minnesota, Institute for Prostate and Urologic Cancers, Masonic Cancer Center, Minneapolis, MN, USA*

Introduction

Worldwide, urothelial carcinoma of the bladder represents the eleventh most frequently diagnosed malignancy and the fourteenth leading cause of cancer-related deaths [1]. Importantly, approximately 75% of the patients with urothelial carcinoma present with non-muscle-invasive bladder cancer (NMIBC; stage Ta/CIS for mucosa infiltration, stage T1 for submucosa infiltration) [2]. According to data from the European Organization for Research and Treatment of Cancer (EORTC), the probability of recurrence 5 years after the initial diagnosis is 31–78%, and the probability of progression at 5 years is <1–45% [3]. These high recurrence and progression rates necessitate long-term surveillance and various adjuvant therapeutic strategies in patients with bladder cancer and come along with a great burden for the respective patient and also the health system in general.

Depending on the estimated aggressiveness of the disease, therapeutic options range from a single transurethral resection of bladder tumor (TURBT) with early post-transurethral-resection instillation therapy over TURBT followed by multiple cycles of intravesical chemo- or immunotherapy (bacillus Calmette–Guérin [BCG]) to radical cystectomy.

The aim of the initial TURBT or biopsy is to obtain tissue for the correct diagnosis and to remove all visible lesions. The resection strategy depends on the size and number of the lesions. A complete and correct transurethral resection has been reported to be essential to optimize outcome [4]. Recently, novel imaging diagnostics including photodynamic diagnosis (PDD) have been introduced to optimize the efficacy of TURBT. Until lately, one immediate postoperative instillation of chemotherapy has been recommended after TURBT of NMIBC. These recommendations have recently been limited to single papillary tumors [5]. The need for further adjuvant intravesical therapy depends on the calculated aggressiveness of the detected tumor. Different chemotherapeutic agents are used in a variety of application schedules.

Finally, there is the option of immediate cystectomy in those patients who present with non-muscle-invasive tumor but may have a high risk of progression based on pathological features. Reported indicators for a higher risk of progression are multiple recurrent high-grade tumors, high-grade T1 tumors, and high-grade tumors with concomitant carcinoma *in situ* (CIS). In such patients, a delayed cystectomy might lead to decreased disease-specific survival [6].

Clinical question 1

In patients undergoing TURBT for urothelial carcinoma, how does fluorescence imaging compare with white light cystoscopy alone?

Background

Current evidence supports the use of fluorescence imaging as it consistently provides increased detection rates for both papillary lesions and CIS. However, its impact on recurrence rates and recurrence-free survival has not been established [7, 8]. O'Brien et al. conducted a prospective trial and included 249 patients who were randomized in a hexyl 5-aminolevulinate (HAL) and a white light cystoscopy group. All patients received a postoperative single dose of mitomycin C [9]. The authors found no significant differences in recurrence rates after 3 or 12 months. These results raised the question of whether the impact of fluorescence cystoscopy is currently overestimated and if the benefits regarding recurrence-free survival would be less evident if all patients received postoperative intravesical mitomycin C instillations

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following current guidelines [9, 10]. However, it has to be kept in mind that PDD has been shown to reduce the recurrence rates independent of the tumor stage. Therefore, fluorescence cystoscopy may useful in cases of NMIBC and CIS that do not benefit as much from perioperative chemotherapy and a potential overestimation of its benefit in reducing recurrence rates might therefore be limited to low-grade NMIBC [7].

Literature search

We searched for systematic reviews, meta-analyses, randomized trials, and observational studies in the Cochrane Library and MEDLINE (January 2009–June 2015) using the search terms "fluorescence imaging," "photodynamic diagnostics," "bladder cancer," and "urothelial carcinoma." Results were limited to publication dates of January 2009 or later, studies involving humans, and reports in the English language. All study designs were accepted except for case reports. Cited references from selected studies were also retrieved. Each article's title and abstract were reviewed for their appropriateness. Results are summarized in Table 29.1.

The evidence

Table 29.1 summarizes data from 15 trials that were published between 2009 and 2013 and includes a total of 4164 patients. Three studies focused on 5-aminolevulinic acid (5-ALA) [11–13], 11 studies focused on hexyl 5-aminolevulinate (HAL) [9, 14–23], and a two-arm study included patients undergoing fluorescence imaging with either 5-ALA or HAL [24].

Based on a recently published review by Rink et al. [25], photodynamic diagnosis using 5-ALA or HAL seems to increase the detection rates of papillary tumors by up to 29% and detection rates of CIS by up to 30%, and significantly reduces residual tumors after TURBT. This leads to an increased recurrence-free survival in those patients compared with white light cystoscopy alone. An increase in overall or cancer-specific survival, however, could not be confirmed [25]. A meta-analysis of randomized controlled trials (RCTs) including 12 studies and 2258 patients showed similar results favoring fluorescence imaging in terms of recurrence rates and recurrence-free survival up to 2 years postoperatively (hazard ratio [HR] 0.65, $p<0.001$). A significant impact on progression rates in muscle-invasive bladder cancer was not observed [8]. Another recent meta-analysis focusing on HAL showed favorable results for HAL regarding detection rates of both papillary tumors (14.7%; $p<0.001$; odds ratio [OR] 4.898; 95% CI 1.937–12.390) and CIS (40.8%; $p<0.001$; OR 12.372; 95% CI 6.343–24.133). Nearly 25% of all patients had at least one lesion that was just detected by HAL, regardless of respective risk group and recurrence history. Recurrence rates after up to 12 months were significantly lower (45.4 vs. 34.5%; $p=0.006$) in the HAL group [7].

The current best evidence indicates slightly better results for HAL compared with 5-ALA, leading to widespread use of HAL. However, a meta-analysis demonstrated comparable results for 5-ALA and HAL with a patient-related sensitivity of 96% (5-ALA) vs. 90% (HAL) and a specificity of 56% (5-ALA) vs. 80% (HAL),and also a biopsy-related sensitivity of 95% (5-ALA) vs. 85% (HAL) and a specificity of 57% (5-ALA) vs. 80% (HAL) [26]. To date, there has been no RCT comparing HAL with 5-ALA. It is currently accepted that both drugs may be used [27]. However, side effects such as systemic photosensitivity are more common with 5-ALA and rarely seen with HAL. There is insufficient evidence for an increase in overall and cancer-specific survival after PDD.

Clinical implications

In patients with urothelial carcinoma undergoing TURBT, we suggest fluorescence imaging over white light imaging (conditional recommendation based on high-quality evidence)

Clinical question 2

In patients with bladder tumors, how does en bloc resection compare with standard loop TURBT?

Background

"En bloc" resection techniques use a "no touch" procedure instead of the conventional "incise and scatter" technique, and this has resulted in emerging interest in this approach. There are data that show that en bloc resection is a clinically safe procedure that goes along with low complication rates and that especially laser-based en bloc resection might reduce the therapeutic burden for the patient in terms of catheterization duration and hospital stay. One of the primary goals of en bloc resection is to avoid re-resections due to missing detrusor muscle in the initial specimen and therefore allowing for more correct pathological stage assignment in more cases than conventional TURBT.

Literature search

We searched for systematic reviews, meta-analyses, randomized trials, and observational studies in the Cochrane Library and MEDLINE (January 1996–June 2015) using the search terms "en bloc resection," "laser enucleation," "laser dissection," "transurethral," "bladder cancer," "urothelial carcinoma," and "water-jet." Results were limited to publication dates of January 1996 or later, studies involving humans, and reports in the English language. Each article's title and abstract were reviewed for their appropriateness. All study designs were accepted. Cited references from selected studies were also retrieved. Results are summarized in Table 29.2.

Table 29.1 Summary of trials focusing on the impact of photodynamic diagnosis (PDD) on patient outcome.

Study	No. of participants	Intravesical instillation	Purpose	Results	OR/*p*-value	Design	Level of evidence
O'Brien et al. 2013 [9]	249	HAL	Impact of HAL on NMIBC recurrence rates	3-mo RR: 20% (WLC) vs. 17% (HAL); 12-mo RR: 16% (WLC) vs. 22% (HAL)/diagnosis of concomitant CIS: 14% (WLC) vs. 26% (HAL)	$p=0.7$; $p=0.4$/$p=0.04$	Randomized, open-label, prospective, single-center	No significant difference in recurrence rates if postoperative mitomycin C instillation/HAL effective diagnostic tool to diagnose CIS; **level 1b**
Karaolides et al. 2012 [14]	102	HAL	Impact of HAL on NMIBC recurrence rates	3-mo RR: 13% (WLC) vs. 2% (HAL)/18-mo RFS: 51% (WLC) vs. 83% (HAL)/no statistical significant benefit if solitary tumors treated ($p=0.3525$)	$p<0.001$/$p<0.0006$	Open-label, randomized, prospective, single-center	HAL decreases recurrence rates for multifocal NMIBC significantly; **level 1b**
Lapini et al. 2012 [15]	96	HAL	Diagnostic accuracy of HAL	Sensitivity: 77% (WLC) vs. 99% (HAL)/specificity: 30% vs. 37%/PPV per biopsy: 51% (WLC) vs. 55% (HAL)/NPV per biopsy: 65% (WLC) vs. 97% (HAL)	$p<0.00001$	Open-label, observational, prospective, multi-center	HAL enhances diagnostic accuracy; **level 2b**
Grossmann et al. 2012 [16]	516	HAL	Impact of HAL on long-term NMIBC recurrence rates	Median follow-up: 53 mo (WLC) vs. 55 mo (HAL; n.s.)/median time to recurrence: 9 mo (WLC) vs. 16 mo (HAL)	$p<0.04$	Randomized, prospective, multi-center	HAL significantly improves time to recurrence/trend towards improved bladder preservation in HAL patients; **level 1b**
Geavlete et al. 2012 [17]	362	HAL	Impact of HAL on diagnostic accuracy, treatment changes and recurrence rates	3-mo RR: 16% (WLC) vs. 7% (HAL)/12-mo RR: 33% vs. 22%/24-mo RR: 46% vs. 31%	$p=0.003$/$p=0.005$/$p=0.001$	Randomized, prospective, single-center	Improved tumor detection rates and decreased recurrence rates for HAL, consecutive significant rate of treatment changes; **level 1b**
Hermann et al. 2011 [18]	233	HAL	Recurrence rates in stage Ta and T1 NMIBC using HAL or WLC	4-mo RR: 31% (WLC) 17% (HAL)/12-mo RR: 24% vs. 16%/false-positive rate: 16% (WLC) vs. 25% (HAL)	n.r.	Randomized, prospective, two-center	Improved detection rates after HAL resulting in reduced recurrence rates; **level 1b**
Lerner et al. 2012 [19]	551	HAL	Impact of HAL on diagnostic accuracy and CIS detection rates	CIS detection rates: 75% (WLC) vs. 87% (HAL)/rates significantly lower in patients treated with chemotherapy or BCG/rates significantly increased when urine cytology positive	$p=0.0006$/$p=0.01$, $p=0.03$/$p=0.02$	Reanalysis from 3 Phase III studies	Increased CIS detection rates with HAL/HAL particularly helpful when cytology positive; **level 1b**
Stenzl et al. 2011 [11]	370	5-ALA	Diagnostic efficacy of 5-ALA on tumor recurrence of NMIBC	PFS: 89% (placebo) vs. 89% (5-ALA)/12-mo RFS: 73% (placebo) vs. 64% (5-ALA)	$p=0.9101$/$p=0.2216$	Randomized, prospective, double-blind, placebo-controlled, multi-center	No superiority of 5-ALA vs. placebo in terms of PFS and RFS after 12 mo/higher detection rates do no not have a significant impact on long-term outcome; **level 1b**

(*continued overleaf*)

Table 29.1 (Continued)

Study	No. of participants	Intravesical instillation	Purpose	Results	OR/*p*-value	Design	Level of evidence
Blanco et al. 2010 [20]	30	HAL	Impact of HAL on detection rates of premalignant lesions in selected high-risk patients	Specificity: 88%/sensitivity: 90%/PPV: 95%/NPV: 78%		Nonrandomized, prospective, open-label, single-center	HAL reliable diagnostic tool in the detection of flat lesions; **level 2b**
Stenzl et al. 2010 [21]	814	HAL	Impact of improved detection rates with HAL on short-term recurrence-free survival	16% with lesion that was not detected during WLC/9-mo RR: 56% (WLC) vs. 47% (HAL)	$p=0.026$	Randomized, prospective, multi-center	Improved detection rates of Ta and T1 NMIBC lead to significantly improved 9-mo RR; **level 1b**
Stanislaus et al. 2010 [24]	153	5-ALA/HAL	Impact of 5-ALA/HAL on RFS of patients initially diagnosed with T1G3 NMIBC	Man follow-up: 53.9 mo/RR: 57% (WLC) vs. 40% (HAL/5-ALA)/CIS detection rate: 22% (WLC) vs. 35% (HAL/5-ALA)	$p<0.001/p=0.077$	Retrospective, single-center	Significantly reduced RR in T1G3 NMIBC; **level 3**
Schumacher et al. 2010 [12]	300	5-ALA	Impact of 5-ALA on RFS and PFS	CIS detection rate: 4% (WLC) vs. 13% (5-ALA)/more malignant and premalignant lesions detected by 5-ALA vs. WLC/no significant differences regarding PFS and RFS	$p=0.109/p=0.689$	Randomized, prospective, multi-center	No clinical advantages of fluorescence cystoscopy and TURBT with 5-ALA; **level 1b**
Draga et al. 2010 [13]	306	5-ALA	Predictors for false-positive rate using 5-ALA	Significant univariate associations: gender, previous intravesical therapy, previous BCG instillations, TURBT in the past 90 days/multivariate associations: female gender; TURBT in the past 90 days	$p=0.009$, OR=0.51; $p=0.03$, OR=1.78; $p=0.03$, OR=2.05; $p=0.01$, OR=2.37/$p=0.005$, OR=0.41; $p=0.01$, OR=2.38	Nonrandomized, open-label, prospective, single-center	Female gender and TURBT in the past 90 days as independent predictors for false-positive 5-ALA results; **level 2b**
Geavlete et al. 2009 [22]	64	HAL	Diagnostic accuracy of HAL in patients with NMIBC	Correct diagnosis: 66% (WLC) vs. 96% (HAL)/false positive: 10% (WLC) vs. 14% (HAL)/18-weeks RR: 23% (WLC) vs. 5% (HAL)	n.a.	Nonrandomized, open-label, prospective, single-center	HAL reliable diagnostic tool in the detection of NMIBC; **level 2b**
Ray et al. 2009 [23]	18	HAL	Impact of HAL on improved multifocal recurrent NMIBC therapy	Sensitivity: 70% (WLC) vs. 98% (HAL)/false-positive rate: 29% (HAL)	n.a.	Nonrandomized, open-label, prospective, single-center	Improved management of multifocal NMIBC recurrence when using HAL; **level 2b**

5-ALA, 5-aminolevulinate acid; BCG, bacillus Calmette–Guérin; CIS, carcinoma *in situ*; HAL, hexyl 5-aminolevulinate; mo, month; NMIBC, non-muscle-invasive bladder cancer; NPV, negative predictive value; n.r., not reported; n.s., not significant; OS, overall survival; PFS, progression-free survival; PPV, positive predictive value; RFS, recurrence-free survival; RR, recurrence rate; TURBT, transurethral resection of bladder tumor; WLC, white light cystoscopy.

Table 29.2 Summary of trials focusing on the impact of en bloc resection techniques on patient outcome.

Study	No. of participants/lesions	Technique	Purpose	Results	Design	Level of evidence
Ukai et al. 2000 [29]	88/108	Monopolar current	Clinical usefulness of en bloc resection using the monopolar J-loop	Sample size up to 20 mm, center of the tumor determined correctly the depth of cancer invasion (pTa or pT1) in all cases, no complications	Prospective, single-center, case reports	Monopolar J-loop feasible, safe and accurate; **level 3**
Ukai et al. 2010 [28]	97/132	Monopolar current	Comparative analysis of en bloc resection or divisional resection using the monopolar J-loop	Sample size up to 55 mm/median follow-up 27 mo (3–84)/*n*=36 pTa, *n*=58 pT1, *n*=7>pT1/27-mo RR: 37%/correct pathological stage assignment possible in 93%, 2 cases without muscularis propria	Prospective, single-center, case reports	En bloc resection with muscle layer in 93% of specimen; **level 3**
Lodde et al. 2003 [30]	37/62	Monopolar current	Feasibility and safety of transurethral en bloc resection using a monopolar flat loop	Sample size up to 25 mm/mean follow-up 14 mo (10–24)/*n*=51 pTa, *n*=11 pT1/RR: 42%/complications: 1× extraperitoneal perforation/correct pathological stage assignment in all cases	Prospective, single-center, case reports	En bloc resection with monopolar current safe and feasible; offers good quality of histopathological specimen; **level 3**
Saito 2001 [31]	35/50	Ho:YAG laser	Technical feasibility of Ho:YAG laser en bloc resection	Sample size up to 30 mm/44% pTa, 52% pT1, 4% pT2/no intraoperative complications	Retrospective, single-center, case reports	Ho:YAG laser safe and feasible; **level 3**
Song et al. 2010 [32]	64/n.r.	Ho:YAG laser vs. TURBT	Efficacy and safety of Ho:YAG laser en bloc resection compared with standard TURBT	Sample size up to 36 mm/mean follow-up 24 mo/*n*=36 pTa, *n*=23 pT1, *n*=5 pTis/24-mo RR 32%/complications: 1× urethral stricture	Prospective, single-center, case reports	Ho:YAG laser safe and feasible; **level 3**
Zhu et al. 2008 [33]	101/152	Ho:YAG laser vs. TURBT	Efficacy and safety of Ho:YAG laser en bloc resection compared with standard TURBT	Sample size >30 mm/mean follow-up 34 mo (18–43)/*n*=67 pTa, *n*=34 pT1/significantly lower catheterization time and longer operation time for Ho:YAG laser/no significant difference in the overall RFS between Ho:YAG laser and standard TURBT	Retrospective, single-center	Ho:YAG safe and feasible, no significant differences in RFS after 24 mo; **level 3**
He et al. 2014 [34]	45/n.r.	Green light KTP laser	En bloc resection using the green light KTP laser	Sample size up to 30 mm/mean follow-up 6 mo/*n*=27 pTa, *n*=15 pT1, *n*=3 pT2a/no intraoperative complications/6-mo RR: 0%	Prospective, single-center, case reports	KTP laser en bloc resection safe and efficient in the short-term follow-up; **level 3**
Muto et al. 2014 [35]	55/61	Tm:YAG laser vs. TURBT	Potential advantages of Tm:YAG laser en bloc resection compared with standard TURBT	Sample size up to 30 mm/mean follow-up 16 mo (8–25)/*n*=31 pTa, *n*=18 pT1, *n*=6 pT2/16-mo RR: 14.5%/no intraoperative complications/correct pathological stage assignment possible in all cases	Prospective, single-center, case reports	Tm:YAG laser en bloc resection safe and efficient in the short-term follow-up; **level 3**
Wolters et al. 2011 [36]	6/6	Tm:YAG laser	Initial experience with Tm:YAG en bloc resection focusing on safety and accurate pathological staging	Sample size up to >30 mm/*n*=3 pTa, *n*=3 pT1/mean follow-up 6 weeks/6-weeks recurrence rate: 0%/no intraoperative complications/correct pathological stage assignment possible in all cases	Prospective, single-center, case reports	Tm:YAG laser en bloc resection safe and efficient in the ultra-short-term follow-up; **level 3**
Gao et al. 2008 [37]	32/39	Tm:YAG laser	Initial experience with Tm:YAG en bloc resection focusing on RR	Sample size up to 30 mm/mean follow-up 12 mo/12-mo RR: 28%	Prospective, single-center, case reports	Tm:YAG laser en bloc resection clinically feasible with acceptable RR in the short-term follow-up; **level 3**

(*continued overleaf*)

Table 29.2 (Continued)

Study	No. of participants/lesions	Technique	Purpose	Results	Design	Level of evidence
Yang et al. 2009 [38]	9/11	Tm:YAG laser	Initial experience with Tm:YAG laser en bloc resection	Sample size up to 30 mm/mean follow-up 8 mo (6–9)/*n*=6 pT1, *n*=3 pT2a/complications: 1× bladder perforation/8-mo RR: 0%	Prospective, single-center, case reports	Tm:YAG laser en bloc resection clinically feasible and efficient in the short-term follow-up; **level 3**
Liu et al. 2013 [39]	64/n.r.	Tm:YAG laser vs. TURBT	Safety and efficacy of Tm:YAG laser en bloc resection compared with standard TURBT	Sample size up to 31 mm/*n*=37 pTa, *n*=27 pT1/follow-up: 36 mo/36-mo RR: 31%/significantly shorter catheterization time and hospital stay for Tm:YAG/complications: 2× urethral stricture/no significant difference regarding RR (p=0.892)	Prospective, single-center, randomized	Tm:YAG decreases the clinical burden for the patient without significant impact on RR; **level 1b**
Zhong et al. 2010 [42]	30 (Tm:YAG); 25 (Ho:YAG)/n.r.	Tm:YAG laser vs. Ho:YAG laser vs. TURBT	Safety and efficacy of Tm:VAG laser en bloc resection compared with Ho:YAG laser en bloc resection and standard TURBT	Sample size up to 30 mm (Tm:YAG), 20 mm (Ho:YAG)/follow-up 24 mo/24-mo RR: 27% (Tm:YAG), 24% (Ho:YAG)/no intraoperative complications	Retrospective, single-center	Tm:YAG and Ho:YAG lasers safe and equally efficient in the 2-year follow-up; **level 3**
Nagele et al. 2011 [40]	5/5	Water-jet	Initial experience using water-jet hydrodissection of the bladder wall	Sample size up to 20 mm/*n*=1 papilloma, *n*=4 pTa/no intraoperative complications/correct pathological stage assignment possible in all cases	Prospective, single-center, case reports	Water-jet hydrodissection clinically feasible and safe; **level 3**
Fritsche et al. 2011 [41]	17/30	Water-jet	Prospective clinical trial to analyze safety and feasibility of water-jet hydrodissection	Sample size up to 75 mm/*n*=7 pTa, *n*=5 pT1, *n*=1 pT2/follow-up 4–14 mo/no intraoperative complications/RR: 24%/correct pathological stage assignment possible in all cases	Prospective, multi-center	Water-jet hydrodissection clinically feasible and safe; **level 2b**

CIS, carcinoma *in situ*; HAL, hexyl 5-aminolevulinate; mo, month; NMIBC, non-muscle-invasive bladder cancer; NPV, negative predictive value; n.r., not reported; RFS, recurrence-free survival; RR, recurrence rate; TURBT, transurethral resection of bladder tumor.

The evidence

Table 29.2 summarizes data from 15 clinical trials and case series that were published between 2000 and 2014. Three studies investigated monopolar current [28–30], three studies investigated the Ho:YAG laser [31–33], one study investigated the potassium titanyl phosphate (KTP) green light laser [34], five studies focused on the Tm:YAG laser [35–39], and two studies analyzed water-jet hydrodissection [40, 41]. In addition, one study included patients treated with both Ho:YAG and Tm:YAG lasers [42]. Overall, these studies provide data on 710 patients and at least 884 lesions. In a recently published review, Kramer et al. analyzed 10 studies focusing on laser en bloc resection of bladder tumors, of which four studies compared laser en bloc resection with conventional TURBT [43]. The authors described shorter hospitalization times in favor of the en bloc resection by about 1 day and shorter operation duration, but reaching statistical significance in only one study [33, 43].

Regarding the correct staging of bladder tumors, Ukai et al. reported detrusor muscle presence in 93% of specimens using the monopolar loop [28]. Lodde et al. reported that correct pathological stage assignment was possible in 100% of specimens [30]. Saito stated that tissue slides crossing the center of the tumor correctly determined its invasion depth [31] and Zhu et al. stated that there was sufficient material for the pathological evaluation [33]. Neither study stated the percentage of specimens actually showing detrusor muscle [31, 33]. Liu et al. reported 100% of specimens being suitable for correct pathological staging without stating whether they included detrusor muscle in all cases [39]. Muto et al. reported detrusor muscle in 100% of the analyzed specimens [35]. The remaining authors did not make any statements about the histopathological quality of the resected specimen. Regarding peri- and postoperative complications, bladder perforation was observed in two cases [30, 38] and urethral stricture occurred in three cases [32, 39]. Referring to recurrence rates, none of the comparative studies that provided recurrence rates could demonstrate any statistically significant differences in terms of recurrence-free survival.

Surprisingly, only a minority of the analyzed studies presented data addressing the histopathological quality of the retrieved tumor specimen. When detrusor muscle presence rates were given, they seemed to be comparatively high and reached 100% in the majority of patients. Regarding recurrence rates, it has to be stated that only limited data are currently available. The reported studies differ considerably in terms of quality and length of follow-up analyses and most of the data are based on small prospective case series. A definitive statement about a potential impact of en bloc resection on recurrence-free survival is therefore not possible. There are indications that en bloc resection might improve diagnostic accuracy but prospective randomized trials (e.g. using the IDEAL framework) are urgently needed to provide further evidence. Moreover, feasibility and learning curve issues have to be considered when applying a novel technique in routine clinical practice.

Clinical implications

In patients undergoing a bladder tumor resection, we suggest against the of use of en bloc resection (conditional recommendation against based on low-quality evidence).

This recommendation is based on the fact that despite improved diagnostic accuracy, there are no documented benefits with regard to patient-important outcomes such as rate of disease recurrence. Meanwhile, TURBT is the standard approach in which all urologists are trained and skilled, whereas en bloc resection poses potential learning curve and feasibility challenges.

Clinical question 3

In patients with pathological T1 urothelial carcinoma, does a second resection improve outcomes compared with no second resection?

Background

There is ongoing discussion about how a second transurethral resection improves outcome for patients with pT1 NMIBC. It is generally accepted that a second resection provides certain benefits, including restaging (diagnostic benefit) and removal of potential residual malignant lesions (potential therapeutic benefit) [44]. In a review, Kulkarni et al. also highlighted the potential prognostic effect of a second resection [44]. Regarding prognosis, Herr et al. found that evidence of residual pT1 NMIBC can predict future muscle invasion [45] and Dalbagni et al. showed that pT stage during second resection can predict disease-specific mortality [46].

Literature search

We searched for systematic reviews, meta-analyses, randomized trials, and observational studies in the Cochrane Library and MEDLINE (January 1996–June 2015) using the search terms "pT1," "second resection," "bladder cancer," and "urothelial carcinoma." Results were limited to publication dates of January 1996 or later, studies involving humans, and reports in the English language. Each article's title and abstract were reviewed for their appropriateness. All study designs were accepted. Cited references from selected studies were also retrieved. Results are summarized in Table 29.3.

The evidence

Table 29.3 summarizes data from 13 trials published between 1999 and 2013 and includes data from 2422 patients with T1 NMIBC. The time interval between first and second

Table 29.3 Summary of trials focusing on the impact of a second resection on outcome for pT1 carcinoma patients.

Study	No. of participants with pT1	Interval to second resection (weeks)	Adjuvant therapy	Results	Design	Level of evidence
Herr 1999 [49]	58	2–6	n.r.	$n=23$ no detrusor muscle in primary specimen/second resection: 22% pT0, 26% pTa/pTis, 24% pT1, 28% pT2; change in treatment: 36%	Retrospective, single-center	Second resection with significant upstaging and change in treatment strategy; **level 3**
Schwaibold et al. 2006 [54]	136	4–6	n.r.	Second resection: 48% pT0, 8% pTa, 11% pTis, 24% pT1, 10% pT2; worsened prognosis in 21%/86% residual malignant tissue in the area of the primary lesion/radical cystectomy: 21%	Retrospective, single-center	Significant rate of residual malignant tissue after first resection; **level 3**
Brauers et al. 2001 [51]	42	2–6	n.r.	Mean follow-up: 60 mo/second resection: 36% pT0, 17% pTa, 24% pT1, 24% pT2/pTis/radical cystectomy: 24%/60-mo RR: 55%	Retrospective, single-center	Significant rate of upstaging after second resection/RR of 55% in the long-term follow-up; **level 3**
Divrik et al. 2006 [55]	80	2–6	n.r.	Second resection: 66% pT0, 9% pTa, 18% pT1, 4% pT1 + pTis, 4% pT2/60% residual malignant tissue in the area of the primary lesion	Prospective, single-center	High rate of residual malignant tissue after first resection; **level 2b**
Divrik et al. 2006 [47]	142 (74 second resection/68 no second resection)	2–6	Mitomycin C within 24 h	Mean follow-up: 32 mo (6–48)/overall RFS: 74% (second resection) vs. 36% (no second resection; $p<0.0001$)/OS: 92 vs. 90%, $p=0.732$)	Prospective, randomized, single-center	Significantly increased RFS if second resection performed, no impact on OS; **level 1b**
Herr et al. 2007 [45]	352	2–4	6 weeks of BCG after second TURBT	Median follow-up: 8 years/8-years RR: 66%/median time to recurrence for pT1G3 NMIBC: 16 mo (95% CI 12–20)/risk factors associated with tumor progression: number of tumors, grading, complete first cystoscopy, restaging after second TURBT	Retrospective, single-center	Restaging after second TURBT as prognostic factor for RFS; **level 3**
Takaoka et al. 2013 [52]	73	1.6–11	n.r.	Median follow-up 49 mo/second resection: 49% pT0, 29% pTa/pTis, 18% pT1, 4% pT2/risk factor for tumor presence at second resection: concomitant Cis ($p<0.01$)/3-years RFS (if pTa, pTis, pT0 in second resection): 81%/3-years PFS (if pTa, pTis, pT0 in second resection): 96%	Retrospective, single-center	Good RFS and excellent PFS if no > pT1 in second resection; **level 3**
Divrik et al. 2010 [48]	210 (105 second resection/105 no second resection)	2–6	Mitomycin C within 24 h	Mean follow-up 66 mo/second resection: 67% pT0, 13% pTa, 4% pTis, 9% pT1, 8% pT2/overall RFS: 52% vs. 21% ($p=0.0001$); median time-to-recurrence: 47 mo vs. 12 mo/overall PFS: 93% vs. 76% ($p=0.0001$)/cystectomy rate: 13% vs. 24% ($p=0.031$)/OS: 68% vs. 64% ($p=0.363$)	Prospective, randomized, single-center	PFS and RFS significantly improved if second resection is performed; cystectomy rate significantly decreased; no significant impact on OS; **level 1b**

Zurkirchen et al. 2004 [56]	115	4–6	n.r.	Second resection: 63% pT0/no significant influence if urologist is in training or not ($p=0.08$)	Retrospective, single-center	High rate of residual tumor after first resection independent of whether urologist is well experienced or not; **level 3**
Schips et al. 2002 [50]	76	4–6	n.r.	Second resection: 67% pT0, 11% pTa, 14% pT1, 8% pT2	Retrospective, single-center	High rate of residual tumor after first resection; **level 3**
Jahnson et al. 2005 [57]	129	4–8	n.r.	Second resection: 40% pT0/multiple tumors at primary resection risk factor for residual tumor at second resection	Retrospective, single-center	High rate of residual tumor after first resection, especially if multiple tumors at first resection; **level 3**
Vasdev et al. 2012 [53]	486 (172 second resection/314 no second resection)	6	Mitomycin C in 88%	Median follow-up: 50 mo/second resection: 2% pTx, 43% pT0, 12% pTa, 12% pTis, 24% pT1, 7% pT2/ RR: 35% vs. 42% ($p=0.1562$)	Retrospective, single-center	No significant difference in RR after a median follow-up of 50 mo; **level 3**
Dalbagni et al. 2009 [46]	523	12	n.r.	Second resection: 50% < pT1, 30% pT1, 20% pT2/ disease-specific mortality (5 years): <pT1: 8% (95% CI: 5–13), pT1: 10% (5–17), pT2: 44 (35–56)/ overall mortality (5 years): <pT1: 15% (95% CI: 5–13), pT1: 22 (16–32), pT2: 57% (47–68)	Retrospective, single-center	T stage at second resection predicts disease-specific mortality; **level 3**

BCG, bacillus Calmette–Guérin; CI, confidence interval; CIS, carcinoma *in situ*; mo, months; NMIBC, non-muscle-invasive bladder cancer; NPV, negative predictive value; n.r., not reported; n.s., not significant; OS, overall survival; PFS, progression-free survival; PPV, positive predictive value; RFS, recurrence-free survival; RR, recurrence rate; TURBT, transurethral resection of bladder tumor; WLC, white light cystoscopy.

resections varied and was up to 12 weeks [46]. Most of the cited studies are retrospective and from a single center, but there are also data from prospective randomized trials [47, 48]. The rate of residual malignant tissue was consistently high and the pT0 rate during the second resection varied between 22 and 67% [48–50]. Muscle-invasive disease was found in 4–24% [47, 51] and cystectomy rates, if reported, varied between 13 and 24% [48, 51].

Three studies investigated recurrence rates of pT1 NMIBC after a second resection without a control group and found recurrence rates between 55% (after a mean follow-up of 60 months) and 66% (after a median follow-up of 8 years) and a 3-year recurrence-free survival of 81% (if pTa, pTis, or pT0 in second resection) [45, 51, 52]. Divrik et al. compared patients who received a second resection and patients without second resection in two prospective randomized trials and found a significantly increased recurrence-free survival for the former group after a mean follow-up of 32 months (74 vs. 36%, $p<0.001$) and 66 months (51 vs. 21%, $p<0.001$) without significant differences in overall survival [47, 48]. In contrast, Vasdev et al. did not detect a significant difference in recurrence rates after a mean follow-up of 50 months (35 vs. 42%, $p=0.156$) [53].

In summary, it has been shown that a second resection can increase the recurrence-free survival for patients with T1 urothelial carcinoma of the bladder [47, 48]. However, a significant impact on overall survival of patients with stage T1 disease still remains to be proven. According to the recent literature, a second resection should be considered in patients with pT1 and high-grade tumors except those with primary CIS.

Clinical implications

In patients with high-grade pathological T1 urothelial carcinoma of the bladder, we suggest re-resection of the tumor (conditional recommendation based on low-quality evidence).

Clinical question 4

In patients with pT1 bladder cancer, does immediate radical cystectomy improve outcomes compared with intravesical therapy?

Background

As indicated in clinical question 3, there is strong evidence that stage T1 NMIBC during TURBT is associated with a significant risk of stage misclassification and also cancer-related death. However, to date, no randomized studies have evaluated survival of patients treated with immediate cystectomy compared with intravesical therapy. The alternative approach, early cystectomy following a single induction course of intravesical therapy, has also not been evaluated in a randomized fashion so far.

Literature search

We searched for systematic reviews, meta-analyses, randomized trials, and observational studies in the Cochrane Library and MEDLINE (January 1996–June 2015) using the search terms "pT1," "immediate cystectomy," "early cystectomy," "bladder cancer," and "urothelial carcinoma." Results were limited to publication dates of January 1996 or later, studies involving humans, and reports in the English language. Each article's title and abstract were reviewed for their appropriateness. All study designs were accepted. Cited references from selected studies were also retrieved. Results are summarized in Table 29.4. According to the convention put forward by Babjuk et al., cystectomy after initial TURBT or second resection was termed "immediate cystectomy" and cystectomy after BCG failure was termed "early cystectomy" [5].

The evidence

Table 29.4 summarizes data from 14 case series published between 2001 and 2013 and includes data from 11 743 patients with T1 NMIBC, of whom 2667 underwent immediate or early radical cystectomy. Three studies reported the outcome after immediate radical cystectomy without comparison with a control group [58–60]. Upstaging occurred in 27–50% [59, 60]. Fritsche et al. found non-organ-confined disease in 33% and lymph node involvement in 17% [60]. Bianco et al. found a 10-year cancer-specific survival of 92% for true pT1 [59], whereas Fritsche et al. reported an 8-year cancer-specific survival of 65% for all T1 patients who underwent immediate radical cystectomy [60]. Overall survival varied between 47% (after 8 years) and 60% (after 10 years) [58, 60]. On comparing immediate radical cystectomy for stage T1 urothelial carcinoma with bladder-preserving therapies (e.g. BCG immunotherapy) with or without delayed cystectomy, the results are conflicting. Most studies do not show significant differences between effects of immediate cystectomy and bladder-preserving strategies on cancer-specific survival and/or overall survival [46, 61–64]. Moreover, two studies observed more favorable results after immediate cystectomy [65, 66], and one study showed improved outcome after BCG treatment [67].

In summary, to date the data are too limited to allow definite statements in favor of immediate cystectomy in patients without prior intravesical therapy. Clinicians may consider risk groups that might benefit the most from an immediate/early definitive treatment. For instance, Kulkarni et al. concluded that young patients with T1G3 NMIBC might benefit the most from immediate cystectomy in terms of quality of life-adjusted life expectancy [68]. Moreover, de

Table 29.4 Summary of trials focusing on the impact of radical cystectomy (RC) on T1G3 NMIBC patient outcome.

Study	No. of participants	Interval to RC	Purpose	Results	Design	Level of evidence
Sternberg et al. 2013 [61]	150 ($n=57$ immediate RC vs. $n=93$ delayed or no RC)	Within 3 mo	OS and CSS for immediate RC vs. bladder-preserving strategies	Median follow-up: 4 years/muscle-invasive TCC: 25% (immediate RC; 5% lymph node metastases) vs. 19% (delayed RC)/no significant association between immediate RC and CSS (HR 1.15, 95% CI 0.43–3.09, $p=0.8$) and OS (HR 0.79, 95% CI 0.4–1.53, $p=0.5$)	Retrospective, single-center	Immediate RC with no significant impact on OS and CSS vs. bladder-preserving strategies; **level 3**
Canter et al. 2013 [62]	8467 ($n=397$ immediate RC vs. $n=8070$ no RC)	Within 12 mo	RC as initial treatment strategy for T1G3 NMIBC using the SEER database	Mean follow-up <3 years/no significant differences in CSS and OS between the two groups ($p=0.70$, $p=0.91$)	Retrospective, multi-institutional database	Immediate RC with no significant impact on OS and CSS vs. no immediate RC; **level 2b**
de Berardinis et al. 2011 [63]	152 ($n=72$ second TURBT, immediate RC vs. $n=80$ second TURBT, BCG maintenance)	Within 60 days	Immediate RC as treatment strategy for T1G3 NMIBC compared with BCG maintenance	Median follow-up 8 years/progression rates: 25% (median time 26 mo; RC) vs. 31% (median time 25 mo; BCG)/10-years OS: 58% (RC) vs. 42% (BCG; $p=0.0487$)/CSS: 78% (median 46 mo; RC) vs. 78% (median 48 mo; BCG; $p=0.9762$)	Retrospective, single-center	No statistical significant effect of immediate RC on CSS and OS; multifocal tumors and CIS with higher progression rates; **level 3**
Dalbagni et al. 2009 [46]	523 ($n=84$ second resection, immediate RC vs. $n=439$ second resection, surveillance)	Within 3 mo	Indications for immediate RC and outcome of immediate RC compared with surveillance	Median follow-up 4 years/restaging at second resection: <pT1 50%, pT1 30%, pT2 20%/immediate RC more likely if pT1 at restaging (37% vs. 10%, $p=0.001$)/$n=138$ treated with BCG/no significant difference in CSS ($p=0.7$)/5-years OS: 79% immediate RC; (95% CI 66–88%) vs. 84% (no immediate RC; 95% CI 78–88%)	Retrospective, single-center	Improved staging accuracy when restaging performed, no significant differences in CSS; **level 3**
Hautmann et al. 2009 [65]	274 ($n=175$ immediate RC/$n=99$ delayed RC)	Within 3 mo	Survival of patients with T1G3 NMIBC treated with immediate vs. delayed RC	Mean follow-up 58 mo/understaging rate: 20%/10-years CSS: 79% (early RC) vs. 65% (delayed RC)	Retrospective, single-center	Improved CSS if immediate RC; **level 3**
Kulkarni et al. 2007 [68]	1 artificial case: 60 years old, no comorbidities, potent, newly diagnosed pT1G3 TCC	n.r.	LE and QALE for immediate cystectomy vs. conservative management using a decision-making Markov model	Mean LE for 60-year-old male: 14 years (immediate RC) vs. 14 years (conservative management)/mean QALE 12 years (immediate RC) vs. 12 years (conservative management)/LE for immediate RC decreases with higher comorbidities/switch in LE for patients >70 years old (conservative > RC)	Literature review, estimation model generation	Higher LE and QALE for younger patients with pT1G3 for immediate RC; **level 2b**
Ali-El-Dein et al. 2011 [64]	204 ($n=134$ immediate RC/$n=70$ delayed RC)	n.r.	CSS in immediate vs. delayed RC	Mean follow-up 79 mo vs. 66 mo/5-years CSS: 78% (immediate RC) vs. 71% (delayed RC); 10-years CSS: 69% vs. 64%/CSS in the delayed RC group significantly lower if RC after >2 years and if >3 TURBTs	Retrospective, single-center	CSS increased for immediate RC, but not reaching significance; **level 3**

(*continued overleaf*)

Table 29.4 (Continued)

Study	No. of participants	Interval to RC	Purpose	Results	Design	Level of evidence
Thalmann et al. 2004 [67]	121 (n=29 immediate RC/n=92 BCG)	Within 3 mo	Long-term outcome of T1G3 NMIBC treated with immediate RC vs. BCG	Median follow-up: 7 years/progression rate: 21% (immediate RC, median time to progression 13 mo) vs. 33% (BCG; 11 mo; p=0.09)/5-years OS: 54% vs. 69% (p=0.1243)/5-years CC: 69% vs. 80% (p=0.33)	Retrospective, single-center	CSS and OS decreased for immediate RC compared with BCG treatment with/without delayed RC without reaching statistical significance; **level 3**
Chalasani et al. 2011 [58]	306	n.r.	Outcome of patients undergoing RC for T1 NMIBC	Mean follow-up 35 mo/upstaging in 48%/5-years OS: 71% (95% CI 64–77%), 10-years OS: 60% (50–69%)/positive margin status and lymph node invasion as independent predictors for decreased OS	Retrospective, multi-center	High rate of upstaging after RC, poor OS after immediate RC for pT1 NMIBC; **level 3**
Denzinger et al. 2008 [66]	105	Within 4 weeks	Outcome of patients with recurrent high-risk T1G3 NMIBC treated with early or delayed RC	Upstaging in 30%/10-years CSS 78% (early RC) vs. 51% (delayed RC; p<0.01)/concomitant CIS related to decreased survival rate in delayed RC subgroup (p<0.001)	Retrospective, single-center	Early RC increases CSS in patients with recurrent high-risk T1G3; **level 3**
Bianco et al. 2004 [59]	66	n.r.	Disease-free survival and CSS after RC for T1G3 NMIBC	Median follow-up 4 years/upstaging in 27%, nodal disease in 12%/4-years CSS 78%, 10-years CSS 92% for pT1	Retrospective, single-center	Good CSS for early RC if no upstaging in RC specimen; **level 3**
Fritsche et al. 2010 [60]	1136	n.r.	Characteristics and long-term outcome of patients with T1G3 NMIBC treated with RC	Median follow-up 4 years/upstaging in 50%, non-organ-confined disease in 33%, lymph node involvement in 17%, downstaging in 21%/2-years CSS: 93%, 5-years CSS: 70%, 8-years CSS: 65%/2-years OS: 92%, 5-years OS: 56%, 8-years OS: 47%	Retrospective, multi-center	High upstaging rates, identification of high-risk patients crucial; **level 3**

BCG, bacillus Calmette–Guérin; CI, confidence interval; CIS, carcinoma *in situ*; CSS, cancer-specific survival; HR, hazard ratio; LE, estimation of life expectancy; mo, month; NMIBC, non-muscle-invasive bladder cancer; n.r., not reported; OS, overall survival; PFS, progression-free survival; QALE, quality-adjusted life expectancy; RC, radical cystectomy; RFS, recurrence-free survival; RR, recurrence rate; TURBT, transurethral resection of bladder tumor.

Berardinis et al. found that patients with multifocal NMIBC and concomitant CIS benefited the most from immediate cystectomy [63]. In addition to the potentially beneficial effect of early cystectomy for these high-risk patients, perioperative mortality, morbidity, and future quality of life issues regarding incontinence, erectile dysfunction, and body image have to be considered [69]. Hence the decision whether to perform a cystectomy for BCG-naive stage T1 urothelial cystectomy should be discussed individually and individual risk factors should be considered.

Clinical implications

In patients with high-risk pT1 urothelial carcinoma of the bladder, we suggest early cystectomy after a single course of intravesical therapy (conditional recommendation based on very low-quality evidence).

Clinical question 5

In patients not responsive to BCG therapy, do innovative intravesical therapies such as gemcitabine instillation result in improved outcomes?

Background

Despite data from various well-designed studies, there is still conflicting evidence regarding the efficacy of intravesical gemcitabine instillations. In a systematic review, Shelley et al. summarized evidence regarding intravesical gemcitabine instillations and concluded that it might have its role in intermediate-risk patients and also BCG refractory patients not undergoing cystectomy – a patient collective that still represents a certain therapeutic dilemma [70].

Literature search

We searched for systematic reviews, meta-analyses, randomized trials, and observational studies in the Cochrane Library and MEDLINE (January 1996–June 2015) using the search terms "intravesical," "gemcitabine," "bladder cancer," and "urothelial carcinoma." Results were limited to publication dates of January 1996 or later, studies involving humans, and reports in the English language. Each article's title and abstract were reviewed for their appropriateness. All study designs were accepted. Cited references from selected studies were also retrieved. Results are summarized in Table 29.5.

The evidence

Table 29.5 summarizes data from 10 trials published between 2005 and 2014 and includes data from 826 patients who underwent treatment with intravesical gemcitabine [71–80].

Addressing intravesical gemcitabine instillation therapy, there are data from six randomized controlled multi-center studies. Gardmark et al. included 32 patients with recurrent NMIBC TaG1 or TaG2 and found a single-dose treatment to be inferior to sequential instillations [75]. Porena et al. compared adjuvant gemcitabine and BCG instillations in 64 patients with high-risk NMIBC and found gemcitabine to be inferior in terms of recurrence-free survival [76]. Di Lorenzo et al. included 80 patients with recurrent high-risk NMIBC after BCG instillation therapy and found a significant increase in recurrence-free survival in the intravesical gemcitabine subgroup compared with BCG maintenance therapy [77]. In the only existing placebo-controlled, double-blind study, Bohle et al. analyzed the impact of single-dose gemcitabine versus saline instillation in 248 patients with primary or recurrent NMIBC. The study was terminated after an interim analysis owing to the low number of events, showing no benefit of an adjuvant single-dose treatment with intravesical gemcitabine [78]. Addeo et al. focused on the impact of intravesical gemcitabine instillations compared with mitomycin C instillations in patients after BCG failure and found a significantly increased disease-free survival in the gemcitabine subgroup [79]. Although gemcitabine instillations seem to be superior to mitomycin C alone [79], a combination of the two agents may also be considered and has been shown to be effective in patients after BCG failure [74, 80]. All studies analyzed indicate that intravesical gemcitabine instillations are well tolerated.

In summary, intravesical gemcitabine instillations appear to be effective if administered to intermediate-risk patients and might reach similar efficacy to standard BCG treatment in this particular subgroup [75]. However, it appears to be inferior to standard BCG treatment in BCG-naive high-risk NMIBC patients [76]. Single-dose regimens seem to be ineffective and are therefore not a preferable alternative [75]. In addition, comparability between the studies is generally limited owing to differences in patient cohorts and therapy regimens.

Clinical implications

In patients with urothelial carcinoma receiving TURBT, we suggest against intravesical gemcitabine (conditional recommendation against based on low-quality evidence). Intravesical gemcitabine might be a useful alternative in selected patients after BCG failure or not tolerating BCG treatment and also in those unable or unwilling to undergo cystectomy.

Table 29.5 Summary of trials focusing on the impact of innovative secondary therapies on patient outcome.

Study	No. of participants	Agent	Treatment course of study drug	Study population	Results	Design	Level of evidence
Sternberg et al. 2013 [71]	69	Intraves. GEM	GEM (2000 mg/50 mL; 1 h) twice weekly for 6 weeks	High-risk NMIBC after BCG treatment failure	$n=37$ BCG refractory/median follow-up 3years in progression-free patients/5-years OS: 58% (BCG refractory) vs. 71% (other type of BCG failure; $p=0.096$)/no significant differences in PFS, CSS, and RFS ($p=0.9$, $p=0.7$, $p=0.2$)/RC rate: 29%/no severe AE	Retrospective, single-center	GEM instillations useful in patients with high-risk NMIBC and BCG failure who are not suitable for RC; **level 3**
Skinner et al. 2013 [72]	47	Intraves. GEM	GEM (2000 mg/100 mL) once weekly for 6 weeks, then monthly for 12 mo	Recurrent NMIBC after at least 2× BCG instillation	3-mo RR: 53%, 1-year RR: 72%, 2-years RR: 78%	Prospective, observational, multi-center	GEM instillations with low RFS after 12 mo after BCG failure; **level 2b**
Gontero et al. 2013 [73]	120	Intraves. GEM vs. 1/3 BCG	GEM (2000 mg/50 mL) once weekly for 6 weeks, then monthly for 12 mo vs. 1/3 dose BCG weekly for 6 weeks and maintenance	Intermediate-risk NMIBC	No significant differences in QOL (QLQ-C30) in multivariate analysis/higher rate of side effects in BCG (40% vs. 34%, $p=0.6$)	Randomized, open-label, multi-center	Despite higher rate of side effects, no significant differences in QOL between GEM and 1/3 dose BCG; **level 1b**
Lightfoot et al. 2014 [74]	47	Intraves. GEM and MMC sequence	GEM (1000 mg/50 mL, 90 min) followed by MMC 40 mg/20 mL once weekly for 6 weeks, then monthly for 12 mo	Recurrent NMIBC after at least 6 weeks intraves. treatment	Median follow-up 26 mo/complete response: 68%/1-year RFS: 48%, 2-years-RFS: 38%, 30% without recurrence during median follow-up/median time to recurrence: 4 mo (1–33)/no significant difference in RFS between high- and low-risk NMIBC ($p=0.39$)/no significant difference in RFS between BCG-naive and BCG failure group ($p=0.69$)	Retrospective, multi-center	GEM/MMC sequence instillations potentially useful treatment option in high-risk NMIBC; **level 3**
Gardmark et al. 2005 [75]	32	Intraves. GEM	GEM (2000 mg/100 mL; 1 h) as a single dose, twice weekly for 3 weeks or once weekly for 6 weeks	Recurrent NMIBC TaG1, TaG2	Overall complete remission rate: 31%/response rate: 10% (single dose), 44% (once weekly), 40% (twice weekly)/most common side effect: nausea; 6% reversible hematological toxicity (mild anemia, mild thrombocytopenia)	Randomized, open-label, multi-center	Single dose inferior to multi-dose treatment strategies in Ta NMIBC/GEM instillation well tolerated; **level 1b**
Porena et al. 2010 [76]	64	Intraves. GEM vs. BCG	GEM (2000 mg/50 mL) once weekly for 6 weeks vs. BCG once weekly for 6 weeks	High-risk NMIBC	Mean follow-up 44 mo/RR: 53% (GEM) vs. 28% (BCG; $p=0.037$)/time to recurrence: 39 mo (GEM) vs. 26 mo; $p=0.042$)/progression rate: 0%/GEM better tolerated than BCG	Prospective, randomized, open-label, multi-center	Adjuvant intraves. GEM inferior to BCG treatment in terms of RFS in high-risk NMIBC; **level 1b**

Di Lorenzo et al. 2010 [77]	80	Intraves. GEM vs. BCG	GEM (2000 mg/50 mL) twice weekly for 6 weeks, weekly for 3 weeks after 3 mo, 6 mo, 12 mo vs. BCG (6 weeks induction, then maintenance)	Recurrent high-risk NMIBC after BCG instillation	Median follow-up 15 mo/RR: 53% (GEM) vs. 88% (BCG; $p=0.002$)/time to first recurrence: 4 mo (GEM) vs. 3 mo (BCG; $p=0.09$)/ estimated 2-years RFS: 19% (GEM) vs. 3% (BCG; $p<0.002$)/progression/RC rate: 33% (GEM) vs. 38% (BCG; $p=0.12$)	Randomized, open-label, multi-center	GEM instillation as possible second-line therapy after BCG failure in high-risk NMIBC; **level 1b**
Bohle et al. 2009 [78]	248	Intraves. GEM vs. placebo	Single dose, postoperative 30–40 min instillation of GEM (2000 mg/100 mL) vs. 100 mL saline	Primary or recurrent NMIBC	Median follow-up 24 mo/1-year RFS: 78% (GEM; 95% CI 69–84) vs. 75% (saline; 66–82)/concomitant BCG used in 14%/AE 7% (GEM) vs. 4% (saline)	Controlled, randomized, double-blind, placebo-controlled, multi-center	Study terminated early after interim analysis/single dose GEM does not increase RFS; **level 1b**
Addeo et al. 2010 [79]	109	Intraves. GEM vs. MMC	2000 mg/50 mL GEM 6× weekly induction therapy, responders with 10× monthly maintenance therapy vs. 40 mg MMC for 1 h, first instillation up to 2 days after TURBT, then 4× weekly, responders with 10× monthly maintenance therapy	Recurrent NMIBC after BCG instillation	Median follow-up 36 mo/relative risk of recurrence: 0.72 (GEM) vs. 0.94 (MMC; $p=0.291$)/DFS significantly increased for GEM vs. MMC ($p=0.0021$)/AE 39% (GEM) vs. 72% (MMC; $p=0.021$), rate of chemical cystitis increased in GEM ($p=0.013$)	Randomized, open-label, multi-center	GEM increases DFS significantly compared with MMC in BCG-refractory patients; **level 1b**
Breyer et al. 2010 [80]	10	Intraves. GEM and MMC sequence	GEM (1000 mg/50 mL, 90 min) followed by MMC 40 mg/20 mL once weekly for 6 weeks, then monthly for 12 mo	Recurrent NMIBC after BCG instillation	Median follow-up 27 mo/14-mo RFS: 60%/ median time to recurrence: 6 mo (4–13)/RC rate: 20%/AE 20%	Retrospective, single-center	GEM/MMC as possible treatment option in BCG-refractory patients not suitable for RC; **level 3**

AE, adverse events; BCG, bacillus Calmette–Guérin; CI, confidence interval; CIS, carcinoma *in situ*; CSS, cancer-specific survival; GEM, gemcitabine; HR, hazard ratio; intraves., intravesical; MMC, mitomycin C; mo, month; NMIBC, non-muscle-invasive bladder cancer; n.r., not reported; OS, overall survival; PFS, progression-free survival; QOL, quality of life; RC, radical cystectomy; RFS, recurrence-free survival; RR, recurrence rate; TURBT, transurethral resection of bladder tumor.

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CHAPTER 30

Treatment of muscle-invasive bladder cancer

Justin R. Gregg and Sam S. Chang
Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA

Background

Bladder cancer is the fourth most common cancer in men and the tenth most common cancer in women in the United States. There were approximately 74 690 new cases of urothelial carcinoma of the bladder and over 15 000 deaths from the disease in the United States in 2014 [1]. The majority of new cases of urothelial carcinoma of the bladder are diagnosed when the disease is not muscle invasive. However, approximately 25% of new cases are muscle invasive at the time of diagnosis and a significant proportion of patients diagnosed with noninvasive disease will eventually progress to muscle-invasive bladder cancer (MIBC) [2]. The current standard for treatment of muscle-invasive urothelial carcinoma is radical cystectomy with pelvic lymphadenectomy combined with neoadjuvant systemic chemotherapy [3]. Overall 5-year survival after cystectomy has been estimated to be 25–80% and is largely dependent on tumor stage and lymph node status [4]. Traditionally, approximately 50% of patients who undergo cystectomy for MIBC have metastatic disease within 2 years [5]. Multiple randomized trials have been completed investigating the efficacy of neoadjuvant chemotherapy, and a 2005 meta-analysis including individual data from 3005 individuals enrolled in 11 trials confirmed previous analyses showing an overall survival in those who received chemotherapy prior to cystectomy [6]. Chemotherapeutic regimens that are approved by the US Food and Drug Administration are gemcitabine with cisplatin (GC), methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), cisplatin, methotrexate, and vinblastine (CMV), and gemcitabine plus carboplatin. Data regarding the efficacy of neoadjuvant chemotherapy were reviewed in the previous edition of this book [7].

Although the potential benefit of radical cystectomy with neoadjuvant chemotherapy is rarely disputed, interest remains in bladder-sparing protocols, including maximal transurethral resection of bladder tumor (TURBT), chemotherapy, and/or radiation, to limit morbidity and quality of life changes that are associated with the current therapy for MIBC. In the previous review, we recommended against the use of bladder-sparing protocols owing to a lack of evidence. This chapter aims to update and evaluate evidence for bladder-sparing therapy in MIBC.

Finally, a commonly cited risk of neoadjuvant chemotherapy is delay of definitive surgical treatment, particularly in patients with MIBC who do not respond to chemotherapy [4]. These concerns raise the question of whether neoadjuvant chemotherapeutic regimens may be shortened without compromising survival, and these are an additional topic of review in this chapter.

Clinical question 1

In patients with clinically localized muscle-invasive urothelial cell carcinoma, how do bladder-sparing therapies (trimodal therapy) compare with radical cystectomy with regard to survival and rates of local recurrence?

Literature search

A systematic search was conducted using Ovid MEDLINE from January 1990 to October 2014 using the terms (and related derivatives) of the following: "urinary bladder neoplasms," "surgical procedures, operative," "drug therapy" "antineoplastic agents," "radiotherapy," "cystectomy," and "bladder sparing," and the names of various chemotherapeutic agents. Articles meeting the above criteria published from October 2014 to June 2015 were also reviewed and included if particularly relevant (large prospective series or randomized trials). A literature search was also conducted

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using the Cochrane Database of Systematic Reviews (up to September 2014), Health Technology Assessment, National Health Sciences Economic Evaluation Database, and Database of Abstracts of Reviews of Effects (the last three up to the third quarter of 2014). These databases were searched using similar terms.

The evidence

Radical cystectomy with lymphadenectomy remains the mainstay of treatment for cancer control in patients diagnosed with MIBC. Cystectomy does expose patients to risks of major surgery, however, and patients with advanced age, female gender, prior treatment, medical comorbidities, and malnutrition, among other factors, are at increased risk of postoperative complications [8, 9]. As a result, interest remains in bladder-sparing protocols that have the potential to limit the morbidity and mortality associated with surgery and improve quality of life without compromising cancer control.

Although a number of individual institutions have developed bladder-sparing protocols using trimodal therapy [10], few of these compared outcomes with concurrent patients who had radical cystectomy. Individual protocols demonstrate that 5–10-year survival can be as high as 40–60% in selected patients, although these results are likely dependent, at least in part, on prompt cystectomy at recurrence [11]. Studies evaluating bladder-sparing approaches compared with cystectomy are summarized in the following and unfortunately are lacking in both quantity and quality. Many are limited by bias and also utilize protocols not used commonly in contemporary clinical practice. Furthermore, the majority of studies (or study arms) compared only radiation therapy with cystectomy. Given randomized evidence regarding improved mortality in patients who undergo bladder-sparing treatment with both chemotherapy and radiation compared with radiation alone [12, 13], these data are insufficient to determine any true mortality difference that may be seen with bladder-sparing treatment compared with cystectomy.

In order to best review the evidence, we utilized a recent high-quality systematic review that identified and summarized the following studies used as evidence [14]. One randomized controlled clinical trial (RCT) [15], seven retrospective cohort series [16–22], and one nonrandomized controlled clinical trial [23] compared bladder-sparing therapy with radical cystectomy in patients with clinically nonmetastatic MIBC. Unfortunately, only two of these studies involved a comparison of true trimodal therapy (cisplatin-based chemotherapy, radiotherapy, and TURBT) with cystectomy. The studies generally included patients with MIBC, although three studies included patients with clinical stage T1 tumors (2.3–24% of the population) [20–22]. A summary of the study characteristics and evaluated interventions is given in Table 30.1.

The randomized controlled trial by Sell et al. evaluated bladder-sparing EBRT with 60 Gy versus preoperative external beam radiation therapy with 40 Gy followed by radical cystectomy in 183 patients [15]. This study did not show a statistically significant difference in overall survival between the EBRT group (median 18 months) and the neoadjuvant EBRT with cystectomy group (median 20 months) ($p = 0.21$). There was, however, a significant increase in local recurrence in patients who received just EBRT (35.8%) compared with patients in the surgery arm (6.8%), with a relative risk (RR) of recurrence of 5.25 (95% confidence interval [CI] 2.31 to 11.9). This study had a high risk of bias, due to methodological shortcomings including baseline differences between treatment groups, poor reporting of attrition, and loss to follow-up. Additionally, its results were imprecise, which is perhaps attributable to sample size. Therefore, it is considered low-grade evidence. Finally, it tested dated interventions that are rarely used in contemporary treatment of MIBC.

Two of the cohort studies evaluated bladder-sparing therapy that included both radiation and chemotherapy [16, 22]. The study by Bekelman et al. compared variable doses of EBRT with cisplatin-based chemotherapy and TURBT with surgery [16]. This study was a population-based cohort in the USA (all other studies were in Europe) and it showed a decreased likelihood of survival in patients who underwent bladder-sparing therapy; however, this finding was not statistically significant. This study had a medium risk of bias due to groups differing in baseline characteristics, although these were adjusted using a propensity scored analysis. The study by Rincón Mayans et al. evaluated two bladder-sparing regimens compared with radical cystectomy [22]. From 1997 to 2003, bladder-sparing therapy involving chemotherapy with paclitaxel, methotrexate, 5-fluorouracil, and cisplatin was given for two cycles, followed by EBRT with 45–65 Gy concurrently with 5-fluorouracil and cisplatin, then with an additional two cycles of the original regimen. Patients from 2003 to 2007 had two cycles of paclitaxel, gemcitabine, and cisplatin for two cycles, followed by EBRT with 55–65 Gy, then received an additional two cycles of chemotherapy. Median follow-up was 18 months and no differences were seen in progression-free survival between groups. This study was from a single institution and had a high risk of bias due to a lack of adjustment for potential confounders.

Three of the cohort studies examined EBRT with at least 55 Gy as the bladder-sparing portion of the study [18–20]. Furthermore, the study by Holmäng et al. included patients who underwent maximal TURBT, although some received lower dose (21 Gy) radiation therapy [18]. This study evaluated ERBT, TURBT, and radical cystectomy and showed an increased risk of 5-year bladder cancer-specific mortality with both bladder-sparing treatments, although only EBRT was statistically significant (RR 1.44, 95% CI 1.02–2.05) [18]. This study had a high risk of bias as it did not adjust for potential confounders and involved population-based data.

Table 30.1 Summary of results for bladder-sparing therapies compared with radical cystectomy.

Study and methodology	Interventions (*n*)	Recurrence	Mortality
Bekelman et al. 2013 [16] • Retrospective cohort • SEER–Medicare • 1995–2005	1 Bladder-sparing chemoradiation (cisplatin based) with TURBT (*n*=473) 2 RC with or without lymphadenectomy	Not reported	OS: 28% vs. 47% (NS) DSS: 52% vs. 65% (NS)
Goossens-Laan et al. 2014 [17] • Retrospective cohort • Netherlands, population-based cancer registry 1995–2009	1 Radical cystectomy (*n*=835) 2 EBRT (*n*=859) 3 Interstitial radiotherapy/ brachytherapy (*n*=172) 4 Maximal TUR (*n*=417)	Not reported	Unadjusted 5-year survival, 1 vs. 2 vs. 3 vs. 4: 48% vs. 29% vs. 70%. vs. 19% (no statistical test)
Holmäng et al. 1997 [18] • Retrospective cohort • Sweden population-based cancer registry 1987–1988	1 EBRT with three-field box, 60 Gy or more (*n*=42) 2 Radical TURBT alone (*n*=70) 3 RC (unknown number received radiation, 2 received NAC, no lymphadectomy)	Not reported	T2 or T3 tumors: ACM: 85% vs. 86% vs. 67% (NS) BCM: 82% vs. 75% vs. 57% (NS) T4 tumors: 100% ACM
Kalogeras et al. 2008 [19] • Retrospective cohort • Greece, single institution 1995–2006	1 EBRT with box configuration, 64 Gy (*n*=119) 2 RC with no radiation (*n*=26)	Local control: 42% vs. 88% (RR 2.08, 95% CI 0.37 to 0.61)	3-year overall survival: 39% vs. 69% (*p*=0.03)
Kotwal et al. 2008 [20] • Retrospective cohort • UK, single institution • 1996–2000	1 Radiotherapy with 50–55 Gy (*n*=97) 2 RC with lymphadenectomy in 52 patients (*n*=72)	Local or distant recurrence: 34% vs. 38% (NS)	ACM: 71% vs. 62% (NS) 5-year OS: 35% vs. 41% (NS) 8-year OS: 18% vs. 36% (NS) BCM: 38% vs. 44% (NS) 5-year DSS: 57% vs. 53%
Nieuwenhuijzen et al. 2005 [21] • Retrospective cohort • Netherlands, single institution 1988–2003	1 EBRT with 30 Gy followed by brachytherapy (*n*=108) compared with partial cystectomy in 24 patients 2 RC with lymphadenectomy (*n*=77)	Local recurrence: 21% vs. not reported	5-year OS: 62% vs. 67% (NS) 10-year OS: 50% vs. 58% (NS) 5-year DSS 73% vs. 72% 10-year DSS 67% vs. 72%
Rincón Mayans et al. 2010 [22] • Retrospective cohort • Spain, single institution 1994–2007	1 EBRT with two different cisplatin-based chemotherapy regimens (switched in 2003) (*n*=43) 2 RC, no radiotherapy (*n*=145)	3-year PFS: 69% vs. 72% (NS) 5-year PFS 61% vs. 63% (NS)	Not reported
Sell et al. 1991 [15] • Randomized control trial • Denmark, multi-center 1983–1986	1 Radical EBRT with 60 Gy (*n*=95) 2 Preoperative EBRT with 40 Gy followed by radical cystectomy (*n*=88). Lymphadenectomy in 40 patients	Local recurrence: 35.8% vs. 6.8% (RR 5.25, 95% CI 2.31 to 11.9)	OS (median): 18 vs. 20 months (*p*=0.21)
Solsona et al. 2009 [23] • Nonrandomized clinical trial • Spain, multi-center 1980–1990	1 Bladder-sparing cisplatin-based chemotherapy (*n*=75) 2 RC with lymphadenectomy (*n*=71)	Need for cystectomy: 72% vs. not reported	5-year DSS: 65% vs. not reported

RC, radical cystectomy; OS, overall survival; DSS, disease-specific survival; NS, not significant; NAC, neoadjuvant chemotherapy; TURBT, transurethral resection of bladder tumor; ACM, all-cause mortality; BCM, bladder-cancer mortality; PFS, progression-free survival.

The study by Kotwal et al. showed a decreased likelihood of 5- and 8-year survival in patients who underwent at least 55 Gy EBRT compared with those who had cystectomy, although the results were not significant [20]. Similarly, the study by Kalogeras et al. showed a decreased rate of survival at 3 years in patients who had radiation; however, these findings also were not significant ($p=0.03$) [19]. Further, both studies had a high risk of bias, as the former did not clearly report results of adjusted analyses and the latter did not adjust for potential confounders.

One cohort study evaluated bladder-sparing therapy using EBRT with 30 Gy combined with brachytherapy (delivered via suprapubic cystotomy), with or without partial cystectomy (depending on the initial response), compared with cystectomy [21]. The bladder-sparing approach was associated with a lower likelihood of disease-specific mortality after adjusting for confounders, although the result was not significant. This study had a medium risk of bias due to failure to report a consecutive random sample and the fact that comparison groups were not entirely concurrent.

The cohort study by Goossens-Laan et al. utilized population-based registry data to compare EBRT, brachytherapy, TURBT, and radical cystectomy, although details were not provided about the interventions [17]. This study found that brachytherapy had a higher unadjusted 5-year survival compared with the other three groups; however, there were large differences between groups in terms of age and bladder cancer stage. For this reason, the study was classified as having a high risk of bias.

Finally, the nonrandomized clinical trial by Solsona et al. compared bladder-sparing therapy using one of three different cisplatin-based regimens with cystectomy [23]. No differences were found in cancer-specific survival between bladder-sparing therapy and cystectomy, although the data were not significant. Notably, 72% (54/75) of patients who underwent bladder-sparing chemotherapy subsequently required cystectomy. This trial had a high risk of bias, in part because statistical analyses did not include adjustment for confounding variables. Therefore, studies comparing bladder-sparing therapies with cystectomy have been widely disparate in terms of methodology and types of therapy offered and include, at most, low-level evidence. They are commonly hampered by a high likelihood of bias, including a lack of consideration of confounding factors. Furthermore, few studies (and no randomized controlled trials) have compared contemporary trimodal therapy with cystectomy. Notably, the two cohort studies that compared bladder-sparing chemoradiation with cystectomy did not show a significant difference in terms of mortality. Regarding cancer recurrence, the same aforementioned limitations to the available literature remain. Retrospective cohorts offer mixed results, although the randomized trial comparing radiation alone with radiation and cystectomy did show higher rates of recurrence with the bladder-sparing approach. Therefore, high-quality cohort studies and prospective trials comparing trimodal bladder-sparing therapy with cystectomy are needed before conclusions can be drawn about the safety and efficacy of this approach.

Clinical implications

In patients with clinically localized muscle-invasive urothelial cell carcinoma who are candidates for radical cystectomy, we suggest against bladder-sparing therapies (trimodal therapy) (conditional recommendation based on low-quality evidence). This recommendation assumes that patients place a relatively high value on overall and recurrence-free survival, and relatively lower value on the avoidance of the associated complications of radical cystectomy and urinary diversion. Patients should be counseled that all studies of contemporary bladder-sparing protocols have been nonrandomized and that cystectomy remains the most proven option. A randomized controlled trial of bladder-sparing therapy for patients with good-risk tumor features versus radical cystectomy is needed before this approach can be safely recommended to patients who are candidates for cystectomy.

Clinical question 2

In patients with clinically localized muscle-invasive urothelial cell carcinoma, how does neoadjuvant dose-dense MVAC compare with standard dose cisplatin-based chemotherapy in terms of overall survival?

Literature search

The literature search was the same as for clinical question 1, with the additional search term "dose dense MVAC."

The evidence

Full-dose MVAC (henceforth referred to as MVAC) is one of multiple cisplatin-based chemotherapeutic regimens found on meta-analysis to improve survival when used in the neoadjuvant setting for MIBC [6]. An EORTC randomized trial reported in 2006 compared dose-dense MVAC given with granulocyte colony-stimulating factor (G-CSF) with MVAC in patients with advanced bladder cancer. This trial showed a higher response rate and a borderline statistically significant reduction in risk of death at 5 years, with a survival rate of 21.8% in the dose-dense group and 13.5% in those who received MVAC. Given a relatively low rate of severe side effects, the regimen was soon extrapolated to include clinically localized MIBC.

Two single-arm prospective studies evaluated dose-dense MVAC in the neoadjuvant setting. Plimack et al. treated 44 patients with MIBC and N0 or N1 disease [24]. Forty patients had a cystectomy and 15 (38%) of these had pT0 disease (the primary outcome of the study). With a median follow-up of 20 months, nine patients had recurrence and five cancer-related deaths were recorded. Choueiri et al. performed a similar study on 39 patients and found that 26% had pT0 disease after cystectomy [25]. Patients had a median follow-up of 24 months and eight had died of their disease at this point. Finally, a meta-analysis by Blick et al. of 80 consecutive patients with MIBC treated with dose-dense MVAC at two UK institutions showed that unadjusted 2-year disease-free and overall survival were 65 and 77%, respectively [26].

One retrospective study with a high risk of bias, by Galsky et al., compared MVAC (in whom 77% of patients received higher density dosing) with GC as neoadjuvant therapy for MIBC [27]. The primary outcome was not survival, although an exploratory analysis was completed examining this outcome. This study included 212 patients from 28 international institutions who met the inclusion criteria (localized disease) and received either MVAC or GC. Sixty-six patients received MVAC prior to cystectomy, of whom 51 (77.3%) were on a dose-dense administration schedule. pT0 disease was the primary outcome, and the study found no difference between the two treatments after adjusting for propensity scores. In an exploratory survival analysis, patients with MVAC had a longer overall survival time (35.5 months) compared with GC (26.8 months), although this was not statistically significant. Despite its use of propensity scoring, this study has a high risk of bias given the sample size, inability to account for confounders such as comorbidity, and dilution of its MVAC group with patients who did not receive dose-dense timed therapy.

Therefore, limited data suggest that dose-dense MVAC is at least equal to full-dose MVAC in patients with metastatic disease, and efficacy in clinically localized disease has been shown in Phase II trials. Although a single retrospective study examining dose-dense MVAC is encouraging, the data are limited in their scope and quality. Fortunately, a recently initiated Southwest Oncology Group trial (SWOG 1314) randomizing patients with MIBC to neoadjuvant GC versus dose-dense MVAC may elucidate any differences in these treatments, although the trial is not designed to compare the two treatment regimens (its primary objective is to investigate a gene expression model-based approach).

Clinical implications

In patients with clinically localized muscle-invasive urothelial cell carcinoma, we suggest neoadjuvant standard-dose MVAC over dose-dense MVAC (conditional recommendation based on low-quality evidence). Prospective studies are needed to show efficacy in terms of disease-related mortality or response. Clinicians are encouraged, as always, to consider individual patient preferences and to await results of future studies prior to recommending dose-dense MVAC uniformly in the neoadjuvant setting.

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31 CHAPTER 31

Management of upper tract urothelial carcinoma

Ilaria Lucca[1,2]*, Romain Mathieu[1,3]*, Tobias Klatte[1], and Shahrokh F. Shariat[1,4,5]

[1] *Department of Urology, Medical University of Vienna, Vienna General Hospital, Vienna, Austria*

[2] *Department of Urology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland*

[3] *Department of Urology, Rennes University Hospital, Rennes, France*

[4] *Department of Urology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA*

[5] *Department of Urology, Weill Cornell Medical College, New York, NY, USA*

Introduction

Urothelial upper tract carcinoma (UTUC) is relatively rare among urothelial cancers, with an incidence of about two cases per 100 000 person-years [1]. Despite earlier diagnosis, noninvasive surgical managements, and the increased use of perioperative chemotherapy, UTUC is associated with poor oncological outcomes [2, 3]. According to the current guidelines, the gold standard treatment for UTUC is radical nephroureterectomy (RNU) with bladder cuff resection [4]. Methods of surgery and ancillary neoadjuvant or adjuvant may impact patient outcomes. In this chapter, we systematically review the current evidence addressing questions about the surgical and medical management of UTUC.

Literature search

Eligible articles were identified through the electronic databases MEDLINE, EMBASE, and Web of Science. The time period included articles in the English language published between January 2000 and July 2015. The search was limited to randomized controlled trials or comparative studies that provided measures of effect (e.g. hazard ratio [HR]) and confidence interval (CI). Additional informative articles were collected by cross-referencing the bibliography of previously selected articles. Review articles, case reports, and case series with fewer than 15 patients were excluded. The article selection process was conducted according to the PRISMA guidelines [5]. Two authors (I.L., R.M.) independently extracted data variables for each study included and disagreements were discussed with the two senior authors (T.K., S.F.S.).

For each question, a systematic review and meta-analysis were performed. Numbers, proportions, means, and standard deviations were extracted. If means and standard deviations were not reported, the values were estimated from the data provided. We used 0.5 for fixed continuity correction if zero counts were reported. Study heterogeneity was assessed using I^2 statistics and the chi-squared test for homogeneity. Random effects models were used as default. Analyses were performed using STATA 12.0 (StataCorp, College Station, TX, USA).

Clinical question 1

In patients undergoing radical nephroureterectomy for UTUC, what is the best management for bladder cuff resection regarding oncological outcomes: open (transvesical or extravesical) or endoscopic approach?

Literature search

We conducted a systematic literature search through the electronic databases MEDLINE, EMBASE, and Web of Science using the search terms "upper tract urothelial carcinoma," "radical nephroureterectomy," and "bladder cuff." The literature search retrieved 203 records. After duplicates had been removed and records screened, 18 full-text articles were assessed for eligibility. According to the inclusion criteria, five studies were finally selected for quantitative synthesis [6–10].

The evidence

We identified five relevant multi-institutional retrospective studies but no randomized controlled study that compared oncological outcomes after endoscopic versus open (extravesical or/and transvesical) management of bladder cuff (Table 31.1). Three studies assessed the risk of

* These authors contributed equally as co-first authors.

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Table 31.1 Selected studies comparing endoscopic versus open management of bladder cuff in UTUC patients treated with RNU regarding oncological outcomes.

Study	Study design	No. of patients	No. with endoscopic approach	No. with open approach	Median follow-up (months)	No. with IVR after open RNU	No. with IVR after no open RNU	Time to IVR after open RNU	Time to IVR after no open RNU	5-years IRFS open RNU (%)	5-years IRFS no open RNU (%)	No. of recurrences after open RNU	No. of recurrences after no open RNU	5-years RFS open RNU (%)	5-years RFS no open RNU (%)
Xylinas et al. 2014 [7]	Retrospective multi-center	2681	85	1811	57.5	Trans: 388 Extra: 160	56	39.9	23.9	Trans: 58 Extra: 51	42	Trans: 526 Extra: 204	18	Trans: 66 Extra: 66	69
Xylinas et al. 2013 [6]	Retrospective multi-center	482	61	421	39.5	143	26	NR	NR	NR	NR	NA	NA	NA	NA
Fradet et al. 2014 [8]	Retrospective multi-center	743	76	Trans: 267 Extra: 251	24.8	Trans: 70 Extra: 71	20	NR	NR	NR	NR	NA	NA	NA	NA
Walton et al. 2011 [10]	Retrospective multi-center	773	90	683	34	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kapoor et al. 2014 [9]	Retrospective multi-center	820	98	Trans: 406 Extra: 316	24.6	Trans: 66 Extra: 77	23	NR	NR	NR	NR	Trans:134 Extra: 112	38	Trans: 46.3 Extra: 35.6	30.10

RNU, radical nephroureterectomy; IVR, intravesical recurrence; IRFS, intravesical recurrence-free survival; RFS, recurrence-free survival; NR, not reported; NA, not assessed; Trans, transvesical approach; Extra, extravesical approach.

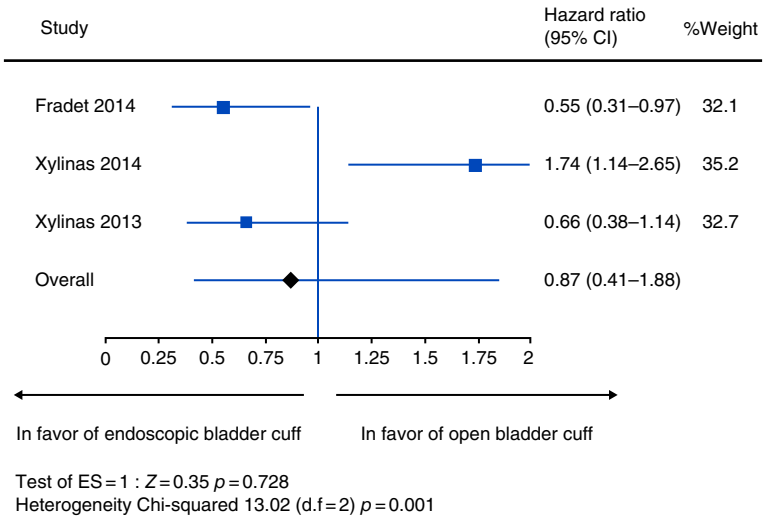

Figure 31.1 Forest plot comparing endoscopic versus open management of bladder cuff in UTUC patients treated with RNU regarding the risk of intravesical recurrence.

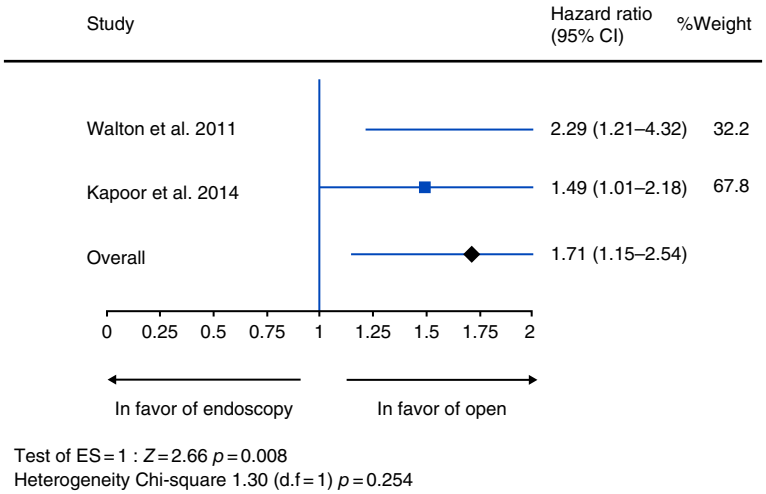

Figure 31.2 Forest plot comparing endoscopic versus open management of distal ureter in UTUC patients treated with RNU regarding the risk of RFS.

intravesicle recurrence (IVR) according to bladder cuff management and reported conflicting results (Figure 31.1). Endoscopic removal of the bladder cuff was not associated with a higher risk of IVR when a meta-analysis of reported HR was performed (HR 0.85, 95% CI 0.41–1.86). The interpretation of the results is limited as the standard open technique varied according the studies: extravesical [8], transvesical [7], or both approaches [6] were considered as the technique of reference.

Two studies [9, 10] specifically assessed recurrence-free survival (RFS) in RNU patients treated with open versus endoscopic bladder cuff removal (Figure 31.2). Compared with an open surgical approach, endoscopic removal was associated with worse RFS (HR 1.71, CI 1.15–2.54). However, the definition of RFS was different between studies, since IVR was not considered as a disease recurrence in the study by Walton et al. [10] This study was, indeed, the only one that assessed a surgical approach to the bladder cuff as an independent predictor of cancer-specific survival (CSS) and showed that endoscopic management of the bladder cuff was associated with a significantly higher risk of cancer-specific death (HR 2.26, 95% CI 1.18–4.27).

In summary, there is no high level of evidence to recommend any single technique for removal of the bladder cuff. The limited data to date suggest that endoscopic bladder cuff removal has worse outcomes compared with open

approaches Until comparative randomized studies are performed, patients should be counseled regarding the lack of data on the optimal surgical approach to remove bladder cuff during RNU and a possible risk of worse outcome with endoscopic management.

Clinical implications

In patients undergoing a radical nephroureterectomy, we suggest open excision of the distal ureter and bladder cuff over endoscopic excision (weak recommendation based on low-quality evidence). This recommendation assumes that patients place a high relative value on improving oncological outcomes and a relatively low value on the short-term perioperative morbidity.

Clinical question 2

How does laparoscopic/robotic-assisted RNU compare with open RNU?

Literature search

We conducted a systematic literature search through the electronic databases MEDLINE, EMBASE, and Web of Science using the search terms "upper tract urothelial carcinoma," "open," "laparoscopic," and "robot-assisted radical nephroureterectomy." The literature search retrieved 249 records. After duplicates had been removed and records screened, 38 full-text articles were assessed for eligibility. According the inclusion criteria, 12 studies were finally selected for quantitative synthesis [6–8, 10–18].

The evidence

We identified only one randomized controlled study and 11 retrospective comparative studies (with adjusted HRs for standard oncological outcomes) that compared laparoscopic RNU with open RNU (Table 31.2). To date, no comparative study has compared robot-assisted RNU with the open approach. In the single randomized study, 40 UTUC patients treated with open RNU were compared with 40 patients treated with laparoscopic RNU [18]. Within a median follow-up of 44 months, CSS was 90 versus 80%, respectively, but the difference was not statistically significant ($p=0.2$). However, in patients with ≥pT3 disease, metastasis-free survival and CSS were significantly worse with laparoscopy compared with open surgery ($p=0.004$ and $p=0.039$, respectively).

Among the other historical cohort studies, seven provided IVR information (Figure 31.3), four addressed any recurrence (Figure 31.4), and four reported cancer-specific death (Figure 31.5). Meta-analyses revealed that a laparoscopic approach was associated with a higher risk of IVR (HR 1.57, 95% CI 1.17–2.11) but similar rates of RFS (HR 1.12, 95% CI 0.90–1.39) and CSS (HR 0.77, 95% CI 0.55–1.06) compared with open RNU. Significant heterogeneity was observed between studies regarding IVR ($I^2=70.5\%$).

Finally, although no difference in survival rates was found between the two techniques, minimal invasive surgery may have advantages of shorter hospital stay and earlier recovery time.

Given the decreased morbidity with laparoscopic renal surgery, it is reasonable to assume that a laparoscopic approach is preferred if oncological outcomes are equivalent to open surgery. The limited available data suggest that laparoscopic RNU may be associated with a higher incidence of IVR but equivalent CSS and RFS compared with open RNU. Given that the single prospective randomized study suggested worse outcomes in patients with pT3, further investigations should be performed in this setting to confirm the safety of the laparoscopic approach in patients with locally advanced disease.

Clinical implications

In patients with ≤cT2 UTUC receiving radical nephroureterectomy, we suggest a laparoscopic approach over an open approach (conditional recommendation based on low-quality evidence). This recommendation assumes that patients place a relatively high value on reducing perioperative morbidity and recovery time and a relatively low value on the risk of intravesical recurrence (conditional recommendation based on low-quality level evidence).

Further, in patients with ≥cT3 UTUC undergoing radical nephroureterectomy, we suggest an open approach (conditional recommendation based on low-quality evidence)

Clinical question 3

In patients having undergone RNU, does postoperative intravesical chemotherapy reduce the risk of bladder cancer recurrence after RNU?

Literature search

We conducted a systematic literature search through the electronic databases MEDLINE, EMBASE, and Web of Science using the search terms "upper tract urothelial carcinoma," "mitomycin C," and "bladder recurrence." Of the 47 studies selected through the literature search, 19 full-text articles were assessed for eligibility. Three studies with 446 patients in total were finally analyzed according to the inclusion criteria [19–21].

The evidence

We identified two randomized controlled studies and one retrospective comparative study that investigated intravesical instillation of chemotherapy after RNU (Table 31.3). In the first multi-center randomized controlled study, 105 patients received a single postoperative dose of intravesical MMC after RNU, and 115 patients were treated with standard care [19]. IVR was recorded in 17 of 105 patients (16%) in the MMC arm and 31 of 115 patients (27%) in the standard

Table 31.2 Selected studies comparing laparoscopic and open approaches for bladder cuff during RNU.

Study	No.of patients	No. of patients treated with open RNU	No. of patients treated without open (= lap/robotics) RNU	Median follow-up (both procedures) (months)	Median follow-up (open) (months)	Median follow-up (no open) (months)	No. of patients with IVR open	No.of patients with IVR no open	5-years IRFS open (%)	5-years IRFS no open (%)	5-years RFS open (%)	5-years RFS no open (%)	5-years CSS open (%)	5-years CSS no open (%)
Zou et al. 2014 [11]	122	101	21	53	NR	NR	NR	NR	NR	NR	NR	NR	79.2%	85.7%
Kitamura et al. 2014 [12]	99	34	65	60	NR	NR	NR	NR	71.1	69.2	57.1	69.2	74.2	87.4
Fradet et al. 2014 [8]	612	267	345	24.8	NR	NR	62	245	NR	NR	NA	NA	NA	NA
Xylinas et al. 2013 [6]	482	350	132	39.5	NR	NR	116	53	NR	NR	NA	NA	NA	NA
Xylinas et al. 2014 [7]	2681	2170	511	57.5	NR	NR	NR	NR	NR	NR	NA	NA	NA	NA
Fairey et al. 2013 [13]	849	403	446	26.4	NA	NA	NA	NA	NA	NA	43	33	73	76
Kobayashi et al. 2012 [14]	288	124	164	20.2	NR	NR	42/151	61/137	NR	NR	NA	NA	NA	NA
Walton et al. 2011 [10]	773	703	70	34	36	17	NA	NA	NA	NA	73.7	63.4	75.4	75.2
Ariane 2012 [15]	609	459	150	27	NR	NR	NA	NA	NA	NA	50.7	52.2	78	90.7
Favaretto 2010 [16]	162	109	53	23	NR	NR	51	15	NR	NR	NR	NR	NR	NR
Taweemonkongsap 2008 [17]	60	31	29	NR	27.9	26.4	13	9	NR	NR	NR	NR	NR	NR
Simone et al. 2009 [18]	80	40	40	44	NR	NR	9	10	NR	NR	NA	NA	89.9	79.8

RNU, radical nephroureterectomy; IVR, intravesical recurrence; IRFS, intravesical recurrence-free survival; CSS, cancer-specific survival; NR, not reported; NA, not assessed.

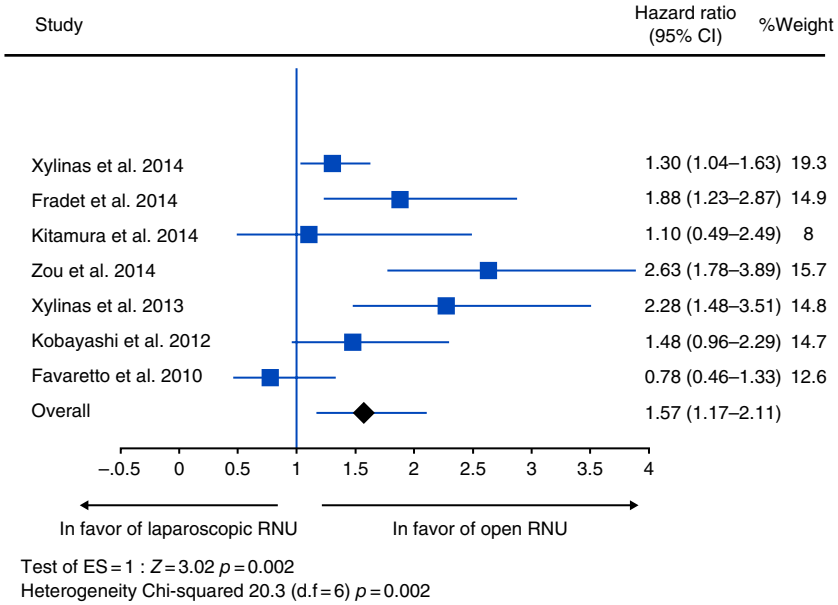

Figure 31.3 Forest plot comparing laparoscopic versus open RNU for UTUC regarding the risk of IVR.

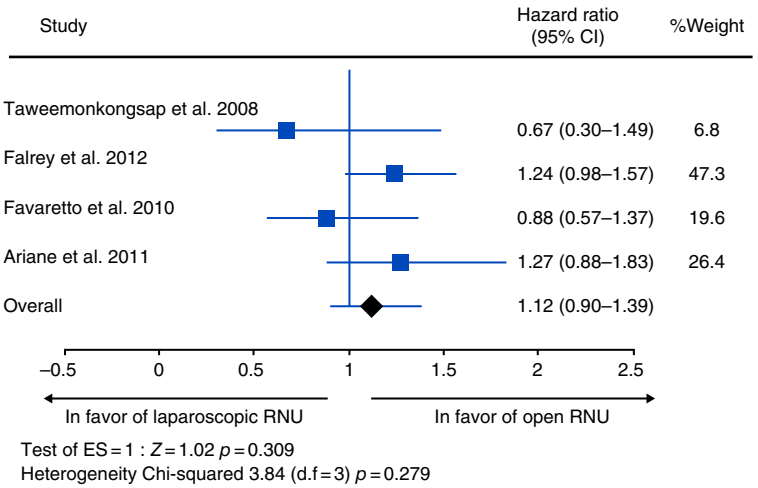

Figure 31.4 Forest plot comparing laparoscopic versus open RNU for UTUC regarding the risk of RFS.

treatment arm. In the subgroup analysis, IVR was higher in moderately and poorly differentiated UTUC. In the second randomized controlled study, the instillation group ($n = 12$) received postoperative intravesical instillations of MMC and cytosine arabinoside (Ara-C), with a total of 28 instillations over a period of 2 years [20]. The 1- and 2-year intravesical recurrence-free survival (IRFS) rates were 92.3 and 80.8%, respectively, in the instillation arm, and 57 and 57%, respectively, in the control group. Finally, of the 196 UTUC patients included in the only retrospective study available, 27 were treated with 6–8 doses of intravesical MMC after RNU [21]. After a mean follow-up of 36 months, 7 of 27 (26%) were diagnosed with a bladder cancer. On multivariable analysis, MMC instillation decreased the risk of IVR ($p = 0.043$).

The meta-analysis revealed a significantly longer IRFS for patients with postoperative intravesical instillations of chemotherapy, with a pooled HR of 0.41 (95% CI 0.31–0.74, $p = 0.01$) (Figure 31.6).

Randomized studies support the use of intravesical chemotherapy to prevent bladder cancer recurrence compared with standard care, especially in moderately and poorly differentiated UTUC with no previous history of bladder cancer. However, the level of recommendation is low because of the limited number of patients in these studies and the variability in treatment between studies. Further investigations to confirm the benefits, assess potential harms, and define the best instillation schedule would optimize this recommendation.

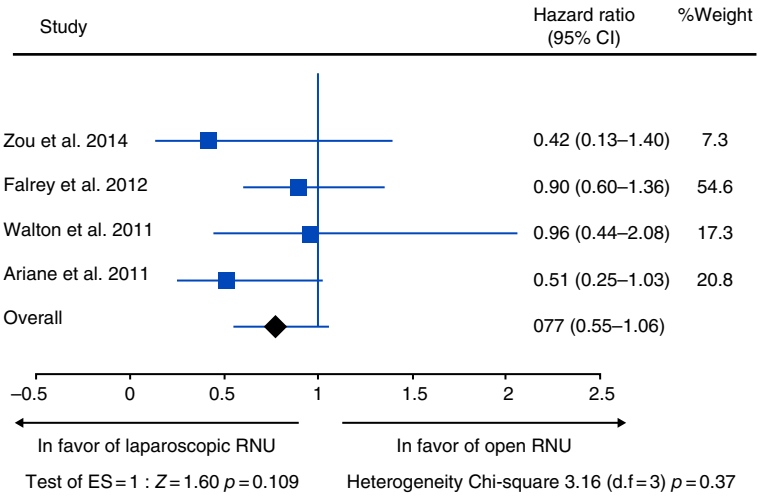

Figure 31.5 Forest plot comparing laparoscopic versus open RNU for UTUC regarding the risk of CSS.

Table 31.3 Selected studies investigating the role of postoperative instillation of MMC after RNU in bladder cancer recurrence-free survival.

Study	Study design	No. of patients	No. of patients treated with MMC	Time to bladder cancer recurrence (months)	IRFS if treated with MMC (%)	IRFS if not treated with MMC (%)	No. of instillations	Time to instillation (days)
O'Brien et al. 2011 [19]	Prospective randomized	225	105	12	84 (1 year)	73 (1 year)	Single	7
Sakamoto et al. 2001 [20]	Prospective randomized	25	12 (+ Ara-C)	45	92 (1 year) 80 (2 years)	57 (1 year) 57 (2 years)		7–14
Wu et al. 2010 [21]	Retrospective	196	27	36 (MMC) 11 (no MMC)	74 (3 years)	59 (11 months)	6–8	14

IRFS, intravesical recurrence-free survival; RFS, recurrence-free survival; MMC, mitomycin C; Ara-C, cytosine arabinoside.

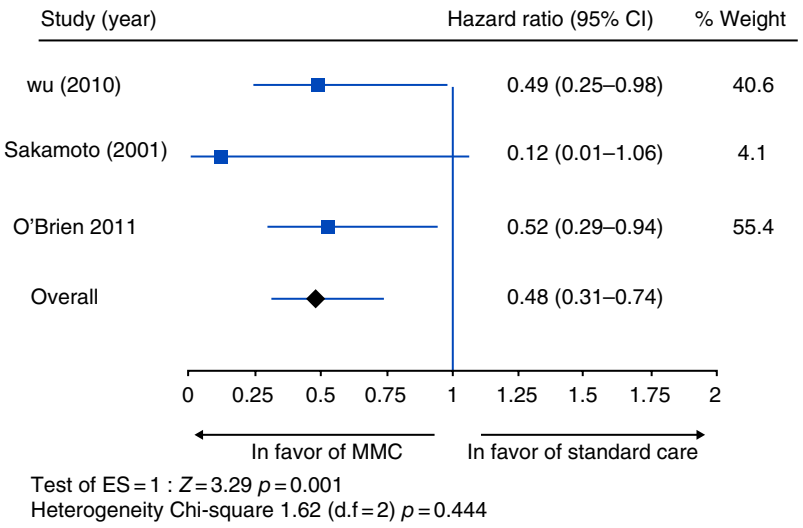

Figure 31.6 Forest plot comparing the use of MMC after RNU versus the standard treatment for UTUC patients regarding the risk of IVR.

Table 31.4 Selected studies investigating the effect of neoadjuvant chemotherapy in high-risk UTUC.

Study	Design	No. of patients	No. of patients treated with NAC	Chemotherapy regimen	Pathological stage NAC group	Downstaging to ≤pT0N0M0 with NAC (%)	Downstaging to ≤pT1N0M0 with NAC (%)	5-years OS NAC	5-years OS no NAC	5-years CSS NAC	5-years CSS no NAC
Porten et al. 2014 [22]	Retrospective	112	31	Cisplatin or ifosfamide (71%) Modified cisplatin (13%) NS combination (16%)	pT0/Tis/Ta/T1 (*n*=20; 65%) pT2 (*n*=6; 19%) pT3–4 (*n*=5; 16%) pN0-Nx (*n*=29; 94%) pN+ (*n*=2; 6%)	13	65	80	62	90	62
Margulis et al. 2009 [24]	Retrospective	1363	47	M-VAC (34%) CMV (29%) GC (20%) Others (17%)	_	11	_	_	_	_	_
Matin et al. 2010 [25]	Retrospective	150	43	M-VAC (44%) CGI (21%) GTA (14%) GC (15%) Others (9%)	pT0/Tis/Ta/T1 (*n*=23; 54%) pT2 (*n*=10; 23%) pT3–4 (*n*=10; 23%) pN0-Nx (*n*=35; 81%) pN+ (*n*=8; 19%)	14	_	_	_	_	_
Rajput et al. 2011 [26]	Retrospective	82	26	M-VAC (23%) CGI (19%) GTA (15%) M-VAC + bevacizumab (15%) Others (28%)	pT0/Tis/Ta/T1 (*n*=51; 63 %) pT2 (*n*=12; 15%) pT3–4 (*n*=19; 23%)	15	_	_	_	_	_
Youssef et al. 2011 [23]	Retrospective	313	18 (N+)	GC (78%) M-VAC (22%)	pT0/Tis/Ta/T1 (*n*=6; 33%) pT2 (*n*=3; 17%) pT3–4 (*n*=9; 50%) pN0-Nx (*n*=9; 50%) pN+ (*n*=9; 50%)	28	_	_	_	44 (N+)	36 (N+) 69 (N0)

IAG, ifosfamide, doxorubicin, gemcitabine; CGI, cisplatin, gemcitabine, ifosfamide; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; GC, cisplatin, gemcitabine; GTA, gemcitabine, paclitaxel, doxorubicin; DD-MVAC, dose-dense M-VAC; CMV, vinblastine, doxorubicin, cisplatin; NAC, neoadjuvant chemotherapy; OS, overall survival; CSS, cancer-specific survival.

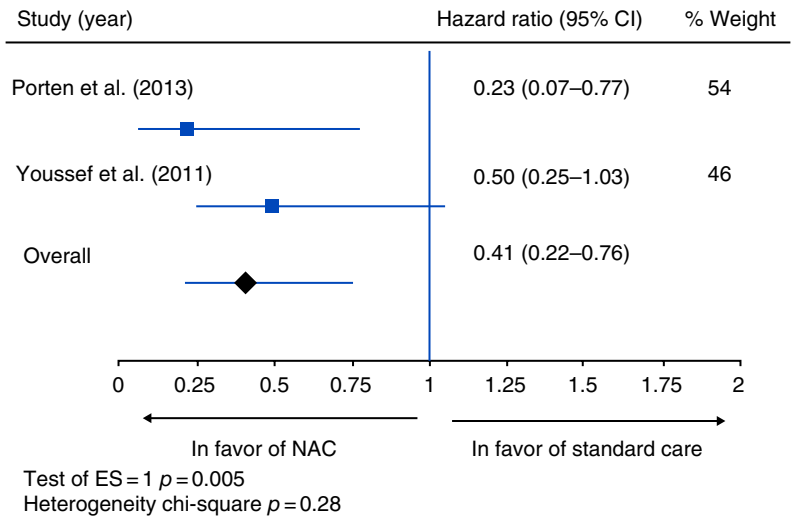

Figure 31.7 Forest plot: CSS of studies investigating NAC for high-risk UTUC.

Clinical implications

In patients having undergone RNU, we suggest postoperative intravesical installation of chemotherapy (conditional recommendation based on low-quality evidence)

Clinical question 4

In patients with high-risk UTUC, does neoadjuvant chemotherapy improve cancer-specific survival?

Literature search

We conducted a systematic literature search through the electronic databases MEDLINE, EMBASE, and Web of Science using the search terms "upper tract urothelial carcinoma" and "neoadjuvant chemotherapy" (NAC). Of the 53 studies selected through the literature search, eight full-text articles were assessed for eligibility. Two studies with 425 patients in total were finally analyzed according to the inclusion criteria [22, 23].

The evidence

We identified five retrospective comparative studies investigating NAC in UTUC, but only two presented sufficient information to be included in a meta-analysis (Table 31.4). No prospective randomized controlled studies were available. Downstaging to pT0N0M0 was recorded in 11–28% of all stages UTUC treated with NAC.

In the first study included in the meta-analysis, 31 patients were treated with NAC before RNU, compared with 81 who were treated only with RNU [22]. The 5-year overall survival and CSS were 80 and 90%, respectively, in the NAC group, and 57.6 and 57.6%, respectively, in the control group. The second study included 138 N+ and 175 N0 UTUC patients treated with RNU with ipsilateral bladder cuff resection and with or without NAC [23]. The NAC group included only patients with clinical evidence of positive locoregional nodal metastasis ($n=18$). The group treated only with RNU included 120 pN+ and 175 pN0 patients. The 5-year CSS and RFS were similar in the NAC group and RNU group if pN0 ($p=0.06$ and $p=0.14$). However, oncological outcomes were significantly worse in the pN+ RNU group compared with the pN0 RNU group ($p<0.001$) and the NAC group ($p=0.06$ for CSS and $p=0.04$ for RFS).

Overall, meta-analysis revealed a significant benefit for NAC in UTUC patients, with a pooled HR of 0.41 (95% CI 0.22–0.76, $p=0.005$) (Figure 31.7).

The meta-analysis, which included only historical cohort studies, showed a significant benefit of NAC in UTUC patients, especially for those with advanced disease. This, together with the decrease in glomerular filtration rate after RNU (which may preclude adjuvant chemotherapy) and available evidence in bladder cancer, suggests that NAC is a valid option for high-grade UTUC.

Clinical implications

In patients with high-risk UTUC planning to undergo RNU, we suggest neoadjuvant chemotherapy (conditional recommendation based on low-quality evidence). This recommendation assumes that patients place a high value on potentially improving oncological outcomes and a relatively low value on the adverse effects of neoadjuvant chemotherapy.

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32 CHAPTER 32

Metastatic bladder cancer

Louise Harris[1], Caitlin Bowen[2], Satish Kumar[2], Bernadette Coles[3], and Malcolm Mason[2]

[1] *Velindre Cancer Centre, Velindre NHS Trust, Cardiff, UK*
[2] *School of Medicine, Cardiff University, Velindre Hospital, Velindre NHS Trust, Cardiff, UK*
[3] *University Library Service, Cardiff University, Cancer Research Wales Library, Velindre NHS Trust, Cardiff, UK*

Introduction

Bladder cancer is the ninth most common cancer worldwide and the fifth most common cancer in Europe. It was estimated that in (2015). there would be 74 000 cases of newly diagnosed bladder cancer in the USA and 16 000 deaths [1]. About 90% of people diagnosed will be over the age of 55 years. Half of cases are confined to the bladder mucosa, in 35% of patients the cancer is muscle invasive but confined to the bladder, and the remaining patients have metastatic disease to local tissues, and 4% of patients present with distant metastases.

Metastatic bladder cancer has been treated for decades with chemotherapy and has a relative 5-year survival rate of less than 10% [2]. There is new interest in alternative therapies for metastatic disease, including immunotherapies. This chapter focuses on the effectiveness and toxicity of chemotherapy regimens used in the metastatic setting and strives to make recommendations clinically relevant.

Literature search

Search strategies were developed in MEDLINE (OVID) using both MeSH and textword terms. Both generic and commercial product drug names were used where appropriate and combined with the MeSH term "urinary bladder neoplasms" and other textword combinations to describe metastatic bladder cancer. Comprehensive literature searches were performed covering the years (1966)–(2016). Updated search strategies were developed based on the original strategies in the first edition of this book and used to search (1966)–(2009). Controlled vocabularies were checked to ensure that any changes or additions to the databases' thesauri were taken into account. This strategy was then used as a basis to produce database specific strategies for use in EMBASE (OVID), the Cochrane Library (Wiley), Web of Science (Thomson Reuters), and PubMed (for non-MEDLINE and e-publications). Update searches were run from (2009). to January (2016). and were limited to randomized controlled trials and systematic reviews. Searches were limited to publications in the English language. All strategies are available from the authors.

Clinical question 1

In patients with metastatic bladder cancer, how do cisplatin-based regimens compare with regimens without cisplatin?

The evidence

It is widely accepted that cisplatin is the basis of standard chemotherapy for bladder cancer. However, the level 1 evidence for cisplatin, as opposed to another drug as the backbone of systemic chemotherapy, rests on a single randomized trial [3]. The UK Medical Research Council trial randomized 214 patients with advanced bladder cancer to cisplatin, methotrexate, and vinblastine (CMV), or to MV (Table 32.1). One-year survival was 16% for MV compared with 29% for CMV; median survival was 7 months for MV versus 14 months for CMV. Progression-free survival (PFS) was significantly improved in patients receiving CMV ($p = 0.0001$). There was significantly more toxicity associated with CMV than MV. There were five (4%) treatment-related deaths in patients receiving CMV but none in those treated with MV. In addition, 16 (15%) patients were unable to complete treatment with CMV owing to toxicity and three patients refused to continue. Only one patient refused to continue MV. There was also significantly more neutropenic fever requiring IV antibiotics, 11 CMV vs. 4 MV. Long-term neurological toxicity was associated with CMV.

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Table 32.1 Comparison of MV with and without cisplatin.

Study	No. of patients	Comparators	Response rate	Survival	Grade 3–4 toxicity
Mead et al. [3]	214	q21 Days 1 and 8: (MV) methotrexate 30 mg/m^2 + vinblastine 4 mg/m^2 ± Day 2 (C): cisplatin 70 mg/m^2	46% RR CMV vs. 19% RR MV	52% RRR in symptomatic progression or death with CMV 32% RRR in death with CMV	Leucopenia and thrombocytopenia: 5 CMV vs. 0 MV Neutropenic fever: 11 CMV vs. 2 MV. (4% deaths CMV vs. 0% MV)

RR, response rate; RRR, reduction relative risk.

Clinical implications

We recommend the use of cisplatin as the basis for systemic chemotherapy (strong recommendation based on moderate-quality evidence). This recommendation is based on a single, relatively small and therefore imprecise, randomized trial.

Clinical question 2

In patients with chemotherapy-naive metastatic transitional cell carcinoma, is cisplatin alone as effective as cisplatin in combination?

The evidence

Five randomized trials have compared cisplatin alone with cisplatin in combination chemotherapy [4–8]. Two of these trials compared cisplatin with doublet chemotherapy, using either methotrexate (108 patients) [4] or cyclophosphamide (131 patients) [5]. Neither demonstrated an improvement in response rate. The addition of methotrexate also failed to show a statistically significant improvement in overall survival.

Similarly, cisplatin alone was compared with cisplatin plus adriamycin and cyclophosphamide in two studies, enrolling 87 and 135 patients respectively [6, 7]. There was no significant difference in response rate or survival in either study. In both studies, the combination regime was significantly more toxic. For example, Khandekar et al. [7] reported that grade 3–4 hematological toxicity was 34% in the combination arm versus 0% with cisplatin alone.

Loehrer et al. compared single-agent cisplatin with the combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) in a randomized trial of 269 patients [8]. There was a significant improvement in response rates (39% MVAC vs. 12.1% for cisplatin, $p<0.001$). Median survival was also significantly improved with MVAC (12.5 vs. 8.2 months, $p=0.0002$). However, this was at the expense of increased toxicity in terms of hematological toxicity, mucositis, and nausea/vomiting [8].

Clinical implications

We recommend the use of cisplatin in combination using MVAC in preference to cisplatin as a single agent in the palliative treatment of patients with metastatic bladder cancer (strong recommendation based on moderate-quality evidence).

We recommend against cisplatin as a doublet in combination with methotrexate or cyclophosphamide, or as a triplet in combination with doxorubicin and cyclophosphamide (strong recommendation based on moderate-quality evidence). This recommendation assumes that patients place a high value on improving survival and a relatively low value on treatment-related toxicity. This recommendation does not imply that MVAC is necessarily the combination regime of choice, and its comparison with other regimes is discussed next.

Clinical question 3

In patients with chemotherapy-naive metastatic bladder cancer, how do methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) compare with other combination chemotherapy regimes?

The evidence

Although it is almost a decade since the last publication on this topic, there has been little progress in this area. The evidence consists of four randomized trials, which are summarized in Table 32.2:

1 Logothetis et al. compared MVAC with cisplatin, cyclophosphamide, and adriamycin (CisCA) and demonstrated improved response and median survival in the MVAC-treated patients [9].

2 Siefke-Radtke et al. compared MVAC with fluorouracil, interferon alpha, and cisplatin (FAP), and showed no significant differences in toxicity, response rates, or survival between the two regimes [10].

3 Bamias et al. conducted a prospective Phase III trial comparing dose-dense (DD) MVAC with DD gemcitabine and cisplatin (DD-GC) [11]. A total of 133 patients from 12 Greek centers were randomly assigned to either DD-MVAC or DD-GC. PFS (median 8.5 versus 7.8 months) and overall survival (OS) (19 versus 18 months) were similar in the two arms. However, DD-GC was better tolerated, with significantly more patients receiving six cycles. In addition, there were

Table 32.2 Randomized trials comparing MVAC with other combination regimes.

Study	No. of patients	Comparator	Response rates	Survival	Grade 3–4 hematological toxicity
Logothetis et al. [9]	110	CisCA	65% MVAC vs. 46% CisCA, $p<0.05$	48.34 months (MVAC) vs. 40.4 months (CisCA), $p=0.0003$	5% MVAC vs. 14% CisCA, NS
Siefke-Radtke et al. [10]	172	FAP	59% MVAC vs. 42% FAP, NS	12.5 months both arms, NS	11.6% MVAC vs. 12% FAP
Bamias et al. [11] (DD-MVAC)	130	GC Dose dense		19 months MVAC vs. 18 months GC, NS	8% neutropenic sepsis MVAC vs. 0% GC
von der Maase et al. [12, 13]	405	GC	46% MVAC vs. 49% GC, NS	15.2 months MVAC, 14 months GC, NS	12% neutropenic sepsis MVAC vs. 1% GC, $p<0.001$

NS, not significant.

no cases of neutropenic fever or toxic deaths, as opposed to 5 and 3%, respectively, with DD-MVAC.

4 von der Maase et al. compared MVAC with gemcitabine and cisplatin (GC) and, with 405 patients TCC randomized, it is the largest reported trial [12, 13]. There was no statistical difference between overall survival or response rates. However, toxicity was increased in the MVAC arm, with a death rate of 3% compared with 1% in the GC arm. There was also increased neutropenia (82 versus 71%) and neutropenic fever (12 versus 1%).

Clinical implications

In patients with chemotherapy-naive metastatic bladder cancer, we recommend GC over MVAC based on equivalence in terms of response rates and survival, but improved tolerability, with fewer toxic deaths or neutropenic fever (strong recommendation based on high-quality evidence). However, these studies do not address the question of whether MVAC at standard doses is better tolerated with growth factor support. The comparison of DD-MVAC with DD-GC is based on a small number of patients, and is therefore subject to imprecision.

We recommend against the use of other regimens such as CisCA (strong recommendation against based on moderate-quality evidence)

Clinical question 4

In patients with chemotherapy-naive metastatic bladder cancer, how does dose-dense MVAC compare with standard dose MVAC?

The evidence

The standard dose regime of MVAC was compared with high-dose intensity (HD) MVAC plus granulocyte colony-stimulating factor (HD-MVAC) in an international randomized EORTC Phase III study [14]. A total of 263 patients with advanced bladder cancer were randomized. An objective response (complete and partial) was seen in 72% of patients on HD-MVAC compared with 58% on the standard MVAC. The median time to progression was significantly improved with the HD-MVAC regime (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.56–0.95, $p=0.017$). At a median follow-up of 7.3 years, the median overall survival was 15.1 and 14.9 months for the HD-MVAC and MVAC regimes, respectively. Five year survival rates were 21.8% (95% CI 18.4–34.0%) and 13.5% (95% CI 7.4–19.6%) for HD-MVAC and MVAC, respectively. There was one toxic death in both arms of the study. Grade 4 leukopenia was worse with MVAC (16 versus 8%), as was neutropenic fever (26 versus 10%), although grade 4 thrombocytopenia was more evident with HD-MAVAC (6 versus 11%).

Clinical implications

In patients with chemotherapy-naive metastatic bladder cancer, we suggest DD-MVAC over standard dose MVAC (conditional recommendation based on low-quality evidence). This is based on indirect evidence for improved survival (based on time to disease progression) and assumes that patients place a relatively high value on improving oncological outcomes and a relatively low value on the adverse effects of treatment.

Clinical question 5

In patients with chemotherapy-naive bladder, how do regimens that substitute carboplatin for cisplatin compare with cisplatin-based regimens?

The evidence

One systematic review has been published, which identified four randomized Phase II studies, all of which, although heterogeneous in their design and interventions, compared cisplatin with carboplatin in their respective regimes [15]. In this review, a meta-analysis was conducted, which concluded that cisplatin increased the likelihood of OS and complete response (CR) compared with carboplatin. However, the impact of improved response rates could not be

related to survival endpoints. A randomized Phase II/III trial has been reported, which compared gemcitabine plus carboplatin versus methotrexate, vinblastine, and carboplatin (MCAVI) in 238 elderly, unfit patients with advanced urothelial cancer [16]. There were no significant differences in efficacy between the two regimes, but the MCAVI regime was more toxic. There have been no randomized controlled trials that have directly compared the regime of cisplatin and gemcitabine with carboplatin and gemcitabine.

Clinical implications

In patients undergoing primary chemotherapy for metastatic bladder cancer, we suggest against substituting carboplatin for cisplatin (conditional recommendation against based on low-quality evidence).

In patients unable to receive cisplatin-based chemotherapy, we recommend the combination of gemcitabine and carboplatin (strong recommendation based on low-quality evidence).

Clinical question 6

In patients with chemotherapy-naive metastatic bladder cancer, how do cisplatin-based regimens that include taxanes compare with cisplatin-based chemotherapy without taxanes?

The evidence

A systematic review has reported outcomes with taxane-containing chemotherapy regimes [17]. In this review, 32 studies were included, but only two randomized trials were found; one was a Phase III trial, the other a randomized Phase II trial. Three other randomized trials were included in the review, but they were not investigating taxane-containing regimens, and are all included in Table 32.2 [17].

The Phase III randomized study compared paclitaxel, cisplatin, and gemcitabine (PCG) with gemcitabine and cisplatin (GC) [18]. A total of 626 patients were randomly treated with GC or PCG. There was a 3.1-month improvement in OS with PCG but this did not reach statistical significance. However, the overall response rate was increased with PCG compared with GC (55.5 versus 43.6%, $p=0.0031$). The addition of paclitaxel resulted in higher levels of grade 4 neutropenia (35.8 versus 20%, $p<0.001$) and febrile neutropenia (13.2 versus 4.3%, $p<0.001$).

The randomized Phase II study enrolled 85 patients, and compared GC with GC plus paclitaxel (GCP). Response rates were 44% for GC and 43% for GCP; median survival was 49 vs. 61 weeks for GC and GCP, respectively. Grade 3 neutropenia was seen in 35 vs. 49% for GC vs. GCP, respectively, $p=0.05$ [19].

A further Phase III trial compared cisplatin plus the taxane larotaxel (LC) or cisplatin plus gemcitabine (GC), but closed prematurely [20]. In this trial, 337 patients were randomized. Overall response rates were 31% for LC compared with 43% for GC. Median overall survival was 13 months for LC versus 14.3 months for GC, and PFS was 5.6 months for LC and 7.6 months for GC. There was more sensory neuropathy with LC.

Clinical implications

In patients undergoing first-line chemotherapy for metastatic bladder cancer, we recommend against the addition of taxanes based on the lack of a survival benefit and increased toxicity (strong recommendation against based on high-quality evidence).

Clinical question 7

In patients with relapsing or progressing metastatic bladder cancer following first-line chemotherapy, how does second-line chemotherapy compare with best supportive care?

The evidence

There is no standard second-line treatment for metastatic bladder cancer. However, docetaxel has been accepted as standard in some Phase III trials. A recent meta-analysis looked at the use of single-agent taxane compared with taxane-containing combination chemotherapy [21]. It concluded that there was improved OS in favor of combination chemotherapy. A second meta-analysis from (2015). looked at second-line single-agent versus doublet chemotherapy as salvage treatment [22] and concluded that there was an improvement in PFS but not OS with combined chemotherapy. Both of these meta-analyses used small Phase II data using different chemotherapy combinations, such as the addition of cyclophosphamide or gemcitabine to a taxane, or in some cases triplet regimens, such as the addition of cisplatin and ifosfamide (Table 32.3).

A single Phase III trial has compared vinflunine with best supportive care (BSC) [23]. A total of 370 patients were randomized in a 2 : 1 ratio. This study reported a statistically significant improvement of 2.6 months in OS with vinflunine, in the "eligible" population (excluding patients with major protocol violations), and vinflunine therapy was associated with survival in a multivariate analysis. However in the intention-to-treat analysis, the survival advantage did not reach significance.

Albers et al. randomized 102 patients to a prolonged versus a short-term schedule of gemcitabine and paclitaxel (GP) in the second-line setting [24]. In this study, the prolonged regime was judged not to be feasible, but a response rate of 40% was noted. However, BSC was not included as a comparator.

Clinical implications

We suggest that patients with relapsing or progressing metastatic bladder cancer following first-line chemotherapy

Table 32.3 Randomized trials and systematic reviews of second-line chemotherapy for relapsing or progressing metastatic bladder cancer.

Study	No. of patients	Comparators	Response rate	Survival	Grade 3–4 toxicity
Sonpavde et al. [21]	370 from 8 trials	Taxane single agent or in combination with at least one other agent after prior platinum exposure	No data	Median OS 6 months (single agent) vs. 9 months (combination) ($p<0.001$)	Hematological toxicity increased in combination group, 80.9 vs. 14.7% ($p<0.001$)
Raggi et al. [22]	(1910). from 146 arms of trials	Meta-analysis (single vs. combination chemotherapy)	RR with single agent was 14.2% vs. 31.9% with combination chemotherapy	Median OS was 6.98 vs. 8.50 months for single and combination chemotherapy, respectively	Increased incidence of leukopenia and thrombocytopenia in combined chemotherapy than in single-agent group ($p<0.001$ and $p=0.024$, respectively) Similar frequencies of anemia, nausea, vomiting, and diarrhea found in the two groups
Bellmunt et al. [23]	317	Vinfluinine + best supportive care (BSC) vs. BSC alone	ORR was 8.6% in the vinfluinine group vs. 0% in the BSC group	6.9 months in the combination group vs. 4.3 months in the BSC group	Main toxicities for the vinfluinine group: neutropenia (50%), febrile neutropenia (6%), anemia (19%), fatigue (19%), and constipation (16%)
Albers et al. [24]	102	Gemcitabine and paclitaxel (GP) (short term, arm A, and long term, arm B)	RR was 37.5% in arm A and 41.5% in arm B	OS 7.8 months in arm A and 8 months in arm B	Grade 3 anemia was 22.2% in prolonged GP arm vs. 4.4% in short-term GP arm. Grade 4 anemia was 4.4% (long-term arm) vs. 2.2% (short-term arm) In the long-term treatment arm there were two deaths (neutropenic sepsis and pulmonary fibrosis)

RR, response rate; ORR, objective response rate; OS, overall survival.

be treated with vinflunine (conditional recommendation based on low-quality evidence). This recommendation assumes that patients place a high value on potentially improved oncological outcomes.

Clinical question 8

In patients with metastatic bladder cancer, do bone-targeting agents reduce skeletal complications due to bone metastases?

The evidence

The only prospective randomized trial of zoledronic acid (ZA) in bladder cancer was a placebo-controlled, randomized, two-arm study in patients with bone metastases from bladder cancer [25]. All patients had received radiotherapy at baseline to the affected bone(s). Following completion of radiotherapy, patients were randomized 1 week later to ZA or placebo. The study concluded that zoledronic acid reduced the rate and time to first skeletal-related event (SRE) and improved overall survival compared with placebo. Results of this study are summarized in Table 32.4.

In this study, an elevated serum creatinine level was seen in seven patients receiving ZA and five patients on placebo, but no other side effects such as osteonecrosis of the jaw or gastrointestinal effects were experienced by patients in either group.

There is increasing evidence that the RANK (receptor activator of nuclear factor-κB) ligand inhibitor denosumab is superior to ZA and older bisphosphonates in a wide range of tumor types metastasizing to the bone. The evidence for its efficacy in the bladder population is limited by the small number of urothelial cancer patients enrolled in these studies, typically ranging from 1 to 5%. In a large subgroup analysis of genitourinary cancer patients enrolled in Phase III

Table 32.4 Results of randomized trial of zoledronic acid versus placebo in bladder cancer metastatic to the bones.

Endpoint	Findings
Reduced proportion of patients with ≥1 SRE	65 vs. 90%; $p=0.010$
Reduced mean no. of SREs	0.95 vs. 2.05; $p=0.001$
prolonged median time to first SRE	112 vs. 56 days; $p=0.0001$
Reduced risk of developing an SRE	50% (HR=0.413; $p=0.008$)
Reduced bone pain score	2.95 vs. 4.37 units; $p=0.015$

trials of denosumab and ZA and reported in abstract form, bladder and transitional cancers comprised only 72/2128 (3.3% of the total number analyzed) [26]. The results were reported for the entire population. Denosumab significantly delayed the time to first on-study SRE by 4.0 months compared with ZA (20.7 versus 16.7 months) in patients with genitourinary cancers. Denosumab also significantly delayed the time to first and subsequent on-study SRE. Time to disease progression and overall survival were similar in the two treatment groups.

Adverse events (AEs) and serious AEs were reported in similar proportions of patients receiving ZA and denosumab (AEs, 96.9% denosumab, 96.8% ZA; serious AEs, 62.8% denosumab, 60.2% ZA); hypocalcemia was reported in 12.9% of denosumab patients and 6.2% of ZA patients. There was no difference between the groups for incidence of osteonecrosis of the jaw (2.2% for denosumab vs. 1.6% for ZA).

Denosumab has been evaluated in systematic reviews and network meta-analyses and shown to be superior to ZA, pamidronate, and placebo in reducing first and subsequent SREs in advanced cancer and bone metastasis. Ideally, the improved SRE outcomes with denosumab would be interpreted alongside pain and quality of life data. Unfortunately, the lack of such published data means that improved SRE rates could not be interpreted in relation to pain and quality of life in bladder cancer patients [27]. In patients with tumors excluding breast and prostate cancer, the rate of renal impairment was higher with ZA (4.5 vs. 2.1%), but hypocalcemia occurred more frequently with denosumab (2.5 vs. 0.9%).

There are sparse data in our population of interest. Most randomized evidence is in breast, prostate, and lung cancer and in myeloma. *Post hoc* analyses of urological cancers, published predominantly in abstract form, show that these patients gain benefit from both bisphosphonates and RANK ligand inhibitors, but these comprise exceedingly small number of bladder cancer patients. There is, however, level one evidence from a single randomized controlled trial of 40 patients with bladder cancer that shows ZA to be superior to placebo in reducing SREs; this study showed an improvement in overall survival. This result is not generalizable to the population owing to the small numbers, and baseline demographics differing from many of the larger clinical trials in that all patients enrolled had to have had palliative radiotherapy to the bone and most patients did not receive concomitant chemotherapy. Based on these issues, the study provides only low-quality evidence.

Clinical implications

In patients with metastatic bladder cancer to the bones, we suggest against the routine use of bone-directed therapy (conditional recommendation against based on low-quality evidence).

Implications for practice

There is strong evidence for the use of palliative chemotherapy in patients with metastatic bladder cancer. MVAC and GC appear to have equivalent efficacy in terms of overall survival, although GC is better tolerated. GC should therefore be considered the standard first-line option in suitable patients. Many patients with bladder cancer are unsuitable for cisplatin chemotherapy owing to either poor performance status or poor renal function. Although carboplatin appears less efficacious than cisplatin, it is a reasonable alternative in this population of patients.

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33 CHAPTER 33

Treatment of localized kidney cancer

Luke T. Lavallée[1,2], Frédérick Pouliot[3], and Rodney H. Breau[1,2]

[1] *Division of Urology, Department of Surgery, The Ottawa Hospital/University of Ottawa, Ottawa, ON, Canada*

[2] *The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada*

[3] *Centre de Recherche sur le Cancer, Université Laval, Ville de Québec, QB, Canada*

Introduction

An estimated 61 560 new cases and 14 080 deaths were expected to be attributed to cancers of the kidney and renal pelvis in the United States in 2015 [1]. Curative treatment of renal cell carcinoma is primarily surgical via partial nephrectomy (removal of the tumor with preservation of the kidney) or total/radical nephrectomy (removal of the entire tumor-bearing kidney). In this chapter, we address the role of ancillary surgical procedures during kidney cancer surgery, namely the benefits and harms associated with lymphadenectomy and adrenalectomy.

Clinical question 1

In patients with a renal tumor who are receiving nephrectomy, should retroperitoneal lymphadenectomy also be performed?

Literature search

The risk of lymph node metastases at the time of nephrectomy for renal cell carcinoma is associated with tumor stage and subtype [2–5]. Lymphadenectomy during surgery improves stage determination by allowing histological examination of locoregional lymph nodes [3]. However, lymphadenectomy requires longer operative times and can result in patient complications. The impact of lymphadenectomy on perioperative complications, cancer recurrence, cancer-related death, and death from any cause is of critical importance to patients. We evaluated the literature examining the effect of lymphadenectomy at the time of nephrectomy for renal cell carcinoma on death and morbidity. We stratified our approach by clinical stage, most notably the presence or absence of clinical adenopathy.

The decision whether or not to perform a lymphadenectomy at the time of nephrectomy should be based on the therapeutic benefit, the prognostic impact, and the harms associated with lymphadenectomy. Recent population-based studies show that the rate of lymphadenectomy at the time of nephrectomy is decreasing overall [6]. However, studies from large academic centers have reported increased use of lymphadenectomy during this time period [7]. These changes may reflect a stage migration of kidney tumors, referral bias to academic centers, or surgeon bias.

The pattern of spread of renal cell carcinoma is not predictable and may be lymphatic or hematological. We have not reviewed the evidence examining templates for lymphadenectomy, but several studies suggest that the extent of lymphadenectomy is important for accurate staging and possibly for survival [4, 8–11]. One study reported that a minimum of 15 lymph nodes needed to be removed to achieve proper staging in 90% of patients [4].

The risk of pathologically malignant lymph nodes has been estimated by tumor stage in several studies (Table 33.1) [5]. These studies may overestimate risk because of selection bias or underestimate risk if the lymphadenectomy was not complete.

A review of the literature identified three systematic reviews published since 2012 examining the effect of lymphadenectomy in patients without clinical adenopathy (Table 33.2) [13–15]. No systematic review was identified examining the benefit of lymphadenectomy in patients with clinical adenopathy. We updated the systematic reviews performed by these authors on 2 October 2015. The previous reviews did not report their search strategies, so we performed an expansive search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials without language restrictions from 1 January 2012 to 2 October 2015.

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The search terms used were "kidney cancer," "nephrectomy," and "lymph node dissection." Review articles, case reports, and duplicates were excluded. The search yielded 111 reports from MEDLINE, 250 from EMBASE, and two from Cochrane. After removing duplicates, 284 reports remained. One author (L.T.L.) screened titles and abstracts of reports and identified 34 potentially relevant articles published since 2012. Full review of these articles identified three retrospective studies that directly compared patients receiving nephrectomy with or without lymphadenectomy [4, 16, 17]. No randomized or prospective studies were identified. Each of these studies had a high risk of bias.

The evidence

We examined the literature for patients with and without clinical adenopathy to determine if and in whom a lymphadenectomy should be performed. The definition of clinical adenopathy varies between studies, but lymph nodes larger than 1 cm in size in the pera-aortic, inter-aortocaval, and pera-caval landing zones are generally considered positive. The risk of malignancy varies by node size. The accuracy of preoperative staging with cross-sectional imaging varies by the prevalence of the disease in the population and the cut-off used for considering a lymph node clinically positive. One study reported sensitivity, specificity, and positive and negative predictive values for preoperative computed tomography of 82, 71, 56, and 90%, respectively [18]. The modest positive predictive value (56%) indicates that clinically enlarged nodes are not malignant almost 50% of the time. The negative predictive value of 90% indicates that few patients without clinical adenopathy will harbor malignancy. These results are consistent with other studies [2, 13, 19, 20]. For example, in the European Organization for Research and Treatment of Cancer (EORTC) trial, 6.3% of clinical T3 patients had positive lymph nodes in the lymphadenectomy arm [2, 13].

Table 33.1 Risk of pathologically malignant lymph nodes by tumor stage [3,5,10,12).

Variable	Risk of malignancy in lymph nodes (%)
pT1	1.1–5.1
pT2	3.6–11.4
pT3–4	12.3–37.1

Survival outcomes in patients receiving lymphadenectomy versus no lymphadenectomy at the time of nephrectomy

Patients with clinical T1–2N0 tumors

One systematic review, by MacLennan et al., published in 2012 examined oncological outcomes for patient with clinical T1–2 renal cell carcinoma and no evidence of clinical adenopathy on preoperative staging [15]. The authors performed a thorough review of existing literature including at a minimum MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and Web of Science without language restrictions. They included evidence from randomized and nonrandomized studies. Nonrandomized studies could be retrospective or prospective and had to include a comparator group. One randomized study was available for review pertaining to the topic of lymphadenectomy at the time or nephrectomy [2]. A formal meta-analysis was not performed because the included studies were heterogeneous, had a high risk of bias, and were deemed to be low-quality evidence.

MacLennan et al. concluded that there was no evidence to support lymphadenectomy for patients with cT1–2 renal tumors without clinical adenopathy. This conclusion was based predominantly on data from the EORTC study by Blom et al. [2]. The EORTC trial reported a hazard ratio (HR) of 1.10 (95% confidence interval [CI] 0.81–1.47) for disease progression or death, indicating no difference between interventions. It is noteworthy that only 4% of the overall patients (cT1–4) in the lymphadenectomy arm of the EORTC

Table 33.2 Published systematic reviews of nephrectomy with or without lymphadenectomy in patients without clinical adenopathy.

Study	Tumor characteristics	Outcome assessed	*p*-Value or risk measurement for survival outcomes (Nx vs. Nx+Ax)	Conclusion
Bekema et al. [13]	T3–4	5-year OS	HR 0.81, 95% CI 0.54–1.20 from EORTC subgroup	No conclusion owing to limitations in data
MacLennan et al. [15]	T1–2	5-year OS	HR 1.10, 95% CI 0.81–1.47 from EORTC subgroup	No conclusion owing to limitations in data
MacLennan et al. [14]	T1–2	Perioperative and quality of life	Not provided.	Lymphadenectomy does not significantly increase morbidity

Ax, adrenalectomy; Nx, nephrectomy; CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; OS, overall survival.

trial had pathological lymph node-positive disease, which indicates that cT1–2 patients randomized in this study were at very low risk of nodal metastases. The low prevalence of lymph node disease in this population made it unlikely that a difference would be found between intervention arms. Furthermore, surgeons performing lymphadenectomy in this trial could not be blinded and the lymph node dissection was not standardized. Therefore, it is likely that the extent of lymph node dissection was biased by the surgeon's assessment of the primary tumor risk.

Patients with clinical T3–4N0 tumors

Bekema et al. performed a systematic review focused on patients with locally advanced (cT3–4N0M0) renal tumors [13]. This review used data from the same randomized EORTC study to perform a subgroup analysis of patients with clinical T3–4 disease to examine outcomes between intervention arms. They reported no difference in overall survival between radical nephrectomy with lymphadenectomy versus radical nephrectomy alone (HR 0.81, 95% CI 0.54–1.20). However a 15% non-statistically significant survival advantage in favor of the lymphadenectomy group was evident at 5 years. This study was limited because it was a subgroup analysis and thus not adequately powered to answer this question. Data from retrospective studies published since 2012 are consistent with these results, showing small advantages to lymph node dissection in locally advanced tumors [4, 16].

Patients with clinical adenopathy (clinical T1–4N+)

No systematic reviews or randomized studies of radical nephrectomy with or without lymphadenectomy are available for patients with clinical adenopathy on preoperative radiographic imaging. Studies of historical cohorts indicate that a proportion of patients with pathologically positive lymph nodes can have long-term survival. In one cohort of 40 patients (median tumor size 11 cm, 80% with stage T3a or greater), 30% of patients had no evidence of disease at a median 17.7 months' follow-up [21]. However, whether survival was impacted by the lymphadenectomy remains unclear. One report of 1983 patients treated with partial or radical nephrectomy at one institution indicates that a more extensive lymph node dissection in patients with either stage pT2a–4, sarcomatoid features, or tumors >10 cm is associated with improved cancer-specific survival [4]. These findings are supported by a population-based study that reported a 10% absolute improvement in cancer-specific survival at 5 years for every 10 lymph nodes removed in patients with at least one positive node [10].

Lymphadenectomy does provide prognostic information. In the study by Canfield et al., more than one positive lymph node was independently predictive of recurrence-free (HR 2.33, 95% CI 1.06–7.61) and overall survival (HR 9.33, 95% CI 1.85–47.09) [21]. Blute et al. also reported that node involvement increased the risk of death by a factor of 8 (relative risk [RR] 7.87, 95% CI 5.98–10.36) [3]. They reported 1-, 5-, and 10-year cancer-specific survival rates for pN0/pNX of 95.5, 82.1, and 72.5%, respectively, compared with 52.2, 20.9, and 11.4%, respectively, for pN1/pN2 patients [3].

Perioperative morbidity and quality of life

The systematic reviews by Bekema et al. and McLennan et al. each examined quality of life and morbidity outcomes [13, 14]. Each relied on data from the sole randomized study by Blom et al. [2]. In the EORTC 30881 trial, perioperative morbidity was similar in the nephrectomy and nephrectomy plus lymphadenectomy groups overall and in the cT3 subgroup (Table 33.3) [2, 13]. Overall, surgical morbidity was low, with 93 events noted in 362 patients randomized to receive nephrectomy with lymphadenectomy compared with 82 events in 370 patients randomized to receive nephrectomy without lymphadenectomy. The lymph node dissection in this study was not standardized and therefore the extent of dissection is not known. Based on the low yield of lymph node metastases detected in the trial, it is possible that the retroperitoneal lymph node dissection was not extensive.

Table 33.3 Complications of surgery in patients receiving nephrectomy without and with lymphadenectomy in the EORTC 30881 trial [2, 13].

Complication	Nephrectomy without lymphadenectomy: No. (%)		Nephrectomy with lymphadenectomy: No. (%)	
	Overall	cT3 subgroup	Overall	cT3 subgroup
Bleeding >1 L	24 (6.5)	14 (13.9)	34 (9.4)	18 (16.1)
Pleural damage	19 (5.1)	7 (7)	16 (4.4)	6 (5.4)
Infection	21 (5.7)	6 (5.4)	19 (5.2)	8 (7.9)
Bowel damage	5 (1.4)	3 (3)	2 (0.6)	0 (0)
Embolism	4 (1.1)	3 (3)	8 (2.2)	3 (2.7)
Lymph fluid drainage	9 (2.4)	3 (3)	14 (3.9)	3 (2.7)

Clinical implications

Patients without clinical adenopathy

Clinical stage T1–2N0

In patients with clinical stage T1–2 renal tumors without clinical adenopathy, we suggest against routine regional lymphadenectomy (conditional recommendation against based on moderate-quality evidence).

Patients with clinical T1–2 tumors have a low risk of metastases to the lymph nodes (Table 33.1) and a randomized trial has demonstrated no benefit in this population of patients [2]. Given that there is a question about the extent of lymphadenectomy performed in the single randomized trial, we believe that some uncertainty still exists and the evidence strength has been downgraded given this limitation.

Clinical stage T3–4N0

In patients with clinical stage T3–4 renal tumors without clinical adenopathy, we suggest regional lymphadenectomy (conditional recommendation based on low-quality evidence).

Many patients with clinical T3–4 disease without adenopathy do not have lymph node metastases (Table 33.1) and therefore will not benefit from, and may be harmed by, routine lymphadenectomy. However, several risk factors have been proposed to help identify higher risk patients, including performance status, patient symptoms, elevated lactate dehydrogenase, tumor necrosis, sarcomatoid features, high nuclear grade, and tumor size [3, 20, 22]. The available data suggest that some benefit may be gained by resecting lymph nodes in high-risk patients [13]. Given the uncertainty in patients at high risk for occult lymph node metastases, the surgeon and patient should discuss the potential harms and benefits of lymphadenectomy prior to surgery.

Patients with clinical adenopathy (clinical T1–4N+)

In patients with renal tumors and clinical adenopathy, we suggest regional lymphadenectomy (conditional recommendation based on very low-quality evidence).

The potential benefit of lymphadenectomy must be placed in the context of a disease that has no curative treatment options for patients with lymphatic spread other than surgery. Some patients with clinical adenopathy due to tumor metastases will be cured following nephrectomy and lymphadenectomy and all patients will receive important prognostic information to guide future therapy based on their lymph node pathological evaluation. However, lymphadenectomy exposes patients to potential harm and therefore we believe that patients should be informed of the potential benefits and risks of lymphadenectomy prior to surgery.

Clinical question 2

In patients with a renal tumor who are receiving nephrectomy, should ipsilateral adrenalectomy also be performed?

Literature search

Routine ipsilateral adrenalectomy has been included during radical nephrectomy since the procedure was first described by Robson et al. in 1969 [23]. In recent years, this dogma has been questioned, in part because the prevalence of ipsilateral adrenal involvement has decreased owing to earlier tumor detection. Despite this, population-based studies reveal that ipsilateral adrenalectomy continues to be performed in a high proportion of patients [24]. We reviewed the literature evaluating adrenalectomy at the time of nephrectomy. We examined survival and morbidity. Renal cell carcinoma may directly invade the adrenal gland or metastasize to it. Invasion has been reported in 1–10% of patients, depending on the population examined [25–27]. Numerous studies have shown an increased risk of adrenal involvement when tumors are large, are of advanced stage, are located in the upper renal pole, or when there are multifocal lesions. Indeed, tumor size and stage are associated with an increased use of ipsilateral adrenalectomy at the time of nephrectomy [7, 24, 28, 29].

Risk of ipsilateral adrenal involvement in patients with renal tumors

Su et al. calculated diagnostic test characteristics for computed tomography or magnetic resonance imaging to predict adrenal involvement at the time of nephrectomy in high-risk patients [30]. The high-risk patients they examined had a 12.3% incidence of adrenal involvement [30]. They identified 11 studies with 1757 patients and used individual patient data to populate a 2×2 table to calculate the sensitivity, specificity, positive predictive value, and negative predictive value of preoperative imaging (Table 33.4).

The positive predictive value of 71.6% indicates that a fair number of patients will have suspicion for adrenal involvement when in fact they do not have it pathologically. The high negative predictive value (98.5%) indicates that in cases where preoperative imaging does not suggest adrenal involvement, there is a very low probability (1.5%) that it is present. These findings are consistent with a recent publication that reported a sensitivity (100%), specificity (94.3%), and negative predictive value (100%) of preoperative imaging in a single-institution cohort [29].

Table 33.4 Diagnostic test characteristics of preoperative imaging for predicting adrenal involvement at the time of radical nephrectomy from Su et al.'s meta-analysis [30].

Test characteristic	Measurement (95% CI)
Sensitivity (%)	92 (84–97)
Specificity (%)	95 (93–96)
Positive predictive value (%)	71.6 (62.4–77.3)
Negative predictive value (%)	98.5 (97.5–99.6)

A review of existing literature identified five systematic reviews published since 2009 examining the role of ipsilateral adrenalectomy compared with no adrenalectomy in patients receiving nephrectomy (Table 33.5) [13–15, 27, 30]. We updated the systematic reviews on 2 October 2 2015. The previous reviews did not all report their search strategies, so we performed an expansive search. We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials without language restrictions from 1 January 2012 to 2 October 2015. The search terms used were "nephrectomy" and "adrenalectomy." Review articles, case reports, and duplicates were excluded. The search yielded 109 reports from MEDLINE, 116 from EMBASE, and two from Cochrane. After duplicate reports had been removed, a total of 223 reports remained. One author (L.T.L.) screened titles and abstracts of reports and identified 15 potentially relevant articles published since the 2012. Full review of these articles identified five duplicate publications (identified in abstract and full manuscript format) and one article that was present only in abstract form, and these were not examined further.

The evidence

Survival of patients receiving nephrectomy versus nephrectomy and ipsilateral adrenalectomy

Four systematic reviews evaluated survival in patients with or without ipsilateral adrenalectomy. The reviews used variable inclusion criteria and methods, hence the studies identified in each review were different. In all reviews, no randomized trials were identified and all of the evidence is based on cohort studies. A summary of findings is presented in Table 33.5.

In our updated literature search, no randomized controlled studies were identified. Five single-/multi-institutional cohort studies and four population-based cohort studies addressing the role of ipsilateral adrenalectomy during nephrectomy were identified [7, 24, 28, 29, 31–35]. All studies were historic patient cohorts. Two studies published since 2012 compared overall or cancer-specific survival in patients receiving nephrectomy versus nephrectomy and adrenalectomy [32, 33]. In each of the more recent publications, overall survival and cancer-specific survival slightly favored the adrenal-sparing group, although not all comparisons were statistically significant. Overall, based on the available data, no survival benefit of routine adrenalectomy has been observed.

Morbidity of ipsilateral adrenalectomy

Three systematic reviews evaluated perioperative outcomes and quality of life of patients receiving nephrectomy with adrenalectomy compared with those receiving nephrectomy alone [13, 14, 27]. Unfortunately, limited information was available to review. Most patients are not harmed in the short term by the addition of ipsilateral adrenalectomy [36]. Long-term effects of ipsilateral adrenalectomy have not

Table 33.5 Published systematic reviews of adrenalectomy versus no adrenalectomy at the time of nephrectomy.

Study	Tumor characteristics	Outcome assessed	*p*-Value or risk measurement for survival outcomes (Nx vs. Nx+Ax)	Conclusion
Bekema et al. [13]	T3–4	Oncological, morbidity, quality of life	None provided	No conclusion owing to limitations in data
MacLennan et al. [15][a]	T1–2	5-year OS 10-year OS	85% vs. 82% ($p=0.56$) 68% vs. 72.4% (*p*-value not reported)	No evidence to support routine removal of ipsilateral adrenal gland
MacLennan et al. [14]	T1–2	Perioperative and quality of life	None provided	No conclusion owing to limitations in data
O'Malley et al. [27]	No restrictions	Incidence, risk factors, morbidity, survival outcomes	Multiple outcomes examined	No evidence to support routine adrenalectomy in patients with normal preoperative imaging Consider removal in select cases with risk factors for adrenal involvement
Su et al. [30]	T1–4	5-year OS 5-year CSS	HR ratio 0.89 (95% CI 0.67–1.19), favors adrenal sparing Odds ratio 1.10 (95% CI 0.84–1.44), favors adrenal sparing	Remove adrenal gland only in cases where preoperative imaging or intraoperative assessment is suspicious

Ax, adrenalectomy; Nx, nephrectomy; CSS, cancer-specific survival; OS, overall survival.
[a] Includes one study [34].

been well studied. The procedure exposes the patient to an increased risk of adrenal insufficiency, especially if a contralateral adrenal metastasis develops, which occurs as frequently as ipsilateral metastasis [25, 37].

Clinical implications

In patients with a renal mass suspicious for renal cell carcinoma and an unremarkable ipsilateral adrenal on cross-sectional imaging, we suggest against ipsilateral adrenalectomy at the time of radical nephrectomy (conditional recommendation based on low-quality evidence).

This recommendation is based on the fact that no survival benefit has been observed in observational studies. However, a small minority of patients may have ipsilateral adrenal involvement that is not detected on preoperative cross-sectional images. Factors associated with adrenal involvement include venous tumor thrombus to the level of the adrenal vein, and large upper pole tumors [27, 30]. In a higher risk patient, the potential benefits and harms of adrenalectomy should be considered.

In patients with a renal mass suspicious for renal cell carcinoma and cross-sectional imaging findings suggestive of ipsilateral invasion or metastases, we recommend ipsilateral adrenalectomy at the time of radical nephrectomy (strong recommendation based on very low-quality evidence).

Although there are no comparative data on the use of adrenalectomy in this setting, we believe that ipsilateral adrenalectomy should be performed. This recommendation is based on the low morbidity of the procedure and on the durable survival observed in cohorts of patients with adrenal tumor extension or synchronous adrenal metastases following complete resection [38]. The potential benefit of adrenalectomy must be placed in context of a disease that has no curative treatment options for patients with unresected disease.

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34 CHAPTER 34

Treatment of metastatic kidney cancer

Przemyslaw W. Twardowski[1] and Robert A. Figlin[2]

[1] *Department of Medical Oncology and Therapeutics Research, City of Hope National Medical Center, Duarte, CA, USA*

[2] *Samuel Oschin Comprehensive Cancer Institute, Cedar Sinai Medical Center, Los Angeles, CA, USA*

Introduction

With 61 000 new cases and 14 000 deaths in the United States every year, kidney cancer represents a major oncological therapeutic challenge [1]. Approximately one-third of patients present with metastases at initial diagnosis and between 20 and 40% relapse after nephrectomy. Several clinical prognostic factors stratify patients with metastatic disease to low-, intermediate-, and high-risk groups with median survival ranging from 43 months in the low-risk, to 22.5 months in the intermediate-, and to 7.8 months in the high-risk groups [2–4] (Table 34.1). Only a small number of patients with metastatic kidney cancer can be cured using existing therapies. Renal cell carcinoma (RCC) is generally resistant to chemotherapy [5, 6]. Owing to a possible immunological influence in well-documented cases of spontaneous regression of renal cell carcinoma metastases, attention has focused, historically, on the possible means of modifying biological response in these patients. In the 1980s and 1990s, immunocytokines interleukin-2 (IL-2) and interferon-alpha (IFN-α) became the standard systemic therapy for metastatic renal cell carcinoma based on documented durable responses in some patients.

A better understanding of signaling pathways and targets important in the development and progression of renal cell carcinoma has resulted in the last decade in a significant expansion of therapeutic options for patients affected with this disease. Sunitinib, sorafenib, bevacizumab ± IFN-α, axitinib, pazopanib, cabozantinib, temsirolimus, and everolimus have improved clinical outcomes in randomized clinical trials by inhibiting the vascular endothelial growth factor (VEGF), mesenchymal epithelial transition (MET), mammalian target of rapamycin (mTOR), and related pathways [7, 8]. The programmed death 1 (PD1) inhibitor nivolumab demonstrated survival improvement in patients who progressed on antiangiogenic therapy [9]. Many other targeted agents and immunotherapies are in clinical development, representing the main focus of clinical research in renal cell carcinoma. The rapidly changing therapeutic landscape of metastatic renal cell carcinoma raises several important questions related to the relevance of debulking nephrectomy, treatment of non-clear cell subsets of RCC, appropriate selection and sequence of available agents, and the role (if any) of adjuvant therapy.

Clinical question 1

In patients with asymptomatic metastatic renal cell carcinoma, does debulking nephrectomy provide a benefit?

Background

Historically, the hypothesis that cytoreductive nephrectomy may play a role in the therapy of metastatic kidney cancer was based on observation of occasional "spontaneous" regressions of metastatic tumors after nephrectomy. Other possible advantages of debulking nephrectomy include prevention of complications during subsequent treatment and improving patient performance status by elimination of the source of additional metastases, hemorrhage, and discomfort. Additional interest in debulking nephrectomy came to light in the context of immunotherapy for metastatic renal cell carcinoma and the hypothesis that persistence of a large primary tumor may generate immunosuppressive cytokines and negate the therapeutic benefits of immunostimulatory agents. Two prospective randomized clinical trials in patients with ECOG performance status of 0–1: the Southwest Oncology Group (SWOG) 8949 trial [10] and European Organization for Research and Treatment of Cancer (EORTC) 30947 trial [11] reported a statistically significant survival

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Table 34.1 Memorial Sloan Kettering Cancer Center (MSKCC) risk factor stratification scale[a].

Factor	Poor prognosis
KPS (Karnofsky Performance Score)	<80 (WHO >1)
Time from diagnosis to treatment	<12 months
Hemoglobin	<low normal range
Lactate dehydrogenase	>1.5 upper limit of normal
Calcium	>10 mg/dL

[a] Good risk, 0 prognostic factors; intermediate risk, 1–2 prognostic factors; poor risk, >2 factors.

advantage for the combination of nephrectomy and IFN-α. Pooled analysis of these two trials demonstrated a median survival of 13.6 months for the combined arm versus 7.8 months for IFN-α alone which represented 31% reduction in the risk of death ($p = 0.002$) in patients treated with nephrectomy and IFN-α [12]. Cytoreductive nephrectomy improved overall survival independently of patient performance status (0 or 1) and the site of metastases.

More recently, the introduction of the VEGF pathway and mTOR inhibitors that exhibit more potent systemic activity against renal cell carcinoma than legacy immunotherapies led, yet again, to the re-emergence of the question of the contribution of debulking nephrectomy to patient outcomes in the era of targeted therapies.

Literature search

Potentially relevant studies were identified by a computerized search, restricted to the English-language literature, of the MEDLINE electronic database (source PubMed, 1966 to July 2015), ASCO abstracts, and GU ASCO abstracts (2010–2015) using relevant text and keywords in combination as follows: "metastatic renal cancer and nephrectomy," "cytoreductive nephrectomy," and "debulking nephrectomy." The reference list of retrieved eligible articles was reviewed to identify additional relevant articles.

The evidence

A recent analysis of International Metastatic Renal Cell Carcinoma Database Consortium suggests that cytoreductive nephrectomy continues to benefit patients in the era of targeted treatments [13]. Before adjusting for prognostic factors, patients who had undergone cytoreductive nephrectomy were found to have a significantly better median overall survival (OS) of 20.6 versus 9.5 months. In addition, even after accounting for prognostic factors, the hazard ratio (HR) for death after nephrectomy was 0.6 (95% confidence interval [CI] 0.52–0.69), and there was a definitive survival benefit across all prognostic groups. Although retrospective, these data suggest that patients continue to derive benefit from cytoreductive nephrectomy in the era of targeted therapies. Two ongoing randomized clinical trials (CARMENA and SURTIME) are attempting to provide a definitive answer to the question of cytoreductive nephrectomy. The CARMENA trial randomizes patients to undergo nephrectomy and sunitinib versus sunitinib alone. SURTIME compares the timing of nephrectomy with patients randomized to receive upfront surgery followed by sunitinib, or three cycles of neoadjuvant sunitinib followed by nephrectomy and resumption of sunitinib.

There are no reported prospective randomized trials addressing this issue, but it is important to stress that most patients (>90%) treated in pivotal trials [14, 15] that established the beneficial effect of VEGF and mTOR therapies in metastatic kidney cancer underwent prior nephrectomy. The quoted retrospective analysis also suggests continued benefit of cytoreductive nephrectomy in patients treated with modern therapies.

Clinical implications

In asymptomatic patients with metastatic renal cell carcinoma, we suggest debulking nephrectomy prior to initiation of targeted therapy (conditional recommendation based on moderate-quality evidence).

Clinical question 2

In patients with metastatic, non-clear cell kidney cancer, how does sunitinib compare with alternative treatment regimens (other VEGF pathway inhibitors, mTOR inhibitors, or chemotherapy)?

Background

The remarkable progress in the management of advanced kidney cancer over the last decade focused primarily on the most common histological type – clear cell renal cell carcinoma (ccRCC), which accounts of about 75% of cases [16]. Less common histological subtypes have been traditionally categorized as "non-clear cell RCC" (nccRCC), although they form a heterogeneous group of tumors and have been underrepresented in drug development efforts. nccRCC includes papillary renal cell carcinoma (pRCC), which is the most common nccRCC and accounts for approximately15% of RCCs. Chromophobe RCC, although considered more indolent than the other major subtypes, usually presents with a larger tumor size [17]. Despite this, these tumors are generally confined to the kidney (stages I and II). Other rare histologies include collecting duct, medullary, unclassified, and sarcomatoid RCC. Collecting duct RCC (CDRCC) arises in collecting ducts in the renal medulla and biologically overlaps to some extent with urothelial carcinoma. Cisplatin-based chemotherapy is used in the management of CDRCC. The response rate reported in a Phase II study of combination of gemcitabine and platinum was 26%, median PFS 7.1 months, and OS 10.5 months [18].

Medullary RCC (MRC) is an extremely lethal disease with a mean survival of 15 weeks after surgery [19]. It occurs in patients with sickle cell trait or hemoglobin sickle cell disease. Although standard of care for this disease has not been established, based on the overexpression of DNA topoisomerase II, most with advanced MRC receive cytotoxic chemotherapy including topoisomerase II inhibitors such as doxorubicin and etoposide [20].

Sarcomatoid differentiation can be identified across all RCC histologies. It is characterized by the occurrence of spindle-shaped mesenchymal cells. The presence of sarcomatoid features has been reported in up to 29% of collecting duct carcinomas, in 9–11% of clear cell, chromophobe, and unclassified RCCs, and less frequently in papillary RCC (3%). Sarcomatoid differentiation is associated with a more aggressive disease phenotype. The combination of doxorubicin and gemcitabine can result in durable remissions in some patients, but the median duration of response is only 5 months [21].

Literature search

Potentially relevant studies were identified by a computerized search, restricted to the English-language literature, of the MEDLINE electronic database (source PubMed, 1966 to July 2015), ASCO abstracts, and GU ASCO abstracts (2010–2015) using relevant text and keywords in combination as follows: "metastatic non-clear renal cell carcinoma," "papillary kidney cancer," "chromophobe kidney cancer," "collecting duct kidney cancer," "medullary kidney cancer," "sarcomatoid kidney cancer," "VEGF inhibitors," "mTOR inhibitors," and "chemotherapy." The reference list of retrieved eligible articles was reviewed to identify additional relevant articles.

The evidence

VEGF pathway inhibitors

In an expanded access trial of sunitinib in RCC, 588 patients (13% of total) with non-clear cell histologies were identified. A majority of them had prior cytokine therapy. A response rate of 11% and a median PFS of 7.8 months were noted [22]. A small Phase II trial of sunitinib in patients with nccRCC enrolled 26 patients. There were no objective responses and the median PFS was 48 days [23]. The retrospective analysis of sunitinib and sorafenib identified 53 patients with nccRCC who had been treated at five different cancer centers in the USA and France [24]. The response rate was 15% and the median PFS was 7.6 months. A subset of patients (13%) participating in the AVOREN trial that established the role of combination of bevacizumab and interferon-α 2A (IFN-α 2A) in the management of RCC exhibited mixed histology, including the nccRCC component. These patients demonstrated overall inferior PFS compared with patients with pure clear cell histology, but they also benefited from a combination of bevacizumab and IFN-α 2A over IFN-α 2A alone, as demonstrated by increased PFS (5.7 vs. 2.9 months) [25].

mTOR inhibitors

Temsirolimus was evaluated in previously untreated patients with metastatic RCC and unfavorable clinical characteristics [26]. This study included a significant number of patients with non-clear cell histology. In a subset analysis, the median PFS of 7 months was similar to the PFS of the overall group. Another mTOR inhibitor, everolimus, was evaluated in an open-label Phase II study (RAPTOR) that assessed 83 previously untreated patients with diagnosis of papillary RCC confirmed by central pathology review. The median PFS was 7.6 months as determined by local investigators, but only 3.7 months by central radiological review [27]. REACT was an expanded-access clinical trial of everolimus in patients with metastatic RCC who progressed on or were intolerant to VEGF-targeted therapy. A total of 75 patients (5.5%) had non-clear histology. The response rate was 1.3% (versus 1.7% in the overall population) and the median duration on therapy was 12.14 weeks versus 14.0 weeks for the whole group. The authors concluded that everolimus had activity in nccRCC [28].

VEGF versus mTOR inhibitors in nccRCC

A randomized multi-center Phase II trial (ESPN) [29]. evaluated 73 patients with nccRCC and no prior systemic therapy. Patients were randomized to everolimus or sunitinib with allowance for cross-over at progression. Sunitinib demonstrated a numerically superior (although not statistically significant) response rate, PFS, and OS compared with everolimus. In a subset of 49 patients with no sarcomatoid features, the median OS on sunitinib was 33 months versus 10.5 months on everolimus ($p = 0.07$).

Clinical implications

In patients with metastatic papillary or chromophobe renal cell carcinoma, we suggest sunitinib over everolimus (conditional recommendation based in low-quality evidence).

In patients with collecting duct and medullary RCC, we suggest chemotherapy (conditional recommendation based on low-quality evidence)'

In patients with sarcomatoid variant RCC, we suggest chemotherapy or targeted therapies (conditional recommendation based on low-quality evidence).

Clinical question 3

In patients with metastatic kidney cancer who have failed first-line therapy with VEGFR TKI (tyrosine kinase inhibitor), how do mTOR inhibitors compare with vascular endothelial growth factor receptor TKIs and PD1 inhibitors?

Background

VEGFR-TKIs (usually sunitinib or pazopanib) are utilized as first-line therapy in the majority of patients presenting with metastatic RCC. Even though these drugs have

revolutionized the treatment and improved outcomes of patients with advanced kidney cancer, almost all of the patients eventually progress after a median time of about 9–11 months [14, 30]. Most of these patients are candidates for second-line therapy. Second-line treatment with the mTOR inhibitor everolimus became a standard after the report of the RECORD-1 study comparing everolimus with placebo in patients who progressed after one or more prior therapies [31]. For the overall population, the median PFS was 4.6 versus 1.8 months favoring everolimus and in the subset analysis of patients treated with only one prior VEGFR TKI a similar improvement of 5.2 versus 1.8 months was observed. The VEGFR TKI axitinib was compared with another agent in the same class, sorafenib, in patients who progressed after one prior therapy and demonstrated superior PFS (6.7 vs. 4.7 months), establishing it as an option in the second-line therapy of RCC, but no survival improvement was noted in this study [32]. Recently, the results of two pivotal trials with nivolumab (a monoclonal antibody that targets the PD1 immune checkpoint) and cabozantinib (a multi-TKI of VEGF, MET, and AXL) comparing these agents with everolimus were published [8, 9].

Literature search

Potentially relevant studies were identified by a computerized search, restricted to the English-language literature, of the MEDLINE electronic database (source PubMed, 1966 to July 2015), ASCO abstracts, and GU ASCO abstracts (2010–2015) using relevant text and keywords in combination as follows: "metastatic renal cancer and drug sequencing," and "metastatic renal cancer and second- line therapy." The reference list of retrieved eligible articles was reviewed to identify additional relevant articles.

The evidence

The INTORSECT trial was the first randomized clinical trial directly comparing VEGFR TKI and an mTOR inhibitor after progression of prior VEGFR TKI [33]. A total of 512 patients who progressed after sunitinib were randomized to the mTOR inhibitor temsirolimus or VEGFR TKI sorafenib. The primary endpoint of PFS was equivalent (4.3 vs. 3.9 months); the secondary endpoint of OS favored the sorafenib arm over temsirolimus (16.5 vs. 12.3 months). This study suggested a preference for VEGFRI TKI over mTOR inhibitor in the second-line setting but was not conclusive. Two recent publications heralded a new era in the management of RCC patients who progressed after therapy with VEGFR inhibitor. The Phase III Checkmate-025 study demonstrated that nivolumab was superior to everolimus (hazard ratio [HR] 0.73, 95% CI 0.57–0.93; $p<0.002$) in VEGF-refractory renal cancer, with a median OS of 25 months (95% CI 21.8 to not estimable) for nivolumab and 19.6 months (95% CI 17.6–23.1) for everolimus [9]. Patients who had failed multiple lines of VEGF-targeted therapy were included in this trial, making the results broadly applicable. Treatment was well tolerated, with a low incidence of grade 3 or 4 adverse events (19% for nivolumab versus 37% for everolimus). There was no PFS advantage with nivolumab despite the OS advantage, not an unusual experience with immune therapy in other tumor types.

Results of the METEOR trials indicated that cabozantinib delayed progression or death compared with everolimus in VEGF-targeted therapy–refractory disease by 42% (HR 0.58, 95% CI 0.45–0.75) [8]. The median PFS for cabozantinib was 7.4 months (95% CI 5.6–9.1) versus 3.8 months (95% CI 3.7–5.4) for everolimus. The trial recruited 658 patients, although PFS was assessed for the first 375 patients. Interim OS results showed a strong trend favoring cabozantinib (HR 0.67, 95% CI 0.51–0.89; $p=0.005$); however, this was not significant at the predefined levels at this interim stage. A final planned mature OS analysis was expected later in 2016. Grade 3 or 4 adverse events occurred in 68% of patients who received cabozantinib and 58% who received everolimus. Although 60% of patients required a dose reduction of cabozantinib, discontinuation due to toxicity was not significantly different with the two drugs [8].

Clinical implications

In patients with metastatic kidney cancer who have failed first-line therapy with VEGFR TKI, we recommend nivolumab or cabozantinib over everolimus (strong recommendation based on high-quality evidence). Of the two, we suggest nivolumab over cabozantinib as the initial choice owing to its better safety profile (conditional recommendation based on low-quality evidence).

Clinical question 4

In patients with resected, localized, high-risk renal cell carcinoma, how does adjuvant therapy compare with observant management?

Background

The concept of applying agents that exhibit activity in metastatic disease to the adjuvant setting has a long and often successful history in oncology. Endocrine agents, targeted therapies, and chemotherapies have demonstrated substantial benefit when utilized in the adjuvant setting of microscopic disease following resection of the primary tumor in various types of malignancies [34–36]. The same idea has been investigated in kidney cancer, but multiple adjuvant clinical trials completed in the era of older immunotherapy agents failed. It included INF-α [37, 38], interleukin-2 [39], and a combination of he two [40]. Multiple reasons can explain these negative results, with the very modest anticancer activity of IL-2 and INF-α being probably the most important.

Table 34.2 Ongoing adjuvant RCC clinical trials.

Trial	Randomization	Duration of therapy (years)	*n*	End date (month/year)	Primary endpoint	Clear cell required?	Eligibility
ATLAS (Pfizer)	Axitinib vs. placebo	3	592	6/2017	DFS	Yes	pTabN0M0 (grades 3–4) or pT2–4 N1–3 M0 RCC
EVEREST (SWOG)	Everolimus vs. placebo	1	1218	10/2021	DFS	No	pTabN0M0 (grades 3–4) or pT2–4 N1–3 M0 RCC
PROTECT (GSK)	Pazopanib vs. placebo	1	1500	4/2016	DFS	Yes	pT2N0M0 (grades 3–4) or pT3–4N0M0 or pTxN1M0
SORCE (MRC)	Sorafenib vs. placebo	3	1420	12/2012	DFS	No	Intermediate or high-risk RCC Leibovich score 3–11
S-TRAC (Pfizer)	Sunitinib vs. placebo	1	720	11/2015	DFS	Yes	pT2N0 (grades 3–4) or pT3–4N0Mo or Pt#-4N0M0 or pTxN1M0

With the improved effectiveness of novel targeted agents, renewed interest has focused on translating these compounds into adjuvant therapy.

Literature search

Potentially relevant studies were identified by a computerized search, restricted to the English-language literature, of the MEDLINE electronic database (source PubMed, 1966 to July 2015), ASCO abstracts, and GU ASCO abstracts using relevant text and keywords in combination as follows: "renal cancer, "adjuvant therapy," "adjuvant immunotherapy," and "adjuvant targeted therapy." The reference list of retrieved eligible articles was reviewed to identify additional relevant articles.

The evidence

The majority of complete and ongoing clinical trials are examining VEGF-directed agents. In the largest of these studies (ECOG 2805, ASSURE), 1943 patients with ≥ T1bNxM0 disease (Furhman grades 3–4) were randomized followed nephrectomy to sunitinib, sorafenib, or placebo for 1 year. Stratification factors included histology (clear cell versus non-clear cell), performance status (ECOG 0 versus 1–2), and nature of surgery (open versus laparoscopic). Although the study was originally designed to evaluate full doses of sunitinib and sorafenib, patients faced great difficulty in tolerating full doses of the drugs and midway through the trial the dose of sunitinib was reduced to 37.5 mg daily (4 weeks on, 2 weeks off) and of sorafenib to 400 mg daily, with subsequent escalation as tolerated. The primary endpoint of the study was disease-free survival (DFS). The study results were presented at the 2015 GU ASCO Symposium [41] and they were negative. The 5-year DFS rates varied little across the three arms at 52.8–55.8%, yielding hazard ratios of 0.98 for sorafenib and 1.01 for sunitinib in comparison with placebo. There was no signal that any subset of patients derived benefit from adjuvant therapy. The study demonstrated that the threshold for tolerability of side effects is significantly lower for patients who receive targeted therapy in the adjuvant setting than for the treatment of life-threatening metastatic disease, and that might have contributed to the lack of success of this trial. Several other trials evaluating the role of targeted agents in kidney cancer are ongoing (Table 34.2).

Clinical implications

In patients with resected localized kidney cancer, we recommend against adjuvant systemic therapy (strong recommendation against based on high-quality evidence). However, enrollment of eligible patients in clinical trials is encouraged.

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PART 6

Testis and penile cancer

Michael C. Risk

35 CHAPTER 35

Early-stage (stage I) seminoma

Sia Daneshmand[1] and Cory Hugen[2]

[1] *USC Institute of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA*

[2] *School of Medicine, University of California, Irvine, CA, USA*

Introduction

It was estimated that there would be 8430 new cases of testicular cancer diagnosed in the United States in 2015 [1], of which 95% would be primary germ cell tumor, 60% seminoma, and approximately 80% would present as a stage I cancer [2, 3]. Although the overall incidence of testicular cancer is low, it remains the most common cancer diagnosed in men aged 20–34 years [4].

Testicular cancer is staged using a group staging system that incorporates the commonly used American Joint Committee on Cancer (AJCC) Tumor–Node–Metastasis (TNM) staging system along with serological tumor markers. These tumor markers include human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH), and are measured both pre- and postorchiectomy. HCG is produced by syncytiotrophoblasts in germ cell cancers and is elevated in approximately 10% of all patients with pure seminoma and up to 30% of patients with advanced disease. Whereas LDH can also be elevated in patients with pure seminoma, AFP should never be elevated. Elevations of AFP in patients diagnosed with pure seminoma should prompt pathological review and treatment should proceed as with a nonseminomatous tumor [5].

Stage I testicular cancer includes both cancer confined to the testicle and tumors with local extension into the epididymis and even scrotal wall (T1–4) but without any lymph node involvement (N0), metastasis (M0), or elevation of serological tumor markers (S0).

In this chapter, we systematically review the evidence relating to stage I seminoma treatment options, risk factors for recurrence, and surveillance regimens.

Clinical question 1

Are tumor size and rete testis invasion predictive of recurrence in stage I seminoma?

Literature search

We conducted a literature search in PubMed spanning 1966–2015. We initially limited the search to randomized controlled trials and systematic reviews; however, no randomized controlled trials were identified that address recurrence risk factors, so observational studies and single-institution series were also included.

The evidence

Four studies were identified that address recurrence risk factors for stage I seminoma.

The first study, by Warde et al., reported the results for 201 patients who were managed with surveillance for stage I seminoma and identified patient age >34 vs. ≤34 years and tumor size >6 cm vs. ≤6 cm as risk factors for recurrence [6]. Of note, rete testis invasion was not evaluated as a potential risk factor in this study.

A later study by Warde et al. used a pooled analysis of 638 patients from four surveillance studies to identify risk factors for recurrence. On multivariate analysis they reported tumor size ≤4 cm vs. >4 cm (hazard ratio [HR] 2.0, 95% confidence interval [CI] 1.3–3.2) and invasion of the rete testis (HR 1.7, 95% CI 1.1–2.6) as significant predictors of recurrence [7].

A study by Chung et al. was performed as a validation study to confirm that tumor size and rete testis invasion were risk factors for recurrence [8]. The authors reported that neither factor was associated with disease recurrence. A more recent study by Chung et al. demonstrated that tumor size was

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a risk factor for recurrence at 3 years, ranging from a 9% recurrence rate for 1 cm tumors to 26% for 8 cm tumors [9].

The lack of agreement and validation of recurrence risk factors is also reflected in published guidelines from various organizations. The National Comprehensive Cancer Network (NCCN) Testicular Cancer Guidelines do not recommend the use of tumor size and rete testis involvement in determining management of stage I seminoma. The European Association of Urology (EAU) Guidelines on Testicular Cancer however, do use rete testis involvement and tumor size >4 cm versus ≤4 cm to classify patients as low and high risk for recurrence.

Clinical implications

We suggest against using tumor size and rete testis involvement as prognostic factors to determine the management of patients with stage I seminoma (conditional recommendation based on very low-quality evidence).

Clinical question 2

In patients diagnosed with stage I seminoma, how does active surveillance compare with adjuvant treatment?

Literature search

We conducted a literature search in PubMed spanning 1966–2015. We limited the search to randomized controlled trials and systematic reviews; however, we did not identify any randomized controlled trials, so observational studies and retrospective reviews were also included.

The evidence

A meta-analysis by Petrelli et al. included 11 retrospective and two prospective cohort series comprising 12 705 patients [10]. They calculated a 5-year relapse-free survival rate of 3.9 vs. 14.8% for those patients treated with either adjuvant chemotherapy or radiotherapy versus active surveillance, respectively. This translates to a 10.9% (95% CI –9.3 to 12.5) absolute risk reduction for those treated with adjuvant therapy and a number needed to treat of 10 (95% CI 7.9–10.7) to prevent a single recurrence. They also calculated a 5-year overall survival that did not demonstrate improved survival when adjuvant therapy was compared with active surveillance, as shown in Figure 35.1.

Three systematic reviews were identified that focused on surveillance. The review by Mok and Warde included the outcomes of nine studies with 1844 patients on active surveillance for stage I seminoma and reported cause-specific survival ranging from 98.4 to 100% [11]. An earlier Cochrane review by Shelley et al. concluded that "Survival for patients with stage I seminoma following orchiectomy is likely to be similarly high whether they are managed by surveillance or adjuvant radiotherapy and the advantage and disadvantages of each approach need to be weighed" [12].

A systematic review by Chung et al. reported on the late effects of treatment with respect to additional outcomes that we considered important but not critical to decision-making according to the GRADE criteria [13]. With regard to secondary malignancy, they reported a relative-risk of 3.4 for developing a secondary malignancy in the radiation field for those treated with adjuvant radiotherapy. Cardiac toxicity was also higher for patients treated with radiotherapy, with a relative risk of 2.74 for those treated with radiotherapy compared with active surveillance. The review was unable to comment on quality of life or sexual function for those on active surveillance owing to lack of data.

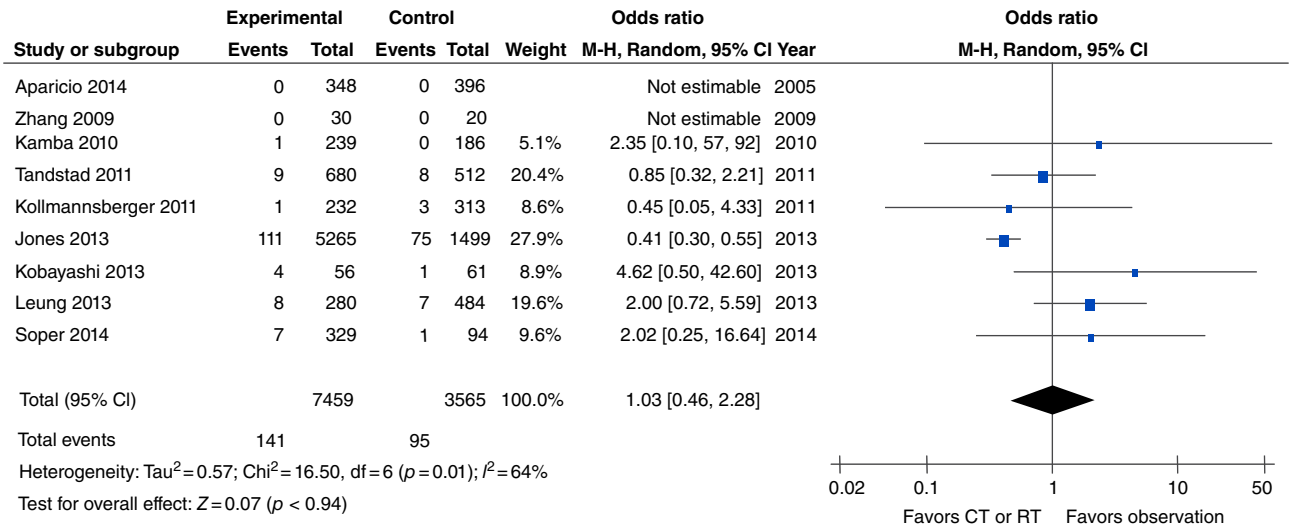

Figure 35.1 5-Year overall survival for adjuvant therapy versus observation in stage i seminoma. Source: Adapted from Petrelli et al. 2015 [11]. Reproduced with permission of Elsevier.

Two retrospective series reported on outcomes of active surveillance. The study by Kollmannsberger et al. included 1344 patients with stage I seminoma who were managed with active surveillance [14]. Recurrence occurred in 173 patients (13%) recurred with a median follow-up of 52 months. The median time to recurrence was 14 months and 92% of recurrences occurred within 3 years of orchiectomy. When recurrences occurred, 61% were managed with chemotherapy. The overall survival rate for patients managed with active surveillance was 99% at 5 years.

The largest reported series in the literature is a Danish study by Mortensen et al. reporting on the outcomes of 1954 patients managed with active surveillance [15]. The authors reported that 369 (18.9%) patients relapsed with a median follow-up of 15.1 years. The 5-, 10-, and 15-year disease-specific survival rates were 99.6, 99.4, and 99.3%, respectively.

Clinical implications

We suggest that patients with stage I seminoma undergo active surveillance rather than adjuvant treatment (conditional recommendation based on very low-quality evidence). The recommendation is based on very favorable disease-specific survival of patients managed by active surveillance that appears not to be inferior to that of patients receiving adjuvant treatment, and places a high value on the presumed wish of patients to avoid long-term complications such as cardiac toxicity and secondary malignancies.

Clinical question 3

In patients diagnosed with stage I seminoma who are managed using active surveillance, how do follow-up regimens of different intensity compare?

Literature search

We conducted a literature search in PubMed spanning 1966–2015. We initially limited the search to randomized controlled trials and systematic reviews; however, no randomized controlled trials could be identified so, in addition to systematic reviews, we also included Guideline Panel schedules and retrospective studies that included surveillance strategies.

The evidence

Several published surveillance regimens exist for patients managed with active surveillance for stage I seminoma and, as noted in the review paper by Mok and Warde [11], a universally accepted schedule and agreement on what clinical variables to assess has yet to be created.

A systematic review by Martin et al. was performed with the purpose of formulating an evidence-based follow-up schedule regarding the frequency, duration, and imaging protocols for the different management strategies [16]. After reviewing the literature, they formulated hazard plots based on timing to recurrence and also the location of the recurrence, and formulated the surveillance schedule shown in Table 35.1.

Nearly all recurrences in stage I seminoma are diagnosed by abdominal imaging; however, the use and timing of abdominal imaging are controversial [14]. Because of the lack of high-level evidence to guide imaging frequency, published schedules vary enormously)[17]. We have included some of these schedules for patients managed with active surveillance in Tables 35.2–35.4.

Although most centers utilize traditional computed tomography (CT) scanning to image the abdomen, some have begun to use low-dose CT scans or magnetic resonance imaging (MRI) to image the abdomen. Fortunately, there is a randomized clinical control trial currently accruing patients to evaluate frequency and imaging modality. It is hoped that the Trial of Imaging and Schedule in Seminoma Testis (TRISST) will provide answers regarding the frequency and modality (CT vs. MRI) utilized in surveillance imaging for stage I seminoma.

Another controversial topic concerning surveillance schedules is whether to include serological tumor markers as part of the surveillance program. The NCCN guidelines consider markers to be optional, whereas other surveillance schedules measure them routinely [14] and often [15]. Kollmannsberger et al. [14] identified relapse by tumor marker

Table 35.1 Recommended follow-up frequency and imaging studies.

Annual hazard rate (%)	Year	Visit frequency (months)	CT abdomen/pelvis	Chest X-ray
>5	1	4	Yes	Yes
1–5	2	4	Yes	Yes
1–5	3	6	Yes	Yes
0.3–1	4	12	Yes	Yes
0.3–1	5–10	12	Yes	Yes
<0.3	>10	Cease	Yes	Yes

CT, computed tomography.

Source: Adapted from Martin et al. 2007 [16]. Reproduced with permission of John Wiley & Sons.

Table 35.2 NCCN Guidelines: surveillance for stage I seminoma – observation.

Surveillance	Year 1	Year 2	Year 3	Year 4	Year 5
H&P	3–6 months	6–12 months	6–12 months	Annually	Annually
CT	3, 6, 12 months	6–12 months	6–12 months	12–24 months	12–24 months
CXR	As clinically indicated, consider CT chest if symptomatic				

H&P, history and physical examination; CT, computed tomography; CXR, chest X-ray. Tumor markers are considered optional.
Source: Adapted from National Comprehensive Cancer Network 2015 [18].

Table 35.3 Surveillance schedule utilized by the Danish Surveillance Program.

Surveillance	Time (months)														
	2	4	6	8	10	12	15	18	21	24	30	36	42	48	60
Physical examination	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
CT scan			×			×		×		×					×
Tumor markers	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Free and total testosterone	×					×				×					×
FSH and LH	×					×				×					×

CT, computed tomography; FSH, follicle-stimulating hormone; LH, luteinizing hormone.
Source: Adapted from Mortensen et al. 2014 [15]. Reproduced with permission of Elsevier

Table 35.4 Surveillance schedule as recommended by Kollmannsberger et al. [14].

Surveillance	Frequency (months)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Physical examination	3	6	6	6	6
Tumor markers	3	6	6	6	6
Chest X-ray	6, 12	18, 24	–	–	–
CT/MRI abdomen	6, 12	18, 24	30, 36	–	60[a]

CT, computed tomography; MRI, magnetic resonance imaging.
[a] Some advocate for scan at this time.
Source: Adapted from Kollmannsberger et al. 2015 [14].

elevation in six patients whereas the study by Mortensen et al. [15] identified only three patients, whose sole abnormality was an elevation of tumor markers. Furthermore, Vesprini, et al. reported that 65 (12%) of 527 patients on active surveillance relapsed within the first 3 years [19]. Despite the elevation of tumor markers in 11 of these patients at the time of relapse, the tumor marker was not the initial indicator of relapse, which was diagnosed by CT scan in 64 patients and by physical examination in one patient.

Clinical implications

We suggest that patients with stage I seminoma undergo a less intense surveillance strategy as shown in Table 35.4 (conditional recommendation based on low-quality evidence). This recommendation is based on evidence suggesting that a less intense regimen performs similarly to a more intense regimen in detecting clinically important recurrences and results in similar outcomes. It places a high value on patients' desire to avoid unnecessary follow-up visits and blood and imaging tests (and costs).

Clinical question 4

In patients diagnosed with stage I seminoma, what is the evidence for management with adjuvant chemotherapy?

Literature search

We conducted a literature search in PubMed spanning 1966–2015. We limited the search to randomized controlled trials and systematic reviews. Because only a single randomized

controlled trial was identified, we also included nonrandomized trials and retrospective reviews.

The evidence

One randomized controlled trial was identified comparing adjuvant chemotherapy with adjuvant radiation. This study was downgraded to low quality by GRADE guidelines owing to study limitations and indirectness of the evidence. Oliver et al. published a noninferiority trial comparing a single infusion of carboplatin dosed at AUC 7 with 20 or 30 Gy radiotherapy [20]. At 6.5 years' median follow-up, they reported 5-year relapse-free rates of 94.7 and 96.0% ($p = 0.37$) for the chemotherapy and radiotherapy arms, respectively.

Several nonrandomized trials using adjuvant chemotherapy have been reported. A study by Dieckmann et al. reported on 93 patients treated with single cycle carboplatin versus 32 patients treated with two cycles of carboplatin [21]. At a median follow-up of 48 months, they reported a recurrence rates of 8.6 and 0% in the one- and two-cycle treatment arms, respectively. In a later study, Steiner et al. compared their retrospective series of patients treated with two cycles of chemotherapy with the published recurrence rates in studies of patients treated with single-cycle carboplatin and concluded that two cycles of chemotherapy resulted in fewer recurrences [22].

We also identified three risk-adapted nonrandomized studies performed by the Spanish Germ Cell Cancer Group, where stage I seminoma patients were managed either with active surveillance or with adjuvant chemotherapy based upon risk factors for recurrence. The risk factors used to determine management changed with each study. In the first trial, 60 patients with >T1 disease and/or vascular invasion were treated with two cycles of carboplatin whereas 143 patients lacking those risk factors were managed with observation. At a median follow-up of 52 months, two patients (3.3%) treated with chemotherapy and 23 patients (16.1%) on observation relapsed; the disease-specific survival at 5 years was 100% for both groups [23]. In the second trial, 214 patients with tumors larger than 4 cm and/or rete testis invasion were treated with two cycles of carboplatin dosed at AUC 7 and 100 patients without risk factors were managed with active surveillance. After a median follow-up of 34 months, six patients (6%) on surveillance and seven patients (3.3%) on chemotherapy relapsed [24]. The 5-year overall survival was 100% for both groups. In the third study, 74 patients with both size >4 cm and rete testis invasion were managed with two cycles of adjuvant carboplatin dosed at AUC 7 whereas 153 patients with either one or no risk factors were managed with active surveillance. After a median follow-up of 34 months, 15 patients (9.8%) on surveillance and one patient (1.6%) treated with chemotherapy experienced relapse [25]. The 3-year overall survival rate was 100%. A fourth study by the same group combined the patient data from the three previous studies to report outcomes and showed that with a median follow-up of 80 months those patients managed with active surveillance had a 14.8% recurrence rate compared with 3.2% for those patients managed with adjuvant chemotherapy [26].

Bamias et al. reported the results of a study using two cycles of etoposide and cisplatin in 64 patients with stage I seminoma [27]. After a median of 60 months, no patients had experienced recurrence, although one patient did develop a metachronous tumor.

With regard to treatment-related toxicities, sparse data are available. Several studies did not report any treatment-related toxicities. One study was carried out to compare treatment-related toxicities in 199 patients treated with either one or two cycles of carboplatin and at 9 years' median follow-up did not show any increased risk of cardiovascular events or secondary malignancies compared with the general population [28].

Clinical implications

In patients with stage I seminoma who opt against active surveillance, we suggest against the use of adjuvant chemotherapy (conditional recommendation based on low-quality evidence). This recommendation is based on low-quality evidence for the GRADE critical outcome of noninferior mortality rates but very low-quality evidence suggesting increased rates of long-term adverse events such as secondary malignancies, cardiac toxicity, sexual function, and quality of life.

Clinical question 5

In patients diagnosed with stage I seminoma, what is the evidence for management with adjuvant radiotherapy?

Literature search

We conducted a literature search in PubMed spanning 1966–2015. We limited the search to randomized controlled trials and systematic reviews.

The evidence

We identified three randomized controlled trials involving patients with stage I seminoma. The first trial compared treating patients with a para-aortic (PA) radiation field versus a dogleg (DL) field that also included the ipsilateral pelvic nodes [29]. This study demonstrated an overall survival at 3 years of 100 and 99.3% and recurrence-free survival at 3 years of 96.6 and 96.0% in the DL and PA fields, respectively. The PA-treated group also had less nausea/vomiting, diarrhea, and leukopenia and improved sperm counts compared with the DL group.

The second randomized trial involved 625 patients who were randomly assigned to 30 or 20 Gy radiotherapy treatment [30]. At a median follow-up of 61 months there were 11 recurrences in the 30 Gy cohort versus 10 recurrences in the

Table 35.5 Outcomes of stage I seminoma patients managed with surveillance.

Study	Study period	No. of patients	Relapse rate (%)	Cause-specific survival rate (%)
Santoni et al.	1970–1999	487	4.3	99.4
Bayens et al.	1975–1985	132	4.5	99.0
Hultenschmidt et al.	1978–1992	188	1.0	100.0
Coleman et al.	1980–1995	144	4.2	100.0
Warde et al.	1981–2002	283	5.0	100.0
Kamba et al.	1985–2006	182	4.9	99.5
Fosså et al.	1989–1993	242	3.7	100.0

Source: Adapted from Mok and Warde 2011 [11].

20 Gy cohort. The 20 Gy cohort experienced less acute toxicity with lower rates of leukopenia and also had no reported secondary malignancies compared with six reported in the 30 Gy treatment cohort.

The third randomized controlled trial compared single-dose carboplatin with either 30 or 20 Gy of radiotherapy treatment [20]. These findings have already been discussed earlier in the chapter and showed no difference in relapse-free rate.

Several retrospective series have reported their experience and published similar relapse and cause-specific survival rates. A summary of these studies can be found in the review by Mok and Warde [11] and is presented in Table 35.5.

Two large SEER Medicare Database studies were identified and reported long-term outcomes and complications. The first, by Jones et al., included 6764 patients of whom 5265 received adjuvant radiotherapy and 1499 underwent surveillance [31]. With a median follow-up of 7.6 years, they reported significant differences in overall survival for radiotherapy versus observation at 5 and 10 years, with rates of 97.9 vs. 95.0% and 94.8 vs. 92.2%, respectively. At 20 years' follow-up, the overall survival for the surveillance group was higher at 84.1% vs. 83.5% ($p=0.0047$) for the radiotherapy group. They also reported significant differences for disease-specific survival at 5, 10, and 20 years for radiotherapy versus surveillance at 99.6 vs. 98.7%, 99.4 vs. 98.7%, and 99.2 vs. 98.7% ($p=0.0015$), respectively.

Both SEER studies showed an increased risk of secondary malignancies in patients treated with radiotherapy [31, 32]. The paper by Beard et al. [32] did not identify increased risks of cardiovascular disease among men treated with radiotherapy.

Clinical implications

In patients with stage I seminoma electing to undergo adjuvant radiation over active surveillance, we suggest a dose of 20 Gy to be delivered including the PA field (conditional recommendation based on low-quality evidence). This recommendation is based on evidence for similar recurrence rates but with fewer adverse events and secondary malignancies.

The overall quality of the studies identified as low by GRADE criteria. Because of the increased risk of secondary malignancies and unknown data regarding sexual function and quality of life – along with the near 100% survival for patients treated with salvage therapy following surveillance – we do not recommend adjuvant radiation therapy as standard management. However, if adjuvant therapy is to be used, the studies mentioned indicate that 20 Gy should be delivered including the PA field.

Implications for research

The clinical challenge in early-stage testicular cancer is that our best clinicopathological predictors of relapse do not sufficiently identify patients at high and low risk for relapse. A more objective and highly discriminant predictive system in early-stage testicular cancer would identify patients at high risk for recurrence to receive adjuvant therapy while allowing for less stringent active surveillance for those at very low risk for recurrence. We believe that the identification of molecular markers and gene expression profiles associated with relapse would allow for improved stratification between patients at high and low risk for recurrence and is an area in need of further research.

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36 CHAPTER 36

Advanced (stage II and III) and recurrent seminoma

Peter C. Black[1] and Christian Kollmannsberger[2]

[1] *Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada*

[2] *Division of Medical Oncology, British Columbia Cancer Agency–Vancouver Cancer Centre, University of British Columbia, Vancouver, BC, Canada*

Introduction

Since the advent of cisplatin-based chemotherapy, advanced seminoma has become a highly curable disease entity [1]. To some extent, the high cure rate has stifled clinical research towards further improvements in the therapy of seminoma. Nonetheless, two critical areas of investigation have been addressed with recent trials.

First, efforts have been focused on reducing the toxicity of treatment. This is particularly important in young patients with a long life expectancy after diagnosis and therapy. Studies aimed at reducing the burden of treatment while maintaining excellent outcomes can be framed around three clinical questions. One important question is whether radiation or chemotherapy offers the best balance between efficacy and toxicity for patients with clinical stage IIA/B seminoma. The same balance is questioned in the selection of three cycles of bleomycin, etoposide, and cisplatin (BEP) versus four cycles of etoposide and cisplatin (EP) for patients with clinical stage IIC and III seminoma. A third question pertains to the need for postchemotherapy retroperitoneal lymph node dissection in these patients, and the use of positron emission tomography (PET) imaging (in comparison with conventional computed tomography [CT]) to make this determination. Given the technical difficulty of this surgery and the high risk for complications, it is particularly important to avoid unnecessary interventions.

Second, there is an urgent need for better treatment options for patients who fail first-line cisplatin-based chemotherapy. Several salvage regimens have been suggested, including the use of high-dose chemotherapy with subsequent autologous stem-cell transplant. This latter regimen is potentially efficacious, but also potentially highly toxic.

In this chapter, we systematically review the evidence behind each of these clinical questions pertaining to the management of patients with advanced and recurrent seminoma.

Clinical question 1

In patients with clinical stage IIA/B seminoma, how do radiation and chemotherapy compare in terms of oncological efficacy and adverse effects?

Literature search

We conducted a systematic literature search in PubMed (1966–2015) using the search terms "seminoma," "radiotherapy," and "chemotherapy." The search was limited to randomized controlled trials and systematic reviews in the English and German languages with a human population.

The evidence

Radiation was the standard of care for decades in clinical stage IIA/B seminoma, with chemotherapy reserved for clinical stage IIC and III disease. However, recognition of late toxicity and secondary malignancies after retroperitoneal radiation has led to wider implementation of chemotherapy in this setting. There have been no randomized trials comparing radiotherapy with chemotherapy.

One recent systematic review compared radiotherapy with chemotherapy for clinical stage IIA and IIB seminoma, with a primary focus on relapse rates [2]. This analysis identified 13 relevant studies between 1990 and 2014, four of which were prospective and nine retrospective. In total, 607 patients received radiotherapy and 283 received chemotherapy. In 11 studies, the radiation was administered at

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least to the para-aortic/paracaval and ipsilateral iliac lymph nodes. The radiation dose was heterogeneous but measured ≥30 Gy in 10 studies. Three studies reported on the use of BEP or EP chemotherapy, while three others studies used nonstandard regimens. The relapse rate was similar between the two treatments (radiotherapy 0.11, 95% confidence interval [CI] 0.08–0.14, versus chemotherapy 0.08, 95% CI 0.01–0.15). In a subgroup analysis of patients with clinical stage IIB seminoma, the relapse rate was 0.12 (95% CI 0.06–0.17) for radiotherapy but only 0.05 (95% CI 0–0.11) for chemotherapy. A meta-regression model did not find a significant difference between groups with respect to relapse rate (odds ratio [OR] = 1.26, 95% CI 0.35–4.56, $p = 0.613$).

In the same systematic review, the mortality rate was analyzed from eight studies meeting the inclusion criteria. For radiotherapy, the mortality rate was 0.02 (95% CI <0.01–0.04) and for chemotherapy it was 0.01 (95% CI <0.01–0.02). These results did not differ substantially in subgroup analyses.

The same review also addressed treatment toxicity related to both treatment modalities. Acute toxicity has been reported almost exclusively with chemotherapy, whereas late toxicity has been described primarily with radiotherapy. Acute toxicities included especially nausea, vomiting, diarrhea, alopecia, peripheral neuropathy, and bone marrow suppression. Bowel toxicity was the most relevant late toxicity, although long-term cardiovascular toxicity was not captured. The rate of second nontesticular malignancies was 0.04 (95% CI 0.01–0.02) in the radiotherapy group and 0.02 (95% CI 0.003–0.04) in the chemotherapy group.

The available evidence for treatment efficacy is summarized in Table 36.1. Figure 36.1 presents Forest plots for relapse (a, b) and mortality (c, d) for radiotherapy (a, c) and chemotherapy (b, d).

Clinical implications

In patients with clinical stage IIA seminoma, we suggest radiotherapy or chemotherapy (conditional recommendation based on very low-quality evidence). Both treatments appear equally efficacious. Although the toxicity of radiation appears to be higher, current best evidence appears insufficient to suggest chemotherapy over radiation.

In patients with clinical stage IIB seminoma, we suggest chemotherapy over radiation therapy (conditional recommendation based on very low-quality evidence). This recommendation is based on the better efficacy and long-term tolerability of chemotherapy.

Clinical question 2

In patients with clinical stage IIC and good prognosis clinical stage III seminoma, how do BEPx3 and EPx4 compare in terms of oncological efficacy and adverse effects?

Literature search

We conducted a systematic literature search in PubMed (1966–2015) using the search terms "seminoma," "chemotherapy," "cisplatin", "bleomycin," and "etoposide." The search was limited to randomized controlled trials and systematic reviews in the English and German languages with a human population.

The evidence

Once four cycles of BEP had been established as a remarkably effective regimen for advanced germ-cell tumors [1, 3], efforts began to reduce the toxicity of therapy in patients with good prognosis. These efforts included removing the bleomycin from the regimen to reduce pulmonary toxicity and reducing the treatment to three cycles. These trials in patients with good prognosis included both seminomatous and nonseminomatous germ-cell tumors.

An EORTC/MRC trial demonstrated that BEPx3 is as efficacious as BEPx4 in 812 patients with good prognosis metastatic germ-cell tumors (22% seminoma) [4], which subsequently established BEPx3 as the standard of care in this cohort. Similar findings were made in a Southeastern Cancer Study Group trial that predated the IGCCC risk stratification [5]. In the EORTC/MRC trial, the complete response rate, including those with complete surgical resection of residual viable disease after chemotherapy, was 73.1% after BEPx3 and 74.9% after BEPx4 (OR 1.10, 95% CI 0.80–1.52). The 2-year progression-free survival was 90.4% for BEPx3 and 89.4% for BEPx4 (hazard ratio 0.93, 80% CI 0.71–1.24). The study concluded noninferiority of BEPx3 in comparison with BEPx4. Adverse effects and quality of life were similar between regimens, except for increased acute and late sensory neuropathy in the BEPx4 arm.

The EP arms of two older prospective randomized trials that compared four cycles of EP with other regimens in patients with good-risk disease as defined by Memorial Sloan Kettering Cancer Center criteria were reviewed retrospectively with *post hoc* assignment of IGCCC risk criteria [6]. Only 28% of 289 patients had pure seminoma and the remainder were nonseminomatous germ-cell tumors. The complete response rate, including those with complete surgical resection of residual viable disease after chemotherapy, was 98%. Relapse was observed in 6% of the patients, and 3% died of disease at a median follow-up of 7.7 years. Based primarily on these outcomes, which are very similar to the already described EORTC/MRC results, four cycles of EP are widely considered to be equivalent to three cycles of BEP in patients with good prognosis.

One prospective, randomized trial has been conducted to compare BEPx3 with EPx4, but it included only patients with good prognosis nonseminomatous germ-cell tumors [7]. Although this French study demonstrated no difference in the primary endpoint of favorable response between the

Table 36.1 GRADE evidence profile for clinical question 1.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiation**	**Chemotherapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Relapse												
13	Observational studies	Serious[a,b,c]	Serious[d]	Serious[e,f]	Serious[a,b,c,g]	Publication bias strongly suspected[h]	71/607 (11.7%)	27/283 (9.5%)	Not estimable	–	⨁◯◯◯ [a,b,c,d,e,f,g,h]	CRITICAL
Mortality												
8	Observational studies	Serious[a,b,c]	Serious[d]	Serious[e,f]	Serious[a,b,c,g]	Publication bias strongly suspected[h]	15/384 (3.9%)	5/272 (1.8%)	Not estimable	–	⨁◯◯◯ [a,b,c,d,e,f,g,h]	CRITICAL

[a] Retrospective studies.
[b] Single arm studies.
[c] Lack of randomization.
[d] I^2 14.6–82.5%.
[e] Differences in intervention (radiation dose/field; chemotherapy agents/dose/schedule).
[f] Different follow-up duration for outcome measure.
[g] Small sample size of included studies and overall number of patients.
[h] Visual inspection of funnel plots of the primary outcome and analytical appraisal based on the Egger's and Peters' linear regression test.

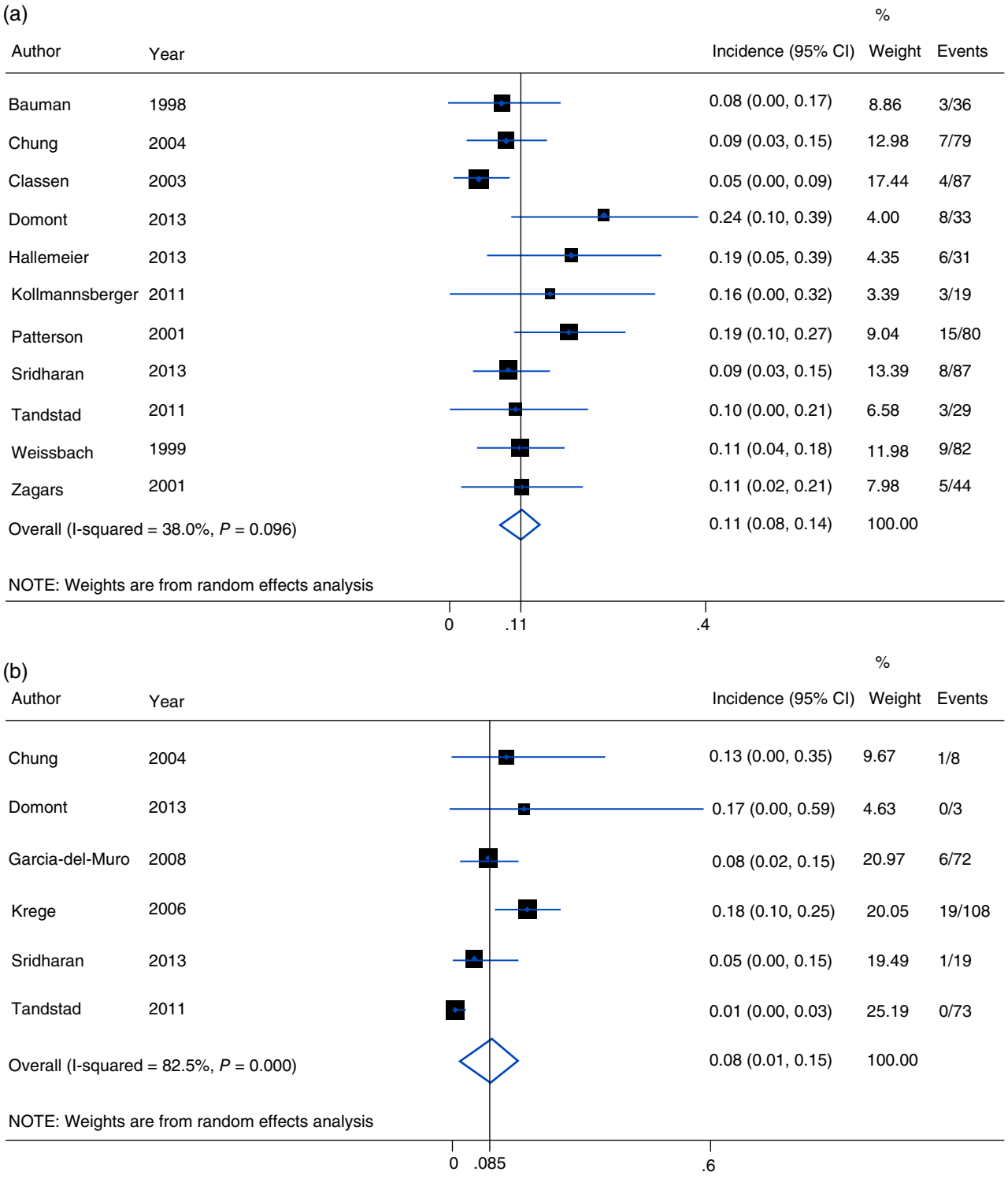

Figure 36.1 Forest plots demonstrating (a) relapse rate of radiation trials, (b) relapse rate of chemotherapy trials, (c) mortality of radiotherapy trials, and (d) mortality rate of chemotherapy trials in patients with stage IIA/B seminoma. Source: Giannatempo et al. 2015 [2]. Reproduced with permission from the European Society of Medical Oncology.

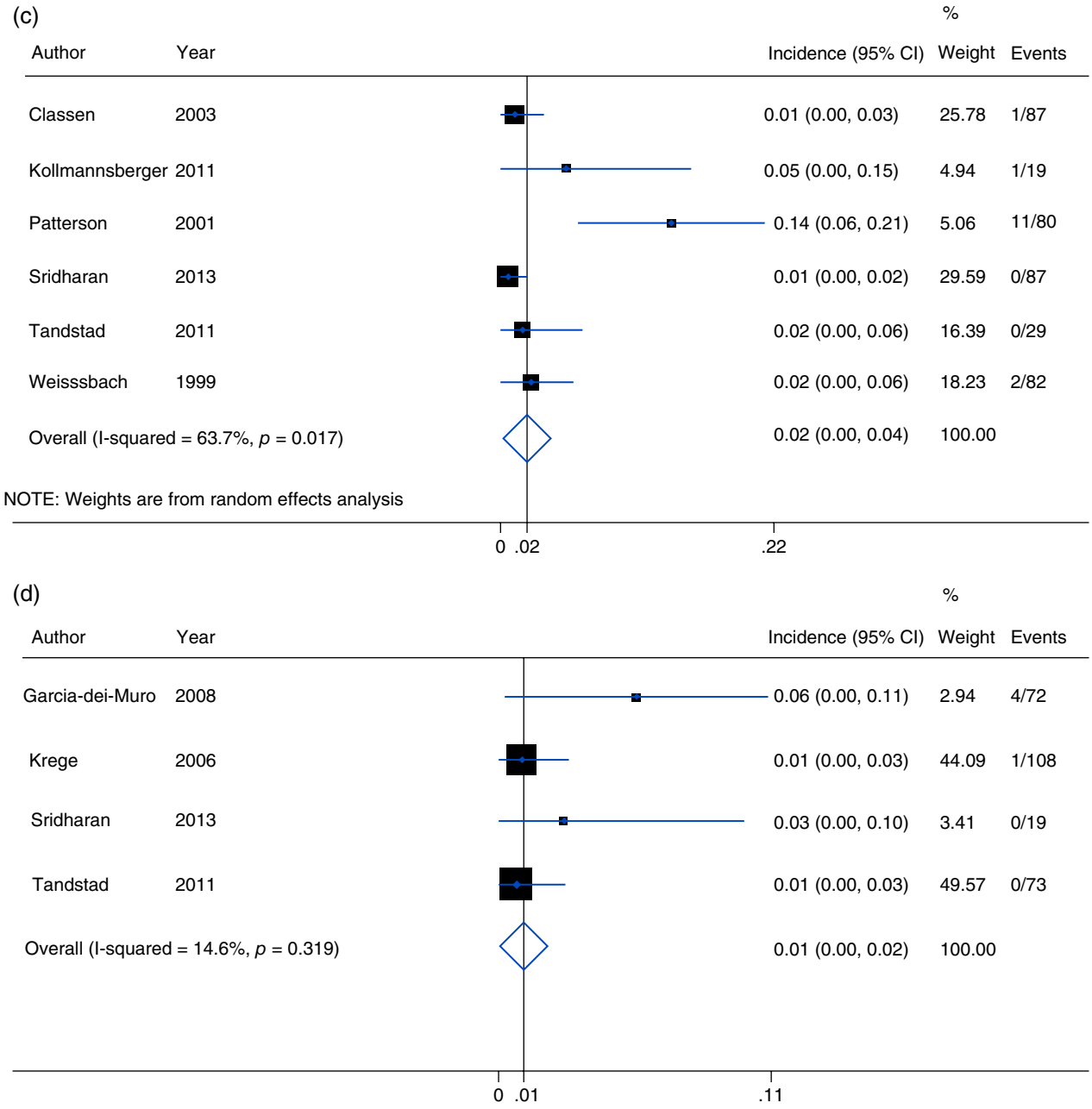

Figure 36.1 (Continued)

regimens, it must be considered inconclusive because it was underpowered for survival, with only 257 assessable patients [8]. Event-free survival at 4 years was 91% for BEP and 86% for EP ($p=0.135$). There were five deaths in the BEP arm and 12 deaths in the EP arm ($p=0.096$).

The evidence from this prospective randomized trial is supported by the prospective risk-adapted therapy implemented by Fizazi et al. [9]. Patients with good prognosis disease received EPx4 and those with intermediate-risk disease received etoposide, ifosfamide, and cisplatin (VIP). Although there was no comparator arm, this study demonstrated that essentially all patients with good prognosis seminoma are cured by EPx4. At 3 years, the progression-free survival rate was 93% and the overall survival rate was 99%.

The French prospective trial revealed a more favorable toxicity profile for EPx4 in comparison with BEPx3. The most significant difference was in neurotoxicity (any grade), which was observed in 16% of BEPx3 and 5% of EPx4

patients ($p=0.006$). Raynaud's phenomenon, which is considered a measure of general vascular toxicity, was observed in 29% of BEPx3 and 8% of EPx4 patients ($p=0.0001$). Dermatological toxicity was observed in 29% of BEPx3 and 8% of EPx4 patients ($p<0.0001$). There was no difference in pulmonary toxicity between the two arms (9% for BEPx3, 6% for EPx4).

The debate between BEPx3 and EPx4 holds only for good prognosis seminoma. Standard therapy for intermediate-risk patients (approximately 10% of all clinical stage III seminoma) is four cycles of BEP. If bleomycin is contraindicated, VIP is usually administered [9]. Two randomized trials that included patients with predominantly (85%) [10] or exclusively [11] nonseminatous germ-cell tumor guide this treatment decision. If it is desirable to avoid exposure to bleomycin owing to poor renal function or the risk of lung toxicity, low-level evidence suggests that four cycles of EP are a safe alternative [12].

Clinical implications

In patients with stage IIC and good prognosis stage III germ-cell tumors, regardless of whether seminomatous or nonseminomatous, we recommend BEPx3 over EPx4 (strong recommendation based on high-quality evidence).

In patients in whom it is desirable to avoid exposure to bleomycin owing to poor renal function or the risk of lung toxicity, we suggest EPx4 as an alternative (conditional recommendation based on low-quality evidence).

Cinical question 3

In patients with seminoma and a postchemotherapy residual mass, how does positron emission tomography (PET) compare with computed tomography (CT) in predicting viable cancer in the residual mass?

Literature search

We conducted a systematic literature search in PubMed (1966–2015) using the search terms "seminoma," "chemotherapy," and "PET." The search was limited to randomized controlled trials and systematic reviews in the English and German languages with a human population.

The evidence

Three prospective trials compared the utility of fluorine-18-fluorodeoxyglucose ([^{18}F]FDG) PET with CT in predicting the presence of viable cancer in postchemotherapy residual mass [13–15]. All three of these trials and six additional studies (five retrospective and one unspecified) were included in a recent systematic review investigating the diagnostic performance of [^{18}F]FDG-PET (with and without CT) in this patient cohort [16]. This analysis included 375 patients. Only two studies evaluated PET–CT and the others evaluated PET alone, all in comparison with CT alone.

The sensitivity of PET was found to be 78% (95% CI 67–87%). The specificity was 86% (95% CI 81–89%), positive predictive value 58% (95% CI 48–68%), and negative predictive value 94% (95% CI 90–96%). The overall accuracy of PET was 84% (95% CI 80–88%). The area under the curve (AUC) on the receiver operator curve (ROC) was 0.90.

Since other retrospective series have shown that residual masses <3 cm in diameter rarely contain viable residual seminoma, a subgroup analysis was performed on lesions <3 cm or >3 cm based on seven studies with 303 patients. In lesions >3 cm the sensitivity increased to 89% (95% CI 75–97%) and the specificity decreased to 81% (95% CI 73–88%). For masses <3 cm, the sensitivity was 47% (95% CI 21–73%) and the specificity was 89% (95% CI 82–94%). The authors concluded that the diagnostic accuracy of PET was higher in lesions >3 cm than in those <3 cm.

Heterogeneity of studies, low number of patients with resultant low statistical power, and publication bias were limitations of this systematic review.

The available evidence from the three prospective trials is summarized in Table 36.2.

In summary, seminoma differs critically from nonseminoma with respect to postchemotherapy residual masses because of the absence of residual teratoma, the lower risk of viable seminoma, and the technical difficulty of surgical resection. The utility of PET–CT is therefore vital for determining the need for postchemotherapy retroperitoneal lymph node dissection (RPLND) in these patients.

Despite only low-quality evidence for its utility, [^{18}F]FDG-PET and PET–CT appear to be accurate in determining viable cancer in postchemotherapy residual masses in patients with seminoma, especially when these masses are >3 cm in diameter, and they have therefore been implemented broadly in clinical practice.

Clinical implications

In patients with seminoma and a postchemotherapy residual mass, we suggest PET over CT scanning (conditional recommendation based on low-quality evidence).

Clinical question 4

In patients with advanced seminoma who fail first-line chemotherapy, how do the oncological outcomes in high-dose chemotherapy with stem-cell transplant compare with standard salvage chemotherapy?

Literature search

We conducted a systematic literature search in PubMed (1966–2015) using the search terms "seminoma," "high dose chemotherapy," and "stem cell transplant." The search was limited to randomized controlled trials and systematic reviews in the English and German languages with a human population.

Table 36.2 GRADE evidence profile for clinical question 3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PET**	**CT**	**Relative (95% CI)**	**Absolute (95% CI)**		
Sensitivity and specificity												
3	Observational studies[a]	Serious[b,c]	Serious[b]	Serious[d]	Serious[b]	None	105	105	–	–	– [2 3 4]	CRITICAL

[a] Cohort studies.
[b] Small sample size of included studies and overall number of patients.
[c] Incomplete follow-up.
[d] Use of clinical follow-up for relapse and not pathology as correlate.

The evidence

High-dose chemotherapy (HDCT) has been studied in the salvage setting in patients with refractory nonseminomatous (NSGCTs) or seminatous germ-cell tumors (SGCTs), but not specifically for seminoma.

Encouraging results in early-phase, single-arm trials [17] led to a prospective randomized Phase III trial comparing HDCT with conventional-dose chemotherapy (CDCT) in the salvage setting [18]. The IT-94 trial randomized 280 patients from 43 centers in 11 countries to four cycles of VIP or VeIP (vinblastine, ifosfamide, and cisplatin) versus three cycles of the same CDCT followed by one cycle of HDCT using carboplatin, etoposide, and cyclophosphamide followed by autologous stem-cell rescue. The complete response rate was 42% for CDCT and 43% for HDCT ($p=0.71$). The 3-year event-free survival was 35% in the CDCT arm versus 42% in the HDCT arm ($p=0.16$), indicating no clear benefit of HDCT.

The IT-94 trial, however, has been criticized for deficiencies in design, and the results are not considered definitive. In particular, previous studies suggesting an advantage of HDCT over historical results for CDCT typically used two or more cycles of HDCT [19]. Another Phase III trial randomized 211 patients in the first-line salvage setting to either three cycles of VIP followed by one cycle of high-dose carboplatin, etoposide, and cyclophosphamide or to one cycle of VIP followed by three cycles of high-dose carboplatin and etoposide [20, 21]. There was no difference in event-free survival, progression-free survival, or overall survival (80 vs. 61%), but the toxicity was reduced in patients receiving three cycles of HDCT (4 vs. 16% treatment-related deaths). The study was close early based on these toxicity findings, and the conclusion was drawn that sequential therapy is preferable because it is better tolerated. The main limitations of this study are differences in dosing between the study arms and the fact that one arm received two agents compared with three in the other arm.

An additional prospective randomized Phase III trial is under way comparing CDCT using paclitaxel, ifosfamide, and cisplatin (TIP) with HDCT using paclitaxel followed by carboplatin and etoposide (TI-CE) as first salvage treatment in relapsed or refractory germ-cell tumors (TIGER trial) [22].

In summary, although the only prospective randomized trial addressing this clinical question showed no survival advantage for HDCT over CDCT, several retrospective trials, including large multi-center reports, support the use of HDCT with stem-cell transplant, and this is considered a standard for salvage after failure of first-line cisplatin-based therapy. Multiple cycles of HDCT are preferred over a single cycle, and the backbone of therapy is carboplatin with etoposide. Alternatively, some experts prefer to administer CDCT as the first salvage option and reserve HDCT for the second salvage therapy. This is justified by the increased toxicity of HDCT. The management decisions do not differ between NSGCTs and SGCTs.

Clinical implications

In patients with advanced NSGCTs and SGCTs who have failed first-line chemotherapy, we suggest HDCT with stem-cell transplantation over CDCT (conditional recommendation based on low-quality evidence). In patients in whom there is increased concern about the higher toxicity of HDCT, CDCT is an appropriate alternative (conditional recommendation based on low-quality evidence).

Implications for research

None of the selected questions in this review have been addressed with good-quality, prospective randomized trials, thereby underlining the need for more high-quality trials for patients with advanced seminoma. Survival rates for patients with stage II/III seminoma are excellent, but there remains a need to minimize the toxicity of therapy. This includes a significant unmet need for predictive markers to guide therapeutic choices. Furthermore, patients with seminoma that recurs or persists after first-line cisplatin-based chemotherapy should be considered for clinical trials whenever possible.

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37 CHAPTER 37

Early-stage nonseminomatous germ-cell tumor

Justin T. Matulay and James M. McKiernan
Department of Urology, Columbia University Medical Center, New York, NY, USA

Background

Testicular cancer is the most common malignancy in men aged 15–35 years. As a result of therapeutic advances over the past several decades and the integration of multimodal treatment, testicular cancer is now one of the most curable neoplasms. The term nonseminomatous germ-cell tumor (NSGCT) includes embryonal carcinoma, choriocarcinoma, teratoma, and yolk sac tumor. Despite favorable long-term survival, the multimodal treatment of NSGCT is constantly evolving and incorporating new paradigms. This chapter aims to present evidence available for several controversies regarding the management of NSGCT.

Clinical question 1

How should patients with scrotal violation be managed?

Literature search

A search of MEDLINE and PubMed databases was conducted to retrieve available publications pertaining to each clinical question. Each database search was limited to articles published between 1960 and 2008 and included only English-language reports. All clinical studies were eligible for inclusion and reports utilizing all levels of evidence were considered for inclusion. The reference list from all included publications was scrutinized to identify potentially relevant publications. Search terms included "testicular neoplasm," "germ cell tumor," "scrotal violation," "trans-scrotal orchiectomy," "trans-scrotal biopsy," and "postorchiectomy complications."

The evidence

An inguinal orchiectomy with high ligation of the spermatic cord is the standard of care for managing a testicular mass that is suspicious for neoplasm. Whereas this technique is undisputed, management of the violated scrotum is more controversial. Scrotal violation can occur during scrotal orchiectomy, percutaneous testicular biopsy, percutaneous fine-needle aspiration, or inguinal–scrotal orchiectomy. Prior inguinal or scrotal surgery could also alter the normal lymphatic drainage of the testis. Scrotal violation before or during orchiectomy leads to concern for higher rates of local and distant recurrence outside conventional retroperitoneal templates.

In the past two decades, three retrospective reviews and one meta-analysis have specifically examined the impact of scrotal violation on recurrence in patients with NSGCT (Table 37.1). The incidence of scrotal violation ranged from 5 to 17% [1–3].

A retrospective analysis by Leibovitch et al. noted that 11% of patients who underwent a hemiscrotectomy after scrotal violation were found to have residual tumor and 66% of these patients experienced local recurrence even after local resection [3]. The same study also noted that no patient treated with chemotherapy after scrotal violation experienced local recurrence. A retrospective study by Giguere et al. noted that 68% of patients with scrotal violation underwent hemiscrotectomy and were found to have no residual tumor [2]. Despite the absence of residual tumor, the authors reported a 17% recurrence rate in the group that underwent local excision versus 40% in patients with scrotal violation who did not undergo hemiscrotectomy. A more recent study by Aki et al. found no local recurrence after scrotal violation and no significant difference in recurrence rates between patients with scrotal violation and those who underwent a standard orchiectomy [4]. Of note, all patients included in the study had negative surgical margins after orchiectomy. Despite these favorable results, the authors

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Table 37.1 Management of the violated scrotum.

Study	Methods	Intervention	Participants	Outcomes	Results	Notes
Aki et al. [4]	Retrospective review Mean FU 45 months	Orchiectomy	62 control patients with stage I NSGCT 13 patients with stage I NSGCT + scrotal violation	Local + distant recurrence	3/35 (17%) scrotal violation No local recurrence No sig. difference in relapse rate of scrotal violation patients (38%) vs. control patients (27%)	All patients had negative surgical margins No mention of adjuvant therapy Scrotal violation before or during orchiectomy
Capelouto et al. [1]	Meta-analysis 1958–1993 Mean FU 22–116 months	Orchiectomy	7 series, 1182 patients 976 control patients with NSGCT 206 patients with NSGCT, scrotal violation ± adjuvant therapy	Local + distant recurrence Overall survival	206/1182 (17%) scrotal violation No sig. difference in distant recurrence or survival Sig. difference in local recurrence rates of 0.4% for control vs. 2.9% for scrotal violation patients No sig. difference in local recurrence when NSGCT patients isolated No sig. difference in local or distant recurrence or survival between scrotal violation patients who underwent surveillance vs. adjuvant therapy	
Leibovitch et al.[3]	Retrospective review Median FU 33 months	Orchiectomy + RPLND (2 delayed postchemotherapy)	78 patients with NSGCT+ scrotal violation	Local + distant recurrence	78/1708 (4.5%) scrotal violation 56 (72%) underwent hemiscrotectomy → tumor Found in 6 (11%), gross tumor spillage noted in 5 5 (6.4%) had local recurrence → 4 after hemiscrotectomy No patient treated with chemotherapy had local recurrence	Scrotal violation during orchiectomy
Giguere et al. [2]	Retrospective review Median FU 36 months	Orchiectomy + RPLND Pathological stage 1 → observation with salvage chemotherapy Pathological stage II → 2 cycles chemotherapy or observation	35 patients with stage I or II NSGCT, scrotal violation, and no adjuvant chemotherapy	Local + distant recurrence	47/462 (10%) scrotal violation 15/22 (68%) patients with gross tumor contamination underwent hemiscrotectomy (no residual tumor) → 17% recurrence in posthemiscrotectomy group vs. 40% in patients without hemiscrotectomy 8/35 (23%) recurrence in scrotal violation group vs. 21% in routine orchiectomy group No scrotal recurrence	Scrotal violation during orchiectomy

FU, follow-up; sig., significant.

did not provide information regarding adjuvant treatment for patients with scrotal violation, so few conclusions can be drawn from this study.

A meta-analysis by Capelouto et al. examined 206 cases of scrotal violation and found no difference in distant recurrence or survival between patients with scrotal violation and patients who underwent standard orchiectomy [1]. When NSGCT cases were isolated, there was also no significant difference in rates of local recurrence. The analysis also reported no significant difference in local or distant recurrence rates for patients with scrotal violation who received local adjuvant therapy and those who did not receive additional local treatment. The authors did not provide information regarding the presence or absence of residual tumor in hemiscrotectomy specimens.

Clinical implications

In patients with stage I NSGCT with scrotal violation, we suggest adjuvant chemotherapy or retroperitoneal lymph node dissection (RPLND) with simultaneous hemiscrotectomy and excision of the spermatic cord remnant (conditional recommendation based on very low-quality evidence).

Clinical question 2

For patients undergoing RPLND, which template has the best survival with least morbidity?

Literature search

A MEDLINE and PubMed search was conducted using the previously described methods. Search terms included "testicular neoplasm," "germ cell tumor," "lymphadenectomy template," and "RPLND template."

The evidence

RPLND has been a mainstay in the surgical management of testicular germ-cell tumors since the late 1940s [5]. The durable cure rate achieved with surgery for low-stage NSGCT is approximately 85–90% and avoids the nearly 30% of patients who are understaged owing to missed retroperitoneal disease on computed tomography (CT) or magnetic resonance imaging (MRI) [6, 7]. The retroperitoneum is the sole location of metastasis in 80% of NSGCTs and it may harbor chemoresistant teratoma that can only be cured with surgical resection [8]. Early surgical templates were based on studies of testicular lymphatic drainage published in 1910 by Jamieson and Dobson [9] showing the primary landing zone to be the retroperitoneum around the site of embryological development of the testes. Surgeons used these data and focused on removing as many retroperitoneal lymph nodes as possible – extending as far cephalad as the crura of the diaphragm, laterally between the ureters, and caudally to the bifurcation of the common iliacs – given that there was no effective adjuvant therapy (chemotherapy or radiation) available should a relapse occur. The end results were high rates of injury to foregut organs, chylous ascites, and vascular injury of the kidney, not to mention nearly universal occurrence of retrograde ejaculation [10]. Trying to address these issues, limited modifications to the suprahilar RPLND template were already being practiced as early as 1955 by Whitmore's group at the Memorial Sloan Kettering Cancer Center (MSKCC). The progressive trend towards exclusion of the suprahilar region in the standard template was driven by three main factors: (1) the introduction of platinum-based chemotherapy regimens that could effectively treat nonteratomatous metastases remaining after surgery, (2) the unlikely scenario of low-stage germ-cell tumors involving the suprahilar lymph nodes to begin with [11], and (3) increased morbidity associated with suprahilar dissection.

During the ensuing decades three major groups attempted to identify the most common sites of retroperitoneal metastasis in order to develop the template that offered the best cancer control with the least morbidity (Table 37.2). Ray, Hajdu, and Whitmore at MSKCC published their retrospective experience in 1974, including 283 patients who underwent either standard bilateral template or modified bilateral template RPLND [12]. The modified bilateral template for right-sided tumors extended from the renal vessels superiorly, to the ipsilateral right ureter. They identified 61 patients with right-sided tumors who had retroperitoneal metastases, of which 52 were ipsilateral, eight bilateral, and one contralateral. In the 61 patients with left-sided tumors, there were 49 with ipsilateral and 12 with bilateral retroperitoneal involvement.

In 1982, Donohue's group at Indiana University reported results from 104 consecutive RPLNDs performed for stage II NSGCT at their institution [11]. They were specifically interested in the rate of suprahilar involvement, so all patients underwent full template dissections as far cephalad as the diaphragmatic crura. There was very limited involvement of the suprahilar nodes for stage B1 (IIA) disease at 7.5%, but only one of those patients had a single suprahilar positive lymph node. For stage ≥ B2 (IIB or higher), the rate was 33–100% with increased incidence at higher stage. Additionally, they identified contralateral cross-over in two low-stage right-sided tumors (left para-aortic and left iliac) but in no left-sided tumors. The rate of cross-over, regardless of primary tumor laterality, increased with more advanced disease, including three late-stage patients with cross-over from left to right. The iliac vessels were involved in only 10% of all early-stage patients. It is important to note that Donohue et al. used a stricter definition of contralateral than did Ray et al. For their purposes, contralateral includes only the region lateral to the inferior vena cava (IVC) for left-sided tumors and lateral to the aorta for right sided tumors. The authors concluded that for low-stage NSGCT, a modified template with unilateral dissection for left-sided tumors and

Table 37.2 Templates used in RPLND.

Study	Methods	Intervention	Participants	Outcomes	Results	Notes
Ray et al. [12]	Retrospective review	Standard bilateral or modified bilateral RPLND	283 patients with "resectable" tumors	Location of nodal metastases	Right to left cross-over in 9/61 (15%) Left to right cross-over in 12/61 (20%) Only 1 patient with solitary contralateral lymph node from right-sided primary	Interaortocaval region defined as contralateral No clinical follow-up
Donohue et al. [11]	Retrospective review	Full template suprahilar RPLND	104 patients with pathological stage II NSGCT	Location of nodal metastases	Infrequent suprahilar involvement for PS IIA disease: 0% right-sided and 7.5% left-sided primaries Rate of suprahilar involvement up to 33% for PS IIB or greater PS IIA cross-over in 8% right- and 0% left-sided primaries	Strict definition of contralateral region; lateral to IVC and aorta for left- and right-sided primaries, respectively No clinical follow-up
Weissbach and Boedefeld [13]	Retrospective review	Standard bilateral infrahilar RPLND	214 patients with pathological stage II NSGCT	Location of nodal metastases	Single positive node: infrequent cross-over with left primary (5%) slightly more common than right primary (3%) Multiple positive nodes: cross-over more common for right-sided tumors (15%) than left-sided tumors (5%)	Interaortocaval region common to both sides No clinical follow-up
Weissbach et al. [18]	Prospective, multi-center study Median FU 30 months	Radical bilateral infrahilar RPLND or modified unilateral RPLND	229 patients with pathological stage I NSGCT	Recurrence, post-operative ejaculatory function	Relapse occurred in 15% of rRPLND and 17% of mRPLND Relapse was retroperitoneal in 1.5% of rRPLND vs. 2.4% of mRPLND Perioperative morbidity was similar for rRPLND (10%) and mRPLND (12%) Antegrade ejaculation preserved in 74% of mRPLND vs. 34% of rRPLND	Unable to control for surgical quality among the 26 different sites If positive nodes encountered intraoperatively then converted to rRPLND and excluded from analysis
Richie [15]	Prospective study Median FU 38 months	Modified template bilateral infrahilar RPLND	85 patients with clinical stage I NSGCT	Recurrence, post-operative ejaculatory function	1 (1.2%) retroperitoneal relapse occurred during follow-up (retrocrural space) 6 additional pulmonary relapses occurred for a total of 7 (8.2%) 80 of 85 patients (94%) regained antegrade ejaculation	Bilateral dissection between renal vessels and IMA; below IMA unilateral dissection including ipsilateral iliac
Eggener et al. [19]	Prospective study	Standard template infrahilar RPLND	500 patients with clinical stage I or IIA NSGCT	Extra-template disease from 5 modified templates	CS I missed disease 1–5% CS IIA missed disease 3–18% PSII missed disease by open template: MSKCC (3%), IU (11%), TTSG (23%) PSII missed disease by lap template: Innsbruck (23%), JHU (19%) Reduced rate of missed disease to <3% if all regions inferior to renal vessels included except for contralateral iliac	Underestimates extranodal disease since not all patients underwent contralateral iliac dissection

FU, follow-up.

limited contralateral dissection of only the preaortic zone for right-sided disease would be adequate to capture nearly all retroperitoneal metastases. Furthermore, as late-stage disease would require adjuvant chemotherapy regardless of the template employed, they suggested remaining infrahilar to avoid the added morbidity.

These conclusions are supported in a paper published a few years later by a German multi-institutional cooperative called the Testicular Tumor Study Group (TTSG) [13]. Using prospectively collected data from 214 consecutive patients treated with RPLND for clinical stage IIA or B disease, the authors found that patients were very unlikely to have a single positive contralateral lymph node, with a prevalence of 3 and 5% for right- and left-sided primaries, respectively. The authors defined ipsilateral versus contralateral lymph node regions similarly to Ray et al., but the latter included the interaortocaval region is as "ipsilateral" for right-sided tumors only. For their purposes, the TTSG considered the interaortocaval region as a common zone and, as such, it would be "ipsilateral" to primaries originating from either side. They recommended that ipsilateral dissection alone is performed for patients with clinical stage I disease with radical bilateral RPLND being reserved for stage II disease. For right-sided tumors, the dissection includes the preaortic area from the renal artery to the inferior mesenteric artery (IMA), the interaortocaval region from the IMA to the bifurcation, and the right common iliacs. In cases of left-sided tumors, the dissection should be limited to the para-aortic region from the renal hilum to the bifurcation and the preaortic area from the renal artery to the IMA, eliminating the interaortocaval and right iliac regions from the Indiana University template.

One major advantage of the templates proposed by Weissbach and Boedefeld [13] and Donohue et al. [11] is the avoidance of contralateral dissection in stage I patients with complete preservation of the sympathetic chain unilaterally. The rate of antegrade ejaculation postoperatively for clinical stage I patients who underwent one of these modified templates has been reported at 74–100% [14–18]. In the only prospective trial to date, Weissbach et al. compared 168 patients undergoing the TTSG-modified template with 67 patients undergoing full template dissection for clinical stage I NSGCT [18]. They found that ejaculation could be preserved in 74% versus 34% without increasing the relapse rate.

Pizzocaro et al. reported on 61 patients with stage I NSGCT who underwent a unilateral lymph node dissection from the diaphragmatic crura to the inguinal ligament ipsilaterally [17]. They excluded the interaortocaval region for left-sided tumors and the preaortic region for right-sided disease. The end result was preserved ejaculation in 82% but a recurrence rate of 15%, over double the 6% recurrence rate observed in historical controls at their institution. Richie reported on a series of 85 patients with early-stage NSGCT who underwent a modified template that included bilateral dissection between the renal vessels and the IMA but unilateral dissection inferior to the IMA [15]. Their rate of antegrade ejaculation was 94% with a relapse rate of only 6% for stage I and 15% for stage IIA patients.

There is concern that modified templates can potentially leave behind disease that would have otherwise been excised with a standard template, illustrated by the common criticism that the landmark studies by the Ray, Donohue, and Weissbach groups lack recurrence and survival data for the study populations [5, 10]. More recently, Eggener et al. analyzed the pathological results for 364 clinical stage I and 136 clinical stage IIA patients who underwent standard template RPLND at MSKCC between 1989 and 2004 [19]. The anatomical distribution of disease found at surgery was superimposed on five modified templates (MSKCC, IU, TTSG, Innsbruck, and JHU). Extra-template disease was found in 1–11% of patients with pathological stage IIA disease and in 3–23% of patients with pathological stage IIB–C disease. The common sites of missed disease were the para-aortic nodes for right-sided tumors and the interaortocaval, precaval, and paracaval nodes for left-sided tumors.

In summary, there is currently no definitive evidence to support one template over another for primary RPLND in early-stage NSGCT.The goal is to maximize cure in pathological stage II patients while minimizing dissection in stage I. The availability of effective chemotherapy has meant an almost universal recommendation to avoid suprahilar dissection, the most morbid portion of the RPLND, except in cases where extensive retroperitoneal disease is encountered at the time of surgery. The most limited templates may be missing up to 23% of positive lymph nodes. By including the interaortocaval, precaval, and paracaval region for left-sided tumors, the para-aortic region for right-sided tumors, and the ipsilateral iliac vessels, the rate of missed disease drops to <3%.

Clinical implications

We are unable to recommend one template over another owing to insufficient evidence.

Clinical question 3

For patients undergoing primary RPLND, how do open and laparoscopic approaches compare regarding benefits and harms?

Literature search

A MEDLINE and PubMed search was conducted using the previously described methods. Search terms included "testicular neoplasm," "germ cell tumor," "laparoscopic RPLND," "laparoscopic lymphadenectomy," "robotic lymphadenectomy," and "robotic RPLND."

The evidence

Laparoscopic RPLND (L-RPLND) was developed in the early 1990s in an effort to reduce perioperative morbidity while maintaining the diagnostic and therapeutic benefits of an open RPLND. The indications for L-RPLND mirror those for a primary open RPLND: stage I or IIA NSGCT, negative serum markers, and absence of surgical contraindications. L-RPLND was initially accepted as a diagnostic tool and controversy still surrounds its ability to match the therapeutic benefit of an open RPLND. Multiple reviews published in the last decade have addressed the role of L-RPLND (Table 37.3).

Several series have demonstrated that L-RPLND is associated with less perioperative morbidity. Although operative times are typically longer with L-RPLND, studies by Abdel-Aziz et al. [20] and Poulakis et al. [21] reported that L-RPLND resulted in significantly less blood loss and a shorter length of hospital stay. Poulakis et al. also reported that patients who underwent L-RPLND had significantly less narcotic requirement, a shorter time to oral intake, and faster return to normal activity compared with nonrandomized historical controls. In addition, open RPLND was associated with significantly higher rates of early and late postoperative complications. Open conversion was required in 2.7–6.9% of cases, primarily for intraoperative bleeding.

In order to provide comparable therapeutic benefit, L-RPLND should produce similar lymph node yields to the open technique. This comparison is difficult to assess, however, since many of the studies in the recent literature did not perform L-RPLND as a completely therapeutic intervention. Whereas one study noted that L-RPLND "is used for diagnostic purposes only," another reported that L-RPLND was not completed if grossly positive nodes were encountered during dissection [22, 23]. The latter study also noted that lymph node yield was higher for patients with negative nodes (25 ± 3) compared with patients found to have positive nodes (14 ± 2). Another study that employed a similar template for both L-RPLND and open RPLND reported a significantly higher lymph node yield in the open group (33 ± 11) compared with the L-RPLND group (17 ± 10) [20]. Poulakis et al. reported no significant difference in the lymph node yield between open RPLND (11, range 6–15) and L-RPLND (10, range 7–16), but the lymph node yields reported in their study were considerably lower than those in other current series so no conclusion can be made based on these data [21].

In order to compare accurately the therapeutic efficacy of open and laparoscopic techniques, series would have to employ similar templates. Even when similar templates were employed, L-RPLND did not uniformly involve dissection of lymph nodes behind the great vessels [20]. The decision to forego dissection behind the great vessels during L-RPLND is based on a study by Höltl et al., which documented the lack of isolated retroaortic or retrocaval lymph nodes [24]. Although this study demonstrates that patients will likely be properly staged based on a laparoscopic dissection that does not include lymph nodes behind the great vessels, the authors made the supposition that all pathological stage II patients will receive adjuvant chemotherapy that will theoretically treat any residual retroaortic or retrocaval germ-cell tumor.

The therapeutic benefit of L-RPLND is also difficult to assess since most pathological stage II patients in the L-RPLND studies received adjuvant chemotherapy [21, 23–26]. Despite this pervasive treatment algorithm, several studies have included patients with pathological stage II disease who have undergone surveillance. Studies by Abdel-Aziz et al. [20], Bhayani et al. [22], and Nielsen et al. [27] included a total of 14 patients with nodal involvement who were initially observed after L-RPLND. With a mean follow-up ranging from 12 to 72 months, two patients experienced relapse with serum tumor markers and one patient suffered recurrence in his chest. No retroperitoneal recurrences were noted.

Robotic surgery has been successful in making otherwise technically demanding laparoscopic operations accessible to a wider range of urological surgeons and may soon be employed for RPLND. The first description of this technique was by Davol et al. in 2006, who described a case report of an 18-year-old boy with teratoma predominant mixed germ-cell tumor who underwent bilateral robot-assisted laparoscopic RPLND [28]. The total operating time was 235 min, estimated blood loss (EBL) 125 mL, and he was discharged home on postoperative day 2. Since that time, only two small case series of three patients each have been published. Williams et al. performed unilateral right-sided RPLND with operating times ranging from 150 to 240 min, lymph node yields of 12 to 33, and a length of stay of 2 days for all patients [29]. Antegrade ejaculation was preserved in all cases and no positive lymph nodes were obtained. In the other series, de Cobelli et al. reported slightly longer operating times (240–275 min) with similar lymph node yields of 13–19 [30].

In summary, the contemporary literature demonstrates that L-RPLND is a well-tolerated procedure with less perioperative morbidity than open RPLND when the procedure is performed by skilled laparoscopic surgeons. Despite this benefit, the literature has not demonstrated that the therapeutic efficacy of L-RPLND currently matches that of open RPLND. Ultimately, a randomized study of laparoscopic versus open RPLND utilizing similar templates is needed to compare the two techniques definitively. In the meantime, more evidence regarding the efficacy of L-RPLND will come from patients with pathological stage II NSGCT who elect to undergo observation after RPLND. The role of robot-assisted laparoscopic RPLND remains to be seen, as there are only case reports available at present.

Clinical implications

In patients undergoing primary RPLND, we suggest an open approach versus a laparoscopic or robotic-assisted laparoscopic approach (conditional recommendation based on very low-quality evidence).

Table 37.3 Role of laparoscopic RPLND.

Study	Methods	Intervention	Participants	Outcomes	Results	Notes
Bhayani et al. [22]	Retrospective review Mean FU 72 months	L-RPLND	29 patients with clinical stage I NSGCT	Operative + pathological parameters	2/29 (6.9%) required open conversion Mean OR time = 258 min (157–380) Mean EBL = 389 mL (75–3000) Mean node yield = 20 nodes (7–53) Mean node yield higher for negative nodes (25 ± 3) than positive nodes (14 ± 2) 17/29 (59%) negative nodes → observation until failure (2 recurrences: chest at 3 months, serum markers at 5 months) 12/29 (41%) positive nodes → chemotherapy (n = 10) or observation (n = 2) (1 observation patient salvaged with chemotherapy at 13 months for elevated serum markers) Complications: 2 hemorrhage, 1 retrograde ejaculation	RPLND not completed if grossly positive nodes encountered Retroaortic + retrocaval nodes not routinely removed Long-term FU Included pathological stage II patients who were initially observed after RPLND
LeBlanc et al. [25]	Prospective study Median FU 15 months	L-RPLND using extraperitoneal approach	20 patients with clinical stage I NSGCT+ 5 patients with clinical stage IIA NSGCT	Operative + pathological parameters	No patient required open conversion Mean OR time = 230 min (180–300) EBL <50 mL for all cases Mean LOS = 1.2 days (1–3) Mean node yield = 9.8 (right) + 17.7 (left) 10/25 (40%) positive nodes → chemotherapy No recurrence	4/5 patients with clinical stage IIA had positive nodes Retroaortic + retrocaval nodes not routinely removed
Janetschek et al. [23]	Prospective study Mean FU 43 months	Lap. RPLND	73 patients with clinical stage I NSGCT	Operative + pathological parameters	2/73 (2.7%) required open conversion Mean OR time = 297 min (150–630) Mean EBL = 156 mL (10–350) Mean LOS = 3.3 days (2–5) 19/73 (26%) positive nodes → chemotherapy 1 contralateral recurrence in pathological stage I group	Retroaortic + retrocaval nodes dissected only in early cases No mention of node yield
Poulakis et al. [21]	Retrospective review Mean lap. FU 4 months Mean open FU 26 months	L-RPLND (21 patients) or open RPLND (29 patients)	50 patients with clinical stage I NSGCT	Operative + QOL parameters	No lap. case required open conversion Mean OR time = 233 min (lap.) vs. 203 min (open) Mean EBL = 270 mL (lap.) vs. 422 mL (open) Mean LOS = 2 days (lap.) vs. 7 days (open) Sig. more early + late complications in open group Lap. group had sig. less narcotic requirement, shorter time to oral intake + faster return to normal activity No sig. difference between mean node yield for lap. (10, 7–16) vs. open (11, 6–15) Positive nodes in 4/21 (19%) lap. + 7/29 (24%) open → chemotherapy (all NED at last FU)	Direct comparison with open RPLND

(*continued overleaf*)

Table 37.3 (Continued)

Study	Methods	Intervention	Participants	Outcomes	Results	Notes
Nielsen et al. [27]	Retrospective review Mean FU 36 months	L-RPLND	120 patients with clinical stage I NSGCT	Operative + pathological parameters	74/120 (62%) negative nodes → observation (7 recurrences → 1 elevated serum markers + 6 outside conventional RPLND template) 46/120 (38%) positive nodes → 36 chemotherapy + 10 observation (2 recurrences in observation group → 1 elevated serum markers + 1 chest) Median node yield = 20	Included excision of retroaortic + retrocaval nodes Included pathological stage II patients who were initially observed after RPLND
Abdel-Aziz et al. [20]	Retrospective review Mean lap. FU 12 months Mean open FU 15 months	L-RPLND (22 patients) or open RPLND (6 patients)	28 patients with clinical stage I NSGCT	Operative + pathological parameters	Mean OR time = 313 min (lap.) vs. 284 min (open) Mean EBL = 159 mL (lap.) vs. 254 mL (open) Mean LOS = 1.2 days (lap.) vs. 8.5 days (open) Node yield sig. higher in open (33 ± 11) vs. lap. (17 ± 10) Positive nodes in 7/22 (32%) lap. + 0/6 open → 5 chemotherapy + 2 observation (all NED at last FU)	Similar modified template for lap. + open Open group with sig. more pT2 patients Included pathological stage II patients who were initially observed after RPLND
Höltl et al. [24]	Retrospective review Mean FU 55 months	Group 1 (29 patients): clinical stage I, L-RPLND with retroaortic/ retrocaval dissection Group 2 (64 patients): clinical stage II, chemotherapy Group 3 (46 patients): clinical stage I, L-RPLND without retroaortic/ retrocaval dissection	75 patients with stage I NSGCT + 64 patients with stage II NSGCT	Distribution of Nodal metastases	Group 1: 10/29 (34%) positive nodes exclusively ventral to great vessels → chemotherapy Group 2: no patient with enlarged node(s) only dorsal to great vessels Group 3: 6/46 (13%) positive nodes → chemotherapy	Basis for excluding retroaortic + retrocaval dissection Assumes that all patients upstaged from stage I to stage II will receive chemotherapy
Neyer et al. [26]	Retrospective review Median FU 72 months	L-RPLND	136 patients with clinical stage I NSGCT	Operative + pathological parameters	7/136 (5%) required open conversion Mean OR time = 261 min (115–570) Median EBL = 50 mL (20–3000) Mean LOS = 4.1 days 25/136 (18.4%) positive nodes → 2 cycles of adjuvant chemotherapy (NED at last FU) 111/136 (81.6%) negative nodes → observation (8 relapsed → 6 chest + 1 elevated serum markers + 1 contralateral retroperitoneum)	

EBL, estimated blood loss; FU, follow-up; lap., laparoscopic; LOS, length of stay; NED, no evidence of disease; OR, operating room; QOL, quality of life sig., significant/significantly.

Clinical question 4

In patients with stage IS NSCGT, how does chemotherapy compare with primary RPLND in terms of overall survival?

Literature search

A MEDLINE and PubMed search was conducted using the previously described methods. Search terms included "testicular neoplasm," "germ cell tumor," "stage IS," "tumor markers," and "elevated serum markers."

The evidence

Clinical stage IS NSGCT is defined by persistently elevated serum markers after orchiectomy with no radiographic evidence of metastatic disease or nodal involvement. Historically, these patients were treated with RPLND in the belief that the persistently elevated serum markers were indicative of occult disease in the retroperitoneum. Several small retrospective reviews provide evidence supporting the trend away from primary RPLND for clinical stage IS patients (Table 37.4).

A study by Saxman et al. included 30 patients with clinical stage IS NSGCT who were treated with primary RPLND [31]. With a median follow-up of 36 months, 24% of patients with no detected nodal involvement at the time of RPLND required chemotherapy for later disease progression. A significant limitation of the study was the omission of post-RPLND serum markers, which would have allowed the detection of patients who experienced serological remission after surgery. In contrast to this surgical series, a study by Culine et al. included 20 patients with clinical stage IS NSGCT treated with induction chemotherapy [32]. All patients had normalization of serum markers after chemotherapy. Although no direct comparison can be made with the Saxman et al. study, only 15% of patients treated with induction chemotherapy required later salvage therapy for radiographic recurrence.

Two nonrandomized studies compared patients with clinical stage IS NSGCT who were treated with either induction chemotherapy or primary RPLND. Davis et al. noted that 100% of patients treated with primary RPLND required chemotherapy for retroperitoneal recurrence or persistent elevation of serum markers, whereas only 25% of patients treated with induction chemotherapy required delayed RPLND for radiographic recurrence [33]. Similarly, Dash et al. reported that 100% of patients who did not receive adjuvant chemotherapy after RPLND required salvage chemotherapy for later recurrence [34]. In the group that received induction chemotherapy, all patients achieved serological remission. Seven patients (41%) underwent RPLND, three electively and four for radiographic recurrence. Of patients undergoing RPLND, five were found to have teratoma and one patient had viable germ-cell tumor, further supporting the conclusion that absence of radiographic abnormality following chemotherapy does not guarantee an absence of retroperitoneal disease.

Clinical implications

In patients with stage IS NSCGT, we suggest induction chemotherapy over RPLND (conditional recommendation based on very low-quality evidence). Persistently elevated serum markers after orchiectomy in a patient with a normal retroperitoneum are indicative of systemic disease and patients should be treated accordingly.

Clinical question 5

In patients with high-risk stage I NSGCT, does RPLND offer any benefit over chemotherapy?

Literature search

A MEDLINE and PubMed search was conducted using the previously described methods. Search terms included "testicular neoplasm," "germ cell tumor," "stage I," "embryonal carcinoma," "lymphovascular invasion," and "high risk."

The evidence

The goal of risk stratification of stage I NSGCT patients is to identify high-risk patients who will likely benefit from adjuvant therapy and low-risk patients who can avoid the associated toxicity of additional treatment. The presence of lymphovascular invasion (LVI) and a predominance of embryonal histology are the factors most commonly used to identify high-risk patients. Other high-risk factors include stage ≥ T2, the presence of malignant teratoma or undifferentiated histology in the primary tumor, or the absence of yolk sac elements. Although the literature provides guidelines to aid in identifying high-risk patients, the optimal treatment of these patients is still a question of significant debate (Table 37.5).

Several retrospective studies in North America have examined the role of RPLND in the treatment of high-risk clinical stage I patients [35–37]. Two studies included one treatment arm and demonstrated that predominance of embryonal histology and presence of LVI were associated with higher rates of upstaging to pathological stage II disease [36, 37]. Although these studies also demonstrated good control of the retroperitoneum, no comparison was made with similar patients who underwent active surveillance or chemotherapy. A study by Al-Tourah et al. included high-risk patients who underwent either RPLND or surveillance and reported no significant difference in chemotherapy-free survival between the two groups [35]. Despite the inclusion of two treatment arms, no statistical comparison of high-risk features was included and the study was not randomized.

The role of adjuvant chemotherapy for high-risk patients is largely addressed by European studies. Studies using one or two cycles of platinum-based chemotherapy for high-risk patients reported favorable relapse rates of ≤7% [38–43]. The recurrence rates, which are comparable if not better than those for RPLND, are tempered by the potentially significant long-term toxicity documented in patients

Table 37.4 Management of stage IS NSGCT.

Study	Methods	Intervention	Participants	Outcomes	Results	Notes
Davis et al. [33]	Retrospective review Mean FU 81 months	Group 1 (11 patients): primary RPLND Group 2 (4 patients): induction chemotherapy	15 patients with clinical stage IS NSGCT	Recurrence	Group 1: 11/11 (100%) required chemotherapy for RP disease or persistent serum marker elevation Group 2: 1/4 (25%) required postchemotherapy RPLND for recurrence	
Saxman et al. [31]	Retrospective review Median FU 36 months	RPLND	30 patients with clinical stage IS NSGCT	Recurrence	9/30 (30%) positive nodes 5/21 (24%) patients with negative nodes required chemotherapy for later disease progression	Excluded patients given adjuvant chemotherapy after RPLND No clarification of which patients experienced serum marker normalization after RPLND
Culine et al. [32]	Retrospective review FU range 14–112 months	Induction chemotherapy	20 patients with clinical stage IS NSGCT	Recurrence	100% of patients achieved normal serum markers after chemotherapy 3/20 (15%) recurrence (8–9 months postchemotherapy)	Equal distribution of recurrences among chemotherapy regimens
Dash et al. [34]	Retrospective review Median FU 35 months	Group 1 (7 patients): primary RPLND Group 2 (17 patients): induction chemotherapy	24 patients with clinical stage IS NSGCT	Recurrence	Group 1: 6/7 (86%) positive nodes, 3 patients received chemotherapy → NED at last FU, 4 patients observed → all required chemotherapy for recurrence Group 2: all patients had normal markers postchemotherapy, 3 patients underwent elective PC-RPLND + 14 patients observed → 4 patients required later PC-RPLND for recurrence • PC-RPLND histology: 1 fibrosis, 5 teratoma, 1 viable germ-cell tumor	

FU, follow-up; NED, no evidence of disease.

Table 37.5 Management of high-risk stage I NSGCT.

Study	Methods	Intervention	Participants	Outcomes	Results	Notes
Albers et al. [45]	RCT Median FU 56 months	RPLND (191 patients) or 1 cycle BEP (191 patients)	382 patients with clinical stage I NSGCT	Recurrence	Sig. difference between relapse rate of 1% in BEP group vs. 8% in RPLND group (p=0.001) 2 year DFS 99.5% for BEP vs. 91.9% for RPLND HR for recurrence with RPLND vs. BEP=7.937 (95% CI 1.8–34.4)	Intention-to-treat analysis (17 lost from BEP+18 lost from RPLND) Powered to detect 7% reduction in recurrence with BEP vs. RPLND Largest RCT for adjuvant therapy in clinical stage I NSGCT No comparison of embryonal component or LVI, not necessarily high-risk patients All patients with nodal metastases treated with 2 cycles of adjuvant BEP
Stephenson et al. [36]	Retrospective review Median FU 53 months	RPLND	267 patients with clinical stage I–IIA NSGCT + embryonal predominance or LVI	Pathological staging, recurrence	112/267 (42%) pathological stage II → 54% with low-volume N1 disease, 50% received adjuvant chemotherapy Patients with both embryonal predominance + LVI had higher rate of pathological stage II disease compared with patients with either embryonal predominance or LVI (54 vs. 37%, $p=0.009$) Estimated 52% of clinical stage I patients overtreated with RPLND (no recurrence in 5 years)	No comparison with surveillance or chemotherapy No comparison with low-risk clinical stage I patients "Embryonal predominant" = >50% embryonal histology
Sweeney et al. [37]	Retrospective review Median FU 46 months	RPLND	292 patients with clinical stage I NSGCT → 125/292 (43%) embryonal predominance	Pathological staging, recurrence	66/292 (22%) pathological stage II → 32% embryonal predominant vs. 16% nonembryonal predominant ($p=0.002$), 36% LVI vs. 15% non-LVI ($p<0.0001$) Recurrence rate significantly higher for embryonal predominant pathological stage I (21%) compared with nonembryonal predominant (3%, $p<0.0001$) Recurrence rate significantly higher for LVI pathological stage I (20%) compared with non-LVI (7%, $p<0.001$) 1/292 relapsed in retroperitoneum (embryonal predominant pathological stage I)	"Embryonal predominant" = most common histology Good control of RP

(*continued overleaf*)

Table 37.5 (Continued)

Study	Methods	Intervention	Participants	Outcomes	Results	Notes
Al-Tourah et al. [35]	Retrospective review Median FU 48 months	Surveillance (72 patients) or RPLND (32 patients)	104 patients with embryonal predominant clinical stage I NSGCT → 46/104 (46%) LVI	Pathological staging, recurrence	Surveillance: 24/72 (33%) recurrence → 10 biochemical recurrence + 10 RP mass + 4 chest metastasis (all salvaged with chemotherapy ± RPLND, 1 dead of stroke) RPLND: 14/32 (44%) pathological stage II, no RP relapse for pathological stage I or II No sig. difference in 4-year chemotherapy-free survival between surveillance and RPLND groups	"Embryonal predominant" = ≥50% embryonal histology Initial therapy determined by patient 13% recurrence rate during surveillance for nonembryonal predominant patients
Oliver et al. [42]	Retrospective review Median FU 84 months	Surveillance (234 patients) or adjuvant chemotherapy with 1–2 cycles BEP (148 patients) for high-risk patients (i.e. LVI, malignant teratoma, absence of yolk sac elements, undifferentiated histology)	234 patients with clinical stage I NSGCT	Recurrence	Surveillance group after 1986: 27% recurrence Adjuvant chemotherapy: 4% recurrence	Patients enrolled between 1978 and 2000, adjuvant chemotherapy not offered until 1986 No indication of how patients relapsed
Böhlen et al. [38]	Prospective study Median FU 93 months	Adjuvant chemotherapy (2 cycles PVB before 6/87 → 2 cycles BEP after 6/87)	59 patients with clinical stage I NSGCT and ≥1 risk factors (embryonal histology, LVI, stage > T1)	Recurrence, toxicity	2/59 (3%) completed only 1 cycle of chemotherapy owing to toxicity (1 paralytic ileus, 1 suspected cardiotoxicity) WHO grade 4 toxicity observed in 9/59 (15%) patients Most common toxicities included myelosuppression, nausea/vomiting, and alopecia 2/59 (3%) recurrence (1 ipsilateral pelvis, 1 metachronous second testicular primary)	No quantification of embryonal component

Pont et al. [43]	Prospective study Median FU 79 months	Surveillance (42 patients) or adjuvant chemotherapy with 2 cycles BEP (42 patients) for patients with LVI	84 patients with clinical stage I NSGCT ± LVI	Recurrence, toxicity	Adjuvant chemotherapy: 2/29 (7%) recurrence among patients with >2 years' FU (1 retroperitoneum + 1 iliac fossa, no recurrence in patients with <2 years' FU) Short-term toxicity of BEP: no WHO grade 4 toxicity, most common WHO grade 3 toxicity included transient neutropenia + alopecia No patient developed ischemic heart disease, cerebrovascular disease, or Raynaud syndrome No long-term pulmonary sequelae, high-tone hearing loss, or hematological malignancies in BEP group	Age-matched controls used from surveillance group to perform matched-pair analysis for toxicity No long-term comparison of recurrence rates between adjuvant chemotherapy + surveillance groups
Cullen et al. [41]	Prospective study Median FU 48 months	2 cycles BEP	114 patients with clinical stage I NSGCT and ≥3 high-0risk features (LVI, undifferentiated histology, absence of yolk sac elements)	Recurrence, toxicity	3/114 (3%) recurrence (1 RP/chest/liver, 1 metachronous second testicular primary, 1 groin) Short-term toxicity of BEP: 4% WHO grade 3 leukopenia, 27% WHO grade 3 emesis, 11% peripheral neuropathy, 8% tinnitus 1/114 died of cerebrovascular accident during second cycle	1 patient with groin relapse not confirmed to have NSGCT upon final pathological review
Maroto et al. [46]	Prospective study Median FU 40 months	Surveillance (358 patients) or adjuvant chemotherapy with 1–2 cycles BEP (231 patients) for patients with ≥1 high-risk features (embryonal histology, LVI, stage > T2)	589 patients with clinical stage I NSGCT	Recurrence, toxicity	Recurrence rates: 17% non-LVI on surveillance, 55% + LVI on surveillance, 1.3% + LVI with adjuvant chemotherapy (majority of relapses limited to RP) Embryonal predominance and LVI were sig. predictors of recurrence in multivariate model Most common toxicity included transient neutropenia and nausea/vomiting	22 patients with LVI chose surveillance over chemotherapy → highest recurrence + lowest DFS

(*continued overleaf*)

Table 37.5 (Continued)

Study	Methods	Intervention	Participants	Outcomes	Results	Notes
Westermann et al. [44]	Prospective study Median FU 96 months	1 cycle BEP	40 patients with clinical stage I NSGCT with embryonal predominance and/or LVI	Recurrence, toxicity	5/40 (13%) recurrence (1 chest recurrence, 2 metachronous second testicular primary, 2 unknown recurrence pattern) Long-term toxicity minimal → 1 patient with NCI grade 2 peripheral neuropathy after salvage chemotherapy, 2 patients with intermittent tinnitus after 1 cycle of BEP (no cardiotoxicity)	"Embryonal predominant" = >50% embryonal histology Central pathology review
Vidal et al. [40]	Prospective, Phase II study Median FU 186 months	1 cycle BEP	40 patients with high-risk clinical stage I NSGCT	Recurrence, toxicity, secondary malignancy	1 patient (2.5%) had pulmonary relapse and died of pulmonary distress following salvage BEP × 3; NED on autopsy 3 patients (7.5%) developed secondary malignancy; 1 with leukemia and 2 with colorectal cancer 3 patients (7.5%) developed metachronous contralateral disease; grade 1 tinnitus in 5% and grade 2 tinnitus in 2.5% Patient with leukemia developed NSTEMI and stage III CKD at 210 months post-therapy No other pulmonary, renal, or cardiac toxicity reported	Does not classify metachronous contralateral tumors as a recurrence
Tandstad et al. [39]	Prospective study Median FU 4.8 years	1 cycle BEP or surveillance	745 patients with low-risk (495) and high-risk (250) clinical stage I NSGCT	Recurrence, short-term toxicity	High-risk relapse rate: 3.2% BEP group vs. 42% surveillance group Toxicity reported in 80% Grade 3/4 toxicity: leukopenia (33%), infection (2%), obstipation (1%), neurological (<1%)	Vascular invasion was the only criterion used to determine low vs. high risk Patients given option of surveillance or treatment

BEP, bleomycin, etoposide, and platinum (cisplatin); DFS, disease-free survival; FU, follow-up; HR, hazard ratio; LVI, lymphovascular invasion; PVB, platinum (cisplatin), vinblastine, and bleomycin; RCT, randomized controlled trial; RP, retroperitoneal; sig. significant.

receiving platinum-based chemotherapy. In an effort to limit cumulative chemotherapy exposure, Westermann et al. treated 40 high-risk patients with one cycle of BEP (bleomycin, etoposide, and platinum [cisplatin]) [44]. The recurrence rate of 13% was higher than those when patients predominantly received two cycles of platinum-based chemotherapy, but long-term toxicity was minimal with a median follow-up of 96 months.

A randomized clinical trial by Albers et al. is a valuable addition to the literature [45]. Although the study was not limited to high-risk clinical stage I patients, the design allowed direct comparison of RPLND and one cycle of BEP. The authors reported a significant decrease in the recurrence rates after patients received one cycle of BEP compared with RPLND.

A prospective Swedish and Norwegian Testicular Cancer Project (SWENOTECA) evaluated 745 clinical stage I NSGCT patients who were treated with surveillance or a single cycle of BEP [39]. High risk was determined by the presence of vascular invasion alone and in those 250 patients there was a relapse rate of 3.2% in the BEP group compared with 42% in the surveillance group. The authors estimated that if all patients (high- and low-risk) were to undergo surveillance, the relapse rate would be 21% and require approximately 77 additional courses of salvage chemotherapy. If single-cycle BEP was given, then the relapse rate would decrease to 2% and only seven additional cycles of chemotherapy would be needed.

Clinical implications

In patients with clinical stage I NSGCT and high-risk features, we recommend against surveillance (strong recommendation based on very low-quality evidence). In these patients, we suggest either RPLND or a single cycle of BEP, but we are unable to make a recommendation of one treatment over another.

The perioperative morbidity of RPLND is balanced by more accurate staging, control of the retroperitoneum, and potential avoidance of chemotherapy and its associated toxicity. Adjuvant chemotherapy offers the advantage of providing systemic treatment with fewer cycles than salvage chemotherapy. In centers that lack appropriate expertise and experience to perform a diagnostic and potentially therapeutic RPLND, we suggest adjuvant chemotherapy (conditional recommendation based on low-quality evidence).

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38 CHAPTER 38
Advanced nonseminoma

Michael C. Risk[1] and Clint Cary[2]
[1] *University of Minnesota and Minneapolis VA Medical Center, Minneapolis, MN, USA*
[2] *Indiana University School of Medicine, Indianapolis, IN, USA*

Introduction

Cisplatin-based chemotherapy has changed the outlook of metastatic testis cancer, including seminoma and nonseminoma, into a model for a curable neoplasm [1, 2]. The 5-year overall survival in those with metastatic testis cancer and good-, intermediate-, or poor-risk disease as classified by IGCCCG criteria is estimated at 94, 83, and 71%, respectively [3]. These excellent overall outcomes in those with advanced testis cancer is dependent on appropriate treatment at each stage of disease, and deviation from this has been associated with worse outcomes. Some aspects of care in advanced nonseminoma are standardized, such as chemotherapy regimens based on risk category and need for retroperitoneal lymph node dissection in those with a residual mass after chemotherapy. In some situations, however, there remains controversy. Our goal in this chapter is to evaluate the evidence for treatment at some critical points in the clinical pathway where which the urologist is actively involved and some controversy remains.

Clinical question 1

In patients with clinical stage 2A–B nonseminoma, how does primary surgical management compare with chemotherapy in oncological outcomes and adverse effects?

Introduction

For those who present with small-volume retroperitoneal nodal disease only and normal serum tumor markers after orchiectomy, primary treatment options consist of retroperitoneal lymph node dissection (RPLND) or induction chemotherapy. This applies only to those who have normalized serum tumor markers following orchiectomy, as recurrence rates after RPLND in those with elevated markers are high [4]. Hence induction chemotherapy is the primary option in the setting of elevated markers after orchiectomy. Given that all those with clinical stage (CS) 2A–B and normal tumor markers have IGCCCG good-risk disease, their 5-year overall survival exceeds 90% regardless of treatment approach. Therefore, treatment options need to be weighed not only based on clinical efficacy, but also on minimizing the short- and long-term morbidity of the various approaches.

Literature search

We conducted a search of the PubMed/MEDLINE database with no limitation on publication year but restricted our search to English-language reports. We searched for "testicular cancer" combined with "retroperitoneal lymph node dissection" and/or "chemotherapy." As identification of reports on the appropriate stage by electronic search was difficult, we performed a manual review of the studies to determine those appropriate to the clinical question. As only one clinical trial had been performed, we also utilized prospective and retrospective series utilizing primary RPLND and primary chemotherapy to examine oncological outcomes. For adverse events, we also analyzed data from studies on adverse effects of RPLND and chemotherapy for testis cancer regardless of stage.

The evidence

One clinical trial attempted to examine this treatment decision directly in 187 evaluable patients with CS 2A–B nonseminoma [5]. In a prospective multi-center clinical trial from 1991 to 1995, 57 centers in Germany and Austria participated although only one-quarter of the sites agreed to randomization, hence the treatment arms were not equally distributed. Overall, 137/187 (73%) were randomized, and 109 men who underwent RPLND with or without adjuvant

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chemotherapy were compared with 87 who underwent primary chemotherapy with or without postchemotherapy RPLND (PCRPLND). Some factors to consider in this trial include the fact that all pathological stage (PS) 2 patients underwent two cycles of adjuvant chemotherapy, some patients who underwent induction or adjuvant chemotherapy received carboplatin-based regimens rather than cisplatin-based regimens as part of a separate trial, and a majority of patients had elevated postorchiectomy markers. The authors found that, regardless of treatment approach, survival was similar (100% in the RPLND arm vs. 97% in the chemotherapy arm) and relapse rates at 3 years were statistically similar (7% in the RPLND arm, 11% in the chemotherapy arm). In the RPLND arm, 12% had no cancer found in the resected nodes, hence they were pathological stage 1 (PS1), although 12 of the 13 patients with PS1 were CS 2A. Surgical complication rates were higher with PCRPLND than with primary RPLND (27 vs. 12%), although only 33% of patients in the chemotherapy arm required PCRPLND. The most common complications were minor, described as impaired wound healing and lymphatic injuries. Loss of ejaculatory function, as would be expected, was higher in the RPLND arm than the chemotherapy arm (29% vs. 16%), although the acute toxicity of chemotherapy was higher in the chemotherapy group, particularly in hair loss, paresthesias, and pulmonary toxicity. There were only two deaths in this series, both in the chemotherapy arm, due to complications of chemotherapy. Quality of life was also analyzed both during and following treatment, and these were fairly similar between the two groups. The authors concluded that primary RPLND is most appropriate in CS 2A–B, given lower risk of complications with primary RPLND and adjuvant chemotherapy, and also avoidance of overtreatment in PS1 patients.

This is the only prospective trial comparing these two approaches in CS 2A–B patients, but it is limited by lack of complete randomization and differences relative to current practice. These differences include management of those with elevated serum markers, observation rather than adjuvant chemotherapy in some patients with PS 2A–B, and use of carboplatin-based chemotherapy in some patients. As stated earlier in this section, those with elevated markers are at high risk of recurrence with RPLND alone, and relapse rates following primary RPLND are reported to be as high as 80% [4]. Therefore, patients with elevated postorchiectomy markers are now uniformly given induction chemotherapy. Current practice includes observation rather than adjuvant chemotherapy for most patients with PS 2, particularly those with PS 2A, as will be discussed in a subsequent section of this chapter. The prospective trial included the use of carboplatin-based regimens, although these have been found to be inferior to cisplatin-based regimens in randomized trials [6–9], hence this is not the current standard of care. The inferiority of this regimen was also demonstrated in this study, as four of five patients with viable cancer on PCRPLND received carboplatin rather than cisplatin [5].

In both arms of the prospective trial, and indeed in all of the retrospective RPLND and primary chemotherapy series for CS 2A–B in the modern era with cisplatin-based chemotherapy, the disease-specific survival is >90% regardless of the treatment chosen (Tables 38.1 and 38.2). Treatment decisions are then made based on minimizing the treatment volume or intensity and minimizing the likelihood of adverse events. One way to examine minimization of treatment burden is to compare the likelihood of needing double therapy – needing chemotherapy after RPLND or needing PCRPLND after chemotherapy. Tables 38.1 and 38.2 outline the outcomes in CS 2A–B nonseminoma for initial RPLND and initial chemotherapy, respectively, including the frequency of double therapy for each. Following RPLND, the likelihood of subsequent chemotherapy was 35–91%, and is related to institutional practice and both clinical and pathological stage. Institutional practice can vary regarding which patients with pathological stage 2 disease are recommended for adjuvant chemotherapy. For example, the highest rate of postoperative chemotherapy was seen in the study in which all PS 2 patients underwent adjuvant chemotherapy; however, many PS 2 patients can safely be observed and this topic is covered further later in this chapter.

Chemotherapy following RPLND is also linked to clinical and pathological stage, which in turn are related to one another. In those with CS 2A and negative serum markers, as shown in Table 38.1, about 50% of patients have PS 1 disease and another 15–35% have PS 2A, while those with CS 2B, even limited disease (tumor size <3 cm), have comparatively lower rates of PS 1 and PS 2A. As recurrence rates for both PS 1 and PS 2A are low, these patients do not receive adjuvant chemotherapy at most centers. Assuming a <10% recurrence rate in those with PS 1, and a 20–33% rate of recurrence in those with PS 2A without adjuvant treatment, the majority of these patients could avoid chemotherapy following RPLND. This leads to a decreased likelihood of receiving chemotherapy with CS 2A alone (35% in [10]) compared with RPLND series which include CS 2B and/or elevated postorchiectomy markers (45–60%).

Similarly to the RPLND series, the likelihood of double therapy in those who undergo initial chemotherapy is dependent on institutional practice and clinical stage. Some centers recommend PCRPLND for all patients who undergo chemotherapy (e.g. [10]) whereas others, including most of the series presented here, do not perform PCRPLND in those with a complete clinical response (i.e. normal postchemotherapy serum tumor markers and no residual mass >1 cm). The management of patients with clinical complete response (cCR) is reviewed in the next section, but we will presume that patients with cCR do not undergo PCRPLND for the sake of argument. Based on data presented in Table 38.2, 53–87% of CS 2A–B patients achieve a cCR and could avoid

Table 38.1 RPLND series in CS 2A–B nonseminoma.

Study	Type	Population (*n*)	Elevated markers (%)	PS 1–2A (%)	Chemotherapy (%)	Survival (%)	Notes
[5]	Prospective	109	Yes (>50)	PS 1: 12 PS 2A–B: 70	91	100 (OS)	All PS 2 received chemotherapy
Cohort 1 [11]	Retrospective	34	Yes	PS 1: 26 PS 2A: 29	62	88 (OS)	Included CS 2C patients
Cohort 2 [11]	Retrospective	140	Yes	PS 1: 23 PS 2A: 36	56	98 (OS)	
[12]	Retrospective	91	Yes (54)	PS 1: 22 PS 2A: 12 PS 2B: 30	52 (no adjuvent treatment in PS 2A–B)	98 (DSS)	All with nodes ≥3 cm had PS 2B or worse disease
1985–1991 cohort [13]	Retrospective	20 CS 2A	No	PS 1: 50 PS 2A: 15	N/A	100 (DSS)	
1985–1991 cohort [13]	Retrospective	20 CS 2B <3 cm	Yes	PS 1: 0 PS 2A: 5	N/A	92.7 (DSS)	
1989–1993 [10]	Retrospective	57 (23% CS 2B)	Yes (16)	PS 1: 30 PS 2A: 9	60	100 (DSS)	
1994–1998 [10]	Retrospective	56 (7% CS 2B)	Yes (14)	PS 1: 36 PS 2A: 21	45	96 (DSS)	
1999–2002 [10]	Retrospective	23 (no CS 2B)	No	PS 1: 47 PS 2A: 35	35	100 (DSS)	

DSS, disease-specific survival; OS, overall survival; N/A, not available.

Table 38.2 Chemotherapy series in CS 2A–B nonseminoma.

Study	Type	Population (*n*)	Regimen	Complete response (%)	Surgery (%)	Survival (%)	Notes
[5]	Prospective	49	BEP	69	31	97 (OS)	
[5]	Prospective	29	CEB	62	38		
[14]	Retrospective	19 (CS 2B)	CISCA/VB	79	21	96 (RFS)	
[15]	Retrospective	28	BEP	71	29	96 (RFS)	
[16]	Retrospective	58 (CS 2A)	Platinum-based	83	17	98.5 (DSS)	Most with cisplatin
[16]	Retrospective	64 (CS 2B)	Platinum-based	61	39		Most with cisplatin
[17]	Retrospective	47 (CS 2A)	Platinum-based	87	6	98 (OS)	
[17]	Retrospective	175 (CS 2B)	Platinum-based	67	23	96 (OS)	
[18]	Retrospective	15 (CS 2A)	Platinum-based	60	40	100 (DSS)	
[18]	Retrospective	43 (CS 2B)	Platinum-based	53	47	93 (DSS)	
[10]	Retrospective	116	EPx4	59	100	100 (DSS)	All pts underwent PCRPLND

BEP, bleomycin, etoposide, platinum (cisplatin); CEB, carboplatin, etoposide, bleomycin; CISCA, cisplatin, cyclophosphamide, doxorubicin; EP, etoposide, platinum (cisplatin); VB, vinblastine, bleomycin; DSS, disease-specific survival; OS, overall survival; RFS, recurrence-free survival.

PCRPLND, and this is directly related to clinical stage at presentation. For those with CS 2A the rates of cCR are 60–87% and for CS 2B the cCR rates are lower at 53–79%. Hence for both CS 2A and 2B, initial chemotherapy results in lower rates of double therapy, similar to the findings of the prospective trial (91% of the RPLND arm versus 33% of the chemotherapy arm).

Another likely more relevant outcome to examine when making this decision is the likelihood of adverse effects. This was considered in the prospective trial, where adverse effects of chemotherapy were higher in the initial chemotherapy arm than in the initial RPLND arm, despite the fact that 91% of the RPLND arm underwent chemotherapy. This is likely due to the fact that the majority of the RPLND patients received less chemotherapy (two cycles of adjuvant versus three or four cycles for induction chemotherapy), and the receipt of chemotherapy would be even less in modern series where at least PS 2A patients would not receive chemotherapy in most cases. Additionally, the complication rates following PCRPLND were higher than in primary RPLND (27 vs. 12%), although only one-third underwent PCRPLND so total postsurgical complications were fewer in the chemotherapy arm (9 vs. 12%).

Given that the majority of men are diagnosed with testicular nonseminoma at ages 20–40 years, and most have long-term survival from their cancer, the late and long-term effects of these therapies also need to be considered in the treatment decision. Late effects of RPLND are similarly low between primary RPLND and PCRPLND at around 7% [19]. These include incisional hernia, small bowel obstruction, and ureteral stenosis/obstruction, with most treated surgically with resolution. The main potential long-term effect of RPLND is on fertility due to loss of antegrade ejaculation. This occurs as a result of injury of the bilateral lumbar postganglionic sympathetic nerves as part of a full bilateral RPLND. This injury can be avoided by performance of either prospective nerve sparing as part of the dissection, or a modified template dissection to avoid the nerves on one side. In the primary RPLND setting, modified template dissection without nerve sparing the dissected side results in preserved ejaculatory function in 90%, and with prospective nerve-sparing ejaculatory function this improves to 99% [20]. The results in the postchemotherapy setting are not as good, in part because only 20–40% of those undergoing PCRPLND are candidates for a nerve-sparing procedure [21, 22]. The tumor location and desmoplastic reaction in the retroperitoneum can make identification and nerve sparing difficult, and as a result the antegrade ejaculation is preserved in 74–79% with bilateral PCRPLND with nerve sparing and in 85–100% if a modified template can be utilized.

The late effects of chemotherapy are currently an area of extensive research and much still needs to be elucidated to determine absolute risk. Both persistent and late adverse effects of chemotherapy are known. Persistent effects are those that begin acutely during or soon after chemotherapy and do not resolve with time, and include neuropathy, nephropathy, pulmonary toxicity, hypogonadism, and metabolic syndrome. Peripheral neuropathy is a side effect of cisplatin, has been correlated with serum platinum levels, which can persist for years following therapy [23], and is present in 20–30% long term following up to four cycles of cisplatin-based chemotherapy [24, 25]. Nephropathy is also caused by cisplatin, and is related to cumulative dose [26]. Although recovery can occur in some patients, about 20–30% have persistent renal dysfunction [26], which, although often not symptomatic, may have a role in the risk of future cardiac events in these patients [27]. Pulmonary toxicity is a known effect of bleomycin, and in the prospective trial led to the only two deaths in that study [5]. Modern trials report acute mortality from bleomycin-induced pulmonary toxicity to be <1% [28, 29]. Long-term studies suggest that 8% of patients develop restrictive lung disease following cisplatin-based chemotherapy [30]; however, this effect appears to be minimal in those who require only standard chemotherapy (BEPx3 or EPx4) for good-risk disease. Hypogonadism is known to occur in survivors of testicular cancer regardless of treatment, although chemotherapy puts them at higher long-term risk than surgery alone (odds ratio [OR] 5.2, 95% confidence interval [CI] 3.5–7.9 versus 2.0, 95% CI 1.3–3.2 for surgery) [31]. Hypogonadism in turn can result in higher rates of metabolic syndrome, which includes obesity, hypertension, hyperlipidemia, and insulin resistance. Higher rates of metabolic syndrome are found in testicular cancer survivors, particularly those with a history of combination chemotherapy and low testosterone, with a 2–3-fold increased risk of metabolic syndrome in those with prior chemotherapy in most series [32, 33]. Metabolic syndrome can predispose patients to the cardiovascular disease (CVD) [34] that is considered a late effect of chemotherapy.

Late effects of chemotherapy are often not apparent acutely but rather manifest over time. Late effects of chemotherapy include CVD and secondary malignancies. There is a known increased rate of mortality in testicular cancer survivors relative to the general population, and in particular there is evidence for increased rates of death from CVD and secondary malignancies [35]. Many of the adverse effects of chemotherapy discussed above, including nephropathy, hypogonadism, and metabolic syndrome, are known to increase the risk of CVD. Several groups have demonstrated increased risk of CVD in testis cancer survivors who had received chemotherapy, with a range of 1.5–7.1-fold increased risk of CVD among different studies [36–39]. One study also found a 3.1-fold increase in myocardial infarction [36]. Secondary leukemia is a known potential adverse effect of etoposide, and although the relative risk is estimated as high

as sevenfold, the absolute risk in those who receive only an induction regimen (BEPx3 or EPx4) appears to be around 0.5% or less [40–43]. Cisplatin has also been associated with a risk of secondary leukemia, although the absolute risk is similarly about 0.16% at 15 years [43]. Solid malignancies are also increased following chemotherapy for nonseminoma. A fairly recent study examining only the era of modern cisplatin-based chemotherapy found a 40% increased risk of solid malignancy in nonseminoma patients treated with chemotherapy compared with those treated with surgery alone (standardized incidence ratio [SIR] 1.43, 95% CI 1.18–1.73), and this risk persisted more than 20 years after treatment [44]. The sites of greatest risk were kidney (SIR 3.37), thyroid (SIR 4.40), and soft tissue (SIR 7.49). Other series have had a similar risk demonstrated, but were contaminated by likely variable chemotherapy regimens, and the use of radiation in some patients. It should be noted that this is a population-based study with inherent limitations, including no data on chemotherapy regimen/dose or other risk factors for subsequent cancer.

Clinical implications

In patients with CS 2A nonseminoma with negative serum markers, we suggest RPLND over chemotherapy (conditional recommendation based on low-quality evidence). This recommendation assumes that patients place high value on the avoidance of short- and long-term side effects of cytotoxic chemotherapy and may elect to undergo a modified template or nerve-sparing RPLND designed to preserve antegrade ejaculation.

In patients with CS 2B nonseminoma, we suggest induction chemotherapy over primary RPLND (conditional recommendation based on low-quality evidence). Most will require double therapy if RPLND is performed upfront, whereas only about 25–45% will require PCRPLND if chemotherapy is the initial treatment. Induction chemotherapy has a higher adverse effect rate in the randomized trial, however, hence this decision should also take into account the potential for higher acute and long-term effects with induction chemotherapy.

For those with CS 2B, this decision is less clear, as most will require double therapy if RPLND is performed upfront, whereas only about 25–45% will require PCRPLND if chemotherapy is the initial treatment. Therefore, no strong recommendation can be made for this scenario, although it is hoped that the evidence provided here will help patients and providers make an informed decision.

Clinical question 2

In patients with stage 2–3 nonseminoma who have a complete clinical response to chemotherapy, how does surgical management (i.e. RPLND) compare with observation in terms of disease-specific and overall survival?

Introduction

Approximately 70–80% of patients with good-risk metastatic nonseminoma will experience a clinical complete response (CR) with induction chemotherapy, defined as normalization of tumor markers and reduction in the metastatic lesions to <1 cm in largest dimension. Early trials examining the necessity for maintenance chemotherapy in patients with a CR to chemotherapy with or without surgery demonstrated recurrence rates of 7–10% in the observation arms, with the majority of these patients having CR with chemotherapy alone [45, 46]. The management of these patients remains controversial, however, owing to evidence that about 25% of these patients harbor residual teratoma or viable germ-cell tumor (GCT) found at RPLND when performed [47]. As a result, some centers routinely perform postchemotherapy retroperitoneal lymph node dissection (PCRPLND) in these patients owing to the potential for untreated disease, whereas others have maintained that the low recurrence rates in these patients, and also the ability to treat effectively those who suffer recurrence, mandate observation as the preferred option in this population.

Literature search

We conducted a search of the PubMed/MEDLINE database with no limitation of publication year but restricted our search to English-language reports. We searched for "testicular cancer" combined with "retroperitoneal lymph node dissection" and/or "chemotherapy." As identification of reports on the appropriate stage by electronic search was difficult, we performed a manual review of the studies to determine those appropriate to the clinical question. As only one systematic review had been performed, we also examined the retrospective series evaluating outcomes in patients with a CR to chemotherapy, although all were referenced in the systematic review.

The evidence

Although no randomized trials on this subject have been performed, a number of centers have published their data on clinical outcomes with the management strategy utilized by those institutions. A recent systematic review addressed this question of management in the setting of sub-centimeter residual retroperitoneal disease following induction chemotherapy [48]. Owing to the nature of the data available in appropriate studies, the authors focused mainly on histology found at RPLND, disease relapse, and survival when provided. The analysis of PCRPLND histology was taken from six studies, with three published only in abstract form, and pooled histological data from 558 patients demonstrated necrosis, teratoma, and viable GCT in 71, 24 and 4% of patients, respectively. The recurrence-free survival in two series with a total of 228 patients was reported as 97–98%. The four surveillance series in patients with a clinical CR to chemotherapy included 455 patients, and the

relapse rate was 5% with a retroperitoneal relapse rate of 3%. Median follow-up in these series ranged from 4.3 to 15.5 years and reported overall relapse-free survival ranged from 92 to 100%.

As relapse-free survival does not appear to differ significantly between the two strategies (95% for observation versus 97% for PCRPLND), observation would seem the logical conclusion to avoid treatment and the potential adverse effects of surgery in the majority of patients. The reporting of this outcome is limited in the PCRPLND series, as only two studies, both available only in abstract form, contain these data. Other series, which have data on patients who underwent PCRPLND for masses up to 2 cm in size, have a similar relapse-free survival of 96%. Hence PCRPLND does not eliminate the risk of recurrence in those with a clinical CR to PCRPLND. Additionally, the majority of the relapses in those who pursued a surveillance strategy were salvageable, with 21 of the 25 relapses (84%) without evidence of disease at last follow-up, and the disease-specific survival based on these data was estimated as 99% (4/455), although only one series included significant follow-up beyond 5 years.

The main risk with observation is residual disease in the retroperitoneum, which would include viable GCT in 4% and teratoma in 24% of patients based on the PCRPLND data presented in the meta-analysis. In most of the observation series, viable GCT was responsible for recurrence, accounting for 15 of the 25 recurrences (60%). This differed in various reports: 83–100% were due to GCT in two series, whereas in the third only 20% were due to GCT, the remainder being retroperitoneal teratoma only managed with RPLND. The fourth series reported no recurrence in 106 patients. The reasons for these differences may be o differences in the patient populations, as the two series with mainly GCT at recurrence had higher populations of IGCCCG intermediate- and poor-risk disease (21–23%) compared with the series with mainly teratoma (6%).

Teratoma can represent a risk of growth, malignant transformation, and late relapse of disease, even beyond 5 years, and this argument leads many to continue the practice of PCRPLND in this population. The Indiana series contained the longest follow-up for patients managed by observation after clinical CR over a median 15.5 years in 141 patients [49]. Among the 12 relapses in this series, retroperitoneal relapses occurred in six and all contained active GCT. Based on the 24% rate of teratoma in those with clinical CR found at PCRPLND, one would expect 34 patients in the Indiana series to have residual teratoma in their retroperitoneum. Only two relapses – one primitive neuroectodermal tumor (PNET) and one sarcoma – suggest a specific relation to residual teratoma, and neither of these occurred in the retroperitoneum. Therefore, the risk related to residual subcentimeter retroperitoneal teratoma appears low within 15 years of chemotherapy treatment.

Clinical implications

In patients with stage 2–3 nonseminoma who have a complete clinical response to chemotherapy, we suggest surveillance over RPLND (conditional recommendation based on low-quality evidence). This avoids overtreatment in most men. Additionally, the small percentage of patients who relapse are able to be salvaged with surgery with or without chemotherapy.

Clinical question 3

In patients with pathological stage 2A–B nonseminoma following primary RPLND, what is the oncological efficacy of observation compared with adjuvant chemotherapy?

Introduction

A staging and potentially therapeutic option for those with clinical stage 1–2B nonseminoma and normal tumor markers following orchiectomy is retroperitoneal lymph node dissection (RPLND). Those who are found to have cancer in the retroperitoneal nodes are classified as pathological stage 2 (PS 2), with further staging based on the size and number of involved lymph nodes (Table 38.3). Those with PS 2C disease are extremely rare with appropriate preoperative imaging, and all are treated with induction chemotherapy following RPLND according to current recommendations given the high risk for relapse. The more difficult question is the next step in those with PS 2A–B disease, as many of these patients are cured by RPLND alone.

Literature search

We conducted a search of the PubMed/MEDLINE database with no limitation of publication year but restricted our search to English-language reports. We searched for "testicular cancer" combined with "retroperitoneal lymph node dissection" and/or "chemotherapy." As identification of reports on the appropriate stage by electronic search was difficult, we performed a manual review of the studies to

Table 38.3 AJCC stratification of pathological stage 2 nonseminoma.

AJCC stage	Pathological node stage	Nodal criteria
2A	pN1	Metastasis with a lymph node mass ≤2 cm and ≤5 nodes positive
2B	pN2	Metastasis with lymph node mass 2–5 cm or >5 nodes positive or evidence of extranodal extension
2C	pN3	Metastasis with lymph node mass >5 cm in greatest dimension

Source: Adapted from NCCN Guidelines Version 1.2016 (http://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf).

determine those appropriate to the clinical question. As only two clinical trials had been performed and only one was published with appropriate follow-up, we also utilized prospective and retrospective series utilizing observation and/or adjuvant chemotherapy following primary RPLND to examine oncological outcomes.

The evidence

We identified one randomized controlled trial (RCT) that directly compared surveillance with adjuvant chemotherapy in men with PS 2 disease following primary RPLND [50]. This trial enrolled 195 patients with PS 2 disease and randomized them to observation ($n=98$) or two cycles of adjuvant chemotherapy ($n=97$). Inclusion criteria allowed for elevated serum tumor markers at the time of RPLND, and more than one-third in each arm had elevated markers. Nearly all of these patients had pathological stage 2A–B disease, and the chemotherapy regimens were either combinations of cisplatin, vinblastine, and bleomycin (PVB) or these three agents with the addition of dactinomycin and cyclophosphamide (VAB). Disease recurrence was significantly higher in the observation group (49 vs. 6%, $p<0.001$), and only one patient who actually received the intended adjuvant chemotherapy regimen experienced recurrence. The overall survival at a median follow-up of 4 years was not significantly different between the two groups (observation 95% vs. adjuvant 97%, p-value reported as not significant). Recurrence in the observation arm was not significantly different when examined by pathological nodal stage, suggesting no difference in recurrence rates between PS 2A and 2B. The toxicity of the regimens included thrombocytopenia and mucosa, skin, and ear toxicity with the VAB regimen and leukopenia with the PVB regimen. Over half of the VAB group and 20% of the PVB group required dose modification related to toxicity, and there were no deaths related to chemotherapy.

One other randomized clinical trial reported preliminary results in 48 men with PS 2A disease following RPLND, with 16 randomized to observation and 32 randomized to adjuvant treatment with two cycles of PVB [51]. At a median follow-up of 18 months, one patient (6%) in the observation arm and none in the adjuvant developed recurrence. Mature data for this portion of the trial was not identified in our literature search, although the same group ran a concomitant randomized trial on two versus four cycles of PVB in 225 men with PS 2B disease [52]. The relapse rate did not differ between the two arms (6/111 [5%] with two cycles versus 1/114 [1%] with four cycles, $p=0.75$), nor did overall survival (100% with two cycles at median follow-up 42 months versus 97% with four cycles at median follow-up 44 months). The treatments differed in terms of toxicity, and 29% of patients randomized to four courses were unable to complete the treatment (versus 4% in those randomized to two courses). Hence two courses of adjuvant chemotherapy are adequate to minimize the risk of relapse without excessive toxicity.

Currently, adjuvant regimens utilize etoposide in place of vinblastine based on the findings of decreased toxicity of the former in the primary treatment of metastatic disease, and potentially improved response rates with more advanced disease [53, 54]. Retrospective studies on adjuvant regimens utilizing etoposide rather than vinblastine in patients with PS 2A–B have examined two courses of etoposide and cisplatin (EP), and also bleomycin with etoposide and cisplatin (BEP). The utility of BEP in PS 2A–B patients was evaluated in a series of 82 evaluable patients at Indiana University [55]. At a median follow-up of 85 months, there was only one recurrence, teratoma in a cervical node, which required only surgical management. Neutropenic fever occurred in 12% and no significant pulmonary toxicity was seen. The success of two courses of EP was demonstrated in a series of 87 patients with PS 2A–C disease (11% pN1, 84% pN2, and 5% pN3) [56]. This regimen prevented recurrence in 98.9% of patients at a median follow-up of 8 years, and all patients were alive with no evidence of disease at last follow-up. The sole recurrence was in a patient with pN3 disease who developed hepatic metastasis and elevated α-fetoprotein 4 months following his adjuvant EP. Salvage chemotherapy with four cycles of paclitaxel, etoposide, and cisplatin (TIP) resulted in a complete response with no further recurrence. This relapse may have been prevented by full induction chemotherapy currently recommended treatment for PS 2C (pN3) disease. Hence, overall, adjuvant chemotherapy following RPLND with PS 2A–B on pathology is effective at preventing recurrence in >95% of patients, although, based on the initial randomized trial already discussed, at least half will not relapse without treatment.

There is some controversy regarding patient selection for observation or adjuvant therapy. The discussed randomized trial did not find a significant difference in recurrence rates between PS 2A and PS 2B [50], suggesting that they have an equivalent risk of recurrence under observation at 49% overall. However, the caveat of that trial is that a number of men underwent RPLND with elevated markers, and clinical staging during the study period was not as precise as in the current era. More contemporary studies have reported lower risks of recurrence in those with PS 2A and PS 2B [57–60], and suggest that recurrence rates on observation are 25–33% in both PS 2A and PS 2B disease. Some centers, however, have reported higher rates of recurrence in those with PS 2B disease [61, 62], and suggest that the majority of those with PS 2B should undergo adjuvant treatment. The recurrence rates are highly variable in these series, however, with a range of recurrence of 0–42% in PS 2A and 33–93% in PS 2B. Other retrospective studies selecting only PS 2A for observation have reported very low recurrence rates of 10% or less with this strategy [63, 64]. Part of this variability is likely due to different rates of inclusion of those with

elevated markers prior to RPLND, which is known to predict recurrence [4].

Ultimately, the difference between the two strategies (adjuvant versus surveillance) is in the chemotherapy treatment burden – either treating all with two cycles of adjuvant chemotherapy or treating about one-third of patients with three or four cycles of induction chemotherapy. The acute burden of induction chemotherapy is greater than that of adjuvant chemotherapy [5], although little is known about the differences in long-term effects. As survival is the same in the two scenarios, treatment decisions should be based on available knowledge regarding these issues.

Clinical implications

In patients with pathological stage 2A–B nonseminoma following primary RPLND, we suggest observation over adjuvant chemotherapy (conditional recommendation based on moderate-quality evidence). This recommendation assumes that patients place a high value on the avoidance of chemotherapy with its short- and long-term side effects. In surgical series, the majority of patients are cured with surgery alone and the observation approach avoids overtreatment. This recommendation could change in the future depending on the availability of more information regarding differences in short- and long-term side effects between adjuvant versus induction chemotherapy.

Clinical question 4

In patients with postchemotherapy residual retroperitoneal masses following chemotherapy, how do outcomes compare in those who undergo unilateral template-based RPLND versus full bilateral RPLND?

Introduction

For those with normalized tumor markers and a residual retroperitoneal mass >1 cm in size following chemotherapy, PCRPLND is normally performed owing to the risk of cancer or teratoma in the specimen. Upon resection, the residual mass contains necrosis/fibrosis in about 45%, teratoma in about 45%, and active residual GCT in about 10% [65], although this can vary based on the clinical scenario. Prediction models generated to determine the histology of the residual mass based on clinical features have not proven helpful enough to change management [66, 67], hence resection is warranted in these patients. The survival benefit of PCRPLND, although not directly demonstrated by RCTs, is suggested by numerous studies [66, 68–70]. Although the indication for PCRPLND in this scenario is undisputed, there is some controversy regarding whether the extent of resection can be tailored based on the clinical setting, with some suggesting that unilateral, template-based resection can be performed in appropriately selected cases.

Literature search

We conducted a search of the PubMed/MEDLINE database with no limitation of publication year but restricted our search to English-language reports. We searched for "testicular cancer" combined with "retroperitoneal lymph node dissection" and/or "chemotherapy." As identification of reports on the appropriate stage by electronic search was difficult, we performed a manual review of the studies to determine those appropriate to the clinical question. As no clinical trials had been performed to address our question, we utilized prospective and retrospective series on postchemotherapy lymph node dissection to evaluate outcomes of interest.

The evidence

The standard technique for PCRPLND includes a full, bilateral template of dissection delineated laterally by the ureter on each side, superiorly by the renal vessels and diaphragmatic crus, and inferiorly by the common iliac arteries. Investigations in the setting of primary RPLND determined the main sites of retroperitoneal metastases based on tumor side, being in the interaortocaval region for right-sided tumors and the para-aortic region for left-sided tumors [71, 72]. A variety of templates were then created in the interest of resecting all areas most likely to harbor metastases while excluding areas along the path of the contralateral lumbar sympathetic nerves to maintain antegrade ejaculation. Donohue et al. demonstrated the oncological safety of modified templates in the primary RPLND setting [73], and also the efficacy in preserving ejaculatory function, and this was also shown in a prospective multi-center trial [74]. Despite this, in those patients with evidence of cancer at the time of primary RPLND, conversion to full bilateral RPLND is performed by some groups owing to the risk of extra-template disease [72, 75], although the need for this is debated.

Similar concern about extra-template disease exists in the postchemotherapy setting, and a variety of mapping studies have examined this to determine the necessary boundaries of resection (Table 38.4).

As shown in Table 38.4, there is wide variability in the frequency of disease outside the margins of a modified template of dissection. The reasons for this include differences in the borders of the modified template, and also differences in the clinical stage and extent of disease before and after chemotherapy, elevated markers at the time of surgery, and need for salvage chemotherapy prior to surgery [78, 79]. It should be noted that some of the patients included in these studies had extra-template disease noted on preoperative imaging or palpable extra-template disease at the time of surgery [77–79], which would normally exclude consideration for a modified resection. As shown also in Table 38.4, the majority of the extra-template disease in these series was teratoma and, as discussed in the earlier section regarding those with a complete clinical response to chemotherapy, the outcome of sub-centimeter teratoma is

Table 38.4 Series examining the incidence of disease outside the confines of modified template in patients who underwent bilateral PCRPLND.

Study	Years	*n*	Clinical stage	Positive markers[a]	Outside template	Extra-template teratoma (%)[b]	Survival	Notes
Wood et al. [76]	1979–1988	113	≥2B	No	14 (12%)	N/A	N/A	
Rabbini et al. [77]	1985–1995	39	≥2B	18%	1 (2.6%)	100	5-year DSS 95%	Extra-template case visible on CT
Ehrlich et al. [78]	1996–2005	50	≥1S	No	9 (18%)	100	82% RFS at 53 months	In ≤2B only 1 (5%) with extra-template disease
Carver et al. [79]	1989–2003	269	≥1S	16%	7–32% depending on template	80	N/A	All had cancer or teratoma

CT, computed tomography; N/A, data not available in the report.

[a] Positive markers denotes presence of positive serum tumor markers following chemotherapy and prior to PCRPLND.

[b] Extra-template teratoma denotes the percentage of extra-template disease that was teratoma, as opposed to viable germ-cell tumor.

uncertain. The benefits of less extensive dissection, which would include increased rates of antegrade ejaculation and potentially lower complication rates related to shorter operating times and decreased fluid shifts in postchemotherapy patients, need to be weighed against the risks of recurrence and the need for repeat RPLND. Furthermore, the majority of these studies were in an unselected cohort with elevated markers and performed in a retrospective fashion. It is difficult to know how the lymph node packets were split and labeled to establish the true area of metastatic disease in a retrospective design.

Investigations in selected patients for modified template PCRPLND have been performed in more recent years to determine the safety and oncological efficacy of this approach. Older series examining resection of the retroperitoneal mass only have had unacceptable outcomes, including high rates of retroperitoneal relapse. More recent series have limited modified template PCRPLND to those with normalized serum tumor markers, more limited disease pre- and postchemotherapy, and no evidence of extra-template disease on preoperative imaging. Table 38.5 presents the results of series describing the indications and outcomes following modified template PCRPLND.

As shown in Table 38.5, there is some variability regarding indication for utilization of a modified template of dissection in the postchemotherapy setting. The first study utilized a frozen section of the residual mass to determine candidacy, with the modified template used if only necrosis/fibrosis was found on frozen section. More recent series depend on the imaging findings both pre- and postchemotherapy to determine candidates for modified template PCRPLND, with most limiting it to those with retroperitoneal disease confined to the template both before and after chemotherapy with the postchemotherapy mass ≤5 cm in diameter. As shown in Table 38.5, reported retroperitoneal relapse rates are low in these series, and similar to rates seen in those with full bilateral RPLND in series that reported both. Nearly all studies report recurrence-free survival and disease-specific survival of ≥95%, which also suggests the efficacy of this approach in appropriately selected patients. The median follow-up in these studies varied, although in four it was longer than 5 years and in the longest it was 10 years.

Aside from efficacy, another consideration in the comparison of the two approaches (bilateral PCRPLND versus modified template PCRPLND) is adverse effects. Many of these series did not report these outcomes in a comparative fashion. Two series examined the surgical complication rates between the two: Herr reported a higher complication rate in those who underwent bilateral PCRPLD (20 vs. 2.7%) [80], whereas Heidenreich et al. reported a minimal difference in major complications (5.6% with bilateral PCRPLND vs. 4.1% with modified template PCRPLND) and no difference in minor complication rates [84]. These findings should be interpreted with caution as the burden of disease between the two groups is significantly different; for example, the average diameter of the retroperitoneal mass in the Heidenreich series was 4.5 cm in the modified template group versus 10.9 cm in the bilateral dissection group. Loss of ejaculation is the most common long-term adverse event related to RPLND, as discussed in earlier sections. Two series examined this and reported similar outcomes, finding antegrade ejaculation to be preserved in 79–85% of those who underwent modified template PCRPLND compared with 25% following bilateral PCRPLND [81, 84]. These differences may again be related in part to disease burden, and very few patients underwent prospective nerve sparing within the template during PCRPLND in these series. Prospective nerve sparing with bilateral PCRPLD is successful when performed, with the largest series reporting a 79% postoperative antegrade ejaculation rate in this setting [22], although nerve sparing could only be performed in 40% of all PCRPLND cases in

Table 38.5 Outcomes of modified template RPLND.

Study	Years	*n*	Median follow-up	Indication	RP recurrence[a]	Survival	Notes
Herr [80]	1988–1994	37	6 years	Necrosis on frozen section of RP mass	1 (3%)	At median follow-up of 6 years: 86% RFS 95% DSS	
Jacobsen et al. [81]	1980–1994	93	96 months	Disease confined to template	4 (4%)	Not stated	3% RP relapse rate in 99 who had full bilateral RPLND
Rabbani et al. [77]	1985–1995	9	56 months	Not stated	0	100% RFS at median follow-up of 56 months	
Cho et al. [82]	1991–2004	100	10 years	Disease confined to template pre- and post-chemotherapy; CS 2 only	0	10-year RFS: 92% 10-year OS: 99%	
Steiner et al. [83]	1988–2005	102	102 months	Disease confined to template pre- and post-chemotherapy; CS 2 only	1 (1%)	97% RFS and 99% DSS at median follow-up of 102 months	
Heidenreich et al. [84]	1999–2007	98	39 months	Confined to template pre- and postchemotherapy, PC mass <5 cm; CS 2–3	0	97% RFS at 2 years	1 (1.8%) RP relapse in 54 who had full bilateral RPLND
Vallier et al. [85]	2007–2013	17	54 months	Confined to template pre- and postchemotherapy, PC mass <5 cm	1 (6%) – in field[b]	2-year RFS: 96%	

DSS, disease-specific survival; OS, overall survival; RFS, recurrence-free survival; PC, postchemotherapy.

[a] RP recurrence denotes recurrence within the template of a full bilateral RPLND.

[b] In field denotes that this recurrence occurred within the modified template used for resection.

this series, suggesting that many are not candidates owing to mass size or desmoplastic reaction.

Clinical implications

In patients with postchemotherapy residual retroperitoneal masses following chemotherapy, we suggest modified template PCRPLND over full bilateral RPLND in appropriately selected patients as described (conditional recommendation based on low-quality evidence). This recommendation is limited to patients with disease confined to the template both pre- and postchemotherapy and postchemotherapy mass <5 cm in largest diameter.

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39 CHAPTER 39
Penile cancer

Oliver W. Hakenberg
Department of Urology, Rostock University, Rostock, Germany

Introduction

Penile cancer is an orphan disease. Owing to its rarity, the published evidence consists mostly of retrospective case series, which do not suffice for adequate meta-analysis, and there are hardly any prospective trials at all. This dilemma cannot be resolved at present. However, penile cancer is an aggressive disease, which, when metastatic, has a very poor prognosis. Furthermore, local treatment often is debilitating for the patient. Rational, evidence-based treatment recommendations are therefore of great importance and we have to make the best possible use of the existing evidence while taking into account its limitations.

Guidelines on penile cancer have changed considerably in recent years [1–3]. While traditional teaching recommended wide surgical resection with a safety margin of 2 cm, the focus has shifted to organ sparing and reconstruction of penile appearance as far as is feasible, while at the same time preserving function as much as possible.

The incidence of penile cancer seems to be increasing in some European countries [4]. With appropriate treatment, the survival rates of patients with localized penile cancer are well over 90% and a local recurrence can still be cured, leading to survival rates of around 90% [5]. Therefore, with organ-sparing treatment, the risk of local recurrence has to be taken into account but does not endanger the patient's life significantly. Cure is also possible in limited regional lymph node disease with multimodal treatment, but the survival rate is less than 40% [5]. In systemically metastasized disease, there is no cure. The appropriate treatment of early-stages disease is therefore of paramount importance.

Clinical question 1

When is organ-sparing treatment indicated in penile cancer?

Literature search

A search was performed using the search terms "penile neoplasm," "penis," or "penile carcinoma," "neoplasm," "malignancy," "carcinoma, squamous cell," and "surgery," "amputation," and "excision." The Cochrane Library was also searched and available guidelines were screened.

The evidence

The published evidence consists of retrospective case series. A recent Cochrane Review assessed this evidence for local interventions in penile cancer with respect to the primary outcome measures cancer-specific and recurrence-free survival, adverse treatment effects, and urinary and sexual function, assessing the existing nonrandomized comparative studies and case series using both full-text articles and meeting abstracts [6].

The conclusions of this Cochrane Review were that for CIS (carcinoma *in situ*) or Ta lesions, provided that staging is correct, conservative treatment with topical chemotherapy (5-fluorouracil, imiquimod), ablation with CO_2 or an Nd:YAG laser, or glans resurfacing is effective, with good cosmetic results if treatment is applied to the whole glans [6, 7]. Topical chemotherapy for CIS has been reported in one large retrospective series with recurrence or a persistence rate of 50% [8] and in one smaller series with a persistence rate of 26% when combined with circumcision [9]. The best oncological outcomes have been reported for glans resurfacing [10, 11].

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For T1 G1/G2 disease, penile-preserving treatments include wide local excision, partial glansectomy, glansectomy, laser ablation, or radiotherapy (external beam radiotherapy [EBRT] or brachytherapy) [12]. Laser ablation of T1 tumors carries a higher recurrence rate than laser ablation for CIS [7]. Amongst these options, glansectomy is reported to offer the best cancer outcome [11]. Glansectomy achieves better local control rates than local excision or partial glansectomy [13]. A decrease in sexual function as assessed using the International Index of Erectile Function (IIEF) Questionnaire has been reported in a series of 23 patients with glansectomy [14].

Clinical implications

In patients with CIS or Ta lesions, we suggest glans resurfacing over topical chemotherapy (5-fluorouracil, imiquimod) and ablation with CO_2 or an Nd:YAG laser (conditional recommendation based on very low-quality evidence). This recommendation assumes that patients place a high value on optimizing oncological outcome and preservation of penile anatomy.

In patients with T1 G1/G2 disease, we suggest glansectomy over wide local excision, partial glansectomy, laser ablation or radiotherapy (conditional recommendation based on very low-quality evidence). This recommendation assumes that patients place a higher value on reducing the risk of recurrence and improving disease-specific survival than on sexual function.

In patients with T2 or T3 disease, irrespective of grade, we recommend a partial penectomy (with documentation of negative margins) or a total penectomy (strong recommendation based on very low-quality evidence). In this setting, in which patients are at high risk for local recurrence and also death from penile cancer, the benefits of radical surgery far outweigh any potential benefits of penile preservation in most patients.

Clinical question 2

In patients undergoing organ-sparing surgery for penile cancer, what surgical resection margins are adequate?

Literature search

A search was performed using the search terms "penile neoplasm" and "carcinoma, squamous cell" with "surgery," "amputation," and "excision." The Cochrane Library was also searched and available guidelines were screened.

The evidence

Several authors have compared partial and radical penectomy and the influence of the resection margins on outcome in terms of local recurrence. In a retrospective examination of the microscopic extension of the tumor beyond the macroscopically visible margin in 64 cases, only 19% of all cases had microscopic extension beyond the macroscopic margin [15] and, of those 12 cases, only three grade 3 tumors had extensions of 10–15 mm. The other nine tumors had extensions of 5–10 mm. Another series of 51 cases [16] reported clear surgical margins of <10 mm in 48% of cases and of <20 mm in 90% of cases. In a series of 17 cases [17], the average resection margin was 14.8 mm, with seven cases with margins <10 mm. The largest series of 179 cases with organ-conserving surgical treatment reported an average surgical margin of 5.23 mm [18].

The rates of local recurrence in series reporting the results of organ-preserving surgical treatment are variable depending on tumor stages included and organ-sparing techniques used, and are given in Table 39.1. The data show that local recurrence rates are higher with organ-sparing treatment compared with amputation [19, 20]. Glansectomy as a more radical organ-preservation approach leads to relatively low recurrence rates [21, 22]. Two very large series have shown that organ-sparing treatment is safe in that disease-specific survival is not significantly impaired with local recurrence that is adequately treated [5, 18].

In some series, it is unclear whether local recurrence or secondary tumors should be the correct diagnosis. With organ-sparing treatment, a late local recurrence may also be a secondary tumor. In the series of Feldman and McDougal [23], 25% of local "recurrences" occurred over 5 years after primary treatment.

Clinical implications

In patients with penile cancer, we recommend routine intraoperative frozen section to assess for surgical margin status (strong recommendation based on low-quality evidence). We further recommend that the final surgical margin be 5 mm or more depending on the grade of the lesion to ensure an adequate local resection (strong recommendation based on very low-quality evidence). Should the definitive pathology report a positive margin, a re-resection is recommended. This recommendation assumes that patients place a high value on the preservation of penile length.

Clinical question 3

Is radiotherapy effective in treating localized penile cancer?

Literature search

A search was performed using the search terms "penile neoplasm" and "carcinoma, squamous cell" with "radiotherapy" and "brachytherapy." The Cochrane Library was also searched and available guidelines were screened.

The evidence

EBRT and brachytherapy alone or in combination are considered options for T2 tumors <4 cm in size [1]. However, there are more reviews than original publications on the

Table 39.1 Reported rates of local recurrence with organ-sparing treatment for localized penile cancer.

Study	*n*	Details	Local recurrence (%)	Survival
Hoffman et al. (1999) [17]	17		0	
Minhas et al. (2005) [16]	51		4	
Lont et al. (2006) [19]	257	T1 and T2 only	37 (compared with 22% for partial amputation)	
Leijte et al. (2008) [5]	415	5.3% for amputation in the same series	27.7	Overall disease-specific survival with local recurrence 92%
Morelli et al. (2009) [22]	15	Glansectomy only	0	
Feldman and McDougal, (2011) [23]	56	CIS and pT1	21.4	
Philippou et al. (2012) [18]	179		8.9	Disease-specific 5-year survival 91.7%
Veeratterapillay et al. (2012) [21]	65	Only partial or total glansectomy	6	
Veeratterapillay et al. (2015) [20]	99	4% for amputation in the same series	18	

use of EBRT for penile cancer and the latter largely base their deductions on analogies made with anal and vulvar squamous cell carcinoma (SCC).

In a series of 60 patients treated by surgery with or without adjuvant EBRT or definitive EBRT alone, local recurrence was more common in the definitive EBRT group (56%) versus the surgery group (13%), and in multivariate analysis, surgery was the only independent factor predicting locoregional control [24]. In an EBRT series of 41 patients, the local control rate was 62%, nodal relapse 12%, relapse-free rate 51%, and overall survival 88% at 5 years [25]. In a larger series of 101 patients treated between 1960 and 1990 (59 treated by EBRT, 13 by brachytherapy, and 29 by surgery) with radiotherapy or surgery used as salvage treatment, the local failure rate with EBRT was 60% compared with 55% for surgery.

For brachytherapy, a large multi-center survey series of 259 patients treated between 1959 and 1989, of whom 184 underwent brachytherapy as monotherapy and 75 combinations with either EBRT or surgery [26], reported a 5-year disease-specific survival of 78% for brachytherapy monotherapy and an overall local complication rate of 53% [26]. In a large series of 144 patients with penile cancer confined to the glans treated by brachytherapy plus circumcision and resection of inguinal nodal metastases, the reported 10-year local and regional recurrence rates were 20 and 16%, respectively [27]. In a series of 67 patients, Crook et al. reported a disease-specific survival of 83.6% and a penile preservation rate of 67% at 10 years [28]. In a three-center retrospective series of 47 patients, a disease-specific survival of 87.6% and a penis-preservation rate of 66% were reported with potency preservation in 55.8% of those previously potent and sexually active [29]. A study of a series of 49 patients reported local recurrence in 5/49 cases and disease-free status in 42/49 patients with 22/27 previously potent patients retaining erectile function [30]. A small series of 12 patients treated with high dose rate brachytherapy showed a local recurrence rate of 17% and disease-specific survival of 100% [31]. A recent meta-analysis of 2178 men with penile cancer of whom 673 underwent brachytherapy and the others surgery reported better local control with surgery (84 vs. 79%, with an odds ratio of 1.45; 95% confidence interval [CI] 1.09–1.92, $p=0.009$) but no significant differences in local control and survival between brachytherapy and surgery in early disease stages [32]. In an age-matched comparison of 19 brachytherapy patients with healthy controls, only moderate impairment of sexual function after brachytherapy was reported [33].

In summary, radiotherapy (EBRT or brachytherapy) for the local treatment of penile cancer offers the promise of complete organ preservation and perhaps the preservation of erectile function. For EBRT, these claims are not supported by evidence. Local control is better with surgery than with EBRT and there are no data on erectile function after EBRT for penile cancer. There is more evidence supporting the use of brachytherapy for penile cancer, but the expertise for this technique is not universally available. For both EBRT and brachytherapy, the reported local recurrence rates are higher than for surgery and reported tumor-specific survival is not as good as in recent series of organ-sparing surgery. Local complications, with meatal stenosis being the most common, occur in one-third of patients or more after radiotherapy.

The evidence for radiotherapy for penile cancer is very poor, consisting of series of patients treated over periods of several decades and different techniques and radiation dosages. On the basis of the available evidence, it seems that radiotherapy should be offered only to patients who refuse surgery as a primary treatment.

Clinical implications

In patients with T2 penile tumors, we recommend against radiotherapy treatment (strong recommendation based on very low-quality evidence). This recommendation assumes that patients place a high value on oncological outcomes and less on the preservation of penile anatomy.

Clinical question 4

Which lymph node management is indicated in patients with clinically negative inguinal nodes**?**

Literature search

A search was performed using the search terms "penile neoplasm" and "carcinoma, squamous cell" with "lymph node," "metastasis," and "lymphadenectomy." The Cochrane Library was also searched and available guidelines were screened.

The evidence

For the management of inguinal lymph nodes in patients with clinically negative nodes, the options are active monitoring (surveillance) or invasive staging by either dynamic sentinel node biopsy (DSNB) or bilateral modified or radical inguinal lymphadenectomy, depending on the grade and stage of the primary tumor [1].

The reported rates of inguinal recurrence with surveillance range from 11% [34] to 36% [35–37]. Hence surveillance carries a considerable risk of inguinal recurrence. Inguinal recurrence reduces the survival rate from over 90% to under 40% [5].

Early inguinal lymphadenectomy improves survival. This has been reported by a large retrospective series from the Brazilian Cancer Institute with 688 patients showing a marked overall 10-year survival difference in those with early lymphadenectomy (71%) versus delayed lymphadenectomy (30%) performed when inguinal recurrence occurred [38]. In a retrospective SEER database analysis of 593 patients, a markedly better overall survival (hazard ratio 0.54; 95% CI 0.36–0.79) was reported for patients undergoing lymph node surgery versus those not undergoing any lymph node surgery [39].

Open surgical sentinel node biopsy as proposed by Cabanas [40] was not successful since there was no way of individually identifying a sentinel node. Sentinel node surgery based on lymphography was reported to have a relative sensitivity of 66% and a relative specificity of 79% compared with modified inguinal lymphadenectomy as the gold standard treatment [41].

For scintigraphy-based sentinel node surgery (DSNB), there is good evidence for its safety and efficacy from several large retrospective series [42–45]. A prospective trial in 264 patients reported a 91% sensitivity [46]. There have been variable false-negative rates reported for DSNB: 0–6% per patient [46–48] and in one large retrospective study 7% per groin [44]. In a national multi-center study in Denmark with 222 patients, the overall false-negative rate was 13.3% per patient [49]. Interpretations have to take into account the tumor stages of the patient cohorts examined, which differ between studies. The learning curve is associated with a higher false-negative rate (15% reported) [50].

Modified inguinal lymphadenectomy is an alternative to DSNB for invasive inguinal node staging. In contrast to radical inguinal lymphadenectomy, modified inguinal lymphadenectomy is anatomically not well defined. Based on patterns of lymph node metastasis, the upper medial inguinal quadrant and the deep inguinal zone at the venous confluens are the locations of most early inguinal nodal metastases [51] and should be removed.

The complications of lymphadenectomy are related to wound healing and disturbance of lymphatic drainage. The complications with DSNB are much lower [44] than those with open lymphadenectomy. However, the reported complication rates known from large retrospective series (around 25% [52, 53] and up to 50% [54]) refer to radical inguinal lymphadenectomy whereas those of modified lymphadenectomy are not known.

Clinical implications

In patients at increased risk for occult lymph node involvement (≥pT1 and > grade 2), we suggest early invasive inguinal lymph node staging by DSNB or modified lymphadenectomy (conditional recommendation based on low-quality evidence). This recommendation assumes that patients place a higher value on increasing disease-specific survival than on the avoidance of potential perioperative complications.

Clinical question 5

Should patients with positive inguinal lymph nodes receive adjuvant chemotherapy after radical inguinal and/or pelvic lymphadenectomy?

Literature search

A search was performed using the search terms "penile neoplasm" and "carcinoma, squamous cell" with "lymph node," "surgery," "lymphadenectomy," and "chemotherapy." The Cochrane Library was also searched and available guidelines were screened.

The evidence

Adjuvant treatment by systemic chemotherapy is recommended in patients with positive inguinal and/or pelvic lymph nodes after radical lymphadenectomy [1]. However, this recommendation is based on little evidence. One series comparing adjuvant chemotherapy with historic controls without adjuvant chemotherapy reported a marked difference in long-term oncological control (84 vs. 55%) [55]. Using a different (taxane-based) chemotherapy protocol, the same group

reported a 36.9% recurrence-free survival in 19 patients with adjuvant chemotherapy in node-positive patients [56].

In a retrospective four-center data collection of 84 patients with pelvic nodal disease treated between 1978 and 2013, 34 patients received adjuvant chemotherapy. Overall survival was better in those receiving adjuvant chemotherapy after a median follow-up of 12 months [57]. In another series with 19 patients, adjuvant taxane-based chemotherapy with cisplatin or carboplatin was used; after 15 months of follow-up, six relapses and one treatment-related death were seen [58].

In summary, there is limited evidence to suggest that adjuvant chemotherapy improves oncological control in patients with limited lymph node disease after adequate surgical lymphadenectomy.

Clinical implications

We suggest that patients with lymph node involvement (pelvic and/or inguinal) receive adjuvant chemotherapy after lymph node removal (conditional recommendation based on very low-quality evidence). This recommendation assumes that these high-risk patients place a higher value on the potential (albeit uncertain) prospects of reduced disease-related morbidity and mortality than on the avoidance of chemotherapy-related adverse effects.

Clinical question 6

Is inguinal adjuvant radiotherapy after radical inguinal lymphadenectomy in node-positive disease effective?

Literature search

A search was performed using the search terms "penile neoplasm" and "carcinoma, squamous cell" and "surgery," "lymphadenectomy," and "radiotherapy." The Cochrane Library was also searched and available guidelines were screened.

The evidence

Data on the use of adjuvant radiotherapy for regional lymph nodes after lymphadenectomy in penile cancer are extremely sparse. There is one randomized controlled trial comparing immediate bilateral groin dissection versus inguinal radiotherapy versus surveillance in 64 patients with clinically negative inguinal nodes. Bilateral lymphadenectomy had lower recurrence rates and the highest 5-year survival (74 vs. 66% with radiotherapy) [34].

One very small series reported improved inguinal control with adjuvant EBRT without statistical significance [59]. Another series reported 40% locoregional recurrence after adjuvant EBRT and showed local control with adjuvant EBRT only in pN1 patients with extracapsular extension [60]. In another series evaluating patients with inguinal recurrence after inguinal lymphadenectomy, adjuvant radiotherapy in patients with two or more positive inguinal nodes did not improve the inguinal recurrence rate significantly [61].

A large retrospective assessment of the SEER database on the use and outcomes of pSCC patients treated with radiotherapy in conjunction with surgery of 2458 patients concluded after multivariable analysis that "radiotherapy had neither a harmful nor beneficial effect on cancer-specific survival" for all stages [62].

Clinical implications

In patients with lymph node-positive penile cancer who have undergone lymph node dissection, we recommend against adjuvant radiotherapy (strong recommendation based on very low-quality evidence). This recommendation is based on the lack of evidence to support improved disease-related outcomes yet potentially considerable side effects, which likely translates into an unfavorable benefit-to-risk ratio.

Clinical question 7

Should patients with enlarged inguinal lymph nodes receive neoadjuvant chemotherapy or neoadjuvant radiotherapy before radical inguinal lymphadenectomy?

Literature search

A search was performed using the search terms "penile neoplasm" and "carcinoma, squamous cell" with "lymph node," "metastasis," "chemotherapy," and "radiotherapy." The Cochrane Library was also searched and available guidelines were screened.

The evidence

In one series of 26 patients with fixed inguinal nodes, 10 were treated with radiotherapy (with or without additional chemotherapy) and 16 were treated with neoadjuvant chemotherapy only. Only one patient in the neoadjuvant radiotherapy group could subsequently be operated on and all radiotherapy patients died of cancer, whereas 56% of the neoadjuvant chemotherapy group could undergo subsequent surgery and 5/16 (31%) had 5-year recurrence-free survival [55].

In a series of 24 patients with fixed inguinal nodes treated with neoadjuvant chemotherapy with bleomycin, methotrexate, and cisplatin, a good response allowing for surgery was seen in 15 patients. The reported 5-year survival was 73.3% in responders and 0% in non-responders [63]. A recent series by the same group reported 43% clinical responses and 14% complete pathological remissions in N2/N3 disease with neoadjuvant chemotherapy in 28 patients, but these responses were not associated with improved survival [56]. In a series of 10 patients treated with neoadjuvant cisplatin, ifosfamide, and paclitaxel chemotherapy, five patients responded and five had stable disease. After surgical treatment, the patients with three or fewer involved lymph nodes had a better survival (median 48 months) than those with more than three involved nodes (median 23 months) [64].

Clinical implications

In patients with extensive inguinal nodal disease (N2/N3), we suggest neoadjuvant chemotherapy in combination with surgery (conditional recommendation based on very low-quality evidence). This recommendation is based on the assumption that these poor-prognosis patients place a higher value on the potential (albeit very uncertain) prospects of reduced disease-related mortality than the avoidance of chemotherapy-related adverse effects.

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PART 7

Female urology, trauma, and reconstruction

Roger R. Dmochowski

40

CHAPTER 40

Medical management of urinary incontinence in women

Joshua A. Cohn[1], Elizabeth Timbrook Brown[2], W. Stuart Reynolds[1], Melissa R. Kaufman[1], and Roger R. Dmochowski[1]

[1] *Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA*

[2] *Department of Urology, Georgetown University School of Medicine, Washington, DC, USA*

Background

Urinary incontinence (UI) is an important health concern that has a substantial effect on an individual's perception of well-being, body image, and quality of life (QOL). As many as one-quarter to one-third of adult women in the United States suffer from UI [1, 2], with a prevalence of <5% in younger women and up to 50% or more in the elderly [3]. Stress urinary incontinence (SUI) is the most common type of UI and is present in approximately 50% of incontinent women, whereas pure urge urinary incontinence (UUI) is present in approximately one-quarter of women [3]. The prevalence of SUI and UUI may be underestimated in all age groups, as most who experience UI never seek or receive treatment [3].

Depending on severity, etiology, and patient comorbidity and preferences, UI may be managed by a variety of nonoperative or operative approaches. Nonoperative, or medical, management of female UI is a broad term that encompasses several modalities, including behavioral therapy, pelvic floor muscle therapy (PFMT), and pharmacological therapy. Antimuscarinic agents and β_3-adrenergic agonists are the primary pharmacological options for UUI; there is no US Food and Drug Administration (FDA)-approved medication for SUI.

Before initiating treatment, it is imperative that patients undergo an appropriate clinical evaluation. A careful history and physical examination may elicit concomitant and potentially serious medical conditions, reversible causes of UI, UI-related perineal skin breakdown, or contributing factors such as pelvic organ prolapse or vaginal atrophy. DIAPPERS (Delirium, Infection, Atrophic urethritis and vaginitis, Pharmaceuticals, Psychological disorders, Excessive urine production, Restricted mobility, Stool impaction) is a helpful mnemonic summarizing potentially reversible causes of incontinence particularly prevalent in the elderly and infirm [4].

In addition to addressing reversible contributing factors, European Association of Urology (EAU) and American Urological Association (AUA) guidelines recommend patient education and behavioral therapy as first-line management for non-neurogenic UUI or overactive bladder (OAB) with or without UI [5, 6]. Behavioral modification includes a variety of activities such as education, lifestyle changes, keeping micturition charts and diaries, development of timed voiding and bladder training regimens, and physiotherapy with or without biofeedback. Guideline recommendations are based on available high-level evidence supporting the efficacy of these interventions; however, data regarding the use of these interventions in clinical practice are more limited.

Clinical question 1

Is there a role for education, behavioral, and lifestyle modification alone for female urinary incontinence (stress and urge)?

Literature search

Evidence for the following clinical recommendations was obtained using three separate methods to ensure completeness and timeliness. First, PubMed searches were conducted including all forms of published English-language studies using the keywords "education," "behavioral modification," "lifestyle modification," and "female urinary incontinence." The references for these studies were in turn examined for further relevant studies that may have been missed in the search. Next, texts and clinical guidelines considered authoritative in the field were reviewed, with specific attention to

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the studies used to form those resources' clinical recommendations. This also included searches at meta-analyses clearing houses. Finally, active practitioners and researchers within the field were queried about recent evidence on the topic and what studies they used to inform their own clinical decision-making. The sum of information found through all the above means was reviewed and the following clinical recommendations are made based on this evidence.

The evidence

Weight loss

Lifestyle interventions for the treatment of UI are of significant interest to patients, yet there is limited high-level evidence to guide practice recommendations. Weight reduction is the behavioral and lifestyle change that has received the most attention as a treatment option for UI. Hunskaar published a well-researched review of the epidemiological literature of UI with respect to overweight and obesity as risk factors [7]. The association between UI and being overweight or obese is well established, but epidemiological evidence is only fair (level 2 and 3 evidence). Many of the studies are composed of samples of patients planning bariatric surgery; hence they are biased populations and contain a large number of very obese patients who are not found in population-based studies. However, there is credible evidence from longitudinal studies that links high body mass index (BMI) to subsequent new-onset UI. The connection between obesity and incontinence is greater for SUI and mixed urinary incontinence (MUI) than for UUI and OAB [7].

The first large-scale randomized controlled trial (RCT) to examine weight loss was the Program to Reduce Incontinence by Diet and Exercise (PRIDE) study. This was carried out at two US sites and enrolled 338 overweight or obese women reporting >10 episodes of incontinence weekly [8]. Participating women were randomized 2 : 1 to an intensive 6-month lifestyle and behavior change weight intervention program ($n=226$) or to a structured education group (control group, $n=112$). Stratification was also performed according to clinical center. Participants were aware of their treatment, but staff members who collected the outcomes data were blinded. All women received an instructional guide of standard behavioral therapy for incontinence and were trained to complete a 7-day voiding diary. The primary outcome measure was the percentage change in the number of incontinence episodes reported in the 7-day diary at 6 months after randomization. Results showed that the characteristics of the participants in the two groups were similar at baseline, and rates of UUI were greater than those of SUI. At 6 months, the weight loss group had a mean loss of 8.0% of bodyweight from baseline and a 47.4% mean decrease in the total number of incontinence episodes per week compared with a 1.6% weight loss ($p<0.001$) and a 28.1% mean decrease in incontinence episodes in the control group ($p=0.01$). The main reduction in incontinence episodes from baseline was related to significantly decreased SUI relative to controls (57.6% reduction versus 32.7%, $p=0.02$). The decrease in UUI episodes was greater in the intervention group (42.4 vs. 26.0%) but not to a statistically significant extent ($p=0.14$). Women in the weight loss group also were more likely to have a >70% reduction in UI episodes ($p<0.001$), to perceive a greater decrease in the frequency UI episodes and a lower volume of urine loss, and to report higher satisfaction with change ($p<0.001$). Increased awareness of bladder habits resulting from voiding diary compliance likely contributed to improvement in both groups. Similarly, at 1 year, fewer patients randomized to intensive lifestyle intervention in the Look AHEAD (Action for Health in Diabetes) trial reported UI (25.3 vs. 28.6%, $p=0.05$) or developed new-onset UI (10.5 vs. 14.0%, $p=0.02$) [9]. Weight loss of 5–10% reduced the odds of developing UI by 47% ($p=0.002$). Lastly, a recently published prospective study (level 2 evidence) found a significant reduction in UI in female subjects at 3 years following bariatric surgery (adjusted relative risk [RR] of UI remission 1.08 per 5% weight loss, 95% confidence interval [CI] 1.06–1.10), further supporting an important role for weight reduction in morbidly obese woman with UI [10].

Fluid and caffeine restriction

Fluid restriction is typically supported for the treatment of UUI. Although there is evidence to support a reduction in urinary frequency and SUI, it has not clearly been demonstrated to limit UUI. Hashim and Abrams reported a small randomized, two-group, prospective, cross-over trial in adults with symptoms of OAB (level 2 evidence) [11]. Twenty-four adult men and women with significant OAB symptoms on frequency/volume charts and having urgency and/or UUI were assigned to either an increased or a decreased fluid intake regimen. The primary endpoint was the change in the frequency of "unwanted events" (i.e. urgency, nocturia, and/or UI episodes) during a 24 h period. A key finding was that adults find it easier to increase or decrease fluid intake by 25% of baseline rather than 50% (a target in earlier trials [12] that led to poor compliance with study design). The study demonstrated a significant reduction in frequency, urgency, and nocturia when patients decreased their fluid input by 25% but did not demonstrate a significant improvement in QOL.

More recently, Swithinbank et al. conducted a 4-week prospective, randomized, cross-over study in 39 and 30 women with urodynamically demonstrated SUI and detrusor overactivity (DO) incontinence, respectively (level 2 evidence) [13]. After a baseline week, patients underwent 3 weeks of caffeine restriction. In week 2, women consumed a normal volume of liquid followed by randomization to either increased and then decreased fluid intake or vice versa in weeks 3 and 4. On average relative to baseline,

fluid was decreased by approximately 50% per 24 h in restricted fluid weeks and increased by approximately 40% during increased fluid weeks. In patients with SUI, wetting episodes per 24 h decreased significantly with decreased fluid intake. In the DO group, episodes of UI and urgency/frequency decreased significantly with fluid restriction. Importantly, reduction in caffeine intake was not demonstrated to have a significant impact on storage lower urinary tract symptoms (LUTS).

Although it is common to recommend decreased caffeine intake because of its impact on urinary frequency [13–15], its reduction has not been clearly demonstrated to reduce episodes of UI in any randomized trials. An analysis of 65 176 women in the Nurses' Health Study, however, did demonstrate a significantly elevated risk of at least weekly incontinence in women with the highest (>450 mg) versus the lowest (<150 mg) caffeine intake (RR 1.19, 95% CI 1.06–1.34) (level 2 evidence) [16]. Incident UUI (rather than SUI or MUI) was primarily responsible for the overall increased risk of developing UI in those women with the highest caffeine intake. A similar study of 2005–2006 and 2007–2008 National Health and Nutrition Examination Survey (NHANES) data also suggested a relationship between caffeine intake and UI (odds ratio [OR] 1.47, 95% CI 1.07–2.01, for highest quartile) (level 2 evidence) [17].

Pelvic floor muscle therapy

PFMT for UI is one of the best-studied nonpharmacological interventions. It is useful for both SUI and UUI because it improves the strength of pelvic floor musculature and thus urethral support, and contraction of striated paraurethral musculature simultaneously causes reflex inhibition of detrusor contractions. It has been well studied as solitary therapy with or without biofeedback and less extensively in conjunction with common additional therapies such as bladder training or pharmacological treatment.

In 2014, the Cochrane Incontinence Group Specialized Trials Register published a large-scale review synthesizing evidence on the effectiveness of PFMT versus no treatment or sham treatment for female UI [18]. All included trials were randomized or quasi-randomized. Twenty-one trials met inclusion criteria, inclusive of 1281 women (665 PFMT, 616 controls). Relative to controls, women with SUI undergoing PFMT were significantly more likely to report cure (RR 8.38, 95% CI 3.68–19.07) and cure or improvement (RR 17.33, 95% CI 4.31–69.64). Mean episodes of SUI in 24 h decreased by 1.21 (95% CI 0.89–1.52) with PFMT relative to controls. In general, the pooled relative risk for continence after PFMT and PFMT with biofeedback was significant and consistent. However, pooled absolute risk differences of resolved or improved UI were inconsistent across the studies. Analysis between studies was hampered by the difference in behavioral training/PFMT protocol between studies. Furthermore, the utility of PFMT in MUI or UUI remains relatively unclear.

A 2013 systematic review evaluated randomized or quasi-randomized trials in which active treatment plus PFMT was compared with active treatment alone [19]. Eleven trials met eligibility criteria. A single trial comparing a combination of PFMT and heat and steam generation with heat and steam alone in women with SUI, UUI, and MUI provided moderate-quality evidence in favor of PFMT (RR for cure 2.38, 95% CI 1.19–4.73). Evidence of the impact of PFMT added to vaginal cones (RR 1.27, 95% CI 0.94–1.71), bladder training (RR 1.71, 95% CI 0.84–3.46), or pharmacological therapy (RR 0.84, 95% CI 0.45–1.60) as it related to cure was rated as very low quality. Moderate-quality evidence suggested no benefit in achieving cure with PFMT added to a continence pessary (RR 0.88, 95% CI 0.67–1.16). In a 2008 systematic review, pooled analysis supported PFMT and bladder training in comparison with regular care (pooled risk difference 0.13, 95% CI 0.07–0.20) with moderate-quality evidence [20]. More recently, Shamliyan et al. reported a number needed to treat (NNT) for PFMT and PFMT with bladder training of 3 (95% CI 2–5) and 6 (95% CI 4–16), respectively [21]. In general, factors that portended a favorable prognosis/outcome for PFMT were PFMT in groups with skilled physical therapists, individualized behavioral intervention with PFMT, and community-based interventions including education, bladder training, and PFMT [20]. Five-year adherence to PFMT in patients with SUI has been reported at approximately 40%; however, its efficacy in the long term is unclear [22].

Biofeedback (BF) uses visual cues and verbal coaching to teach patients how to control the physiological responses of the bladder and pelvic floor muscles that control continence. BF-assisted PFMT has been shown to be as effective as pharmacotherapy for UUI and superior to immediate-release oxybutynin in one randomized trial [23]. A systematic review in which 24 trials met inclusion criteria demonstrated that women undergoing BF had a lower likelihood of reporting no improvement (RR 0.75, 95% CI 0.66–0.86) but no significantly increased likelihood of cure (RR 0.92, 95% CI 0.81–1.05) [24]. Nonetheless, in clinical practice, physicians may find BF a useful adjunct to PFMT, particularly in women who have difficulty isolating pelvic floor muscles. Large-scale RCTs are needed to study the best use of BF in PFMT [25].

The literature on predictors of response to behavioral therapy is sparse and inconsistent. In an attempt to identify predictors of outcome of a multicomponent behavioral training program for UI (SUI and UUI), a secondary analysis of data from three prospective, randomized clinical trials was performed [26]. In multivariable regression analyses, none of the factors relied upon for diagnostic evaluation, such as age, race, type of incontinence, obstetric history, medications, pelvic examination, BMI, urodynamic parameters, or distress

level with the condition, was associated with outcomes. Overall, previous treatment and indicators of severity, number of incontinence episodes at baseline, and lack of need for incontinence pads showed an association with outcomes of behavioral therapy. A mean reduction in incontinence episodes of 80.7, 68.8, and 39.4% was experienced with behavioral treatment, drug treatment, and placebo, respectively. More recently, 446 women were randomized to pessary, behavioral, or combined therapy for SUI as part of the Ambulatory Treatments for Leakage Associated with Stress Incontinence (ATLAS) trial [27]. At 3 months, behavioral therapy and combination therapy demonstrated superior outcomes with respect to incontinence and patient satisfaction. Additional predictors of patient-reported success, presented in a later study, included college education or greater, no previous incontinence surgery, postmenopausal status, and fewer than 14 incontinence episodes per week [28]. Although further study is required, existing data suggest that behavioral therapy is applicable to patients in any age group and, since most motivated patients do receive benefit from behavioral treatment without any risk, no incontinent woman should be discouraged from exploring this therapeutic option.

Clinical implications

In women with urinary incontinence, we recommend behavioral therapies of education, diet modification, fluid restriction, and weight loss (strong recommendation based on high-quality evidence).

These interventions are of low risk to all populations, easy to access, and inexpensive relative to other forms of therapy (pharmacological and surgical). Despite the added expense associated with PFMT if used in combination with biofeedback and/or trained physical therapists, the role for PFMT in treating SUI is well supported. The use of PFMT with selective use of additional modalities is worthwhile and may even benefit patients with MUI and UUI. Indeed, there is little reason not to offer behavioral therapies and PFMT as options in the care of UI, especially in light of the excellent risk/benefit ratios associated with these interventions and the presence of randomized, prospective evidence supporting them.

However, as these modalities are often not curative and are dependent on patient motivation, counseling should include a discussion of reasonable expectations and also options in the event of treatment failure. Women should be made aware of efficacy in relation to other therapies, any risks associated with behavioral therapy, and limitations in available evidence.

Clinical question 2

Is there evidence to support pharmacological treatment of stress urinary incontinence?

Literature search

Evidence for this question was obtained in a similar manner to question 1, starting with a PubMed search using the keywords "stress incontinence," "medical management," "anticholinergics," "estrogen," "alpha-adrenergic," "imipramine," "duloxetine," and "SNRI." The references in the papers found were also evaluated for studies missed by the search. Authoritative texts and systematic reviews clearinghouses were then consulted for the identification of further studies. Finally, practicing researchers and clinicians in the field were asked about studies they used to inform their own decision-making.

The evidence

Estrogens

Although rarely used as primary therapy, estrogens have been advocated for UI. The rationale behind their use is based on the presence of estrogen receptors in the bladder base and urethra. Estrogens may affect continence by increasing urethral resistance, raising the sensory threshold of the bladder, increasing α-adrenoreceptor sensitivity in the urethral smooth muscle, or promoting β_3-adrenoreceptor-mediated relaxation of the detrusor muscle [29, 30]. Postmenopausal women with SUI have significantly lower serum estradiol levels than those without UI [31]. Hormone replacement therapy (HRT) is thought to increase the number of epithelial cells lining the bladder and urethra, improve the thickness and quality of the subepithelial vascular plexus, and thus improve the coaptation of urethral walls and urethral resistance [31, 32]. Recent data from several large studies have elucidated the effect of conjugated estrogens on SUI.

A 2012 Cochrane Incontinence Group systematic review identified 34 randomized or quasi-randomized trials including estrogens in at least one arm in women with SUI, MUI, or UUI [33]. A total of 19 676 incontinent women were included, of whom 9599 received estrogen in a variety of combinations, dosages, routes of administration, and durations of therapy. In a pooled analysis of the six trials involving systemic estrogens, risk of incontinence not improving was significantly greater for estrogen than placebo (RR 1.32, 95% CI 1.17–1.48). The same increased risk for nonimproved incontinence was observed for women on combined estrogen/progesterone therapy. In contrast, local estrogens were associated with a decreased risk of UI (RR 0.74, 95% CI 0.64–0.86) in the pooled Cochrane analysis [33].

Two RCTs merit specific mention. The Women's Health Initiative (WHI), a multi-center double-blind placebo-controlled randomized trial of HRT in 27 347 women, studied the impact of systemic estrogen or estrogen plus progesterone on the development of UI or change in UI if present at baseline. Women randomized to systemic estrogen replacement alone had double the risk of developing SUI (RR 2.15, 95% CI 1.77–2.62) relative to placebo and were 59% more likely to have worsening of baseline UI (RR 1.59,

95% CI 1.39–1.82) [34]. The Heart and Estrogen/Progestin Replacement Study (HERS) study was an RCT designed to evaluate daily oral conjugated estrogen plus medroxyprogesterone acetate therapy for the prevention of coronary heart disease events in postmenopausal women with known coronary disease [35]. A total of 1525 of the 2763 women who had at least weekly UI at the initiation of the study were evaluated for change in the severity of incontinence and followed for 4.1 years. Incontinence improved in 26% in the placebo group compared with 21% in the HRT group. Additionally, 27% of the placebo group and 39% of the HRT group realized a worsening of symptoms ($p=0.001$), with the incidence of incontinence episodes per week increasing in the HRT group by an average of 0.7 and decreasing in the placebo group by 0.1 ($p<0.001$). A reasonable conclusion from the available data, particularly the most recent clinical trials, is that conjugated estrogens with or without medroxyprogesterone are not indicated for the treatment of SUI and in fact may worsen the condition. In women with SUI where local estrogen therapy is indicated (e.g. atrophic vaginitis), topical estrogens may reduce UI and should be comfortably prescribed in the absence of contraindication.

Imipramine

The tricyclic antidepressant imipramine is indicated for nocturnal enuresis and has historically been used off-label for SUI, MUI, and UUI. Despite its long use for UI, the exact mechanism most responsible for action on the lower urinary tract is not clear because it has so many pharmacological actions [36, 37]. In theory, imipramine is used for the treatment of SUI owing to its alpha-stimulating effect at the urethra, which can increase the urethral closure pressure and functional urethral length. Available data on the use of imipramine are largely anecdotal. No randomized placebo-controlled trials of imipramine for SUI have been published. In small, uncontrolled studies (level 2 and 3 evidence), cure rates of 35–70% have been reported [38, 39]. Side effects are numerous and related to its anticholinergic properties: dry mouth, weakness, fatigue, sedation or mania, parkinsonian effects, orthostatic hypotension, sweating, arrhythmia, and sexual dysfunction, which may preclude use of the drug [40]. Imipramine is toxic in high doses, and overdose can produce lethal cardiac dysrhythmia or conduction blocks [41]. Although studies demonstrating myriad actions of imipramine on the lower urinary tract exist, there are few clinical data showing a significant positive effect for SUI.

Alpha-adrenergic agonists

Increased outlet resistance theoretically should be possible with the use of α-adrenergic agonists to stimulate the large number of α_1-receptors at the proximal urethra and sphincter. Contraction of the α_1-receptors in the proximal urethra leads to an increase in the maximum urethral pressure and maximum urethral closure pressure. However, currently available agents are nonselective and produce significant adverse side effects, including elevated blood pressure, anxiety, insomnia, headache, tremor, weakness, palpitations, cardiac arrhythmias, and respiratory difficulties. These drugs must be used with caution, particularly in women with hypertension, cardiovascular disease, or hyperthyroidism.

Ephedrine and its stereoisomer pseudoephedrine are sympathomimetic agents that increase the release of norepinephrine from sympathetic neurons and stimulate α- and β-adrenergic receptors [42]. Few studies exist to support the use of ephedrine. In an older study of 38 patients with sphincteric incontinence, 27 achieved a "good to excellent" result with ephedrine sulfate at doses of 44–200 mg in four divided doses (level 3 evidence) [43]. Continence was improved mostly in the patients who experienced mild SUI. In patients with favorable responses, UDS revealed improved urethral pressure profiles. More recently, Weil et al. showed no improvement in objective measurements of urinary function in an RCT of the α_1-agonist midodrine, although the drug was well tolerated [44]. With α-adrenergic agents, tachyphylaxis may develop after prolonged use, perhaps owing to depletion of norepinephrine stores.

Serotonin–norepinephrine reuptake inhibitors (SNRIs)

Duloxetine is not approved for SUI in the United States but has been well studied for this condition. Its mechanism of action is inhibition of serotonin (5-HT) and norepinephrine reuptake (SNRI) in Onuf's nucleus where the pudendal motor neurons are located in the spinal cord. Resultant higher levels of 5-HT and norepinephrine increase activity on a greater number of postsynaptic receptors, a greater activation of pudendal nerve motor neurons, and increased urethral sphincter tone. Duloxetine has shown little or no inhibition of dopamine reuptake or affinity for histaminergic, dopaminergic, adrenergic, or cholinergic receptors; therefore, potentially it may produce few side effects. It has been shown to be beneficial for UI, with relative risk of decreased incontinent episode frequency of 1.24 (95% CI 1.14–1.36) versus placebo in a meta-analysis using data from several systematic reviews [45]. The largest of these reviews included 3327 women and compared duloxetine with placebo with endpoints of subjective cure of SUI and results of pad tests [46, 47]. Duloxetine was significantly better than placebo in improving QOL (weighted mean difference 5.26, 95% CI 3.84–6.68). Incontinence frequency decreased by approximately 50%, but subjective cure had a much lower success rate, at 3% over placebo (10.8 vs. 7.7%, $p=0.04$). Side effects with duloxetine were common but tended to be mild. Although tending to resolve within 1 week to 1 month, nausea is the most common reason for discontinuation [48].

Clinical implications

In women with stress urinary incontinence, we recommend against the use of oral conjugated estrogen (strong recommendation against based on moderate-quality evidence). This is based on randomized trial evidence that does not support the claim that oral conjugated estrogens improve stress incontinence and also in light of their side-effect profile.

We suggest against the off-label use of imipramine or α-agonists in women with stress incontinence (conditional recommendation based on low-quality evidence). There are only anecdotal reports of their efficacy and they have potential side effects.

We also suggest against the use of duloxetine in women with stress incontinence (conditional recommendation based on high-quality evidence). Although prospective, randomized studies have demonstrated both decreased frequency of incontinent episodes and increased QOL in patients with SUI, these effects are typically small and the chance of cure is remote. As this medication is not approved by the FDA for this indication owing to concerns about increased risk of suicide and hepatotoxicity, the off-label use of duloxetine for SUI is recommended only in selected patients who are not surgical candidates or who do not desire surgery and after extensive counseling, including depression screening, and the formation of a care plan to cover adverse effects (grade B recommendation). Where this medication is approved for SUI, our recommendations remain the same, with emphasis that it be used with counseling on realistic expectations. Perhaps most reasonably, when providers prescribe duloxetine for approved uses such as major depressive disorder or fibromyalgia, it is worth considering the potential added benefit of improvement in SUI when it is concomitantly present.

Clinical question 3

What are the efficacy and side-effect profiles of the anticholinergic and β_3-adrenergic class of drugs for urge urinary incontinence?

Literature search

Evidence for this question was obtained in a similar manner to that for the previous questions, starting with a PubMed search using the keywords "anticholinergic," "beta-3 adrenergic," "detrusor overactivity," "side effects," "urge incontinence," "oxybutynin," "tolterodine," "fesoterodine", "trospium," "darifenacin", "solifenacin," and "mirabegron." The references in these papers were used to broaden the search. Textbooks and meta-analysis clearinghouses aided in the identification of further studies. Finally, practicing researchers and clinicians in the field were asked about studies they used to inform their own decision-making.

The evidence

Anticholinergics

Anticholinergics are the standard of care for the first-line pharmacological treatment of OAB and UUI. The efficacy and side effects of this class of drugs have been well studied in multiple randomized placebo-controlled studies and in subsequent meta-analyses. Studies on individual anticholinergics consistently show statistically significant improvement versus placebo, in both subjective measures such as perception of cure and objective measures such as maximum cystometric capacity [49–51]. However, long-term compliance with anticholinergics is relatively poor, owing to inefficacy and side effects such as dry mouth (reported in approximately one-third of patients), pruritis, vertigo, constipation, and confusion. To this end, a recent meta-analysis reported persistence rates across 14 trials of only 12–39% at 12 months, 8–15% at 18 months, 6–12% at 24 months, and 0–16% at 36 months [52].

Across all age groups, a 2006 meta-analysis of 61 trials (42 parallel-group, 19 cross-over) encompassing 11 956 subjects found the relative risk of cure or improvement of OAB to be 1.39 (95% CI 1.28–1.51) and the decease in number of leakage events per 24 h to be 0.54 (95% CI 0.41–0.67) [50]. The rate of dry mouth with active treatment was reported as 29.6% versus 7.9% with placebo. More recently, the Anticholinergic vs. OnabotulinumtoxinA for Urgency Urinary Incontinence (ABC trial) study, a double-blind, double-placebo-controlled randomized trial, illustrated the potential benefits and certain challenges associated with anticholinergic therapy [53]. Women with idiopathic UUI with five or more episodes of UUI per 3-day period were followed for 6 months following randomization to anticholinergic therapy (solifenacin 5 mg, possible increase to 10 mg, change to trospium ER 60 mg if necessary) plus intradetrusor saline injection or injection of intradetrusor onabotulinumtoxinA 100 U plus daily placebo. Women in the anticholinergic group experienced a mean decrease of 3.4 episodes of UUI daily, similar to that with onabotulinumtoxinA injection, but only 13% were cured (versus 27%, $p=0.003$), and 46% experienced dry mouth. This trial highlights the relatively low but not insignificant potential for cure of UUI with anticholinergics balanced against the risks of unsatisfactory efficacy and side effects. In the clinical setting, however, response to anticholinergics can be augmented by concomitant behavioral training [23].

A 2012 Cochrane review aimed to determine which anticholinergic is best in the general population [54]. In the meta-analysis of 70 parallel trials, no significant differences were found with respect to tolterodine versus oxybutynin; however, tolterodine was better tolerated (RR for withdrawal 0.52, 95% CI 0.40–0.66; RR for dry mouth 0.65, 95% CI 0.60–0.71). Compared with tolterodine, solifenacin demonstrated significantly improved patient-reported cure or improvement (RR 1.25, 95% CI 1.13–1.39) and

leakage episodes in 24 h (0.30 fewer, 95% CI 0.08–0.53). In addition, dry mouth was less frequent for solifenacin (RR 0.69, 95% CI 0.51–0.94) compared with immediate-release tolterodine. Fesoterodine similarly performed better than tolterodine, including a relative decrease in leakage episodes per day of 0.19 (95% CI 0.09–0.30), but was associated with an 80% higher risk of dry mouth (RR 1.80, 95% CI 1.58–2.05). Evaluation of various dosing regimens demonstrated improved efficacy at higher doses but greater risk of dry mouth. In general, extended-release preparations were associated with decreased risk of dry mouth. Transdermal oxybutynin was not associated with a remarkably improved side-effect profile. A separate 2012 systematic review of 94 RCTs inclusive only of women with UUI reported that per 1000 women treated, continence was restored in 130 with fesoterodine (95% CI 58–202), 85 with tolterodine (95% CI 40–129), 114 with oxybutynin (95% CI 64–163), 107 with solifenacin (95% CI 58–156), and 114 with trospium (95% CI 83–144); rates of discontinuation due to side effects per 1000 treated were reported at 31 with fesoterodine (95% CI 10–56), 63 with oxybutynin (95% CI 12–127), 18 with trospium (95% CI 4–33), and 13 with solifenacin (95% CI 1–26).

Although dry mouth is the most frequent side effect of therapy, one of the primary concerns with anticholinergic treatment of older women with UUI is the risk of cognitive impairment. Existing studies examining cognitive function and sleep while using anticholinergics have suggested that differential binding to the muscarinic receptor M1 subtype may be a determining factor for these drugs. An RCT in young, healthy volunteers showed that sleep architecture and random eye movement sleep were not affected by trospium or tolterodine, and none of the drugs studied had significant differences in subjective or cognitive assays [55]. A 2008 meta-analysis of five RCTs supports the use of M3 selective drugs, concluding that there is compelling evidence of cognitive impairment with oxybutynin, whereas darifenacin demonstrated no impairment of memory or other cognitive functions [56]. This trial drew conclusions only on oxybutynin and darifenacin, citing incomplete evidence to allow judgment on tolterodine, solifenacin, and trospium, although each of these medications either demonstrated better cognitive outcomes than oxybutynin or did not demonstrate significant differences in cognitive function relative to placebo. A 2013 systematic review evaluating 13 moderate- to high-quality trials inclusive of women older than 65 years with UUI treated with anticholinergics found insufficient evidence regarding cognitive outcomes [57]. Indeed, even in two studies with a goal of evaluating the efficacy of anticholinergics in cognitively impaired older adults with OAB, the impact of the medication on cognition was not clear, highlighting the need for further study to guide practice in this patient population better [58, 59].

Mirabegron

A novel therapeutic option for OAB and UUI emerged in 2012 following FDA and subsequent European Medicines Agency approval of the β_3-adrenergic agonist mirabegron. In contrast to antimuscarinic agents, which work by inhibition of micturition, mirabegron facilitates urine storage by relaxing smooth muscle during the storage phase [60]. The first randomized Phase III trials comparing mirabegron with placebo or active treatment were published in 2013 [61].

In the 933 patients in the trial with baseline UI, Nitti et al. found statistically significant improvements at 12 weeks in incontinence episodes per 24 h relative to placebo at the 50 and 100 mg doses (decreases for placebo, 50 mg, and 100 mg 1.13, 95% CI 0.91–1.35, 1.47, 95% CI 1.25–1.63, and 1.63, 95% CI 1.40–1.86, respectively) [61]. Across all patients, significant improvements relative to placebo were observed in micturition frequency per 24 h and also all significant secondary endpoints. There were no significant differences in adverse events between placebo and treatment groups (hypertension, urinary tract infection, headaches, nasopharyngitis), and notably the incidence of dry mouth was 0.5 and 2.1% in the 50 and 100 mg dosing groups, respectively.

A concurrent Phase III double-blinded, randomized placebo-controlled trial conducted in 27 countries in Europe and Australia compared mirabegron at 50 and 100 mg doses with placebo, with tolterodine ER (extended release) 4 mg as a second control [62]. At 12 weeks, among the 1165 patients with at least one episode of incontinence at baseline, patients receiving mirabegron experienced reductions in incontinence episodes per 24 h of 1.57 (95% CI 1.35–1.79) and 1.46 (95% CI 1.23–1.68), respectively, a significant improvement relative to those receiving placebo (mean decrease 1.17, 95% CI 0.95–1.39). Primary treatment outcomes were similar between mirabegron and tolterodine ER. A similar rate of reported adverse events was observed between placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER (43.3, 42.8, 40.1, and 46.7%, respectively).

Chapple et al. presented 12-month follow up data in a trial in the United States and Europe in which patients with OAB were randomized 1 : 1 : 1 to mirabegron 50 mg, mirabegron 100 mg, or tolterodine ER 4 mg [63]. With mirabegron, significant improvements in OAB symptomatology relative to baseline were observed at as early as 4 weeks and maintained at 12 months. The rate of adverse events was similar for all patients, with a greater incidence of dry mouth in patients treated with tolterodine ER but no difference in hypertension: 9.2, 9.8, and 9.6% for patients on mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER, respectively. Discontinuation rates due to adverse events were 6.4, 5.9, and 6.0%, respectively.

A 2014 systematic review aimed at assessing the efficacy and tolerability of mirabegron 50 mg relative to antimuscarinics identified 44 RCTs encompassing 27 309 patients [64].

Bayesian mixed treatment comparisons found mirabegron 50 mg to be as efficacious as antimuscarinics in reducing the frequency of micturition and UUI episodes. The exception was solifenacin 10 mg, which was found to be more efficacious than mirabegron 50 mg in reducing voiding frequency (relative additional mean decrease of 0.584 voids per 24 h) and UUI (relative additional mean decrease of 0.422 UUI episodes per 24 h). The incidence of dry mouth was found to be higher for all antimuscarinics relative to mirabegron, for which the incidence of dry mouth was similar to that for placebo.

The updated AUA Guideline for the Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults addressed the role of mirabegron in the treatment armamentarium [6]. Mirabegron and antimuscarinics received a grade C recommendation for use as first-line therapy in conjunction with behavioral therapies and a grade B recommendation as second-line therapy. The expert panel interpreted the existing data on mirabegron to reflect similar efficacy to antimuscarinic medications with a lower risk of dry mouth and possibly lower risk of constipation, particularly relevant in patients with baseline conditions that may make these side effects particularly untoward. The 100 mg dose is not recommended, as there is no evidence suggesting a significant improvement compared with the 50 mg dosage. Although the existing studies have been of high quality and encouraging, the panel cautioned that there are limited data on the long-term use of mirabegron, the reduction in symptoms is relatively modest, and the severity of OAB in most trial patients is relatively low on the OAB spectrum. In addition, the use of mirabegron in patients with comorbidities such as cognitive impairment, glaucoma, and uncontrolled hypertension has received relatively little study, suggesting the need for particular caution with its use in patients with these conditions. Subsequent to the publication of the updated AUA guidelines, a review of the cardiovascular safety of mirabegron in the treatment of OAB concluded that the cardiovascular safety was acceptable at therapeutic doses and comparable to those of antimuscarinic agents [65]. In addition, two recent publications, one a subanalysis of previous trials in patients older than 65 years [66] and the other a, RCT comparing mirabegron alone, solifenacin alone, mirabegron plus solifenacin, and placebo in patients older than 65 years [67], specifically supported the safety and efficacy of mirabegron in elderly patients in the short term. Nevertheless, as the guidelines suggest, caution is advised in vulnerable populations.

Combined treatment with anticholinergics and mirabegron

Three recent publications reported on the efficacy of mirabegron in combination with solifenacin. Yamaguchi et al. conducted an open-label Phase IV study of patients with OAB in which mirabegron 25 mg was added to the treatment regimen of patients on solifenacin 2.5 or 5 mg for 16 weeks (level 2 evidence) [68]. After 8 weeks, mirabegron could be increased to 50 mg. Significant improvements were observed in all efficacy endpoints from baseline to end of treatment in all patient groups. The overall drug-related adverse event rate was 23.3%, and no meaningful changes in post-void residual, QT interval, or blood pressure were observed. In the aforementioned randomized trial evaluating solifenacin and mirabegron alone or in combination in patients older than 65 years, significant improvements in multiple parameters were observed in patients receiving combination therapy without increasing side effects [67]. Specifically, incontinence episodes decreased by 3.5 per day in the combination group compared with decreases of 2.3 and 2.2 per day in the mirabegron alone and solifenacin alone groups, respectively ($p<0.05$ for both comparisons). Third, a Phase II efficacy and safety trial randomized 1306 patients with OAB to 12 weeks of combination therapy with solifenacin 2.5, 5, or 10 mg plus mirabegron 25 or 50 mg, monotherapy with solifenacin 2.5, 5, or 10 mg or mirabegron 25 or 50 mg, or placebo [69]. Compared with solifenacin 5 mg monotherapy, three combination groups significantly improved voiding frequency (ranging from 0.80 to 0.98 fewer voids), and five combination therapies significantly reduced urgency episodes (ranging from 0.98 to 1.37 fewer episodes). There were no reported dose-related trends in adverse events or blood pressure, heart rate, or post-void residual. All three of these studies suggest the potential benefit of combination therapy but highlight the need for further study. The efficacy of combination therapy in refractory OAB with UUI, long-term efficacy and safety, compliance, and optimal dosing are unknown, as are efficacy and tolerability relative to established third-line therapies. In addition, the cost of mirabegron monotherapy remains a certain drawback to both patients and payers, let alone as part of combination therapy with currently uncertain benefit.

Clinical implications

In women with UUI refractory to behavioral therapy, we recommend antimuscarinic medications (strong recommendation based on high-quality evidence).

In women who have not undergone prior behavioral therapy, we suggest antimuscarinic medications in combination with behavioral therapy (conditional recommendation based on moderate quality evidence).

There is limited evidence that one agent is more effective than another; however, although dry mouth is common to all agents, side-effect profiles may differ. The choice of a specific agent should be tailored to the individual patient and made based on side-effect profile, dosing regimen, and cost (clinical principle).

We suggest against mirabegron as primary medical treatment in women with UUI (conditional recommendation against based on low-quality evidence). This is based on

similar treatment efficacy, reduced rates of dry mouth, but also much higher costs.

We suggest mirabegron as secondary medical treatment in women with UUI who have failed antimuscarinic medications (conditional recommendation based on low-quality evidence).

We suggest against mirabegron in older adults or those with cognitive impairment (conditional recommendation against based on low-quality evidence). This recommendation is based on the lack of sufficient safety data. Initial studies of combination therapy with antimuscarinics and mirabegron have been encouraging, but caution is advised outside select clinical scenarios until Phase III studies better establish efficacy, tolerability, and optimal dosing regimens in the general population.

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CHAPTER 41

Surgical treatment of female urinary incontinence

Alex Gomelsky
Department of Urology, Louisiana State University Health – Shreveport, Shreveport, LA, USA

Introduction

Stress urinary incontinence (SUI) is defined by the International Continence Society as the involuntary loss of urine through an intact urethra in response to a sudden increase in intra-abdominal pressure, in the absence of a detrusor contraction or an overdistended bladder [1]. Although the pathophysiological mechanism responsible for SUI is complex and incompletely understood, it is accepted that continence depends on the interaction of urethral and bladder neck support, intrinsic urethral properties, urethral sphincter mechanism, and pelvic floor musculature. At rest, a "mucosal" seal composed of submucosal connective tissue and luminal secretions from the periurethral glands compresses mucosal urethral folds to create a watertight closure. During stress maneuvers, a reflex contraction of the levator ani musculature and urogenital diaphragm elevates suburethral supporting tissue and compresses the proximal urethra ("hammock hypothesis") [2]. Additionally, the urethropelvic ligaments augment the muscular closure of the pelvic floor by enveloping the proximal urethra and bladder neck medially and inserting laterally onto the arcus tendineus fascia pelvis. Furthermore, striated muscles in the urethrovaginal sphincter and compressor urethrae compress the urethra during stress maneuvers. The net effect of these changes is equal transmission of abdominal pressure to the bladder and urethra, leading to increased outlet resistance and continence. Conversely, in women with loss of anatomical support, the proximal urethra descends during stress maneuvers and rotates out of the pelvis.

Petros and Ulmsten suggested that the midurethra, rather than the bladder neck, may be the linchpin for urinary continence [3]. Their "integral theory" proposed that contraction of the pubococcygeus pulls the anterior vaginal wall forward and closes off the urethra during an increase in intra-abdominal pressure. This response is contingent on an intact attachment between the anterior vaginal wall and the pubourethral ligaments, which act as a fulcrum at the midurethra. Laxity in the pubourethral ligaments contributes to incontinence during increases in intra-abdominal pressure.

The goal of anti-incontinence surgery is to prevent involuntary urine loss during periods of increased intra-abdominal pressure. Procedures can be broadly divided into several classes, based on the mechanism that they address. Buttress operations, such as anterior colporrhaphy (AR), support the urethrovesical junction by plicating the pubocervical fascia. Retropubic and transvaginal bladder neck suspensions (RBNS and TNS, respectively) provide support by suspending and elevating lateral periurethral tissues. Pubovaginal slings (PVS) placed at the bladder neck augment normal lateral urethral support structures and buttress the bladder neck to prevent descent and funneling during stress maneuvers. Midurethral slings (MUS; retropubic [RP], transobturator [TO], and single-incision mini slings [SIMS]) support the midurethra in a tension-free fashion to prevent SUI. Finally, urethral bulking procedures augment the "mucosal seal" mechanism to aid in apposition of the urethra in a watertight fashion.

The purpose of this chapter is to review the available evidence regarding the efficacy of surgical treatment options for female SUI, focusing specifically on the questions in Table 41.1. The specific procedures and materials compared in this chapter are summarized in Table 41.2. Owing to length constraints, comparisons of perioperative morbidity are fairly cursory. Furthermore, treatment of side effects and assessments of cost-effectiveness of a particular procedure are not included in this chapter. Grading of the quality of evidence and strengths of recommendations in this chapter

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Table 41.1 Clinical questions.

Clinical question 1	In women undergoing surgery for SUI, do RBNS provide a greater durable subjective and objective improvement of preoperative symptoms over sling procedures?
Clinical question 2	In women undergoing surgery for SUI, do open RBNS provide a greater durable subjective and objective improvement of preoperative symptoms over laparoscopic (lap) RBNS procedures?
Clinical question 3	In women undergoing surgery for SUI, does one type of RBNS provide a greater durable subjective and objective improvement of preoperative symptoms over another RBNS?
Clinical question 4	In women undergoing surgery for SUI, do lap RBNS provide a greater durable subjective and objective improvement of preoperative symptoms over MUS procedures?
Clinical question 5	In women undergoing surgery for SUI, does one type of PVS provide a durable subjective and objective resolution of preoperative symptoms compared with another PVS?
Clinical question 6	In women undergoing surgery for SUI, do PVS provide a durable subjective and objective resolution of preoperative symptoms compared with MUS?
Clinical question 7	In women considering surgery for SUI, do MUS provide a durable subjective and objective resolution of preoperative symptoms over no treatment?
Clinical question 8	In women considering surgery for SUI, do RP MUS provide a durable subjective and objective resolution of preoperative symptoms over TO MUS?
Clinical question 9	In women considering surgery for SUI, do bottom–top RP MUS provide a durable subjective and objective resolution of preoperative symptoms over top–bottom RP MUS?
Clinical question 10	In women considering surgery for SUI, do medial-to-lateral TO MUS provide a durable subjective and objective resolution of preoperative symptoms over lateral-to-medial TO MUS?
Clinical question 11	In women considering MUS surgery for SUI, do different tape properties contribute to a durable subjective and objective resolution of preoperative symptoms?
Clinical question 12	In women considering surgery for SUI, do SIMS provide a durable subjective and objective improvement of preoperative symptoms over RP MUS?
Clinical question 13	In women considering surgery for SUI, do SIMS provide a durable subjective and objective improvement of preoperative symptoms over TO MUS?
Clinical question 14	In women considering surgery for SUI, does one SIMS procedure provide a durable subjective and objective improvement of preoperative symptoms over another SIMS procedure?
Clinical question 15	In women undergoing surgery for SUI, do bulking agents provide a durable subjective and objective resolution of preoperative symptoms over surgical therapy?
Clinical question 16	In women undergoing surgery for SUI, does one bulking agent provide a durable subjective and objective resolution of preoperative symptoms over surgical therapy over another bulking agent?

are based on the guidelines proposed by the international Grading of Recommendations Assessment, Development, and Evaluation Working Group (GRADE) [4].

Furthermore, there has been no new published evidence regarding AR and TNS for the treatment of SUI since the previous edition of this book. The conclusions that there is no evidence to support the use of either procedure over RBNS, PVS, or MUS in women with primary SUI remain valid. Hence these procedures are not included in this chapter.

Literature search

Potential studies were identified by a computerized search of the MEDLINE electronic database (PubMed, 1966–2015). Relevant text and keywords were "incontinence" OR "stress urinary incontinence" OR "female incontinence," AND "randomized controlled trial" OR "controlled trial" OR "meta-analysis." The search was limited to the English-language literature. Several recently updated Cochrane Reviews represented a starting point for the evidence-based evaluation of SUI treatment. In their assessment, relevant studies were identified from a register of controlled trials identified from MEDLINE, CINAHL, the Cochrane Central Register of Controlled Trials, and manual searching of journals and conference proceedings. Details regarding review methods, including identification of primary studies, quality assessments, and data extraction, are described in detail in each Cochrane Review. The findings in the Cochrane Reviews were augmented by additional meta-analyses and randomized controlled trials (RCTs) located by a manual search of the MEDLINE database by the author.

Despite RCTs and meta-analyses of RCTs representing the highest level of evidence, interpretation of these types of trials poses some challenges. First, lack of blinding procedures is common in the surgical literature, and may not be practical in many trials. Second, randomization procedures may be inappropriate, or simply not described. Third, outcome measures, such as nonvalidated questionnaires, may not be appropriate. Fourth, short-term follow-up periods may not be representative of durable, long-term cure rates. Fifth, significant heterogeneity may exist between trials, contributing to wide confidence intervals (95% CI).

Table 41.2 Procedures for female SUI included in this chapter.

Retropubic suspensions (RBNS)	Burch	
	Marshall–Marchetti–Krantz (MMK)	
	Laparoscopic colposuspension (lap RBNS)	
Pubovaginal slings (PVS)	Autologous	Rectus fascia (ARF)
		Fascia lata (AFL)
		Dermis
	Allograft (cadaver)	Fascia lata (CFL)
		Dura mater
	Xenograft (porcine)	Dermis (PD)
		Small intestinal submucosa (PSIS)
	Synthetic (nonabsorbable)	Polytetrafluoroethylene (PTFE)
		Expanded PTFE (Gore-Tex)
		Teflon
Midurethral slings (MUS)	Retropubic (RP)	Tension-free vaginal tape (TVT)
		SPARC
		Intravaginal slingplasty (IVS)
	Transobturator (TO)	TVT-obturator (TVT-O)
		Monarc
Single-incision mini-slings (SIMS)	TVT-Secur (Gynecare),	
	MiniArc (AMS)	
	Ajust (C.R. Bard)	
	Needleless (Mayumana Healthcare, Lisse, The Netherlands)	
	Ophira (Promedon, Cordoba, Argentina)	
	Tissue Fixation System (TFS Pty Ltd., Sydney, Australia)	
	CureMesh (D.Med. Co., Inc., Seoul, Korea)	
Bulking agents	Autologous fat cells	
	Bovine collagen (Contigen)	
	Carbon-coated zirconium beads (Durasphere)	
	Silicone (Macroplastique)	
	Calcium hydroxyapatite (Coaptite)	
	Porcine dermal collagen (Permacol)	

Additionally, dropout or failure to follow-up rates may be substantial in some trials. Furthermore, many trials are small and underpowered to detect a significant difference between two treatment arms.

The SUI literature presents additional unique challenges during interpretation. First, patient populations may be different between trials. Women may present with SUI only or with mixed (urge and stress) incontinence. Some women may have also undergone previous anti-incontinence surgery or have pelvic organ prolapse (POP) eligible for concomitant repair. Second, the quality of SUI may also vary. Women may have the symptom of SUI based on clinical evaluation alone or urodynamic stress incontinence. Additionally, some women may have "occult" SUI, which is diagnosed only after concomitant POP has been reduced in a subjectively dry woman. Third, extensive procedural variations may exist even for established surgeries, making a meta-analysis difficult. Fourth, the generalizability of the results of a particular operation may be brought into question, as the results of many trials represent the experience of a single surgeon or a single institution. Additionally, the follow-up period may vary. For the purpose of this chapter, follow-up periods are defined as short-term (<12 months), medium-term (12–60 months), and long-term (>60 months).

Perhaps the most difficult issue in evaluating the SUI literature is a consistent definition of success or cure. Measures may be subjectively based on a woman's report or a validated questionnaire, or objectively based on a voiding diary, pad tests, cough-stress testing (CST), or urodynamics. At present, there is no consensus on which measures are vital to a trial's validity, but it is widely accepted that both subjective and objective outcomes should be reported. In some trials, definitions of success may also include improved patients, whereas in some studies, cure of SUI may be at the expense of worsened postoperative urge incontinence or an increased incidence of obstructive symptoms and urinary retention.

Clinical question 1

In women undergoing surgery for SUI, do RBNS provide a greater durable subjective and objective improvement of preoperative symptoms over sling procedures?

The evidence

RBNS, and the Burch colposuspension in particular, have been evaluated extensively in a Cochrane Review encompassing 53 trials and 5244 women (updated 13 March 2012) [5]. Seven new trials and updated reports from three previously included trials were incorporated into the current evidence-based review.

Twenty trials with 2170 randomized patients compared open RBNS with sling procedures [5]. Six trials involved PVS and 14 used the TVT as the sling procedure. Eight trials with short-term follow-up compared RBNS with either PVS or MUS and showed no significant difference between the two treatment groups in the risk for subjective incontinence (relative risk [RR] 0.90; 95% CI 0.69 to 1.18). Likewise, subgroup analyses of the PVS and MUS groups failed to show a statistically significant difference between either of these procedures and RBNS. Incontinence rates at medium-term follow-up were lower with sling procedures (six trials; RR 1.18; 95% CI 1.01 to 1.39), which was primarily driven by the findings of one large trial by Albo et al. [6]. In this Urinary Incontinence Treatment Network (UITN) trial, 655 women underwent either Burch or ARF PVS, with 520 (79%) completing the outcome assessment at 24 months. Overall success rates were significantly higher for women who underwent PVS (47 vs. 38%), as were SUI-specific

success rates (66 vs. 49%). Two additional trials had long-term results, and neither showed a significant difference in subjective outcomes [7, 8].

Objective incontinence rates were not statistically different within short-term (RR 1.21; 95% CI 0.84 to 1.75), medium-term (RR 1.12; 95% CI 0.82 to 1.54), and long-term follow-up (RR 0.70; 95% CI 0.30 to 1.64). There were significantly fewer perioperative surgical complications in the RBNS group, again reflecting the results from UITN trial (RR 0.76; 95% CI 0.66 to 0.87). In the subgroup analysis looking at perioperative complication rates between RBNS and MUS, there was no significant difference (RR 1.11; 95% CI 0.66 to 1.87).

Clinical implications

In women with SUI undergoing concomitant abdominal surgery, sling surgery is suggested over RBNS (conditional recommendation based on moderate-quality evidence). This recommendation is based on better outcomes with regard to continence rates. Owing to potentially fewer perioperative complications, RBNS is suggested in those women undergoing concomitant abdominal surgery and those wishing to minimize their mesh load from concomitant MUS.

Clinical question 2

In women undergoing surgery for SUI, do open RBNS provide a greater durable subjective and objective improvement of preoperative symptoms over laparoscopic (lap) RBNS procedures?

The evidence

Twelve trials compared RBNS with lap RBNS [5]. Short-term outcomes did not favor either intervention (RR 0.97; 95% CI 0.79 to 1.18), whereas in the medium term, the combined estimate favored open RBNS (RR 0.88; 95% CI 0.75 to 1.03), albeit not with statistical significance. Without the data from the trial by Ankardal et al., which reported highly significantly better results with open RBNS and was heavily weighted in the meta-analysis, there was no difference in the cure rates between the open and lap RBNS (RR 0.95; 95% CI 0.80 to 1.11) [9]. In the long term, a single trial with 64 participants tended to favor lap RBNS (RR 1.89; 95% CI 0.99 to 3.59), but was not statistically significant [10]. The meta-analyses of short-term data (six trials; RR 0.88; 95% CI 0.64 to 1.21) and medium-term data (seven trials; RR 0.92; 95% CI 0.71 to 1.19) did not show any significant differences in objective continence rates between RBNS and lap RBNS. A meta-analysis by Tan et al. encompassing 16 studies and 1807 women revealed similar outcomes between these procedures at 2 years of follow-up [11].

Clinical implications

In women undergoing surgery for SUI, lap is suggested over open RBNS (conditional recommendation based on moderate-quality evidence) based on similar outcomes and less invasive nature. This recommendation hinges on the availability of the necessary instrumentation, and also of an appropriately trained and skilled surgeon (which is increasingly the case in many parts of the world).

Clinical question 3

In women undergoing surgery for SUI, does one type of RBNS provide a greater durable subjective and objective improvement of preoperative symptoms over another RBNS?

The evidence

Limited data were available from two trials with short-term follow-up comparing different RBNS and the outcomes were not conclusive regarding total number of women with incontinence (9 vs. 12%; RR 0.35; 95% CI 0.10 to 1.26). However, in medium-term follow-up, women treated with a Burch procedure were less likely to be incontinent than those after MMK (four trials: 23 versus 34%; RR 0.72; 95% CI 0.52 to 0.99). Medium-term, objective incontinence rates also favored Burch, but were not statistically significant (19 vs. 30%; RR 0.64; 95% CI 0.39 to 1.05).

Clinical implications

In women considering RBNS for SUI, the Burch procedure is suggested over other surgical alternatives (conditional recommendation based on moderate-quality evidence).

Clinical question 4

In women undergoing surgery for SUI, do lap RBNS provide a greater durable subjective and objective improvement of preoperative symptoms over MUS procedures?

The evidence

Outcomes after lap RBNS have also been evaluated in a Cochrane Review (updated 15 December 2009) [12]. The lap approach theoretically confers less postoperative discomfort and shorter convalescence; however, it may be associated with a learning curve, longer operating times, and greater expense. Most of the 22 eligible RCTs had fewer than 50 women in each arm.

Eight trials compared lap RBNS with MUS [12]. Overall, there was no significant difference in subjective cure rates within 18 months (RR 0.91, 95% CI 0.80 to 1.02). In longer follow-up (4–8 years), TVT had similar subjective cure rates to lap RBNS (RR 1.18, 95% CI 0.36 to 3.81) [13]. Objective cure rates assessed in all but one study were higher for women after MUS compared with lap RBNS using sutures (RR 0.92, 95% CI 0.85 to 0.99) and mesh (RR 0.66, 95% CI 0.51 to 0.86). Of note, a trial by Valpas et al. comparing lap RBNS and TVT reported a significant difference in favor of TVT in both objective (CST) and subjective (King's Health

Questionnaire) outcome measures [14]. Although this trial presented 1-year data and there was a lack of appropriate blinding procedures, the randomization technique was appropriate and subjective and objective outcome criteria were used.

Clinical implications

In women undergoing surgery for SUI, MUS is suggested over lap RBNS (conditional recommendation based on moderate-quality evidence), based on better outcomes and a less invasive approach. Lap RBNS is suggested in those patients placing a relatively higher value on reducing the mesh load than maximizing continence outcomes. It also hinges on the availability of the necessary instrumentation and an appropriately trained and skilled surgeon.

Clinical question 5

In women undergoing surgery for SUI, does one type of PVS provide a durable subjective and objective resolution of preoperative symptoms compared with another PVS?

The evidence

Twenty six trials including 2284 women who underwent PVS were evaluated in a Cochrane Review (updated 2 June 2010) [15]. The quality of evidence was moderate for most trials and the follow-up typically ranged from 6 to 24 months.

Six trials compared one type of PVS with another [15]. Women who underwent ARF PVS (35%, 56/161) had similar short-term, subjective incontinence rates to those who had PVS made from porcine dermis, porcine SIS, and ARF of shorter length (sling on a string) (34%, 49/146) (RR 0.89; 95% CI 0.66 to 1.19). ARF PVS was associated with significantly higher improvement rates compared with another biological PVS (two trials: RR 0.22; 95% CI 0.08 to 0.59). There was no significant difference in medium-term incontinence rates (379 women: RR 0.89; 95% CI 0.72 to 1.10); however, medium-term improvement rates favored ARF PVS (RR 0.33; 95% CI 0.17 to 0.64). Long-term incontinence rates were assessed in only one trial and showed no statistically significant difference between different lengths of ARF used (RR 1.17; 95% CI 0.86 to 1.59) [16]. A single trial revealed more complications with the use of non-absorbable Gore-Tex.

Clinical implications

In women with SUI who choose a bladder neck sling, ARF PVS is suggested over alternative approaches (conditional recommendation based on moderate quality evidence).

Clinical question 6

In women undergoing surgery for SUI, do PVS provide a durable subjective and objective resolution of preoperative symptoms compared with MUS?

The evidence

Twelve trials addressed the comparison between PVS and MUS operations [15]. There was no significant difference in short-term subjective continence rates (eight trials: RR 0.97; 95% CI 0.78 to 1.20). This translates to 267 per 1000 women being incontinent after a PVS vs. 275 per 1000 after an MUS. There was also no statistically significant difference in trials with medium- or long-term follow-up (four trials: RR 1.23; 95% CI 0.91 to 1.66). Two trials with short- and medium-term follow-up assessed objective continence rates [17, 18]. There was no statistically significant difference between the two groups (RR 1.29; 95% CI 0.45 to 3.71). In pooled data analyses of a relatively small number of trials, PVS were associated with more perioperative complications (other than bladder puncture), more postoperative voiding and storage symptoms, and more requirements for sling release.

Clinical implications

In women with SUI considering a sling procedure, an MUS is suggested over a PVS (conditional recommendation based on moderate-quality evidence). This recommendation is based on the higher rates of postoperative adverse sequelae and the need for an additional harvest site with PVS surgery. Hence PVS may be best reserved for those women with complex or recurrent SUI.

Clinical question 7

In women considering surgery for SUI, do MUS provide a durable subjective and objective resolution of preoperative symptoms over no treatment?

The evidence

Commensurate with its status as the primary anti-incontinence surgical procedure worldwide, the MUS has been the most-researched operation since the previous evidence-based review. To date, one multi-center prospective RCT has compared MUS versus no treatment. Campeau et al. randomized women over 70 years of age to undergo immediate TVT or to wait 6 months to undergo the same surgery (control group) [19]. Although continence was not an endpoint, quality of life indices were significantly higher in the immediate surgery group.

Clinical implications

In women considering surgery for SUI, MUS is suggested over no surgical treatment at all (conditional recommendation based on moderate-quality evidence).

Clinical question 8

In women considering surgery for SUI, do RP MUS provide a durable subjective and objective resolution of preoperative symptoms over TO MUS?

The evidence

The results of the Cochrane Review evaluating MUS outcomes have recently been updated (26 June 2014) [20]. Eighty-one trials evaluating 12 113 women were included in the review.

Fifty-five studies compared the RP route of insertion with the TO route [20]. Short-term subjective cure ranged from 62 to 98% for TO and from 71 to 97% for RP, with no statistically significant difference between the two approaches (36 trials, 5514 women: RR 0.98, 95% CI 0.96 to 1.00). The mean subjective cure rate across both groups was 83.3% and, for every 1000 women, there were 17 fewer cured in the TO group (95% CI from 0 fewer to 33 fewer per 1000). This was not statistically significant and the difference is unlikely to be clinically significant. Medium-term subjective cure rates were also not significantly different between the two groups (five trials, 683 women: RR 0.97, 95% CI 0.87 to 1.09). Subjective cure rates ranged from 82 to 91% for the TO group and from 77 to 98% for the RP group. The average medium-term subjective cure rate across both groups was 86.9% and, for every 1000 women, there were 26 fewer women cured in the TO group (95% CI from 26 per 1000 more to 70 per 1000 fewer). There was no statistically significant difference in long-term subjective cure (four trials, 714 women: RR 0.95, 95% CI 0.80 to 1.12). Subjective cure rates ranged from 43 to 92% in the TO group and from 51 to 88% in the RP group. The average long-term subjective cure rate across both groups was 84.3% and, for every 1000 women, there were 42 fewer women cured in the TO group (95% CI from 110 per 1000 less to 34 per 1000 more).

Short-term objective cure rates were 85.7 vs. 87.2% for the TO and RP approaches, respectively (40 trials, 6145 women: RR 0.98, 95% CI 0.96 to 1.00). As the CI was narrow, the 2% statistically nonsignificant difference between the approaches is unlikely to represent a clinically significant difference. The small difference in the short-term objective cure plus improved rate was not statistically significant (10 studies, 1478 women: RR 0.98, 95% CI 0.96 to 1.01). The same holds true for the medium-term objective cure rates (five trials, 596 women: RR 1.00, 95%CI 0.95 to 1.06), and long-term objective cure rates (three trials, 400 women: RR 0.97, 95% CI 0.90 to 1.06).

There were some significant differences in the complication rates between the two approaches. Major vascular or visceral injury occurred significantly less often with the TO approach (28 trials, 4676 women: RR 0.33, 95% CI 0.19 to 0.55). The rate of bladder perforation was significantly lower in the TO group (40 trials: RR 0.13, 95% CI 0.08 to 0.20). The average bladder perforation rate across both groups was 2.54% and there were 22 fewer perforations per 1000 in the TO group (95% CI from 20 to 23 per 1000 fewer). The TO approach was associated with significantly lower rates of postoperative voiding dysfunction (37 trials, 6200 women: RR 0.53 95% CI 0.43 to 0.65). There was no statistically significant difference between the two approaches in reported rates of *de novo* urgency and urgency urinary incontinence (UUI) (31 trials, 4923 women: RR 0.98, 95% CI 0.82 to 1.17). The mean short-term rate of *de novo* urgency/UUI across both groups was 8.35%. Similarly, the medium-term rates of *de novo* urgency/UUI were not significantly different (RR 0.98, 95% CI 0.55 to 1.73). A single long-term study showed no difference between the groups (253 women: RR 0.81, 95% CI 0.18 to 3.53) [21]. The average rate of vaginal extrusion across both groups was 2.09% and there was no significant difference between the groups (31 trials, 4743 women: RR 1.13, 95% CI 0.78 to 1.65). The average rate of groin pain across both groups was 4.51% and there was a significantly higher occurrence after a TO approach (RR 4.12, 95% CI 2.71 to 6.27). Conversely, the rate of suprapubic pain was significantly lower after a TO approach (RR 0.29, 95% CI 0.11 to 0.78).

Clinical implications

In women with SUI planning to undergo a MUS, TO MUS is recommended over RP MUS (strong recommendation based on high-quality evidence). This recommendation is based on similar continence outcomes, but a better adverse sequelae profile for the TO approach. I The RP approach is recommended owing to its predictable location, with the knowledge that there may be more persistent or *de novo* storage and emptying symptoms afterwards. Owing to the greater potential for neurological sequelae and groin pain, the TO approach may not be the optimal choice in younger, more physically active women. It is important to note that, since the compilation of this review, several of the MUS included in the trial have been removed from the market.

Clinical question 9

In women considering surgery for SUI, do bottom–top RP MUS provide a durable subjective and objective resolution of preoperative symptoms over top–bottom RP MUS?

The evidence

Five trials with 636 women addressed the comparison between bottom–top RP MUS (TVT) with top–bottom RP MUS (SPARC) [20]. Short-term continence rates were significantly higher after the TVT (87.34%) vs. SPARC (79.58%) (three trials, 477 women: RR 1.10, 95% CI 1.01 to 1.19). Objective cure rates using a variety of measurements were similar between the two groups (five trials, 622 women: 94.19 vs. 89.10%; RR 1.06, 95% CI 0.97 to 1.17). No statistically significant difference was seen in overall perioperative complications (RR 0.98, 95% CI 0.53 to 1.84); however, significantly fewer women experienced bladder perforation

(RR 0.55, 95% CI 0.31 to 0.98), voiding dysfunction (RR 0.40, 95% CI 0.18 to 0.90), and vaginal extrusion (RR 0.27, 95% CI 0.08 to 0.95) after the TVT. There were no statistically significant differences between the two groups with respect to postoperative *de novo* urgency/UUI (RR 0.84, 95% CI 0.52 to 1.34).

Clinical implications

In women with SUI planning to undergo RP MUS, the bottom–top approach is suggested over the top–bottom approach (conditional recommendation based on moderate-quality evidence). Since the overall difference in outcomes and complications is fairly low, the prudent approach should be for the practitioner to continue the approach with which they are most comfortable. It is important to note that, since the compilation of this review, several of the MUS included in the trial have been removed from the market.

Clinical question 10

In women considering surgery for SUI, do medial-to-lateral TO MUS provide a durable subjective and objective resolution of preoperative symptoms over lateral-to-medial TO MUS?

The evidence

Ten trials compared the medial-to-lateral (inside-to-out) TO approach with the lateral-to-medial (outside-to-in) TO approach [20]. There were no statistically significant differences in either short-term subjective cure rates (six trials: RR 1.0, 95% CI 0.96 to 1.06) or short-term subjective cure or improved rates (five trials: RR 1.02, 95% CI 0.97 to 1.08). There was no statistically significant difference in medium-term subjective cure (two trials: RR 1.06, 95% CI 0.91 to 1.23) or subjective cure or improved rate (two trials: RR 1.00, 95% CI 0.90 to 1.11). Objective cure was not significantly different between the two groups (six trials: RR 0.99, 95% CI 0.95 to 1.04). There was also no statistically significant difference in the objective cure or improved rate between the two groups (RR 1.00, 95% CI 0.95 to 1.07). There are no published trials with long-term data. The average rate of vaginal wall perforation across both groups was 7.39% and was significantly less likely to occur with the medial-to-lateral approach (RR 0.25, 95% CI 0.12 to 0.53). The average rate of postoperative voiding dysfunction across both groups was 5.53% and occurred significantly more in the medial-to-lateral approach (eight studies, 1121women: RR 1.74, 95% CI 1.06 to 2.88). There were no statistically significant differences between the two groups in terms of: overall perioperative complication rate, major vascular/visceral injury, bladder perforation, *de novo* urgency/UUI rates, detrusor overactivity, vaginal extrusions, and groin/thigh pain (six studies, 837 women: 9.2 vs. 8%; RR 1.15, 95% CI 0.75 to 1.76).

Clinical implications

In women with SUI planning to undergo TO MUS, the inside-out approach is suggested over the outside-in approach (conditional recommendation based on moderate-quality evidence) based on lower rates of intraoperative vaginal wall perforation. Since the overall difference in outcomes and complications is fairly low, the prudent approach should be for the practitioner to continue the approach with which they are most comfortable.

Clinical question 11

In women considering MUS surgery for SUI, do different tape properties contribute to a durable subjective and objective resolution of preoperative symptoms?

The evidence

Ten trials compared different methods of carrying out TO and RP MUS surgeries using the same route [20]. Although there were no statistically significant differences reported for all outcomes in each trial, the small size of each comparison group precluded any meaningful statistical analysis of the outcomes measured.

Four trials compared different MUS operations based on their tape properties, for example monofilament versus multifilament tapes [20]. In the short and medium term there was no statistically significant difference between mono- and multifilament tapes in terms of their subjective cure rates. The objective cure rate was not significantly different between the groups (RR 1.07, 95% CI 0.96 to 1.19). There were few perioperative complications with no statistically significant difference between the groups (RR 1.16, 95% CI 0.36 to 3.69). Bladder perforation occurred in 4.49% of monofilament and 3.67% of multifilament tape procedures (RR 1.15, 95% CI 0.49 to 2.70). There were no statistically significant differences between the groups for postoperative voiding dysfunction, *de novo* urgency/UUI, and detrusor overactivity. In three trials, vaginal extrusions were more common in the multifilament group, but this did not reach statistical significance (RR 0.79, 95% CI 0.09 to 6.84).

Clinical implications

In women considering MUS surgery for SUI, monofilament, polypropylene MUS are suggested based on their history of stable tissue integration and the high complication rates seen with other materials (conditional recommendation based on low-quality evidence).

Clinical question 12

In women considering surgery for SUI, do SIMS provide a durable subjective and objective improvement of preoperative symptoms over RP MUS?

The evidence

SIMS are short polypropylene slings placed through a small suburethral, vaginal incision. The aim of any SIMS procedure is to avoid blind trocar placement through the pelvis while maintaining the success rates of traditional MUS placed through either the RP or TO approach. In light of early low objective cure rates and concerns regarding adverse events, in 2012 the US Food and Drug Administration ordered SIMS manufacturers to complete postmarket studies to assess sling safety and efficacy (522 orders). In the same year, the European Association of Urology analyzed SIMS data and found that there was a paucity of level I evidence to support SIMS implantation [22].

The data regarding SIMS were assessed in a Cochrane Review (updated 6 February 2013) [23]. Overall, 31 RCTs or quasi-randomized trials involving 3290 women were identified. Data from five trials revealed that significantly more women had subjective persistent urinary incontinence after SIMS versus RP MUS (121/292, 41 vs. 72/281, 26%; RR 2.08, 95% CI 1.04 to 4.14). Objective success also statistically significantly favored RP MUS (two trials: RR 4.44, 95% CI 2.06 to 9.56). Statistical heterogeneity, disparity in study sample size, and variable follow-up length made summarizing results challenging.

Clinical implications

In women considering surgery for SUI, RP MUS are suggested over SIMS (conditional recommendation based on low-quality evidence).

Clinical question 13

In women considering surgery for SUI, do SIMS provide a durable subjective and objective improvement of preoperative symptoms over TO MUS?

The evidence

In 10 trials, significantly more women had subjective urinary incontinence after SIMS than inside-out TO MUS (172/572, 30% vs. 55/481, 11%; RR 2.55, 95% CI 1.94 to 3.36) [23]. Women were nearly three times more likely to be objectively incontinent after SIMS, and the overall result was statistically significant in favor of inside-out TO MUS (RR 2.91, 95% CI 2.00 to 4.25). Seven trials compared SIMS versus outside-in TO MUS and the overall result was not statistically significant (36/306, 12% vs. 38/296, 13%; RR 0.91, 95% CI 0.60 to 1.39). Although there was no statistical difference in objective continence when comparing SIMS and outside-in MUS, the overall results obtained when both types of TO MUS were combined still favored the TO MUS (RR 1.88, 95% CI 1.49 to 2.36).

Clinical implications

In women considering a surgical approach that avoids the retroperitoneum, either the TO MUS or SIMS are suggested (conditional recommendation based on low-quality evidence). SIMS may offer the capacity for an even less-invasive approach than the TO MUS, but the documented difference is insufficient to drive a recommendation for SIMS.

Clinical question 14

In women considering surgery for SUI, does one SIMS procedure provide a durable subjective and objective improvement of preoperative symptoms over another SIMS procedure?

The evidence

Nine trials compared one type of SIMS versus another SIMS [23]. There was no statistically significant difference in subjective or objective success rates in any of the studies.

Clinical implications

In women considering surgery for SUI, one type of SIMS cannot be suggested over another in women considering SIMS for surgical correction of SUI (no recommendation can be made owing to insufficient evidence).

Clinical question 15

In women undergoing surgery for SUI, do bulking agents provide a durable subjective and objective resolution of preoperative symptoms over surgical therapy?

The evidence

A Cochrane Review (updated 6 May 2011) addressing the efficacy of periurethral bulking therapy included 14 trials and 2004 women [24]. One study compared paraurethral injection of autologous fat with placebo injection of saline in 68 women [25]. At 3 months, six of 27 (22%) women reported cure or improvement compared with six of 29 (21%) women after saline injection (RR 0.98, 95% CI 0.75 to 1.29). There was a similar reduction in 1 h pad weight for both groups.

Two trials compared bulking therapy with surgical therapy. In one trial, complete satisfaction was not significantly different in women undergoing bulking therapy and surgery with Burch, PVS, or TVS [26]. More women were objectively cured in the surgery group based on the pad weight test. In another trial, nine of 22 women (41%) were not satisfied after Macroplastique injections compared with four of 21 (19%) after PVS (NS; RR 2.15, 95% CI 0.78 to 5.92) [27]. When cure was defined as subjective incontinence occurring once or less per week, there was no statistically significant difference between the two therapies.

Clinical implications

In women undergoing surgery for SUI, PVS are suggested over bulking agents (conditional recommendation based

on low-quality evidence). This recommendation is based on limited evidence of a more durable response. Bulking remains an option for those women interested in an office procedure and those who accept the possibility of requiring multiple treatment sessions.

Clinical question 16

In women undergoing surgery for SUI, does one bulking agent provide a durable subjective and objective resolution of preoperative symptoms over surgical therapy over another bulking agent?

The evidence

Eight trials compared one bulking agent with another. Lightner et al. reported that 76 of 115 women (66%) undergoing injection of Durasphere reported cure or improvement in their SUI compared with 79 of 120 (66%) women having injection of bovine collagen (NS; RR 0.99, 95% CI 0.70 to 1.42) [28]. Andersen reported a trend towards better outcomes after 1 year of treatment with Durasphere with regard to cure (40 vs. 14.3%; RR 0.70, 95% CI 0.49 to 1.01) and improvement of symptoms (80 vs. 61.9%; RR 0.53, 95% CI 0.20 to 1.36); however, the results were not statistically significant [29]. There was no significant difference in objective urine loss between the two groups in the first study, and there were no data on quantification of symptoms in the second study.

A meta-analysis of two trials revealed that 65 of 145 women (44.8%) reported being dry/cured following injection of Macroplastique, compared with 46 of 134 women (34.3%) injected with bovine collagen at 12 months of follow-up [24]. Analysis suggested a nonstatistically significant trend towards better outcomes after Macroplastique injections (RR 0.85, 95% CI 0.71 to 1.03). Also not statistically significant, 36 of 111 women (32.4%) had no improvement following Macroplastique injections, compared with 48 out of 108 women (44.4%) injected with collagen (RR 0.73, 95% CI 0.52 to 1.03). Urinary loss as measured by pad test decreased in both groups following treatment, but there no significant differences were found between the two groups at 1, 6, or 12 months of follow-up.

Coaptite was compared with Contigen in a large multicenter RCT [30]. At 12 months of follow-up, 83 of 131 women (63.4%) receiving Coaptite reported improvement of one Stamey grade or more, compared with 57 of 100 (57%) receiving Contigen injections (NS; $p = 0.34$). In another study, porcine dermal implant (Permacol) was compared against Macroplastique [31]. There was no significant difference in improvement using a validated questionnaire or an objective pad test. In addition, although not statistically significant, women who underwent transurethral injection may have a greater rate of improvement than those who were treated with a periurethral injection technique.

Clinical implications

In women undergoing surgery for SUI, one bulking agent cannot be suggested over another (no recommendation can be made owing to insufficient evidence). Furthermore, several of the agents included in the trials are no longer available.

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42 CHAPTER 42

Diagnosis and treatment of overactive bladder

Nadir I. Osman, Altaf Mangera, and Christopher R. Chapple
Department of Urology, Royal Hallamshire Hospital, Sheffield, UK

Introduction

Overactive bladder syndrome (OAB) is a common and highly bothersome chronic symptom complex that has a negative impact upon quality of life. It affects both men and women in similar proportions and its prevalence increases in the older population. Incontinence is far more common as a problem in women than men, affecting approximately 30% of females affected by OAB. There are significant economic costs associated with OAB, both on individuals and society as a whole, owing to the expense related to direct care in addition to that incurred by lost productivity. OAB consists of a collection of storage lower urinary tract symptoms (LUTS) and was defined by the International Continence Society (ICS) as "urinary urgency with or without urgency incontinence usually accompanied by frequency and nocturia" [1]. The *sine qua non* of OAB is urinary urgency, which is described by the ICS as "a sudden and compelling desire to void that is difficult to defer" [1].

Clinical question 1

What is the evidence for the definition of overactive bladder?

Literature search

We performed a systematic search of the literature using the terms "overactive bladder" and "detrusor overactivity."

The evidence

The older terminology regarding OAB was related to pathophysiology as defined by a pressure/flow urodynamic study, referring to the finding of involuntary detrusor contractions during the filling phase of the micturition cycle. This was termed "detrusor instability" (idiopathic etiology) or "detrusor hypereflexia" (neurogenic etiology) [1]. In contemporary times, the ICS refers to this finding as "detrusor overactivity" (DO). In 1996, it was proposed by Paul Abrams and Alan Wein that a symptom-based definition be introduced, based on the observation that patients who complain of bothersome symptoms were not always found to have DO on urodynamics testing. Moreover, it was considered unnecessary to subject all patients with symptoms to invasive urodynamics before commencing drug therapy [2]. The term "overactive bladder" (OAB) was proposed to describe the symptoms associated with DO, as it was considered to be easier for patients to understand and identify with this concept. This was subsequently rapidly adopted by the healthcare professions, regulators, and the pharmaceutical industry. Consequently, there has been a rise in the public profile of OAB and a boon in related clinical and scientific research and also an expansion in the marketed agents used for its treatment.

Notwithstanding the advantages resulting from the development of a symptom-based definition and the adoption of the term OAB, the symptom complex of OAB continues to generate considerable controversy. It has been argued that the definition of OAB is too vague, with the inclusion of terms such as "usually" and "with or without" [3]. It must also be emphasized that only a proportion of people with the symptoms of OAB have demonstrable DO. In addition, the lack of standardized outcome measures for symptom severity (e.g. how many voids, the degree of frequency, and the degree of incontinence) in the definition has been criticized with the suggestion that individuals with mild or occasional symptoms who may actually be normal will be included. In particular, the voiding frequency threshold for normality of less than eight times in a 24 h period that has been adopted has not been supported by any clear evidence base. The implication of this is possible overmedicalization and an overestimation of the scale of the

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Table 42.1 Studies correlating the symptom complex of overactive bladder (OAB) with detrusor overactivity (DO).

Study	Definition of OAB	No. of subjects	% of OAB-DRY patients with DO	% of OAB-WET patients with DO	Overall % of OAB patients with DO
Hashim and Abrams 2006 [5]	ICS 2002	Male	69	90	–
		Female	44	58	–
Sekido et al. 2006 [6]	ICS 2002	Male: 12	–	–	75
		Female: 38	–	–	37
Hyman et al. 2001 [7]	"Urge incontinence"	Male: 28	–	–	75
Al Ghazo et al. 2011 [8]	ICS 2002	Male: 92	63	93	76
		Female: 117	61	70	59
Giarenis et al. 2013 [9]	ICS 2002	Female: 556	–	–	43
Digesu et al. 2003 [10]	ICS 1988	Female: 457	–	–	54.2
Jeong et al. 2013 [11]	ICS 2002	Female: 513	–	–	32.6

problem, particularly in view of the fact the large epidemiological surveys reported to date have relied upon subjective estimations such as using telephone interviews and online questionnaires.

In practical terms, the interpretation of the symptom of urinary urgency can be challenging. The ICS definition does not detail whether urgency is a discrete or a continuous phenomenon. Furthermore, a compelling desire to void is arguably also felt by normal individuals when the bladder is over-full. It has been suggested that what truly defines patients with urgency from normal individuals is a "fear of leakage" [4]. When the patient does not reach the toilet in time, incontinence results, termed urgency urinary incontinence (UUI), which occurs in around 30% of patients (usually female) with OAB. In men, such episodes are highly correlated with DO [5], this being more common in the absence of DO in women as the bladder outlet is relatively weaker, meaning that leakage is more likely to occur. A further important issue is that the word urgency is not differentiated from urge in many languages, which makes applying the definition problematic. In particular from a methodological standpoint, there is a conundrum: while the definition and assessment of the term urgency have not been adequately validated using modern criteria, nevertheless it represents the pivotal symptom upon which the diagnosis of the whole symptom complex is based.

Clinical implications

Overactive bladder is the accepted term by the ICS, which proposed a definition that has been used in clinical practice and research for over a decade. Despite the limitations of the definition, its use is recommended to ensure consistency in practice and standardization in research (clinical principle).

Clinical question 2

How does overactive bladder relate to detrusor overactivity?

Literature search

We performed a systematic search of the PubMed database to identify studies that sought to correlate the symptoms of OAB with the urodynamic finding of DO. No systematic reviews were found; the articles retrieved are summarized in Table 42.1.

The evidence

Several investigators have sought to assess objectively the relationship between the symptom complex of OAB and the urodynamic diagnosis of DO. Most of these studies were retrospective case series of patients undergoing urodynamic studies. Summarizing these studies, it is apparent that OAB symptoms are more strongly correlated with underlying DO in men than women. In both sexes, OAB with incontinence (OAB wet) is more strongly associated with DO than OAB without incontinence (OAB dry). Work by our group has demonstrated that ambulatory urodynamics have a much higher sensitivity for detecting DO than standard urodynamics [12], raising the possibility that DO is simply missed in the latter in a proportion of patients, potentially as a consequence of the nonphysiological filling rates used during urodynamic testing.

Clinical implications

Clinicians should consider that OAB symptoms may be due to alternative diagnoses to DO when assessing and treating patients with symptoms of OAB (clinical principle).

Clinical question 3

What is the evidence base relating to the use of placebo treatments in overactive bladder?

Literature search

A systematic review of the literature was conducted, looking for randomized controlled trials (RCTs) that assessed the

efficacy of antimuscarinic agents versus placebo. Full details of the search are described elsewhere [13].In brief; 12 781 references were retrieved, of which 83 were RCTs and, of those, 62 trials were placebo controlled. Five parameters were assessed against a null hypothesis of "no effect" for change in incontinence episodes per day, change in micturition episodes per day, change in urgency episodes per day, change in mean volume per micturition, and change in maximum cystometric capacity. Each study was weighted by its inverse variance.

The evidence

This systematic review revealed that patients in the placebo arm of RCTs had a reduction in incontinence episodes, micturition episodes, and urgency episodes of 1.1 per day. The mean micturition volume increased by 11 mL and cystometric capacity decreased by 17 mL. The conclusions were that bladder diary parameters are prone to a placebo effect, but this does not extend to improvements in urodynamic effects. The effects were not related to study size.

The potential rationale reasons for a "placebo effect" in OAB trials are manifold. A placebo is pharmacologically "inert" and by itself should not lead to any response. The effect seen is therefore likely to be attributable to the subjective perception of improvement; clearly, with a quality of life-impacting condition such as OAB, this will have important perceptual consequences for the individual affected by OAB. In addition, in OAB trials a bladder diary is used to assess response to treatment, and this in itself leads to a bladder retraining effect and behavioral changes and may be responsible for an improvement in symptoms. Patients in trials are also educated about their diagnosis and counseled regarding conservative measures, and this will inevitably lead to some improvement in symptoms.

Interestingly, there were no urodynamic improvements, but many patients with OAB do not have urodynamic abnormalities to start with, as discussed above. Interestingly, clinicians with enthusiasm for a new drug in placebo-controlled RCTs may lead to increased placebo effects through a phenomenon called experimental subordination, whereby a patient will attempt to please the enthusiastic clinician conducting the study.

Clinical implications

Ethically, administration of a placebo is considered a form of deception as the patient has to believe that they are actually receiving an active pharmaceutical; therefore, it should not be used in routine clinical practice (clinical principle).

However, one could argue that placebos are "doing no harm" and are "without side effects," and utilizing the mind to help retrain the bladder is not an entirely useless approach. Should a physician withhold a treatment that has the potential to heal? Also, the benefit that some patients may gain can be considered complementary to conservative measures such as bladder drill and caffeine restriction. Indeed, although the evidence for conservative therapies is not of great quality, nevertheless, we still advocate these to all our patients.

From the data in the literature, the true benefit of a placebo is only speculative. Until a trial compares conservative measures alone versus placebo with conservative measures, we will remain unsure of the true potential for placebo treatments. In such a trial, the placebo would have to be administered with the implication that it was a new therapeutic agent. This would have ethical issues; nevertheless, we can agree that using such an approach would utilize the "placebo effect" and therefore have some benefit to the patients being studied, and could therefore be justified.

Clinical question 4

What is the evidence base relating to antimuscarinic therapy for overactive bladder?

Literature search

This section is based on a previously published systematic review and meta-analysis by our group [14]. In addition, we undertook a further comprehensive search for systematic reviews on this topic in the PubMed database from 2008 to May 2015. Since our earlier publication, further systematic reviews have been published reporting the efficacy of antimuscarinic agents [15, 16], constipation seen with antimuscarinic agents [17], adverse events of antimuscarinic agents [18], central nervous system adverse events [19], and antimuscarinic use in men [20]. Systematic reviews for individual antimuscarinic agents include fesoterodine [21], tolterodine extended release (ER) [22], and solifenacin [23].

The evidence

Meta-analysis has shown the improvements reported by patients in both symptoms and health-related quality of life with antimuscarinic agents in addition to reporting their safety [14]. Pooled differences showed a reduction of 0.5–1.3 micturition episodes per day and 0.4–1.1 incontinence episodes per day. With very few trials comparing selective antimuscarinic agents against each other, a meta-analysis of such data is not available. Therefore, researchers have addressed differences in antimuscarinic agent profiles by comparing the outcomes across studies.

Meek et al. reported the odds of developing constipation with various antimuscarinic formulations [17]. It is clear that all antimuscarinic agents increase the odds of developing constipation, with varying risk attributed to each, but the differences between agents have overlapping confidence intervals and so the differences seen cannot be said to be significant. Another concern with analyses of this sort is that study inclusion and exclusion criteria and assessment

tools will have varied, and this is a potential source of bias. Similarly, a network meta-analysis reported similar adverse event profiles with all currently used antimuscarinic agents except oxybutynin >10 mg/day [18].

Paquette et al. suggested that there is inadequate assessment and reporting of cognitive side effects in antimuscarinic trials in their systematic review [19]. The majority of studies reported spontaneous cognitive adverse events and only 1/72 trials used an objective measure such as the mini-mental state examination.

Clinical implications

There appears to be little difference in efficacy between the different selective antimuscarinic agents. Given the different sub-receptor affinities for each antimuscarinic preparation, if one drug fails then a different formulation may be of benefit. Preparations with adjustable dosing are also beneficial here as they allow for a balance between efficacy and side effects (clinical principle).

In almost all RCTs, cognitive impairment is a real concern, especially when treating the elderly population and those with conditions such as diabetes, Alzheimer disease, stroke, trauma, multiple sclerosis, and Parkinson disease, due to increased permeability of the blood–brain barrier [24]. Trospium, a quaternary amine, has been shown not to cross the blood–brain barrier, but whether this translates to a clinically detectable difference in cognitive impairment compared with the other selective antimuscarinics remains to be proven [25].

The majority of RCTs were conducted over a 12-week period and the natural history of the OAB syndrome complex seems to fluctuate, probably owing to its multifactorial nature. Therefore, discontinuation rates, which are obtained from post-market analysis, are up to 50% [26, 27]. More work is required to assess the potential benefits of re-challenging patients who relapse after ceasing their medication or who discontinue it owing to lack of efficacy or side effects.

Given that the majority of patients in OAB trials are women, clinicians have debated the utility of antimuscarinics in men. This is especially important given the potential risk of precipitating urinary retention. Kaplan et al. systematically reviewed the evidence for antimuscarinics in men and reported a rate of urinary retention of <3% with non-significant changes in post-void residue [20]. A combination of an antimuscarinic and an alpha-antagonist was found to lead to greater symptomatic improvements than antimuscarinics alone, although antimuscarinics alone are efficacious and safe.

Clinical question 5

What is the evidence base relating to β_3-agonist therapy in overactive bladder?

The evidence

β_1-, β_2-, and β_3-adrenoreceptors have been shown to be present in the detrusor and urothelium. When stimulated, these receptors lead to G-protein and adenylcyclase activation, which leads to an increase in cyclic AMP levels and relaxation of the detrusor; in humans this effect is mediated via the β_3-receptors. Mirabegron, an agent that specifically agonizes the β_3-receptors, has recently become available for use. Mirabegron facilitates detrusor relaxation during the storage phase of the micturition cycle and, in contrast with antimuscarinic agents, improves the storage capacity of the bladder without impairing the amplitude of the detrusor contraction during the voiding phase of the micturition cycle. Mirabegron has been studied in several industry-sponsored clinical trials over the past decade, including a total of approximately 10 000 patients. We performed a systematic search of the PubMed database to identify the relevant safety and efficacy data from the pivotal Phase III studies.

The Phase III program comprised three 12-week double-blind RCTs that were conducted in North America, Australia, and Europe [28–30]. These studies compared mirabegron with placebo or with the antimuscarinic tolterodine in terms of safety and efficacy. Inclusion criteria included adults (>18 years old) with daytime urinary frequency (≥8) and urinary urgency with or without urgency incontinence (at least three leakage episodes in a period of 3 days in bladder diary). The secondary endpoints were mean number of urgency episodes per 24 h and mean volume voided per void. Primary endpoints were change in mean number of leakage episodes and the mean number of voids in a 24 h period.

A pooled analysis of efficacy data from the three pivotal Phase III studies was performed by Nitti et al. [31]. Statistically significant decreases in the mean number of leakage episode per 24 h of –1.10, –1.49, and –1.50 were observed at 12 weeks for placebo, mirabegron 50 mg and mirabegron 100 mg, respectively ($p < 0.05$ for all comparisons). In terms of mean number of voids, reductions of –1.20, –1.75, and –1.74 were observed for placebo, mirabegron 50 mg, and mirabegron 100 mg, respectively ($p < 0.05$ for all comparisons). Both number of leakage episodes per 24 h and number of voids per 24 h, were significantly improved for mirabegron at both doses compared with placebo. For the secondary endpoints of mean volume voided per void, mean level of urgency, mean number of urgency episodes (grade 3 or 4) per 24 h, and mean number of urgency incontinence episodes per 24 h, there were significant decreases at 12 weeks for both doses of mirabegron compared with placebo. The higher dose of mirabegron did not appear to confer any additional benefit over the lower dose and, although a statistically significant reduction in nocturia episodes of –0.55 compared with placebo –0.042 was observed, the clinical significance of this difference is highly doubtful.

In terms of safety and tolerability, the profile of mirabegron appears to be acceptable. The pooled analysis of safety data of the three pivotal Phase III studies by Nitti et al. showed the most common treatment-emergent adverse events (TEAEs) to be hypertension, nasopharyngitis, and urinary tract infection (UTI) [31]. These incidences were similar to those with placebo and tolterodine. Dry mouth is one of the most bothersome side effects of antimuscarinic treatment, and the incidence of this was at the placebo level for mirabegron. The incidence of urinary retention was also similar to that with placebo. Mirabegron was associated with approximate increases of ≤1 mmHg in blood pressure and ≥1 bpm in pulse rate compared with placebo. A 12-month study by Chapple et al. demonstrated a similar incidence of TEAEs for mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg [32]. Dry mouth was more common with tolterodine than mirabegron, 8.6% versus 2.3–2.8%, respectively. Discontinuation due to TEAEs was similar amongst all groups, 6.4, 5.9, and 6.0% of subjects receiving mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg, respectively.

In summary, mirabegron 50 and 100 mg has demonstrated significant and clinically meaningful efficacy in terms of improving the symptoms of OAB, with no significant advantage conferred at the higher dose. In the pooled dataset, approximately half of OAB patients had been previously treated with antimuscarinic agents but had discontinued because of either unacceptable efficacy and/or poor tolerability. The efficacy of mirabegron has been evaluated in both treatment-naive subjects and those who had previously been treated with antimuscarinics. This is important as antimuscarinics are associated with poor persistence, with discontinuation rates of >50% reported at 6 months and >75% reported at 1 year [33, 34]. Mirabegron was associated with placebo rates of dry mouth, a common cause of discontinuation of antimuscarinics, while the safety profile appears to be acceptable.

Clinical implications

In patients with an OAB, we suggest mirabegron over tolterodine in patients with or without a history of prior antimuscarinic use (conditional recommendation based on moderate-quality evidence). Whether the lower rate of dry mouth compared with tolterodine leads to better adherence and persistence outside the clinical trial setting remains to be established.

Clinical question 6

What is the evidence base relating to the use of botulinum toxin in overactive bladder?

Literature search

We recently performed a systematic review of the use of botulinum toxin in OAB [35]. The review protocol was registered a priori (PROSPERO 2013:CRD42013003724) and consisted, in brief; of a search of the PubMed, Scopus and EMBASE databases utilizing the MeSH term "botulinum toxin" and combined search terms "overactive bladder" and "incontinence." Data were differentiated into level 1 and 2 studies and level 3 studies. Individual study data were converted into a "percentage change" format so that they were comparable between studies. Thereafter, a statistical comparison was made with standardized mean outcomes. High-level studies were assessed for risk of bias using a Cochrane Collaboration tool.

The evidence

In total, 16 high-level studies were included, which reported on 1380 patients. Standardized mean changes included a reduction in daily frequency of 29%, daily urgency of 38%, and daily incontinence episodes of 59%. Urodynamic changes included an increase in maximum cystometric capacity of 32% and a reduced maximum detrusor pressure of 31%. The need for intermittent self-catheterization was 16%, and 21% developed a UTI. These changes were all significantly greater than those with placebo.

Comparison could also be made of 100 and 200 IU of onabotulinumtoxinA (Table 42.2). The higher dose leads to greater reductions in frequency and incontinence episodes but increases the risk of UTI and need to self-catheterize. Therefore, a suggested starting dose is 100 IU.

Many regulatory authorities such as the US Food and Drug Administration (FDA) have granted a license for onabotulinumtoxinA use in the bladder. Other formulations include abobotulinumtoxinA and incobotlinumtoxinA. The systematic review showed very few data reflecting their use in the bladder. Owing to the different manufacturing processes, different formulations, and different therapeutic doses, clearly these agents should not be considered as generic equivalents [36].

Despite the common use of onabotulinumtoxinA, some questions still remain to be answered. For instance, what

Table 42.2 Standardized mean outcomes of changes in symptomatic and urodynamic parameters after injection of onabotulinumtoxinA.

Injection	%Δ daily frequency	%Δ daily leak	%Δ MCC	ISC (%)	UTI (%)
OnabotulinumtoxinA 200 IU	–40	–69	52	24	34
OnabotulinumtoxinA 100 IU	–28	–30	23	7	18

ISC, intermittent self-catheterization; MCC, maximum cystometric capacity; UTI, urinary tract infection.

is the best injection strategy, including dilution and site of administration? Is it better to inject into the detrusor or into the suburothelial layer? Should the trigone be injected routinely? To date, only one small study has looked at injection depth and trigone inclusion and showed a mild benefit from including the trigone and injecting submucosally [37]. The volume and number of injections have also not been standardized between many of the studies.

Botulinum toxin has been shown to have a therapeutic effect for 6–9 months and can be repeated multiple times. The formation of antibodies to BTX-A has been a real concern. Antibody tests are occasionally positive in patients postinjection [38]. They may be responsible for failure, but some authors have shown that with time a re-trial of BTX-A may achieve good results [39]. Biopsies after repeated injections have not shown significant differences in inflammation or dysplasia in the bladder wall of patients who have received onabotulinumtoxinA [40].

The place of BTX-A has traditionally been after failure of drug therapy. A 2012 trial assessed this and found that botulinum toxin led to increased rates for resolution of incontinence and less dry mouth but with higher rates of UTI and urinary retention [41]. The issue of whether it can be offered prior to antimuscarinic therapy requires further study. On the other hand, the outcomes from the ROSETTA trial are eagerly awaited, as this compares sacral neuromodulation with botulinum toxin. The trial will provide information regarding efficacy, adverse events, and cost-effectiveness.

Newer methods for botulinum toxin delivery, including electromotive drug administration and liposome instillation, have been reported in the literature. The data for these is currently too poor to be able to draw any meaningful conclusions but further research is warranted as these options remain in the realms of clinical research.

Clinical implications

In patients with OAB who have failed other forms of therapy, we suggest the use of botulinum toxin as second-line treatment (conditional recommendation based on moderate-quality evidence).

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43 CHAPTER 43

Urethral stricture disease

Robert A. Goldfarb[1] and Sean P. Elliott[2]

[1] *Chesapeake Urology Associates, Baltimore, MD, USA*

[2] *Department of Urology, University of Minnesota, Minneapolis, MN, USA*

Background

Urethral stricture disease is one of the oldest maladies known in urology. In current practice, the term "urethral stricture" is used to describe to injuries to the anterior urethra characterized by scarring of the surrounding corpus spongiosum, or "spongiofibrosis." In contrast, narrowing of the posterior urethra, which includes the membranous and prostatic urethra, which are not surrounded by corpus spongiosum, is referred to as "urethral stenosis" or "urethral distraction defect," as appropriate. In general, etiology can by divided into inflammatory/infectious (i.e. lichen sclerosus or gonococcal), iatrogenic (i.e. post-instrumentation or catheterization), traumatic (i.e. straddle or pelvic fracture injury), or congenital/idiopathic.

Patients with symptomatic stricture disease often present with obstructive voiding symptoms; however, some patients will report a history of recurrent urinary tract infections, dysuria, prostatitis, epididymitis, bladder calculi, or urethrocutaneous fistula. In cases where there is sufficient clinical suspicion, diagnostic testing is recommended to demonstrate urethral narrowing; additional information, such as anatomical location and length, is useful for management decisions. Urethrography has been used for over 100 years to diagnose urethral strictures and is still the most commonly used method [1]. Retrograde urethrography (RUG) combined with voiding cystourethrography (VCUG) is an easy to perform, well-tolerated procedure that provides detailed anatomical information about stricture presence, severity, and location [2, 3]. Sonourethrography (SUG) and magnetic resonance urethrography (MRU) provide additional assessment of periurethral tissues; this information may be useful in certain situations, such as competing diagnoses, extensive fistulization, or suspected malignancy [4, 5].

Treatments options for urethral stricture disease can be divided into minimally-invasive techniques and urethroplasty. Minimally-invasive procedures generally include urethral dilation or direct-vision internal urethrotomy (DVIU). Urethroplasty is considered the definitive treatment and can generally be understood to involve excision and re-anastomosis or substitution with grafts or flaps. Over the past 20 years, the utilization and options for buccal mucosal grafting (BMG) have increased significantly [6]. The properties of buccal mucosa that are well suited for substitution urethroplasty include availability and ease of harvest, a thick, hairless, elastin-rich epithelium, and thin vascular lamina propria to facilitate imbibition and inosculation. The decision between dorsal versus ventral placement of BMG involves consideration of surgeon experience, stricture location, and patient-specific factors. Theoretical advantages of ventral placement include less extensive urethral dissection and improved visibility, especially in the proximal bulbar urethra. Dorsal placement is thought to be associated with improved structural graft support from corporal fixation, facilitating graft take and minimizing graft sacculation.

Pelvic fracture results in urethral injury in approximately 2.5% of cases [7]. This injury can manifest as a laceration or a disruption. In some cases, a urethral catheter can bridge the defect with or without the use of a guidewire. This is one form of primary realignment (PR) of the urethra. When this is unsuccessful, suprapubic cystostomy (SPC) is required. One can then elect to delay management until urethroplasty in a few months or make an attempt at PR using a combined antegrade/retrograde approach. Historically, antegrade/retrograde PR was performed blindly or through an open incision, but is now performed endoscopically with a flexible cystoscope through the suprapubic tract and a flexible or rigid cystoscope through the urethral meatus. The goal of

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urethral realignment is either to avoid urethroplasty or at least to make the subsequent urethroplasty easier to perform.

Clinical question 1

What is the most accurate modality to diagnose an anterior urethral stricture?

Literature search

The PubMed, MEDLINE, and EMBASE databases were electronically searched for original articles published between 1990 and 2014 using a combination of controlled vocabulary search terms and free-text keywords that included "urethral stricture" and reference to any of the following diagnostic modalities: "retrograde urethrogram," "voiding cystourethrogram," "sonourethrogram," or "urethral ultrasound," "radiourethrogram," or "urethroscopy." Advanced search strategies were used to isolate articles whose primary objective included identification and evaluation of strictures. The abstracts from the search were evaluated and studies related to the question were evaluated in further detail. A total of 10 case series and four cohort studies were selected to comprise the body of evidence.

The evidence

There were 10 studies that compared the accuracy of sonourethrography (SUG) with RUG for diagnosing urethral strictures [8–17]. The evidence generated from these 10 studies comprised of nine low-quality studies and one moderate-quality study. In all studies, the gold standard for determining test accuracy was cystoscopy or open surgical findings. The sensitivity of RUG for the detection of anterior urethral stricture ranged from 82 to 100%; SUG demonstrated equivalent or superior diagnostic accuracy in all but one study [12]. SUG was consistently more sensitive than RUG in estimating stricture length in the bulbar urethra; in two studies, these findings resulted in a change in the intervention from endoscopic urethrotomy to urethroplasty in 18 and 50% of cases [9, 10].

Three studies compared RUG with MRU [8, 18, 19]. All three studies were small and the quality of evidence is low. MRU showed equivalent or slightly better accuracy than RUG in the detection of urethral strictures, particularly in the proximal bulbar or membranous urethra. In one study, MRU showed superior visualization of the proximal urethra and detection of two membranous urethral strictures missed on RUG [19]. There were two additional studies that compared urethroscopy with RUG and VCUG [20, 21]. Urethroscopy showed improved accuracy in detecting anterior urethral strictures compared with RUG and posterior strictures compared with VCUG; however, both studies were of low quality.

Clinical implications

In patients with suspected anterior urethral stricture disease, we suggest RUG/VCUG over SUG (conditional recommendation based on low-quality evidence). The recommendation places a high value on its utility to assess the entire urethra, widespread availability, and urologists' familiarity with this imaging technique.

We recommend against MRU (strong recommendation based on low-quality evidence) given its nonsuperior diagnostic accuracy, limited availability, and higher costs. Its value is for patients with suspected urethral stricture secondary to malignancy or in the presence of extensive fistulization to the perineal skin, in which case it may guide operative management.

Clinical question 2

What is the role of primary realignment versus suprapubic cystostomy with delayed repair in pelvic fracture urethral injury (PFUI)?

Literature search

The PubMed, MEDLINE, and EMBASE databases were electronically searched for original articles published between 1990 and 2014 using a combination of controlled vocabulary search terms and free-text keywords that referred to "pelvic fracture urethral injury" (or similar) and any of the following: "realignment" (primary or early), "endoscopic," or "suprapubic cystostomy." Additional references from systematic reviews were also used to identify potential studies. The abstracts from the search were evaluated and studies related to the question were evaluated in further detail. A total of 30 studies published between 1990 and 2014 were identified and further reviewed. In order to minimize bias, we chose to exclude case series and include only studies directly comparing PR with SPC. Our primary outcome of interest was stricture formation; type of repair (endoscopic versus urethroplasty) and success were also assessed when available. A total of seven studies, one prospective and six retrospective, were fully reviewed and served as the body of evidence.

The evidence

We found no randomized controlled trials comparing long-term complications of PFUI in patients managed with PR versus SPC. The studies selected for inclusion were limited by small cohorts, imprecise reporting of time to realignment, and incomplete reporting of the degree of urethral injury. The initial technique for PR was retrograde catheterization in two studies [22, 23]; other methods included careful retrograde catheterization or attempted union through a cystotomy, such as antegrade/retrograde cystoscopy or interlocking sounds. Only four studies addressed the determining factors involved in the management with PR or SPC; factors associated with PR included surgeon preference and hemodynamic stability [22–25].

Despite the heterogeneity between the studies, especially regarding methods of realignment, there was a significant reduction in the rate of urethral occlusion in patients with PR versus SPC (odds ratio [OR] 0.12, 95% confidence interval [CI] 0.02–0.23, $p<0.01$) [22–28]. Only one additional study reported exclusive use of PR, however, time to realignment in this group was significantly longer than in other studies (within 2 weeks) and all injuries were complete disruption [29]. In patients who developed urethral occlusion, those initially managed with PR were less likely to require urethroplasty. Additionally, there were no significant differences in rates of erectile dysfunction or incontinence.

There are several methodological flaws in the literature regarding this topic. The small sample size, retrospective nature, lack of standardized definitions of severity and/or success, limited follow-up, outdated techniques, and unclear quality of life assessments are some of the limitations and potential sources of bias. Although several case series reported significant reductions in the incidence of urethral occlusion with EPR, there is a paucity of comparative studies and lack of other outcomes. Regardless of whether it reduces the incidence of urethral occlusion, we, and others, have anecdotally noted that PR can make urethroplasty easier.

Clinical implications

We suggest that patients with pelvic fracture urethral injury who are hemodynamically stable undergo endoscopic primary alignment (conditional recommendation based on very low-quality evidence).

Clinical question 3

What is the optimal initial treatment for short (1–2 cm) bulbar urethral strictures?

Literature search

The PubMed, MEDLINE, and EMBASE databases were electronically searched for original articles published between 1990 and 2014 using a combination of controlled vocabulary search terms and free-text keywords that included "bulbar urethra" and reference to specific treatment types including "visual urethrotomy," "dilation," and "urethroplasty." Additional strategies were used to focus on initial treatment or primary therapy. The abstracts from the search were evaluated and studies related to the question were evaluated in further detail. There were no studies that provided comparative data to address this question. As a result, case series with long-term follow-up were used to extrapolate the relative efficacy of individual treatment modalities.

The evidence

Although there are no studies that compare the success of different treatments for primary short, uncomplicated bulbar urethral strictures, there are several case series with long-term follow-up that can help guide management decisions. Santucci et al. reported on a cohort of 168 patients treated with anastomotic urethroplasty (AU) for bulbar urethral strictures with a mean length of 1.7 cm [30]. At a mean of 70 months, the success rate was 95% with a <5% rate of complications, all of which were minor. Other single-institution case series with extended follow-up showed similar success rates (91–99%) for AU as initial treatment [31, 32]. Pansadoro and Emiliozzi reported one of the largest case series evaluating the long-term results of visual internal urethrotomy (VIU) for anterior urethral strictures [33]. They showed a success rate of 47% for VIU in patients with previously untreated bulbar urethral strictures with at least 5 years of follow-up. Stricture length greater than 1 cm and caliber less than 15 French were both associated with lower success rates. Similar case series examining long-term results of urethrotomy have shown average success rates of 20–30% [33–35].

In addition to measurements of success, other outcomes of interest have been evaluated to compare urethroplasty with urethrotomy. Wright et al. reported on the cost-effectiveness of PAU versus VIU [36, 37]. For bulbar urethral strictures 1–2 cm in length, the most cost-effective approach was a single VIU before urethroplasty. In addition, if the predicted success of VIU was less than 35%, then the most cost-effective treatment was primary urethroplasty [37, 38]. In a meta-analysis, the incidence of adverse events associated with VIU was approximately 6.5% [39]. The most common events included erectile dysfunction, urinary incontinence, urinary extravasation, and infection. In comparison, most series of AU report a complication rate of less than 5%, with neuropraxia, wound infections, and urinary tract infections as the most common [30–32].

Clinical implications

We are unable to make a recommendation for the initial management of a short, uncomplicated bulbar stricture (insufficient evidence); urethral dilation, direct vision internal urethrotomy, or urethroplasty should all be discussed. Patients should be informed that urethral dilation and urethrotomy may be associated with less perioperative morbidity and shorter recovery, but urethroplasty results in better long-term success rates.

Clinical question 4

Is there a benefit to dorsal versus ventral placement of a buccal mucosa graft (BMG) in substitution bulbar urethroplasty?

Literature search

The PubMed, MEDLINE, and EMBASE databases were electronically searched for original articles published between 1990 and 2014 using a combination of controlled vocabulary search terms and free-text keywords related to "anterior

urethra," "urethroplasty," and any of the following: "buccal mucosa," "substitution," "non-transecting," "onlay," "dorsal," and "ventral." The abstracts from the search were evaluated and studies related to the question were evaluated in further detail. A total of one randomized controlled trial and six cohort studies were selected for analysis.

The evidence

We found one randomized controlled trial that compared a dorsal versus a ventral approach [40]. Forty patients with anterior urethral strictures were randomized to receive either dorsal or ventral onlay BMG urethroplasty. The stricture was located in the bulbar urethra in 55% of patients, with the remainder classified as penobulbar or penile. There were 20 patients in each group with a mean follow-up of 12 months. In each group, 90% of patients rated their subjective symptoms as "excellent"; stricture recurrence occurred in two patients from each group (10%); however, subjective assessment of symptoms in these patients was "good." The quality of evidence was downgraded to low based on risk of bias (no allocation concealment, lack of blinding) and imprecision (not all cases were bulbar stricture; Table 43.1).

Kaggwa et al. conducted a prospective cohort study of 72 patients with bulbar urethral strictures [41]. At a mean follow-up of 1 year, the success rate was 80% (32/40 patients) for dorsal onlay grafts and 84% (27/32 patients) for ventral onlay grafts. There no significant differences in the rates of failure, need for repeat urethroplasty after failure, or complications between the groups. There were five retrospective studies comparing ventral versus dorsal BMG in patients with bulbar urethral strictures. There were no significant differences in success rates between the groups: 80–95% for dorsal and 79–86% for ventral onlay [42–46].

Clinical implications

In patients with bulbar strictures undergoing substitution urethroplasty with buccal mucosa, we recommend graft location (dorsal or ventral) be based on surgeon experience

Table 43.1 Summary of findings table.

Dorsal compared with ventral in BMG urethroplasty

Patient or population: BMG urethroplasty
Setting:
Intervention: dorsal
Comparison: ventral

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with ventral	Risk with dorsal				
Treatment success Assessed with: "Excellent" rating of voiding symptoms Follow-up: mean 12 months	90 per 100	**0 per 100** (0 to 0)	Not estimable	40 (1 RCT)	⨁◯◯◯ VERY LOW	
Q_{max} Scale: from 0 to 100 Follow-up: mean 12 months	The mean Q_{max} was **19.6**	The mean Q_{max} in the intervention group was 0.8 higher (0 to 0)	–	40 (1 RCT)	⨁⨁⨁⨁ HIGH[1]	
Stricture recurrence (recurrence) Assessed with: RUG follow-up: mean 12 months	10 per 100	**0 per 100** (0 to 0)	Not estimable	40 (1 RCT)	⨁⨁⨁◯ MODERATE	
Complications assessed with: Clavien–Dindo classification II–III Follow-up: mean 12 months	The mean complications were **12** events	The mean complications in the intervention group were 12 events	–	40 (1 RCT)	⨁⨁⨁◯ MODERATE	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; HR, hazard ratio; MD, mean difference; RCT, randomized controlled trial.
GRADE Working Group grades of evidence:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

(clinical principle). For surgeons proficient with dorsal graft placement, we suggest dorsal placement in strictures located in the distal bulbar or penile urethra (conditional recommendation based on very low-quality evidence).

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44 CHAPTER 44

Genitourinary trauma

Paul Chung[1] and Bryan B. Voelzke[2]

[1] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA*

[2] *Department of Urology, Harborview Medical Center, University of Washington School of Medicine, Seattle, WA, USA*

Background

Prospective, randomized trials to assess the treatment of genitourinary trauma are limited owing to the unpredictable nature of trauma. Hence most research in this field has focused on retrospective case studies, case reports, and expert opinion. The American Urological Association (AUA) and the European Association of Urology (EAU) have both independently convened panels of experts to conduct systematic reviews of published genitourinary literature [1, 2]. Guideline statements were created to aid clinicians regarding the most effective method to evaluate and treat genitourinary trauma. In 2002, the Society of International Urology published consensus statements providing a similar comprehensive review of renal, ureter, bladder, urethral, and external genitalia trauma [3–7]. These statements also serve as excellent resources for interested clinicians. In this chapter, we review the literature to examine important genitourinary trauma questions. We aimed to examine clinical questions not posed in the previous edition of this book.

Clinical question 1

In patients who sustain a blunt testicular injury, does immediate testicular exploration compared with observation decrease the incidence of future complications?

Literature search

A search of PubMed from 1985 to 2015 was conducted using the MeSH search terms "testis" and "wounds and injuries." After narrowing the search to publications involving humans and written in the English language, 316 articles were identified. The abstracts were examined and articles related to the clinical question were identified for evidence review.

The evidence

Blunt testicular injury can manifest with various clinical findings that can affect the decision to recommend immediate surgical management. There is an injury scoring system for testicular injuries provided by the American Association for the Surgery of Trauma [8]; however, it is sparsely utilized in published manuscripts. Instead, testicular injuries are commonly categorized as contusion, hematoma, rupture, or shatter. Among patients with a contusion, this can manifest as bleeding into the tunica vaginalis sac (hematocele) or bleeding within the testicular capsule (subcapsular hematoma).

Immediate surgery following testicular rupture or shatter is recommended; however, there is controversy regarding the management of a testicular contusion or hematoma. In such a setting, scrotal ultrasound can be utilized to differentiate testicular rupture from a less serious contusion and hematoma. Although contour irregularity, heterogeneous testicular parenchyma, and low blood flow on color Doppler have been reported to be predictors of testicular rupture on ultrasound, contour irregularity is thought to be the best predictor for testicular rupture [9].

Owing to concern that ultrasound may not be able to assess testicular parenchyma adequately in the setting of a large scrotal hematoma, Cass and Luxenberg examined the value of immediate scrotal exploration following *blunt testicular contusion with hematocele* [10]. Among this cohort of patients, who were initially managed in a conservative manner (i.e. non-surgical), delayed scrotal exploration (40%) and subsequent orchiectomy (15%) were necessary. These patients experienced persistent pain, swelling, and fever, despite antibiotics, that prompted delayed surgery. The tunica was intact at the time of delayed surgical exploration, and the orchiectomy specimens revealed infection

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and/or necrosis on histology in all cases. Time to delayed surgery was between 6 and 35 days from the initial injury. Among the remaining patients who underwent immediate surgical management following blunt testicular contusion with hematocele, drainage of the hematocele and evacuation of subcapsular testicular hematoma, if present, were performed. No patient required immediate or delayed orchiectomy. When expanding immediate surgical therapy for *any form of testicular injury*, the same authors noted a higher orchiectomy rate following initial conservative management (21 vs. 6% immediate surgery) [11].

Advocates for immediate surgical exploration following suspected blunt testicular injury cite the potential impact of testicular trauma on fertility and hormone function. To date, one article has assessed this question in humans [12]. Of 15 patients who underwent immediate scrotal exploration, eight returned for assessment of fertility and hormone function. Their original injuries consisted of hematoma and tunica rupture. Surgical repair included incision of the tunica for subcapsular testicle hematomas and excision of protruding seminiferous tubule with reapproximation of testicular tunica albuginea for tunica ruptures. Hormonal status was normal for all eight patients; however, six men were noted to have suffered a negative impact on fertility evident based upon semen analysis. Additionally, testicular atrophy was present in five of nine injured testicles (one patient had bilateral testicular injury). Surgical exploration did not appear to have a major impact on the development of anti-sperm antibodies, as only one patient had anti-sperm antibodies. Limitations of this report include the follow-up of only a limited number of the initial cohort. Since the authors only assessed patients who were managed with immediate surgery, it is not possible to draw conclusions regarding the impact of early exploration versus conservative management on future fertility.

Although most published series have adhered to the recommendation for early exploration following blunt testicular injury, conservative management has also been reported. Conservatively managed patients have primarily included those who report their injury in a delayed setting and patients with no evidence of testicular rupture on sonography following blunt testicular trauma. Of note, conservative management of a hematocele following blunt testicular injury has not been recommended owing to concerns that unresorbed hematocele can become infected over time, leading to orchitis, abscess, and eventually secondary necrosis [13]. In a recent 10-year review of genital trauma, 18/25 patients elected for conservative management in the setting of no pain and abnormal testicular echogenicity without evidence of tunica rupture [14]. Orchiectomy rates were similar to those in the immediate surgical therapy cohort (18 vs. 20% initial conservative management). Meacham has published a report from a colleague who treated a patient with delayed presentation of a testicular rupture [15]. The patient was noted to have a hydrocele months later that required surgery. At the time of hydrocele surgery, a thin membrane was covering the site of rupture. No orchiectomy was performed, and the patient did not report pain from the injured testicle. Stillwell et al. also noted a similar thin membrane covering the site of testicular rupture during delayed scrotal exploration [16]. In this report, the patient first presented 6 weeks after injury with no pain. Surgery was recommended based on existing guidelines; however, orchiectomy was not necessary.

Based on these encouraging case reports, Cubillos et al. reported their experience with seven adolescent boys who presented in a delayed setting following blunt testicular rupture [17]. All seven boys were managed in a conservative manner. They presented 1–5 days following injury with heterogeneous blunt testicular injuries. Scrotal ultrasound of the seven boys revealed testicular heterogeneity (7/7), hematocele (7/7), irregular tunica contour (3/7), subcapsular hematoma (3/7), tunica tear (3/7), scrotal wall edema (3/7), and seminiferous tubule extrusion (1/7). After 6 months' follow-up, all boys in the series were successfully managed with conservative management. Five boys underwent delayed ultrasound that demonstrated no evidence of atrophy and resolution of testicular echogenicity.

Conservative management following blunt testicular injury has also been reported among patients without hematocele, an intact tunica albuginea, and lack of fracture on ultrasound [18]. Unfortunately, only 4/44 patients (9%) were seen after discharge, and there was no attempt to call the patients. The lack of follow-up precludes the ability to realize fully the success of conservative management among this particular cohort.

Since blunt testicular injury can present as a contusion, hematoma, rupture, or shatter, the recommendation for immediate surgery can depend on the severity of the testicular injury. Among patients who present in a delayed setting, successful conservative treatment has been reported in select clinical circumstances (primarily contusion and hematoma); however, clinicians are advised that these reports have included very small cohorts of patients. Further, an acceptable hematocele size or tunica albuginea rupture that can be safely observed has not been reported. Lastly, clinicians who recommend conservative management should be mindful to counsel patients that there is a possibility of chronic testicle pain, infection, atrophy, and prolonged recovery. Immediate surgery should be strongly considered if there is concern about the patient's ability to follow up after hospital discharge.

Clinical implications

In patients who sustain blunt testicular injury, we suggest immediate surgical exploration over observation (conditional recommendation based on moderate-quality evidence).

Clinical question 2

In a patient with an uncomplicated extraperitoneal bladder rupture, does conservative management with catheter drainage versus early surgical closure increase the risk for delayed complications?

Literature search

A search of PubMed from 1970 to 2015 was conducted using the MeSH search term "extraperitoneal bladder trauma," and 136 articles were identified. The abstracts were examined and articles related to the clinical question were identified for evidence review.

The evidence

Bladder rupture is a rare event that coincides with an 11% risk for mortality among patients who experience blunt trauma [19, 20]. Bladder rupture can have a blunt, penetrating, or spontaneous etiology. A large series from a major trauma center reported their experience with bladder rupture as 63% nonpenetrating, 25% penetrating, 10% iatrogenic, and 2% spontaneous [21]. Of these bladder injuries, 62% were extraperitoneal, 25% intraperitoneal, and 6% combined.

Intraperitoneal bladder ruptures most often occur from nonpenetrating, deceleration injuries. Rapidly rising intravesical pressures cause rupture at the dome of the bladder, which has the least resistance and structural support. The AUA and EAU recommend surgical repair of intraperitoneal ruptures since open communication between the bladder and abdominal organs increases the risk for bacterial seeding, peritonitis, sepsis, and death [1, 2].

Extraperitoneal bladder rupture can be divided into uncomplicated and complicated injuries. The AUA and EAU guidelines advise that uncomplicated bladder ruptures can be treated with catheter placement and observation [1, 2]. According to the AUA guidelines, catheter drainage should continue for 2–3 weeks, and cystography should be performed to confirm resolution of the bladder injury. Open repair should be considered for patients with injuries unresponsive to catheter drainage for longer than 4 weeks. The AUA and EAU guidelines advise that formal surgical repair should be performed for complicated extraperitoneal bladder ruptures to avoid prolonged and delayed recovery. Complicated ruptures may include exposed bone fragments within the bladder, vaginal or rectal lacerations, or bladder neck injuries. Repair should also be considered for any extraperitoneal bladder rupture in patients undergoing surgery for a concurrent injury.

Historically, formal surgical closure was the recommended treatment for uncomplicated extraperitoneal bladder ruptures. Starting in the 1970s, a paradigm shift occurred as reports suggested that conservative management with urinary diversion was sufficient to treat extraperitoneal bladder ruptures and even select intraperitoneal ruptures [22–24]. These reports were careful to recommend several key points for conservative management: (1) no other complicating injuries requiring surgical exploration, (2) diagnosis made in less than 12 h, (3) no active urinary infection or genitourinary disease, (4) no difficulty in using a wide-bore catheter, (5) inpatient monitoring or urinary drainage, and (6) surgical exploration if clinical condition worsens or inadequate response drainage alone [22, 23].

Current AUA and EAU recommendations for the conservative treatment of uncomplicated extraperitoneal bladder ruptures are based on clinical and observational studies without randomized trials [1, 2]. Only one study exists that compared conservative urinary drainage with early operative closure for uncomplicated extraperitoneal bladder ruptures [25]. This study compared catheter drainage versus early surgical closure of extraperitoneal bladder ruptures. A total of 80 patients were identified with uncomplicated extraperitoneal bladder ruptures; 56 (70%) patients were treated with catheter drainage alone and 24 (30%) were treated with early closure as secondary procedures during concomitant surgery for nonurological reasons (i.e., exploratory laparotomy or open reduction internal fixation [ORIF]). There were no significant differences in gender, arrival condition, incidence of pelvic fracture, or mean injury severity score (ISS) between the two groups. Further, there were no differences in median time in the intensive care unit (ICU) (5.5 vs. 4.0 days, $p = 0.351$) or hospital length of stay (10.5 vs. 10.6 days, $p = 0.990$). Minor urological complications (Clavien grade 2 or lower) were similar between the two groups ($p = 0.806$). Major urological complications (Clavien grade 3 or higher) were numerically greater in the catheter drainage cohort ($n = 10$, urinary tract fistula, urosepsis, infected pelvic hardware, prolonged urinary extravasation) compared with the early closure cohort ($n = 1$, clot retention; $p = 0.103$). The median number of days to negative cystography was similar between the two groups (18.5 days for catheter drainage vs. 20 days for early closure, $p = 0.826$).

A subgroup analysis was performed comparing those who underwent early extraperitoneal bladder closure ($n = 24$) with those managed with catheter drainage alone despite surgery for other traumatic injury ($n = 21$). There were no differences in hospital admission characteristics between the two groups. Patients who did not undergo extraperitoneal bladder repair had a higher incidence of urological complications ($p < 0.05$), median time in the ICU (9.0 vs. 4.0 days, $p = 0.02$), hospital length of stay (18.9 vs. 10.6 days, $p = 0.02$), and longer time to negative cystogram (25.5 vs. 20.0 days, $p = 0.023$). Patients who did not undergo early bladder closure more frequently underwent exploratory laparotomy (57%) than ORIF (43%), whereas patients who underwent early closure more frequently underwent ORIF (71%) than exploratory laparotomy (29%). Patients in this study who did not undergo early closure may have had more serious

concomitant injuries contributing to their more prolonged recovery, despite similar ISS scores. Owing to the retrospective nature of the study, the authors could not provide further details of the extent bladder injuries attributed to the overall recovery process and why some patients received early closure and others did not.

Clinical implications

In patients with an uncomplicated extraperitoneal bladder rupture undergoing surgery for a concomitant injury, we suggest early closure (conditional recommendation based on low-quality evidence).

Recent evidence shows that conservative management with catheter drainage compared with early surgical closure does not increase the risk for delayed complications, except in patients who undergo surgery for a concomitant injury. Based on the evidence, we recommend repair of extraperitoneal bladder injuries in the setting of concomitant orthopedic hardware insertion for pelvic fracture. Primary closure of extraperitoneal bladder injuries may allow for quicker healing and minimize delayed complications.

Clinical question 3

In patients with pelvic fracture(s) and suspicion for bladder rupture, is imaging with computed tomographic (CT) cystography equivocal to conventional cystography?

Literature search

A search of PubMed from 1990 to 2015 was conducted using the MeSH search terms "cystography" and "bladder trauma," and 15 articles were identified. The abstracts were examined and articles related to the clinical question were identified for evidence review.

The evidence

Pelvic fractures are the most common etiology of bladder rupture; however, only 3.4% of patients with pelvic fractures suffer from bladder injury [26]. The AUA and EAU recommend conventional or CT retrograde cystography in patients with pelvic fracture and gross hematuria but not in patients with pelvic fracture or hematuria alone [1, 2]. Additional clinical indicators of bladder injury, such as difficulty voiding, low urine output, increased BUN/creatinine, incomplete bladder emptying, and suprapubic/abdominal fullness, may be used to determine whether imaging is indicated in patients with pelvic fractures and or microscopic hematuria. Patients with penetrating injuries and microscopic or gross hematuria should undergo further evaluation with retrograde cystography, cystoscopy, or surgical exploration.

Both the AUA and EAU guidelines leave the option of using conventional versus CT cystography to the clinician [1, 2]. Conventional cystography is the gold standard for evaluating bladder injuries. It is performed using slow retrograde filling of the bladder with a minimum of 300 mL of dilute contrast agent. Complete filling and post-drainage films are the minimum images required, and oblique films can be obtained to provide further information. In the 1990s, CT imaging emerged as the modality of choice to evaluate patients who had sustained blunt trauma; however, detection of a bladder injury was initially poor compared with conventional cystography. The initial protocols relied on delayed contrast from the excretory phase to fill the bladder and catheter plugging to distend the bladder. High rates of missed bladder injuries were seen in these initial reports since the intravenous contrast did not apply sufficient bladder distension for injury assessment [27, 28]. CT cystography protocols now involve similar retrograde filling as in conventional cystography.

Two of the larger retrospective studies evaluated 316 and 216 trauma patients with blunt pelvic injury and concern for bladder injury [27, 29]. CT cystography was performed and confirmed by surgical exploration or follow-up conventional or CT cystography in both studies. Chan et al. reported sensitivities and specificities of CT cystography to diagnose any type of bladder rupture (100 and 100%), extraperitoneal rupture (92.8 and 100%), and intraperitoneal rupture (100 and 99%) [27]. Similarly, Deck et al. reported sensitivities and specificities of CT cystography for diagnosing overall bladder rupture (95 and 100%) and intraperitoneal rupture (78 and 99%) [29]. Causes of missed intraperitoneal ruptures in these studies included a large extraperitoneal rupture that did not allow for sufficient bladder distension and a streak artifact from an external fixation device.

Evaluation of conventional and CT cystography following blunt abdominal trauma has been assessed in a prospective manner [28]. CT cystography was performed in 212 patients ($n = 19$ bladder ruptures) who were at risk for bladder injury and underwent screening CT imaging of the abdomen and pelvis. A conventional cystogram was then performed for the following circumstances: (1) to confirm a negative CT cystogram, (2) to confirm a positive finding if there was clinical [28] or radiological doubt, or (3) to clarify further the type of injury (intraperitoneal versus extraperitoneal) if the CT cystogram was equivocal. Intraoperative evaluation was the gold standard to determine the absence or presence of bladder injury. In the absence of surgical intervention, conventional cystography was used as the second gold standard. The sensitivities and specificities of both CT and conventional cystography in detecting bladder rupture were 95 and 100%, respectively [28]. There was concordance between CT cystogram and conventional cystography, except in two cases, in which each radiographic modality failed to make a diagnosis when the other was positive for bladder injury. Compared with conventional cystography, CT cystography had decreased sensitivity and positive predictive value (equivalent specificity and negative predictive value) when evaluating for extraperitoneal and intraperitoneal injuries. These findings where validated in a second cohort of 283

patients ($n=27$ bladder ruptures) who underwent CT cystography without conventional cystography. The sensitivity and specificity of CT cystography to diagnosis bladder rupture and extraperitoneal versus intraperitoneal injuries were each 100%, and they were confirmed by either surgery or uneventful clinical follow-up. The authors stated that they had greater confidence in their ability to localize the site of contrast extravasation with CT cystography but did not qualify their clinical gestalt further.

Clinical implications

In patients with pelvic fracture and suspected bladder rupture, we suggest CT cystography over conventional cystography (conditional recommendation based on moderate-quality evidence).

Although studies show that CT cystography and conventional cystography are equivalent in their ability to detect the presence and location of bladder rupture, CT imaging has several advantages: it can be performed in the same setting as abdominal and pelvic CT imaging, can help detect other abdominal or pelvic injuries, can provide a multiplanar view, and may be less time consuming than conventional cystography. CT cystography, however, does come at a higher cost and with increased radiation exposure.

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PART 8

Male LUTS and sexual dysfunction

John M. Hollingsworth

45 CHAPTER 45

Medical management of benign prostatic hyperplasia

Paholo G. Barboglio Romo and John M. Hollingsworth
Department of Urology, University of Michigan Medical Center, Ann Arbor, MI, USA

Clinical question 1

In men with lower urinary tract symptoms (LUTS) and evidence of benign prostatic hyperplasia (BPH), does combination medical therapy (i.e. use of an α_1-adrenergic-antagonist [AB] plus a 5α-reductase inhibitor [5-ARI]) reduce symptoms and the risk of disease progression more than AB or 5-ARI monotherapy alone?

Background

Whereas surgery was historically the mainstay of BPH care, the preferred initial treatment for the majority of men with symptomatic BPH today is either with an AB, a 5-ARI, or a combination of the two. Indeed, up to 88% of urologists in the United States recommend AB monotherapy for the initial care of men with moderate LUTS and evidence of prostate enlargement [1].

High-level evidence supports the use of such medical therapies. Several short- to moderate-term studies demonstrated the ability of ABs both to relieve symptoms and to improve urinary flow rates [2–5]. Long-term trial data showed that the 5-ARI finasteride not only ameliorates symptoms but also halts disease progression [6]. ABs decrease smooth muscle tone in the prostate and bladder neck, whereas 5-ARIs reduce prostate volume through induction of epithelial atrophy. Given that the effects of these two medication classes are mediated by different mechanisms, investigators hypothesized an additive effect of using the combination of them.

Literature search

A literature search was conducted in PubMed from January 1993 – the year that the US Food and Drug Administration (FDA) approved the first AB for BPH treatment – to July 2015. The following Medical Subject Heading (MeSH) terms were used: "lower urinary tract symptoms or prostatic hyperplasia" and "drug therapy combination or 5-alpha reductase inhibitors." Filters were used to limit the search to clinical trials and reviews in the English language. Systematic reviews and randomized controlled trials (RCTs) comparing combination medical therapy with placebo or an active control were included. Studies were evaluated in accordance with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group statement. Specifically, the quality of evidence was classified into one of four levels: high, moderate, low, or very low [7–10].

The evidence

The literature search yielded a total of 179 citations, from which five RCTs and two systematic reviews were selected. Systematic reviews by the Cochrane Collaboration and Füllhase et al. [11] examined the outcomes from combination medical therapy compared with AB or 5-ARI monotherapy. Although detailed data syntheses were performed, summary estimates of effect including the majority of the important RCTs assessing combination therapy were limited owing to the heterogeneity between included trials [11, 12]. For this reason, we describe the main outcomes of each RCT (Table 45.1).

The first trial was the 52-week, multi-center Veterans Affairs Cooperative study, which randomized 1229 men aged 45–80 years to receive placebo, terazosin, finasteride, or a combination of the two drugs [13]. Eligibility criteria included a mean American Urological Association (AUA) Symptom Index score of at least 8 and a mean peak urinary flow rate (Q_{max}) of 4–15 mL/s. Among the 1007 men who completed the study, the authors found that although the terazosin and combination therapy groups had similar symptomatic relief (mean changes from baseline in symptom scores were decreases of 6.1 and 6.2 points, respectively) and improved $\mathbf{Q}_{max}$ (mean changes were increases of

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2.7 and 3.2 mL/s, respectively) compared with the placebo and finasteride groups, the combination of terazosin and finasteride offered no additional benefit over terazosin alone with respect to those outcomes [13].

The European ALFIN Study Group in 1998 published an RCT on alfuzosin, finasteride, and combination therapy [14]. This was a 36-week, multi-center, double-blind study of 1051 men aged 50–75 years treated with alfuzosin, finasteride, or alfuzosin plus finasteride. Patients with a total International Prostate Symptom Score (IPSS) of at least 7 and a mean Q_{max} between 5 and 15 mL/s were eligible. There were 133 men who did not complete (13%) the study and there was no difference among the drug arms when assessing withdrawal. Alfuzosin, finasteride, and combination therapy showed significant improvements in urinary symptoms (mean decreases in IPSS of 6.3, 5.2, and 6.1 points respectively) compared with baseline status and significant improvements from baseline in Q_{max} (mean increases of 1.8, 1.8, and 2.3 mL/s, respectively). However, there was no significant difference between combination therapy and the alfuzosin groups when assessing both subjective and objective outcomes [14].

The Prospective European Doxazosin and Combination Therapy trial followed [15]. This 52-week, multi-center study randomized 1095 men aged 50–80 years to treatment with doxazosin, finasteride, doxazosin plus finasteride, or placebo. Patients with a total IPSS of at least 12 and a mean Q_{max} between 5 and 15 mL/s were eligible for inclusion. Although only 771 subjects (71%) completed the study, the discontinuations were evenly distributed among all four groups. Compared with the placebo and finasteride monotherapy groups, both the doxazosin and doxazosin plus finasteride groups experienced similar and statistically significant improvements from baseline in Q_{max} (mean increases of 3.6 and 3.8 mL/s, respectively) and IPSS (mean decreases of 8.3 and 8.5 points, respectively). However, no statistically significant difference was demonstrated between the doxazosin and doxazosin plus finasteride groups when assessing urine flow parameters and symptom score outcomes [15].

The preceding two 52-week trials primarily assessed longitudinal changes in urinary symptom scores and flow rates. The Medical Therapy of Prostatic Symptoms (MTOPS) trial was conducted in order to examine the long-term effect of combination medical therapy on risk of clinical progression [16]. This 6-year, multi-center study randomized 3047 men aged 50 years and older to receive placebo, doxazosin, finasteride, or combination medical therapy of doxazosin plus finasteride. Over a mean follow-up of 4.5 years, combination medical therapy significantly reduced the risk of overall clinical progression by 66% compared with placebo. This reduction in risk was significantly greater than that associated with doxazosin or finasteride alone. Of note, approximately 78% of the primary outcome events took the form of improvement in AUA Symptom Index scores. Further, doxazosin, finasteride, and combination medical therapy each resulted in significant improvements in AUA Symptom Index scores (median changes were decreases of 6.0, 5.0 and 7.0 points, respectively), with combination medical therapy superior to either monotherapy alone. Subsequent *post hoc* analysis of these data suggested that larger prostate volume was a strong predictor of benefit from combination medical therapy, and the risk of clinical progression among prostate volumes less than 25 mL was not statistically different between combination medical therapy and either monotherapy alone [17].

To address further the role of combination medical therapy for men with larger prostate glands, the Combination of Avodart® and Tamsulosin (CombAT) trial was conceived [18]. This 4-year, multi-center trial randomized 4844 men aged 50 years and older to receive dutasteride and tamsulosin-matched placebo, tamsulosin and dutasteride-matched placebo, or combination medical therapy. Inclusion criteria included men with prostate volumes of 30 mL or greater and a total IPSS of at least 12. The withdrawal rate was around 20% at the end of study. Tamsulosin, dutasteride, and combination therapy had superior objective outcomes (mean decreased Q_{max} of 0.7, 2, and 2.4 mL/s, respectively) compared with baseline; the improvement was significant also when assessing subjective measures (mean IPSS decreases of 3.8, 5.3, and 6.3 points, respectively) compared with baseline. This is the only trial where a 5-ARI was superior to the AB.

The CombAT trial confirmed that combination therapy is associated with improved long-term outcomes compared with either AB or 5-ARI monotherapy in subjects with larger prostates. Further subgroup analyses when assessing for predictor variables of enlarged prostate showed that either a prostate volume of >30–40 mL or a prostate-specific antigen (PSA) value >4 ng/mL benefit from combination therapy with AB and 5-ARI when given long term. Adverse events (AEs), including erectile dysfunction, retrograde ejaculation, decreased libido, ejaculation failure, decreased semen volume, and nipple pain occurred more frequently in combination therapy groups compared with either monotherapy or placebo. This appeared to be an additive effect since drug-specific AEs were not significantly increased in the combination group compared with the monotherapy drug in question [19, 20].

In summary, the reviewed trials on combination medical therapy are of moderate to strong quality (Table 45.1). Findings from these trials are critical and support the use of long-term combined use of doxazosin and finasteride to reduce the risk of BPH progression (strong recommendation). Further critical outcomes from the use of combination therapy with tamsulosin and dutasteride support a greater symptom amelioration compared with either therapy alone in men with large glands (volumes >30 mL). It remains uncertain whether there is a "class effect" (i.e. ability to

Table 45.1 Randomized clinical trials comparing combination medical therapy with placebo or an active control.

Study ID	Intervention	No. completed/ randomized	Therapy duration	Combination therapy results	Adverse events	Limitations and quality of evidence GRADE
Lepor [13] (VA Cooperative)	Treatment 1: terazosin (10 mg daily) Treatment 2: finasteride (5 mg daily) Treatment 3: combination of the two drugs	Treatment 1 = 256/305 Treatment 2 = 243/310 Treatment 3 = 254/309 Placebo = 254/305	1 year	Improved urinary symptom scores and mean peak urinary flow rates compared with baseline, placebo, and terazosin monotherapy Combination therapy provided no further benefit to that achieved by doxazosin alone	Treatment 1 = 18 Treatment 2 = 15 Treatment 3 = 24 Placebo = 5	1-year follow-up GRADE high
Debruyne [14] (ALFIN)	Treatment 1: alfuzosin (5 mg twice per day) Treatment 2: finasteride (5 mg daily) Treatment 3: combination of the two drugs	Treatment 1 = 318/358 Treatment 2 = 305/344 Treatment 3 = 295/349	6 months	Improved urinary symptom scores compared with baseline and terazosin monotherapy Improved mean peak urinary flow rates compared with baseline only Combination therapy provided no further benefit to that achieved by terazosin alone	Treatment 1 = 25 Treatment 2 = 18 Treatment 3 = 24	No placebo arm Short follow-up GRADE moderate
Kirby [15] (PREDICT)	Treatment 1: doxazosin (8 mg daily) Treatment 2: finasteride (5 mg daily) Treatment 3: combination of the two drugs	Treatment 1 = 250/275 Treatment 2 = 239/264 Treatment 3 = 265/286 Placebo = 253/270	1 year	Improved urinary symptom scores and mean peak urinary flow rates compared with baseline, placebo, and finasteride monotherapy Combination therapy provided no further benefit to that achieved by doxazosin alone	Treatment 1 = 32 Treatment 2 = 34 Treatment 3 = 35 Placebo = 30	Industry sponsored 1-year follow-up DRE used for prostate enlargement GRADE high
McConnell [16, 17] (MTOPS)	Treatment 1: doxazosin (8 mg daily) Treatment 2: finasteride (5 mg daily) Treatment 3: combination of the two drugs	Treatment 1 = 582/756 Treatment 2 = 565/768 Treatment 3 = 598/786 Placebo = 534/737	6 years	Improved urinary symptom scores compared with baseline, placebo, and both monotherapies Improved mean peak urinary flow compared with baseline and both drugs alone Combination therapy significantly decreased the risk of overall BPH clinical progression compared with both monotherapies and placebo The risks of AUR and need for surgery were significantly reduced by combination therapy and finasteride monotherapy	Treatment 1 = 22.22[a] Treatment 2 = 17.37[a] Treatment 3 = 28.51[a] Placebo = 14.25[a]	Industry sponsored GRADE high
Roehrborn [18–20] (CombAT)	Treatment 1: tamsulosin (0.4 mg daily) Treatment 2: dutasteride (0.5 mg daily) Treatment 3: combination of the two drugs	Treatment 1 = 1254/1611 Treatment 2 = 1301/1623 Treatment 3 = 1267/1610	4 years	Improved urinary symptom scores compared with baseline and both monotherapies Improved mean peak urinary flow compared with baseline and both drugs alone Decreased total prostate volume (adjusted mean percentage change from baseline) Decreased RR of BPH clinical progression and AUR compared with tamsulosin monotherapy but not dutasteride alone	Treatment 1 = 136 Treatment 2 = 108 Treatment 3 = 154	No placebo arm Very large population size Prostate volume >30 mL GRADE moderate

AUR, acute urinary retention; CombAT, combination of Avodart® and tamsulosin; MTOPS, medical therapy of prostatic symptoms; PREDICT, Prospective European Doxazosin and Combination Therapy; RR, relative risk; VA, Veterans Affairs.

[a] Rate/100 person-years of follow-up.

generalize these findings to other pharmacotherapies within the same classes). The literature does not support the use of combination medical therapy over monotherapy in men with smaller prostates or when treatment is planned for only a short time period.

Treatment decisions should include a discussion on AEs, which are more common with combination therapy than monotherapy. Although these were not categorized as critical, it is important to describe the possible side effects from the two drugs alone in addition to the additive effect from combination therapy.

Clinical implications

In men with LUTS and evidence of BPH with a large prostate (>30 mL), we recommend combination medical therapy over an AB or 5-ARI monotherapy alone (strong recommendation based on moderate-quality evidence).

In men with LUTS and evidence of BPH with a small prostate (30 mL or less) or in whom only short-term treatment is planned, we suggest against combination medical therapy (conditional recommendation against based on moderate-quality evidence) versus an AB alone.

Clinical question 2

In men with BPH and storage symptoms (i.e. urinary frequency and urgency), does the use of an antimuscarinic agent (alone or in combination with an AB) offer more symptom relief than AB monotherapy or placebo?

Background

Storage symptoms, characterized by urinary urgency and increased day and night-time micturition frequency [21], may coexist with bladder outlet obstruction caused by BPH. They may also be secondary to the obstruction itself [22]. When the former situation exists, treatments targeted at the prostate exclusively, such as ABs, may not relieve a man's storage symptoms [23]. This is the rationale behind the use of antimuscarinic therapy in men with storage symptoms and evidence of BPH.

Literature search

A literature search was conducted in PubMed from January 1993 to July 2015. With an English-language restriction, the following MeSH terms were used: "lower urinary tract symptoms or prostatic hyperplasia" and "muscarinic antagonists or cholinergic antagonists." Filters were used to limit the search to clinical trials and reviews in the English language. Systematic reviews and RCTs comparing antimuscarinics combined with ABs versus AB monotherapy or placebo were included. Studies were evaluated in accordance with the GRADE Working Group statement. Specifically, the quality of evidence was classified into one of four levels: high, moderate, low, or very low [7–10].

The evidence

The literature search yielded a total of 386 citations, including two systematic reviews and 15 RCTs. Füllhase et al. conducted a systematic review that included eight trials [11], but the authors were unable to pool data from these trials owing to differences in study design. Only one RCT included in this systematic review – Kaplan et al.'s randomized, double-blind, placebo-controlled multi-center trial evaluating tolterodine and tamsulosin (TIMES) – evaluated antimuscarinic therapy alone versus AB monotherapy versus an antimuscarinic in combination with an AB versus placebo [24]. For the remaining trials included in this systematic review, study participants were already on AB monotherapy at baseline and the antimuscarinic agent was added after randomization. There was also substantial clinical heterogeneity due to dissimilar inclusion criteria, varying lengths of follow-up, varying degrees of storage symptoms that were not well characterized by validated instruments, and unknown prostate size. Nonetheless, this systematic review suggests that the addition of an antimuscarinic agent to AB therapy leads to a significant decrease in storage symptoms (compared with AB monotherapy). However, there were no significant differences in quality of life (QOL) measures and peak urinary flow rates (Q_{max}) between groups. Although there was no difference in the rate of acute urinary retention (AUR), patients taking an antimuscarinic had higher postvoid residual (PVR) urine. Mild AEs were drug dependent and resolved upon discontinuation of the treatment [11].

A more recent systematic review by Hao et al. included 18 trials [25]. RCTs comparing AB monotherapy versus an AB plus an antimuscarinic agent were included. Prior AB therapy use was not considered an exclusion criterion. Outcomes assessed included IPSS, QOL score, Q_{max}, and bladder diaries. The authors pooled data. Follow-up was short and varied from 4 to 12 weeks. Data for IPSS were available for 15 trials and the weighted mean difference (MD) favored the addition of an antimuscarinic agent by –0.88 points (95% confidence interval [CI] –1.64 to –0.12 points; $p=0.02$). There was no statistically significant difference in Q_{max} between the two pooled groups (MD –0.05 mL/s; 95% CI –0.27 to 0.17 mL/s; $p=0.64$) based on 14 studies. Data assessing PVR were taken from 12 trials and favored AB monotherapy (MD 6.53 mL; 95% CI 3.06 to 10.00 mL, $p=0.0002$). The authors found no difference in the rate of AUR [25].

Findings from 15 trials with a follow-up period of longer than 4 weeks are displayed in Table 45.2. The majority of these compared AB monotherapy versus combination with an antimuscarinic. Subjects were already on AB monotherapy before randomization and had moderate to severe storage symptoms as an inclusion criterion in the majority of the studies, as assessed by the storage component of the IPSS questionnaire or by the number of daily urgency episodes. Exclusion criteria included an elevated PSA, low urinary flow rates, history of urinary retention, and a PVR >200 mL

Table 45.2 Randomized clinical trials comparing an antimuscarinic agent (alone or combined with an α_1-adrenergic antagonist) with placebo or an active control.

Study ID GRADE	Inclusion criteria	Intervention	No. completed/ randomized	Length (weeks)	IPSS (total)	IPSS (stor)	IPSS (void)	Q_{max}	QOL	PVR	AUR	AEs
					Statistical significance favors higher							
Athanasopoulos 2003 [29]	BOO and IDO, prostate vol. >40 mL	Tamsulosin vs.	25/25	12	NA	NA	NA	NA	*com*	ND	AB 0	3
GRADE	Tamsulosin 1 wk prior randomize	Tamsulosin Tolterodine	23/25								*com* 0	1
Lee 2005 [30]	BOO and daily urgency	Doxazosin	67/69	8	ND	*com*	ND	AB	ND	*com*	AB 0	7
GRADE	Unclear if taking alpha-antagonist	vs.										
Moderate		Doxazosin Toleterodine	131/142								*com* 2	50
Maruyama 2006 [31]	IPSS ≥8	Naftopidil	44/48	12	ND	*com*	ND	ND	ND	*com*	AB 0	1
GRADE	Unclear if taking alpha-antagonist	vs.										
Moderate		Naftopidil Propiverine Oxybutynin	36/53								*com* 0	3
Kaplan 2006 [24, 26]	3 urgency events in 24 h	Tamsulosin	186/215	12	ND	NA	NA	NA	*com*	ND	AB 0	60
GRADE	No prior therapy for LUTS/BPH	vs.										
Strong		Tamsulosin Tolterodine	191/225								*com* 2	106
Yang 2007 [32]	PVR <51	Terazosin	36	6	*com*	*com*	ND	ND	ND	NA	AB 0	1
GRADE	Terazosin 1 wk prior randomize	vs.										
Very low		Terazosin Tolterodine	33								*com* 0	6
MacDiarmid 2008 [33]	SPSS ≥8 and urgency	Tamsulosin	206/209	12	*com*	*com*	ND	ND	*com*	*com*	AB 0	89
GRADE	Tamsulosin 4 wk prior	vs.										
Moderate	randomize	Tamsulosin Oxybutinin	203/209								*com* 0	89
Chapple 2009 [34]	Daily urgency	Alpha-antag.	292/323	12	ND	*com*	ND	ND	ND	com	AB 2	89
GRADE	Alpha-antagonist 4 wk prior	vs.										
Strong	randomize	Alpha-antag. Tolterodine	283/329								*com* 3	114
Kaplan 2009 [35]	IPSS >12 and daily urgency	Alpha-antag.	174/195	12	ND	ND	ND	ND	ND	*com*	AB 0	77
GRADE	No prior therapy for LUTS/BPH	vs.										
Moderate		Alpha-antag. Solifenacin	167/203								*com* 7	91
Bae 2011 [36]	SPSS >3; IPSS ≥12	Alfuzosin	77	8	*com*	*com*	ND	ND	ND	ND	AB 0	3
GRADE	Unclear if taking alpha-antagonist	vs.										
Low		Alfuzosin Propiverine	132								*com* 0	9

(*continued overleaf*)

Table 45.2 (Continued)

Study ID GRADE	Inclusion criteria	Intervention	No. completed/ randomized	Length (weeks)	IPSS (total)	IPSS (stor)	IPSS (void)	Q_{max}	QOL	PVR	AUR	AEs
					Statistical significance favors higher							
Yamaguchi 2011 [37]	Already taking antimuscarinic	Tamsulosin	394/423	12	ND	*com*	ND	ND	ND	*com*	AB 0	NA
GRADE	Alpha-antagonist 4 wk prior	vs.										
Moderate	randomize	Tamsulosin Solifenacin	197/215								*com* 4	NA
Lee 2011 [38]	SPSS ≥8; IPSS >13	Doxazosin	63/91	12	ND	*com*	ND	ND	*com*	*com*	AB 0	1
GRADE	No prior therapy for LUTS/BPH	vs.										
Moderate		Doxazosin Tolterodine	64/85								*com* 1	3
Seo 2011 [28]	IPSS >12; excluded if PVR >100 mL	Tamsulosin	29/30	12	ND	ND	ND	ND	ND	ND	AB 0	NA
GRADE	Unclear if taking alpha-antagonist	vs.										
Moderate		Tamsulosin Solifenacin	27/30								*com* 0	NA
Kaplan 2012 [39]	3 urgency events in 24 h	Alpha-antag.	424/473	12	ND	*com*	ND	ND	*com*	ND	AB 1	243
GRADE	Alpha-antagonist 6 wk prior	vs.										
Moderate	randomize	Alpha-antag. Fesoterodine	401/474								*com* 1	418
Van Kerrebroeck 2013 [27]	IPSS >12	Tamsulosin	177/179	12	ND	ND	ND	ND	ND	*com*	AB 1	33
GRADE	No prior therapy for LUTS/BPH	vs.										
Moderate		Tamsulosin Solifenacin	532/536								*com* 4	104
Lee 2014 [40]	SPSS ≥6; IPSS >14	Tamsulosin	69/80	12	ND	ND	ND	ND	ND	ND	AB 0	3
GRADE	3 urgency events in 24 h	vs.										
Moderate	No prior therapy for LUTS/BPH	Tamsulosin Solifenacin	70/76								com 1	6

AB, alpha-antagonist; AE, adverse events; AUR, acute urinary retention, ND, no difference; BOO, bladder outlet obstruction; *com*, combination therapy; IDO, idiopathic detrusor overactivity; IPSS, International Prostate Symptom Score; NA, none available; PVR, postvoid residual volume; Q_{max}, peak flow; QOL, quality of life.

(unless specified otherwise in Table 45.2). In addition to differences between these trials with regard to their inclusion criteria, it is important to note that variability in the use of a placebo arm and differences in the drug type and dose prescribed and the follow-up period complicate comparisons between them.

Only two trials included a placebo arm. The first was the TIMES study. This multi-center, double-blind study was also one of the few trials to start all interventions after randomization. It had four arms, including both antimuscarinic and AB monotherapy groups, a combination therapy group, and a placebo group. Inclusion criteria included, among others, at least three episodes of urgency on daily bladder diary. The main outcome measure was binary, assessing the benefit (yes/no) from treatment. For patients who reported benefit, the degree of benefit was characterized on a subcategory scale. The results showed that the combination of AB plus an antimuscarinic agent was associated with more benefit in storage symptoms compared with either drug individually or placebo. With regard to secondary outcomes, there was no difference in Q_{max}, PVR, or rates of AUR [24]. In a *post hoc* analysis, the study team adjusted for prostate size, finding that the benefits of combination therapy were realized mainly in subjects with larger prostates (volume ≥30 mL). Men with smaller prostates (<30 mL) had significant improvement with AB monotherapy on total IPSS and voiding parameters, and with antimuscarinic monotherapy on IPSS storage parameters compared with placebo [26].

The trial by Van Kerrebroeck et al. was the second RCT on antimuscarinic therapy that included a placebo arm [27]. In this multi-center, double-blind trial, all interventions were started after randomization. Study subjects had a 2-week placebo run-in period. There were multiple arms, including three solifenacin monotherapy arms (with different doses), one tamsulosin monotherapy arm, three different combination therapy arms (with different antimuscarinic doses), and a placebo group. Inclusion criteria included a total IPSS score of >12 with no particular requirement for storage symptoms or urgency episodes. Analysis of baseline variables revealed that half of the subjects had less than one urgency episode per day. Findings from the study revealed no significant difference in total IPSS (main outcome) on comparing all interventions versus placebo. Subgroup analyses revealed a benefit of combination therapy over AB monotherapy in subjects with at least two urgency episodes per day, as assessed by storage symptoms on the IPSS. Combination therapy was well tolerated, despite a higher AE rate. The most common AEs in all treatment groups containing solifenacin were dry mouth and constipation. Higher PVR was associated with all solifenacin arms (compared with placebo), but this was not considered clinically significant. AUR was low in all solifenacin groups and showed no association with increasing dose [27].

Additional studies are characterized in Table 45.2 and QOL outcomes were assessed in all trials, but the instruments used varied between studies. Of note, there was no benefit from the addition of an antimuscarinic agent in 10 of 15 trials. The five studies in which a QOL benefit was observed had more stringent inclusion criteria (persistent LUTS despite prior AB therapy or pre-existing moderate to severe urinary storage symptoms). Total IPSS was used in 14 of 15 studies. In 11 of these studies, there was no significant difference in IPSS between the AB monotherapy and combination therapy groups. An improvement favoring the addition of an antimuscarinic agent was observed in the storage subscore of the IPSS in nine of 13 trials. In two of the three trials associated with no improvement in storage subscores, there were no eligibility criteria based on storage symptoms and/or urinary episodes [27, 28]. PVR was assessed in 14 of 15 studies. Although the addition of an antimuscarinic agent was associated with a higher PVR in eight of 14 studies, this was not described as clinically significant in any. Rates of AUR were not more common in the combination therapy groups. Detailed AEs were reported in six trials. Antimuscarinic therapy use was associated with higher rates of AEs, the most common being dry mouth [11, 25].

In summary, the reviewed trials of antimuscarinic therapy for treatment of storage symptoms in men with BPH are of low to moderate quality (Table 45.2). Findings from these trials are important and provide some evidence to support benefit from the addition of an antimuscarinic agent to AB therapy for the management of urinary urgency and daytime frequency. These findings rely only on short-term outcomes and long-term safety and efficacy data are not currently available. Moreover, given the variety of antimuscarinic agents available, the optimal combination and regimen have yet to be determined. It is important to recommend caution when prescribing antimuscarinic agents to men with large PVRs, low Q_{max}, or prior history of AUR, as subjects with these problems were excluded from RCTs. Treatment decisions should include a discussion on AEs, which are more common when an antimuscarinic is used.

Clinical implications

In men with BPH and storage symptoms (i.e. urinary frequency and urgency), we suggest the use of an antimuscarinic agent (alone or in combination with an AB) over AB monotherapy (conditional recommendation based on low-quality evidence).

Clinical question 3

In men with LUTS secondary to BPH, does the use of saw palmetto provide greater symptom relief than placebo?

Background

Treatment of BPH with phytotherapy was described as early as the fifteenth century BCE [41]. Widely used in Europe

for BPH symptom relief [42–45], plant extracts offer an alternative to pharmaceutical agents and their related side effects. Indeed, the popularity of phytotherapy is growing in the United States, with an estimated 1% of American adults reporting the use of extracts of the *Serenoa repens* fruit [46], one of the most extensively studied herbal remedies for BPH. Acting through multiple mechanisms, including modulation of human 5α-reductase [47], the active ingredient from the *Serenoa repens* berry is thought to be the lipid/sterol extract saw palmetto. A high-profile systematic review and meta-analysis of the available literature published in 1998 by Wilt et al. suggested that saw palmetto extracts improved LUTS and urinary flow measures [48]. However, the effect sizes reported in the pooled studies were small, partially due to small sample sizes and relatively short study durations. Hence the authors fell short of giving saw palmetto extracts unequivocal endorsement for the management of BPH.

Literature search

The English-language literature was searched for human studies relating to saw palmetto for the treatment of BPH using the MEDLINE database from January 1999 (the year after Wilt et al.'s meta-analysis [48]) to July 2015. The search was conducted by exploding the following MeSH terms: "lower urinary tract symptoms or prostatic hyperplasia" and "plant extracts" and "phytotherapy" and "serenoa." Filters were used to limit the search to clinical trials and reviews in the English language. Systematic reviews and RCTs comparing saw palmetto with placebo were included. Studies were evaluated in accordance with the GRADE Working Group statement. Specifically, the quality of evidence was classified into one of four levels: high, moderate, low, or very low [7–10].

The evidence

The literature search yielded a total of 146 citations. From these, one Cochrane Review and five RCTs were identified and reviewed in detail (Table 45.3). The Cochrane Review was an update of the systematic review carried out in 2012 by Wilt et al. It included 5666 men assessed from 32 RCTs with a follow-up period ranging from 4 to 72 weeks. Twenty-seven trials were double blinded and treatment allocation concealment was adequate in 14. According to the authors, there were only three high-quality, moderate- to long-term trials that showed no difference between *Serenea rapens* and placebo when assessing urine peak flow parameters. They concluded that there was no improvement in urinary flow measures or prostate size in men with LUTS [49].

The same group performed a meta-analysis including 17 RCTs (a total of 2008 subjects) that compared saw palmetto extract with placebo. Only five studies reported AUA Symptom Index scores or IPSS. Sixteen trials described an adequate blinding process and six trials described treatment allocation concealment. Synthesis of the trial data led the authors to conclude that saw palmetto does not improve urinary flow measures or prostate size in men with LUTS

Table 45.3 Randomized clinical trials comparing saw palmetto extract with placebo or an active control.

Study ID GRADE	Intervention	No. completed/ randomized	Therapy duration	Results	Adverse events
Marks [51] GRADE Moderate	Saw palmetto herbal blend (320 mg daily)	Treatment: 20/21 Placebo: 23/23	6 months	Both treatment and placebo groups had similar small improvements in clinical parameters from baseline	Treatment: 0 Placebo: 0
Debruyne [52] GRADE Moderate	Treatment 1: Permixon (320 mg daily) Treatment 2: tamsulosin (0.4 mg daily)	Treatment 1: 296/340 Treatment 2: 298/345	1 year	Improvements in symptom scores were similar between Treatments 1 and 2 Increases in urinary flow rates were similar between Treatments 1 and 2	Treatment 1: 28 Treatment 2: 30
Willetts [53] GRADE Moderate	*Serenoa repens* extract (320 mg daily)	Treatment: 46/50 Placebo: 47/50	12 weeks	There was no significant difference in the decrease in symptom scores over time between the treatment and placebo groups There was no significant difference between treatment and placebo groups in peak urinary flow rates after the trial	Treatment: 4 Placebo: 3
Bent [54] GRADE Strong	Saw palmetto extract (160 mg twice daily)	Treatment: 102/112 Placebo: 104/113	1 year	Both treatment and placebo groups had similar small decreases in their mean symptom scores There was no significant difference between treatment and placebo groups in the change in peak urinary flow rates	Treatment: 8 Placebo: 18
Barry [55] GRADE Strong	Saw palmetto extract (320, 640, and 960 mg daily)	Treatment:155/186 Placebo: 151/183	72 weeks	No difference in main and secondary outcomes using AUA Symptom Index scores	Treatment: 530 Placebo: 476

consistent with BPH. They were not able to pool data for all the outcomes because of significant heterogeneity between studies (I^2 76%). For this reason, we describe the RCTs of higher quality that used validated questionnaires to assess symptom improvement [50].

The first was reported by Marks et al., in which 44 men from a single general urology practice in metropolitan Los Angeles were randomized to receive a saw palmetto herbal blend versus placebo [51]. Following a 1-month placebo lead-in, subjects were treated and followed for 6 months. Throughout the study and at completion, a variety of clinical parameters were assessed, including IPSS, urinary flow rate and PVR.

A slight decrease in symptom scores (mean changes were decreases of 3.05 points for the placebo group and 5.58 points for the saw palmetto group) and a slight increase in urinary flow rates (mean changes were increases of 0.58 and 2.65 mL/s, respectively) were noted for subjects in both groups [51]. Although these changes were slightly greater in the saw palmetto group, the differences were not statistically significant. Overall, the saw palmetto extract was well tolerated and no adverse events were noted.

Two years later, Debruyne et al. published the results of an equivalency trial, comparing Permixon® (a trade name for the *Serenoa repens* lipid/sterol extract) with tamsulosin [52]. In this multi-center trial, 704 men were randomized to one of the two treatment arms and followed for 1 year. Eligibility criteria included an IPSS of at least 10 and a peak urinary flow rate between 5 and 15 mL/s. After study completion, IPSS decreased by 4.4 in both groups. No differences were noted between groups for either the irritative or obstructive IPSS domains. In addition, Q_{max} increased similarly in both treatment groups. The treatments were well tolerated with only a similarly small number of subjects discontinuing therapy in each group. Given these data, the authors concluded that Permixon and tamsulosin were clinically equivalent [52]. However, in the absence of a placebo arm, the investigators were unable to comment on the efficacy of Permixon.

In 2003, an Australian group reported the results of a single-institution clinical trial in which 100 men with symptomatic BPH were randomized to receive *Serenoa repens* extract versus placebo. Men with at least three symptoms related to BPH (e.g. frequency of micturition, nocturia, hesitancy, poor force of stream, etc.) were eligible for participation. After 12 weeks of treatment, the mean IPSS scores and improvements in Q_{max} were not significantly different between the treatment and control groups [53].

A subsequent long-term, multi-center trial confirmed those results. In total, 225 men with moderate to severe BPH symptoms, based on the AUA Symptom Index score, were randomized to receive saw palmetto extract versus placebo. After 12 months of treatment, both groups had small decreases in symptom scores, but those differences were insignificant over time between groups. In addition, Q_{max} did not differ between the treatment and placebo groups at any time during the study period. These data led the authors to conclude that saw palmetto did not improve LUTS caused by BPH [54].

In 2011, a multi-center, double-blind, placebo-controlled trial was conducted in the United States by the Complementary and Alternative Medicine for Urological Symptoms (CAMUS) Study Group [55]. This was powered to detect a two-point group MD in AUA Symptom Index score between the saw palmetto extract and placebo groups at 72 weeks. Subjects older than 44 years of age, with Q_{max} ≥4 mL/s and an AUA Symptom Index score ≥8 and ≤24 at two screenings were included. There were 369 men randomized to receive a standardized saw palmetto fruit extract with dose escalations at 24 and 48 weeks or similarly escalated placebo. The mean AUA Symptom Index score at baseline was 14.4. The mean change in AUA Symptom Index score was not statistically different between both groups. Per protocol analysis of the main outcome favored placebo when assessing saw palmetto extract (151) versus placebo (155) at 72 weeks (MD 0.82; $p = 0.89$). There were no significant differences in the rates of AEs between the two groups, regardless of the saw palmetto dose [55].

In summary, the reviewed trials on saw palmetto therapy for symptomatic BPH are of moderate to high quality (Table 45.3) and do not support the use of saw palmetto in the management of LUTS compared with placebo.

Clinical implications

We recommend against the use of saw palmetto in men with LUTS (strong recommendation against based on moderate-quality evidence).

Clinical question 4

In men with LUTS secondary to BPH, does the use of a phosphodiesterase type 5 inhibitor (PDE5I) improve symptoms compared with placebo or active control?

Background

Men complaining of LUTS due to BPH are usually affected by some degree of erectile dysfunction (ED) and, although the relationship between LUTS and ED is not well understood, men receiving PDE5Is to treat ED have been found in multiple observational studies to have improvement in their LUTS on validated questionnaires. Proposed mechanisms of action include impaired nitric oxide/cycle guanosine monophosphate signaling, increased RhoA/Rho-kinase pathway activation, pelvic ischemia, autonomic overactivity, and increased bladder/prostate afferent activity [56].

PDE5Is are known to target the prostate, urethra, bladder, and pelvic vasculature [57]. Buoyed by this, a randomized, placebo-controlled trial was conducted by McVary et al. in 2007, showing favorable results [58]. Subsequent to this

and several other RCTs that reproduced these findings, the FDA approved the use of tadalafil in October 2011 for men with ED and concomitant LUTS [59]. However, questions regarding the effect of other PDE5Is on LUTS, assessed with validated questionnaires, and flow parameters remain.

Literature search

The English-language literature was searched for human studies relating to PDE5Is for the treatment of LUTS in men with BPH using the MEDLINE database from January 1993 to July 2015. The search was conducted by exploding the following MeSH terms: "lower urinary tract symptoms or prostatic hyperplasia" and "phosphodiesterase inhibitor." Filters were used to limit the search to clinical trials and reviews in the English language.

Systematic reviews and RCTs comparing PDE5Is (alone or in combination with an AB) versus AB monotherapy or placebo were included. Studies were evaluated in accordance with the GRADE Working Group statement. Specifically, the quality of evidence was classified into one of four levels: high, moderate, low, or very low [7–10].

The evidence

The literature search yielded a total of 205 citations, from which one systematic review and 10 RCTs were selected (Table 45.4). Wang et al. recently conducted a systematic review, identifying 12 studies. They pooled data to characterize different outcomes at 12 weeks [60]. Of note, the identified studies had a limited description of randomization and allocation concealment, thus increasing the risk of bias. Seven trials were pooled that included comparisons between PDE5I and AB monotherapy. The pooled MD in IPSS change was not significant. There was also no difference with respect to flow parameters (MD –0.55; 95% CI –1.20 to 0.10) or QOL (MD –0.02; 95% CI –0.50 to 0.46), and PVR was actually lower in the AB monotherapy arm (MD 9.82; 95% CI 3.80 to 15.85). Eight studies were included comparing the combination of a PDE5I plus an AB with AB monotherapy. The pooled MDs in IPSS, Q_{max}, PVR, and QOL were –1.86 (95% CI –2.45 to –1.27), 0.81 (95% CI 0.37 to 1.24), –5.37 (95% CI –10.14 to –0.60), and –0.84 (95% CI –1.32 to –0.35), respectively, all of which favored combination therapy. The authors also looked at the comparison between PDE5I monotherapy and the combination of an AB plus a PDE5I (five studies with data on this comparison). The pooled MDs in IPSS, Q_{max}, PVR, and QOL were –3.97 (95% CI –5.40 to –2.53), 2.22 (95% CI 1.63 to 2.82), –23.43 (95% CI –36.54 to –10.32), and –0.81 (95% CI –1.41 to –0.2), respectively, all of which favored combination therapy. Reported AE rates did not differ across the comparison groups [60].

Ten of the 12 studies included in Wang et al.'s systematic review were identified in the search described because of the English-language restriction. Detailed results of these studies are summarized here.

As mentioned previously, McVary et al. published the first RCT comparing LUTS outcomes between dose-escalation tadalafil and placebo. Tadalafil was superior to placebo at 6 weeks (IPSS change –2.8 vs. –1.2) and at 12 weeks (–3.8 vs. –1.7) in a study of 280 subjects. Improvement was also noticed in erectile function in most men with ED who were sexually active [58]. Later, Kaplan et al. published the first trial comparing AB monotherapy versus PDE5I monotherapy versus a combination of the two. Subjects with both LUTS and ED were enrolled and randomized to alfuzosin 10 mg, sildenafil 25 mg once daily ($n=21$), or combination therapy for 12 weeks. Improvement in IPSS was significant across all three groups relative to baseline, but the trend in symptom IPSS favored combination therapy. Frequency, nocturia, PVR, and Q_{max} were improved significantly with alfuzosin monotherapy and combination therapy. No serious AEs were noted [61].

Several smaller studies were later published with shorter follow-up periods. Findings from these studies were consistent with those from McVary et al. and Kaplan et al. (see Table 45.4). Two were of strong quality and included a placebo arm for the comparison of AB and PDE5I monotherapy. Oelke et al. conducted a multi-center RCT comparing tadalafil 5 mg daily with tamsulosin 0.4 mg daily ($n=168$) and placebo [62]. Inclusion criteria included a baseline IPSS ≥13 and Q_{max} from ≥4 to ≤15 mL/s. After a 4-week lead-in period, almost 90% of subjects completed the study. The investigators observed a significant improvement in IPSS (including both the storage and voiding subscales) over baseline for both the tadalafil and tamsulosin groups compared with placebo. However, only tadalafil was superior to placebo when assessing the IPSS QOL score at 12 weeks. Improvements in Q_{max} were significantly greater with tadalafil and tamsulosin than with placebo. There was no difference in the rate of AEs across all three groups. A *post hoc* analysis by the same investigators showed higher treatment satisfaction among tadalafil users compared with placebo. This was not observed for tamsulosin [62].

The second high-quality study was performed by Yokoyama et al. [63]. This multi-center, double-blind, placebo-controlled trial included a screening/washout period to control for other drugs that may have influenced LUTS. Eligible men were randomized to oral placebo, tadalafil (2.5 or 5.0 mg), or tamsulosin (0.2 mg) daily for 12 weeks. Findings from this study revealed a statistically significant improvement in total IPSS and QOL compared with baseline for tadalafil and tamsulosin users versus placebo (regardless of the dose prescribed). However, there was no improvement in urinary flow studies. Common reported AEs included myalgia, headache, back pain, nasopharyngitis, and dizziness [63].

The eight other RCTs identified in this search examined the combined effect of PDE5Is and ABs. The inclusion and exclusion criteria were similar across these studies. In addition, validated instruments were used in all to measure patient symptoms. Based on data from Wang et al., results from the pooled analyses, estimating the impact of

Table 45.4 Randomized clinical trials comparing phosphodiesterase type 5 inhibitors with placebo or active controls.

Study ID GRADE	Trial duration (weeks)	Intervention	No. completed/ randomized	Adverse events	Results
Kaplan [61]	12	Alfuzosin 10 mg q.d.	18/20	2/20	IPSS improvement in all intervention arms compared with baseline and the trend favored combination therapy
GRADE		Sildenafil 25 mg q.d.	19/21	2/21	
Low		Combination	18/21	3/21	Frequency, nocturia, flow, and PVR were significantly improved with alfuzosin monotherapy and combination therapy (vs. baseline)
Bechara [64]	12	Tamsulosin 0.4 mg q.d.	15	6/27	IPSS improvement in both intervention arms compared with baseline
GRADE		Tamsulosin 0.4 mg + tadalafil 20 mg daily	15	17/27	IPSS total score and QOL item significantly favored the combination group
Moderate			Cross-over 27/30		Q_{max} and PVR improved from baseline in both groups but there was no difference among these
Tuncel [65]	8	Tamsulosin 0.4 mg q.d.	20/20	NA	IPSS, Q_{max}, and PRV significantly improved in each group from baseline. Statistical significance on these outcomes favored both combination and tamsulosin monotherapy arms compared with the sildenafil arm
GRADE		Sildenafil 25 mg (4 d/wk)	20/20	NA	
Moderate		Combination	20/20	NA	
Jin [66]	24	Sildenafil 25–100 mg	66/82	12/82	IPSS and QOL only improved at 3 and 6 months in the combination therapy arm
GRADE		Doxazosin 4 mg + sildenafil 25–100 mg q.d.	137/168	26/168	Combination therapy was superior to sildenafil monotherapy based on IPSS and QOL
Moderate					
Öztürk [67]	12	Alfuzosin 10 mg q.d.	47/50	NA	IPSS, QOL, PVR, and Q_{max} improved in both groups compared with baseline
GRADE		Alfuzosin 10 mg + sildenafil 50 mg q.d.	45/50	NA	There was no statistical difference in outcomes between the two therapies
Moderate					
Oelke [62]	12	Tadalafil 5 mg q.d.	156/171	40/171	Both drug arms were superior to placebo when assessing IPSS and its voiding and storage subscales
GRADE		Tamsulosin 0.4 mg q.d.	150/168	40/168	
High		Placebo	148/172	35/172	Only tadalafil was superior to placebo when assessing IPSS–QOL Index. Improvements in Q_{max} were significantly greater than for placebo with tadalafil and with tamsulosin
Gacci [68]	12	Tamsulosin 0.4 mg + placebo q.d.	30/30	3/30	Improvement from baseline parameters was detected for combination therapy in all outcomes and for tamsulosin monotherapy only in IPSS and overactive bladder questionnaire and not for flow parameters
GRADE					
High		Tamsulosin 0.4 mg + vardenafil 10 mg q.d.	29/30	2/30	Combination therapy arm achieved better IPSS and flow parameters than tamsulosin monotherapy
Yokoyama [63]	12	Tadalafil 2.5 mg q.d.	136/151	5/151	Improvement from baseline on IPSS and QOL favored tadalfil 2.5 and 5 mg, and also tamsulosin compared with placebo. There was no difference in flow parameters among the drug therapy groups compared with placebo
GRADE		Tadalafil 5 mg q.d.	137/155	7/155	
High		Tamsulosin 0.2 mg q.d.	143/152	2/152	
		Placebo	145/154	1/154	
Abolyosr [69]	16	Doxazosin 2 mg q.d.	50	NA	Improvement from baseline was detected in all groups in IPSS, urine flow, PVR
GRADE		Sildenafil 50 mg q.d.	50	NA	
Moderate		Combination	50	NA	
Regadas [70]	4	Tamsulosin 0.4 mg q.d.	20	0/20	Total IPSS, storage, and voiding subscore improved significantly in tamsulosin/tadalafil compared with tamsulosin/placebo group
GRADE		Tamsulosin 0.4 mg + tadalafil 5 mg daily	20	1/20	
Low					Urodynamic parameters significantly favored combination therapy when assessing $P_{det}Q_{max}$

NA, none available.

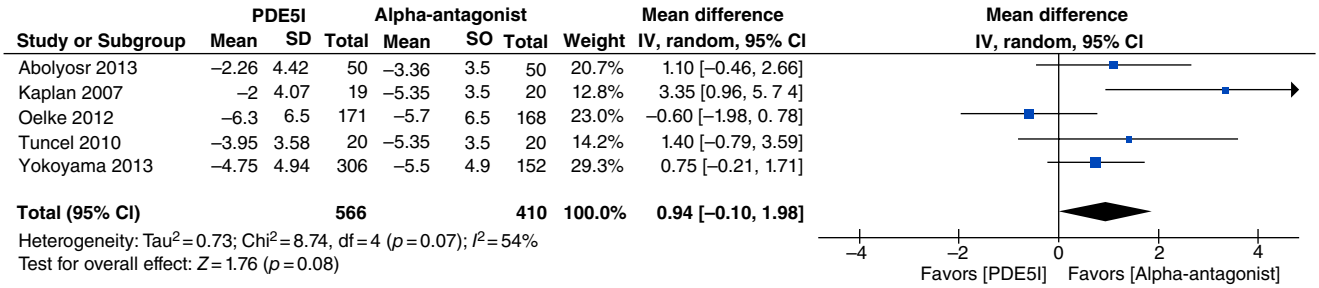

Figure 45.1 IPSS total score: PDE5I.

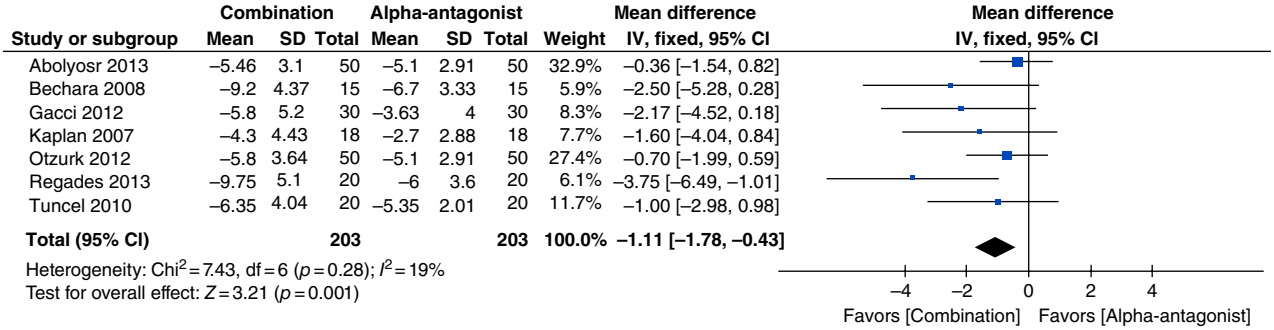

Figure 45.2 IPSS total score: combination.

combination therapy on outcomes [60], we calculated the summary estimate using RevMan and illustrated the results by the forest plots shown in Figures 45.1 and 45.2. These plots reveal no difference between changes in IPSS scores between AB and PDE5I monotherapies. However, there appears to be a significant benefit associated with combination therapy compared with AB monotherapy, which was also noted by Wang's group [60].

In summary, data from RCTs and one meta-analysis on PDE5I compared with placebo or active control in men with LUTS secondary to BPH are of moderate quality (Table 45.4). The results from short and 1-year follow-up show important outcomes that support the use of tadalafil (when combined with an AB) in reducing moderate to severe LUTS in men (weak recommendation). Additionally, there are no data supporting an effect of PDE5I use on flow parameters. Finally, the evidence on other PDE5Is is more limited and optimal dosing regimens remain unclear.

Clinical implications

In men with LUTS secondary to BPH, we suggest tadalafil (combined with an AB) over no treatment (conditional recommendation based on moderate-quality evidence).

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CHAPTER 46

Surgical management of lower urinary tract symptoms secondary to benign prostatic hypertrophy

Derek J. Lomas and Amy Krambeck
Department of Urology, Mayo Clinic, Rochester, MN, USA

Introduction

Benign prostatic hyperplasia (BPH) is a common urological issue facing the aging male. Epidemiological studies have shown that BPH affects over 70% of men in the seventh decade of life and 80% of patients over age 70 years [1]. Lower urinary tract symptoms (LUTS) secondary to BPH can be managed both medically and surgically. Typically, patients with mild symptoms or bother can be managed with medical therapy and/or behavior modification. However, patients who either poorly tolerate medication or have refractory symptoms may require surgical management. Indications for surgical management of BPH include acute urinary retention (AUR), bladder calculi, azotemia, recurrent urinary tract infection (UTI), recurrent hematuria, or worsening LUTS refractory to medical therapy [2]. Historically, surgical management of BPH has been accomplished through transurethral resection of the prostate or open simple prostatectomy (OP). Transurethral resection of the prostate (TURP) was pioneered in the 1930s and since then has remained the gold standard for endoscopic management of BPH due to its long-term effectiveness and wide availability in most urological practices. Simple prostatectomy continues to be performed through either open or robotic approaches for large prostates where endoscopic techniques may be ineffective or time consuming. Both TURP and OP remain effective treatments for BPH, but their associated morbidity and even mortality have given rise to the development and rise in popularity of multiple additional minimally invasive surgical procedures to relieve outlet obstruction. These newer BPH procedures offer an alternative to patients who are either unfit or unwilling to undergo TURP or OP. In this chapter, we evaluate the alternatives to TURP and OP and review the evidence supporting the alternatives in order to make clinical recommendations for index patients.

Methods

We formulated four clinical questions to guide our literature search, and we attempted to identify recent high-quality systematic reviews with meta-analysis that addressed these questions. We focused on both efficacy and safety outcomes in order to make recommendations based on the quality of evidence available. The efficacy outcomes of importance varied by technique, but included International Prostate Symptom Score (IPSS), maximum flow rate (Q_{max}) (mL/s), quality of life (QOL), and reoperation rate. Emphasis was placed efficacy data at 12 months or longer. Safety outcomes of importance again varied by technique, but included: blood transfusion rate and incidence of transurethral resection (TUR) syndrome. Perioperative outcomes including catheterization time (hours) and hospital stay (hours) were also reviewed. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to assess the quality of evidence of the available meta-analyses [3].

Clinical question 1

In a patient with an enlarged prostate and moderate to severe LUTS and/or who is significantly bothered by these symptoms, how do OP and robot-assisted simple prostatectomy (RASP) compare?

Literature search

A comprehensive search of several databases from each database's inception to 13 July 2015, in any language, was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled

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Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for studies comparing RASP with OP for enlarged prostate with LUTS. Keywords included "robotic," "robot," "da vinci," "prostate," "benign," and "simple." Emphasis was placed on systematic reviews, meta-analyses, and randomized controlled trials (RCTs). The actual strategy is available from the corresponding author (A.K.).

The evidence

OP has been shown to be an efficacious and durable treatment of BPH [4]. Morbidity associated with the procedure has led to the development of alternative deobstructing surgical procedures. RASP has become increasingly popular among urologists. The use of the Da Vinci Surgical System has been extensively studied for radical prostatectomy, but many fewer data exist for its use for simple prostatectomy.

Our review of the literature did not identify any RCTS comparing OP and RASP. We did identify a systematic review assessing the outcomes of RASP in a non-comparative fashion [5]. This systematic review by Banapour et al. included nine noncomparative case series with 125 patients. No meta-analysis was performed. The authors reported a low prevalence of perioperative transfusion, with transfusions given in only two (1.6%) patients of the 125 patients across all series. Length of hospital stay ranged from 1.3 to 3.2 days across the series. Mean preoperative IPSS ranged from 17.7 to 24 and postoperative mean IPSS ranged from 5 to 8.13 with follow-up ranging from 1 to 6 months. Mean operating time ranged from 128.8 to 228 min across the series. Mean catheterization time was reported in eight series and ranged from 110 to 312 h. In one series, one patient was converted to OP.

The same group published another paper in 2014 with an updated review of the case series available [6]. None of the methodological details were provided for the review. The review contained four additional case series comprising a total of 50 patients. In addition, complication rates across all 13 series were summarized and ranged from 7.7 to 33%. Transfusion was required in six (3.2%) out of the 176 patients included in the review and the rate ranged from 0 to 33% across the series.

An additional systematic review was identified that compared minimally invasive simple prostatectomy (MISP) with OP [7]. MISP included both laparoscopic simple prostatectomy (LSP) and RASP. Twenty-seven observational studies were analyzed, including four nonrandomized studies comparing MISP with OP. RASP was the focus of eight studies, which were noncomparative. All four of the nonrandomized studies compared LSP with OP. The data pooled for meta-analysis was were differentiated by technique. Nevertheless, the combined data on LSP and RASP showed a mean increase in Q_{max} of 14.3 mL/s and a mean IPSS improvement of 17.2. The mean length of catheterization was 144 h and the mean length of hospital stay was 4.2 days. Blood transfusions were required in 6.4% of cases, UTIs occurred in 2.2%, and reoperation was required in 1.8% of cases. Again, these data represent both LSP and RASP, with the majority of the studies evaluating LSP.

We identified one large retrospective review that included 1330 consecutive cases of MISP across several institutions [8]. It contained data on 487 RASPs. The median length of hospital stay was 2 days (range 1–4) and the median catheterization time was 168 h (range 120–216 h). At a median follow-up of 12 months, the median Q_{max} was 25 mL/s, up from a preoperative value of 8 mL/s. There was also an improvement in IPSS from a median of 23 preoperatively to 7 at a median follow-up of 12 months. Complication data were reported for the 90-day postoperative period. Blood transfusion was required in five patients (1%) and there were 10 patients with AUR (2%).

Another retrospective review comparing perioperative outcomes of OP versus MISP, conducted by Parsons et al. using the Nationwide Inpatient Sample (NIS) database, was also identified [9]. MISP included both LSP and RASP. The outcomes were not separated by the specific minimally invasive procedure. The data showed that patients in the MISP group were approximately 50% less likely to receive a blood transfusion (10.8 vs. 20.9%), however, this difference was not statistically significant ($p=0.13$). Mean length of hospital stay was 1 day shorter (3.7 vs. 4.7 days) in the MISP group, but again this was not statistically significant ($p=0.19$).

Clinical implications

In a patient with an enlarged prostate and moderate to severe LUTS with significant bother, we suggest RASP over OP (conditional recommendation based on very low-quality evidence).

The current evidence is derived from noncomparative case series, and also indirect evidence including MISP from retrospective studies. This recommendation is based on the comparable efficacy results between the two groups, together with the significant morbidity associated with OP. Meanwhile, it should be noted that at this time, RASP is considered an investigational procedure by the American Urological Association guideline on the management of benign prostatic hyperplasia [2]. Although noncomparative case series and retrospective reviews have shown promising results, comparative prospective studies are needed.

Clinical question 2

In a patient with an enlarged prostate and moderate to severe LUTS and/or who is significantly bothered by these

symptoms, how do holmium laser enucleation of the prostate (HoLEP) and OP compare?

Literature search

A comprehensive search of several databases from each database's inception to 13 July 2015, in any language, was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for studies of HoLEP versus OP for enlarged prostate with LUTS. Keywords included "prostate," "holmium," "Ho laser," "Ho YAG laser," "HoLEP," "StoneLight," "Versa Pulse," "benign," "simple," "open," "transvesical," "lower urinary tract symptoms," "LUTD," "LUTS," and "BPH." Emphasis was placed on systematic reviews, meta-analyses, and RCTs. The actual strategy is available from the corresponding author (A.K.).

The evidence

OP has traditionally been the treatment of choice for patients with symptomatic BPH and significantly enlarged prostates. This invasive procedure is associated with significant early and late complications, including blood transfusion, prolonged hospitalization and recovery, and even death [4, 10]. HoLEP is a minimally invasive alternative with durable results that is increasingly being used in patients with significantly enlarged prostates who would otherwise be offered OP [11].

We identified four relevant systematic reviews [12–15], of which one was available only as a meeting abstract [13] and two were available only in Chinese [12, 15].

The systematic review by Cornu et al. [14] included three RCTs comparing HoLEP with OP in patients with prostates >100 mL [16–18]. This review did not contain a formal meta-analysis. Two of the RCTs included were by the same group and contained the same patient population, with one focused on cost analysis [17, 18]. The authors found that operating time was significantly longer in the HoLEP group (mean difference 24.9 min, $p = 0.01$). A shorter hospital stay (mean difference 4.3 days, $p = 0.004$) and catheter duration (mean difference 98 h, $p = 0.01$) were found in the HoLEP group. Efficacy comparisons were made by two of the included trials. The authors reported that IPSS and Q_{max} improvements were comparable between OP and HoLEP, but no mean differences were reported. With regard to complications, blood transfusions were more common in the OP group (relative risk 6.09, $p < 0.0001$). The authors reported that the rates of stricture, incontinence, and reoperation were comparable in the two groups, but no statistical analysis was performed.

The outcomes of interest that were addressed by the studies included in this review were IPSS at 12 months, Q_{max} at 12 months, blood transfusion rate, hospital stay, and catheterization time. As the Cornu review only summarized the data and did not include a meta-analysis, we therefore performed our own meta-analysis of the two unique RCTs and generated forest plots for these outcomes (Figure 46.1). A summary of findings is presented in Table 46.1.

Clinical implications

In a patient with an enlarged prostate and moderate to severe LUTS with significant bother, we suggest HoLEP over OP (conditional recommendation based on very low-quality evidence).

This recommendation is based on the comparable efficacy of results between the two groups, and also the significantly lower morbidity associated with HoLEP. One limitation to the recommendation is the steep learning curve associated with HoLEP, which has hampered its dissemination into general urological practice [19, 20].

Clinical question 3

In a patient with an enlarged prostate and moderate to severe LUTS and/or who is significantly bothered by these symptoms, how do photovaporization of the prostate (PVP) and monopolar transurethral resection of the prostate (M-TURP) compare?

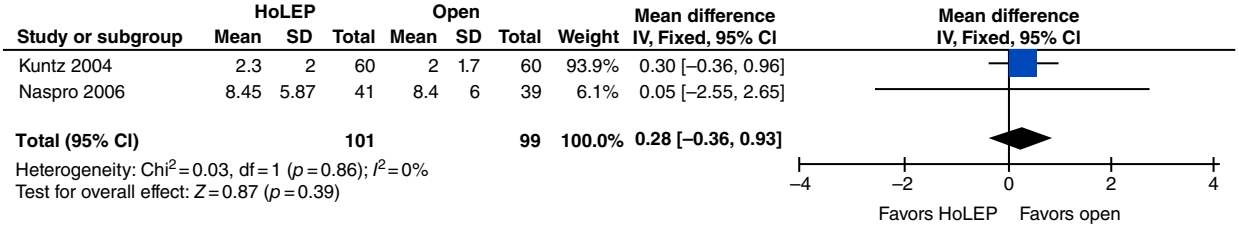
Literature search

A comprehensive search of several databases from each database's inception to 14 July 2015, in any language, was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for studies of PVP laser prostatectomy versus TURP for enlarged prostate with LUTS. Keywords included "laser prostatectomy," "green light," "greenLight," "potassium-titanyl-phosphate (KTP)," "photoselective laser*" or "photoselective vaporis*" or "photoselective vaporiz*" or "potassium titanyl phosphate," "PVP," "contact laser ablation*," "transurethral resection," "transurethral resection of prostate," "TUR," "TURP," "prostate," "lower urinary tract symptoms," "LUTD," "LUTS," and "BPH." Emphasis was placed on systematic reviews, meta-analyses, and randomized controlled trials. The actual strategy is available from the corresponding author (A.K.).

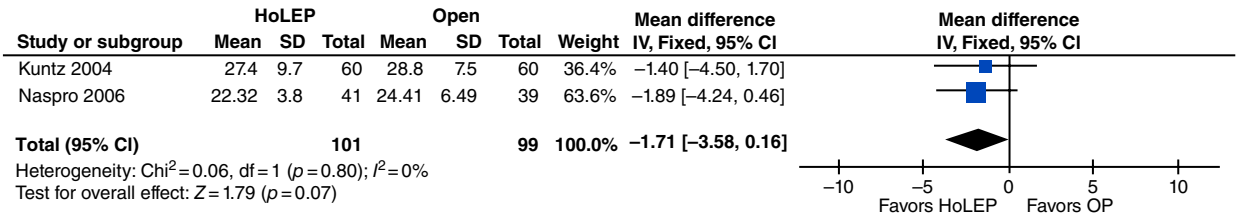
The evidence

Potassium titanyl phosphate (KTP) laser prostatectomy is another alternative to the traditional M-TURP developed in an effort to reduce morbidity. The procedure, also referred

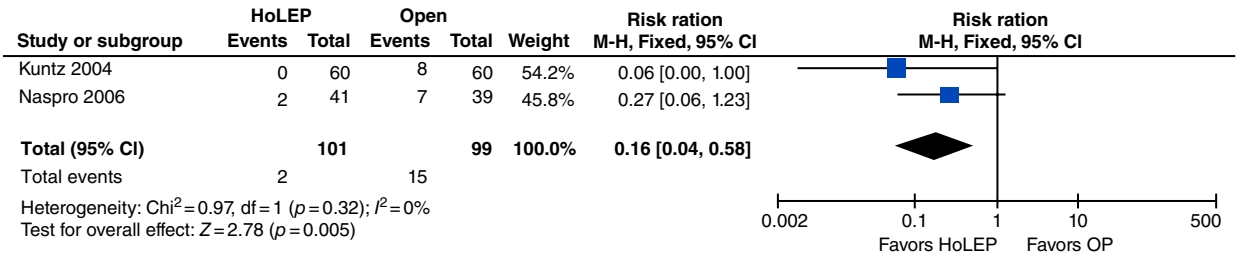
(a) IPSS at 12 months



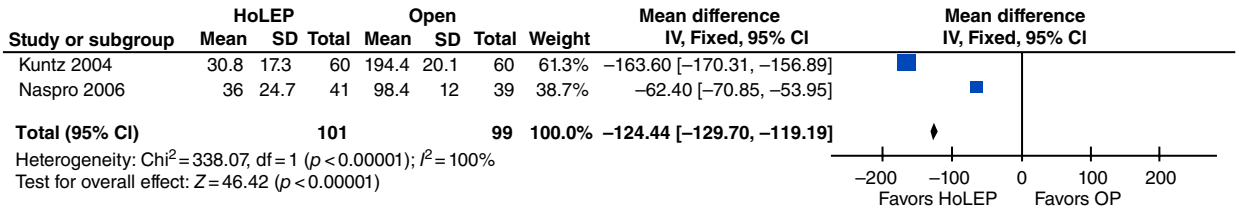
(b) Q_{max} at 12 months



(c) Blood transfusion



(d) Length of catheterization (h)



(e) Length of hospital stay (days)

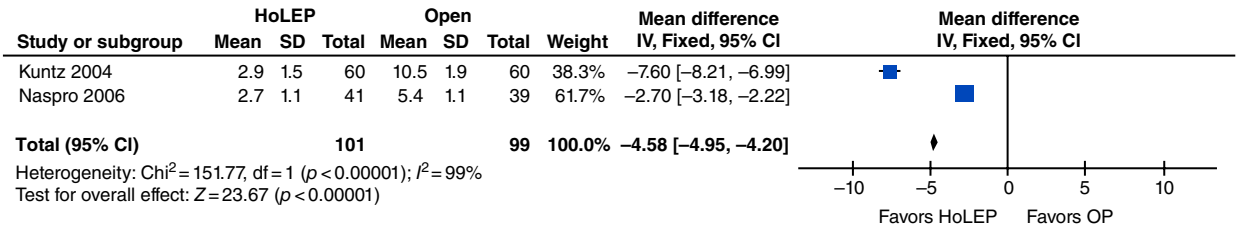


Figure 46.1 Meta-analysis of efficacy and complications in studies comparing HoLEP to OP.

to as photoselective vaporization of the prostate (PVP), uses Nd:YAG laser light passed through a KTP crystal at a wavelength of 532 nm. This laser light is selectively absorbed by hemoglobin, leading to vaporization of prostatic tissue and hemostasis with a necrosis depth of 1–2 mm. Given that the tissue is destroyed through the vaporization, no samples are recoverable for pathological analysis. Since 2000, when the original 60 W system was introduced, 80, 120, 160, and 180 W systems have been developed and evaluated. Currently, the two commercially available systems are the AMS GreenLight HPS 120 W and GreenLight XPS 180 W.

We identified seven systematic reviews comparing PVP laser prostatectomy with M-TURP [14, 21–26]. We chose to focus on reviews that included RCTs that evaluated either the 120 or 180 W devices to increase clinical relevance.

Table 46.1 Summary of findings: HoLEP compared with OP in a patient with an enlarged prostate and moderate to severe LUTS.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with OP	Risk with HoLEP				
IPSS Follow-up: mean 12 months	The mean IPSS was **5.2**	The mean IPSS in the HoLEP group was 0.28 higher (0.36 lower to 0.93 higher)	–	200 (2 RCTs)	⨁⨁⨁◯ MODERATE[a,b]	
Q_{max}	The Q_{max} was **26.5** mL/s	The mean Q_{max} in the HoLEP group was 1.71 mL/s lower (3.58 lower to 0.16 higher)	–	200 (2 RCTs)	⨁⨁⨁◯ MODERATE[a,b]	
Blood transfusion	**Study population** 152 per 1000	**2 per 1000** (6 to 88)	**RR 0.016** (0.040 to 0.580)	200 (2 RCTs)	⨁⨁◯◯ LOW[a,b,c]	
Catheterization time	The mean catheterization time was **146.4** h	The mean catheterization time in the HoLEP group was 124.44 h fewer (129.7 fewer to 119.19 fewer)	–	200 (2 observational studies)	⨁◯◯◯ VERY LOW[a,b,d]	
Length of hospital stay	The mean length of hospital stay was **8** days	The mean length of hospital stay in the HoLEP group was 4.58 days fewer (4.95 fewer to 4.2 fewer)	–	200 (2 observational studies)	⨁◯◯◯ VERY LOW[a,b,e]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; MD, mean difference; RR: risk ratio.

[a] Unclear allocation concealment in 2/2 studies.

[b] Unclear if incomplete outcome data adequately addressed in 1 study.

[c] Small number of events.

[d] I^2 value 99%. No overlap in 95% CI.

[e] I^2 value 100%. No overlap in 95% CI.

The most recently published systematic review and meta-analysis was by Cornu et al. [14]. In this study, six RCTs comparing the GreenLight HPS 120 W with M-TURP were included [27–32]. Efficacy data on IPSS, Q_{max}, and PVR were available for 12 months' follow-up and were of moderate quality. On meta-analysis, there was no significant difference in IPSS (mean difference 0.02, $p=0.92$), Q_{max} (mean difference 0.06, $p=0.94$), and PVR (mean difference 3.21, $p=0.15$). Operating time was longer in the PVP group (mean difference 9.37 min, $p<0.0001$). Catheter duration (mean difference 32.36 h, $p<0.0001$) and hospital stay (mean difference 1.85 days, $p<0.00001$) was shorter in the PVP group. The need for transfusion was lower in the PVP group (odds ratio [OR] 0.10, $p=0.0001$), but the rates of AUR (OR 1.18, $p=0.67$) and UTI (OR 1.23, $p=0.56$) were not significantly different between the groups. Long-term complications of bladder neck contracture (OR 0.85, $p=0.79$) and urethral stricture (OR 1.01, $p=0.99$) did not vary between the groups. M-TURP was favorable with regard to decreased need for reoperation due to recurrent symptoms (OR 3.87, $p=0.04$).

Six additional systematic reviews and meta-analyses were identified in our literature search. Two of the identified reviews contained RCTs evaluating only the 80 W device [21, 22]. The remaining four systematic reviews and meta-analyses identified no further contributory trials or data [23–26].

A summary of findings is presented in Table 46.2.

Clinical implications

In a patient with an enlarged prostate and moderate to severe LUTS with significant bother, we suggest PVP over M-TURP (conditional recommendation based on low-quality evidence).

This recommendation considers that the functional outcomes at 12 months' follow-up were not significantly different between the groups whereas length of hospital stay, rate of transfusion, and catheter duration favored PVP. This recommendation assumes that patients place a high value on reducing the immediate morbidity of the procedure (i.e. lower risk of transfusion, shorter length of stay) and a relatively low value on the possible need for future reintervention. The reoperation rates were significantly higher in the PVP group, leading to concerns over the durability of the procedure. Longer follow-up studies focusing on outcomes after PVP would be beneficial to assess the durability of PVP compared with M-TURP.

Table 46.2 Summary of findings: PVP compared with M-TURP in a patient with an enlarged prostate and moderate to severe LUTS and/or who is significantly bothered by these symptoms.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with M-TURP	Risk with PVP				
IPSS Scale: from 0 to 35 Follow-up: 12 months	The mean IPSS was **6.6**	The mean IPSS in the PVP group was 0.02 lower (0.45 lower to 0.41 higher)	–	360 (4 RCTs)	⨁⨁⨁◯ MODERATE[a]	
Q_{max}	The mean Q_{max} was **20.7** mL/s	The mean Q_{max} in the PVP group was 0.06 mL/s higher (1.41 lower to 1.53 higher)	–	340 (3 RCTs)	⨁⨁⨁◯ MODERATE[b]	
Reoperation	**Study population** 15 per 1000	**56 per 1000** (16 to 178)	**OR 3.87** (1.06 to 14.04)	393 (3 RCTs)	⨁⨁◯◯ LOW[c,d]	
Blood transfusion	**Study population** 77 per 1000	**8 per 1000** (3 to 26)	**OR 0.10** (0.03 to 0.32)	697 (6 RCTs)	⨁⨁◯◯ LOW[d,e,f]	
Catheterization time	The mean catheterization time was **64.9** h	The mean catheterization time in the PVP group was 32.36 h fewer (48.17 fewer to 16.54 fewer)	–	440 (4 RCTs)	⨁⨁◯◯ LOW[f,g,h]	
Hospital stay	The mean hospital stay was **4.6** days	The mean hospital stay in the PVP group was 1.85 days fewer (2.48 fewer to 1.21 fewer)	–	438 (3 RCTs)	⨁⨁◯◯ LOW[b,i]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; MD, mean difference; OR, odds ratio.
[a] Allocation concealment unclear in 3/4 studies, No sample size calculation in 2/4 studies.
[b] Allocation concealment unclear in 2/3 studies.
[c] Allocation concealment unclear in all 3 studies.
[d] Small number of events.
[e] Allocation concealment unclear in 5/6 studies.
[f] Unclear completeness of outcome data in 1 study.
[g] Allocation concealment unclear in all 4 studies.
[h] I^2 value 95%. Some studies have little or no overlap of 95% CI.
[i] I^2 value 83%. Two studies without overlap in 96% CI.

Clinical question 4

In a patient with an enlarged prostate and moderate to severe LUTS and/or who are significantly bothered by these symptoms, how do monopolar TURP and bipolar TURP compare?

Literature search

A comprehensive search of several databases from each database's inception to 14 July 2015, in any language, was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for studies of monopolar versus bipolar TURP for enlarged prostate with LUTS. Keywords included "transurethral resection," "transurethral resection of prostate," "gyrus plasmakinetic," "trans-urethral*," "bipolar," "transurethra resection in saline" or "trans-urethra resection in saline" or "transurethral resection in saline" or "trans-urethral resection in saline,""TUR," "TURis," "TURP," "Vista CTR," "prostate," "lower urinary tract symptoms," "LUTD," "LUTS," and "BPH." Emphasis was placed on systematic reviews, meta-analyses, and RCTs. The actual strategy is available from the corresponding author (A.K.).

The evidence

The bipolar transurethral resection of the prostate (B-TURP) system was developed in an effort to reduce the complications associated with conventional monopolar TURP while attempting to preserve good surgical outcomes. Traditional monopolar transurethral resection of the prostate (M-TURP)

requires nonionic irrigation solutions, typically mannitol or glycine. The use the these hypotonic fluids can lead to transurethral resection (TUR) syndrome and dilutional hyponatremia. In order to limit the likelihood of developing TUR syndrome, most M-TURP procedures are limited to a resection time of 1 h.Thus, M-TURP has traditionally been limited to smaller prostates (<100 g) that can be successfully treated during the time constraint. Unlike M-TURP, B-TURP can be performed using isotonic saline irrigation, thus eliminating the risk of TUR syndrome and allowing for longer resection times.

There are several bipolar devices currently in use, available from Olympus, Wolf, and Karl Storz. These devices include the Olympus TURis system, the Gyrus PlasmaKinetic, the ACMI Vista Controlled Tissue Resection system, the Wolf Bipolar system, and the Karl Storz Bipolar system. We identified four systematic reviews and meta-analyses comparing B-TURP with M-TURP [14, 33–35], of which two were by the same authors with the more recently published review being an update of the original [34, 36].

The most recently published systematic review and meta-analysis was by Cornu et al. [14]. The authors identified 24 independent RCTs comparing B-TURP with M-TURP and performed a meta-analysis [37–60], The articles included in this review were subsequently used to create our GRADE evidence profile.

When evaluating the efficacy outcomes of IPSS (mean difference 0.12, $p=0.31$), QOL (mean difference 0.1, $p=0.32$), and PVR (mean difference 4.15 mL, $p=0.11$) at 12 months, there were no significant differences between the M-TURP and B-TURP groups. Maximum flow rate (Q_{max}) at 12 months was higher in the B-TURP group (mean difference 1.26 mL/s, $p=0.009$). Fewer efficacy data are available with long-term (>12 months) follow-up. Follow-up in the three studies varied from 24 to 60 months. There were no significant differences in Q_{max} (mean difference 1 mL/s, $p=0.14$), PVR (mean difference 1.1 mL, $p=0.83$), and IPSS (mean difference 0.49, $p=0.06$) between M-TURP and B-TURP at long-term follow-up.

Operating time was not significantly different between the procedures (mean difference 1.51 min, $p=0.41$). Immediate complications favored B-TURP with significant differences seen in transfusion rates (OR 0.49, $p=0.0009$), hemoglobin reduction (mean difference 0.43, $p=0.00001$), decrease in serum sodium (mean difference 3.01, $p=0.0001$), clot retention (OR 0.47, $p=0.0002$), AUR (OR 0.68, $p=0.04$), and TUR syndrome (OR 0.22, $p=0.002$). Immediate reoperation rates were also significantly lower in the B-TURP group (OR 0.43, $p=0.02$). There was no difference in UTIs (OR 1.03, $p=0.9$) and recatheterization rates (OR 0.86, $p=0.73$). Length of hospital stay was shorter in the B-TURP group (mean difference 0.79 days, $p=0.003$). A shorter catheterization time was also seen in the B-TURP group (mean difference 17.14 h, $p<0.00001$). At 12 months' follow-up, the rates of urethral stricture, incontinence, and reoperation were not significantly different between the groups. At long-term follow-up, the rates of urethral stricture, bladder neck contracture (OR 1.14, $p=0.75$) and reoperation (OR 1.25, $p=0.40$) were again not significantly different between the groups.

A systematic review and meta-analysis by Tang et al. also compared B-TURP and M-TURP [35], and 31 RCTs comparing M-TURP with B-TURP were included. The review focused on efficacy and safety outcomes. Efficacy was assessed by Q_{max} and IPSS at 12 months. The authors reported a significant difference in Q_{max} at 12 months (mean difference 0.36, $p<0.12$) favoring B-TURP. The forest plot included in the review, however, supports favoring M-TURP. Upon closer examination, it appears that for some studies, the M-TURP and B-TURP data for Q_{max} had been reversed, which would explain the discordant finding. No difference was reported between the two modalities with regard to IPSS at 12 months, but a mean difference was not supplied in the review. The meta-analysis also included safety outcomes. The risk of TUR syndrome was significant lower in the B-TURP group (OR 0.02, $p=0.0004$). Clot retention was found to be higher in the M-TURP group. There were no significant differences in transfusion rates or late complications, including urethral stricture and bladder neck contracture. The authors concluded that given the favorable increase in Q_{max} and the improved safety outcomes of TUR syndrome and clot retention, B-TURP should replace M-TURP as a treatment option for BPH. Again, serious statistical issues may be present in this review, which may decrease the validity of its conclusions.

The third systematic review and meta-analysis, by Omar et al., included 24 RCTs comparing B-TURP with M-TURP [34]. It included one RCT not included in the two more recent reviews [61]. Nevertheless, the outcomes of this review mirror those of the later reviews. With regard to efficacy, there were no significant differences between the two techniques concerning IPSS and QOL. The difference in Q_{max} favored B-TURP at 3, 6, and 12 months. The authors commented that the largest mean difference for Q_{max} was at 3 months and was 3.04 mL/s ($p<0.001$). By 12 months, the mean difference has decreased to 1.3 mL/s ($p<0.001$). Although statistically significant, it is unlikely to be appreciable by the patient and the difference is not likely to be clinically significant. With regard to safety, the need for blood transfusion, risk of clot retention, and incidence of TUR syndrome were lower in the B-TURP group. There were no differences in urethral stricture, UTI, or AUR after catheter removal.

A summary of findings is presented in Table 46.3.

Clinical implications

In a patient with an enlarged prostate and moderate to severe LUTS with significant bother, we recommend B-TURP

Table 46.3 Summary of Findings: B-TURP compared to M-TURP in a patient with an enlarged prostate and moderate to severe LUTS based on systematic review by Cornu et al [14].

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with M-TURP	Risk with B-TURP				
IPSS	The mean IPSS was **6.7**	The mean IPSS in the B-TURP group was 0.12 lower (0.34 lower to 0.11 higher)	–	1302 (10 RCTs)	⨁⨁⨁◯ MODERATE[a,b]	
Q_{max}	The mean Q_{max} was **19.5** mL/s	The mean Q_{max} in the B-TURP group was 1.26 mL/s higher (0.31 higher to 2.21 higher)	–	1499 (12 RCTs)	⨁⨁◯◯ LOW[c,d]	
TUR syndrome	**Study population** 14 per 1000	**3 per 1000** (1 to 8)	**OR 0.22** (0.09 to 0.56)	2668 (19 RCTs)	⨁⨁◯◯ LOW[e,f,g]	
Catheterization time	The mean catheterization time was **67.7** h	The mean catheterization time in the B-TURP group was 17.14 h fewer (22.94 fewer to 11.35 fewer)	–	2053 (15 RCTs)	⨁⨁◯◯ LOW[h,i]	
Length of hospital stay	The mean length of hospital stay was **3.6** days	The mean length of hospital stay in the B-TURP group was 0.79 days fewer (1.32 fewer to 0.27 fewer)	–	1276 (9 RCTs)	⨁⨁◯◯ LOW[i,j]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, confidence interval; MD, mean difference; OR, odds ratio.
[a]Most studies with unclear allocation concealment. Unclear random sequence generation in 4 studies. No explanation for incomplete outcome date in 2 studies.
[b]No explanation was provided.
[c]Most studies with unclear allocation concealment. Unclear random sequence generation in 5 studies. No explanation for incomplete outcome date in 4 studies.
[d]I^2 value 56%. Some studies with minimal or no overlap in 95% CI.
[e]Most of the studies had unclear allocation concealment, 1 study with no explanation for incomplete outcome data.
[f]Most studies have unclear allocation concealment, 6 studies with unclear random sequence generation, 3 studies with unclear completeness of outcome data, and 1 study with no explanation for incomplete outcome data.
[g]Small number of events.
[h]Most studies with unclear allocation concealment. Unclear random sequence generation in 6 studies. No explanation for incomplete outcome date in 4 studies.
[i]I^2 value 95%. Some studies with minimal or no overlap in 95% CI.
[j]Most studies with unclear allocation concealment. Unclear random sequence generation in 3 studies. No explanation for incomplete outcome date in 1 study.

over M-TURP (strong recommendation based on low-quality evidence).

This recommendation considers that minimal differences are seen with regard to efficacy between B-TURP and M-TURP, but the safety profile appears to be improved with B-TURP.

Conclusion and implications for future research

As our population continues to age, more men will require treatment for BPH. Newer minimally invasive therapies are attractive to those that are unwilling or unable to accept the morbidity and risk associated with traditional M-TURP or OP. In this chapter, we set out to evaluate the evidence supporting these. Robot-assisted laparoscopic surgery has become increasingly common among urologists and has been instituted as an aid in BPH surgeries. From our review, early results are promising, but long-term data are sparse and there is still considerable morbidity associated with RASP. The lack of comparative prospective studies provides an opportunity for future research. Our review of the literature for the second clinical question revealed that HoLEP compares favorably with OP with regard to both efficacy and safety. It is important to consider that the efficacy and safety data published on HoLEP tend to come from experienced surgeons and the results are likely not applicable to novices. A major limitation to the widespread use of HoLEP has been steep learning curve associated with the procedure and, although it is an excellent option, its availability is not as widespread as the other modalities discussed in this chapter. When available, however, HoLEP should be favored

over OP. The third clinical question addressed the use of PVP laser prostatectomy over M-TURP. PVP laser prostatectomy is widely available and our review of the literature shows it to be a viable alternative to M-TURP. Lastly, we looked at B-TURP compared with M-TURP. Based on the available literature, B-TURP should be used over the older M-TURP.

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CHAPTER 47

Chronic prostatitis/chronic pelvic pain syndrome (NIH category III)

Giuseppe Magistro[1] and Florian M.E. Wagenlehner[2]

[1] *Department of Urology, Campus Grosshadern, Ludwig-Maximilians-Universität München, Munich, Germany*

[2] *Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig-Universität Giessen, Giessen, Germany*

Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common condition affecting 8.2% of aging men [1]. According to the consensus definition established by the US National Institutes of Health, prostatitis syndromes are classified in infectious forms (acute bacterial prostatitis [NIH category I] and chronic bacterial prostatitis [NIH category II]), noninfectious forms termed chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) (inflammatory CP/CPPS [NIH category IIIA] and noninflammatory CP/CPPS [NIH category IIIB]), and asymptomatic prostatitis (NIH category IV) (Table 47.1) [2]. Whereas the treatment of acute and chronic bacterial prostatitis depends on the adequate use of antibiotics, the management of CP/CPPS has always been challenging for both urologists and patients. The exact pathophysiology underlying this bothersome condition is poorly understood. Therefore, an efficient monotherapy is not available. With the introduction and validation of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) as an objective assessment instrument and outcome measure [3, 4], a plethora of clinical trials were conducted to evaluate various treatment modalities. In this chapter, we systematically review published data on the treatment of CP/CPPS.

Clinical question 1

How do antimicrobial agents compare with placebo in the treatment of patients diagnosed with CP/CPPS?

Literature search

A systematic literature search in PubMed and the Cochrane Database from January (1988). to December (2014). was performed. The search strategy included the following terms and their combinations: "chronic prostatitis," "chronic pelvic pain syndrome," "antibiotic," "antimicrobial agents," and "anti-infective agents." We searched for randomized controlled trials (RCTs) that classified patients as chronic prostatitis category IIIA or IIIB according to the NIH consensus definitions and reported the NIH-CPSI score as outcome measure.

The evidence

Three RCTs were eligible for inclusion (Table 47.2). Neither a 6-week course of treatment with ciprofloxacin (500 mg b.i.d.) [5] nor therapy with levofloxacin (500 mg q.i.d.) [6] resulted in a statistically significant therapeutic benefit as measured by the NIH-CPSI compared with the placebo arm. Only the clinical trial by Zhou et al. observed a significant mean decrease of 18.5 points in the NIH-CPSI after a 12-week course with 500 mg tetracycline per day [7]. No change was reported for the placebo group.

In a systematic review and meta-analysis by Cohen et al. [8], no significant therapeutic effect was reported for the use of antibiotics for NIH-CPSI total score ($n=167$; mean difference –1.8, 95% confidence interval [CI] –5.9 to 2.3). A subdomain analysis for the pain, voiding, and quality of life subscores also failed to reveal clinical efficiency. The included studies [5, 6] were well conducted and of good quality. Meta-analysis showed modest heterogeneity for NIH-CPSI total score ($Q=2.85$, df = 1; $p<0.0005$; $I^2=0.0\%$). Meta-regression and sensitivity analyses were applied, but failed to identify the reason for heterogeneity.

Clinical implications

We recommend against the use antibiotics as monotherapy for the treatment of patients diagnosed with CP/CPPS (strong recommendation against based on high-quality evidence). Available RCTs and meta-analysis failed to demonstrate a

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statistically significant therapeutic effect for antimicrobial agents compared with placebo. Nevertheless, antibiotics may be considered in a multimodal treatment approach in antibiotic-naive patients.

Clinical question 2

Is there a benefit of phytotherapeutics in alleviating pain in patients with CP/CPPS?

Literature search

A systematic literature search in PubMed and the Cochrane Database from January (1988). to December (2014). was performed. The search strategy included the following terms and their combinations: "chronic prostatitis," "chronic pelvic pain syndrome," and "phytotherapy."

The evidence

Two eligible RCTs were identified (Table 47.3). The small trial conducted by Shoskes et al. evaluated the efficacy of quercetin, a bioflavonoid with antioxidative and anti-inflammatory properties [10]. A course of 4 weeks of quercetin (500 mg b.i.d.) showed a significant benefit compared with placebo as measured by the NIH-CPSI. The total symptom score decreased significantly by –7.1 points (35% improvement; p =0.003) after treatment. This amelioration in total score resulted from improvements in the pain and quality of life subdomain. In the treatment arm, the pain score was reduced by 4.1 points (p=0.005) and quality of life improved by 3.1 points (p=0.004). No significant change was reported for the placebo group. The other trial investigated the therapeutic effect of Cernilton, a standardized rye pollen extract, over 12 weeks (two capsules q8h) [11]. The mean change in NIH-CPSI total score was –7.7 points (p=0.01), with a statistically significant decrease of –4.5 points in the pain subdomain for the pollen extract group compared with –2.92 points in the placebo arm (p=0.009). Also, the quality of life subdomain demonstrated a significant improvement of –2.23 points compared with placebo (p=0.03).

A meta-analysis [8] confirmed the statistically significant effect of the pollen extract on NIH-CPSI total score with a mean difference of –3.5 points (95% CI –6.2 to –0.8). A significant reduction in the pain subdomain was further determined (mean difference –1.78, 95% CI –3.09 to –0.47).

Table 47.1 NIH consensus definitions and classification of prostatitis [2].

Category	Definition
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)
IIIA	Inflammatory
IIIB	Noninflammatory
IV	Asymptomatic prostatitis

Clinical implications

We recommend the use of the tested phytotherapeutics as primary treatment or in combination in multimodal approaches for the treatment of CP/CPPS (strong recommendation based on high-quality evidence).

Clinical question 3

Do randomized controlled trials support the use of alpha-blockers for the treatment of CP/CPPS?

Table 47.2 RCTs on the impact of antibiotics for the treatment of CP/CPPS [9].

Treatment	Duration	Patients (n)	Basic mean NIH-CPSI total score	Mean change	Significance	Jadad total score	Ref.
Ciprofloxacin vs.	6 weeks	49	24.2	–6.2	No (p>0.05)	≥3	5
tamsulosin vs.		49	24.6	–4.4			
combination vs.		49	25.3	–4.1			
placebo		49	25.0	–3.4			
Levofloxacin vs.	6 weeks	45	24.4	–5.6	No (p>0.05)	≥3	6
placebo		35	21.3	–3.1			
Tetracycline vs.	12 weeks	24	35.6	–18.5	Yes (p<0.01)	<3	7
placebo		24	NR	NR			

NR, not reported.

Table 47.3 RCTs on the benefit of phytotherapeutics for the treatment of CP/CPPS [9].

Treatment	Duration	Patients (*n*)	Basic mean NIH-CPSI total score	Mean change	Significance	Jadad total score	Ref.
Cernilton	12 weeks	70	19.3	–7.7	Yes ($p<0.05$)	≥3	11
vs.							
placebo		69	20.3	–5.2			
Quercetin	4 weeks	15	21.0	–7.9	Yes ($p<0.01$)	≥3	10
vs.							
placebo		13	20.2	–1.4			

Literature search

A systematic literature search in PubMed and the Cochrane Database from January (1988). to December (2014). was performed. The search strategy included the following terms and their combinations: "chronic prostatitis," "chronic pelvic pain syndrome," "α-adrenergic receptor blockers," and "α-adrenergic receptor antagonists."

The evidence

We identified seven RCTs evaluating the efficacy of a monotherapy with α-adrenergic receptor blockers versus placebo [5, 12–17] (Table 47.4). Of note, clinical outcomes as determined by NIH-CPSI were fairly heterogeneous. Different substances over various periods of time were evaluated. A meta-analysis ($n=770$) [8] analyzed the benefit of α-blockers over placebo. With regard to NIH-CPSI total score, a decrease of 4.8 points was reported (95% CI –7.1 to –2.6) with high heterogeneity ($Q=29.49$, df = 7, $p<0.0005$, $I^2=76.3\%$). A mean change of 2.1 points (95% CI –3.1 to –1.2) for the pain subdomain with moderate heterogeneity ($Q=18.24$, df = 7, $p=0.01$, $I^2=61.6\%$) was determined. The reduction in the voiding subscore was 1.1 points (95% CI –1.7 to –0.4) with moderate heterogeneity ($Q=17.7$, df = 6, $p=0.0007$, $I^2=66.1\%$). Quality of life was improved by 1.4 points (95% CI –2.3 to –0.4) compared with placebo with high heterogeneity ($Q=36.8$, df = 6, $p<0.0005$, $I^2=83.7\%$).

In summary, treatment with α-blockers did not result in a global clinical improvement compared with the placebo group (relative risk [RR]: 1.1, 95% CI 0.86–1.39) [8]. Furthermore, the high degree of heterogeneity of clinical trials must be acknowledged. However, a prolonged treatment, especially in α-blocker-naive patients, may be considered in a multimodal treatment approach. With a calculated decrease of 0.23 points each week, a significant clinical outcome as determined by a 6-point reduction in NIH-CPSI total score requires a duration of α-blocker treatment of at least 26 weeks [8]. Indeed, clinical trials investigating longer durations of at least 12 weeks observed a significant benefit of α-blockers over placebo [12, 13, 16, 17].

Clinical implications

We suggest against the use α-adrenergic receptor blockers as monotherapy for the treatment of patients diagnosed with CP/CPPS (conditional recommendation against based on moderate-quality evidence).

As part of a multimodal treatment approach, we suggest the use of α-adrenergic receptor blockers as monotherapy for an extended treatment course of at least 12 weeks (conditional recommendation based on moderate-quality evidence).

Clinical question 4

In patients with CP/CPPS, is the combination of antibiotics and α-blockers more efficacious than monotherapy with either drug class?

Literature search

A systematic literature search in PubMed and the Cochrane Database from January (1988). to December (2014). was performed. The search strategy included following terms and their combinations: "chronic prostatitis," "chronic pelvic pain syndrome," "combination therapy," "α-adrenergic receptor blockers," "α-adrenergic receptor antagonists," "antibiotic," "antimicrobial agents," and "anti-infective agents."

The evidence

In the meta-analysis by Cohen et al. [8], five clinical trials were identified and the direct comparison of the two drug classes and the combination therapy versus either modality alone was analyzed [5, 18–21] (Table 47.5). No statistically significant difference was observed between α-blockers and antibiotics with regard to clinical outcome as measured by NIH-CPSI total score and subscores. When the combination of the two substances was investigated, no relevant therapeutic benefit was observed over either drug class alone (Table 47.5).

In summary, even the combination of the two modalities failed to improve clinical outcome. Nevertheless, α-blockers are beneficial in patients suffering from lower urinary tract symptoms, whereas antibiotics may be helpful in treatment-naive patients. In a multimodal treatment approach addressing the individual clinical profile of patients with CP/CPPS, the combination of the two options may be considered. Indeed, for selected patients, a stronger therapeutic effect may be achieved by the combination of α-blockers and antibiotics [22, 23].

Table 47.4 RCTs on the impact of α-blockers for the treatment of CP/CPPS [9].

Treatment	Duration	Patients (*n*)	Basic mean NIH-CPSI total score	Mean change	Significance	Jadad total score	Ref.
Ciprofloxacin	6 weeks	49	24.2	–6.2	No ($p>0.05$)	≥3	5
vs. tamsulosin		49	24.6	–4.4			
vs. combination		49	25.3	–4.1			
vs. placebo		49	25.0	–3.4			
Tamsulosin	6 weeks	27	26.4	–9.1	Yes ($p<0.05$)	≥3	15
vs. placebo		30	26.2	–5.5			
Alfuzosin	12 weeks	138	23.8	–7.1	No ($p>0.05$)	≥3	14
vs. placebo		134	25.1	–6.5			
Silodosin 8 mg	12 weeks	45	26.8	–10.2	Yes ($p<0.05$)	≥3	16
vs. silodosin 4 mg		52	26.0	–12.1			
vs. placebo		54	27.9	–8.5			
Doxazosin	24 weeks	30	23.1	–10.6	Yes ($p<0.001$)	<3	17
vs. DIT		30	21.9	–10.2			
vs. placebo		30	22.9	–0.7			
Terazosin	14 weeks	43	25.1	–14.3	Yes ($p=0.01$)	<3	12
vs. placebo		43	27.2	–10.2			
Alfuzosin	24 weeks	17	26.0	–9.9	yes ($p=0.01$)	<3	13
vs. placebo		20	23.0	–3.8			

Table 47.5 Direct comparison and combination therapy of α-blockers and antibiotics [8].

Treatment	NIH-CPSI total score	NIH-CPSI pain	NIH-CPSI voiding	NIH-CPSI quality of life
Antibiotic vs. α-blockers	–1.89 (–7.5 to 3.67)	0.96 (–1.31 to 3.23)	–0.04 (–1.41 to 1.34)	0.22 (–2.4 to 2.84)
Antibiotic vs. antibiotic + α-blockers	1.38 (0.54 to 3.30)	0.74 (–0.85 to 2.33)	0.54 (0 to 1.08)	0.64 (–0.26 to 1.54)
α-Blockers vs. antibiotic + α-blockers	1.78 (–0.85 to 4.41)	0.23 (–2.43 to 2.9)	0.27 (–0.3 to 0.85)	0.51 (–0.52 to 1.54)

Clinical implications

We suggest against the use of either α-blockers or antimicrobials alone for the management of CP/CPPS (conditional recommendation against based on high-quality evidence). We suggest the use of combination therapy as part of a multimodal approach (conditional recommendation based on moderate-quality evidence).

Conclusion

The management of CP/CPPS has always been a formidable task in clinical practice. With its enigmatic pathophysiology, no promising treatment targets have been identified so far. This is mirrored by a plethora of unsuccessful clinical trials evaluating various single therapeutic options. At least modalities such as phytotherapeutics have been shown to provide some relief with regard to pain. Published data do not speak in favor of the current sequential monotherapy. A multifactorial etiology appears to contribute to this highly variable syndrome. New approaches addressing the individual clinical profile with a phenotypic-directed multimodal treatment concept are promising and clinical trials are ongoing to evaluate its therapeutic benefit for clinical practice [9].

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48 CHAPTER 48

Management of erectile dysfunction

Hunter Wessells
Department of Urology, University of Washington School of Medicine, Seattle, WA, USA

Introduction

Erectile dysfunction (ED), defined as the inability to obtain and maintain erection sufficient for sexual activity [1], affects one in five men in the United States, with the prevalence increasing every decade to reach over 60% by the time a man reaches his 70s [2, 3]. As the male population ages and its overall health and fitness worsen, the incidence and prevalence of erectile dysfunction will continue to increase [4]. Combining these trends with men's expectations for quality of life throughout the lifespan, a significant burden will be placed on healthcare systems to diagnose and treat male sexual dysfunctions. Such expectations will increasingly come into conflict with fiscal and regulatory constraints.

Annual medical expenditures for ED in the United States have increased substantially with the introduction of major pharmaceutical costs, which now make up the majority of treatment-related ED costs. For example, worldwide sales of the phosphodiesterase 5 enzyme (PDE5) inhibitors (PDE5-I) were over $3 billion in 2006 (www.wikinvest.com/concept/Erectile_dysfunction_drug_market). It is certain that policy makers and third-party payers will seek evidence-based approaches to determine the feasibility and appropriateness of coverage for the evaluation and treatment of ED. The stakes are not trivial: if all men in the United States sought treatment for ED, the yearly total costs, including pharmaceutical costs, could exceed $10 billion [4].

Pharmacological treatments for ED primarily target the NO-cGMP–PDE5 pathway [5] to initiate or enhance vascular processes that mediate penile erection. Treatment options for ED span the range from psychological counseling to oral, topical, intraurethral, and intracavernosal vasoactive therapy, vacuum constriction devices, and surgery, including vascular procedures and penile implants [6]. The goal of treatment is to preserve or restore satisfactory penile erections with minimal adverse effects. Men have demonstrated a strong preference for oral treatments even if they have lower efficacy [5], suggesting that efforts to optimize treatment of ED should address patient/partner satisfaction and preference in addition to the more standard physiological and clinical measures of improvement. Men with ED want a safe, well-tolerated, convenient treatment requiring little or no invasiveness that is reliably effective in all types of ED. Unfortunately, no single therapy is satisfactory for every patient. The American Urological Association Guidelines Development Panel has not updated their guideline for the treatment of erectile dysfunction since 2005 [6]. However, because the field has not seen major changes in medical or surgical therapies for ED since the introduction of PDE5-I, the general findings of this document remain relevant. Subsequent to publication of our chapter in the previous edition of this book, synthesis of data through meta-analysis and the Cochrane Database have expanded the evidence base for consideration.

Definition and measurement of erectile dysfunction

The diagnosis of ED requires a detailed sexual and medical history, evaluation of psychosocial factors, physical examination with a focus on the genitalia, neurological, and vascular systems, and selected laboratory tests [6]. Comprehensive, validated scales to quantify reproducibly the presence and severity of ED have become useful adjuncts to the case history, but are not sufficient to diagnose ED correctly or treat it safely.

The International Index of Erectile Function (IIEF) [7] is an example of such a symptom-based definition; it has been fundamental to the development of objective primary

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endpoints for randomized clinical trials (RCTs) of pharmaceutical agents, and has replaced the use of physiological measures of erectile function in Phase II and III clinical trials. This 15-item questionnaire addresses several domains of sexual function. Responses to the Erectile Function (EF) domain (range 0–30) allow categorization of ED as severe (<10), moderate (11–16), mild to moderate (17–20), mild (21–25), or no erectile dysfunction (26–30). Trials usually also include Sexual Encounter Profile (SEP) questions and a Global Assessment Question (GAQ) relating to improvement in erection and or intercourse success.

Rosen et al. [8] provided important context for the interpretation of treatment-related changes in the IIEF EF domain. Using aggregated data from 17 trials of tadalafil in 3345 patients, they established that the minimal clinically important difference (MCID) in the EF domain of the IIEF was 4, with significant variation based on severity of baseline ED (mild, 2; moderate, 5; severe, 7). Future trials may consider responder classification based on absolute change in IIEF EF domain (e.g. meeting MCID) or achieving a "normal" EF domain score of >25 [9].

It should be noted that trials of vardenafil and tadalafil in general had higher baseline IIEF-EF domain scores than sildenafil; this is a known effect in studies of subsequent drugs introduced in patient populations already exposed to agents in the same drug class. Finally, results from clinical trials are not uniformly generalizable to clinical practice. Patients in clinical trials will have fewer and less severe comorbid conditions, better control of diabetes, and absence of hypogonadism. Placebo run-ins, common in the PDE5-I trials, also may bias towards better responses.

The ability to measure objectively the response to ED treatments is foundational to the value of this chapter to clinicians and policy makers; although pharmaceutical trials have most successfully used these outcome measures, definitional questions limit the ability to analyze and compare results from intervention and prevention trials focused on radical prostatectomy-associated ED and many studies of penile implants. Finally, the importance of partner perspective is well recognized in the clinical evaluation and treatment of ED; how these parameters are measured in clinical trials, and how the data should be interpreted, are less well defined.

Literature search strategy

Potentially relevant studies were identified by computerized search of MEDLINE (1966 to December 2015), restricted to English-language human randomized controlled studies, meta-analysis or controlled clinical trial article types. In the case of penile implant surgery, we included large case series of currently available devices approved by the US Food and Drug Administration (FDA).

Estimates for efficacy and safety outcomes in patients treated with the various pharmacological and surgical treatments were tabulated. Levels of evidence quality were assessed for each study using the GRADE system [10] and included in the tables. Owing to the widely divergent outcome measures, risks, and safety issues, we did not attempt to compare between broad categories of treatment. Recommendations were developed based on subsequent GRADE publications [11].

Clinical question 1

In a patient presenting for initial treatment of ED, what are the effectiveness and safety of phosphodiesterase type 5 inhibitors?

The evidence

Randomized placebo-controlled trial data strongly and uniformly indicate a significant improvement in erectile function with the use of all available oral PDE5-I (Table 48.1). Overall, the quality of evidence for the three most frequently prescribed agents is high. Fewer studies exist for the most recently approved PDE5-I, avanafil. Many studies of approved agents (e.g. vardenafil, tadalafil, avanafil) do not include treatment-naive patients, which influences outcomes (see the previous discussion). Patients expected to be the most refractory to treatment, such as those with diabetes, multiple sclerosis, radical prostatectomy, and other comorbidities, were found to have significant improvement in erectile function in clinical trials [12–16].

Sildenafil administered on demand at either fixed doses (ranging from 25 to 100 mg) or in flexible dosing leads to statistically significant increases in the IIEF-EF domain of 6.4–11.7 points (all studies $p<0.001$). This difference is of clinical significance. Sildenafil demonstrates excellent drug efficacy in patients over a wide range of ages, with different causes of ED (organic, psychogenic, and mixed causes) and in all severities of ED [17].

Men administered vardenafil exhibit statistically and clinically significant increases in IIEF-EF score (3–8 points) versus placebo. Improvements were dose responsive in patients taking 5–20 mg, and were independent of disease severity [18].

Tadalafil has been extensively studied in a variety of administration schedules. Owing to the long 17.5 h half-life of this medication, efficacy has been demonstrated when taken on demand, three times per week and daily [19–22]. Some men may find alternative dosing schedules attractive. Studies evaluating daily tadalafil use at various doses indicate that doses as low as 2.5 or 5 mg daily improve IIEF-EF scores by 6–8 points over placebo, with higher IIEF-EF scores and more patients reporting improved erections at the 5 mg dose. However, no additional benefit was derived at 10 mg daily doses. At fixed doses ranging from 5 to 25 mg, IIEF-EF scores were 6–10 points higher than with placebo in a dose–response fashion.

Table 48.1 Efficacy and safety of oral phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction.

Study	Trial year	*n*	Study design	Baseline IIEF-EF domain	IIEF-EF domain (treatment vs. placebo)	GEQ (treatment vs. placebo)	Grade
Sildenafil							
Goldstein et al. [49]	1998	861	Multi-center, RCT, flexible dose	12	22.1 vs. 12.2 ($p<0.001$)	74% vs. 19% ($p<0.001$)	High
Montorsi et al. [50]	1999	514	Multi-center, RCT, fixed dose	12.5	~19–25 mg ~21–50 mg ~22.5–100 mg vs. ~12.6 placebo ($p<0.001$)	67–86% (25–100 mg) vs. 24% ($p<0.0001$)	High
Dinsmore et al. [17]	1999	220	Multi-center, RCT, flexible dose	10.3	21.8 vs. 10.1 ($p<0.0001$) healthy controls 25.8	81% vs. 18% ($p<0.0001$)	High
Tan et al. [51]	2000	254	Multi-center, RCT, flexible dose	13.3	25.1 vs. 15.5 ($p<0.0001$)	87% vs. 33% ($p<0.0001$)	Mod
Fink et al. [52]	2002	27 trials (6659 men)	Systematic review and meta-analysis	N/A	N/A	78% vs. 25% ($p<0.0001$)	Low
Vardenafil							
Porst et al. [53]	2001	601	Multi-center, RCT, fixed dose	14.0	20.9–5 mg 22.1–10 mg 22.8–20 mg vs. 15.6 placebo	66–80% (5–20 mg) vs. 30% ($p<0.001$)	High
Hatzichristou et al. [54]	2004	323	Multi-center, RCT, flexible dose	12.8	24.2 vs. 15.6 ($p<0.005$)	86% vs. 36% ($p<0.005$)	High
Markou et al. [55]	2004	10 trials (6809 men)	Systematic review	N/A	Increase 5–7.5 points over placebo	69% vs. 26% ($p<0.00001$)	Low
Potempa et al. [56]	2004	398	Multi-center, open-label, flexible dose. No placebo	13.9	25.9	92%	Low
Tadalafil							
Padma-Nathan et al. [57]	2001	179	Multi-center, RCT, fixed dose	15.0	19.3–2 mg 22.9–5 mg 23.6–10 mg 24.2–25 mg vs. 14.7 placebo	51–81% (2–25 mg) vs. 17% placebo ($p<0.005$)	High
Porst et al. [22]	2006	268	Multi-center, RCT, 5 or 10 mg daily dose vs. placebo	13.4	22.8–5 mg 22.8–10 mg vs. 15.0 placebo ($p<0.001$)	85% vs. 28% ($p<0.001$)	High
Rajfer et al. [21]	2007	287	Multi-center, RCT, 2.5 or 5 mg daily dose vs. placebo	13.4	19.1–2.5 mg 20.8–5 mg vs. 14.6 placebo ($p<0.001$)	63–73% (2.5–5 mg) vs. 26% placebo ($p<0.001$)	High
McMahon et al. [58]	2005	140	Multi-center, RCT, 20 mg fixed dose	15.6	22.8 vs. 12.7 ($p<0.001$)	78% vs. 12.8% ($p<0.001$)	Mod
Carson et al. [59]	2005	195	Multi-center, RCT, 20 mg fixed dose	13.0	19.5 vs. 13.5 ($p<0.001$)	73% vs. 15% ($p<0.001$)	Mod
Carson et al. [60]	2004	11 trials (2102 men)	Systematic review	N/A	21.1–10 mg 23.2–20 mg vs. 15.3 placebo ($p<0.001$)	71–84% (10–20 mg) vs. 33% placebo ($p<0.001$)	Low

(*continued overleaf*)

Table 48.1 (Continued)

Study	Trial year	*n*	Study design	Baseline IIEF-EF domain	IIEF-EF domain (treatment vs. placebo)	GEQ (treatment vs. placebo)	Grade
Yip et al. [61]	2006	242	Multi-center, RCT, 20 mg fixed dose	N/A	Increase 8.5 points vs. 2.1 for placebo	86% vs. 30%	Low
Montorsi et al. [62]	2011	217	Multi-center, RCT, 5 mg daily fixed dose	15.6	Increase 7.3 points vs. 3.4 for placebo	39.5% vs. 21.5%	Low
Avanafil							
Goldstein et al. [23]	2012	646	Multi-center, RCT, 50, 100, 200 mg fixed dose	12.6	Increase 9.4 points (200 mg) vs. 2.9 for placebo	57% (200 mg) vs. 27%	Low
Special populations							
Diabetes							
Rendell et al. [63]	1999	268	Sildenafil, multi-center, RCT, flexible dose	9.7	17.5 vs. 10.4 ($p<0.001$)	74% vs. 12% ($p<0.001$)	High
Goldstein et al. [12]	2003	452	Vardenafil, multi-center, RCT, fixed dose, diabetic men	11.2	17.1–10 mg 19.0–20 mg vs. 12.6 placebo	57–72% (10– 20 mg) vs. 13% ($p<0.0001$)	Mod
Vardi and Nini [13]	2007	8 trials (1759 men), meta-analysis	Any PDE5-I, diabetic men	N/A	Increase 6.6 points (95% CI 5.2–7.9) over placebo	3.8-fold higher in treatment group	Meta-analysis
Multiple sclerosis							
Xiao et al. [15]	2012	2 trials (406 men), meta-analysis	Sildenafil	N/A	N/A	2.72-fold higher in treatment group	Meta-analysis
DeForge et al. [14]	2006	2 trials (205 men)	Sildenafil, systematic review of RCT, spinal cord injury	N/A	N/A	75–76% vs. 4–7% ($p<0.001$)	Low
Radical prostatectomy							
Montorsi et al. [64]	2004	303	Tadalafil, multi-center, RCT, 20 mg fixed dose, men 12–48 months after BNSRP	13.0	17.1 vs. 12.5 ($p<0.001$)	62% vs. 23% ($p<0.001$)	High
Wang et al. [16]	2014	8 trials	PDE5-I, multi-center, RCT, men after BNSRP		Mean difference 5.63 PDE5-I vs. placebo	N/A	Meta-analysis

BNSRP, bilateral nerve-sparing radical prostatectomy; CI, confidence interval; GEQ, global efficacy question.

Avanafil has a rapid T_{max} (20–30 min) and short half-life, making its use on demand within 15 min efficacious. In RCTs it has shown improvements in IIEF EF domain of 9 points versus 2.9 points for placebo [23].

Regardless of the oral PDE5-I studied, the majority of patients in flexible-dose trials concluded the trial at the highest allowed dosage. There was strong evidence across studies of improved response at higher doses, although side effects also increased with increased dosages. With improvement in erectile function, men tend to note improvements in self-esteem, confidence, and relationship satisfaction, which correlate with improvement in IIEF-EF scores [24]. In another study [25], patients on PDE5-I reported improved sexual self-confidence and spontaneity in addition to expected and previously document improvements in GAQ and SEP responses, IIEF-EF, orgasmic function, sexual desire, and overall satisfaction domains.

Mechanism of action

Sildenafil, vardenafil, tadalafil, and avanafil are competitive inhibitors of the PDE5 enzyme. Although of varying molecular structure, each acts via inhibition of PDE5 to block cGMP hydrolysis in corporal tissues. This results in sustained increased levels of cGMP, consequent amplification of neural and endothelium-dependent NO release, and smooth muscle relaxation, resulting in enhanced erectile responses.

There have been no rigorous RCTs designed to evaluate the comparative efficacy of the available PDE5-I. A meta-analysis attempted to pool RCT data from fixed-dose studies involving sildenafil, vardenafil, and tadalafil [26]. It concluded that at maximum doses, all three drugs improve IIEF-EF scores by 7–10 points compared with placebo treatment. Scores from the pooled studies indicated that sildenafil might be slightly more efficacious than vardenafil, but the differences between drugs were slight. Other randomized cross-over studies have demonstrated similar improvements in IIEF-EF score, similar sexual attempts during treatment, and similar safety profiles, but a 52–73% patient preference for tadalafil over sildenafil or vardenafil [27, 28]. Patient preference appears to be primarily due to differences in dosing schedule and reduced performance pressure. These data were of moderate- and low-quality evidence owing to methodological and study design issues, with one study comparing the highest recommended dose of tadalafil with an intermediate dose of sildenafil. A recently published trade-off network meta-analysis included 47 626 patients in 82 trials with efficacy data and 20 325 patients in 72 trials with adverse event data [29]. The authors concluded that for men who prioritize high efficacy, sildenafil 50 mg appears to be the treatment of choice. For men wishing to optimize tolerability, tadalafil should be considered.

Safety

Overall, oral PDE5-I are well tolerated, with few patients in any of the studies terminating treatment due to adverse effects [6]. The side effects of these medications tend to be dose related. In general, men may report headaches (8–14%), flushing (4–6%), dyspepsia (5–18%), rhinitis (5%), and visual effects and blue vision (3%). Sudden hearing loss is rare, as is nonarteritic anterior ischemic optic neuropathy, which may occur in patients with underlying risk factors

The Princeton III Consensus recommendations [30] describe relative and absolute cardiovascular contraindications to sexual activity and thus use of ED medications. Absolute contraindications to all PDE5-I include unstable angina, active heart failure, and concurrent nitrate use. Caution should also be exercised in patients taking alpha-adrenergic antagonists or CYP3A4 inhibitor drugs (phenytoin, ketoconazole, rifampin, HIV protease inhibitors, erythromycin, grapefruit juice), those with excessive alcohol intake, and those with low baseline blood pressure, active coronary ischemia not on nitrates, and congestive heart failure.

Clinical implications

In men with ED, we recommend PDE5-I as first-line therapy (strong recommendation based on moderate-quality evidence). The overall class effect is consistent and well characterized, justifying the strength of the recommendation. However, evidence varies as to the efficacy and safety of the various specific PDE5-I agents, and reasons for patient preference are poorly studied overall.

In men with diabetes, spinal cord injury, or multiple sclerosis, and after nerve-sparing radical prostatectomy, we also recommend PDE5-I (strong recommendation based low-quality evidence). The quality of evidence and the probability of selection bias in the recruitment of subjects, leading to lesser generalizability, temper the confidence we have in the underlying evidence.

Clinical question 2

Should men with ED who fail a trial of one PDE5-I be offered a trial of another PDE5-I?

The evidence

Success at the first attempt is an important aspect of ED therapy, since this has a great effect on the patient's sexual confidence and long-term compliance with the selected ED treatment [31]. First-time response is a marker of continued response, and PDE5-I medications tend to remain effective for men even after years of use. With repeat challenges and counseling, a percentage of initial nonresponders may be salvaged; treatment should be continued at increased doses in up to three separate attempts before conceding failure of a medication [32, 33].

Table 48.2 Efficacy and safety of alprostadil for the treatment of erectile dysfunction.

Study	Trial year	*n*	Study design	Control group	GEQ (vs. placebo) (%)	Pain (%)	Grade
Intracavernosal							
Godschalk et al. [36]	1994	15	RCT[a]	Placebo	66	10	Moderate
Linet et al. [37]	1996	296	Prospective	Placebo			Moderate
		683	Prospective	None[b]	94	11	High
Intraurethral							
Padma-Nathan et al. [39]	1997	996	RCT[c]	Placebo	65 vs. 19	10	Moderate
Williams et al. [40]	1998	159	RCT[d]	Placebo	69 vs. 11	17	Moderate
Urciuoli et al. [38]	2004	528	2 studies	Placebo	Odds of at least 1 success 7.22 (95%CI 5.68–9.18)	29	Meta-analysis

[a] In-office administration only.
[b] No placebo arm to at-home study.
[c] RCT was of in-clinic responders. Response rate in clinic was 66% of 1511 patients.
[d] RCT was of in-clinic responders. Response rate in clinic was 64% of 259 patients.

Nevertheless, adherence is relatively poor and reasons for this include lack of efficacy and constraints due to time window of use with various agents [34]. Evidence from single-institution cohort studies suggests that inappropriate medication use causes a significant amount of treatment failure, and that instruction and dose optimization can salvage between 30 and 50% of nonresponders to a PDE5-I [35].

Clinical implications

In men with ED who fail a trial of one PDE5-I with at least three attempts and optimal dosing of their PDE5I of choice, we recommend a trial of a second PDE5 inhibitor (conditional recommendation based on low-quality evidence).

Clinical question 3

In men who fail a PDE5-I trial, what are the effectiveness and safety of alprostadil (prostaglandin E1) in the treatment of ED?

The evidence

With the approval of alprostadil (prostaglandin E1 [PGE1]; EDEX™ or Caverject™) by the FDA in 1996, patients were given an easily accessible and standardized treatment for ED. Before this, off-label intracavernosal injection (ICI) of drugs such as papaverine (a nonspecific PDE inhibitor) and phentolamine (an alpha-adrenergic antagonist) was used. After in-clinic studies showed the efficacy of PGE1 intracavernosal compared with placebo controls [36], subsequent at-home testing in "responders" demonstrated success rates (e.g. as evaluated by the global efficacy question [GEQ]) above 90% [37]. The lack of at-home placebo controls, and selection of responders for home-use studies, lowered the quality of evidence as reflected in the GRADE ratings.

A Cochrane review [38] of PGE1 for the treatment of ED focused primarily on intraurethral PGE1 due to the single RCT for intracavernosal injection. The authors concluded that regardless of etiology, PGE1 improves ED with adverse effects commensurate with dosage. The inconvenience of ICI and the relatively high percentage of patients reporting pain with alprostadil (Table 48.2) led to the development of an intraurethral delivery system for alprostadil, MUSE™ [39]. Its easier application via the urethra made placebo-controlled in-office and home trials more feasible. For example, the main Phase III study of intraurethral alprostadil [39] consisted of an in-clinic component and a home-use component. Approximately two-thirds of men responded to intraurethral alprostadil when challenged in the clinic and, of these approximately 60–70% achieved erections sufficient for sexual activity in the home setting [39, 40]. Only in-clinic responders were included in an at-home RCT, thus biasing the study towards better outcomes. These selection biases may explain the lesser response to MUSE in clinical situations and comparison trials, and thus the conditional recommendation for its use. For example, in two studies in which subjects were randomized to ICI or MUSE, the overall intercourse success rate for MUSE was 53% [41, 42].

Vasoactive compounds directly initiate penile erection via intracavernosal sites of action. Alprostadil causes cavernosal smooth muscle relaxation via cAMP-mediated mechanisms. Evidence from RCTs and large prospective studies supports the proerectile effect, dose–response relationship, and at-home efficacy of intracavernosal and intraurethral PGE1 (see Table 48.2).

Priapism is a rare but serious complication of all proerectile pharmacological agents. The rates of priapism in the pivotal Phase III trials for intracavernosal and intraurethral alprostadil were 1 and 0%, respectively. Hypotension may occur with either delivery method but is very rare. Nevertheless, American Urological Association (AUA) guidelines recommend that the first dose of PGE1, whether intracavernosal or intraurethral, should be administered in a clinical setting [6]. Pain from the medication, as distinct from the route of injection, occurs via an unclear mechanism that may involve nerve sensitization. The incidence and severity of pain vary

Table 48.3 Oral PDE5 inhibitor prevention trials for post-radical prostatectomy-associated erectile dysfunction.

Trial	Year	Agent	*n*	Study design	Pre BNSRP IIEF-EF domain	Change in IIEF-EF domain	End-of-study GEQ (treatment vs. placebo) (%)	Grade
Montorsi et al. [45]	2008	Vardenafil nightly or on demand vs. placebo	628	RCT	N/A	No difference	62.60 59.8 57.1	High
Padma-Nathan et al. [47]	2008	Sildenafil vs. placebo	76	RCT			27 vs. 4	Moderate
Bannowsky et al. [46]	2008	Sildenafil (nightly) vs. none	43	Cohort	21.0[a]	4.8[a]	47 vs. 28	Very low
Montorsi et al. [48]	2014	Tadalafil daily vs. on demand vs. placebo	423	RCT	>22	6.2 (5 mg daily) vs. 5.8 (20 mg) vs. 6.0	N/A	High

GEQ, global efficacy question.
[a]IIEF-5 – an abbreviated five-item version of the IIEF (range 0–25).

but, as shown in Table 48.2, are higher for ICI than intraurethral alprostadil. The risk of penile nodules and fibrosis is 2% with ICI.

Clinical implications

In patients who have failed first-line therapy for ED, we recommend intracavernosal alprostadil for ED regardless of the underlying etiology (strong recommendation based on low-quality evidence).

In patients who have failed first-line therapy for erectile dysfunction, we suggest intraurethral alprostadil (conditional recommendation based on low-quality evidence). This recommendation is based on the assessment that intraurethral delivery is both less invasive but also less efficacious that intracavernosal injection.

Clinical question 4

Should a potent man be offered on-demand or daily PDE5-I to improve recovery of erectile function after bilateral nerve-sparing radical prostatectomy?

The evidence

ED associated with radical prostatectomy (RP) is prevalent, severe, and difficult to treat. Even nerve-sparing techniques fail to preserve normal sexual functioning in a substantial majority of previously potent men [43]. Therefore, strategies aimed at preventing ED are an important area in urological and sexual medicine research.

Although the pathophysiology of erectile impairment after prostatectomy remains incompletely understood, neural injury, smooth muscle apoptosis, and cavernosal fibrosis are the major proposed mechanisms. Montorsi et al. [44] first reported the use of thrice-weekly ICI alprostadil after nerve-sparing RP using an RCT design. The small sample size, lack of objective endpoints, and lack of baseline pre-RP erectile function measures reduced the GRADE rating of the study, but it remains a seminal publication with far-reaching impact. Small studies of vacuum erection devices and intraurethral alprostadil were similarly flawed and have not been validated. A small number of trials provide evidence regarding the role of oral PDE5 inhibitors for post prostatectomy penile rehabilitation and are listed in Table 48.3.

The use of PDE5-I in penile rehabilitation after RP remains controversial. One large, multi-center RCT compared on-demand and nightly vardenafil with placebo in a 9-month study [45]. No differences in end-of-study erectile function were noted after a 2-month single-blind washout period. Smaller, controlled clinical studies suggested an effect of nightly sildenafil but involved single-surgeon series [46] or unexpectedly low potency rates in controls [47]. The REACTT study [48] randomized patients to daily tadalafil 5 mg, on demand tadalafil 20 mg, or placebo for 9 months. Early initiation of tadalafil had no effect on unassisted erectile function at the end of the study. As in other studies, erectile function recovery rates were lower than expected. Overall, the data are discouraging. The large number of men at risk, and the high cost associated with nightly drug administration, make strong recommendations imperative. The relatively small number of studies, and the potential for bias from inadequate length of the study period, reduce the strength of the recommendation.

Clinical implications

We suggest the use of oral PDE5-I to prevent or mitigate the development of ED after bilateral nerve-sparing radical prostatectomy (conditional recommendation based on very low-quality evidence).

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CHAPTER 49

49 Update on treatment of bladder pain syndrome: does anything work?

Yahir Santiago-Lastra[1], Ann Oldendorf[1], and J. Quentin Clemens[2]

[1] *University of Michigan Medical Center, Ann Arbor, MI, USA*

[2] *Division of Neurourology and Pelvic Reconstructive Surgery, University of Michigan Medical Center, Ann Arbor, MI, USA*

Introduction

For many clinicians, the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) has become a lesson in the treatment of chronic pain. The American Urological Association defines IC/BPS as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of infection or other identifiable causes" [1]. Specifically, it is a diagnosis of exclusion and there is no perfect test to establish its diagnosis. Both patients and clinicians can become frustrated because of the lack of effective treatment options. There are multiple theories regarding the pathogenesis of the condition, resulting in considerable variability of the treatments offered. Often, these treatments are combined in the hope of improving effectiveness.

Our objective in this chapter is to focus on frequently prescribed behavioral, oral, and intravesical therapies, in order to update the reader on the most recent levels of evidence and recommendations for treatment.

Methods

A MEDLINE and EMBASE literature search was performed for the period 1980–2015 to identify all randomized controlled trials (RCTs), systematic reviews, and meta-analyses related to the use of: pentosan polysulfate sodium (PPS), amitriptyline, intravesical instillations, and physical therapy for the treatment of IC/BPS. An individual literature search was performed for all four treatment variables. These were identified by using a keyword search for "interstitial cystitis," "pentosan polysulfate," "amitriptyline," "physical therapy," and "intravesical therapy" using exploded terminology. The search was limited to English-language publications. All abstracts identified through this process were reviewed t manually o identify publications that addressed the efficacy of the various treatment methods.

Clinical question 1

In patients with IC/BPS, is pentosan polysulfate, compared with placebo, effective at reducing IC/BPS symptoms?

The evidence

We identified two meta-analyses, five systematic reviews and seven RCTs that addressed the efficacy of PPS in the treatment of IC/BPS [2–14]. Five RCTs tested the efficacy of PPS versus placebo [2, 3, 5, 10, 11, 15]. Efficacy was defined by improvements in one or more of the following parameters: symptom scores as quantified via validated questionnaires (Interstitial Cystitis Symptom Index [ICSI], Patient's Overall Rating of Improvement of Symptoms [PORIS]), visual analog scale (VAS), cystometric capacity, and cystoscopic appearance of the bladder after treatment. All studies recruited a largely female population, with the percentage of female patients ranging from 89 to 100%. Most trials administered a dose of 300 mg, in divided doses of 100 mg, administered three times per day. Nickel et al. compared the dose–response effect of PPS, and their results did not demonstrate any difference in efficacy, as measured by improvement in the VAS scale, among the different doses [14]. The treatment duration of the trials ranged from 12 to 32 weeks. The reported overall response rate to treatment varied between 15 and 67% of treated patients in individual trials, compared with 13–49% of placebo, which reveals substantial overlap between the proportions of patients who are expected to derive benefit from the treatment. Dimitrakov et al. performed a systematic review of the literature and performed a pooled analysis of the RCTs using a standardized

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Table 49.1 Symptom response to pentosan polysulfate therapy.

Outcome	Standardized mean difference (95% CI)[a]
Effect on patient-reported pain	
Mulholland et al. [11]	–0.15 (–0.53 to 0.22)
Parsons and Mulholland [15]	**–0.74 (–1.34 to –0.14)**
Sairanen et al. [6]	–0.48 (–1.01 to 0.04)
Sant et al. [10]	–0.11 (–0.62 to 0.40)
Effect on patient-reported urinary frequency	
Parsons and Mulholland [15]	**–0.62 (–1.14 to –0.10)**
Sant et al. [10]	0.06 (–0.45 to 0.56)
Effect on Interstitial Cystitis Symptom Index score	
Sairanen et al. [6]	**–0.89 (–1.49 to –0.28)**
Sant et al. [10]	–0.26 (–0.77 to 0.25)
Relative risk of overall improvement	
Holm-Bentzen et al. [2]	1.25 (0.76 to 2.04)
Mulholland et al. [11]	1.84 (0.81 to 4.17)
Parsons and Mulholland [15]	**2.67 (1.20 to 5.91)**
Parsons et al. [3]	**2.15 (1.21 to 3.82)**
Sant et al. [10]	1.91 (1.00 to 3.64)
Overall	**1.78 (1.34 to 2.35)**

[a] Values in bold type have 95% CIs that do not cross 1.
Source: Adapted from Dimitrakov et al. 2007 [12].

mean difference (SMD), which suggested benefit of active treatment compared with placebo, with a relative risk of 1.78 for patient-reported "global improvement" in symptoms (95% confidence interval [CI] 1.34–2.35). The subjective symptom response to PPS therapy in the RCTs, measured via questionnaire data, is summarized in Table 49.1 [12].

Giannantoni et al. also conducted a systematic review of the literature through 2010 to assess original research articles published on the management of IC/PBS [13]. Included in their analysis were five RCTs that reported on the efficacy of oral PPS. Only two of the five trials were graded as high-quality RCTs based on a Jadad score ≥3 [3, 10]. The data from the clinical trials were abstracted as an SMD, with the aim of producing measures of effect for each treatment trial on a similar metric. Improvements in individual domains of pain, frequency, urgency, and ICSI scores were reported. Many of these improvements were of a small effect size. Hwang et al. completed another meta-analysis of the five trials that studied PPS versus placebo, and they reported a relative risk ratio of 1.69 (95% CI 1.16–2.46) of improvement in pain symptoms with PPS versus placebo, as measured by VAS [1, 4].

In summary, PPS is the only oral medication for IC/BPS approved by the US Food and Drug Administration, and it is the most studied oral therapy for the condition. Although individual trials were well designed and implemented, the variability in the results and the weak clinical improvements in subjective scores do not support a stronger recommendation. There are limited data to suggest that PPS, in combination with other therapies, provides improved benefit. Longer-term data are needed to assess what subsets of patients derive the most benefit and what treatment duration is optimal. Meanwhile, the current literature does not suggest any benefit in offering continued therapy with PPS to patients who do not respond to the initial 12–24-week trial of the medication.

Clinical implications

We suggest that IC/BPS patients be treated with PPS to improve their pain (conditional recommendation based on low-quality evidence).

Clinical question 2

In patients with IC/BPS, does intravesical instillation therapy, compared with placebo, reduce bladder symptoms?

The evidence

We identified 13 RCTs with a total of 797 subjects. Seven different intravesical preparations (lidocaine, heparin, bacillus Calmette–Guérin [BCG], oxybutynin, PPS, resiniferatoxin, and dimethyl sulfoxide [DMSO]) were evaluated with a clinical trial versus placebo [5, 10, 16–18]. In addition, several of these intravesical agents (lidocaine, PPS, heparin, BCG and DMSO) were compared with another intravesical agent in a cross-over design, with no placebo group. A 2012 systematic review standardized the outcome measures for 12 of these trials using the SMD for ICSI scores, pain, urgency, and frequency in order to determine effect size of the different intravesical treatments across the different outcome measures [1, 13]. These outcomes were obtained by extracting the individual domains from the ICSI and Interstitial Cystitis Problem Index (ICPI) questionnaire results reported by the individual RCTs. No treatment showed benefit over placebo across all four outcomes measured. An earlier systematic review by Dawson and Jamison reported that outcome measures for RCTs testing the efficacy of intravesical instillations were variable [19]. The quality of the RCTs was limited by small sample sizes, lack of blinding in many smaller trials, and poor study design. Retention times of the intravesical agent were not confirmed for most of the trials. The reporting of adverse events varied widely among the different trials. This is likely due, in part, to the use of different intravesical agents but also to varying investigator thresholds for reporting adverse events. For many trials, the rate of adverse events was not reported at all, except as 'rarely seen' [20]. Adverse events mentioned in other trials included pain with instillation, hematuria, arthralgias, chemical cystitis, and foul urine odor [19].

Intravesical lidocaine

Nickel et al., in a multi-center RCT on 102 patients, reported clinically significant improvement in pain scores measured by VAS in 30% of those treated with intravesical lidocaine

plus bicarbonate, compared with 10% in the placebo group at 3 days post-treatment [21]. Re-evaluation at 10 days did not demonstrate a statistically significant difference in treatment benefit, suggesting a short-lived effect of treatment. An open-label phase of the trial followed, with 54% of patients experiencing improvement at 3 days and 48% at 10 days after treatment [22]. The optimal dosing of intravesical lidocaine has not been reported in the literature, as no trials have compared different preparations. There are no randomized trials comparing lidocaine cocktails (heparin, PPS, or bicarbonate) with lidocaine alone. One open-label study demonstrated clinical benefit, as measured by improvement on VAS scores, and also a reduction in ICSI score, in the lidocaine plus PPS group compared with lidocaine alone [7].

Intravesical DMSO

Two randomized cross-over trials reported on the efficacy of DMSO for IC/BPS patients [17, 23]. One of the trials compared DMSO with placebo with a 93% subjective rate of improvement, and the other compared DMSO with BCG therapy, with a 47% subjective rate of improvement compared with 0% for BCG. The methods for instillation of DMSO varied between the two trials. Adverse events associated with DMSO were reported as minor, including a foul urine odor, discomfort on intravesical administration, and a transient chemical cystitis lasting up to 72 h [17].

Intravesical heparin

There is one randomized double-blind placebo-controlled cross-over study that reported that 50% of patients experienced reduction in pain symptoms at 12 h after a single heparin instillation, compared with 13% of patients in the placebo arm reporting a reduction in pain symptoms, which was statistically significant ($p < 0.0032$). Adverse events associated with heparin instillation were minor, and included pain with instillation and low-grade hematuria that resolved within 24 h of initial treatment [20].

BCG and RTX

Although early pilot studies of BCG demonstrated a favorable response rate compared with placebo, subsequent higher-powered RCTs failed to generate statistically significant results [16, 17, 24]. Resiniferatoxin (RTX) held early promise as an intravesical treatment in observational studies, but three large RCTs did not demonstrate a statistically significant benefit of RTX over placebo [25–27]. In addition, the trials of RTX demonstrated a high rate of adverse events, most commonly dysuria and suprapubic pain during instillation [1, 25–28].

In summary, the available data suggest that intravesical lidocaine can provide significant but short-term benefit in the treatment of IC/BPS. Intravesical DMSO and heparin demonstrated a modest benefit in a small number of RCTs, but the lack of substantial, high-quality RCT data makes it difficult to determine the risk/benefit ratio. In the case of BCG and RTX, the absence of clear benefit, combined with the undesirable adverse effects of the two therapies, warrants a recommendation against their use. Table 49.2 summarizes the different RCTs that evaluated intravesical instillation treatments and their available SMDs for the following outcomes: ICSI score, urgency, frequency, and pain domains [13].

Clinical implications

We suggest that that patients with ICS/PBS be treated with intravesical lidocaine. (conditional recommendation based on moderate-quality evidence).

We further suggest that that patients with ICS/PBS be treated with intravesical DMSO (conditional recommendation based on low-quality evidence) or intravesical heparin (conditional recommendation based on very low-quality evidence).

We recommend against the use of BCG (strong recommendation against based on moderate-quality evidence) or RTX (strong recommendation against based on moderate-quality evidence).

Clinical question 3

In patients with IC/BPS, is amitriptyline effective, compared with placebo, at reducing IC/BPS symptoms?

The evidence

Two RCTs reported the efficacy of oral amitriptyline to be superior to that of placebo. van Ophoven et al. reported on 50 patients in a parallel design trial of oral amitriptyline, with increasing doses once daily from 25 to 100 mg titrated over several weeks for a 4-month period. The treatment group demonstrated a 63% improvement in ICSI score and global pain scale compared with 4% of the placebo group. Medication side effects were common (79% of patients in treatment group reported dry mouth as a side effect) and were a major reason for participant withdrawal from the study (17% study withdrawal rate in the treatment group). Other side effects reported (nausea, sedation, drowsiness) were considered to have the potential to impact quality of life [29].

Foster et al. reported on a parallel-design RCT of 231 patients treated with amitriptyline plus behavioral modifications versus placebo plus behavioral modifications. The dose of amitriptyline was titrated from 10 to 75 mg over 12 weeks. Patients who were able to titrate up to at least 50 mg had a significantly greater improvement than the placebo group (66% success rate in the treatment arm). Adverse events were also common in this study (fatigue, dry mouth, and dizziness) [1, 30].

Table 49.2 Response to intravesical instillation therapy in randomized controlled clinical trials [13].

Trial	Agent	Comparator	No. of patients	Design	Standardized mean difference (SMD) (95% CI)				Adverse events (if reported)
					ICSI	Pain	Urgency	Frequency	
Peters et al. [24]	BCG	Placebo	33	Parallel	N/A	–0.63 (–1.36 to 0.11)	Not extractable (–)	–0.4 (–1.17 to 0.28)	Dysuria (placebo and treatment groups)
Peeker et al. [17]	BCG	DMSO	21	Cross-over	N/A	–0.13 (–0.74 to 0.48)	Not extractable (–)	–0.45 (–1.1 to 0.17)	Dysuria and increased lower urinary tract symptoms in 52.3% of patients in BCG group vs. 5 in DMSO group
Mayer et al. [16]	BCG	Placebo	265	Parallel	–0.18 (–0.42 to 0.07)	0.22 (–0.02 to 0.46)	–0.28 (–0.52 to –0.04)	–0.13 (–0.38 to 0.11)	Gastrointestinal disturbances in 49% of patients in treatment group
Propert et al. [18]	BCG	Placebo	44	Parallel	–0.51 (–1.2 to 0.2)	–0.44 (–1.13 to 0.26)	–0.45 (–1.14 to –0.25)	–0.48 (–1.17 to 0.22)	Not reported
Nickel et al. [21]	Lidocaine + bicarbonate	Placebo	102	Parallel	–0.42 (–0.83 to 0)	–0.40 (–0.81 to 0.01)	–0.51 (–0.92 to –0.1)	0.07 (0 to 0.48)	Bladder pain during instillation in 2% of treatment group
Barbalias et al. [34]	Oxybutynin	Placebo	36	parallel	Not extractable (+)	N/A	N/A	–1.59 (–2.4 to –0.80)	Not reported
Bade et al. [20]	Heparin	Placebo	20	Parallel	N/A	N/A	Not extractable (–)	–0.30 (–1.19 to 0.58)	No adverse events encountered
Davis et al. [7]	PPS	Placebo	41	Parallel	Not extractable	Not extractable (+)	Not extractable (+)	Not extractable	Headache, hair loss in 3 patients in treatment group
Lazzeri et al. [25]	Resiniferatoxin (RTX)	Placebo	18	Parallel	N/A	–4.01 (–5.67 to –2.34)	Not extractable (+)	–1.57 (–2.64 to –0.50)	Suprapubic burning sensation in one patient in treatment group
Chen et al. [26]	RTX	0.10 μM RTX vs. 0.05 μM RTX vs. placebo	22	Parallel	0.05 μM RTX: –0.27 (–1.44 to 0.89); 0.10 μM RTX: –0.69 (–1.93 to 0.55)	0.05 μM RTX: 0.05 (–1.15 to 1.25); 0.10 μM RTX: –0.32 (–1.48 to 0.85)	0.05 μM RTX: –0.26 (–1.43 to 0.90); 0.10 μM RTX: –0.84 (–2.10 to 0.41)	0.05 μM RTX: –0.19 (–1.35 to 0.97); 0.10 μM RTX: –0.68 (–1.92 to 0.56)	Pain during instillation (80, 87.5, and 25% in 0.10 μM RTX, 0.05 μM RTX, and placebo, respectively
Payne et al. [27]	RTX	0.10 μM RTX vs. 0.05 μM RTX vs. 0.01 μM RTX vs. placebo	163	Parallel	Not extractable (–)	0.01 μM RTX: 0.02 (–0.98 to 0.33); 0.05 μM RTX: –0.26 (–0.91 to 0.39); 0.10 μM RTX: –0.52 (–1.18 to 0.39)	0.01 μM RTX: –0.20 (–0.85 to –0.45); 0.05 μM RTX: –0.05 (–0.70 to 0.60); 0.10 μM RTX: 0.12 (–0.53 to 0.77)	0.01 μM RTX: 0.00 (–0.42 to 0.42); 0.05 μM RTX: 0.06 (–0.37 to 0.48); 0.10 μM RTX: 0.19 (–0.25 to 0.64)	Dose-dependent increase in pain during instillation

(–) reported as not effective but data not extractable; (+) reported as effective but data not extractable.

In summary, amitriptyline has a clinically significant benefit over placebo in the treatment of IC/BPS, and current evidence suggests that the benefit is dose dependent. The high risk of experiencing adverse events encountered in the RCTs makes its risk/benefit profile equal.

Clinical implication

We suggest the use of amitriptyline in patients with IC/BPS using the lowest effective dose (conditional recommendation based on moderate-quality evidence).

Clinical question 4

In patients with IC/BPS, is pelvic floor physical therapy effective, compared with controls, at reducing IC/BPS symptoms?

The evidence

Many patients with IC/BPS also present with considerable soft tissue tenderness, myofascial pain, and banding of the pelvic floor musculature. Most data on the benefits of directed pelvic floor or myofascial physical therapy are observational. Two randomized multi-center clinical trials were identified that determined the efficacy and safety of pelvic floor myofascial physical therapy. FitzGerald et al. compared myofascial physical therapy versus global therapeutic massage in 81 women. They reported a statistically significant global response of 26% in the therapeutic massage group and a 59% response rate in the myofascial physical therapy group. Pain, urgency, frequency, and ICSI scores were decreased in both groups but were not statistically different between the two groups. No serious adverse events were reported [28, 31–33].

In summary, the evidence for pelvic floor myofascial physical therapy for the treatment of IC/BPS is scarce. To date, only two high-quality RCTs have tested its efficacy in the treatment of IC/BPS. They are categorized as high-quality studies given their intention-to-treat analysis, low rate of patient exclusion, high rate of patient adherence to the therapy, and high rate of availability of questionnaire data from patients who completed the RCT. Both studies demonstrated a significant clinical benefit and a very low adverse event profile, with desirable effects clearly outweighing undesirable effects.

Clinical implications

We recommend the use of pelvic floor myofascial physical therapy in patients with IC/BPS (strong recommendation based on high-quality evidence).

Conclusion

Further characterization of IC/BPS into clinically relevant subpopulations, and also further investigation into the pathophysiology of disease, may help target treatment strategies and document better clinical outcomes. In addition, adherence to standardized methods of reporting outcomes, by way of collaborative networks, will help create a standardized metric by which all treatment modalities can be compared.

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50 CHAPTER 50
Male infertility

Bryan Hinck[1], Ashok Agarwal[2], Fnu Deepinder[3], and Edmund S. Sabanegh, Jr.[4]

[1] *Department of Urology, Glickman Urological and Kidney Institute, The Cleveland Clinic, Cleveland, OH, USA*
[2] *Andrology Center, The Cleveland Clinic, Cleveland, OH, USA*
[3] *Department of Endocrinology, Cedars Sinai Medical Center, Los Angeles, CA, USA*
[4] *Department of Urology, Cleveland Clinic Lerner College of Medicine, The Cleveland Clinic, Cleveland, OH, USA*

Background

Male infertility is a broad and complex topic, and this chapter addresses several pertinent questions in the field: (1) what is the effect of varicocelectomy on semen parameters and pregnancy rate?; (2) what is the role for clomiphene citrate in the treatment of male infertility?; (3) what is the difference between modified two-layer and formal two-layer anastomosis in vasovasostomy?; and (4) what is the difference in outcomes for microsurgical vasovasostomy and robotic-assisted vasovasostomy?

Varicocele is present in approximately 40% of men presenting with infertility [1]. Although varicocele repair is widely used in the management of male-factor infertility, the effectiveness of varicocelectomy has been intensely debated, and there is still no consensus on the topic. The exact mechanism by which varicocelectomy improves fertility in affected men remains unknown. Oxidative stress and DNA damage to sperm, which are well-documented components of varicocele pathophysiology, have shown improvement after varicocele repair. Several studies have suggested that varicocele repair decreases the levels of oxidative stress as a mechanism for improving fertility [2–4].

The existing literature is conflicting, and very few sufficiently large and adequately controlled prospective trials evaluating the efficacy of varicocelectomy in improving pregnancy outcomes are available. Two published meta-analyses evaluating prospective randomized trials came to the same conclusion that varicocele repairs do not improve subfertility [5, 6]. A 2008 Cochrane Review recommended against varicocele repair for unexplained infertility [7]. However, these meta-analyses have been criticized for methodological flaws that may have biased their results [8]. Consequently, they have not resolved the issues surrounding varicocelectomy and subfertility.

The development of assisted reproductive techniques (ART) has led to increased use of intracytoplasmic sperm injection (ICSI) for all causes of male infertility, including varicoceles. However, these techniques have safety issues, deprive patients of the satisfaction of natural conception, and are less cost-effective [9].

The 2001 guidelines from the Best Practice Policy Committee of the American Urological Association (AUA) and the American Society for Reproductive Medicine (ASRM) recommended varicocele repair for infertile men with a clinically palpable varicocele and at least one or more abnormal semen parameters with the female partner having either normal or potentially treatable fertility [10]. The most recent update from the European Urological Association (EUA) guidelines in 2014 indicated that varicocele repair should be considered in cases of clinical varicocele, oligospermia, infertility duration of more than 2 years, and otherwise unexplained infertility in a couple [11]. This represents a meaningful change, considering that the guidelines prior to 2012 indicated that varicocele treatment for infertility should not be undertaken unless a full discussion of the uncertainties of treatment benefit is completed [12].

Selective estrogen receptor modulators (SERMs), also known as antiestrogens, are used as empirical nonspecific therapy in the management of idiopathic male infertility. The two most commonly used nonsteroidal antiestrogens are clomiphene citrate and tamoxifen. Clomiphene is a synthetic compound similar in structure to diethylstilbestrol. Clomiphene indirectly stimulates the secretion of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) by binding to estrogen receptors in the hypothalamus and pituitary, thereby blocking estrogen feedback inhibition. The resultant increase in intratesticular testosterone concentration

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is believed to boost the gametogenic function of the testis. Men treated with clomiphene consistently demonstrate elevation of serum FSH, LH, and testosterone levels. However, it is essential to maintain serum testosterone within normal limits because higher levels may negatively influence spermatogenesis [13, 14]. Application of clomiphene citrate in males with nonobstructive azoospermia may result in sufficient sperm for ICSI, either identified in the ejaculate or by successful surgical testicular sperm extraction [15]. Clomiphene citrate is usually prescribed in doses of 12.5–50 mg per day either continuously or on a 25-day cycle with a 5-day rest period each month [13, 14].

Although numerous investigators have studied the effect of clomiphene on male infertility, controversy still exists with regard to its efficacy. Many well-designed prospective randomized controlled trials (RCTs) failed to demonstrate any significant improvement with clomiphene compared with placebo [16–22]. However, a few studies have shown a positive effect of clomiphene on pregnancy outcomes, including a study that combined clomiphene with vitamin E [23–25]. The Cochrane Review that was updated more than a decade ago found no significant benefit with clomiphene in increasing the fertility rates of men with idiopathic oligospermia [26]. In another meta-analysis, Kamischke and Nieschlag demonstrated no significant therapeutic effect of antiestrogen therapy with clomiphene and tamoxifen on pregnancy outcomes [27].

Approximately 500 000 vasectomies are performed annually in the United States and, of these, nearly 6% of men will request vasectomy reversal [28, 29]. The history of vasectomy reversal is less than a century old and progressed from a macroscopic technique to a highly refined microsurgical procedure following the implementation of the microscope. Edward Martin performed the first epididymovasostomy (EV) in 1902 and William Quinby reported the first successful vasovasostomy in 1919 [30]. Vasal reconstruction continued to evolve, but success was limited, as is evident in an AUA survey in 1948 that revealed a patency rate of 38% and a pregnancy rate of 19.5% [31]. Silber [32] and Owen [33] independently described the first microsurgical technique for vasectomy reversal in 1977, which marked a new era of vasal reconstructive surgery. Vasal reconstruction utilizing a microscopic technique has since become the gold standard. Series comparing microsurgical, Loupe magnification, and unmagnified vasovasostomy have shown improved patency and pregnancy rates with higher magnification [34–36].

There has recently been interest in utilizing a robot for robotic-assisted vasovasostomy (RAVV). Previous animal studies suggested potential advantages of RAVV over microsurgical vasovasostomy (MVV), although the cost of the equipment remains a significant issue [37].

Clinical question 1

What is the effect of varicocelectomy on semen parameters and pregnancy rate?

The evidence

There have been several well-designed meta-analyses in the last decade showing a positive impact of varicocelectomy on semen parameters and pregnancy rates [12, 38–42].

The most recent meta-analysis by the Cochrane Collaboration [42] identified 10 RCTs that met the inclusion criteria [43–52]. Studies included were RCTs that reported pregnancy rates or live birth rates as an outcome measure. Interventions included were surgical ligation or radiological embolization compared with untreated or placebo groups. The meta-analysis included 894 men with a combined fixed-effect odds ratio (OR) for the outcome of pregnancy of 1.47 (95% confidence interval [CI] 1.05–2.05) favoring intervention. The authors noted that this was a new finding from a previous Cochrane Review in 2009 [53] that failed to offer evidence of a treatment benefit.

The authors also performed a subgroup analysis with more restrictive inclusion criteria. These criteria included men with a clinical varicocele, an abnormal semen analysis, and pregnancy rate as the primary outcome. Five of the 10 studies met these requirements [43, 46, 50–52]. The subgroup analysis also favored intervention for these men with a combined OR of 2.39 (95% CI 1.56–3.66). The authors conclude that their review "suggests a benefit from treatment of varicocele for subclinical and clinical varicocele in subfertile men with normal and abnormal semen analysis and with otherwise unexplained subfertility" [42]. However, they noted that the quality of the evidence is very low. Only one of the included studies reported the outcome of adverse events [45], with no events reported.

Schauer et al. investigated the impact of varicocelectomy on sperm parameters with a new meta-analysis in 2012 and included three surgical techniques, high ligation, inguinal varicocelectomy, and the subinguinal approach [41]. Their meta-analysis concluded that varicocelectomy, regardless of the surgical technique, is associated with significant improvements in sperm count and motility.

With regard to the surgical technique, there have been two well-designed analyses that addressed this question. In 2009, Cayan et al. analyzed the pregnancy rate from 36 studies [54]. They concluded that the microsurgical varicocelectomy technique has high spontaneous pregnancy rates and lower postoperative recurrence than conventional varicocelectomy techniques and radiological embolization. Diegidio et al. also reported similar findings in 2011 after a review of 33 studies with over 5000 pooled patients [55]. The overall pregnancy rate was 38.37% (954/2486). The pregnancy rate was

Table 50.1 Effect of empirical clomiphene citrate therapy on pregnancy outcomes.

Study	Clomiphene dose (mg/day)	Treatment group (*n*/*N*)	Control group	Control group (*n*/*N*)	OR (95% CI)
WHO [22]	25	7/70	Placebo	6/71	1.20 (0.39–3.75)
Sokol et al. [20]	25	1/11	Placebo	4/9	0.17 (0.02–1.21)
Micic and Dotlic [24]	50	7/56	Placebo	0/45	6.81 (1.46–31.69)
Wang et al. [21]	25 or 50	4/29	Placebo	0/7	3.89 (0.29–51.80)
Abel et al. [19]	50	15/93	Vitamin C 200 mg/day	10/86	1.45 (0.62–3.37)
Ronnberg [18]	50	1/14	Placebo	1/15	1.07 (0.06–18.10)
Paulson [17]	25	7/17	Cortisone 10 mg/day	2/15	4.55 (0.77–26.83)
Total	25–50	42/298		23/248	1.35 (0.75–2.42)

CI, confidence interval; OR, odds ratio; WHO, World Health Organization; *n*, number of couples achieving pregnancy; *N*, total number of cases.

highest for the microsurgical subinguinal technique (44.75%) and the microsurgical inguinal technique (41.78%).

Clinical implications

We suggest that infertile men with palpable lesions and at least one abnormal semen parameter seeking to establish fertility undergo surgical varicocelectomy (conditional recommendation based on moderate-quality evidence). We further suggest that patients should undergo a microsurgical approach rather than a conventional approach or radiological embolization (conditional recommendation based on low-quality evidence).

Efficacy of clomiphene citrate in male infertility treatment

Clinical question 2

Is clomiphene citrate effective for male infertility treatment?

Literature search

Studies were identified by performing an extensive MEDLINE search (from 1975 to the present) with the help of a professional librarian and also by manually searching review articles and cross-references. The following keywords were used to search the databases: "clomiphene citrate," "antiestrogens," "oligospermia," "infertility," "semen parameters," and "pregnancy rate or outcome." RCTs of clomiphene therapy for at least 3 months or more compared with placebo or an alternative treatment for subfertile males among couples where subfertility was attributed to male factors were selected.

The evidence

A total of 22 studies were identified, of which only eight met our inclusion criteria [17–22, 24, 25]. Five studies used placebo as a control group [18, 20–22, 24] and one each compared antioxidant vitamin C [19] and low-dose cortisone acetate [17] with clomiphene citrate therapy, and one study compared combined clomiphene citrate and vitamin E against a placebo control [25]. Couples who failed to achieve pregnancy after at least 12 months of unprotected intercourse were chosen. The male partners of the couples included were diagnosed with idiopathic infertility and had oligo- and/or asthenozoospermia. Any patients with a known cause of infertility, such as a history of toxin or drug exposure, varicocele, undescended testis, primary germinal infertility, or known endocrine disorder, were excluded. The female partners had no demonstrable cause for infertility as they had normal menstrual and ovulatory patterns and no significant mechanical abnormalities by laparoscopy or hysterosalpingography. Pregnancy data were recorded for 6–12 months after the clomiphene empirical therapy and the overall odds were calculated; p-values <0.05 were used as a cut-off point for significance testing in all statistical tests.

The odds of "spontaneous" pregnancy after at least 3 months of clomiphene therapy compared with no or alternative empirical treatment for male subfertility did not differ significantly: 1.55 (95% CI 0.66–3.68) by fixed effect model and 1.35 (95% CI 0.75–2.42) by random effect model (Table 50.1). These odds ratios suggest some increased "risk" of pregnancy with treatment. Other potential side effects of clomiphene treatment include headache, dizziness, blurred vision, nausea, vomiting, gynecomastia, weight gain, and hypertension [56]. There have also been reports of a paradoxical response in testosterone level and/or semen parameters [25, 57].

However, some of the trials demonstrated significant improvement in semen parameters, especially the total motile sperm count. Unfortunately, insufficient studies and heterogeneity among these trials precluded us from conducting a meaningful meta-analysis evaluating the improved outcomes in semen parameters.

The most recent trial, by Ghanem et al. in 2010, was not included in the meta-analysis given that the trial compared clomiphene citrate (25 mg/day) plus vitamin E (400 mg/day)

versus placebo [25]. The trial included 60 infertile men aged 20–40 years who met the mentioned selection criteria. The results from this trial found a higher pregnancy rate in the treatment arm of 36.7% (11 pregnancies) versus 13.3% (four pregnancies) with an OR of 3.76 (95% CI 1.03–13.64; $p=0.037$). The results were not significant until months 4–6. In months 1–3 there were four pregnancies in the treatment group and three pregnancies in the placebo group, whereas in months 4–6 there were seven additional pregnancies in the treatment group and only one additional pregnancy in the treatment group. Semen parameters of sperm concentration ($p=0.0025$) and forward motility ($p=0.0286$) showed a statistically significant improvement in the treatment group. No significant change in other semen parameters was observed. This study shows a benefit with clomiphene citrate with vitamin E; however, given that the study did not include a clomiphene citrate-only arm, it is not possible to assess the impact of combination treatment versus clomiphene citrate treatment alone on pregnancy rates.

Clinical implications

We suggest that subfertile men with oligo- and/or asthenozoospermia undergo treatment with clomiphene 25–50 mg/day, with possible addition of vitamin E 400 mg/day, for at least 3–6 months with discretion before proceeding to advanced ART techniques such as ICSI (conditional recommendation based on low-quality evidence).

With regard to vitamin E, clinicians should counsel patients regarding the potential increase in prostate cancer and select patients carefully [58]. This recommendation assumes that patients place a high value on avoiding more invasive and resource-intense alternatives.

Impact of surgical technique on outcomes of vasovasostomy

Clinical question 3

What is the difference in outcomes for vasectomy reversal between microsurgical modified two-layer and formal two-layer anastomosis?

Literature search

Studies were identified by performing an extensive PubMed search. The following keywords were used to search the databases: "vasovasostomy," "vasectomy reversal," "two-layer technique," "modified two-layer technique," and "single-layer technique." Studies were selected that included comparison between the formal two-layer and the modified two-layer technique.

The evidence

The formal two-layer and the modified one-layer techniques are the most commonly described approaches in the literature. Formal two-layer anastomosis begins by opposing the adventitia and muscularis of the vasal ends on the posterior side of the anastomosis with one or two interrupted 9–0 nylon stitches. The mucosal layers are then carefully approximated with interrupted 10–0 nylon sutures beginning on the far side of the anastomosis. Care is taken to place the stitches so that the knot resides outside the lumen and six to eight mucosal stitches are generally required. The second layer is completed by placing four or five interrupted 9–0 nylon sutures in the serosal and muscularis layers [59].

The modified one-layer anastomosis technique varies from the formal two-layer technique in the size of suture material used and the layers incorporated in the mucosal stitches. Four to six full-thickness 9–0 nylon stitches are placed to create a well-spaced anastomosis. The stitches are placed so that the knots are on the serosa. The first one or two stitches, placed on the deep side of the anastomosis, may be tied immediately, and the remaining stitches are tied once all stitches have been placed to allow for maximum visualization of the lumen. Following the approximation of the lumen, a second layer of 9–0 nylon stitches through the adventitia and some muscularis is placed to ensure a watertight anastomosis [59].

Only two studies have reported the outcomes comparing the formal two-layer against the modified two-layer technique. In their landmark paper in 1991, the Vasovasostomy Study Group reported the results from 1469 patients who underwent a microscopic vasectomy reversal [60]. The study compared the outcomes from the five participating microsurgical specialists from August 1976 through May 1985. Three surgeons performed only the formal two-layer anastomosis and the remaining two surgeons performed either the formal two-layer or the modified one-layer technique. Neither the patency rate, 85.8 vs. 89.1%, respectively ($p=0.160$), nor the pregnancy rate, 51.2 vs. 56.7%, respectively ($p=0.136$), showed a statistically significant difference.

Fischer and Grantmyre reported the results for 40 men who underwent microscopic vasectomy reversal from January 1992 through December 1994 [61]. Seventeen men underwent modified one-layer anastomosis (group 1) and 23 underwent a formal two-layer anastomosis (group 2) by a single microscopic surgeon. Different techniques were used at two different locations owing to the availability of a microsurgical assistant. The patient characteristics were similar between the two groups, except for the mean obstructive interval, which was longer for patients in group 1 (56.3 vs. 35.0 months). Interestingly, the patency rates were similar between the two groups, indicating that the modified two-layer technique can be successful even in patients with factors that may compromise the outcome. They found, similarly to other reports, that the modified two-layer anastomosis technique was faster to perform and resulted in shorter operating room time.

A recent retrospective review by Nyame et al. reported the economic differences between the modified one-layer and the formal two-layer anastomosis techniques [62]. They identified 106 men who had undergone bilateral vasovasostomy by a single surgeon from 2010 to March 2015. The surgeon had changed surgical technique from the formal two-layer to the modified one-layer approach in May 2014, and they identified 20 patients who had undergone the modified anastomosis. They found no significant difference in patency rates between the modified one-layer and the formal two-layer technique (93.3 vs. 89.3%, $p=0.22$); however, there was significant cost savings associated with the modified repair, estimated at US$1036.10. The cost savings were due both to the elimination of the 10–0 nylon sutures and to decreased operating time (120.0 vs. 165.0 min, $p=0.006$).

Clinical implications

We suggest that the urologist perform a modified one-layer microsurgical anastomosis (conditional recommendation based on low-quality evidence). Given well-established comparable outcomes for both techniques, preference is given to the approach that is easier to perform with shorter operating room times and lower costs.

Clinical question 4

What is the difference in outcomes for vasectomy reversal between microsurgical vasovasostomy (MVV) and robotic-assisted vasovasostomy (RAVV)?

Literature search

Studies were identified by performing an extensive PubMed search. The following keywords were used to search the databases: "vasovasostomy," "vasectomy reversal," "microsurgical vasovasostomy," and "robotic-assisted vasovasostomy." Studies were selected that included comparison between MVV and RAVV.

Outcomes

Only two studies have reported the outcomes of comparing MVV with RAVV, both by Parekattil et al., first in 2010 and more recently in 2012 [63, 64]. The more recent report contained updated data and is discussed here.

Between August 2007 and February 2012, 155 vasectomy reversals were performed by a single fellowship-trained microscopic surgeon [64]. The primary endpoint was operative duration and the secondary endpoint was total motile sperm count at various months postoperatively. Looking only at the MVV and RAVV groups (excluding the EV patients), there were 110 men in the RAVV group and 28 in the MVV group. Selection of approach was based on patient preference. Patient characteristics were similar in both groups; importantly, the median obstructive interval was similar at 7 years for the RAVV group and 6.5 years for the MVV group ($p=0.3$). The same suture and suturing techniques were used in both groups (formal two-layer with 10–0 and 9–0 nylon suture). Patency was defined as >1 million sperm per ejaculate and was found to be 96% in the RAVV group and 80% in the MVV group ($p=0.02$). The pregnancy rate was not significantly different within 1 year postoperatively at 65 vs. 55%, respectively. The authors noted a possible confounding factor given that the majority of the MVV procedures were completed earlier in the surgeon's experience and RAVV was performed "almost exclusively in the later part of the series." The authors also highlighted the important learning curve associated with RAVV, noting that the operating time decreased rapidly after the first 10 cases.

Clinical implications

We suggest that urologists perform microsurgical MVV rather than RVV (conditional recommendation based on very low-quality evidence). In the setting of short-term data suggesting comparable outcomes, this recommendation favors MVV owing to reduced resource utilization/costs.

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51 CHAPTER 51
Premature ejaculation

Josip Vukina, J. Abram McBride, Culley C. Carson, and R. Matthew Coward
Department of Urology, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Introduction

Premature ejaculation (PE) is the most common sexual dysfunction in men, with global prevalence estimates ranging from 20 to 40% [1–3]. Men with PE report high levels of distress and interpersonal difficulty related to ejaculation, low satisfaction with intercourse, low sexual self-confidence, and lower overall quality of life [1, 4, 5]. PE has been poorly defined historically until more recent attempts at consensus definitions. Both the International Society for Sexual Medicine (ISSM) and the *Diagnostic Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) offer definitions for PE, both of which focus on the bother, in addition to the unintended brevity, of sexual intercourse [6–8]. The ISSM defines PE as "a male sexual dysfunction characterized by ejaculation which always or nearly always occurs before or within approximately one minute of vaginal penetration; the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy" [9]. In contrast to the DSM-IV-TR criteria, these criteria offer both subjective and objective measures of dysfunction. DSM-IV-TR defines PE as a persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it, and is associated with marked distress or interpersonal difficulty [6]. The DSM-V has been updated to include intravaginal ejaculatory latency time (IELT) as an objective measure of PE; however, the older DSM-IV-TR criteria have been widely used and are pervasive in the literature [10]. Generally, two types of PE are recognized: lifelong (primary) and acquired (secondary). Primary PE is present from the first sexual encounter whereas the onset of secondary PE occurs after a perceived normal period of ejaculation [11].

Prior treatment approaches for PE have included behavioral therapies, topical medications, and off-label use of tramadol and oral selective serotonin reuptake inhibitors (SSRIs). Unfortunately, behavioral and cognitive therapies have not been shown to have long-term improvements [12, 13]. Topical agents, such as lidocaine, EMLA cream, severance secret cream (SS-cream), and topical eutectic mixture for premature ejaculation (TEMPE) have been shown to be successful in delaying ejaculation. Off-label SSRIs have demonstrated significant success; however, pharmacologically, they are intended for long-term use and may take several hours to reach desired plasma concentrations [14]. Dapoxetine is the only SSRI licensed and formulated for the treatment of PE, but it is not approved for use in the United States by the US Food and Drug Administration [15]. The drug is rapidly absorbed after oral administration, with peak plasma concentrations being achieved in about 1 h, and is rapidly eliminated with a half-life of about 1.4 h. This can be compared with 21 h to 4 days for other off-label SSRIs [14, 16, 17]. Tramadol was initially developed as an analgesic, but recently it has shown efficacy for the treatment of PE. This chapter aims to review the available evidence on topical agents, dapoxetine, off-label SSRIs, and tramadol in the treatment of PE.

Clinical question 1

In patients with lifelong PE, are topical anesthetics an effective, safe, and satisfying treatment option compared with placebo for improving IELT?

Literature search

We conducted a systematic literature search in PubMed, EMBASE, and Web of Science using the search terms "premature ejaculation" and "topical, anesthetic, lidocaine,

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EMLA, severance secret cream (SS-cream), topical eutectic mixture for premature ejaculation (TEMPE) or PSD502." Studies were excluded if they did not report IELT. The search was limited to RCTs, systematic reviews, and meta-analyses in English within a human population with no time limits. Reference lists were evaluated for additional studies.

The evidence

We identified a total of eight RCTs and two meta-analysis systematic reviews. The two meta-analyses [18, 19] were both from 2013 and evaluated eight RCTs available at the time, all of which measured baseline IELT and used stopwatch-measured IELT by the patient's partner, although one meta-analysis excluded an RCT for including multiple treatment arms [19]. Only one additional RCT on the subject has since been published [20]; however, this study was excluded from our review because IELT was not a treatment outcome. In total, two RCTs evaluated the topical agent severance secret cream, or "SS-cream," a concoction of nine naturally occurring herbal products that is only available for use in Korea [21, 22]. Four RCTs evaluated the use of EMLA cream (2.5% lidocaine and 2.5% prilocaine), three of which compared EMLA cream versus placebo, and one compared EMLA cream with placebo, sildenafil only, and combination EMLA cream and sildenafil [20, 23–25]. Lastly, three RCTs evaluated the use of TEMPE (PSD502) spray (an aerosol-delivery form of lidocaine–prilocaine [7.5/2.5 mg per actuation] with three actuations equating one dose) versus placebo [26–28]. The critical outcomes reported in the RCT data providing the basis of recommendation for use of topical anesthetics in this chapter were based on IELT, side-effect profile, and patient satisfaction.

The 2013 meta-analysis by Pu et al. [18] consisted of eight RCTs including 860 patients demonstrating a statistically significant improvement in stopwatch IELT with topical anesthetic over placebo across all eight studies [21–28]. Of note, not all studies used the same exact definition of PE, since the accepted definition changed over the period of time spanning the RCTs, but all essentially included men with lifelong PE (Table 51.1). Of the studies reporting median

Table 51.1 Study characteristics of RCTs on topical therapy for the treatment of PE.

Study ID	Design	*n*	Diagnostic criteria	Intervention (dose/time before intercourse)	IELT (min) before treatment (SD)	IELT (min) after treatment (SD)	Side effects (%)
Choi [22] (1999)	RCT	50	IELT <3 min	SS-cream (0.2 g, 1 h) Placebo	1.3 (0.1)[a]	D: 11.0 (1.1) P: 2.2 (0.3)[b]	D: 13.2 mild burning, 0.5 penile pain P: 1.6 mild burning
Choi [21] (2000)	RCT	106	IELT <3 min	SS-cream (0.2 g, 1 h) Placebo	1.3 (0.1)[a]	D: 10.9 (0.9) P: 2.4 (0.2)[b]	D: 14.7 mild burning, 3.7 penile pain P: NR
Atikeler [23] (2002)	RCT	40	IELT <1 min	EMLA cream (2.5 g, variable) Placebo	1.0[a]	D: 6.7 (2.5) P: 1.0 (0.1)[b]	D: 53 penile numbness and DE P: NR
Busato [24] (2004)	RCT	29	DSM-IV	EMLA cream (2.5 g, variable) Placebo	D: 1.4 (0.9) P: 1.6 (0.7)	D: 8.4 (0.9) P: 1.9 (0.1)[b]	D: 6.9 penile burning, 6.9 DE P: 0
Atan [25] (2006)	RCT	84	DSM-IV	EMLA cream (2.5 g, 15 min) -Sildenafil (50 mg, 45 min) Placebo	NR	No change between EMLA and EMLA+sildenafil, both better than placebo	0
Dinsmore [27] (2007)	RCT	54	DSM-IV	TEMPE spray (3 actuations, 15 min) Placebo	D: 1.0 (1.2) P: 0.9 (0.7)	D: 4.9 (4.9) P: 1.6 (1.6)[b]	D: 11.5 penile numbness, 3.8% ED P: 3.5 mild burning
Dinsmore [28] (2009)	RCT	290	DSM-IV, ISSM	TEMPE spray (3 actuations, 5 min) Placebo	D: 0.6 (0.3) P: 0.6 (0.5)	D: 3.8 (9.5) P: 1.1 (2.5)[b]	[c]D: 2.6 vaginal burning, 1 ED P: 0
Carson [26] (2010)	RCT	249	DSM-IV, ISSM	TEMPE spray (3 actuations, 5 min) Placebo	D: 0.5 (0.2) P: 0.5 (0.2)	D: 2.6 (6.7) P: 0.8 (1.3)[b]	[c]D: 7.8 vaginal burning, 5.4 ED P: 2.4 vaginal discomfort

D, drug being evaluated; P, placebo; ED: erectile dysfunction; DE, delayed ejaculation >45 min; NR, not recorded. The two most common side effects for each drug are listed. Standard deviations are listed if provided in the original literature.

[a] Study only reported baseline IELT for all participants not stratified by placebo or treatment.

[b] Statistically significant, $p<0.05$.

[c] Study also evaluated partner related side effects.

time to IELT, pooled analysis demonstrated a mean improvement of 5.8 min (95% confidence interval [CI] 3.5–8.1) with topical anesthetic over placebo. In the two trials [26, 28] reporting geometric mean IELT, IELT (minutes) of 0.6/0.56 at baseline improved to 1.1/0.8 with placebo and to 3.8/2.6 with treatment, respectively, in each study. The application time varied across all RCTs, but one study suggested optimal treatment outcome with application of EMLA cream 20 min before intercourse [23]. TEMPE spray was associated with easier use and faster onset of action without the need for a condom [27].

Data evaluating subjective patient-reported sexual intercourse satisfaction demonstrated significant improvements over placebo with topical treatment. Specifically, two studies evaluated satisfaction as a percentage of patients satisfied. Satisfaction increased from 18 and 16.2% at baseline to 26 and 19.8% with placebo, versus 90 and 79.8% with 0.20 g of SS-cream [21, 22]. Busato et al. reported similar results, with 31% of patients in the EMLA group reporting "excellent" sexual satisfaction versus 0% in the placebo group [24]. Objective patient-reported outcomes for sexual intercourse satisfaction using validated patient questionnaires (IPE, PEP, IEC, and SQOL) were utilized in three studies [26–28], and all three showed either overall trends towards significance or statistically significant improvements in sexual intercourse satisfaction with topical treatment.

Lastly, side-effect reporting in all eight RCTs revealed a statistically significant increase in side effects with treatment (relative risk [RR] 4.3, 95% CI 1.6–11.2), including penile erythema, burning, numbness, pain, and, in some, loss of erection. Importantly, the two most recent RCTs also included partner-reported side effects and included vaginal burning, discomfort, and numbness [26, 28]. However, nearly all reported side effects were localized to the application site, or were transient and did not result in any study participant withdrawals [18]. Systemic side effects were rare [23, 24].

It must be noted that there was substantial heterogeneity across all eight RCTs in terms of inclusion criteria, randomization process, drug dosages, and type of treatment used (Table 51.1). The data are also somewhat indirect given the transformation of the definition of PE over the time period in which the RCTs were published. Similarly, the data demonstrate a degree of imprecision given the small number of treated patients in several of the RCTs. Based on these limitations, the overall quality of these studies is poor.

The 2013 meta-analysis reported by Xia et al. [19] included seven of the same RCTs as Pu et al. and confirmed a statistically significant improvement in IELT and patient sexual intercourse satisfaction with a minor burden of side effects with topical treatments over placebo [21–24, 26–28]. Statistical analyses unique to this meta-analysis included random-effect modeling to account for individual study heterogeneity, which demonstrated a standard mean difference of 5.0, favoring a statistically superior effect of improving IELT with topical treatments [19]. Also, meta-regression was performed, establishing that IELT was not associated with the heterogeneity otherwise appreciated in each study [19]. Sensitivity analysis was performed and showed very little change in the pooled positive standard mean difference consistent with stable meta-analysis results [19]. Lastly, fixed-effect modeling was used to evaluate side effects and demonstrated a combined odds ratio of 3.3 (95% CI 1.71–6.36, $p=0.64$) favoring a higher side-effect rate with topical treatment versus placebo.

Clinical implications

We suggest that patients with lifelong PE be treated initially with topical anesthetic agents (weak recommendation based on low-quality evidence). This recommendation assumes that the benefits of treatment (increased IELT) clearly outweigh its side effects, which are mild and transient in nature. In our practice, we prefer to recommend the topical spray formulation owing to its demonstrated efficacy, lower rate of patient and partner side effects, and availability over the counter.

Clinical question 2

Is on-demand dapoxetine safe and effective versus no treatment at all for improving IELT in men with lifelong or acquired PE?

Literature search

We conducted a systematic literature search in PubMed, EMBASE, and Web of Science using the search terms "premature ejaculation" and "dapoxetine." Studies were excluded if they did not report IELT. The search was limited to RCTs, systematic reviews, and meta-analyses in English within a human population with no time limits. Reference lists were evaluated for additional studies.

The evidence

Four eligible RCTs were identified, all of which measured baseline IELT and used stopwatch-measured IELT by the patient's partner (Table 51.2). Three studies randomized participants to placebo versus dapoxetine 30 and 60 mg as needed for intercourse [29, 30]. One study randomized participants to scheduled dapoxetine 30 mg twice daily versus placebo [31].

The first RCT, published by Pryor et al. in 2006 [32], randomized 2614 men from 121 clinical research sites in the United States to a 12-week course of placebo, on-demand dapoxetine 30 mg, or on-demand dapoxetine 60 mg. Inclusion criteria were based on the DSM-IV. Baseline IELT was similar across the groups. The doses were taken as needed 1–3 h prior to intercourse. Dapoxetine significantly prolonged IELT in both dosage groups. There was a statistically significant difference between 30 mg versus placebo, 60 mg

Table 51.2 RCTs evaluating dapoxetine for the treatment of PE.

Study ID	Design	*n*	Diagnostic criteria	Intervention	IELT (min) before treatment (SD)	IELT (min) after treatment (SD)	Effect size	Side effects
Pryor [32] (2006)	RCT	2614	DSM-IV	Placebo p.r.n. 30 mg p.r.n. 60 mg p.r.n.	0.90 (0.47) 0.92 (0.50) 0.91 (0.48)	1.75 (2.21) 2.78 (3.48)[a] 3.32 (3.68)[a,b]	1.11 (0.8–1.43) 1.66 (1.35–1.98) (LSMD)	P: nausea 1.9%, diarrhea 1.4% 30 mg: nausea 8.7%, diarrhea 3.9% 60 mg: nausea 20.1%, diarrhea 6.8%
Buvat [29] (2009)	RCT	1162	DSM-IV and IELT <2 min	Placebo p.r.n. 30 mg p.r.n. 60 mg p.r.n.	0.9 (0.51) 0.9 (0.50) 0.9 (0.49)	1.9 (2.89) 3.1 (4.88)[a] 3.5 (3.80)[a]	1.5 (1.05) 2.5 (1.05) 3.3 (1.05) (GMFI)	P: headache 8.3%, nasopharyngitis 3.4% 30 mg: nausea 16.5%, dizziness 7.7% 60 mg: nausea 30.6%, headache 13.6%
McMahon [30] (2010)	RCT	858	DSM-IV and IELT <2 min	Placebo p.r.n. 30 mg p.r.n. 60 mg p.r.n.	1.0 (0.47) 1.0 (0.45) 1.0 (0.48)	2.4 (2.05) 3.9 (3.95)[a] 4.2 (3.97)[a,c]	2 (1.04) 2.8 (1.05) 3.3 (1.05) (GMFI)	P: dizziness 3.9%, nausea 2% 30 mg: dizziness 10.5%, nausea 10.5% 60 mg: nausea 26.4%, dizziness 18.8%
Safarinejad [31] (2008)	RCT	212	IELT <2 min	Placebo b.i.d. 30 mg b.i.d.	0.46 0.52	0.9 3.2[a]	1.4 (0.84–1.63) 2.9 (1.84–4.16) (GMFI)	P: ED 2%, loss of libido 2% 30 mg: nausea 5.4%, diarrhea 5.4%

LSMD, least square mean difference; GMFI, geometric mean fold increase from baseline; P, placebo. The two most common side effects for each drug listed. Standard deviations are listed if provided in the original literature.

[a] Statistically significant versus placebo ($p<0.05$).

[b] Statistically significant versus 30 mg dose ($p<0.05$).

[c] Not statistically significantly different between 30 and 60 mg doses.

versus placebo, and 60 mg versus 30 mg. The most common side effects were nausea, diarrhea, and headache. The incidence of severe side effects was low: 2.9% for placebo, 2.3% for dapoxetine 30 mg and 4.3% for dapoxetine 60 mg.

An RCT by Buvat et al. randomized 1162 subjects to a 24-week course of placebo, on-demand dapoxetine 30 mg, or on-demand dapoxetine 60 mg [29]. Inclusion criteria were based on the DSM-IV definition and a baseline IELT of less than 2 min. The Baseline International Index of Erectile Function (IIEF-5) score was similar between the three groups. Results were reported with both arithmetic and geometric means. Dapoxetine was found to be significantly better than placebo at improving IELT with both the 30 and 60 mg doses. No statistical information was given regarding the comparison of 30 and 60 mg doses. Rates of serious side effects were 1, 0.8, and 1% in the placebo, 30 mg, and 60 mg dose groups, respectively.

The third RCT, by McMahon et al., evaluated 858 patients in 52 centers in Australia, China, Korea, Taiwan, Malaysia, the Philippines, Thailand, Singapore, and Hong Kong [30]. Inclusion criteria were based on the DSM-IV definition and an IELT of less than 2 min. Participants were randomized to a 12-week course of placebo, dapoxetine 30 mg, and dapoxetine 60 mg taken on demand prior to sexual intercourse. There was a statistically significant increase in IELT compared with placebo with both 30 and 60 mg doses of dapoxetine as outlined in Table 51.2. There was no statistically significant difference between the 30 and 60 mg doses. Rates of discontinuation due to treatment-emergent side effects were placebo 0.3%, dapoxetine 30 mg dose 1.7%, and dapoxetine 60 mg dose 5.1%.

Lastly, Safarinejad randomized 212 patients with IELT less than 2 min to scheduled dapoxetine 30 mg twice daily versus placebo [31]. Efficacy assessments were made every 2 weeks until the end of the 12-week study period and 3 months after cessation of treatment. Geometric means were reported. IELT increased from 0.52 to 3.2 min in the treatment group compared with an increase from 0.46 to 0.9 min in the placebo group. At 3 months' follow-up after discontinuation of the drug, there was no statistically significant difference in mean IELT between the two groups. The most common side effects were nausea (5.4%), diarrhea (5.4%), insomnia (4.3%), headache (4.3%), and dizziness (3.2%).

The overall quality of evidence of these studies is moderate, as all studies were placebo controlled and randomized, sample sizes were robust, and two of the four studies were multi-centered. There was downgrading due to study limitations including unclear randomization concealment [31], lack of description of study dropouts [29–32], and absence of intention-to-treat analysis [31].

Clinical implications

We suggest that patients with lifelong or acquired PE be treated with dapoxetine (conditional recommendation based on moderate-quality evidence). This recommendation is based on the judgment that the small increase in IELT experienced by patients treated with dapoxetine outweighs the potential minor and transient side effects of the drug.

Clinical question 3

For patients with PE, which SSRIs are more effective with continuous versus as-needed dosing at improving IELT?

Literature search

We conducted a systematic literature search in PubMed, EMBASE, and Web of Science using the search terms "selective serotonin reuptake inhibitor" and "premature ejaculation." Studies were excluded if they did not report IELT. Studies exclusively evaluating dapoxetine were excluded, as this topic was previously evaluated in Clinical question 2. The search was limited to RCTs, systematic reviews, and meta-analyses in English within a human population with no time limits. Reference lists were evaluated for additional studies.

The evidence

In 2004, Waldinger et al., the most prolific authors on the topic, published a systematic review on all studies performed between 1943 and 2003 for the treatment of PE [33]. This was the most comprehensive and methodologically sound review to date looking at all known therapies for PE. Within this review, serotonergic antidepressants were specifically evaluated. Only studies reporting quantitative data on IELT were used. Because of the variability in measurement of the IELT (clock, stopwatch, questionnaire, or subjective assessments), the effect was calculated as the percentage change from baseline. Unfortunately, the review did not include assessment of side effects.

The review included open design trials, RCTs, and case reports, and reported on a total of 35 studies evaluating serotonergic antidepressants for PE. Within this group, Waldinger et al. performed a separate subgroup analysis of prospective, double-blind, stopwatch-assessed studies, as these showed significantly less variability in outcome measures [33]. There were only eight studies that fitted these criteria. Based on this subgroup analysis, the rank order was found to be (1) paroxetine (783% IELT increase, 95% CI 499–1228%), (2) clomipramine (360% IELT increase, 95% CI 201–644%), (3) sertraline (313% IELT increase, 95% CI 161–608%), (4) fluoxetine (295% IELT increase, 95% CI 200–435)%, and (5) placebo (47% IELT increase, 95% CI 29–76%) [33].

Another separate subgroup analysis was performed specifically evaluating on-demand dosing of SSRIs. Eight studies, a mixture of double-blind, single-blind, and open studies, fitted these criteria and showed a similar rank order of efficacy of paroxetine (929%, 95% CI 398–2166%), sertraline (553%, 95% CI 210–1457%), and clomipramine (263%, 95% CI 60–1152%). A meta-analysis could not be performed on these studies owing to insufficiently provided data from the original studies. The authors cautioned against any final conclusions from this part of the analysis owing to the low number of studies and the fact that there was only one double-blinded study using a stopwatch [33].

We then performed a search using the same criteria and examined RCTs published since 2003 until the present in order to evaluate new data published since the Waldinger review.

We identified seven studies evaluating dapoxetine, fluoxetine, sertraline, paroxetine, citalopram, and escitalopram as outlined in Table 51.3. There were insufficient studies per drug to allow meta-analysis. Manasia et al. compared fluoxetine 90 mg once weekly with fluoxetine 20 mg daily and found that both doses are associated with a statistically significant difference in IELT compared with placebo, with no difference found between the two doses [34]. In a single-blinded cross-over study, Arafa et al. randomized two groups of 70 and 77 men to sertraline followed by a washout period and then placebo, and placebo followed by a washout period and then sertraline, respectively [35]. The results showed a significant increase in IELT from baseline in both groups and also mild side effects. In two separate studies, Safarinejad and Hosseini showed citalopram and escitalopram to be associated with statistically significant increases in IELT and observed the drugs to be well tolerated [36, 37]. Perhaps more interestingly, in a separate study, Safarinejad compared dapoxetine 60 mg with paroxetine 20 mg and found that, in the dapoxetine group, IELT increased from 38 to 179 s (4.7-fold increase), compared with 31 to 370 s (10.9-fold increase) in the paroxetine group [38]. The difference between the efficacies of the two SSRIs was found to be statistically significant, leading to the conclusion that paroxetine outperforms dapoxetine with regard to prolonging IELT. However, the timing of the dose (i.e. on-demand versus daily dosing) of dapoxetine was not reported. The most common side effects of both drugs included nausea and headache [38]. This finding is in contrast to Simsek et al., who found an improvement in IELT in the dapoxetine 60 mg on demand group from 43.5 to 118 s (2.7-fold increase) compared with an increase from 45.2 to 98.4 s (2.2-fold increase) in the paroxetine 20 mg group ($p < 0.05$) [39]. The discrepancy between these studies may be explained by the difference in timing of the dose of dapoxetine. Lastly, Rezakhaniha and Sirosbakht evaluated fluoxetine and citalopram in a randomized trial including patients with anxiety disorder [40]. In those with and without anxiety disorder, both fluoxetine and citalopram were associated with a significant increase in IELT with no difference in efficacy noted between the two drugs. Interestingly, in the fluoxetine group,

there was a higher increase in IELT in those without anxiety, whereas the citalopram group showed a better response in IELT in those with anxiety. Unfortunately, no statistical analysis was presented regarding these subgroups [40].

Side effects reported in each of the above trials are presented in Table 51.3 in greater detail; however, the rates were relatively low and most commonly included gastrointestinal symptoms and headache.

The overall quality of evidence of these studies is poor, with downgrading for many limitations; all studies were performed at single centers with small sample sizes ranging from 58 to 340 patients. Only the Safarinejad studies described methods of randomization [36–38]. The Rezakhaniha study did not provide information on drug side effects [40].

Clinical implications

We suggest that patients undergoing treatment for PE with an SSRI take daily medication rather than using on-demand dosing (conditional recommendation based on low-quality evidence). This recommendation is based on the paucity of evidence to provide assurance that on-demand treatment is as effective as continuous treatment. With regard to choice of SSRI, studies show that paroxetine may have a slight

Table 51.3 Studies of SSRIs for the treatment of PE since 2003.

Study ID	Design	n	Diagnostic criteria	Intervention	IELT (min) before treatment (SD)	IELT (min) after treatment (SD)	Side effects
Manasia [34] (2003)	RCT	80	IELT <2 min	Fluoxetine 90 mg once weekly Fluoxetine 20 mg q.d.	0.48 0.5	90 mg: 3.57[a] 20 mg: 3.37[a]	90 mg: nausea 7.5%, headache 5% 20 mg: nausea 12.5%, headache 5%
Arafa [35] (2006)	Randomized cross-over	127	IELT <2 min and AIPE questionnaire	Sertraline 50 mg q.d. Placebo	Group 1: 0.7 (0.12) Group 2: 0.8 (0.15)	Group 1: sertraline 3.3 (0.22)[a] P: 0.7 (0.11) Group 2: 3.4 (0.26)[a] P: 0.8 (0.16)	GI upset: 1.5% Anorexia: <1%
Safarinejad [38] (2006)	RCT	340	IELT <2 min	Dapoxetine 60 mg q.d. Paroxetine 20 mg q.d. Placebo	0.63 0.33 0.56	Dapoxetine: 2.98[a] Paroxetine: 6.1[a] P: 0.92	Dapoxetine: nausea 9.6%, diarrhea 5.4% Paroxetine: nausea 7.6%, diarrhea 7.7% P: nausea 1%, ED 6%
Safarinejad [36] (2006)	RCT	58	IELT <2 min	Citalopram 20 mg q.d. Placebo	0.53 0.47	Citalopram: 4.47[a] P: 0.63	Citalopram: nausea 20%, dry mouth 10% P: ED 1%, insomnia 1%
Safarinejad [37] (2007)	RCT	276	IELT <2 min	Escitalopram 10 mg q.d. Placebo	NR	Escitalopram: 4.9-fold increase[a] P: 1.4-fold increase	Escitalopram: nausea 4.7%, headache 3.9%. P: not listed
Rezakhaniha [40] (2010)	RCT	77	Not defined	Fluoxetine 20 mg b.i.d. Citalopram 40 mg q.d.	Fluoxetine without anxiety: 0.97 (0.69) Fluoxetine with anxiety: 0.82 (0.67) Citalopram without anxiety: 0.86 (0.57) Citalopram with anxiety: 1.08 (0.69)	Fluoxetine without anxiety: 7.77[a] (0.18) Fluoxetine with anxiety: 6.33[a] (0.11) Citalopram without anxiety: 6.7[a] (0.13) Citalopram with anxiety: 8[a] (0.11)	NR
Simsek [39] (2014)	RCT	150	IELT <1 min	Dapoxetine 30 mg Dapoxetine 60 mg p.r.n. Paroxetine 20 mg q.d.	0.77 (0.39) 0.73 (0.34) 0.75 (0.53)	1.67 (0.41)[a] 1.97 (0.68)[a] 1.64 (0.44)[a]	Paroxetine: yawning 10%, akathisia 6% Dapoxetine 60 mg: nausea 14%, headache 10% Dapoxetine 30 mg: nausea 8%, headache 4%

AIPE, Arabic Index of Premature Ejaculation; GI, gastrointestinal; P, placebo; NR, not reported. Standard deviations are listed if provided in the original literature.

[a] Statistically significant ($p<0.05$) compared with placebo.

advantage in efficacy compared with other off-label SSRIs, but all are considered effective.

Clinical question 4

Is on-demand tramadol a safe and effective treatment option compared with placebo or other treatments for men with RE at improving IELT?

Literature search

We searched MEDLINE, EMBASE, and Web of Science for "tramadol" and "premature ejaculation." Studies were excluded if they did not report IELT. The search was limited to RCTs, systematic reviews, and meta-analyses in English within a human population with no time limits. Reference lists were evaluated for additional studies.

The evidence

Eight studies fitted the inclusion criteria and were included in the review (Table 51.4). Two studies compared with other drugs, with one study comparing tramadol with paroxetine [41] and another study comparing it with sildenafil, paroxetine, and lidocaine gel in a multi-arm design [42]. The remainder of the studies either compared tramadol with placebo [43–47] or compared different doses of tramadol [48]. The study designs were all prospective and randomized with varying criteria for PE as shown in Table 51.4. The duration of treatment ranged from 4 to 24 weeks and the sample size varied from 35 to 604 subjects. Although the majority of the studies were small and from single institutions, Bar-Or et al. evaluated 604 patients from centers in 11 countries and found a statistically significant improvement in IELT with tramadol 62 and 89 mg using on-demand dosing [43].

Table 51.4 RCTs comparing the effects of tramadol on PE.

Study ID	Design	*n*	Diagnostic criteria	Intervention	IELT (min) before treatment (SD)	IELT (min) after treatment (SD)	Side effects
Alghobary [41] (2010)	RCT	35	DSM-IV	T 50 mg on demand Paroxetine 20 mg q.d.	0.6	Tramadol 6 wks/12 wks: 3[a]/2.22[a,b] Paroxetine 6 wks/12 wks: 3.83[a]/7.22[a,b]	NR
Bar-Or [43] (2012)	RCT	604	IELT <2 min	P T 62 mg on demand T 89 mg on demand	1.03 (0.04) 0.98 (0.04) 1.02 (0.04)	2.67 (0.20) 3.28 (0.27)[a] 3.38 (0.24)[a]	P: 1.5% 62 mg: 5.0% 89 mg: 8.2%
Eassa [48] (2013)	RCT	300	Not defined	T 25 mg on demand T 50 mg on demand T 100 mg on demand	2.82 (0.89) 2.79 (0.95) 2.99 (0.86)	13.17 (1.83)[a] 23.43 (1.78)[a] 36.49 (3.25)[a]	Somnolence and pruritus in 100% all groups
Khan [44] (2013)	RCT	60	Not defined	P T 100 mg daily × 4 weeks then on demand × 4 weeks	0.98 0.99	P daily: 1.58 P p.r.n.: 1.61 T daily: 3.375[a] T p.r.n.: 3.97[a]	6.7% placebo 12.4% tramadol (specifics not reported)
Kaynar [45] (2012)	RCT	60	IELT <1 min	P T 25 mg on demand	0.51 (0.31) 0.65 (0.26)	0.93 (0.56)[a] 2.57 (0.65)[a]	P: NR T: 20% nausea, 20% headache
Safarinejad [46] (2006)	RCT	64	IELT <2 min	P T 50 mg on demand	0.35 0.32	0.56 4.05[a]	P: 15.6% T: 28.1% Not specified
Kurkar [47] (2015)	RCT	180	IELT <2 min	P T 50 mg on demand T 100 mg on demand	1.2[c]	P: 1.36[a] T 50 mg: 2.5[a] T 100 mg: 4.53[a]	T 50 mg: 13.6% nausea, 12.8 post void dribble T 100 mg: 36.8% nausea, 33.6 post void dribble. NR for placebo
Gameel [42] (2013)	RCT	150	IELT <2 min	P T 50 mg on demand Sildenafil 50 mg on demand Paroxetine 20 mg on demand Lidocaine gel 2.5%	P: 1.02 (0.51) T: 1.12 (0.44)	P: 1.35 (0.54) T: 5.85 (1.98)[a]	P: 7% constipation T: 55% sleep disturbance, 35% nausea

P, placebo; T, tramadol; NR, not reported.

[a] Study only reported baseline IELT for all participants not stratified by placebo or treatment.

[b] $p<0.05$ comparing drug with baseline/placebo.

[c] $p<0.05$ comparing 12- and 6-week dosing.

Every study showed a statistically significant improvement in IELT with tramadol administration. All studies evaluated exclusively on-demand dosing with the exception of the Khan and Rasaily study, which randomized 60 patients to either tramadol 100 mg daily or placebo and then at 4 weeks switched them to as-needed dosing 2–8 h prior to intercourse [44]. From a baseline IELT of 59.2 s (mean), IELT after daily treatment was 202.5 s and after on-demand treatment was 238.2 s. The difference between treatment and baseline was reported to be statistically significant for both the daily and on-demand groups; however, no statistical information was given comparing the two dosing schemes. Rather than studying this head-to-head, following one dosing scheme with another leads to significant difficulty in interpretation because of issues with tolerance. Alghobary et al. compared on-demand tramadol 50 mg with daily paroxetine 20 mg. Although there was a statistically significant difference with both tramadol and paroxetine compared with baseline, the study showed a decreased efficacy of on-demand tramadol at 12 weeks compared with 6 weeks [41]. This may indicate some tolerance effect; however, this was not corroborated by any of the other studies. Of note, this trial was the only to reassess response to continuous dosing of tramadol at two time points [41]. In studies comparing multiple doses of tramadol, the higher doses had a larger effect on lengthening IELT, as shown in Table 51.4 [43, 47, 48].

All of these trials, with the exception of the Kurkar et al. study, as it was published more recently, were included in a systematic review and meta-analysis by Martyn-St. James et al. [49] published in 2015. In the studies comparing tramadol with placebo, the pooled mean difference in IELT at 8 or 12 weeks was 1.2 min with a 95% CI of 0.52–1.95 ($p=0.009$). There was high heterogeneity of the studies with $I^2=74\%$. The remainder of the comparison groups did not have sufficient studies to be able to perform further meta-analysis.

Seven of the eight trials in this review reported specific side effects. In general, tramadol was well tolerated, with the most common side effects being somnolence and gastrointestinal issues. Not surprisingly, mirroring the increase in efficacy with higher doses, there is also an increase in adverse events with dose escalation. This is well illustrated by the study by Eassa and El-Shazly, in which men were randomized to tramadol 25, 50, or 100 mg [48]. Approximately 20 and 17% of the 100 mg group experienced nausea and vomiting, respectively, whereas none of the participants in the 50 or 25 mg group experienced these effects. With regard to dizziness and headache, 38 and 30% of the 100 mg group suffered from these side effects, whereas none did in the 25 mg group. Notably, 100% of participants reported somnolence and pruritus [48]. The adverse event rate reported by Bar-Or et al. was 6.7, 12.5, and 16.5% for the placebo, tramadol 62 mg, and tramadol 89 mg groups, respectively [43]. In an earlier study, Cossman et al. reported on combined data for over 21 000 patients taking tramadol and noted that the most frequently reported side effects were gastrointestinal issues, dizziness, and drowsiness [50].

Owing to its opioid characteristics, there has been concern regarding addiction or dependence with tramadol. Earlier studies showed a physical dependence, but these investigated higher doses and chronic users [51–55]. Long-term exposure to opiates has been shown to decrease gonadal hormones in both human and animal studies [56, 57]. Although this is well documented with morphine administration, a recent study confirmed similar effects with tramadol [58]. No studies in our review examined this as an outcome; however, hypogonadism may be attributed to tramadol use, which could potentially lead to worsening of ED.

The quality of evidence of these studies is poor, with downgrading for small sample sizes [41, 44, 45], single-institution studies (all but one), lack of randomization [45], and lack of description of study dropouts [47].

Clinical implications

We suggest the use of tramadol to treat refractory PE (conditional recommendation based on low-quality evidence). This recommendation applies only to patients who can be carefully monitored for the development of dependence on this agent. Further studies are needed to understand better the relationship between tramadol and hypogonadism, as this could theoretically lead to worsening ED.

Conclusion

This chapter provides a systematic review of the current best evidence for the treatment of PE. The particular questions were chosen based on the current, most commonly used medications for PE. Studies included were exclusively RCTs and meta-analyses, mostly of low to moderate quality, resulting in conditional recommendations. Topical anesthetics, dapoxetine, off-label SSRIs, and tramadol all show efficacy in the treatment of PE. However, the current data supporting all agents could be bolstered by larger randomized trials including direct comparison between different agents within each class. Specifically, data comparing EMLA cream with TEMPE spray would help determine treatment superiority regarding efficacy and side effects. Likewise, further comparisons of dapoxetine on-demand with other off-label SSRIs given continuously or on demand are needed to allow stronger recommendations regarding dosing and timing of these medications. Lastly, data examining tramadol used on demand with longer follow-up may help address underlying dependence and side effect concerns, and also issues with hypogonadism. In our current practice, we recommend topical lidocaine spray initially as it has significant effects on IELT, fairly minimal side effects, is available in the United States, and avoids the issues of dependence associated with tramadol. Additionally, we feel that providers will be more comfortable

prescribing this medication compared with SSRIs. This review outlines numerous treatment options for PE; however, more high-quality research is needed to offer definitive therapies to patients suffering from this life-altering disorder.

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