Absolute Clinical Radiation Oncology Review

Daniel M. Trifiletti
Nicholas G. Zaorsky
Editors

Springer

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Abbreviations

2D	Two-dimensional
3D	Three-dimensional
3D-CRT	Three-dimensional conformal radiation therapy
5-FU	5-Fluorouracil
ABMT	Autologous bone marrow transplant
APBI	Accelerated partial breast irradiation
abnl	Abnormal
ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
adj	Adjuvant
Adr	Adriamycin
AFP	Alpha-fetoprotein
AIDS	Acquired immune deficiency syndrome
AJCC	American Joint Committee on Cancer
aka	Also known as
alk phos	Alkaline phosphatase
Alt	Alternated with
am	Morning (ante meridian)
ANC	Absolute neutrophil count (lab)
ant	Anterior
anterolat	Anterolateral
AP	Anterior-posterior
APC	Adenomatous polyposis coli (gene mutation)
appx	Approximately
APR	Abdominoperineal resection
ARUBA	A Randomized Trial of Unruptured Brain Arteriovenous Malformations
ASCUS	Atypical squamous cells of undetermined significance
ASTRO	American Society for Radiation Oncology
AUC	Area under the curve
avg	Average
BAT	B-mode acquisition and targeting
b/c	Because
b/t	Between
bFFP	Biochemical freedom from progression
b-HCG	Beta-human chorionic gonadotropin
bid	Twice daily

bilat	Bilateral
BM	Bone marrow
BMI	Body mass index
BMP	Basic metabolic panel
BMT	Bone marrow transplant
BTSG	Brain Tumor Study Group
BWS	Beckwith-Wiedemann Syndrome
Bx	Biopsy/biopsies
C	Cervical (spine level)
c/w	Compared with
CA19-9	Cancer antigen 19-9
CA 125	Cancer antigen 125
CALGB	Cancer and Leukemia Group B
C/A/P	Chest/abdomen/pelvis
CBC	Complete blood count (lab)
CCCG	Colorectal Cancer Collaborative Group
cCR	Clinical complete response
CD	Cone-down
CD4	Cluster of differentiation 4 (for immune cells)
CEA	Carcinoembryonic antigen
CESS	Cooperative Ewing Sarcoma Study
CHART	Continuous Hyperfractionated Accelerated Radiotherapy Trial
chemo	Chemotherapy
CHF	Congestive heart failure
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in situ
cm	Centimeter/centimeters
CMP	Complete metabolic panel (lab)
c-myc	Proto-oncogene, part of the Myc gene family
cN0	Clinically node-negative
CN	Cranial nerve
CNS	Central nervous system
Co-60	Cobalt-60
COG	Children's Oncology Group
contralat	Contralateral
CPT	Common procedural terminology
Cr	Creatinine
CR	Complete response
CRT	Chemoradiation
CSF	Cerebrospinal fluid
CSI	Craniospinal irradiation
CSM	Cancer-specific mortality
CSS	Cause-specific survival
CT	Computed tomography
cT	Clinical T-stage
CTV	Clinical target volume
Cx	Cervical (spine level)
CXR	Chest x-ray

D/C	Discontinue/discontinued
D&C	Dilation and curettage
DCC	Deleted in colorectal cancer (gene)
DDx	Differential diagnosis
DFS	Disease free survival
DI	Diabetes insipidus
DLBCL	Diffuse large-B cell lymphoma
DLCO	Lung diffusion capacity testing
DM	Distant metastasis
DMFS	Distant metastasis free survival
DOI	Depth of invasion
DRE	Digital rectal examination
DSS	Disease-specific survival
d/t	Due to
DVH	Dose volume histogram
DVT	Deep venous thrombosis
Dx	Diagnosis/diagnoses
Dz	Disease/diseases
EB	External beam
EBRT	External beam radiation therapy
EBUS	Endobronchial ultrasound
EBV	Epstein-Barr virus
ECE	Extracapsular extension
ECOG	Eastern Cooperative Oncology Group
EFRT	Extended field radiotherapy
EFS	Event free survival
e.g.	For example
EGFR	Epidermal growth factor receptor
EM	Electron microscopy
ENI	Elective nodal irradiation
EORTC	European Organisation for Research and Treatment of Cancer
Epo	Erythropoietin
ESR	Erythrocyte sedimentation rate (lab)
et al.	And others
EUA	Exam under anesthesia
EUS	Endoscopic ultrasound
EWS	Ewing sarcoma
exam	Examination
f/b	Followed by
FAP	Familial adenomatous polyposis
FDA	Food and Drug Administration
FDG	Fluorine-18 2-fluoro-2-deoxy-D-glucose
FEV	Forced expiratory volume
FFS	Failure-free survival
FFTF	Freedom from treatment failure
FIGO	International Federation of Gynecology and Obstetrics
FH	Favorable histology
FHIT	Fragile histidine triad

FISH	Fluorescence in situ hybridization
FKHR	Forkhead (Drosophila) homolog 1 (rhabdomyosarcoma) (gene)
FLAIR	Fluid attenuation inversion recovery
F:M	Female to male ratio
FN	Rate false-negative rate
FNA	Fine needle aspiration
FOLFOX	5-FU/leukovorin/oxaliplatin
FPR	False-positive rate
FSH	Follicle-stimulating hormone
FSR	Fractionated stereotactic radiotherapy
fx	Fraction/fractions
GBM	Glioblastoma multiforme
GH	Growth hormone
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GnRH	Gonadotropin-releasing hormone
GTR	Gross total resection
GTV	Gross target volume
GU	Genitourinary
Gy	Gray
gyn	Gynecologic
H&N	Head and neck
H&P	History and physical
HA	Headache
HAART	Highly active antiretroviral therapy
HCG	Human chorionic gonadotropin (lab test)
HDC+SCT	High-dose chemotherapy with stem cell transplant
HDR	High dose rate
Hgb	Hemoglobin
HGG	High-grade glioma
HGSIL	High-grade squamous intraepithelial lesion
HIV	Human immunodeficiency virus
HNPCC	Hereditary nonpolyposis colon cancer
HPV	Human papilloma virus
hr/hrs	Hour/hours
HR	Hazard ratio
HRT	Hormone replacement therapy
HSV	Herpes simplex virus
HTN	Hypertension
HVA	Homovanillic acid
Hx	History/histories
Hyperfx	Hyperfractionation
IBCSG	International Breast Cancer Study Group
IC	Internal carotid
ICP	Intracranial pressure
IDL	Isodose line
i.e.	That is

IFN	Interferon
IgA	Immunoglobulin A
IGF	Insulin-like growth factor
IgG	Immunoglobulin G
IGRT	Image-guided radiation therapy
IJROBP	International Journal of Radiation Oncology, Biology, and Physics
IMA	Inferior mesenteric artery
IMRT	Intensity-modulated radiation therapy
inf	Inferior
INR	International normalized ratio
intraop	Intraoperative
IORT	Intraoperative radiation therapy
ipsi	Ipsilateral
IQ	Intelligence quotient
ITV	Internal target volume
IVC	Inferior vena cava
JAMA	Journal of the American Medical Association
JCO	Journal of Clinical Oncology
JCOG	Japan Clinical Oncology Group
JCRT	Joint Center for Radiation Therapy
JHH	Johns Hopkins Hospital
JNCI	Journal of the National Cancer Institute
JPA	Juvenile pilocytic astrocytoma
KPS	Karnofsky Performance Status
L	Lumbar (spine level)
LA	Lymphadenopathy
lab	Laboratory/laboratory test
LAD	Lymphadenopathy
LAMP	Locally Advanced Multimodality Protocol
LAO	Left anterior oblique
lat	Lateral
LC	Local control
LDH	Lactate dehydrogenase
LDR	Low dose rate
LE	Lower extremity
LEEP	Loop electrosurgical excision procedure
LF	Local failure
LFT	Liver function test
LGSIL	Low-grade squamous intraepithelial lesion
LH	Luteinizing hormone
LINAC	Linear accelerator
LLL	Left lower lobe
LML	Left middle lobe
LN	Lymph node
LND	Lymph node dissection
LOH	Loss of heterozygosity
LP	Lumbar puncture

LPO	Left posterior oblique
LR	Local recurrence
LRC	Locoregional control
LRF	Locoregional failure
LRFS	Local recurrence free survival
LRR	Locoregional recurrence
LUL	Left upper lobe
LVI	Lymphovascular invasion
LVSI	Lymphovascular stromal invasion
MALT	Mucosa-associated lymphoid tissue
max	Maximal/maximum
MB	Medulloblastoma
MDACC	MD Anderson Cancer Center
med	Medication
MEN	Multiple endocrine neoplasia
mets	Metastasis/metastases
M:F	Male to female ratio
MFS	Metastasis free survival
MGMT	O6-methylguanine DNA-methyltransferase
MI	Myocardial infarction
MIBG	Metaiodobenzylguanidine
min	Minimal/minimum
MLD	Mean lung dose
MN	Mediastinal node
mo/mos	Month/months
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MS	Median survival
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated/tolerable dose
Mtx	Methotrexate
MVA	Multivariate analysis
NB	Neuroblastoma
N/C	Nuclear to cytoplasm ratio
NCCN	National Comprehensive Cancer Network
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
NED	No evidence of disease
NEJM	New England Journal of Medicine
neoadj	Neoadjuvant
NF	Neurofibromatosis
NGGCT	Nongerminomatous germ cell tumor
NHL	Non-Hodgkin lymphoma
NPCR	National Program of Cancer Registries
NPV	Negative predictive value
NPX	Nasopharynx
NR	No response

NSABP	National Surgical Adjuvant Breast and Bowel Project
NSAID	Nonsteroidal anti-inflammatory drug
NSE	Neuron-specific enolase
NSS	Not statistically significant
NTR	Near-total resection
n/v	Nausea/vomiting
NWTS	National Wilms Tumor Study
NZ	New Zealand
OPX	Oropharynx
OR	Odds ratio
ORN	Osteoradionecrosis
ORR	Overall response rate
OS	Overall survival
PA	Posterior-anterior
PAP	Papanicolaou smear
PCI	Prophylactic cranial irradiation
PCNSL	Primary CNS lymphoma
PCP	Pneumocystic pneumonia
PCR	Polymerase chain reaction
pCR	Pathologic complete response
PDGFR	Platelet-derived growth factor receptor
PEG	(Tube) Percutaneous endoscopic gastrostomy tube
periop	Perioperative
PET	Positron emission tomography
PF	Posterior fossa
PFS	Progression free survival
PFT	Pulmonary function test
Plt	Platelets
pm	Afternoon (post meridian)
PM	Para-meningeal (for rhabdomyosarcoma)
PMH	Princess Margaret Hospital
pN0	Pathologically node negative
PNET	Primitive neuroectodermal tumor
PNI	Perineural invasion
PNS	Paranasal sinuses
PORT	Postoperative radiation therapy
post	Posterior
posterolat	Posterolateral
postop	Postoperative
PPV	Positive predictive value
PR	Partial response
PrA	Para-aortic (for lymph nodes)
PrT	Paratesticular (for rhabdomyosarcoma)
preop	Preoperative
PS	Performance status
PSA	Prostate-specific antigen
pt/pts	Patient/patients
PTHrP	Parathyroid hormone–related peptide

PT	Prothrombin time
pT	Pathologic tumor stage
PTV	Planning target volume
PUVA	Psoralen and long-wave ultraviolet radiation
q	Every
qd	Daily
QOL	Quality of life
QUANTEC	Quantitative analysis of normal tissue effect in the clinic
R1	Microscopically positive margin
R2	Macroscopically positive margin
RAO	Right anterior oblique
RASSFIA	Ras association (RalGDS/AF-6) domain family member 1A
RB	Retinoblastoma
RBE	Relative biologic effectiveness
RCC	Renal cell carcinoma
RCT	Randomized controlled trial
rcv	Receive/received
RFS	Relapse free survival
RLL	Right lower lobe
RML	Right middle lobe
RMS	Rhabdomyosarcoma
r/o	Rule out
ROM	Range of motion
RPO	Right posterior oblique
RR	Relative risk
RT	Radiation or radiation therapy
RTOG	Radiation Therapy Oncology Group
RUL	Right upper lobe
RUQ	Right upper quadrant
Rx	Prescription/prescriptions
S	Sacral (spine level)
SBO	Small bowel obstruction
SC	Spinal cord
SCC	(or SCCa) Squamous cell carcinoma
SCV	Supraclavicular
Sg	Surgery
SEER	Surveillance Epidemiology and End Results (data)
SFOP	French Society of Pediatric Oncology
Sg	Surgery
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
SIL	Squamous intraepithelial lesion
SQ	Subcutaneous
s/p	Status post
SPECT	Single photon emission computed tomography
SRS	Stereotactic radiosurgery
SS	Statistically significant
SSD	Source to skin distance
ST	Soft tissue (as in sarcoma)

STD	Sexually transmitted disease
STR	Subtotal resection
STS	Soft-tissue sarcoma
sup	Superior
SVC	Superior vena cava
Sx	Symptom/symptoms
T	Thoracic (spine level)
TD	Tolerance dose
TFT	Thyroid function test
tid	Three times a day
TMZ	Temozolomide
TNM	Tumor/node/metastasis
trilat	Trilateral
TRUS	Transrectal ultrasound
TSH	Thyroid-stimulating hormone
Tx	Treatment/treatments
UA	Urinalysis
UCSF	University of California at San Francisco
UE	Upper extremity
UH	Unfavorable histology
UK	United Kingdom
unilat	Unilateral
US	Ultrasound
U.S.	United States
UV	Ultraviolet
VALCSG	Veterans Administration Lung Cancer Study Group
VCE	Vincristine, carboplatin, etoposide (chemo regimen)
VMA	Vanillylmandelic acid
vs.	Versus
w	With
WBC	White blood cell
WBRT	Whole brain radiation therapy
WHO	World Health Organization
wk/wks	Week/weeks
WLE	Wide local excision
yo	Year old/years old
yr/yrs	Year/years

Symbols

+	Meaning with or and (as in Surgery + RT)
→	Meaning followed by
↑	Meaning increasing, high(er), or elevated
↓	Meaning decreasing or low(er)

General Principles of Radiation Oncology

1

Nicholas G. Zaorsky, Daniel M. Trifiletti, and Daniel W. Golden

Abstract

This chapter discusses the general management and thought process used by radiation oncologists. Several broad and basic principles of radiation oncology are discussed.

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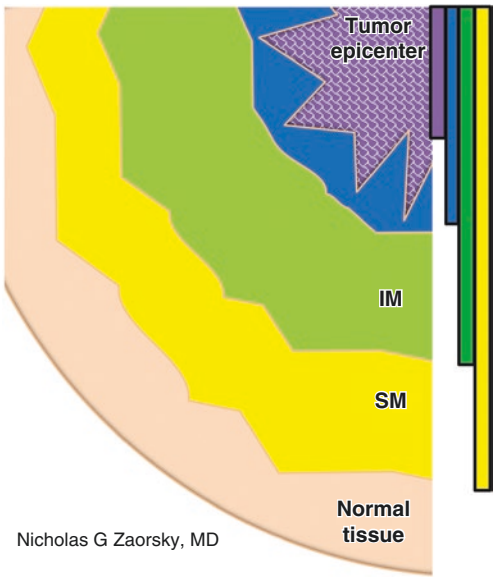


GTV: gross tumor volume

- All tumor that can be seen on a scan
- For reference, a 1 cm tumor has about 10^9 billion cells

CTV: clinical target volume

- The volume that has to be treated to achieve cure or palliation
- Should be defined before choosing a treatment modality
- Includes "crablike" extensions of the cancer, which contain:
  - microscopic cancer cells that cannot be seen on a scan
  - “Elective” lymph nodes that we think the cancer spread to
- CTV = GTV + a margin of where we think microscopic disease is located

IM: internal margin

- Variations in size, shape, and position of CTV relative to anatomic reference points (e.g. from breathing)

ITV: internal target volume

- Volume that encompasses movement of the CTV and the IM
- ITV = CTV + IM

SM: setup margin

- Uncertainties in patient positioning and alignment of therapeutic beams during treatment planning, and all treatment sessions

PTV: planning target volume

- Volume that encompasses movement of the CTV, the IM, and errors in setup / position of the patient and penumbra
- PTV = CTV + IM + SM

Disease	Scenario	General protocol	CTV	PTV	Dose	Chemo	Outcome
WHO IV (GBM) and WHO III (AA, AO, AOA) 1p19q non-codel; Unidel; AA Rim-enhancing (signifying central necrosis), irregular. Pathology: pseudo-palisading necrosis. High grade = Mitoses, Endothelial prolif, Atypia, Necrosis. IDH 1 WT = molecular GBM IDH1 = 2ndary GBM (LGG =>HGG)	Standard (Supp): < ~65–70 yo, KPS > ~60–70	MRI in 48h of surg. Send tissue for MGMT, IDH1/2, TERT promoter, EGFR	CTV46 = Post-op T2 **FLAIR** + cavity **+ 2 cm** CTV60 = **post-op** cavity + residual **enhancement + 2 cm** (cropped to 5 mm at natural barriers)	+ 3 mm w daily CBCT	46 Gy to **FLAIR**, 60 Gy to **enhancement**	+TMZ 75 mg/m2 QD, then 1m break, then 150 mg x 5d q 28d x 6c. Consider TTF No Avastin upfront	GBM RPA III: 22 m RPA IV: 15 m RPA V: 10 m
	>65–70 yo and good KPS	Decadron + PPI Keppra 500 mg BID if sz	CTV = T1post enhancement + **2 cm**	+ 3 mm w daily CBCT	**40 Gy / 10 @** 4 + TMZ → TMZ (Perry) **40.05 Gy / 15** @2.7 Gy (Roa 1; also WHO III KPS≤60), 75% of dose **25 Gy / 5 @ 5** Gy (Roa 2: 40/15=25/5) **34 Gy / 10** @ 3.4 Gy (Nordic: 34/10 better than 60/30)	No TMZ in Canada/Roa, yes TMZ in Nordic/Perry	Perry: MST 9.3 vs 7.6 m
	KPS ≤ 60				**TMZ alone** (Nordic) for poor KPS		
	Recurrence		GTV	+ 3 mm w daily CBCT	35 Gy / 10	Bev alone	
WHO III (AA, AO, AOA);	1p19q co-del (all are IDH1mut); others per WHO IV standard	MRI in 48h of surg. Send tissue for 1p/19q and IDH1 for oligo (all 1p19q codel are also IDH1 mut)	CTV45 = Post-op T2 FLAIR + cavity + 2 cm (cropped to 5 mm at natural barriers) CTV59.4 = If enhancing: post-op cavity + residual enhancement **+ 2 cm** (cropped to 5 mm at natural barriers). If non-enhancing: T2-FLAIR **+5mm**	+ 3 mm w daily CBCT	**45 Gy** to FLAIR, and **59.4 Gy** to conedown / 1.8 Gy	Adjuvant PCV q6w x 6c	94–02 GIII AO, AOA: RT vs RT, adj PCV 1p/19q co-del (all IDH1 mut): 7yr vs. 14.9yr 1p/19q intact, IDH1 mut: 3.3 vs. 5.5 Intact/WT: 1.3 vs. 1.0
LGG (diffuse astro: oligo, astro, mixed oligoastro; pilomyxoid; pleomorphic xanthoastro) G1 subtypes: JPA, pleomorphic xanthoastro, SEGC astrocytoma, subependymoma, gangliogliomas	**New hi risk**: > 40 yo or STR **Old hi risk** (also): size 6+ cm, astrocytoma, neuro deficit preop, cross midline, 1p19q non-co-del, IDH1/2 non-mut	**options:** RT + adjuvant PCV RT + concurrent TMZ (prefer for MGMTm) Decadron + PPI Keppra 500 mg BID if sz	CTV = T2 FLAIR + tumor bed + **1 cm**	+ 3 mm w daily CBCT	**50.4–54 Gy**	**High Risk options:** RT + adjuvant procarbazine POD8–21, CCNU d1, vincristine (PCV) RT + concurrent TMZ **Low risk option:** TMZ alone if 1p19q co deleted	Low risk: OS5 = 90%; PFS5 = 50% High risk: OS5 = 70%; PFS5 = 50%
	Low risk: <40 yo AND GTR	**Options:** Obs vs RT alone if sx or difficult to salvage vs. TMZ alone if 1p19q codel					
Ependymoma, brain	G1 = subependymomas and **myxopapillary** G2 = classic ependymomas G3 = **anaplastic** ependymomas	MRI in 48h of surg. RT in 8w.	CTV = initial tumor vol, tumor bed + 1 cm	+ 3 mm w daily CBCT	G2: **54 Gy** G3: **59.4 Gy**. If MRI spine/LP+, CSI to 36 Gy. Boost spine GTVs to **45 Gy**	Chemo no proven benefit	EFS5 GTR: 80% EFS5 STR: 40%
Ependymoma, spine		R0 = observe (only G1/2) R+ = limited field RT Spine mets = CSI + boost		+ 3 mm w daily CBCT	Limited field = **50.4 Gy.** If MRI spine/LP+, CSI to 36 Gy. Boost spine GTVs to **45 Gy**		
Ependymoblastoma	treat like STPNET/high risk medullo				CSI 36 Gy. Boost to **55.8 Gy**		
Meningioma		G1 Simpson1–3 (R0): obs G1 Simpson4–5 (R+): obs vs RT hi risk vol Recur: surg vs RT G2-3 (<10%): EBRT	Do not cover dural tail!!! **G1:** CTV54 = GTV + bed + **1 cm** **G2/3:** CTV54 = GTV + bed + **2 cm** CTV60 = GTV + bed + **1 cm**	+ 3 mm w daily CBCT	RTOG 0539: **PTV54** to tumor/bed +1–2 cm **PTV60** to G2/3 tumor bed + 1 cm Consider SRS 13 Gy (up to 17 Gy if G3), but not 1st choise. Optic n sheath: 45 Gy		G1: 90% LC in def EBRT, R0, R1+EBRT G2: MST 12y. LC 60% if R0, 70% LC surg + EBRT G3: MST 3y. OS5 50%.
Pituitary adenoma: Macro: ≥ 1 cm, micro < 1 cm PRL (30%), GH (25%), ACTH (15%). PRL: amenorrhea, galactorrhea. Cushing (ACTH): obesity, HTN, DM, hirsutism, skin, osteoporosis. Acromegaly (GH): bones, HA, cardiac dz	**RT if:** Inoperable; TSH secreting (always post-op); R+ with persistent hypersecretion or residual near critical structures; Recur after surg	Endo panel: TSH, FSH, LH, GH/IGF-1, cortisol, ACTH, PRL. Dex text.	CTV= GTV + bed + **2 mm**	+ 3 mm w daily CBCT	Functioning: **54 Gy**. Or SRS 20 Gy Non-functioning **50.4 Gy.** Or SRS 18 Gy	GH or TSH: Somatostatin ACTH: Ketoconazole	If no hormone normalization after surg, RT, meds,: Cushing's => adrenalectomy TSH => thyroidectomy
AVM	SRS best if < 3 cm, deep, defined focus			+ 1 mm	SRS 16–20 Gy	None	SRS reduces bleed risk 50% in latency period, 88% after obliteration. 2y obliteration = 90%
Acoustic neuroma	No mass effect. If mass effect, needs surg	Audiometry to check serviceable hearing	SRS: if < 3 cm. GTV = PTV. FSRT: if > 3 cm. PTV = GTV + 3 mm.	SRS = none FSRT = +3 mm w daily CBCRT	SRS = 12.5 Gy FSRT = 50.4 Gy in 1.8 Gy or 25 Gy / 5	No	
PCNSL		Vz exam. Slip lamp exam (20% ocular involvement). CBC, CMP, HIV, EBV, testicular exam, MRI spine. Bx first. No steroids bc 40% response.	If no ocular involvement, iso at bony canthi and ½ beam block. Cover post 1/3 orbit if slit lamp neg. Cover brain and cribriform, down to C2/3.		Chemo. If CR, WBRT to 23.4 Gy. If PR, WBRT to 30, boost GTV to 45 Gy If orbit involved, and if CR, 23.4 Gy to orbit; if PR 36 Gy. If no chemo: WBRT 36 Gy, boost GTV to 45 Gy. Avoid RT if > 60yo	R-MPV x 7c + IT MTX first (per RTOG 93–10)	80% CR to chemo OS5: 80% for pts who received WBRT PCNSL = Ocular involvement in 20% Ocular lymphoma = 80% risk of PCNSL later
Primary ocular DLBCL			36 Gy / 1.8 Gy fx. Half beam block post at post optic canal (tx CN II). If only 1 eye, tx ipsi globe, CN II.				
Trigeminal neuralgia		MRI thin slices	Single 4-mm isocenter; target is 3–6 mm anterior from junction of the trigeminal nerve and pons		**SRS 80 Gy to 100 % IDL.**		Median time to pain relief: 1–2m 60% pain free, 20% have decrease, 15% no change. <10% facial numbness
Brian mets		MRI w contrast. Always do workup for primary: breast, lung, RCC most common	Intact = GTV Post-op = cavity + 2 mm	+ 1 mm	RTOG 90–05. SRS to 80% IDL on linac. 0–2cm: 24 Gy, but use **22 Gy,** >2–3 cm: **18 Gy,** >3–4 cm: **15 Gy**		

Disease	Association	Workup	Treatment
HL CD15/30+, I-II F	MC = EBV LD = HIV, old	CBC, CMP, LDH, HIV, pregnancy test, EBV, albumin, ESR, albumin, echo, excisional bx, CSF if HIV+/testicular	**ABVD x 2**, restage w/ PET , Deauville 1–3, **ISRT 20 Gy,** Deauville 4, **ISRT 30 Gy** UK RAPID: ABVD x3, interim PET. D1–2: observe or ABVDx1; D3–4 ABVDx1, then ISRT 30 Gy.
HL CD15/30+, I-II UF		+ BM bx	**ABVD x 4**, restage w/ PET, Deauville 1–3 = **ISRT 30 Gy** Deauville 4 , **ABVD x 2**, restage w/ PET Deauville 1–3, **ISRT 30 Gy** Persistent Deauville 4 or 5 needs bx, if (+) it is refractory
HL III-IV (MASH ALL): Male, Age ≥45, Stage IV, Hgb <10.5, Alb <4, Leukocytosis >15k, lymphocytopenia <0.6k/mL (or <8%)]		+ BM bx	**ABVD x 2**, restage w/ PET Deauville 1–3 = **ABVD x4**, then observe Deauville 4 = **ABVD x 4**, restage w/ PET Deauville 1–3 ISRT to bulky sites to **36 Gy**
NLPHL CD20/45+, I-II			**ISRT 30 Gy (larger margin than HL)**, then PET. CR = observe. PR = R-CHOP or ABVD.
NHL relapse/refractory			RT after salvage chemo in pero-txp prior. Pre transplant 24–30 Gy / 20 fx BID 6 hours apart. Post txp 30 Gy in 17–20 Gy. If non-txp candidate, then 30 Gy for CR.
NHL, high grade: • Burkitt, lymphoblastic	t(8:14): Burkitt's lymphoma	+ beta2 micro, + LDH, + HBV, + EGD, + CSF, + BM bx	da-R-EPOCH or R-CHOP x 6c, then PET-CT, then **30 Gy ISRT** for PR
NHL, G2, Stage I–II: • follicular (G3B), mantle cell, DLBCL, T/NK cell, peripheral T cell, anaplastic large cell IPI: APLES: Age > 60, Performance >2, LDH > ULN, 2+ E sites, Stage III/IV	t(11:14): BCL-1, mantle cell lymphoma "Double hit": bcl-2, c-myc "Triple hit": above + bcl-6	Above, but no CSF + c-scope for mantle	I-II (non-X, i.e. < 7.5 cm): For IPI 0-1, **RCHOP x 3c**. Then PET. Then ISRT **30–36 Gy.** Boost FDG-avid residual dz to 40–46 Gy. For IPI 2–4 or X, **RCHOP x 6c.** Then PET. Then **+/–ISRT 30–36 Gy.** If unable to tolerate chemo, then 36–45 Gy ISRT,boost to 40–46 Gy. If high IPI, clinical trial for high dose chemo with autologous stem cell rescue. ISRT 36 Gy only to initial bulk dz.
NHL, intermediate grade, III–IV			III-IV: If high IPI, clinical trial for high dose chemo with autologous stem cell rescue. **R-CHOP x 4**, restage w/ PET. If CR, **R-CHOP x 2**, observe. Consider ISRT only to initial bulk (**36 Gy**), per German group. If PR, R-CHOP x 2, restage w/ PET. If PET negative: ISRT only to initial bulk (**36 Gy**) If PET positive: refractory, go to transplant.
• DLBCL, gastric			R-CHOP x 3, ISRT **30 Gy**
• DLBCL, testicular			Orchiectomy, R-CHOP x 6 w/ IT-MTX, scrotal RT to **30 Gy.** Electrons 9–12 MeV. No bolus.
• DLBCL, bone			R-CHOP x3c, ISRT **30 Gy if CR, 40 if PR**
• DLBCL, breast			R-CHOP x 6c + RT **36 Gy** to whole breast
Primary mediastinal B cell lymphoma (PMBCL)	35yo woman		DA-EPOCH-R x 6c. **NO RT** unless persistent focal dz, then 30 Gy.
Mediastinal gray zone lymphoma (GZL)	35yo man		DA-EPOCH-R or R-EPOCH x 6c. Always consolidate **30 Gy** + 10 Gy boost for PR.
NHL, low grade / indolent: • FL G1–2, MZL, MALT, SLL/CLL, MF FLIPI for FL ("*NoooooLASH*"): Sites: ≥5, LDH > ULN, Age ≥60, Stage III/IV, Hgb < 12. FLIPI-2: B2 micro, BM, Hgb < 12, LN > 6 cm, age ≥ 60	t(14:18), BCL 2, follicular lymphoma del13, t(14,19), tri12, SLL, CLL		Stage I–II, G1, no X: ISRT, **24–30 Gy** / 2 Gy fx Stage I–II, X, or unfav molecular: Chemo w R-bendamustine, then ISRT, **24–30 Gy** / 2 Gy fx Stage I–II G1, non-X and non-contiguous: chemo alone Stage III–IV: no cure. Palliate PRN. **2 Gy x 2**
• MALT, gastric	t(11:18) usually abx refractory	EGD, urea breath test, bacteria test	Bismuth, lansoprazole, tetracycline, metronidazole. Wait 1 year. **30 Gy / 20 (@1.5)** ISRT if refractory. Tx planning: NPO, 4D, 100 cc PO contrast.
• MALT, orbital	Chlamydia psittaci	bacteria test	Doxycycline. RT if refractory, **24 Gy / 12 fx.** Treat whole orbit.
• MALT, salivary	Sjogren		Abx. Surg. If R0, observe. Else, RT **24 Gy / 12 fx.**
• MALT, small bowel	Campylobacter jejuni	bacteria test	Abx. Surg. If R0, observe. Else, RT **24 Gy / 12 fx.**
• MALT, testis			RT **24 Gy / 12 fx** to contralattestis.
• MALT, thyroid	Hashimoto		Surg. If R0, observe. RT **24 Gy / 12 fx.**
• MALT, spleen	HCV		Surg. If R0, observe. RT **24 Gy / 12 fx.**
• MALT, breast			RT **24 Gy / 12 fx.** WBI.
• MALT, lung			Surg. If R0, observe. RT 24 Gy / 12 fx. Advanced stage: chemo + ISRT
• MALT, skin (Primary cutaneous MZL)	Borrelia burgdorferi		Surg. If R0, observe. RT 24 Gy / 12 fx. CTV = GTV + 1 cm. Palliate 2 Gy x 2.
Plasmacytoma			
• SEP	Lesion visible, plasmacytoma by bx (<5% plasma cells), no CRAB	CRP, LDH, ALP, albumin, B2 micro, Ca, SPEP/UPEP, serum free light chain. Bx. No Tc99 BS.	PTV1 to 50.4 Gy, ENI to 40 Gy.
• SBP			Bone with 2–3cm margin. Spine: whole VB Standard tx is RT, 40–50 Gy
MM	BM bx > 10% plasma cells, M-spike on SPEP or UPEP, CRAB		Bortezomib and dexamethasone x 2 c. Palliative **30 Gy / 10 fx**
MF			T1: PUVA, steroids, topical chemo, local electrons **24 Gy / 2 Gy** T2–4: TSEBT **24 Gy / 12 fx**, 4 days per week, 3 positions QOD.
Nasal NK/T cell NHL	EBV		Concurrent Chemo-RT (54 Gy) to involved dz w/ concurrent cisplatinum, 3c DeVIC
Chloroma / myeloid sarcoma			**24 Gy / 12 fx**

Site	Work-Up	Scenario	Treatment	CTV	PTV	Dose	Chemo	Follow-Up	Outcomes
Esophageal	- H/P: GERD, alcohol, smoking, dysphagia, weight loss - EGD + Bx -CT C/A/P +C -EUS if M0 -PET/CT -Smoking Cessation -PEG/PEJ -Bronch if above carina (25cm)	T2–4 or N+	Neoadjuvant CRT (followed by restaging PET/CT +/– EGD w/ Bx in 4 weeks) → surgery Or Definitive CRT	ITV + 4cm sup/inf and 1cm radial ENI: SCLV if proximal 1/3; celiac if distal 1/3; paraesophageal for everyone	CTV + 0.5cm	50.4Gy [can also do 45Gy + 5.4Gy CD if preop – CD volume = GTV + 1cm per RTOG 1010]	Neoadjuvant: Carbo AUC 2/ Taxol 50mg/m2 weekly Definitive: cisplatin 75mg/m2 + 5FU 1000mg/m2 on weeks 1, 5, 8, 11	H/P Q 3–6mos for yrs 1–2, then Q6–12mos for yrs 3–5, then annually CT C/A/P Q4–6mos yr 1, then decr freq EGD Q 3–6mos for yrs 1–2, then Q6mos yr 3	5-Yr OS: Stage I: > 90% Stage II: 40% Stage III: 10% Stage IV: < 5% pCR=30% R0=90%
Gastric	-H/P: satiety, hematemesis, detailed nodal exam (cervical axillary, periumbilical, SCLV), ascites, HSM -EGD + Bx -CT C/A/P +C -PET/CT if >T2,N+,M0 -EUS if M0 -Nutritional c/s +/– PEJ -Laparoscopy if >T1b or N+	High risk T2 [G3, LVSI, PNI, no D2 dissection] T3–4 or N+	Surgery → Adjuvant CRT	Gastric Bed Anastomosis LNs: SMA, perigastric, celiac for all; add paraesophageal + splenic If proximal/GEJ; add pancreaticoduodenal and splenic if middle; add pancreaticoduodenal + duodenal stump if distal	CTV = 0.5cm	45Gy in 25 fractions 5.4Gy boost if +SM 9Gy boost if GRD	1c of capecitabine (1000mg/m2 BID)D1–14 followed by 825mg/m2 BID capecitabine concurrent with RT followed by 2c of capecitabine (1000mg/m2 BID)D1–14	H/P Q 3–6mos for yrs 1–2, then Q6–12mos for yrs 3–5, then annually Monitor for B12 and iron deficiency Labs, imaging and EGD as clinically indicated	5-yr OS: Stage I: 65% Stage II: 40% Stage III: 15% Stage IV: 5%
Pancreas	-H/P: painless jaundice, abdo exam, weight loss -Pancreatic protocol CT -EUS + FNA Bx -ERCP w/ stent if obstructed -CT chest	Any	If resectable: resect → chemo (4c Gem/abraxane or FOLFOX) → CRT If unresectable: 4c chemo → CRT	Resected: CTV: [(proximal 1.5cm of CA, prox 3cm of SMA, PV, PJ, preop tumor volume) + 1cm] + [Aorta + (3cm to the R + 1cm to the L + 2cm anteriorly + 0.2cm posteriorly)] Definitive: ITV (gross disease and involved LNs) + 1cm	CTV + 0.5cm	50.4Gy in 28Fx	Capecitabine 825mg/m2 BID on radiation days	H/P Q3–6mos for 2 yrs, then Q6–12mos w/ CA 19–9 and CT (cat 2B) Pancreatic enzyme replacement	Resectable: MS 2 yrs , 3-yr OS=30%, LC 70–80% Unresectable: MS 10mos, 2-yr OS 10–20%
Rectal	-H/P: anemia, prior RT, IBD, DRE, pelvic exam in women, FHx -CEA -colonoscopy, proctoscopy -EUS or MRI -CT C/A/P +C	[TAE alone if: <8cm from verge, <30% circum, <3cm, G1, margin >3mm, no LVSI] T3–4 or N+	Neoadjuvant CRT → Surgery → adjuvant CT If cT1/2 taken for surgery and found to be T3/4 or N+ or +SM, give postop CRT → CT	Mesorectum up to rectosigmoid or 2cm superior to gross dz (whichever is more proximal) and 2cm distal to gross dz Presacral and internal iliac LNs If T4 : ext iliac If anal canal involved:+/– inguinals	CTV + 0.7cm Fields: PA: L5/S1 → 3cm below tumor + 2cm on pelvic brim laterally Lats: behind PS (in front if T4) → behind sacrum	45Gy to whole pelvis f/b 5.4Gy boost to GTV + 2cm	Concurrent Capecitabine 825mg/m2 BID on radiation days f/b 4 months of CAPOX or FOLFOX [total of 6 months of chemo]	H/P Q3mos for 2yrs w/ CEA if elevated at dx, then Q6 mos for yrs 3–5 Colonoscopy in 1 yr then Q5yrs CT C/A/P annually for 5yrs	50% LRF reduction w/ RT LRR < 10% at 10yrs with naCRT; 30% DMs 5-yr OS: Stage I: 90% T3 or N+: 75% T4N+: 50% M1, resectable liver: 30–40%
Anal	-H/P: sphincter tone, HIV, IBD, prior RT, pelvic exam with pap and HPV testing in women -Labs: HIV -Anoscopy + Biopsy -CT C/A/P +C -PET/CT	Any	Definitive CRT	CTV_A: [GTV + anal canal] + 2–2.5cm CTV_B: Involved LN(s) + 1cm CTV_C: Elective LNs (internal iliac, external iliac, inguinal) + 1cm	CTV + 1cm	T2N0: 50.4 Gy in 28Fx to CTV_A and 42Gy in 28Fx to CTV_C T3/4N0: 54Gy in 30Fx to CTV_A and 45GY in 30Fx to CTV_C N+: 54Gy in 30Fx to CTV_A., 54Gy in 30Fx to CTV_B if LN > 3cm OR 50.4Gy in 30Fx to CTV_B if LN < 3cm; 45Gy in 30Fx to CTV_C	Concurrent MMC 10mg/m2 and 5-FU 1000mg/m2 on D1 and D29	H/P in 8–12 weeks. If CR, DRE and inguinal nodal exam Q3–6mos for 5 yrs; Anoscopy Q6–12mos for 3 yrs, CT C/A/P annually for 3 yrs If persistent disease at 8–12 weeks, re-evaluate at 4 weeks. If persistent disease, restage. If progressive dz at 8–12 weeks, re-stage.	5-yr OS: Stage I: 85% Stage II: 75% Stage III: 50% Stage IV: 5%

Disease	Workup	Scenario	Contraindications	Treatment	CTV	PTV	Dose	Systemic tx
Prostate	PSA, MRI, Biopsy	VLR, LR		AS			PSA q 6m, DRE/bx no more than q 12m After 12-month bx, alternate mpMRI w/ bx. Indications to tx: ↑ in # cores, % involvement, ≥ G4; PSA DT < 3 years	No
		LR (T1-T2a, GS6, PSA <10)		EBRT	Prostate + prox SVs	+ 5 mm	78 Gy	No
	+ BS if T2 and PSA >10	IR (T2b-c, GS7, PSA 10–20)		EBRT	Prostate + prox SVs Distal SVs	+ 5 mm	PTV1 = 80 Gy PTV2 = 46 Gy	Consider ADT 6m in unfav IR
	+ BS + T, LFTs, CBC, CMP, Dexa, Ca, Vit D	HR (GS 8+, T3+, PSA >20)		EBRT + ADT	Prostate + prox SVs Distal SVs + pelvic LNs	+ 5 mm	PTV1 = 80 Gy PTV2 = 46 Gy	ADT x 2–3y Lupron (7.5 mg = 1 month; 22.5 mg = 3 months) = GnRH agonist (Degarelix = GnRH antagonist). Menopausal sx. Bicalutamide (50 mg/day) = anti-androgen. Check LFTs monthly. Diarrhea.
			> 60 cc, < 20 cc (if too large give ADT to shrink by 1/3) TURP defect Large median lobe	LDR-BT	Prostate	0 mm	I125, 145 Gy mono 110/50.4 Gy boost Pd103, 110 Gy mono, 100/50.4 Gy boost	
			Pubic arch interference IPSS > 15 (> 20 absolute) Anesthesia/sedation risk IBD/prior RT	HDR-BT	Prostate	0 mm	13.5 x 2, one week apart 15 Gy + 50.4 Gy	
	MRI BS if PSA > 10	Post RP Adjuvant: T3, R+ Salvage: Persistent or rising PSA post-RP			1 cm below UVA, lat to obturator internus, post to rectum, ant entire bladder below pubic symphysis, and 1 m of it superior to it. Pelvic LNs if pLN+	+ 5 mm	68 Gy. 74 Gy if GTV	aRT, N0 = RT alone (shared decision making about ADT) aRT, N+ = RT + 2y of ADT (Messing was life) sRT, N0 = RT + 6 months ADT if pre-RT PSA <0.7 ng/mL; else, 2y sRT, N+ = RT + 2y of ADT
Bladder	GU/rectal/GYN exam Cystoscopy w/ mapping + TURBT + random biopsies [Trigone/neck → urethral] CT C/A/P w/ CT urethrogram to evaluate UUT for synchronous lesions and evaluate LN ALP or sx → BS	Ta-LG		Obs				
		CIS		BCG x 6				
		cT1/Ta-HG		reTURBT, then BCG x6 → residual: BCG x 6 or cystectomy				
		cT2-T4aN0	Tumor>5cm, Hydronephrosis, multifocal, poor bladder fx, carcinoma in situ (CIS), incomplete TURBT, non-TCC histology, M+ disease, near ureteral orifices	RT	Bladder, prostate, prox urethra	+ 5–7 mm	60 Gy, 66 Gy / 30 fx	Cisplatin (40 mg/m2 weekly)
Testicular	LDH, HCG, AFP; do bilat testicular exam, supraclav and inguinal LN exam; CBC, CMP; CT CAP; fertility; sperm bank	IS: Any pT N0 M0 S1-3 IA/B: T1-T4 but N0 M0 S0		obs				
				Carbo1c AUC7				Carbo1c AUC7
				20 Gy PA	T11/12-L5/S1 CTV= (IVC+1.2cm) + (Aorta + 1.9cm)	PTV= CTV + 0.5 cm. A 0.7cm uniform margin around PTV to block edge accounts for penumbra.		
		IIA: T1–4 N1 (all ≤ 2cm (no more than 5 total pN+) S0-2		20 Gy DL + 10 Gy CD	From T11/T12, contour aorta and IVC down to the ipsilateral iliac arteries and veins stopping at the top of the acetabulum	PTV = CTV + 0.7cm to block edge Block edge CD = LN + 2 cm		
		IIB: T1–4 N2 (all 2 -≤ 5cm, or more than 5 pN+, or ECE) S0-2		20 Gy DL + 16 Gy CD				
		III						BEP 3c

General Principles [1–22]

Cancer Death Worldwide

1. Lung 1.59 M
2. Liver 745 K
3. Stomach 723 K
4. Colorectal 694 K
5. Breast 521 K
6. Esophagus 400 K

Cancer Visibility and Tumoricidal Dose

Number of cells	CT scan visibility	Example case	Dose necessary to kill cells (EQD2)
10^8	Not visible	R1 resection status post-chemo with CR	~50 Gy
10^9	1 cm^3	R2 resection Most visible cancers, including LNs	~66–70 Gy
10^{10}	10 cm^3	Bulky disease	

Dose necessary to kill 1 log = ~10–20 Gy

Resection Nomenclature

Resection type	Definition	CNS and peds protocol terms	CNS and peds protocol description
R0	Negative margins	GTR1	Not visible on operative microscope or postoperative imaging
R1	Grossly negative but pathologic positive margin	GTR2	Visible on operative microscope Not visible on postop imaging
R2	Grossly positive margin (surgeon can see with their eye)	NTR	Residual evident on postop imaging, nodularity <5 mm. Linear "streak" enhancement
		STR	Surgically removing tumor tissue Residual evident on postoperative imaging, nodularity >5 mm

Radiobiology

The "4 Rs" of Radiobiology

- Redistribution
- Repopulation
- Repair
- Reoxygenation
- Lethal damage = DNA double-strand breaks
- 1 Gy of radiation = ~20–40 DSBs
- Majority of radiation-induced cell death = mitotic catastrophe

Cell Cycle and Radiosensitivity

- Cell cycle: G1 → S → G2 → M
- Cells in late G2/mitosis = most radiosensitive
- Cells in late S/early G2 = most radioresistant

Blood Vessel Radiosensitivity

- Capillaries > arteries > veins.
- Arteries can tolerate 50–70 Gy CFRT.
- Veins are highly radioresistant.

Physics

- 1 Gray (Gy) = 1 Joule/Kg energy deposited in tissue
- The difference between γ-rays and X-rays is the source. γ-ray = natural decay of radioisotope, e.g., Cobalt-60, X-ray = manmade, e.g., linear accelerator
- Photon nuclear interactions:
  - (1) Coherent scattering (≈E)
  - (2) Photoelectric effect (≈Z^3/E^3) used for diagnostic imaging
  - (3) Compton effect (≈electron density) **dominates in radiotherapy**
  - (4) Pair production (≈E)

Clinical Care Path

- Consultation → Simulation → Treatment planning → Quality assurance → Treatment → Follow-up

LN Metastasis Nomenclature

- Sister Mary Joseph nodule: periumbilical met through falciform ligament
- Virchow's node: L supraclavicular mass where thoracic duct inserts into left venous angle and thoracic duct drains from cisterna chyli
- Krukenberg tumor: ovarian metastasis from breast, gastric, and others
- Irish LN: L axillary mass
- Blumer's shelf: tumor spread to retrouterine or rectovesical space (pouch of Douglas)

Preoperative vs Postoperative RT

Advantages of preop	Advantages of postop
Improved blood supply/ tumor oxygenation	Smaller target volume after resection/debulking
Target delineation more clear	Plan based on pathologic information
Radiated tissue is resected	
No tumor repopulation during healing	

Young Patients

- Fertility counseling
- Pregnancy testing
- Consider options to minimize normal tissue exposure (reduced RT protocol, protons)

Life Expectancy (US Social Security Data)

	M	F
65 y/o	18 y	20 y
70 y/o	14 y	17 y
75 y/o	11 y	13 y
80 y/o	8 y	10 y
85 y/o	6 y	7 y

TEACHH Model: Life Expectancy of M+ Patients

- Type of cancer. +1 if not breast or prostate
- ECOG. +1 if 2. + 2 if 3–4.
- Age. +1 if > 60
- Chemo (prior courses). +1 if >2
- Hospitalizations. +1 if yes
- Hepatic mets. +1 if yes

Groups

- A (0–1): 20 m
- B (2–4): MST 5 m
- C (5, 6): MST 2 m

Palliative Care

- Temel, NEJM, 2010: 151 NSCLC M+ patients randomized to SOC +/− early palliative care. Palliative care is meeting with palliative care team member within 3-week enrollment, and then monthly. Improved QOL, lower depression, less aggressive end-of-life care (54% vs 33%), more resuscitation preferences documented in medical record, and longer OS (11.6 m vs 8.9 m MST).
- ENABLE II: n = 322. Randomize to nursing-led multicomponent psycho-educational intervention vs usual care. Improved QOL, symptom intensity, and mood. No difference in resource usage.
- ENABLE III, Alabama (Bakitas, 2015): advanced cancer patients and oncologist determined prognosis 6–14 months. Randomize to early (at enrollment) vs delayed (after 3 m) palliative care. Palliative care is telehealth RN coaching session, monthly FU. One year OS was improved in early intervention group. KM

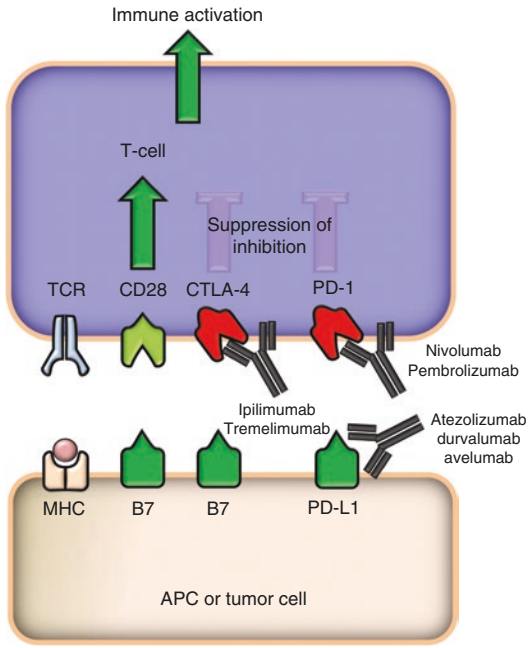
1-year OS 63% vs 48%, a 15% absolute benefit. No change in QOL between groups.

– Kumar, JCO 2017: interview 2300 families of deceased patients with advanced lung or colorectal cancer. Patients enrolled in hospice had more pain, the right amount of pain med, help with dyspnea, EOL wishes followed, excellent quality with EOL care, and highest QOL.

KPS vs ECOG

KPS	ECOG	Description
90	1	Restricted in strenuous activity
70	2	Unable to work. Out of bed >50% of waking hours
50	3	Limited self-care. Out of bed <50% of waking hours
30	4	No self-care

Immunotherapy



Plan Evaluation

– CB CHOP – contours, beams, coverage, hot/cold spots [23], organs at risk, and prescription

Not Meeting Dose Constraints

– Consider reducing PTV (probably don't want to do this if possible).
– Consider induction chemo to shrink tumor.
– Consider gating or DIBH.
– Consider resimulation with alternative patient positioning (prone, full bladder, belly board, etc.)
– Review QUANTEC and national protocol OAR constraints; they may provide protocol deviation/not violation options (less stringent constraints).
– Consider resimulation/replan during treatment.
– Hyperfractionate to reduce late effects (e.g., HNSCC), or use 1.8 Gy instead of 2 Gy doses for CNS or the breast.

CT Scans

– 0 Hounsfield units (HU) = density of water, air = −1000 HU, bone = >1000 HU level is the HU at the center of the window/level scale.
– Window is the HUs displayed across the available shades of gray.
– Anything outside of range is black (less dense than lower end of window) or white (more dense than upper end of window).
– Must consider window/level of CT scans when contouring target volumes.

Depression

Symptoms

Five symptoms × 2 weeks:

– Sleep changes: increase during day or decreased sleep at night
– Interest: loss of interest in activities
– Guilt (worthless)
– Energy (lack): common presenting symptom (fatigue)
– Cognition/concentration: reduced cognition and concentration
– Appetite (wt. loss): usually declined
– Psychomotor: agitation (anxiety) or retardations (lethargic)
– Suicide/death ideation

Nausea/Vomiting

- Ondansetron, orally dissolving tablet (ODT) available.
- Compazine.
- Reglan.
- Olanzapine. 2.5 or 5 mg. ODT available. Sedating, so start at bedtime.
- Dexamethasone.
- Lorazepam.

Pituitary hormones

~100% of patients will develop deficiency in at least one

Timing: ("G FLAT")

- GH.
- FSL/LH.
- TSH/ACTH.
- No effect on ADH; thus, there is no DI (however, DI is a common complication after pituitary surgery).

Disorders, Syndromes, and Genetics

Disorder or syndrome	Chromosome (sorted by #)	Tumor, disorders
Li-Fraumeni	p53	Glioma, choroid plexus papilloma, osteosarcoma
Cowden		Meningioma
Gorlin		Basal cell carcinoma, Medulloblastoma
Turcot		Medulloblastoma (Wnt), GBM, GI polyps
FAP	APC gene, causes WNT/beta catenin pathway irregularity	Desmoid tumors
VHL	**3p**	Hemangioblastoma, clear cell RCC, pheochromocytoma, pancreatic neuroendocrine tumors
	Trisomy 12	MALT lymphoma
	4q	GIST
	t(**8**:14) and t(**8**:22)	Burkitts, B-cell ALL
Tuberous sclerosis	**Chromosome 9**	Subependymal giant cell astrocytoma, retinal hamartoma
Gardner		"SOD": sebaceous cysts, osteomas, desmoid tumors
	t(9;22)	CML
WAGR	del **11p13**, WT1	Wilms, aniridia, GU anomalies,
Denys-Drash	**11p**, WT1 mutation	renal dz, male pseudohermaphroditism, Wilms
Retinoblastoma		Pineoblastoma, osteosarcoma
MEN-1	**11q13**.	3Ps: pituitary, parathyroid, pancreas
	t(11;14)	Mantle cell lymphoma
	t(11;18)	MALT lymphoma
	t(11,22)	Ewing sarcoma, PNET
ATM		PCNSL
Beckwith-Wiedemann	WT2 mut, **11p15.5**: IGF-2 overactivity, no active copy of CDKN1C	Macroglossia, gigantism, hernia, macrosomia, inc risk Wilms, pancreatic hepatoblastoma, rhabdomyosarcoma, macrosomia, macroglossia, omphalocele, prominent facial features (earlobe pits, creases), large kidneys, hemihypertrophy
	Gain **chr12**→ ↑MDM2→↓p53	PCNSL
	12q amp → ↑MDM2→↓p53	Well-differentiated/dedifferentiated liposarcoma
	t(**12**;16)	Myxoid round cell liposarcoma
	t(2:**13**) and t(1:**13**)	Alveolar Rhabdomyosarcoma
	t(14;18) → ↑Bcl-2	Intraocular lymphoma, follicular B-cell lymphoma
	t(X:18)	Synovial cell sarcoma
	t(14:19)	CLL (BCL3)
NF-1	**17q11**.1/neurofibromin	Optic glioma, JPA
NF-2	**chr 22** tumor suppressor missing	Bilac acoustic neuroma, spinal ependymoma
	22q deletion, INI-1/hSNF5 inactivation	ATRT and malignant rhabdoid
Osler-Weber-Rendu		AVM
Sturge-Weber		AVM
Tolosa-Hunt		OP with cavernous sinus involvement

High-Yield Neoadjuvant RT and pCR Rates

Study	Site	Treatment	pCR % (w NA-RT)	pCR % w/o NA-RT
SWOG 9416/INT 0160 [24]	NSCLC – pancoast/ superior sulcus	Of T3/4 N0/1 induction CRT to 45 Gy/25 with cis 50 mg/m^2 + etop 50 mg/m^2. Repeat CT during last week of RT (week 5) to allow surgeon to make decision resectability. If ineligible, continue RT to 61.2/1.8. Then surgery and postop chemo. 20% of unresectable went to complete RT. Of 80% going to surg, 94% had R0	29 (26% with minimal residual)	0
SAKK [25]	NSCLC	IIIA/N2 NSCLC. Rando to (1) neoadjuvant chemo (cis 100 mg/m^2 and docetaxel 85 mg/m^2) then RT (42/22) then surg vs (2) 3 c neoadjuvant chemo, then surg	16	12
POET [26]	Esophagus	T3-4 Nx adeno of lower esoph and gastric cardia → neoadjuvant chemo 2.5 c of cis/5-FU/leucovorin vs 2 c same chemo followed by CRT (30/15 + etoposide/cis). All got surg	15.6	2
CROSS [27]	Esophagus	368 patients (75% adeno, 23% SCC, 2% large cell undif) → surgery +/−preop CRT. 41.4 Gy in 23 fx with carbo/taxol. Carbo was AUC 2 and paclitaxel was 50 mg/m^2 weekly during RT	29% overall. pCR 23% adeno and 49% SCC	0
RTOG 9904 [28]	Gastric	Preop CRT (45 Gy with 5FU + taxol)	26%	
ACCORD-12 [29]	Rectal	T3-4 Nx resectable rectal cancer. *n* = 598. Rando to 45/25 + cape vs 50/25 + cape + oxali. TME planned 6w after CRT. 3 year OS 88% for both. Similar pCR	19	14
German [30]	Rectal	T3+ or N + → preop 50.4 + 5FU (1000 mg x2c) vs postop 55.8/31 + 5FU (1000 mg x2c on d1-5, w1 and w5). All patients got postop 5FU (500 mg/m^2/day × 4c)	8	0
Polish [31]	Rectal	T3-4 resectable rectal cancer. Rando to 25/5 + surgery in 7d vs NA CRT 50.4/28 with concurrent bolus 5-FU and leucovorin, surg in 4-6w	16, long course	
			1, short course	
TROG 01.04 [32]	Rectal	T3 N0-2 rectal adeno. 5x5, surg, 6 x 5FU vs 50.4/1.8 + 5FU, surg, and then 5FU × 4c. DFS, OR no difference. Similar G3+ acute tox: 6%; chronic: 8%. Increased pCR in long-course arm	15, long course	N/A
			1, short course	N/A
Meta-analysis RTOG 8802, 9506, 9706, 9906, and 0233 [33]	Bladder	Chemo-RT per protocol for MIBC	69	
GOG 205 [34]	Vulvar	Phase II, T3-4 unresectable→inguinal LND → preop CRT (cisplatin 40 mg/m^2 qw + 57.6Gy/32fx). 45 Gy AP/PA pelvis, 12.6 Gy boost. Then resection or biopsy to confirm CR. 78% pCR, 64% cCR, 40% 2 yr OS	78	
GOG 101 [35]	Vulvar	Advanced primary or nodes→cisplatin/5FU + RT; 47.6 Gy BID. 97% converted to resectable	31	
GOG 123 [36]	Cervix	WPRT 45 Gy then LDR BT, total point A dose of 75 Gy. Concurrent RT arm was cis 40 mg/m^2 qw × 6w. Wait 3–6 weeks, and then the surgery was class I extrafacial histo	52	41

CTCAE v4.0 Grading [6]

	1	2	3	4
General	Asymptomatic or mild, clinical or diagnostic observations; intervention not indicated	Moderate symptoms; limiting instrumental ADL; endoscopic or minor procedure indicated; medical management indicated	Severe sx; limiting self-care ADL, elective operation indicated	Almost died; emergent care needed (e.g., ICU admission)
		Instrumental ADLs: preparing meals, shopping for groceries, using phone managing money	**Self-care ADLs**: bathing, dressing, feeding, using toilet, taking meds, not bedridden	
Headache	Mild	Moderate	Severe	
Memory	Mild; forgetting car keys, grocery list	Moderate		
Eye blindness		> 20/40	<20/40 but >20/200	Blindness (*unilateral or bilateral*)
Eye dryness	Relieved with lubricants	Multiple agents needed	Vis acuity <20/40 but >20/200	N/A
HN dysgeusia	Altered taste, no change in diet	Altered taste, change in diet (e.g., supplement), unpleasant taste, loss of taste	N/A	N/A
HN – odynophagia		Moderate pain	Severe pain; TFs or TPN	
Ear – desquamation		External otitis with moist desquamation, edema, cerumen; TM perf; tympanostomy	Mastoiditis, stenosis or osteomyelitis, necrosis of the soft tissue or bone	Urgent op
Ear – hearing		Hearing loss but aid not indicated	*Unilat* hearing loss and aid or intervention indicated	Profound bilateral hearing loss, non-serviceable
Breast		Brisk erythema, patchy moist desquamation	Moist desquamation outside of creases, bleeding	Skin necrosis or ulceration, spontaneous bleeding, skin graft
Heart	EKG or physical findings only	Symptomatic pericarditis (i.e., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening; urgent intervention needed
Lung – dyspnea	SOB with moderate exertion	SOB with minimal exertion	SOB at rest	Urgent care needed
Lung – cough	Mild dry cough or DOE, no intervention	Requires narc antitussives	Severe cough not response to narcs or dyspnea at rest,+/− intermittent O2 or steroids	Continuous O2 or vent

	1	2	3	4
GI – diarrhea	<4 stools over baseline, mild increase ostomy output	4–6 stools/d over baseline, mod increase ostomy output, antidiarrheal med	7+ stools/d over baseline, incontinence; hospitalized, severe increase in ostomy output, parenteral support	Acute or subacute obstruction, fistula or perforation' GIB requiring transfusion
GI – constipation	Occasional sx, occasional stool softeners, laxatives, enema	Persistent sx with regular use of laxatives or enema	Obstipation with manual evacuation indicated	Urgent intervention indicated
GI – LGIB	Mild, no intervention	Moderate, medical intervention, or minor cauterization	Transfusion, radiologic, endoscopic, or elective operation indicated	Urgent care needed
GI – fistula		Altered GI function	TPN or hospitalized, elective operation	Life threatening
GU renal (units for CrCl are ml/min/1.73 m^2)	eGFR < LLN – 60 or proteinuria 2+	59–30	29–15	<15
GU sexual		Meds or penile pump	Penile prosthesis	
GU frequency	Present	Meds indicated	N/A	N/A
GU ejaculation	Diminished	Anejaculation or retrograde		
GU sperm	N/A	N/A	Azoospermia (absence of sperm in ejaculate)	N/A
GYN – menopause			Menopause: ovarian failure prior to 40 y/o	
GYN – dyspareunia	Mild pain, relieved with lubricants or estrogen	Moderate pain, *partially* relieved with lubricants or estrogen	Severe discomfort or pain, unrelieved with lubricants or estrogen	
Weight	Loss 5–10%	Loss 10–20%, nutritional support indicated	Loss 20 + %, TF or TPN needed	N/A
WBC	< LLN – 1500/mm^3	<1500–1000/mm^3	<1000–500/mm^3	<500/mm^3
Limb length	< 2 cm discrepancy	2–5 cm discrepancy, shoe lift indicated	>5 cm discrepancy, operation indicated	
Lethargy	Reduced alertness and awareness	Moderate, limited instrumental ADLs	N/A	N/A
Somnolence	Mild drowsiness or sleepiness	Moderate sedation, limiting instrumental ADLs	Obtundation or stupor	
Hypohidrosis, body temp	N/A	Symptomatic, limiting instrumental ADL	Increase in body temp	Heat stroke

Dose Constraints

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QUANTEC Dose Constraints

Critical structure	Volume	Dose/ volume	Max dose	Toxicity rate	Toxicity endpoint
Brain			<60 Gy	<3%	Symptomatic necrosis
Brain			72 Gy	5%	Symptomatic necrosis
Brain			90 Gy	10%	Symptomatic necrosis
Brain stem			<54 Gy	<5%	Neuropathy or necrosis
Brain stem	D1–10 cc	<= 59 Gy		<5%	Neuropathy or necrosis
Brain stem			<64 Gy	<5%	Neuropathy or necrosis
Optic nerve/chiasm			<55 Gy	<3%	Optic neuropathy
Optic nerve/chiasm			55–60 Gy	3–7%	Optic neuropathy
Optic nerve/chiasm			>60 Gy	>7–20%	Optic neuropathy
Spinal cord			50 Gy	0.2%	Myelopathy
Spinal cord			60 Gy	6%	Myelopathy
Spinal cord			69 Gy	50%	Myelopathy
Cochlea	Mean	<=45 Gy		<30%	Sensory-neural hearing loss
Parotid, bilateral	Mean	<=25 Gy		<20%	Long-term salivary function <25%
Parotid, bilateral	Mean	<=39 Gy		<50%	Long-term salivary function <25%
Parotid, unilateral	Mean	<=20 Gy		<20%	Long-term salivary function <25%
Pharyngeal constrictors	Mean	<=50 Gy		<20%	Symptomatic dysphagia and aspiration
Larynx			<66 Gy	<20%	Vocal dysfunction
Larynx	Mean	<50 Gy		<30%	Aspiration
Larynx	Mean	<44 Gy		<20%	Edema
Larynx	V50	<27%		<20%	Edema
Lung	V20	<=30%		<20%	Symptomatic pneumonitis
Lung	Mean	7 Gy		5%	Symptomatic pneumonitis
Lung	Mean	13 Gy		10%	Symptomatic pneumonitis
Lung	Mean	20 Gy		20%	Symptomatic pneumonitis
Lung	Mean	24 Gy		30%	Symptomatic pneumonitis
Lung	Mean	27 Gy		40%	Symptomatic pneumonitis
Esophagus	Mean	<34 Gy		5–20%	Grade 3+ esophagitis
Esophagus	V35	<50%		<30%	Grade 2+ esophagitis
Esophagus	V50	<40%		<30%	Grade 2+ esophagitis
Esophagus	V70	<20%		<30%	Grade 2+ esophagitis
Heart (Pericardium)	Mean	<26 Gy		<15%	Pericarditis
Heart (Pericardium)	V30	<46%		<15%	Pericarditis
Heart	V25	<10%		<1%	Long-term cardiac mortality
Liver	Mean	<30–32 Gy		<5%	RILD (in normal liver function)
Liver	Mean	<42 Gy		<50%	RILD (in normal liver function)
Liver	Mean	<28 Gy		<5%	RILD (in Child-Pugh A or HCC)
Liver	Mean	<36 Gy		<50%	RILD (in Child-Pugh A or HCC)
Kidney, bilateral	Mean	<15–18 Gy		<5%	Clinical dysfunction
Kidney, bilateral	Mean	<28 Gy		<50%	Clinical dysfunction
Kidney, bilateral	V12	<55%		<5%	Clinical dysfunction
Kidney, bilateral	V20	<32%		<5%	Clinical dysfunction
Kidney, bilateral	V23	<30%		<5%	Clinical dysfunction
Kidney, bilateral	V28	<20%		<5%	Clinical dysfunction
Stomach	D100	<45 Gy		<7%	Ulceration

Critical structure	Volume	Dose/ volume	Max dose	Toxicity rate	Toxicity endpoint
Small bowel (individual loops)	V15	<120 cc		<10%	Grade 3+ toxicity
Small bowel (peritoneal cavity)	V45	<195 cc		<10%	Grade 3+ toxicity
Rectum	V50	<50%		<10%	Grade 3+ toxicity
Rectum	V60	<35%		<10%	Grade 3+ toxicity
Rectum	V65	<25%		<10%	Grade 3+ toxicity
Rectum	V70	<20%		<10%	Grade 3+ toxicity
Rectum	V75	<15%		<10%	Grade 3+ toxicity
Bladder (bladder cancer)			<65	<6%	Grade 3+ toxicity
Bladder (prostate cancer)	V65	<50%			Grade 3+ toxicity
Bladder (prostate cancer)	V70	<35%			Grade 3+ toxicity
Bladder (prostate cancer)	V75	<25%			Grade 3+ toxicity
Bladder (prostate cancer)	V80	<15%			Grade 3+ toxicity
Penile bulb	Mean dose to 95% gland	<50 Gy		<35%	Severe erectile dysfunction
Penile bulb	D90	<50 Gy		<35%	Severe erectile dysfunction
Penile bulb	D60–70	<70 Gy		<55%	Severe erectile dysfunction

Site	Organ at risk	Dose constraint 1	Dose constraint 2	Dose constraint 3	Notes
Pediatrics	Long bone	V40 < 64%	Mean < 37 Gy	Max 59 Gy	
Pediatrics	Kidney	V10 < 80%			
Pediatrics	Flat bone	Minimize V35			
Pediatrics	VB	V18 all or none			18 Gy over entirety if receiving any RT; this will prevent scoliosis
Pediatrics	Skin/lymphedema				Keep longitudinal 2–3 cm strip of extremity to <15 Gy
Pediatrics	Soft tissue (to prevent RT-induced sarcoma)	V60			
CNS	Cauda equina	0.03 cc < 16 Gy	5 cc < 14 Gy		
CNS (SRS)	Brain stem	0.5 cc < 10 Gy			
CNS (SRS)	Optic nerves/ Chiasm	0.2 cc < 8 Gy			
CNS (SRS)	Spinal cord	0.35 cc < 10 Gy	Max 18 Gy / 3 fx (RTOG 0236, 0618)		Kilpatrick (2010) [1]
H&N	Mandible	0.1 cc < 70 Gy			
H&N	Temporal Lobe	0.03 cc < 68 Gy	1 cc < 58 Gy		
H&N/Lung	Brachial Plexus	0.1 cc < 66 Gy			
H&N	Brainstem	0.1 cc < 55 Gy			
H&N	Optic Nerves/ Chiasm	0.1 cc < 55 Gy			
H&N	Spinal cord (+ 3 mm)	0.1 cc < 50 Gy			PRV
H&N	Uninvolved constrictor	Mean < 45 Gy			
H&N	Contralateral SMG	Mean < 39 Gy			
H&N	GSL	Mean < 35 Gy			
H&N	Cochlea [2]	Mean < 35 Gy	<12–14 Gy/1 fx		For mean < 45 Gy, risk of hearing loss <30%.
H&N	Oral cavity	Mean < 30–40 Gy			
H&N	Lacrimal gland	Mean < 34 Gy			
H&N	Combination parotid [3]	Mean < 25 Gy			
H&N	Contralateral parotid	Mean < 20 Gy			
GI	Small bowel/ Stomach	1 cc < 60 Gy	V50 < 2%		
GI	Duodenum	2 cc < 55 Gy			
GI	Liver	V30 < 60%	Mean < 25 Gy		
GI (SBRT)	Liver	700 cc < 21 Gy			
GI (SBRT)	Duodenum	V15 < 9cc/1 fx V20 < 3cc/1 fx Dmax <23 Gy			Murphy (2010) [4]
GI	Kidney [3]				
GI	Kidney	V18 < 66%			
GI	Bladder	V40 < 35%			Same as prostate
GI	Femoral heads	1 cc < 45 Gy	V40 < 35%		
GI	Heart	V40 < 100%	V50 < 33%		

Site	Organ at risk	Dose constraint 1	Dose constraint 2	Dose constraint 3	Notes
GI	Lung	V5 < 50%	V20 < 20%	Mean < 12 Gy	
Thoracic	Lung (−PTV)	V5 < 60%	V20 < 30%	Mean < 18 Gy	Lung V5 not associated with toxicity per secondary analysis of RTOG 0617 [5]
Thoracic	Lung [3]				<20% risk of pneumonitis
Thoracic	Contra lung after EPP [6]	V20 < 7%			Rice (2007) [6]
Thoracic	Heart	V45 < 2/3	V50 < 25%	V60 < 30%	RTOG 0617
Thoracic	Heart	V30 < 50%	V45 < 35%		RTOG 1308
Thoracic	Heart				
Thoracic	Esophagus	V60 < 30%	Mean < 34 Gy		
Thoracic	Spinal cord	0.1 cc < 45 Gy			Max dose 54 Gy has <1% RT myelopathy per QUANTEC
Breast	Heart	V30 < 1%	Mean < 4 Gy		NSABP B51
Breast	Lung	V20 < 15%			
Breast	Breast	0.03 cc < 115%			NSABP B51
GU	Bladder	V40 < 50%	V65 < 25%		
GU	Femoral heads	V50 < 10%			
GU	Rectum	V40 < 35%	V65 < 17%		
GU	Rectum	V50 < 3cc (50 Gy SBRT)	V24 < 35% of rectal wall circumference		Kim (2014). Using 45–50 Gy/5 fractions for prostate cancer [7]
GU	Penile bulb				
GU	Kidney				
GU (HDR)	Bladder	V75 < 1 cc			
GU (HDR)	Rectum	V100 < 1 cc			
GU (HDR)	Urethra	V125 < 1 cc	V150 = 0 cc		
GYN	Rectum	V40 < 60%			RTOG 0724 (postop cervix)
GYN	Rectum	V40 < 80%			RTOG 1203 (cervix + endometrial)
GYN	Bowel space (SB, colon, sigmoid)	V40 < 30%			RTOG 0724, RTOG 1203
GYN	Bladder	V45 < 35%			RTOG 0724, RTOG 1203
GYN	Bone marrow	V10 < 90%	V40 < 37%		RTOG 1203
GYN	Bladder pt	<75 Gy, <80% of dose,	D2cc < 90 Gy		
GYN	Rectal pt	<70 Gy, <70% of dose	D2cc < 75 Gy		
GYN	Sigmoid		D2cc <75 Gy		
GYN	Small bowel	D2cc < 60 Gy	V55 < 15 cc		Verma (2014) [8]
Gyn (HDR)	Rectum/Sigmoid	2cc < 75 Gy			D2cc = the minimum dose to the maximally irradiated 2cc
Gyn (HDR)	Bladder	2cc < 90 Gy			
Gyn (HDR)	Upper vagina	Point <120 Gy			
Gyn (HDR)	Lower vagina	Point <90 Gy			

HN, CNS

	Protocols, institutional	SRS (for brain)
PTV	HN: Max < 110% Rx. D95% > 100% Rx. D99% > 93% Rx | GBM: D95% = 60 Gy D99% = 54 Gy	CI < 1.5–2
Temporal lobe	max < 68 Gy, 1 cc < 58 Gy	
Normal brain	Max 60 Gy	V12 < 10 cc (RN predictor)
Brainstem	Max < 54 Gy (HN), 60 Gy (RTOG 0529, 0825), 64 Gy (QUANTEC) V54 < 20% (ependymoma)	Max 12 Gy (required) Max 45 Gy (for trigem neuralgia)
Chiasm; Optic N	Max 54 Gy (HN) – 55 (GBM)	Max 8–10 Gy (prefer), 12Gy (required). Stay >3 mm from GTV
Pituitary	max 50 Gy	
Hippocampus (RTOG 0933)	Max 16–17 Gy D100 < 9 Gy	
Spinal cord PRV	max 45–50 Gy	Max 14 Gy
Retina	max < 45 (HN) – 50 (GBM)	
Lens	max < 7–10 Gy	
Lacrimal gland	mean < 34 Gy (41.4in RMS)	
Cochlea	max 35 Gy. 55 in NPX. mean < 35–45 Gy (also peds) V30 < 50%	Max 9 Gy Mean < 4 Gy
Inner ear	max < 50 Gy	
Dorsal vagal complex	mean < 12 Gy	
Parotid, contra	mean < 20 Gy (<20% Δ salivation)	
Parotids, combo	mean < 26 Gy	
SMG, contra	mean < 35–39 Gy	
GSL (larynx)	max < 66 Gy mean < 35–45 Gy (involved) mean < 20 Gy (uninvolved) V55 < 10%	
Oral cavity, ant	V35 < 35% V30 < 65%	
Oral cavity, uninvolved	max < 60 Gy mean < 30–40 Gy	
Lips	mean < 20 Gy	
Mandible	0.1cc < 70 Gy, 1 cc < 75 Gy	
Pharyngeal constrictor, sup	V65 < 30% V55 < 80%	
Pharyngeal constrictor, mid	V65 < 75%	
Pharyngeal constrictor, uninvolved	V60 < 15% V50 < 33% mean < 45 Gy	
Esophagus	mean < 30–34 Gy	Max < 16 Gy V11 < 5 cc
Brachial plexus (1 of 2)	Max < 66–70 Gy	

Lung

	Lung, 5 fx SBRT (RTOG 0813)	Lung, 30-35 fx (RTOG 1306/1308, LungART)
PTV	Rx to 60–90% IDL V100 > 95% Max < 120%	
Cord	Max 30	Max < 45–50 (<36–41 if BID) Block at 41.4 (meso)
Brachial plexus	Max 32 (say 30)	Max 66–70 Gy
Trachea/PBT	105% PTV Rx 18 Gy to < 4 cc	
Great vessels	105% PTV Rx 18 Gy to < 4 cc	
Chest wall (lung + 2 cm rind)	V30 < 30 cc V60 < 1 cc	
Skin	Skin max 32 Gy	
Esophagus	105% PTV Rx 27.5 Gy to < 5cc	105% PTV Rx Mean < 34 V60 < 17%
Lungs (-PTV or ITV)	V20 (bilat) < 10% V20 (ipsi) < 25% D1.5L max 12.5 Gy D1L max 13.5 Gy	V20 < 35% (<25% if BID) V20 < 31% (if PORT) V20 < 8% (if meso) V5 < 60% Mean < 20 (<13 if BID, <8 if meso)
Heart	32 Gy to < 15 cc 105% PTV Rx	V60 < 30% V45 < 35% (1308) V35 < 30% (Lung ART) V30 < 50% (1308) Mean < 26 Gy (not 35), < 9 for meso heart block at 19.8 (meso)
Stomach	NS	Block entirely for meso
Liver		Block entirely for meso

GI

	Esophagus (RTOG 1010) IMRT	Gastric (RTOG 0114) IMRT	Liver SBRT, 5 fraction (RTOG 1112) IMRT	Pancreatic (RTOG 0848)	Rectal (RTOG 0822) 3D	Anal (RTOG 0529)
PTV	Max < 110% D95 = 100					
Cord	Max <45	Max <45	Max 20–25 Gy	Max < 45		
Esophagus			Max 32 Gy			
Lungs (-PTV or ITV)	V30 < 20% V20 < 25% V10 < 40% V5 < 50% Mean < 20 (5–8)	V30 < 20% V20 < 25% V10 < 40% V5 < 50% Mean < 20 (5–8)				
Heart	Max 50 Gy Mean < 30 Gy V40 < 30–50%	Max 50 Mean < 30 V40 < 30%				
Stomach			Max 30 Gy			
Liver	Mean < 21 V30 < 30%	V30 < 60%	700 cc < 21 Gy Mean < 15 liver < 35 (10% risk) liver < 50 (50% risk)	Mean < 21–25 V30 < 30%		
Small bowel		Max < 56	Max 30 Gy	Max < 54 D15% < 45 D10% < 50	V45 < 65 cc V40 < 100 cc V35 < 180 cc V30 < 300 cc	Max < 50 Gy V45 < 20 cc V35 < 150 cc V30 < 200 cc
Large bowel			Max 32 Gy		V50 < 0.5 cc	V45 < 20 cc V35 < 150 cc V30 < 200 cc
Kidneys (1 of 2)	Max 45 V20 < 30%	Mean < 18 V20 < 30%	Mean < 10 Gy	D30-50% < 18 Mean < 18	V18 < 2/3 of kidney	
Kidney (1 of 1)	V20 < 20%	V20 < 20%	V10 < 10%	D15% < 18 V20 < 20%		
Femoral heads					V50 < 0.5 cc	V44 < 5% V40 < 35% V30 < 50%
Bladder					V50 < 0.5 cc V40 < 40%	V50 < 5% V40 < 35% V35 < 50%
Iliac crest						V50 < 5% V40 < 35% V30 < 50%
Genitalia						V40 < 5% V30 < 35% V20 < 50%

GU

	Prostate conventional 80 Gy/20 (Pollack/FCCC)	Prostate hypofrac 70.2 Gy/26 (Pollack/FCCC)	Prostate hypofrac 70 Gy/25 (RTOG 0415)	Prostate post-op 68 Gy/34 (Pollack/RTOG 0534)	Prostate SBRT 36.25/7.25 Gy (RTOG 0938)	Prostate LDR 145 Gy mono I125	Prostate HDR 13.5 Gy x 2 mono Ir192	Bladder 45 Gy, CD to 64.8 Gy	Seminoma 20–36 Gy
PTV	D100% > 95% V95% > 100%	D100% > 95% V95% > 100%	V100 >98% Max < 107%	D100% > 95% V95% > 100% Dmax < 115%	D0.03cc <107% Rx CK D0.03cc <120% Rx non-CK V100 >95% D0.03 >95% Rx	D90 > 100% of dose V100 > 90–95% V150 < 50–60%	V100 > 90–95% of dose		
Kidney (1 of 2)									D50 < 8 Gy
Kidney (1 of 1)									D15 < 20 Gy
Small/large bowel potential space				V45 < 150 cc				V50 < 5%	
Urethra					D1cc <107% Rx	UV150 ~0 (in volume) UV5 < 150% UV30 < 125%	D0.1 ≤ 120 Gy EQD2 D10 ≤ 120 Gy EQD2 D30 ≤ 105 Gy EQD2 D1cc < 150% dose (FCCC)		
Bladder (-CTV)	V65 <25% V40 < 50%	V50 < 25% V31 < 50%	V79 <15% V74 <25% V69 <35% V64 <50%	V65 < 50% V40 < 70%	D1cc <105% D90% <90% Rx D50% <50% Rx				
Rectum	V65 < 17.5% V40 <35%	V50 < 25% V31 < 50%	V74 <15% V69 <25% V64 <35% V59 <50%	V65 < 35% V40 < 55%	D1cc <105% D90% <90% Rx D80% <80% Rx D50% <50% Rx	RV100: <1 cc on day 0; and < 1.3 cc on day 30 D2cc < prescribed dose; and D0.1cc < 200 Gy	D2cc ≤ 75 Gy EQD2 D1cc < 100% of dose (FCCC)	V60 < 5% V30 < 50%	
Testis *Sterilize: 2 Gy*									PA: < 0.1 Gy DL: < 0.3–0.4 Gy
Penile bulb	Dmax < 50 Gy		Mean ≤51 Gy	D90 < 50 Gy	D1cc <100% Rx V20 <3cc				
Femoral head	V50 < 5%			V50 < 10%	V20 <10cc (both) D1cc <81% Rx			V50 < 10%	

GYN/STS

	Cervix 45 Gy WPRT+ CD to 54 Gy PMB +/– CD 60 to LN + 6 Gy x 5 BT	Endometrial 6 Gy x 3 BT boost + 45-50.4 WPRT Vag 45 Gy + 6x3 (RTOG 0418; GOG 279) RT alone: 5x5 + 45 Gy	Sarcoma 50 Gy / 25
PTV	HR-CTV = 85 Gy Point A = 85 Gy Point B = 60 Gy		
Kidney (1 of 2)			
Kidney (1 of 1)			
Small/large bowel potential space	Dmax 60 Gy	V55 < 5 cc V45 < 200 cc SB V40 < 30%	
Bladder (-CTV)	D2cc ≤ 90 Gy (4 Gy/fx in 5 fx) Bladder pt ≤ 70 Gy	D2cc ≤ 90 Gy V45 < 35% V40 < 50%	
Rectum	D2cc ≤ 70 Gy (4.5 Gy/fx in 5 fx) Rectal point ≤ 70 Gy	D2cc ≤ 70 Gy V40 < 80% V30 < 60%	
Sigmoid	D2cc ≤ 70 Gy		
Vagina	Surface < 140% pt A dose	Upper 1/3: 120 Gy Mid 1/3: 90 Gy Low 1/3: 70 Gy VSD = ~150% rx	Anus/vulva: V30 < 50%
Ovary *Sterilize: 2 Gy; Fail: 5-10 Gy*			
Testis *Sterilize: 2 Gy*			V3 < 5%
Vagina	upper third: 120 Gy middle third: 80–90 Gy lower third: 60–70 Gy	upper third: 120 Gy middle third: 80–90 Gy lower third: 60–70 Gy	
Femoral head		V30 < 15% V44 < 5%	V60 < 50%
Wt bearing bone			V50 < 50% Epiphysis max 20
Skin strip			V20 < 50%

Lymphoma

	Constraint
Rule of thumb use mean 5 Gy on every OAR. If can't meet this, then use constraints below.	
Lung	V20 < 20% Mean < 12 Gy
Heart	Mean < 15 Gy
Bone	Mean < 8 Gy
Breast	< 5–10 Gy
Thyroid	Mean < 15 Gy
Kidney	Mean < 20 Gy
Liver	V25 < 50%
Testes	2 Gy – sterility 0.5 Gy – acute azospermia
Ovary	5-10 Gy failure 2 Gy – sterility

Peds

Organ	Constraint
Lacrimal gland	Max 41.4 Gy (RMS)
Lens	Max 14.4 Gy
Globes	Max 35 Gy (Ependymoma)
Optic N	Max 56 Gy (Ependymoma) Max 45–54 Gy (RMS)
Brainstem	Max < 63 Gy (Ependymoma) D90% < 44 Gy (Ependymoma)
Cord	Max < 56 Gy D90% < 3 Gy (Ependymoma)
Chiasm	Max 46.8–54 Gy (RMS)
Heart	Max 30.6 Gy (RMS, Wilms)
Lungs (<1/2 of combined lung volume in PTV)	15 Gy/1.5 Gy max (RMS) V15 < 33% (NB)
Kidney	V14.4 Gy < 100% (NB/Wilms) 100% kidney < 14.4 Gy (NB/Wilms) Ipsi V19.8 Gy < 50% (NB/Wilms) Contra kidney V12 < 20% (NB/Wilms) Max 19.8Gy (RMS)
Liver	V9 < 50% (NB/Wilms) V18 < 25% (NB/Wilms) V30 < 15% (NB/Wilms) Max 23.4 Gy (RMS, Wilms)
Bladder	Max 45 Gy (Wilms)
Vertebral body	If in close proximity, treat whole VB to 18 Gy.
Small bowel	V45 < 50% (RMS)
Rectum	Max 45 Gy (Wilms)

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Pediatrics Cancers

2

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Abstract

This chapter discusses the general management of patients with various pediatric solid tumors, with special focus on principles that guide radiotherapy management. Several key components of pediatric cancer care are discussed.

Pediatrics Pearls [1]

DDx Posterior Fossa Tumor

- **Mnemonic: MADE JAM**
- Medulloblastoma
- Astrocytoma
- DIPG (pontine expansion)
- Ependymoma (solid + calcs may track into foramina of Luschka-Magendie)
- JPA (cystic/solid w/ enhancing mural nodule)
- ATRT
- Mets

Posterior Fossa Syndrome

- **Mnemonic**: **SAME**
- Swallowing dysfunction
- Ataxia
- Mutism
- Emotional lability
- *Occurs postop after resection*

DDx Suprasellar Mass

- **Mnemonic: COP GEMM**
- Craniopharyngioma
- Optic glioma
- Pituitary adenoma
- GCT
- Ependymoma
- Meningioma
- Mets

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DDx Pineal Tumor

- GCT
- Pineoblastoma
- Pineocytoma
- Glioma
- Meningioma
- Lymphoma
- Benign cyst

Small-Round-Blue-Cell Tumors (SRBCTs)

- **Mnemonic**: **LEARN NMR**
- Lymphoma
- Ewing family: Ewing sarcoma, extraskeletal Ewing, Askin (small cell of thoracopulmonary region), PNET
- ALL
- Rhabdomyosarcoma
- Neuroepithelioma
- All blastomas
  - Neuroblastoma
  - Nephroblastoma (Wilms)
  - Medulloblastoma
  - Retinoblastoma

BM Biopsy for

- Basically everything except medullo, non-clear cell Wilms, most brain tumors
- ATRT
- Rhabdoid/clear cell Wilms, Ewing, RMS, NMS
- HL III/IV or B

LP for

- **Mnemonic**: (PAGE Neurosurgery)
- Parameningeal RMS
- ATRT
- Germ cell tumors
- Ependymoma
- Medullo/Medullo-like (SPNET) (neuroendocrine)

Molecular Markers

	NSE	Desmin	Actin	Vimentin	LCA
PNET	+	–/+	+/–	+/–	–/+
Neuroblastoma	+	+	–	–	–
RMS	+/–	+	+	+	–
Ewing sarcoma	–	–	–	+	–
Lymphoma	–	–	–	+	+

CSI

Sim:
- Consent patient and family.
- Discuss need for anesthesia.
- Protons are preferred.
- Supine in five-point face mask with head extended and shoulders pulled down. Supine has easier access to airway, more reproducible head tilt, and it is more comfortable.
- Make sure spine is straight.
- Scan top of skull to coccyx.
- Contour the CSF. In spine include the FULL roots. In the brain, include all of CN II to the back of globe and the cribriform.

1. *Upper spine should be planned first.*
   - Each half must be <18 cm to allow feathering.
   - If the spine is too long, do extended SSD or split field into two, but leave gap at cord and feather jxn weekly (every 9 Gy).
     - Extended SSD causes more divergence, scatter, and MUs.
     - Two PA beams: preferred, match beams ant to cord at posterior VB (avoid overlap in cord).
   - **inf**: bottom of thecal sac + margin (determined from MRI, ~S2-3).
   - **sup**: C5–6 or as low as possible while still clearing shoulders on WB.
     - This low border makes sure you won't go through the brain or mouth when you feather up.
   - **Lateral**: ~1 cm lateral to pedicles of VB and catch sacral nerve roots inferiorly; field widens within the pelvis. Typical field width is 4–6 cm.
   - Gap calculation usually around 3 mm
   - If you have to use two fields:
     - **Skin gap** = ([0.5 × Length1 × d]/SSD1) + ([0.5 × Length2 × d]/SSD2): where d is the distance from the skin to were fields match.
     - **Feather**: avoids hotspots on cord. Move the junction superiorly 0.5 cm on 7th and 13th fraction or every 9 Gy. Cold spine match is preferred over hot. In doing so, WBRT collimator angle will stay the same, but the couch kick would need to be recalculated (below).
   - Therapist will put marker on patients' back each day to label field edges.
   - Prescribe to post aspect of VB at central axis. If too much variation, use compensators
2. *WBRT should be planned second.*
   - Iso behind lenses.
   - Two angles.
   - **Rotate collimator** to match divergence of spine field.
     - θ = arctan (½ length of thorax field/SSD)
     - ~10.5 degrees
   - **Kick couch**, feet toward gantry, to avoid divergence of WBRT field into spine field
     - θ = arctan (½ length of cranial field/SAD)
     - ~7.5 degrees
   - Also, angle WB gantry to avoid contralateral retina/lens.
     - Photons: RAO and LAO
     - Protons: RPO and LPO
   - Be sure to contour and cover the cribriform plate (1 cm to block edge), prost 1/3 orbits, and temporal lobes.
   - Block anterior to VB.
   - Inf border as low as possible, just sup to shoulders.

Protons

- Always consider protons, unless covering large volume (e.g., WART in Wilms)
- For CSI, protons decrease dose anterior to VBs
- If child is growing, the entire VB should be covered, or there will be growth asymmetry with aging. Proton planning differs significantly and should be done at a specialized center.

Pain Management in Peds

- Opioids often used as early intervention.
- NSAIDs and acetaminophen are avoided because NSAIDs have antiplatelet activity, the antipyretic effects may mask neutropenic fever, RCTs have shown inefficacy of NSAIDs for pain management, and there are renal/GI toxicities with combination chemos.

Second Neoplasm

- Childhood Cancer Survivor Study, Friedman, 2010: Overall, peds cancer survivors have six-fold increase in malignancy after treatment vs general population. At 30y, for 5-year-old peds patients, there is a 21% risk of *subsequent neoplasms* (0.7%/year) and 8% risk of *secondary malignant neoplasms* (0.4%/year) survivors. HL has the greatest incidence, with SIR of 8.7 at 30 y. Sarcoma has RR of 3.1.

Treatment Comparison for Pediatric Tumors

Tumor	Location and classic presentation	Med age	Buzzwords	Bad prognostics	Bx tumor?	BM bx?	Tx paradigm	Start RT by	CSI	Dose	Volumes
RMS	Mass. Fav or unfav subsites	2–6 emb15–19 alv	FOXO1, FKR t(2:13) t(1:13) NF1, Li-Fraumeni, Beckwith-Wiedemann SRBCT	FOXO1, FKR (bad)	Yes, can plan w surgery	Y	Surg, then risk adapted Group I tage 1–3: VAC, no RT Everyone else: VAC and RT	LR: 13w IR: 4w HR: 20w CNS: 0w	N	Group I: UH gets 36 Gy Group II: R1: 36 Gy; 41.4 Gy pLN+ to entire LN chain Group III: 45 Gy orbit; 50.4 Gy others	CTV = preop, pre-chemo GTV + 1 cm PTV = CTV + 0.5; or PTV = preop, pre-chemo GTV + 1.8–2 cm
NRSTS	Bone pain		Synovial sarcoma, t(X;18) MPNST		Yes	Y	Surg, then PORT for R1 HGs + chemo if >5 cm HGs		N	All LG → observe HG, ≤ 5 cm R0 → observe HG, ≤ 5 cm R1 → 55.8 Gy HG, > 5 cm → 55.8 Gy + Ifos/Doxo x 5 Unresected → NA CRT (45 Gy)	GTV = tumor on MRI post contrast CTV = 1.5 cm radially and longitudinally PTV = CTV + 0.5 cm w/ daily KV imaging
Langerhans cell histiocytosis (LCH)	HSC: skull lesions, DI, exophthalmos LSD: hepatosplenomegaly, LAD, lung lesions, bone lesions	2	Birbeck granules Hand-Schuller-Christian dz Letterer-Siwe disease	LSD, multisystem involvement	Yes	Y/N	If multiorgan involvement: HD pred + vinblastine If single bone, then RT	14d for DI	N	DI: 15 Gy to pituitary/hypothalamus Bone: 5–10 Gy (e.g., 3 Gy x 3 fractions with small margin) Adult: 15–24 Gy/2 Gy fraction	

Tumor	Location and classic presentation	Med age	Buzzwords	Bad prognostics	Bx tumor?	BM bx?	Tx paradigm	Start RT by	CSI	Dose	Volumes
Ewing sarcoma	Soft tissue (e.g., femur), "awakens from sleep," "growing pains"	14, skewed right	t(11:22), t(21:22), EWS SRBCT "moth eaten," "sunburst," "onion skin," "laminated," Codman's triangle, sclerosis		Yes	Y	Neoadj chemo w VDC-IE x 12w. Restage at week 12 MRI + PET. Then surg or RT. PORT if indicated. Hold adria and actinomycin during RT. Adj chemo for all 48 w. PORT if R+ (<5 mm), spill, >10% viable	chemo, restage, then week 13	N	R1/pN+/definitive VB: **50.4 Gy**/25 fxs R2/definitive elsewhere: **45 Gy** to pre-chemo preop +1.5 cm, boost GTV + 1 cm to **55.8 Gy**/31 fxs All w concurrent chemo (VC/IE), but hold adria M+: after all chemo, WLI to 15 Gy. Boost residual to 43 Gy	GTV1 = pre-chemo dz in tissue + bone CTV1 = GTV1 + 1–1.5 cm GTV2 = pre-chemo dz in the bone and post-chemo dz in tissue CTV2 = GTV2 + 1 cm
Nephro-blastoma/ Wilms (WT)	Intrarenal, circumscribed Can spill Abdominal mass Wilms = well. Rarely crosses midline. Won't move w inspiration. Macroglossia, aniridia, GU hypospadias or cryptorchidism. CCSK: the bone, brain mets; Rhaboid: brain mets. Lung mets > bone (vs NB).	4y unilat2.5y bilat 90% are <5yo	WT1: WAGR (del 11p13, WT1) Denys-Drash (WT1 mut) WT2: Beckwith-Wiedemann (11p) No calcs Stage III = BSS-LURPP SRBCT	Del ch22q, LOH 1p, LOH 16q, gain 1q, blastemal histo, anaplasia, CCSK, Rhabdoid	No (becomes Stage III), unless Stage V suspected Avoid vigorous exam	Y, for rhab-doid and CC	Surg for all. Then risk adapted Chemo for low risk Chemo, then RT for std risk	POD 8 (UH), max 14 for FH	N	Stages I–II, FH: no RT Stage III *or* UH: **10.8 Gy** to flank Diffuse anaplasia or rhabdoid: **19.8 Gy** to flank R2: boost another **10.8 Gy (21.6 Gy total)** Spill or rupture: **10.5 Gy** WART + boost residual by **10.5 Gy**/7 (**21 Gy** total) All w concurrent vinc Liver or unresected LN: **19.8 Gy** Whole lung **12/8** + boost residual to **19.5** or resect WBRT: 21.6 Gy/12 Focal liver: 19.8 Gy/11 fxs	usually AP/PA, Preop GTV + 1–2 cm based on CT, US, MRI, IVP

Neuro-blastoma (NB)	Extrarenal, ill-defined margins. 65% have abd mass (adrenal or paraspinal). "Not well." Cross midline. HTN, renal art compression. Opsoclonus. Calcified. HMA/VMA+. Bone mets > lung (vs WT)	1.5y	#1 extracranial solid tumor in peds Homer-Wright rosette Calcified Blueberry muffin. Raccoon eyes SRBCT	SANDS: ↑stage, ↑age, n-myc, diploid (hypodiploid good), Shimada 1p/11q loss	Yes, after ruling out Wilms +BM bx +MIBG	Y	Surg for all. Chemo for low risk+. RT rarely needed for low or std risk. For high risk (Stage 2–4 N-myc+; Stage 4 N-myc+), induct chemo, surg resection, myeloblat chemo, SCT, EBRT, immunotherapy	4–6 weeks after ASCT with CAPE	N	No RT for low or int risk; 24 Gy if cord compression, residual High risk: PTV = GTV + 1.5 cm. **21.6**/1.8 Gy +/– **14.4 Gy** for residual dz (> 1 cc or MIBG-avid) Met site: **21.6 Gy**, no boost If cord compression: surg, then chemo Cord compression: 9 Gy if <3. 21.6 if >3yo After RT, cis-retinoic acid Massive HSM: 4.5 Gy/1.5 Gy	preop, post-chemo tumor vol + 1.5 cm Boost postop M2: CTV = 1 cm to 55.8 Gy M3 Diffuse: CSI 39.6 GTV above vs below conus: 45 vs 50.4 Gy
Retino-blastoma	Retina. Opthalm sx: leukocoria, strabismus	infant	RB1 on ch13, G1/S checkpoint Flexner-Wintersteiner rosette "trilateral" SRBCT	ON involvement, extraocular m involvement. Thus, need bone scan, BM bx, CSF.	No bx will seed. EUA by opthalmologist w retinal mapping	N	Chemo w vinc/carbo.etop x 6c. Then local therapy (cryo, surgery, or RT) Bilat are txd as separate primaries.		N	EBRT to 40 Gy I125 plaque BT 40 Gy to apex ARET0321: Induction chemo, consolidation w SCT (stage IVA/IVB only), and response-adapted EBRT: II–III: if residual, dose is 45 Gy IVA: <5 mm residual or CR: no RT IVA: > 5 mm residual, 36 Gy IVB: 36 Gy CSI, 45 Gy to cranium, 50.4 Gy to pineal gland	Pre-chemo and presurgical disease +5 mm = CTV PTV = CTV + 5 mm

(continued)

Tumor	Location and classic presentation	Med age	Buzzwords	Bad prognostics	Bx tumor?	BM bx?	Tx paradigm	Start RT by	CSI	Dose	Volumes
Medulloblastoma (and supratent PNET)	CNS. 4th vent. Neuro sx Child = mid Adult = lat Blocks Aqueduct of Sylvius	7-9yo + 25yo	Chang staging COG: avg or High risk WNT (good) Group 4 (intermed) MYC (bad) Group 3 (v bad) Post-fossa syndrome Homer-Wright rosette Perivascular pseudorosette SRBCT	Myc Group 3	No bx. Surg for all. No LP if hi ICP	N	Resection. If <3yo, chemo. If >3yo, Then RT w vincristine.RT dose depends on risk group. Avg risk is >3 yo, < 1.5 cm2, M0, not PNET.	MRI brain 24–48 h postop.MRI spine 10–14d postop Then CSI by POD31	Y	**<3yo:** Resect, chemo, some centers radiate tumor bed only Consider CSI at 3yo. **Std risk:** CSI 23.4. Cavity boost to 54 Gy. **High risk:** CSI to 36 Gy. Cavity boost to 54–55.8 Gy Brain mets: 55.8 Gy Spine mets: 45 Gy	CTV = preop tumor + postop cavity +1.5 cm PTV = CTV + 5 mm
ATRT	CNS. 4th vent. Neuro sx	<3	INI-1/ SMARCB1 *loss* Vimentin, EPA, SMA		No bx. Surg for all. No LP if hi ICP	Y	Like high risk medullo Surg for all. Chemo investigational. PORT	MRI brain 24–48 h postop, MRI spine 10–14d postop Then CSI by POD31	Y	>3yo: 36 Gy CSI; boost to 54–55.8 Gy. If M+, boost spine dz to 45 Gy < 3yo: 50.4–54 Gy to primary alone	CTV = preop tumor + postop cavity +1 cm PTV = CTV + 5 mm
Pineoblastoma	CNS		Homer-Wright rosette Flexner-Wintersteiner rosette		Surg for all. No LP if hi ICP		Like high risk medullo, but lower boost. Surg for all. Adj RT		Y	If >3yo, CSI to 36, boost to 54 Gy. If <3yo, 50.4–54 Gy to primary site	
Pineocytoma					Surg for all	N	Like LGG		N	If R0, obs. If R+, 54 Gy	

Ependy-moma	CNS. 4th vent. 70% infratent, 30% supratent. Neuro sx, Calcified	5yo + 35yo	WHO G1–4 Ependymal rosettes Perivasc pseudoro-settes NF2 Calcs usually PNET is G4		Surg for all. No LP if hi ICP	N	Surg for all. MRI brain >10d postop if wasn't done preop RT if R+ or G2+. Role of chemo unknown	MRI spine and CSF cytology 10–14d postop	N, usly	Resid tumor + bed to 54, G3 or R1, boost to 59.4 respecting brainstem CSI only if M+ in CSF, to 36 Gy, boost to 45 Gy or 50–54 if no cord in field	Pre- and postop CTV = GTV + 1 cm
Optic pathway glioma	Vis sx		NF-1, café au lait		No bx, esp. if NF1	N	<10yo: surveil-lance, carbo+vinc. >10yo: RT+ carbo+vinc	N/A	N	50–54 Gy Never SRS	
LGG (JPA, DFA)	CNS. Neuro sx		Rosenthal fibers (JPA) Loss of 1p or 19q (oligode-nodglioma)		Surg	N	Can observe JPA in very young. Surg w GTR sufficient. Consider chemo and/or RT if unresectable or recurrent. NF-1 kids can regress		N	<5 yo: vinc+carbo to delay RT 10 + yo: 50.4–54 Gy in 1.8 Gy	GTV = visible tumor on MRI (T1 post and T2/FLAIR) CTV = GTV + 0.5 cm PTV = + 3 mm
HGG	CNS. Neuro sx				Surg	N	Adjuvant RT + temodar	~1–2 m	N	MSR, then RT + TMZ FLAIR to 45 Gy, then CD to enhancement 59.4 Gy	CTV1 = T2 FLAIR +2 cm CTV2 = T1 post con + GTV + 1.5PTV = + 0.5 mm
DIPG/ midline glioma	Brainstem. Neuro sx for 6+ months		Palsy of VI, VII; then IX, X, XI, XII; then III, IV, V		No bx	N	Steroids for upfront sx management. Definitive RT for all. Chemo only on study	N/A	N	54–55.8 Gy. Re-RT 2 Gy dx 12 fractions to GTV + 0.5 cm	CTV = GTV + 1 cm including entire BS. limited by bone, falx, tent

(continued)

Tumor	Location and classic presentation	Med age	Buzzwords	Bad prognostics	Bx tumor?	BM bx?	Tx paradigm	Start RT by	CSI	Dose	Volumes
Cranio-pharyn-gioma	Rathke's pouch. Neuro sx. Pituitary abnormalities		BRAF mutated Bimodal (10 or 50yo)		Surg	N	Limited surgery with RT at time of recurrence or after STR. Bleo, β-emitters. No chemo	N/A	N	RT to 54 Gy SRS 12 Gy if <2 cm and > 5 mm from optics	GTV = residual dz, inc cysts CTV = GTV + 0.5–1 cm PTV = + 3 mm
GCT/ NGGCT	Pineal or suprasellar. Parinaud's. DI. Bi temp hemianopsia. GCT and NGGCT look similar on MRI		Chang Staging isochromo 12 Poly-X Loss 1p and 6q Germinoma C-Kit+, HCG+/−, AFP- Endodermal sinus: AFP+, HCG-, c-Kit- Choriocarci-noma: HCG+, c-Kit- Teratoma: all neg	NGGCT do worse	Shunt for hydro, vis sx Bx if normal HCG, AFP No surg for germi-noma	N	GCT: CSF-, then WVRT only If CSF+, treat like low-risk medullo: CSI to 24, WVRT 21 Gy. If PR or PD, consider different dx. No chemo	N/A	If + CSF	Control: If CSF-, WVRT is 21–24 Gy If CSF+, CSI is 24 Gy, plus WVRT. Boost gross dz to 45 Gy Experimental: 2-4c carbo/etop. If CR: 21 Gy WVRT; 30 Gy IFRT	CTV1 = pre-chemo GTV + 1 cm CTV2 = WVW + 1 cm PTV = CTV + 5 mm
					Possible		NGGCT: all get chemo (carbo, ifos, etop) and CSI. May need surgery and then adj chemo, CSI, and IFRT	N/A	Y	All get chemo. Assess response. If RT, then 36 Gy CSI, then 54 Gy PF boost. If PR/SD, surg, if R+, HDSCT, then RT	

Pediatric Leukemia (T-ALL, B-ALL) [2, 3]

Pediatric leukemia (T-ALL, B-ALL)[2,3]

CNS stage	Definition	Notes	Incidence, %
1	neg cytology (no blasts)		27
2	< 5 WBCs/uL, age 1–20		32
3	≥5 WBCs/uL (or > 50/10^3 uL), CN deficit, or CNS lesion on imaging	CNS involvement found in 3% children at diagnosis w ALL. More common in AMML (20%) > ALL > AML, CML, CLL	37
"very high risk"	t(9:22): (Ph+ ALL) BCR-ABL fusion +/– t(9:22) hypodiploid (<44 chromosomes) DNA index < 0.98	Any of these criteria!	4

B-cell risk group	Definition
Low	Favorable response to treatment Favorable age (<10 yo) Low WBC count Hyperploidy, ETV6-RUNX1 positive(t[12;21] translocation associated w fusion protein formerly known at TEL-AML1), trisomies of Ch 17,10,4 Neg cytology (no blasts)
Standard	Favorable response to treatment Favorable age (<10 yo) < 5 WBCs/uL (aka < 50,000) No cytogenetic changes as seen in low risk group
High	Residual dz in bone marrow after induction chemo (>0.01% at d28–36) Age > 10 yo Unfavorable cytogenetic findings (e.g. ,9:22) (note, <1 yo not included in risk groups, but considered high risk)
Very high risk	No remission after induction (>5% blasts d28) Hypodiploid (<44 chromosomes), DNA index < 0.98 t(9:22): (Ph+) BCR-ABL fusion +/– t(9:22) T(4;11) MLL rearrangement iAMP21 amplification

Treatment

Risk group	Treatment
Low risk CNS 1–2	No cranial RT
T-ALL, no CNS disease, intermediate or high risk, CNS 1-2 Lymphoblastic leukemia CNS 1–2	No cranial RT (COG 1231)
High risk because age > 10 or < 1, >50K WBC, 9:22, T-cell	PCI 12 Gy at 1.5 Gy / fx
Any CNS3	Therapeutic WBRT 18 Gy / 1.8 Gy fx
Relapsed < 18 mo	CSI 24 Gy

General
- Leukemia is the most common pediatric malignancy (30%), followed by CNS malignancies (20–25%).
- Risk factors: Down syndrome, Bloom syndrome, Fanconi anemia, ATM, radiation exposure, and chemicals.

Presentation
- Fever, bleeding, bone pain, and lymphadenopathy
- Testicular enlargement
- Mediastinal mass (more common in boys w/ T-cell ALL)

Workup
- HP, labs, peripheral blood smear, LP, MRI brain, BM biopsy, US, or MRI testes

Histology
- 80% are B-cell origin.
- 20% are T-cell origin.

Genetics
- t(12:21): TEL/AML1. Good prognosis
- t(9:22): (Ph+ ALL)
- BCR-ABL fusion +/– t(9:22): poor prognosis
- hypodiploid (<44 chromosomes): poor prognosis
- DNA index < 0.98

Treatment
- Induction chemo→ intensification/consolidation → CNS-directed tx as indicated → maintenance chemo
- *Multi-agent chemo (i.e., hyper-CVAD [cyclophosphamide, vincristine, adria, dexamethasone])

ALL Chemo
- Very commonly used. Causes neuropathic pain in 35%.
- For CNS-directed therapy, IC MTX is usually used.

T-cell Acute Lymphoblastic Leukemia (T-ALL) Literature
- AALL0434: T-ALL w testicular involvement. Get four drug inductions. Response adapted. CNS 3 gets 18 Gy. CNS 1–2 intermediate- or high-risk get 12 Gy. Testic RT only if testicle remains positive (often by bx) at the end of induction for both newly dxd and relapse. Dose to testicle is 24 Gy/12 fx.

Target
- Posterior ½ of globes and optic nerves
- Inf border is C2/C3. Rationale for this is that dura is thicker above this level and high-dose chemo is less likely to penetrate (as opposed to spinal cord)

Testicular Leukemia
- If ever involvement of one testicle must bx other side.
- Standard tx is chemo, response eval, and SCT +/− maintenance chemo.
- If bulky dz, orchiectomy or **24 Gy.**
- Can also treat per AALL0434, where pts undergo four drug inductiona, and then according to response, they get different dose levels of MTX. If CNS 1 or 2 and intermediate or high-risk, then 12 Gy. If CNS 3, then 18 Gy. Patients only receive testicular RT if testicle remains positive, by bx, at end of induction for both nely dxd and testicular relapse patients. Dose is 24/2.

Rhabdomyosarcoma (RMS) [4–15]

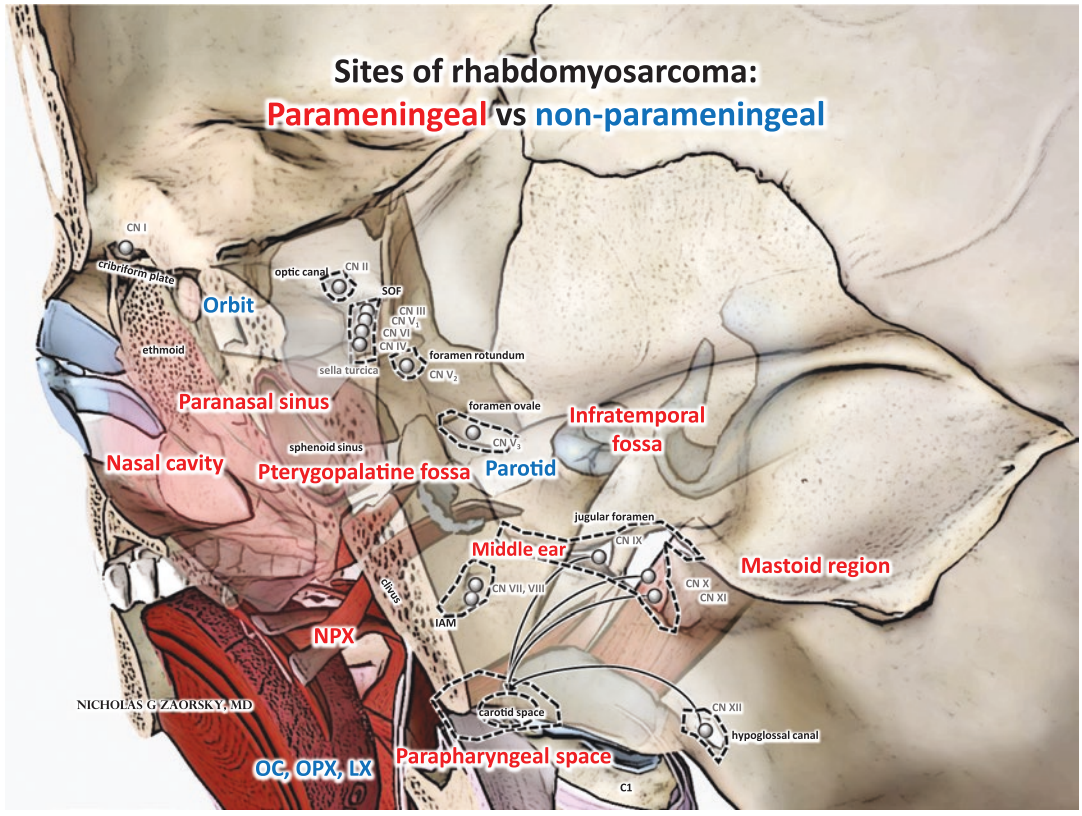
Histology (Green = fav; red = unfav)	Freq	Genetics	Locations	Age	OS
Fusion-negative (formerly embryonal)	65%	LOH 11p15 (IGF2 deletion) poly Ch8	orbit, H&N or GU	2–6 yo	66%
Botryoid	10%		GU (vag, bladder), NPX, biliary	Infant	95%
Spindle cell	<5%		paratesticular		88%
Alveolar FOX01-		FOXO1-			>90%
Undiff	5%				40%
Fusion-positive (formerly Alveolar)	25%	FOXO1+; t(2;13): PAX3/FKHR t(1;13): PAX7/FKHR	Trunk or abd	15–19	54%

- **T1** – confined to site of origin
  - T1a – ≤5 cm
  - T1b – >5 cm
- **T2** – extension beyond site of origin
  - T2a – ≤5 cm
  - T2b – >5 cm
- **N1** – nodes

Risk group (in color)	Stage	Group	When to start RT
Low risk	EMB 1 (fav site) EMB 2–3 (unfav site)	I–III, fav sites; I–II (R1, LN)	13w post-op
Intermediate risk	EMB 2–3 ALV	III any	4w post-op
High risk	4	IV	20w post-op

Risk group [in color] as a function of stage, group, and histology

						Group (post-op; not after induction chemo)						
		Description	Sites	TNM	5 yr OS	I: (R0, localized)		II: (IIA: R1/IIB: pLN+/IIC: A+B)		III: (GTV: unresectable/ R2/ excis bx)		IV: (M+)
Stage (pre-op)	1	*Fav site, M0*	*Fav site*: Orbit, non-PM H&N, non-Bladder/Prostate GU, Biliary	Any T, Any N	90%	Low (embryonal)	Intermed (alveolar)	Low (embryonal)	Intermed (alveolar)	Low (embryonal)	Intermed (alveolar)	High
	2	*Unfav site, small*	*Unfav site*: Parameningeal, Bladder/Prostate, Extremity, Trunk, retroperitoneal, Other	≤5cm and N0	85%	Low (embryonal)	Intermed (alveolar)	Low (embryonal)	Intermed (alveolar)	Intermed (alveolar)		High
	3	*>5 cm or N1*	Unfav site	>5cm or N1	70%	Low (embryonal)	Intermed (alveolar)	Low (embryonal)	Intermed (alveolar)	Intermed (alveolar)		High
	4	*M+*	–	M1	30%	High		High		High		High


Sites of rhabdomyosarcoma:
Parameningeal vs non-parameningeal
CN I
cribriform plate
optic canal
CN II
SOF
Orbit
CN III
CN V1
CN VI
CN IV
ethmoid
sella turcica
foramen rotundum
CN V2
Paranasal sinus
foramen ovale
Infratemporal fossa
CN V3
sphenoid sinus
Nasal cavity
Pterygopalatine fossa
Parotid
jugular foramen
CN IX
Middle ear
Mastoid region
CN VII, VIII
CN X
CN XI
clivus
IAM
NPX
NICHOLAS G ZAORSKY, MD
carotid space
CN XII
hypoglossal canal
OC, OPX, LX
Parapharyngeal space
C1

Overview
- ~3% of childhood cancers
- 50% of child soft tissue malignancy
- Arises from mesenchymal stem cells
- **SRBCT**
- VAC: vincristine/actinomycin-D/cyclophosphamide

Genetics: NF1, Li-Fraumeni, Beckwith-Wiedemann, Costello, and Noonan

Parameningeal Sites
- (**IMMNNOPPP – "I Make Money Nuking Numerous Petite Pediatric Patients"**) [***not orbital***]
- **I**nfratemporal fossa
- **M**iddle ear
- **M**astoid region
- **N**asal cavity
- **N**asopharynx
- **P**terygopalatine fossa
- **P**aranasal sinus
- **P**arapharyngeal region
- Non-PM HN sites: scalp, cheek, parotid, OC, OPX, LX
- Favorable sites: biliary, orbit, non-parameningeal HN, and non-bladder/prostate GU (vaginal or paratesticular) ("**BONG**")

Workup
- H&P and labs.
- CT/MRI.
- PET.
- BM bx.
- If parameningeal: LP with cytology +/− neuraxis MRI.
- If bladder: EUA and cystoscopy.
- If T1 N0 then no metastatic workup necessary.
- If T2 N0 FH, then CT chest +/− bone scan. If N+ or UH, then full metastatic workup.

Natural history: LN involvement varies widely by primary site. Orbit <1%. Extremity 15%. Paratesticular 30%. DMs in <25%, most common: the lung and bone.
- Most are v radiosensitive and chemosensitive
- 65% embryonal, 25% alveolar, and 10% other

IHC: Myogenin and MyoD1+ 97% sensitivity. In alveolar RMS, most cells stain +for MyoD; in embryonal RMS, only select cells stain.

Genetics
- Alveolar associated with:
  - **t(2;13): PAX3 + FKHD**
  - **t(1;13): PAX7 + FOXO1.** Not all alveolar are FOXO1. **PAX/FOXO1** is more important than histology.
- Embryonal associated with **LOH 11p15.5**. **LOH 11p15**; **Ch8** gains are good; hyperdiploid is good.

Chemo
- VAC: vincristine, actinomycin-D, and cyclophosphamide. SOC for M0 RMS.
- Vincristine causes neurotoxicity, CNS depression, palsies, bowel atonis, cramping, diarrhea, bladder atonia, leukopenia, and thrombocytopenia.
- Cyclophosphamide causes alopecia, infertility, second malignancy, gonadal suppression, hemorrhagic cystitis, leukopenia, SIADH, vasogenic sx, and renal failure.
- Actinomycin D causes sloughing, erythema, stomatitis, mucositis, myalgias, hepatotoxicity, ascites, abdominal pain, and myelosuppression.
- VAC/VI may have improved efficacy in intermediate-risk patients.

Trials
- Heyn 1974: VA after surgery improved OS.
- IRS I: group I patients didn't benefit from RT unless alveolar/undiff. Huge RT fields don't help. No dose response. 5-yr OS 55%.
- IRS II: LC improved for >40Gy (93% LC). RT was tumor +5cm. 5 yr. OS 63%.
- IRS I-II: prostate had 40% LN+ dz.
- IRS III: RT was tumor+2 cm, and bladder/vagina/uterus doesn't need RT after CR to chemo. 5-yrOS 73%.
- IRS IV: VIE, VAC, and VAI have the same PFS. QD or BID RT has the same PFS. oc cN0, 17% were pN+; thus, LND became routine. 3-y FFS for pts w 1–2 mets were 40%.

- IRS V: EFS for low risk ~87%, intermed risk 73%, high risk 32%. Intermed pts rando to VAC vs VTC + 2nd look surg. VAC alone won. High-risk pts VCR + I vs I alone. VCR + I won.
- IRS-VI:
- COG D9803: intermed risk→ VAC vs VAC alt with VTC. No difference in DFS or LF.
- Mandell 1990: retrospective of group II pts. No LC difference between <40 and >40Gy.
- ARST0331: goal to decrease Cytoxan dose to decrease sterility. RCT initially allowed omission of RT for group II/III females w vaginal RMS w excellent response to chemo but amended to mandate RT for them.

Management
- GTR. RPLND for paratesticular, axillary or inguinal LND for extremity, and if positive, then they are M+.
- Bladder/prostate → pelvic LN sampling (if + → LND). NPX has high LN involvement, but no LND unless cN+.
  - →VAC
  - →RT
  - →chemo
- Start RT based on risk classification.
- Dose of RT based on grouping.

No Surgery for
- Parameningeal
- Bladder/prostate (except if residual dz)
- Vagina/cervix/uterine
- Orbit

No RT Given Only if
- Vagina/cervix/uterus AND embryonal with CR after induction chemo
- Bx→VAC
- Group I extremity s/p amputation
- Group I paratesticular s/p orchiectomy
- Metastatic site R0

General Guidelines
- **Low Risk**
  - Stage 1–3, Group I: surgery→chemo (VA or VAC). No RT
  - Stage 1, Group II: surgery→chemo(VA) + RT at week 13 (36Gy for N0, 41.4Gy for N1)
  - Stage 1, Group III: surgery→chemo (VA) + RT (50.4Gy except orbit = 45Gy)
  - Stage 2 Group II: surgery→VAC → RT at wk 13 (36Gy)
  - Stage 3, Group II: surgery→VAC → RT at wk 13 (36Gy for N0, 41.4 for N1)
- **Intermed Risk**
  - Surgery→chemo→(repeat surgery if possible)→RT(50.4Gy).
- **High Risk**
  - Chemo (VCPT→VAC). RT to primary and metastatic sites (45–50.4Gy). RT may be initiated week 0 for symptomatic intracranial extension or cord compression. Dose is 50.4 for Group 3 tumors, unless orbital, where dose is 45 Gy.
  - For M+ PAX/FOXO1 negative, usually no RT to mets.
  - For M+ PAX/FOXO1 negative, RT to mets.
  - **High-risk non-CR/R0 mets:**
    - Try to tx at week 20 when tx primary, if not possible give at end
    - R0 resection or CR after chemo = No RT
    - R1 resection = 36 Gy
    - R2 resection or no surgery = 50.4 Gy

Lung Mets
- Always treat lung mets even if CR. Give WLI at the end of all tx
- WLI **15 Gy/1.5** (**12 Gy** if <6yo),
- then boost limited gross lung disease to 50.4 Gy if feasible
- boost limited lung disease to 54 Gy (give at end of all chemo).

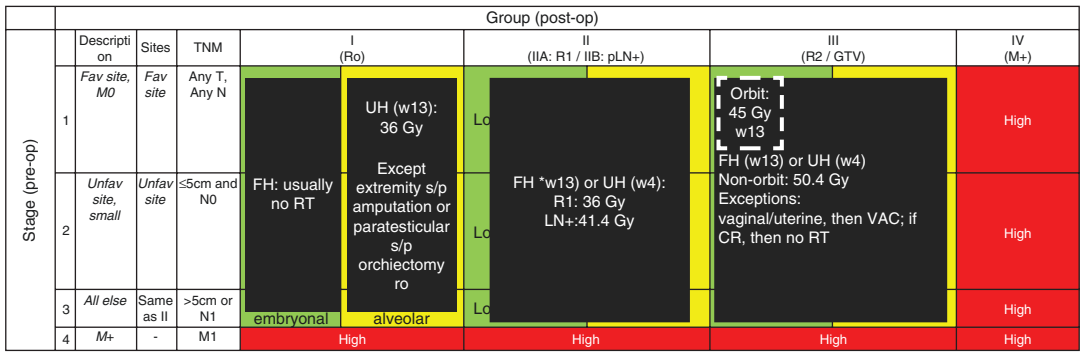
Technique
- Orbit: biopsy only→45 Gy to tumor+1 cm (5 mm CTV and 5 mm PTV; per IRS-VI), crop anatomic boundaries (pre-chemo scans).
- Otherwise CTV = GTV + 1–1.5 cm. Note 1 cm used on IRS-VI. **Definitive** non-orbit dose is 50.4 Gy.
- Contours should be *preop* and *pre-chemo* volume.

– PTV = CTV + 0.5 cm, i.e., PTV = GTV + 1.8–2 cm
– Include the entire LN chain if N+
– Site-specific recs:
  - Confine orbital CTV to orbit unless tumor extent beyond.
  - Boys 10+ with paratesticular tumors need aggressive LN sampling. Boys <10yo should have thin-cut CT (5 mm slices) or retroperitoneum and pelvis, w further workup for suspicious LNs. Boys all ages need LND if cLN+.
  - Radiate only regionally involved LN basins.
  - Gen no ENI in orbit, HN, and female GU.
  - Can move and replant gonads.
  - LND required for paratesticular, pelvic, and extremities (>20% LN+ rate).
  - CR after chemo in bladder/vagina/uterus doesn't need RT.
  - Never deliver actinomycin or adria w RT.
  - Cytoxan + RT can cause mucositis and consider dose reduction.
  - Lung metastases are not common, and management is not well studied, but whole-lung RT (15 Gy in 10 fractions) may be considered in setting of multiple lung metastases.

Timing

- For FH: usually w 13 unless reason to delay (e.g., marrow preservation).
- For UH: w4.
- If symptomatic intracranial extent can consider RT at w0.
- Timing (week 4 vs 13) probably is not important (Spalding, IJROBP, 2013).
- WLI, if indicated, may be deferred until completion of planned chemotherapy.

Group (Risk in color)	Other	RT timing		Dose
I FH	Embryonal	N/A		0 (NONE)
I UH	Alveolar	w4		36 Gy
II R1	FH and UH get the same dose	FH: w13	UH: w4	36 Gy
II pN+				41.4 Gy
III R2/bx	Orbit (w/ VAC)	w13		45 Gy
III	Non-orbit	w4		<5 cm: 50.4 Gy >5 cm: 59.4 Gy
IV	M+	w20 to primary and mets; or finish all chemo if too many mets; w0 if CNS sx not responding to chemo		R1: 36 Gy R2+: 50.4 Gy Lung mets 15/1.5 or 12/1.5



High-Yield Cases

Orbit: stage I, group III
- GTV = pre-chemo volume, CTV = GTV + 1 cm (do not need to include whole orbit)
  - Dose = 45 Gy, wk 13
  - Constraints: lacrimal gland = 41.4 Gy, lens = 14 Gy, optic nerve = 45 Gy. IMRT or wedged pair

HN, Non-PM
- **Oral cavity:** stage I, group I, embryonal
  - No RT
- **Oral cavity:** s/p bx only. stage I, group III. Low risk. 50.4 Gy/28

HN, PM
- **Middle ear: stage II, group III**
- GTV = pre-chemo volume, CTV = GTV + 1 cm
- Dose = 50.4 Gy, wk 4
- IMRT

GU, Non-BP

Paratesticular: stage I, group I, alveolar

- Surgery with inguinal orchiectomy with high ligation of spermatic cord + ipsilateral RPLND if <10 and CT + or ≥ 10 yo
- No RT (tumor bed has been removed)
- *if +pN (Group 2) → 41.4 Gy dog leg, wk 4
- *if residual (Group 3) → 50.4 Gy

Vaginal/uterine: stage I, group III

- Bx → VAC. If CR, no RT

Bladder/prostate: stage II, group III

- w/u = EUA w/cystoscopy
- Bx + pelvic LN sampling → VAC → RT → salvage surgery if necessary (60% bladder preservation)
- Dose = 50.4 Gy, wk 4

Extremity: stage III, group 1

- Sx = WLE + SLNBx
- Dose = 36 Gy
- *amputation → no RT (tumor bed has been removed)

Organ	Dose constraint from COG-D9602
Kidney	19.8 Gy max
Liver max	23.4 Gy max
Chiasm	46.8 Gy max
Heart	30.6 max
Abd/pelvis	24 Gy/1.5 Gy max
Lungs (<1/2 of combined lung volume in PTV)	15 Gy/1.5 Gy max
Lacrimal gland	41.4 Gy max
Lens	14 Gy
Optic N	45 Gy max

Non Rhabdoid Soft Tissue Sarcoma (NRSTS)

Most Common Histologies
- Synovial sarcoma, t (X;18)
- MPNST

ARST0332 Treatment Paradigm
- All LG → observe
- HG, ≤ 5 cm R0 → **observe**
- HG, ≤ 5 cm R1 → **55.8 Gy**
- HG, > 5 cm → 55.8 Gy + Ifos/Doxo x 5
- Unresected → Neoadjuvant CRT (45 Gy)
- COG volume definition (≤ 18 y)
  - GTV = tumor on MRI post contrast
  - CTV = 1.5 cm radially and longitudinally
  - PTV = CTV + 0.5 cm w/daily KV imaging

Ewing Sarcoma [4–8, 16–21]

Overview
- Three hundred cases/yr. Median age 14, skewed right.
- Caucasian.
- Can arise in bone or soft tissue.
- Tends to be radiosensitive.
- Ewing sarcoma is generally staged as local vs metastatic but refers to STS chapter for reference for a formal staging system

Natural History
- Location
  - 25% in axial skeleton (CW, spine, skull)
  - 20% in pelvis
  - 65% in lower skeleton (30% in femur, 10% in tibia)
  - 15% in upper skeleton
- 80% localized but 25% have macromets and nearly all have micromets
- Strong rationale for local therapy to DM, being investigated on open COG study currently
- DM sites: the lungs, bone, marrow

Histology
- **SRBCT**
- Ewing family: Ewing sarcoma (87%), Extraosseous Ewing (8%), PNET (5%), Askin's tumor (a Ewing of the chest wall)
- EWS: RNA-binding protein
- EWS and FLI work as chimeric TF
- **t(11:22):** involves the FLI1 on ch11 and EWS gene on ch22
- **t(21:22):** 5–10%. ERG and EWS
- ↑c-myc activity (↑n-myc in neuroblastoma)
- CD99+, vimentin+, NSE- (PNETs are CD99+, vimentin+, NSE+)

Disease	5y OS %
Localized	70
Single met	50
Diffuse mets	30

Workup
- H&P, labs, plain film
- CT/MRI, bone scan or PET-CT, CT chest
- Chest imaging necessary to rule out RMS, Wilms
- LDH
- Bx: open is best. Longitudinal cut
- BMBx
- Cytogenetics bc t(11;22) found in 85%
- Fertility preservation
  - Male (infertility = 2 Gy) → sperm bank + clam shell
  - Female (ovarian failure = 8 Gy) → ovarian transposition
- **DDx ("EGMODE")**
  - Epiphysis = **Giant cell**
  - Soap bubble appearance
  - Metaphysis = osteosarcoma
  - Sunburst, Codman's triangle
  - Diaphysis = Ewing
  - Moth-eaten, onion skin
  - MRI findings: T1 hypointense, T2 heterogeneous
  - Other: met, trauma, osteomyelitis, lipoma, Legg-Calve-Perthes, osteosarcoma, RMS, sarcoma, lymphoma, neuroblastoma
- DMs are principle concern
- Plain film: "moth eaten," "sunburst," "onion skin," "laminated," Codman's triangle, sclerosis, permeative. Usually lytic at diaphysis

Poor prognostics: central lesions, >8 cm (200 cc), M, high LDH, soft tissue extension, poor chemo response

Trials
- IESS-1: nonmetastatic dz → VAC + D vs VAC vs VAC + prophylactic whole-lung RT. VAC + D won. 5 yr. RFS (60 → 24 → 44%).
- IESS-2: VAC + D high dose vs continuous. High dose improved RFS but not OS.
- IESS-3: VACD +/− IE. More chemo won. 5 yr OS 61 → 72%. Did not improve OS for M1 disease.
- CESS 86: chemo→ surgery vs surgery+PORT vs RT alone. No difference in 5 yr OS (69%). LC worse without surgery (100 → 95 → 86%).
- POG 8346, Donaldson 1998: chemo→surgery or RT. RT was randomized whole bone 39.6 + boost 16 Gy vs 4 cm margin to

55.6 Gy/1.8 Gy fx. Central path and RT review. No difference in LC or RFS. LC was 53% in both RT arms. Thus, do not treat whole bone. LC was 80% in extremity, 69% proximal, 82% central, 44% pelvis. Protocol deviation → poor outcomes.
- EICESS analysis: any patients with lung mets benefited from WLI with improved EFS.
- Schuck 2002: Askin tumors. 7 yr EFS improved with hemithorax RT and boost to primary.
- No RCTs to guide surgery, RT, surg + RT. Selection bias confounds data; central tumors likey to get RT, while peripheral likely to get surgery.
- AWES0031: chemotherapy Q2 weeks improved EFS compared to Q3 weeks.
- AEWS 1221: current COG M+ ES protocol examining anti IGF-1R mAb ganitumab. All pts have local therapy to primary + DMs. RT to metastatic sites is a study question. SBRT recommended for DMs in bone <5 cm in max dimension.

Chemo
- **VDC/IE**: vincristine, adriamycin, cyclophosphamide, ifosfamide, and etoposide. The standard in the USA.
- **VTC/VDC**: vincristine, topotecan, and cyclophosphamide/VDC. This is on AEWS1031
- **VIDE**: vincristine, ifosfamide, doxorubicin, and etoposide. The standard in Europe.

Ewing Treatment Paradigm
- (1) NAC w VDC, alt with IE x 12 weeks. Note that on AEWS1031, randomization to VDC/IE vs VTC/VDC.
  Preop RT indications: Expect R+. Preop dose 36–45 Gy.
- (2) Then at week 12, local treatment: surgery or RT (try to avoid both). Surgery is preferred, unless unresectable.
  - "Expendable bones" are ribs, fibula, clavicle (lateral 4/5ths), and ilium.
  - "Borderline resectable" bones are long bones and mandible. With wide resection and good response, 1% LR rate. If poor response, 12% LR.
  - Surg margin: 2–5 cm is preferable for bone but accepts >1 cm, >0.5 cm for soft tissue (fat, muscle, medullary bone), >0.2 cm for fascia, periosteum, and septae.
  - Unresectable bones (more likely axial) are maxilla, BOS, vertebrae, and periacetabular pelvis. Also soft tissue. These typically receive RT.
  - If giving RT, adriamycin and actinomycin-D are held during RT.
- (3) PORT if necessary. Indications: R+ (<5–10 mm) and poor response from chemo (<90% tumor necrosis)
- (4) Adjuvant chemo, up to 48w
- LC w RT alone is >70%. LC is lowest in pelvis is 70–80% and 90–95% in the extremities
- Doses >60 Gy have high-risk bone malignancy
- Doses <40 Gy have high LR rates

NCCN
- **Preop RT (Rare to do this!)**
  - 36 Gy.
- **Definitive RT**
  - MRI essential, inc T2/FLAIR.
  - GTV1 = *pre*-chemo dz in tissue + bone.
  - CTV1 = GTV1 + 1–1.5 cm.
  - GTV2 = *pre*-chemo dz in bone and *post*-chemo dz in tissue. If dz is pushing on an organ but not invading, and has response, do not pre-chemo volume.
  - CTV2 = GTV2 + 1 cm.
  - PTV = CTV + ~0.5 cm.
  - PTV1: **45 Gy/25 fxs.** Exception is extraosseous ESFT with CR to chemo, then dose is **50.4/28 fx** and then no PTV2.
  - PTV2: boost **10.8 Gy/6 fxs**, total to **55.8 Gy** (unless at cord tolerance, then stop at **45–50.4 Gy).** COG and IESS both have definitive dose of 55.8 Gy.
  - All w concurrent chemo hold adria and actinomycin.
  - Consider boosting to 59.4 for chemo response <50%.

– **Postop RT**
  - Wire scars and drain sites. Bolus.
  - GTV1 and CTV1 are the same.
  - GTV2 is residual bone, microscopic margin soft tissue abnormality.
  - R0: **observe.**
  - R1: **50.4 Gy/28 fxs.**
  - R2/bx/GTV: 45–50.4 Gy + boost to **55.8 Gy/31 fxs** (like in definitive).
  - Concurrent chemo.

Other Treatment Considerations
– **N+**
  - If resected, 50.4 Gy to nodal bed.
  - If not resected, 55.8 to gross sz.
– **Bladder**: avoid bladder RT w cyclophosphamide or ifosfamide bc of risk of hemorrhagic cystitis
– **Paraspinal tumors** stop at **45–50.4 Gy** (cord tolerance)
– **Lung primary (Askin's):** hemithorax RT (15–20 Gy at 1.5/fx) followed by boost of primary
  - Recommended if pulm mets. Level 4 evidence for improved EFS.
  - Target bilat lungs. No cardiac shield. Shield bilat shoulders.
– **Metastatic disease**: current study is AEWS 1221 and requires RT.
  - M+ has same tx paradigm, except 42 w of chemo (VAI). Local tx is w13 to all M+ sites except the lung, which is treated with WLI.
– **Lung mets:** WLI.
  - <6 yo: 12 Gy at 1.5/fx.
  - 6–14 yo: 15 Gy at 1.5/fx.
  - >14 yo: 18 Gy at 1.5/fx.
  - Even if CR, some institutions omit WLI with CR to chemotherapy.
  - Boost residual mets (if no CR to chemo) 27 Gy, to 43 Gy total.
– Preop CRT to 36 Gy may be used to improve chance of R0 resection, *not* to covert inoperable to operable.

Chemotherapy Toxicity
– Secondary leukemia (AML): Ifos, Cyc, Etoposide, and Dox (higher doses in arm C/INT 0091 ~11%)
– Cardiomyopathy (Dox): doses < 450 mg/m2 or 300 mg/m2 with thoracic RT
– Infertility: > males (Cyc, Ifos) sperm banking
– Renal toxicity: Ifosfamide
– Cystitis: cyclophosphamide

Follow-Up
– Physical exam and imaging or primary site and chest q2–3 months.
– Labs as necessary.
– Can make imaging annual after 5 y.
– Most common second malignancy after RT is sarcoma.

Nephroblastoma (Wilms' Tumor/WT) [4–8, 22–29]

	Description	Incidence	4y OS DA	4y OS FA
Stage I	R0, Limited to kidney, capsule intact, LN neg	40	83	100
Stage II	R0, capsule broken, into vessels/sinus	20	83	93
Stage III	Some dz may be left in abdomen ("**BSSLURPP**"): **B**iopsy **S**ubtotal residual (R1, R2) c/p**L**N+ **U**nresectable (get pre-op chemo) **R**upture/**s**pillage **P**iecemeal **P**eritoneal implant	20	65	90
Stage IV	Distant mets or LN outside abd/pelv Location: lung (80%) > liver > bone > brain (CC) *Note: adrenal+ is not M+*	10	33	80
Stage V	Bilateral tumors	5		

Risk class (all POSTOP)	Meaning	Tx after nephrectomy	RT on POD
Very low risk FH	Stage I, <2 yo, tumor <550g, no LOH (1p, 16q), no gain of 1p, FH	Obs (on AREN 0532; note these are the risk factors on trial)	N/A
Low risk FH	Stage I-II, ≥2 yo, tumor ≥550g, no LOH (1p, 16q), no gain of 1p, FH	VA (vinc, actinomycin) chemo x 18w. No RT.	N/A
Standard risk	Stage III, FH Stage III, FH, *local* spillage Stage I–II, FH, but LOH 1p, 16q Stage I–II, UH (e.g. *focal* anaplasia), <16 yo	Flank **10.8 Gy**/6 fxs at1.8 Gy w concurrent vinc **+ 10.8 Gy** for gross residual (total **21.6 Gy**) Then chemo usually VAD x 24w	8–10
High Risk (ruptured)	Stage III with *SPAR* (spillage in abdomen, peritoneal seeding, ascites, rupture)	FH: Whole abdomen, **10.5 Gy**/7 fxs at 1.5 Gy w concurrent vinc + Boost residual by **10.5 Gy**/7 fxs at1.5 Gy to **21 Gy** total. UH: Whole abdomen, **19.8 Gy**/11 fx at 1.8 Gy Then VAD chemo x 24w	8–10
High Risk (non-ruptured)	Stage III, UH, > 16 yo Stage I–III Rhabdoid > 12 mo Stage I–III, *diffuse* anaplasia	Flank **19.8 Gy**/1.8 w concurrent vinc GTV/R2: **+ 10.8 Gy** (total **30.6 Gy**) Shield kidney after to limit dose to < 14.4 Gy Then VAD/C/E chemo x 24w for UH.	8–10
Special scenario	unresected LNs	GTV, 19.8 Gy/11 fxs or **21 Gy**/14 fxs.	8–10
	Lung mets	Whole lung: >12 mo: **10.5 Gy**/7 vs. <12 mo: **12 Gy**/8 fxs. Boost residual to **19.5 Gy** or resect w concurrent vinc. If rapid CR with chemo, omit RT(on ARST0533) Histology affects WLI dose and chemo type	With flank or after 6w chemo
	Liver mets (diffuse)	Whole liver **19.8 Gy**/1.8.	8–10
	Brain mets	Per AREN 0532/0533 >16yo: 30.6/1.8 Gy WBRT, no boost <16yo: 21.6 Gy WBRT in 12 fxs + 10.8 Gy boost (total 32.4 Gy) Historical dose: 25.2 Gy + 10 Gy	
	Bone mets	<16 yo: 25.2 Gy >16 yo: 30.6 Gy	

Overview
- 450 cases/yr usually 3–4 year olds. 2.5y for V
- Fourth most common childhood cancer
- Intrarenal
- **Favorable histo (FH, 90% of cases):** Blastemal, stromal, and epithelial. Mixed histology is most common (~40%)
- **Unfavorable histology (UH)**: anaplastic, sarcomatous, clear cell sarcoma of kidney (CCSK), and rhabdoid (RTK, technically not Wilms)
  - **Diffuse anaplasia (DA):** nonlocalized, localized w severe dysplasia elsewhere, anaplasia outside capsule or M+, and anaplasia in random bx
- **SRBCT**
- Most common abdominal tumor of children
- Very radiosensitive. Typical doses 10.5–21 Gy
- 90% will be resectable
- AA > white > Asian

Genetics
- **WT1 tumor** suppressor gene on 11p13. Associated syndromes
  - **WAGR syndrome** (del 11p13, WT1): Wilms, aniridia, GU anomalies, and retardation
  - **Denys-Drash syndrome** (WT1 mutation. WT1 is a Zn finger protein): renal dz, male pseudohermaphroditism, and Wilms
- **WT2 tumor** suppressor gene on 11p15. Associated syndromes
  - **Beckwith-Wiedemann syn** (WT2 mut, 11p15.5): IGF-2 overactivity, no active copy of CDKN1C, macrosomia, macroglossia, omphalocele, prominent facial features (earlobe pits, creases), large kidneys, and hemihypertrophy
- 2% of Wilms is familial.
- 10% of Wilms is assoc with congenital abn.
- **Del ch22q**, **LOH 1p** and **LOH 16q**, **gain 1q** have poorer RFS and OS.
- **Clear cell** and **Rhabdoid** are not actually Wilms tumors and are treated differently.
- FH: fathers who are welders (RR 5.3); mothers who use hair dyes (RR 3.6).

Presentation
- Smooth, nontender abdominal mass or swelling, in absence of other sx
- Wilms = "well"; Neuroblastoma = "not well"
- Bilat dz 7%
- Multifocal dz 12%
- Renal v invasion 10%
- LN+ 20%
- M+ 10%

DDx: Wilms, neuroblastoma, nephroma, and RCC

Workup
- H&P, US abd is the first test of choice: CT/MRI, CT chest (not CXR), urine catecholamines, LFTs, CMP, ECG, and echo
- Will be intrarenal
  - CT assesses mass size, contra involvement, capsule rupture, and ascites (most likely from rupture). CT for Wilms has calcs in 10% vs 70–90% of neuroblastomas have calcs.
- *Do not do*: Bx, unless unresectable or bilat, vigorous abdominal exams. Auto-upgrade to stage III and PORT recommended bc of seeding
- Bx for: unresectable, bilateral dz. If possible, use post approach
- **After surgery:**
  - **Rhabdoid**: add MRI brain (15% have synchronous brain tumor, 2nd primary ATRT), BMBx
  - **Clear cell**: add MRI brain, BMBx, bone scan (25% have bone mets)
- **Prognosis:** DA < rhabdoid, < clear cell < others
- OS5:
- FH > 90% (stage IV 80%)
- FA/DA 80%
- CCSK 75%
- RTK 30%

Treatment Paradigms
- Biopsy is avoided because it may cause tumor spill.
- **NWTS**: The USA. Surgery, then adjuvant tx.

  - Note: USA staging typically postop must assess regional LNs, contra kidney, peritoneum, liver, and renal vein/IVC involvement
- **SIOP**: Europe. Preop chemo, and then resect. And then assess adjuvant tx. Consider if stages IV and V or if would likely be stage III (R+/spill). Gain of 1q has worse 5y EFS 88% vs 75% and OS, 94% vs 88%.
- UKW3: RCT of NWTS vs SIOP approaches. SIOP has imp stage dist, 20% reduced use of RT, doxorubicin. Similar EFS and OS.

What Do You Want to Know from Surgery?
- Extent of resection
- Nodal status
- Extent outside kidney
- Spillage (focal or diffuse), cytology, and implants
- Pathology: FH versus FA/DA/CCSK/RTK
- 1p, 16q, del ch22q status
- Review by central pathology

Trials
- NWTS 1: showed no RT needed for group 1, <2 yo if given chemo. RT starts <9d after surgery. FH 2y CSM 7% vs 44% for UH. V + A better than V or A alone. WAI is not needed if local spill; just use flank.
- NWTS 2: showed RT not needed for all group 1. Adding Adriamycin can improve OS for group 2–4.
- NWTS 3: showed RT is not needed for stage II if chemo given. 10 Gy for stage III if Adriamycin used. *Must start RT w/in 9 days, at latest 14d*.
- NWTS 4: showed pulse-intensive chemo (6 m vs 15 m) less toxic than standard
- NWTS 5: stage I, FH and <550 g tumor can be observed after surgery (2 yr DFS 87%, OS 100%). *LOH 1p or 16q assoc with relapse and death.* For UH, etoposide improved OS. Vinc/Adr/cyclophos/etoposide improved outcomes in II-IV w DA.
- AREN 0533: higher risk FH WT. Resection, local RT, chemo, RT to non-lung mets. If rapid responder (CR after 2 cycles DD4A), and then omit WLI. Slow responders get WLI and different chemo.

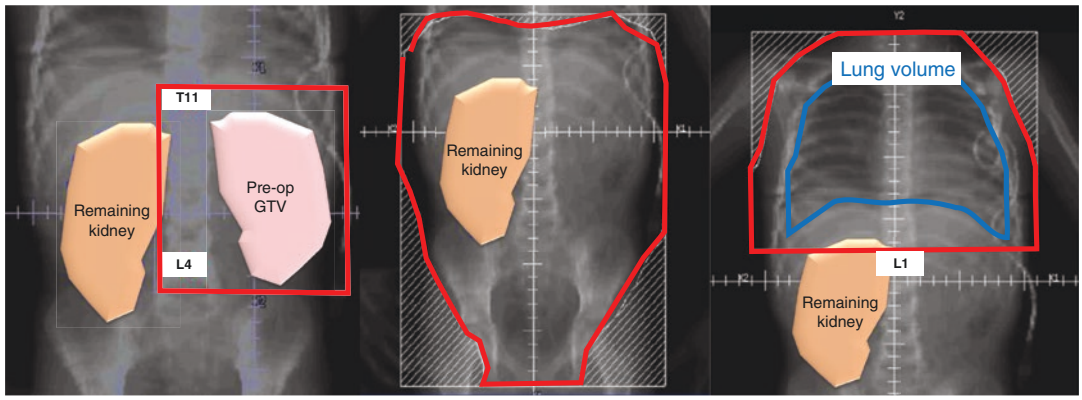
Chemo Types
- **EE4A (VA)**: vincristine and dactinomycin. Used in FH
- **DD4A (VAD)**: EE4A + doxorubicin. Used when inc risk (e.g., FH w lung mets, UH)
- **M**: DD4A + cytoxan+etoposide
- **CAVE** for CCSK: cytoxan, adriamycin, vincristine, and etoposide
- **CEC** for RTK: carbo, etoposide, and cytoxan

RT General Rules
- All patients get an overall stage and a local stage.
- All get postop RT except FH I/II and CCSK I (review by central pathology).
- **RT to primary site:** for all pts w unfavorable histology (e.g., focal anaplasia).
- RT should be initiated by day 10 concurrent with start of chemo. Hold adria during RT.
- Treat abdominal stage when pt has stage IV dz (i.e., if stage IV by pulm mets, but abdomen is stage II, and FH do not tx abdomen).
- When to WART: ("SPAR") tumor spill, peritoneal mets, Ascites/gross dz, and preop rupture. Note that Bx not always = spill.
- When to use >10 Gy: any residual dz (e.g., unresected, mets).
- Always RT for anaplasia. 10.8 Gy for focal anaplasia and 19.8 Gy for stage III–IV diffuse anaplasia.
- RTK stage I–IV all need RT, 19.8 Gy; some centers use higher doses.
- Only stage III–IV w FH require RT.

Bilateral Wilms' Approach
- Bx and stage each site.
- Ex-lap w bilateral renal bx.
- Preop chemo by worst histo.
- Then, either bilatal partial nephrectomy or additional chemo if unresectable. Once it is resectable, do bilat partial nephrectomy and then adjuvant chemo and RT by most aggressive dz. If it never becomes unresectable, preop RT 12–16 Gy reassess.

Technique

– All AP/PA, all fields treated together
– *Not* held for low counts and unless life-threatening (ANC < 300, platelets<40), give G-CSF. If 4–7-d breaks, add 1 fx. If >7d and add 2 fx.
– CT sim under anesthesia, non-contrast. 3D planning can be used, but 2D is acceptable. Usually no IMRT for the abdomen. Consider arms up since preop imaging usually arms up.
– Start by day 9 postop, max 14 (for FH).
– **Flank RT**:
  • Usually AP/PA, 1.8Gy/fx. ***Preop*** GTV + 1 cm based on CT, US, MRI, and IVP.
  • Include diaphragm and shield fem heads.
  • Treat the entire vertebral body to avoid scoliosis.
  • If abdomen pLN+, then tx PA LNs from diaphragm crux to bottom of obturator foramen. Cross midline 1 cm beyond VB if treating AP PA.
  • Stage I-II, FH: no RT.
  • Stage III or UF: 10.8 Gy to flank.
  • Diffuse anaplasia or rhabdoid: 19.8Gy to flank.
  • R2: boost another 10.8 Gy.
  • If LN+, treat paraaortics, T11-L4.



Flank RT:
- usually AP/PA, 1.8Gy/fx.
- ***Preop*** GTV+1 cm based on CT, US, MRI, IVP.
- Include diaphragm, shield fem heads,
- Treat entire vertebral body to avoid scoliosis
- If abdomen pLN+, then txPA LNs from diaphragm crux to bottom of obturator foramen. Cross midline 1 cm beyond VB if treating AP PA.
- If LN+, treat para-aortics, T11-L4

Whole abdominal RT (WART):
- Indications: Spillage, Peritoneal seeding, Ascites, Rupture ("*SPAR*")
- Sup border 1.5 cm above diaphragm, inf border pubic symphysis, flash skin, block femoral heads.

Whole lung irradiation (WRI):
- full lung, costophrenic recesses, and mediastinum + 1 cm to block edge. Flash laterally, supraclav fossa.
- Tx concurrently w one large field vs two separate fields matching w appropriate gaps and feathering to avoid excessive liver RT, kidney RT.
- If treating flank, give flank 10.5 Gy and raise inf border for last WLI fraction
- Both lungs irradiated regardless of location or numbers of mets.
- Block humeral heads.
- Sup is 1 cm above 1st rib. inf is L1. Check sagittal view to ensure coverage of lung tissue.

– **Whole abdomen RT (WART):**
  - Indications: spillage, peritoneal seeding, ascites, and rupture ("*SPAR*").
  - Sup border 1.5 cm above the diaphragm, inf border pubic symphysis, flash skin, and block femoral heads.
  - Opposite kidney ≤14.4 Gy.

– **Whole lung irradiation (WLI)**:
  - AREN 0533: flank/abd RT and WLI occur together on w1. If unresectable primary, LOH, lung mets, and then do both on w7.
  - AREN 0334 showed that lung RT can be avoided if a CR to first 6 weeks of chemotherapy. For patients with lung mets who need flank or abdominal RT, DELAY until restaging at 6 weeks. At that point, treat flank or abdominal field with or without WLI, depending on treatment response.
  - If treating include full lung, costophrenic recesses and mediastinum +1 cm to block edge. Flash laterally, supraclavicular fossa.
  - **12 Gy in 8 fx if > 12 mos**, not mandated on NWTS-5.
  - **10.5 Gy if < 12 mos**.
  - Historical AP/PA was from above clavicles to below L1. Now, consider IMRT for cardiac sparing.
  - Persistent mets should get resection or boost to 19.5 Gy.
  - Tx concurrently w one large field vs two separate fields matching w appropriate gaps and feathering to avoid excessive liver RT, kidney RT.
  - If treating flank, give flank 10.5 Gy and raise inf border for last WLI fraction.
  - Add PO Bactrim.
  - Both lungs irradiated regardless of location or numbers of mets.
  - Block humeral heads.
  - Sup is 1 cm above 1st rib. inf is L1. Check sagittal view to ensure coverage of lung tissue.
  - SIOP trials show 5-year OS 83% w preop chemo and metastasectomy or WLI if no CR.

– **Brain mets**
  - <16 yo: 21.6 Gy WBRT with 10.8 Gy boost (if <4 lesions).
  - >16 yo: 30.6 Gy in 17 fx WBRT.
– **Liver mets:**
  - If solitary met removed prior to chemo, R0, then no RT.
  - All other situations: Met +2 cm to **19.8 Gy. Boost limited vol + 5.4–10.8 Gy.**
– **Bone mets**
  - 25.2 Gy in 14 fx (2–3 cm margin); 30.6 Gy if >16 yo.

Late Effects
– **OM25y**: 6%
– **Renal**: more common in bilateral, RT nephritis, Denys-Drash, and WAGR. Reirradiation tolerance of kidney decreases w time. TD 5/5 is 23 Gy.
– **Cardiac**: doxorubicin-induced cardiomyopathy, 50%.
– **Hepatic**: dactinomycin-induced hepatotoxicity, ~10%.
– **Reproductive**: female pts more likely to have IUGR, perinatal complications, perinatal mortality, breast hypoplasia (80% of female getting WLI). After WART, risk of oocyte damange resultin in infertility is 60–70%.
– **Ovarian failure:** 10 Gy: low risk; 20 Gy: high risk.
– **Second malignancy**: 1.6% at 15 years, all were solid tumors within the RT field. Excess risk of 1.4x baseline for every 10Gy.
– **Spine**: scoliosis, muscular hypoplasia, kyphosis, and iliac hypoplasia. 10 Gy → 3 cm shortening; > 10 Gy → 7 cm shortening.
– **GI**: SBO in 15%.

Organ	Dose constraints, cutoffs
Contra kidney, 1/3	< 14.4 Gy
<1/2 of uninvolved liver	<19.8 Gy
¾ of liver w mets	<30.6 Gy

Neuroblastoma [4–8, 30–35]

Prognostic factors ("*SANDS*")			
Stage	1,2,4S	3	4
Age	<1 yo	1–4 yo	5–9 yo
N-myc	–		+
DNA ploidy	Hyperdip or near triploid (DI > 1)	DI = 1, no MYCN	Diploid, DI = 1, MYCN+
Shimada (INPC) "SAD MiNd"	Schwann cells stroma rich Young age G1/FH Low MI Non-nodular		

COG RISK GROUPINGS		
Low Risk	*Intermediate risk*	*High risk*
Any stage 1		Stage 2-4S with N-myc+
Stage 2, no RF		Stage 3 w/ ≥ 18mo *AND* UH
Stage 4S (no RF)		Stage 4 w/ N-myc or ≥ 18mo or diploid
Note: R+ disease for neuroblastoma can be low risk, and no RT recommended. In contrast, for Wilms, R1/2 is stage III, treatment is flank vs abdomen +/– boost.		

INRGSS clinical staging (preop). *New!*	
Stage L1	Localized tumor
Stage L2	Locally invasive by defined criteria
Stage M	Metastatic disease except MS
Stage MS	Metastatic to only the skin/liver/marrow and <18 m

INSS OLD staging (still used for risk groups)	
I	GTR (R0/1); Can include adherent LN
II	STR (R2) or ipsi LN
III	Unresectable or crosses midline (dz or LNs)
IV	Distant mets: distant LN or the bone, liver skin
IVS	< 1 yo, stage I–II, w/ BM < 10%, the liver, or skin

Overview

- 650 cases/yr, the most common extracranial childhood tumor and most common cancer for children <18 m.
- Median dx is 17–22 m (Wilms is 3–4 yo).
- Represents ~8% of childhood cancers.
- Primitive neural crest cells (usually calcified; Wilms isn't).
- SRBCT.
- Suprarenal (vs intrarenal for Wilms).
- Homer-Wright rosettes.
- Stains NSE+, synaptophysin+, and neurofilament+.
- Shimada classification: based on stroma, age, diff, mitoses, and nodular/diffuse (SAD MiNd).
- Poorer prognosis: ↑stage, ↑age, n-myc amp, diploid, and Shimada (SANDS).
- Also poorer prognosis: LOH 1p or 11q,↑telomerase.
- **Screening**: Tumors can spontaneously regress, so screening is not helpful (Japan, Canada, Austria trial); only recommend if familial.
- **Location**: adrenal (35–40%), post-mediastinum (20%), paraspinal ganglion (25–32%), and the pelvis (5%). Thus, ~65% are abdominal.
- **Associations**: NF1, Hirschsprung, central hypovent, familial ALK mutations, Turner, and material opiates.

Features	Neuroblastoma	Ganglioneuroblastoma	Ganglioneuroma
Neuroblast	Neuroblast dominant	Mix	Schwann dominant
Maturity	Immature	Mix	Mature ganglions
Aggressiveness	Y		N

Manifestation
- "Sick kid" (vs Wilms).
- Abdominal mass, large, firm, and crossing midline.
- Pain and fever (30%).
- HTN from ↑catecholamines or by compression of renal art.
- Thoracic tumor: respiratory sx.
- Paravertebral tumor: cord compression and Horner syndrome.
- M+ disease: Blueberry muffin sign, raccoon eyes (from retrobulbar or orbital mets causing periorbital ecchymosis), and opsoclonus-myoclonus-truncal ataxia.
- Paraneoplastic syndrome: Opsomyoclonus – from Igs anti-muscle, in 2%, dancing eyes/dancing feet syndrome (50% have NB), favorable prognosis, but symptoms persist after NB treatment.

Chemos
- Cis or carboplatin, etoposide, cyclophosphamide, doxorubicin, ifosfamide, topotecan, and vincristine

Workup
- H&P, labs, urine catecholamines (VMA, HVA), EKG, and MUGA/echo.
- BMBx: analyze **n-myc** and **DNA ploidy.**
- MRI, CT CAP, ***MIBG scan*** *(better than bone scan)*, and PET if negative**.** MIBG is NE analog concentrated in adrenergic tissue. + in 90% of neuroblastomas.
- Audiogram.
- Tumor biopsy, after all other workup, unlike in Wilms, Tx is not driven based on "tumor spillage" like it is for Wilms.

Studies

Low Risk
- POG 8104: 101 pts with INSS 1 → GTR → obs. 2 year DFS 89%
- CCG 3881: 374 pts with INSS 1-2B → surgery alone → stage 1 EFS 93%, stage 2 81%. Patients with n-myc amp, UF, LN+ at higher risk

Intermediate Risk
- Castleberry 1991: phase III, 62 pts >1 yo, INSS 2B-3 → surgery→ postop chemo +/− RT → surgery→ chemo. RT was 24–30 Gy based on age. CRT improved DFS (31 → 58%)
- POG 8742: phase II, INSS 2B-3 → surgery → chemo x5c → surgery → RT for residual→chemoRT. 24-30Gy based on age. 2 year EFS was 85%

High Risk
- Historically, 15% survival.
- No RCTs re RT.
- CCG 3891, Matthay, 2009: phase III, 539 pts → chemo x5m → surgery (+10Gy if STR; +10Gy/2 Gy fx to abdomen; 20 Gy/2 Gy to extra-ab sites) → bone marrow transplant +/− TBI (3.33 Gy x 3 d). Then randomized to +/− cis-retinoic acid. TBI and cis-retinoic acid improved 5 yr. OS.
- Matthay 2007: phase II of refractory NB. Showed a 36% response rate with I-131 MIBG
- **ANBL0532**: (1) induction chemo; (2) radical surg; (3) randomization of single vs tandem myeloablative consolidation; (4) local RT to 21.6 Gy to GTV based on preop scans w boost to 36 Gy permitted if still residual postop tumor, directed at MIBG-avid sites; and (5) cis-retinoic acid. Results at ASCO 2016: tandem had better EFS (61% vs 48%) but not OS (~72%). Benefit of tandem ASCT preserved in pts also getting anti-GD2 tx, w 3y EFS 74% vs 56%. Toxicity similar.

Guidelines

- **Low risk (includes 4S w FH and no N-myc)**
  - Surgery
    - obs if GTR
    - STR or recur→chemo w carbo/VP-16 or carbo/cyclophos/doxorubicin
  - RT rarely needed
    Residual dz, recurrence, persistence: 21Gy in 1.5 Gy/fx (COG 9641)
    Cord compression:
    < 3 yo, 9 Gy in 1.8 Gy/fx
    > 3 yo, 21.6 Gy in 1.8 Gy/fx
    Can obs if clinically stable 4S low risk
- **Intermediate risk**
  - Possible neoadjuvant chemo 4–8 months (to increase resectability)
  - Surgery → chemo
  - RT rarely needed
    Residual dz, recurrence, persistence: 21-24Gy in 1.5 Gy/fx. CTV + 2 cm (A3961)
    Cord compression: 21.6 Gy in 1.8 Gy/fx
    RT if there is bulky tumor causing organ damage
- **High-risk** treatment paradigm (Pinto, *JCO* 2015):
  - (1) Chemo induction (CAPE: cyclophosphamide, adria, cisplatin, etoposide). Restage after chemo.
  - (2) Surgery.
  - (3) Then stem cell harvest.
  - (4) Consolidation with myeloablative chemo (e.g., cis, etoposide, melphalan, or busulfan, melphalan), stem cell infusion/rescue, MIBG scan.
  - (5) ~4-6w after transplant or after 4c chemo, **RT** (**21.6 Gy at 1.8/fx**, see below) to the primary site and MIBG-avid sites after chemo. Boost gross residual to **36 Gy. M+ sites:** 21.6 Gy (no boost).
  - (6) Post-consolidation: immunotherapy (ch 14.18 mAb, GM-CSF, IL-2) + isotretinoin (13-cis-retinoic acid) for minimal residual disease. GMCST improves antiGD2 efficacy.

Current High-Risk Studies

- ANBL09P1 examines use of therapeutic ^{131}I-MIBG in induction chemo.
- ANBL12P1 examines use of Busulfan and Melphalan in consolidation.

Technique

- Initial GTV is the extent of dz at time of surgery, whenever surgery occurs. Typically, induction chemo provides dramatic response. If resected before induction, initial GTV will be larger.
- Pts often txd under anesthesia
- 4D planning to minimize PTVs

General Doses (per A3973)

- **GTV1**: extent of dz at time of resection, whether it is prior to or after induction chemo. Since NB is sensitive eto chemo, the ***post-chemo***, ***preop*** tumor based on CT /MIBG scans is preferred (this minimizes the volume).
- **CTV1** = GTV1 + 1 cm, anatomically confined. Crop the kidney, liver, and bone.
- **PTV1** = CTV1 + 0.5 cm. Txd to **21.6 Gy** in 12 fx.
- **GTV2** = residual dz >1 cc or MIBG-avid. This is a boost volume. On ANBL09P1, boost is required for residual dz.
  CTV2 = GTV2 + 1 cm, anatomically confined.
  PTV2 txd to **14.4 Gy in 8 fxs** (on ANBL0532).
  Thus, will be **36 Gy** total for gross residual.
- RT for DMs is controversial. The standard practice remains treating mets that remain MIBG-avid on the pre-transplant MIBG scan. Usually **21.6 Gy** in 12 fx for up to 5 mets.
- **Other scenarios:**
- **4S, asymptomatic:** observe!
- **4S symptomatic** liver involvement (Pepper syndrome: symptomatic w SOB, SVC syndrome, dec renal perfusion). Chemo first. Then 4.5Gy at 1.5/fx to whole liver. Can avoid parts to spare the ovaries and kidney.
- **cord compression:** chemo first if life-threatening. 9 Gy if <3 yo. 21.6 Gy if >3 yo.

– **M:**
– If >5 sites, repeat MIBG 28
– If <5, treat with RT

Dose Constraints

– Tumor usually near the heart and liver. High risk of cardiac dz (bc of adria) and sinusoidal obstructive liver dz
– ANBL0532 constraints (likely over conservative):
  – Kidneys: mean < 14.4 Gy, V19.8 < 50%
    • Ipsilateral: V19.8 < 50%, V14.4 < 100%
    • Contralateral: V12 < 20%, V8 < 50%
  – Liver: V9 < 50%, V18 < 25%
  – Lungs: V15 < 33%

Outcomes

– 5y OS for LR is 95%, IR is 80%, HR is 30%

Retinoblastoma [4–8, 36–38]

Stage	
0	Conservative tx
I	Enucleated, R0
II	Enucleated, R1
III	(a) R2/overt dz, (b) preauric or cervical LN+
IVA, heme mets	(1) Single met; (2) multiple mets
IVB, CNS mets	(1) Prechiasmatic lesion (e.g., bilateral retinoblastoma and pineoblastoma), (2) CNS mass, (3) LMD

A	≤3 mm height, ≥3 mm from fovea, ≥1.5 mm from ON
B	>3 mm height, clear subretinal fluid
C	C1: localized subretinal seeding C2: ≤3 mm from tumor margin C3: both
D	Same as Group C but diffuse seeding
E	No visual potential: tumor in anterior segment, ON, ciliary body, neovascular glaucoma, hemorrhage, phthisical eye, orbital cellulitis, extraocular disease

Overview

- 250 cases/yr.
- Bilateral is hereditary, presents at younger age, and has higher risk of second malignancy (and that malignancy will likely cause death).
- Unilateral is incidental.
- Trilateral RB: bilateral RB + midline CNS PNET: uniformly fatal.
- Pts are prone to osteosarcomas.
- Leukocoria: white pupillary reflex caused by tumor growing in the globe. Parents notice white reflection behind the pupil of affected eye in flash photos of child.

Genetics and Pathology

- **RB1** tumor suppressor on ch13 → defect in G1/S checkpoint
- Flexner-Wintersteiner rosettes

Workup

- H&P, ophthalmology exam, labs, and genetic counseling
- Bilateral ultrasound, MRI brain, and spine
- BM biopsy and bone scan
- If extraocular: bone scan and LP
- EUA, no biopsy bc it will seed

Trials

- Shields 1997: retrospective of chemo +/− local therapy. Local treatment reduced LC from ~70 → 0%
- **ARET0321**: Induction chemo, consolidation w SCT (stage IVA/B only), and response-adapted EBRT.
- **Stage II and III** pts get induction chemo and response-adapted RT w/o consolidation tx.
- If there is residual stage II (orbital) or III (orbital and regional /LN) after induction chemo, dose is ***45 Gy*****.**
- **Stage IV** pts get induction, SC harvest, consolidation w SC rescue, and response-adapted EBRT.
- For IVa disease, <5 mm residual or CR gets no RT. If >5 mm, then tx residual to 36 Gy. If residual dz for IVB (CNS dissemination) dose is ***36 Gy CSI*****,** ***45 Gy to cranium*****,** ***50.4 Gy to pineal gland*****.**

Technique

- Anesthesia.
- Supine, mask, IMRT, +/− bolus.
- Cover entire retina and 5-8 mm of optic nerve.
- Dose is 36–40Gy in 1.8–2/fx (26Gy if post-chemo).
- Protons spare orbital bone and lens.
- RT increases risk of secondary malig from 25 → 50% at 50 years (1% per year).

Guidelines

– RT is rarely used in management of retinoblastoma bc of high risk of second malignant neoplasms; ~50% of pts w hereditary Rb develop second malignancy in 50 years (Wong 1997)
– Unilateral: eye/sight preservation ~75% with EBRT
  • *Chemo*: vincristine/carbo/etoposide x6c
  • Laser: small, far from fovea
  • EBRT (36-40Gy): small tumors or failed non-RT therapy
  • Pre-chemo and presurgical disease + 5 mm = CTV
    • PTV = CTV + 5 mm
  • I-125 plaque: dose is 40Gy to apex
  • Cryotherapy, photocoagulation
  • enucleation
– Bilateral: treat as separate primaries
– Extraocular: orbital EBRT and chemo (high-dose chemo + SCT?)
– Trilateral: treat the eyes, chemo, CSI? (MS is 11 m)

Langerhans Cell Histiocytosis (LCH)

Risk group	Definition
Low	1 lesion in bone, LN, GI, CNS
High	<2 yo w organ dysfunction; liver, spleen, BM

Background

- 1200 cases/y
- 1–3 yo
- M > F
- Dysregulation of monocular cell line
- Previously called eosinophilic granuloma and histiocytosis X
- LCs are SPCs to lymphocytes in the skin, mucosa, and spleen.
- **Hand-Schuller-Christian dz:** proliferation of histiocytes causing exophthalmos, skull lesions, DI, and hemangiomas; lytic bone lesions (thus, negative BS). Good prognosis. > 2 yo
- **Litterer-Siwe disease**: Hepatosplenomegaly, lymphadenopathy, pulmonary lesions, and bone lesions. Widespread seborrheic rash. <2yo
- **Manifestation**: the bones in children and the lungs in adults. In children, usually bone pain, soft tissue mass, the lung, or oral mucous membrane involvement
- **Workup**: HP, labs, skeletal survey (appears "punched out"), NOT BS, biopsy
- **Histology**: Birbeck granules on EM. CD1a, S100, and CD207 (Langerin)

Treatment

System involvement	If asymptomatic	Tx modality	RT	Outcomes
Single	Observed because typically self resolves	For single lesion, esp symptomatic, local therapy w surgery (e.g. ,surgery, curettage). If the skin, then nitrogen mustard, steroids, systemic tx	RT if not healing after surgery, potential compromise of critical structures, pain relief, DI (within 14d of dx) Also consider if in the eye,ear, spine, weight-bearing bone	LC = >90% OS = 100%
Multi	Observed because typically self resolves	If multisystem (e.g. fever, pain, severe skin involvement), then chemo w **prednisone**(1st line), then **vinblastine**. Single agent chemo is as good as multi-agent.		OS: 33–54 if no organ dysfunction 82–96 if organ dysfunction

Planning

DI: 15 Gy to pituitary/hypothalamus within 14 d
Bone: 5–10 Gy (e.g. 3 Gy x 3 fractions w small margin) or 1.5 Gy x 8 fractions
Adult: 15–24 Gy/2 Gy fraction

Medulloblastoma (and Supratentorial PNET, Pineoblastoma) [4–8, 36, 39–44]

T1	T2	T3a	T3b	T4
< 3 cm diam In vermis, roof of 4th vent, or cerebellar hemisphere	≥3 cm diam, invades one adjacent struct or part filling 4th vent	Invades two adjacent struct or complete filling of 4th vent, extensions into aqueduct of foramina, w marked hydro	Arises from floor of 4th vent	Penetrates aqueduct to involve 3rd vent or midbrain or cord
M1	**M2**	**M3a**	**M3b**	**M4**
CSF micro mets	Macro mets in brain	Macro mets in spinal subarachnoid, but no M2	M2 + M3a	Mets outside CNS

Note: Use Chang system, like germinoma, though not used as much as the risk groups

Risk group	Classic criteria *(technically only avg and high risk)*			5 yr EFS	Molecular markers (Ellison, JCO, 2011)	Signaling	Anaplasia (new, from ACNS 0332)
	Age	Residual post-op (cm^2, not cc)	M				
Low (*classic + moleculars*)	>3 yr	<1.5	0	>90%	MYC(–) β-catenin(+)	WNT	
Avg/std risk (*all* of these factors)	>3 yr	<1.5	0	75–80%		SHH	Nodular, desmoplastic, classic
High risk (*any* of these factors)	<3 yr	>1.5	+, or PNET	50%	MYC(+), or diploid DNA, or LOH 17p, or p53 mut, or low TrkC, or HER2(–)	Non-WNT Non-SHH MYC	Diffuse anaplasia (large cell)

General

- 500 cases/yr US.
- Bimodal (7–9 y/o and 25 y/o).
- Most common infratentorial CNS malignancy (~45%), followed by JPAs (~30%).
- Assoc with:
  - **Gorlin syndrome** (PTCH1), activation of SHH pathway. Nevoid BCC of skin
  - **Turcot syndrome** (APC). Familiar polyposis, brain tumors
- Cell of origin is neuroectodermal cells from the germinal matrix of the cerebellum. Thus, arises in posterior fossa w high potential for CSF spread (33% present w CSF dissemination). Obstructs cerebral aqueduct (Aqueduct of Sylvius), which connects 3rd and 4th ventricle.
- In adult, medullo usually in lateral cerebellum.
- Medullo has an intact INI1.
- 94% in children, 52% in post fossa, 39% supratent, 5% pineal, and 2% spinal.
- Homer-wright rosettes (same as all blastomas but retinoblastoma).
- **Posterior fossa tumors (Ddx):** brainstem glioma, ependymoma, astrocytoma, atypical teratoid/rhabdoid (ATRT), and medulloblastoma.
- **Medulloblastoma variants**
- Classic.
- Nodular/desmoplastic: good prog (LOH 9q).
- Large cell/anaplastic: poor prog.
- Four genetic subgroups:
  1. **WNT group**: CTNNB1 mut, β-catenin(+), APC mutation, assoc with Turcot (10%, good prog)
  2. **SHH group**: PTCH1, GLI3, MYCN mut, SMO, SUFU usually desmoplastic (30%, int prog)
  3. **Group 3**: MYC amp, usually M+, usually large cell (poor prog)
  4. **Group 4**: isochromosome 17q, MYCN, CDK6 amp (int prog)

Workup
- H&P, labs, fundoscopic exam, audiometry, IQ, and growth measures.
- If ATRT, then need CT CAP to scan for concurrent renal rhabdoid tumors (not mets).
- No role for VP shunt now. Try high-dose steroids. Can place at time of surg, remove before pt dcd.
- Preop MRI brain/spine. To avoid artifacts from resection; also guides aggressiveness of surgery.
- MRI brain 24–48 hours postop.
- MRI spine 10–14 days postop.
- CSF cytology 10–14 days postop. Check WNt, SHH, c-myc. If too early, then contaminated from surgery, high FPs.
- After surgery, posterior fossa syndrome occurs in 20%. Mutism, dysphagia, truncal ataxia, hypotonia, head titubation, increased mood lability, gaze palsy, and occas resp failure.

Trials for Child Medulloblastoma
- POG 8631/CCG 923, Thomas, 2000: std risk → 36 vs 23.4 Gy CSI, then PF boost to 54 Gy. No chemo. Closed early due to inc relapse rate in low-dose arm, 5y EFS 67% vs 52%.
- Note there have been no RCTs of 36 Gy vs 23.4 Gy CSI w concurrent chemo.
- CCG 9892, Packer, 1999: std risk → 23.4 with vincristine→55.8 Gy PF boost→adj chemo. Favorable EFS (phase II), 79% 5-year EFS (which is excellent). Thus, 23.4 Gy + chemo became SOC on COG trials.
- Baby POG: <3 yo treated with chemo alone until 3 yo. 5-yr OS was 40%.
- German BTSG: similar to baby POG (58% 5 yr OS)
- **ACNS 9961** (Packer, 2006, 2013). Adjuvant chemo question. Note, not a CSI dose trial. 23.4 Gy CSI + 55.8 Gy PF boost + concurrent VCR, then rando: (1) Packer Regimen of CCNU/CDDP/VCR; vs (2) CTX/CDDP/VCR. Similar 10 year EFS (76%), OS (81%). Ten-year incidence secondary cancer was 4%. Twenty percent of pts developed PF syndrome after surg.
- Retrospective series and ACNS0331 show low failures outside tumor bed.
- ACNS0331. What is role of reduced dose CSI and reduced boost field in avg risk medullo? Pts are 3+, have ≤1.5 cm2 residual, M0. Pt 3-7yo rando to 23.4 Gy vs 18 Gy CSI. All pts. rando to entire PF boost vs involved surg field boost to GTV + cavity +1.5 cm margin, excluding bone and tentorium. PTV = +0.3–0.4 cm. Vcr qw concurrent. Then adjuvant Vcr + cis + CCNU alternative w vcr/cyclophos x9c q6w. No difference for involved field vs entire PF boost for 5y OS (84%), EFS (~82%), and LR (~3%). However, improved outcomes w 23.4 Gy CSI vs 18 Gy CSI, 5 yr OS: 78% vs 86%, EFS 72% vs 83%. 5y DM 13% vs 8% (NSS). Two percent of pts had second malignancies in 6.5y.
- ACNS 0332: high-risk medullo gets 36 Gy CSI + 9 Gy boost to spinal dz (45 Gy total above terminus) and 19.8 Gy boost to post fossa (55.8 Gy total). Examining efficacy of carbo concomitantly w RT and isotretinoin as pro-apoptotic agent.

Trials for Adult Medulloblastoma
- Brandes, 2007. Low-risk disease given CSI to 36 Gy, then boost PF 18.8 Gy to total 54.8 Gy. High-risk pts received combination chemo + RT. PFS and OS at 5 years were 72% and 75% for all pts.

Simulation/Planning
- Consent pt, family
- Discuss anesthesia
- Supine 5-pt mask, head extended, and shoulders down
- PCP ppx (TMP/SMX) if being treated
- Prone, neck extended, mask, and protons
- CSI, within 31d of surgery
- Classic PF fields:
  Ant: post clinoid
  Sup: 1 cm higher than midpoint bw foramen magnum and vertex
  Post: internal occipital protuberance
  Field = PF + 1 cm
- New standard risk fields: cavity +1.5 cm
- Sparing: supratentorial brain, cochlea, hypothalamus, the eyes, optic structures, cervical spine, and the skin

– The entire tx takes ~1y. ACNS 0331 RT takes 6w. Concurrent chemo for 6w w vcr, then 9c of chemo q6w. Total = 55w tx

Dose Constraints
– Cochlea: V30 < 50%, max 35 Gy

Special Considerations (Mostly High Risk)
– **M2/Brain/thecal mets** 54–55.8 Gy.
– **Spinal mets** 45 Gy if above terminus, 50.4 Gy if below terminus. per ACNS 0332.
– **Diffuse spinal disease** 39.6 Gy.
– **Pineoblastoma**: Treat like a high-risk medullo (CSI to 36, boost to 54 Gy).
– **Adult medullo**. Adults cannot tolerate chemo like peds patients. Further, since adult is fully grown, there is less concern about long-term toxicity. Some argue tx like peds, others advocate RT alone.
– **Standard risk cannot get chemo**: treat like high risk, 36 Gy CSI + 19.8 Gy boost.

Follow-up
– **Second malignancy** rate is 0.4% per year (from ACNS 9961).

COG Approach

COG approach

Risk group	Age (y)	Surgery	RT: Chemo	RT: CSI	RT: Boost	Trials	SJMB12 (approximate groups; note supratentorial PNET excluded):	
Low	>3	MSR	RT with vincristine 1.5 mg/m2, start 4 weeks after surg, then qw x 7c. Then adjuvant cis. Note: concurrent chemo not used on SJMB12 Adjuvant: Cis, vincristine, + either cyclophosphamide or CCNU 8 cycles q6w	15 Gy	*Tumor bed* to 54 Gy		Stratum W1 (WNT): 15 Gy CSI, 51 Gy boost	4 cycles cyclo, cis, VCR.
Avg/Std Risk	>3	MSR		**23.4 Gy** /13 fx If chemo not given, then use 36 Gy/ 20 fx	*Tumor bed* to **54 Gy** CTV = GTV + 1.5 cm. PTV = CTV + 0.3–0.5 cm	**ACNS 0331 reported**: RT to tumor bed > posterior fossa. Still need 23.4 Gy CSI	Stratum S1 (SHH) 23.4 Gy CSI, 54 Gy boost.	4 cycles cyclo, cis, VCR. Then maintenance vismodegib x 12 months
							Stratum N1 (Non-SHH, Non-WNT, Non-MYC):23.4 Gy CSI, 54 Gy boost.	4 cycles cyclo, cis, VCR.
							Stratum N2 (Non-SHH, LCA or MYC gain; standard risk): 23.4 Gy CSI, 54 Gy boost.	AABAABB (7 cycles) A: cyclo, cis, VCR B: pem, gem
							Stratum S1 (SHH): 23.4 Gy CSI, 54 Gy boost	4 cycles cyclo, cis, VCR.
							Stratum W2 (WNT, atypical): 23.4 Gy CSI, 54 Gy boost	4 cycles cyclo, cis, VCR.
High Risk	>3	MSR. If unresectable, proceed w CRT		36 Gy / 20 fx	*Posterior fossa* to 54-55.8	3-21 yo. Rando to (1) concurrent VCR + RT vs (2) Concurrent VCR + carbo + RT. Then 2nd rando for both for chemo alone vs chemo + isotretinoin	Stratum S2 (SHH + MYC): 36-39.6 Gy CSI, 54 Gy boost.	4 cycles cyclo, cis, VCR. Then maintenance vismodegib x 12 months
							Stratum W3 (WNT, MYC): 36-39.6 Gy CSI, 54 Gy boost.	4 cycles cyclo, cis, VCR.
							Stratum N3 (Non-SHH, Non-WNT, MYC amp; high risk): 36–39.6 Gy CSI, 54 Gy boost.	AABAABB (7 cycles) A: cyclo, cis, VCR B: pemetrexed, gemcitabine
	<3	MSR	Avoid RT (in general) bc of long-term sequelae. Consider adjuvant chemo until 3 yo. Otherwise, tx per high risk				`	

Pineoblastoma

- Treat like a high-risk medulloblastoma patient.
- CSI to 36 Gy with boost to 54 Gy, with CVP chemo.

Pineocytoma

- Treat like LGG.
- If GTR: observe.
- If < GTR: RT to 54 Gy.

Atypical Teratoid Rhabdoid Tumor (ATRT)

Overview

- Median age < 3 yo.
- 94% in <5 yo.
- Has loss of INI1 in 85%. ATRT prev misclassified as PNET until ~1995. Have rhabdoid cells +/− fields that resemble PNET. Vimentin, EPA, and smooth muscle actin (SMA) are in ATRT but not in medulloblastoma.
- 52% in PF, 39% supratentorial, 5% pineal, and 2% spinal.
- MST 1 y.

Workup

- H&P, labs, fundoscopic exam, audiometry, and IQ.
- Unlike in medullo, for ATRT you need CT CAP to scan for concurrent renal rhabdoid tumors (not mets).
- No role for VP shunts now. Try high-dose steroids. Can place at time of surg; remove before pt dcd.
- Preop MRI brain/spine. To avoid artifacts from resection; also guides aggressiveness of surgery.
- MRI brain 24–48 hours postop.
- MRI spine 10–14 days postop.
- CSF cytology 10–14 days postop. If too early, then contaminated from surgery, high FPs.
- After surgery, posterior fossa syndrome occurs in 20%. Mutism, dysphagia, truncal ataxia, hypotonia, head titubation, increased mood lability, gaze palsy, and occas resp failure.

Treatment

- Patients need multimodality therapy.
- Chemotherapy regimens vary, but use multiple IV and IT drugs. The IRS-3 regimen is used at many institutions.
- Mainstay of tx is resection.
- Radiation treatment paradigms are similar to those for high-risk medulloblastoma.
- If >3yo, CSI to 36, boost to 54–55.8 Gy.
- If <3yo, 50.4–54 Gy to primary site only. No CSI.
- If diffuse spinal involvement, boost spine to 39.6 Gy. If focal, boost to 45 Gy in cord and 50–54 Gy in cauda.

Ependymoma [4–8, 45–47]

General
- Bimodal (5 yo and 35 yo).
- Assoc with NF2 (ch 22).
- WHO classification (2016).
  (a) **I:** myxopapillary and subependymoma, indolent, and adults
  (b) **II:** classic
    (i) Test for RELA fusion, associated with supratentorial tumors in children
  (c) **III:** anaplastic
- Perivascular pseudorosettes, ependymal rosette. Tumor cells oriented radially around central lumen. Gland-like structures.
- Poor prognosis.
  - ErbB-2/erbB-4 overexpression
  - Age <4 yo
  - Supratentorial location

Natural history
- Cell of origin is the ependymal cell.
- 95% intracranial, with 70% infratentorial and 1/3 supratentorial.
- Classic natural history is tracking out of foramen of Lushka through foramen magnum.
- Thus tends to fail locally, and CSI is usually not necessary.

Surgery
- Resection more difficult in PF vs supratent bc tumors extend to CPA and can have postop MM

Workup
- Similar to medullo
- H&P, labs, fundoscopic exam, audiometry, and IQ
- Preop MRI brain/spine. 10% w spinal primary. < 10% CSF seeding: 9% infratent and 2% supratent
- MRI spine 10–14 days postop, if not done preop
- CSF cytology 10–14 days postop
- CT*: usually have calcifications*

Trials
- Rogers 2005: posterior fossa ependymomas, retrospective. GTR, 10 yr LC improved with RT (50% → 100%). For STR + RT, 10 year LC was 36%. Thus, RT was recommended even for GTRs.
- St. Jude experience (Merchant, 2009): Phase II. n = 153. 51% < 3 yo. GTR, then second-look surg if < GTR. Results: GTR rate was 82%. Seven-year EFS 77% GTR vs 34% STR. Seven-year EFS: 69% for all, 79% if G1, 61% if G2–3, 77% if GTR, 34% if STR.
  Seven-year OS: 88% if GTR, 52% if STR. Probability of failure more common in dedifferentiated tumors, 17% vs 5%.
- Merchant 2009 and Koshy 2011 suggest RT → ↑OS in children under 3yo.
- Retrospective series show no benefit to CSI.
- Retrospective evidence reveals improved outcomes of 54 vs 50.4.
- Extent of resection is most important prognosticator.

Chemo
- Role of chemo is not well established. No known chemo response. Baby POG trial sometimes used to support chemo until 3, but very few ependymomas on trial.
- Response rate 5–15%.
- No improvement as adjunct to RT.
- May improve GTR rate (COG ACNS 0121).
- Being explored in ACNS 0831.

Relative Indications
- STR
- Child <3yo (to delay use of RT)

COG Approach
- Everyone gets upfront maximum safe resection. Consider re-resection if STR.
  - Establishes diagnosis, reestablishes CSF flow. Extent of resection is most important prognostic factor.
  - If **GTR and Grade 1**, then observe. Rate of GTR = 85%. More difficult to get R0 for infratent tumors. If infratentorial, harder to get R0.

- If **STR** then push for induction chemo, 7w of vcr, carbo cpm OR vcr, carbo, etop. Then re-resection so there is a GTR or NTR. On ACNS 0831, pts with STR do not receive RT.
- **If GTR and high-risk features** (e.g., G2/3; adult patient), then adjuvant RT. Note that RT usually local.
  (i) > 3 yo: Resection and adj RT. R1 or G3 above the cord to **54, then comes down (off brainstem, chiasm, cord) to 59.4 Gy.**
  (ii) < 3 yo: Need to delay RT. Resection and chemo (cisplatin-cyclophos-etoposide) Can give 2 cycles then re-resection vs RT. If used, RT should be to 54 Gy.
- **Indications for CSI (ideally after 3 yo):**
  (iii) M+ (e.g. +CSF, MRI positive)
  (iv) Grade IV (treat like medullo)
- **ACNS0831**. Supratent ependymoma. Phase III study of:
  (1) Obs after GTR, differentiated supratent ependymoma
  (2) After STR, induction chemo cinv carbo cyclosphos, and etopo, second-look surg, then RT, then chemo
  (3) All others get RT, then rando +/− chemo. Supratent ependymomas get 59.4/1.8. GTV is any residual tumor+bed. Pre- and postop imaging used to define GTV. CTV = GTV + 0.5 cm. PTV = CTV + 3–5 mm (3 if IGRT)

– **If Spinal met:** RT for incomplete resection or anaplastic histology
  (a) Two vert bodies above/below to **45 Gy.**
  (b) Boost to **50.4–59.4** Gy if no cord in field.
– **Ependymoblastoma**
  (c) Treat like high-risk medulloblastoma

Simulation/Planning

1. Local therapy (volumes from ACNS0831)
   (a) **CTV1** = residual & cavity *+1 cm*
   CTV2 = residual tumor and resection bed above the cord
   PTV1 = CTV1 + 0.3–0.5 cm
   PTV2 = CTV2 + 0.3–0.5 cm
   (b) Dose: Treat PTV1 to **54 Gy/1.8 Gy fx**. Boost PTV2 to **59.4 Gy** if >18 m, However, if pt < 18 m w GTR, then no focal boost.
   (c) No RCT for 54 vs 59.4. However, brainstem toxicity can be fatal. Consider treating to only 54 Gy if close proximity to brainstem.
2. If delivering CSI
   (a) Dose is **36 Gy**
   (b) If gross spine dz, would boost to **45 Gy**

Follow-Up

1. For >10 yrs, late recurrences happen.
2. Craniospinal MRI Q3-6 m then Q1yr.

Risk of brainstem toxicity: chemo, age < 3 yo, ATRT, and multiple surgeries

Germ Cell and Non-Germ Cell Tumors (GCT/NGGCT/Germinoma) and Pineal Tumors [4–8, 48–50]

T1	T2	T3a	T3b	T4
< 3 cm diam In vermis, roof of 4th vent, or cerebellar hemisphere	3+ cm diam, invades one adjacent struct or part filling 4th vent	Invades 2 adjacent struct or complete filling of 4th vent, extensions into aqueduct of foramina, w marked hydro	Arises from floor of 4th vent	Penetrates aqueduct to involve 3rd vent or midbrain or cord
M1	**M2**	**M3**		**M4**
CSF micro mets	Macro mets in brain	Macro mets in spinal subarachnoid		Mets outside CNS

Note: no AJCC staging. Chang's system used

General

- Histology
  - Germinomas (65%)
  - NGGCT (35%)
    1. Choriocarcinoma (5%)
    2. Endodermal sinus tumor (yolk sac) (18%)
    3. Teratoma (20%)
    4. Embryonal carcinoma (7%)
    5. Mixed (25%)
- Peak age: 10–12 yrs. Majority (90%) before 20 yo and most others before 30 yo
- Very rare in early child hood
- Younger pts tend to have NGGCTs
- Older pts tend to have pure germinomas
- Usually arise from proximal 3rd ventricle and affect supratentorial midline structures, e.g., pineal, hypothalamus, and BG
- Natural history: subependymal spread near 3rd and 4th vent

Clinical Presentation: Pineal Tumors

- Obstructive hydrocephalus (compression of aqueduct of Sylvius in 3rd ventricle)
  - ⇧ICP (25–50%): H/A, N/V, papilledema, lethargy, and somnolence
  - Ataxia
  - Seizures
  - Behavioral changes/decline in academic performance
- Neuro-ophthalmologic abnormalities (up to 50%)
  - Parinaud syndrome: poor upward gaze, accommodates but abnl light response (caused by pressure on the superior colliculus)
  - Pseudo-Argyll-Robertson pupils
- Endocrinopathy (rare): diabetes insipidus (occult tumor in floor of 4th ventricle or suprasellar region)
- "Bifocal" (synchronous suprasellar + pineal): M+ in USA but M0 in Europe

Clinical Presentation: Suprasellar Tumors

- Hypothalamic/pituitary dysfunction
  - Diabetes insipidus due to reduced ADH secretion
  - GH abnormality: delayed or precocious puberty
  - Isolated growth hormone deficiency
  - Hypothyroidism
  - Adrenal insufficiency
- Ophthalmologic abnormalities: usually bitemporal hemianopsia

Workup

- H&P
- **Serum**: labs, bHCG, and AFP
- **CSF cytology** with AFP, bHCG, PLAP, and c-KIT
- **MRI brain/spine**. Note: cannot distinguish NGGCT vs germinoma
- Surgery
  - Place shunt (do this before LP)
    - Endoscopic third ventriculostomy (ETV): opening from 3rd vent to prepontine space
  - Ventriculoperitoneal shunt (VPS): rarely get shunt met
  - To obtain tissue diagnosis
  - If germinoma, then no need for resection

When to Biopsy
- SOC was historically to biopsy. ACNS 1123 allows for tx stratification based on CSF and serum tumor markers of AFP and BHCG.
- Per ACNS 1123, if normal serum/CSF β-HCG and AFP, should biopsy to distinguish pure germinoma/mature teratoma from other tumors.

Germinoma Diagnostic Markers
- Always AFP negative or < 10 ng/mL (if pure)
- β-HCG typically <50 ng/mL, << 100 ng/mL
  - Minority of germinomas have ⇧β-HCG (from syncytiotrophoblasts). If pt. has path revealing GCT, but has high BHCG, then path should be reviewed, but the tx will be for a NGGCT.
- c-Kit positive
- PLAP positive
- Stains with placental alkaline phosphatase
- **Molecular biology**
  - Isochromosome 12p in adults.
  - Poly-X in CNS teratoma.
  - Young children loss of 1p and 6q.

Prognosis
- Best: pure germinomas and teratomas
- Intermediate: germinoma w high HCG; immature teratomas
- Poor: choriocarcinoma, yolk sac, embryonal

Chemo
- Balmaceda, MSKCC, 1996: 45 germinomas and 26 NGGCTs. Treat with CEP x4c. 57% had CR. If <CR, then proceed to intensified chemo or second surgery. Overall, 78% achieved CR without RT. However, 50% of these patients recurred, and 10% had a tx-related mortality. Thus, chemo alone not SOC for GCTs**.**

Trials
- MAKEI 83/86/39, Bamberg, 1999. RT alone. MAKEI 83/86 (Pilot studies) – 36 Gy CSI + 14 Gy (N = 11). MAKEI 89–30 Gy CSI + 15 Gy boost. Chemo only for salvage. High vs low dose had similar outcomes; all pts had CR after RT. Five-year RFS 91% vs 88%. Five-y OS 94% vs 92%. In 83/8 trial, no relapse after 10y. In 89 trial, 5 pts relapsed at 10–33 m, 1 isolated spine met and 4 outside CNS, salvaged w chemo. Tox was worse w 36 Gy > 30 Gy. Study demonstrated (1) exquisite radiosensitivity; (2) 30/15 has 100% CR. Thus, 30 Gy won.
- SIOP CNS GCT96: M0 → CSI 24 Gy + 16 Gy boost vs chemo+IFRT 40 Gy. All CRT failures were in the ventricles.
- Rogers 2005, 2008: lit review with similar results. >90% OS at 10y.
- Rogers, 2015.

Rogers relapse review, 1988–2004	WVRT or WBRT	CSI
Overall relapse (%)	7.6	3.8
Spinal relapse (%)	2.9	1.2

Conclude that WVRT+boost should replace CSI in completely staged germinoma.

- ACNS 0122: Stratum 1 is for NGGCT. HCG > 100; any elevation AFP > 10 ng/mL or on bx/rxn, yolk sac, embryonal carcinoma, choriocarcinoma, teratoma, mixed GCT. Stratum 2 for pure germinoma. Normal AFP, HCG < 50. Bifocal or pineal lesion w DI and HCG < 100 + normal AFP.
- ACNS1123: Stratum 1 is NGGCT, serum and/or BHCG >100 mIU/mL, any elevation of serum and CSF AFP > 10 ng/mL, or any of the following on bx/rsxn: yolk sac tumor, embryonal carcinoma, choriocarcinoma, malignant/immature teratoma, mixed GCT w malignant elements. Stratum 2 is pure germinoma: normal AFP and BHCG <50; b bifocal involvement or pineal w DI and BHCG <100 mIU and normal AFP; histologically confirmed germinoma or mixed w mature teratoma and BHCG <100 mIU/mL and normal AFP. Stratum 2 receives (1) WVI + focal boost vs (2) 4 cycles carbo/etoposide, then WVRT to 18 Gy and IFRT to total of 30 Gy. CTV = GTV + 5 mm, limited by bone, falx, tent.

Planning

- CT sim w ≤ 3 mm image thickness. Contrast is not required.
- Fuse MR, post-Gt T1W, post-chemo T2W.
- GTV + 5 mm = CTV.
- WVRT + pineal cistern + suprasellar cistern + prepontine cistern (optional).
- CTV + 3–5 mm = PTV. Need daily IGRT w 3 mm. This is boost volume.
- Whole ventricular volume (WVV)-CTV + 3 mm = PTV.
- OARs: hypothalamus, pituitary, optic Ns, retina, cod, brainstem, and cochlea.

COG Approach

1. **Localized germinoma**: RT only. Cure >90%. Historically, tumor was diagnosed by giving 20 Gy and watching it melt.
   (a) ACNS1123: Chemo then RT. For pure germinoma w/o CNS dissemination and CR to chemo, dose is **18 Gy WVRT + 12 Gy boost (total of 30 Gy)** to tumor bed/residual dz using 1.5 Gy fractions.
   - If PR or SD w chemo, then dose **is 24 Gy WVRT** and then **12 Gy boost (total of 36 Gy)**.

   (b) Non-protocol standard therapy:
   - WVRT to **21–24 Gy**. PTV = CTV + 3–5 mm
   - Boost primary to **40–45 Gy**
   - If PR or PD, consider a different diagnosis!
   - No CSI!
   - If using chemo alone, relapse is 50%, and mortality is 10%; thus, not SOC.
2. Bifocal/biphasic germinoma: involvement near third ventricle (usually pineal and suprasellar). Treat as local-regional dz. WVRT without CSI.
3. **+CSF germinoma** (like low-risk medullo)
   (a) The same as previous, but **CSI to 24 Gy**
   (b) Boost GTV to **45 Gy**
   - Alternative: clinical trial with neoadjuvant chemo (2–4 cycles carbo/etop) then response-based RT
   - If CR: 21 Gy; WVRT; 30 Gy IFRT; CSI
   - If PR or PD, consider a different diagnosis!

   (c) ACNS 0112 Stratum 2: 4c carbo/etoposide, then WVRT 18 Gy + IFRT to 30 Gy to primary.
4. **NGGCT**: if labs suggest NGGCT, even w path showing GCT, then treat as NGGCT. Treat like high-risk medullo: all get chemo, usually get CSI. Usually worse prognosis than germinomas. In comparison to NSGCTs (of testes), RT plays a big role for NGGCTs
   (a) Certain tumors do not need histo confirmation per ACNS 1123, e.g., bifocal pineal + suprasellar tumors, pineal lesions w DI, or mild elevation of HCG or AFP)
   (b) Chemo RT
   (i) Induction platinum-based chemo
   (ii) Then CSI 30–36 Gy
   (iii) Then boost 50.4–54 Gy
   (c) Surgery + chemo
   (i) Resection
   (ii) Adj platinum-based chemo
   (iii) Restage
   (iv) CSI (36 → 50.4) vs IFRT
   (d) Note: surgery not encouraged due to morbidity risk. Tumors are in midline structures.
   (e) **ACNS 0122**:
   Randomize to.
   (1) Standard dose, CSI **36 Gy + boost to 54 Gy**; vs
   (2) **30.6 Gy WVRT + boost to 54 Gy** for pts w CR.
   (f) On current COG trial, ACNS 1123, NGGCT get chemo identical to ACNS 0122, then
   (1) Control: **36 Gy CSI**, then **54 Gy PF boost;** vs
   (2) Experimental: **30.6 Gy WVRT then boost to 54 Gy** if CR to chemo.
5. **Pineocytoma**: treat like low-grade glioma (delayed RT)

Craniopharyngioma [4–8, 51–53]

General
- Rathke's pouch origin
- Histologically *benign* but locally destructive
- Bimodal (10 yo and 50 yo)

Subtypes
- Papillary
- Adamantinomatous

Workup
- H&P and labs
- MRI brain
- CSF cytology with AFP and bHcG
- Check all anterior and posterior pituitary hormones
  (a) **Post pituitary**:
    (i) ADH
    (ii) Oxytocin
  (b) **Ant pituitary**:
    (i) GH
    (ii) TSH
    (iii) LH/FSH
    (iv) ACTH
    (v) PRL

Trials
- Stripp (2004): 10 yr LC with surgery worse than surgery+RT (42% → 84%), but if RT used as salvage 10 yr LC was unchanged.
- Varlotto (2002) recommend doses of 54–60 Gy for craniopharyngiomas bc lower doses have more failures

COG approach
1. Max safe resection (usually STR) then RT (or can observe). Fluid that drains is like "crank-case oil" – dark brown, thick.
2. GTV = residual dz, inc cysts.
   - CTV = GTV + 0.5–1 cm
   - PTV = CTV + 0.3–0.5 cm
   - Dose ***50.4–54 Gy***. Prefer 54 bc doses <54 Gy associated worse LC.
     (a) Mind hot spots in chiasm
     (b) Watch for swelling
3. During RT, weekly MRIs should be obtained to determine if there is reaccumulation of the cyst. CT scans (e.g., CBCT) not sensitive enough to clearly define reaccumulating cyst.
4. Can use intracystic bleomycin.
5. SRS 12 Gy if <2 cm and > 5 mm from optics.
6. Can use β-emitters (Y90, P32, Rh186). Rx is 200–250 Gy to cyst wall.
   (a) P32 is 0.7 MeV, t1/2 14 days, effective depth is 4 mm

Toxicity/outcomes
1. Long-term dz control after GTR and RT 90%.
2. Neuro-cognitive is the primary concern.
3. Endocrine is secondary concern. DI: 30% get it after RT. Presents as hypernatremia, polyuria, and thirst. Tx with desmopressin.

Hemangioblastoma

Background
- 20–50yos
- Arises in cerebellum
- VHL association
- WHO I
- Made of endothelial stem cells, "foamy cells" that make "clear cell" morphology
- Single lesion = sporadic, older
- Multiple lesions = familiar, younger

VHL Hemangioblastomas
- Young age, mean 29, 50% in cord, 40% cerebellum, 10% brainstem
- PCV bc of EPO production by tumor
- Have better prognosis after EBRT

Workup
- MRI: eccentric, peripheral cystic mass, and 70%. Intensely enhancing

Treatment
- **Surgery** w MSR preferred
  - **No need to remove entire cyst if R0.**
  - **15% M/M**
  - **50–80% LC**
- **SRS** is alternative, typically reserved for LR:
  - 15–21 Gy to 50% IDL
  - 90% LC at 2y, 75% at 5y
- **EBRT** is for multiple tumors, after STR for recurrence, large (>3 cm), lesions in eloquent brain regions
  - 50–55 Gy/2

Optic Pathway Glioma (OPG)

General
- Bimodal distribution: 5y and 52y.
- 5% of CNS peds tumors.
- Usually G1.
- F > M in peds; M > F in adults.
- NF-1 association, 20% of NF-1 pts will get OPG.
- Presents as painless proptosis.
- 5y OS 89%.
- Optic N sheath better than chiasm, PFS 80% vs 50%.
- In adults, these behave like HGGs. In peds, esp with NF-1, they may regress.

Workup
- HP, ophthalmology exam, MRI brain and orbits, genetics eval, and endocrine eval
- No bx necessary: imaging and exam enough

Studies
- CCG A9952. Compares chemos carbo and vinc vs thioguan, procarbazine, lomustine, and vincristine

Treatment
- Controversial.
- Chemo first, esp if < 10yo. Carbo and vincristine.
- RT: delay due to possible toxicity. Consider if >10 yo, progression, declining visual acuity.
- RT is 45–54 Gy/1.8 Gy fx.
- Never SRS bc CNII tolerance is 8 Gy.
- Surg: if refractory and no useful vision.
- Should include learning to read Braille at time of diagnosis.

Low-Grade Gliomas (LGG)

General
- In children low grade > high grade
- JPA is the second most common pediatric brain tumor, after medullo

Histology
- JPA: Rosenthal fibers
- Oligodendroglioma: Loss of 1p or 19q

WHO Grading
- I. JPA
- II. Diffuse fibrillary astrocytoma

Treatment paradigm
- Observation w MRI to determine pace of progression. NF-associated can regress.
- Surgery w GTR sufficient.
- Chemo can delay RT. Reasonable in <10yo, prefer if <5yo and NF1+. Typically cannot observe pts with G2+ tumors and sx. If >10yo and not surgical candidate, then RT encouraged.

Chemo Options
- Carbo 175 mg/m2 + vinc 1.5 mg/m2 induction, then maintenance x 12c
- 6-thioguanine, procarbazine, dibromodulcitol, CCNU, and vinc
- Avastin + irino: recurrence

Indications for Adjuvant RT
- R+
- Progressive/symptomatic
- Chemo refractory
- Unresectable

RT Options
- 50.4–54 Gy in 1.8 Gy fractions

Technique
- GTV = visible tumor on MRI (T1 post and T2/FLAIR)
- CTV = GTV + 0.5 cm
- PTV = CTV + 0.3–0.5 cm

Toxicity
- Endocrine
- Moya-moya: vascular complications near circle of Willis, constricted, develop collaterals as “puff of smoke” requires surgery.
- Cognition decline
- second malignancy

High-Grade Glioma (HGG)

Histology
- JPA: Rosenthal fibers (low grade)
- Oligodendroglioma: Loss of 1p or 19q

WHO Grading
- III: anaplastic astrocytoma
- IV: GBM

Chemo
- No consensus on what is best.
- PEI =cisplatin, etoposide, ifosfamide.
- PEV = cisplatin, etoposide, vincristine.
- VCR = vincristine.

Management
- Maximal Safe Resection and RT + TMZ
- FLAIR to 45 Gy, then comes down to enhancement to 59.4 Gy
- CTV1: T2 FLAIR+2 cm
- CTV2: T1 post contrast + GTV + 1.5 cm
- PTV = CTV1 or CTV2 + 5 mm
- **Outcomes**: 3-year EFS for AA and GBM is 13% and 7%

Diffuse Intrinsic Pontine Glioma (DIPG)/Midline Glioma/Brainstem Glioma [4–8, 51, 54–62]

General

- 80% arise in pons, and the rest are in the cervicomedullary junction, midbrain, and medulla
- Two classes
  (a) Focal: upper midbrain/lower medulla
  (b) Diffuse: pons and upper medulla

Workup

- H&P and labs
- MRI brain/spine. MRI will have indistinct margins, T1 hypointest, T2hyperintense, irregular enhancement w Gd, or none at all, no cystic or exophytic parts
- No biopsy
- IDH1, Histone 3 K27M mutation, MGMT promoter methylation, 1p/19q co-deletion status.

Genetics

- Histone 3 K27M mutation: associated with worse OS. Eighty percent of DIPGs have this mutation.

Trials

- Cohen 2011: no benefit to concurrent/adj TMZ.
- POG/CCG trials showed no benefit to hyperfrac or dose escalation.
- Janssens 2013: hypofractionated treatment has same OS and PFS.
- No benefit has been shown for chemo in DIPG.

COG Approach

- Steroids. Alternative is bev. This will help control peritumoral edema. In general surg is not recommended due to likely damage to brainstem.
- IMRT 54Gy/30 fx.
- CTV = tumor + brainstem +0.5–1 cm. Current trial COG-ADVL 1217 recommends GTV-CTV expansion of 1 cm, limited at calvarium, falx, tentorium.
- No role for dose escalation or hyperfractionation (per POG). MST is 9–12 months.
- Due to poor prognosis, other option is hypofrac: 3 Gy x 13 or 5.5 Gy x 6. Similar outcomes to CFRT.
- Recurrence: 2 Gy x 12 fractions. GTV + 0.5 cm margin.

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Central Nervous System Cancers

3

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Abstract

This chapter discusses the general management of patients with central nervous system tumors, with special focus on principles that guide radiotherapy management. Several key components of radiotherapy and radiosurgery care are discussed.

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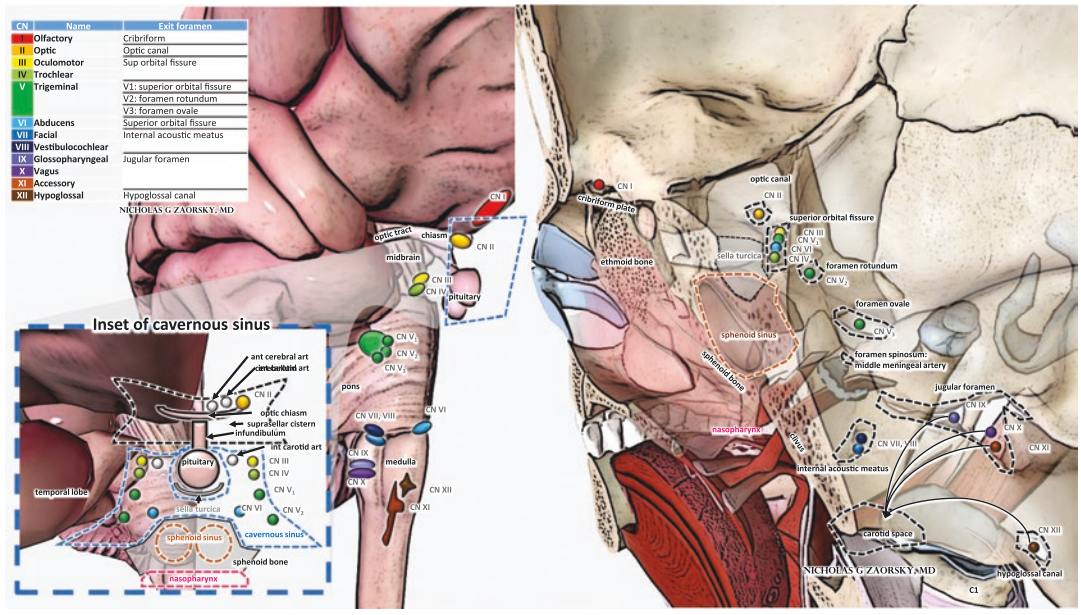
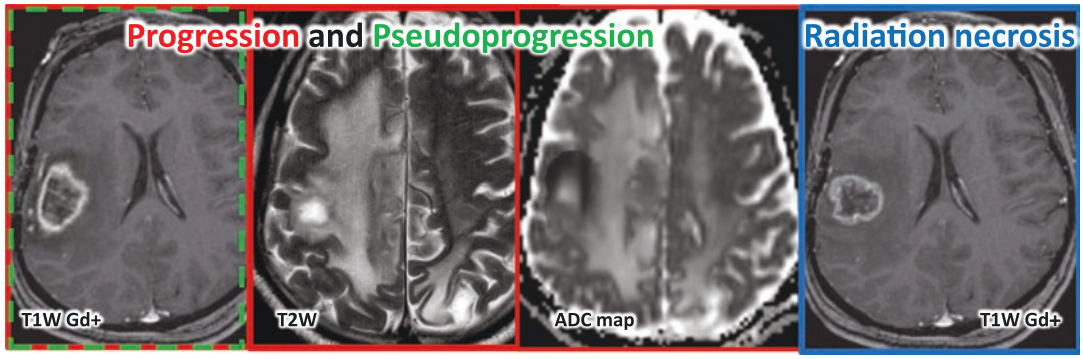
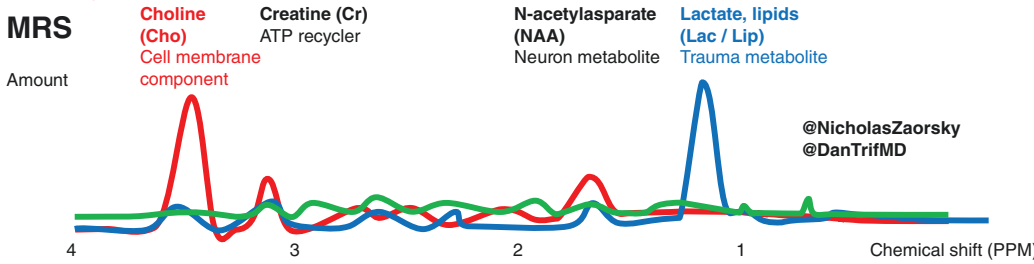


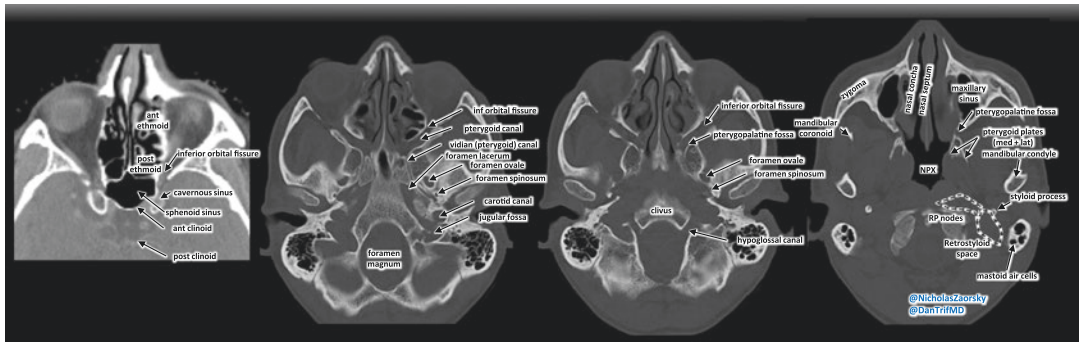


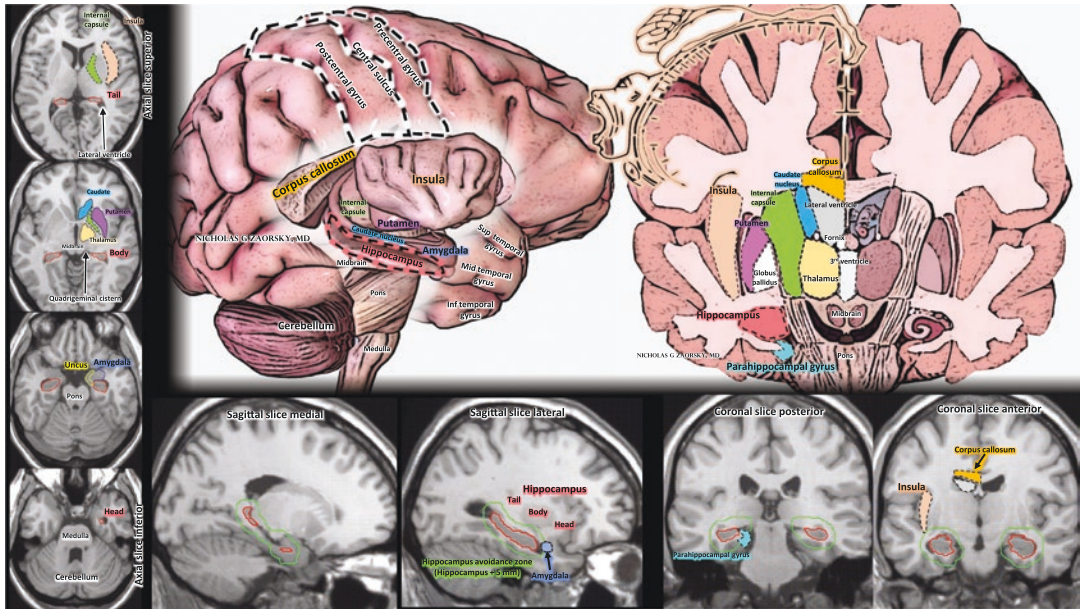
- Months – years after RT
- RANO: T1W is >25% ↑, T2/FLAIR is ↑, new lesion, ↓ clinical status
- Imaging:
  - T1 Gd+ MRI: Ring -like enhancement
  - T2W: hyperintense core, surrounding edema
  - ADC map from DWI: *hypointense* signal surrounding hyperintense core
  - DWI: ↓ diffusion around ring
  - MR perfusion: ↑ blood volume

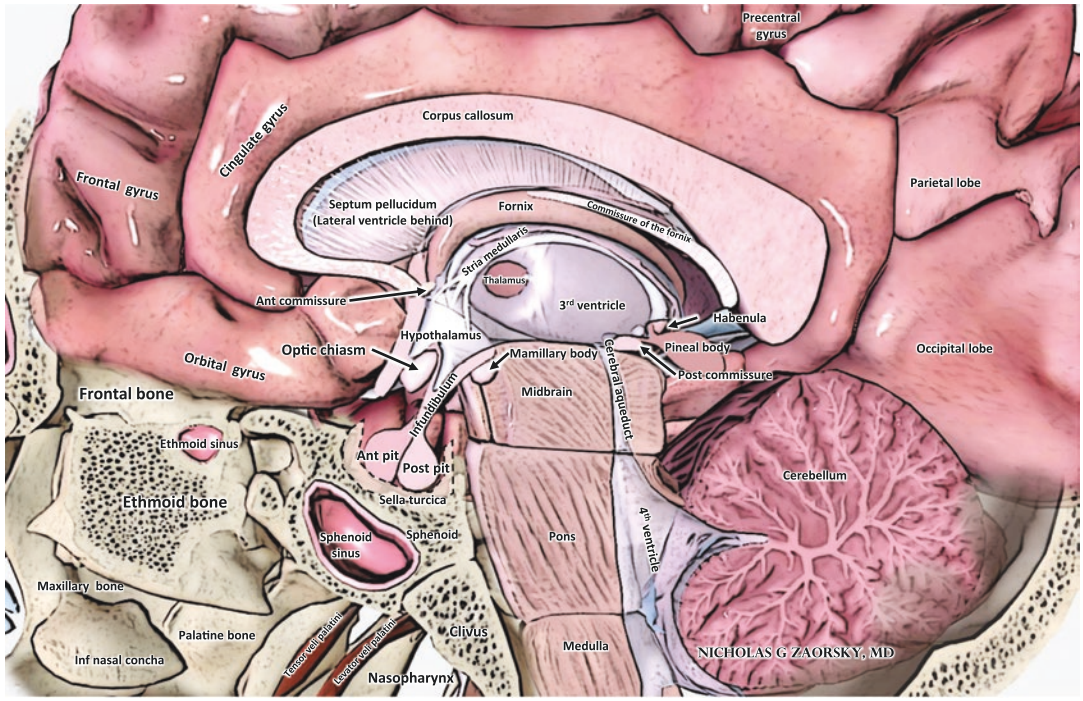
- ~2-6 months after RT
- Damage to oligodendrocytes, transient interruption of myelin synthesis
- More common in MGMTm
- Imaging:
  - T1W Gd+ MRI: Ring-like enhancement
  - T2W MRI: *hyperintense* around ring
  - DWI: ↑ diffusion around ring

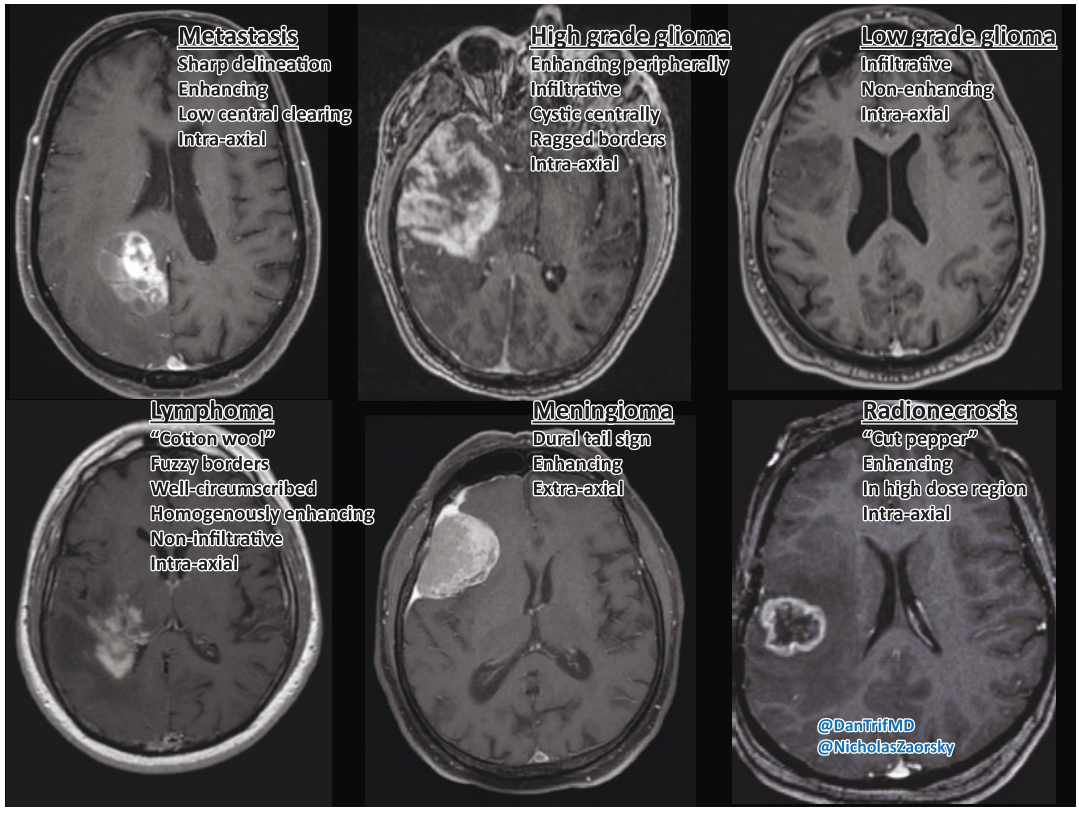
- Months–years after RT
- T2W MRI: "cut pepper" appearance




ant ethmoid
post ethmoid
inferior orbital fissure
cavernous sinus
sphenoid sinus
ant clinoid
post clinoid
inf orbital fissure
pterygoid canal
vidian (pterygoid) canal
foramen lacerum
foramen ovale
foramen spinosum
carotid canal
jugular fossa
foramen magnum
clivus
inferior orbital fissure
pterygopalatine fossa
mandibular coronoid
foramen ovale
foramen spinosum
hypoglossal canal
sinus
nasal concha
nasal septum
maxillary sinus
pterygopalatine fossa
pterygoid plates (med + lat)
mandibular condyle
NPX
styloid process
RP nodes
Retrostyloid space
mastoid air cells
@NicholasZaorsky
@DanTrifMD


Axial slice superior
Internal Capsule
Insula
Tail
Lateral ventricle
Caudate
Putamen
Thalamus
Midbrain
Body
Quadrigeminal cistern
Uncus
Amygdala
Pons
Axial slice inferior
Head
Medulla
Cerebellum
Precentral gyrus
Postcentral gyrus
Central sulcus
Corpus callosum
Insula
Internal Capsule
Putamen
Caudate nucleus
Hippocampus
Amygdala
Midbrain
Pons
Sup. temporal gyrus
Mid temporal gyrus
Inf temporal gyrus
Cerebellum
Medulla
NICHOLAS G ZAORSKY, MD
Corpus callosum
Caudate nucleus
Insula
Internal capsule
Lateral ventricle
Putamen
Fornix
3rd ventricle
Globus pallidus
Thalamus
Hippocampus
Midbrain
Pons
Parahippocampal gyrus
Sagittal slice medial
Sagittal slice lateral
Hippocampus
Tail
Body
Head
Hippocampus avoidance zone (Hippocampus + 5 mm)
Amygdala
Coronal slice posterior
Parahippocampal gyrus
Coronal slice anterior
Corpus callosum
Insula


Precentral gyrus
Corpus callosum
Cingulate gyrus
Frontal gyrus
Parietal lobe
Septum pellucidum (Lateral ventricle behind)
Fornix
Commissure of the fornix
Stria medullaris
Thalamus
Ant commissure
3rd ventricle
Habenula
Hypothalamus
Optic chiasm
Mamillary body
Pineal body
Occipital lobe
Orbital gyrus
Post commissure
Frontal bone
Infundibulum
Midbrain
Cerebral aqueduct
Ethmoid sinus
Ant pit
Post pit
Cerebellum
Ethmoid bone
Sella-turcica
4th ventricle
Sphenoid sinus
Sphenoid
Pons
Maxillary bone
Palatine bone
Clivus
Medulla
Inf nasal concha
Tensor veli palatini
Levator veli palatini
Nasopharynx
NICHOLAS G ZAORSKY, MD


Metastasis
Sharp delineation
Enhancing
Low central clearing
Intra-axial
High grade glioma
Enhancing peripherally
Infiltrative
Cystic centrally
Ragged borders
Intra-axial
Low grade glioma
Infiltrative
Non-enhancing
Intra-axial
Lymphoma
"Cotton wool"
Fuzzy borders
Well-circumscribed
Homogenously enhancing
Non-infiltrative
Intra-axial
Meningioma
Dural tail sign
Enhancing
Extra-axial
Radionecrosis
"Cut pepper"
Enhancing
In high dose region
Intra-axial
@DanTrifMD
@NicholasZaorsky

CNS Pearls [1–10]

Brain pathology	
Nuclear **A**typia **M**itotic index **E**ndothelial proliferation **N**ecrosis	GBM
Rosenthal fibers	JPA
Psammoma bodies, whorls	Meningioma
Verocay body	Schwannoma
Schiller-Duval bodies	Yolk sac
Fried egg	Oligodendroglioma
Pseudorosettes	Ependymoma: cystic, cerebellar
Homer-Wright rosettes	Medulloblastoma, neuroblastoma, PNET, +/−pineoblastoma
Flexner-Wintersteiner rosettes	Retinoblastoma, +/−pineoblastoma

Structure	Constraint	Risk	End point	Resource
Standard fractionation				
Optic N/chiasm	Dmax <55 Gy Dmax 55–60 Gy Dmax >60 Gy	<3% 3–7% >7–20%	Optic neuropathy	QUANTEC
Retina	Dmax <45 Gy (acceptable 45–50)		Retinopathy	NRG BN001
Lens	Dmax <7 Gy (acceptable 7–10)		Cataracts	NRG BN001
Cochlea	Mean < 45 Gy (preferable <35)		Hearing loss	QUANTEC
Brainstem	D1–10 cc < 59 Gy Dmax <60–64 Gy	<5%	Neuropathy/necrosis	QUANTEC
Brain	Dmax <60 Gy Dmax = 72 Dmax = 90	<3% 5% 10%	Necrosis	QUANTEC
Spinal cord	Dmax 45 Gy Dmax 50 Gy Dmax 54 Gy Dmax 60 Gy Dmax 69 Gy	<0.1% 0.2% <1% 6% 50%	Myelopathy	QUANTEC
Single- fraction SRS				
Optic N/chiasm	Dmax 8 Gy/1 fx (preferred) Dmax 12 Gy/1 fx (required)	Rare <10%	Optic neuropathy	QUANTEC
Brain	V12 < 5–10 cc/1 fx		Radiation necrosis	QUANTEC
Brainstem	Dmax <12.5 Gy/1 fx	<5%	Neuropathy/necrosis	QUANTEC
Cochlea	Mean dose <4 Gy/1 fx	<25%	Hearing loss	Kano 2009 Tamura 2009
Spinal cord	Dmax 14 Gy/1 fx Subvolume V10 < 10%/1 fx		Myelopathy	Yamada 2008 Ryu 2007
Esophagus	Dmax <16 Gy V11.2 < 5 cc		Ulceration	RTOG 0631

Additional resources for single and multi-fraction radiosurgery constraints:
UK Consensus on Normal Tissue Constraints for Stereotactic Radiosurgery (Hanna 2018)
Stereotactic body radiation therapy: the report of AAPM Task Group 101 (Benedict 2010)

CNS Workup

- History: ask about risk factors for extracranial disease (e.g., smoking) if it could be mets. For meningioma: ionizing radiation, NF-2, and hormone replacement therapy (70% of gr1 tumors are PR+).
- If NF2: check for café au lait spots.
- Physical exam: Neuro exam, HA, vision change, CN deficits, hypopituitarism, or overproduction.
  - Prolactinoma: amenorrhea, infertility, and galactorrhea.
  - Cushing's disease (ACTH): central obesity, HTN, DM, hirsutism, the skin changes, and osteoporosis.
  - Acromegaly (GH): changes in bones, HA, and cardiac disease.
- Differential: lymphoma, GBM, anaplastic astrocytoma, metastasis, meningioma, and abscess/infection ("L-GAMMA").
- Labs: CBC/CMP.
  - For pituitary tumor: endocrine panel (TSH, FSH, LH, GH/IGF-1, cortisol, ACTH, PRL).
  - Dex suppression test (Cushing's disease is not suppressed by low dose but is suppressed by high dose).
- CT head thin cuts.
  - Dural tail sign ddx: chloroma, lymphoma, sarcoid, meningioma (***cats like spilled milk***).
- MRI brain w/ and w/o contrast, thin slices.
- Consider CT c/a/p if suspecting brain metastasis.
- Neurosurgical consultation.
- Bx.
  - Biopsy if MRI compatible for lymphoma. No steroids before bx.
  - Send tissue for MGMT, IDH 1/IDH 2, EGFR, TERT promoter (WHO III–IV), 1p/19q (WHO II).
- Decadron + PPI – if low likelihood of lymphoma.
- Keppra (500 mg BID) if seizure risk.
- After surgery, need MRI within 48 h
- If ependymoma: MRI brain and spine preop (if spine MRI not done preop, then must wait until >10 days post-op)

MRI

- T1: longitudinal relaxation. Ideal for soft-tissue/normal anatomy. Enhances fat and soft tissues, does not enhance fluid. T1 + Gad contrast is ideal for visualizing brain tumors.
- T2: transverse relaxation. Ideal for fluid/edema.
- FLAIR: T2 with moving fluid (i.e., CSF) signal subtracted out.

MRI Spectroscopy

- Tumors have ↑ choline.
- Necrosis has ↓ choline, ↑ lactate, and ↑ lipid.
- Both have ↓ creatinine and NAA.

CSF flow

- Choroid plexus is present in all four ventricles and produces CSF. CSF flows from lateral ventricles → foramen of Monroe → 3rd ventricle → cerebral aqueduct of Sylvius → 4th ventricle → foramen of Magendie and lateral foramina of Luschka → subarachnoid cisterns

Intradural Intramedullary Spinal Cord Tumors

Differential Diagnosis

- **Extradural spinal cord tumors:** usually mets. Primary tumors are chordomas, sarcomas, lymphomas, plasmocytomas, MM, and Langerhans.
- **Intradural extramedullary spinal cord tumors** are 50% mets and 50% primary. Most

common are nerve sheath tumors (schwannomas, neurofibromas) and meningiomas.
– **Intradural intramedullary spinal cord tumors** are usually primary tumors. **Subtypes**: ependymoma (90%), astrocytoma, hemangioblastoma, subependymoma, and ganglioglioma.

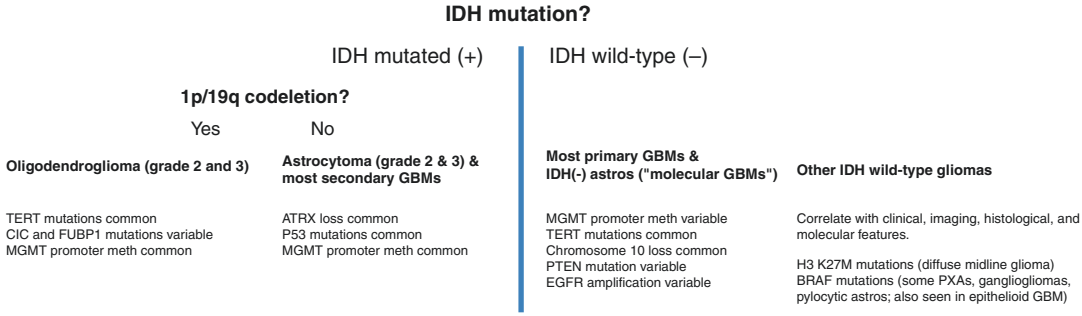
SRS Evaluation

– **Gradient index (GI):** (volume of half the prescription isodose)/(volume of the prescription isodose).
  • Preferred to be ~1.0 in CNS.
  • For example, for a plan normalized to the 50% IDL, it is 25% isodose volume/50% isodose volume. GI will differentiate between plans of similar conformity but with different dose gradients, for example, where isocenters have been inappropriately centered on the edge of the target volume.
– **Conformity index (CI):** (Rx isodose volume)/(PTV).
  • Preferred <1.2 in lung SBRT
  • Controversial use in CNS

Radionecrosis

– Central hypodensity, ring enhancement, high edema to enhancing tumor ratio, T1/T2 mismatch, low PET avidity, ↓ choline peak, ↑ lactate peak, and ↑ lipid peak occur at >6 m post RT. Necrosis may have decreased blood flow on perfusion series (e.g., arterial spin labeling [ASL]), while some tumors (e.g., GBM, metastases) will have increased blood flow.

Molecular Pathways for Adult Gliomas in 2018



The classification of gliomas has evolved significantly in the past decade. Historically, WHO grades I and II gliomas were broadly classified and treated as "low-grade" tumors, and WHO grades III and IV tumors were classified and treated as "high-grade" tumors based on light microscopy features. In the 2016 edition of the WHO classification of tumors of the CNS, gliomas are now classified according to both histopathologic and defining molecular features. Some of the most important updates are related to the recognition of IDH mutations as early, stable driver mutations in the majority of grades II and III gliomas, as well as a characteristic feature of most secondary GBMs (i.e., those GBMs that arise from lower-grade tumors). IDH-mutated tumors that subsequently develop downstream codeletion of chromosomal arms 1p and 19q are now classified as oligodendroglial tumors by definition, whereas IDH-mutated tumors without 1p/19q codeletion are classified as astrocytic tumors and commonly have downstream ATRX loss and p53 mutations (Eckel-Passow 2005, Cancer Genome Atlas Research Atlas 2015) [3, 4].

The assignment of WHO grades II, III, and IV is still dependent on histopathologic features including atypia, mitoses, microvascular proliferation, and necrosis. However, both IDH-mutated oligodendrogliomas and astrocytomas will typically retain their characteristic molecular driver mutations after transformation to higher-grade tumors, suggesting that grade II and III oligodendrogliomas represent different points in the phenotypic evolution of tumors from a common molecular lineage and the same could be said of IDH-mutated astrocytomas of grades II, III, and IV (i.e., secondary GBMs).

Primary GBMs, which are more common (~90%) than secondary GBMs (~10%) and tend to occur in older adults, typically do not have IDH mutations and are instead driven by other characteristic molecular features, including but not limited to TERT mutations, chromosome 10 loss, PTEN mutations, and EGFR amplification. IDH wild-type astrocytomas often exhibit molecular profiles and clinical behaviors that are more similar to primary GBMs than to IDH-mutated astrocytomas and are sometimes referred to as "molecular GBMs."

In 2018, the majority of the available clinical data is based on older WHO classification systems, and guideline-endorsed treatment paradigms are driven more by histologic grade than molecular profile (see below). However, it is clear that future risk stratification and treatment algorithms will be increasingly based on genomic alterations.

General Glioma Treatment Paradigms in 2018

Grade 2, astrocytomas and oligodendrogliomas

Trial justification for *preferred* strategies

Notes

"High-Risk" → RT + chemo (preferred)
RT alone
Max safe resection → Chemo alone
Observation

RTOG 9802 (Bucker, NEJM 2016)

Grade 2 risk stratification is based on RTOG 9802 inclusion criteria: High-risk is either ≥40y OR a subtotal resection. Low-risk is <40y AND a gross total resection. However, additional high-risk criteria have been used in other studies (eg, large tumors, crossing midline, symptomatic, recurrent).

"Low-risk" → Observation (preferred)
RT + chemo
RT alone
Chemo alone

EORTC 22845 "non-believers" trial (van den Bent, Lancet 2005)

Caution should be exercised when deeming an IDH(-) astrocytoma as "low-risk", as these tumors can exhibit molecular profiles and natural histories similar to primary GBMs.

Grade 3, anaplastic astrocytomas and oligodendrogliomas

Max safe resection → RT + chemo (preferred)
RT alone
Chemo alone

EORTC 26951 (van den Bent, JCO 2012)
RTOG 9402 (Cairncross,JCO 2012)
CATNON (van den Bent, Lancet 2017)

-Level 1 evidence supports RT + concurrent and adjuvant TMZ as preferred treatment for GBM regardless of age for both younger (Stupp 2005) and elderly patients (Perry 2017) who are suitable candidates for combined therapy.

Grade 4, glioblastomas

Max safe resection → RT + TMZ (preferred) +/– TTF
RT alone
TMZ alone

(Only in MGMT+; Wick 2012, Malmstrom 2012)

EORTC/NCIC (Stupp, NEJM 2005)
EORTC/NCIC/TROG Elderly Trial (Perry, NEJM 2017)
TTF-trial (Stupp, JAMA 2015)

-Hypofractionated RT may be selected or preferred for elderly or those with poor performance status (Perry 2017, Roa 2004, Roa 2015, Malmstrom 2012).

Low-Grade Glioma (WHO Grades I–II, Oligo, Astro, and Mixed Oligo-Astro) [11–25]

General

- Frequently diagnosed in 30s and 40s.
- Approx 20% of gliomas are low grade.
- Protracted natural hx often undergo high-grade transformation in the years after dx. RT not assoc with ↑ malignant trans (EORTC 22845).

Histology

- Historically, four determinants of grade: atypia, mitosis, microvascular proliferation, and necrosis.
- Grade I subtypes: JPA, pleomorphic xantho-astrocytoma, subependymal giant cell astrocytoma, subependymoma, and gangliogliomas.
- Grade II subtypes (common): diffuse astrocytomas and oligodendrogliomas.
- Oligo-astrocytoma no longer exists in WHO. These are now oligo lineage (IDH+, 1p/19q codel+) or astrocytoma lineage (IDH+ but 1p/19q neg or IDH wild-type astros).
- Juvenile pilocytic astrocytoma (JPA):
  (a) Rosenthal fibers histologically.
  (b) WHO I: treat with surgery; consider PORT if STR or recurrent.
  (c) Pilomyxoid astrocytoma is an atypical JPA, more aggressive.
- Subependymal giant cell tumor:
  (a) Associated with tuberous sclerosis (ch9)
  (b) WHO I

Symptoms

- Seizures: common presenting symptom due to superficial location of tumor, infiltration into brain parenchyma, and slow growth rate.
- Other symptoms include, but are not limited to, motor or language deficit, personality changes, headaches, and vomiting.

Workup

- H&P and neurological exam.
- History: previous scans, cancer history, and cancer screening.
- Basic labs to rule out infection.
- CT CAP or PET/CT sometimes appropriate to rule out metastases if diagnosis in question.
- Decadron or anti-seizure meds: appropriate for symptoms, generally not indicated prophylactically.
- MRI w/ or w/o gad. LGGs commonly do not enhance with contrast, usually show T2 bright signal, and often appear mass-like (gyral fullness, sulci effacement). Although most non-enhancing gliomas are low grade, foci of higher-grade disease may be found on pathology.
- Calcifications may be seen with oligos.
- Hearing/ophtho eval as indicated.
- Surgery eval for maximum safe resection. Rarely biopsy first, unless unresectable or diagnosis in question.
- Post-op MRI indicated within 72 hrs of surgery and within 24 hrs when possible.

Surgery for LGGs

- **Smith 2008**: retro, 216 pts, resection >90% correlated with 5yr OS (97% vs 76%)
- **Jakola 2017**: parallel Norwegian pop-based cohorts received watchful waiting vs resection for grade II lesions. Median OS 14 yrs (resection) vs 6 yrs (obs)

RT for LGGs

- **EORTC 22845 Non-Believers trial** (van den Bent, Lancet 2005). 314 patients randomized to early radiation (54 Gy/30 Fx) vs observation and RT at progression. No chemo. OS similar (median 7.4 vs 7.2 yrs, NS). Early RT assoc with improved PFS (5.3 vs 3.4 yrs, HR 0.59, $p < 0.001$) and better seizure control at 1 year. Salvage RT recorded in 46% of the obs pts. Seventy percent of pts had transformation to HGG irrespective of early vs delayed RT. Study can be used to argue for obs (delay RT until progression) due to lack of OS difference but can also be used to argue for early RT due to improved PFS. Prognostic factors for worse OS on MVA: age >40, astro histo, 6+ cm, crossing midline, and neuro deficit prior to surgery.

– **EORTC 22844 Believers (dose-esc) trial** (Karim, IJROBP 1996). 379 patients with LGG randomized to 45 Gy/25 Fx vs 59.4 Gy/33 Fx. No difference in OS.
– **Intergroup (dose-esc) trial** (Shaw, JCO 2002): 203 patients randomized to 50.4 Gy/28 Fx vs 64.8 Gy/36 Fx. No difference in OS. High-grade neurotox worse with high-dose RT. Ninety-two percent of failures were infield. OS better with age <40, oligo histo, and smaller size.

RT +/– Chemotherapy for LGGs

– **RTOG 9802** (Buckner NEJM 2016). High-risk LGG (defined as age ≥ 40 or STR), 251 patients randomized to 54 Gy/30 Fx +/– PCV chemo x 6 cycles. 43% oligodendro. With 12-yr follow-up, PCV dramatically improved OS (median 13.3 vs 7.8 yrs) and PFS (10.4 vs 4.0 yrs). Curves separate at 4y.
– **RTOG 0424** (Fisher 2015): Single-arm phase II. 129 patients with high-risk LGG, with 3 or more risk factors (age ≥ 40, astro, bi-hemispherical tumor, ≥6 cm, or preop neuro function status of >1), were treated with RT (54 Gy/ 30 Fx) plus concurrent and adjuvant TMZ. Three-year OS of 73% improved vs historical control of 54%.
– **EORTC 22033-26033** (Baumert, Lancet Oncol 2016): Randomized single-modality comparison of RT alone (50.4 Gy) vs TMZ alone (max 12 cycles) in high-risk supratent LGG, with at least one of these features: age >40, progressive dz, size >5 cm, cross midline, and neuro sx. No diff in median PFS, 46 months for RT vs 39 months for TMZ. OS results still maturing and not reported in 2016 publication. Results should be taken in context of the RTOG 98-02 results showing best outcomes with RT + chemotherapy.

PFS and OS in Major LGG Randomized Trials

Trial	Treatment	PFS (years)	OS (years)
Non-Believers	Obs (delayed RT)	3.4	7.2
	RT (54 Gy)	5.3	7.4
Believers	RT (45 or 59.4 Gy)	4 to 5	6 to 7
Intergroup	RT (50.4 or 64.8 Gy)	5.5	9.3
EORTC 22033	RT (50.4 Gy)	3.8	–
	TMZ	3.2	–
RTOG 9802	RT (54 Gy)	4.0	7.8
	Combined RT (54 Gy) and then PCV x6c	10.4	13.3

NEW NCCN high risk	OLD high risk (*SATANIC*)
>40 yo or STR	**S**ize ≥6 cm
	Age >40yo
	Tumor crossing midline
	Astrocytoma (pure)
	Neuro deficit preop
	IDH1/2 non-mutated as high risk
	1p/19q non-**C**odeleted

Treatment Paradigms in 2018

– Cranial LGGs need max safe resection first. Per 2017 NCCN, if low risk (GTR and age <40 per RTOG 9802), may follow with close observation.
– If high-risk (STR or age >40y), then adjuvant RT + chemo. PCV is category-1 based on RTOG 9802, but many centers use TMZ.
– The contemporary NCCN stratification of high vs low risk provides a useful backbone for LGG management; however, we would caution the conceptual overreliance on the high- vs low-risk inclusion criteria from a single trial (i.e., RTOG 9802). Additional clinical risk factors have been identified and used in other trials (e.g., tumor size, histology, symptoms, crossing midline, progressive, etc.). Molecular-based

stratifications (IDH, 1p/19q) are also likely to gain increasing importance in future trials. IDH-negative astros, in particular, may exhibit natural histories similar to primary GBMs (Cancer Genome Atlas Research Network, NEJM 2015).
– For spinal LGGs, the adj RT paradigm is similar, although the role of chemotherapy is currently undefined. Surgery with max safe resection first. If GTR, role of adj RT is controversial and may be individualized. If STR or less, adj RT is usually advocated because failure is typically local.

Simulation/Planning: Brain
– Supine, aquaplast, and fuse post-op MRI. Fusion of preop MRI may be useful for reference.
– **GTV** = post-op cavity + any T1 post-contrast and T2 FLAIR abnormality. Most LGGs will not have T1 post-contrast enhancement.
– **CTV** = 0.5–1.0 cm exp, cropped at anatomic boundaries (e.g., falx, tentorium, bone, cisterns). CTVs should be allowed to cross white matter tracts commonly including corpus callosum but where appropriate consideration should also be given to cerebral/cerebellar peduncles and ant/post commissures.
– **PTV** = 2–5 mm with daily IGRT. *PTVs should be based on institutional technical standards.
– Two dedicated randomized RT dose-esc trials from the pre-chemo era (EORTC 22844 and Intergroup) do not support an advantage of RT doses above 45–50.4 Gy. The RTOG 9802 used **54 Gy/30 fx.** EORTC used **50.4 Gy/28 fx.** Consequently, 2017 NCCN acknowledges doses from 45–54 Gy.
– New CODEL trial incorporates boost for GRD to 59.4 Gy.

Simulation/Planning – Spine
– Supine, vacloc, aquaplast mask if above T4.
– MRI should be used to define the GTV.
– Classically, fields targeted 2 VBs above and below the myelogram-defined tumor. With modern MRI-based planning, a CTV of GTV + 0.5–1.0 cm is reasonable.
– PTV = 3–5 mm with daily IGRT.
– Dose: 45–50.4 Gy are reasonable for LGG; extrapolated from cranial disease; higher doses can be considered based on size, location, tumor grade, and risks of radiation-induced myelopathy vs myelopathy from tumor regrowth.

Follow-Up
– NCCN advocates MRI Q6m for 5 years and then annually.
– Lifelong surveillance recommended.

High-Grade Glioma (WHO Grades III–IV) [11–15, 26–86]

General

- Most common primary malignant brain tumor.
- Majority are sporadic.
- Some hereditary syndromes (e.g., Cowden, Turcot, Lynch, Li-Fraumeni, NF1).
- Symptoms may include headache, seizure, focal neuro deficits, and personality changes.
- MRI typically shows T1p enhancing lesion with T2-bright vasogenic edema.
- DDx may include brain metastases, lymphoma, infection, stroke, and demyelinating lesion.
- In GBM, defining histopath features include necrosis and microvascular proliferation.
- H3 K27M mutations define diffuse midline gliomas (WHO grade IV).

Molecular

- Grade III (anaplastic) gliomas.
  - Anaplastic oligos (IDH+, 1p/19q codeleted), same molecular signature as grade II oligos.
  - Anaplastic astros (IDH+, 1p19q non-codel) or (IDH-negative, sometimes referred to as "molecular GBMs"), same as grade II astros.
  - Oligo-astro no longer recognized; now classified as oligos or astros based on molecular signatures above.
- Primary vs secondary GBM: molecularly related to IDH mutational status.
  - Primary GBMs (90%): typically IDH wild type, worse prognosis, older patients, usually not preceded by a lower-grade tumor.
  - Secondary GBMs (10%): typically IDH-mutated, better prognosis, younger patients, often preceded by a lower-grade tumor. May have molecular features similar to IDH+ astro (e.g., ATRX loss, p53 mutation).
- MGMT (O-6-methylguanine-DNA-methyltransferase).
  - DNA repair enzyme that removes alkyl groups from O6 guanine.
  - Methylation of the MGMT promotor silences MGMT, increasing the antitumor effects of alkylating agents like temozolomide (TMZ).
  - MGMT promoter meth observed in 35–45% of primary GBMs and ≥ 80% of secondary (IDH+) GBMs and IDH+ grade III gliomas
  - MGMT status is a well-validated predictor of improved TMZ response.
  - MGMT status has not reliably predicted as outcomes in patients treated with RT alone (Malmstrom 2012, Wick 2012, Perry 2017).
  - A subset of pts without MGMT promoter meth still benefit from TMZ (Stupp 2009, Perry 2017), but features identifying these patients have not yet been defined.

Workup

- H&P, neuro exam
- MRI w/ or w/o gad
- History: prior MRIs, cancer hx, cancer screening
- Basic labs to rule out infection
- CT CAP or PET/CT sometimes appropriate to rule out metastases if diagnosis in question
- Decadron or anti-seizure meds: appropriate for symptoms, generally not indicated prophylactically. If longer-term steroids needed, consider PPI and PCP prophylaxis
- Hearing/optho eval as indicated
- Surgery eval for maximum safe resection. Typically no need for biopsy, unless unresectable or diagnosis in question.

Extent of Resection (EOR)

- **Vuorinen 2003**. Finland. Small randomized trial ($N = 30$) of resection plus RT vs biopsy plus RT for suspected HGG in the elderly

(>65 yrs). Resection associated with improved OS (5.7 vs 2.8 mo, $p = 0.035$).
- **Brown 2016**: Meta of >41,000 pts; improved OS with GTR >STR and STR >biopsy alone.
- **Lacroix 2001**: $n = 416$. Ninety-eight EOR was cut off and contributed to all or none surgical philosophy.
- **Sanai 2011**: $n = 500$. EOR as low as 78% beneficial. Stepwise improvement in OS for EOR thresholds of 95%, 98%, and 100%.
- **Chaichana 2014**: $n = 259$. EOR at >70% beneficial.

BCNU/Carmustine (Gliadel) Wafers in the Surgical Cavity
- **Westphal 2006**: RCT ($N = 240$) of newly diagnosed HGG. Improved OS with wafers, 13.8 vs 11.6 mo ($p = 0.017$).
- **Valtonen 1997**: RCT ($N = 32$) of newly diagnosed HGG. Improved OS with wafers, 53 vs 40 weeks ($p = 0.008$) for GBM.
- **Brem 1995**: RCT ($N = 222$) of recurrent HGG. Improved OS with wafers, 31 vs 23 weeks ($p = 0.006$).
- 2017 NCCN acknowledges wafers in cavity at resection as an option for both newly diagnosed and recurrent HGGs, but note that this can be an exclusion criterion for some clinical trials.

Surgery +/– RT in the Pre-TMZ Era
- **Laperriere 2002.** Systematic review and pooled analysis of six RCTs from the pre-TMZ era (Shapiro 1976, Walker 1978, Anderson 1978, Walker 1980, Kristiansen 1981, Sandberg-Wollheim 1991). OS favored RT (HR 0.81, $p < 0.0001$). These historic trials used doses from 45 to 60 Gy and most involved whole-brain RT.

WBRT vs Limited-Field RT
- **Shapiro 1989**: Trial included a randomization of WBRT 60 Gy vs WBRT 43 Gy and then cone down to 60 Gy. No differences in OS.

RT Dose
- **RTOG 74-01** (Nelson 1988): No benefit to 70 Gy over 60 Gy for GBM
- **MRC** (Bleehen 1991): 474 pts. 45/20 vs 60/30. 60 Gy improved OS (12 vs 9 mo)

Strategies that Have not Improved on 60 Gy/30 Fx
- SRS boost (e.g., RTOG 9305, RTOG 0023)
- Hyper Fx (e.g., RTOG 9006, RTOG 8302)
- Brachytherapy (e.g., BTCG NIH 8701)

Elderly: RT vs Best Supportive Care
- **Keime-Guibert 2007**: 81 patients >70 yrs. RCT of 50.4 Gy vs best supportive care. No chemo. Trial stopped at first interim analysis with superior OS with RT, 7.3 vs 4.3 mo.

Elderly/Poor KPS: Hypofractionation, No TMZ
- **Roa 2004 ("Roa 1")**: 100 elderly (>60 yo) GBM patients. Surgery, then randomize 60 Gy/30 Fx vs hypofractionated RT 40 Gy/15 Fx. No chemo. No difference in median OS: 5.1 vs 5.6 mo. No change in average KPS score or KPS over time.
- **Roa 2015 ("Roa 2"):** 98 with GBM. Three patient types included: frail = age 50+ and KPS 50–70, elderly = age 65+ and KPS 80–100, and elderly and frail. Note that 40/15 is 70% BED of 60 Gy/2. Randomized to 25 Gy/5 Fx vs 40 Gy/15 Fx. No chemo. No diff in OS, PFS, or QOL. Dose constraint is the max dose (40 Gy).

Elderly/Poor KPS: Hypofractionation and + TMZ
- **Nordic trial** (Malmstrom 2012): Single-modality comparisons – TMZ alone vs hypofrac RT 34/10 alone vs standard RT 60/30 alone for GBM in >60yo. OS outcomes with TMZ alone (8.3 mo) similar to 34/10 (7.5 mo) and superior to 60/30 (6 mo). Standard RT 60/30 patients were less likely to complete treatment. MGMT+ patients did best with TMZ alone. In MGMT-negative, RT alone was superior to TMZ alone. Supports use of 34/10 over 60/30 for elderly.
- **NCI Canada/EORTC/TROG** (Perry 2017): Elderly pts ≥70 yrs**,** randomized to hypofractionated RT (40 Gy/15 Fx) +/− conc/adj TMZ. Improved OS (9.3 vs 7.6 mo) with TMZ overall and in MGMT methy ($p < 0.001$) and unmeth patients ($p = 0.055$). This trial effectively ended the preceding debate about the

role of single-modality therapy in elderly GBM patients: RT + TMZ is the gold standard in elderly patients who are suitable for combined therapy.

TMZ

- **EORTC/NCIC** (Stupp 2005, 2009): 573 GBM pts (≤70 years). RCT of RT (60 Gy) +/− conc/adj TMZ. Median OS improved with TMZ (14.6 v 12.1 mo), and 2-year 27% vs 11%, and 5-year 10% vs 2%. Largest benefit of TMZ in MGMT+, but a subset of MGMT unmethylated patients also benefited, making TMZ the guideline standard irrespective of MGMT status.
- **RTOG 0525** (Gilbert 2013): RCT of standard TMZ vs dose-dense TMZ; no diff in OS or PFS.
- **NOA-08** (Wick 2012): German elderly trial. Single-modality comparisons for standard RT 60/30 alone vs dose-dense TMZ alone in patients 65+ years. No difference in OS or PFS. TMZ alone reasonable for MGMT+ patients unsuitable for combined RT + TMZ.
- **Rusthoven 2016**. NCDB: over 16,000 GBM patients ≥65y in the TMZ era (2005+). OS best with chemoRT (9 mo); OS with RT alone (4.7 mo) and chemo alone (4.3 mo) was similar; no-RT/no-chemo cohort associated with shortest OS (2.8 mo).

Bevacizumab in Up-Front GBM

- **RTOG 0825** (Gilbert 2014): 637 pts with GBM: RCT of RT/TMZ +/− conc/adj Bev. No diff in OS. Bev was assoc with superior PFS but also inferior QOL and more adverse events.
- **AVAGLIO** (Chinot 2014): 921 patients with GBM: RCT of RT/TMZ +/− conc/adj/maintenance Bev. No diff in OS. Bev was assoc with superior PFS and QOL but also higher adverse events.
- Bevacizumab is not considered standard therapy for newly diagnosed GBM.

Tumor-Treating Fields (TTF)

- **Stupp 2015, 2017**: 695 GBM patients completed RT/TMZ and then randomized 2:1 to TTF plus TMZ or TMZ alone. TTF associated with improved OS (21 v 16 mo) and PFS (6.7 v 4 mo). Criticisms: no sham device (i.e., no placebo) and increased support in TTF patients. No palliative care (see Temel NEJM); Currently category-2A for adjuvant GBM treatment.

Grade 3 Glioma: RT +/− Chemotherapy

- **RTOG 9402** (Cairncross 2013). 289 patients w/grade III oligos or oligo-astros. RCT of RT (59.4 Gy) +/− neoadj PCV. No diff in OS overall, but curves split after 5 yrs. In 1p/19q codeleted, OS dramatically improved with PCV (median 14.7 vs 7.3 years, $p = 0.03$). Subsequent analysis (Cairncross 2014) also showed a benefit to PCV in IDH-mutated, 1p/19q non-codeleted (i.e., molecular astrocytomas in the contemporary WHO).
- **EORTC 26951** (van den Bent 2012): 268 pts w/ grade III oligos or oligo-astros. RCT of RT (59.4 Gy) +/− PCV. PCV improved OS in the overall cohort (median 42.3 vs 30.6 mo). The benefit was largest for 1p/19q codeleted.
- **CATNON: EORTC 26053-22054.** (van den Bent 2017). Patients with grade III astros without 1p/19q codeletion. Two-by-two design randomizing patients to RT (59.4 Gy) +/− conc TMZ +/− adj TMZ. Interim results in 2017 specifically reporting on the +/− adjuvant TMZ randomization showed improved OS with adj TMZ (5-year OS, 56 vs 44%).

Grade III Gliomas: RT vs Chemotherapy

- **NOA-04** (Wick 2009). 318 patients with grade III gliomas. RCT of up-front RT alone (60 Gy) vs chemo alone (PCV or TMZ). Comparable outcomes (TTF, PFS, and OS) with up-front RT alone vs chemo alone.

Patterns of Failure and Evolving RT Treatment Technique

- RTOG and EORTC have historically used 2+ cm CTV margins for GBM based on autopsy and recurrence series from the pre-MRI era showing most recurrences within 2 cm of the resection cavity and contrast enhancement.
- More recent clinical series have suggested comparable outcomes with smaller CTV margins ranging from 0.5 to 1.5 cm, with most failures remaining infield (Paulsson 2014, Gebhardt 2014, McDonald 2011). As a result, the 2016 ASTRO GBM consensus statement (Cabrera 2016) acknowledges that margins <2 cm are acceptable.
- **RTOG cone-down technique**: Initial treatment to larger T2 abnormality, then cone down for last 14–16 Gy to cavity+T1 post-contrast abnormality.
- **EORTC single-volume technique**: Cavity+T1 post-contrast abnormality to full dose. No dedicated coverage of T2 abnormality.
- **Minniti 2010**: failure patterns in the TMZ era using EORT single-volume technique, analyzed by MGMT +/−. Recurrences were infield for 64% of methylated, 91% for unmethylated.
- **Chang 2007**: MDACC study, edema not included in target volumes; patterns of recurrence reviewed and patients re-planned based on RTOG guidelines; including edema would not have altered failure patterns.

WHO IV/GBM Simulation/Planning

- Post-op MRI within 72 h (preferably within 24 hours when possible)
- Supine, aquaplast. Fuse post-op MRI for volumes. Fusion of preop MRI may be useful in some cases for reference.
- Primary techniques are RTOG-style cone down and EORTC-style single-volume technique as noted above.
- CTV46 = **post-op T2 FLAIR** + cavity +2 cm (cropped to 5 mm at natural barriers).
- CTV60 = post-op cavity + residual enhancement +2 cm (cropped to 5 mm at natural barriers).
- PTV = CTV + 3 mm (only if using daily CBCT).
- Goal is to start within 4 weeks of surgery.
- TMZ is 75 mg/m^2/day 7 days per week concurrent, then 1 m break, and then 150 mg/m^2/day d1–5 q28 days x 6–12 cycles adjuvant. Give Bactrim for PCP ppx.
- Do not give bevacizumab up-front (two negative RCTs).

Special Scenario: Elderly >65 yo and KPS >60–70

- Old Roa: Hypofractionated RT to 40 Gy in 15 fractions + concurrent TMZ. CTV = T1 post enhancement +2 cm, PTV = CTV + 3 mm.
  - No TMZ on trial.
- New Roa: Ultra-hypofrac RT to 25 Gy in 5 fractions
  - No TMZ on trial.
- Nordic: 34 Gy in 10 fractions alone
- Perry: 40 Gy/10 fractions + TMZ → TMZ alone

Special scenario: KPS <60–70

- Nordic: If MGMT methylated → TMZ alone (150–200 mg/m^2 × 5d q28d × 6).

Response Assessment in Neuro-Oncology (RANO) Criteria for GBM Recurrence

	CR	PR	SD	PD
T1 Gd+ dz	None	>50%	<50% if ↓ <25% if ↑	>25% ↑
T2/FLAIR	Stable or improved			↑
New lesion	No			Yes
Steroid use?	No	Stable or ↓		N/A
Clinical status	Stable or improved			↓
Requirement for response	All	All	All	Any

- Simplified RANO: new enhancement outside RT field, increase >25% in size, unexplained clinical deterioration

- Call progression within 3 months of RT only if new enhancement is beyond 80% IDL
- Unequivocal pathological evidence of viable tumor

Revised EORTC RPA for GBM
- III: age <50 and PS 0
- IV: age <50 and PS 1–2
- Age >50, GTR/STR, and MMSE>27
- V: age >50 and bx only or MMSE<27

Median Survival w/ TMZ + RT
- RPA III – 21–24 mo
- RPA IV – 14–16 mo
- RPA V – 9–10 mo

Follow-Up
- 2017 NCCN: MRI q2–4 months x 3 years and then 6 q months indefinitely.
- Majority of HGG recurrences (80–90%) are local; 20–30% of patients have pseudoprogression after RT + TMZ (Taal 2008).
- MGMT methylation status increases the incidence of pseudoprogression after TMZ + RT (Brandes 2008).

Recurrence
- Approx 80–90% recurrences are local/infield
- There is no universal standard of care for recurrent HGG. Cases should ideally be discussed in multidisciplinary setting. Clinical trials are preferred when available.
- Options for therapy may include combinations of re-resection +/− chemotherapy wafer placement in the cavity, chemo/systemic therapy (e.g., TMZ re-challenge, alternative systemic agent, bevacizumab), TTF (Stupp 2012), and re-irradiation.
- ReRT carries increased risk of side effects and should generally be delayed to at least >6 months and ideally >12 months after prior RT.
- **Combs 2005**. Series of reRT in 172 patients, conventional fractionation 36 Gy/18 Fx
- **Fogh 2010**. Series of reRT in 145 patients, hypofractionated RT 35 Gy/10 Fx
- **Shapiro 2013**. Series of 24 patients reRT with, SBRT 30 Gy/5 Fx + bevacizumab
- **RTOG 1205 (ongoing)**: RCT of bevacizumab alone vs bevacizumab plus reRT. RT is 35 Gy/10 Fx to cavity and T1 post-contrast abnormality with tight margins.

Grade III Glioma (AA, AO, AOA) management

- Maximal safe resection (or stereotactic biopsy if not feasible)
- Send tissue for: 1p/19q and IDH1 for oligos (all 1p/19q codel also are IDH1 mut)
- Post-op MRI w/ in 48 hr
- **If codeleted:** RT → PCV six cycles. PCV = procarbazine, CCNU, vincristine q6 weeks × six cycles
- **If non-codeleted or AA:** Stupp regimen as per GBM. Concurrent TMZ and RT → adjuvant TMZ

RT Details
- Simulation: Supine, three-point face mask. CT sim w/o contrast, and MRI sim with contrast. Ensure to obtain T1 post and T2-FLAIR sequences
- CTV45 = Post-op T2 FLAIR + cavity +2 cm (cropped to 5 mm at natural barriers)
- CTV59.4 = If enhancing: post-op cavity + residual enhancement +2 cm (cropped to 5 mm at natural barriers). If non-enhancing: T2-FLAIR+5 mm
- PTV = CTV + 3 mm (only if using daily CBCT)
- Planning:
- Dose: 45 Gy to FLAIR and 59.4 Gy to cone down
- IMRT
- Daily CBCT

Special Scenario: Elderly or Low KPS. See GBM

Outcomes:

RTOG 94-02 (Grade III AO or AOA)
RT vs PCV → RT

	RT	PCV → RT
Median OS (yrs):		
1p/19q codel (all IDH1 mut)	7	15
1p/19q intact, IDH1 mut	3.3	5.5
Intact/WT	1.3	1.0

Primary CNS Lymphoma (PCNSL) [11–15, 87–103]

Prognostics, Ferreri, JCO, 2003			
Age > 60	Risk group	# Factors	2y OS %
ECOG > 1	Low risk	0–1	80
LDH > UNL	Int risk	2–3	50
CSF prot > UNL	High risk	4–5	15
Deep brain involved			

Stage: All Are Stage IE (Extranodal NHL)

General

- 4% of primary CNS tumors.
- In immunocompetent pts, most dx between 45 and 65 years of age.
- The primary risk factor is immunodeficiency: HIV, iatrogenic immune deficiency, autoimmune disorders, and genetic immune deficiency syndromes.
- EBV+ in 60% of immunocompetent cases.
- Gain of **chr12** → ↑MDM2 → ↓p53.
- Most (>95%) have a negative systemic lymphoma workup. If lymphoma found outside CNS, it is NHL with CNS involvement.
- The majority of PCNLS are DLBCL.
- There are normally no B cells in the CNS.
- Clinical prognostic groups (Ferreri JCO 2003) based on age, PS, serum LDH, CSF protein concentration, and deep brain involvement: **a**ge >60, **E**COG >1, **e**levated LDH, elevated **C**SF protein, deep **b**rain involvement.
- "ABCDE"
- Abrey/MSKCC, 2006 nomogram:
  - RPA1: Age <50. MST 8.5 y
  - RPA2: Age >50, KPS >70: MST 3.2 y
  - RPA3: Age >50, KPS <70: MST 1.1 y

Imaging

- T1p homogenously enhancing mass, pre-con T1 hypointense, T2 iso to hyperintense.
- Majority (60–70%) are solitary lesions in immunocompetent pts, with higher rates of multifocality in the immunocompromised.
- Lesions tend to be nonhemorrhagic, periventricular masses, in deep white matter.
- Thalamus, basal ganglia, and corpus callosum are common areas, followed by frontal, parietal, temporal, and occipital lobes.
- Borders tend to be sharply circumscribed in most cases but can be ill-defined (~15%).
- Differential may include lymphoma, brain metastases, glioma, infection, demyelination, and neurosarcoid. Considerations specific to HIV may include toxoplasmosis and progressive multifocal leukoencephalopathy (PML).

Workup

- H&P, CBC, CMP, LDH, HIV
- Stereotactic brain biopsy; hold steroids until path bc of 40% response rate
- CSF cytology if safe
- Slit lamp exam to rule out ocular involvement
- MRI +/−spine if spinal canal involvement suspected. MRI has classic "cotton" wool appearance with fuzzy borders
- CT CAP or PET-CT to rule out systemic NHL
- Testicular ultrasound for men >60 years
- Consider BM biopsy
- SPECT if immunocompromised
- Vitrectomy for diagnosis if ocular lymphoma suspected

Chemo +/– RT

- **G-PCNSL-SG-1** (Thiel 2010): Phase 3 noninferiority trial. 551 enrolled (318 treated per protocol), immunocompetent patients randomized to high-dose MTX (with or without ifosfamide) +/− WBRT (45 Gy/1.5 Gy Fx daily). No diff in OS (but failed to reach noninferiority margin). WBRT assoc with improved PFS and more neurotox.
- **RTOG 1114** (ongoing): R-MVP and consolidative Ara-C +/− low-dose WBRT (23.4 Gy)

Chemo + Low-Dose WBRT

- **Morris 2013.** Multicenter phase II, 52 patients. R-MVP (MTX, procarbazine, VCR, ritux) + reduced dose RT to 23.4 Gy in the case of CR or 45 Gy for PR, then consolidation cytarabine. 2-year PFS 77%, median PFS 7.7 years. 3-year OS 87%. Median OS not reached.

– **Shah 2007**: methotrexate, vincrist, procarb + rituximab (R-MVP) + RT 23.4 Gy in the case of CR or 45 Gy for PR, then consolidation cytarabine. 2 year OS 67%. 2/3 had CR. With CR to chemo, 2-year OS 89%, PFS 79%. Note reduced dose used bc earlier trials showed v high rates of neurotoxicity if >60 yo and 45 Gy.

Chemo + Hyper-fractionated RT

– **RTOG 93–10** (Fisher 2005): All receive induction chemo 5 cycles MVP (MTX 2.5 m/m^2, vincrist, procarb) and then WBRT. Initially RT to 45 Gy (1.8 Gy Fx), until awareness of delayed neurotoxicity: 80% of patients >60y had neurocognitive defects vs 6% in patients <60y. RT dose was decreased to 36 Gy (1.2 Gy Fx BID).
– **RTOG 0227** (Glass 2016): Phase I/II, 65 patients. MTX + TMZ + rituximab. Hyper-fractionated WBRT 1.2 Gy BID to 36 Gy. 2-year OS and PFS were 81% and 64%, respectively.

Chemotherapy Alone (Without RT)

– **NABTT 9607** (Batchelor 2003): Phase 2, HD MTX, no RT. MS 22.8 mo. No reported neurotox
– **MSKCC** (Gavrilovic 2006): Series of 57 patients treated with high-dose MTX with or without WBRT. Median OS 51 mo. Median OS for pts >60y was 29 mo irrespective of WBRT
– **EORTC 26952** (Hoang-Xuan 2003). Phase 2 in patients over 60y, MTX, no WBRT. 55 patients. 42% CR, 6% PR. Median OS 14.3 mo. 1-yr PFS 40%
– **Illerhaus 2009**: Phase 2, 30 elderly pts (57–79 y, median 70 y). MTX + CCNU + procarbazine, no WBRT. CR 44%, PR 25%. 5-year OS 33%.
– **Juergens 2010**: Phase I/II, 65 patients, treated with systemic and intraventricular chemo, no WBRT. Concluded that half of patients could achieve long-term DFS without WBRT.

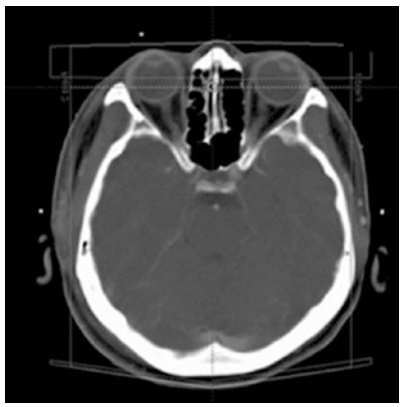
Salvage WBRT

– **Nguyen 2005**. Series of 27 pts treated with salvage WBRT (median 36 Gy). 74% had a response (37% CR, 37% PR). Medians OS 11 mo after WBRT. Neurotox higher if >60 yo and if >36 Gy.

Treatment Paradigms in 2018

– High-dose IV methotrexate induction therapy is the backbone of contemporary management.
– Historically, PCNLS was managed WBRT alone, but responses were not durable, and median OS was only 10–18 months (e.g., RTOG 8315). With MTX-based therapy (with or without WBRT), median OS may range from 3 to 5 years.
– Therapy is divided into induction (with high-dose MTX-based regimens) and consolidation.
– **Induction:**
  – MTX may be monotherapy or delivered with other chemotherapy agents and/or rituximab.
  – Goal a complete response (CR).
– **Consolidation after CR:**
  – NCCN recognizes options include high-dose chemotherapy + autologous stem cell rescue, non-myeloablative chemotherapy, consolidative MTX, and low-dose WBRT (23.4 Gy).
  – Role of WBRT after CR is controversial. The one RCT of WBRT after CR (Thiel 2010) found improved response rates but no difference in OS. Several trials involving WBRT randomizations are ongoing (RTOG 1114, IELSG 32, PRECIS).
  – When WBRT offered after a CR, low-dose WBRT **23.4 Gy/1.8 Gy** is preferred.
  – If <CR: **30–36 Gy,** WBRT **+ involved field boost to 45 Gy** is reasonable (NCCN 2017).
  – If unable to tolerate high-dose MTX, consider alternate chemo or WBRT to 24–36 Gy + involved field boost to 45 Gy (NCCN 2017).

  - If ocular involvement alone (primary ocular lymphoma), options include intraocular chemotherapy and/or systemic therapy and/or RT to eyes (~36 Gy, Yahalom 2014).
  - Due to concerns over neurotox, many centers defer WBRT up-front and reserve WBRT for salvage. There is particular concern for neurotox in patients >60 yrs.
- **Relapse:**
  - Options may include chemotherapy, high-dose chemo + stem cell rescue, WBRT if not previously given, and palliative/best supportive care.
  - The NCCN 2017 stratifies relapse paradigms by duration of initial response to up-front therapy >12 months.
- **Patients unable to tolerate high-dose MTX:**
  - May be offered and alternate chemotherapy regimen or WBRT (per NCCN 2017, 24–36 Gy followed by focal boost to 45 Gy)
- **Patients with HIV:**
  - Treated with MTX-based therapy in conjunction with anti-retrovirals, with or without WBRT



Simulation/Planning

- Place BBs at the lateral canthi to approximate posterior third of orbit
- Helmet field, treat down to C2/3
- If no ocular involvement, treat posterior 1/3 of the globe. If ocular involvement, include entire orbits (Yahalom 2014).

Primary Ocular DLBCL

- RT is primary tx
- Orbits only 36 Gy in 1.8/fx w/ half beam block posteriorly at posterior optic canal (treat optic nerves up to chiasm)
- If only one eye involved, treat ipsilateral globe + optic nerve up to the chiasm

Meningioma [11–15, 96, 104–127]

Simpson resection grade (1957)	5-y LRR	G1, surg + RT5-y LRR	G3, surg+RT 5-y LRR	10-y LRR	15-y LRR
0: GTR + dural attachment + bone + 2cm dural strip	5				
1: GTR + dural attachment + bone	10	N/A	33	20	24
2: GTR + ***coagulation*** of dural attachment	20			25	32
3: GTR tumor only, extradural extension	30				
4: STR	40	90	55	60	80
5: Decompression +/– biopsy	100		55		

General

- 34% of all primary tumors.
- From arachnoid cap cells in arachnoid villi.
- Approximately 2–3% of the population may have meningiomas.
- Second most common primary brain tumor (at 15–30%), and the incidence increases with age.
- Two percent of the population may have meningiomas (based on autopsy series), though 90% are benign.
- Median age 65, rare in children (increased in NF2 or after early RT exposure).
- Female:male ratio 2–3:1 for grade I s but less pronounced in grades II–III s.
- Risk factors: RT, hormone therapy, NF2, schwannomatosis, and MEN1 syndrome.
- Somatic NF2 mutations may be present in up to 1/2 of sporadic meningiomas.
- Psammoma bodies and calcifications and keratin whorls (Starry Night by Van Gogh sign).
- Factors predicting slow progression: calcifications, hypointense on T1 MRI, old age, and no growth on serial scans.

WHO grade	Rate	Name	Mitosis	Cellularity
I	>80%	**Benign**, Angioblastic, All others	<4 /10 HPF	
II	7–15%	**Atypical** Clear cell Chordoid OR benign w/ *brain invasion*	≥4 /10 HPF Brain invasion *or* ≥3 of the following:	Increased cellularity Small cells, high N:C Prominent nucleoli Patternless or sheetlike growth Foci necrosis
III	4%	**Anaplastic** Rhabdoid Papillary	≥20 /10 HPF *And/or*:	Resemble carcinoma, sarcoma, melanoma Loss of usual patterns Infiltration of brain Mitoses + atypical forms Multifocal foci necrosis

History

- Many are asymptomatic: HA, personality changes, CN deficits, paresis, paresthesias, and seizures.
- If suspecting NF-2, check for café au lait spots.

Workup

- Make the diagnosis radiographically. If not possible, then consider biopsy or octreotide scan.
- CT head thin cuts w/ and w/o contrast.
- MRI brain w/ and w/o contrast.

MRI

- Extra-axial, dural-based mass.
- Classically pre-contrast T1 isointense or hypointense, T2 isointense or hyperintense.
- Strong, homogenous T1 post-contrast enhancing.
- Frequently have adjacent dural thickening that tapers peripherally ("dural tail").
- Features which may suggest a grade II–III meningioma: brain invasion, brain edema, intratumoral cystic change, extension through bone, hyperostosis or adjacent bone destruction, and elevated blood volume.
- No imaging feature is pathognomonic for high-grade meningiomas in the absence of pathology.

CT Head Thin Cuts w/ and w/o Contrast

- Majority contrast enhancing, peritumoral edema in 60%, bony changes (hyperostosis) in 15–20%; 15% have calcification.

Extent of Resection

- GTR often attempted for tumors located along convexities, anterior parasagittal/sagittal sinus area, olfactory groove, and some tentorial and posterior fossa lesions.
- STR may be attempted for less accessible tumors including the skull base, clivus, and posterior parasagittal/sagittal sinus area. The risks and benefits of partial resection need to be weighed on an individual basis. For example, an attempt to relieve mass effect or debulking of large tumors may warrant planned STR when GTR is unfeasible.
- Biopsy alone or empiric radiation therapy without biopsy may be appropriate for high-risk areas, such as the cavernous sinus, skull base, and optic nerve sheath.

General Outcomes with/Without RT (RANO Review, Rogers 2015; Gr2/3 Review, Sun 2015)

- Grade I s, reported tumor control rates
  (a) GTR without RT: approx. 80–90% control at 5 yrs, 60–80% at 10 yrs, and 40–75% at 15 yrs
  (b) STR without RT: approx. 40–60% control at 5 yrs, 0–50% at 10 yrs, and 0–30% at 15 yrs
  (c) After RT (EBRT or SRS) as primary or post-op treatment: approx. 70–95% control at 10 yrs.
- Grade II s, reported tumor control rates
  (a) GTR, approx 60–90% control at 5 yrs without RT and 70–100% control with EBRT
  (b) STR, approx 0–60% control at 5 years without RT and 45–90% control with EBRT
  (c) SRS for recurrent or residual grade II s, reports are heterogeneous with widely ranging control from 0% to 90%, with most reports ranging from 50% to 80% at 2 yrs (Rogers 2015)
- Grade III s
  (a) GTR/STR + RT: 5-year PFS 0–60%, OS 30–60%

Observation

- **Observation alone, Yano 2006**: 351 patients with asymptomatic meningiomas were observed without surgery. Among patients with 5-yr follow-up, 37% progressed; only 6% of those observed had symptomatic progression.
- **Observation after surgery (grade I): RTOG 0539 low-risk cohort.** Rogers 2016 (ASTRO abstract 2016). Prospective phase II study. Sixty-five patients with grade I meningioma s/p GTR or STR (only 5 had STR) prospectively observed without RT. 3/5 year: LC 93/87%, PFS 92/86%, and OS 98/98%.

Conventionally Fractionated RT

- **RTOG 0539: Intermediate-risk cohort:** Rogers 2017. Recurrent grade I or grade II after GTR. Treated to 54 Gy/30 Fx. 3/5 year: LC 96/86%, PFS 94%/84%, and OS 96/96%
- **Tanlzer 2011:** 88 patients treated to mean 52.5 Gy. Median follow-up 8 years. 10-year LC 99%
- **Solda 2013**: 222 patients treated with 50–55 Gy. Five- or 10-year LC were 93%/86% and OS 93%/84%
- **Fokas 2014**: 318 patients treated with RT (80%), hypofractionated SRS (15%), SRS 5%. 5/10-year LC 93%/88%, OS 89%/74%, and CSS 97%/97%

Stereotactic Radiosurgery (SRS)

- Considered most appropriate for smaller lesions (often <3 cm or <10 cc), tumors with distinct margins, and those at sufficient distance from functionally important areas (e.g., optic nerves, chiasm)
- Excellent local control rates (80–95% at 10 yrs) have been reported with single-fraction doses from 12 to 16 Gy for grade I meningiomas (Rogers 2015), with no clear dose response with higher doses (Stafford 2001, Kondziolka 1998)
- **Kondziolka (2008).** Series of 972 patients treated with GK-SRS, mean marginal dose of 14 Gy. Median follow-up 4 yrs. Ten-year control in grade I s was 91%. Overall morbidity 7.7%.
- **Santacroce (2012).** Multicenter retrospective of 15 centers, 4565 patients treated with GK SRS (median marginal dose of 14 Gy) for grade I s. Median imaging follow-up 63 months. PFS at 5/10 yrs was 95%/87%. Permanent morbidity in 6.6%.

- Reports of SRS for grade II s are primarily in the setting of STR or recurrence, with widely ranging control rates from 0 to 90% at 2 yrs, with most between 50 and 80% (Rogers 2015).
- Symptomatic edema is reported more commonly after single-fraction SRS for larger meningiomas and those in parasagittal/parafalcine or convexity locations (Sheehan 2015; Patil 2008; Girvigian 2008). Some authors have advocated fractionated SRS or conventional RT for such cases.
- Multi-fraction SRS (frequently in the range 20–25 Gy delivered in 3–5 fx) has been associated with encouraging LC and may represent an attractive option for tumors located near critical structures such the optic nerves/chiasm or brainstem (Marchetti 2016; Navarria 2015). Overall, the available follow-up durations in series of multi-fraction SRS are shorter than the single-fraction SRS literature.

Treatment Paradigm

Grade I

- Small (typically <2–3 cm but no strict size criteria), asymptomatic:
  (a) Up-front observation preferred. Growth rate = 4 mm/y
- Symptomatic, large (>~3 cm), or growing:
  (a) Max safe resection preferred:
    (i) GTR: Observation preferred
    (ii) STR: Observation generally preferred for grade I. If close to critical structures, consider RT
  (b) Unresectable: Radiation alone. FSRT preferred. SRS cat 2b
- Growth after surgery:
  (a) RT and/or re-resection depending on scenario
- RT technique:
  (a) SRS generally preferred for suitable lesions due to similar efficacy to conventional RT, favorable toxicity, and convenience.
  (b) SRS dose is typically 12–16 Gy for grade I.
  (c) Conventionally RT is typically 45–55 Gy for grade I.

Grade II

- Max safe resection:
  (a) GTR: Role of adj RT is controversial. Either RT or close observation may be acceptable:
    (i) Ongoing NRG BN003 and ROAM/EORTC 1308: Grade II s post-GTR randomized to RT (59.4 or 60 Gy) vs close observation
  (b) STR: Post-op RT is standard.
- RT technique:
  (a) Conventionally fractionated RT is typically standard, 54–60 Gy.
  (b) SRS can be considered in select cases.

Grade III

- Max safe resection - >adj RT (59.4–60 Gy) is standard.

Pediatric Meningioma

- Very rare.
- Manage primarily w/ surgery.
- Consider adjuvant RT if anaplastic, R+, brain invasion, and benign meningioma at a site where risks of recurrence outweigh risks of RT, progressive, or unresectable.

Conventional fractionation planning: RTOG 0539					
Risk group	**Definition**	**Treatment**	**3y PFS /LC/OS**	**5y PFS/LC/OS**	**Follow-up:** MRI at 3 m, then every q6m for 3y, and then q12m for 10 y.
Low	GTR G1 (Simpson I–III) STR G1(Simpson IV–V)	**observe**	92/93/98	86/87/98	RTOG 05-39: MRI q6m for 3y, then q12m for 10y
Intermed	GTR G2 Recurrent G1	GTV=tumor bed and enhancement **CTV54**=GTV + ***1cm*** **PTV54**=CTV54 + 3-5mm	94/96/96	84/86/96	RTOG 05-39: MRI at 3, 6, 12 months, then every 6-12m for 5y, then MRI q1-3y.
High	GTR G3 Recurrent G2 STR G2	**CTV54**=GTV + ***2cm*** **PTV54**=CTV54+ 3–5mm Then followed by 6 Gy boost CTV60 = GTV + ***1cm*** **PTV60** = CTV54 + 3–5mm	59/69/79	–	RTOG 05-39: MRI at 3 m, then every q6m for 3y,then q12m for 10 y.

Optic Nerve Sheath Meningioma

Literature

- **Paulsen 2012**: 109 patients treated with 54 Gy. Radiographic tumor control 98% at 5 yrs. Visual acuity preserved in 91% at 5 yrs.
- **Milker-Zabel 2009**: 32 patients. Median RT dose 54.9 Gy. Median follow-up was 4.5 yrs. LC 100%.
- **Saeed 2010:** Br J Opthalmol, 2010. 34 patients treated with fractionated RT. At median of 58 months, 41% showed improved visual acuity, vision stabilized in 50%, deteriorated in 9%.

RT Technique

- Simulate supine, aquaplast mask.
- At minimum, fuse with T1 post-contrast MRIs. T2 series are frequently helpful in distinguishing tumor from normal tissues. Neuroradiology review recommended for complex cases.
- Conventionally fractionated RT:
  (a) GTV = gross tumor, typically defined on T1 post-contrast MRI:
    (i) Surgical cavity typically included in adjuvant RT cases.
    (ii) The dural tail is generally not included in protocols.
  (b) CTV = 3–5 mm expansion on GTV for grade I–II meningiomas:
    (i) CTVs can be shaved off anatomic barriers of spread and can be minimized at brain parenchymal interface in the absence of pathologic brain invasion. Brain parenchyma should be included in the setting of brain invasion.
    (ii) In the setting of suspected or confirmed bone involvement, CTVs should not be shaved off bone.
    (iii) The RTOG 0539 used larger expansions (1 cm for int risk and 1–2 cm for high risk); however, due to the predominately infield pattern of failure and low rates of marginal failures, the follow-up NRG BN003 (grade II meningiomas s/p GTR) uses smaller margins with 5 mm CTV expansions which can be shaved down to 3 mm around critical structures.
  (c) CTVs for grade III s may be 0.5–2 cm depending on institutional practice and generally include brain parenchyma
  (d) PTV: Typically 2–5 mm based on institution-specific technical and IGRT standards
- Stereotactic radiosurgery
  (a) GTV = gross tumor, typically defined on T1 post-contrast MRI
  (b) CTV/PTV expansions: dependent of institutional practice: often no expansion or 1–2 mm.

Brain Metastases [11–15, 128–161]

General

- Brain metastases are the most common adult brain tumor.
- Occur in approximately 20–40% of patients with advanced cancers.
- Lung, breast, melanoma, and renal cell carcinomas are the most common.
- Hemorrhagic metastases are more common in melanoma and renal cell.
- The blood-brain barrier (BBB) can significantly reduce the concentrations of many systemic agents, which can make the CNS a pharmacologic sanctuary for metastatic progression.
- Approximately 80% occur in cerebral hemispheres, 15% in the cerebellum, 5% in the brainstem.
- Nomenclature: "solitary" brain metastasis = only metastatic lesion in the entire body; "single" brain metastasis = only metastatic lesion in the brain.

Workup

- MRI brain with and without gadolinium.
- Brain metastases are typically T1 post-contrast enhancing.
- Hemorrhage is intrinsically T1 hyperintense on non-contrast images.
- Brain metastases may be single or multiple, typically have circumscribed margins, often occur preferentially at the gray-white matter interface, may have areas of central necrosis/hemorrhage/or cyst, and may be associated with large amounts of vasogenic edema or mass effect in relation to the lesion size.
- Differential may include metastases, primary brain tumors (e.g., GBM, high-grade gliomas), primary CNS lymphoma, and infection. Multiple lesions raise suspicion for metastases, though not pathognomonic.
- Brain biopsy is often not necessary when the probability of metastases is considered high based on the overall clinical picture (e.g., cancer history, prior brain metastases, multiple brain lesions, metastases to other organs, rising tumor markers, etc.).
- Spinal axis MRI and CSF analysis may be appropriate when concerned for spinal metastases and/or leptomeningeal spread.

Symptomatic Brain Metastases

- For patients with symptomatic brain metastases, corticosteroids are usually appropriate.
- Corticosteroids are generally not indicated in the absence of symptoms; anticonvulsants are generally not indicated in the absence of seizures.
- For patients with large and/or symptomatic brain metastases associated with significant vasogenic edema, midline shift, or risk of herniation, urgent neurosurgical consult is indicated.
- Neurosurgical resection for large and/or symptomatic lesions is often preferred for single brain lesions.
- Resection may also be appropriate in select cases of multiple metastases when surgery is considered the best approach to relieve mass effect or prevent herniation from a larger lesion.
- If resection is not appropriate or not offered, corticosteroids and evaluation for potential radiation therapy should be pursued.

General Management Paradigms for Asymptomatic Brain Metastases in 2018

- Single brain lesions:
  - SRS alone
  - Neurosurgical resection +/− postoperative SRS to the resection cavity:
    - Resection often preferred for large, symptomatic, or threatening lesions.
- Limited brain metastases:
  - SRS alone preferred
- More extensive brain metastases:
  - WBRT
  - SRS to multiple lesions with close MRI surveillance:
    - SRS candidacy is evolving. Historically, SRS was offered for 1–3 or 4 lesions based on the inclusion criteria of the randomized SRS +/− WBRT trials (Aoyama 2006; Chang 2009; Kocher

2011; Brown 2016); however, there is a growing literature supporting SRS for 4–10+ lesions (Yamamoto 2014), suggesting that SRS candidacy should be increasingly individualized.

Evolution of Prognostic Models

- Older trials incorporated the RTOG **recursive partitioning analysis (RPA)** (Gaspar 1997), stratifying Class 1 (KPS ≥70, age <65, controlled primary, and no extracranial metastases: median OS 7.1 months), Class 3 (KPS <70; median OS 2.3 months), and Class 2 (not Class 1 or 3: median OS 4.2 months). Original RPA underestimates OS in the modern era, but familiarity remains useful for historical purposes and interpreting the literature.
- **Graded prognostic assessment (GPA)** (Sperduto 2008) adds # of mets.
- **Diagnosis-specific GPA (DS-GPA)** (Sperduto 2012) modified GPA by histo.
- **Lung molecular GPA (lung-molGPA)** (Sperduto 2017) adds EGFR and ALK to GPA. Includes 2186 patients, 2006–2014 with NSCLC (1521 adenocarcinoma and 665 non-adenocarcinoma). Median OS 12 months in the entire cohort (better than any group in the original 1997 RPA). Patients with high lung-molGPA scores had prolonged median OS of nearly 4 yrs after brain mets.

Clinical Data

Whole-Brain Radiation (WBRT)

WBRT vs Supportive Care

- **MRC "QUARTZ" trial** (Mulvenna 2016). 538 patients with NSCLC, randomized to supportive care +/− WBRT 20 Gy/5 Fx. No significant difference in OS or quality of life.

WBRT +/− Up-Front Surgery (Sx) for Single Met

- **Patchell 1990**. 48 patients with single met, received WBRT 36 Gy/12 Fx randomized to +/− up-front Sx. Median OS improved with Sx (40 vs 15 weeks). Sx reduced rates of neurologic death (20% vs 52%).
- **Vecht 1993.** 63 Patients with single met, received WBRT 40 Gy/20 Fx BID randomized to +/− up-front Sx. Sx improved median OS (10 vs 6 mo).
- **Mintz 1996**. 84 patients with single met, received WBRT 30 Gy/10 Fx randomized to +/− up-front Sx. No difference in OS.

Stereotactic Radiosurgery (SRS)

WBRT +/− SRS

- **RTOG 9508** (Andrews 2004): 331 patients with 1–3 mets, received WBRT 37.5 Gy/15 Fx randomized to +/− SRS. SRS assoc with improved OS for single met (6.5 vs 4.9 mo), LC, KPS, and steroid independence at 6 mo. No diff in OS for all patients with 1–3 mets, neurologic death, or time to any intracranial failure.
- **Kondziolka 1999**. 27 patients with 2–4 mets randomized to WBRT +/− SRS. Stopped early due to LC benefit with SRS on interim analysis. 1-yr LC 100% vs 8%. Time to local failure 36 vs 6 months.

SRS +/− WBRT

- **JROSG 99-1** (Aoyama 2006): 132 patients with 1–4 mets, randomized to SRS +/− WBRT 30 Gy/10 Fx. No difference in OS or neurologic death. WBRT assoc with improved LC, distant brain control.
- **MDACC** (Chang 2009): 58 patients with 1–3 mets randomized to SRS +/− WBRT 30 Gy/12 Fx. Stopped early due to worse cognitive outcomes in WBRT arm. SRS alone assoc with improved 4-month Hopkins verbal learning test and improved median OS (15 vs 6 mo). WBRT assoc with improved LC and CNS DFS.
- **EORTC 22952** (Kocher 2011): Local therapy (surgery or SRS) randomized to +/− WBRT. No difference in OS or time to KPS deterioration with WBRT. WBRT reduced LR, distant recurrence, and decreased neurologic deaths. **Soffietti 2013** Patient-reported QOL analysis of the EORTC 22952. WBRT assoc with decline in global health at 9 mo, cognitive function at 12 mo, physical function and fatigue at 2 mo.

– **Brown 2016.** 213 patients with 1–3 mets, randomized to SRS +/− WBRT 30 Gy/12 Fx. SRS alone assoc with less cognitive decline at 3 mo (and 12 mo in longer-term survivors). QOL improved with SRS alone. WBRT assoc with better CNS control. No diff in OS or functional independence.

SRS Alone for Multiple Metastases

– **LGK0901** (Yamamoto 2014): Prospective observational study. 1194 patients with 1–10 brain metastases treated with single-fraction SRS alone. Median OS: best for single lesion (13.9 mo) but no diff in OS between 2–4 lesions (10.8 mo) vs 5–10 lesions (10.8 mo). No diff in toxicity. Neurologic mortality rates were low overall with SRS alone (8%), with no diff between groups.

SRS Alone for Multiple Metastases and Targetable Mutations

– **Colorado** (Robin 2017): Cohort of ALK and EGFR NSCLC, SRS alone to ≥4 mets in a single session (range 4–26). Median OS in yrs from brain mets was 4.2 (ALK) and 2.4 (EGFR). Five-year freedom from WBRT was 97% and from neurologic death was 84%. For patients treated to >10 mets in single SRS session, mean whole-brain and hippocampal doses were only 1.2 Gy and 0.8 Gy, respectively.

SRS Dose

– **RTOG 90-05** (Shaw 1996, 2000): Prospective SRS dose-escalation study. 156 patients who received prior conventionally fractionated radiation. One-third had recurrent brain tumors and two-thirds had recurrent brain mets. Trial established safe single-fraction SRS doses of 24 Gy for ≤2 cm, 18 Gy for 2–3 cm, and 15 Gy for 3–4 cm. Neurotoxicity associated with tumor size, SRS dose, and KPS.

Multi-fraction SRS for Larger Targets

– **Minniti 2016.** Cohort of 289 patients treated with single-fraction vs multi-fraction (27 Gy/3 Fx) SRS for unresected lesions >2 cm. Multi-fraction assoc with better 1-yr LC (91% vs 77%) and lower rates radionecrosis (11% vs 20%).
– **Eaton 2015**. Cohort of 76 resected brain metastases cavities ≥3 cm treated with single-fraction SRS ($N = 40$) or three-to-five fraction SRS ($N = 36$). LF was equivalent at 1-yr (27 vs 25%). Radionecrosis was lower with multi-fraction at 1-yr (10 vs 19%).

Postoperative Radiation

Surgery +/− Postoperative WBRT

– **Patchell 1998**. 95 Patients, status post complete resection of single met randomized to +/− WBRT 50.4 Gy/28 Fx. No diff in OS or length of functional independence. WBRT reduced local and distant brain recurrence, decreased neurologic deaths.
– **EORTC 22952** (Kocher 2011). Local therapy (surgery or SRS) randomized to +/− WBRT. No diff in OS or time to KPS deterioration with WBRT. WBRT reduced LR, distant recurrence, and decreased neurologic deaths.

Surgery +/− Postoperative SRS to the Cavity

– **MDACC** (Mahajan 2017): RCT of 132 patients status post complete resection of 1–3 mets <4 cm randomized to +/− single-fraction SRS to the cavity (volume-based dosing, 12–16 Gy). SRS assoc with improved LC at 1 year (72% vs 43%). No diff in OS.

Surgery + Post-op Fractionated SRS to the Cavity

– **Stanford** (Soltys ASTRO 2015). Single-arm phase I/II dose-escalation from 24 to 33 Gy in 3 Fx. 50 patients. At 12 mo: local failures 7%, distant 50%, leptomeningeal disease 15%. Authors recommend 27–30 Gy/3 Fx for cavities 2–4 cm.
– **MSKCC** (Brennan 2014). Single-arm phase II trial. Forty-nine patients treated with 15–22 Gy (median 18 Gy). At 12 mo, local failures 22%, distant 44%. Tumors ≥3 cm with superficial dural/pial involvement had the highest risk of local failure.

Surgery + Post-op SRS vs Post-op WBRT

- **NCCTG N107C** (Brown 2017). 194 patients status post resection of one brain metastasis randomized to WBRT or single-fraction SRS (volume-based dosing, 12–20 Gy). Improved cog deterioration-free survival with post-op SRS over WBRT. SRS assoc with shorter time to any intracranial tumor progression. No diff in OS.

Clinical Data Summary Notes

- For single brain metastases, tumor ablation (surgery or SRS) has been associated with improved OS in RCTs.
- Compared to supportive care, surgery alone, and SRS alone, the addition of WBRT improves CNS disease control, but does not improve OS.
- WBRT is associated with measurable declines in cognitive function and QOL.
- SRS alone was historically offered for one to three or four lesions based on the inclusion criteria of SRS +/− WBRT trials. Growing data suggests that SRS may be appropriate for patients with ≥4 lesions in the setting of close MRI surveillance.
- Postoperative SRS to the surgical cavity improves LC but not OS (Mahajan 2017).
- Multi-fraction SRS has been associated with encouraging LC and toxicity rates and may be particularly useful for larger intact or postoperative targets.
- As emerging systemic agents demonstrate improved CNS penetration and activity (Peters 2017; Mok, 2017; Davies 2017), brain metastases paradigms are likely to evolve to incorporate multidisciplinary approaches involving local and systemic therapy.

Planning

- Sim supine, head neutral, and aquaplast mask.
- For WBRT:
  - Opposed lateral beams, block orbits, cover below foramen magnum, and flash skin.
  - Confirm adequate coverage of intracranial contents including temporal fossa and cribriform plate on lateral fields and 3D dose eval.
  - Dose: commonly 30 Gy/10 Fx for better KPS, 20 Gy/5 Fx reasonable for poor KPS.
- For SRS, fuse with thin-slice T1 post-contrast MRI images.
- For post-op cases, fuse post-op T1 post images at a minimum. Preop MRIs may also be useful.
- Target definition:
  - For intact (unresected) targets = gross tumor.
  - For post-op cases: surgical cavity + any residual tumor at a minimum. In some case, more generous volumes at postoperative dural areas may be appropriate in an effort to lower risk of dural/leptomeningeal recurrence.
  - A postoperative SRS contouring consensus paper (Soliman 2018) recommends inclusion of the surgical tract, a CTV expansion of 5 to 10 mm along the dura in cases of preoperative dural contact, and a margin of ≤5 mm into the adjacent venous sinus when preoperative venous sinus contact was present. The recommended inclusion of the entire surgical tract and relatively large expansions remain controversial.
- Expansions:
  - For intact cases, typically 0–1 mm.
  - For postoperative cases, typically at least 1–2 mm around the resection cavity and possibly larger expansions in the case of preoperative dural or venous sinus contact (Soliman 2018).
  - In general, expansions for SRS are individualized based on institutional practices, physician comfort level, and IGRT/immobilization standards.
- Typical SRS dose fractionation
  - Single fraction:
    - 20–24 Gy for <2 cm,
    - 18 Gy 2–3 cm,
    - and 15 Gy for 3–4 cm are common.
  - Multi-fraction, 24–30 Gy/3 fraction, and 25–30 Gy/5 fractions are common.
- SRS often prescribed to the 50–80% isodose lines (corresponding to central hot spots of 125–200% of the prescription dose).

Ependymoma

Background
- Most common intramedullary tumor in adults
- Peak 30–40yo
- Arises from filum terminale, a filamentous process that anchors the dural sac inferiorly to coccyx
- Follow for >10y because late recurrences occur in 10% of pts
- Grade I = subependymomas and myxopapillary
- Grade II (classic ependymomas)
- Grade III (anaplastic ependymomas)

Brain Ependymoma Management

- Maximum safe resection (reresect if STR; try to get GTR). EFS5 if GTR = 80%. EFS5 if STR = 40%.
- Consider induction chemo → 2nd look surgery for GTR.
- MRI post-op (w/ in 48 hr).
- Chemo has no proven benefit.

Simulation
- Supine in 3 point face mask.
- CT sim w/o contrast and MRI sim w/ contrast.
- Fuse preop MRI.
- Use IMRT.

Contours
- CTV: drawn out initial tumor volume; tumor bed +1 cm.
- PTV: CTV + 3 mm (with daily CBCT).
- RT to involved fields to 54 Gy (grade II) or 59.4 Gy (grade III) (start within 56 days).
- If MRI spine/LP+ = CSI to 36 Gy.
- Boost gross spinal dz to 45 Gy.

Spinal Cord Ependymoma Management

Grade I/II
- If GTR = observe
- If STR = limited field RT to 50.4 Gy
- Spine mets present = CSI to 36 Gy and boost to 54 Gy tumors

Grade III
- If GTR/STR = limited field RT to 50.4 Gy
- Spine mets present = CSI to 36 Gy and boost to 54 Gy tumors

Contours
- For caudal ependymomas, should cover thecal sac down to S2–3.
- The typical sup-inf margin is 3–5 cm.

Ependymoblastoma (Actually Medullo)
- Treat like STPNET/high-risk medullo with CSI to 36 Gy + boost to 55.8 Gy

Intradural Spinal Cord Astrocytoma

- Rare, aggressive
- Usually in C/T spine
- Associated w/ cysts
- MST 6 months
- 2/3 of patients die of local and disseminated disease
- Typically occurs in 2 yrs, infield
- **Treatment**: 50.4 Gy–54 Gy

Pituitary Tumors [11–15, 162–173]

Type and notes	% incidence	Sx	Normal range	Surgical, medical tx (rec if secretory)	Stop drugs prior to RT?	RT		Response to RT (%)
Non-secretory *Chromophobic Males, elderly*	25			Surgery first line. 95% LC after transsphenoidal resection overall. Risk for ↓ LC: ↑age, >2cm,		45–50.4 Gy for no GTV or non-functioning	14–18 Gy/1 fx	5 y LC 94%, 10 y LC 76%
Prolactinoma DA secreted by hypothalamus, suppressing PL production in pituitary. Compression of pituitary stalk inhibits DA suppression,leading to overproduction of PL. Common to have *calcifications, amyloid*	30	Galactorrhea, amenorrhea, infertility, vaginal dryness, alibido, ED	**2–25**	DA agonists e.g. **bromocriptine** are first line and work in 85% of pts. 30% cannot tolerate bromo bc of N/V, HA, fatigue. Surgery if medical failure fails or visual sx.	Stop bromocriptine 2-4 mos prior to RT	50-54 Gy if GTV	20 Gy/1 fx Optic nerve max 8 Gy, need 3–4 mm distance from tumor to chiasm	25–50
GH	25	Acromegaly, HA, cardiac dz, bone changes	**<10**	**Somatostatin (octreotide),** lancreotide. DA agonists are ineffective in acromegaly, but can be used in 2nd line.	Hold for 2–4 months. Patients on octreotide reach normal GH and IGF-1 level after significant longer interval (radioprotective?).			80–100
ACTH Nelson syndrome: ACTH adenoma develops after adrenalectomy *Males, elderly*	15	Cushings, HTN, DM, hirsutism, skin changes, osteoporosis	**15**	**Ketoconazole** (the best), cyproheptadine (inhibits ACTH), RU-486 Consider adrenalectomy	Pegvisomant and ketoconazole can be given during RT			50–80
TSH	<1%	Hyperthyroid	**<1**	**Somatostatin (octreotide)**	Hold for 2–4 months.			

General
- 75% functional, 25% nonfunctional.
- Associated with MEN-1.
- Macroadenoma (≥1 cm) (more common in nonsecretory).
- Microadenoma (<1 cm).
- Prolactinomas are most common (30%).

DDx Sellar Mass
- Craniopharyngioma
- Glioma
- Pituitary adenoma or carcinoma
- Germ cell tumors
- Ependymomas
- Meningioma
- Metastasis
- Benign: cyst, abscess, cavernous sinus AVM

Presentation
- Symptoms due to mass effect or ↑hormone secretion
- Bitemporal hemianopsia or other patterns of vision impairment
- Headache
- Pituitary apoplexy (sudden hemorrhage)
- Prolactinomas: galactorrhea, amenorrhea, infertility, or hypogonadism
- GH-secreting adenomas: acromegaly
- ACTH-secreting adenomas: Cushings

Differential Diagnosis
- Craniopharyngioma, meningioma, cyst, GCT, chordoma
- Metastases to the pituitary: most likely from breast and lung cancer
- Benign pituitary hyperplasia due to pregnancy, lactation, long-standing primary hypothyroidism or hypogonadism, cirrhosis

Workup
- H&P, labs: serum prolactin, IGF-1, 24-h urine-free cortisol, LH/FSH, and free/total T4/TSH.
- Thin-cut MRI is only imaging needed; normal pituitary and adenomas are isointense to slightly hyperintense on T1 and may have T2

signal intensity due to cystic changes. Normal pituitary tissue enhances with gadolinium; however, adenomas typically have lesser enhancement than normal pituitary tissue.
– Formal visual field testing as indicated.

Histology
– IHC stains for synaptophysin, chromogranin, hormone-specific stains.
– 2017 WHO classification includes increasing role of transcription factors, PIT-1 and SF-1, for characterization.
– Special variants of adenomas with aggressive behavior and higher recurrence rates include sparsely granulated somatotroph, plurihormonal PIT-1-positive, silent corticotroph, lactotroph in men, and crooke cell (Lopes 2017).

General Principles of Treatment
– Up-front surgery, usually by a transsphenoidal approach, is the mainstay of therapy for all except prolactinomas.
– For prolactinoma, DA agonist (bromocriptine) is first-line therapy and causes 90% PRL normalization.
– Radiation is reserved for patients who have exhausted surgical and medical options.
– Adjuvant RT can be considered for STR or if persistent function/growth after surgery.
– RT is very effective at stopping tumor growth but less effective at normalizing hormone levels; higher RT doses are required for hormone normalization (Sheehan 2011; McCollough 1991). RT has 90% PFS, 88% for all patients, 92% for non-functioning adenoma.
– Hormone normalization, when achieved, may take several years (median ~1–5 years in studies). While monitoring for hormone remission, continued medical therapy is often necessary.
– Asymptomatic adenomas can be observed up front or after STR.
– Prolactinomas are managed medically first.
– Literature suggests that it may be beneficial to hold antisecretory meds during RT (e.g., dopamine agonists, ketoconazole, or somatostatin analogs) and for several weeks before RT. However, the data is non-randomized, and the need for concurrent secretory medications may be a surrogate for worse tumors.

Nonsecretory Adenomas
– Treat like meningioma. Transsphenoidal surgery fist.
– If no residual disease seen on MRI (suggestive of GTR), then chance of regrowth is <5% at 5 years, and observation is recommended.
– If STR, then chance of regrowth is ~50%; adjuvant RT could be given or close follow-up with RT offered as an alternative to surgery at the time of regrowth.
– There is a higher risk of regrowth if there is residual disease outside of the sella.
– Local tumor control is >90% in most RT series.
– Key studies: Brochier 2010; Chang 2008, Sheehan 2013.

Lactotroph Adenomas (Prolactinoma)
– 90% respond to dopamine agonists and can then be treated with surgery as second-line
– RT is rarely used as the initial modality but is indicated in patients who have failed surgical or medical management. As such, patients undergoing RT typically have a more aggressive phenotype.
– Endocrine remission defined as normal serum prolactin level.
– Endocrine remission rates are more variably reported but average ~25% for medically refractory adenomas; higher marginal doses may be associated with better remission rate.
– Median time to hormone remission is ~24 months.
– Local control in RT series is ~90%.
– Key studies: Pouratian 2006; Liu 2013.

Corticotroph Adenomas (Cushings)
– Radiation is indicated for patients who fail to obtain endocrine remission or tumor control from surgical or medical management.
– Endocrine remission defined as normal 24-h urine-free cortisol and serum cortisol.
– Endocrine remission rate is ~50% in major series but increases with longer follow-up and higher marginal doses.
– Mean time to hormone remission in successful cases is ~12 months.

– Local tumor control in RT series is ~95%.
– Key series: Jagannathan 2007; Minniti 2007; Sheehan 2013.

Somatotroph Adenomas (Growth Hormone)
– Radiation is indicated for patients who fail to obtain endocrine remission or tumor control from surgical or medical management.
– Endocrine remission defined as normalization of serum GH and IGF-1 levels; some studies use oral glucose tolerance test results to define remission.
– Endocrine remission rates vary across series but average ~50%.
– Mean time to hormone remission is ~24 months but can take up to 15 years.
– Local tumor control in RT series is ~95%.
– Key studies: Losa 2008; Lee 2014.

RT indications
– Inoperable
– STR with persistent hypersecretion or residual near critical structures
– Recurrence/progression after surgery
– TSH secreting (always give post-op RT)

Radiation Technique
– SRS or fractionated RT can be considered. The literature suggests that both are equally effective in local control, although non-randomized comparisons suggest a shorter interval to hormone normalization with SRS. However, these are retrospective studies, and SRS may have been preferentially used on smaller tumors.
– SRS is appropriate for tumors <3 cm and at least 3–5 mm from the optic pathway.
– The majority of SRS series have used GK, but linac-based approaches are reasonable.
– Standard doses for **nonfunctional** adenomas are 14–16 Gy in 1 fraction or 45–50.4 Gy in 1.8 Gy fractions.
– Standard doses for **functional** adenomas are 16–25 Gy in 1 fraction or 50.4–54 Gy in 1.8 Gy fractions.
– Constraints:
  • Chiasm = 54 Gy
  • SRS = 8 Gy (need 3–4 mm distance from tumor to chiasm)

If no hormone normalization after full surgical + RT treatment and med management:

– Cushings → adrenalectomy
– TSH → thyroidectomy

Outcomes
– Non-functioning adenomas: LC is >90%.
– Functioning adenomas (rates of hormone normalization):
  • 50% with RT alone vs >80% with RT + medical therapy
  • >2 years to hormone normalization
  • PRL: 50% with RT alone vs >80% with RT + medical therapy.
    • Time to normalization is 2–8 years.
  • ACTH: 50% with RT alone vs >80% with RT + medical therapy:
    • Time to normalization is 1–4 years.
  • GH: 50% w/ RT alone at 10 years, with medical therapy is 70%:
    • Time to normalization is 3–10 years.

Toxicity/Follow-up
– 100% will get some deficiency.
– Panhypopituitarism is most common. Hypopituitarism occurs in about 20% at 5 years but may rise up to 80% at 10 years (Sheehan 2011; Minniti 2007):
  • GH deficiency, 100% at 5y
  • GnRH 60% at 10y
  • ACTH <60% at 10y
  • TSH <30% at 10y
  • HyperPRL 20–50%
– Sensitivity of hormones to RT (**"G FLAT"**): (1) GH, (2) FSH/LH, (3) TSH/ACTH. Because prolactin should not be elevated in a nonpregnant adult, it is not reported as suppressed after RT to the pituitary. Vasopressin and oxytocin are made in posterior pituitary and are resistant to RT. Thus, RT is not linked to DI.
– Low risk for optic pathway injury or second malignancy.
– MRI and labs q6–12 months.
– Endocrinology evaluation and follow-up recommended.

Vestibular Schwannoma (VS)/ Acoustic Neuroma (AN) [9, 174–207]

Koos Grade

I	Intracanalicular
II	<2 cm
III	Extracanillicular, <3 cm
IV	Displaces trunk or CNs, >3 cm

General

- Arise from Schwann cells of CN8.
- 5–10% of intracranial, 80% of CPA tumors.
- Mostly sporadic, minority related to NF2.
- Bilateral VS are associated NF2.
- Sporadic VS is usually unilateral, occurring in ages of 40s–60s.
- Typically slow growing, median <2 mm/yr.
- Intracanicular and small tumors associated with slower growth.
- Tinnitus associated with increased odd ratio of growth (Agrawal 2010).
- 10% show spontaneous shrinkage.
- Malignant transformation is extremely rare.

Risk Factors

- NF2
- Radiation exposure
- History of parathyroid adenoma
- Loud noise exposure, although recall bias may confound self-report series

Histopathology

- Most commonly arise from superior or inferior vestibular nerve, rarely cochlear branch
- Characterized by alternate dense (Antonin A) and sparse (Antonin B) cellularity
- S100+

Symptoms (Mathias 1997)

- Hearing loss in 95%
- Tinnitus 63% (may be associated with increased risk of growth)
- Vestibular symptoms 61%
- CN5 symptoms 17%
- CN7 symptoms 6%
- Compressive symptoms (ataxia, lower CN deficits, hydrocephalus)

Workup

- H&P
- MRI, with gadolinium, with thin (1–1.5 mm) slices. On T1 gad, VS will appear as a homogenously enhancing mass in the CPA
- Audiometry: asymmetric sensorineural loss, more prominent in higher frequencies
- Rene, Weber tests
- If NF, image neuroaxis
- Weber test – differentiates conductive vs sensorineural hearing loss
  - Conductive loss → sound toward bad ear
  - Sensorineural loss → sound toward good ear

Grading Systems

- **Koos**: Tumor extent
  - (1) IAC only, (2) CPA, (3) brainstem contact, and (4) 4th vent shift
- Hearing function:
  - **AAO-HNS**
    - Class A (good) to D
  - **Gardner-Robertson**
    - Grade I (good) to V (deaf)
  - AAO-HNS class A/B and GR I/II typically = preserved/serviceable hearing in studies
- **Audiogram**: Gardner-Robertson scale to assess serviceable hearing
  - Often have **high frequency sensorineural hearing loss.**
  - Serviceable hearing = >50% on speech discrimination and can hear at less than 50 dbs.
  - **Speech reception threshold (SRT)** is lowest intensity level (in db) at which the patient can correctly identify 50% of common two-syllable words (baseball).
  - **Pure-tone average (PTA)** is the average of hearing sensitivity at 500, 1000, and 2000. This average should approximate the speech reception threshold (SRT), within 5 dB.
    - If the SRT is significantly better than the PTA, the possibility of pseudohypoacusis should be considered.
    - If the PTA is significantly better than the SRT, the possibility of central involvement should be considered.

- **House-Brackman**: CN7 motor dysfunction
  - 1 = normal, 2 = slight, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = total paralysis

Treatment Paradigms in 2018

- Options include observation, RT (SRS or fractionated), and surgery.
- In the absence of randomized trials, optimal VS management is individualized based on factors including tumor size and extent, age, performance status, hearing, and other CN symptoms.
- Ideally, cases should be reviewed by both a radiation oncologist and surgeon.
- In a contemporary systematic review (Carlson 2018), all approaches (observation, radiation, surgery) are associated with poor serviceable hearing preservation in the range of 25–50% with long-term (>10-yr) follow-up. Thus, while RT and surgery improve LC over observation, long-term hearing preservation rates remain suboptimal.
- Comparisons of surgery and RT suggest comparable LC rates, with improved QOL, hearing, and CN preservation with RT (Pollock 2006, Myrseth 2009). However, the potential for selection bias (i.e., surgery for worse tumors) is acknowledged.

Observation

- May be preferred initial approach intracanicular or small (<2 cm) without tinnitus (Germano 2018) and attractive for some elderly pts with comorbidities (Tsao 2017).
- Hearing preservation rates: 75–100% at 2 yrs, 50–75% at 5 yrs, and 25–50% at 10 yrs (Carlson 2018).
- Factors associated with improved hearing preservation are good hearing at diagnosis and tumor non-growth (Sughrue 2010, 2011).
- **Stangerup 2010**. 1144 patients initially observed, 377 with ≥5 yr and 102 with ≥10 yr follow-up. 249 of 455 (55%) patients who presented with class A/B hearing maintained serviceable hearing at last follow-up.
- **Ferri 2008**. Prospective study of 123 patients initially observed. At a median of 4.8 yrs, of the 56 presenting with serviceable hearing, 41 (73%) maintained useful hearing at last follow-up.

Surgery

- Often preferred for large (>3 cm), symptomatic tumors, mass effect, and sometimes for younger patients.
- Three main approaches:
  - Middle cranial fossa: for small tumors in IAC with intact hearing
  - Retrosigmoid: can attempt GTR of larger tumors and can attempt hearing preservation
  - Translabrynthine: can attempt GTR of larger tumors, sacrifices hearing. Preferred in some cases where hearing is already lost
- Complications from surgery include mortality 0.2–1%, CN deficits 5–15%, and CSF leak 8–15%.
- Hearing preservation rates range from approximately 25–75% at 0–2 yrs, 25–75% at 5 yrs, and 25–50% at >10 yrs (Carlson 2018).
- Surgery is associated with an increased risk of immediate hearing loss compared to RT and observation. If hearing is maintained postoperatively, it can be durable in a subset of cases.
- Factors associated with better hearing preservation rates after surgery include good pretreatment hearing, small (<1 cm) tumors, and presence of a "fundal cap" of CSF distal to the tumor in the IAC.
- Outcomes appear best with high-volume surgeons and centers (Barker 2003).

Radiosurgery (SRS) and Fractionated RT

- LC excellent >80–90% with either approach (Tsao 2017).
- Larger tumors and NF2 have worse LC.
- Hearing preservation: 75–100% at 2 yrs, 50–75% at 5 yrs, 25–50% at 10 yrs (Carlson 2018).
- Hearing preservation, CN5, and CN7 function appear comparable with SRS and FSRT (Tsao 2017), although better hearing with FSRT has also been suggested (Andrews 2001).

- SRS usually preferred over FSRT in cases suitable for either intervention. Some use SRS if <3 cm, FSRT if >3 cm.
- Prospective observational studies have shown mixed results regarding the effect of SRS on hearing preservation compared to observation (Regis 2010, Breivik 2013).
- Some retrospective data suggests hearing preservation is better with SRS vs observation in patients with good baseline hearing (Apkinar 2016).
- SRS dose 12–13 Gy. Dose >13 Gy associated with more toxicity, without improved LC (Germano 2018, Lunsford 2005).
- Fractionated RT doses 45–57.6 Gy in 1.8–2 Gy fractions.
- Various multi-fraction SRS/hypofractionated RT doses: 6 Gy x 3 Fx, 5 Gy x 4–5 Fx, 3 Gy x 10 Fx (Meijer 2003, Hansasuta 2011, Puataweepong 2013)

Radiation Technique

- **SRS:**
  - GTV per post-contrast MRI +/− FIESTA sequence.
  - No CTV.
  - PTV 0–2 mm.
  - Perform CT when using GK due to artifacts from MRI at this level.
  - Most common dose selected is 12–13 Gy, to 50% IDL with GK or 80% IDL with a LINAC.
  - Cochlear dose <4 Gy with SRS has been associated with better hearing preservation (Kano 2009, Yomo 2012).
  - Repeat SRS for progression may be considered and appears to be associated with good LC but decreased hearing preservation and mildly increased cranial neuropathy rates based on small retrospective series (Germano 2018).
- **FSRT**:
  - GTV per post-contrast MRI +/− FIESTA sequence
  - No CTV expansion
  - PTV 1–3 mm
  - Cochlear mean dose <35 (Quantec 2010) and ALARA

Toxicities from RT

- CN5 numbness 0–10% for FSRT, up to 20% with SRS.
- CN7 neuropathy, palsy: 0–5% in FSRT, 20% with SRS.
- CN8, hearing preservation: 64–97% in FSRT, 50% with SRS.
- Tinnitus <5%.
- Vestibular symptoms <5–15%.
- Tinnitus and vertigo can improve or arise after treatment (Badakhshi 2014).
- Cranial neuropathy is associated with larger tumors (Spiegelmann 2001) and pre-existing deficits (Kondziolka 1998).
- Serviceable hearing rates continue to decline with long-term follow-up (25–50% at 10 yrs)

Follow-Up

- MRI q6–12 months initially and spaced out more over time.
- Audiogram q12 months as indicated.
- Pseudoprogression is known to occur in 20–30% vestibular schwannoma patients treated with RT. For asymptomatic enlargement within 3 years of RT, observation is favored (Tsao 2017).
- There may also be alternating enlargement and regression of the tumor at up to 50 months post treatment (Nakamura 2000).
- Malignant transformation is extremely rare (1/1000 to 1/10,000).

NF2 patients

- NF2 patients require imaging of the entire cranial spinal axis.
- Typically have a more aggressive disease course and lower hearing preservation rates.
- Bevacizumab may be a targeted therapy for VSs due to the high VEGF expression in NF2 patients (Plotkin 2009).
- Radiation is a reasonable option for NF2 patients with enlarging VS or hearing loss (Germano 2018).

Trigeminal Neuralgia (TN) [208–214]

Background

- Increases with age; most occur after age 50.
- More common in women than men (approx. 1.5:1).
- Classical TN is either related to vascular CN5 compression or idiopathic.
- Secondary TN, or *trigeminal neuropathy*, may arise from herpes zoster, postherpetic neuralgia, MS, CN5 trauma, and nonvascular CN5 compression. Sensory loss, bilateral involvement, and younger age are associated with a higher risk of secondary TN.
- Classical TN pain is paroxysmal, unilateral, lancinating, and provocable (e.g., by talking, brushing teeth, chewing).
- Classic TN has the following features:
  (a) Paroxysmal attacks lasting 1 s–2 min, affecting any branch of CN5.
  (b) Pain has at least one feature: sharp, intense, stabbing, or superficial.
  (c) Attacks are stereotyped in the patient.
  (d) Not attributed to another disorder.
- Pretreatment MRI to rule out structural causes.
- CISS and 3D FIESTA sequences can offer high-resolution views of the TGN.

BNI Grade

- (I) No pain, taking no med
- (II) Occasional pain, but taking no med
- (III) Some pain, controlled w/ meds
- (IIIa) No pain, continued med
- (IIIb) Persistent pain, controlled w/ med
- (IV) Some pain, not controlled w/ meds
- (V) Severe pain or no relief

Studies

- **Flickinger 2001**: RCT of 87 pts comparing one vs two isocenters. Two isocenters increased length of trigeminal nerve being treated. Sixty-eight percent of pts w/ response. Pain relief was equivalent between two arms, but two-isocenter arm had more toxicity.
- **Maesawa 2001**: n = 220. GKRS. Median age 70. Sixty-one percent previous surgery. Complete or partial pain relief in 86% at 1 y. Complete pain relief 65% at 6 m, 70% at 1 yr and 75% at 33 m. Only 10% of pts developed new of increased facial numbness. Facial numbness was a predictor of long-lasting pain relief.
- **Lopez 2004**: Systematic review. Seventy-five percent of pts have CR after SRS at 1 yr. Only 50% maintain this at 3 yrs.
- Patients with classic TGN features felt to have better responses to therapy (Taich 2016).

Treatment

- **Medical therapy**: first-line therapy. Carbamazepine (Tegretol) or other anticonvulsants. Side effects may be intolerable in some patients.
- **Microvascular decompression (MVD)** is preferred if compressing vessel is found
- **Other surgical procedures**: RFA, glycerol injection, balloon compression.
- **Gamma Knife SRS**: reserved for medically refractory cases. A single 4 mm collimator gamma knife "shot" is placed on the dorsal root entry zone where CN5 exits from the pons, with the 50% IDL placed at the interface of the entry zone and the brainstem. 80–85 Gy max point dose prescribed to the 100% IDL. Brainstem max 45 Gy.

Follow-Up

- Median time to some pain relief is 1–2 mo.
- 60–80% some pain relief at 6 mo.
- 50% complete relief.
- TN pain can recur during follow-up. Repeat SRS may be an option for carefully selected patients (Herman 2004, Pollock 2005, Hasegawa 2002).
- Check for loss of corneal reflex.

Arteriovenous Malformation (AVM) [215–223]

Background
- Congenital lesions with a risk for hemorrhage.
- Occurs in 0.1% of the population.
- Underlying pathophysiology involves an aberrant connection between an artery and vein without an intervening capillary bed.
- Abnormal development of the vessel and increased blood flow/pressure lead to rupture.
- A variety of flow-related phenomenon are often seen, including vascular tangles, aneurysms, and adjacent gliotic brain.

Natural History
- 2–4% annual risk of bleeding.
- 30–50% risk of morbidity/bleed.
- Ten percent risk of death/bleed.
- 6–8% harbor aneurysms.
- Risk factors for future hemorrhage include prior hemorrhage, associated aneurysms, and deep brain location.

Presentation
- Intracranial hemorrhage
- Seizure
- Neurologic deficits
- Intractable vascular headache

Diagnosis
- CT is often the initial study, which may show hemorrhage, flow voids, and edema.
- MRI useful for identifying the location of the nidus.
- Angiography is the gold standard for diagnosis and treatment planning.

Grading System
- Spetzler-Martin system historically used to determine the risk of open neurosurgery for an AVM

Spetzler-Martin grading system (1986)				
Points	0	1	2	3
Size (cm)		<3	3–6	>6
Location	Non-eloquent	Eloquent		
Venous drainage	Superficial	Deep		

Eloquent are sensorimotor, language, visual, thalamus, hypothalamus, internal capsule, brainstem, cerebellar peduncles, and deep cerebellar nuclei. Various combinations result in cumulative grades of I–V.

Treatment
- Consider the risk of rupture as well as risks of intervention when deciding to intervene.
- Microsurgery is the mainstay of treatment, best for small, superficial lesions in non-eloquent brain.
- Embolization is typically not curative but can be combined with SRS or surgery.
- SRS is best for small (<3 cm), deep AVMs with a well-defined focus.
- Goal of SRS is obliteration and works by vascular wall thickening and luminal thrombosis.
- Lag time of 1–3 yrs to complete obliteration, during which bleeding is still possible but reduced by 50% (Marayuma 2005).
- Dose: 16–22 Gy at margin in one fraction, depending on size.
- If large, consider volume-staged procedure (Kano 2012). Dose-staged has also been used, although one systematic review found inferior outcomes compared to volume-staged (Moosa 2014).

Outcomes/Studies
- Lunsford 1991: $n = 227$. Two-year obliteration rates according to volume were 100% for AVMs <1 cc, 85% for AVMs 1–4 cc, and 58% for AVMs greater than 4 cc.
- Friedman 1995: $n = 158$. Mean dose 15.6 Gy to periphery. Mean FU of 33 months. 1–4 cc, 81% obliteration. 4–10 cc, 89% obliteration. >10 cc, 69% obliteration.
- Maruyama 2005: $n = 500$. 81% obliteration at 4y wth GK.
- ARUBA trial (Mohr 2014): Brain AVMs randomized to (1) medical management vs (2) same + intervention (surgery, embolization, SRS alone, or in combination). Trial stopped early due to superiority of medical management. Risk of death or stroke from intervention was higher than medical therapy (31% vs 10%)

SRS Toxicity

- Early: seizures in 10%, N/V, H/A.
- Late: Symptomatic radionecrosis (1–3%), edema, cyst formation.
- Factors associated with a higher risk of developing symptomatic toxicity include larger volume, higher dose, larger 12 Gy volume, and higher Spetzler-Martin grade (Kano 2017).

Follow-Up

- MRI every 6 months
- Angiogram to confirm obliteration

Hemangiopericytoma (HPC) [224–227]

Background

- Rare, dural-based tumors, <1% of CNS tumors.
- Arise from smooth muscle cells or fibroblasts (mesenchymal cells).
- Occur in adults, aged 40–50 on average.
- Appear on imaging as an extra-axial mass. Enhance with contrast-like meningiomas but lack calcifications. May have a dural tail or adjacent bone erosion.
- Seventy percent supratent, 15% post fossa, and 15% spinal.
- WHO categorizes solitary fibrous tumors (SFT) (gr I) and HPC (gr II and III) on a phenotypic spectrum.
- Both SFT and HPC are characterized by NAB2-STAT6 fusion protein.

Studies

- Rutkowski 2012: *N* = 40. Median survival 16 years. 5-year OS 92%, but 5-year PFS ~50%. RT improved local control but did not impact survival or development metastases. Extracranial mets occurred in 20%.
- Schiariti, 2011. *N* = 39. 15-year recurrence 92%. Extracranial mets were common (26%), occurring at a median of 126 mo after initial surgery. RT decreased risk of recurrence by one-third.
- Soyuer 2004: *N* = 29. Five-year OS 85%; 5-yr LC 68%. LC better if GTR. Adjuvant RT given to ten patients, median dose 54 Gy. Concluded attempted GTR with limited field RT is a reasonable initial approach.
- Staples 1990: *N* = 15. LC after RT was 100% if dose >55 Gy.
- Guthrie 1989; *N* = 44. 10 developed extracranial mets a median of 99 mo after first operation.

Treatment paradigm

- Complete surgical resection is the mainstay of therapy.
- Adj RT (54–60 Gy) is generally recommended for all tumors with HPC phenotype.
- During RT target delineation, it is important to remember that HPCs are meningeal-based tumors.
- There is some data on the feasibility of SRS (Spina 2016, Cohen-Inbar 2017).
- Recurrent tumors after radiation may benefit from anti-angiogenic therapies.

Follow-Up

- MRI brain surveillance similar to gliomas protocols.
- Consider systemic surveillance imaging for extracranial metastases.

Thyroid Ophthalmopathy (TO) [228–232]

Background
- Autoimmune disease of the retro-orbital tissues.
- Caused in part by a T-cell lymphocytic infiltration.
- Associated with Graves' disease and Hashimoto thyroiditis.
- Variable natural history may worsen or improve without treatment.

Symptoms
- Exophthalmos, impaired EOM, diplopia, edema/redness, lid retraction.
- Mild symptoms per EUGOGO (Bartalena 2016): minor lid retraction (<2 mm), mild soft-tissue involvement, exophthalmos <3 mm above normal for race and gender, no or intermittent diplopia, and corneal exposure responsive to lubricant.
- Moderate-severe symptom per EUGOGO: lid retraction ≥2 mm, moderate or severe soft-tissue involvement, or exophthalmos ≥3 mm above normal for race and gender, inconstant, or constant diplopia.
- Sight-threatening per EUGOGO: dysthyroid optic neuropathy or corneal breakdown; loss of color vision may be an early sign.

Workup
- HP, Hertel exophthalmometer, CBC, CMP, TFs, and CT/MRI orbit

Treatment
- Treat underlying disorder and reverse hyperthyroidism.
- Smoking cessation (exacerbates orbital dz).
- Local measures to reduce surface irritation: eye shades, artificial tears, and raising head of bed at night.
- Additional therapy should be tailored based on severity of symptoms:
  - Mild: local measures only, NSAIDs, consider a 6-month course of Selenium.
  - Mod-severe: high-dose steroids are SOC (prednisone 30 mg qday x 4 weeks vs IV steroids if more severe) and response in ~60%, if refractory consider rituximab, mycophenolate, surgery, or RT.
  - Sight-threatening: this is a medical emergency; initiate high-dose steroids, and consider urgent orbital decompression surgery.

Radiation Therapy
- External orbital radiation is rarely used for TO in modern times and is typically reserved for those patients with moderate-to-severe symptoms who cannot tolerate or fail to respond to steroids.
- The benefit of RT for TO is controversial with conflicting evidence from RCTs.
- RT may improve eye motility and diplopia compared to sham tx; however, the duration of benefit may be limited, and RT may not improve quality of life (Prummel 2004).

Studies
- **Prummel 2004**: mild TO. RCT of RT vs sham. RT won, 52% vs 27% response. No QOL or cost change.
- **Gorman 2001**: mild TO. RCT w/ crossover, to 1 orbit, then opposite at 6 m. At 6 m, no difference in results w/ either eye. At 12 m, minor improvement in the first treated eye. Concluded RT not justified.
- **Mourits 2000:** Double-blind, RCT of RT vs sham RT. RT improved diplopia 60% vs 31% at 24 w but had no benefit for proptosis or eyelid swelling. Seventy-five percent of RT patients still required strabismus surgery.
- **Prummel 1993**: Severe TO. RCT RT vs sham. RT improved diplopia but not proptosis and eyelid edema. Conclude that RT best for motility EOM impairment only.

RT planning
- 20 Gy in ten fractions is the most common regimen.
- Other less common options: 10 Gy in ten fractions or 20 Gy/1 per week × 20 weeks.
- Opposed laterals, half beam block to minimize divergence to contralateral lens.
- Try to limit lens dose to <8–10 Gy to prevent cataracts.

Follow-up

- Ophthalmology follow-up
- Toxicity: cataracts, dry eye, retinopathy, and optic neuropathy

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Head and Neck Cancers

4

Daniel M. Trifiletti, Nicholas G. Zaorsky, and Henry S. Park

Abstract

This chapter discusses the general management of patients with head and neck cancers, with special focus on principles that guide radiotherapy management. Several key components of trimodality care and radiation field design are discussed.

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HN Pearls [1–9]

History and Physical

- History
  - Neck mass
  - Tobacco and EtOH
  - Odynophagia and dysphagia
  - CN deficits, trismus and dysarthria
  - "Hot potato" voice = BOT involvement
  - Otalgia (inner/middle ear) = Jacobson (CN IX)
  - HPV risk factors (M, high SES, never married, smoker)
  - SGL = dysphagia/odynophagia, otalgia (Arnold). Ask about voice changes (hoarseness), swallowing, aspiration, and pulmonary status (can the patient climb a set of stairs)
- Physical
  - OPX: oral cavity inspection w/ BOT palpation, "stick out your tongue," LN exam, CN exam.
  - OC: oral cavity inspection w/ palpation of tongue and FOM; examine tongue mobility (CN XII), sensation (V), and taste (VII, IX); LN exam, CN exam.
  - LX: palpate larynx (mass at thyroid notch = pre-epiglottis space/PES invasion), gently move (loss of laryngeal click = post-cricoid area/PCA invasion), palpate tongue, and BOT, LN exam
  - "fixed" = when you move the mass, the patient moves with it. Implies ECE/attachment to soft tissue or musculature.
- Labs: CBC, SMP, EBV for NPX
- Imaging: CT neck w contrast, MRI, PET-CT
- Referrals ("SANDS"): speech/swallow, audiometry, nutrition, dental, smoking cessation

Pre-RT Dental Evaluation

- Complete oral and HN exam, radiographs of all teeth.
- Risk assessment and tx for caries, periodontal dz.
- Eliminate potential sources of infection.
- Extractions.
  - 2+ wks prior to start of RT
  - Teeth w non-restorable caries or those extending to gum line
  - Teeth w large compromised restorations, significant periodontal loss (pocket >5 mm)
  - Teeth w severe erosion or abrasion or if in high-dose region
- For metal restorations: silicone guards to minimize RT backscatter.
- Return visit for re-eval and prevention in last week of RT (e.g., fluoride trays).
- Eval for oral candidiasis.
- Bite block or tongue depressor can be considered to displace tongue during sim and RT to decrease integral dose. Bite block looks like a mouth guard for athletes.

Differential Diagnosis

- Benign
  - Developmental (thyroglossal duct cyst, branchial cleft cysts, inclusion cysts)
  - Inflammatory (e.g., lymphadenitis, benign reactive hyperplasia, infected sebaceous cyst)
  - Benign neoplasm (e.g., lipoma, fibroma, hemangioma, neurofibroma, schwannoma, parathyroid adenoma, goiter)
- Malignant
  - Primary HN SCC >>adeno
  - Metastatic cancer
  - Lymphoma, leukemia
  - Carotid body tumor
  - Thyroid cancer
  - Parathyroid cancer
  - Histiocytosis
  - Carcinoid

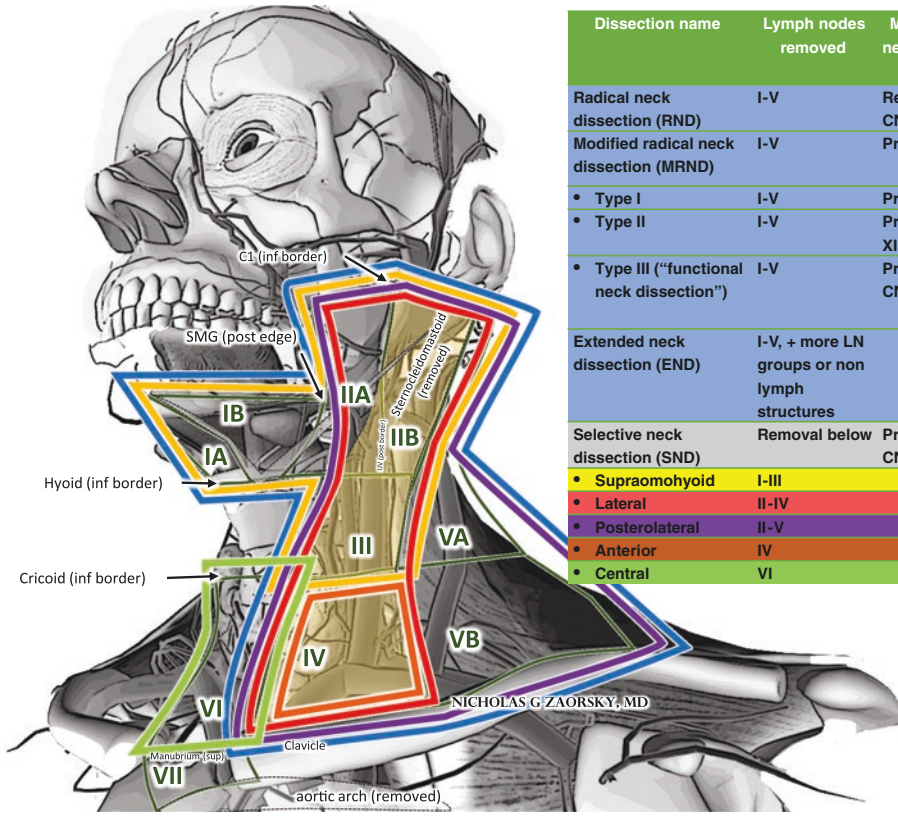
Biopsy

- FNA preferred
- Open biopsy
  - Alters lymphatics
  - Seeding or dissemination of tumor
  - Wound necrosis

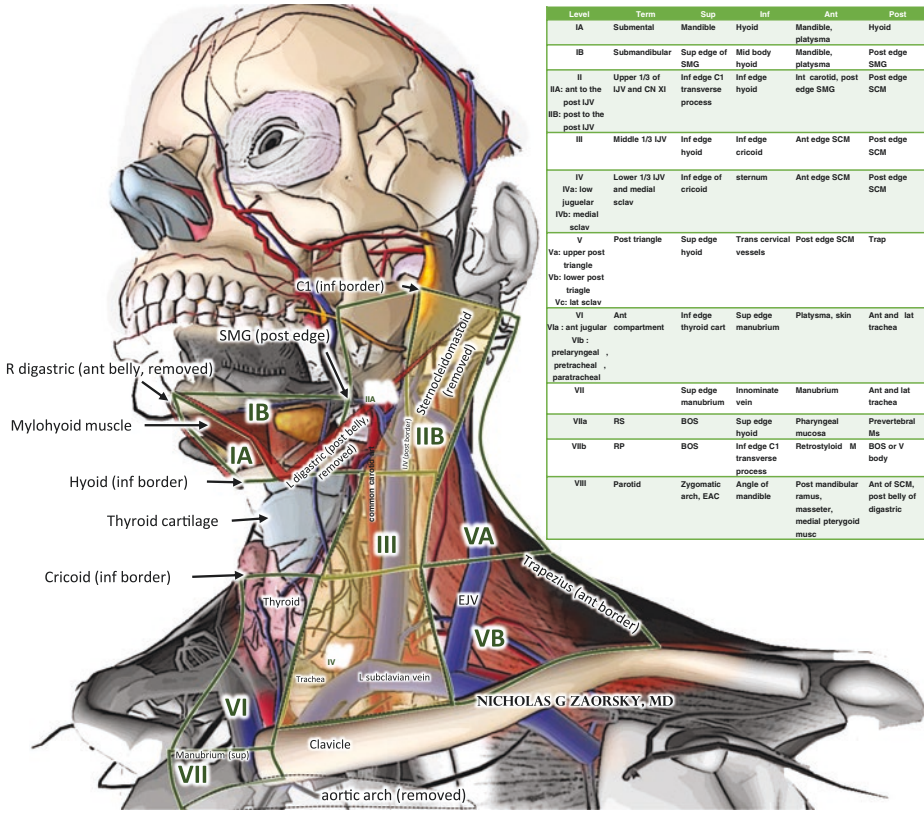
Types of Neck Dissections

- Radical neck dissection (RND)
  - Removes levels I-V
  - Removes SCM, IJV, CN XI
- Modified radical neck dissection (MRND)
  - Removes levels I–V.
  - Preserves other parts, per subtypes.
  - Type I MRND preserves CN XI.
  - Type II MRND preserves CN XI and IJV.
  - Type III MRND ("functional neck dissection") preserves the CN XI, IJV, and SCM.
- Extended neck dissection (END)
  - Removes levels I–V.
  - Additionally removes more LN groups or non-lymphatic structures.
- Selective neck dissection (SND)
  - Supraomohyoid: removes levels I–III (not IV or V)
  - Lateral: levels II–IV
  - Posterolateral: levels II–V
  - Anterior: level VI

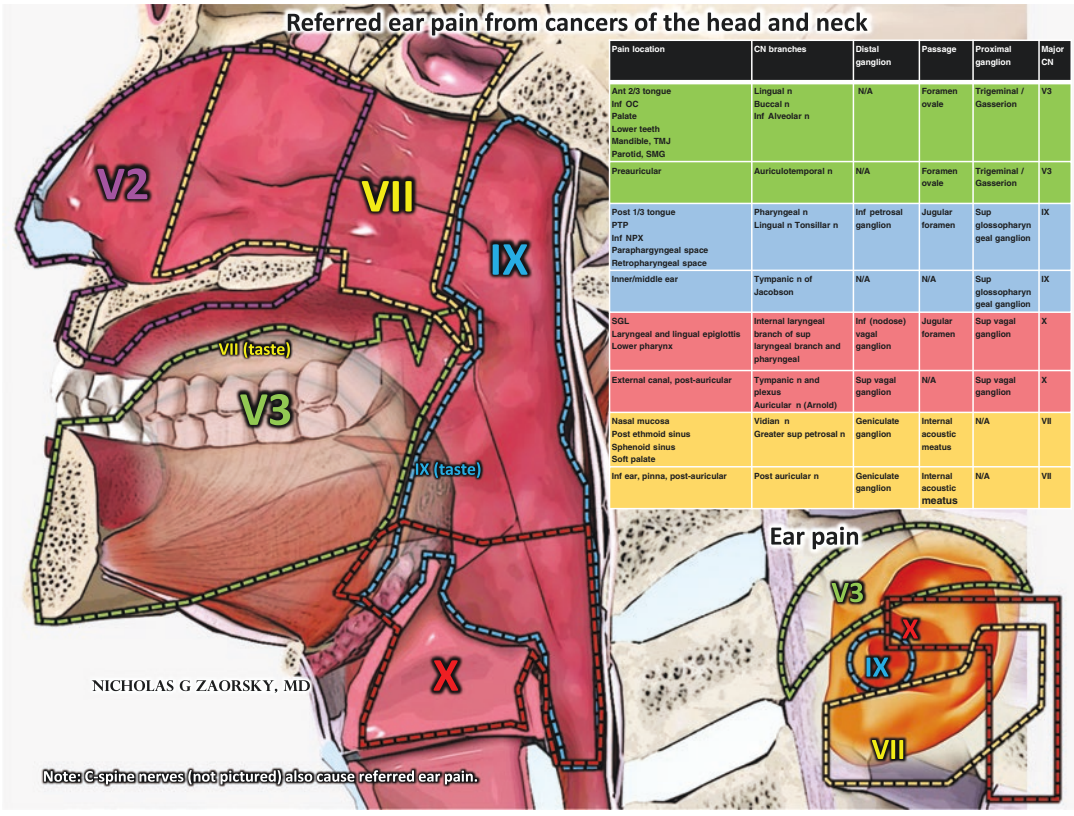
No further treatment	Post-op RT Alone	Post-op CRT
Margin ≥5mm	Close margin	Positive Margin
Ø PNI	PNI	ECE
Ø LVSI	LVSI	4+ other factors
N0-N1	2+ LN	
	Bulky LN (>3cm)	
	T3-T4	
	OPX/OC level IV-V LN	



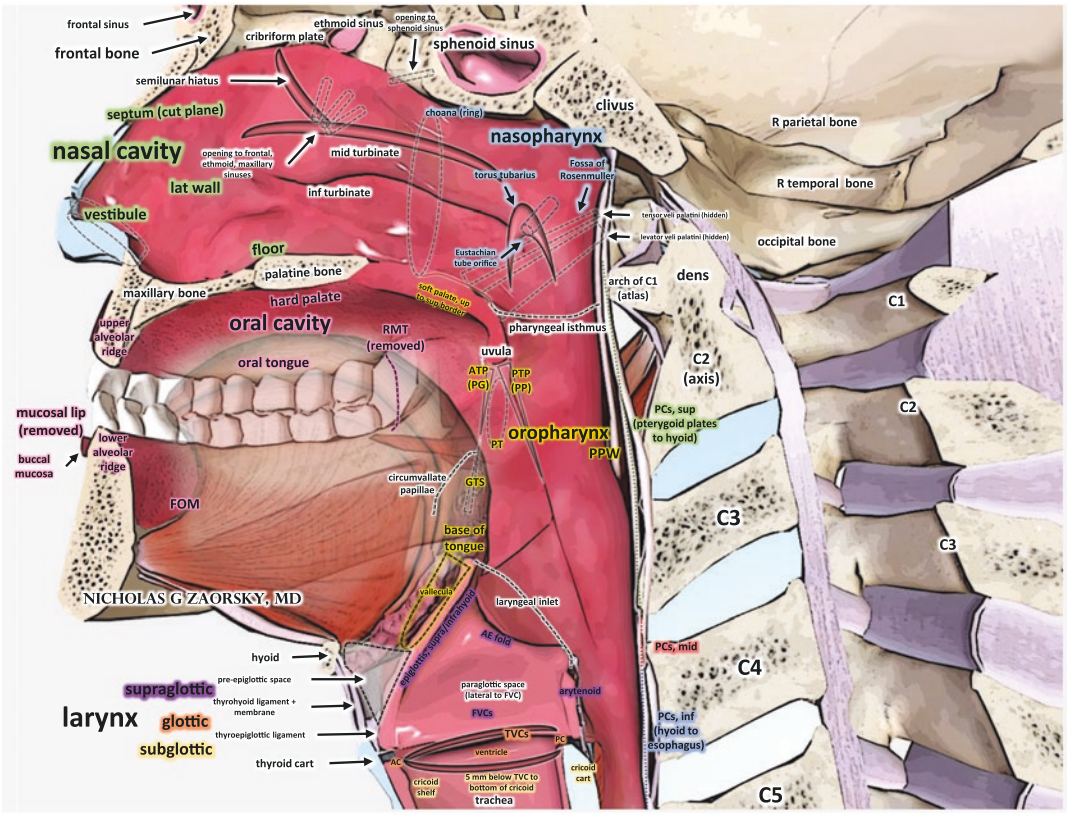
Dissection name	Lymph nodes removed	Muscles, vessels, nerves removed or preserved
Radical neck dissection (RND)	I-V	Removes SCM, IJV, CN XI
Modified radical neck dissection (MRND)	I-V	Preservation below
• Type I	I-V	Preserves CN XI
• Type II	I-V	Preserves IJV, CN XI
• Type III ("functional neck dissection")	I-V	Preserves IJV, SCM, CN XI
Extended neck dissection (END)	I-V, + more LN groups or non lymph structures	
Selective neck dissection (SND)	Removal below	Preserves IJV, SCM, CN XI
• Supraomohyoid	I-III	
• Lateral	II-IV	
• Posterolateral	II-V	
• Anterior	IV	
• Central	VI	

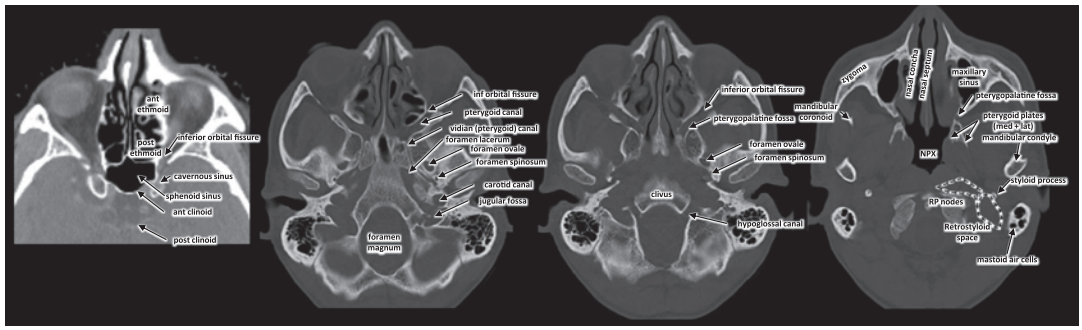


Level	Term	Sup	Inf	Ant	Post	Lat	Med
IA	Submental	Mandible	Hyoid	Mandible, platysma	Hyoid	Ant digastric	--
IB	Submandibular	Sup edge of SMG	Mid body hyoid	Mandible, platysma	Post edge SMG	Mandible, platysma	Ant digastric
II IIA: ant to the post IJV IIB: post to the post IJV	Upper 1/3 of IJV and CN XI	Inf edge C1 transverse process	Inf edge hyoid	Int carotid, post edge SMG	Post edge SCM	Medial SCM	Int carotid, levator scap
III	Middle 1/3 IJV	Inf edge hyoid	Inf edge cricoid	Ant edge SCM	Post edge SCM	Medial SCM	Int carotid, paraspinal M
IV IVa: low jugular IVb: medial sclav	Lower 1/3 IJV and medial sclav	Inf edge of cricoid	sternum	Ant edge SCM	Post edge SCM	Medial SCM	Int carotid, paraspinal M
V Va: upper post triangle Vb: lower post triagle Vc: lat sclav	Post triangle	Sup edge hyoid	Trans cervical vessels	Post edge SCM	Trap	Platysma, skin	Paraspinal M
VI VIa : ant jugular VIb : prelaryngeal , pretracheal , paratracheal	Ant compartment	Inf edge thyroid cart	Sup edge manubrium	Platysma, skin	Ant and lat trachea	Thyroid and SCM	None or midline
VII		Sup edge manubrium	Innominate vein	Manubrium	Ant and lat trachea	Carotids or mediastinum	---
VIIa	RS	BOS	Sup edge hyoid	Pharyngeal mucosa	Prevertebral Ms	Styloid, deep parotid lobe	Medial edge ICA
VIIb	RP	BOS	Inf edge C1 transverse process	Retrostyloid M	BOS or V body	Parotid	Midline
VIII	Parotid	Zygomatic arch, EAC	Angle of mandible	Post mandibular ramus, masseter, medial pterygoid musc	Ant of SCM, post belly of digastric		Styloid process



Pain location	CN branches	Distal ganglion	Passage	Proximal ganglion	Major CN
Ant 2/3 tongue Inf OC Palate Lower teeth Mandible, TMJ Parotid, SMG	Lingual n Buccal n Inf Alveolar n	N/A	Foramen ovale	Trigeminal / Gasserion	V3
Preauricular	Auriculotemporal n	N/A	Foramen ovale	Trigeminal / Gasserion	V3
Post 1/3 tongue PTP Inf NPX Paraphargyngeal space Retropharyngeal space	Pharyngeal n Lingual n Tonsillar n	Inf petrosal ganglion	Jugular foramen	Sup glossopharyngeal ganglion	IX
Inner/middle ear	Tympanic n of Jacobson	N/A	N/A	Sup glossopharyngeal ganglion	IX
SGL Laryngeal and lingual epiglottis Lower pharynx	Internal laryngeal branch of sup laryngeal branch and pharyngeal	Inf (nodose) vagal ganglion	Jugular foramen	Sup vagal ganglion	X
External canal, post-auricular	Tympanic n and plexus Auricular n (Arnold)	Sup vagal ganglion	N/A	Sup vagal ganglion	X
Nasal mucosa Post ethmoid sinus Sphenoid sinus Soft palate	Vidian n Greater sup petrosal n	Geniculate ganglion	Internal acoustic meatus	N/A	VII
Inf ear, pinna, post-auricular	Post auricular n	Geniculate ganglion	Internal acoustic meatus	N/A	VII


frontal sinus
frontal bone
cribriform plate
ethmoid sinus
opening to sphenoid sinus
sphenoid sinus
semilunar hiatus
septum (cut plane)
choana (ring)
clivus
nasopharynx
R parietal bone
nasal cavity
opening to frontal, ethmoid, maxillary sinuses
mid turbinate
lat wall
inf turbinate
torus tubarius
Fossa of Rosenmuller
R temporal bone
vestibule
tensor veli palatini (hidden)
levator veli palatini (hidden)
occipital bone
floor
palatine bone
Eustachian tube orifice
dens
arch of C1 (atlas)
C1
maxillary bone
hard palate
soft palate, up to uvula border
upper alveolar ridge
oral cavity
RMT (removed)
pharyngeal isthmus
C2 (axis)
oral tongue
uvula
ATP (PG)
PTP (PP)
C2
mucosal lip (removed)
lower alveolar ridge
buccal mucosa
PCs, sup (pterygoid plates to hyoid)
oropharynx
PT
PPW
circumvallate papillae
GTS
FOM
C3
base of tongue
C3
NICHOLAS G ZAORSKY, MD
vallecula
laryngeal inlet
AE fold
hyoid
epiglottis, supra/infrahyoid
PCs, mid
C4
supraglottic
pre-epiglottic space
paraglottic space (lateral to FVC)
arytenoid
thyrohyoid ligament + membrane
larynx
glottic
FVCs
PCs, inf (hyoid to esophagus)
thyroepiglottic ligament
TVCs
subglottic
ventricle
thyroid cart
AC
cricoid cart
cricoid shelf
5 mm below TVC to bottom of cricoid
trachea
C5


ant ethmoid
post ethmoid
inferior orbital fissure
cavernous sinus
sphenoid sinus
ant clinoid
post clinoid
inf orbital fissure
pterygoid canal
vidian (pterygoid) canal
foramen lacerum
foramen ovale
foramen spinosum
carotid canel
jugular fossa
foramen magnum
inferior orbital fissure
pterygopalatine fossa
mandibular coronoid
clivus
foramen ovale
foramen spinosum
hypoglossal canal
zygoma
nasal concha
nasal septum
maxillary sinus
pterygopalatine fossa
pterygoid plates (med & lat)
mandibular condyle
NPX
styloid process
RP nodes
Retrostyloid space
mastoid air cells

Surgical Margins

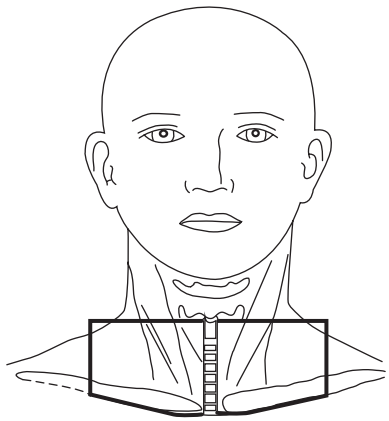
– Positive surgical margins at initial frozen section despite negative final path being a strong predictor of LR (HR 3.3). PORT should be considered for these patients even when final path margins were negative (Ettl, 2016).

Flap Coverage

– In PORT for the head and neck, the entire post-op bed and flap should be covered in case of ECE.

Split-Field vs. Whole-Neck IMRT

– **Whole-neck IMRT**: easier setup; fewer hot spots at junction; potential for inadequate dose.
– **Split-field:** allows better larynx sparing (V10 = 100% vs V10 = 45%); has more complicated setup – higher potential setup errors. Low anterior neck (LAN) is prescribed to 3 cm depth. Can't match through gross dz or for high-risk dz s/p surgery (e.g., advanced larynx s/p TL ad BL LND).
  – LAN borders: sup border is match line (level of thyroid notch); inf border is 1 cm below the clavicles; lat border is medial; 2/3 of clavicle mid border is the larynx.
  – Place Iso in the middle of the vertebral body at level of thyroid notch.
  – Dosimetric match at 50% IDL line of IMRT and LAN fields.
  – Can feather the junction to spread out dose.



CTV Expansions

– 0.5–1.0 cm GTV to CTV margin
– Indications to cover level VI: emergent trach, > minimal subglottic space extension, extension thru thyroid cartilage, apex, or pyriform sinus involvement for hypopharynx primaries

PTV Expansion

– 0.3–0.5 cm CTV to PTV margin if using daily KV and/or CBCT

PET-CT

– Often in N+ pts when conventional imaging is equivocal, if primary site unknown, if recurrent, and if salvage.
– Consider in stages III–IV OC, OPX, HPX, LX, NPX (non-keratinizing, N2–3), and unknown primary before EUA
– Mehanna, 2016: Is PET noninferior to planned neck dissection for HNSCC N2–3? n = 564, 2007–2012, N2–3 M0. 84% OPX. 57% T1–2. 79% N2a-2b. Randomize: (1) PET/CT surveillance 12w after end of CRT. If <CR, then undergo ND in 4w after PET-CT. vs (2) Planned ND. CT or MRI at 12w. Nineteen percent of PET-CT pts needed ND. Two-yr OS 85% vs 82%, slightly favoring surveillance, meeting noninferiority criteria. Small QOL benefit for PET at 6mo, similar thereafter. LRC 91% in both. DMs similar in both. Thus, after CRT, surveillance PET-CT preferred for OS, QOL, and cost

Mastication

- Lateral pterygoid originates from lat pterygoid plate and inserts onto the neck of condyloid process of the mandible –> opens jaw
- Masseter and medial pterygoid –> closes jaw

Speech and Swallow

- Baseline eval for speech and swallowing dysfunction.
- Dysphagia/aspiration-related structure (DARS): pharyngeal constrictors, supraglottic, and glottic larynx.
- For patients receiving CRT, SLP improves swallowing at up to 9 months of follow-up.

PEG or NG Tube

- Not routinely recommended
  - Higher G-tube dependence
  - Higher late esophageal stricture
- Consider w severe weight loss (5% in 1 month, 10% in 6 months), dehydration, dysphagia, anorexia, significant comorbidities, aspiration risk, and large RT fields

Treatment Initiation

- Ideally start definitive therapy within 4 wks and post-op therapy with 6 wks

Induction Chemo

- **Current indications**: Possibly T4b or N3 non-oropharynx cancers, metastatic NPX cancer to gain control over DMs prior to LR RT, borderline/unresectable sinonasal neuroendocrine tumors, pt unable to lie flat
- In general, not recommended over concurrent CRT. PARADIGM and DeCIDE negative for OS advantage of induction vs concurrent.

Immunotherapy

- Checkmate 141, Ferris, UPMC, 2016. M HN SCC w dz. progression 6 m after platinum chemo. Nivo > standard tx, 1-year OS 36% vs 17%, response rate 13% vs 6%. Response in both p16+/−. Nivo had stable physical and social function, which worsened w chemo. If >1% PD-L1 expression, then favorable OS, HR 0.55. No further benefit if >5% of >10% expression.

Contouring Normal Structures

Brainstem

Spinal cord

Dorsal vagal complex (**DVC**), area postrema – Level of inferior cerebellum (on sag), contour two to three slices of posterior brainstem going inf (1 above level of hemisphere, 1 at, and 1 below level of hemisphere)

Cochlea: lucency anterior to IAC on bone windows. Prefer slices ≤1 mm. Avg volume 0.13–0.56 mL. Note cochlea has no known threshold for sensorineural hearing loss, rec to keep dose ALARA.

Vestib complex: lucency post to IAC

Pharyngeal constrictors: three sets of contours. Contour 3 mm slice of posterior pharynx. Sup: when pterygoid plates disappear, superior PC begins. Goes inf to sup hyoid bone.

Middle: spans hyoid bone (sup to inf). Inf: start when hyoid no longer visualized and ends at the esophagus. Make wider near the inferior aspect (cricopharyngeus muscle joins pharynx to esophagus and is wide)

Esophagus

Parotids: starts at superior level of the external auditory canal and ends at angle of mandible.

SMG: under the mandible, sup aspect ends under floor of mouth (mylohyoid muscle).

OC: contains minor salivary glands

Lips: for OC, look on sagittal view.

Glottic/Supraglottic larynx (**GSL**): spans C3-C6 – prism-shaped volume. Start at the bottom of hyoid, large contour, between pharyngeal constrictors and submandibular glands. Continue contouring external all of thyroid cartilage. Inf border is inf cricoid cartilage, stops at the esophagus. Trachea does not have cartilage all the way around, cricoid does and includes AC to arytenoids.

Mandible

Maxilla

Brachial plexus: 5 mm diameter, start at C5, end at T1.

CNV1: ophthalmic division arises from sup aspect of TG ganglion, courses along lateral wall of cavernous sinus, and enters orbit via sup orbital fissure.

CN V2: maxillary division arises from inf portion of TG ganglion, courses along lat wall of cavernous sinus, and enters pterygopalatine fossa via foramen rotundum.

CN V3: mandibular division arises from inf portion of TG ganglion and passes through foramen ovale to inf surface of skull.

CN VII: exits via stylomastoid foramen. Branches are temporal, zygomatic, buccal, mandibular, and cervical ("Two Zebras Bit My Coccyx").

CN XII: hypoglossal. W/ neuro deficit, tongue points to affected side. BOS tumor may damage it in the hypoglossal canal.

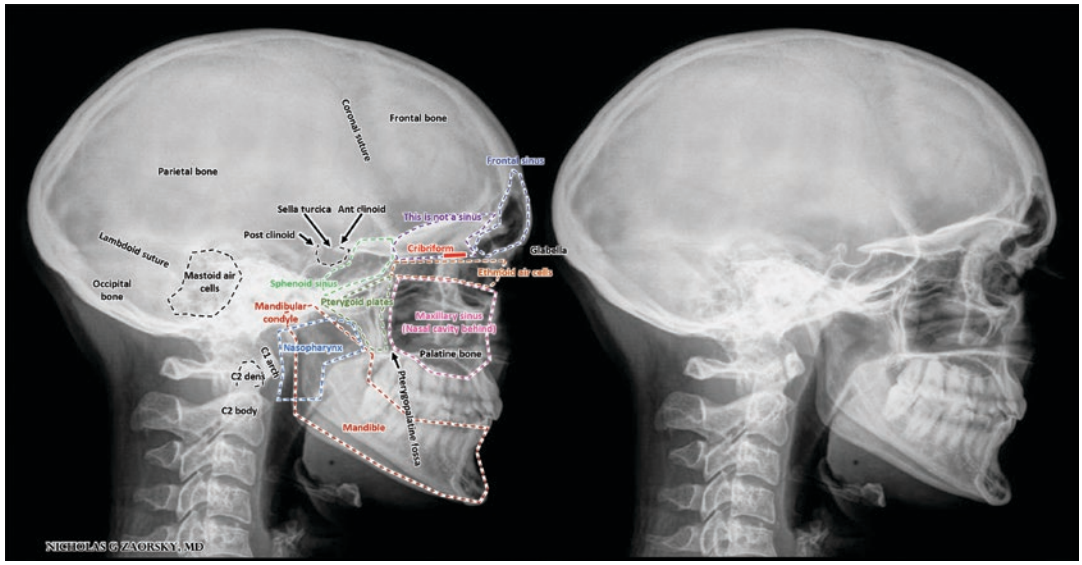
Dose Constraints (Guidelines Vary Depending on Proximity/Importance of PTV Coverage)

Spinal cord PRV	0.1 cc < 50 Gy
DVC	Mean < 12 Gy
Brainstem	0.1 cc < 54 Gy
Contralateral parotid	Mean < 20 Gy
Combination parotids	Mean < 26 Gy
Contra SMG	Mean < 39 Gy
GSL (larynx)	Mean < 35 Gy; V55 < 10%
OC, ant	V30 < 65%; V35 < 35%
OC	Mean < 30 Gy; 0.1 cc < 60 Gy
Lips	Mean < 20 Gy
Mandible	0.1 cc < 70 Gy
Pharyngeal constrictor, sup	V55 < 80%; V65 < 30%
Pharyngeal constrictor, mid	V65 < 75%
Pharyngeal constrictor, uninvolved	V50 < 33%; mean < 45 Gy; V60 < 15%
Esophagus	Mean < 30 Gy
Brachial plexus (L or R)	0.03 cc < 70 Gy
Optic N	0.1 cc < 54 Gy
Chiasm	0.1 cc < 54 Gy
Temporal lobe	0.1 cc < 68 Gy; 1 cc < 58 Gy
Lens	0.1 cc < 10 Gy
Cochlea	V30 < 50%, max 35 Gy
Retina	0.1 cc < 45 Gy
Lacrimal gland	Mean < 34 Gy

Nodal Stations and Boundaries of the HN [10, 11]

Level	Term	Sup	Inf	Ant	Post	Lat	Med	Drainage from	When to treat
IA	Submental	Mandible	Hyoid	Mandible, platysma	Hyoid	Ant digastric	--	Skin of the chin, mid-low lip, tip of the tongue, ant FOM, ant oral tongue, and mandibular alveolar ridge	
IB	Submandibular	Sup edge of SMG	Mid body hyoid	Mandible, platysma	Post-edge SMG	Mandible, platysma	Ant digastric	IA, lower nasal cavity, hard/soft palate, maxillary and mandib alveolar ridges, cheek, lips, ant tongue, OC, ant NC, midface, SMG	
IIIIA: ant to the post IJV**II**B: post to the post IJV	Upper 1/3 of IJV and CN XI	Inf edge C1 transverse process	Inf edge hyoid	Int carotid, post edge SMG	Post edge SCM	Medial SCM	Int carotid, levator scapulae	"Grand central station": face, parotid, SMG, IA, IB, VIIa, NC, NPX, OC, OPX, LX, HPX, EAC, middle ear IIB: OPX, NPX >> OC, LX, HPX	Standard hemi -neck
III	Middle 1/3 IJV	Inf edge hyoid	Inf edge cricoid	Ant edge SCM	Post edge SCM	Medial SCM	Int carotid, paraspinal M	NPX, OC, OPX, LX, HPX	
IV IVa: low juguelar IVb: medial sclav	Lower 1/3 IJV and medial sclav	Inf edge of cricoid	Midway b/w cricoid and clavicle head	Ant edge SCM	Post edge SCM	Medial SCM	Int carotid, paraspinal M	NPX, OPX, LX, HPX. Infrequently: OC	
V Va: upper post triangle Vb: lower post triangle Vc: lat sclav	Post triangle	Sup edge hyoid	Trans cervical vessels	Post edge SCM	Trap	Platysma, skin	Paraspinal M	NPX	Post-op, node-positive hemi rt neck

VI VIa: ant jugular VIb: prelaryngeal, pretracheal, paratracheal	Ant compartment	Inf edge thyroid cart	Sup edge manubrium	Platysma, skin	Ant and lat trachea	Thyroid and SCM	None or midline	thyroid, LX (subglottic involvement), extension through the thyroid cartilage, HPX	
VII (older)		Sup edge manubrium	Innominate vein	Manubrium	Ant and lat trachea	Carotids or mediastinum	---		
VIIa/RP	Retropharyngeal	BOS	Sup edge hyoid	Pharyngeal mucosa	Prevertebral Ms	Med edge int carotid	Midline	Paranasal sinuses	If gross positive or PPW involved. Anything with "pharynx" in name of dz
VIIb/RS	Retrostyloid	BOS	Inf edge C1 transverse process	Retrostyloid M	BOS or V body	Parotid	Lat edge int carotid		Post-op, cLN+ hemi-neck
VIII	Parotid	Zygomatic arch, EAC	Angle of mandible	Post mandibular ramus, masseter, medial pterygoid musc	Ant of SCM, post belly of digastric		Styloid process		
Supraclav		Inf border level 4–5	Sup edge manubrium	SCM and clavicle	Carotid and paraspinal MS	Clavicle or fat space	SCM, carotid, med clavicle		
SMG								typically none bc encapsulated	Primary SMG cancer
Parotid									


Coronal suture
Frontal bone
Parietal bone
Frontal sinus
Sella turcica
Ant clinoid
This is not a sinus
Post clinoid
Lambdoid suture
Cribriform
Glabella
Ethmoid air cells
Occipital bone
Mastoid air cells
Sphenoid sinus
Pterygoid plates
Mandibular condyle
Maxillary sinus (Nasal cavity lateral)
Nasopharynx
Palatine bone
C1 arch
C2 dens
C2 body
Mandible
Pterygopalatine fossa
NICHOLAS G. ZAORSKY, MD

HN Toxicity Management [12–18]

Mucositis Most common cause of tx breaks. It causes severe pain, dysphagia, and weight loss.

- **Risk factors**: poor hygiene, nutrition, immunosuppression, poorly fitting dentures, spicy food, betel nut, EtOH, tobacco, prior RT, chemo, dec saliva, concurrent chemo, dose, site, location, transplanted tissue, metallic dental work

- **Prevention**
  - 4–6x/d w 1 qt water: 1 tsp salt: 1 tsp baking soda
  - Soft toothbrush and mild toothpaste after every meal/QHS
  - Don't start flossing during RT. Gentle if you already do
  - Avoid alcohol mouthwash
  - Lip moisturizer
  - Fluoride trays
  - Humidifier in bedroom
  - Avoid oral irritants

- **Management**
  - Magic mouthwash before meals, QHS, up to 8x/day: Mylanta 160 ml, Benadryl 160 ml, and Viscous Xylocaine 2% 160 ml
  - Doxepin mouthwash before meals
  - Pain medications (narcotics)
  - Antibacterial or antifungal prn
  - Manuka honey vs. placebo (Bardy, OMS, 2011): no difference in G3 mucositis, severity, or duration of mucositis
  - Palifermin, a recombinant keratinocyte factor, decreases oral mucositis. However, no change in tx breaks, opiate use.
- **Oral candidiasis:** from candida colonization. Worsened by xerostomia. Before treatment, must check meds and LFTs. Treatment:
  - Nystatin. Unpleasant taste. Can cause N/V.
  - Fluconazole: possible hepatotoxicity. P450 inhibitor and can interact w other meds, e.g., coumadin.
  - Amphotericin B: possible liver toxicity.

Xerostomia Defined by symptoms (taste, dryness not relieved by sipping water, difficulty chewing, swallowing), quantify by salivary production.

- SMGs for basal flow produce predominance of unstimulated saliva (65%) vs parotids (20%). SMG secretions are more mucinous and results in more moisture in mouth and alleviate feeling of xerostomia.
- Parotid for saliva bolus; thus, sparing at least one parotid reduces xerostomia. PARSPORT was RCT of conventional vs IMRT, 60–65 Gy/30 fx. IMRT decreased G2+ xerostomia at 12 and 20 months (83% vs 29%), but fatigue is more prevalent in IMRT group.
- Minor salivary glands thought to be important for resting salivation, a key component of sensation of dry mouth.

Hiccups Treat w chlorpromazine, 25 mg PO TID or QID. Often, a single dose will break the cycle. If this does not work, try baclofen, 5 mg PO TID.

Osteoradionecrosis (ORN)

- **Pathophys**: Non-vital bone in site of prior RT. Occurs secondary to hypocellularity, hypoxia, and hypovascularity.
- **Risk factors**: pre- or post-RT extraction or surgery, close to tumor, location: post mandible > ant mandible > post maxilla > ant maxilla, dental dz., dose >60 Gy, time from pre-RT extractions to start of RT < 14 d.
- **Work-up**: rule out tumor recurrence, bx PRN, imaging w CT and/or MRI
- **Presentation**: pain, swelling, trismus, exposed bone, path fx, malocclusion, oral cutaneous fistula formation.
- **Clinical criteria**: exposed bone and fistula. *But not* pain, dysesthesia, trismus, fistula
- **Radiographic criteria**: diffuse radiolucency + bone exposure and sequestration, *but not* periosteal thickening, mottled areas of osteoporosis, increased density

- **Grading**:
  - I: exposed alveolar bone
  - II: above, doesn't respond to HBO
  - III: full thickness involvement +/− path fx
- **Incidence**: 3–12%. 12% if tx prior to 1968. Three percent in studies since 1997. Rare if dose to mandible <60 Gy
- **Prevention**: dental eval, extractions of non-restorable teeth prior to RT start. Daily fluoride treatment (1% NaF gel) for life
- **Treatment**:
  - **PENTOCLO** regimen: trental 400 mg BID, vit E 500 IR, BID, clodronate 1600 mg QD, prednisone 20 mg QD, cipro 500 mg BID. Must be taken for 8–9 months. In the U.S., vit E is in 400 mg capsules. Trental reduced to BID for avoidance of vascular effects. Clodronate is not available, so Fosamax may be used.
  - **HBO**: Marx protocol is 20 dives prior to operation and 10 dives after, to 2.4 ATM × 90 min. Would do 30 + 10 dives if there is already necrosis.
  - Yes if dose to tooth >50 Gy.
  - Consider if dose 40–50 Gy.
  - No HBO if <40 Gy.

- **HBO literature**.
- ORN 96 (Annane, JCO, 2006). RCT of HBO vs sham HBO for ORN. No difference in outcomes. However, used imprecise definition of ORN compared to standard clinical practice (see criteria above), excluded grade III. Also, HBO was BID and not QD; 75% of tx group did not get full 30 dives. Sham HBO was actually ~21% O2.
- Marx (Marx, JADA, 1986). RCT of HBO (20 sessions prior +10 after extraction) vs penicillin for ORN. HBO decreased rate of ORN 30% vs 5%.

Brachial Plexopathy

- **Classical type** (unlikely w <60 Gy): chronic progressive fibrosis, variable time to onset (0.25–26 years post-RT), presents w sensory or motor sx in ipsi limb, less likely to have pain. Twenty percent of pts will develop this in 5y, more likely if treated w 3D, getting chemo.
- **Transient type**: ~4 month onset, resolves spontaneously

Thyroid Dysfunction

- **Hypothyroidism** rates in 22–48% at 5 years, ~50% at 10 years
- Check serum TSH q6m for first 5 years, then yearly

	NPX	Maxillary sinus	Nasal cavity/ Ethmoid	Salivary gland	OC	OPX	Supraglottis	Glottis	Subglottis	Hypopharynx	Thyroid	Melanoma	Skin SCC/BCC	Merkel
anatomy	Ant: choanae Post: clivus, C1, C2 Sup: sphenoid sinus Inf: soft palate		***Subsites of nasal cavity of nasal cavity: septum, floor, lateral wall, vestibule.*** Note: that most vestibule cancers are skin cancers, have different tx	Stage only applies to major salivary glands (parotid, SMG, SL). Minor salivary gland = stage as primary site!	Subsites: mucosal lips, buccal mucosa, sup and inf alveolar ridge (aka upper, lower gingiva), retromolar trigone (RMT), hard palate, floor (FOM), ant 2/3 tongue (anterior to terminal sulcus, aka vallate papillae).	**Subsites:** tonsil, (includes ATP, PTP, GTS), vallecula, BOT, PPW, soft palate	*5 Supraglottic subsites ("A VISA"): **a**rytenoids, false cords (**v**entricular bands), **i**nfrahyoid epiglottis, **s**uprahyoid epiglottis, **a**ryepiglottic folds,	TVCs, ant/post commissures	5mm below glottis to inferior cricoid or 1st tracheal ring	* 3 Hypopharynx subsites ("3 Ps"): **P**yriform sinus, Hypo**p**haryngeal wall (lateral and post), **p**ostcricoid region (mucosa overlying cricoid cartilage, w arytenoids mucosa superiorly and esophageal mucosa inferiorly) **Borders:** hyoid bone or tip of epiglottis (sup); bottom of cricoid cart or cricopharyngeus muscle (inf)			HR factors: area L > 20 mm, M >10 mm, H > 6 mm; poorly defined; recurrent; immune suppressed; prior RT; rapid growth; PNI; G3; adenoid; Clark IV+	
T1	NPX, OPX, or nasal cavity	Limited to maxillary sinus without bone erosion	1 subsite*, no bony invasion	≤2 cm w/o extraparenchy-mal extension	≤2 cm *(new in AJCC 8: and ≤5 mm DOI)*	≤2 cm	1 subsite*, normal VCs	Normal VC movement (**T1a** one cord, **T1b** both)	Subglottis only	One subsite**, ≤2 cm	T1a - ≤1cm T1b – 1-2 cm	≤1mm thick T1a – no ulcer, < 0.8mm T1b –ulcer or 0.8-1.0 mm	≤2 cm	≤2 cm
T2	Parapharyngeal space *(AJCC 8: +/- med or lat pterygoid, prevertebral muscles, carotid space)*	Invading *hard palate*, middle nasal meatus	2+ subsites* (doesn't matter if invading hard palate or middle nasal meatus)	2—4cm w/o extraparenchymal extension	2–4cm *or 5-≤10 mm*	2–4cm	2+ subsites or glottis, or region outside supraglottis (BOT [e.g. hot potato voice], vallecula, medial wall pyriform)	Supra/subglottis or VCs w impaired mobility (previously T2b)	VCs w normal mobility VCs w impaired mobility	2+ subsites, 2–4cm	2–4 cm, capsule intact	1.01-2mm thick T2a - no ulcer T2b - ulcer	2–4 cm	2–5cm
T3	Bony structures, skull base, or paranasal sinuses	Posterior wall of *maxillary sinus, subQ, orbital wall,* ***pterygoid fossa****, ethmoid*	Maxillary sinus, medial orbital wall, palate, cribriform plate ("COMP")	>4 cm or extraparenchymal extension	>4 cm *or >10 -≤20 mm DOI*	>4 cm or lingual surface of epiglottis	**Fixed cord** **P**ost-cricoid area, **p**araglottic space, **pre**-epiglottic space	**P**araglottic space	>4 cm, **esophagus**		T3a - > 4 cm but limited to thyroid T3b – Gross extrathyroidal extension into strap muscles	2.01–4mm thick T3a - no ulcer T3b - ulcer	>4cm or minor bone erosion, or *c/p/rPNI* or deep	>5cm
T4a	Intracranial,*any CNs*, infratemporal fossa, hypopharynx, orbit, parotid, masticator space, soft tissue beyond lat pterygoid, parotid gland, masseter muscle	T4a – anterior orbit, skin, **pterygoid plates**, infratemporal fossa, cribriform plate, sphenoid/frontal sinuses	Anterior orbit, skin, **pterygoid plates**, cranial fossa, sphenoid/frontal sinuses ("POS CSF")	Skin, mandible, ear canal, *CN VII*	Non-lip:>20 mm DOI, cortical bone, maxillary sinus, deep muscles of tongue (genio, hyo, stylo, palatoglossus). *Note: superficial bone does not count* lip: through cortical bone, inf alveolar N (V3), FOM, skin of face (skin, nose)	(p16- is split a/b, however p16+ is lumped together into T4 alone) larynx, deep tongue muscles, medial pterygoid, hard palate, mandible *No mention of PNI	Inner thyroid cartilage Through thyroid cartilage Beyond larynx (e.g.**esophagus,** soft tissues of neck, extrinsic tongue muscles, strap muscles, thyroid)		Cricoid, thyroid cartilage invasion (AJCC 7:*any* cartilage was T4a)	Thyroid/cricoid cartilage, hyoid, central compartment	T4a – subQ, larynx, trachea, esophagus, recurrent laryngeal, or any anaplastic	>4 mm thick T4a - no ulcer	Gross cortical bone invasion	Into bone, muscle, fascia, cartilage
T4b		Orbital apex, dura, brain, middle cranial fossa, *CNs other than V2*, nasopharynx, clivus	Orbital apex, dura, brain, middle cranial fossa, *CNs other than V2*, nasopharynx, clivus	Skull base, **pterygoid plates**, carotid	Masticator space, **pterygoid plates**, skull base, encases carotid	Lateral pterygoid (e.g. trismus < 4 cm),**pterygoid plates**, lateral nasopharynx, skull base, carotid	Prevertebral space, carotid, mediastinum				T4b – prevertebral fascia, carotid, mediastinum (anaplastic out of thyroid)	T4b – ulcer	BOS	

	NPX **EBV + SCCUP (T0 NPX)**	**OPX p16+** **p16+ SCCUP (T0 OPX)**		**Maxillary sinus** **Nasal cavity** **OC** **OPX p16-** **SCCUP p16- and EBV-** **All LX** **HPX** **All Salivary** **Skin SCC, BCC**		**Thyroid**	**Melanoma**	**Merkel**	
		cN	pN	cN	pN			cN	pN
What is important?	6 cm, ipsi/bilateral, above vs below cricoid	6 cm, ipsi/contra/bilateral	4 vs 4+	3 cm/6 cm, ipsi/contra/bilateral, single/multiple, ECE	3 cm/6 cm, ipsi/contra/bilateral, single/multiple, ECE	VI-VII (central) vs I-V (lat) or RP	1 vs 2–3 vs 4+ occult vs matted	Regional vs in transit	Regional vs in transit
N1	**Unilateral**, ≤6 cm, above inf cricoid; or any RPs	Ipsi nodes, all ≤ 6 cm	≤ 4 nodes, any location	**Single ipsi node ≤ 3 cm**, no ECE	**Single ipsi node ≤ 3 cm**, no ECE	N1a – level VI-VII N1b – level I-V or RPs	1 node N1a – clinically occult node (SLNBx) N1b – clinically apparent node N1c – no nodes, but in-transit/satellite/microsatellite	Regional	pN1a: clinically occult LNs pN1b: clinically apparent LNs
N2	**Bilateral**, ≤6cm, above inf cricoid	Contra or bilateral, all ≤ 6 cm	> 4 nodes, any location	N2a: Single ipsi, **3–6 cm**, no ECE	Single ipsi, **3–6 cm**, no ECE; *or* **ipsi/contra < 3 cm with ECE+**		2–3 nodes N2a – clinically occult N2b – at least one clinically apparent N2c – 1 clinical node, and in-transit/satellite/microsatellite	In transit mets, no LNs	In transit mets, no nodes
				N2b: **Multiple ipsi**, ≤6cm, no ECE	Multiple ipsi, 3-6 cm, no ECE				
				N2c: **Bilateral or contralat**, ≤6 cm, no ECE	Bilateral or contralat, 3-6 cm, no ECE				
N3	**>6 cm** and/or **below inf cricoid**	Any node **> 6 cm**		N3a: **>6 cm**, no ECE	**>6 cm**, no ECE		≥4 nodes N3a - ≥4 nodes, all occult N3b - ≥4 nodes some felt, or matted nodes N3c –2+ clinical nodes, and in-transit/satellite/microsatellite	In transit mets AND nodes	In transit mets AND nodes
				N3b: **Any clinically overt ECE**	**Single >3 cm with ECE**; *or* **multi nodes with any ECE+**				

Ocular/Uveal Melanoma [19–29]

COMS staging				
	Apical height (AH)	Basal diameter (BD)	10yr OS	Treatment
Small	≤3 mm	≤5 mm	80%	Observation or local therapy. 33% progress with obs
Medium	3–8 mm	<16mm	60%	Enucleation, plaque, SRS (25–40Gy to 50% isodose), or protons (56 cGyE)
Large	>8 mm	>16 mm	40%	Enucleation (SOC) or protons. Protons best as substitute for BT or enucleation and for tumors near macula or near orbital muscles
Diffuse	Thickness <20% basal			
Metastatic	N1, M1		<7 m	

Overview

- 2000 cases/yr (1/3 asymptomatic), 4/1 million.
- 98% Caucasians.
- Ocular melanoma is the #1 eye malignancy of primary cancers.
- Usually arises from choroid (85%) > adnexa (10%) > conjunctiva (5%).
- Melanocytes of uveal stroma (neural crest origin) give rise to ocular melanoma.
- 1–2% present w DM. Usually mets to liver (90%). Twenty percent will had DM over 5y, 50% at 15y.
- BAP1 inactivation found in most ocular melanoma.

Anatomy

- Layers of globe: outer fibrous layer (sclera), middle vascular layer (choroid), inner nerve layer (retina)
- Macular important for color vision
- Optic disk is 2 mm medial to macula, 1.5 mm diameter

Presentation Thirty percent asymptomatic. Most have vision loss, scotoma, flashing lights.

Work-up H&P, eye exam, slit lamp, B-scan u/s, LFTs, liver u/s, biopsy *not* necessary

Histology Spindle cell (best), mixed, epithelioid (worst)

Trials

- COMS 1997: obs small tumors. Five-yr OS 94%, 33% progressed
- COMS 28, 2006: (COMS medium)→enucleation vs eye plaque. Same 12-yr OS (~20%), 13% of plaque pts ended up getting enucleations 2/2 tumor or pain
- COMS medium, Quivey 1993: retrospective I-125. 13% local failure at 5y, due to tx failure or pain from BT complications
- COMS large: preop RT does not improve DFS or OS between two tx groups.

Plaque Technique

- I-125 seeds, 0.7–1 Gy/h. Treatment time 4–7 days.
- Ru-106, a beta emitter may be used, because it has limited dose penetration vs I-125, so it results in less toxicity and is easier to insert.
- 85 Gy to apex (if less than 5 mm apex→Rx to 5 mm).
- 2 mm around tumor.
- LC 93%.

Protons

- 70 Cobalt Gy Equivalent in 5 fractions over 10 days
- LC 93%

Toxicity

- Loss of vision: 50% of pts lose >5 lines vision
- Cataracts: 83%

Nasopharyngeal (NPX) Cancer [19–23, 30–41]

- **T1** – NPX, OPX, or nasal cavity
- **T2** – parapharyngeal space (*AJCC 8 adds: +/− med or lat pterygoid, prevertebral muscles, carotid space*)
- **T3** – bony structures, skull base, or paranasal sinuses
- **T4** – intracranial, CNs, infratemporal fossa, hypopharynx, orbit, parotid, masticator space, soft tissue beyond lat pterygoid, parotid gland, masseter muscle

– **N1** – **unilateral**, ≤6 cm, above inf cricoid, or any RPs
– **N2** – **bilateral**, ≤6 cm, above cricoid
– **N3** – **>6 cm** or **below cricoid cartilage**

	T1	T2	T3	T4
N0	I	II	III	IVA
N1	II	II	III	
N2	III	III	III	
N3	IVA			
M1	IVB			

Pathology

WHO	Old WHO	keratin	EBV assoc?	Differentiated	Notes
I		Keratinizing	N	Differentiated	Smokers, radioresistant, U.S.
II	IIA	Non-keratinizing (EBV associated)	Y	Differentiated	
III	IIB		Y	Undiff, lymphoepithelioma	
Basaloid					Rare

– EBV: titers >1500 copies/ml→ ↓OS. Persistent EBV after tx → ↓OS (Lin et al)
– EBV/HPV
  – EBV+: best prognosis
  – HPV+: intermediate
  – EBV-/HPV-: poor prognosis
– 70% cN+, 90% pN+, 50% BL N+
– Poor prognosticators: high stage, male, age > ~45, WHO I, high EBV (>1500 copies/mL), detectable EBV after RT

	LRC w RT alone, %
T1–2	75–95
T3–4	50–75
N0–1	90
N–3	70

Anatomy

– Borders
  – Ant: choanae
  – Post: clivus, C1, C2
  – Sup: sphenoid sinus
  – Inf: soft palate
  – Lat: eustachian tube, torus tubarius, fossa of Rosenmuller (deep is parapharyngeal space)
– **Villaret/Jugular foramen syndrome**: parapharyngeal space invasion (CN IX-XII, sympathetic nerve palsy)
  – Jugular foramen: IX, X, XI
  – Hypoglossal canal: XII
– **Foramen Spinosum**: middle meningeal artery/vein, CN V3 recurrent branch, lesser superficial petrosal nerve
– **Foramen Rotundum**: V2
– **Foramen Ovale**: V3, lesser petrosal nerve, accessory meningeal art, emissary veins
– **Foramen Lacerum**: carotid→cavernous sinus→cranial fossa (Jacod syndrome)
– **Cavernous sinus**: carotid, III, IV, V1, V2, VI
– **Triangle of Ho**: superior clavicle point where the neck meets the shoulder

Workup

– H/P: hearing loss, otalgia; nasal congestion, epistaxis
  • CN deficits (vision) or trismus.
  • First nerve affected: CN VI through foramen lacerum, then V1 and V2
  • If spread through foramen rotundum: V2 and V3

  - If parapharyngeal extension: IX-XI
  - Trismus bc of involvement of masticator space
- Usually presents w unilat LN mass (75%) or bilat LN masses (505). M+ in 5–10%.
- H&P, FNL, otoscopy, CN exam, labs (EBV IgA/DNA).
- MRI (thin cuts), CT w con, PET-CT.
- Level 5 LAD is suspicious for NPX cancer.
- Parapharyngeal tumors (differential): paraganglioma, schwannoma, sarcoma.
- Level 4 LAD is suspicious for malignancy below clavicles (e.g., lung, breast, cervix).
- DDx: lymphoma, minor salivary gland tumor, plasmacytoma, melanoma, chordoma, RMS.

RT +/– chemo
- Al-Sarraf, 1998. Int 0099 / RTOG 88–18 (mostly WHO I) stage III/IV:70/35 + – HD cis d1,22,43 and adj cis/5FU q4w × 3c. RT to GTV + 2 cm margin was 70 Gy. cN- neck gets 50. LNs <2 cm get 66 Gy. CRT won; 3-yr OS 47→78%, PFS 24→65%. Purportedly the largest OS difference in a RCT? Mostly WHO I, which is radioresistant.
- Wee, 2005: confirmed Int 0999 for WHO III: 2-yr OS 78→85%
- Chen, 2005: RT +/– LD cis: 59→70%, lower toxicity
- Baujet: meta-analysis, chemo improved OS when given concurrent
- Chen 2012: NPX Stage III/IV, but not T3–4No. CRT +/–adj cis/5FU. Cis is 40 mg/m^2 qw × 7c. RT was 2–2.27 Gy/fx to 66 Gy to primary, or 60–66 to involved neck. Adj chemo was 80 mg/m^2 cis and 800 mg/m^2 5-FU for 120 h q4w for 3c. no benefit to added chemo for FFS, OS, DMFS, LCFS, long-term data pending. Not designed as noninferiority. Twenty percent of pts randomized to adj chemo arm did not actually get adj chemo.
- Blanchard, 2015: meta-analysis: CRT improves OS by 5% vs RT alone.

Neoadj Chemo
- Debated, mostly no benefit in phase III trials

IMRT
- Lee et al. IMRT to 70 Gy: 4-yr OS 88%, LRC 87%.
- RTOG 0225: phase II to investigate feasibility of IMRT w or w/o chemo, assess toxicity, failure patterns, survival. GTV based on MRI, PET, CT. Treatment; 70 Gy at 2.12, 59.4 at 1.8, 50.4 at 1.8 w/ cis + adj cis/5FU. All SIB.
  - CTV70 = GTV + 5 mm.
  - CTV 59.4 = CTV-70 + 5 mm + areas at risk for microscopic involvement, including NPX, RP LNs, skull base, clivus, pterygoid fossae, sphenoid sinus, posterior 1/3 of nasal cavity/max sinuses, including pterygopalatine fossae and levels I–V.
  - CTV 50.4/1.8 = optional inclusion of low neck; otherwise, could use split field, and treat to 50.4
  - PTV margin = 3–5 mm. May reduce to 1 mm near brainstem. Two-yr LRC 91%, OS 79%. Note this is a benchmark vs historical control (at 50–70%)
- RTOG 0615.
- Kam (2007): IMRT has lower xerostomia vs 2D: 39% vs 82%.
- Pow (2006) IMRT has better recover of pre-RT whole saliva (50% vs 5%) and parotid saliva (83% vs 10%).

Sim
- Dental eval, Aquaplast, supine, MRI fusion.
- CT sim through BOS should be 1–2 mm slices. Can be 3 mm through the neck.

NCCN

T1N0 →**RT alone**
- 70(2)/63(1.8)/56(1.6) in 33 fractions
- b/l: RP, II-V w/ RSS

≥T2 or N+ CRT → chemo
- 70(2.12)/59.4(1.8)/54.12(1.64) in 33 fractions
- cN0: RP, II-V w/ RSS
- cN+: RP + IB-V w/ RSS
- Cis (100 mg/m^2) days 1, 22, 43 → Cis/5-FU × 3
  - *residual disease → neck dissection
- **Metastatic**: chemo. Focal RT for palliation

CTV70 = 70Gy in 2Gy fx to primary + positive nodes
- Any abnormal LN is suspicious (>10 mm short-axis or centrally necrotic).
- CTV70 = GTV + 3 mm (per HN-001).
- Nancy Lee: CTV70: @2.12 = GTV.
- PTV = CTV + 3 mm.

CTV63 = 63 Gy/35 fx to 1st echelon LN:
- High-risk subclinical disease including CTV70 + 5–10 mm, **entire NPX**, anterior 1/3 **clivus** (entire if involved), **skull base** including bilateral **foramen ovale** (V3) and **foramen rotundum** (V2), bilateral **pterygoid fossa** (V2) and **parapharyngeal space**, inferior **sphenoid sinus**, posterior 1/4 nasal cavity and maxillary sinuses (covering **pterygopalatine fossa** where V2 resides), and **soft palate inferiorly** always include **retrostyloid space** (inf edge of transverse process of C1 to BOS).
- **Pterygoid fossa** is bordered by the medial and lateral pterygoid plates and contains the medial pterygoid muscle.
- T3/T4: add **entire sphenoid sinus and cavernous sinus.**
- Nancy Lee: CTV59.4 at 1.8 = nasopharynx, sphenoid sinus, cavernous sinus, skull base, clivus, RPN, post 1/3 maxillary, post 1/3 nasal, pteryopalatine fossa (V2), pterygopharyngeal space (V3).

CTV56 = 56Gy/35fx to elective LN
- Always treat bilateral levels **II–V (including VB), RP, Sclav. Ib in cN+ neck.**
- cN0: consider omitting IB.
- Nancy Lee: CTV 54 at 1.64

Dose Limits
- Target coverage:
  D95 (dose to 95% of the PTV) ≥100% Rx
  D99 (dose to 99% of the PTV) ≥93% Rx
  Dmax: no more than 110% Rx dose
- Brainstem: 54 Gy (60 Gy max)
- Optics: 54 Gy
- Retina 45 Gy, lens 10 Gy
- Parotid mean < 26Gy
- Inner ear <50 Gy
- Larynx: V50 < 30%

Not Meeting Constraints Shrink PTV margin to 1 mm if using Exactrac; go w QUANTEC constraints (up to 59 to brainstem); induction chemo instead of adjuvant; hyperfractionation

Follow-up
- q3 mo × 1 year, **q4** mo × 2 years, **q6** mo for years 3, 4, and 5
- **Follow-up of initially positive neck**:
  - Reimage with PET/CT in 12 weeks
  - If node (+) on PET, do FNA
    - If FNA (+), send for neck dissection
  - If node (−) on PET, observe

Maxillary Sinus Cancer
[19–23, 42–44]

- **T1** – limited to maxillary sinus without bone erosion
- **T2** – invading *hard palate*, middle nasal meatus
- **T3** – posterior wall of *maxillary sinus, subQ, orbital wall, pterygoid fossa, ethmoid*
- **T4** -
  - T4a – anterior orbit, skin, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid/frontal sinuses
  - T4b – orbital apex, dura, brain, middle cranial fossa, CNs other than V2, nasopharynx, clivus

    Note pterygoid plate is T4a; pterygoid fossa is T3

	T1	T2	T3	T4a	T4b
N0	I	II	III	IVA	IVB
N1	III	III	III		
N2	IVA				
N3	IVB				
M1	IVC				

Anatomy
CN V2 is the most likely CN to be involved.

Studies
– Le et al. 2000: retrospective, +/− surgery, +/− RT: 20% neck failure without ENI but 0% neck failure with ENI
– Bristol et al. 2007: retrospective, surgery + adj RT: clinical outcomes similar but justifies base of skull and ENI coverage in at-risk patients

NCCN
Resectable = Sx +/− PORT

PORT indications

1. + margin
2. PNI
3. ACC
4. Locally advanced (pT3-T4)
5. N+
6. Undifferentiated

Neck RT indications Cover ipsi neck only, unless tumor crosses midline or invades structures with bilateral lymphatics (i.e., nasal cavity, soft palate, upper lip)

1. pT3-T4
2. N+
3. Undifferentiated

cN1	Single ipsi node ≤3 cm, no ECE	**pN1**	Single ipsi node ≤3 cm, no ECE
cN2		**pN2**	
cN2a	Single ipsi, 3–6 cm, no ECE	pN2a	Single ipsi, 3–6 cm, no ECE; OR <3 cm with ECE
cN2b	Multiple ipsi, 3–6 cm, no ECE	pN2b	Multiple ipsi, 3–6 cm, no ECE
cN2c	Bilateral or contralat, 3–6 cm, no ECE	pN2c	Bilateral or contralat, 3–6 cm, no ECE
cN3		**pN3**	
cN3a	>6 cm, no ECE	pN3a	>6 cm, no ECE
cN3a	Any clinically overt ECE	pN3b	Single >3 cm with ECE; *or* multi-nodes with any ECE

Maxillary Sinus RT Volumes
– Post-op RT dose and coverage for MAXILLARY primary:
  – CTV60–63 = surgical bed and grossly enlarged nodes preop (2–2.12Gy × 30 fractions)
  – CTV50–54 = CTV60 + 1 cm mgn and ipsi maxillary sinus, nasal cavity, ethmoid sinus, ipsi PPF, pterygoid space, and NPX (CTV P)
    - ipsi level IB, II, RP, RSS if indicated (CTV N) (1.7–1.8Gy × 30 fractions)
  – *__Bilateral__ neck if invades the nasal cavity, soft palate, upper lip
  – If PNI present, cover cranial nerve to base of skull foramina (e.g., if V2 involved, go to foramen rotundum, cavernous sinus)
– Treatment of the neck
  – Controversial. Consider elective nodal coverage for T3-T4 or undifferentiated histology. If so, cover level IB-II and RP

Nasal Cavity (Aka Nasal Fossa) and Ethmoid Sinus Cancer [19–23, 42–46]

- **T1** – one subsite*, no bony invasion
- **T2** – two subsites*, +/− bony invasion (doesn't matter if invading hard palate or middle nasal meatus)
- **T3** – maxillary sinus, medial orbital wall, palate, cribriform plate ("COMP")
- **T4** -
  - T4a – anterior orbit, skin, pterygoid plates, cranial fossa, sphenoid/frontal sinuses ("POS CSF")
  - T4b – orbital apex, dura, brain, middle cranial fossa, CNs other than V2, nasopharynx, clivus

***Subsites of nasal cavity:** septum, floor, lateral wall, vestibule. Note that most vestibule cancers are skin cancers and have different tx.

Wang Classification for Nasal Vestibule Carcinoma

- T1 – superficial
- T2 – skin of nose, upper lip, nasal septum
- T3 – bone (e.g., paranasal sinus, hard palate, turbinates, septum, buccogingival sulcus)

Esthesioneuroblastoma, Kadish Staging

A: Confined to nasal cavity
B: Nasal cavity + paranasal sinus
C: Beyond nasal cavity/paranasal sinus
D: LN or distant mets

Histology (MDACC/Allen, 2008)
– SCC most common (60–80%), also Adenoid cystic (18%), minor salivary gland, plasmacytoma, lymphoma, SNUC (4%), etc.

Outcomes (5y OS)
– SCC, Adeno, ACC = 50–60% (SCC > Adeno)
– SNUC = 30%

Anatomy
– **Nasal cavity** borders: limen nasi (ant), choana (post), hard palate (inf), BOS (sup), mucosa-covered bone (lateral walls) w 3 turbinates.
– **Communications w nasal cavity:** NPX; nasal vestibule.
– **Paranasal sinuses (4 in #):** frontal, ethmoid, maxillary, and sphenoid. These drain primarily to RP LNs.
– Lamina papyracea: medial wall of orbit (thin bone).
– Ohngren's Line: medial canthus to angle of mandible (superior-posterior to this is worse).
– Lymph drains to IB, parotid, RPN, and II.
– Paranasal sinuses have limited lymph and capillary supply, so incidence of cervical LN+ is 5–10%, higher if invasion into sites w extensive LN drainage (OC, skin, NPX).
– Cantu (2008): n = 704 pts w paranasal sinus tumors. Two percent of ethmoid cancers had cLN+; 8% of maxillary cancers had cLN+. Incidence of LN recurrence 4% for ethmoid group, 12% maxillary sinus.

Work-up
– H&P, FNL, CN exam, biopsy
– CT/MRI, CT chest, +/− PET

Nasal Cavity Studies
– Dulguerov et al. 2001: mixed group, 5-yr OS 40%, LRC 59%. Worse prognosis: pterygomaxillary fossa, frontal/sphenoid sinuses, cribriform/dural erosion. If periorbital fat or ocular muscle invasion →enucleation (no enucleation if just bone)

Management
– T1 or T2 lesions located in the infrastructure: surgery alone (usually partial (or total) maxillectomy to neg. margins).
– T3 or T4 lesions in patients that can undergo surgery; the combination of surgery and RT (usually postoperative) is the treatment of choice.
– Radical maxillectomy +/− orbital exenteration is often necessary.

- Indications for adjuvant radiation therapy include:
  - T1N0 w positive margins
  - Consider for T2N0
  - T3 or T4
  - Perineural invasion
  - Adenoid cystic histology
  - For any N+, add neck RT
- Radiation therapy alone can be used as a primary modality for inoperable patients.

Chemo?

- Sinus cancers are not included in post-op CRT trials, but indications (i.e., margins, ECE) usually extrapolated from SCC histology.

Historical Treatment

3D-CRT w 4 field: AP photons, wedged opposed la photons, and interorbital anterior electron field. Wedge pairs were also used.

Sinus Sim/Planning (Based on Nancy Lee's Recs)

- Dentistry, supine, mask, eyes straight, bite block.
- Diagnostic MRI co-registered with planning CT for contouring.
- Standard is 1.8–2 Gy daily.
  - 50 Gy if neoadjuvant
  - 60–66 if post-op
  - 70 Gy if definitive
- Esthesioneuroblastoma can do cist/estopo x2 cycles, then 50 Gy (with ENI), then resection.
- Dose limits:
  - Brainstem: 54 Gy (60 Gy max)
  - Optics: 54 Gy
  - Retina 45 Gy, lens 10 Gy
  - Parotid mean < 26Gy
  - Pituitary/thyroid (62% develop hormone deficiencies)

NCCN

- Resectable: surgery + RT for T3, T4,+margin, PNI, ACC, ethmoid (all ethmoid tumors need adj RT)
  - Add chemo for +margin, ECE, SNUC
  - 60–66 Gy to primary, 50–54 to necks
- T2+/N + = Sx → PORT
  - 66/60/54 (same for all nasal cavity/paranasal sinus)
    - Bilateral IB-II
- N+: IB, RSS/II-V
- *posterior 2/3 involvement: cover RP nodes
- *nasal vestibule involvement: cover facial nodes
- Unresectable: chemo-RT to 70 Gy, cisplatin
- When to cover elective LNs in N0 dz: (1) involvement of NPX bc of high rate of lymphatic spread; (2) T3/4; (3) PNI, G3–4, olfactory neuroblastoma
- LN volumes controversial
- Consider alt fractionation for tissue sparing
  - Accelerated: BID once per week (6 fx/wk)
  - Concomitant boost: BID last 2 wks
  - Hyperfractionation: BID throughout
  - CTV1 = GTV + 1–1.5 cm margin, modified at natural barriers + ENI (bilateral RP + level II-IV)
  - Phase I (initial volume): 48.4 Gy in 44 fx at 1.1 Gy BID
  - CTV2 = GTV + 0.5–1 cm margin, modified by natural barriers.
    - Phase II (small field boost): 24.2 Gy in 22 fx @ 1.1 Gy BID
    - PTV = CTV + 3 mm
    - Total PTV dose: 72.6 Gy in 66 fx @ 1.1 Gy BID
    - IMRT preferred for normal tissue sparing
    - Preop RT or CRT to 50 Gy accepted

SNUC

- A, B, C = Surgery → PORT (for low-grade A, can consider RT alone)
- B, C = + bilateral RP, IB-II
- Consider adj cis/etop bc SRBCT

Nasal NK/T-cell Lymphoma/Lethal Midline Granuloma [47, 48]

Overview
- Locally aggressive extranodal lymphoma that can lead to progressive midline facial destruction.
- Usually originates from NK cell, sometimes from cytotoxic T cells
- Sometimes EBV associated.
- Isobe, 2006: Doses >50 Gy had improved LC.
- Kim, 2009: Concurrent CRT is best tx option.

Sites
- Nasal cavity/paranasal sinus
- Waldeyer's ring (more aggressive, usually nodal involvement +/− advanced stage)

Workup
- H&P: ENT exam, nasopharyngoscopy, testicular exam, skin exam
- Labs: CBC/CMP/LDH, serum EBV
- Procedures/imaging:
  - Biopsy tumor: stain for CD56 and pcr for EBV
  - PET/CT and CT w/ contrast and MRI of head and neck
  - BM biopsy

Treatment

Localized (Stage I–II)
- Concurrent Chemo-RT (**50 Gy/2 Gy fractions**) to involved dz w/ concurrent **cisplatinum** → 3c DeVIC (Dexamethasone, Etoposide (VP-16), Ifosfamide, Carboplatin)
- Unfit for chemo = RT alone (**54 Gy**)

Stage IV
- Concurrent chemo-RT → likely transplant

RT Targets
- Stage IE → primary site only
  - Cover nasal cavity and adjacent paranasal sinuses
  - If posterior nasal tumor, include nasopharynx
  - If adjacent structures involved, include those too
- Stage IIE (i.e., N+) → include involved nodal levels, but no ENI

Outcomes
- OS5 70%

Oral Cavity (OC) Cancer [19–23, 49–66]

	T1	T2	T3	T4a	T4b
N0	I	II	III	IVA	IVB
N1	III	III	III		
N2	IVA				
N3	IVB				
M1	IVC				

- **T1** – ≤2 cm and ≤5 mm DOI (note DOI new in AJCC8 vs 7)
- **T2** – 2–4 cm or >5 – ≤10 mm DOI
- **T3** – >4 cm or >10 mm DOI
- **T4**
  - T4a (everything but lip) – cortical bone, maxillary sinus, deep muscles of tongue (genio, hyo, stylo, palatoglossus). *Note: superficial bone does not count.*
  - T4a (lip) – through the cortical bone, inf alveolar N (V3), FOM, skin of face (chin, nose)
  - T4b – masticator space, pterygoid plates, skull base, encases carotid

cN1	Single ipsi node ≤3 cm, no ECE	**pN1**	Single ipsi node ≤3 cm, no ECE
cN2		**pN2**	
cN2a	Single ipsi, 3–6 cm, no ECE	pN2a	Single ipsi, 3–6 cm, no ECE; *or* <3 cm with ECE+
cN2b	Multiple ipsi, 3–6 cm, no ECE	pN2b	Multiple ipsi, 3–6 cm, no ECE
cN2c	Bilateral or contralat, 3–6 cm, no ECE	pN2c	Bilateral or contralat, 3–6 cm, no ECE
cN3		**pN3**	
cN3a	>6 cm, no ECE	pN3a	>6 cm, no ECE
cN3b	Any clinically overt ECE	pN3b	Single >3 cm with ECE, *or* multi-nodes with any ECE+

Anatomy

– **Subsites**: mucosal lips (most common), FOM (2nd most common), buccal mucosa, superior alveolar ridge (aka upper gingiva), inferior alveolar ridge (aka lower gingiva), retromolar trigone (RMT), hard palate, ant 2/3 tongue (anterior to terminal sulcus, aka vallate papillae).
  - The circumvallate papilla differentiates the oral tongue from BOT; on axial CT it is separated by uvula.
– **Extrinsic tongue muscles**: genioglossus, styloglossus, palatoglossus, hyoglossus

	5y OS
Lip	89%
Oral tongue	65%
FOM	52%
Gum	59%

LN drainage

Lip

– Upper (10%, worse prognosis) → Facial, IB, II
– Lower (90%) → IA, IB, II
– Oral commissure → 15% LN risk

Alveolar Ridge

– Lower (80%), often involves molars, presents as ill-fitting dentures
– Alveolar ridge w/ PNI need to cover length of IAN

RMT

– Anterior spread along alveolar ridge, IAN
– Pterygomandibular raphe → masticator space and FOM

Oral Tongue

– LN drainage
  - Tip of tongue = IA
  - Anterior tongue = IB and III
  - Posterior tongue = IB and II

- Anterior and midline = more likely to be bilateral
  - 5% bilateral overall
  - If N+ ipsilateral, 30% bilateral

Floor of Mouth
- DOI ≥ 1.5 mm = high risk of LN involvement, therefore needs neck dissection
- LN drainage = IB
- Often invades oral tongue, alveolar ridge, and mandible
- Mylohyoid muscle divides sublingual space from submandibular space

Workup
- H&P
- Tobacco, ETOH, poor hygiene, betel/areca nuts
- Oral leukoplakia (10% risk)
- Erythroplakia (30% risk)
- CN XII, motor; CN V, sensory; CN VII, taste (BOT CN IX taste)
- Otalgia: auriculotemporal nerve (CN V3)
- palpation, FNL, CN exam, bx, labs
- MRI + CT, CT chest, +/− PET
- Dentistry

Studies

Altered Fractionation (No Chemo)
- RTOG 9003: advanced H&N SCC→ 70/35 (std) vs 81.6 at 1.2 BID (hyperfrac) vs 67.2 at 1.6 BID split (split) vs 72 w/ last 12fx BID (conboost). Hyperfrac and Conboost won (LRC 54%, DFS 39%, OS 53%). ↑toxicity
- MARCH meta-analysis: 6515 pts. 3.4% OS benefit at 5 years for altered fractionation, mostly for young pts

Chemo-RT
- MACH-NC meta-analysis, Pignon, 2009: 17,346 pts from 87 RCTs. Median 5.6y follow-up. At 5y, 4.5% OS benefit with any chemotherapy (neoadjuvant, concurrent, adjuvant), HR 0.88. The greatest benefit with concurrent (6.5%). Platinum-monotherapy is a gold standard, no benefit if age >71.
- MACH-NC update, Blanchard, 2011: benefit broken down by dz sites:
  - OC: 9%, NSS
  - OPX: 8%, SS
  - LX: 5%, SS
  - HPX: 4%, NSS

Post-op RT, CRT
- Ang 2001: OC SCC: *n* = 213. Aim to determine validity of previously reported path risk factors. All pts had surgery. RFs were then: primary site (OC), +margin, PNI, ECE, number and location of post LNs. Pts w no risk factors (low risk) observed. Pts w 1 RF besides ECE (intermed risk) got 57.6/32. Pts w 2 RFs or ECE (high risk) randomized to either CFRT 63/35 in 6.5 w vs AFRT 63/35 in 5 wks. Risk groups were validated and had ↑failure without post-op RT. For high risk, trend for improved LRC and OS for AFRT vs CFRT.
- EORTC 22931: operable stage III/IV H&N SCC of OC, OP, larynx, hypopharynx. pT3–4 any nodal, except T3N0 of LX, w R0, or T1–2 w N2–3 M0. Patients w Stage T1–2 N0–1 w unfavorable path findings (e.g., ECE, R+, PNI, LVI) also eligible. Randomize: post-op 66/33 +/− concurrent cisplatin (100 mg/m^2 Q3wks). CRT won: 5-yr DFS 36→47%, OS 40→53%, LRC 69→82% (DM unchanged ~25%). ↑toxicity (21→41%).
- RTOG 9501: operable H&N (≥2 LN, ECE, +margin): 66/33 +/− concurrent cisplatin (100 mg/m^2 Q3wks): CRT won: 2 yr DFS 43→54%, LRC 72→82%, trend for OS. ↑toxicity.
- Meta-analysis of 9501 and 22,931: CRT improved OS, DFS and LRC for ECE or + margins. Trend for stage III/IV, PNI, LVSI, low neck nodes.
- MDACC: Peters, *IJROBP*, 1993, RCT to determine optimal dose. Pts stratified by adverse path features (e.g., ECE, SMs, 2+ LN+, T stage, PNI, OC primary) into low and high risk. Subsequently, low-risk patients observed. Intermediate-risk patients randomized to 57.6 Gy/32 or 63 Gy/35; high risk to

63 Gy/35 or 68.4 Gy /38. <54 Gy had higher failure. ECE >63 Gy. # adverse features (0–1; 2–3; ECE; 4 or greater; in order or worsening prognosis) predicted for poorer LRC. 4+ negative factors had a similar LRC to ECE.

Post-op RT Timing
- Daly, Stanford, IJROBP, 2011: 37 pts. Worse LC if initiating >6w after vs <6w: LC was 80% vs 40%. Also noted difference in treatment package time of > vs <12 w.

Surgery and Pathology
- Finding PNI raises risk of LR by 20–40%. PNI likely not sign of neurotropism (like in melanoma or adenoid cystic) but for SM.
- Finding LVI likely increases risk of LNMs (similar to cervical cancer).

Neck Dissection
- For oral SCC neck dissection needs at least 16 LNs
- **Tata Memorial / D'Cruz, NEJM, 2016**: ipsi elective ND vs therapeutic ND (at time of relapse) for cT1–2N0 OC SCC. *n* = 500. At 3 y, END had improved OS 80% vs 68%. Rate of LN positivity in END arm is 30%. Correlated with DOI: 3 mm = 6%, for 4 mm = 17%. Rate of adverse events 6.6% vs 3.6%. Thus, need ND if 3+ mm DOI. Thirty-three percent of END group recurred vs 58% in the therapeutic ND recurred. Of the therapeutic ND pts who recurred, 53% died of PD, emphasizing limited success of salvage.

Sim/Planning
- Dental eval, PEG?, aquaplast, supine, bite block
- Sim: supine on head rest, neck extended, shoulders down, immobilization with thermoplastic mask, wire scars/nodes, IV contrast, Iso typically placed at thyroid cartilage notch. Bolus for tumor invading skin/violated neck w/ECE

Volumes
- CTV66 = include areas at very high risk of recurrence such as close/+mgn and ECE, though volume should be kept as small as possible
- CTV60 = preop GTV + entire post-op bed including residual tongue, BOT, FOM, glossotonsillar sulcus, and anterior tonsillar pillar (CTV P):
  - For R0 resection in pT4 mandible, go 1 cm into bone
  - For midline OC tumor, always treat contra IB
  - If pN+, include ipsilateral hemineck (CTV N)
    - Note: if using LAN to 50 Gy, can do 10 Gy ipsi boost on involved side
  - CTV54–56 = low-risk subclinical disease, often contralateral neck, ipsi RSS
- Dose limits:
  - Cord <45 Gy max
  - Parotid mean <26Gy
  - Larynx mean <43.5 Gy
  - Mandible <70 Gy max

Management

General Oral Cavity

T1–2N0
- Surgical resection preferred
- No commissure involvement: surgery (Mohs or WLE). Indications for adj RT: + margin, PNI, LVI. Oral Tongue requiring LND: >3 mm DOI, grade 3, +LVSI, recurrence
- Adequate margin in OC SCC: 1 cm (1.5 cm for tongue)
- Commissure involved: RT 66–70 Gy to primary only
- EBRT and BT generally not done as definitive therapy for oral cavity because of morbidity.
- EBRT + brachy boost (50Gy + 21Gy/7fx HDR boost)
- For HDR, must be >1 cm from mandible

T3–4N0
- Surgical resection +/− neck dissection
- Concurrent CDDP chemo with RT 70 Gy standard frac, treat full neck inc LAN for T4N0
- Altered frac RT 70 Gy alone for T3
- Bone/nerve invasion = Surgery + RT (RT alone = 90% LF)

N+

- Surgical resection (w/ reconstruction prn) and neck dissection (preferred). Post-op RT: pT3/4, close margin, multiple LN, PNI, and LVSI
- Concurrent cisplatin with RT 70 Gy /35fx to primary/involved LN; 50–63/1.8–2Gy/fx
- EBRT + brachy boost (50Gy + 21Gy/7fx HDR boost)

Lip

- Commissure involvement→↑nodal risk
- Surgery preferred unless concern for post-op function. ND for: >3 mm DOI, T2+
- T1/2: electrons (+bolus), orthovoltage, brachy (50/25 + boost of 10–16 Gy), no neck tx
  - Upper lip = bilateral facial, IB, II
  - Lower lip = bilateral IA, IB, II
- T3: 50/25 + boost of 20 Gy, treat neck levels I/II
- T4 or N+: same as T3 but treat neck I-IV

Oral Tongue

T1–2N0

- Surgery – hemiglossectomy + elective neck dissection for T2 (and lesions >1.5 mm: 30% fail in neck)
- Adjuvant (C)RT for high-risk features. Volumes:
  - Consider covering the entire residual tongue in post-op volume.
  - CTV_66 = + margin/gross residual/ECE. If extensive PNI, consider tracing V3 to foramen ovale.
  - CTV_60 = cN+ neck; +tumor Bed, entire oral tongue (+muscles), BOT, GTS, ATP, FOM.
  - CTV_54 = cN0 neck. Cover bilateral levels I-IV for oral tongue primary; RP nodes rarely involved. If II-III involved, cover RSS and V. Unilateral neck RT can be considered for a well-lateralized T1–2 lesion not including anterior 1/3 of tongue, though controversial.
  - PTVs = CTVs +5 mm.
  - If chemo RT indications, then Cis (100 mg/m^2), days 1, 22, 43.

T3–4N+

- 1. Surgery + post-op RT +/− concurrent chemo
- RT dose: 60Gy/30fx to primary/involved LN levels; 54Gy/30fx (1.8Gy/fx) to elective LN, Boost ECE/positive margin to 66Gy/30fx.
- 2. Definitive Chemoradiation with cisplatin, less preferred than upfront surgery
- RT dose (EBRT alone): 70Gy/35fx to primary and involved LN, 56Gy to intermediate risk

Oropharyngeal (OPX) Cancer
[19–23, 49–61, 67–73]

- **T1** – ≤2 cm [74–77]
- **T2 –** 2–4 cm
- **T3** – >4 cm or lingual surface of epiglottis
- **T4** (p16- is split a/b; however p16+ is lumped together into T4 alone)
  - T4a – larynx, deep tongue muscles, medial pterygoid, hard palate, mandible
  - T4b – lateral pterygoid (e.g., trismus <4 cm), pterygoid plates, lateral nasopharynx, skull base, carotid
    Subsites: tonsil, (includes ATP, PTP, GTS), vallecula, BOT, PPW, soft palate

p16+ Oropharynx neck staging			
cN1	Ipsi nodes, all ≤6 cm	**pN1**	≤4 nodes, any location
cN2	Contra or bilateral, all ≤6 cm	**pN2**	>4 nodes, any location
cN3	Any node >6 cm		

p16+ Oropharynx clinical group staging				
	T1	**T2**	**T3**	**T4**
N0	I		II	III
N1				
N2	II			
N3	III			
M1	IV			

p16+ Oropharynx pathologic group staging				
	T1	**T2**	**T3**	**T4**
N0	I		II	
N1				
N2	II		III	
M1	IV			

AJCC 7 Staging
- N2 was stage IVA.
- T3N0 T1-3N1 was stage III.

International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S)
- O'Sullivan, 2016: Aims to develop staging for HPV+. Smoking was prognostic in cohort w HR of 1.01 but was not included in final model.
- Husain, 2016: Validated in NCDB.

p16- Oropharynx neck staging			
cN1	Single ipsi node ≤ 3 cm, no ECE	**pN1**	Single ipsi node ≤3 cm, no ECE
cN2		**pN2**	
cN2a	Single ipsi, 3–6cm, no ECE	pN2a	Single ipsi, 3–6 cm, no ECE; *or* <3 cm with ECE+
cN2b	Multiple ipsi, 3–6 cm, no ECE	pN2b	Multiple ipsi, 3–6 cm, no ECE
cN2c	Bilateral or contralat, 3–6 cm, no ECE	pN2c	Bilateral or contralat, 3–6 cm, no ECE
cN3		**pN3**	
cN3a	>6 cm, no ECE	pN3a	>6 cm, no ECE
cN3b	Any clinically overt ECE	pN3b	Single >3 cm with ECE; *or* multi nodes with any ECE+
Note: both radiographic **AND** clinical findings (e.g. skin involvement) needed to achieve cN3b			

p16-Oropharynx group staging					
	T1	**T2**	**T3**	**T4a**	**T4b**
N0	I	II	III	IVA	IVB
N1	III	III	III		
N2	IVA				
N3	IVB				
M1	IVC				

ICON-S (O'Sullivan)				
	T1	**T2**	**T3**	**T4**
N0	I		II	III
N1				
N2a				
N2b				
N2c	II			
N3	III			
M1	IV			

Anatomy

- Vallecula: part of boundary bw LX and OPX
- ventricle / Morgangi's sinus: part of LX bw TVC and FVC

HPV+ vs HPV–
- RTOG 0129, 0522 patients
- Similar rates of DM, but improved OS for HPV+

SS in yellow	HPV+	HPV–	pval
Median time to progression, m	8	7	NS
patients w DM, %	46	43	NS
First site of progression LRR only, %	55		Similar patterns of failure
First site of progression DM only, %	39		
LRR+DM, %	2		
DM 2y after dx	13%	4%	SS
2y OS, %	55	28	SS
MST after progression, y	2.6	0.8	SS

HPV+ SCC
- Younger, nonsmokers (~60% of new cancers)
- subtypes 16(80%), 18: ↑nodes, ↑mets
- E6→↓p53; E7→↓Rb→↑p16
- Chin / Wash U St Louis, 2011: p16+ OPX w ECE or close/R+. 60 vs 66Gy IMRT. No difference in LRC 2 years 99% vs 99%
- RTOG 0129: CFX + concurrent chemo (cis 100 mg/m^2 d1,22,43) vs AFX + concurrent chemo (cis 100 mg/m^2 d1,22). Three-year OS was 70% vs 64% (NSS). ECOG 0–1. No diff in PFS, patterns of failure, acute/late tox. Subgroup analysis: better 3-yr OS for HPV+ (57→82%)
  - RPA: (1) HPV; (2) PYs: 10, 20 cut points; (3) T-Stage; (4) N-stage
  - Low risk: HPV+ and < 10 PY; or HPV+ and > 10 PY and N0-2
  - High risk: HPV- and > 10 PY; or HPV- and < 10 PY and T4
  - Three-year OS for 93% for low, 71% for intermed, and 46% for high-risk groups

Anatomy
- Subsites: soft palate, palatine tonsils, tonsillar pillars, base of tongue, pharyngeal wall
- Borders: superior soft palate to superior hyoid bone (floor of vallecula)
- Ear pain?
  - Oral tongue: auriculotemporal nerve (CN V)
  - BOT: Jacobson's nerve (CN IX) – innervates the post 1/3 of the tongue and tonsillar fossae/pillars and the ear (via tympanic nerve)
  - Larynx/HPX: Arnold's nerve (CN X)

Work-up
- H&P, palpation, FNA, CN exam, biopsy (p16)
- MRI + CT, CT chest, +/− PET, dentistry

Surgery
- Need 18+ LNs for LN dissection, diagnostic, and therapeutic (Ebrahimi, Cancer, 2010; Divi, Cancer, 2016).
- For tonsil primary with cN0 neck, the rate of contra LNs is 10–15%.

Preop vs Post-op RT
- RTOG 7303 *HN Surg*, 1987, advanced HNSCC, preop RT (50 Gy) vs. post-op RT (60 Gy) vs. definitive RT alone (65–70 Gy) +/− salvage surgery (the third arm was not offered to patients with cancer of the supraglottic larynx or HPX). Post-op RT vs. preop RT vs. RT alone had marginally improved OS (36% vs. 33%, vs. 33%, NS) and LRC (65% vs. 48% vs. 38%). Thus, preop RT typically not used for SCC. The benefit of RT is likely secondary to preservation of the surgical site. The 60 Gy dose became the "standard" Fletcher dose for subsequent HN RCTs.

Altered Fractionation (RT Alone, NO CHEMO)
- IAEA ACC, Overgaard, 2010. 9 centers. *N* = 908. Stage I-IV larynx, pharynx, OC. No NPX or stage I glottic. Pts got either 6fx/w for 40d vs 5fx/w for 47d. Total dose 66–70/2. 5-year DSS 50% vs 40%, LRC 42% vs 30%. OS 35% vs 28%. favoring ACC.

- RTOG 00–22: T1–2N01 OPX SCC: 66 Gy in 30 fx (@2.2). Accelerated hypofrac IMRT. Treatment to primary dz and bilat neck. RT was 66/2.2, over 6w. PTVs received 54–60 Gy at 1.8–2 Gy/fx w SIB. 2 yr LRC 91% (N staging clinical only), DFS 82%, OS 96%.
- RTOG 9003: advanced HNSCC→ 70/35 (std) vs 81.6 @1.2 BID (hyperfrac) vs 67.2 @1.6 BID (split) vs 72 w/ last 12fx BID (conboost). Hyperfrac and Conboost won (LRC 54%, DFS 39%) though ↑toxicity. No difference in OS 53%.
- EORTC 22791: T2/3 oropharynx 70/35 vs 80.5/70 @1.15 BID. 1980–87. *n* = 356. T2–3 N0–1 < 3 cm, age < 75, KPS >60. No BOT in this trial. Hyperfrac ↑LRC 40→59%, OS 31→47% at 5y. Greatest benefit in T3N0, T3N1. Acute tox worse; 7.5 vs 4.5% had tx interruption. Thus, for pts unfit for chemo, hypofx an option.
- MARCH meta-analysis, Baujat, 2010: 6515 pts 3.4% OS benefit and 6.4% LC benefit at 5 yrs for altered frac, mostly in young pts., mostly with the use of hyperfractionated RT (rather than accelerated RT)
- DAHANCA, 2003: *n* = 1476. RT in 5 vs. 6 weeks to 66–68/2. 5-yr LRC 70% vs 60% for accelerated. DFS: 73% vs 66%. No OS difference. Acute mucositis worse w accelerated: 53% vs 33%, but all pts healed within 3 months of start. No difference in severe late tox.

Chemo-RT

- GORTEC 9401, Denis, 2004: stage III/IV oropharynx: 70/35 +/− *carbo/5-FU*. Carbo 70 mg/m^2 and 5-FU 600 mg/m^2 on d1,22,42. CRT improved 5-yr LC 25→48%, DFS 15→27%, OS 16→23%.
- INT, Adelstein 2003: *unresectable* stage III/IV H&N SCC. Excludes NPX, parotid, paranasal sinus. (1) RT 70 /2 (2) + cisplatin (100 mg/m^2 Q3wks) (3) split course CRT w 3 courses 4-day CI 5-FU 1 g/m^2 + cisplat bolus 75 mg/m^2 on d1 q4w. RT was 30, then 30–40 Gyk, for total of 60–70 Gy. RT break was planned for possible surg. Arm 2/CRT won. 3 yr OS 23% vs 37% vs 27%, compliance 93% vs 85% vs 73%. cCR 27% vs 40% vs 49%. Concurrent CRT became SOC for *unresectable* dz after this trial.
- GORTEC 99–02, Bourhis, 2012: Stage III/IV OC, OPX, HPX, LX. 66% OPX, 55% T4, 25% N2c. *n* = 840. SCC. Randomize: (1) 70/35+ *carbo/5FU* vs (2) 70/30 (6w) + *carbo/5FU* vs (3) very accelerated RT (VART), 64.8/18, *no chemo*. Best outcomes and toxicity in conventionally fractionated + chemo. ↑acute tox, feeding tube dependence in 64.8/18 arm. Pts receiving accel frac + chemo only received 2c chemo. Conclusion is *not* to do altered fx + chemo or VART bc no change in outcome, but worse tox.
- MACH-NC meta-analysis: see OPX section.

RT +/– Cetuximab

- Bonner 2006: advanced OP, larynx, hypopharynx: RT vs CRT (cetuximab). RT was 70/35, 72–76.8/1.2 BID, or 72/42 concomitant boost, with 32.4/1.8 followed by 21.6/1.8 in AM and 18.0/1.5 in PM. RT per tx institution. Cetux was initial loading of 400 mg/m^2 1w prior to RT, then weekly 250 mg/m^2 during RT. CRT won, 3-yr LRC 34→47%, OS 45→55%. Rash with cetuximab, and those pts. w G2–4 rash did better: MST 69 vs 26 m, HR 0.5. Delayed accelerated CB + cetux did the best.

CRT +/– Cetuximab

- RTOG 0522 (Ang, 2014): T2N2–3M0 or T3–4 any N SCC OPX, HPX, LX. Randomize to (1) RT (either 72 Gy/42 over 6 w, BID RT for 12 d; or 70 Gy/35) + cis 100 mg/m^2 vs (2) RT + cis + cetux 400 mg/m^2. Three-year OS (73% vs 76%), PFS (61% vs 59%), LRF (20% vs 26%), DMs (13% vs 10%) were similar. Cis-cetux-RT had more interruptions (27% vs 15%) and G3 mucositis (43% vs 33%).
  - pCR is 86% for HPV associated OPX SCC.
- MSKCC retrospective (Koutcher, 2011): 2 year LRF of cis-RT vs. cetux-RT is 6% vs 40% – 8x the failure! 2-year OS 92% vs 67%.

Post-op RT +/– Chemo

- EORTC 22931, Bernier: operable stage III/IV H&N SCC of OC, OP, larynx, hypopharynx

(ECE, +margin, PNI, LVSI, level IV/V nodes): post-op 66/33 +/− concurrent cisplatin (100 mg/m^2 Q3wks): CRT won: 5-yr DFS 36→47%, OS 40→53%, LRC 69→82% (DM unchanged ~25%). ↑toxicity (21→41%).
– **RTOG 9501**, Cooper: operable H&N (≥2 LN, ECE, +margin): 66/33 +/− concurrent cisplatin (100 mg/m^2 Q3wks). CRT won: 2-yr DFS 43→54%, LRC 72→82%, trend for OS. ↑toxicity. On unplanned subset analysis, R+ and/or ECE had benefit in LRC (33% vs 21%) and DFS (12% vs 18%). Lack of OS benefits likely bc of high OPX proportion, in comparison to EORTC.
– Meta-analysis of 95–01 and 22,931 (Bernier, 2005): CRT improved OS, DFS and LRC for ECE or + margins. Trend for stage III/IV, PNI, LVSI, low neck nodes

Induction Chemo
– TAX 323: unresectable H&N SCC: TPF vs PF induction →RT alone. TPF increased MS 16→19 months.
– TAX 324, Lorch 2011: See LX section. Posner: unresectable H&N SCC: taxotere + cisplatin +5-FU (TPF) vs PF induction →CRT with *carboplatin*. Induction CRT won. Three-yr OS 48→62%. Five-year OS 52% vs 42% MST 71 m vs 35 m. PFS 38 m vs 13 m. Twenty-five percent of patients never made it to RT (progressed, died, withdrew). Concluded that taxotere needed for induction.
– DeCIDE trial, Chicago, Cohen, 2014: locally advanced H&N SCC: (1) CRT with docetaxel, 5FU, hydroxyurea, BID fx vs (2) TPF induction then same CRT. CRT was 1.5 Gy BID, 74–75 Gy to GTV, 54 Gy to high risk, and 39 Gy to low risk. More adverse events w induction. No difference in DFS, RFS, and OS. Underpowered. Fifty-eight percent of deaths were from HNSCC; remainder due to PNA, PE, drug toxicity, and other cancers.
– PARADIGM trial, Harvard (Haddad, 2013): 2004–2008. *N* = 145. Unresectable or unlikely to be cured surgically. III/IV, N2–3. TPF induction + CRT with docetaxel or carboplatin vs CRT with cisplatin: no difference (3-yr OS 73% induction; 78% CRT)). More adverse events.
– Madrid, Hitt 2014: Induction then concurrent RT vs concurrent CRT. Induction w TPF or PF. Chemo-RT was cis 100 mg/m^2 q3w. No benefit in OS of induction over concurrent.

Sim/Planning
– Dental eval, PEG?, aquaplast, supine, 35 fx IMRT
– Bilateral neck unless T1–2N0 tonsil with <1 cm BOT of soft palate invasion (O'Sullivan 2001: 3.5% contralateral neck failure, all N+)

Recurrence
- All pts should be seen at 6 week post-tx clinical assessment, and if there is primary progression, then consider surgery. PET is preferred to post-tx neck dissection. Post-chemo-RT PET-CT should be at 3 months. If negative, 0% recurrence. Ninety percent of equivocal PET CTs will become negative.
- Recurrent p16 positive has MST of 2.6 years vs. PST negative of 0.8 years MST. Surgery is better than reRT.

NCCN
Early Stage

T1N0(</= 2 cm)/ T2N0 (>2 cm, </= 4 cm) / Or N1

Surgery or RT: results are equivalent.

1. Surgery+/-PORT: Tonsillectomy/hemiglossectomy w/elective neck dissection or WLE of soft palate
2. RT alone:
   - High-risk CTV:66–70Gy/30–35fx (boost primary to 66 Gy for T1, 70Gy for T2). Includes tumor +1 cm margin (min 5 mm) and involved LNs.
   - Intermediate-risk CTV(optional): 63Gy/35fx rest of level with involved LN/1st echelon LNs
   - Low-risk CTV:56 Gy/35fx to elective neck (levels II-IV, ipsi RP).
   - LAN: 50Gy/25 fx; boost 10Gy/5fx if LN+ hemineck.

- HPV positive: most commonly use 50 Gy/25 fractions in 5 weeks, QD; 64 Gy/40 fractions. 4 w, BID is the second most common.

  Well-lateralized tonsil/soft palate: treat unilaterally, for N0-1. All N2b + should get bilateral neck RT.

3. Altered fract ≥T2N0 (BID, concomitant boost, DAHANCA (Easiest: 2Gy/fx; 6fx/wk, add extra fraction on Fridays starting week 2.)

**Can boost w 20–30 Gy boost via Ir-192 implant

Tumor	Nodal coverage	Primary coverage
Tonsil	N-hemineck: II–IV* N+ hemineck: RS, RP, IB-V, SCV	Ipsilateral soft palate, BOT, GTS
BOT	N-hemineck: II–IV* N+ hemineck: RS, RP, IB-V, SCV	GTS, vallecula, pre-epiglottic space
Soft palate	N-hemineck: RP, II–IV N+ hemineck: RS, RP, IB-V, SCV	Entire soft palate, adj NPX, sup tonsil

*Coverage of RP nodes on "involved" node-negative hemineck is recommended

Advanced Stage
Chemoradiation is preferred.

1. Definitive Chemoradiation: 70Gy + concurrent cisplatin (100 mg/m^2, q3 weeks or 40 mg/m^2 weekly); carbo/taxol if poor kidneys; cetuximab
   - High-risk CTV (i.e., CTV1): 70Gy/35fx (include gross dz +1–2 cm margin)
   - Intermediate-risk CTV (i.e., CTV2; optional): 63Gy/35fx rest of level with involved LN/1st echelon LNs
- **For BOT:**
  High-risk subclinical disease includes CTV70 + 5–10 mm expansion, plus entire BOT, vallecula, generous portions of oral tongue, and if vallecula involved include suprahyoid epiglottic larynx (CTV P); as well as involved neck levels plus one level above and below (CTV N).
- **For tonsil:**
  High-risk subclinical disease includes CTV70 plus adjacent buccal mucosa, palate, and BOT, as well as first echelon nodes
  More advanced tonsil include mandibular bone, ipsi pterygoid muscle, parapharyngeal space, and adjacent NPX
  - Low-risk CTV (i.e., CTV3):56 Gy/35fx to elective neck (levels II-V, RP, retrostyloid space)
  - LAN: 50Gy/25 fx; boost 10Gy/5fx if LN+ hemineck
  - Post-LN-positive hemineck should treat II–IV and RP LNs; and *additionally*, treat level V

    HPV-: lower threshold for neck dissection after chemo-RT
2. Altered frac RT (RTOG 9003) if pt. refuses chemo
3. Surgery (total glossectomy) + post-op RT or CMT for T4/+margin/ECE

Post-op RT Indicated for
Neck
- Multiple positive nodes
- >3 cm
- Extracapsular spread of nodal disease
- Close or positive margins
- Prior biopsy/violation of neck/trach prior to laryngectomy

Primary tumor
- T4
- Extensive subglottic extension
- + Margin/close margins (<5 mm)
- Perineural/vascular invasion
- High-grade histology
- Concerned surgeon

Squamous Cell Cancer Metastatic to Cervical Nodes from Unknown Primary (SCCUP) [19–23, 78–85]

p16+ Neck staging			
cN1	Ipsi nodes, all ≤6 cm	**pN1**	≤4 nodes, any location
cN2	Contra or bilateral, all ≤6 cm	**pN2**	>4 nodes, any location
cN3	Any node >6 cm		

p16-Neck staging			
cN1	Single ipsi node ≤3 cm, no ECE	**pN1**	Single ipsi node ≤3 cm, no ECE
cN2		**pN2**	
cN2a	Single ipsi, 3–6 cm, no ECE	pN2a	Single ipsi, 3–6 cm, no ECE; *or* <3 cm with ECE
cN2b	Multiple ipsi, 3–6 cm, no ECE	pN2b	Multiple ipsi, 3–6 cm, no ECE
cN2c	Bilateral or contralat, 3–6 cm, no ECE	pN2c	Bilateral or contralat, 3–6 cm, no ECE
cN3		**pN3**	
cN3a	>6 cm, no ECE	pN3a	>6 cm, no ECE
cN3b	Any clinically overt ECE	pN3b	Single >3 cm with ECE; *or* multi nodes with any ECE

Epidemiology

- 1–4% of HNSCCs
- Increasing bc of HPV
- Diagnosis of exclusion
- Usually presents w painless neck mass
- NCCN: painless neck mass in >40yo is cancer UPO
- **DDx:**
  - **Branchial cleft cyst**: congenital abnormality manifesting in adulthood. Appear in 20s–30s, usually not >40. Note that HPV-assoc LNs are usually cystic.
  - **PTC:** if FNA suggests thyroid ca, then must do thyroid US and biopsy.
  - **Skin SCC of the LNs:** may also be p16+. Rarely in level II. Usually in >70yos, immunocompromised. LNs of skin SCC that is p16+ typically will not have HPV DNA.
  - **Adenocarcinoma, lymphoma, thyroid, melanoma, salivary, and sarcoma.**

Staging

- Primary T category: T0.
- N-category designated according to anatomic site based on EBV and HPV status:
  - EBV+ Stage like NPC
  - HPV+ Stage like p16+ OPC
  - HPV- Stage like p16- OPC
- Usually N2a or N2b (AJCC 7).
- The most common primary is tonsil or BOT.
- 40% w single enlarged LN, typically level 2.
  - This suggests OPX primary
- 80% of patients with bulk of dz in level 2, with smaller volume of dz in level 3.
- LAD in level 3 w/o level 2 suggests supraglottic LX or HPX because these drain to the mid neck.
- LAD in level 4 and/or supraclav fossa are seldom result of a primary above the clavicles.
- 45% tonsil, 40% BOT, and 10% pyriform sinus.
- Waldeyer's ring: palatine, tubal, pharyngeal, and lingual tonsils.
- When primary is found:
  ~50% of time by directed Bx
  ~25% of time by tonsillectomy
  ~25% of time by PET
  ~10% w/bilateral neck disease
- If just neck dissection alone:
  ~50% fail at primary
  ~15% fail in the dissected neck (~60% if ECE)
- ~40% fail in node (−) neck if you treat only ipsilateral.

Suspicion Based on Nodal Station

- Level I = OC. If not SCC, may be salivary, skin, malar face

- Level II = OPX; for Level 2B close to parotid consider skin met to parotid or salivary gland primary
- Level V or RP = HPX or NPX
- Level IV = often outside H&N. The lung and esophagus (left SCV is Virchow's node so look below diaphragm!)
- Level VI = thyroid

Work-up

– **FNA** of LN is preferred. If non-dx, then repeat with US.
– **Open biopsy contraindicated because of:**
  – Potential tumor spill and disruption of fascial planes (which naturally prevent tumor spread)
  – Limitation of future treatments
  – Scar formation and increased morbidity (biopsy wound must be excised or covered in higher dose volume)
  – Necessitation of second operation if path staging pursued
  – **"Neck violation":** incisional/excisional biopsy of node
– **CT +/− MRI.**
– **PET-CT:** detects tumors in 25% of patients. Can show DMs, non-HN primary. FPR: 20%; thus, confirmatory bx necessary. PET scan PPV 90%, NPV 75%.
– **Fiberoptic endoscopy.**
– **EUA** (DL and direct bx): not necessary if primary found otherwise. For level 2/3 LNs, biopsy of **NPX**, b/l **BOT**, b/l **pyriform** sinuses, **SGL** recommended. Tonsil cancers in crypts may not be seen. B/l tonsillectomy recommended if tissue present. If HPX ca suspected, then biopsy the pyriform sinus.
– **Pathology**:
  • SCC or undifferentiated ➔ HPV (p16 staining) and EBV testing
  • Adenocarcinoma ➔ TG and calcitonin staining. If TG and calcitonin negative (and level I-III) likely parotid origin
– **Triple endoscopy** if levels IV–V.
– **EBV**: rarely elevated in North American patients w SCCUP. Can check EBV in FNA specimens. Recommended to direct bx for patients from endemic area.
– **HPV**: can be detected in FNA specimen. Should check in all. If positive, tonsillectomy (usually b/l) recommended. TORS results in 63–100% detection of primary.
– **Thyroglobulin, calcitonin, PAX8, or TTF** for anaplastic/undifferentiated tumors

Retrospective Reports

– McQuone 1998: improved diagnostic yield with tonsillectomy over biopsy.
– UF 2001: LC 78%, OS 47%.
– Baker 2005: larynx-sparing RT is just as effective, less toxic.
– Loyola 1997: unilateral neck RT led to 44% contralateral neck failure and 44% primary emergence rate.
– Soushtari 2011 (UVA): all IMRT. Five-yr OS 71%, DFS 85%. All nodal failures had bulky disease.

Treatment Paradigm

– Natural history: Failure usually in ipsi neck > distal. Among surgically treated patients, mucosal progression is 18% in old series, likely <10% now.
– Typically, multimodal.
– Usually neck dissection + aRT
– ECE_{mic} in p16+ patients: unknown if aCRT is beneficial. Currently, any ECE is indication for aCRT.

RT Planning

– Timing of RT does not appear to influence DFS.
– **Volumes:**
  – Contra neck and mucosal subsites (b/l tonsil, BOT) controversial, sometimes excluded in p16+/EBV- with N1 disease.
  – NPX is typically included; consider excluding in non-Asian with p16+/EBV- LNs. NPX contour: base of skull to soft palate, posterior choana and posterior pharyngeal wall, and laterally cover fossa of Rosenmuller.
  – LN volumes: bilat RP nodes, bilat IB-IV, ipsi V. Neck RT will include the RS space and RP LNs (level VII) with IMRT. Thus, NPX will receive considerable dose even if not in CTV.

- Include oral cavity only if LN in IA/IB (can exclude NPX then).
- Larynx-sparing RT inappropriate for SCCUP of level 3 w/o level 2 bc primary likely in LX or HPX. Otherwise, Larynx/HPX = hyoid to bottom of cricoid
- Include OC and exclude NPX if level IB node

- **Doses**:
  - GTV: 66–70 Gy.
  - Adjuvant: 60–66 Gy. Elective: 45–54 Gy.
  - Mucosa: 50–60 Gy/25 (per NCCN) or 54Gy/30 (per EORTC 22205). Sometimes inc ipsi OPX to 60.

Chemo

- Use mainly for ECE, R+.
- Also for aCRT in T0N3.
- Main benefit for chemo is inc LRC. Distant benefit dubious.

Stage	Incidence	Outcomes	Treatment	Post-tx
T0N1	Rare	Good	Unimodal, usually neck dissection or RT. May consider aRT omission	
T0N2a	Common	Good	P16+, <10PYs, no ECE: as above	
		Good	P16– or >10PYs: neck dissection + RT	
		Variable	ECE: CRT because aCRT would be required post-surgery	ECE should receive CRT. PET-CT 12 w post-tx. If no CR, neck dissection
T0N2b	Common	Good. Unknown which tx better	Neck dissection + RT	
			CRT	
T0N2c	Rare		CRT	PET-CT 12 w post-tx. If no CR in hemineck, neck dissection
T0N3	Common		CRT bc most N3 LNs have ECE Surg only if no ECE. Then aRT	PET-CT 12 w post-tx. If no CR, neck dissection. Neck dissection with <CR still reasonable
Gross ECE			CRT	

Likely primary site of SCC when no primary found			
Smoker	Never smoker, level II–V		
Level III/IV	EBV+	HPV+	EBV–/HPV–
NPX	NPX	NPX	NPX
OPX		OPX	OPX
HPX, SGL			

Likely primary site of adenocarcinoma when no primary found	
Thyroglobulin–/calcitonin	
Level Ib-III	Level IV–V
Parotid. Perform neck dissection, ipsilateral Parotidectomy –> PORT	Infraclavicular, e.g., the breast, lung, and GI

Salivary Gland Cancer [19–23, 86–93]

- **TX**: cannot be assessed. **T0**: no tumor
- **T1** – ≤2 cm w/o extraparenchymal extension
- **T2 –** 2–4 cm w/o extraparenchymal extension
- **T3** – >4 cm or extraparenchymal extension
- **T4**
  - T4a – skin, mandible, ear, CN VII
  - T4b – skull base, pterygoid plates, carotid
    *Only applies to major salivary glands (parotid, SMG, SL). Minor salivary gland = stage as primary site!

cN1	Single ipsi node ≤3 cm, no ECE	**pN1**	Single ipsi node ≤3 cm, no ECE
cN2		**pN2**	
cN2a	Single ipsi, 3–6 cm, no ECE	pN2a	Single ipsi, 3–6 cm, no ECE; *or* <3 cm with ECE
cN2b	Multiple ipsi, 3–6 cm, no ECE	pN2b	Multiple ipsi, 3–6 cm, no ECE
cN2c	Bilateral or contralat, 3–6 cm, no ECE	pN2c	Bilateral or contralat, 3–6 cm, no ECE
cN3		**pN3**	
cN3a	>6 cm, no ECE	pN3a	>6 cm, no ECE
cN3b	Any clinically overt ECE	pN3b	Single >3 cm with ECE; *or* multi-nodes with any ECE

	T1	T2	T3	T4a	T4b
N0	I	II	III	IVA	IVB
N1	III	III	III		
N2	IVA				
N3	IVB				
M1	IVC				

– **Benign**: pleomorphic (most common), Warthin's, Godwin's, oncocytoma, basal cell adenoma, myoepithelioma
  – Negative SM is *1 cell* (i.e., no tumor on ink)
  – Usually mobile superficial lobe, slow growth, no pain, VII intact, no LNs
– **Low grade**: acinic cell; basal cell adenocarcinoma; low-grade mucoepidermoid (G1); oncocytic carcinoma
  – Negative SM is *1 cell*
  – No further treatment unless positive margins typically
– **High grade**: adenoid cystic carcinoma (ACC; sometimes called "low grade", but treat like high grade), high-grade mucoepidermoid carcinoma (most common; the more epidermoid, the worse, since more like SCC), malignant mixed, adenocarcinoma, SCC
  – Negative SM is 5 mm.
  – All get adjuvant RT. Consider chemo-RT.
  – ACC, ductal, undifferentiated → ↑DM (lung, bone, liver).

Glands
– Major glands: parotid, SMG, SL.
– Minor glands: submucosa and the mouth (90% malignant).
– Typically, the smaller the gland, the more malignant the tumor

Anatomy
– **Parotid**: facial nerve divides superfic and deep lobes, has Stensen's duct, most common location, malignant less common (20%).
  – Most common histo: pleomorphic
  – Most common malignant: mucoepidermoid
  – Anatomic landmarks: ECA, retromandibular vein, CN VII (all behind mandible)
  – Frey's syndrome, auriculotemporal nerve syndrome, and gustatory sweating (CN VII damage)
– **Submandibular**: lingual nerve (V3) and XII, Wharton's duct, more likely malignant (50%).
– **Sublingual**: superior to mylohyoid, Rivinus/Bartholin's ducts, incidence debated (90%?).
– **Minor salivary**, 90% malignant. Usually ACC.

LN drainage
– **Parotid**: preauricular, peri/intraparotid, levels II–IV
– **SMG/sublingual**: levels I/II, less often III/IV
– **Minor salivary:** depends on location, have highest propensity for LN spread

Histologies	Benign (B) v cancer (C) and G	Incidence among B and C	Common location	Occult LNMs+	DM potential	Her-2	EGFR	c-kit	AR	ER or PR
Adenoid cystic carcinoma (ACC)	C. Treat as G3. tubular, cribriform (~G1), solid (~G3)		Most common cancer in SMG, minor SGs predilection for PNI	<10%	Sporadic can have >10y to DM. Forty percent have lung mets	<5%	variable	>50%	<5%	<5%
Adenocarcinoma				35%		<25%	<25%	Vvariable	<25%	<5%
Mucoepidermoid	C, most G1	>50	Parotid	35%		<25%	>50%	<5%	<5%	<5%
Salivary duct	C, most G3					>50%	>50%	<5%	>50%	<5%
Carcinoma ex pleomorphic adenoma (CexPA)	C, most G3 Surrogate name for salivary ductal ca Microscopically similar to breast ca				High					>50%
Acinic cell	C, most G1									
Pleomorphic adenoma	B	65	Usually parotid							

Work-up

- History: Duration of mass/speed of growth, painless or painful, numbness/CN deficit, neck mass
  - DDx = recent infection, salivary cysts, salivary gland stones, sarcoid, Sjogren's syndrome, other malignancy (salivary primary, lymphoma, met)
- Physical: oral cavity inspection w/ palpation of tongue and FOM; examine tongue mobility (CN XII), sensation (V), and taste (VII, IX); LN exam, CN exam (especially VII, V, and XII)
- FNL, biopsy (FNA). MRI + CT, CT chest, +/− PET, dentistry

Post-op RT and Elective Nodal Irradiation

- Terhaard 2005: retrospective; surgery +/−RT: 10 yr LC improved (T3–4 18→84%) (close 55→95%) (+margin 18→84%) (+bone 54→86%) (PNI 60→88%)
- Chen 2007: cN0 salivary gland→surgery+RT: ENI reduced nodal failure from 26→0% (more with ↑T, SCC, undiff, adeno). Usually ipsilateral only

Adenoid Cystic Carcinoma

- Slow growing, not expected to benefit from chemo. PNI w skip lesions and facial nerve involvement common.
- Chen 2006: ACC is locally infiltrative, spreads along CNs, has skip lesions, and can recur in >10y. Minimize time bw surg and RT to <42 days.
- Garden 1995: ACC→surgery+RT: 10 yr LRC 86%, worse for +margins and clinical PNI. Provides justification for definitive tx if M1 (long natural hx).
- Mendenhall 2004: ACC: surgery+RT better than RT alone (91% vs 43%) worse for T3–4 and clinical PNI.
- For ACC irradiate nerve to skull base, ultimately 40% will develop lung mets

RT+/–Chemo

- Currently no prospective data.
- NCDB: no improvement w post-op CRT vs RT. However, the CRT group had more high-grade cases and some had adenoid cystic.

Neutrons
- RTOG-MRC trial: 32 inoperable salivary gland: neutron vs photon/electron: closed early, neutrons won: 10 yr LRC 17→56%, OS unchanged (15→25%)
- 19.2nGy to GTV (1.2nGy x4/wk), 13.2nGy to PTV2

NCCN
- Surgery is the mainstay of treatment. LND indications (supraomohyoid, I-III): HG (except ACC), cN+,4+ cm.
- **Parotidectomy subtypes:**
  - Superficial = superficial
  - Total = superficial + deep, spares VII
  - Radical = includes VII and skin/fascia
  - Indications for post-op RT:
    1. high grade
    2. PNI or LVI
    3. LN + or ECE
    4. Recurrent
    5. Adenoid cystic histology
- Indications for post-op chemo-RT:
  1. close (<2 mm)/positive margins
  2. ECE
- Indications to treat LNs (N0: IB-III; N+: IB, RSS/II-V)
  1. HG (except ACC)
  2. pN+
  3. Recurrent

RT Doses
- **Post-op:**
  - 60–63 Gy @ 1.8 Gy–2Gy, 66Gy for positive margin
  - When to treat BOS: cPNI, rPNI, named nerve involved, "extensive" PNI; adenoid cystic
- **PNI considerations:**
  - Parotid:
  - VII: track to styloid foramen; if VII grossly involved, extend to include facial canal through petrous bone
  - Submandibular:
  - V3 (lingual): track nerve to foramen ovale, include Meckel's cave
  - XII: track nerve to hypoglossal canal
  - VII: track to styloid foramen

Definitive for Unresectable/nonsurgical
70Gy/35fx for gross dz

Treat elective neck to 50–54 Gy in 1.8-2Gy/fx
Consider neutrons

Laryngeal (LX) and Hypopharyngeal (HPX) Cancer [19–23, 94–111]

Laryngeal (LX) and Hypopharyngeal (HPX) Cancer[19-23,94-111]

	Supraglottis	Glottis	Subglottis	Hypopharynx
% of LX cancer	35	60	2	
anatomy	*5 Supraglottic subsites ("A VISA"): **a**rytenoids, false cords (**v**entricular bands), **i**nfrahyoid epiglottis, **s**uprahyoid epiglottis, **a**ryepiglottic folds,	TVCs, ant/post commissures	5mm below glottis to inferior cricoid or 1st tracheal ring	** 3 Hypopharynx subsites ("3 Ps"): Pyriform sinus, Hypo**p**haryngeal wall (lateral and post), **p**ostcricoid region (mucosa overlying cricoid cartilage, w arytenoids mucosa superiorly and esophageal mucosa inferiorly) **Borders**: hyoid bone or tip of epiglottis (sup); bottom of cricoid cart or cricopharyngeus muscle (inf)
LNM	Rich LN supply 55% N1+, 16% N2c, 33% occult	for T1, <2%; for T2 <7%; for T3, 20%; for T4, 25%	~20%	60%+
T1	1 subsite*, normal VCs	Normal VC movement (**T1a** one cord, **T1b** both)	Subglottis only	One subsite**, ≤2 cm
T2	2+ subsites or glottis, or region outside supraglottis (BOT, vallecula, medial wall pyriform)	Supra/subglottis or VCs w impaired mobility (AJCC6 T2b)	To VCs w normal or impaired mobility	2+ subsites, 2–4 cm
T3	**Fixed cord**			
	Post-cricoid area, **P**araglottic space, **Pre**-epiglottic space	**P**araglottic space		>4 cm, **esophagus**
	Inner thyroid cartilage			
T4a	**Outer** thyroid cartilage		Cricoid invasion, **ANY cartilage invasion**	Thyroid/cricoid cartilage, hyoid, central compartment
	beyond larynx(e.g. **esophagus,** soft tissues of neck, extrinsic tongue muscles, strap muscles, thyroid)			
T4b	Prevertebral space, carotid, mediastinum			

	T1	T2	T3	T4a	T4b
N0	I	II	III	IVA	IVB
N1	III	III	III		
N2	IVA				
N3	IVB				
M1	IVC				

Risk Factors

– Smoking, EtOH, GERD, asbestos, paint fumes, Ni, soot, tar, vitamin deficiencies (Fe, B12, C), betel nuts

Anatomy

cN1	Single ipsi node ≤3 cm, no ECE	**pN1**	Single ipsi node ≤3 cm, no ECE
cN2		**pN2**	
cN2a	Single ipsi, 3–6 cm, no ECE	pN2a	Single ipsi, 3–6 cm, no ECE; *or* <3 cm with ECE
cN2b	Multiple ipsi, 3–6 cm, no ECE	pN2b	Multiple ipsi, 3–6 cm, no ECE
cN2c	Bilateral or contralat, 3–6 cm , no ECE6cm, no ECE	pN2c	Bilateral or contralat, 3–6 cm, no ECE
cN3		**pN3**	
cN3a	>6 cm, no ECE	pN3a	>6 cm, no ECE
cN3b	Any clinically overt ECE	pN3b	Single >3 cm with ECE; *or* multi nodes with any ECE

- Larynx innervation: all vagus (X), via recurrent laryngeal nerve and the superior laryngeal nerve
- Note: thyroid cartilage invasion and extralaryngeal spread difficult to determine by CT (PPV, 81%; NPV, 71%; sens, 49%; spec, 92%) Ear pain?
  - Oral tongue: auriculotemporal nerve (CN V)
  - BOT: Jacobson's nerve (CN IX)
  - Larynx/HPX: Arnold's nerve (CN X)
- Anatomic landmarks:
  - Hyoid = C3
  - Superior border of thyroid = C4
  - Cricoid cartilage = C6

Work-up
- FNL, biopsy
- History: SGL = dysphagia/odynophagia, and otalgia (Arnold)
- Voice changes (hoarseness), swallowing, aspiration, and pulmonary status (can the patient climb a set of stairs)
- Physical: palpate larynx (mass at thyroid notch = preepiglottis space/PES invasion), gently move (loss of laryngeal click = postcricoid area/PCA invasion), palpate tongue and BOT, LN exam
- CT +/− MRI, CT chest, +/− PET, dentistry
- PFTs

Studies

RT Alone Fractionation
- Yamazaki 2006: phase III, T1 glottis: 2Gy/fx to 60–66 Gy vs 2.25 Gy/fx to 56–63 Gy. Hypofrac won. Five-yr LC 77→92%, CSS, OS, toxicity unchanged (Bledsoe 2017 showed possible OS advantage to hypofrac in T1-T2 from NCDB)
- RTOG 9512: T2 glottis. *N* = 250. 70/35 vs 79.2 BID (1.2 Gy). No change, trend for ↑LC w hyperfrac (70→79%, $p > 0.11$), LRC 67% vs 73%, DFS 50% vs 49%, OS 63% vs 72%. Hyperfrac better numerically, but not SS, likely bc underpowered. Similar late G3+ tox, 8%. For cost and pt convenience, consider other fractionation regimens, e.g., 2.25 Gy/d
- **RTOG 9003**, Fu, 2009: compared
  - CFRT (70/35over 7 weeks) vs.
  - Hyperfrac RT (81.6/68over 7 weeks, i.e., 1.2 Gy BID) vs.
  - Accelerated frac w split course (67.2/42 fractions over 6 weeks, i.e., 1.6 Gy BID; with a split course where there was a break in the middle of treatment) vs.
  - Accelerated frac with delayed concomitant boost (1.8 Gy/fx 5d/w w 1.5 Gy/fx as boost field as second daily tx over the last 12d; total, 72/gy42 fractions). All tumors from lip to esophageal verge eligible, except glottic larynx. Parallel opposed field.
  - LRF: 29% vs 51% vs 58% vs 52%.
  - OS 30% vs 37% vs 31% vs 34%. Both hyperfrac and DCB had improvement in *LRF*.
  - *OS and LRF* improved in the hyperfrac arm. 1% LRC improvement for each day tx shortened. CFRT had lowest acute tox vs all others. Worse outcomes in on-tx smokers, more so than previous heavy smokers.

LX Cancer – Larynx Preservation
- **VA Larynx Trial (Wolf, 1991):** III/IV larynx: (1) surgery+PORT vs (2) Chemoselection: induction cis/5FU x 2c, then re-eval, then 1c (total 3c), then RT if PR+ or surg/PORT if <PR. At 4y, LX preservation was 12% vs 64%. OS ~50% (NSS). TL 88% for surg vs 38% CRT. Pts alive w larynx 5% vs 31%, favoring CRT. LC lower for CRT (98→88%). Salvage laryngectomy rate 56% in T4, 29% in < T4 tumors. Note, most T4 is now T3 (bc any thyr ctx invasion was T4, now minor invasion T3)
- **RTOG 91–11 (Forastiere, 2003; 2013):** III/IV larynx, T2/T3/ "early T4" (now T3) of glottic/supraglottic. Technically some resectable. Randomize: (1) RT alone vs (2) induction chemo (cis 100 mg/m^2 on d1 and 5-FU 1000 mg/m^2 q24h CI, qw, x2c), followed by RT if PR+ or surg/PORT if <PR vs (3) concom CRT (cis 100 mg/m3 q3w × 3c). RT 70/2 and 50/2 to elective neck and sclav. All cN2 patients got planned neck dissection after RT. Endpoint: LX preservation. Concurrent CRT won for LC and LRC (69→55→51%),

established it as SOC. Concurrent CRT was better for LX preservation vs RT alone, but there was no difference bw two chemo groups. Five-yr larynx preservation 84→71→66%. Chemo reduced DMs (13% vs 22%). OS unchanged. Some argue induction arm is the best (esp if w TPF and not PF). Larynx preservation acceptable for T3

Induction

- TAX 324 (Posner, Lorch 2011): unresectable head and neck (33% larynx/hypopharynx): induction taxotere + cisplatin +5-FU (TPF) vs induction PF x3 cycles, then 70 Gy CRT. CRT was 70–74 Gy w concurrent carbo AUC 1.5. Induction TPF won. Three-yr OS 48 vs 62%, 5-yr OS 52% vs 42%. MST 71 m vs 35 m. LRC 62→70%, DM unchanged. TPF was toxic.
- EORTC 24891: same as VA trial but with pyriform sinus and required CR. Same OS (~40%). 5-yr functional larynx 35%.
- GORTEC 2000–01, Janoray, 2015: III-IV LX, HPX SCC who required TL randomized to TPF vs PF induction. Responders get RT. Primary endpoint was LX preservation. TPF increased LX preservation and larynx function. No change in OS, DFS, LRC. TPF also w less G3–4 tox, 17% vs 9%.

Chemo-RT

- See oropharynx (RTOG 9501, EORTC 22931).
- For larynx and hypopharynx, the rate of long-term G-tube placement after tx is 50% (vs. 40% for oral cavity and OPX).
- For just hypopharynx, the rate is 25%.
- In the MACH-NC meta-analysis, the benefit of chemo-RT is not higher than that for other dz sites.
- If no pCR, the median DFS is 12 months.

HPX Trials

- Treatment paradigm similar to LX cancer
- EORTC 24891 Lefebvre, 1996, 2012. Rando (1) surgery, PORT, or (2) induction chemo (i.e., with cisplatin and 5-FU x3), then (2a) patients with CR get RT, (2b) patients w PR or NR get surg, then PORT. No OS difference. However, CT + RT +/− surgery had 17% LX preservation rate at 5 years (EORTC 24891 Lefebvre, JNCI, 1996) and 8.7% at 10 years. Ten-year DM 36% with surgery and RT, 25% with chemo, RT, +/− surgery, low OS in both arms likely due to poor salvage success

Sim/Planning

- Mask, shoulders down

General Treatment Recommendation

- **Stages I–II:** unimodal therapy
- **Stages III–IV:** multimodal therapy (e.g., chemo-RT)

Surgery Types

- **SGL**
  - Supraglottic laryngectomy (T1, T2, T3 by PES only)
  - Removes: upper 1/2 thyroid cartilage, preepiglottic space, epiglottis, AE folds, false cords, up to one arytenoid (need to preserve one)
- Contraindications:
  - **B**/L arytenoids
  - **F**ixed cord/any true cord
  - **I**nadequate pulmonary reserve/ "cannot walk up two flights" (unable to tolerate aspiration)
  - **T**hyroid/cricoid cartilage

GL

- Mucosal stripping (CIS)
- Transoral laser excision/cordectomy (T1a). Contraindicated for AC involvement
- Vertical partial laryngectomy (T1a, T1b, select T2)Removes: 1/2 thyroid cartilage + ≤ 1 and 1/3 TVC

SGL/GL

- Total laryngectomy (T3, T4a)Removes: hyoid, thyroid, cricoid w/ entire larynx +strap muscles

- Patient left with permanent tracheostomy and pharynx reconstruction (by suturing to BOT)
- Most common failure sites = BOT and stoma

Speech After Laryngectomy

- Esophageal speech
- Tracheoesophageal puncture
- Electrolarynx

Treatment for Supraglottic Larynx

- **T1N0**
  - Supraglottic laryngectomy w/bilateral MRLND
  - RT alone 66 Gy to primary, 50 Gy to bilat neck
- **T2N0**
  - (1) Supraglottic laryngectomy with bilateral modified radical LND
  - (2) RT alone 70 Gy to primary, 50 Gy to bilat neck (for bulky T2, could consider altered fractionation schedule but not standard)
- **T3-4N+**
  - CTV70. avoid SIB, esp >2Gy per fraction, due to risk of late toxicity.
  - High-risk CTV 63Gy/35fx. Includes CTV70 + entire larynx (top thyroid notch to bottom cricoid), paraglottic and preepiglottic space, pyriform sinuses, vallecula, and up to 1 cm BOT, as well as high-risk first echelon nodes
  - Elective LN: 56Gy/35fx., e.g., upper level II, RPLNs. LAN: 50Gy/25 fx; boost 10Gy/5fx if LN+ hemineck

Treatment for Glottic Larynx

- **Early larynx options**: stripping, laser, RT, cordectomy, vertical hemilaryngectomy
  - **Contraindications to vertical hemilaryngectomy:** Involves more than one true cord, epiglottic invasion, fixed cord, bilateral arytenoids involvement, 5 mm subglottic extension.
  - After CO2 laser, do not need adjuvant RT if no tumor on ink.
  - Stripping uses H2O jet to lift the tumor off; it is not an oncologic procedure and needs adjuvant RT.
  - Failure rate is local only (not LNs), so need very close follow-up, q 3 m.
  - Tis: *cord stripping (laser/CO2)* or RT.
  - **RT:**
  - **T1: 63 Gy/28 fractions at 2.25 Gy**
  - **T2: 65.25 Gy/ 29 fractions at 2.25 Gy**
  - Historically 5 × 5 field for T1 or 6x6 field for T2, now more based on anatomic borders. Treat in <43 days
  - Iso @TVC
  - 6MV photons, wedges w heels anterior
  - Bolus if AC involved
  - Hotspot <110%
  - **3D: CTV** covers entire larynx, including glottis (TVCs, anterior and posterior commissures), part of supraglottis (FVCs, arytenoids) to top of thyroid notch and subglottis inferiorly to cricoid cartilage (can extend to first tracheal ring for T2); paraglottic space and thyroid cartilage can be included if deemed at risk. CTV should extend ≥2 cm craniocaudally.
  - **2D: superior border** is the top of the thyroid cartilage; **inferior border** is the bottom of the cricoid (at C6) or one tracheal ring below cricoid if T2 for subglottic involvement; **anterior border** has a 1 cm flash; and **posterior border** is the anterior edge of the vertebral body.
  - Alternative for favorable T2a is 79.2 Gy @ 1.2 BID, per RTOG 95–12.
  - **Unfavorable T2: "old T2b,"** if there is more extensive disease (e.g., cord hypomobility), then consider chemo-RT and 70 Gy w RNI w concurrent cis. Argument for this is comparing CRT arm of 91–11 vs. HFX arm of 9512.
  - **T3 or N+:** CRT (surgery salvage) or induction chemo or laryngectomy.
  - Primary and involved LN: 70Gy in 35 fx.
  - High risk CTV 63Gy/35fx. CTV70 + entire larynx (top thyroid notch to bottom cricoid), paraglottic and preepiglottic space, pyriform sinuses, vallecula, and up to 1 cm BOT, as well as high risk first echelon nodes.

  - If level II/III involvement, do not need to cover RP, level IB, level V.
  - If dz. breaks through cartilage, cover level VI.
- Primary + b/l neck: 70/63/54 in 35 fx.
- cN0: II-IV.
  - [+ VI for subglottic extension, HPX involvement, emergent trach, soft tissue extension of primary to neck
  - + VII involvement for subglottic extension, HPX involvement, SCV node]
  - cN+: IB + RSS/II–V.
- [+ VI for subglottic extension, HPX involvement, emergent trach, soft tissue extension of primary to neck
- + VII involvement for subglottic extension, HPX involvement, SCV node]
- *with any HPX involvement add b/l RP.
- CTV70 = primary, gross LN.
- CTV63 = [CTV_70 + 5 mm], remaining larynx, piriform sinuses, paraglottic space, PES, vallecula, cN+ neck.
- CTV56 = cN0 neck.
- Cis (100 mg/m^2) days 1, 22, 43.
- **T4**: laryngectomy preferred over chemo-RT because of failure rates on VA larynx.
- PO(C)RT.
  - Post-op bed + b/l neck: 66/60/54 in 30 fx
  - Cis (100 mg/m^2) days 1, 22, 43.
- CTV66 = post-op bed if + margin or ECE.
- CTV60 = post-op bed, cN+ neck.
- CTV54 = stoma, cN0 neck.

Treatment for Subglottic Larynx

T1-2N0 RT alone
- RT alone 70 Gy to primary + b/l neck (II-IV + VI): 70/60/54 in 35 Fx, BID Friday
- For bulky T2, could consider altered fractionation schedule but not standard

T3-4N+

- Cisplatin 100 mg/m^2 on day 1, 22, 43 w/concurrent CTV70 = GTV + 5–10 mm, carving out bone/air
- CTV60–63 = high-risk elective, consider N+ neck plus one level above/below. For subglottic involvement, always treat level VI and consider superior mediastinum. Always cover LN levels III-IV bilaterally, and add level II for advanced T stage or N+
- CTV50–56* = low-risk elective, including entire larynx (top thyroid notch to bottom cricoid), paraglottic and preepiglottic space, pyriform sinuses, vallecula, as well as first echelon nodes (see above)

Covering level VI indications: emergent trach, subglottic extension, apex or pyriform sinus involvement

Treatment for Hypopharynx

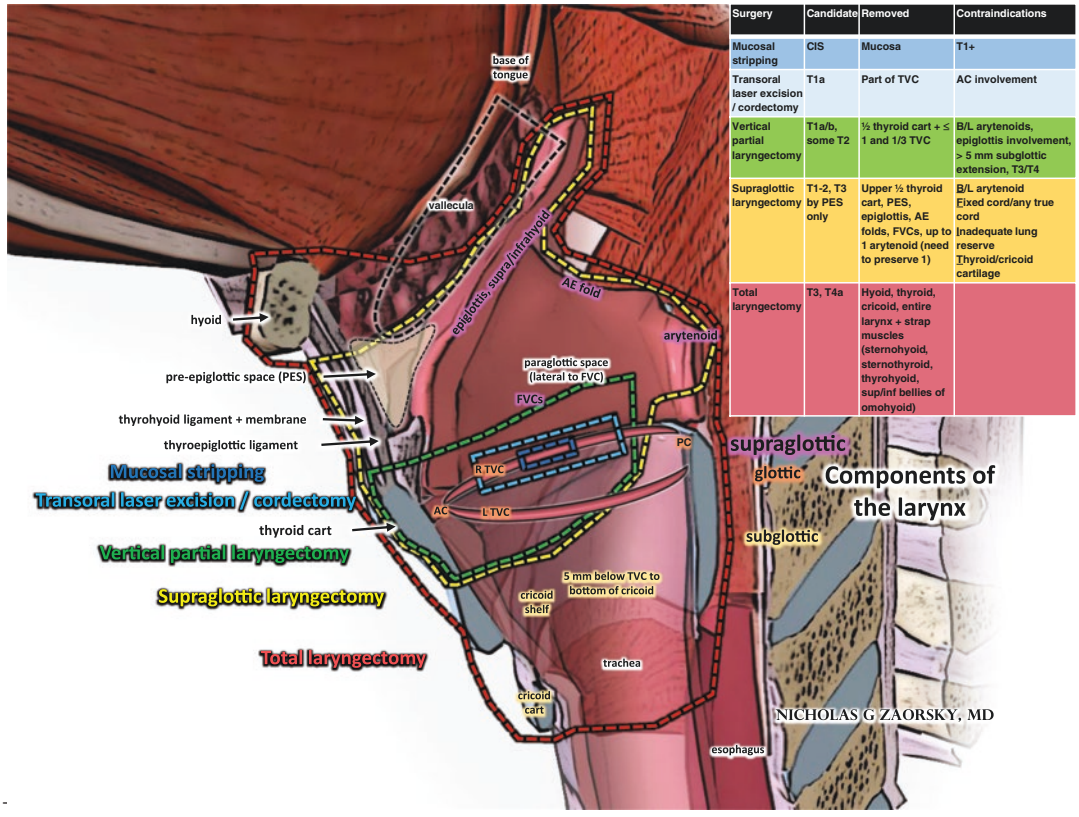
- **T1N0**
  - (1) Partial laryngopharyngectomy w/ bilateral MRLND
  - (2) RT alone 70 Gy to primary, 50 Gy to bilat neck

T2N0
- (1) Partial or total laryngopharyngectomy with bilateral modified radical LND
- (2) RT alone: altered fractionation

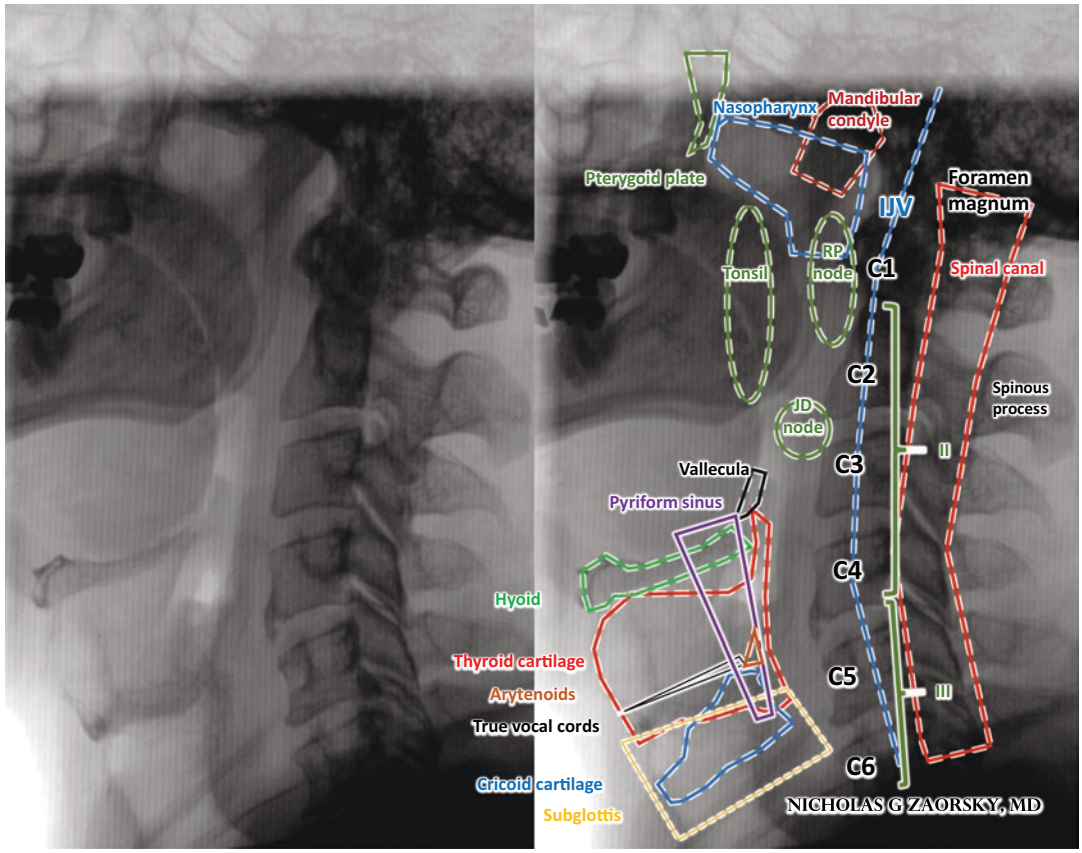
T3N+: Chemo-RT if functional larynx and not aspirating
- Primary + b/l neck: 70/60/54 in 35 fx
- cN0: RP (stop at C1), II-IV [+ VI for extension below cricoid or into PS apex]
- cN+: RP (stop at BOS), IB + RSS/II-V [+ VI for extension below cricoid or into PS apex]
- CTV70 = primary, gross LN
- CTV63 = CTV_70 + Entire LX/HPX (hyoid to cricoid), 3 cm sup/inf if pharyngeal wall involvement, cN+ neck
- CTV_56 = cN0 neck
- **T4a**
- Total laryngectomy +/− post-op RT or CRT

Indications for Treating Stoma ("No ESCAPE")

- Nodes: multiple LNs or positive LN close to stoma
- Emergency tracheostomy
- Subglottic extension >5 mm
- Surgical scar crosses stoma
- Anterior soft tissue/skin involvement
- Positive/close margins



Surgery	Candidate	Removed	Contraindications
Mucosal stripping	CIS	Mucosa	T1+
Transoral laser excision / cordectomy	T1a	Part of TVC	AC involvement
Vertical partial laryngectomy	T1a/b, some T2	½ thyroid cart + ≤ 1 and 1/3 TVC	B/L arytenoids, epiglottis involvement, > 5 mm subglottic extension, T3/T4
Supraglottic laryngectomy	T1-2, T3 by PES only	Upper ½ thyroid cart, PES, epiglottis, AE folds, FVCs, up to 1 arytenoid (need to preserve 1)	B/L arytenoid Fixed cord/any true cord Inadequate lung reserve Thyroid/cricoid cartilage
Total laryngectomy	T3, T4a	Hyoid, thyroid, cricoid, entire larynx + strap muscles (sternohyoid, sternothyroid, thyrohyoid, sup/inf bellies of omohyoid)	


Nasopharynx
Mandibular condyle
Pterygoid plate
IJV
Foramen magnum
Tonsil
RP node
C1
Spinal canal
C2
Spinous process
JD node
II
C3
Vallecula
Pyriform sinus
C4
Hyoid
Thyroid cartilage
C5
III
Arytenoids
True vocal cords
C6
Cricoid cartilage
Subglottis
NICHOLAS G ZAORSKY, MD

Thyroid Cancer: PTC, FTC, MTC, and ATC [19–23, 112–120]

- **T1** –
  - T1a – ≤1 cm
  - T1b – 1–2 cm
- **T2** – 2–4 cm, capsule intact
- **T3** –
  - T3a – >4 cm but limited to thyroid
  - T3b – Gross extrathyroidal extension into strap muscles
- **T4** –
  - T4a – subQ, larynx, trachea, esophagus, recurrent laryngeal, or any anaplastic
  - T4b – prevertebral fascia, carotid, mediastinum (anaplastic out of thyroid)
- **N1a –** level VI-VII
- **N1b –** level I-V or RPs

Papillary/follicular		Papillary/follicular, medullary		Anaplastic	
<55 years old		≥55 years old (and all medullary)			
M0	I	T1 or T2	I		
M1	II	T1-2 & N1 or T3	II		
		T4a	III		
		T4b	IVA	N0	IVA
		M1	IVB	T3b-4 or N1	IVB
				M1	IVC

Pathology

- Differentiated thyroid cancer (DTC) = papillary and follicular
- **Papillary** carcinoma (follicular cells)
  - Has a "follicular variant"
  - Good prognosis except diffuse sclerosing, tall cell, columnar cell
  - Takes up RAI
  - Hurthle cell is a variant (does not take up RAI)
  - 30% LN+, 5% DM+
- **Follicular** carcinoma (Follicular cells)
  - Looks like follicular adenoma but invasive
  - Takes up RAI
  - Requires capsular or vascular invasion, cannot be diagnosed on FNA
  - 10% LN+, 15% DM+
- **Medullary** carcinoma (parafollicular/C cells)
  - Excrete calcitonin (↓serum calcium), can be tracked
  - 25% associated w/ MEN syndrome(RET, Ch 10)
    - MEN2A: pheochromocytoma, hyperparathyroid, MTC
    - MEN2B: marfanoid, ganglioneuromas, pheochromocytoma, MTC
  - Don't take up RAI
  - Test RET on all patients
- **Anaplastic** carcinoma
  - ↑ age, mets, does not take up RAI

Work-up

- H&P, TSH, T3, T4
- CT (no iodine), +/– CT chest, +/– RAI scan
- For MTC: calcitonin, CEA, catecholamines, RET
- BRAF + TERT mutation: poor prognostic markers for PTC
- MEN2: rule out pheochromocytoma with serum and urine catecholamines. Rule out hyperparathyroidism with PTH and Ca
- US, then FNA. ↓TSH ➔ thyroid radionuclide scan:
  - If functional ➔ no FNA
  - If nonfunctional ➔ FNA

Differentiated Thyroid Cancer

- PMH and Hong Kong retrospective reviews show ~90% LC, improved with RAI if stage II+, >45 y/o. EBRT ↑LRC, but not OS or CSS

Anaplastic Thyroid Cancer

- SEER (Chen): EBRT improved OS for patients with >1 m survival and ETE, by no mets
- De Crevoiser 2004: suggests treating with surgery, then chemo, then 40 Gy BID, then chemo again (cisplatin and doxorubicin)

For Primary Therapy
- Total thyroidectomy for cT3 or cN1 or M1
- Lobectomy or total thyroidectomy for cT1-2 cN0
- Lobectomy for cT1a
- If cN+/pN+, then bilateral neck dissection + VI
- With total thyroidectomy, can follow thyroglobulin for recurrence (should be undetectable after total thyroidectomy)
- Anaplastic rarely early stage. If early, still recommend resection.

Post-op

- Check thyroglobulin, Tg ab. If pt has Tg ab, then the Tg is not interpretable.
- Check TSH should be >30.
- If distant mets seen on cross-section imaging need 123-I imaging.

Radioactive Iodine
- Use in PTC, FTC, HTC
- Avoid iodine contrast 4–6 months prior to treatment
- ^{131}I: 8d half-life, 364 keV, beta minus
- Rx is 100–200 mCi with 5 days of scan
- Rescan 7–10 days following to ensure uptake, then 4–6 months later to eval for new sites
- Low iodine diet, stop levothyroxine for 6 wks (can give T3 for the first 3 weeks)
- Recombinant TSH (thyrogen) avoids withdrawal symptoms prior to RAI scan
- Side effects: sialadenitis, xerostomia, cystitis, gastritis, diarrhea, oligospermia
- Maximum lifetime RAI dose is ~800 mCi

Adjuvant Therapy RAI for any high risk

- Low risk: typically no RAI.
- Intermediate risk is aggressive histology, minor ETE, vascular invasion, or >5 LNs involved. Give 30 mCi (for ablation) – 150 mCi (residual dz. in neck)
- High risk is gross ETE, margin-positive, elevated post-op Tg, metastatic, give 100–200 mCi
- Medullary: no RAI. Check RET proto-oncogene. Get liver MRI
- Max lifetime dose 800 mCi

After RAI

- Resume levothyroxine 2–3 d after I–131.
- Restage.
- Excellent response is negative imaging and either suppressed Tg (<0.2 ng/mL) or TSH stimulated Tg <1 ng/mL. see yearly.
- Indeterminate response is indeterminate imaging, non-stimulated Tg low (<1 ng/mL).
- Biochemical incomplete response. Suppressed Tg >1 ng/mL

NCCN
- Contains criteria for biopsy (anything >1 cm)
- Surgery if feasible
- Neck dissection if <15 y/o, >45 y/o, RT history, T3+, N+
- RAI indications: ETE, >4 cm, post-op Thyroglobulin>5 ng/mL (consider for N+, >1 cm, LVSI, anti Tg antibodies, poorly differentiated)
- EBRT: no defined role, consider for:
  - Extensive R+ or ECE
  - Unresectable disease that doesn't take RAI
  - Tracheal involvement
  - Post-op locally invasive MTC (50/25)
  - Anaplastic histology (>5% of cells)
  - Bulky mets after RAI
  - Doses similar to SCC (50→70Gy)

RT
- Primary + b/l neck: 70/66/60/54 in 35 Fx
- PET/CT simulation
- 70 for gross disease
- 66 for + margin/microscopic disease
- 60 for HR neck
- 54 for bilateral II-V + VI, VII and include mediastinal LN to carina for N+
- Anaplastic = + low-dose Adriamycin or taxol

Melanoma [19–23, 121–139]

- **T1** – ≤1 mm thick
  - T1a – nonulcerated <0.8 mm
  - T1b – ulcerated or 0.8–1.0 mm
- **T2** – 1.01–2 mm thick
  - T2a – nonulcerated
  - T2b – ulcerated
- **T3** – 2.01–4 mm thick
  - T3a – nonulcerated
  - T3b – ulcerated
- **T4** – >4 mm thick
  - T4a – nonulcerated
  - T4b – ulcerated

– **N1**–1 node
  - N1a – clinically occult node (SLNBx)
  - N1b – clinically apparent node
  - N1c – no nodes but in transit/satellite/microsatellite

– **N2**–2–3 nodes
  - N2a – clinically occult
  - N2b – at least one clinically apparent
  - N2c – 1 clinical node and in transit/satellite/microsatellite

– **N3** – ≥ 4 nodes
  - N3a – ≥ 4 nodes, all occult
  - N3b – ≥ 4 nodes some felt or matted nodes
  - N3c – 2+ clinical nodes and in transit/satellite/microsatellite

- **M1a** – skin, subQ, distant nodes
- **M1b** – lung
- **M1c** – visceral non-CNS mets
- **M1d** – CNS mets

Clinical staging					
	T1a	T1b/T2a	T2b/T3a	T3b/T4a	T4b
N0	IA	IB	IIA	IIB	IIC
cN+	III				
M1	IV				

Pathologic staging					
	T1a/T1b	T2a	T2b/T3a	T3b/T4a	T4b
N0	IA	IB	IIA	IIB	IIC
N+					
pIIIA	T1-T2a and N1a/N2a				
pIIIB	T1-T2a N1b/c r N2b *or* T2b-T3a NN1a-N2b				
pIIIC	T1-T3a N2c/N3 *or* T3b-4aN+ *or* T4b N1-2c				
pIIID	T4bN3				
M1	IV				

General

– Subtypes: superficial spreading (65%), nodular (25%) lentigo maligna, and acral lentiginous.
– Wu, 2016: **Sunburns** are associated w increased risk of melanoma (vs any other type of cancer): RR 2.41 in melanoma, 1.48 for SCC, 1.18 for BCC.
– ABCDE (for melanoma): asymmetry, borders, color, diameter >5 mm, enlargement.

Workup

– WLE with SLN
– <1 mm: nothing special
– >1 mm, labs, CXR, consider CT for nodes
– No shave biopsy unless index of suspicion low
– LN+: PET-CT, MRI
– SLNB if 1+ mm thickness. If pos, then complete dissection of all involved LN basins. Twenty percent chance more LNs. Must do dissection if cLN+.

- **Imaging:**
  - Stages 1–2: consider nodal US for equivocal exam findings
  - Stage 3: obtain PET and brain MRI
  - In transit: intra-lymphatic tumor in skin or subQ tissue >2 cm from primary but not past nearest regional nodes

Pathology
- On report:
  - Breslow thickness
  - Mitotic rate
  - Ulceration
  - Margin status
  - Microsatellitosis
  - PNI
  - Clark Level (if <1 mm)
  - LVSI
- Breslow method: path assessment of primary tumor *thickness*
- Clark method: path assessment of primary tumor level of *DOI*
- Clark Levels
  - I: epidermis only
  - II: into papillary dermis
  - III: filling papillary dermis, compressing reticular dermis
  - IV: invading reticular dermis
  - V: into subQ
- S-100+, melan-A+, HNB-45
- BRAF if M1

Surgical Margins

- The UK melanoma study group: 1–2 cm vs 3–5 cm margins. For >1 mm depth, 2 cm surg margins wins. In case of LRR, 5-year OS is 10%. If no LRR, 5-y OS 86%.

Adjuvant Therapy

- **Interferon alpha (ECOG 1684/1690/1694):** IFN-alpha for T4 or N+ pts provided ↑ 10% RFS, not OS.
- **Ang 1994:** phase II. patients had high-risk features, inc Breslow >1.5 mm, clinically LN+, recurrent dz. 79 pts WLE + 30 Gy/5 twice weekly over 2.5w (some patients got LND). Five-yr LRC 88%, OS 47%. This was better than historical outcomes. Toxicity tolerable. OS better if LN burden lower. Based on these results, RTOG 9302 closed early due to poor accrual.
- **Chang 2006:** 56 pts retrospective, 30/5 vs 60/30: no difference, more complications with 30/5.
- **TROG 96.06:** 234 pts, 48/20 (if +margin got 50/21). 5 yr in field failure 6.8%, OS 36%. Rate of G3 lymphedema 19% in gorin and 9% in axilla. This RCT is precursor to 02.01.
- **MDACC/Ballo et al.:** Risk factors for nodal recurrence: ECE, 4+ LNs involved, any LN measuring >3 cm, cervical LN location, recurrence.
- **TROG 02.01:** phase III, 250 pts. Resection+LND, then observation vs 48/20. Dose technically designed for lymphatics. Had to have at least 1 high-risk feature: 1+ *parotid LN,* 2+ *axillary LN,* 3+ *groin LN, any ECE*, LN ≥3 cm in neck, LN ≥4 cm in axilla or groin. RT ↑LRC (60→82%, SS) but did not affect RFS, OS.
- Overgaard: primary RT. 50 Gy in 20 fx with 100–250 kv, 1.5 cm margin and hyperthermia. Consider in lentigo maligna of the face.

Surgery
- IA: WLE alone, no SLNB
- IB2: WLE + SLNB. 1 cm margin for T1. 2 cm margin for T2 4
- III: WLE

Adjuvant Ipilimumab
- Ipi is anti-CTLA4 antibody
- **Eggermont, 2016:** Stage III melanoma randomized to placebo vs ipi. Five-year RFS 41 vs 30%; 5-year OS 65% vs 54%, favoring ipi
- Hodi, 2010: M+ melanoma. Ipi improved MST by 10 mos vs gp100. Median OS 9 m vs 11 m. >10% OS advantage at 1-, 2-, 3-year time points
- Robert, 2011: M+ melanoma. Dacarbazine +/− ipi. MST w ipi 9–11 mos. 3–y OS 20 vs 12%

Definitive RT
- RTOG 8305: Showed 32/4 same as 50/20, CR ~25%
- Overgaard 1995: 24 or 27 Gy in 3 fx over 8 days followed by hyperthermia. Hyperthermia and 27 Gy improved LC (each ~25→50%)

NCCN
- Surgery for everyone
- Stage 1: T1-T2a, N0
  - WLE [w 1 cm margin for T1, 2 cm for T2]
  - (+SLNB if >1 mitosis/HPF or T1b)
- Stage 2: T2b-T4b, N0
  - WLE [w 2 cm margin]
  - + SLNB
- Stage 3: Node (+)
  - WLE w 2 cm margin + LND
  - Systemic options: nivo (preferred), dabrafenib/trametinib for BRAF V600+, high-dose ipi, or interferon alpha.
  - Hold BRAF/MEKi during RT
- Stage 4: M1
  - If limited, resect. Otherwise, systemic tx.

Radiation Therapy

	Primary site	Nodes
Indications for RT	(almost never) R+ extensive neurotropism	ECE 4+ LNs in groin 4+ LN in axilla 2+ cervical 3+ cm LN
Doses	70/35 50/20 (2.5 Gy) 35/5 (7 Gy)	60/30 48/20 (2.4 Gy) 30/5 (6 Gy)
Volume	RT to encompass the site scar with 3–4 cm margin	Nodal basin

- Contouring/planning based on location. Immobilize and use bolus 5 mm
- **Electrons**: Similar to MCC. Primary +4–5 cm margin to blocked edge. Can use smaller margin of 2–3 cm if in head and neck
- **Photons**: same for electrons but mainly when LNs needed to be covered

Metastatic Disease
- Ipilimumab (CTLA4 antibody) improves OS
- Vemurafenib, dabrafenib (BRAF inhibitors, V600 mutation)
- IL-2
- Imatinib (C-kit)

Outcomes
- LC stage I/II: 80–90%
- Stage III w/ adjuvant RT: RR 20%
- OS 50%

Mucosal Melanoma

- T3 and T4 only
- Sinus/nasal cavity: surgery with ND if N1 or def RT if T4b
- PORT to primary site and include neck if N1
- OC/OPX, LX, HPX: surgery, ND, PORT. If T4b, then def RT

Skin Squamous Cell and Basal Cell Carcinoma (SCC/BCC) [19–23, 140–144]

- **T1** – ≤ 2 cm
- **T2–**2–4 cm
- **T3** –> 4 cm or minor bone erosion or PNI 1+ mm or deep
- **T4**
  - T4a – gross cortical bone invasion
  - T4b – skull base invasion

	T1	T2	T3	T4
N0	I	II	III	IV
N1	III			
N2	IV			
N3				
M1				

AJCC8: No staging system for BCC or cutaneous SCC outside H&N

cN1	Single ipsi node ≤3 cm, no ECE	**pN1**	Single ipsi node ≤3 cm, no ECE
cN2		**pN2**	
cN2a	Single ipsi, 3–6 cm, no ECE	pN2a	Single ipsi, 3–6 cm, no ECE; *or* <3 cm with ECE
cN2b	Multiple ipsi, 3–6 cm, no ECE	pN2b	Multiple ipsi, 3–6 cm, no ECE
cN2c	Bilateral or contralat, 3–6 cm, no ECE	pN2c	Bilateral or contralat, 3–6 cm, no ECE
cN3		**pN3**	
cN3a	>6 cm, no ECE	pN3a	> 6 cm, no ECE
cN3b	Any clinically overt ECE	pN3b	Single >3 cm with ECE; *or* multi-nodes with any ECE

Nasal Vestibule SCC

- **T1** – superficial, only in vestibule
- **T2** – skin of nose, upper lip, nasal septum
- **T3** – bone, deep muscle

General

– Associated conditions: albino, xeroderma pigmentosum, Turcot syndrome, Fanconi Anemia, Gorlin syndrome
– Marjolin's ulcer: SCC from chronic inflammation
– BCC: low PNI, LN, or DM
– SCC: PNI in 10%. If G3, >3 cm, DOI >4 mm, lips or temple, then 15% LN met.
– Gorlin syndrome: increase risk BCC, medullo, RT sensitivity

Anatomic Areas

– Nasal vestibule, w epithelium that is hair follicle bearing skin. Triangular space. Nasal vestibule SCCs extremely rare, tend to do worse
  - Borders: Limen nasi (post); alae nasi (lat); membranous septum and coumella (medial); floor of nasal cavity(inf)

Workup

– H&P, exam, biopsy
– Contraindications to RT: XP, Gorlin's syndrome/basal cell nevus syndrome, epidermodysplasia verruciformis
– If HN, then do neuro exam specifically assessing CN5 and seven for PNI
– If medial/let canthus lesion, CT to assess DOI into orbit
– PET if LN+
– MRI if PNI

Retrospective Reports

– Rogers and Coldiron 2009: showed that RT was most expensive treatment of available options
– Roussy 1988: survery vs RT (interstitial or orthovoltage). Surgery won. LC 7.5→0.7%. Orthovoltage was best of RT options (5%)
– Balamucki et al. pts with BCC or SCC with PNI benefit from ENI (18–0% neck failure)

Chemo

– Vismodegib, a SHH inhibitor, approved in 2012, for LA and M+ BCC

Surgery Background

– BCC: 4 mm SMs
– SCC: 5–6 mm SMs
– There has been a RCT of surgery vs RT. RFS is 0.7 vs. 7.5% for surgery vs RT. Cosmetic outcome also better with surgery

High-Risk Factors for Local Recurrence
- Trunk and extremities >2 cm; check/forehead/scalp/neck >1 cm; mask areas of the face, genitalia, hands, feet >6 mm
- Poorly circumscribed
- Recurrent
- Immune suppression
- Prior RT or chronic inflammation
- PNI
- Rapid growth
- G3-4
- adenoid/adenosquamous/desmoplastic
- Clark level IV/V or >2–5 mm thick.
- For SCC: acantholytic, adenosquamous, desmoplastic, or metaplastic
- For BCC: morpheaform, basosquamous, sclerosing, mixed infiltrative, or micronodular

Orthovoltage Background
- Has max dose at surface, less beam constriction at surface and depth, can use smaller fields, has less penetration through eye shields
- However, has higher exit dose than electrons, higher absorption in bone/cartilage, not available in most depths

Electron Background
- Similar outcomes to photons
- Have lower RBE than orthovoltage X-rays by 15–20% and require commensurate increase in dose. Thus, most authors of NCCN will equate electrons dosed to 90% IDL vs orthovoltage dose to dmax
- Require bolus, at least 0.5–1 cm
- Confirm w OSLDs and phantom
- Require larger field size to allow sufficient buildup and account for lateral constriction, usually 1.0–1.5 cm *margin.* Wider margins necessary than w orthovoltage X-rays bc of constriction of higher IDLs at depth
- "Tertiary collimation": using lead on the skin to reduce beam penumbra and make tighter margins for OARs. Does not work for superficial X-rays bc of backscatter
- **4-3-2-2 rule.**
- For an electron beam with energy, E
  - Depth to 90% dose (cm) **at E/4 cm**
  - Depth to 80% dose (cm) **at E/3 cm**
  - Range (<5% dose) **is E/2 (cm)**
  - Required thickness of lead shielding (mm) = **E/2**

Standard Skin SCC, NCCN

- Prefer WLE or Mohs
- PORT for high-risk features
  - T3/4
  - parotid gland
  - R+
  - PNI: should be of a named nerve bc nerves <0.1 mm tend to not have higher LRs vs no PNI.
  - Multi high-risk features (>2 mm thick, clarke ≥IV (invades reticular dermis), pni, poorly/undiff, ear or nonhair bearing lip)
  - Indication for RT to regional LNs: N2+, ECE, T3/4, PNI
- Topical 5FU/imiquimod for low-risk superficial BCC
- Definitive RT for
  - high risk or nonsurgical candidates, e.g., large lesion of scalp, ears, forehead (>2 cm); central face including >0.5 cm involving the eyelids, ala, nose, lips
  - cartilage, bone, muscle involvement
  - recurrent
- Neck treatment same as other H&N cancer. If near parotid, treat parotid and levels II–IV on hemineck

RT Contraindications
- Poor blood supply (shin, back of hand)
- Gorlin's syndrome
- ATM
- Xeroderma pigmentosum
- Scleroderma

Sim
- Based on location. Immobilize and use bolus 5 mm

Contouring/Planning

- **Electrons**
  - Primary/post-op area plus 1.5 cm margin
  - 6–12 MeV
  - Prescribe to 90% IDL
  - Lead eye shield: use if treating medial canthus/eyelid tumors
  - Try to block out lacrimal gland
- **Photons**
  - Use IMRT when covering regional LNs

Tumor diam	RT margins	Dose
<2 cm	1–1.5 cm	60–64 Gy/30–32 fx @ 2 Gy in 6–6.4 w 55 Gy/20 fx @ 2.75 Gy in 4 w 50 Gy/15 fx in 3 w 30 Gy/5 fx in 2–3 w 12–20 Gy/1 fraction for symptomatic management of large bleeding tumors of very ill/nursing home type patient
>2 cm	1.5–2 cm	66–70 Gy/33–35 fx @ 2 Gy in 6.6–7 w 55 Gy/20 fx @ 2.75 Gy in 4w
Post-op		50 Gy/20 fx @ 2.5 Gy 60 Gy/30 fx

Chemo

- BCC: only if metastatic (hedgehog inhibitor)
- SCC: may consider cisplatin for locally advanced cases

Nasal Vestibule SCC

- Behaves like a skin cancer but stages as nasal cavity
- H&P: Nodal exam. Note extension to septum or lip. Intranasal endoscopy and biopsy
- MRI for depth, LN, PNI

Treatment

- Surgery then RT
- Supine with immobilization
- Intraoral stent to displace tongue posteriorly and partially shield upper alveolar ridge
- Fill nasal cavity with bolus as much as possible
- Wax bolus over entire nose to convert it into a box-like contour to improve dose distribution. Lead skin collimation and wax bolus over nose

Tumor	Targets	Dose (Gy)
<1.5 cm and well diff	GTV + 2 cm	66
>1.5 cm or poor diff	GTV + 2 cm	66
	Vestibule, anterior nasal cavity, 2 cm margin above lip	60
	Bilat facial, level IB-II	54
N+: ChemoRT	GTV + 0.5 cm	70
	Vestibule, anterior nasal cavity, 2 cm margin above lip	60
	Bilat facial, level IB-IV	54

Medial Canthus SCC

Treatment Paradigm

- Mohs w flap. If R+, re-resect or RT. Or definitive RT if plan for R2

Indications for Adjuvant RT

- To primary: R+, PNI, DOI >4 mm, multiple HR features
- To regional LNs: N2+, ECE, T3/4, PNI

Technique

- En Face Electrons
  - Always cover CN PNI to BOS
  - 6–9 MeV, prescribe to 90% IDL
  - Pack nose with bolus/saline gauze and lead shielding
  - Custom beeswax bolus over the treatment area
  - Ceramic-coated lead lens cup (Pb mm = MeV/2) during treatment: need anesthetic drops for daily placement, risk of corneal injury due to loss of corneal reflex so must patch the eye after daily treatment
  - Try to block out lacrimal gland
- Photons: Use IMRT when need to cover regional LNs

Merkel Cell Carcinoma (MCC) [19–23, 145–148]

- **T1** – ≤2 cm
- **T2–**2–5 cm
- **T3** – >5 cm
- **T4** – into bone, muscle, fascia, cartilage
- **M1a** – skin, subQ, distant nodes; **M1b** – lung; **M1c** – other

cN1	Regional nodes	**pN1**	
		pN1a	Clinically occult nodes
		pN1b	Clinically apparent nodes
cN2	In-transit mets, no nodes	**pN2**	In transit mets, no nodes
cN3	In-transit mets and nodes	**pN3**	In transit mets and nodes

Clinical staging				
	T1	T2	T3	T4
N0	I	IIA		IIB
N+	III			
M1	IV			

Pathologic staging				
	T1	T2	T3	T4
N0	I	IIA		IIB
N1a	IIIA			
N1b-N3	IIIB			
M1	IV			

General
- Arises from Merkel cells (tactile receptors, maybe neural crest derived)
- "Extrapulmonary small cell"/cutaneous neuroendocrine carcinoma/trabecular carcinoma. Not good
- Risk factors: males, age >70, immunosuppression, CLL, UV rad exposure, Merkel cell polyomavirus

Immunostains
- **Positive**
  - NSE, though also found in SCLC, SC melanoma
  - 80–100% caused by Merkel cell polyomavirus (MCPyV)
  - CK20: + in 95%
- **Negative**
  - TTF1, CK7: found in neuroendocrine ca of lung. Negative in 95% of MC
  - PS100: found in melanoma
  - HMB45
  - CD45: found in lymphoma
  - LCA: found in lymphoma

Anatomy
- HN, 36%; UE, 22%; trunk, 11%; LE, 15%

Workup
- H&P (nodal exam), Biopsy (check CK-20, NSE – should be positive), CT, MR, or PET-CT. For non-HN need SLNB. The use of SLNBx debated for H/N as drainage can be erratic
- SLNB+ ➔ LN dissection and/or RT to LNs
- SLNB- ➔ observe nodal basin

Retrospective Reports
- Mojica 2007: SEER analysis, 1665 pts, surgery +/− PORT. RT improved mean survival for all size tumors.
- TROG 96.07, Poulsen 2003, 2006: phase II, high risk (e.g., primary >1cm_, cLN+, recurrence after initial surgery (outside prior RT field), R2, occult primary w + LNs, biopsy proven MCC: 1996–2001. $n = 53$. 50/25 with concurrent carbo AUC 4.5/etop 80 mg/m^2. For RT, margins were 3–5 cm. Bolus PRN. Dermal lymphatic and regional LNs covered if within 20 cm of primary. Clinically uninvolved LNs txd to 45 Gy. Chemo was q3w × 4c. 3 yr LRC 75%, DMFS 76%, OS 76%. No benefit of CRT over historical controls.
- T1–-2 N0 Merkel: if <1 cm, rate of LNs is 0%; for 1–2 cm, rate of LNs is 25%.

NCCN

– WLE with 1–2 cm SMs. For cN0, do SLNB. For cN1, proceed with biopsy, then imaging. Assess for adjuvant RT.

Scenario	Dose
Gross tumor	60–66 Gy
Microscopic disease (or s/p SLNB or LND)	56–60 Gy
R0 or N0	50 Gy

- **Primary site**
  - **T < 1 cm, N0**: observation is option if margins >1–2 cm. Note this is rare.
  - **All others**: RT to primary, 3–5 cm of margin for risk of in-transit mets.

If PNI, always cover CN5 and 7 to BOS.

- "The RT field for Merkel cells stops when you run into a critical organ. In a few weeks, Merkel cell will fail at your field margin."
- Dose typically ***50–55Gy if R0, 60 if R1, 66 if R2.***
- **Nodal bed**
  - **SLNB:** if SLNB not performed and cN0, LN RT given if suspicion high, ***45–50Gy***; if cN+, ***60-66Gy***
  - **SLNB without LND**:
    - SLNB(−), LN RT not indicated unless large tumor. If in H/N or risk for false neg, then 46–50 Gy
    - SLNB(+), LN RT indicated to regional lymphatics. Treat axilla or groin to 50–54 Gy, HN to 56–60 Gy. If covering regional LNs, always cover in-transit sites.

Outcomes, OS5 by Stage

– 1: 75%
– 2: 50%
– 3: 25%
– 4: <5%

Palliation [149–151]

Pain/Symptom Management

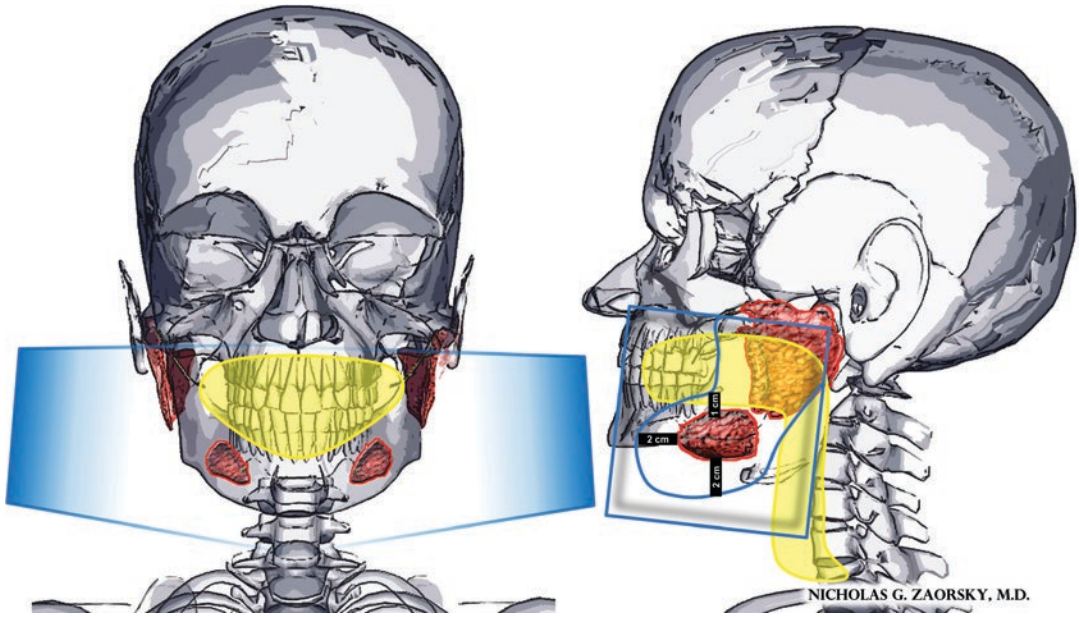
– **QUAD SHOT**: 14 Gy over 4 BID fractions in 2 days. Can repeat x2 every 4 weeks up to a dose of 42 Gy/12 fractions, if tolerated. Provided BED just below the threshold for mucositis; thus, toxicity is minimal.
– **0-7-21**: Give 8 Gy on day 1, then again on day 8, then again on day 22. In a single arm Ontario trial, 40% CR for symptoms, 31% decrease in tumor size, 42% PR symptoms, 50% PR in tumor size
– **Split course**: 20Gy/5 or 30Gy/10, 3–4 week break, then reassess
– **Aggressive palliation**: 50Gy/20, could plan for 2 week break after 10 fx

Sialorrhea

– Treat inferior 2/3 of the parotids and entire SMGs. 81% PR. Median dose is 5 Gy, to 10–15 Gy.

Graves ophthalmopathy

– Autoimmune process of retroorbital space
– Activation of T-cells by TSH antigen, causes cytokine production (TNF and IFN-g), causes retroorbital fibroblasts to produce hydrophilic glycosaminoglycans
– Glycosaminoglycans changes osmotic balance with accompanying influx of fluid and pressure in retroorbital space
– RT rationale: decreases lymphocyte concentration, GAG production
– **Treatment**:
  - For mild sx (e.g., photophobia, wind sensitivity), conservative management recommended. When pt develops chronic irritation, diplopia, and/or proptosis, trial of prednisone 30 mg/d for 4w should be initiated.
  - RT if patients do not have "burnt-out" Graves.
  - 20 Gy/10 fx per eye over 2 w. No benefit to dose escalation (Petersen 1990, 30 Gy no better).


1 cm
2 cm
2 cm
NICHOLAS G. ZAORSKY, M.D.

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Lung Cancer

5

Nicholas G. Zaorsky, Daniel M. Trifiletti, and Henry Wagner Jr

Abstract

This chapter discusses the general management of patients with thoracic cancers, with special focus on principles that guide radiotherapy management. Several key components of trimodality care and stereotactic body radiation therapy (SBRT) are discussed.

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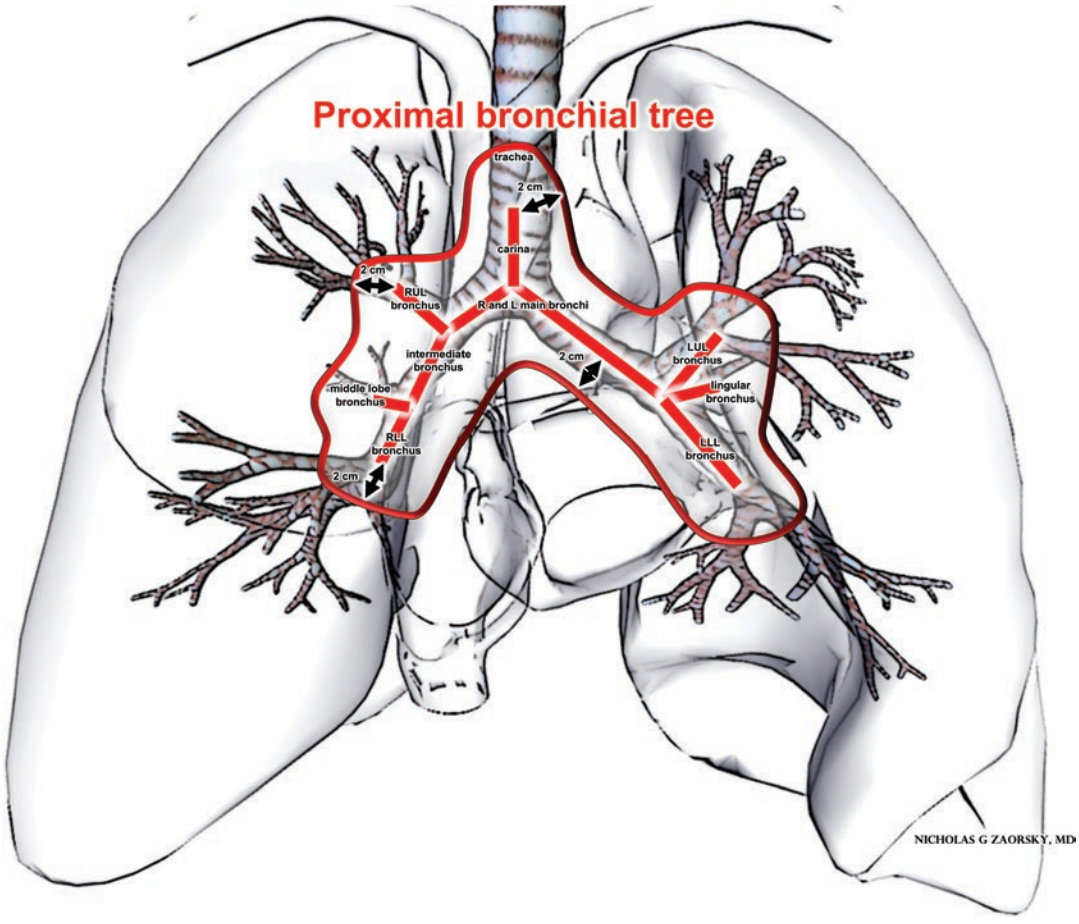
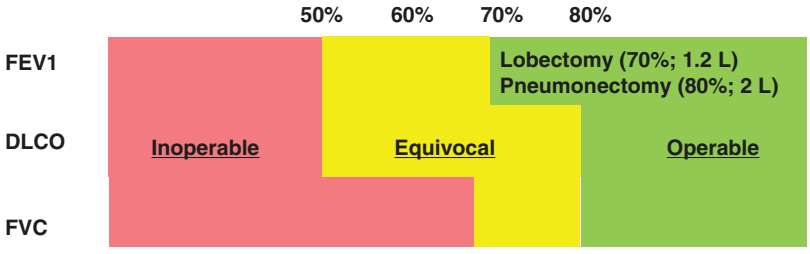

Proximal bronchial tree
trachea
2 cm
carina
2 cm
RUL bronchus
R and L main bronchi
intermediate bronchus
2 cm
LUL bronchus
middle lobe bronchus
lingular bronchus
RLL bronchus
LLL bronchus
2 cm
NICHOLAS G ZAORSKY, MD


50%
60%
70%
80%
FEV1
DLCO
FVC
Inoperable
Equivocal
Lobectomy (70%; 1.2 L)
Pneumonectomy (80%; 2 L)
Operable

Lung Pearls [1, 2]

Nodal and Distant Staging (7th + 8th Edition)

- **N1** – ipsi intrapulmonary, hilar (N10–14)
- **N2** – ipsi mediastinal (N1–9)
- **N3** – contra mediastinal, hilar; BL scalene, supraclav
- **M1a** – tumor in contra lung, pleural nodules, malignant effusion
- **M1b** – 1 distant met
- **M1c** – 2+ distant mets

AJCC 8th Edition Staging

- **T1** – ≤3 cm
  - T1a – ≤ 1 cm
  - T1b – 1.01–2 cm
  - T1c – 2.01–3 cm
- **T2** – 3–5 cm
  - T2a – 3.01–4 cm or main stem bronchus (but not carina), visceral pleura, atelectasis (*VAB*)
  - T2b – 4.01–5 cm
- **T3** – 5.01–≤7 cm
  - or parietal pleura, chest wall, diaphragm, phrenic nerve, pericardium, carina (<2 cm to carina doesn't matter now), whole lung atelectasis, tumor in the same lobe
- T4 – ≥7 cm
  - or mediastinum, heart, great vessels, trachea, recurrent laryngeal, esophagus, vertebrae, carina, separate tumors in ipsi lobes

1	Low cervical, SCV	8	Paraesophageal, ↓carina
2	Upper paratracheal	9	Pulm ligament
3	Pre(3A) & retro(3P) trach	10	Hilar
4	Lower paratracheal	11	Interlobar
5	AP window	12	Lobar
6	Paraaortic	13	Segmental
7	subcarinal	14	subsegmental

AJCC 7	T1	T2a	T2b	T3	T4
N0	IA	IB	IIA	IIB	IIIA
N1	IIA		IIB	IIIA	
N2	IIIA				IIIB
N3	IIIB				
M1	IV				

AJCC 7th Edition Staging

- **T1** – ≤3 cm
  - T1a – ≤2 cm
  - T1b – 2–3 cm
- **T2** – 3–7 cm or main stem bronchus (>2 cm from carina), visceral pleura, atelectasis
  - T2a – 3–5 cm or T2 <3 cm w above features
  - T2b – 5–7 cm
- **T3** – >7 cm
  - or parietal pleura, chest wall, diaphragm, phrenic nerve, pericardium, bronchus <2 cm from carina, whole lung atelectasis, tumor in the same lobe
- **T4** – mediastinum, heart, great vessels, trachea, recurrent laryngeal, esophagus, vertebrae, carina, separate tumors in ipsi lobes

AJCC 8	T1a	T1b	T1c	T2a	T2b	T3	T4
N0	IA1	IA2	IA3	IB	IIA	IIB	IIIA
N1	IIB					IIIA	
N2	IIIA					IIIB	
N3	IIIB					IIIC	
M1	IV						

Overview

- Lung ca: 228,200 cases/yr, 160,000 deaths (U.S. only, increasing in Africa and Asia).
- 5-year OS for severe COPD is 40%.
- Risk factors: smoking, asbestos, radon.
- Five lobes, five segments/lobe (except RUL-3 and RML-2).
- 40% adeno, 35% SCC, 15% large cell, 10–15% SCLC.
- Adeno in situ (BAC): not assc with smoking. Spreads along alveoli, responds to TKIs.
- Stains TTF-1+ (except SCC).
- +/− EGFR (90% SCC, 30% adeno) exon 19.
- TKIs work until T790 M mutation (newer 3rd-gen TKIs target T790 M).
- Kras and ↑ERCC1 don't respond well to platinum. KRAS in 35% of adenos and has the poorest prognoses. EGFR and ALK are targetable.

Screening

- USPSTF: current or recent smokers, 55–79 yo, more than 30 pack/yrs → low-dose CT annually x several years.
- National Lung Screening Trial: 53 K pts at high risk for lung ca in the U.S.. Rando to three annual screening w low-dose CT vs single PA X-ray. Adherence >90%. Rate of + tests 24% vs 7%. A total of 96% vs 95% were false positives. CT screening had relative reduction in mortality vs X-ray by 20%. Rate of death from any cause also decreased by 7%.

Workup

- **History**:
  - Cough (75%), hemoptysis (57%), dyspnea
  - Weight loss
  - Voice changes (common with L lung tumors)
  - Dysphagia (esophageal compression)
  - Apical tumors: arm weakness, pain
  - Smoking history, cancer history, family history
  - Occupation, infectious agents
- **Labs**: CBC, CMP, LFTs, alk phos, LDH
- **CXR**: compare to priors
- **CT**: with contrast, from thyroid to liver/adrenals LN staging – Se 60%, Sp 80%
- **PET scan**: may be used as mediastinal staging. Se 85%, Sp 90%. If PET+ in mediastinum, need path confirmation
- **MRI brain** if symptoms, SCLC, stage IB+, NSCLC
- **MRI thoracic inlet** for superior sulcus
- **PFTs**
- Mediastinal staging: do this first if suspicious mediastinal or hilar lesion since it upstages patient
- Bronchoscopic bx for central lesion
- CT-guided biopsy for peripheral lesion. 20% risk PTX
- Smoking cessation

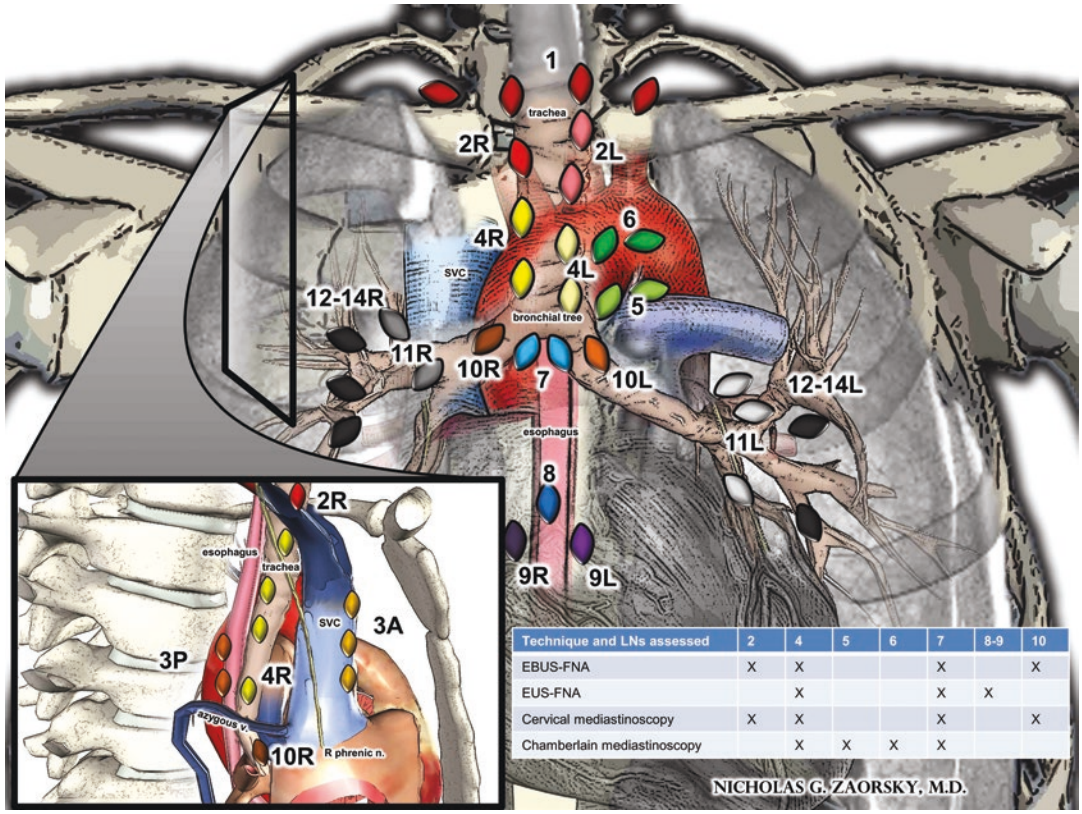
Paraneoplastic Syndromes

- Hypertrophic osteoarthropathy: joint pain without bone mets (can see elevated periosteum on plain films and will be positive on bone scan), adenoCA
- Hypercalcemia: SCC from PTH-related peptide (PTHrP)
- SCLC: SIADH, cerebellar ataxia, Eaton-Lambert

Mediastinal Staging

- NCCN recommends 3+ stations sampled and sampling 8 and 9 (harder to reach).
- For R-sided tumors, 2R, 4R, 7, and 10R should be sampled.
- For L-sided tumors, 5, 6, 7, and 10 L should be sampled.
- Go after highest stage LN.
- If there are suspicious M1 lesions, biopsy these if possible rather than N1 or N2 sites. In general, biopsy most advanced suspicious lesion first.

- **Cervical mediastinoscopy**
  - Levels 1–4R, 7, 10
  - Requires thoracic surgeon, may be omitted in inoperable patients
- **Chamberlain**
  - Levels 4L, 5, 6, 7
  - Left median sternotomy via left second intercostal space
- **EBUS-FNA**
  - Levels 2, 4, 7, 10
  - Great for pts unable to get mediastinoscopy due to medical comorbidity
- **EUS-FNA**
  - Levels 4, 7, 8, 9
- **ACOSOG Z0030,** Darling, 2011: no benefit of complete mediastinal LND if thorough nodal sampling was negative.



Technique and LNs assessed	2	4	5	6	7	8-9	10
EBUS-FNA	X	X			X		X
EUS-FNA		X			X	X	
Cervical mediastinoscopy	X	X			X		X
Chamberlain mediastinoscopy		X	X	X	X		

LN Stations

- Level 1 – low cervical and supraclavicular lymph nodes
- Level 2 – upper paratracheal lymph nodes
- Level 3A – prevascular lymph nodes
- Level 3P – retrotracheal lymph nodes
- Level 4 – lower paratracheal lymph nodes
- Level 5 – subaortic lymph nodes
- Level 6 – para-aortic lymph nodes
- Level 7 – subcarinal lymph nodes
- Level 8 – paraesophageal lymph nodes
- Level 9 – pulmonary ligament lymph nodes

Brachial Plexus

- Find C4–5 and T1–2 neural foramina on sagittal.
- Contour ventral rami of C5–T1 as exiting foramina.
- Contour trunks of BP bw ant and mid-scalene muscles.
- Follow insertion of scalene muscles into first rib.
- Contour BP divisions, cords, and terminal nerves by following subclavian artery into axilla.

PFTs

	Inoperable	Desirable
FEV1	<50% or <1.2 L	1.5 L or 70% predicted for lobectomy 2 L or 80% predicted for pneumonectomy
FVC	<70%	>70%
DLCO	<50%	>60%
Predicted post-op		FEV1 >0.8 L or 40%

NSCLC General Volumes

- Definitive RT for early stage: treat primary and involved nodes only (Sibley review – no benefit to elective nodal RT).
- Conc chemoRT: treat primary and mediastinum 40–45Gy, and boost primary and + nodes to 60 Gy (limited role of ENI; most will say define one volume and treat that volume).
- Post-op RT: role in N2. See doses below.
- Post-op RT for R+: treat margin area only.

Simulation

- Orders: supine, arms raised, alpha cradle, CT sim + contrast, 2.5 mm slice thickness, image thoracic inlet to below diaphragm (s'clav or lower lobe involvement may require extension of image borders). Consider taking bottom of scan to bottom of the liver. Tumor volume outlined. Contours of the lungs, heart, esophagus, spinal cord, and body surface.
- When analyzing DVH for lung dose, should look at whole lung – GTV, per RTOG 1306 and RTOG 1308. Using whole lung, CTV or PTV will decrease apparent lung doses but should not be used when comparing a tx plan to dose criteria per RTOG protocols. The use of contrast varies if there is a recent enhanced scan of CT/PET available for fusion.

Conventional Fractionation Contours

- Standard-free breathing CT w IV contrast
  - GTV: tumor + involved nodes (from CT, PET). Nodes and primary contoured separately.
  - When contouring for SBRT, should use the "pulmonary" window. Other presets will underestimate the size of target.
- 4D CT
  - GTV = primary tumor and involved LNs (>1 cm short axis diameter or PET avid).
  - iGTV = GTV + margin for motion from MIP or on three breath hold scans,
  - ITV: created in one of two ways – (1) iGTV +8 mm to include subclinical miscoscopic dz, shave at natural barriers and (2) combine all CTVs in all respiratory phases.
  - CTV: GTV + ITV + ***6 for SCC and 8 mm for adeno*** for primary (Giraud, IJROBP, 2000) and 3–5 mm for LN. Connect fat betweenLN stations (e.g., cover 4 if 2 and 7 are involved). Otherwise, no ENI.
  - PTV: CTV + 5 mm (setup error).
  - 4D CT takes multiple images in thin sections; then the images in each section are sorted into each breathing phase and reconstructed into a 4D movie. If tumor is EVER in a given area during breathing, that area is included in the ITV.

Chemo for Localized Disease

- Cis**p**latin/**E**toposide (**EP**)* historically the SWOG regimen. SOC for SCLC; can also be used in NSCLC. Cis is 50 mg/m^2 on d1, 8, 29, 36; etoposide is 50 mg/m^2 per day on d1–5, 29–33.
- **C**arbo/**P**aclitaxel (**CP**)* preferred CALGB regimen. Also used for sequential CRT. Used in NSCLC.
- CP is typically given as a weekly regimen and give typical doses (e.g. Carbo AUC 2, paclitaxel 45mg/m2).
- *Depending on med onc, may give additional two cyc after RT.
- **EP vs CP:** previous RCTs show equivalence between EP and CP (Wang, 2012). VA analysis (2015) of concurrent CRT showed no difference in outcomes; however, EP patients are more likely to be hospitalized, have more outpatient clinic visits, and have infections, dehydration, and esophagitis.
- **Cisplatin**: alkylator.
- **Etoposide**: topoisomerase II inhibitor.
- **Taxol**: prevents microtubule disassembly.

Chemo for Advanced/Metastatic Disease

- **Carbo** AUC5 on d1 and **pemetrexed** 500 mg/m^2 on d1, q21 d for 4c: for non-SCC
- **Cis** 75 mg/m^2 on d1 and **pemetrexed** 500 mg/m^2 on d1, q21 d for 3c: for non-SCC
- **Cis** and **gem** for SCC (folic acid premed if using PEM)

Other Chemo Considerations

- Cetux (from RTOG 0617): 400 mg/m^2 d1 and then 250 mg/m^2 weekly (doesn't work).
- Cis is given with dex, Zofran, and aprepitant.
- Cis/etop and cis/vinblast can be given full dose with RT.
- Carbo/taxol, Carbo/gem, and Cis/vinorelbine require dose reduction.

Follow-Up

- H&P and contrast-enhanced chest CT every 4–6 mo for 2 y.
- Then H&P and non-contrast-enhanced chest CT annually.
- Smoking cessation counseling.
- PET or brain MRI is not indicated for routine follow-up.

Common hypofractionated RT doses (Gy)			
Total dose	Dose/fx	fx	Example indications
24–34	34	1	Peripheral, small (<2 cm) tumor, esp >1 cm from CW (RTOG 0915)
45–60		3	Peripheral tumor and >1 cm from CW
48–50	12	4	Central or peripheral tumors <4–5 cm, esp <1 cm from CW
50–55	10	5	Central or peripheral tumors, esp <1 cm from CW
60–70	7.5	8–10	Central tumors
70	4.12	17	Central tumors (CALGB 39904)
60	5	12	Central tumors (the Netherlands)

Common RT doses (Gy)			
Total dose	Dose/fx	fx	Example indications
60–70	2	30–35	Definitive RT, +/− chemo
45–54	1.8–2	~25–28	Pre-op
50–54	1.8–2	25–30	Post-op, R0
54–60	1.8–2	~30	Post-op, ECE or R1
60–66	2	30–33	Post-op, R2 (70 Gy is high)
30–45	3	10–15	Palliation, obstruction
20–30	4–3	5–10	Palliation, bone me, w soft tissue mass
8–30	8–3	1–10	Palliation, bone me, no soft tissue mass
17	8.5	2	Palliation, chest dz, poor PS
8–20	8–4	1–5	Any mets, poor PS

PORT

- CTV: bronchial stump + nodal stations, tumor bed only if parietal pleura invasion

What if Not Meeting Constraints?

- Use more AP/PA beams (vs angled), tighter ITV, do induction chemo first, re-CT after 36–45 Gy, do gating, do IMRT, amifostine.

Toxicity of RT

- Dermatitis
- Esophagitis
- Cough
- Fatigue
- Heme, monitor CBC weekly
- Pulmonary fibrosis
- Pericarditis
- Brachial plexopathy
- Lhermitte's
- Radiation pneumonitis:
  - No clear thresholds, though accepted limits are V20 <30–35% and MLD <20 Gy for 20% risk of pneumonitis.
  - Risk of pneumonitis for V20.
    - <20%: **2%**
    - 20–30%: **10%**
    - >30%: 15–40%
  - Risk of pneumonitis MLD
    - <10: 5%
    - 10–20: 10–15%
    - >20: 25%
  - Type 1 pneumocytes die, and type 2 proliferate. Subacute reaction, occurring 6w to 6 m after RT.
  - Increased levels of TGF-B before and during RT (not after) are correlated with pneumonitis, pulm fibrosis, and RILD. TGF-B activates SMAD3, which binds to type 1 and 2 receptors.
  - Fever, SOB, tachycardia, hypoxia.
  - Diffusing capacity may be decreased.
  - Rule out other processes.
  - Refer to pulmonology.
  - Get PFTs to monitor.
  - Treat with prednisone (1 mg/kg/d). Taper as tolerated.

Dose Constraints in Gy (RTOG 0618, 0813, 0915; QUANTEC) [3–5]

OAR	1 fraction	3 fractions		4 fractions		5 fractions		30–35 fractions	
	Max total	Max total	Max/ fx	Max total	Max/ fx	Max total	Max/ fx	Max total	Others
Cord	14	18	6	26	6.5	30	6	50	
Lung per RTOG, lung – GTV should be used for RTOG 1306, 1308						RTOG 0813: V20 <10% D1.5 L max 12.5 Gy (2.5 Gy/fx) D1L max 13.5 Gy (2.7 Gy/fx)			V20 <35% V5 <65% MLD <20 Gy
Esophagus	15.4	27	9	30	7.5	105% PTV prescription		105% PTV prescription	Mean <34 V60 <17%
Brachial plexus	17.5	24	6	27.2	6.8	32 RTOG 0813: D3cc <6 Gy/fraction	6.4	66	
Heart/ pericardium	22	30	10	34	8.5	105% PTV prescription			V30 <50% (1308) V45 <35% (1308) V60 <30% Mean <35 Gy
Great vessels	37	NS		49	12.25	105% PTV prescription			
Trachea/ proximal bronchi	20.2	30	10	34.8	8.7	105% PTV prescription			
Rib	30	30	10	40	10	NS			
Skin	26	24	8	36	9	32	6.4		
Stomach	12.4	NS	NS	27.2	6.9	NS			

Early-Stage Non-Small Cell Lung Cancer (NSCLC) [6–32]

General

- Raz, 2007. *n* = 1432 registry analysis. Without tx, MST 1 year, and 5-year OS <10%. Most pts died of lung cancer w 5-year CSM ~15%.
- Johnson, 1988: After treatment for early-stage NSCLC, risk is 1–2%/y for another lung cancer. For SCLC, risk is 6%/year.

Inoperability

- Cor pulm or severe CAD
- Renal failure
- Poor pulmonary function:
  - DLCO <60% or FEV1 <40% (~<1.2–1.5 L)
  - FVC <60%
  - FEV1/FVC ratio <50–75% predicted
  - Poor predicted post-op FEV1 <0.8 L or 75%

Surgery

- Cervical mediastinoscopy: evals 1–4R.
- Ant mediastinoscopy (Chamberlain): adds 4 L–7.
- Ginsburg, LCSG 821: T1 N0 → lobe vs wedge w 2 cm margin. Both staged intraop. Wedge ↑LF (6 → 18%). Also trend for ↑ CSM. No diff in periop M/M, functional improvement in wedge group. Established lobectomy as SOC for minimal resection for lung ca. Still, lobectomy not tolerated if poor pulm reserve.
- CALGB 9761 (D'Cunha, 2005): *n* = 489. cT1 undergo resection. Only 72% were pT1. 14% p Stage II. 13% p Stage III. 1% p Stage IV.

Brachytherapy

- ACOSOG Z4043: sublobar resection +/− mesh BT. No benefit for OS for BT, even if suspected R+.

Conventional RT Alone

- Dosoretz, 1996: T1–3 N0 med inop review. Dose >64 Gy improved PFS.
- Sibley, 1998: T1–2 N0 review. 60–66Gy. 5-yr OS was 15%. 50% LF.
- RTOG 9311: dose escalation safe up to 90.3 Gy. 84 Gy recommended LRC ~60%. No ENI given and nodal failure <10%.

RFA

- Option for <3 cm lesions.
- Not recommended by NCCN.
- Hiraki, 2006: 224 lesions. PNX in 52% of sessions, 11% requiring tube. Pleural effusion I 19%. 30-d mortality rate 2.6%. No benefit over SBRT.

SBRT

- RTOG 0236 (Timmerman 2006, 2010): T1–T2 N0 <5 cm treated to 60–66 Gy in 3 fx. 2-yr LC 94%, OS 72%. 3-yr LC 91%, regional control rate 87%, DM 22%, OS 56%. 5-year LC 88%, OS 43%, 9% regional failure. Initially started at 20 Gy × 3.GTV to CTV was 0 mm. PTV margin up to 10 mm in CC dimension and 5 mm radially. If 4D CT scan/gating and IGRT used, then reducing to 5 mm uniform expansion from ITV was appropriate.
  - On review, determined that dose delivered was overestimated because of lack of heterogeneity corrections and charged particle equilibrium. Thus, dose actually 18 Gy × 3. 2-yr LC 95%. 2-year OS 55%. G3–5 tox in 20% and higher for centrally located tumors (46%) vs peripheral (17%).
- Onishi, 2004: 245 pts; BED_{10} ≥100Gy improved LF (26 → 8%) and 3-yr OS (69 → 88%).
- CALGB 39904 (Bogart): 38 inoperable Stage T1–2, <4 cm, N0 patients. Required to have high-risk comorbid medical illness of pulm dysfunction FEV1 <40%, predicted DLCO <50%, predicted PCO2 >45 mmg Hg, VO2 max <15 mg (kg/min), or on O2. Randomized to 70 Gy in 29, 29, 23, 20, or 17 fractions. Allows central tumors <4 cm size. CTV = GTV + 1 cm. PTV = CTV + 1.5 cm. Constraints: V18 <25%, V2.2 <10%. 17 fractions (4.11 Gy/fx) did not have more toxicity. Similar outcomes to SBRT (historic control), 92% LC, 18% DMs. No G3–4 late tox. Only two G3 acute tox, dyspnea, and pain.

- RTOG 0618: operable SBRT. 33 pts, 18 × 3 SBRT. 2-yr LF 19.2%, OS 84.4%.
- Chang/MDACC (Lancet Onc, 2015): STARS + ROSEL. SBRT vs surg. Both RCTs closed due to slow accrual. Median FU 40 m SABR and 35 surg. 3-year OS 95% vs 79%, $p = 0.04$. 3-year RFS 86% vs 80%, $p = 0.05$. More toxicity with surg.
- MSKCC (Mutter, 2012): $n = 126$. 3–5 fraction to 40–60 Gy. No dose constraints initially. Eval for dose-volume metrics. G2+ CW pain if CW3cm V30 Gy >70 cc.
- UVA (Dunlap, 2010): keep CW3cm V30 Gy <30 cc.
- Cleveland Clinic (Woody, 2015): $n = 40$, >5 cm, SBRT, median dose 50/5. 18 m LC 91%. G3+ tox 8%. Conclude that these tumors can be treated w good LC and toxicity.

Ongoing SBRT Trials
- RTOG 0813: Tox results from 0236 drove 0813. SBRT for "central" NSCLC. w/in 2 cm of proximal bronchial tree. 10 Gy × 5 up to 12 Gy × 5. Results pending.
- RTOG 0915: Peripheral I NSCLC only, <5 cm. Most tumors are <3 cm, so may not apply to 3–5 cm. 34 ×1 vs 12 × 4. Expecting to have similar LC w less toxicity vs 54/3 arm of RTOG 0236. Appears promising per ASTRO 2013. Initial LC 97% for 34 × 1 and 93% for 12 × 4. Further results pending.

SBRT Requirements in Pulm Function
- No clear minimum FEV1.
- FEV1 change ~0.05 L, which is about 1.9% decrease in predicted FEV1.
- RTOG 0236 secondary analysis: In 2y, FEV1 and DLCO declined by 6%.

SBRT Eligibility

- T1 or T2 <= 5 cm, N0
- Peripheral vs central/CW approximate
- Goal BED10 >100 Gy
- Match to spine or carina, some match to tumor

Simulation
- Supine, arms up, in alpha cradle.
- CT sim + CONTRAST; 4D CT at level of the tumor. If dramatic excursion → use abdominal compression to get motion down to 1 cm.

Contours
- Fuse PET to planning CT.
- Contour GTV on free breathing CT,
- ITV using 4D CT to expand GTV to encompass tumor on all ten phases of breathing cycle.
- PTV = ITV + 5 mm (no CTV), consider +8 mm sup/inf.
- Contour the esophagus, heart, lungs, cord, CW, and BP.

Planning
- 3D-CRT, usually 7–12 coplanar and noncoplanar beams
- 6 MV
- Tissue heterogeneity corrections required
- No block edge margin, Rx to 60–90% IDL
- V100 >95%, Max 120%
- Dmax in PTV
- Conformality index = Rx isodose volume/PTV <1.2
- R50 = ratio of 50% Rx isodose volume to PTV volume <5 (but varies by PTV volume)
- D2cm = max dose in % of dose prescribed at 2 cm from PTV. Should be <50%

Peripheral SBRT Regimens
- 18 Gy × 3 (RTOG 0236)
- 10–12 Gy × 5 (Cleveland)
- 12 Gy × 4 (Japan)
- 34 Gy × 1 (Japan)

During RT
- CBCT each fraction, not kV-kV!
- 2–3 fx per week, minimum 40 h apart

High-Risk Features Suggesting Failure After SBRT
- (1) Enlarging opacity at primary site
- (2) Sequential enlarging opacity
- (3) Enlarging opacity after 12 months
- (4) Bulging margin
- (5) Loss of linear margin
- (6) Air bronchogram loss

Follow-Up
- CT chest q6–12 months for 2 years
- No definite role for PET because scar tissue may be FDG avid for 1–2 years; useful to guide biopsy if one area very PET avid or for nodal recurrence

Stage (AJCC 7)	NCCN treatment options
IA (T1 N0)	Surgery alone (resection + mediastinal LN dissection) or SBRT (inoper/unwilling for surg). *Prefer lobectomy, if SLR obtain 2 cm margin
T2a/b T2–3(3–7 cm)N0 T1 N1(ipsi peribroch/hil) T2 N1 T4(>7)N0 T3 N1	<5 cm may do SBRT Surgery (SOC is lobectomy, mediastinal sampling/dissection, and resection), +/− risk-adapted cisplatin-based chemo, +/− risk-adapted RT (see next section)

NSCLC: Post-op Therapy [22, 33, 34]

Adjuvant Chemo

- CALGB 9633 (Strauss, JCO, 2008): Stage IB T2 N0 randomized to carbo/taxol vs obs. Stopped early because of OS benefit, though not SS. Exploratory analysis: adjuvant chemo improves outcomes if primary ≥4 cm (controversial) or ≥5 cm (higher SS). Thus, while not level I evidence, should be discussed w patient.

Adjuvant BT

- Allegheny Gen Hosp (Colonias, 2011): Retrospective. Stage I NSCLC get sublobar resection and interop I-125 mesh. 1996–2008. *n* = 145. Mean dose 117 Gy to 33 cm2. Periop mortality 3%. LR 4%, 6% w regional failure, 17% w DMs. On MVA, no factors predictive of LR
- ACOSOG Z4032 (Fernando, 2013). *n* = 224. Sublobar resection +/− BT. No improvement in LR w BT, at 8%

Adjuvant Chemo and RT

- LACE meta-analysis: 5% for OS at 5 yrs for Stages I–II after resection. Most benefit in N1 pts. Subset analysis: no benefit for chemo in IA/B dz. However, CALGB 9633 data not included in this trial.
- Pre- vs post-op chemo: no difference (EORTC 08012, CHEST trial, NATCH Spanish trial).
- Italian study (Trodella, 2002): 104 pts, pN0 → PORT vs obs. 50.4 Gy. PORT improved LF (23 → 2%) and 5-yr OS (58 → 67%).
- **ANITA trial + reanalysis** (Arriagada, 2004; Douillard, 2008): NSCLC w surgery, R0. Adjuvant vinorelbine + cis vs observation. PORT not mandatory, given per each center's policy. Chemo had improved OS, benefit to Stage II/IIIA (pN+), no benefit to Stage I. Chemo and PORT had best outcomes, and PORT is better than obs. PORT techniques relatively modern.
- LCSG 773: T3 or N2 → obs vs PORT (50Gy). PORT improved LR (41 → 3%) but same OS.
- PORT meta-analysis Trialists Group, 1998: ten trials. PORT→↓OS, mostly in Stages I–II. Included old techniques (Co-60 in four trials), large fraction sizes, high total doses delivered, mostly early stage. No detriment to pN2.
- SEER (Lally, 2006): Benefit for pN2 patients, HR of 0.86 for death.
- No benefit to CRT over PORT alone (INT 0115/RTOG 9105/ECOG 3590).
- RTOG 0214: Evaluated PCI. Stage III NSCLC s/p definitive thoracic treatment. PCI 30 Gy/15 reduced brain failure (18% vs 8%), but same OS 76%. No diff in 1 year for QOL, MMSE, or ADLs; however, there were neurocog differences at 3 months (major difference between eligibility criteria and in positive SCLC trials).

Technique

- Need to ask what LN stations were dissected.
- Lung Adjuvant RT Trial (Lung ART): RCT for pN2 to PORT vs obs provides guidelines. In all patients, bronchial stump, ipsi hilum, extension to mediastinal pleura facing resection bed always in CTV. Also cover involved LN level, LN levels at risk.
- For N0–N1 R1, cover region of R1. For N2, cover involved LN region.

AJCC 7 stage	NCCN adjuvant treatment recommendations
pT1 N0 R0	Observe
pT2a N0 R0	**Standard risk**: observe **High risk** (G3, LVI, wedge, tumor >4 cm [i.e., large AJCC 7 pT2a or AJCC 8 pT2b], visceral pleural involvement): chemo
pT2b N0 R0	Chemotherapy alone
pT3 N0 R0	Chemotherapy alone
pT1–3 pN1 R0	Chemotherapy alone preferred If cannot receive chemo, then consider adj RT (soft data, based on ANITA)
pN2 R0 ECE0	Sequential chemo cis (100 mg/m^2), eto (100 mg/m^2), restage, and then PORT to 50.4Gy
pN2 R0 ECE1	Sequential vs concurrent chemo, restage, and then PORT to 54 Gy
R1–2	Concurrent chemo-PORT preferred over sequential chemo and then RT R1: 54–60 Gy. If N0, treat site of R+ only R2: 60–66 Gy at the primary site, and 50–54 to elective mediastinum/hilum

Locally Advanced Non-Small Cell Lung Cancer [3, 6–11, 35–62]

Induction (or Neoadjuvant) Chemo

- MDACC (1998): surgery +/− neoadj cis/etop/cyclophos. Chemo ↑MS (14 → 21 m).
- Madrid (1999): same as MDACC but cis/ifos/mitoC. MS 10 → 22 m.
- Spanish Trial 9901: phase II. N2 or T4 → cis/gem/docetaxel x3c → surgery. pCR 13%. MS 16 m.
- EORTC 08941: IIIA→chemo→ surgery vs RT. PORT permitted. Same OS. Pts did worse after pneumonectomy.
- See CALGB 8433 (Dillman, 1990, 1996) regimen.

Neoadj CRT

- **German LCCGT**: Stage IIIA–B → induction cis/etop x3c → surgery. Randomized to preop CRT or post-op RT. pCR improved with preop CRT (20 → 60%), but same OS. Worse OS if pneumonectomy.
- **INT 0139** (Albain, 2009): IIIA→ neoadjuvant CRT (45Gy) + surgery vs definitive CRT alone (61Gy). Both got post cis/etop. Cis was 50 mg/m^2 and etop 50 mg/m^2 in both arms, with first 2 c given during TRT. For neoadj arm, pts assessed at the end of RT to make sure they don't have PD. Surgery improved LF (22 → 10%) and DFS, but same OS: 27% w trimodality vs 20% w CRT at 5y. Pts w pN0 dz (aka "mediastinal nodal clearance) had median OS 34 m vs 26 m for N1–3. Subgroup analysis: possible that only pts w lobectomy (not pneumonectomy) will benefit. OS at 5y dependent on surgery type 36% lobectomy vs 18% pneumonectomy.
- **ESPATUE** (Eberhardt, 2015): N2 dz. Similar to Albain. Dose for NA RT was 45 Gy/1.5 Gy BID. For definitive RT, dose was up to 61.2 Gy, with a "risk-adapted" boost up to 65–71 Gy. Trial plan for 500 pts, close early w 246 pts bc of lack of funding and lack of accrual. 5-year OS ~42% (NSS). Underpowered for primary endpoint.
- **RTOG 02–29** (Suntharalingam, 2012): purpose to eval mediastinal LN clearance rates after induction CRT. n = 57. Chemo is carbo/taxol. RT is 50.4 to mediastinum and primary, and then boost 10.8 Gy to GTV. Mediastinum reassessed pathologically after completion of RT. 63% achieved mediastinal LN clearance.
- **SAKK 17/04** (Pless, Lancet, 2015): IIIA/N2 NSCLC. Rando to (1) neoadj chemo (cis 100 mg/m^2 and docetaxel 85 mg/m^2) then RT (42/22) then surg vs (2) 3 c neoadj chemo, and then surg. Primary endpoint was LRRFS: 9.4 m vs 7.6 m (NSS). MST 37 vs 26 m (NSS). Critiques: low number of pts to show non-inferiority. The pCR rate was 12% in chemo group vs 16% in chemoRT group, while NA CRT usually around 30%. There were 25 pts in each arm that did not get assigned tx. Finally, this may have been lower-risk population of IIIA without bulky LNs.

Hypofractionation

- Norway (Sundstrom, JCO, 2004): Inoperable, too advanced for cure, chest sx, and tumor threatening airway. n = 421. No concurrent chemo. Only six had recd prev chemo. Rando to 17 Gy/2 fx vs 42 Gy/15 fx vs 50 Gy/25 fx. QOL and sx relief equivalent. MST was 8.2 vs 7.0 vs 6.8 m, though NSS. Hypofrac recommended for these pts.

Definitive CRT

↑Dose

- RTOG 7301: dose escalation. 40 → 60Gy. Arms: (1) split course 40; (2) CFRT 40; (3) CFRT 50; (4) CFRT 60. 60Gy had improved OS. Split course had worst outcomes, 3-year OS 6%, LR 55%.
- RTOG 8311: dose escalation BID. 1.2/fx → 69.6Gy improved OS.
- RTOG 9311: dose escalation with chemo. 70 → 90Gy. 83.8 Gy had best OS.
- RTOG 0617: Stage III. 2 × 2 factorial. 60 vs 74 Gy and +/− cetuximab. All pts rec concurrent chemo, paclitaxel 45 mg/m^2, and carbo qweek AUC2. Mean esophagus dose <34 Gy, suggested. After CRT, given 3-week carbo AUC 6 and taxol 200 mg/m^2. Closed early.
  - 74Gy more toxic, worse OS, worse LR.
  - MST 29 m vs 20 m.

- 1-year LR 15% vs 25%, favoring 60 Gy.
- 2-year LR 31% vs 39%, favoring 60 Gy.
- G3+ tox similar bw RT groups. Esophagitis worse w 74 Gy, 21% vs 7%.
- +/− cetux had the same OS.
- G3+ tox worse w cetux, 86% vs 70%.
- On MVA, factors predicting OS were *RT dose (60 Gy)*, *max esophagitis grade*, *PTV*, *heart V5*, and *heart V30*.
- On MVA, *predictors of G3+ pneumonitis were RT technique*, *Stage IIIA* vs *IIIB*, and *lung V20.*
- RT and chemo compliance, RT technique, not significant for OS. IMRT did reduce pneumonitis.

– RTOG 0617 secondary analysis (Chun, 2016): IMRT associated w less G3+ pneumonitis than 3D CRT (3% vs 8%). No difference in OS, PFS, LR, DMFS. IMRT assoc w lower heart dose. Heart V40 associated w OS. Lung V5 not assoc w G3+ toxicity, but V20 was.
– CHART: 54 Gy at 1.5Gy TID (x12 consec days) vs 60/30. TID improved 3-yr OS by 10% but ↑tox. Mostly SCC.

Induction Chemo + RT vs RT Alone

– Induction generally only appropriate if upfront CRT plan exceeding DVH constraints.
– **CALGB 8433** (Dillman, 1990, 1996): IIIA→60/30 vs cis/vinblast induction +60/30 (sequential). Cis was 100 mg/mq q28d and vinblast was 5 mg/m^2 qw. Sequential CRT improved ↑MS (10 → 14 m). 5-yr OS (7 → 19%).
– **RTOG 9410** (Curran, 2011): Dillman trial worked, so now will concurrent chemo beat sequential? Three arms→Dillman to 63Gy vs concurrent CRT to 63Gy vs 69.6Gy CRT BID. Chemo was cis/vinblast, but BID arm got cis/etop. Conventional CRT improved MS (14.6 → 17 → 15.6 m). More tox with chemo. This RCT defined current SOC. (not cis/vbl).
– **RTOG 8808** (Sause, 2000): II–IIIB→ 60/30 vs 69.6 BID vs cis/vinblast induction +60/30 (Dillman style). CRT improved MS (11.4 → 12 → 13.2 m).
– **CALGB 39801** (Vokes, JCO, 2007): Unresectable Stage III. CRT to 66 Gy +/− induction chemo (carbo/taxol). Chemo was carbo AUC 2 and paclitaxel 50 mg/m^2. Same OS, around 30%. Toxicity worse during induction, 38% w G3+ neutropenia.

Sequential Chemo Versus Concurrent Chemo

– **LAMP trial**: three arms – Dillman (chemo→RT) vs (chemo→CRT) vs (CRT → chemo). Chemo was carbo/taxol. CRT → chemo improved MS (13 → 16.3 → 12.7 m).
– **Auperin meta-analysis** (Auperin, JCO, 2010): sequential vs. concurrent CRT for LA NSCLC – At 5 y, OS was 15.1% vs 10.6%, 4.5% absolute improvement for concurrent. Also has decreased LRP (HR 0.77) but higher G3 esophagitis (18% vs 4%).

Consolidation Chemo

– **SWOG 9504** (Gandara, 2003): path IIIB NSCLC. Concurrent CRT. Chemo is cis 50 mg/m^2 d1, 8, 29, 36 and etoposide 50 mg/m^2 d 1–5, 29–33. Concurrent TRT to 61 Gy. Consolidation docetaxel started 4–6w after CRT, at initial dose 75 mg/m^2. Did not improve OS.
– **HOG**: IIIA/B cis/etop x2c with RT 60 Gy + − consolid docetaxel. No diff OS, more toxicity.
– **SWOG**: IIIA/B cis/etop x2c with RT 61 Gy - > docetaxel + − gefitinib (Iressa). Worse OS with gefitinib.

Immunotherapy

– Checkmate 057, Borghaei, 2015. Nivolumab vs docetaxel in M+. Nivo improved 1-y OS 51% vs 39%, MST 12 vs 9 m.

Toxicity

– Palma, 2013: 1082 patients received concurrent CRT from 4 continents. V60 was best predictor of esophagitis. Cut points of V60 <0.07%, 0.07–17, and >17%. Thus, keep V60 <17%.

ENI

- No great data.
- RTOG 1308. II–IIIB NSCLC. Photons vs protons. 70 Gy RBE. 2 Gy/fx. Concurrent platinum doublet chemo w CP or EP. Heart constraints coming from 0617 analysis.
- Yuan, 2007. China. *n* = 200. Randomized LA NSCLC to IFRT 68–74 Gy vs ENI 60–64 Gy. 4–6c platinum-based chemo is given, and TRT was to start after c2. At 2y, response rate 90% vs 79%, OS 39% vs 26%, all favoring IFRT. OS difference not persisting to 5 years. Because of higher doses of IFRT, there was more pneumonitis than ENI, 17% vs 29% (SS). Other toxicities similar.

PCI for NSCLC

- RTOG 0214: ↓ # of mets, but no Δ OS/DFS
- Differences in eligibility from SCLC

Superior Sulcus Tumors (Pancoast) [63]

Staging
– By definition at least T3

Symptoms
– Pancoast triad: (1) shoulder pain, (2) brachial plexus palsy, (3) Horner's syndrome (ptosis, meiosis, enophthalmos, and ipsilateral anhidrosis)
– Pancoast syndrome: pain in C8/T1, lower brachial plexopathy from invasion of stellate ganglion, + chest wall (rib invasion), has to be at least T3

Outcomes (NCI data)
– 2-yr OS: 55%, 5-yr OS = 44%
– 3-y/5-y OS: 61%/56%
– 3-y OS: 56%

Studies
– INT study (Loehrer, 1997). Evaluating PAC chemo. Pts get 2–4c q3w cis (50 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2). For those without PD, mediastinal RT to 54 Gy was delivered. *n* = 23, with 5 CRs and 11 PRs to chemo. RT converted 80% of pts w SD to a CR or PR. 5-year OS 53%.
– SWOG 9416/INT 0160 (Rusch, 2007): superior sulcus phase II of T3/4 N0/1 induction CRT to 45 Gy/25 with cis 50 mg/m^2 + etop 50 mg/m^2. Repeat CT during last week of RT (week 5) to allow surgeon to make decision regarding resectability. If ineligible, continue RT to 61.2/1.8. Then surgery and post-op chemo. 20% pts unresectable and went on to complete RT to 60 Gy. Of 80% who went to surg, 94% had R0 resection, 29% had pCR, and 26% had minimal microscopic residual, with a combined rate of 56% for response. 5-yr OS 44%. Recurrence: distant (non-brain) only 33%, brain only 33%, local only 17%, local + distant 12%. Created SOC for these tumors.
– SWOG 0220 EP concurrent, docetaxel consolidation.

Treatment
– Trimodality: neoadj cis/etop +45Gy
– Check CT at last week of RT
– If resectable, → surgery →EP consolidation or docetaxel per 0220
– If unresectable at 45Gy, go to 60–66Gy + adj chemo. Thus, need to save immobilization devices until surgeon reviews CTs and pt has surgery. No evidence for boost in patients w R+ resection (per 0160)
– **Contraindications to surgery**: involves brachial plexus, subclavian artery, VB, esophagus, mediastinal LNs, or DMs

Stage	NCCN treatment options
IIIA resectable	**Options:** (1) Surgery, followed by chemo, with or without RT (2) Chemo (Cis 100 mg/m^2 + Eto 10 mg/m^2 × 4), followed by surgery (3) **Trimodality**: chemoRT, followed by surgeryIn the U.S., the standard of care with known Stage III disease is to first receive definitive chemo, or RT, or both, but not go straight to the OR. The patients with IIIA disease who receive surgery first are those where mediastinal LNs were not expected **Good PS and is operable** EP 50/50 × 2: **cisplatin** 50 mg/m^2 D1, 8, 29, 36; with **etoposide** 50 mg/m^2 D1–5, 29–33; with **RT 45 Gy** (per INT 0139, Albain, Lancet, 2009). RT to 60 Gy possible Complete resection and avoid pneumonectomy if possible Then adjuvant EP 75/100: cisplatin 75 mg/m^2 and etoposide 100 mg/m^2 q 21 days × 2c **Poor PS and is operable** **Carboplatin** AUC 2 and **paclitaxel** 50 mg/m^2 weekly with RT to 45 Gy Then complete resection and avoid pneumonectomy Then adjuvant **carboplatin** AUC 6 and **paclitaxel** 200 mg/m^2 q 21 days **Contraindications to surgery in IIIA** Poor PFTs T4 or ECE Multi-station N2 High N2 disease Pneumonectomy required (relative)
IIIA/B unresectable	Concurrent CRT, 60 Gy, + adjuvant carbo/taxol (if carbo/taxol w CRT) × 2–3 (LAMP Regimen) Consider + outback durvalumab q2 w × 12 m (NEJM, 2017) Can also try pemetrexed, works on non-squamous, but not on squamous If inoperable, then do RT with chemo to 60 Gy, and then consolidate as above For definitive RT: treat primary and nodal dz (>1 cm) or hypermetabolic or + meds. No elective nodal irradiation (allows for tumor dose escalation and is associated w low nodal relapse (6% – Rosenzweig 2007) For highly symptomatic dz: can do RT 1st for local relief For bulky dz too large to safely contain in RT port: consider induction chemo 1st
Pancoast T3–4 N0–1	Trimodality (if possible): Neoadj cis/etop +45Gy Check CT at last week of RT If resectable → surgery →EP consolidation or docetaxel per 0220 If unresectable at 45Gy, go to 60-66Gy + adj chemo Thus, need to save immobilization devices until surgeon reviews CTs and pt has surgery. No evidence for boost in patients w R+ resection (per 0160)
T4Nx	Definitive CRT
IIIA/B not curable, central sx	Consider 17 Gy/2 fractions vs 42 Gy/15 fractions (Sundstrom, JCO, 2004)
Contra nodule (M1a)	Contralateral nodules: treat as 2 primary tumors if curable (some may disagree)

Metastatic Lung Cancer

Treatment

- ECOG PS 0–2: Chemo ± palliative RT
- First-line chemo uses two agents for 3–4 cycles
- ECOG PS 3–4: Best supportive care

Novel agents

- EGFR mutated: erlotinib 1st line
- EML4-ALK: crizotinib 1st line
- Non-mutated: platinum doublet
- Addition of bevacizumab to carboplatin-paclitaxel improves survival Bevacizumab criteria = non-squamous, no h/o hemoptysis, no CNS mets, not on therapeutic anticoagulation
- Role of RT is palliative.
- MS? 6–18 mo, usually ~8–10 mo.

Tracheal Cancer [64, 65]

Overview
- 44% SCC
- 16% adenoid cystic
- ~30% are adeno, adenosquam, carcinoid, epidermoid

Studies
Xie, 2012: SEER. Improved outcomes w RT. If treated w RT alone, MST 12 m vs 5 m w/ RT

- Urdaneta, 2011: SEER. No benefit for OS w RT.

Treatment
- Surgery first.
- Then PORT as needed. Typically 50 Gy for microscopic disease and 60–63 for R+. Consider concurrent chemo for macroscopic residual or unresectable disease.

Carcinoid

H/P
- Flushing, diarrhea, wheezing
- Labs: Urine 5HIAA; ACTH/cortisol per NCCN

Imaging
- Octreotide scan
- CT C/A

Diagnostic
- Broch. Mediastinoscopy if LNs on CT

Neuroendocrine
- Typical carcinoid – (<2 mitoses/10 hpf)
- Atypical carcinoid – (2–10 mitoses/10 hpf or + necrosis)
- Large cell neuroendocrine carcinoma (>=11 mitoses/10 hpf, large polygonal cells, necrosis)
- Small cell lung cancer (15% of lung cancers)

Typical Carcinoid
- Lobectomy + LND; N0 and N+ → observation

Atypical Carcinoid
- Lobectomy + LND: N0 → observation; N+ → PORT. Adjuvant dose is 50 Gy. Definitive dose is 60–70 Gy.

Small Cell Lung Cancer (SCLC)
[6–10, 66–81, 82]

Overview
- 15% of lung cancer.
- 1/3 pts present with limited stage dz; 2/3 have mets, and 15% have brain mets.
- Markers: S100, synaptophysin, chromogranin, neurotensin, EGFR.
- Del3p14–25, amplification of bcl2 and c-myc family; inactivation RB1; p53 mutations.
- On spectrum of neuroendocrine tumors (which are CD56+), SCLC has the highest mitotic rate.
- Ki-67 should be >20–25%.
- On imaging classically appears as hilar mass w massive mediastinal LAD.

Presentation
- Hypercalcemia
- Hypercoagulable state
- Hypertrophic osteoarthropathy
- SIADH – headaches, confusion, N/V
- Ectopic ACTH
- Eaton-Lambert
- Cerebellar ataxia
- Retinopathy.

Workup
- H&P.
- CBC, platelets, CMP.
- Biopsy, PET-CT and eval adrenals (should do in all lung cancer), MRI brain, BM bx if ↑LDH or red cell aplasia (this can upstage them). PET will upstage 10% LS to ES,
- 4% abs OS benefit to not smoking during RT (5% vs 9%).
- If CBC abnormal, BM bisy,

Chemo
- Etoposide + platinum (EP) chemo is SOC and cat 1 rec from NCCN. Two dose options.
- Etoposide, ***100*** mg/m^2, d1–3 + cisplatin, ***80*** mg/m^2, d1 q3w. Taken from CALGB 30610.
- Etoposide ***120*** mg/m^2 d1–3 + cis ***60*** mg/m^2 d1 q3w. Taken from INT0096/Turrisi.
- The pt will therefore receive 2c during RT (if getting BID) and 2c after RT for total of 320 mg/m^2 (if using 80 mg/m^2 × 4c). This is similar to HNSCC chemo.

Limited Stage (LS-SCLC, i.e., Stages I–III)
- Definition: one RT port, one hemithorax, excludes contra sclav, malignant effusion. Contra hilar is often considered ES-SCLC.
- ~24-month median OS.
- NCCTG (Schild, 2004): n = 262. Induction chemo w 3c EP. RT on c4. Randomize to 50.4/1.8 vs 48/1.5 BID. In the BID arm, pts could have 2-wk break after initial 24 Gy. No difference in MST (21 m) or 5-year OR (22%). Inc tox in hyperfx arm.
- Pignon 1992: meta-analysis (2140 pts) of chemo +/− thoracic RT. RT improved 3-yr OS (8.9 → 14.3%), 5% absolute OS benefit. Best for <55 yo. Subgroups >55 yo had minimal benefit, esp if >70 yo.
- Fried 2004: meta-analysis of early vs delayed RT. Early improved 2-yr OS by 5.2%.
- Takada 2002: concurrent vs sequential CRT. Concurrent improved 5-yr OS (20 → 30%).
- INT 0096 (Turrisi, NEJM, 1999): 417 pts → cis/etop with RT (45/25 vs 45 Gy at 1.5/fx BID). Chemo was cis 60 mg/m^2 and etopo 120 mg/m^2, given q3w for 4c total. RT was to ipsi hilum and bilat mediastinum. Sclav LNs not routine included. Inf aspect of field was 5 cm below carina or at bottom of involved hilm, whichever was lower. AM+PM tx on cord for w1; then AM dose on cord, PM dose off cord w obliques during w2–3. BID ↓LF (52 → 36%) and ↑5-yr OS (15 → 26%). BID ↑ grade 3 esophagitis (11 → 27%). Cord max 36 Gy. BEDs not equivalent: 45 Gy BID = ~60 Gy/30.
- Komaki, 2013: patterns of care study. Only 20% of physicians use BID 2006–2007, though it increased from 8% in 1998–999.
- CALGB 30610/RTOG 0538. Ongoing. Concurrent chemo and high-dose TRT. Similar to 0096 but at similar BEDs: 45 Gy BID vs 70 Gy/30. 61.2 Gy concomitant boost arm was closed early (planned to close 1 arm, was not

inferior). The better comparison is 70 and 45 Gy BID. MDACC arm was less acceptable. PCI is given 3–6 w after completion of all 4 c chemo.
- CONVERT trial (Faivre-Finn, 2017): International. Concurrent CRT w 45 Gy BID vs 66 QD for LS-SCLC and ECOG 0–1. ASCO 2016: 2-y OS 56% vs 51% and MST 30 m vs 25 m (NSS). No difference in toxicity. Currently supporting either regimen as SOC.
- RTOG 0239: phase II → RT to 61.2 Gy, partially BID. Improved OS compared to Turrisi.
- CALGB 8837: phase I trial, dose escalated to over 70 Gy with good results.
- RTOG 0538: pending. Turrisi vs RTOG 0329 (0239) vs 70/35 (CALGB 8837). This trial includes ENI. The spinal cord tolerance is 36 Gy in the BID arm.

Induction Chemo
- SWOG 7924 (Kies, 1987): All got induction chemo for LS-SCLC and then randomize to post-op tx. If CR, then rando to TRT or further chemo. Those with PR or had SD to induction were rando to TRT to either pre-induction ("wide field") or post-induction ("reduced field") target volume. No difference in OS, patterns of failure

PCI
- 5.4% OS_3 absolute improvement. 25 Gy/10 fx.
- Contraindications: poor mental status, stable, or progressing disease.
- Auperin 1999: meta-analysis of PCI. PCI reduced 3-yr brain mets (59 → 33%) and increased 3-yr OS (15.3 → 20.7%). Better if given early.
- Le Pechoux 2003: randomized LS cCR patients to 25/10 vs 36/18 PCI. Same brain met rate, worse OS in high dose.
- EORTC 08993 (Slotman 2007): ES with any response to 4–6c chemo→ +/− PCI. PCI improved 1-yr OS (13 → 27%). No routine MRIs done. Extracranial progression unchanged (89% vs 93%, NSS).
- Komaki, 1995: MDACC neurocog study. 97% of pts had neuro decline after chemo but before RT. Mostly verbal memory, frontal lobe dysfunction, fine motor coordination. In 11 pts who had post-RT testing, no SS difference in neuro status pre vs post RT.
- NRG hippocampal avoidance trial: improved Hopkins verbal learning.
- Takahashi, 2017: PCI in ES-SCLC with neg MRI prior to randomization. PCI did not improve OS.

Extensive Stage (ES-SCLC, i.e., Stage IV)
- 9-Month OS
- Definition: can't fit in one RT port.
- Yugoslavia, Jeremic 1999: PR or CR after chemo→ chest RT vs more chemo. RT improved 5-yr OS (3.7 → 9.1%).
- Bonner, Mayo, 1995. ES-SCLC gets chemo. If PR or CR, +/−TRT. 3/19 pts alive >5 years.
- CREST (Chest Radiotherapy Extensive-Stage Small Cell Lung Cancer Trial), Slotman 2014: ES-SCLC get chemo. If PR or CR → +/− thoracic RT (30/10). PCI is for all. 90% of pts had residual thoracic dz after initial chemo, only 5% w CR. For TRT, PTV = *post*-chemo volume + 1.5 cm margin, also all LN stations involved pre-chemo, including hilum + mediastinum, even w CR. Lung (defined as lungs minus PTV) V20 <35%. Pts only get CNS imaging if there are clinical sx. 1-year OS similar 28–33%, NSS. However, RT improved 2-yr OS (3 → 13%). Intrathoracic PFS improved 20% vs 47%. Toxicity similar be arms, G3+ esophagitis <2%.
- Giuliani, PMH, 2011: ES-SCLC pts get consolidative TRT, 30+ Gy. LR was 26% in 1 y and 39% in 2 y.
- RTOG 0937: ES-SCLC w up to four extracranial mets get PCI 25/10 +/− consolidative TRT and met-directed RT. Must have at least radiographic PR in one site and no PD. Can have max four extracranial metastatic lesions. Rec max dose is 45 Gy/15 fx at 3 Gy. Alternative is 30–40 Gy/10 fx. Closed due to poor accrual and futility boundary for OS. High G4+ toxicity in TRT arm.

Simulation
- Supine, arms up, in alpha cradle
- CT sim w contrast (from cricoids to include liver); 4D CT

LS-SCLC Contours
- Fuse PET to planning CT and contour GTV on free breathing CT: primary tumor, ipsilateral hilum, and clinically positive lymph nodes (>1 cm in short axis) or pretreatment PET/CT (SUV >3).
- Some patients need 1–2 cycle chemo induction. RT is to post-induction volume acceptable, no apparent increase in marginal failure (SWOG 7924, Kies, 1987; Liengswanwong, JCO, 1994).
- *If no PET, need to treat gross tumor, ipsilateral hilum, and bilateral mediastinum per Turrisi.
- Using 4D CT, create ITV by expanding GTV to encompass tumor on ten phases of breathing cycle.
- CTV = ITV + 1 cm; PTV = CTV + 5 mm.
- OARs: esophagus, heart, lungs, cord, BP.

Dose
- **LS-SCLC:** 45 Gy in 1.5 Gy BID fractions, minimum 6 hours between treatments
- **ES-SCLC**: 30 Gy in 3 Gy fractions

Planning
- 3D CRT, all fields daily
- 6 MV beam energy
- Block edge margin = 5 mm

On Treatment
- Daily KV imaging

Historical, from Turrisi
- PTV: GTV + 1.5–2 cm, ipsilateral hilum, include all mediastinum + involved LNs.
- IFRT appears OK if PET-staged.
- BID:
  - 1st week AP/PA AM and PM
  - Then AP/PA AM, oblique PM
  - Cord tolerance 36 Gy (41 Gy to a point, per CALGB, RTOG 0538)

BID Dose Constraints
- Spinal cord: Dmax <41 Gy (36 Gy)
- Total lung-CTV: V20 <25%, MLD <13 Gy

ES-SCLC Contours (per CREST)
- All patients get PCI.
- TRT is 30 Gy/10.
- PTV = post-chemo GTV + 1.5 cm + initially involved hilar and mediastinal LN stations (even if CR with chemo).

Recurrence

Topotecan is currently the only FDA-approved second-line tx but has poor response rate. Ardizzoni, 1997, four courses of topotecan w 22% response. Depends on response to EP (Brahmer and Ettinger 1998). Responders vs nonresponder MST 12 m vs 5 m.

Prognosis
- Good KPS; weight; females do better

Stage	Tx paradigm
SIADH and hypoNa	Fluid restriction Give hypertonic saline, correct 1–2 nmol/L/h Demeclocycline Antineoplastic therapy Vasopressin receptor inhibitors
Cushing syndrome	Consider ketoconazole and then metyrapone Consider before initiation of antineoplastic tx
T1–2 N0	Mediastinal sampling. If neg → lobectomy and node dissection pN0: post-op chemo pN+: post-op CRT Still recommend PCI
LS-SCLC: "fits in one port"	"Concurrent platin doublet + RT" (Turrisi and Pignon meta-analysis) Four cycles of EP chemo: etoposide, 120 mg/m^2, d1–3 + cisplatin, 60 mg/m^2, d1 q3w Concurrent RT at 1st cycle if possible. Some pts w massive LAD may need 1–2 cycle induction chemo before TRT. In this case, RT is to post-induction volume, no apparent increase in marginal failure (SWOG 7924, Kies, 1987; Liengswanwong, JCO, 1994) RT: 45Gy/1.5Gy/fx >6 h apart or 60–70 Gy 1.8–2Gy (Turrisi or CALGB 39808) "Early RT" (Murray and Fried meta): start date to end date of RT should be 3 weeks w BID Wait for 3–6 w after all chemo, and do CT chest and MRI brain. If CR or PR, then PCI, 25 Gy/10 fx If progression use topotecan
LS-SCLC w SVC syndrome	Try chemo first and then proceed per above.
ES-SCLC: "doesn't"	Platin doublet, four cycle EP chemo (80/80) Then CT chest, to bottom of adrenals and MRI brain If CR or PR: PCI for all. Concurrent consolidative TRT to 30 Gy in ten fractions to GTV + 1.5 cm and ENI if involved up front (EORTC CREST/Slotman) RT to other sites not recommended (RTOG 0937) If progression: topotecan
M1, non-brain met	SVC/lobar obstruction/bone mets: Chemo + RT Cord compression: palliative RT first
M1, brain met	Asx: may do chemo 1st, then WBRT Sx: WBRT and then chemo

Thymoma and Thymic Carcinoma [6–10, 83–89]

AJCC 8th Edition Staging

- **T1** – encapsulated or into mediastinal fat
  - T1a: not into mediastinal pleura
  - T1b: into mediastinal pleura
- **T2** – invasion into pericardium
- **T3** – adjacent organs: into the lung, brachiocephalic vein, vena cava, phrenic nerve, chest wall, or pulm artery/vein
- **T4** – into aorta, arch vessels, heart, trachea, esophagus
  - **N1** – ant mediastinal nodes
  - **N2** – intrathoracic nodes
  - **N3** – supraclav

	T1	T2	T3	T4
N0	I	II	IIIA	IIIB
N1 or M1a	IVA			
N2 or M1b	IVB			

Masaoka Staging

- **T1 –** encapsulated
- **T2 –** through capsule
  - T2a – microscopic invasion
  - T2b – macro invasion, into fat, mediastinal pleura
- **T3** – into organs
  - T3a – into adj organs
  - T3b – into great vessels
- **T4** – pleural/pericardial
  - **N1** – ant mediastinal nodes
  - **N2** – intrathoracic nodes
  - **N3** – supraclav

	T1	T2	T3	T4
N0	I	II	III	IVA
N1-3	IV			
M1				

Overview

- Anterior mediastinal mass: DDx is the four Ts: thymic tumor, thyroid mass, terrible lymphoma, teratoma (GCT)
- Assoc with MG, red cell aplasia, hypogammaglobulinemia
- 50% of ant mediastinal masses are thymomas
- 50% of thymomas have MG, and 15% of MGs have thymoma
- **WHO grading (A, AB, B1–3, C).**
  - **Type A**: spindle cell, medullary. Benign course. 10-year DFS 95%
  - **Type AB:** borderline/mixed. 10-year DFS 90%
  - **Type B1–3**: moderately malignant. 10-year DFS 40–85%
    - **B1**: tumor represents normal functional thymus, "lymphocyte-rich"
    - **B2**: mixed, cortical
    - **B3**: predominantly neoplastic epithelial cells, few lymphocytes
  - **Type C**: highly malignant (***thymic carcinoma***)
- Thymic carcinoid/carcinoma (30% N+)

Paraneoplastic Syndromes

- Myasthenia gravis, present in 30–50% of thymoma patients. Higher OR risk due to crisis. All pts will need AChR inhibition prior to surgery (e.g., neostigmine, pyridostigmine). 15% of myasthenia patients have thymoma.
- Pure red cell aplasia.
- Hypogammaglobulinemia.
- Addison's or Cushing's syndrome.

Workup

- Same as NSCLC, plus rule out germ cell tumor: serum beta-HCG, AFP
- TSH, T3, T4 as needed
- Serum anti-AChR antibodies MUST BE DRAWN BEFORE ANY SURGERY
- Biopsy not needed if suspected clinically and radiographically. If performed, should not use transpleural approach to prevent seeding
- PET-CT
- PFTs
- MRI chest as needed

What You Need to Know From Surgery
- Histology (thymoma can be observed if Stage I R0; thymic carcinoma always gets at least RT)
- Margin status (all R1s get at least RT)
- Capsular status, infiltration of mediastinum or surrounding organs (invasion is at least T2)
- WHO classification

Natural History
- Failure typically pleural or pericardial mets (Stage IVA). Can still attempt resection of implants for long-term survival

Neoadjuvant Chemo
- MDACC (Kim, 2004): unresectable invasive thymoma II–IVB given 3c induction cyclo, doxo, cis, pred q3–4w, then resect, and then PORT. 50 Gy for R0 and 60 Gy for R1 or if <80% tumor necrosis. Then give 3c consolidation chemo. Induction chemo had response of 77%. 76% had R0. 5-year OS 95%. 7-year OS 79%.
- MGH experience (Wright, 2008): ten pts w Masaoka III or IVA. Given 2c cis and etopo and concurrent RT, 40–45 Gy. Re-eval and then resection at 4–8w. 80% w R0 resection.
- INT/Indiana (Loehrer, JCO, 1997): unresectable thymomas given 2–4 cycles of cisplatin, doxorubicin, cyclophosphamide (PAC). If no PD, then RT to primary and regional LNs to 54. 70% response, 22% CR. Overall *5-y freedom from failure 54%*. 5y-OS 52%.
- Hamaji, 2015: meta-analysis of 12 studies, 266 pts, w thymic epithelial tumors (TETs) w cis induction. Response rate to induction chemo 59%. CR 73%. 5-year OS 5%. 10-year OS 76%.

PORT
- Forquer 2009: SEER database. PORT improved 5-yr OS for Stages II–III (5-yr OS 66 → 76%), but not stage I.
- Curren 1988: 103 pts. No recurrence for Stage I without RT. Stage II–III patients had ↓LF with PORT (53 → 0%). 21% if subtotal resection and PORT.
- Mangi 2002 and Haniuda 1996 challenged PORT for Stage II thymoma.

Adj Chemo
- Mornex 1995: +/− cisplatin, unclear benefit.
- Wright 2008: retrospective of ten patients, Stages III–IV. cis/etop + RT. Then resection and post-op chemo. Four had radiographic PR. 5-year OS 70%.

Treatment Paradigm (Based on Masaoka Staging)
- **Operable**: resect, median sternotomy + en bloc thymectomy
- Stage I
  - Thymoma, R0: obs
  - Carcinoma R0: 45–50 Gy
  - Carcinoma R1: PORT +/−chemo, 50–54Gy
  - Carcinoma R2: PORT +/−chemo, 60Gy
- Stage II, R0–R1, B2–B3, 45–50Gy
- Stage III–IVA, R0: 45–50Gy+. R1: 54 Gy. Note R0 for Masaoka Stage III difficult to achieve.
- Stage III–IVA, Unresectable or R2, 60–70 Gy

Inoperable
- Adriamycin-based chemo, usually CAP (cyclophosphamide, adria, cisplatin). Some have tried cis/etop as well. Then surgery if resectable and then RT (≥60Gy) then more chemo.
- If still unresectable, CRT (60–70Gy).
- For R1–2 carcinomas, cis-based chemo with 60–70 Gy RT preferred.

Technique
- Supine, 4D, cast, arms up, IV contrast.
- 3D-CRT w AP/PA or wedged pair or IMRT
- CTV = thymic space, tumor bed, and clips, involved LN. ENI not recommended bc thymomas rarely go to LNs. Talk to thoracic surgeon.
- PTV = CTV + 1.5–2 cm.

Posttreatment
- 50% of MG pts will improve.
- 30% of red cell aplasia will improve.
- Hypogammo does not improve.

Margin	Histology	Post-op paradigm	RT details ("just say 50 or 60")
R0	Thymoma or carcinoma	I: Surveillance w CT chest q6–12 months for 2 y and then annually for 5y for carcinoma and 10 y for thymoma	
	Thymoma	II–IV: +/− post-op RT	Stage II R0–1 B2–3: 45–50 Gy
	Carcinoma	II–IV: + post-op RT (cat 2b)	Stage II R0–1 B3: 50–54Gy Note R0 for Masaoka Stage III difficult to achieve
R1	Thymoma	Post-op RT	50–54Gy
	Carcinoma	Post-op RT +/− chemo Then surveillance w CT chest q6–12 months for 2 y and then annually for 5 y for carcinoma and 10 y for thymoma	50–54Gy
R2	Thymoma	Post-op RT +/− chemo	50–54Gy
	Carcinoma	Post-op RT + chemo	Unresectable or R2, 60–70 Gy
Unresectable		Chemo first. Then CT with contrast and PET-CT. Then reconsider for resection. If unresectable, then RT +/− chemo	

Pleural Mesothelioma [6–10, 90–94]

AJCC8

- **T1** – ipsilateral pleural disease only
- **T2** – into diaphragm muscle or pulmonary parenchyma
- **T3** – endothoracic fascia, mediastinal fat, chest wall, outer pericardium (potentially resectable)

AJCC8	T1	T2	T3	T4
N0	IA	IB		IIIB
N1	II		IIIA	
N2	IIIB			
M1	IV			

- **T4** – multifocal, into peritoneum, contralateral pleura, mediastinal organ, spine, internal pericardium (unresectable)
  - **N1** – ipsi hilar/mediastinal
  - **N2** – contralateral or SVC

AJCC7

- **T1**
  - T1a – ipsi parietal pleura, no visceral
  - T1b – ipsi parietal pleura, +visceral
- **T2** – into diaphragm muscle or pulmonary parenchyma
- **T3** – endothoracic fascia, mediastinal fat, chest wall, outer pericardium
- **T4** – multifocal, into peritoneum, contralateral pleura, mediastinal organ, spine, internal pericardium
- **N1** – ipsi hilar
- **N2** – ipsi mediastinal/IM, or subcarinal, or peridiaphragmatic
- **N3** – contra mediastinal/IM, supraclav

AJCC7	T1a	T1b	T2	T3	T4
N0	IA	IB	II	III	IV
N1	III				
N2					
N3	IV				
M1					

Overview

- 2500 cases/yr.
- 80% involve asbestos. RT, smoking is synergistic.
- Stains for calretinin, vimentin WT1, cytokeratin.
- Arise from pleura, peritoneum, pericardium, and tunica vaginalis (embryonic outpouching of peritoneum).
- 80% of mesos are pleural.
- Majority of pts will die of LR.

Work-Up

- H&P – asbestos exposure, if transthoracic extension, then SC/Ax LNs at increased risk.
- CT CAP.
- MRI chest/abd to rule diaphragm invasion.
- Pleural bx: VATS preferred over open. Needle bx can seed track.
- If surgery planned (clinical Stages I–III):
  - Med/EBUS of nodes
  - PET/CT
  - PFTs and stress test: Goal >40% EF and no reversible ischemia, perfusion studies to assess contralateral lung. Post-op FEV1 expected to be >30% and >0.8 L
- PET/CT optional per NCCN. May be useful for pts with prior talc pleurodesis as this can mimic tumor. If no prior pleurodesis, obtain PET prior to talc.
- Thoracentesis for cytology.

Surgery

- **Extrapleural pneumonectomy (EPP)** removes parietal/visceral pleura, lung, mediastinal nodes, pericardium, and ipsi diaphragm. ~5–15% mortality. 2-year OS is 35%. Contraindicated if extension through diaphragm.

– **Pleurectomy/decortication (P/D)**: more like debulking, resection of pleura w/o lung removal. Possible removal/recon of diaphragm or pericardium. Only 2% operative mortality but only curative for T1, so it is reserved for early stage. Adjuvant RT limited by remaining underlying intact lung.

Adj RT
– Adj RT typically part of package after EPP, but some centers have published good outcomes of post-op IMRT and IMPT after P/D.
– Rusch 2001: phase II → EPP and hemithoracic 54 Gy. MS 34 m for Stages I–II, 10 m for Stages III–IV.
– Flores 2006: induction gem/cis → EPP → 54Gy. MS 33 m.
– Rosenzweig (2012) Good review esp toxicity of IMRT and ways to minimize this.

Chemotherapy
– Vogelzang 2003: metastatic→cis +/−pemetrexed. Pem is 500 mg/m^2 and cis is 75 mg/m^2 q3w. This is superior to cis alone in patients unfit for surg for MST (12 vs 9 m), PFS (6 vs 4 m), and radiographic response (41% vs 17%).

RT
– O'Rourke: $n = 61$. Rate of tract seeding similar bw RT arm (13%) and obs (10%). Questions need for prophylactic tract RT.

NCCN
Early Stage/Resectable
– Highly controversial. Radical pleurectomy increasingly option over EPP. RT after radical pleurectomy only on trial.

Advanced Stage/Unresectable
– Induction chemo (cis and pem) →surgery → +/−RT.
– Surgery (definitive/palliative):
  – EPP
  – P/D
  – *Avoid aggressive surgery if poor PS, N+, or sarcomatoid b/c poor prognosis
    • For N+, palliative chemo is the SOC.
– Chemo: anti-folate/platinum doublet (e.g., cis/pem).
– Thymic carcinoma needs adjuvant therapy.

Radiation
– Post-op after EPP: R0: 50–54Gy; R+ 54–60Gy. 41.4 Gy is prescribed to contra vertebral.
– Prophylactic to prevent tract recurrence: 21Gy/3 fx at 7 Gy.

Technique
– Sim w supine arms akimbo since tx usually AP PA and en face electron patches under shielding.
– Simulation, CTV:
  – Sup: top of T1
  – Inf: bottom of L2
  – Lat: flash skin
  – Medial: 1.5–2 cm beyond contra VB border
– **Stomach** (for L-sided lesion) and **liver** (for R-sided lesion) blocked through *entire* hemithoracic RT course.
– If on L, **ant heart block** at 19.8 Gy to prevent pericarditis.
– **Cord** blocked after 41.4 Gy.
– **Electron field patch** is used centrally to supplement pleural space under block, to treat the diaphragmatic recesses around the liver. Dose usually 1.53 Gy/d. This dose is used because photon field scatters 15% of dose to blocked portion. Electrons prescribed to 90% IDL.

Constraints
– If RT after P/D: lung V20Gy <20% and MLD <9.5 Gy
– Hemithoracic RT 4–8 wks post-op to 54 Gy
– Contralateral lung V20 <7%, V5 <50%, mean <8.5Gy
– Heart V40Gy <50%

SVC Syndrome [95, 96]

Management
- Biopsy (if nonemergent case) to rule out benign causes or other sensitive tumors
- Most commonly seen with lung ca (80%)

Non-life-Threatening
- 1–2c systemic therapy. Has been shown to relieve sx in 80% of SCLC and 60% of NSCLC.
- RT not recommended prior to getting path diagnosis, esp if there is mediastinal mass.

Life-Threatening
- Sx: hoarseness, dyspnea, facial plethora, laryngeal edema.
- Eval for protective intubation, emergent stent placement, steroids.
- Begin immediate RT, AP/PA midplane. Meanwhile, dosimetry will develop conformal plan for definitive treatment.

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Breast Cancer

6

Nicholas G. Zaorsky, Daniel M. Trifiletti, and Jennifer Rosenberg

Abstract

This chapter discusses the general management of patients with breast cancers, with special focus on principles that guide radiotherapy management. Several key components of trimodality care and accelerated partial breast irradiation (APBI) are discussed.

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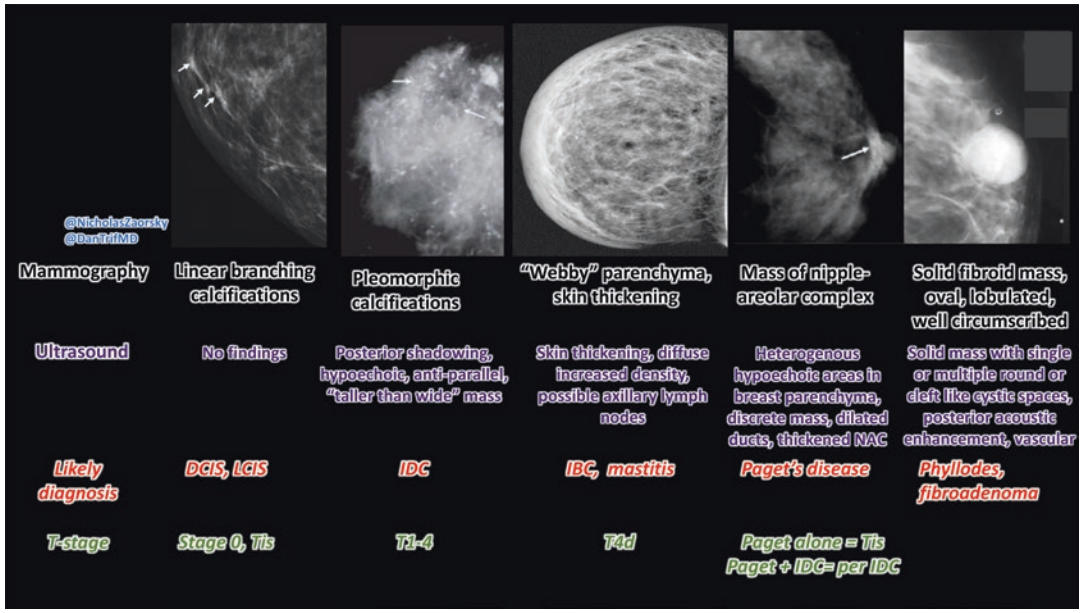
Breast Pearls [1–17]



T1 – ≤2 cm
T1mi – ≤0.1 cm
T1a – >0.1 and ≤0.5 cm
T1b – >0.5 and ≤1 cm
T1c – >1.0 and ≤2 cm
T2 – >2.0 and ≤5 cm
T3 – >5 cm
T4 -
T4a – chest wall (not pec, *but serratus*, *intercostal*, *ribs*)
T4b – ulceration, peau d'orange, nodules, and/or edema that is not T4d
T4c – 4a + 4b
T4d – inflammatory breast cancer (IBC):
Rapid onset of breast erythema, edema, and/or peau d'orange involving >1/3 of breast with or without palpable mass.
<6-month duration.
Pathological confirmation: core bx confirms invasive ca, skin punch bx (minimum of 2). DLI pathognomonic but not required.

cN0	No nodes	**pN0**	No nodes
cN1	Mobile level I-II nodes	**pN1mi**	Micromets (0.2-2mm)
		pN1a	1-3 nodes (>2mm)
		pN1b	Micro IM nodes
		pN1c	pN1a +pN1b
cN2a	Fixed/matted axillary nodes	**pN2a**	4-9 nodes (>2 mm)
cN2b	Clinical IM nodes only	**pN2b**	Clinical IM nodes with pathologically neg axilla
cN3a	Infraclav nodes (ax level III)	**pN3a**	10+ axillary or any infraclav
cN3b	IM + axillary nodes	**pN3b**	IM + axillary nodes
cN3c	Ipsilateral Supraclav	**pN3c**	Ipsilateral Supraclav

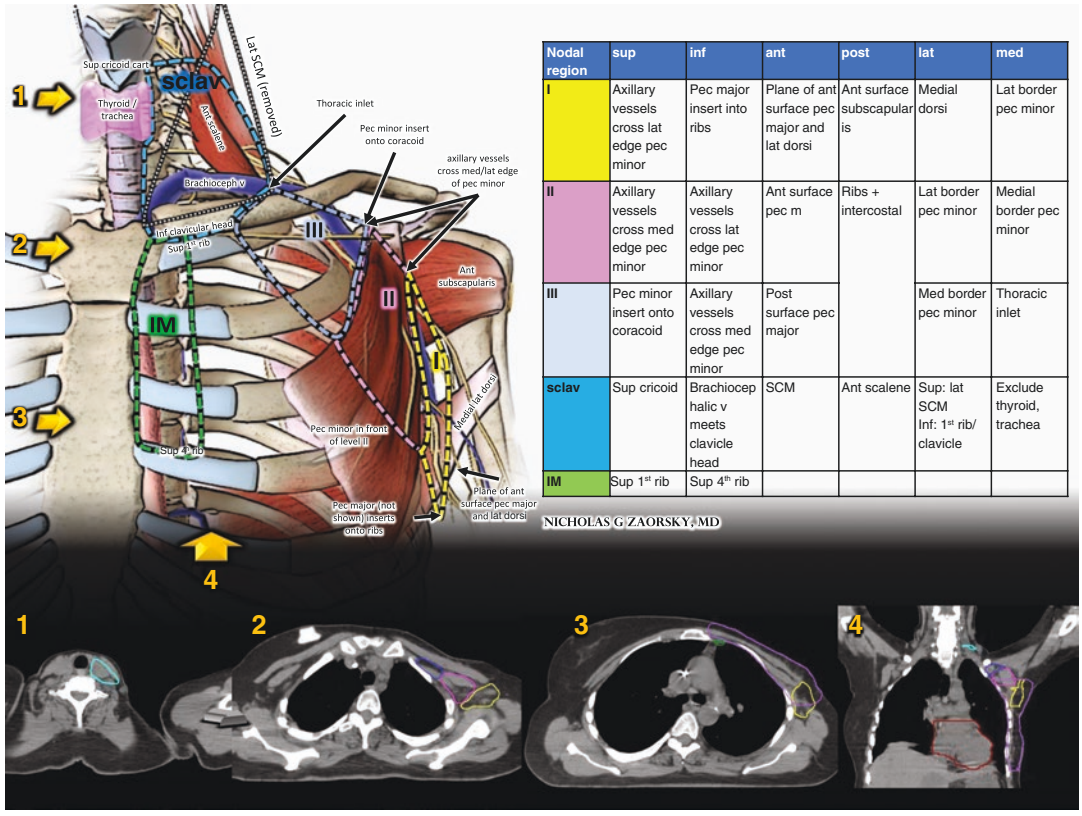
	T1	T2	T3	T4
N0	IA	IIA	IIB	IIIB
	N1mi = IB			
N1	IIA	IIB	IIIA	
N2	IIIA			
N3	IIIC			
M1	IV			

AJCC 8th Edition Changes/Staging Clarifications

- LCIS no longer included in Tis, it is benign.
- Multifocal: 2+ tumors in the same quadrant.
- Multicentric: 2+ tumors in diff quadrants, separated by >5 cm.
- For multifocal disease, use size of max focus (do not sum).
- **Anatomic stage**: Only based on TNM.
- **Prognostic stage**: Includes TNM, ER/PR/Her2 status, +/− Oncotype testing
  - pT1–2 N0 that is ER/PR+ and HER2- and Oncotype <11 is stage IA.
- Intramammary LN count as axillary nodes for staging.

Anatomy

– Chest wall (CW) = ribs, intercostals, serratus anterior



Nodal region	sup	inf	ant	post	lat	med
I	Axillary vessels cross lat edge pec minor	Pec major insert into ribs	Plane of ant surface pec major and lat dorsi	Ant surface subscapularis	Medial dorsi	Lat border pec minor
II	Axillary vessels cross med edge pec minor	Axillary vessels cross lat edge pec minor	Ant surface pec m	Ribs + intercostal	Lat border pec minor	Medial border pec minor
III	Pec minor insert onto coracoid	Axillary vessels cross med edge pec minor	Post surface pec major		Med border pec minor	Thoracic inlet
sclav	Sup cricoid	Brachiocephalic v meets clavicle head	SCM	Ant scalene	Sup: lat SCM Inf: 1st rib/ clavicle	Exclude thyroid, trachea
IM	Sup 1st rib	Sup 4th rib				

Pectoralis Minor
- Arises from third to fifth ribs
- Inserts at coracoid process

Axillary LN Levels
- Level I: lateral to pec minor.
- Level II: behind + including pec minor.
- Level III: medial to pec minor.
- IMNs: lie in first–third intercostal spaces, in between the sternum and rib. Sup border is sup border of the first rib; inf border should be sup to the fourth rib.
- Supraclav:
  - Superior = below cricoid cartilage
  - Inferior = below clavicular head
  - Anterior = SCM
  - Posterior = anterior scalene
  - Medial = trachea
  - Lateral = lateral edge of SCM

Workup

- History
  - Age
  - Early menarche, late menopause, nulliparity, first pregnancy ≥ 30 yo
  - Exogenous estrogen (HRT → 1.24 RR)
  - MMG history, previous breast biopsies, previous breast cancer
  - FH of breast cancer
  - Previous chest RT
  - Pregnancy
  - Scleroderma, active SLE (RA ok)
- Physical exam, including breast and LN exam
- Review previous mammos
- Obtain b/l diagnostic mammo and U/S
  - Calcs → magnification view
  - Palpable → compression views
- HCG
- Fertility counseling/genetics referral PRN
- Breast MRI controversial (consider for young or BRCA+)
- T3, N1+, or symptoms: bone scan and CT chest/abd/pelv, +/− PET, +/− MRI
- Adjunctive markers of progression: CEA, CA 15–3, CA 27.29

Biopsy
- Stereotactic **core** biopsy w/ clip placement.
- US-guided **core** biopsy w/ clip placement.
- What is a suspicious US? Irregular, hypoechoic, posterior shadowing, taller than wide.
- Stereotactic, wire-localized excisional biopsy (near CW, near nipple, very faint calcs).
- Place a clip in both primary mass and any nodes.
- If ADH/LCIS still needs excision, bc could be associated with IDC/DCIS.
- If cN+ → axillary U/S + FNA.

Risk of Axillary LN Involvement
- T1 5–20%
- T2 40%
- T3 75%
- T4 85%

Risk of Level III/SCV Involvement
- 1–3 LN 10%/5%
- 4+ LN 50%/15%

Men Versus Women
- Male breast cancer represents 1% of all breast cancer.
- Men present at later age, median 71 yo.
- Men more likely to have LN+, ER/PR+. 90% IDC. Few DCIS (10%) or LCIS (1%).
- No difference in outcomes of men vs women.
- MKSCC: Male breast CA more likely to be ER+ (87% vs 55%). Gestational breast cancer: definition is during pregnancy, lactation, or first postpartum year. Recommended approach is ALND.

Genetic Testing

	BRCA1	BRCA2	General population (lifetime risk)
Breast cancer	47–66%	40–57%	12.5%
Breast cancer histo	Usually TNBC	Usually ER+	
Contralateral cancer	Up to 65%	Up to 50%	0.5–1% per yr
Ovarian cancer	35–46%	13–23%	1.5%
Male breast	Increased, not as much as BRCA2	3.2–12%	0.1%
Prostate		35–40%	15%
Pancreas		<10%	1.3%
Uveal melanoma		<10%	

- Lifetime risk of breast/ovarian cancer w/ either BRCA 1 or 2 is 60%.
- Risk of endometrial cancer similar between BRCA 1 and 2.
- TNBC: 20% of pts have BRCA mutation.
- 5% of all breast ca pts have a hereditary mutation.
- WECARE study, Malone, 2010: population-based, international. 10y risk of a second contralat breast cancer diagnosed >1y after original breast cancer dx. BRCA1 or 2 carrier, 18%. Noncarrier 5%.

Genetic Referral Indicated If

- Family member with BRCA
- Triple negative breast ca and <60 yo
- Breast ca at age <50
- Personal hx breast or ovarian primaries
- 1+ relative with breast ca <50 yo
- 1+ relative with ovarian ca
- 2+ relatives with breast or pancreas ca
- 2+ same side fam members with breast, panc, prostate (GS7+), sarcoma, adrenocortical, brain, endometrial, leukemia/lymphoma, thyroid, diffuse gastric
- Ashkenazi Jew
- Male breast CA

Screening Mammos Timing

- USPSTF recommends screening patients 50–74 every 2 years. For women <40 or 50 yo, regular screening initiation should be based on a patient's specific context.
- Normal risk.
- ≥20–39 yo clinical exam q 1–3 years.
- ≥40 yo annual mammo and exam.
- Strong FH: 10 years before the age at which youngest family member diagnosed.
- Meta-analyses estimate 20–35% relative risk reduction in breast cancer mortality in women 50–69. In women who are 40–49, the RR reduction is 15%.

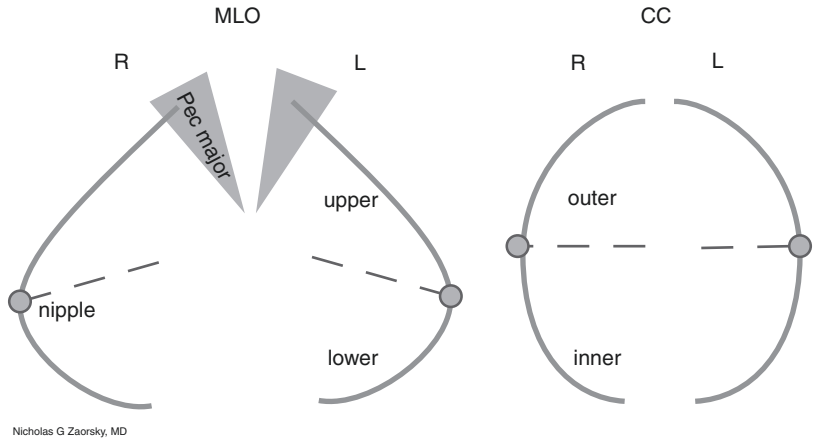
MRI

- **Screening indications**
  - ACS recommends MRI for risk ≥20–25%.
  - BRCA 1 and 2: ≥25yo, annual MMG and MRI (stagger q 6 months).
  - Prior chest RT before age 30: 10 y post RT. Annual mammo and MRI (stagger q 6 months).
- **Diagnostic indications**
  - Multicentric, multifocal
  - Response to NACT
  - Occult primary

What is an Adequate Mammogram?

- MLO: Perpendicular line from the pectoralis to nipple. Inframammary fold should be visible.
- CC: The pectoralis can be visualized in 30%; the nipple is in profile.
- Compare to prior mammos.
- What are suspicious mammo findings/buzzwords? Large size, spiculated/ill-defined borders, architectural distortion, pleomorphic calcifications, microcalcifications in a linear branching pattern, granular calcifications.
- Calcifications present→Mag views. Can be described as a *heterogeneous cluster of pleomorphic calcifications*. Stereotactic biopsy.

– Mass present→compression views. If it persists, then it is a true mass.
– **Screening mammo** = CC, MLO.
– **Diagnostic mammo** = CC, MLO, and additional views (magnification and compression).



BIRADS: Breast Imaging Reporting and Data System

Score	Findings	% Malig	Recs
0	Incomplete study	N/A	Further imaging
1	Normal	<1%	Cont screening
2	Benign lesion	<1%	Cont screening
3	Prob benign	<2%	Short-term fu in 6 months
4	Suspicious	5–95%	Biopsy
5	Highly suspicious	>95%	Biopsy
6	Known cancer	100%	Treatment

Factor Affecting Recurrence (Botteri, 2010)

Local/regional	Distant
Size ER status Ki-67 Young age	LVI LN status

Path Evaluation

- LNs: #, ECE. This is the single most powerful predictor of LRR, DFS, and OS.
- Size and extent (multifocal?).
- Grade (1–3).
- Calcifications and necrosis assoc. w/ DCIS.
- DCIS in non-calcified areas.
- Margins >2 mm for DCIS and post-MRM. Margins are 0 mm for BCT.
- Necrosis.
- LVI.
- ER/PR/Her2 status.

Nottingham Factors for Grade (Elston-Ellis Modification)

- Based on (1) tubular differentiation, (2) nuclear pleomorphism, and (3) mitotic count.
- Each category is given a score from 1 to 3. Final grade is the composite.
  - Grade 1 = score 3–5.
  - Grade 2 = score 6–7.
  - Grade 3 = score 8–9.

Molecular Subtypes (Invasive Disease)

	IHC status	Grade
Lum A	ER+ PR+ Her2− Ki67+	1, 2
Lum B	ER+ PR+ Her2− Ki67−	2, 3
	ER+ PR+ Her2+ Ki67+	
Her2	ER− PR− Her2+	2, 3
Basal	ER− PR− Her2-	3

HER2 (Wolff et al. JCO 2013)

	ISH	FISH single probe	FISH dual probe
Her2+	3+	≥6 copies/cell OR	HER2:CEP17 ratio ≥ 2
Equiv	2+	4–6 copies/cell AND	HER2:CEP17 ratio < 2
Her2−	0–1+	<4 copies/cell AND	HER2:CEP17 ratio < 2

Oncotype DX

- Assessed in NSABP B-14 and B-20, where patients were ER+ and node negative
- High risk: Score 31+
- Intermediate risk: Score 18–30
- Low risk: Score <18

Surgery Types

Surgery type	Breast removed	Muscle removed	Nodes removed	Predictors of LC	Predictors of OS
RM	Yes	Pec major and minor	ALND I, II, III		1. Axl LNs 2. T stage
MRM	Yes	Pec major fascia	ALND I, II	1. # Axl LNs 2. T stage	
TM	Yes	Pec major fascia	No		
WLE	Partial	No	No		
Excisional bx	Partial	No	No		
BCS	Partial	No	Typically w/ SLN (I)	1. R+ 2. young age	

Reconstruction Types

- Gel implants
- Deep inferior epigastric perforator (DIEP) flap
- Nipple sparing

BCS Basics

- SLN biopsy is part of package for invasive. For DCIS, need SLN if palpable/ >4 cm, extensive high grade, microinvasion.
- All BCSs get into-op specimen radiograph to confirm calcs/biopsy clip are in specimen.

BCS Contraindications (NCCN)

Absolute: pregnancy, diffuse microcalcifications, poor cosmesis expected, persistent or diffuse +margin, multicentric (evaluated in Z11102), widespread disease, ATM mutation
Relative: prior RT, connective tissue disease (scleroderma/lupus), T3/tumors >5 cm (cat 2B), focally +margin, genetic predisposition (e.g., BRCA, Li-Fraumeni)

Diagnosis During Pregnancy

- Regardless of trimester, no RT, SNLBx, or Tam/AI during preg.
- US and MRI can be done, not mammo.
- Other staging studies typically cannot be done.
- Chemo can be considered *after* first trimester (usually doxo, cytoxan, 5FU): AC.
- First trimester: consider termination; OR mastectomy and ALND (no SLNB), chemo in second trimester, deliver then XRT and Tam.
- Second: mastectomy/BCS and ALND (no SLNB), chemo as needed, then RT and Tam.
- Third: mastectomy/BCS and ALND (no SLNB), deliver then chemo/RT/Tam.

Surgical Margins (Moran, 2014; Morrow, 2016)

Margins	Tumor	Notes
On ink	IDC	R+ associated w/ 2x increase in IBRT vs R0
≥2 mm	DCIS	If <2 mm, individualize tx

Shave Margins

- Chagpar (NEJM, 2015). Stage 0–III breast ca getting partial mastectomy. 23% IDC, 19% DCIS, 53% both. *n* = 235. Rando to further cavity shave margins vs not. In both arms, surgeons allowed to remove selective margins on basis of gross and radiographic findings. Then, pts randomized intra-op. Primary outcome = tumor on ink and <1 mm of edge of DCIS specimen. Rate of positive margins decreased 19% in shave vs 34% non-shave. Also lower rate of re-resection to clear margins (10% vs 21%). Similar complications.

Systemic Therapy

Chemotherapy Agents

- CMF: cyclophosphamide, methotrexate, 5FU (historical standard).
- AC: Adriamycin, cyclophosphamide (should be "dose-dense" given q2w x 4 cycles).
- AC→T: adding paclitaxel decreases CSM by 4% (RR 0.83, NSABP B-28). Thus, adding a taxol to adj chemo provides the same DSS benefit as adding regional nodal irradiation to early-stage N+ or high-risk node neg pts on MA-20 (HR 0.76, DFS 82 vs 77%).
- Paclitaxel either given q2w x 4c (with G-CSF) or weekly x 12c (no need for G-CSF).
- AC→THP: + Herceptin +Perjeta (if Her2+)
- Herceptin/trastuzumab: neoadjuvant and given for 1 year post BCT.
- Perjeta/pertuzumab: currently approved in the neoadjuvant setting only.
- TC: docetaxel (taxotere), cyclophosphamide given q3w x 4 cycles.
- Trastuzumab: monoclonal antibody for HER2/neu. Give 4 mg/kg IV over 90 min and then 1 mg /kg over 30 min qWeek during chemo for 12 weeks of paclitaxel or docetaxel.
- CDK4/6 inhibitors: palbociclib, ribociclib, abemaciclib; used in metastatic setting with AI in ER+ postmenopausal pts.

Endocrine Therapy

- Menopausal if: prior b/l oophorectomy, age 60+, age <60, and amenorrheic x 12 m.
- Consider FSH/estradiol testing if uncertain status.
- Aromatase inhibitors block peripheral conversion of androgen→estrogen.
- In premenopausal women, main source of estrogen is ovaries (vs peripheral conversion in postmenopausal women). Aromatase can be increased in premenopausal women. Thus, AIs are not as effective in premenopausal women, and the decreased peripheral conversion of estrogen may stimulate ovaries to make more estrogen.
- **Premenopausal**: tamoxifen.
- **Postmenopausal**: raloxifene, tamoxifen, or AI.

Chemoprevention with Endocrine Therapy

- **NSABP P01, Fisher 1998, 2005**: women age >60, or 35–59 with inc risk, or hx of LCIS given Tam or placebo. Tam won.
  56% reduced risk with hx of LCIS
  49% reduced risk of invasive cancer overall
  RR 2.53 for endometrial cancer
- ASCO/NCCN recs for chemoprevention in 35 yo w/ >10 year life expectancy and one of the following:
  - Atypical hyperplasia.
  - LCIS.
  - A >1.7% 5 year risk for breast cancer (per Gail model).
  - Consider w/ flat epithelial atypia.
- Get baseline GYN assessment, bone density scan

Tamoxifen

- Tamoxifen dose usually 20 mg QD x 5–10y.
- SERM: Selective estrogen receptor modulator.
- Toxicity: hot flashes, ↑thromboembolic dz, ↑uterine cancer.
- Follow-up: HP q6–12 m x 5y, then yearly. mammo q12m. annual GYN exam,
- **NSABP B-24**: BCT (lump +50Gy) +/− tamox(5 yrs). At 10 yr tamox improved IBRT (15 → 11%) and contralateral cancer (5.4 → 4.5%). Same DM and OS. If ER+, 50% risk reduction.
- **UKCCR trial** (see DCIS section).
- **TEXT trial**: Oral exemestane 25 mg QD + triptorelin or Trelstar IM injection q28 d vs oral tamoxifen. Bilat oophorectomy or ovarian RT allowed if at least 6 m of triptorelin in both arms.
- **SOFT trial:** Exemestane + ovarian suppression (triptorelin, bilateral oophorectomy, or ovarian RT) vs tamoxifen + ovarian suppression vs tamoxifen alone.

Aromatase Inhibitors (AIs)

- Drugs:
  Exemestane (Aromasin): Irreversible steroidal AI. Dose is 25 mg PO daily x 5 y.
  Anastrozole (Arimidex, 1 mg QD); **letrozole** (Femara): Nonsteroidal reversible AIs.
- Toxicity: Bone pain, osteoporosis, SOB, cough, F/C,
- AIs are superior to Tam in postmenopausal women (ATAC trial, Cuzick 2010; EBCTCG 2015).
- In premenopausal: Tam +/− ovarian suppression or AI + ovarian suppression.
- TEXT/SOFT combined analysis. Pagani (NEJM, 2014): Is exemestane + ovarian suppression better than tam + ovarian suppression? 4690 premenopausal women with operable high-risk breast cancer and ER > 10%+. Randomized to oral exemestane (25 mg QD) + triptorelin (for ovarian suppression) vs tamoxifen (20 mg QD) + triptorelin. Exemestane beat tamoxifen. Improved 5-yr DFS (91% vs 87%), breast cancer FS (93% vs 89%), DMFS (94% vs 92%). Thus, for patients premenopausal women w/ high-risk early breast ca, exemestane + ovarian suppression is an option. Note that in pt not getting chemo, there were fewer DMs and no appreciable DM difference was found for exemestane and tam groups.

AI Versus Tamoxifen in Postmenopausal

- **NSABP B-35** (Margolese, Lancet, 2016): 3104 postmenopausal women. Tam 20 mg QD vs anastrozole 1 mg PO QD for 5 years. Improved *breast cancer-free interval (BCFI)*, mainly in women <60 yo (this was not seen at 5 years, but it was seen at 10 years). Increased thrombosis/embo w/ tam vs anastrozole, 2.7% vs 0.8%.
- EBCTCG meta-analysis Lancet 2015: Recurrence ratio favors AIs in years 0–4 and nonsignificantly thereafter. 10-y CSM lower with AI 12% vs 14%. AI lowers CSM vs tam by 15% and by 40% vs no endocrine therapy.

Length of Endocrine Therapy

- MA-17 (Goss, NEJM, 2016): 10 years of AI >5 years
- DATA trial: equivocal results in 5 vs 10 y
- NSABP B42: equivocal results in 5 vs 10 y

CDK4/6 Inhibitors

- Palbo is a CDK4/6 inhibitor, which regulates cell cycle at the G1/S interface. Palbo blocks cells from moving from G1 to S.
- At this point, approved only for metastatic dz.
- PALOMA-2 (Finn, 2016). 666 postmenopausal women w/ ER+ HER2-M+ breast cancer, 50% w/ prior chemo and 56% had prior endocrine. Rando to letrozole +/− palbo. Palbo improved PFS: 25 m vs 14 m (HR 0.58).
- MONALEESA-2 (Hortobagyu, 2016): similar results.
- PALOMA-3 (Cristofanilli, 2016): HR+ HER2- M+ breast cancer progressed on prior endocrine therapy. Rando to oral palbo + fulvestrant vs placebo + fulvestrant. Median FU 9 months. Median PFS 9.5 m vs 4.6 m. G3–4 tox 73% in combo group vs 22% in fulvestrant group. Mainly heme tox.
- MONARCH2 (Sledge, 2017): ER+ M+ breast cancer pts; PFS improved with addition of abemaciclib to letrozole.

Bisphosphonates

- Z-fast (Brufsky, 2007)
- ZO-FAST (Bundred, 2008)
- SABRE (van Pozkan, 2010)
- All demonstrate effectiveness of bisphosphonates in reducing bone loss in women receiving AIs.
- ASCO Guidelines (JCO 2017): adj bisphosphonates reduce recurrence in postmenopausal pts with nonmetastatic dz.

Chemo Trials

- Joint Center (Recht, 1996; Bellon, 2005). What is best chemo/RT sequence? Stage I–II breast ca. BCS + ALND. Rando to (1) adjuvant

chemo, then RT vs (2) RT, then chemo. Chemo was CMF, prednisone, leucovorin. RT was 45 + 16 Gy. Long-term FU: no benefit for LRR, time to failure, DMs, OS.

Recht trial	Chemo→RT	RT → chemo
10 y rate of any event (IBTR, CBTR, breast cancer, second malignancy, or death)	46%	51%, $p = 0.88$
10 y distant metastases	35%	36%, $p = 0.70$
10 y mortality	28%	33%, $p = 0.41$

- EBCTCG chemo/HT: meta-analysis, 6 m anthracycline-based chemo reduced breast ca death by 38% if <50 yo and 20% if 50–69 yo. Tamoxifen x5 yrs reduced breast ca death by 31%.
- NSABP B-20: surgery and pN0, ER+. Randomized to Tamox vs Tamox +MF chemo vs Tamox + CMF. Chemo improved 12 yr DFS, but not OS (p = 0.068). These pts were used in the validation of Oncotype recurrence score.
- CALGB 9741: showed that dose dense ACT improved 4 yr DFS 75 → 82% as well as OS.
- NSABP B-14: ER+ pts. Tamox 10 mg BID x5 yrs vs placebo. Tamox improved 15-yr DFS/OS.
- NSABP B-18: cT1–3 N01. Preop vs postop AC x4c. n = 1523. At 9 yrs, no difference in DFS or OS. More BCT in preop group (~25% converted), but more LR in those patients (10.7 vs 7.6%). More LR if mastectomy converted to BCT (9.6 vs 15.7%). Main benefit of NA CT was downstaging tumor for BCT. At time of surgery, pts w/ NA CT were ypN = 41% of time vs 57% if no NA CT.
- NSABP B-27: Neoadj ACx4→surg vs ACx4 →docetaxel→surg vs ACx4→surg→docetaxel. More toxicity with AC then docetaxel (G4 = 23% vs 10%). However, response increased (40% vs 64% cCR; 14% vs 26% pCR). Similar rates of BCS.
- B-18 + B-27 combined analysis (Mamounas, 2012): n = 3088. NA chemo with AC or AC-T. Patients who had MRM did not get adjuvant RT. Patients w/ BCS had WBI. 10-year LR was 12% after MRM and 10% after BCS. For any size tumor with pCR, LRR rates were 0%. Highest LRR rates if ypN+.
  - After MRM, predictors of recurrence were (1) tumor size prior to chemo, (2) LN status prior to chemo, and (3) ypN status.
  - Predictors of recurrence in BCS were (1) age, (2) cLN status, and (3) ypN status.
  - The very low LRR rates are the rationale for NSABP B-51.
- NSABP B-28: LN+ pts randomized to AC vs ACT. Taxane improved 5-yr DFS 72 → 76% (RR 0.83). No OS benefit. MA-20 showed similar DSS benefit to adding RNI to early stage N+ patients (HR 0.76, DFS 82 vs 77%).
- NCCTG N9831: HER2 pos women rando to AC, then T vs AC then T then trastuzumab vs AC, then T+ trastuzumab, then transtuzumab alone.
- NSABP B-31: HER2+ pts: ACT vs ACT+H. Herceptin improved 3-yr DFS (75 → 87%) and OS (92 → 94%).
- N9831 and B-31 joint analysis (Perez, 2011): AC→T +/− trastuzumab. 10y DFS 75 vs 84%, OS 62 vs 74%.
- ATAC Trial (Howell, 2005; Cuzick, 2010): ER+/− postmen pts: anastrozole 1 mg QD, tamoxifen 20 mg QD, or both. AI improved DFS over tamox (89 vs 87%); both were 87%, but only for ER+ pts. No dif in OS.

Systemic Therapy, Clinical Use

Indications for Adjuvant Chemo

- ER+, HER2-:
  1. + LN (>2 mm) or
  2. Tumor >0.5 cm → Oncotype, ≥31
- All other subtypes:
  1. + LN (>2 mm) or
  2. Tumor >1 cm

Agents Used and Schedule

- ddAC x 4 → T x 4, q 2 weeks (dose dense).
  *Adriamycin 60 mg/m2 and cyclophosphamide 600 mg/m2 are both on day 1, cycled q 14 days for 4 cycles (2 months total).
  Paclitaxel 175 mg/m2 weekly x 4 weeks.
  Preferred for LN+.

– **TC**
  Docetaxel 75 mg/m2 IV day 1.
  Cyclophosphamide 600 mg/m2 IV day 1.
  Cycled q21d x 4 cycles with filgrastim support for each cycle.
  Some use AC, but not "preferred" per NCCN.
– ER+: Tam (20 mg QD) or anastrozole (1 mg QD) x 5–10 years.
– HER2+: Herceptin (start with first dose of paclitaxel if w/ CT) x 1 year. 4 mg/kg once per week. Cardiac monitoring at 3, 6, and 9 months.
– + herceptin if + LN, > 2 cm (Herceptin: 4 mg/kg loading then 2 mg/kg weekly during chemo, then 6 mg/kg q3wks x 1 y after)

AI Follow-Up
– Check DEXA at baseline
– Toxicities: Osteoporosis, arthralgia, SOB, cough, fever/chills

Oncotype Dx
– PCR study of 21 genes (5 reference/16 cancer)
– **Prediction/prognostication**:
  Likelihood of disease recurrence and survival (prognostic)
  Response to chemo (predictive)
– **Indications**:
  LN(−) and ER(+) who will be tx with tamoxifen
  SWOG 8814 also demonstrated predictive magnitude in ER+ LN+ patients
– 0–17 low risk. 31+ high risk

Relative Indications for Neoadjuvant Chemotherapy (NACT)
– To get to BCS (T2, T3)
– Locally advanced tumors (N2, T3N1, T4, N3)
– Inflammatory

To Ensure Post-NACT SLNBx FNR < 10%
– FNA w/ clip placement so the primary is not lost
– Dual radiocolloid and blue dye tracer
– IHC to define any positivity
– 3+ SLN

Hot Flashes/Antidepressants
– Venlafaxine, paroxetine, fluoxetine, and sertraline all decrease hot flashes vs placebo. Sertraline has been shown to decrease hot flashes in women on hormonal therapy.
– Fluoxetine/paroxetine may decrease formation of tamoxifen metabolites.

RT Simulation/Planning Technique

- Supine, arms up, head turned slightly, angled breast board to make sternum parallel to couch, alpha cradle.
- Wire scar, sup wire at inf clavicular head, inf wire 2 cm below inframammary fold, lateral wire at mid-axillary line, med wire at sternum. Use contralateral breast to identify inframammary fold if postmastectomy.
- DIBH for L sided w/ scout film to check.
- If large/pendulous breasts, consider prone tx vs tx in bra; cut out opposite side most often so contralateral breast falls out of the way.

"Two-Field"/Tangents Only

- Tangents include the sup/inf wire.
- Set medial tangent to stay off the contralateral breast.
- Add collimation to maximize coverage and minimize lung/heart exposure (cannot collimate if treating LNs with three fields).
- Iso: midpoint sup/inf, midpoint enter/exit, just inside CW. Note that if you will treat LNs, you should first try monoisocentric technique and set iso near inf clavicular head. If field size >20 cm, then breast should be treated with couch kicks.
- Oppose beam for lateral tangent.
- Match posterior border or half beam block.
- 1 cm lung = 6% irradiated.
- 2 cm lung = 16% irradiated (goal is <2 cm).
- 3 cm lung = 26% irradiated.
- Iso at midpoint between med and lat wires.
- High tangents: top border 2 cm below humerus.
- Field in field.
- Hot spot <107% is the goal. Max 110%.

Beams Eye View (BEV)

- Superior
  Inferior aspect of head of clavicle
  Below humeral head
- Inferior
  2 cm margin on inframammary fold
- Anterior
  2 cm flash
- Posterior
  Match wire marking midline.
  Adjust block to make straight sup-inf line at the mid-sternum and avoid contralateral breast.

Field in Field (FIF)/Forward Planned IMRT

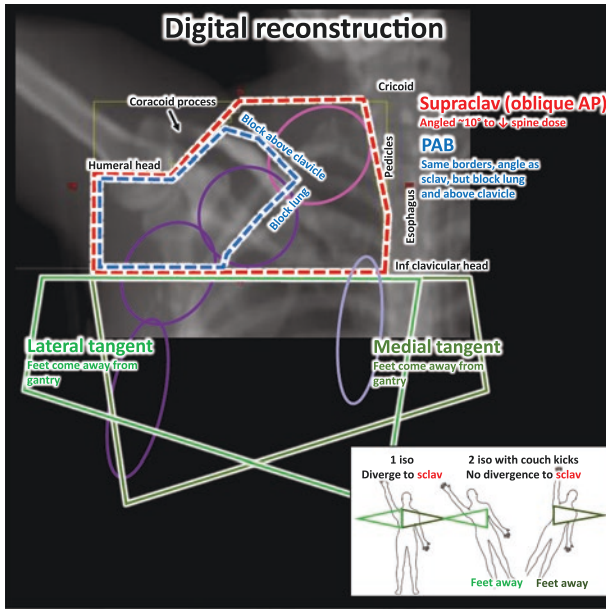
- Copy open medial field. Creating hot spot volume, 120%. Block it in the new field.

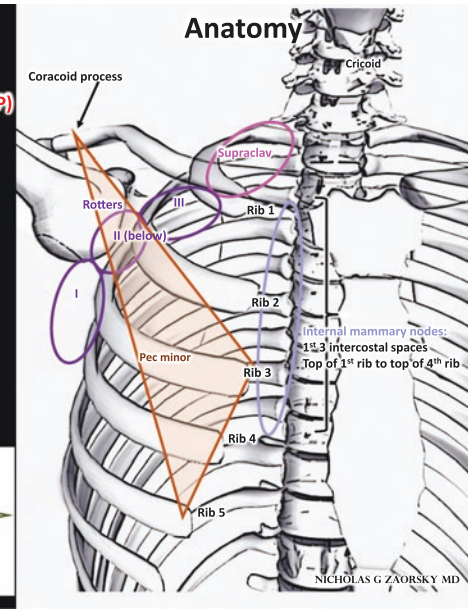
Boost

- Contour seroma and clips.
- Add 2-cm margin for electrons.
- e-cover volume with 90% IDL or use mini tangents.
- Consider re-sim in lateral decub position if tumor bed is far lateral.

"Three-Field" Breast Treatment

- Same setup as two-field but adds sclav field (i.e., treating nodes, levels I–III, and supraclavicular).
- If it is possible to treat the entire breast and the supraclav in one field, set isocenter at clavicular head for single-iso technique (cannot collimate).
- Start with tangent fields, same procedure as above, but half-beam block for superior half of field.
- SCV field: angled 10–15° away from cord. If treating L sided, RAO is used; if treating R sided, LAO is used.
  - Sup: cricoid
  - Inf: bottom of clavicular head/top tangents
  - Lateral: coracoid process or humeral head
  - Medial: pedicles (angle field 10° to stay off cord)
- Look at CT plan to ensure coverage. Use higher E (e.g., 16 MV vs 6 MV) when needed.
- If tangent field too long, need dual-isocenter technique.


Digital reconstruction
Coracoid process
Cricoid
Supraclav (oblique AP)
Angled ~10° to ↓ spine dose
Block above clavicle
Pedicles
PAB
Same borders, angle as sclav, but block lung and above clavicle
Humeral head
Block lung
Esophagus
Inf clavicular head
Lateral tangent
Feet come away from gantry
Medial tangent
Feet come away from gantry
1 iso
Diverge to sclav
2 iso with couch kicks
No divergence to sclav
Feet away
Feet away


Anatomy
Coracoid process
Cricoid
Supraclav
Rotters
III
Rib 1
II (below)
I
Rib 2
Internal mammary nodes:
1st 3 intercostal spaces
Top of 1st rib to top of 4th rib
Pec minor
Rib 3
Rib 4
Rib 5
NICHOLAS G ZAORSKY MD

"Four-Field" Breast Treatment

- Same as three-field, but adds **PAB** field to cover posterior axilla.
- Brings dose up to midplane of axilla to 50 Gy, usually 40–60 cGy/fx b/c; most dose comes from SCV.
- **Uses**: undissected axilla, gross ECE, larger patient (where three-field does not penetrate deeply).
- Field is 180° gantry angle opposite from SCV field.
- Borders the same as full SCV field, except block lung and above clavicle:
  - Sup: clavicle
  - Inf: match line at bottom of clavicular head (with half-beam block)
  - Lateral: include humeral head
  - Medial: clavicle-CW interface

"Kicking the Couch"

- **Use** when breast/CW is >20 cm and need to treat breast and LNs in a two-isocenter technique
- **Options**:
  - Extended SSD with monoisocentric technique OR
  - Dual-isocenter technique
    1. Set patient up as you would for standard tangents and set up supraclav field.
    2. Half beam block, supraclav iso is at the bottom of the field.
    3. Breast isocenter is in the tangent.
    4. Match superior border of tangent to the inferior border of the supraclav by "kicking the couch" (foot of bed) *away* from gantry.
    5. When you collimate the tangents, the superior part of the tangent will overlap w/ the third field.

IMN Field

- Still controversial; ASCO/ASTRO guidelines generally recommend including IM nodes when PMRT is used.
- Hennequin et al.: Randomized trial looking at PMRT +/− IM nodes. Stage I–II pts, did not show benefit of DFS or OS. Old RT techniques, little QA, underpowered.
- DCBG-IMN Trial: Prospective cohort study of 3089 pts with N+ breast cancer. R-sided pts received IM-RT; L-sided pts did not. Improved 8y OS 75% vs 72% with IM-RT (HR 0.82). DSS also improved.

IMN Technique Options

1. Deep tangents: to cover the breast and the IMN, but it is hard to meet the lung/heart dose constraints with deep tangents. Easiest.
2. VMAT/IMRT.
3. Shallow tangents and matching electron field (to cover the IMN). Set match line at 4 cm past midline with 1 cm feathering technique to avoid hot/cold spots. Hot spot would be at depth.
   (a) Target volume: first–third ICSs.
   (b) Medial border of tangent will move laterally when using an IMN field.
   (c) Angle IMN field away from medial tangent 5–10 °.
   (d) Match line is at skin.
   (e) Minimize cold spot and avoid match line fibrosis.
   (f) Up to 12 MeV electrons, usually prescribed to 90%.

Volumes

- PTV_eval created for DVH analysis
- RTOG 1005:
  - Breast CTV = breast tissue (clinically and CT), bound post by surface of pec then cropped 5 mm from skin (see pic)
  - Breast PTV = breast CTV +7 mm (no heart)
  - Breast PTV_eval = PTV cropped 5 mm from skin and at anterior ribs (includes muscle, excludes the rib, lung, heart)

NCCN Dose Guidelines (General)

- **WBRT hypofractionation** (T1–2 BCS):
  42.5 Gy/16 fractions → 10 Gy boost
  NCIC and UK START trials
  Margins –ve, <25 cm sep
- **WBRT conventional fractionation**: 45–50 at 1.8–2/fx, then 10 Gy boost, use if young and G3. CTV_boost is the lumpectomy cavity +1 cm. PTV_boost is +7 mm.
- *APBI* 38.5 Gy in 10 fractions.
- **Inflammatory**: 60 Gy.

Dose Constraints for Conventional

- 95% of volume getting 95% of dose. Relaxed to allow for better cosmesis
- V105 < 10%. Dmax 108%
- Heart: V30 ≤ 1%, mean < 2–3 Gy
- Lung, ipsi: V20 ≤ 15%. three-field: V20 < 30%
- Lung, contra: V5 < 10%
- Breast, contra: Max 3 Gy

If Unable to Meet Heart Constraints

- Heart block in tangents
- Change gantry/collimator angle
- IMRT
- Shallow tangents and match to electron field
- Prone breast board
- Breath-hold techniques
- Undercover IMNs

Breast Reconstruction

- BC retrospective, 2014: MRM with expander placement vs those w/ permanent implant placed 6 m after completion of RT. Rate of G3–4 capsular contracture 22% vs 10% for expander vs not. Rate of revision surgery also higher 30% vs 21%.
- May need to deflate contralateral implant.
- If flap-based reconstruction, these are usually plugged into IM arteries.

Toxicities of RT

Radiation Dermatitis

- G1 Faint erythema, dry desquamation
- G2 Moderate erythema, moist desquamation confined to skin folds
- G3 Moist desquamation in areas other than skin folds, bleeding induced by minor trauma
- G4 Life-threatening skin necrosis, ulceration, spontaneous bleeding from involved site, skin graft indicated
- G5 Death

Treatment

- Early → Aquaphor (dry desquamation); 1% hydrocortisone (pruritus).
- Advanced → Hydrogel wound dressings, Silvadene

Others

- Rib fracture
  - 0.5% with 4–6 MV
  - 1–2% with Co-60
- Pneumonitis
  - 2–3% – tangents
  - 5% – SCV
- Lymphedema – 10%
  - SLN or RT: 5%
  - SLN + RT: 10%
  - ALND: 7–10% (~1% per LN removed)
  - ALND + RT: 13% ("+50% relative increase over ALND alone")
- Axillary vein stripping – 40%
- Brachial plexopathy – 1.8%
- Second malignancies – 0.2–0.9%. 32% increase in lung cancer risk for smokers
- Breast fibrosis/asymmetry: 1/3 of pts
- Capsular contracture
- Cosmesis: 80% good, 5% poor

Heart Disease

- Darby, 2013: 7.4% increase in cardiac events for each 1 Gy mean heart dose. Mean heart dose better predictor than dose to LAD.
- Pericarditis – 2% (for left sided breast).

Follow-Up

- Interval H&P q 6 months x 5 years, then annually.
- Annual mammo.
- Wait at least 6 months from completion of RT.
- Routine imaging of reconstructed breast is not indicated.
- Women on tamoxifen: gynecologic exam if the uterus present.
- Women on AI: periodic bone mineral density.

Ductal Carcinoma In Situ (DCIS) [18–35]

General

- Stage I (Tis N0 M0).
- 15–20% of all breast cancer.
- 95% present with calcs on mammo.
- 1/3 progress to IDC at 10 yrs.
- 50% of DCIS recurrences are invasive (EBCTCG meta-analysis).
- ~10% risk of IBTR for lump only.
- Multicentricity more likely with larger tumors.
- If associated with microinvasion (<1 mm), should consider as DCIS when determining appropriate margin width (2 mm vs no tumor on ink for IDC).
- Post-lumpectomy mammogram should be performed to check for residual calcs.
- No clear role for MRI in DCIS.
- No RCTs for BCT vs MRM for DCIS; extrapolated from IDC.
- RT only adds LC benefit, not OS benefit.

Molecular/History

- Comedo (worse prog), cribriform, papillary, micropapillary, solid
- E-cadherin +
- Grade: 1–3, based on nuclear score

HER2

- HER2 testing not recommended, nor is HER2 therapy.
- G3 DCIS more likely to be HER2 positive.
- If extensive DCIS, and only small component of IDC, HER2 eval should be performed only on the invasive component and not on the DCIS portion bc of high FP rate.
- NSABP B-43: ongoing. Rando to WBI vs WBI + trastuzumab IV once in weeks 1 and 4.

Prognostic Factors for 10-Year EFS (from EORTC 10853, JCO 2006)

- Age < 40: 66% vs 81%
- Detection: 74% (clinical) vs 82% (mammo)
- Size 59% (>2 cm) vs 79% (1–2 cm) vs 82% (<1 cm)
- Histo: 74% (G3+) vs 73% (G2) vs 86% (G1)
- Architecture: 73% (solid/comedo) vs 74% (cribriform) vs 91% (micropap)
- Margin: 68% (R+) vs 81% (R0)

Mastectomy Versus Lumpectomy +/− RT

- B-06 pathology analysis, Fisher 1986, 1991: 78 pt had DCIS. Of 48 pts w/ segmental mastectomy +/−RT, 7% of RT had LR, and 43% in surg alone had LR. 28 pts total mastectomy pts had DCIS, and only 4% had LR. These data provide estimates of LR for DCIS, since there is no RCT comparing them.

DCIS Lumpectomy +/− RT

- **NSABP B-17**, Fisher, 1993, 2001: lump +/− 50 Gy. 9% of pts received a boost. At 12 yrs RT reduced IBTR 32 → 16%. Same DM and OS (87%). 50% of recurrences were invasive.
- **EORTC 10853**: lump +/− 50 Gy. At 10 yrs RT reduced LRF 26 → 15%, same DM and OS.
- **Swedish**: lump +/− 50 Gy. At 5 yrs RT reduced LF 22 → 7%, same DM and OS.
- *UKCCR*: lump then (50Gy, tamox, neither, both). All breast events 8, 18, 22, 6% respectively.
- **Meta-analysis** of above: BCS +/− RT: HR 0.49, all subgroups benefit from RT without significant long-term toxicity.
- **RTOG 98–04** (McCormick, 2015): 636 pts with G1–2 DCIS, <2.5 cm, margins 3 mm or greater randomized to lump +/− RT. Tam optional, given in 62%. RT was WBI 50/2, 50.4/1.8, or 42.5/16. No boost allowed. RT improved 7-year LR *1%* vs *7%*. Similar CBTR (5%), MRM (3%), G3–4 toxicity (4%), DFS, and OS. Late RT toxicity for RT: 30% G1, 5% G2.

BCS Alone, No RT

- MGH (Wong, 2006) *n* = 158. G1–2 DCIS ≤2.5 cm on mammo and SM ≥1 cm or R0 re-excision. Lump alone. No tam. Closed early due to high number of LRs, 12% at 5y. Of these recurrences 69% had DCIS and 31% had invasive dz. Rate of LR too high to warrant surg alone.
- ECOG 5194 (Hughes, 2009; Solin, JCO, 2015): Prospective, nonrandomized. Median age 60. DCIS w/ lump alone. Two cohorts studied (1). G1–2 ≤ 2.5 cm OR (2) G3 ≤ 1 cm. All pts had SMs ≥3 mm, no residual calcs on post-surg mammo. Tam discretionary (used in 30%). This study later used to validate Oncotype Dx DCIS score.

ECOG 5194	Group 1	Group 2
5y LR	6%	15%
7y LR	11%	18%
12y LR	14%	25%

Surgical Margins (Morrow, 2016)

- Neg margins have risk of IBTR vs pos margins.
- 2 mm margin is considered adequate in pts with DCIS treated with WBRT.
- If pt foregoes RT, should have at least 2 mm margin. If SMs are persistently positive, then refer for MRM.
- Re-excision in pts with margins <2 mm should be on case-by-case basis.

Indications for SLNBx

- Palpable/>4 cm
- Extensive high grade
- Microinvasion

NCCN Guidelines

- Lumpectomy (no ALND) + WBRT (cat 1).
- RT is conventional or hypofractionation (for suitable candidates).
- Lumpectomy without WBRT (cat 2B)/omission of RT (per 9804): low G, size <2 cm, SMs 3+ mm, ER+. Counsel on risk of higher LR 6% vs 1% at 7 years.
- Consider boost for margins <1 mm, age < 50, G3. No direct evidence. May improve LC, not OS.
- TM +/− SLNBx +/− reconstruction.
- Tamoxifen/AI x 5 yrs. if ER+.

Follow-Up

- Exam and mammo annually x5 years

Lobular Carcinoma In Situ (LCIS) [18–30, 36, 37]

Background

- The risk of developing breast cancer is 9–12x higher in pt w/ biopsy-proven LCIS vs general population.
- Can present w/ multicentric dz in 90% of mastectomy specimens; bilateral involvement in 35–60% of mastectomy specimens.
- If dx'd on bx, must excise to rule out DCIS/invasive dz as LCIS does not result in mammographic or physical findings. Other options for LCIS include close surveillance w/ exam and imaging and tam.
- Typically not associated with calcs.
- Finding LCIS in path specimen of IDC or DCIS does not change management or outcomes.
- CDH-1 gene loss common, leading to loss of protein e-cadherin.
- E-cadherin negative in 95% (single-file cells).
- Most ER+. Should add tamoxifen for high-risk pts (young age, diffuse involvement, FHx).
- 50/50 lobular/ductal.
- Tam decreases invasive dz by ~50%.

LCIS Lumpectomy

- NSABP P-1: 13 K pts with high risk for breast CA; +/− tamox for risk reduction. Included 180pts with LCIS treated with BCT. At 12y, 14% had IBTR, and 8% had contra CBRT. 1/3 of IBTRs invasive (5% of total cohort). Given low incidence of invasive cancers, these patients typically not treated w/ RT after lumpectomy.

NCCN

- Surgical resection, then cancer risk reduction with tamox, no RT indicated.
- R0 not necessary.
- 15–30% lifetime risk of developing breast cancer, bilateral (but more common in affected breast), so follow closely.
- Surveillance is annual mammo (not MRI).
- Consider chemoprevention w/ tam.

Early-Stage Breast Cancer/Invasive Ductal or Lobular Carcinoma (IDC/ILC) [18–22, 28, 38–62]

General

- 85% IDC.
- Extensive intraductal component (EIC): ≥25% DCIS.
- Tubular/mucinous histologies are favorable.
- Paget's: crusting, bleeding, pruritus, ulceration of nipple. About 50% of women will present with a palpable mass. If mass detected, 90% will be invasive.

Mastectomy +/− RT

- NSABP B-04: 1971. Is less extensive surg +/− RT as effective as Halsted RM? Two groups: (I) cN0: (1) RM vs (2) TM + ALND vs (3) TM + regional RT, without ALND (at the time the LNs were found to be positive). (II) cN+: (1) RM vs (2) TM + regional RT.
  No systemic tx. RT as 50/25 +/− 10–20 Gy boost to LNs if LN+. IMNs and sclav txd to 45/25. At 25 yr. f/u, no difference in DFS or OS.
  In cN0 patients, 25y DFS was 19% vs 13% vs 19% (NSS).
  In cN+ patients, 25y DFS was 11% vs 10% (NSS).
  Nodal treatment (by RT or LND) reduced LRF from 19% to 4%. The ~risk of dz in the axilla was 40%, but regional relapse rate in pts with TM alone was 19%. Overall, B-04 suggested that RT was as effective as RMs in controlling +LNs and that in pts w/ cN- dz, there is no benefit in removing ALNs.

SLNBx

- van der Ploeg, 2008: systematic review, meta-analysis, axillary LN recurrence in SLN-negative patients 0.3%.
- Kim 2006: meta-analysis of SLNBx. False neg rate 7.3%.
- Unaffected by neoadj chemo? (Buchholz 2008).
- NSABP B-32 (Krag, 2007): SLNB vs ALND. n = 561. cN0 axilla. Rando to SLN then immediate ALND vs SLN without ALND if the SLNs were negative on intra-op cytology. Results FNR of 10%. Removal of >1 SLN decreases FNR. Between two groups, similar OS, DFS, regional control.
- SLNB less morbid than ALND, per Z0011, IBCSG 23–01, and AMAROS.

Mastectomy Versus BCS

- **NSABP B-06, Fisher, 1985**: stage I/II, <4 cm, neg margins: TM vs segmental mastectomy vs segmental mastecomy+50Gy. At 20 yrs, same DFS, OS, and DMFS. LR: 3% for mastectomy, 7% for lumpectomy + RT, and 43% for lumpectomy alone. 20y IBTR: 39% vs 14%.
- B-06 pathology analysis: see DCIS section.
- EORTC 10801: stage I/II: MRM vs lump+50Gy + boost. At 10 yrs MRM reduced LF (20 → 12%) but the same OS (65%). 48% in lumpectomy group had pos margins.
- Milan I: T1 N0, RM vs quad+60Gy, at 20 yrs. RM reduced LF 8.8 → 2.3%, same OS.

Lumpectomy +/− RT

- NSABP B-06 above
- **Milan III**: <70 yo, ≤2.5 cm. Quad+ALND +/− 60Gy. At 10 yrs RT reduced LF (23.5 → 8%), same OS. All patients received systemic therapy.
- **Swedish Trial**: ≤3 cm. lump +/− 50Gy. At 5 yrs LR 14 → 4%, same OS.
- **PMH**: stage I/II. Tamox +/−RT. At 8 yrs RT reduced LR (12.2 → 4.1%), same OS.
- **CALGB 9343** (Hughes): >70 yo, pT1 N0, ER+. Tamox +/− RT. RT improved 8 yr LF (7 → 1%), but OS same.
- **NSABP B-21** (Fisher, 2002): Is Tam as effective as RT after BCS in IDC pN0, ≤1 cm? Three arms: tamox vs RT vs both. Tam is given 10 mg BID. Only 70% of pts had known ER/PR status. 13% ER neg; thus, likely that LF would be higher if only ER+ included. At 8 yrs LF 16.5%, 9.3%, and 2.8% (SS), respectively, same OS.
- B-21 subset analysis of available path (Fisher, 2007) *n* = 638. 14-year outcomes: 80% vs 89% vs 90% (SS). The benefit of combination

RT + tam (vs RT alone) is lost w/ long-term follow-up.
- **EBCTCG meta-analysis**, Lancet, 2005, 2011. 10 RCTs evaluating adj RT after BCS. Overall, 5y risk LR reduced from 26% to 7%. In each individual RCT, RR was ~0.3; thus, 70% relative risk reduction with RT. No difference in OS or CSM in individual RCTs. However, overall 15y CSM was reduced from 36% to 30%. Thus a 20% LR decrease in 5y results in reduction in CSM by 5% at 15 years – this is "The 4:1 rule" of breast cancer.
- **EBCTCG** update, 2011: 10y recurrence was decreased by 50% w/ RT 35% vs 19%. The reduction in LRR as the first site of recurrence was still decreased by 66%.
- **PRIME II** (Kunkler, 2015): includes age 65+, BCS and path axillary staging, T1–2, < 3 cm, ER/PR+, SM 1+ mm, G3 or LVI (but not both). Rando to 40–50 Gy/15–25 frax WBRT vs no RT. n = 1326. 5-year IBTR 4.1% vs 1.3% ($p < 0.01$). 5-year CSS and OS similar. Also, results similar to Hughes, 2004 study.

Timing
- JCRT Sequencing: stage I/II. chemoRT vs RTchemo. At 11 yrs, same OS, DM, etc. For close margins (<1 mm), LR improved with RT first (32 → 4%), for +margins, no difference.

Boost
- EORTC Boost Trial: Stage I/II s/p lump +50Gy +/− 16 Gy boost. At 10 yrs boost improved LF 10.2 → 6.2%. All patients benefited but more for <40 yo. Boost had more severe fibrosis (1.6 → 4.4%).
- Lyon Boost Trial: <3 cm. Lump+ALND+50Gy +/−10Gy boost. At 3 yrs boost improved LF 4.5 → 3.6%. Cosmesis unchanged.
- **RTOG 10–05**. Assessing sequential vs concurrent boost.
  CTV = GTV + 1 cm. CTV excludes ant surface of pec major, anterolat 5 mm from skin, and any extension past midline.
  PTV = CTV + 0.7 cm. PTV excludes heart. PTV-eval excludes the part of PTV outside of the ipsi breast, the first 5 mm of tissue under skin, and expansion into CW, pec muscle, and lung.

APBI
- **RTOG 0413/NSABP B-39**. Early stage randomized to 50–50.4 optional boost to 60–66.6 vs PBI. APBI with any of these:

Technique	Interstitial	Intracavitary/ balloon	3D-CRT
Dose	3.4 Gy x 10 BID		3.85 Gy x 10 BID
CTV and PTV	15 mm from cavity	10 mm from cavity	15 mm expansion from cavity, + 10 mm for PTV.
Clip	Limit to 5 mm from skin surface		

- TARGIT A (Lancet, 2014): Pts randomized to single dose IORT vs standard Fx WBRT after surg. All pts. >45y with IDC. 85% <2 cm, 84% G1–2, 93% N0, 82% ER+, 69% PR+. WBRT required if margins <1 mm, EIC or unexpected ILC, and per inst policy (nonuniform). 22% of pts. received subsequent WBRT. Median fu 2.5y. 5y LR 3.3% vs 1.3% ($p = 0.04$) favoring WBRT but met 2.5% non-inferiority threshold of 2.5%. No dif in CSM, OS. Results are controversial.
- **Strnad (Lancet, 2016)**: n = 1184. DCIS or IDC. Age > 40, pTis or pT1–2 (up to 3 cm), pN0 or pN1mi, unifocal, no EIC, no skin involvement or Paget's dz, negative SM > 1 mm and > 5 mm for ILC or DCIS, no LVI, DCIS w/ VNPI <8. If IDC, then SLNBx or ALND w/ 6+ LNs required. Rando to WBI vs APBI. APBI is interstitial, multi-catheter BT, to dose of 32 Gy/8 fx or 30.3 Gy/7 fx (BID) w/ HDR, or 50 Gy w/ pulses of 0.6–0.8 Gy/h (1 pulse/h, 24 he per day) w/ PDR BT. WBI was 50–50.4 Gy, then 10 Gy electron boost. The 5-year LR was 1.4% APBI vs 0.9 WBO (NSS). G2–3 skin toxicity 3% APBI vs 6% WBO ($p = 0.08$). Grade 2/3 subcut late tox 7% vs 6% (NSS). Grade 2–3 breast pain lower w/ APBI (1% vs 3%, $p = 0.04$). Conclusion: APBI is not inferior to WBI in select, low-risk pts.

- Livi, Florence, 2015: PBI 6 Gy x 5 fx vs 50/20 + 10 Gy boost. n = 520. IBRT was 1.5% in both arms. This fractionation scheme adopted by Formenti.
- Formenti, 2012: n = 100 APBI like Florence. IBTR1%.

Hypofractionation
- Whelan (Canadian): invasive, LN neg breast cancer. 50/25 vs 42.5/16. No boost, no >25 cm separation, no tumor >5 cm.10-yr LR unchanged (~6.4%, NSS), cosmesis excellent or good in ~70% (NSS). Only group w/ worse outcomes were high grade (10-yr LR 5% vs 16%, $p = 0.01$).
- Bane, 2014: subset analysis of Whelan trial. Central path review of molecular subtype was predictive of LR (luminal A, B, HER-2 enriched); however, unlike original manuscript, tumor grade did not predict response to hypofractionation.
- START A: 50/25 vs 41.6/13 vs 39/13. ~25% chemo, ~25% N+, ~50% boosted, ~10% PMRT. 5 yr LRR same.
- START B: 50/25 vs 40/15. Boost allowed in both START A and B but not required. Same findings as START A. Less adverse effects with hypofrac. 10-year LRR 6% vs 7% (NSS). 10-year DMFS 16% vs 10% ($p = 0.01$), OM 19% vs 16% ($p = 0.04$), both favoring hypofrac.
- RMH/GO3: similar doses to START A. Showed that 42.9/13 had lowest IBTR.
- FCCC: 45/2.25 + 56/2.8 concomitant boost, in 20 fx. Similar LC, cosmesis.

Invasive Breast Cancer, Management of the Axilla

- **BCS**
  - cN0 → SLNBx
  - SLNBx (−) = done
  - SLNBx (+) =
    1. T1-T2, 1–2 LN+, BCS, getting whole breast RT → done
    2. All others (e.g., T3) → ALND
  - cN+ →Axillary u/s + FNA:
    (−) FNA → SLNBx w/ removal of abnormality
    (+) FNA → ALND
- **TM**: all get ALND after SLNB, except T1–2 N0

NCCN for ≤T3, ≤N1

- **Lumpectomy with SLNBx**
- (If >1 cm, pN+) chemo first
- (pN0) WBRT +/−boost
- (pN+) 3field +/− boost
- (pT1 N0, ER+, >70yo): HT +/− RT
- HT/Herceptin based on N, ER, HER2
- TM + SLNBx (RT if N+)
- Neoadj chemo (aiming for BCT)
- Core bx with clips placed, LN eval

Hypofractionation (ASTRO, 2018):
- All, except if doing RNI

Hypofractionation (ASTRO, 2011):
- Pt > 50yo at dx.
- pT1–2 N0, sp. BCS.
- No systemic chemo.
- In the breast along the central axis, the minimum dose is >93%, and max dose is <107% of prescription dose, as calculated w/ 2D tx planning w/o heterogeneity correction.

Omission of RT
Consider if age > 65–70, ER/PR+, T1 N0 tumors, on hormonal therapy (similar to CALGB 9343, PRIME II inclusion).

Accelerated Partial Breast Irradiation (APBI) [63]

ASTRO APBI Criteria (2016 updates in bold)[63]			
	Suitable	**Cautionary**	**Unsuitable**
Age	**≥ 50 y**	**40-49 y if no other risk factors OR ≥ 50 y and at least 1 pathologic RF, but no other unsuitable factors**	**< 40 y OR 40 -49 not meeting criteria for cautionary**
BRCA1/2	Not present		Present
Tumor size	≤ 2 cm	2.1-3.0 cm	> 3 cm
T-stage	T1 **OR low risk Tis (<2.5 cm, G1-2, ≥ 3 mm SM)**	T2	T3-4
Margins	≥ 2 mm	<2 mm	Positive
Grade	Any		
LVSI	No	Limited/focal	Extensive
ER status	Positive	Negative	
Multicentricity	Unicentric only		Multicentric
Multifocality	Clinically unifocal and pathologic extent of disease ≤ 2 cm	Clinically unifocal and pathologic extent of dz 2-3 cm	Clinically multifocal or microscopically multifocal >3 cm in total size
Histology	Invasive ductal or other favorable subtypes	Invasive lobular	
Pure DCIS	low risk Tis **(<2.5 cm, G1-2, ≥ 3 mm SM, screen detected)**	**≤ 3 cm and not meeting "suitable" criteria**	> 3 cm
EIC	Not allowed	≤ 3 cm	> 3 cm
Associated LCIS	Allowed		
N stage	pN0(i$^-$,i$^+$)		pN1, pN2, pN3
Nodal surgery	SLN Bx or ALND		None performed
Neoadjuvant therapy	No		Yes
IORT	Restrict IORT for suitable pts Low E IORT should be on study		

APBI Planning with EBRT

- CTV = lump +1.5 cm
- PTV = CTV + 1 cm
- PTV_EVAL = PTV – 5 mm at skin surface and pec maj

APBI EBRT Planning Evaluation

- Whole breast V50% Rx < 60%
- Lung ipsi V30% Rx < 15%
- Lung contra V5% Rx < 15%

APBI Planning with MammoSite

- CTV = balloon +1 cm
- PTV = CTV
- PTV_EVAL = PTV – 5 mm at skin surface and pec maj

APBI MammoSite Treatment Planning Evaluation

- Tissue/balloon conformance (no air/fluid cavities)
- Balloon symmetry
- Balloon to skin distance (>7 mm)
- Skin dose <145% prescription
- Breast DVH:
  90% volume gets 90% of dose.
  V150 < 50 cc.
  V200 < 10 cc.

Dose Constraints for APBI

- Contralateral Dmax ≤3 Gy
- Ipsi lung V20 < 15%, V5 < 50%
- Contra lung V5% < 15%
- Heart V20 < 5%, mean < 4 Gy

Breast Cancer, Postmastectomy RT (PMRT) [64, 65]

NSABP pooled analysis of MRM without RT (from NSABP)	
#LNs	**10 year LRF**
1–3	13%
4–9	24%
10+	32%
Tumor size	
≤2 cm	15%
2.1–5 cm	21%
>5 cm	25%

Conventional Fractionation

- **Danish 82b**: premenopausal ("B is pre"). n = 1708. High-risk breast cancer w/ cN+, tumor size >5 cm, or skin/pec fascia involvement. MRM + CMF +/− RT. RT was to CW, sclav LNs, IMNs. At 10 yrs PMRT improved LRF (32 → 9%), DFS (34 → 48%), and OS (45 → 54%). Improvements regardless of tumor size or #LNs (mean 7 LNs excised).
- **Danish 82c**, Overgaard, 1999: postmenopausal, high-risk breast cancer (positive LNs, tumor size >5 cm, or skin/pec fascia involvement). MRM + tamox +/− RT. PMRT was to CW, supraclav LNs, and IMNs. At 10 yrs PMRT improved LRF (*35* → *8%*), DFS (24 → 36%), and OS (36 → 45%). No benefit for N0 patients.
- In both 82b/c, rate of recurrence 3%/y. 20–30%LRR benefit, 10% OS benefit.
- In both 82b and c, criticism was inadequate ALND. Thus, subgroup analysis done of 1152 patients with 8+ LNs removed. In 1–3+ LNs, 15-year LRR 4% w/ RT vs 27% no RT. 15-year OS 57% w/ RT vs 48% no RT (both SS). In 4+ LN benefit, similar benefit for 15-year LRR 10% vs 51% and OS 21% vs 12%.

Hypofractionation

- British Columbia trial (Ragaz, 2005): premenopausal. MRM + CMF +/−RT. Mean 11 LNs excised. RT was five-field. CW to 37.5/16. Bilat IMN chain to 37.5/16. Sclav to 35/15. At 20 yrs PMRT improved LRF (26 → 10%) and OS (37 → 47%).
- EBCTCG meta-analysis, Clark, 2005: 8135 women, 22 RCTs to assess effect of PMRT. PMRT improves LR (~18% at 5 yrs) and breast cancer mortality (5.4% at 15 yrs). 4:1 ratio. RT ↑ contralateral breast cancer, lung cancer, and heart disease.
- EBCTCG meta-analysis, 2016 update: Stratified by #N+. In pts with 1–3 N+, RT decreased 10y LR 20% → 4%, decreased 10y DSM 50% → 42%. Similar benefit for pts with 4+ LN. No benefit for pts who are N0.
- NSABP pooled analysis of 5 RCTs, Taghian, 2004.

EBCTCG data	10y LRR first		10y any recurrence		20y CSM		20y OM	
SS in yellow	RT	No RT	RT	No RT	No RT	No RT	No RT	No RT
pN0	3	2	22	21	29	27	48	42
pN+	8	26	52	62	58	66	65	70
1-3 LN	4	20	34	46	42	50	53	56
4+	13	32	66	75	71	80	75	83

PMRT Technique

- 50/25. Custom wax bolus QOD.
- Include CW, axilla, supraclav and axillary LNs, ipsi IM LNs.
- Tissue expanders (if present) should not be expanded during RT.

Scenario	Absolute indications	Relative indications	Observation (must meet all)
Indications for PMRT	> 5 cm (i.e. T3) R+, which is < 2 mm SMs (this is in contrast to the post-BCT setting, where it is 0 mm) 4+ LNs, or 3+ LNs (EBCTCG) > 20% LNs involved and tumor > 3.5 cm (MDACC)	young age nipple involvement < 10 LNs resected > 20% LN involvement and tumor < 3.5 cm OR < 20% LNs involved and tumor > 5 cm gross multicentric muscle involvement G3 HER2+	T1-2 N0 R0
Indications for PMRT after NA chemo (expert opinion only)			cT1-2 N0-1 tumors, achieving pCR, ypN0; or ypN1 and ER+, age > 40, no LVI, no ECE

Locally Advanced Breast Cancer [18–22, 39, 59, 66–81]

General

- Risk of IMN+
- 5% of tumors have IMN as sentinel node
- 10% if Ax node neg
- 20–50% if Ax node pos

RNI

- **EORTC 22922**, Poortmans, 2015. Stages I–III, central or medial primary, MRM or BCS and ALND. 76% had BCS, 24% MRM. Some w/ SLNB, then ALND if +LN. n = 4004. Rando WBRT or CW RT alone 50 Gy/25+/− RNI RT to first 3 IC spaces, up to first 5 IC spaces for lower inner quad tumors. 99% LN+ and 66% LN- got systemic tx. RNI won. 10 year OS 81% vs 82% ($p = 0.06$). DFS 69% vs 72% ($p = 0.04$) DMFS 75% vs 78% ($p = 0.02$). Any recurrence 23% vs 19% ($p = 0.01$). CSM 14% vs 12% ($p = 0.01$). RNI had worse pulm fibrosis (4 vs 2%) and cardiac fibrosis (1.2% vs 0.6%), but not brachial plexopathy. Thus, for LN+ or high-risk LN- breast cancer, addition of RNI improves DFS, DMFS, and BCSM, without concomitant effect on OS.
- **NCIC MA.20** (Whelan, NEJM, 2016). Women were randomized to BCS (i.e., lumpectomy) + ALND +/− chemo + WBRT vs lumpectomy + ALND +/− chemo + WBRT and RNI (which included SCV and IMNs – the axilla was not treated because it was dissected during ALND). Notably, most patients went straight to ALND; only 40% of patients had a SLNB prior to the ALND. The primary endpoints were OS and morbidity. Of the patients, ~50% were > 2 cm, 42% were Grade 3, 74% were ER+, the median number of LNs removed was 12, 85% had 1–3 + LNs, 10% were high-risk N0 (e.g., triple negative, young), 5% had 4 or more LNs, 91% received AC chemo, and 71% received endocrine therapy. The trial was therefore mostly a trial of women with 1–3+ LNs. The RCT had overlap eligibility with Z0011. The dissected axilla was not in the radiation volume. At 5 years (Whelan, ASCO, 2011), the OS failed to reach SS at 92 vs 91%. LR was SS improved with RNI, at 97% vs 95% (though these values are very close); and the DMFS was improved with RNI at 90% vs 84% ($p = 0.003$). DM was decreased in the group that received RNI (surprisingly, because the benefit for LC was not so drastic); and this benefit likely had an impact on OS. With RT, we typically see large differences in LRR reduction translate to small differences in DMFS improvement, with the idea being that we decrease the source of metastatic disease spread. These results suggest the importance of RNI with treatment of the IMNs: it is clinically negative, not appreciated, not screened. Thus, a patient with a IMN LRR would never be counted, but the patient would be counted with a DM. This is why there is an inverse in the 4:1 ratio of LRR vs OS that we typically quote. These results suggest that a longer follow-up and more detailed analysis of the data are needed; moreover, these patients are very different from the Z0011 data. However, increase risk in pneumonitis (0.2% vs 1.3%) and lymphedema (4.1% vs 7.3%) with RNI though felt to be acceptable. Thus, more time is necessary before this is called practice changing. Nonetheless, the data suggest that RLNI benefits higher-risk patients (from Z11). Moreover, we know from the B-04 trial that the chance of a woman getting lymphedema continues to increase over time.

Local Treatment of Metastatic Patients

- Tata memorial (Bawde, 2015): M+ breast ca, given chemo6–8 cycles, then randomized to locoregional tx (MRM in 72% or BCS in 23%) or not. Median OS similar (20 months). With LRT, LRPFS improved (median not attained vs 18 months). In the no LRT group, only 10% of women ultimately required palliative surgery. Thus, LC for M1 patients not warranted.

Axillary dissection

- ACOSOG Z0011:T1–2, cN0, SLNBx+ (1 or 2 SLN by H&E). Randomization: lumpectomy with neg margins +/− ALND. All got

PORT (tangents). 97% got systemic therapy (HT or chemo) at discretion of physician. 5-yr regional control same (*99 + %*), OS same (92%). Radiation field design varied widely: 89% got WBRT, 15% got RNI (though it wasn't allowed), high tangents used in 50%.

– **Which patients do not quality for Z0011?** If cannot find the node, if gross ECE, if clinically LN+, R+, >3 LNs involved, matted LNs, neoadjuvant systemic tx.

NCCN for T3+, N2+

– Neoadj chemo → MRM → PMRT.
– OR MRM, then chemo and RT.
– If doing NACT, place markers to localize tumor bed.
– If NACT, and given AC x 4 but no response, try taxol x 4 (per B-27).
– **Contraindications to BCT after NACT**: Multicentric, IBC (T4d), diffuse microcalcs, residual skin involvement.

Inflammatory Breast Cancer (IBC) [79, 82]

General

- Definition:
  1. Rapid onset of breast erythema, edema, and/or peau d'orange of >1/3 of the breast:
     +/− calor
     +/− underlying palpable mass
  2. < 6-month duration (i.e., not from neglect).
  3. Histologic dx of breast cancer.
  4. DLI can be seen on path, but not necessary for dx.
- Stage IIIB (T4d N0 M0)
- Metastatic disease in 25–30%
- **Haagensen's grave signs (1943)**. Factors used to determine operability in pts w/ LABC. If two or more of the following present, then it is a contraindication to mastectomy:
  - Skin ulceration
  - Fixation to CW
  - Edema <1/3 of skin of the breast
  - Axillary LNs > 2.5 cm
  - Fixed axillary LNs
- **Haagensen's signs of very poor outcome**
  - >50% skin edema
  - Satellite skin nodules
  - Inflammatory
  - Clinically involved SCF and IM LNs
  - Arm edema

Workup

- HP
- Bilateral mammo
- Full metastatic workup:
  - Breast MRI optional
  - Labs: CBC and CMP including LFT
  - Chest X-ray
  - CT c/a/p (can be performed the same time as PET)
  - Bone scan or sodium-fluoride PET-CT (Category 2B)
  - Fertility counseling
  - Genetic testing

Outcomes

- LRR5: 10–20%. If no RT LRR 50%
- DFS5: 40–50%
- OS5: 50–60%

Chemo

- MDACC retrospective, Cristofanilli (2004). Addition of taxanes to 5-FU/adria/cyclophos improved PFS and OS.

RT

- MDACC (Liao, 2000; Bristol, 2008): Retrospective of trimodality tx for M0 IBC. RT was (1) 50/2 + 10 Gy boost (1977–1981) or (2) 45–51 Gy/1.5 BID w/ 15 Gy boost (1982+). For BID RT, 5-year LRC was 84% (66 Gy BID) vs 58% (60 Gy BID), and 10y LRC was 77% (66 Gy BID) vs 58% (60 Gy BID), all SS. For those txd w/ BID RT, G3+ toxicity was 29% vs 15%, lymphedema 9% vs 25%, fibrosis 6% vs 4%, and brachial plexopathy 2% vs 0%. 66 Gy had improved LRC in those w/ < PR to chemo, R+ or close SMs, and < 45 yo. Thus, do not treat to 66 Gy unless warranted.

Treatment

- Workup! Then, treatment.
- Combined-modality therapy: **ddAC x4 → T x 12 → MRM → comprehensive PMRT**.
- If no response, try different chemo.
- If still no response to NA chemo, *consider* NA RT.
- Then MRM and ALND. Never SLNBx.
- Always need PMRT.
- RT to cover CW for PMRT (or whole breast if preop), RNI. Patient- and institution-dependent: ± IMNs ± PAB ± scar boost.
- RT is to the CW, axilla. Escalate to 66 Gy if <45 yo, close or positive SMs, four or more LNs following preop systemic treatment, or poor response to systemic treatment.
- 5–10 mm bolus QD until desquamation.
- Boost scar 60 Gy if pCR, 66 Gy if <pCR.
- +/− late reconstruction. Never early because it can compromise outcomes.

Phyllodes Tumor [83, 84]

Overview
- Large, fast growing.
- Arises from periductal stromal cells.
- Accounts for <1% of breast neoplasms.
- 30% are malignant.
- Stomal overgrowth, tumor size >7 cm.
- Infiltrative borders, necrosis, and high mitotic count are the main high-risk features for DMs.
- Classification: benign, borderline, and malignant (only malignant get RT).

Differential
- Fibroadenoma, IDC

Treatment
- Optimal management is surgery.
- Re-excise for R+. No axillary staging.
- Consider PORT if unresectable (cat 2b) or if very large and removed w/ MRM (e.g., > 10 cm) or if >5 cm and removed w/ BCS.

Paget Disease

Overview
- Eczematoid changes, crusting, redness, discharge

Workup
- Full thickness skin biopsy
- PE + MMG; if both (−) → MRI for patients who are candidates for BCT

Treatment
- Paget alone (Tis); Paget + DCIS (Tis); Paget + invasive disease (staged per invasive)
- BCS (with removal of full nipple areolar complex) + RT vs TM
- EORTC 10873, Bijker, 2001: 5-year LR 5% after complete excision of nipple-areolar complex and underlying breast + WBI 50 Gy

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Gastrointestinal Cancers

7

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Abstract

This chapter discusses the general management of patients with gastrointestinal cancers, with special focus on principles that guide radiotherapy management. Several key components of trimodality care and stereotactic body radiation therapy (SBRT) are discussed.

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Esophageal Cancer [1–23]

- **T1**
  - T1a – into lamina propria or muscular mucosae
  - T1b – into submucosa
- **T2** – muscularis propria
- **T3** – adventitia
- **T4** – adj structures
  - T4a – pleura, pericardium, azygos, diaphragm, peritoneum
  - T4b – aorta, vertebrae, trachea
- **N1** – 1–2 nodes
- **N2** – 3–6 nodes
- **N3** – 7+ nodes

Additions to AJCC 8th, from 7th

- Changed definition of location of tumor from top to its epicenter.
- Any tumor extending <2 cm into stomach is esophageal; if >2 cm, then it is gastric.
- Added ypTNM prognostic staging, which does not distinguish between adenoCA vs squam.

General Anatomy/Staging

- Tumors arising at the GEJ or in the cardia of the stomach within 5 cm of GEJ *and* extend into the GEJ are staged as esophageal.
- All others with an epicenter in the stomach >5 cm from the GEJ *or* those <5 cm without extension into the GEJ are staged as gastric.
- The staging system differs for N0 patients; it depends on histology.
- Once a pt. is LN+, staging and prognosis are similar.
- Location matters for SCC; prognosis is worse with more proximal tumors.

Siewert (assess for all adenoCA of GEJ; from Siewert, 1998)			
		Epicenter	Treat like
1	Lower esophagus within 1–5 cm above GEJ	Above GEJ	Esoph
2	Cardia within 1 cm above and 2 cm below GEJ	At GEJ	Esoph
3	Subcardinal with center 2–5 below GEJ, infiltrates GEJ from below	Below GEJ	Gastric

(Tx 1–2 like esophageal; 3 like gastric)

AJCC esophagus section	cm from incisors	Landmark
	15	Cricoid
Cervical	15–20	
	20	Thoracic inlet, sternal notch
Upper T	20–25	
	25	Azygous, carina
Mid T	25–30	
	30	Inf pulmonary vein
Lower T	30–40	
	40–42	GEJ

<table>
<tr><td>AJCC 8</td><td>T1a</td><td>T1b</td><td>T2</td><td>T3</td><td>T4a</td><td>T4b</td></tr>
<tr><td rowspan="5">N0</td><td>IA-SCC G1</td><td rowspan="3">IB-SCC G1-3</td><td>IB-SCC G1</td><td rowspan="2">IIA-SCC G1up/mid or G1-3 low</td><td rowspan="5">IIIB</td><td rowspan="5">IVA</td></tr>
<tr><td>IB-SCC G2/3</td><td>IIA-SCC G2/3</td></tr>
<tr><td>IA-aden G1</td><td rowspan="3">IB-aden G1-2</td><td rowspan="2">IC-aden G1/2</td></tr>
<tr><td>IB-aden G2</td><td rowspan="2">IIB-SCC G2/3 up/mid</td></tr>
<tr><td colspan="2">IC-aden G3</td><td>IIA-aden G3</td><td>IIB-aden-G1-3</td></tr>
<tr><td>N1</td><td colspan="2">IIB</td><td>IIIA</td><td>IIIB</td><td>IIIB</td><td></td></tr>
<tr><td>N2</td><td colspan="2">IIIA</td><td>IIIB</td><td>IIIB</td><td>IVA</td><td></td></tr>
<tr><td>N3</td><td colspan="5">IVA</td><td></td></tr>
<tr><td>M1</td><td colspan="5">IVB</td><td></td></tr>
</table>

AJCC 7	T1	T2	T3	T4a	T4b
N0	Depends on histo, G; loc for SC			IIIA	IIIC
N1	IIB	IIB	IIIA	IIIC	IIIC
N2	IIIA	IIIA	IIIB	IIIC	IIIC
N3	IIIC				
M1	IV				

AJCC 8 ypTNM	ypT0	ypT1	ypT2	ypT3	ypT4a
ypN0	I	I	I	II	IIIB
ypN1	IIIA	IIIA	IIIA	IIIA	IVA
ypN2	IIIB	IIIB	IIIB	IIIB	IVA
ypN3	IVA				
M1	IVB				

Overview
- 17, 300 cases/yr., 15, 800 deaths/yr.
- Barrett esophagus annual conversion 0.2–2%/yr.
- Risk factors: tobacco, ETOH, nitrosamines, Plummer-Vinson syndrome, achalasia, GERD.
- Note: no serosal lining of esophagus and rich submucosal lymphatic network; thus, locoregional spread common. 90% of tx failures after definitive CRT are within GTV (Welsh, 2012).

T	Tis	T1a	T1b	T2	T3
Risk LN+	<3%	7	20	40	>40

Workup
- EGD, EUS with FNA.
- On US, layers 1, 3, and 5 are bright, whereas 2 and 4 are dark. Layer 3, submucosa (T1); layer 4, muscularis propria (T2); layer 5, serosa (T4).
- PET-CT or CT chest (40% have lung mets).
- PFTs if planning surgery.
- Barium swallow as needed.
- Nutrition eval.
- Port/J-tube; consider lap (in GEJ adenoCA); Her-2 in M1; CBC; CMP; LFT; EtOH, tobacco abuse.
- Bronch if tumor is above carina (at ~25 cm) and M0 to rule out a tracheoesophageal fistula.
- Staging lap and thoracoscopy in LA dz. to limit futile CMT.
- Assess Siewert.
- Pathological microscopic spread (Gao, IJROBP):
  - AdenoCA: 10 ± 7 mm prox, 18 ± 16 mm distal.
  - SCC: 10 ± 14 mm prox, 11 ± 8 distal.
  - Thus, CTV margin <30 mm OK in 94% of cases, except distal GEJ adenoCA, which need 50 mm.

Surgical Techniques
- Endoscopic mucosal resection
  - No ulceration, no LVSI, <2 cm, G1–2, T1aN0 (SCC), T1a/superficT1b (adenoCA)
  - 98% OS (Ell 2007)
- Transhiatal esophagectomy: no thoracotomy, two incisions, pull up Inability to perform a full thoracic LN dissection, but better tolerated, no mediastinitis risk
- Ivor-Lewis (right thoracotomy): good exposure, risk mediastinitis
- Left thoracotomy: good for lower third resections
- Optimum # nodes = 23 (Peyre 2008); min 15 (NCCN)
- Surgery alone ~20% 3-year OS

Preop/Periop Chemo
- RTOG 8911 (Kelsen 1998): T1–2Nx → surgery +/− preop cis/5-FU. *n* = 440. Same OS, 2.5% pCR.
- MAGIC trial (Cunningham 2006): T1–3 N0–1 gastric/GE/lower esophagus adenosCAs→ surgery +/− periop epirubicin, cisplatin, 5-FU. *n* = 503. Only 42% of patients assigned to periop chemo arm are able to complete all cycles. Only 49% of pts who got all preop chemo completed all three cycles of adjuvant chemo. Chemo ↑ 5-yr OS (23 → 36%).
- FLOT4 (abstract only): MAGIC regimen (3c ECF preop and post-op) vs FLOT (4c docetaxel, oxaliplatin, 5-FU preop and post-op). FLOT improved MST (35 m vs 50 m) and 3-yr OS (48% vs 57%).

Preop CRT

- Michigan (Walsh 1996): RCT specifically for adenosCAs. *n* = 113. Ran to CRT 40 Gy/15 at 2.67 + cis/5-FU, then surg vs surg alone. MST improved w CRT: 16 m vs 11 m. Criticisms: short median FU; 11 pts withdrew from CMT arm vs 1 in surg arm; outcome of surg arm poor (10–20% lower than expected vs Michigan and EORTC trials). 25% pCR.
- EORTC (Bosset 1997): T1–3 N0 or T1–2 N1, SCC only→ surgery +/− preopCRT (cis x2c with 37/10 split course). *n* = 282. pCR 26%, same OS (18 m). 26% pCR.
- Michigan, Urba 2001. *n* = 100. Median FU 8 yrs. NA-CRT 45/1.5 BID w cis, 5-FU, vinblast then surg vs surg alone. No difference in MST 18 m. However, only powered to detect increase from 1–2.2 years. 28% pCR.
- Burmeister 2006: T1–3 N0–1 → surgery +/− preop CRT (cis5-FU with 35/15). *n* = 256. Same DFS and OS but better R0 resection in CMT. 13% pCR.
- CALGB 9781 (Tepper 2008): T1–3 N1 → surgery +/−preop CRT (cis5-FU with 50.4 Gy). CRT ↑5 yr OS (16 → 39%). 40% pCR.
- POET (Preop Chemo versus chemo + CRT in Esophagogastric AdenoCA Trial. [Really, "PreOCOREGAT"])/Stahl 2009: T3–4NX *adenoCA* of lower esoph and gastric cardia → neoadj chemo 2.5 c of cis/5-FU/leucovorin vs 2 c same chemo followed by CRT (30/15 + etoposide+cis). All got surgery 3–4wk after. Closed early but CRT had better pCR (2 → 15.6%) and rate of pathologically involved LNs (38% vs 64%). Also trended better OS (3 yr., 28 → 47%, $p = 0.07$). 3-year LR lower in NA-CRT arm 24% vs 41%, $p = 0.06$. Stopped early bc poor accrual. Authors conclude underpowered for OS benefit.
- CROSS (van Hagen, NEJM 2012): 368 pts (75% adenoCA, 23% SCC, 2% large cell undif) → surgery +/−preop CRT. 41.4 Gy in 23 fx with carbo/taxol. Carbo was AUC 2, and paclitaxel was 50 mg/m^2 weekly during RT.
  - ↑MST (24 m → 49.4 m)
  - 5-year OS 47% vs 34%
  - ↑R0 resection with CRT (69 → 92%)
  - pCR 29% overall. pCR 23% adenoCA and 49% SCC
- Gebski 2007: metanalysis with 1209 pts. Preop CRT improves OS compared to surgery alone.
- Meta-analysis of 12 trials (Sjoquist, Lancet Onc 2011). NA-CRT vs surgery alone in operable esophageal carcinoma. With NA-CRT, there is 8.7% absolute improvement in 2-year OS vs surgery alone. Also, 5.1% absolute improvement in 2-year OS w chemo alone vs surgery.
- RTOG 1010: current RCT. CROSS trimodality +/− trastuzumab to 50.4 Gy. Must have HER2 overexpress.

Definitive RT

- Sai (IJROBP 2005). Retrospective of 34 patients with T1 CA, either EBRT alone (64 Gy) or EBRT (52 Gy) + ILBT (8–12 Gy/2–3 fx). 5-year OS 59%, RFS 68%, CSS 80%

BT for Inoperable Esophageal CA

- RTOG 9207, Gasper, 2000. 50/25 w cis and 5-FU, wait 2w, then HDR 5 Gyx3 or LDR 20 Gy. 1-year OS 49%. Fistulas in 14%. RIP brachy.

Definitive CRT

- RTOG 85–01 (Herskovic 1991; Cooper, 1999): T1–3 N0–1. 86% SCC, 14% adenoCA. Randomize→RT (64 Gy) vs CRT (cis 75 mg/m^2 and CI 5-FU 1000 mg/m^2 with 50 Gy/25). CRT improved 5-year OS (0 → 27%). This RCT established CRT as superior to RT alone for T1–3 N0–1 pts not eligible for surgery. Doses 64.8 and 50.4 later become INT doses by Minsky.
- INT0123 (RTOG 9405): T1–4 N0–1 → CRT to 50 Gy vs 64.8 Gy (50.4 + 14.4 boost to GTV + 2 cm). Chemo was cis 75 mg/m^2 + 5-FU 1000 mg/m^2. Interestingly, mostly SCC > adenoCA. Stopped early because of ↑death (2 → 10%, but 7/11 deaths were prior to 50.4 Gy in high-dose group). 2-year OS 40 vs 31% (NS).
- Stahl 2005: T3–4 N0–1 SCC → chemo x 3c → CRT alone (64–65 (50/25 + BID EBRT boost or HDR boost)) vs CRT + surgery (40/20). Surgery improved LC, but CRT had less treatment-related mortality (13 → 4%–SS).

NCCN

1. Definitive surgery
   - Tis-T1a: EMR vs esophagectomy. Risk of LNMs <3%
   - T1bN0: esophagectomy (EMR for superficial adenosCAs)
   - Adjuvant treatment:
   - AdenosCAs: surveillance or CRT for pT3–T4, bad T2 (high-grade, LVI, PNI, or age <50 yo), LN+, or R1 or R2 resection
   - Squams: CRT only for + margins
   - Nonsurgical candidate:
- 45–50 Gy + 2 drug chemo.
- Higher doses may be considered in cervical.

2. Neoadjuvant CRT
   - T2–T4a or N+.
   - ChemoRT → surgery (non-cervical) by week 6.
- RT: 41.4–50.4 Gy.

   Chemo: weekly carbo (2AUC)/taxol(50) x 5 wks; CP 75–100 on d1 and d29 + 5-FU 750–1000 CI d1–4&d29–32.

3. Definitive CRT (cervical esoph; if decline surg; not candidate for surgery). Consider salvage esophagostomy for persistent disease.

   RT: 50–50.4 Gy.

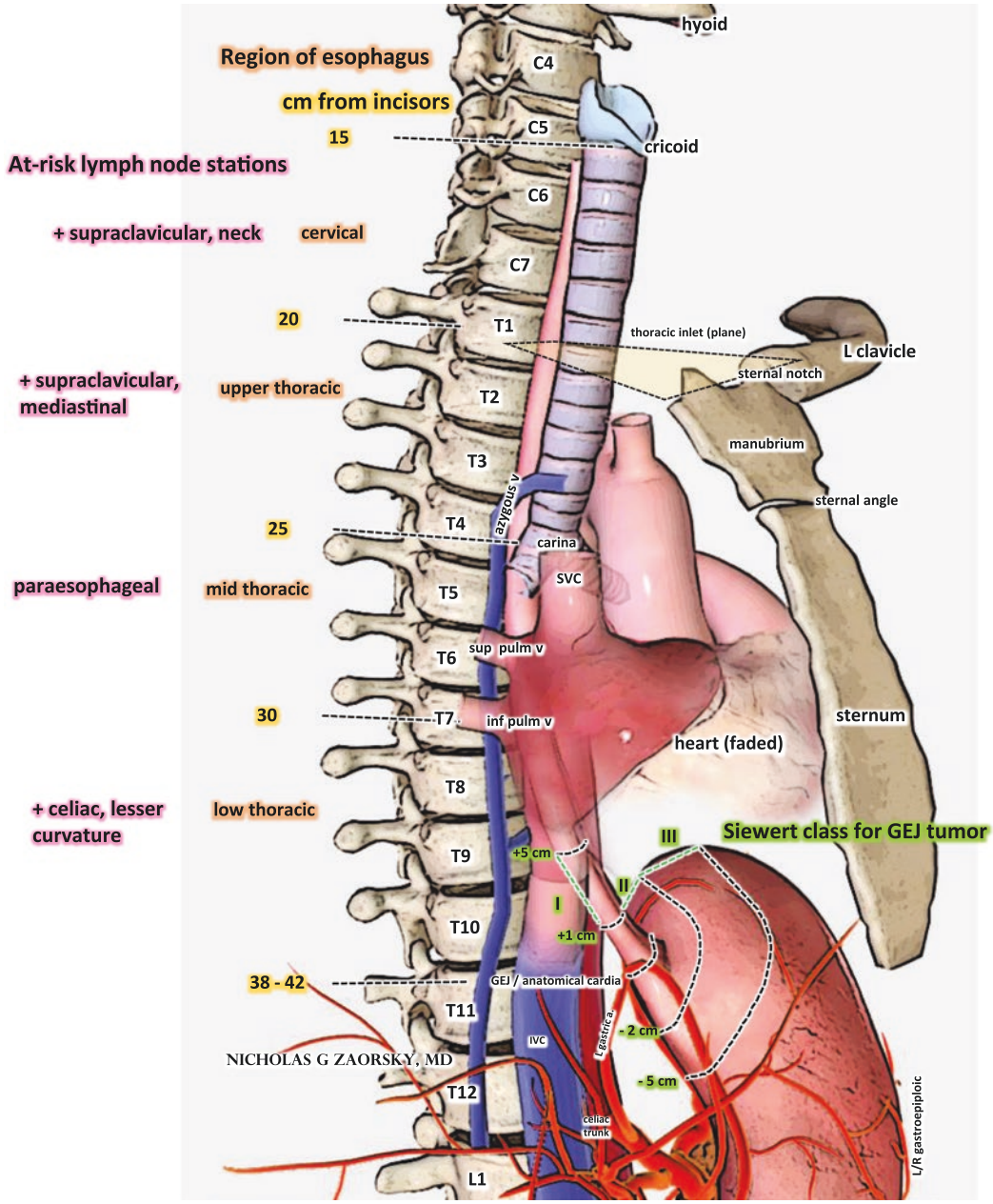
   Chemo: CP 75–100 d1 + 5-FU 750–1000 CI d1–4. Q28d for 2–4 cycles. Another option is FOLFOX. (Note that the chemo is different from the recommended preop carbo/taxol, but weekly carbo/taxol can be considered).
4. Esophagectomy (non-cervical) – if low risk (T1 N0, <2 cm, well-differentiated).
5. Defin CRT
   - If cervical or decline surg (50–50.4)
   - Then PET/EGD. Can observe if cCR and SCC
   - T4b: defin CRT (50–50.4)
   - **Dysphagia palliation**: RT preferred over stent or CRT

Technique

- Generally sim supine, arms up, IV and PO contrast, motion assessment/management for lower tumors.
  - Cervical eso: supraclav, neck nodes
  - Upper thoracic: include SCV and mediastinal nodes
  - Mid thoracic: paraesophageal nodes
  - Low thoracic: consider gastric nodes, celiac axis
- No benefit to dose escalation (INT 0123, Minsky).
- PET SUV of 2.5 at baseline (not post chemo) is good threshold.
- Assimilate EGD and EUS report.
- IMRT:
  - CTV = 4 cm sup/inf mucosal expansion (only 2 cm into stomach if distal) and 1–1.5 cm radial expansion for primary tumor +1–1.5 cm expansion for gross nodal disease. Incorporate CT, US, PET. CTV should be shaved off the bones, aorta, and heart (limit 0.5 cm into the heart but can shave off if motion management is used).
  - Upper 1/3: + SCV.
  - Distal 1/3: + celiac LNs to the bifurcation.
- PTV = 0.5 expansion w daily kV imaging.

Constraints

- Lung: V20 <20%; V10 <40%; V5 <50%; mean ALARA, <5–8 Gy (Wang, 2013)
- Heart: V50 <33%; V30 <30%; V25 <50%; mean <30 Gy
- Liver: mean <25 Gy; V30 <20%; V20 <30%
- Kidney: 2/3 <18 Gy; combined mean <18 Gy


Region of esophagus
cm from incisors
15
20
25
30
38 - 42
At-risk lymph node stations
+ supraclavicular, neck
cervical
+ supraclavicular, mediastinal
upper thoracic
paraesophageal
mid thoracic
+ celiac, lesser curvature
low thoracic
hyoid
C4
C5
cricoid
C6
C7
T1
thoracic inlet (plane)
L clavicle
sternal notch
T2
manubrium
T3
azygos v
sternal angle
T4
carina
T5
SVC
T6
sup pulm v
T7
inf pulm v
sternum
heart (faded)
T8
T9
+5 cm
III
II
I
Siewert class for GEJ tumor
T10
+1 cm
GEJ / anatomical cardia
T11
L gastric a.
- 2 cm
IVC
- 5 cm
T12
celiac trunk
L1
L/R gastroepiploic
NICHOLAS G ZAORSKY, MD

Gastric Cancer [1–5, 9, 24–34]

- **T1**
  - T1a – into lamina propria or muscular mucosae
  - T1b – into submucosa
- **T2** – muscularis propria (this is the "fourth layer" on EUS).
- **T3** – subserosa
- **T4**
  - T4a – serosa
  - T4b – adj structures
- **N1** – 1–2 nodes
- **N2** – 3–6 nodes
- **N3** – 7+ nodes
  - N3a – 7–15 nodes
  - N3b – 16+ nodes

M1: metastatic

Mnemonic: IA (T# + N#; i.e., T1 N0) adds to 1; IB adds to 2 (i.e., T2 N0 or T1 N1); IIA adds to 3; IIB adds to 4

AJCC8	T1	T2	T3	T4a	T4b
N0	IA	IB	IIA	IIB	IIIA
N1	IB	IIA	IIB	IIIA	IIIB
N2	IIA	IIB	IIIA		IIIB
N3a	IIB	IIIA	IIIB	IIIB	IIIC
N3b	IIIB	IIIB	IIIC	IIIC	IIIC
M1	IV				

Overview

– 22,700 cases/yr., 12,000 deaths/yr.
– Risk factors: salt, nitrates, H pylori, pernicious anemia.
– ≈ 20% HER2 positive; MSI/MMR and EBV are other relevant biomarkers
– CDH1 mutation: AD truncating mutation, gene encodes cell adhesion molecule E-cadherin. Found in ≈ 40% of hereditary diffuse gastric cancer (HDGC). For pts w syndrome, avg. age of gastric cancer 37 yo, >70% develop it by age 80. On path, appears diffuse, w signet rings.
– Anatomy
  – GEJ, fundus: 35%, diffuse. Seiwert III esophageal CA treated like gastric
  – Body: 25%
  – Antrum: 40%, intestinal

Workup:

– H&P, nodal eval, CBC, CMP, *H pylori* eval, EGD, EUS, bx, CT CAP w/ IV + oral contrast
– Nutritional assessment and counseling. Consider J-tube (not G)
– HER2 and MSI/MMR testing if M+ adenocarcinoma is documented/suspected
– Assess Siewert category
– Smoking cessation
– Screen for FH
– PET for T2+, suspicious LN
– Laparoscopy if T1b + or N+: 20–35% have occult peritoneal mets

Surgical Anatomy

– What is unresectable? Infiltrating mesenteric root, PA-LNs+, invades major vasculature (not splenic vessels), DMs, peritoneal seeding.
– Need subtotal gastrectomy for distal lesion.
– Aim for >3–5 cm margins, ≥15 LNs.
– D0: no or incomplete perigastric nodal dissection.
– D1: perigastric nodes.
– D2: D1+ left gastric, common hepatic, splenic, celiac ("Gotta Harvest Supplementary Cancer").
– D3: D2 + hepatoduodenal, retropancreatic, mesenteric root, PA, middle colic.
– Extent of dissection controversial. More complications with D2+ but seemingly improved CSS.
– Supplement fat-soluble vitamins (ADEK) and B12 post-op.

LN Anatomy

– Regional LNs of gastric cancer:
  – **Greater curvature**: greater curvature, greater omental, gastroduodenal, gastroepiploic, pyloric, pancreaticoduodenal
  – **Pancreatic and splenic**: pancreatolienal, peripancreatic, splenic

  - **Lesser curvature**: lesser curvature, lesser omental, L gastric, cardioesophageal, common hepatic, celiac, hepatoduodenal
- LNs/spread that is metastatic: retropancreatic, PA, portal, retroperitoneal, mesenteric, positive peritoneal cytology

Surgery
- Note, no RCT reveals OS benefit of D2 versus D1 resection, but there is a CSS (Dutch trial).
- Gouzi 1989: subtotal vs total gastrectomy for gastric antrum cancers: no difference in OS.
- MRC trial (Cuschieri 1996,1999): D1 vs D2. Same 5-yr OS, SS higher M/M with D2 Dutch trial (Bonenkamp 1999,Songun 2010): D1 vs D2. D2 had more complications/deaths. Same 5-yr OS but the 15 yr. data showed D2 ↑CSS (37 → 48%) and ↓ locoregional recurrence.
- For Dutch and MRC, criticism is 10% op mortality, perhaps from inexperience of surgeons.
- Yu, 2006. RCT of splenectomy vs splenic preservation in proximal gastric cancer getting gastrectomy. No OS benefit. NS higher M/M w splenectomy. No impact on OS in pts w mets to LNs at hilum of spleen or along splenic artery.
- Taiwanese trial (Wu 2006): D1 vs D3. D3 ↑ 5-yr OS (54 → 60%). No adj chemo or RT.
- JCOG9501 trial (Sasako 2008): D2 vs D2 + PAs. Longer surgery; no OS or RFS benefit.

Periop/Preop Chemo/CRT
- Theoretical disadvantage is tumor regression and perforation, targeting accuracy, and gastric ulceration.
- MAGIC (Cunningham 2006): mostly gastric but some GEJ/eso → surgery +/− pre-/post-op chemo (ECF). 42% completed all 6c chemo. Only 49% of pts completing preop chemo completed all 3c adjuvant chemo. CR rate 0%. Chemo improved downstaging, R0, 5 yr OS (23 → 36%). Bc of difficulty completing chemo, benefit of post-op chemo component unclear.
- FLOT4 (abstract only): MAGIC regimen (3c ECF preop and post-op) vs FLOT (4c docetaxel, oxaliplatin, 5-FU preop and post-op). FLOT improved MST (35 m vs 50 m) and 3-yr OS (48% vs 57%).
- RTOG 9904 (Ajana 2006): phase II: preop CRT (induction chemo followed by 45 Gy with 5-FU + taxol). pCR 26%.
- Critics (ASCO 2016 abstract): phase II trial of stage IB-IVM0 resectable gastric or GE junction cancers rand to (1) periop ECX/EOX vs (2) ECX/EOX X 3 → surgery → CRT (45 Gy + XP). No difference in OS (41%) or PFS with higher heme tox for arm 1 and higher GI tox for arm 2. 87% of patients had at least a D1+ dissection with median 20 LNs.
- TOPGEAR. Phase III perioperative ECF chemo versus perioperative chemo + preop CRT – awaiting final results.

Post-op CRT and/or Chemo
- INT 0116 (Macdonald 2001,2012): 556 pts, R0 surgery +/− CRT. Stage IB-IVM0. 54% D0 resection. Chemo was 5-FU, leucovorin given once before RT started, then x 5d per w #1 and #5 of RT. RT was 45/25. CRT improved DFS and OS. 3-year OS 50% vs 41%; 3-year RFS 48% vs 31%.
- Kim 2005: retrospective. 990 pts with D2 +/-CRT. 5-yr OS improved with CRT (51 → 57%).
- ARTIST: Adjuvant Chemoradiotherapy in Stomach Tumors (Lee, 2012; Park, 2015): 2004–2008. $n = 458$. South Korea. Gastric adenoCA s/p R0 gastrectomy + D2 LND. Rand: (1) chemo alone ("XP"), 6c cape 2000 mg/mg on d1, 14 and cis 60 mg/mg2 on d1, repeat q3w. vs (2) 2c of cape and cis +, then 45 Gy + concurrent cape 825 mg/m^2 BID, and then 2c of cape and cis. RT decreased LRR (13% vs 7%), but no change in 5-year OS (~74%), DFS (~75%), DMs (~26%). No benefit in DFS for entire group ($p = 0.08$) but CRT beneficial if LN+ ($p = 0.04$), and in pts w *intestinal*-type GC (3 yr. 94% vs 83%). Criticisms: no surg QA. Borderline significance.
- CLASSIC (Noh 2014): 37 centers in SK, China, Taiwan. D2 resected II-IIIB gastric CA. $n = 1035$. Surgically resected then rand:

(1) adjuvant oral cape 1000 mg/m^2 BID on d1,14 x 8c + oxali 130 mg/m^2 on d1 for 6 m; vs (2) obs only. 3-year DFS 75% vs 60%. 5-year OS 78% vs 69%. G3–4 tox in 56% vs 6%, favoring surg only. Chemo arm won for OS, but >9x the severe toxicity.
- CALGB 80101 (Fuchs 2017): Stage IB-IVM0 patients treated with surgery→ chemo→CRT (5-FU + 45 Gy) → chemo sandwich, testing either ECF versus 5-FU/leucovorin. 3-yr data show similar outcomes.
- ARTIST II: ongoing. Looking at adjuvant chemo versus CRT in LN+ patients; chemo is S1 vs S1 and oxaliplatin.

Metastatic
- ToGA trial (Bang 2010): metastatic gastric, cis/5-FU +/− trastuzumab. Improved median OS (11.1 → 13.8 m).

NCCN

Pre-surgical Recommendations
- **Tis-1aN0**: endoscopic resection or gastrectomy alone
- **T1b**: surgery alone
- **T2+ or N+**
  1. Perioperative chemotherapy + surg [5-FU and cis x3 →surgery →5-FU and cis] (cat 1)
  2. Preoperative CRT (carbo/taxol; CP/5-FU) + surgery (cat 2B)
- **Unresectable:** 5-FU-based CRT

Post-surgical R0 with No Preop Treatment
- **Tis or T1**: surveillance.
- **T2 N0** – surveillance or MacDonald or chemo (if D2 dissection); CRT can be considered for pT2 N0 w unfav features (LVSI, <D2 LN dissection).
- **T3+/N+:** MacDonald [MacDonald: surgery + post-op chemoRT: 5-FU (425 mg/m^2) + leucovorin (20 mg/m^2) X 1 cycle → concomitant chemo/RT (45 Gy w/ 2 cycles 5-FU(400 mg/m^2)/LV(20 mg/m^2) → 2 additional cycles 5-FU(425 mg/m^2)/LV (5 cycles of chemo, RT w/cycles 2 + 3)].

Post-surgical R1–R2 ± Preop Chemo Treatment
- **R1:** CRT (chemo alone if received preop can be considered)
- **R2:** CRT or palliative

Technique
- Fast for 3 hrs before sim.
- Supine, arms up, IV contrast, oral contrast, 4D.
- Fuse w preop scans.

"Classic" Four-Field Technique (from Gunderson Patterns of Failure Paper)
- 3D CRT w/ four fields (heavy weighting of APPA with RAO/LPO)
- **Superior** = Level of L hemidiaphragm (unless anastomosis above diaphragm), often T9/10.
- For proximal T3 lesions, cover medial 2/3 L hemidiaphragm.
- **Inferior** = L3/L4 for most pts. If upper 1/3 lesion w/ only 1–2 nodes (+), consider raising border to L2 b/c lower risk of sub-pyloric nodes.
- **Right lateral** = 3 cm to right of vertebral body. Look at preop/post-op imaging to include porta hepatis, gastroduodenal nodes, antrum, medial duodenal wall.
- **Left lateral** = Variable. 2/3 of L hemidiaphragm +1 cm. Shield L kidney in lower portion of field if possible.
- 6 MV beam energy.
- Block edge margin = 5 mm.

- **Volume based:**
- CTVp: residual dz. + remaining stomach + anastomosis, 3–5 cm margin. No need to treat entire gastric volume.
- Consider boost for close SM (<5 mm).
- CTVn (contouring atlas available Wo et al. 2013).
- IGRT Mandatory!

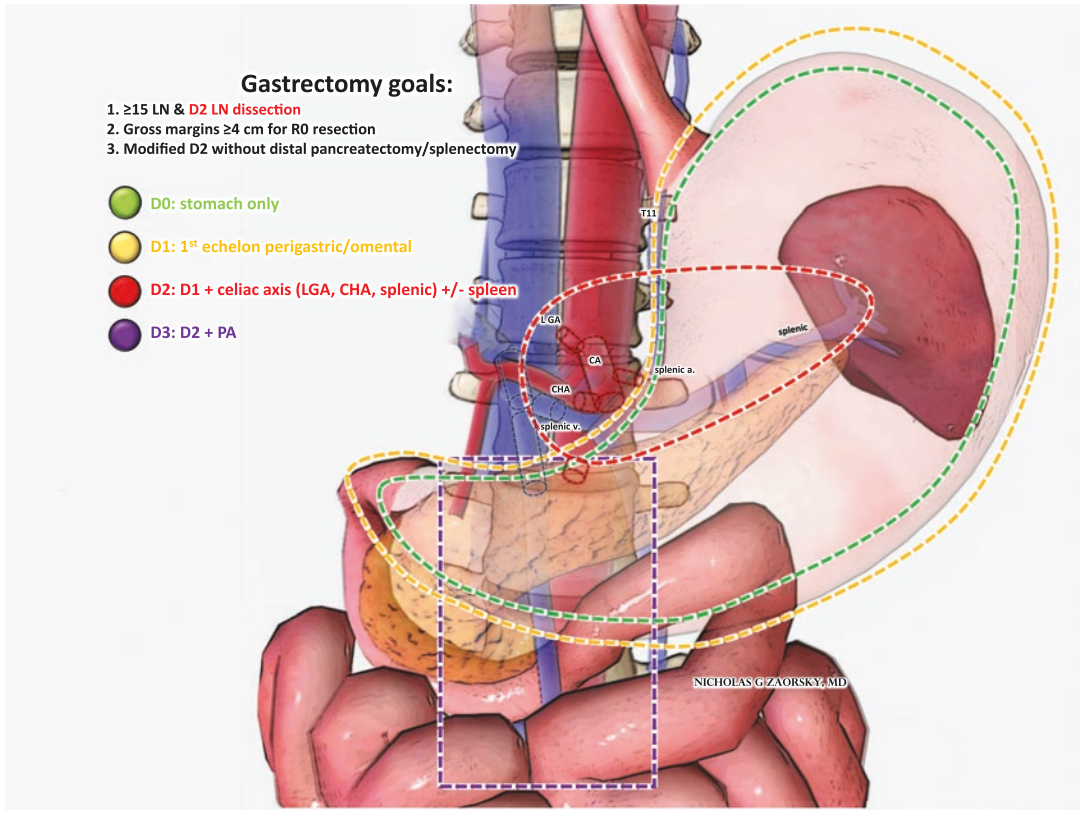
	Tumor location		
Regional sections/LNs to cover	Proximal 1/3 Fundus Cardia GEJ	Middle 1/3 Body	Distal 1/3 Antrum Pylorus
Stomach sections (+ gastric bed, remnant, anastomoses, clips)	x	x	x
Perigastric	x	x	x
Suprapancreatic	x	x	x
SMA	x	x	x
CA	x	x	x
Porta hepatic	x	x	x
Esophageal, 5 cm	x		
splenic	x	x	
supra/sub-pyloric		x	x
pancreaticoduodenal		x	x
duodenal, 5 cm			x

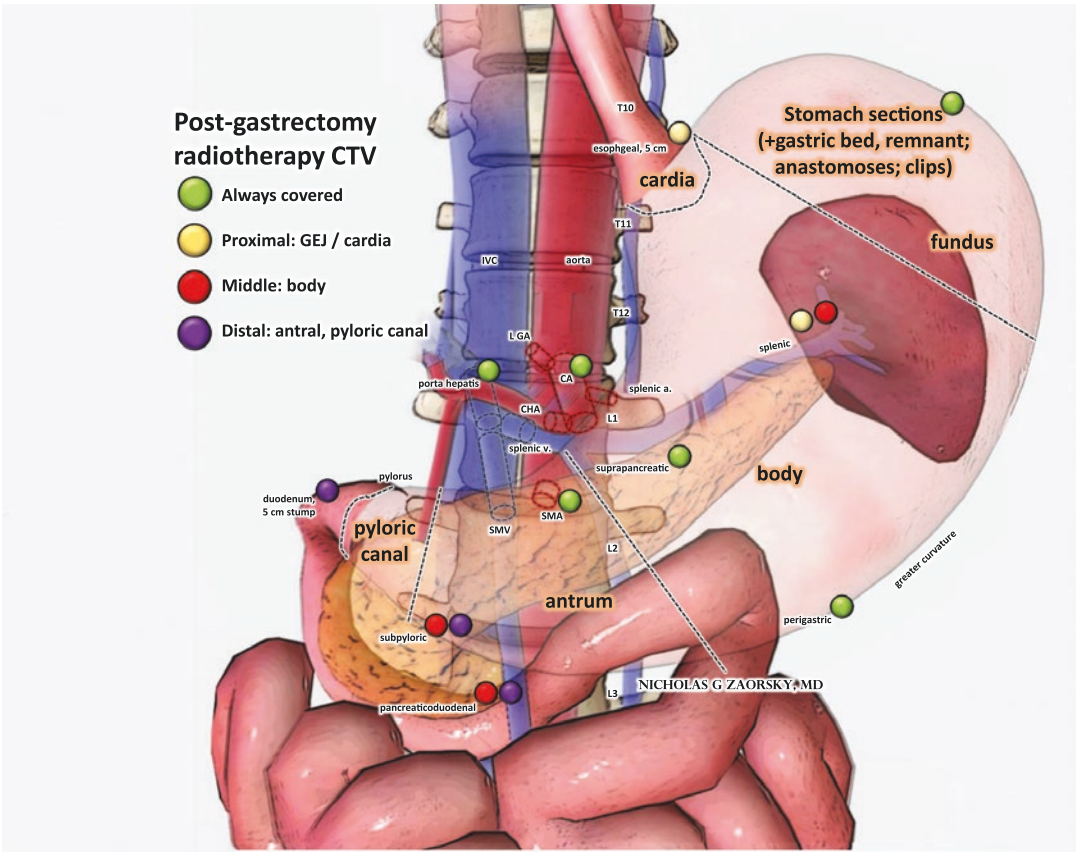
Constraints

- Isodose distribution in PTV <10% variation
- Heart: V30 <30%, mean <30 Gy
- Lung: V20 <30%, V10 <40%, V5 <60%, mean <20 Gy
- Small bowel: V45 <150 cc, V30 <300 cc
- Liver: V30 <33% mean <25 Gy
- Kidney: mean <18 Gy; V20 <33%

Supportive Care

- PPI/H2 blockers
- Supplements: B12, CA++, Fe




Post-gastrectomy radiotherapy CTV
Always covered
Proximal: GEJ / cardia
Middle: body
Distal: antral, pyloric canal
Stomach sections (+gastric bed, remnant; anastomoses; clips)
T10
esophgeal, 5 cm
cardia
T11
fundus
IVC
aorta
T12
splenic
L GA
CA
porta hepatis
splenic a.
CHA
L1
splenic v.
suprapancreatic
body
pylorus
duodenum, 5 cm stump
SMA
SMV
pyloric canal
L2
greater curvature
antrum
perigastric
subpyloric
NICHOLAS G ZAORSKY, MD
L3
pancreaticoduodenal

Gastrointestinal Stromal Tumor (GIST) [35–37]

- **T1-** ≤2 cm
- **T2** – >2 cm but ≤5 cm
- **T3** – >5 cm but ≤10 cm
- **T4** – >10 cm
- **N0** – no regional nodes
- **N1** – + regional nodes

M1: metastatic

Mitotic rate:

Low: 5 or fewer mitoses per 5mm^2 or per 50 HPF

High: >5 mitoses per 5 mm^2 or per 50 HPF

Overview

– Considered a type of sarcoma.
– ≈85% of cases are driven from an activating mutation in either KIT or PDGFRA, leading to active intracellular TK.
– Location: stomach 60%, SB, 35%, rectum, esophagus, omentum, mesentery <5%.
– **There** are different staging systems for gastric/omental versus small intestine/esophageal/colorectal/mesenteric.

Workup

– H&P
– CT abdomen/pelvis and or abdominal MRI ± chest imaging if GIST is T2+
– Testing for KIT and PDGFRA

Predictors of Malignancy

– >5 mitoses/50 HPF = "high"
– High MIB1 index
– Large size (>10 cm)
– Tumor >5 cm w > 5 mitoses/hpf
– Necrosis
– Infiltration of surrounding structures

Studies

– SSG XVIII/AIO (Joensuu 2012, 2016). 36 m imatinib superior to 12 m adjuvantly for RFS and OS (92.0 vs 81.7%) in high-risk* surgically resected KIT-positive GIST.
– Le Cesne, 2010/French. Interrupting imatinib has high risk of progression, 80% vs 16%.

Treatment

– **Surgery**: main treatment for resectable tumors even for metastatic disease.
– **Imatinib (Gleevec):** a TKI for the c-KIT gene product CD-117. 400 mg/d
– Use as primary therapy for unresectable or borderline resectable tumors. Given for at least 6 months to achieve maximal response for resectability.
– Give adjuvant for at least 36 months if high-risk* tumor: >10 cm, >10 mitoses/50 HPF; tumor >5 cm and >5 mitoses/HPF, tumor rupture.
– If pt. had SD on imatinib, do not stop, or there is ↑ risk of progression (80% vs 16%).
– Sunitinib followed by regorafenib can be given for progression.
– **RT** only as palliative therapy (mostly for bone metastases)

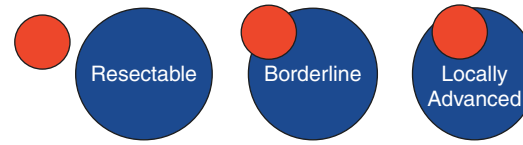
Pancreatic Cancer [1–5, 38–57]

AJCC 8th Edition

- **T1** – ≤2 cm
  - T1a – ≤0.5 cm
  - T1b – >0.5–<1 cm
  - T1c – ≥1.0–≤2.0 cm
- **T2** – >2–≤4 cm
- **T3** – >4 cm
- **T4** – involves celiac, SMA, and/or common HA.
  - **N1**–1–3 nodes
  - **N2**–4+ nodes

AJCC 8	T1	T2	T3	T4
N0	IA	IB	IIA	III
N1	IIB			
N2	III			
M1	IV			

AJCC 7	T1	T2	T3	T4
N0	IA	IB	IIA	III
N1	IIB			
M1	IV			



Criterion	Resectable	Borderline resectable	Locally advanced/unresectable
DMs	No DM	No DM	DM
SMV	No *SMV* or portal vein abutment, distortion, tumor thrombus, or venous encasement	SMV/portal vein abutment/ encasement	Unreconstructable *SMV/PV* (e.g., involvement of splenic v, PV, SMV) Contact w/ proximal draining jejunal branch into SMV
SMA	Clear fat plane around vessel	Abutment of SMA ≤180°	*SMA* >180 Contact w/ first jejunal SMA branch
Celiac axis	Clear fat plane around vessel	Abutment of CA ≤180° for pancreatic body/tail CA >180° w/o aorta and GDA involvement to allow Appleby (controversial)	*CA* >180
IVC		Solid contact with IVC	
Other	Clear fat planes around celiac axis, hepatic artery, SMA	Solid contact w CHA, without extension to CA or HA bifurcation	
Notes	Note: as long as SMV reconstructable, it is resectable		Unreconstructable SMV/PV due to tumor involvement or thrombus

AJCC 7th Edition

- **T1** – ≤2 cm
- **T2** – >2 cm
- **T3** – beyond pancreas
- **T4** – involves SMA or celiac
- **N1** = any LNs

Overview

- 45,000 cases/yr., 35,000 deaths/yr. in US.
- Risk factors: tobacco, dietary fat, RT, chemo.
- First echelon LNs: pancreaticoduodenal, suprapancreatic, pyloric, pancreaticosplenic.
- 50% are M1 at diagnosis.
- 30% are LAPC, M0.

- Most common in 70s.
- **CA 19–9:** use primarily in management of panc CA but can be elevated in colon cancer.
- **Chromogranin A:** can be sign of nonfunctional panc neuroendocrine tumor, esp. if normal amount of gastrin, insulin, glucagon.

LN drainage	Panc head	Panc body/tail
Ant and post pancreaticoduodenal LNs	Y	
Hepatoduodenal ligament (including porta hepatis)	Y	
SMA	Y	Y
Splenic artery		Y
Celiac		Y
PA		Y
Inf panc		Y

Anatomy
- T12: celiac artery.
- L1–2: head of pancreas. SMA originates at lower L1.
- L3: IMA origin.

Workup
- H&P, jaundice, DRE, LFTs, CA19–9, thrombotic events (Trousseau's migratory thrombophlebitis).
- EGD, EUS, ERCP, bx, stent?, CT C/A/P, +/-MRI.
- PET-CT if suspicious LNs.
- **3Ps**: PPI, pancreatic enzymes, pain control.
- **Stent:** only if obstructed. Need to have **metal > plastic** if doing RT. Plastic has short lifespan and higher risk of clot and infection, which is deadly in pancytopenic patient. On the other hand, plastic stent preferred if pt. is preop bc the metal stent makes surgery complicated.
- **CT:** pancreatic protocol. IV and oral contrast. Arterial and venous phase. 2–3 mm cut at level of the pancreas. Pancreatic carcinoma is hypovascular tumor and is seen best on later arterial phase.

Surgery
- For head lesions: Whipple/pancreaticoduodenectomy (classic or pylorus-sparing): ~4% mortality.
- **Whipple**: remove partial pancreas, duodenum, prox jejunum, distal stomach, GB + cystic duct, CBD, regional LNs, +/−spleen.
- Everything needs to be reconnected to jejunum.
- Reconstruction w/Roux-en-Y: *choledochojejunostomy (hepatic duct to jejunum)*, *pancreaticojejunostomy (pancreas to jejunum)*, and *gastrojejunostomy (stomach to jejunum)* or partial pancreatectomy for distal tumors.
- No benefit to extended LND (Riall 2005).
- NCCN recommends high-volume center, >15–20 panc resections/yr.
- JHU rapid autopsy series, Iacobuzio, 2009: 30% of pts had locally destructive panc CA, and 70% died from DMs. Divergent failure patterns at autopsy were unrelated to clinical stage at initial presentation, treatment history, pathology. DPC4 status correlated w M+.

Pro-Post-op CRT

- GITSG 9173 (Kalser, 1985): 43 pts. Surgery +/− CRT (5-FU + 40 Gy split). CRT improved OS (5 → 14%).
- SEER analysis (Hazard 2007): RT → ↑OS (12 → 17 m MS). No benefit for T1–2 N0.
- Mayo Clinic (Corsini 2008): retrospective, 472 pts. T1–3 N0–1 with R0 resection. Patients who got 5-FU + 50.4 Gy did better than observation (MS 19 → 25 m).
- RTOG 9704**,** (Regine 2008, 2011): 451 pts. 86% panc head, others w body and tail→R0–1 → CRT sandwich. Randomization: (1) gem 1000 × 3w, then 5-FU + RT, then gem 1000 mg × 12 w vs (2) 5-FU CI 250 mg/m^2 × 3, then RT+ 5-FU, then 5-FU × 12 w. Gem was Qwk. 5-FU was 250 mg/m^2 w RT. RT was 50.4 Gy, 4 field. ChemoRT is same in both arms. *Classic borders: Sup T10/11. Inf L3/4*. Ant 2–3 cm ant to preop GTV. Post-splits VBs. Lat includes hepatic hilum porta hepatis, pancreatic remnant, 1.5–2 cm off VBs to cover the PA-LNs. Gem arm trended toward 3-yr ↑OS (22 → 31%) but not SS. ~73% of pts failed distantly first; LR was 25% for 5-FU arm and 30% for gem arm. In panc head tumors receiving gem trend to improved OS.

– Johns Hopkins + Mayo (Hsu 2010): adj CRT vs obs. CRT had improved median OS 21.1 m vs 15.5 m.

Anti-Post-op RT

– EORTC 40891 (Klinkenbijl 1999, Smeenk 2007): surgery +/− CRT (5-FU + 40 Gy split). No difference in 5- or 10-yr OS (10-yr OS 18%). Included periampullary (no diff) and pancreas (5-yr OS 20 vs 10% NSS).
– UK, ESPAC-1 (Neoptolemos 2001,2004): surgery→2×2 (+/−5-FU, +/−40 Gy split). Chemo ↑OS (14 → 19 m), but CRT worsened 5-yr OS (20 → 10%). Criticisms: physicians pick tx; crossover allowed; split course; no RT QA (many pts >60 Gy).
– Meta-analysis (Stocken 2005): 875 pts, chemo improved MS (13.5 → 19 m), but not CRT (~15 m). RT improved outcomes for positive margins.

Adjuvant Chemo

– CONKO-001, (Oettle 2007,2013): 368pts → R0 or R1 +/− gemcitabine x6c. Gem → ↑DFS (6.7 → 13.4 m) and 5-yr OS (10% → 20%). No RT
– Krishnan 2007: retrospective. Induction chemo → CRT had longer MS then upfront CRT (8 → 12 m).
– ESPAC-3 (Neoptolemos 2010): panc ductal, R0–1. 5-FU vs gem. No RT. Same MS (~23 m).
– ESPAC-4 (Neoptolemos 2017): panc ductal, R0–1. Gem vs gem+ capecitabine. No RT. MS was 25.5 vs 28 m (SS) favoring gem + cap.

Neoadjuvant CRT for Resectable

– MDACC (Evans JCO, 2008): phase II. Stage I/II resectable panc adenoCA of head or uncinate process treated w/ CRT w 7 weeks gem 400 mg/m^2 IV over 30 m qw + RT 30 Gy/10 fx. Restage in 4–6w, then surg if no PD. 85% taken to surg. 74% had successful Whipple. Median OS 23 m and 5-year OS 36% in those who underwent pancreaticoduodenectomy. If no surg, MST 7 m, 5-year OS 0%.

Borderline Resectable

– MDACC (Katz, 2008): Retrospective. BR panc CA, all get neoadj chemo, 4 c induction gem, then CRT w 5-FU, then resection. *n* = 125. 78% completed preop tx and restaging. 41% underwent pancreatectomy. 94% who had surgery had R0. MST 40 m if receive all tx vs 13 m if no surg.

Unresectable

– GITSG 9273 (Moertel 1981): 40 Gy + concurrent 5-FU 500 mg/m^2 vs 60 Gy + concurrent 5-FU vs 60 Gy/30 alone. All arms use split-course RT. CRT improved MS (5 → 9 m, SS). This is the only old trial to show OS benefit for CRT vs RT alone.
– GITSG 9283. (JNCI 1988). *n* = 43. RT + concurrent 5-FU vs streptozocin, MMC, 5-FU. Concurrent CRT won. MST 10 m vs 7 m.
– Tempero 2003: big bolus vs small bolus gemcitabine. Slow infusion ↑OS (5 → 8 m).
– RTOG 9812 (Rich 2004): phase II: 50.4 Gy + paclitaxel. MS was 11 m.
– Huguet 2007: retrospective of LAPC on GERCOR studies. At 3 months after chemo, 29% had DMs. Thus, avoid upfront CRT in LAPC.
– French FFCD (Chauffert 2008): phase III. Gem +/− RT with 5-FU. CRT had worse survival (13 → 8.6 m).
– ECOG 4201 (Loehrer 2011): closed early. 71 pts → gem +/− RT. CRT improved median OS (9.2 → 11.1 m) but more toxicity.
– LAP-07 (Hammel, 2016): RCT in LAPC of gem +/− erlotinib. If no progression during chemo at 4 months, then rando to chemo vs CRT (54 Gy with Xeloda). RT volumes: GTV (including LNs >1 cm) + 3 cm cm sup/inf and 1.5 cm elsewhere = PTV. Large to account for setup and respiratory motion. No ENI, so no CTV! CRT provided no OS benefit (MST ~15 m) or PFS (~8–10 months). LR improved w CRT, 32% vs 46%. No difference in adverse toxic events generally, except more G3–4 nausea (SS).
– RTOG 1201: dose escalation trial of gem/abraxane ± CRT to either 63 vs 50.4 Gy.

- ALLIANCE trial: chemotherapy ±SBRT for borderline resectable pancreatic head tumors.

Metastatic Pancreatic Cancer

- Conroy 2011: 342 stage IV pancreatic cancer rand: FOLFIRINOX vs gem. MS was 11.1 vs 6.8 m favoring FOLFIRINOX.
- VonHoff 2013: Stage IV pancreatic cancer patients rando: gem vs gem+abraxane. MS 6.7 vs 8.5 m favoring gem+abraxane.

Pancreatic Adenocarcinoma Treatment

- **Resectable**
  - Resection→ chemo (gem x 5c or 5-FU/leuc or gem/cap) *or* sandwich chemo with CRT. No RT right after surgery because of high risk of mets.
  - RTOG 0848: 50.4 Gy, no boost
  - RTOG 9704: 1-month chemo, CRT, 3-month chemo
  - Option: 45–46 Gy (1.8–2/fx) + 5–9 Gy boost.
- **Borderline**
  - Neoadj chemo (FOLFIRINOX *or* gem/abraxane) +/−RT
  - After resection can consider additional chemo
  - SBRT: on trial [ALLIANCE: 25–36 Gy/5Fx]
- **Unresectable**
  - FOLFIRINOX *or* gem+/−abraxane or gem/cap
  - CRT or SBRT after "adequate course of chemo" (4–5 months or RTOG 9704 is 1-month chemo, CRT, then 3-month chemo). Neoadjuvant chemo given to allow occult M+ disease to manifest and spare pts toxicity of RT. Then adjuvant chemo
- CRT: 45–54 Gy (1.8–2.5/fx)
- SBRT: on trial preferred 25–45 Gy in 3–5 fractions.

Sim Technique
- Sim supine, arms up, +IV and PO contrast, 4D CT and/or motion management; fiducials preferred; consider NPO.
- PO contrast does not work well for tail lesions.

Post-op. Indications: R+, LN+
- Abdominal nodal volumes (peripancreatic, celiac, SMA, porta hepatis, para-aortic), anastomoses, tumor bed
- Post-op nodal beds +1 cm
- *Classic borders: Sup T10/11. Inf L3/4*

Per RTOG 0848, Contours
- **Structures**: CA, SMA, aorta, PV, PJ, tumor bed/clips
- **Expansion 1:** CA (1 cm prox); SMA (3 cm prox); PV; PJ; preop tumor volume + 1 cm expansion; post-op bed w clips
- Note that pancreaticogastrostomy is *not included* in CTV.
- **Expansion 2: Aorta** from most cephalad contour of CA, PV, or PJ to bottom of L2. Lower if GTV is lower, to include all L3. **Expand ~ 2.5–3 cm to R, 2–2.5 cm ant, 0.2 cm post, 1 cm L**. Shave bowel, kidneys, VBs.
- For tail lesions: Splenic artery/vein; no PV.
- CTV50.4 = Expansion 1 + Expansion 2.
- IMRT.
- 50.4 Gy in 28 fractions.
- Concurrent chemo: gemcitabine or capecitabine. Capecitabine preferred due to ↓ toxicity.
- **Tolerances:**
  - Kidney V18 <50%.
  - Bowel/stomach max 55 Gy, V45 <15%.
  - Liver mean <25 Gy.

Intact, Conventional Fractionation
- GTV + 2–3 cm
- May consider coverage of pancreaticoduodenal, suprapancreatic, celiac, porta hepatis, duodenal loop (splenic for tail tumors) but ENI is controversial
- See 0848 volumes above

Intact, SBRT
- Contraindicated if duodenal or gastric invasion.
- Fiducials, contour on bone window.
- Empty stomach; NPO 3 h prior.
- IV and PO contrast.
- 4D CT
- Expiratory phase is ideal time for sim and treatment (Taniguchi, 2013) bc of less overlap bw PTV and duodenum, stomach.
- **Volumes:**
  - GTV. If enlarged LN near tumor, then can treat. Otherwise, this is a contraindication.
  - TVI = tumor vessel interface.
  - iGTV = GTV on 4D CT respiratory phase scans or breath-hold scans.
  - PTV = GTV + 3–5 mm.
  - **Dose** is 30–45 Gy/3 fractions vs 25–45 Gy/5 fractions and consideration of dose escalation to TVI.
- **Tolerances:**
  - Kidneys V12 <25%
  - Duodenum/SB/stomach max: 35 Gy, V20 <20 cc, V35 Gy <1 cc
  - Cord V20 <1 cc
  - Liver V12 <50%
  - Single fraction Duodenum (Murphy 2010): V15 <9 cc; V 20 <3 cc; Dmax <23 Gy
  - Liver V30 <10%
  - Cord max 20 Gy
- Hold chemo for 1 week prior to and 1 week after. Total will be 3w off chemo.

Follow-Up

- q3–6, HP, labs, CA 19–9, CT abd x 2 y, then annual.
- Give pancreatic enzyme replacement.

Outcomes

Resectable
- LC 70–80% with chemoRT vs 50% RT alone
- MST 24 months
- OS3 = 30%

Unresectable
- MST 10 mo
- OS2 10–20%

Pancreatic Neuroendocrine Treatment

- Pts w localized disease are managed w/ definitive surgical resection. For panc head, surgery is enucleation of primary tumor + LND (small ≤2 cm), or pancreaticoduodenectomy (Whipple). For distal pancreas, pts should get pancreatectomy + splenectomy and LND.
- CRT is not a curative therapy.
- If M+ but resectable, they can also be treated with surgery. If M+ and unresectable, then systemic agents include octreotide or lanreotide (first line) or everolimus or sunitinib or chemo for progression.

Gallbladder and Biliary Tract/Cholangiocarcinoma: Extrahepatic Cholangiocarcinoma (EHCC), Intrahepatic Cholangiocarcinoma (IHCC) [58–66]

Gallbladder

GB	T1	T2a	T2b	T3	T4
N0	I	IIA	IIB	IIIA	IVA
N1	IIIB				
N2	IVB				
M1					

- **T1a:** lamina propria or **T1b,** muscularis.
- **T2**: perimuscular connective tissue
  - **T2a**: On peritoneal side
  - **T2b**: On hepatic side
- **T3**: into the serosa (visceral peritoneum); liver; other organs
- **T4**: involved PV or HA; or 2+ EH organs
  - **N1**: 1–3 nodes
  - **N2**: ≥4 nodes
  - **M1**: DMs

IHCC (<30% of Tumors)

IHCC	T1a	T1b	T2	T3	T4
N0	IA	IB	II	IIIA	IIIB
N1	IIIB				
M1	IV				

- **T1:** solitary, no vascular invasion
  - **T1a** – ≤5 cm
  - **T1b** – >5 cm
- **T2:** solitary with vascular invasion or multiple tumors
- **T3:** perforates visceral peritoneum
- **T4:** extrahepatic invasion
- **N1**: regional LNs. **M1:** DMs

EHCC: Perihilar/Hilar (40–60% of Tumors)

EHCC-perihilar/hilar	T1	T2a	T2b	T3	T4
N0	I	II	II	IIIA	IIIB
N1	IIIC				
N2	IVA				
M1	IVB				

- **T1:** the bile duct only or muscle or fibrous tissue.
- **T2:** invades beyond the wall of the bile duct.
- **T2a:** invades surrounding adipose tissue.
- **T2b:** invades liver parenchyma.
- **T3:** invades unilateral branches of PV or HA.
- **T4:** invades main PV or bilat PV branches or CHA; or unilateral radicals w/ contralateral PV or HA.
- **N1**: 1–3 nodes.
- **N2**: ≥4 nodes.
- **M1:** DMs.
- Note, preop Blumgart T-stage predicts resectability.

EHCC: Distal (<30% of Tumors)

EHCC-distal	T1	T2	T3	T4
N0	IA	IIA	IIB	IIIB
N1	IIA	IIB		
N2	IIIA			
M1	IV			

- **T1:** confined to the bile duct or invades <5 mm
- **T2:** 5–12 mm depth of invasion
- **T3:** invades >12 mm
- **T4:** invades celiac, SMA, CHA
- **N1**: 1–3 nodes
- **N2**: ≥4 nodes
- **M1:** DMs

Locations

- Biliary tract cancer locations:
  - **Klatskin** (hilar) – 10% of all liver and biliary carcinomas. 60% of biliary tract cancers.
- Surgery: Roux-en-Y, hepatectomy, lobectomy.
- Definition = "a perihilar cholangiocarcinoma involving the confluence of the L and R hepatic bile ducts."

- Type I involves CHD; Type II is bifurcation. IIIA is R IH duct. IIIB is L IH duct. IV is bilateral IH ducts. IV is multicentric.
  - **Distal** – 30%.
- Surgery is a Whipple.
  - **Intrahepatic/diffuse/multifocal** – 10%. Papillary – best prognosis.
- Venous drainage – PV (posterior to CBD).
- Lymphatic drainage – submucosa to porta hepatis, celiac axis, pancreaticoduodenal LN.

- **GB cancer natural history**: tends to metastasize.
- **HCC cancer natural history:** LR spread predominates (e.g., liver, stomach, duodenum, pancreas, colon, omentum, abd wall). LN mets in 40–80%. First echelon: cystic and pericholedochal. Second echelon: pancreaticoduodenal, celiac, PA.
- **DM rate**: adenoCA of GB > IHCC > hilar CC.
- **LR** continues over time (unlike HCC, where LR is in 1 year).

- **E/IHCC risk factors:** gallstones, PSC, UC, family hx, parasites, meds (e.g., INH, thorotrast).
- **GB risk factors:** cholelithiasis; chronic inflammation (e.g., salmonella); porcelain GB; polyps; congenital cysts; obesity.

- **Workup**: HP; labs: CBC, LFT, CA 19–9, coags, CEA, Hep panel; imaging: US will ID obstruction location; CT chest w contrast; multiphasic abdominal/pelvic CT/MRI with contrast; cholangiogram; ERCP/MRCP.

- **Markers**: *CA 19–9* and *CA 50* can be elevated in cholangiocarcinoma.
- CA19–9 also seen in other GI malignancies, e.g., HCC, esophageal, CRC.

- **Initial management**: relieve obstruction w stent or bypass. If incidental finding, consider staging lap.
- **Surgery**: SOC. Staging lap, then resection and LN removal.
- **Resectability criteria:** See Blumgart T-Stage. No RP or paraceliac involvement, no liver mets. No PV, HA invasion. No organ invasion. No DMs.
- **Transplant:** only an option of EHCC (hilar).

Studies

CRT After Surgery
- Limited data.
- Mayo Clinic (Gold 2009). Retrospective. Stage I (T1–2 N0) or II (T3 N0 or T1–3 N1) gallbladder. Median dose 50.4/28. 5-FU-based chemo. Of 73 pts included, 25 received adj CRT. Adj CRT assoc. w improved OS.
- Wang, 2011: Nomogram of OS benefit with adjuvant chemo or CRT for resect gallbladder CA.
- Adjuvant chemo recommended if T4 and/or N+.
- Adjuvant CRT has small benefit in T2–3 N0 and has large benefit in T4 N0 or any N+.
- SWOG 0809 (Ben-Josef 2015). Phase II feasibility study of 79 patients with gallbladder or extrahepatic cholangios (pT2–4 or N+ or positive resection margins) treated with adjuvant chemo + CRT. Chemo is cape 1500 mg/m^2/d (in two doses: 750 mg/m^2 q12h) for 14d; and gem 1 g/m2 on d1 and d8; give for 4 cycles (12 w). Reimage. Then concurrent cape 1330 mg/m^2 (in two doses: 665 mg/m^2 q12h) + RT 45, 5x per week for 5–6w. 2-yr OS was 65%.

CRT Followed by Transplant
- Mayo (Rea, 2005). Hilar cholangiocarcinoma get NA-CRT 45 Gy/1.5 Gy BID w concurrent 5-FU, then 12–16 Gy intracavity BT of 6 Gy x2 or 4 Gy x 4 BID, w concurrent 5-FU, followed by the liver txp compared to similar patients treated with resection. 5-year OS 82% for transplant versus 21% after resection.

Chemo
- ABC-02 (Valle, 2010). n = 410 locally advanced or M+ bile duct, GB, or ampullary carcinoma. Rand to cis 25 mg/m^2, then gem 100 mg/m^2 on d1 and 8 q3w for 8 cycles vs gem alone d 1, 8, 15 q4w for 6c, up to 24w. Primary endpoint was OS. Median OS 12 m

vs 8 m for combination therapy. Median PFS 8 m vs 5 m. Tumor response (CR or PR) 81% vs 72%.

NCCN Treatment Recommendations

Perihilar ± Gallbladder
- Resectable = Extended cholecystectomy + partial hepatectomy+ LND → CapeRT for R1/N+.
- Unresectable = Gem/Cis.

Gallbladder/Extrahepatic Cholangios
- Resectable = Whipple → capeRT for R1/N+
- Unresectable = Gem/Cis

Incidental T1 N0 Gallbladder
- Return to OR for extended cholecystectomy. Remove GB, 2 cm of liver tissue around GB bed, regional LNs.

pT1 N0R0
- Surgery. No adjuvant therapy

pT2-T4
- Observation or adjuvant CRT or chemo

Positive Margins or Positive Nodes
- Adjuvant CRT followed by chemo (SWOG 0809) or adjuvant chemo alone (positive nodes only)

Unresectable
- Chemo w gem/cis. Cis + gem > gem alone (per ABC-2, 2010). (Category 1).
- NRG GI-001 has gem/cis +/− hypofractionated RT. Doses based on remnant liver. Range is from 37.5 in 2.5 s to 67.5 in 4.5 s. Treatment is to tumor alone, no LNs. Keep liver mean <22 Gy.
- CRT should be 50–59.4 Gy with 45 Gy to at risk lymph node volumes. No benefit dose escalation >60 Gy.

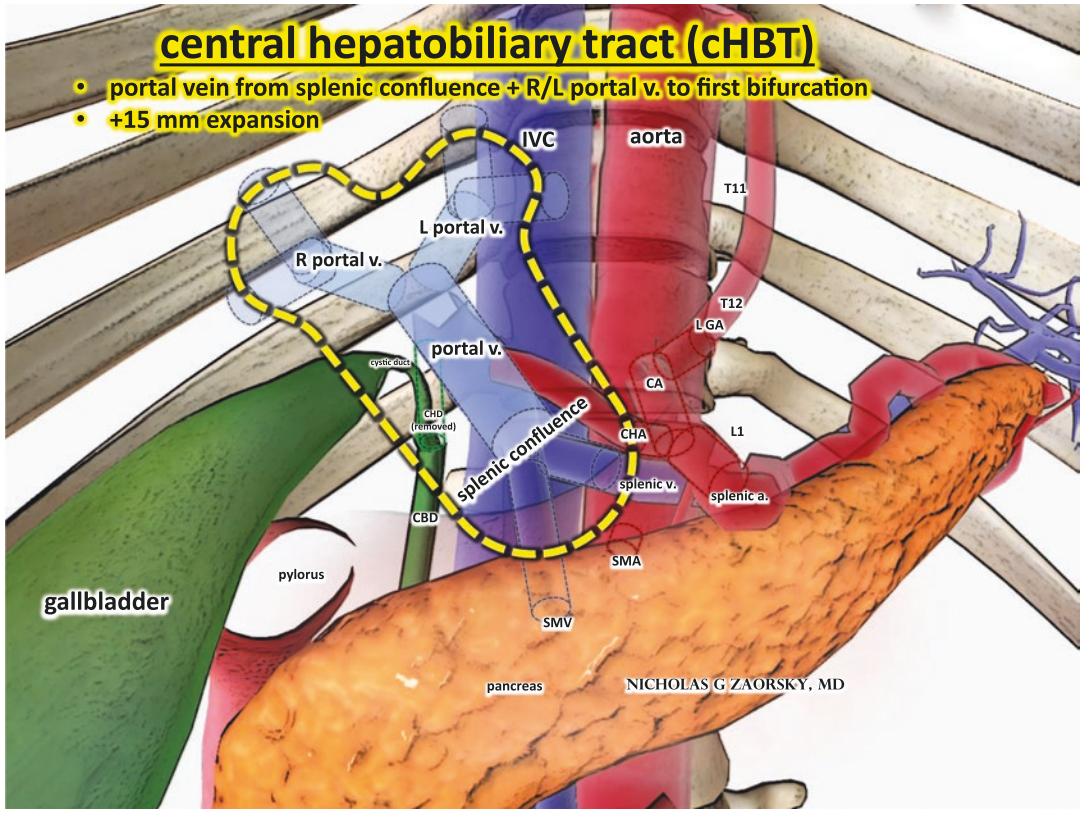
Intrahepatic Cholangios
- Resectable = Partial hepatectomy → CapeRT for R1/N+
- Unresectable = Gem/Cis

R0 Resection, N0
- Observe or clinical trial or adjuvant chemo

Positive Margins or Positive Nodes
- Adjuvant CRT followed or adjuvant chemo alone (positive nodes only).

Unresectable
- Chemo w gem/cis. Cis + gem > gem alone (per ABC-2, 2010) (Category 1).
- NRG GI-001 has gem/cis +/− hypofractionated RT per above.
- CRT should be 50–59.4 Gy with 45 Gy to at risk lymph node volumes. No benefit dose escalation >60 Gy.
- Hypofractionated radiation or SBRT can be considered for intrahepatic cholangios. One option is 75 Gy in 25 fractions with SIB to tumor center 100 Gy in 25 fractions. Make 5 mm PRVs for OARs. Keep BED >80. Gem+cis neoadj OK. Concurrent cape is OK. 89% of recurrences are local.
- NRG-GI001 is ongoing.

Adjuvant CRT Technique (Form SWOG 0809)
- CT sim supine, IV and oral contrast, 4DCT.
- CTV45 = hepaticojejunal (choledochojejunal) anastomosis + celiac LNs (1 cm around vessels) + anterior and posterior pancreaticoduodenal + porta hepatis (1 cm around vessels) + retroduodenal.
- CTV54–59.4 = post-op bed (include all surgical clips), GTV bed + ITV bed. Up to 59.4 Gy at physician's discretion for R1. For positive margin in IMRT patients, dose was 55 Gy at 220 cGy per day.
- PTV=CTV + 5 mm.
- Concurrent capecitabine 1330 mg/m^2 (in two doses: 665 mg/m^2 q12h) 7 days per week.
- **Constraints per SWOG:** Kidneys max dose ≤20 Gy; no more than 10% between 18–20 Gy. Bowel/stomach max ≤54 Gy, V50 <2%, V45 <25%. Duodenum max ≤54 Gy, V45 <33%. Liver mean <30 Gy. Spinal cord ≤45 Gy.


central hepatobiliary tract (cHBT)
• portal vein from splenic confluence + R/L portal v. to first bifurcation
• +15 mm expansion
IVC
aorta
T11
L portal v.
R portal v.
T12
L GA
portal v.
cystic duct
CA
CHD (removed)
CHA
L1
splenic confluence
splenic v.
splenic a.
CBD
SMA
pylorus
gallbladder
SMV
pancreas
NICHOLAS G ZAORSKY, MD

Hepatocellular Carcinoma (HCC)
[1–5, 67–78]

	T1a	T1b	T2	T3a	T4
N0	IA	IB	II	IIIA	IIIB
N1	IVA				
M1	IVB				

- **T1** – single tumor
  - **T1a**: ≤2 cm
  - **T1b**: >2 cm without vascular invasion
- **T2** – single >2 cm with vascular invasion or multiple tumors all ≤5 cm
- **T3 –** multiple tumors, at least one >5 cm
- **T4** – adj organs or visceral peritoneum or involving major branch of portal vein or hepatic vein
  - **N1** – regional nodes
  - **M1** – distant mets

– **Okuda**: >50% liver; ascites; alb ≤3 g/ dL; bili ≥3 mg/dL. Stage A: no factors. Stage C: 3–4 factors.
– **BCLC (more of a tx algorithm rather than staging)**:

– A: All of these: ECOG 0. Single or three tumors <3 cm. Okuda I-II. CP A-B.
– B: Large multinodular + ECOG 0 + CP A-B.
– C: ECOG 1–2 or T4 or N1. CP A-B.
– D: Any of these: ECOG 3–4. Okuda III. CP C.

Child-Pugh (CP) Eval for cirrchosis "Pour Another Beer At Eleven."	**Points.** Score: A = 5–6. 85% 2 year OS B = 7–9. 57% 2 year OS C = 10–15. 35% 2-year OS		
Components	**1**	**2**	**3**
T Bili	<34 (≤2 mg/dL)	34–50 (2–3)	>50 (>3)
Albumin (g/L)	>3.5	2.8–3.5	<2.8
INR or PT	<1.7 <4	1.7–2.3 4–6	>2.3 >6
Ascites	None	Mild–Mod	Sev
Encephalopathy	None	G1–2	G3–4

Overview
– 22,000 cases/yr., 17,000 deaths/yr
– Assoc with cirrhosis, hepB, hepC, aflatoxin B, NASH
– Cirrhosis or HepB+ → screening w/ US every 6 months w/ optional AFP testing

Workup
– Labs, CMP, LFTs, CBC, AFP, hep panels, PT/ INR ultrasound
– Triphasic liver CT or MRI: late arterial, portal venous, and delayed phases. Should enhance, have washout
– chest CT,
– If <1 cm: repeat US in 3 mos
– if >1 cm and classic by imaging, it is HCC. Avoid bx. Tumor seeding in 3%
– Higher hepatocyte growth factor (HGF) (>~2000) correlated w increasing CP score

Surgery
– Partial hepatectomy: 5-yr OS ~50%, recurrence at 5 yrs >70%.
– Transplant: 5-yr OS ~70%.
– Lau 2008: surgery + postoperative 131I- lipiodol→↑OS.
– Penna (2002): 75–80% of the liver in non-cirrhotic can be safely resected.

IR Procedures
– RFA: better for deep tumors <3 cm.
– Cryoablation: can treat up to 6 cm (not in US).
– EtOH injection (not in US).
– TACE: 50% response.
– Prospective studies have shown that down-staging with local therapies prior to transplant improves DFS and recurrence.

Sorafenib
– TKI against c-rad and PDGF-α.
– Llovet 2008: advanced HCC (not eligible for local therapy or had disease progression after locoregional/surgical therapies w/ ECOG ≤2 and CP A) → sorafenib vs placebo. Sorafenib ↑OS (7.9 → 10.7 m)

Treatment Paradigm
1. Surgical assessment first:

  - Resect if feasible: CP A, B. No portal HTN. Good liver reserve. No tumor thrombus.
  - **Milan/UNOS criteria for transplant**:
    - One tumor <5 cm
    - Or 2–3 tumors <3 cm each
    - No vascular involvement
    - N0 M0
    - **UCSD criteria for transplant**:
    - One tumor <6.5 cm
    - Or three tumors all <4.5 cm
    - And cumulative size <8 cm
  - For transplantable candidates, can consider locoregional bridge therapies as indicated.
2. If no resection, consider local therapies:
  - Ablation or arterial directed therapies (TAE, TACE, Deb-TACE, RE). "TACE refractory" = PD in 6 months or need three TACEs in 6 months.
  - EBRT is cat 2B.
  - Avoid RE (Y90) if bili > 2 mg/dL or CP class C.
  - Arterially directed therapies are relatively contraindicated for bili >3 mg/dL, CP C, or main portal vein thrombosis.

Barcelona Clinic Liver Cancer (BCLC – See above)

- Stage 0 (PS 0, Child-Pugh A)
  - (1) Single, <2 cm, Nl bili – resection.
  - (2) Local therapies for non-resection candidates.
- Stage A (single or 3 nodules <3 cm, PS 0)
  - (1) Single or <3 nodules <3 cm, Nl bili – resection.
  - (2) Abnl bili or other diseases – liver transplant or PEI/RFA.
  - (3) Consider local therapies as bridge to transplant.
- Stage B (Multinodular, PS 0)
  - (1) TACE
  - (2) Consider RT if refractory to TACE or if portal invasion
- Stage C (Portal Invasion, N1, M1, PS 1–2).
  - (1) Sorafenib
  - (2) Consider RT if portal invasion
- Stage D (PS >2, Child-Pugh C)

Radioembolization

- Y90: 50–80% response

Liver EBRT and SBRT

- Best for focal (1–3 tumors) disease, hard to access with surgery.
- Traditionally was 50+ Gy (2 Gy/fx) 3D or IMRT but SBRT increasing in frequency.
- Tse 2008: 41 pts CPA HCC or IHCC median 36 Gy in 6 fx. Median OS 11.7 m for HCC.
- Bujold 2013: 102 pts w/ CP A HCC w/ at least 700 cc of uninvolved liver (52% had prior local therapies), median 36 Gy/6, median OS 17 m, LC 87%, 30% grade 3+ tox. Dose >30 Gy had NS ↑ in LC.
- Wahl 2015: Retrospective comparison of outcomes of non-met HCC treated with RFA versus SBRT. FFLP improved in tumors ≥2 cm treated with SBRT. SBRT 3–5 fx, 27–60 Gy. All BED_{10}s ≥100.
- Brade 2016: phase I suggests sorafenib ↑RT toxicity.
- Nugent 2017 GI ASCO abstract: phase II trial of CP A-B (<9) w/ 1–2 HCC tumors treated with either Deb-TACE versus SBRT (40–50 Gy in 5 fx wt uninvolved liver >700 cc) as a bridge to transplant. SBRT had ↓ toxicity and better QOL.
- Criteria per RTOG 11–12.
  - Child-Pugh A.
  - 700–800 cc uninvolved liver.
  - No size criteria, up to four lesions.

SBRT Techniques

- **3–6 fraction SBRT technique:**
  - Best for CP A, B7 patients.

  - CT, MRI, fiducial marker, 4DCT, IV contrast, arms up, vac lock, Abd compression or other motion management.
- **Late arterial phase of CT** should be used bc contrast enhances within tumor allowing superior delineation vs liver parenchyma. This is in contrast to liver mets or IHCC.
- GTV + ITV + 5 mm = PTV.
- SBRT dose varies by institution. 10–20 Gy x 3, 5–12 Gy x 5 are most common. Get BED_{10} to >100.
- More details in liver mets section.
- **QUANTEC Constraints**

QUANTEC	Treating HCC		Treating mets	
Mean liver dose (liver – GTV)	3 fx	6 fx	3 fx	6fx
	<13 Gy	<18 Gy	<15 Gy	<20 Gy
Critical liver vol	>700 mL normal liver receives ≤15 Gy in 3 fx of ≤21 Gy in 5 fx			

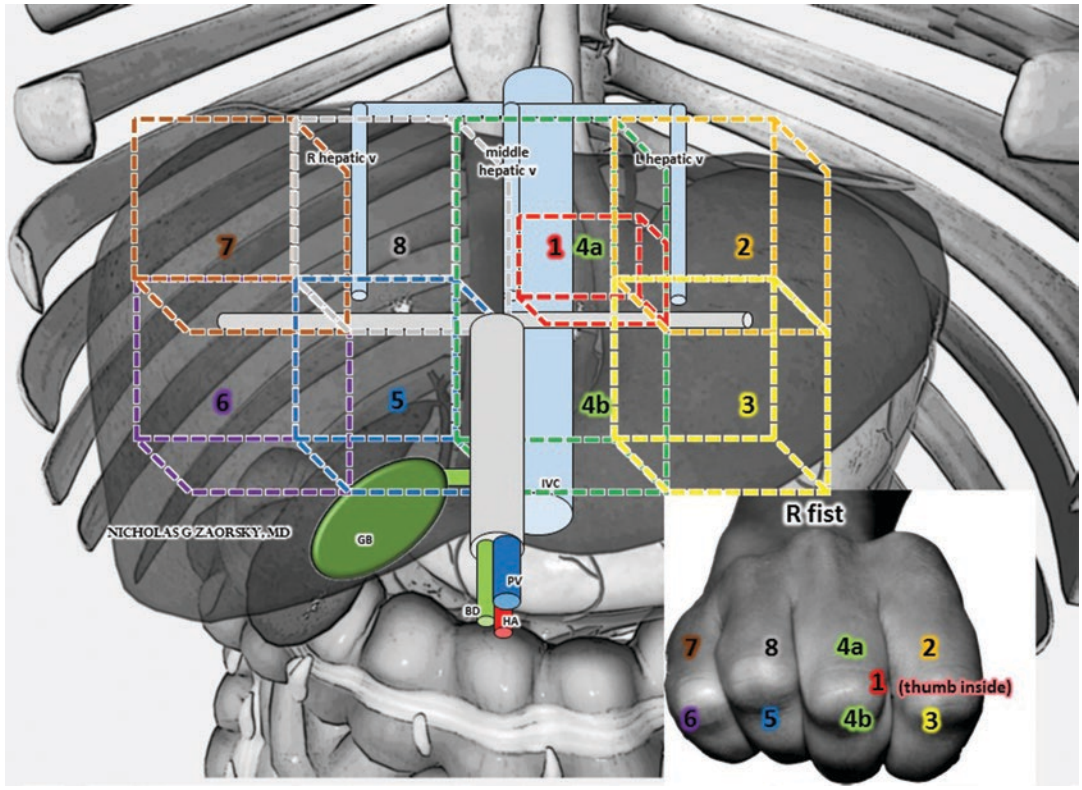
Whole-Liver RT Palliation

- Russell 1993: 1.5 Gy BID dose escalation for patients with liver metastases. Recommended dose of 30 Gy (33 Gy was unsafe). No longer performed.
- Hanson recommends 21 Gy in 7 fx.
- Soliman 2013 (Toronto): phase II of 8 Gy x1 to whole liver for patients with HCC of liver tumor-related pain. Exclusion criteria: systemic tx in 2 w or TACE in 1 month. Plts >25, Hgb <7, INR >3, bili >100 umol/L, AST or ALT >10 x normal. Premed with granisetron, decadron 2 mg 1 h prior to RT. GTV. CTV is majority of the liver. CTV + 1 cm = PTV. 8 Gy x1. 95% of PTV >7 Gy; improved QOL, 48% had ↓symptoms at 1 month.

Non-SBRT Constraint: Mean <25 Gy

Toxicity

- **Classic RILD**: anicteric **h**epatomegaly, **a**scites, elevated **l**iver enzymes. 1–2 months after RT. Fatigue, RUQ pain, ascites, high LFTs (esp ALP). Pathologic: VOD, central venous congestion, spares large veins, entraps RBCs. Supportive management. 10% mortality
- **Non-Classic RILD**: Elevation of liver enzymes, reactivation of hepB or C, liver function decline
- Biliary obstruction
- GI Bleed, obstruction, fistula
- Patients w baseline dysfunction, anything not fitting classic


R hepatic v
middle hepatic v
L hepatic v
7
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1
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IVC
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NICHOLAS G ZAORSKY, MD
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Liver Metastasis [73]

Background
- Usually from CRC. 20% CRC patients have present with mets. 40% will develop.
- Pts w synchronous tumors do worse than metachronous tumors.

Anatomy
- Liver blood supply is 60–80% from hepatic PV, 20–40% from HA.
- **Hepatic PV** is nutrient rich, O2 poor.
- **HA** is O2 rich. Provides 80–100% of the tumor blood supply.

Pre-Tx
- PV embolization: if pt. is unresectable bc of insufficient remnant liver volume, embo will cause hypertrophy of remnant volume.

Treatment Options
- **No therapy**. Median OS 6–9 m
- **Chemo**: irinotecan or oxaliplatin based
- **RFA**: for 1–3 lesions, <3 cm. 5-year OS up to 40%
- **Surgery**
- **TACE**. median OS 5 mos
- **SBRT**
  - 1 year 70% LC for 75 cc treated to median 41.8 Gy in 6 fractions (Lee, 2009) and median OS 17 months vs 95% 1 year LC (100% for tumors <3 cm) (Rusthoven 2009)
  - Rusthoven (JCO 2009): SBRT for 1–3 liver mets. Dose esc from 36 Gy to 60 Gy in Phase I. Phase II, 60 Gy used. Medial tumor diam 2.7 cm. Veff: 700 mL should get <15 Gy. 2-year LC 92%. MST 21 months. G3 tox <2%.

Whole-Liver RT Palliation

- Russell 1993: 1.5 Gy BID dose escalation for patients with liver metastases. Recommended dose of 30 Gy (33 Gy was unsafe). No longer performed.
- Soliman 2013 (Toronto): phase II of 8 Gy x1 to whole liver for patients with HCC of liver tumor-related pain. Exclusion criteria: systemic tx in 2 w or TACE in 1 month. Plts >25, Hgb <7, INR >3, bili >100 umol/L, AST or ALT >10 x normal. Premed with granisetron, decadron 2 mg 1 h prior to RT. GTV. CTV is majority of the liver. CTV + 1 cm = PTV. 8 Gy x1. 95% of PTV >7 Gy; improved QOL, 48% had ↓symptoms at 1 month.

SBRT Technique
- Sim orders: arms up, vac-lock bag, IV contrast, fiducials, 4D CT, motion management, daily cone beam CT.
- **Portal venous phase of CT** should be used, maximizing contrast enhancement in non-diseased portion of the liver, while targets will be hypodense on CT. This is in contrast to HCC.
- Manage motion w abdominal compression (decreases TV), breath-hold (limits diaphragmatic motion), respiratory gating (turns beam on/off w respiratory cycle).
- GTV + ITV + 5 mm = PTV. No ITV if RF beacons used.
- 50–60 Gy in 5 fractions most common. Modify based on constraints. CRC more radioresistant, tend to need 60/5.
- Liver Veff: liver volume minus all GTVs, which, if irradiated uniformly to the treatment dose, would be associated with the same risk of toxicity as the nonuniform dose distribution allowed.

Y90 Radioembolization
- Radioactive beta emitter embedded in resin (SIRS) or glass (TheraSpheres). Max energy 2.3 MeV. Mean range 2.5 mm. Half-life 65 h. Most dose delivered 2–4 mm from source. Virtually none >1 cm from source.
- Pt selection: liver-only or liver-dominant disease. Good liver function w bili <2. ECOG <3. Failed standard therapies (chemotherapy resistant).
- **Absolute** contraindications: shunt >20%; Blood flow to GD region.

- **Relative** contraindications: Prior EBRT to liver. Bili >2. Concurrent chemo w cape.
- **Mapping session:** SPECT scan to determine percent lung shunting. If >20% lung shunting, not eligible. Occlusion of collaterals (GDA) to prevent gastric ulcers. Calculate RT dose based on BSA.
- **Tx session**: Antiemetic and steroids given pre-tx. Can treat whole-liver or sequential segments. Advantage of segmental is can monitor for AE. Deliver spheres until full dose given or until stasis.

Tradename	SIR-Spheres	TheraSpheres
Diam (um)	20–60	20–30
SG (g/dL)	1.6	3.6
Activity per particle (Bq)	50	2500
Number of microspheres/3 GBq	40–80 M	1.2 M
Material	Resin w bound Y90	Glass w Y90 in matrix
Approval	CRC	None. Has rare disease exemption, including HCC
Stasis vs radioembolization	Causes stasis prior to radioablation	Much hotter. Does not causes stasis

Liver Dose Constraints

Liver dose constraints

		Timmerman 5 fraction constraints		Timmerman 3 fraction constraints		Other	
Serial Tissue	**Vol (cc)**	**Volume Max (Gy)**	**Max Point Dose (Gy)****	**Volume Max (Gy)**	**Max Point Dose (Gy)****		**Endpoint (≥Grade 3)**
Spinal cord	<10% subvolume	22	28	18	22.5		
Esophagus*	<5	19.5	35	17.7 Gy	25.2 Gy		stenosis/fistula
Brachial Plexus	<3	27	32.5	22 Gy	26 Gy		neuropathy
Heart/Pericardium	<15	32	38	24 Gy	30 Gy		pericarditis
Great vessels	<10	47	53	39 Gy	45 Gy		aneurysm
Rib	<5	45	57	40 Gy	50 Gy		Pain or fracture
Skin	<10	36.5	38.5	31 Gy	33 Gy		ulceration
Stomach	<5 cc	26.5	35	22.5 Gy	30 Gy		ulceration/fistula
Bile duct			41		36 Gy		stenosis
Duodenum*	<5 <10	18.5 14.5	26	15.6 Gy 12.9 Gy	22.2 Gy		ulceration
Jejunum/Ileum*	<30	20	32	17.4 Gy	27 Gy		enteritis/obstruction
Colon*	<20	28.5	40	24 Gy	34.5 Gy		colitis/fistula
Renal hilum/vascular trunk	15	23	15 cc	19.5 Gy			malignant hypertension
Central biliary system (CBS) = CBD, CHD, HDs, GB						V80 (in EQD2) = 0	Biliary stenosis[79]
Parallel tissue	**vol (cc)**	**Critical Volume Dmax (Gy)**					**Endpoint (≥Grade 3)**
Lung (R + L)	1500	12.5			10.5 Gy		Basic Lung Function
Lung (R + L)	1000	13.5	V-13.5Gy<37%		11.4 Gy		Pneumonitis
Liver	700	21			17.1 Gy	TD 5/5 = 30 Gy	Basic Liver Function
Renal ctx (R+L)	200	18			15 Gy		Basic renal function

*Avoid circumferential irradiation
** “point” defined as 0.035 cc or less

Rectal Cancer [1–5, 80–97]

- **Tis** – mucosa
- **T1** – submucosa
- **T2** – muscularis propria
- **T3** – pericolorectal tissues
- **T4:**
  - T4a – visceral peritoneum
  - T4b – adj organs
- **N1**
  - N1a – 1 node
  - N1b – 2–3 nodes
  - N1c – no nodes, but tumor deposits in subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues
- **N2**
  - N2a – 4–6 nodes
  - N2b – 7+ nodes
- **M1a** – one organ
- **M1b** – multiple organs
- **M1c** – peritoneal surface metastases

<table>
<tr><th></th><th>LN description</th><th colspan="2">T1</th><th colspan="2">T2</th><th>T3</th><th>T4a</th><th>T4b</th></tr>
<tr><td>N0</td><td>0</td><td colspan="3">I</td><td>IIA</td><td>IIB</td><td>IIC</td></tr>
<tr><td>N1a</td><td>1</td><td colspan="3">IIIA</td><td colspan="2">IIIB</td><td>IIIC</td></tr>
<tr><td>N1b</td><td>2-3</td><td colspan="3">IIIA</td><td colspan="2">IIIB</td><td>IIIC</td></tr>
<tr><td>N1c</td><td>0, deposits</td><td colspan="3">IIIA</td><td colspan="2">IIIB</td><td>IIIC</td></tr>
<tr><td>N2a</td><td>4-6</td><td colspan="2">IIIA</td><td colspan="2">IIIB</td><td colspan="2">IIIC</td></tr>
<tr><td>N2b</td><td>7+</td><td colspan="3">IIIB</td><td colspan="3">IIIC</td></tr>
<tr><td>M1</td><td></td><td colspan="7">IVA, IVB, IVC, respectively</td></tr>
</table>

Overview

- *110,000* colon cancer/yr., *41,000* rectal cancer/yr.
- Screening: ≥50-yr colonoscopy Q10yrs.
- FAP: APC gene, HNPCC: DNA mismatch.
- HNPCC affects MMR genes, e.g., MSH2, MLH1, MSH6. 80% lifetime risk of colon cancer, also at risk for endometrial and gastric cancer.
- Ulcerative colitis: risk of colon cancer 0.5%/yr for 10–20 years, then 1% /yr after.
- Rectum: rectosigmoid (S3) to 2 cm prox to dentate line.

Workup

- H&P, symptoms such as change in bowel habits, caliber, bleeding, sx of anemia, weight loss, KPS.
- FH (colorectal CA, FAP, HNPCC).
- DRE: distance from verge, circumference, total length, sphincter function.
- Pelvic for women.
- Labs: CEA, CMP, CBC, LFTs. PSA for all males.
- Colonoscopy: to check for another lesion higher up, bx.
- Prior RT, IBD.
- CT C/A/P, +/− MRI.
- Note, PET-CT not routinely indicated for colon or rectal cancer. Can be used to evaluate equivocal CT findings.
- EUS: 85–90% accuracy T-stage, 75% for N stage.
- CEA can be tracked for response.

Anatomy

- Anal verge: transition to hair-bearing/sweat gland skin.
- Anal canal: sup of the AV. 3–4 cm in length. A surgeon needs 2 cm from the AV to perform LAR.
- Low tumor is <~5 cm. Mid is 5–10 cm. High is 10–15 cm.

Chemo

- **FOLFOX**: folinic acid, 5-FU, oxaliplatin.
- **5-FU** if given for NA-CRT, dose for CI is 225 mg/m^2 over 24 h for 5–7 d /w during RT. Bolus 5-FU is 400 mg/m^2 IV w leucovorin 20 mg/m^2 IV over 4d w1 and 5 of RT.
- **Capecitabine** (Xeloda) is 825 mg/m^2 BID for 5d/w during RT. Cape is reaches optimal blood levels 1–2 h after single oral administration, and doses decrease rapidly thereafter (Yi, 2007). 1 h time can improve pCR (24% vs 10%), T-stage.
- Patients w dihydropyridine dehydrogenase (DPD) deficiency have AR disorder w absent activity of DPD, which metabolizes uracil to thymine. AA > white. May have G4–5 tox after 5-FU or cape infusion.

Abdominoperineal Resection (APR)

- Completely removes the distal colon, rectum, and anal sphincter complex using both anterior abdominal and perineal incisions, resulting in a permanent colostomy
- Necessary for low lesions (<5 cm from AV)

Total Mesorectal Excision (TME)
- Goal to remove micrometastatic dz., reduce radial +margin rate
- Sharp dissection beyond the plane of the mesorectum
- Well-defined circumferential margins
- Surrounding perirectal fat and lymph nodes are removed as a single specimen
- Gold standard for surgery
- Decreases the LR by 50%

Transanal Excision
- Criteria: T1, within 8 cm from anal verge, mobile, <30% circumference, <3 cm tumor, >3 mm margin, grade 1–2, N0, no LVSI, no PNI, reliable pt
- Data supporting this approach: CALGB 89–84 (Greenberg 2008): 10 yr. LF 8%.....RTOG 89–02 (Russell 2000): 5 yr. LF 4%
- Adj CRT or completion APR/LAR if doesn't meet criteria

LAR: Low Abdominal Resection
- Coloanal anastomosis or J-pouch reservoir formation
- Preserves sphincter function

LND
- Need ≥14 LNs removed for adequate dissection in colon cancer

Chemo Recs (per NCCN)
Adjuvant or neoadjuvant if locally advanced:
- FOLFOX: folinic acid, 5-FU, oxaliplatin (preferred). Other options: CAPEOX or 5/FU/lec or capecitabine

Concurrent:
- 5-FU CI: 225 mg/m^2 over 24 h for 5–7 d during RT
- Bolus 5-FU 400 mg/m^2 w leucovorin 20 mg/m^2 over 4d during week 1 and 5 of RT
- Xeloda 825 mg/m^2 BID, 5 d/wk. during RT

Adj Chemo/XRT Studies
- GITSG 7175 (NEJM 1985, Thomas 1988): T3–4 or N+ patients treated with surgery→ obs vs chemo vs RT vs CRT (2x2 randomization). RT was 40 or 45 Gy CFRT. Post-op CRT was 40 or 44 Gy CFRT w concurrent 5-FU 500 m/m2, then adjuvant 5-FU M-CCNU. CRT improved OS 10 yrs. (45 vs 27%) and LRR (10 v 25%).
- NSABP R-01 (Fisher 1988): Dukes B&C pts → obs vs MOF chemo vs 46 Gy. Chemo improved DFS and OS, RT → ↑LRC.
- Intergroup/NCCTG 794751 (Krook 1991): stage II-III T3–4 or N+ post-op→ RT alone 50.4/28 vs chemo (semustine and 5-FU) and CRT w concurrent bolus 5-FU. CRT ↓ death rate by 29%, DM by 37%, and LR by 46%, but had worse toxicity.
- INT NCCTG 86–47-51 (OConnell 1994). 660 post-op pts Stage II-III rectal adenoCA 2x2 randomization. 5-FU and semustine vs 5-FU alone; and type of 5-FU infusion w RT (bolus vs CI). All pts receive 9w systemic chemo, then concurrent RT, 45 Gy to pelvis and boost of 5.4 to 9 Gy to total of 50.4–54 Gy w 5-FU, then additional chemo. Bolus 5-FU was 500 mg/m^2 on d1–3 w 1 + 5 during RT; CI 5-FU was 225 mg/m^2 daily during RT. CI 5-FU won: less relapse (47% vs 37%), DM (40% vs 31%), RFS (63% vs 53%), OS (70% vs 60%) at 4 yrs. CI 5-Fu is superior. No benefit to semustine.
- NSABP R-02 (Wolmark 2000). 694 patients w/ Dukes B/C treated with surgery followed by Adj 5-FU + LV vs 5-FU + LV + RT. Improved LR w adj CRT.

Neoadj Chemo/XRT Studies
- ACCORD-12 (Gerard 2010, 2012): T3–4 Nx resectable rectal cancer. n = 598. Rando to 45/25 + cape vs 50/5 + cape + oxali. TME planned 6w after CRT. 3-year OS 88% for both. Similar pCR, 14–19%. No diff in LR, ~5% or DFS, ~70%. Much higher preop G3+ tox w cape-ox, 25% vs 1%. Over 3-y FU, tox was similar bw arms.

Post-op RT
- MRC 3. (Lancet 1996) Dukes B/C: surg vs surg +40/20. Improved LR (34 vs 21%) w post-op RT
- MRC CR07: preop 5 x5 vs selective post-op 45 + 5 FU. Preop won

Preop RT

- **Swedish Uppsala** (Pahlman 1990, Frykholm 1993): 25/5 preop vs selective 60 Gy post-op (split course – to high-risk patients). No OS difference, but preop ↓LR (13 vs 22%).
- **Wash U** (Myerson 1999). 20 Gy/5 preop. 5 year FU. 95% LC, 77% DSS. G3+ periop or late tox in 13% of pts.
- **Dutch TME trial** (Kapitejin 2001, Peeters 2007): TME +/− preop 25/5, 1 w prior to surg. No chemo. If the pts in the TME alone arm pts had SMs <2 mm, it was mandatory they receive PORT. 5 yrs.: No OS benefit (63%). RT ↓LRR (5.6 vs 10.9%). Effect of RT stronger in tumors 5–10 cm from AV.
- **Swedish** (Folkesson, 2005): *n* = 1168, 908 treated curatively. Surgery +/− preop 25/5. RT ↑OS (38% vs 30%), CSS (72% vs 62%), and LRR (9% vs 26%). TME was not used. RT makes up for bad surgery. Only RCT to show OS benefit for rectal cancer.
- **Peeters**, 2007. Dutch TME subgroup analysis, RT was best in those w LN+, lesions 5–10 cm from the AV, uninvolved circumferential resection margin.
- **Stockholm 3** (Erlandsson 2017). Preop 5x5, wait 1–7d vs 5x5, wait 4–8 w, vs 25 x 2 wait 4–8 w for surg. Similar tox rates among all groups, but, in assessment of two short courses there was higher acute XRT toxicity but sig ↓ postoperative complications w/ delayed short course group.

Preop CRT

- **German (Sauer 2004):** T3+ or N + → preop 50.4 + 5-FU (1000 mg x2c) vs post-op 55.8/31 + 5-FU (1000 mg x2c on d1–5, w1 and w5). All pts got post-op 5-FU (500 mg/m^2/day x 4c). Preop CRT won, but only 54% (vs 92% in preop) of adj pts got full dose.
  - Same 5-yr OS (~75%)
  - 18% patients overtreated bc path revealed pT1–2 dz. at resection
  - **All favoring preop:**
  - LR: 13 → 6%
  - pCR: 8%
  - Sphincter – preservation in subgroup analysis: 28% anticipated →39% (preop CRT) vs only 19% (post-op CRT)
  - Acute tox: 40 → 27%
  - Late tox: 24 → 14%
- **French FFCD 9203** (Gerard 2006): T3–4 NX rectal adenoCA. Preop RT vs preop CRT (5-FU, 350 mg/m^2 and leucovorin on d1–5, w1, 5). RT was 45/1.8. Both groups got adj chemo x4c 5-FU and leucovorin after surg. No difference in 5y OS or sphincter preservation. CRT had worse tox but ↓5-yr LR (16.5 → 8.1%) and ↑pCR (3.6 → 11.4%).
- **EORTC 22921**(Bosset 2006, 2014). T3–4 resectable, *n* = 1011. 2x2 design w 4 arms: (1) neoadj RT alone; (2) neoadj CRT; (3) neoadj RT alone and adj chemo; (4) neoadj CRT and adj chemo. RT was 45/25. Chemo was daily 5-FU 350 mg/m^2 and leucovorin 20 mg/m^2. No difference in 5-y OS, 65%. However, neoadj CRT improved LR 9% vs 17%. The long-term follow-up did not show benefit to adj chemo.
- **Polish** (Bujko 2006). *n* = 312. T3–4 resectable rectal cancer. Rando to 25/5 + surgery in 7d vs NA-CRT 50.4/28 w concurrent bolus 5-FU and leucovorin, surg in 4–6w. No difference in OS, DFS, severe late tox. pCR was improved in long-course arm, 16% vs 1%, and incidence of radial R+ decreased in long course 13% vs 4%. Increased acute G3+ tox 18% vs 3%.
- **RTOG-0012** (Mohiuddin 2006, 2013): randomized phase II of NA-CRT for T3–4 rectal adenoCA 0–9 cm from dentate line (3–12 cm from anal verge) treated w/ 1) CVI 5-FU + HRT (45.6 Gy at 1.2 Gy BID plus 9.6–14.4 Gy boost) or 2) CVI 5-FU + irinotecan + RT (45 Gy at 1.8 Gy Qday +5.4–9 Gy boost). No diff in toxicity, pCR. High pCR and improved DSS w/ 5-FU and higher dose of radiation in T4 cancers.
- **NSABP R-03** (Roh 2009): T3+ or N+. Similar design as GRCT but poor accrual. 5-FU + LV w/ 50.4 Gy pre- vs post-op. Trend toward ↑OS with neoadj. ↑DFS w/ neoadj (65 vs 53%). pCR in 15%. No pat w pCR recurred.

- **TROG 01.04** (Ngan 2012): T3 N0–2 rectal adenoCA. (1) 5x5, wait 1 month, surg, then 6c of 5-FU vs (2) 50.4/1.8 + 5-FU, surg, then 5-FU x4c. LR were 4.4% vs 7.5% (NS). ~28% had DMs in both arms (NS). 5y OS similar, 72%. Similar G3+ acute tox: 6%; chronic: 8%. Increased pCR in long-course arm 15% vs 1%. "Either no difference or favoring LC for distal tumors."
- **NSABP R-04** (Allegra 2015): Stage II-III rectal cancer getting preop RT 45/25 + 5.4–10.8 Gy boost. Chemo CVI 5-FU vs capecitabine +/− oxaliplatin: no difference in OS or LC. Adding oxaliplatin only worsened tox. Cap is SOC.

Local Recurrence

- **MDACC** (Das 2010). 39 Gy in 1.5 Gy BID if re treat >1 y or 30 Gy if <1 yr. Concurrent chemo in 98%. 36% had surg after RT. 3-year OS 39% for all; better if received surg, 66% vs 27%. 3-yr freedom from LP was 33%. G3–4 tox 35%.
- **Italy** (Valentini 2006). 30 Gy in 1.2 Gy BID, then 10.8 Gy boost w concurrent 5-FU. Then surg in 6–8 w. All received adjuvant Ralitrexed. CR and PR 44%. Surgery in 51%. 5-year OS 67% if R0, 22% if R+ or no surg. G3 tox 5%.

NCCN

- For 5 × 5, NCCN recommends surgery 1–2 weeks after radiation, but there is some evidence that waiting 4–8 weeks will ↑ pCR rate and ↓ postoperative complications. 5 × 5 is not recommended for T4 tumors.
- Even if patient needs APR, need to do NA-CRT because of the high recurrence rate.

Rectal

- **Local excision alone requirements (rule of 3 s):**
  - <1/3 bowel circumference
  - <3 cm
  - SM > 3 mm
  - T1 N0
  - Mobile
  - G1–2
  - <8 cm from anal verge
  - Endoscopically removed polyp with cancer of indeterminate pathology
  - No LVI, PNI

- **T1 N0: transanal vs APR/LAR**
  - High-risk features: T2, +margin, LVSI, G3.
  - Post-op dose is 45 Gy + 5.4–9 Gy boost.
  - T2 N0 R0: FOLFOX x 2 m, then capeRT, then FOLFOX.
  - Post-op CRT if R+, T3+ or N+, may also consider after transanal w/ high-risk features that does not have surgical resection as either definitive or neoadjuvant treatment).
  - Adjuvant chemo is FOLFOX (preferred) for 6 months, q 2 weeks.

- **T3+ or N+: neoadj CRT, then TME, then adj chemo**
  - Preoperative capeRT (45 Gy + 5.4 Gy to primary) → surgery → FOLFOX x 8 (4 months).
  - Chemo is CI 5-FU 225 mg/m^2 over 24 h (or capecitabine 825 mg BID) during RT.
  - Surgery is 6 weeks after CRT.
  - Low-lying = <5 cm from anal verge, need APR.
  - IORT (12.5–15 Gy) for positive margin.
  - If obstructing distal lesion → temporary diverting colostomy. Avoid stent.
  - Unresectable: ChemoRT to 59.4 Gy.

Resectable Mets

- FOLFOX × 6 (3 months) → capeRT → surgeries (synchronous/staged)
- Liver/lung rules: Primary tumor out or can be taken out, no unresectable extrahepatic/extrapulmonary disease, Complete resection possible

Technique

- Prone, belly board, PO ± IV contrast, full bladder, (wire scar and include if post-op), fuse CT sim with MRI.
- If there is gross residual in a paracolic gutter, then sim the patient in the contra lateral decubitus (e.g., if dz. in R, then sim L lat decub).

This will push SB away from tx fields, position ipsi kidney out of field. Use daily imaging to verify setup.

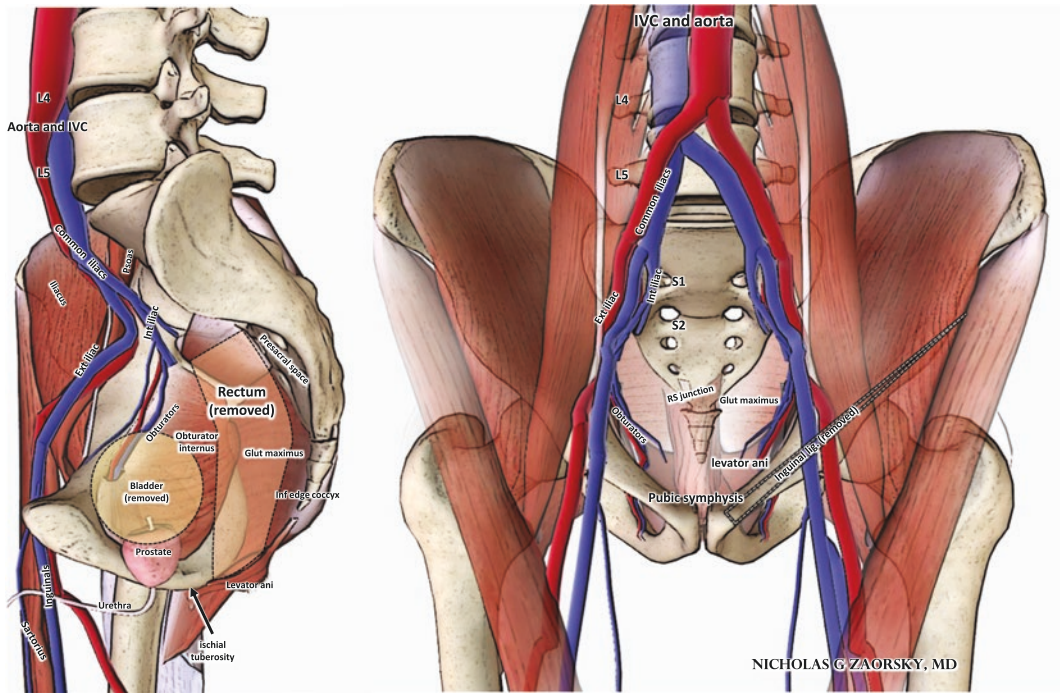
- **3D-CRT (per RTOG-0012):**
  - 3D-CRT, 3F plan, Wedges on laterals with heal toward posterior
  - Often need 16 MV due to patient thickness
  - Sup: L5/S1
  - Inf: >5 cm from inf extent of primary or the anal verge for distal cancers as identified by marker on CT sim
- If not on R-0012: 3 cm below tumor or below obturator foramen
  - Lateral: 2 cm outside pelvic brim
  - Post: entire sacrum and presacral space (for coverage of presacral space)
    T4: 1 cm post to the sacrum:
    T3: 2 cm post to the presacrum. Do not split sacrum since 2/3 LRs are in presacral space
  - Ant:
    T3: cover the lower common and ext. iliac LNs to 1 cm post to the symphysis pubis
    T4: ant to pub symph, but ensure 3 cm margin on tumor
  - Boost GTV +2–3 cm
  - 45 Gy WPRT +5.4 Gy boost if preop
  - Up to 54 if post-op, though no good data on 50.4 vs 54.
  - If R+, IORT to 15 Gy or EBRT 15 Gy
  - On treatment: daily kV imaging
- **IMRT**
  - When to use: young patients, concern for long-term sequelae; LN burden; SB issues; post-op; anal canal involvement; immunosuppressed; bulky disease, re-irradiation.
  - RTOG 0822 (Hong 2015) showed no benefit of IMRT vs 3DCRT. However, IMRT was w oxaliplatin (which increased toxicity and did not improve outcomes), and it was compared to historical control.

Follow-Up

- q3 month H + P exam, CEA if elevated at onset x 2 years, then q6 mo for total 5 years, c-scope in 1 y and then every 5 years, CT c/a/p annually for 3–5 years

Overall Outcomes

- OS5:
- T1–2: 90%
- T3 or N+: 75%
- T4N+: 50%
- ~50% LRF reduction with RT
- All comers LRR <10% with preop CRT
- DM 30%
- M1 resectable liver met: 30–40%


L4
Aorta and IVC
L5
Common iliacs
Psoas
Iliacus
Int iliac
Ext iliac
Presacral space
Rectum
(removed)
Obturators
Obturator internus
Glut maximus
Bladder
(removed)
Inf edge coccyx
Prostate
Levator ani
Inguinale
Urethra
Sartorius
Ischial tuberosity
IVC and aorta
L4
L5
Common iliacs
Int iliac
Ext iliac
S1
S2
RS junction
Glut maximus
Obturators
levator ani
Inguinal lig (removed)
Pubic symphysis
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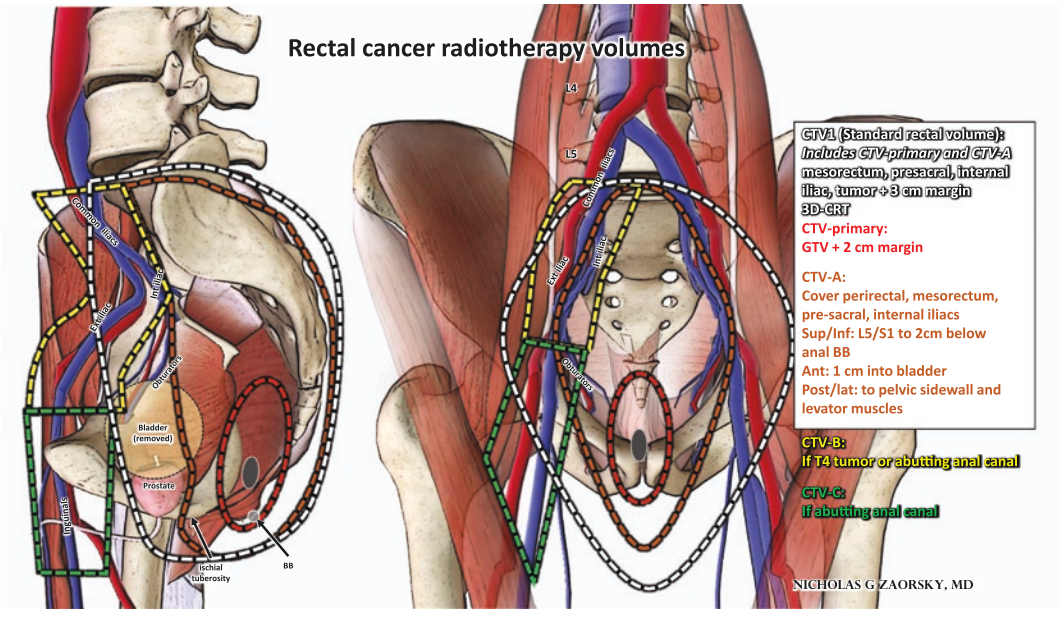
Rectal cancer radiotherapy volumes
L4
L5
Common iliacs
Int iliac
Ext iliac
Obturators
Bladder
(removed)
Prostate
Inguinale
Ischial tuberosity
BB
CTV1 (Standard rectal volume):
Includes CTV-primary and CTV-A
mesorectum, presacral, internal iliac, tumor + 3 cm margin
3D-CRT
CTV-primary:
GTV + 2 cm margin
CTV-A:
Cover perirectal, mesorectum, pre-sacral, internal iliacs
Sup/Inf: L5/S1 to 2cm below anal BB
Ant: 1 cm into bladder
Post/lat: to pelvic sidewall and levator muscles
CTV-B:
If T4 tumor or abutting anal canal
CTV-C:
If abutting anal canal
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Colon Cancer [85, 91, 98]

Anatomy

– Ascending and descending colon are retroperitoneal. They do not move within abdominal cavity and can sometimes be treated similar to rectal CA, i.e., w preop CRT.

Studies

– Intergroup 0130 (Martenson 2004): T4 or T3 N1–2 of retroperitoneal colon (i.e., ascending and descending colon) → adj chemo or adj CRT. No difference in 5-yr OS or DFS and tox worse w CRT. 5y OS 62% vs 58%; DFS was 51%. Toxicity was 54% vs 42% in heme; no difference in nonheme G3 + toxicity, 35% vs 44%. Only accrued 222/700 pts, so may be a Type II error. Consider RT for R+ or tumor adherence noted during surgery.
– MOSAIC (Andre, NEJM, 2004):4-FU + leucovorin +/− oxaliplatin in resected colon cancer, Stage II-III. Established FOLFOX x 12 cycles (6 m) as standard post-op adjuvant chemo regimen w/ better DFS.
– Toronto/Cukier, 2012: retrospective; 33 pts w potentially resectable M0 T4b colon cancer. Received N-CR 45–50 Gy/25 w 5-FU, then multivisceral resection. Median FU 36 m. All pts R0. 3-year OS 86%, DFS 74%. Post-op complications in 36%.

NCCN

– Consider pre- or post-op RT for T4 or pos margins
– 50 Gy with 5-FU for tumor, 45 Gy to LNs

Anal Cancer [1–5, 99–110]

AJCC 8th Edition Staging

- **T1** – ≤2 cm
- **T2 –** 2–5 cm
- **T3** – >5 cm
- **T4** – adj organ

AJCC 8	T1	T2	T3	T4
N0	I	IIA	IIB	IIIB
N1abc	IIIA		IIIC	
M1	IV			

- **N1a** – inguinal, mesorectal, internal iliac
- **N1b** – external iliac only
- **N1c** – external iliac and any N1a node
- **M1** – DMs, e.g., dermal involvement of vulva

AJCC 7th Edition Staging (N Stage Differs from 8th)

- **N1** – perirectal nodes
- **N2** – No perirectal
- But, unilat internal iliac, unilat inguinal, *or* both
- **N3** – perirectal+inguinal, bilateral internal iliac, bilateral inguinal
- **M1** – DMs, e.g., dermal involvement of vulva

AJCC 7 TNM	T1	T2	T3	T4
N0	I	II		IIIA
N1: Perirectal	IIIA			IIIB
N2: Unilat int iliac *or* unilat inguinal *or* both **N3:** perirectal+inguinal, bilateral internal iliac, bilateral inguinal	IIIB			
M1	IV			

Overview

- 7000 cases/yr.
- 80% SCC, 15% adenoCA.
- HPV associated (16, 18), AIDS assoc.
- HPV 16 in 81%, 18 in 2%, 33 in 5%.
- 33% are N+, but only 50% of cN+ are pN+.
- Anatomy: anal canal is 3–4 cm long, from anal verge (inf) to anorectal ring (sup).
- **Dentate line** divides rectum and anus. Perianal skin may have skin cancers. Above dentate drains to rectal nodes. Below drains to inguinals.
- **Anal margin**: 5 cm ring around anus, treat like skin cancer if T1 N0 and well-differentiated; otherwise treat like anal.

Workup

- H&P, GYN exam, DRE, CBC, CMP, *HIV*, PET-CT CAP, +/− MRI, anoscopy, HCG. If cN+, FNA and avoid open bx
- On DRE: note distance from verge, sup extent, clock location, circumferential involvement
- Pelvic exam in women, inc cervical CA screening

Chemo

- Mitomycin C: hypoxic cell radiosensitizer
- 5-FU: 1000 mg/m^2/day continuous infusion
- MitoC: 10 mg/m^2 bolus on days 1 and 29
- Capecitabine: 825 mg/m^2 BID Mon–Fri

HGSIL

- Pineda, 2008 n = 246 HGSIL. Used electrocautery. 57% recurrence but complications in only 9 pts

Local Excision Alone or RT Alone

- **Boman 1984**: T1, G1, neg margins, <40% circumference, no sphincter involvement (LC >90%).
- **Deniaud-Alexandre 2003**: RT alone for T1 N0, 100% LC.

RT vs CRT

- **Nigro 1974**: 30/15 + 5-FU + mitoC. 5-FU is 100 mg/m^2 CI x2c, and MMC is 15 mg/m^2 bolus d1. RT was AP/PA to pelvis and inguinals. Then surgery for some. 71% pCR. Same control with or without APR (~80%). Foundation trial for definitive CRT.
- **UKCCCR ACT I** (Lancet 1996, Northover 2010): anal SCC, excluding T1 N0. Randomize 45 Gy/20–25 fx (institutional preference) + boost w Ir-192 BT+/− 5-FU + mitoC. Split course RT. If no response, then pt. go to salvage surgery. At 12y, CRT improved LRC 66% vs 41%, colostomy-free survival 89% vs 73%, but not OS (27–33%). CRT w 5-FU/MMC became SOC.
- **RTOG 8704** (Flam 1996): 45–50.4 Gy with 5-FU +/− mitoC. 5-FU was 1000 mg/m^2 on d1–4 and d29–32. MitoC was 10 mg/m^2 on d1 and 29. MMC improved CR rate (85 → 92%) and ↓colostomy rate (22% vs 9%) and 4-year DFS (51% vs 73%) but same OS. However, MMC had more G4–5 tox, 26% vs 8%.
- **EORTC trial** (Bartelink 1997): similar ACT I. 45/25 + boost of 15–20 Gy if CR or PR after 6w vs CRT 45/25 + 5-FU CI and MMC. CRT arm had better LC, 68% vs 50% and colostomy-free survival 72% vs 40%. 5-yr OS similar – 56%.
- **Salama 2007**: 53 pts s/p chemoIMRT. Favorable results.
- **CALGB 9281** (Meropol 2008): neoadj chemo phase II trial for T3–4 and/or N2–3. At 4 yrs. showed 68% OS and 50% sphincter preservation.
- **RTOG 9811** (Ajani 2008, Gunderson 2012): T2–4,NX, *n* = 644 patients. 5-FU + cis with induction vs 5-FU + mitoC without induction. RT was 3D CRT. sup L5/S1. Whole pelvis (30.6 Gy): Inf 2.5 cm margin around tumor and anus. Lat to include lat inguinal LNs and 2 cm lat to greater sciatic notch. Then true pelvis (to 45 Gy): same field, but sup border lowed to inf border of the SI joints. If N0, then field reduced off inguinal nodes also. 5 yr OS with mitoC better (71 → 78%). 5-year colostomy-free survival better w MMC 72% vs 65%. 5 yr. DFS (68% vs 58%). G3+ heme acute tox worse w MMC, 62% vs 41%.
- **EXTRA-**(Glynne-Jones 2008): phase II data of mitomycin combined with capecitabine instead of 5-FU. Good results.
- **UKCCCR ACT II** (James 2013): Can we replace MMC w cis? 50.4 Gy with 5-FU + mitoC vs cisplatin. Then +/− maintenance chemo. Superiority trial. *n* = 472. 3-year PFS was 75%. No diff in PFS, OS, colostomy-FS, or CR at 26w. At 26w, CR was 91% in MMC arm and 90% in cis arm. 5-FU/MMC + 50.4 Gy RT in 28 fx w/o maintenance recommended as SOC bc this was not a non-inferiority trial.
- **RTOG 0529** (Kachnic 2013): phase II of dose painted IMRT. Entire pelvis gets up to 54/1.8 (30 fx) depending on stage. Inguinal LNs get 45 Gy if negative, 50.4 if <3 cm (1.68 Gy/fx), and 54 Gy if >3 cm. A T2 N0 tumor in this protocol is treated w 50.4 Gy/1.8 Gy to primary and 42 Gy/1.5 Gy fx to pelvis and inguinal LNs. Less grade 2+ heme, grade 3+ GI, and grade 3+ derm toxicity but primary endpoint (combined acute grade 2 toxicity GI and GU).
- Contours per RTOG 0529.

Anal Cancer Treatment Paradigm

- Everyone gets definitive CRT.
- MMC and 5-FU/capecitabine.
- Chemotherapy wks 1 and 5.
- Capecitabine 825 mg/m^2 PO BID M-F.
- MMC 10 mg/m^2, D1 and 29 (or 12 mg/m^2 on D1 only if capecitabine).
- Do not use cisplatin in place of MMC, unless AIDS. RTOG 98–11: Worse OS and DFS with cis, although confounded by addition of induction cis/5-FU in cis arm. UK ACT II: No difference b/w MMC and cis; no benefit to outback chemo.

Risk Groups (lower rows from 9811)		Treatment
HGSIL		Topical therapy, immune modulation, IR coag, electrocautery ablation.
T1 anal *margin* or perianal	V low risk, tx like skin CA	surg alone, w risk adapted therapy. For R1, re-resect, or RT+5-FU
T1 anal *canal*	V low risk	CRT w 5-FU/MMC
T2-3N0	Low risk	CRT
T4N0, T2N1-3	Intermediate	CRT
T3N1-3, T4N1-2	High risk	CRT

Unique Situations
- SCC of anal margin: Tumors ≤2 cm = WLE alone with ≥1 cm margin. All others treated as SCC of anal canal.
- AdenoCA of anal canal: Preoperative CapeRT → APR → FOLFOX x 8 (4 months). Use IMRT, with regional lymph nodes treated per anal cancer.

Management of AIDS Patient
- Start HAART.
- Ask about CD4 count and if they are on HAART.
- If new dx and CD4 >200 → treat with 5 U/MMC/RT.
- If CD4 <200 →consider holding MMC or substituting CDDP.

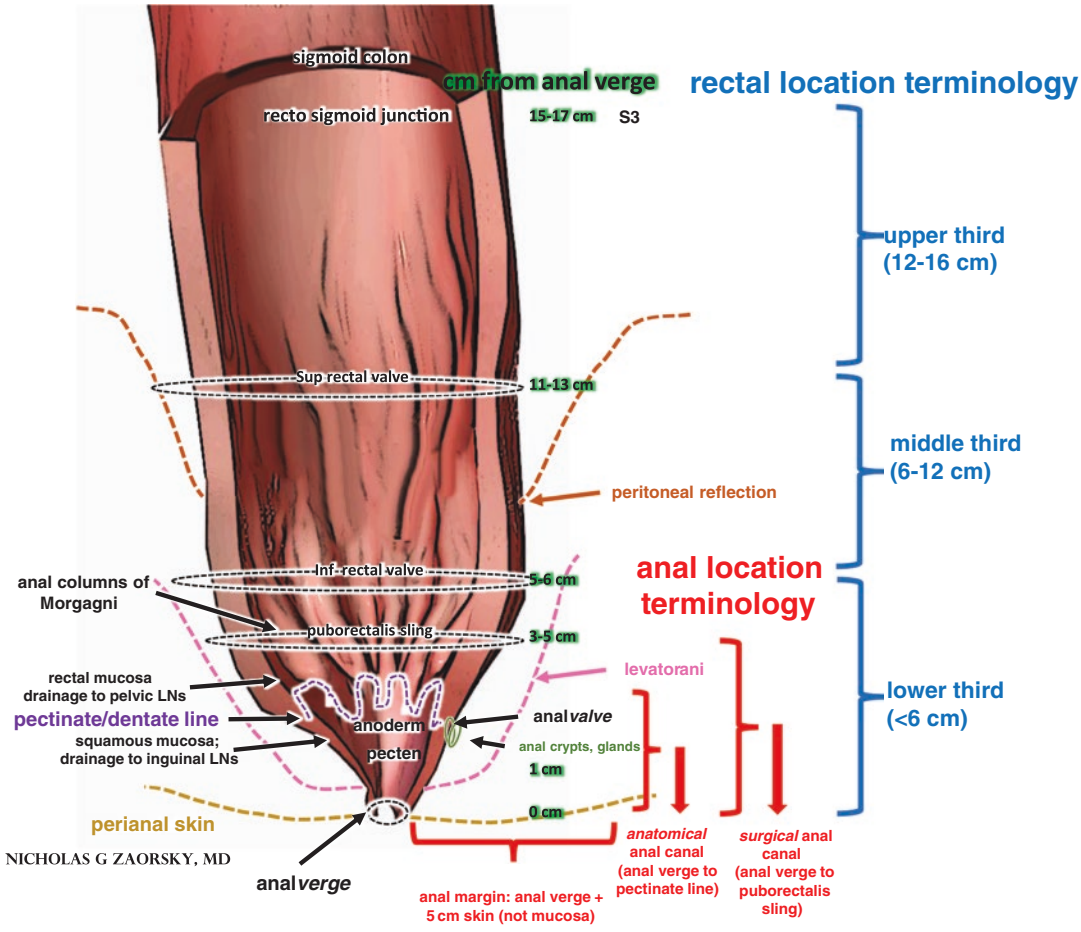
Management of Diarrhea >6 BM/d
- Imodium/lomotil/paregoric (anhydrous morphine).
- Check treatment plan.
- Check for C diff.
- Electrolytes/IV fluids/hospitalize.
- Hold 5-FU.
- Hold RT if unresponsive to above until <7 BM/day.

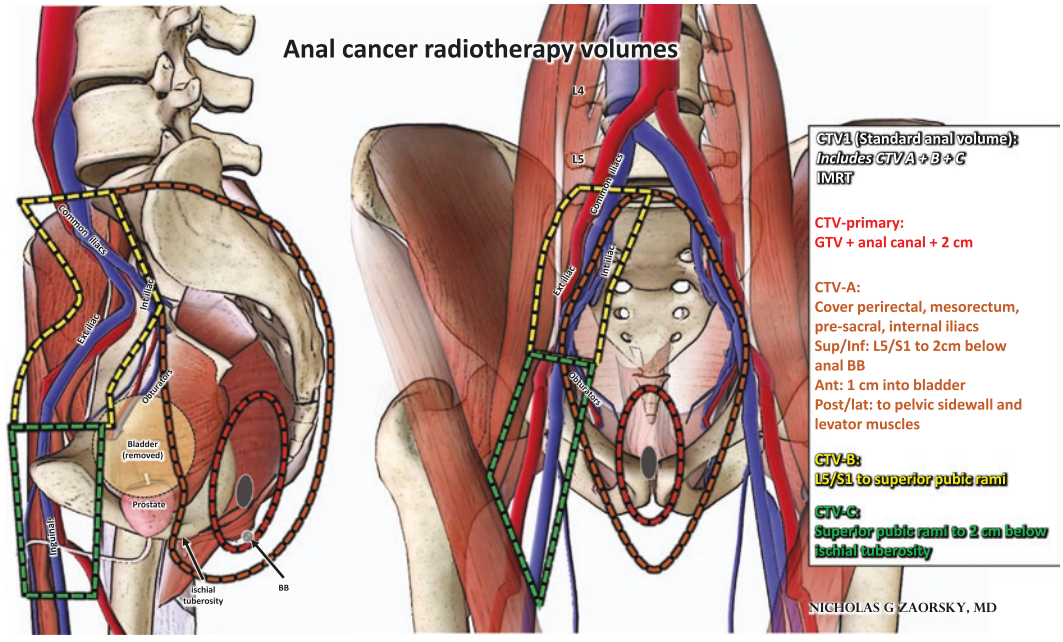
Hold RT If
- ANC <500
- Plts <50
- Diarrhea >7 BM/d
- Grade 4 dermatitis (ulceration)
- Grade 3 vomiting

Anal Cancer Outcomes
- cCR = 90%
- pCR = 80–85%
- Colostomy rate 10%
- LRR (the dominant failure pattern):
  - T1–T3 N0 = 15–20%
  - T2N+ or T4 N0 = 30%
  - T3/T4N+ = 35–40%
- DM: ~ 20%
- Salvage APR success = ~ 50%

Toxicity
- Acute toxicity: Perianal skin reaction, diarrhea, nausea, pain, dehydration, mucositis with 5-FU, heme toxicity with mitomycin C
- Late toxicity: Fistula, fecal incontinence, ulceration, bleeding, colostomy, sexual side effects, sterility, impotence and vaginal dryness/stenosis

Follow-Up
- Follow-up w DRE at 8–12w, then q4w until CR is achieved. Once CR is achieved, DRE and inguinal LN exam q3–6 m for 5 years.
- Anoscope q6-12 m for 3yr.
- CTCAP qy for 3y if T3–4 or inguinal LN+.
- Biopsy only if evidence of PD or significant clinical concern.
- Counsel vaginal dilator use.
- No benefit to routine posttreatment biopsy (Cummings 1991; ACT II, James, Lancet Onc, 2013). Continues to regress for up to 12 months.


sigmoid colon
cm from anal verge
rectal location terminology
recto sigmoid junction
15-17 cm
S3
upper third
(12-16 cm)
Sup rectal valve
11-13 cm
middle third
(6-12 cm)
peritoneal reflection
anal location
terminology
anal columns of
Morgagni
Inf. rectal valve
5-6 cm
puborectalis sling
3-5 cm
levatorani
rectal mucosa
drainage to pelvic LNs
pectinate/dentate line
squamous mucosa;
drainage to inguinal LNs
anoderm
pecten
anal valve
anal crypts, glands
1 cm
lower third
(<6 cm)
0 cm
perianal skin
NICHOLAS G ZAORSKY, MD
anal verge
anatomical
anal canal
(anal verge to
pectinate line)
surgical anal
canal
(anal verge to
puborectalis
sling)
anal margin: anal verge +
5 cm skin (not mucosa)


Anal cancer radiotherapy volumes
L4
L5
Common iliacs
Internal
External
Obturators
Bladder
(removed)
Prostate
Inguinals
Ischial
tuberosity
BB
CTV1 (Standard anal volume):
Includes CTV A + B + C
IMRT
CTV-primary:
GTV + anal canal + 2 cm
CTV-A:
Cover perirectal, mesorectum,
pre-sacral, internal iliacs
Sup/Inf: L5/S1 to 2cm below
anal BB
Ant: 1 cm into bladder
Post/lat: to pelvic sidewall and
levator muscles
CTV-B:
L5/S1 to superior pubic rami
CTV-C:
Superior pubic rami to 2 cm below
Ischial tuberosity
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Anal and Rectal Cancer Planning [111]

Simulation

- Supine and frog leg for anal.
- Prone on a belly board for rectal.
- Anal marker, vaginal marker as indicated.
- Comfortably full bladder.
- Small bowel contrast. IV Contrast.
- BB on anal verge, wire distal edge of tumor if needed for anal.
- CT-based planning. Fuse with PET for treatment planning for anal.
- Place iso in the anal canal.

Pelvic Anatomy: Australasia GI Trials Group Contouring Atlas

	CTVA					CTVB	CTVC
	Mesorectum	Presacral space	Int iliac LNs	Ischiorectal fossa	Obturator LNs	Ext iliac LNs	Inguinal LNs
Cranial	Rectosigmoid junction	Sacral promontory (L5/S1) interspace	Bifurcation of common iliac artery	Apex formed by levator ani, glut maximus, obturator internus	3–5 cranial to obturator canal	Bifurcation of common iliac artery	Ext iliac art leaves bony pelvis to become femoral artery
Caudal	Anorectal junction	Inferior edge coccyx	Level of obturator canal or where no space bw obturator internus and midline organs	Anal verge	Obturator canal, where obt artery exits pelvis	Roof of acetabulum and sup pubic rami	Lower edge of ischial tuberosities, 2 cm caudad to the saphenous/ femoral junction
Post	Presacral space	Post to ant border of sacral bone, include sacral hollow	N/A	Transverse plane bw ant edge of medial walls of glut maximum muscle	Int iliac LNs	Int iliac LNs	Muscle
Ant	Males: penile bulb, prostate, SVs, bladder both: bladder, + 1 cm added to ant border	1 cm ant to sacral border	Obturator internus upper pelvis: 7 mm margin around int iliac vessels	Where obturator internus, levator ani, sphincter muscle fuse inf: 10–20 mm ant to sphincter muscles	Ant extent of obturator internus	7 mm margin ant to ext. iliac vessels	Minimum 2 cm margin on inguinal vessels
Lateral	Lower pelvis: medial edge of levator ani upper pelvis: int iliac LNs	SI joints	Medial edge of muscle or bone	Ischial tuberosity, muscles	Obturator internus	Iliopsoas muscle	Medial edge of sartorius or iliopsoas
Medial	N/A	N/A	Lower pelvis: mesorectum and presacral space upper pelvis: 7 mm around vessel	N/A	Bladder	Bladder or 7 mm margin around vessel	1–2 cm margin around femoral vessels

Anorectal Elective LN Regions per RTOG Anorectal Contouring Atlas (Myerson, 2009)

Volume	Description	Rectal cancer (per RTOG 0822)	Anal cancer
GTV	Part of CTVA		**GTV** = dz. on imaging and DRE
CTVA	**Perirectal, presacral, internal iliacs** **Sup**: ≥2 cm from gross disease, including entire *mesorectum* + pelvic floor, or rectosigmoid junction (whichever is more sup). Follow to where iliac vessels bifurcate to ext./int iliacs (~sacral promontory) **Lateral**: extend to lateral pelvic sidewall musculature or bone. Unless evidence of extension into ischiorectal fossa, no need to go more >mm beyond levator m **Anterior**: 1 cm into the posterior bladder to account for day-to-day variation **Posterior**: posterior internal *obturator vessels* (lie between external and internal iliacs), + 7–8 mm around vessels	***Always treated:*** **CTV50.4** = GTV + 2 cm sup/inf mucosally +1.3 cm radially plus entire mesorectum including the presacral space at the level. Same for 50.4 Gy or 5x5 Gy **CTV45** = at least 2 cm inferior to gross disease or to the pelvic floor, whichever is lower. Lateral to pelvic sidewall muscles, include posterior portion of internal obturator vessels. Sup to bifurcation of common iliacs to int/ext. iliacs. **PTV** = CTV + 3-5 mm, inside skin	***CTV A + B + C always treated*** **CTVA** = GTV + entire anal canal +2–2.5 cm sup/inf expansion +1.5 cm radial expansion. Include pre-sacral space and mesorectum at involved levels. Inf, should extend >2–2.5 cm around anal verge (or from GTV, if perieanal skin involved). Lat, include <3 mm beyond levator ani (unless levator ani involved, then 1–2 cm margin up to bone) **CTV node boost** = GTV node +5-7 mm. No accepted standard. **CTV(42–50):** remainder of the CTV*A + B + C* **T3–4/N+ (30 fractions)** PTV_A = 54/30 at 1.8 PTV_A_B_C = 45/30 at 1.5 PTV_CD ≤3 cm = 50.4/30 at 1.68 PTV_CD ≥3 cm = 54/30 at 1.8
CTVB	**External iliac region** Inf extent of internal obturator vessels (bony landmark: upper edge of sup pubic rami) recommend 7 mm margin in soft tissue around the iliac vessels but at least 1 cm ant, especially if cN+ Trim off uninvolved muscle and bone	***Sometimes treated:*** Cover if tumor extending anteriorly (i.e., T4 lesion – GI/GU structures), or *abutting* anal canal	**T1–2/N0 (28 fractions)** PTV_A = 50.4/28 at 1.8 PTV_A_B_C = 42/28 at 1.5
CTVC	**Inguinal region**. Cover for tumors invading anal canal. Should be 2 cm below saphenous/femoral junction	***Sometimes treated:*** Cover if *invading* anal canal	

(continued)

Volume	Description	Rectal cancer (per RTOG 0822)	Anal cancer		
Treatment paradigm		**T1 N0**: transanal vs APR/LAR If high risk (>2/3 of circumference, G2+), then TME and post-op CRT if T3+ or N+ High risk: pT2, +margin, LVSI, G3 Adjuvant chemo is for 6 months, q 2 weeks **T2+ or N+**: neoadj CRT, then TME, then adj chemo. 50.4 Gy with Xeloda	ChemoRT for all		
			RTOG 98–11 (sequential volume reduction) **Entire pelvis** (L5/S1, 2.5 cm margin on tumor+anus, include lat inguinal LNs on AP field, include 2 cm lat to greater sciatic notch on PA): **30.6/1.8** **Boost**: 14.4/1.8, same field but sup border is SI joints If N0, reduce field off inguinal LNs after **36 Gy** **Primary boost:** For T3–4 dz., N+ dz., or residual dz. after delivery of 45 Gy, a boost of 10–14.4 Gy to GTV + 2–2.5 cm margin allowed, to 54–59 Gy	**RTOG 0529 with SIB:** **T1–2 N0** PTVA (primary): 50.4/28/1.8 PTV42 (all nodal regions): 42/28/1.5 **T3–4 N0** PTVA: 54/30/1.8 PTV45: 45/30/1.5 **N+** PTVA: 54/30 PTV54 (nodes >3 cm): 54/30/1.8 PTV50.4 (nodes <3 cm): 50.4/30/1.68 PTV45: 45/30	**Sequential IMRT boost:** **Entire pelvis:** 45/30/1.8 **Boost** to 54–59.4 to primary T2 should go to 50.4T3–4 should go to 54 **cN0 inguinal LNs:** T3 + N0 36/20/1.8: T2 N0 42/28/1.5 **N+ <3 cm:** 50.4/28/1.8 **N+ >3 cm:** 54/30/1.8 Note: No volume reduction after initial 30.6
Chemo		5-FU-based, 225 mg/m^2 Maintenance used	5-FU 1000 mg/m^2 d1–4 and d29–32, MMC 10 mg/m^2 d1 and d29 Can use cape instead of 5-FU. No maintenance chemo		

Dose Constraints [112]

	RTOG 0822 (rectal)	RTOG 0529 (anal)
Small bowel		Dmax <50 Gy
	V45 <65 cc	V45 <20 cc
	V40 <100 cc	
	V35 <180 cc	V35 <150 cc
	V30 <300 cc	V30 <200 cc
Large bowel		V45 <20 cc V35 <150 cc V30 <200 cc
Femoral heads	V50 <0.5 cc	V44 <5% V40 <35% V30 <50%
Bladder	V40 <40% V50 <0.5 cc	V35 <50% V40 <35% V50 <5%
Kidneys	V18 <2/3 of kidney	
Iliac crest		V50 <5% V40 <35% V30 <50%
Pelvic bone marrow		
Genitalia		V20 <50% V30 <35% V40 <5%

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Genitourinary Cancers

8

Nicholas G. Zaorsky, Daniel M. Trifiletti, and Katherine Tzou

Abstract

This chapter discusses the general management of patients with genitourinary tract cancers, with special focus on principles that guide radiotherapy management. Several key components of trimodality care and brachytherapy are discussed.

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Prostate Cancer

Group	TNM	PSA	GS
I	T1-T2	< 10	3+3
IIA	T1 or T2a T2b-c	10-20 < 20	3+3
IIB	T1-2	< 20	3+4
IIC	T1-2	< 20	4+3 or 4+4
IIIA	T1-2	≥ 20	< 9
IIIB	T3-4	-	< 9
IIIC	-	-	9 or 10
IVA	N1	-	-
IVB	M1	-	-

- **T1** – clinically unapparent
  - T1a: incidental <5% of tissue resected
  - T1b: incidental >5% of tissue resected
  - T1c: needle biopsy (↑PSA)
- **T2** – confined within prostate
  - T2a: ≤½ of one lobe
  - T2b: >½ of one lobe
  - T2c: both lobes
- **T3** – through capsule
  - T3a: EPE or microscopic invasion of bladder neck
  - T3b: seminal vesicles
- **T4** – invades adjacent structures: external sphincter, rectum, levator muscles, and/or pelvic wall
- **N1** – pelvic, hypogastric, obturator, iliac (internal, external), and sacral
- **M1a** – non-regional lymph nodes
- **M1b** – bone
- **M1c** – other sites

WHO 2016 grade	GS
1	<7
2	3 + 4 = 7
3	4 + 3 = 7
4	8
5	9–10

Overview [1–5]

– 230,000 cases, 27,000 deaths annually
– Zones: peripheral (2/3 cancers), transitional (BPH), central, anterior fibromuscular stroma.
– PSA velocity: ≥2 ng/ml/yr. → ↑GS7.
– PSA density (PSA/gland volume): >7% → ↑risk.
– Free PSA <25% → ↑cancer.
– Natural history (JHU, MSKCC): time from BF to DMs is 5–8 years, time from BF to CSM is 10.5y. Time from DM to CSM is 5 years.
– Screening: 50 y/o, DRE & PSA, debated.
  – 1400 screened → 48 cancers → 1 death prevented

Workup

– DRE
– AUA/QOL/SHIM scores, history of IBD, history of prior RT.
– Labs: PSA/testosterone, check LFTs if giving ADT.
– **Bone scan/CT** for unfavorable intermediate risk+.
– **Colonoscopy** within past 5 years.
– TRUS-guided 6–12 core bx of prostate (path: Gleason score, # cores, % of core involved), endorectal MRI, or proctoscopy/cystoscopy if warranted.
– mp MRI, 3 T, no coil.
  • T2: tumor is dark compared to prostate.
  • DWI w/ ADC map: tumor is dark.
– DCE: tumor shows early arterial enhancement.
– Bone scan if unfavorable intermediate or symptoms.

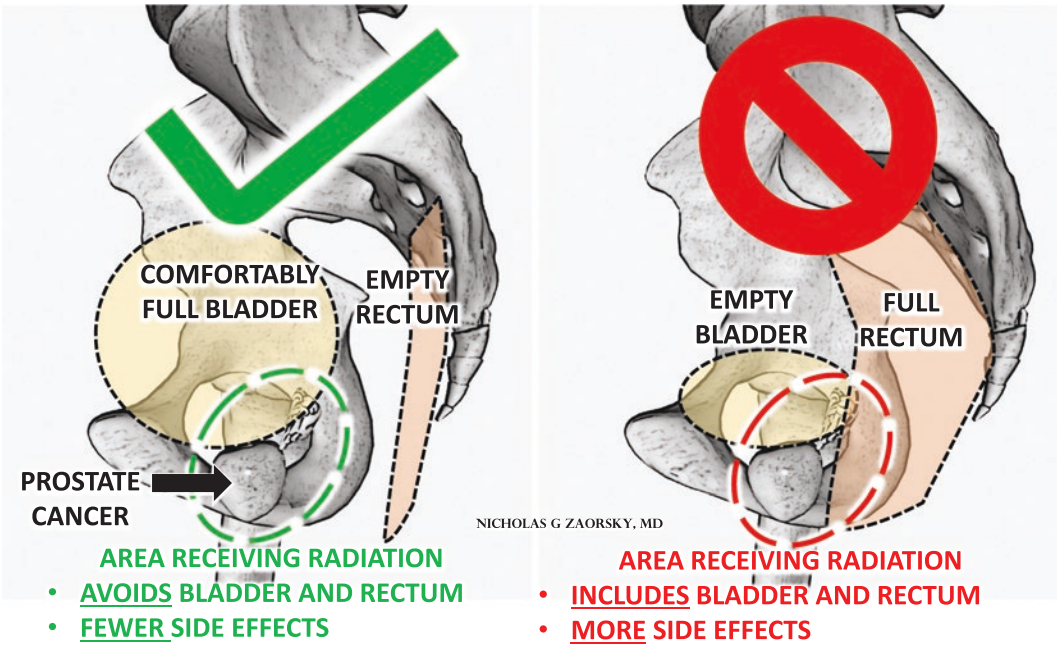
Screening

– ERSPC, Schroder, 2009, 2012, 2014. 21% relative decrease in death (absolute of 0.71 per 1000 men) in PCSM with screening. No difference in OS. Number needed to invite to PSA screening to prevent 1 death = 781; num-

ber needed to detect = 27. Authors did not recommend population-based screening.
- PLCO trial, Andriole, 2009. No benefit for annual screening. However, high contamination rate, with 80% of screening arm screened, while 50% of the non-screening arm was screened.

Roach Formulas
- ECE = 3/2(PSA) + 10(GS-3)
- SVI = PSA + 10(GS-6)
- LN = 2/3(PSA) + 10(GS-6)
  - Treat nodes for >15%

Anatomy
- Prostate apex starts 5 mm above the GU diaphragm, which can be identified on CT sim as the top of the urethrogram beak.



Prostate Cancer Treatment Considerations and Planning

Contraindications to prostate RT modalities

	As first-line therapy				Post-RP
	RT subtypes				
Possible contraindications	BT	EBRT			EBRT
	LDR or HDR	CFRT	HFRT	SBRT	CFRT
Limited life expectancy (e.g. <10 years; patient will not realize benefit of RT in lifetime)					
Unacceptable operative risks, or medically unsuited for anesthesia		**	**	*, **	**
Distant metastases		***	***	*, ***	*
Absence of rectum such that TRUS-guidance is precluded		**	**	**	**
Large TURP defects which preclude seed placement and acceptable radiation dosimetry		**	**	*	N/A
Ataxia telangiectasia					
Preexisting rectal fistula					
Risk of bleeding (e.g. from anticoagulants)		**	**	**	**
Moderate-severe urinary symptoms (e.g. high IPSS score, typically defined as > 20)	Consider CFRT		Consider CFRT	Consider CFRT	
History of prior pelvic radiotherapy				*	*
Large prostate (e.g. >60 cm^3)					N/A
Large median lobes					N/A
Inflammatory bowel disease				*	*
Pubic arch interference (e.g. prior pelvic fracture, irregular pelvic anatomy, or a penile prosthesis)					
Patient peak flow rate <10 cc/s and post void residual volume prior to brachytherapy > 100 cc		N/A	N/A	N/A	N/A
Concurrent androgen deprivation therapy use				*	

Abbreviations: N/A: not applicable; IPSS: International Prostate Symptom Score; TRUS: transrectal ultrasound; TURP: transurethral resection of prostate; RT: radiation therapy

Note: * Excluded on clinical trial; ** Placement of fiducials for IGRT may be difficult; *** Depends on intra-vs. extra-prostatic disease burden

Green color refers to items that are not contraindications for RT.

Yellow color refers to items that may be contraindications for RT, or logistics. Red color refers to items that are contraindications for RT.

RT treatment options for men with NCCN risk group-stratified prostate cancer, in relation to other treatment options.

Options and subtypes		NCCN risk group					
		Very Low T1c, *and* GS <6, *and* PSA <10 ng/mL, *and* <3 positive cores with <50% cancer/core, *and* PSA density <0.15 ng/mL/g	**Low** T1-T2a, *and* GS ≤ 6/GG 1, *and* PSA <10 ng/ml,	**Intermediate** T2b-T2c, *or* GS 7 (3+4)/GG 2, *or* GS 7 (4+3)/GG 3, *or* PSA ≥10 ng/ml ≤ 20 ng/ml	**High** T3a, *or* GS 8/GG 4, *or* GS 9-10/GG 5, *or* PSA > 20 ng/ml,	**Very High** T3b-T4, *or* primary GP 5/GG 5, *or* >4 cores with GS 8-10/ GG 4 or 5	**Post-RP RT**[19] **Adjuvant indications**: pT3; positive SMs, GS 8-10, seminal vesicle involvement **Salvage indications**: suspected LR (e.g. rising PSA, imaging, biopsy-proven)
Active surveillance / watchful waiting / observation		Yes; typically the preferred option	Yes	Usually no	Usually no	Usually No	N/A
Radical prostatectomy (RP)	open, laparoscopic, robotic approaches	Monotherapy if >20 years life expectancy	Monotherapy if >10 years life expectancy	Monotherapy	Monotherapy	Monotherapy	N/A
Brachytherapy	low dose rate	Monotherapy if >20 years life expectancy	Monotherapy if >10 years life expectancy	Monotherapy or boost	Monotherapy or boost	Monotherapy or boost	No
	high dose rate	Monotherapy if >20 years life expectancy	Monotherapy if >10 years life expectancy	Monotherapy or boost	Monotherapy or boost	Monotherapy or boost	No
External beam radiation therapy (EBRT)	conventional fractionation	Monotherapy if >20 years life expectancy	Monotherapy if >10 years life expectancy	Monotherapy or boost	Monotherapy or boost	Monotherapy or boost	Yes
	hypofractionation	Monotherapy if >20 years life expectancy	Monotherapy if >10 years life expectancy	Monotherapy or boost	Monotherapy or boost	Monotherapy or boost	No
	stereotactic body radiation therapy (SBRT)	Monotherapy if >20 years life expectancy* (sometimes)	Monotherapy* (sometimes)	Monotherapy* (sometimes)	Monotherapy* (rarely)	No	No
± Androgen deprivation therapy		No	No	Sometimes*	Almost always, (24–36 months)	Almost always, (24–36 months)	Sometimes*

Abbreviations: BT: brachytherapy; GG: Gleason grade group; GP: Gleason pattern GS: Gleason score; PSA: prostate specific antigen; SBRT: stereotactic body radiation therapy; SMs: surgical margins

Note:

- Green color refers to accepted treatments, NCCN Category 2A[2]. Additionally, NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
- Yellow color refers to controversial topics, or those being explored on clinical trials. * Denotes treatment options that are largely investigational or controversial (clinical trial reference provided, if available).
- Red color refers to treatments that are not recommended.
- For ease of review, subsequent tables will combine very low and low risk together, as well as high and very high risk together

"Boost" refers to the use of BT + EBRT, as opposed to either treatment alone.

Active Surveillance (AS)

- Eligibility: life expectancy <20 years, cancer up to T1c or T2a. PSA <10 ng/mL. GS 6 with no 4 or 5 component. PSA/prostate volume (i.e., the density) <0.15.
- Components: biannual DRE/PSA, annual Bx. Not indicated after age 75 or within 6 months if <10 cores or discordant findings. DRE no more than yearly. 25% will end up getting treated.
- Indications to begin treatment: ↑ in # positive cores/percent involvement, ≥ GS 4; PSA DT <3 years.

Brachytherapy (BT)

Contraindications

- >60 cc, <20 cc (if prostate too large can give ADT to shrink by 1/3)
- Size cutoffs are mostly for LDR-BT
- TURP defect
- Large median lobe
- Pubic arch interference
- IPSS >15 (>20 absolute)
- Anesthesia/sedation risk
- IBD/prior RT
- Unless considering salvage BT for local recurrence. All local recurrences should be biopsied

Definitions

	Prostate brachytherapy terms. Note, these are generally specific to prostate, do not apply to other organs
D0.1 cc or D_{max}	The average dose to the hottest point of a volume. "D0.1 cc" is sometimes used because this approximates the maximum dose to the smallest volume that can be calculated on a computer
D2cc	The average dose to 2 cc of a volume
D10	The average dose to 10% of a volume, in Gy. The urethra D10 should be <150% of the prescribed dose. This constraint limits the dose to the urethra
D30	The average dose to 30% of a volume, in Gy. The urethra D30 should be <130% of the prescribed dose. This constraint limits the dose to the urethra
D90	In prostate cancer brachytherapy, this is the minimum dose in the hottest 90% of a volume, in Gy. The prostate D90% should be >100%. This constraint ensures the prostate volume receives adequate dose
Dwell time	The time that the ^{192}Ir source spends in a predetermined dwell position during HDR-BT. A longer dwell time in a position translates to a greater dose deposited in the volume around the position
Dwell position	The position where a ^{192}Ir source is located during HDR-BT. A combination of dwell positions in different needles allows the delivery of a predetermined dose to the CTV
Hot spot	A colloquialism used to describe volume outside the PTV which receives dose larger than 100% of the specified PTV dose
*R*V100	In prostate cancer brachytherapy, this is the volume of the rectum receiving 100% of the dose and should be <1 cc
V100	In prostate cancer brachytherapy, this is the percentage of a structure receiving 100% of the dose. For example, the V100 for the prostate should be >90%, meaning that 100% of the prostate CTV should receive more than 90% of the prescribed dose. V100 is a surrogate for post-implant D90
V150	In prostate cancer brachytherapy, this is the percentage of a structure receiving 150% of the dose. The V150 for the prostate CTV should be <50–60%, meaning that <50–60% of the CTV should receive >150% of the prescribed dose. V150 is surrogate for chronic urethral toxicity
*U*V5	In prostate cancer brachytherapy, this is the average dose to 5% of the urethral volume receiving the highest dose. The UV5 should receive <150% of the dose
*U*V30	In prostate cancer BT, this is the average dose to 30% of the urethral volume receiving the highest dose. The UV30 should be <125% of the dose
*U*V150	In prostate cancer BT, this is the volume of the urethra receiving 150% of the prescribe dose. *U*V150 of the urethra should be 0%, meaning that 0% of the volume should receive 150% of the prescribed dose

- ^{103}Pd: 17d, 21 keV, EC, 125 Gy mono, 100 Gy w/ EBRT
- ^{125}I: 60d, 28 keV, EC, 145 Gy mono, 110 w/ EBRT
- ^{192}Ir: 74d, 3.8 MeV (~13.5 Gy × 2 or 10.5 Gy × 3 mono, 15 Gy × 1 or 9.5 Gy × 2 w/ EBRT)
- GS 7 can get LDR monotherapy if all this: 3+ 4, PSA <10, ≤4/12 cores, ≤T2a, ≤50% each core, between 20–65 cc gland

Brachytherapy Procedure

1. [Some use Flomax 0.4 mg daily for 1 with prior to implant].
2. Bowel prep evening before.
3. General anesthesia, pre-op abx are institution-dependent (some use Ancef 1 g IV).
4. Place in dorsal lithotomy position.
5. Place Foley, irrigate rectum. Bladder drained and filled w/ 50 cc contrast +100 cc H2O.
6. Prep perineum with betadine, tape scrotum, avoid tape on perineum.
7. Insert TRUS. 5–7.5 Hz. Evaluate prostate size, geometry. Urethra will be midline on sag view. Confirm you can see base through apex. Lock probe/stepper into position and secure template to cradle.
8. Place needles. For LDR: 70% peripherally, 30 centrally. For HDR: keep 1 cm part, no dwell positions in last 9 mm.
9. Confirm needle depths on sagittal US.
10. Capture transverse US images every 5 mm. Some inject aerated KY jelly.
11. Contour prostate, urethra, rectum. CTV = GTV + 3–5 mm. PTV = + 0 mm bc no movement.
12. [For LDR: intraop/real-time. For LDR: remove trocars. Watch for urine or blood leaks). Attach Mick applicator to needle, being careful not to push needle. Use Mick applicator to insert seeds according to plan under US and fluoro guidance.]
    - [For HDR: inverse planning with remote afterloading system.]
13. Withdraw needles, apply perineal pressure.
14. For LDR: cystoscopy by urologist, check bladder for seeds. Rad safety should check room for seeds.
15. Remove Foley, voiding trial. If can't void within 4–8 h, admit as inpatient. Otherwise, discharge with pain meds, Flomax × 1 week, Motrin, Cipro.
16. [For LDR: Follow-up CT after 1 m to assess dosimetry]
    - [For HDR: second fraction in 1 week]
17. Peri-op expect pain, dysuria, hemat, freq, urinary retention (obs ur sx resolve 6–12 m!)
18. Avoid exercise and sex for 2–3 weeks.
19. [For LDR: avoid pregnant women and children for one half-life (60 days/17 days)].

Plan Isodose Evaluation

- On DVH the x-axis is dose and y-axis is volume in percentages.
- Get D90 by going to y-axis and 90% then going across till you cross the curve.
- Get V100 by finding 100% of prescribed dose on x-axis (e.g., 145 Gy for I125) and them moving up vertically where curve crosses. This is the volume of prostate getting 100% of the prescribed dose. V100 cannot be >100%.
- 100% to cover CTV (no PTV).
- 200% are islands.
- 150% may touch occasionally.
- Post implant dosimetry.
- Post-brachy obstruction risk ≈ AUA score (%).

PSA bounces: more common in younger patients.

Management of acute frequency/urgency: NSAIDs, alpha blockers.

Management of acute urinary obstruction: Catheter. Follow until able to void.

Radionuclide	Mono dose (Gy)	Boost dose (Gy)	t1/2 (days)	Average energy (keV)	Prostate (CTV)			Urethra	Rectum	
		EBRT is 45–50.4			D90	V100	V150			
125I	145	110	59.4	28.4	>100% of dose	>90–95%	<50–60%	UV150 ~0 (in volume) UV5 <150% UV30 <125%	V100 <1 cc on day 0; and <1.3 cc on day 30	D2cc < prescribed dose and D0.1 cc <200 Gy
103Pd	110	100	17.0	20.7						
131Cs	120		9.7	30.4						
192Ir	13.5 × 2 9.5 × 4	15 4 × 8.5	73.8	380		>90–95% of dose		D0.1 ≤120 Gy EQD2 D10 ≤120 Gy EQD2 D30 ≤105 Gy EQD2 V150 = 0 cc	D2cc ≤75 Gy EQD2	
								No normal tissue constraints from ABS due to wide range of fractionation options [7]		

EBRT

Conventional and Hypofractionation

- Bowel prep.
- Supine.
- Comfortably full bladder.
- Immobilized w/custom thermoplastic casts.
- CT and MRI (3 mm) images obtained. No MRI for pacer or metal foreign bodies (orbital XR). MRI before Calypso placed.
- **For intermediate risk**, proximal 1 cm of SVs should be covered by CTV (per RTOG 0815).
- Definition of PTV:
  - Prostate +8 mm (except posteriorly)
  - Prostate +5 mm posteriorly
  - Proximal/distal SVs same as prostate
  - LNs → no margin
- CFRT: 75.6–79.2 Gy @ 1.8/fx, 80 Gy @ 2 Gy / fx.
- HFRT:
  - FCCC: 70.2 Gy @ 2.7/fx
  - MDACC: 72 Gy @ 2.4/fx.
  - 0415: 70 Gy @ 2.5/fx
  - Italy: 62 Gy @ 3.1/fx
- NCIC 52.5 Gy @ 2.63/fx
- No nodes/ADT for low risk
- On treatment:
  - Daily KV imaging if fiducials.
  - Daily CBCT if no fiducials. Align to PTV.

SBRT

- Fiducials for guidance.
- Contour prostate urethra (insert Foley if no MRI).
- GTV: prostate w/o SVs.
- PTV: GTV + 3 mm.
- D95 >100% prescription.
- Maximum point dose <120%.
- <15% of the PTV or <10 cc should be treated to >115% of prescription dose.
- Ratio of prescription isodose volume to PTV volume of <1.2.
- Volume outside PTV receiving >100% of dose should be <15% of PTV volume.
- Hot spots in CTV if possible.
- Urethra: maximum point dose 110%, V39.3 *Gy <20%*.

ADT

Studies

– Bria, 2009: meta-analysis of 7 RCTs, ADT improves OS 10%.

Hypothalamic-Pituitary-Gonadal Axis

– Hypothalamus makes GNRH, which is also called LHRH. LHRH is released in pulsatile matter, causing hypothalamus to release FSH and LH from pituitary. LH stimulates Leydig cells in testes to make T, which is then converted by 5-alpha-reductase to DHT.
– For men with BF after RT, should observe if PSA-DT is >12 months. Can start ADT if high absolute PSA level, PSA-DT <12 months.

Types of ADT

– **Castration**
– **GnRH analogue**
  – Goserelin (Zoladex) GnRH analogue/LHRH agonist induces hypogonadism by reducing the secretion of gonadotropin and therefore testosterone. 3.6 mg implant SC q28 days or 10.8 mg SC q12 weeks.
  – Leuprolide (Lupron) inhibits LH production, which in turn causes a suppression of testosterone and dihydrotestosterone, 1 mg SC qday, 7.5 mg IM q month, 22.5 mg IM q 3mos
– Triptorelin (Trelstar).
  – Toxicity: All analogues can cause initial T flare, followed by suppression. Hot flashes, bone loss, anemia, fatigue, decreased libido, impotence, decreased insulin sensitivity, dyslipidemia, increased BMI.
  – Increased risk of DM and CAD but no increase in cardiac deaths.
  – Get baseline bone scan.
  – All men should be started on vit D 1000 IU/d and Ca 1200 mg/d prophylaxis.
– **Antiandrogens**
  – Bicalutamide (Casodex). 50 mg po QD. Causes gynecomastia, hepatotoxicity, diarrhea. Check LFTs monthly; d/c if 2.5x ULN
  – Nonsteroidal antiandrogen: flutamide. 250 mg po q8 hours.
– **Estrogens**
  – Ketoconazole: blocks P450
  – Degarelix: GnRH antagonist, no initial flare
– **NCCN**
  – Up to 81 Gy permitted
  – +/− 4–6 m ADT unfavorable intermediate risk
  – + 2–3 yrs. ADT high risk

Postoperative EBRT

- Indications for **adjuvant RT**: pT3a/b, SM+. Always check PSA before RT.
  - Wait for urinary function to stabilize before starting RT. Once RT is delivered, urinary QOL is locked in place.
  - PSA half-life 2–3 days so must wait ~1 month before PSA will be undetectable post-RP.
- Indications for **salvage RT**: persistent or rising PSA post-RP (BF = >0.2 ng/ml on 2 separate PSA tests). "Early salvage" is recommendation for RT for *any* rising PSA, per updated Stephenson analysis. 5-yr FFBF was 56% overall, improved with RT was given with lower pre-SRT PSA level:
  - 71% for those with 0.01 to 0.2 ng/mL
  - 63% for those with a PSA of 0.21 to 0.50 ng/mL
  - 54% for those with a PSA of 0.51 to 1.0 ng/mL
  - 43% for those with a PSA of 1.01 to 2.0 ng/mL
  - 37% for those with a PSA >2.0 ng/mL

Workup
- MRI pelvis to determine gross LR.
- Bone scan if PSA >10.
- Do not use fiducials.

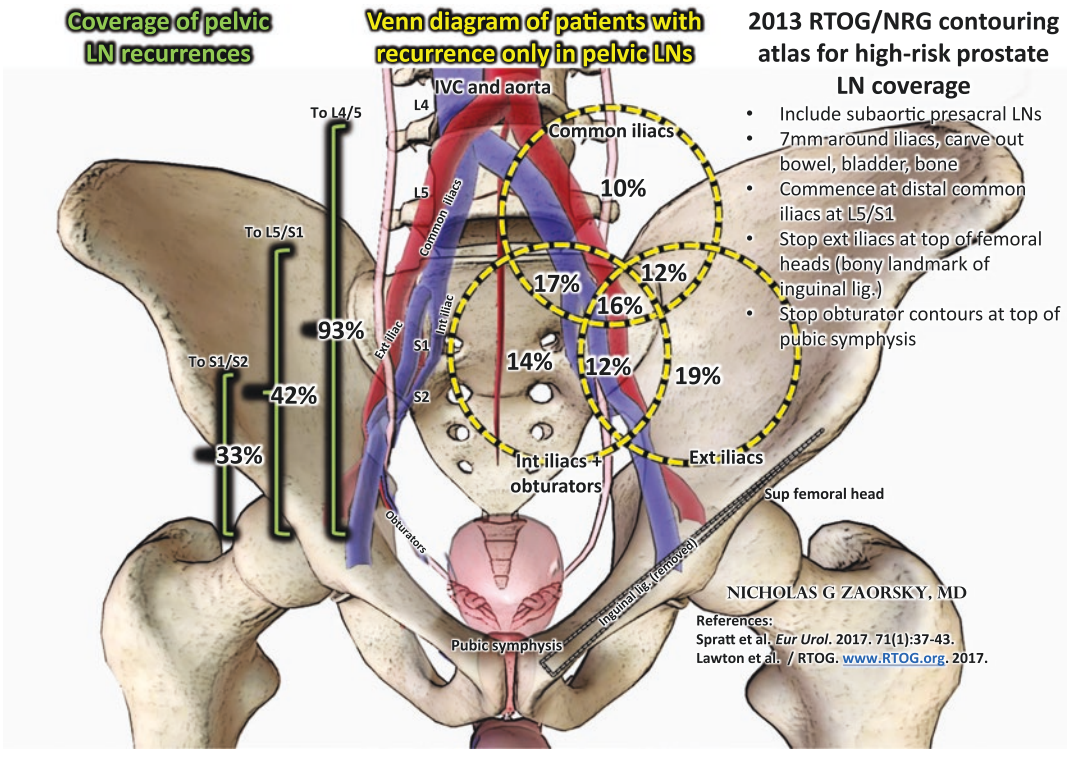
Simulation
- Full bladder (two cups an hour before) and empty rectum (have a BM before sim)
- Supine, arms on chest, in Aquaplast mold
- CT sim +/− PO contrast

Post-op Dosing
- 64–72 Gy @ 1.8-2 Gy/fx.
- Some physicians treat to 65–66.6 Gy in adjuvant setting and 66.6–72 Gy in the salvage setting.
- If gross local recurrence, then treat GTV to 74 Gy, standard-risk volume to ~68 Gy. All dose escalation trials went to 74–80 Gy for GTV.

Volumes, Michalski, 2010
- CTV extends sup from approximately the caudal vas deferens remnant to >8–12 mm inf of the UVA.
- **Superior**: level of vas deferens or 3 cm above pubic symphysis
- **Inferior**: 1 cm below VUA
- **Lateral**: obturator internus
- **Posterior**: rectum.
- **Anterior**: entire bladder below pubic symphysis and 1 cm of it superior to it.
- PTV = CTV +5–6 mm.
- Do not routinely cover pelvic LNs, unless LN+.
- Contour bladder, rectum, bowel, cord.

Constraints (RTOG 05–34)
- Rectum V65 <35% and V40 <55%.
- Bladder (defined as bladder – CTVp) V65 <50%, V40 <70%.
- Constraints relaxed because dosimetric relationship of volume exposed to marker doses is less clear, and bladder neck is in CTVp.
- Femoral heads: V50 <10%.
- Penile bulb: D90 <50 Gy to keep risk of severe ED <35%.

Post-op ADT
- Indications are unclear.
- High-risk features supporting ADT are short PSA-DT (<6–12 m), GS 8+, detectable PSA post-op, if PSA >0.7–1.5 ng/mL (continuous variable, see RTOG 96–01).
- Adjuvant setting, N0 = RT alone. Discuss risks/benefits of ADT.
- Adjuvant setting, N+ = RT + 24 months of ADT. Messing was lifelong ADT.
- Salvage setting, N0 = RT +/− 6–24 months ADT.
- Salvage RT, N+ = RT + 24 months of ADT.


Coverage of pelvic LN recurrences
To L4/5
To L5/S1
To S1/S2
93%
42%
33%
Venn diagram of patients with recurrence only in pelvic LNs
IVC and aorta
L4
L5
S1
S2
Common iliacs
Common iliacs
Int iliac
Ext iliac
10%
17%
12%
16%
14%
12%
19%
Int iliacs + obturators
Ext iliacs
Sup femoral head
Obturators
Inguinal lig. (removed)
Pubic symphysis
2013 RTOG/NRG contouring atlas for high-risk prostate LN coverage
• Include subaortic presacral LNs
• 7mm around iliacs, carve out bowel, bladder, bone
• Commence at distal common iliacs at L5/S1
• Stop ext iliacs at top of femoral heads (bony landmark of inguinal lig.)
• Stop obturator contours at top of pubic symphysis
NICHOLAS G ZAORSKY, MD
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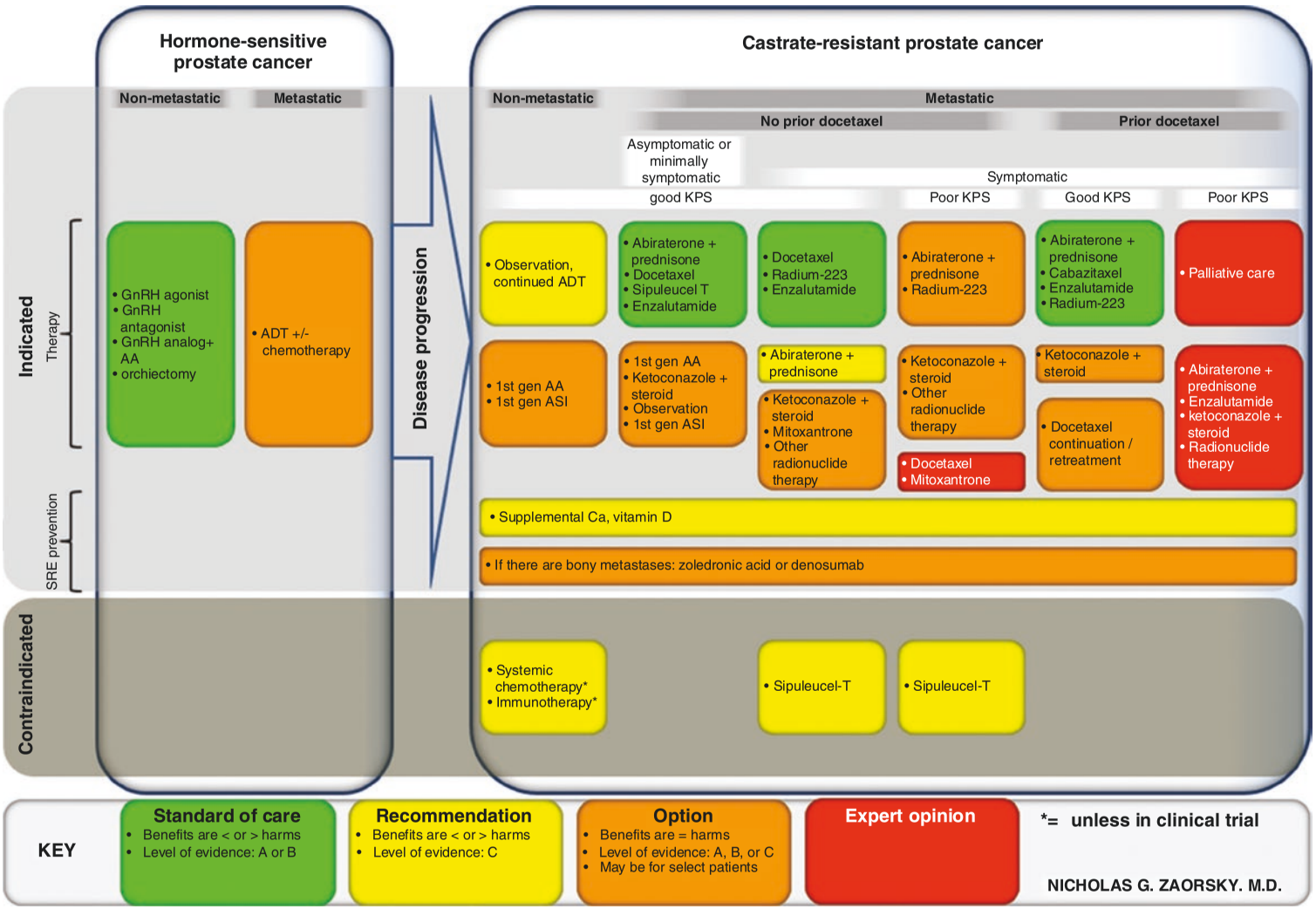
M+ Prostate Cancer Systemic Therapy

- **Metastatic**
  - First line: ADT
  - Second line: docetaxel/prednisone
    - SWOG 9916
    - TAX 327
  - ^{223}Ra (Alpharadin): bone only mets
    - 11.4d, alpha emitter, 5.8 MeV avg
    - 1000 kBq/ml, Rx is 50 kBq/kg Q4wks x 6 treatments
  - Requires
    - ANC $\geq 1.5 \times 10^9$/L
    - PLT $\geq 100 \times 10^9$/L
    - Hgb ≥ 10 g/dL

Rising PSA Systemic Therapy Options:



Low-Risk Studies [8–31]

Lifestyle

- Nobes, 2012: men on ADT randomized to metformin, low glycemic diet, and exercise. At 6 m, men had improvement in abdominal girth, weight, BMI, SBP. No difference in biomarkers of insulin resistance.
- SELECT: Screening study with men randomized to Vit E, selenium, or both. Men with Vit E and selenium had more aggressive prostate cancers.

RP Versus RT

- ProtecT, Hamdy, 2016. UK. Randomize between (1) active monitoring; (2) EBRT; (3) RP. Men 50–69 yo, mostly low risk, median age 62, median PSA 4.6, 77% GS6, 76% cT1c, 90% PSA <10, only 1% of patients nonwhite, 76% cT1c, the rest had cT2. At 10 y, no difference in PCSM (1%), OM (10%). AS more likely to have progression (20% vs 8%), DM (6% vs 2.5%). 55% of AS patients eventually got tx. No difference in RP vs EBRT. For urinary function, RP had worse impact on incontinence at all time points, but there was some recovery after 6 m. Voiding sx were worse with RT at 6 m but then returned to baseline by 1 y. Nocturia worsened in all groups, esp. in RT, but at 1 y was at baseline. Sexual function declined in all, but worse in RP; 12% of men had erections firm enough for intercourse, vs 22% in RT, and 52% in AS. Erections remained worse at all time points for RP group. In RT group number of erections for intercourse rose between 6–12 m, then seclined again to 27% at 6y. However, most of these men got 3–6 m of NA-ADT. Bowel function was worse only in RT group, pronounced at 6 m. QOL better in EBRT.

EBRT Trials

- Swedish Trial (Bill-Axelson): mixed group, RP vs WW: RP improves CSS, not OS. Before PSA-era.
- RP vs EBRT vs brachy (Kupelian 2004) ≈ 80% 5 yr. FFS (51% if <72 Gy).

Dose escalation trials: (↑ bPFS ~20%, no change in OS)

- PROG 9509, Zietman, 2005, 2010: 58% low risk, 37% intermediate risk, and only 4% high risk; 50.4 then proton boost to 70.2 vs 79.2 GyE. No ADT for anyone. 10 yr. bFail: *32 → 17%*. Salvage ADT in *11%* vs *6%*.
- MDACC (Pollack 2002, Kuban 2008, 2010): mixed risk, 205 low, 46% intermediate, 34% high. No ADT for anyone. 70 vs 78 Gy to isocenter; 8 yr. FFF 59 → 78%; CSS (97%) and OS (78%) unchanged. G2 rectal toxicity 26% vs 13%. G3 rectal toxicity 7% vs 1%.
- Peeters, 2006, Netherlands: 68 vs 78 Gy; 7 yr. bPFS 45 → 56%. Stratified by use of ADT.
- MRC, Dearnaley, 2007, 2014: All patients received ADT, neoadjuvant, 3–6 m before start of RT, and continued until end of RT. High dose won. 64 vs 74 Gy, 5 yr. bPFS 60 → 71%.
- GETUG: 70 vs 80 Gy; 5 yr. PSA failure 31 → 24%.
- Zelefsky, 2008. Retrospective. 3D CRT. n = 339 with post-tx biopsied after median time of 6.25 yrs. For intermediate-risk patients, if dose >75.6, then 24% positive biopsy; if <70.2, then 42% positive biopsies. For high risk, it was 33% vs 51%. For patients who did not get NA-ADT, 42% had +bx vs 16% who did get NA-ADT.

HFRT Trials

- CHHiP, Dearnaley, 2016: phase 3, non-inferiority. T1b-T3N0M0. n = 3216. Randomize to one of 3 tx regimens: 74/2 vs 60/3 (EQD2 ~77 Gy) vs 57.3 (EQD2 ~73 Gy). 5y FFBF similar, 97% among all. Worse acute bowel toxicity with hypofrac, 25% vs 38% vs 38%. Acute bladder toxicity similar between both fractionation regimens.

SBRT

- Kim, 2014. using 45–50 Gy/5 fractions for prostate cancer. 7% rectal toxicity. Recommend keep V50 <3 cc and V24 <50% circumference of rectal wall.

Intermediate-/High-Risk Studies [8–12, 18, 31–50]

SV Involvement

– Kestin, 2002: 7% of SV invasion extends >1 cm; only 1% extends >1 cm in low-risk patients RTOG 0815 recommends including prox 1 cm for intermediate-risk patients

High-Risk Chemo

– STAMPEDE (James, Lancet Onc, 2016): high-risk, LA, M1, or recurrent PCa get ADT +/− zolendronic acid, docetaxel, or both. 2:1:1:1 randomization. Docetaxel was 75 mg/m2 q3w × 6c with prednisolone 10 mg daily. OS improved for both arms with docetaxel by 10 months. G3–5 toxicity increased with docetaxel: 52% vs 32%.

ADT +/− RT

– Scandinavian (SPCG-***7***) : intermediate/high risk; ***3*** m ADT +/− ***7***0 Gy. RT was delivered using ***3***D CRT prescribed to central dose of 50 Gy. Boost was 20 Gy to prostate. 10 yr. FFBF ***7***5% vs 26%, a ***three***fold difference. OS 61 → 70%, CSS 76 → 88%.

BT Boost

– ASCENDE-RT: RCT of EBRT to 78 Gy vs EBRT + LDR-BT. EBRT was dose escalated, 46 Gy to pelvis, boost to 78. Both arms got 12 m ADT for intermediate- and high-risk patients n = 400. 9-y FFBF was better with CMT 83% vs 62%. However, there was worse G3+ late GU toxicity, 19% vs 5%, mostly urethral stricture.
– RTOG 0232, Prestige, 2006. Intermediate risk. cT1c-T2b GS 6 PSA 10–20 or GS 7 and PSA <10 rando to 45 Gy EBRT + LDR-BT boost vs BT mono. No difference in PFS, 85% for both arms at 5y. Acute G3 toxicity similar, 8% for both. Late G3 toxicity 12% for CMT and 7% for brachy alone.
– Hoskin, 2012: RCT in UK. 55 Gy/20 fx EBRT (non-dose escalated) vs 35.75 Gy/13 fx EBRT + HDR-BT 8.5 × 2. Improved DFS in boost arm.

Intermediate-Risk RT +/− ADT: Most Improve OS 5–10%

– RTOG 8610: high risk, T2–4 bulky dz., +/− cLN+; 70 Gy +/− 4 m ADT neoadjuvantconcurrent +/− additional 2y ADT; 10 yr. CSS 64 → 77%, ↓DM, ↑OS trend.
– RTOG 9408: intermediate risk. 68 Gy +/− 4 m ADT; 12 yr. OS 51 → 56%.
– Harvard/DFCI, D'Amico, JAMA, 2008: T1b-T2b and GS 7 dz. OR PSA >10 ng/mL OR ECE. mostly intermediate risk; 70 Gy +/− 6 m ADT, given as 2 m neoadjuvant, 2 m concurrent, 2 m adjuvant; 8 yr. OS 61 → 74% in the intermediate-risk group. (*13% difference!*) Men with no/minimum comorbidity had the most benefit. If mod-severe comorbidity, then worse survival, 25% vs 54%, though not SS. Findings being re-examined in RTOG 0815, which uses higher doses.
– TROG 96.01 (Denham, 2011): mostly high risk; 3 arms: 66 Gy +/− ADT (3 m, 6 m); DFS 32 → 49 → 52%, local progression 28% vs 16% vs 13% (NSS). ↑PCSM with ADT: at 10 y, 22% vs 19% vs 11%. 10y ↑OM: 42% vs 37% vs 29% (SS for 6 m). Thus, 6 m of NADT +66 Gy superior to 3 m for intermediate-and high-risk patients.
– Crook: mixed risk: 66 Gy + ADT (3 m vs 6 m); no differences (longer better for high risk).
– RTOG 9413: intermediate/high risk, 2 × 2 (+/− WP, neoadj/adj ADT): mixed data, no clear result.
– RTOG 0815. Ongoing. Dose escalated RT +/− ST-ADT for intermediate risk. Maximum dose in PTV is 107%, to volume at least 0.03 cc. minimum dose in PTV is >95% of prescribed dose. Hotspots 107–110 are acceptable. Coldspots 93–95 are acceptable.

High-Risk RT +/− ADT: Improves OS

– RTOG 8531, Pilepich, 2005: T3 or N+, non-bulky patients WP RT; 70 Gy +/− indefinite goserelin; 10 yr. OS 39 → 49% for GS 7–10.
– EORTC 22863, Bolla, 2010: cT1–2 WHO G3 or T3–4 any G with WHO PS of 0–2 randomized: WP RT 70 Gy, with 50 Gy to WP and

20 Gy boost to prostate) +/− 3 yr. goserelin. ADT started first day or RT and continued monthly injections for 3 y. Oral AA cyproterone 50 mg TID orally for 1 m prior to start of goserelin to prevent flare from T surge. 10 yr. OS 32 → 42%. PCSM 10 vs 30% LRF 6 vs 24%. FFDM 51% vs 30%.

ADT Duration

- RTOG 92–02, Hanks, 2003. cT2c-T4, PSA <150 ng. mL, KPS >70. Rando to 4 m goserelin and flutamide, 2 m before and 2 m during RT (65–70 Gy to prostate and 44–50 Gy to PLNs) with short-term ADT vs same RT + long-term ADT (additional 24 months, for a total of 2 y 2 m). 5-y DFS 28% vs 46%. DM 17% vs 11%. CSS 91% vs 95%. Local progression 12% vs 6%. All favored LTADT.
- EORTC 22961, Bolla, 2009: phase 3 non-inferiority. pT1c-T2a/b, pN1or2 M0 patients or cT2c-T4 N0–2 M0. PSA <40. All had high risk. WP RT; 70 Gy + 6 m vs 3 yr. ADT. The first 6 m of ADT was CAB wLHRH analogue on d1 of RT and AA agent, 750 mg flutamide/d or 50 mg bicalutamide QD, started 1w before LHRH analogue. 5 yr. OS 81 → 85% with 3 yrs. 5y PCSM 3% vs 5%, SS. Note good outcomes, long disease course.
- RTOG 9910, Pisansky: localized dz., intermediate and high risk. ADT 8w vs 28w before RT. Both groups get 8-week ADT during RT also, so really 16w vs 34w. No difference in DM, OS, CSS. Death was much lower than expected.
- DART 01/05, GICOR, Zapatero, 2015: RCT of intermediate- and high-risk patients to 4 vs 28 m ADT. There was an OS benefit to 28 m.

Salvage ADT?

- King (2004): Salvage RT +/− ADT; 5 yr. OS 87 → 100%, bPFS 31 → 57%.

Whole Pelvis RT?

- All failed to show a clear subgroup with benefit.
- RTOG 7706.
- RTOG 9413.
- GETUG-01.
- RTOG 09–24. Ongoing. ADT + RT +/− WPRT in unfavorable intermediate or favorable high risk. Total dose 79.2 Gy. Arm 1: 45 Gy to prostate and SVs, then 34.2 Gy to prostate and prox SVs. Arm 2: 45 Gy to prostate and SVs and whole pelvis, then 34.2 Gy to prostate and prox SVs. The WP volume goes to L4/L5, if feasible; if not feasible, then can go to L5-S1 or S3 to meet dose constraints to rectum. CTV = iliac vessels +7 mm margin in 3D, not extending outside true pelvis, into musculature, or organs. PTV = CTV + 0.5 cm minimum and 1.5 cm maximum.
- Spiotto, 2007. WPRT vs prostate bed RT after RP. 160 patients included. WPRT superior to prostate bed only in high risk, and only with concurrent ADT. No difference in low risk.

PA LN RT

- RTOG 7506, Hanks. 90 patients with pelvic LN+ treated with definitive RT. Randomize to pelvic vs pelvic + PA LN RT. 2% of patients were cured. 10y OS 29%. 10y NED rate of 7%.

Adjuvant/Salvage and Metastatic Prostate Cancer Studies [6, 8–12, 40, 51–62]

PSA Failure

- After RP: >/0.2 ng/mL rise with second confirmatory level detected at >/= 0.2 ng/mL.
- 1996 ASTRO definition: 3 consecutive rises, then backdated.
- 2005 Phoenix definition: rise of 2 ng/mL over nadir.
- This is the definition you should use.
- PSA bounce: ↑2 ng/mL ~12 m out (~20% risk).

Location of Failure Post RP

- Sella, 2004: 82 patients with endorectal coil MRI after RP. Sensitivity 95%, specificity 100%. LR at retrovesical space in 40%, peri-anastomotic site 29%, retained SV remnants 22%, ant or lat SMs 9%.

Adjuvant RT

- Definition = undetectable post RP PSA.
- Note GS 8–10 not enrollment criterion for any adjuvant or salvage RCTs.
- Note, all 3 RCTs treated prostate bed only, not pelvis.
- German ARO 96–02: pT3 N0 or + M, PSA 0. Note, the only RCT to require undetectable PSA. *n* = 385. rando: "wait and see" policy vs adj RT, 60 Gy; bPFS 54 → 72%, OS same.

"Adjuvant" but Really "Early Salvage" RT

- Definition = detectable post RP PSA.
- SWOG 8794: pT3 N0 or + SM; obs with salv RT vs adj RT; 15 yr. OS 37 → 47%, LF 22 → 8%.
- EORTC 22911, Bolla, 2005, 2012: criteria: cT0-3 N0 with either ECE, SVI (i.e., pT3a/b), or + SM. All patients <76 yo. RT within 16w of surgery. *n* = 1005. Randomize: obs with salv RT 60 Gy vs adj RT; 5 yr. bPFS 53 → 74%, OS same. LRFS same.

Salvage at Different PSAs

- Swanson analysis of 8794 (JCO <2007): all PSA levels (<0.2, 0.2–1.0, >1.0) benefit from adjuvant RT. Absolute reduction in 10y risk of BF 30%, LR 13%, DM 8% with postsurgical PSA ≤0.2. If >1, then 10y risk reduction for BF 6%, LR, 16%, DM 26%.
- King IJROBP 2012: systematic review, 41 studies, 5597 patients. PSA level pre-RT and RT dose independently associated with RFS. 2.6% decline in RFS for each 0.1 ng/mL increase in PSA at time of salvage RT.
- Stephenson, 2004: 501 patients got salvage RT at 5 U.S. institutions. Median Fu of 45 months, 50% had disease progression. On MVA, predictors of progression were GS8–10, pre-RT pSA >2 ng/mL, negative SMs, PSA-DT <10 m, and SV invasion.
- Tendulkar/Stephenson, 2016: *n* = 2460. Improved FFBF with lower pre-tx PSA. if <0.2, then 71%. If >2, then 37%. Same trend for DMs: if <0.2, then 10y DM rate 9%; if >2.0, then 37% DM rate.
- In the original nomogram, the trigger for adjuvant RT was PSA >0.2 ng/ml x2 or PSA >0.5 × 1.

Salvage RT + ADT

- RTOG 9601, Shipley, NEJM, 2017. *n* = 760. all post RP with LND, with elevated PSA of 0.2–4 ng/mL, pT3 N0 or pT2N0 with + SM. Randomize: (1) RT + ADT; (2) RT alone. RT was 64.8 in 36 fx. ADT was 24 m of Casodex 150 mg QD, during and after RT. Primary endpoint was OS. 10y OS was 76% vs 71%, SS. 12y FFMD 14% vs 23%, SS. 12y PCSM 6% vs 13, SS. Late adverse effects similar. Gynecomastia 70% vs 11%. Thus, addition of 24 m ADT to salvage RT improves all outcomes.
- GETUG-AFU 16, lancet Onc, 2016: 742 patients randomized to RT alone or RT + ADT. RT was 66 Gy. ADT was 6 m starting on d1 RT. ITT analysis showed improved PFS for RT + ADT 62% vas 80% for combo. ADT increased toxicity with hot flashes, sweating. No OS differences.

Node Positive

- Messing trial: pN+; RP +/− ADT. Immediate ADT FFBF is 7% vs 18% observation. 12 yr. MS 11.3 → 13.0 yrs.
- ADT was for life.

- RTOG 8531, Lawton, 2005: Subset analysis of N+ patients of 8531. 173 patients had pN+ dz. in this group 98 received RT + immediate goserelin, and 75 patients got RT alone with goserelin at relapse. 9 yr. OS 38 → 62%. 95 PFS 33% vs 4%. Thus, immediate ADT won.
- Abdollah, 2014: Milan + Mayo data. 1107 pN1 patients analyzed to determine benefit of aRT. All had RP + EPLND, then aRT within 90d. 35% received aRT. The CSS rate at 5y was 96% vs 82%, favoring CMT. 2 groups benefits (1) Patients with <3 + LNs and GS7–10 with pT3b/pT4 dz. or R+; (2) Patients with 3–4 + LNs, regardless of any other characteristics. Other patients (e.g., >5) did not benefit from aRT, suggesting extra-pelvic dz.
- Zagars, 2001. 255, retrospective. ADT vs ADT + RT. improves 10y OS, 46% vs 67%.

Gynecomastia Prophylaxis

Studies

– Perdona, 2005: tam vs RT for prevention of breast pain and gynecomastia during bicalutamide monotherapy. n = 151. Rando to 3 arms: (1) bicalutamide 150 mg QD; (2) bicalutamide 150 mg QD + tam 10 mg QD; (3) bicalutamide 150 mg QD + RT, one 12 Gy fraction when starting bic. In these arms, development of gynecomastia was 35/51, 4/50, and 17/50. Breast pain: 29/51, 3/50, and 15/50. Thus, both tam and RT reduce risk of breast pain and gynecomastia for men taking AA. RT good as tam alternative.

Regimens

– 4 Gy × 3 or 10 Gy × 1 with en face electrons prescribed to 85% IDL. 10 cm diameter circular block centered over the nipple. No bolus since skin not target.

Bladder Cancer [3, 8–12, 63–75]

Stage	Nodal risk	LR with cystectomy	5 yr OS
pT1	5%	<5%	88%
pT2	18%	10%	63%
pT3a	26%	30%	46%
pT3b	46%		
pT4	42%	50%	15%

- **Tis, Ta** – CIS, noninvasive, papillary
- **T1** – subepithelial
- **T2** – muscularis propria
  - T2a – inner half
  - T2b – outer half
- **T3** - perivesical tissue
  - T3a – microscopic
  - T3b – macroscopic
- **T4** – adjacent organs
  - T4a – prostatic stroma, uterus, vagina
  - T4b – pelvic wall, abd wall
- **N1**– 1 LN below common iliac
- **N2** – multiple LNs below common iliac
- **N3** – common iliac LN

AJCC8	Ta,Tis	T1	T2	T3	T4a	T4b
N0	0a,0is	I	II	IIIA		IVA
N1	IIIA					
N2, N3	IIIB					
M1	IV					

AJCC7	Ta,Tis	T1	T2	T3	T4a	T4b
N0	0a,0is	I	II	III	III	IV
N+	IV					

Overview

- Risk factors: smoking, dyes, irritation (Foley), chronic UTI, schistosoma, aromatic amines, prior pelvic RT.
- 93% TCC (5% SCC, 2% adenocarcinoma).
- 75% Ta, Tis, T1 at presentation.
- 20% T2
- 8% M+.
- 60% NMIBC will recur, and 15% of superficial will progress to MIBC.

Workup

- H&P: ask about smoking and work. Examine external genitalia (penis/testicular for males and rectal exam, pelvic exam for women), LN, CVA tenderness.
- Labs: CBC, CMP, *UA, alk phos*, *urine cytology.*
- Cystoscopy, biopsy, bladder mapping, EUA, TURBT+ random biopsies. Make sure you ask to assess for muscle invasion on TURBT path. If trigone/bladder neck → urethral biopsies.
- Check eGFR if planning cisplatin. Rule out hydro; stent if planning bladder preservation.
- Superficial: CT pelv + IVP to evaluate upper urinary tract (UUT) for synchronous lesions and evaluate LN.
- Muscle invasive: CT chest/abd/pelv +/− MRI.
- Increased alk phos or symptoms → bone scan.

Neoadjuvant Chemo and RT

- Chemo meta-analysis 2003: 5% OS advantage at 5 yrs. with multiagent cisplatin.
- Cole 1995: MDACC: pre-op 50/25 vs no pre-op therapy 5 yr. LC improved 72 → 91%, but nothing else.

Chemo Options

- Based on meta-analysis of RCTs, neoadjuvant *cisplatin-based* chemo is recommended because it confers a 5% OS benefit.
- **ddMVAC**: methotrexate, vinblastine, doxorubicin, cisplatin. dd is preferred over standard. Standard MVAC is q4w for 12 weeks total; dd-accelerated MVAC is q2weeks, 6 weeks total.
- **gem + cis** (4 cycles). Acceptable alternative to ddMVAC with similar PFS and OS, per Danish study,
- **CMV**: cisplatin, methotrexate, vinblastine.

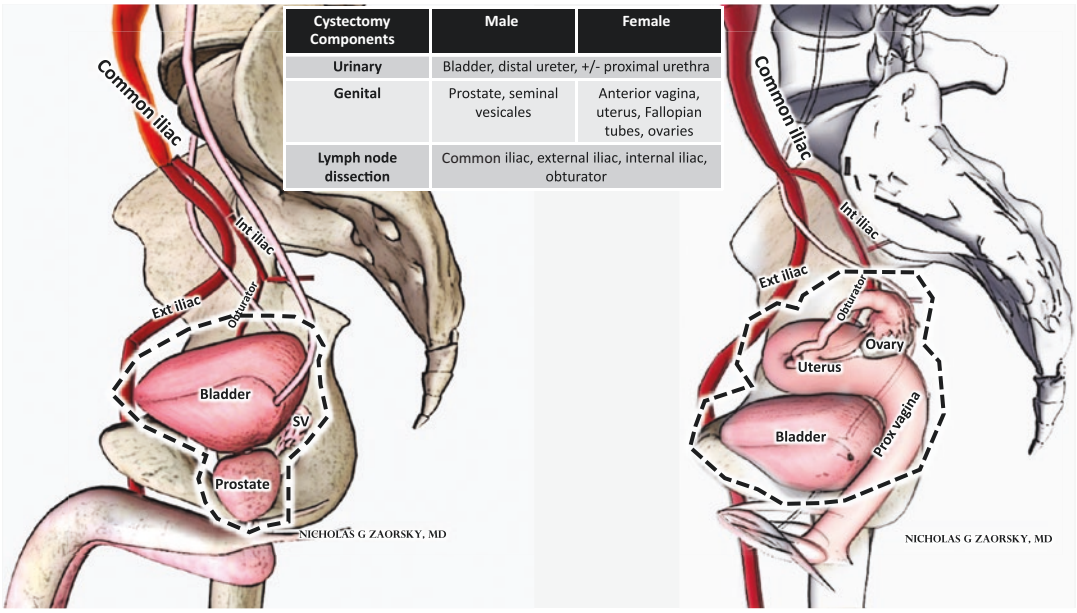
Cystectomy

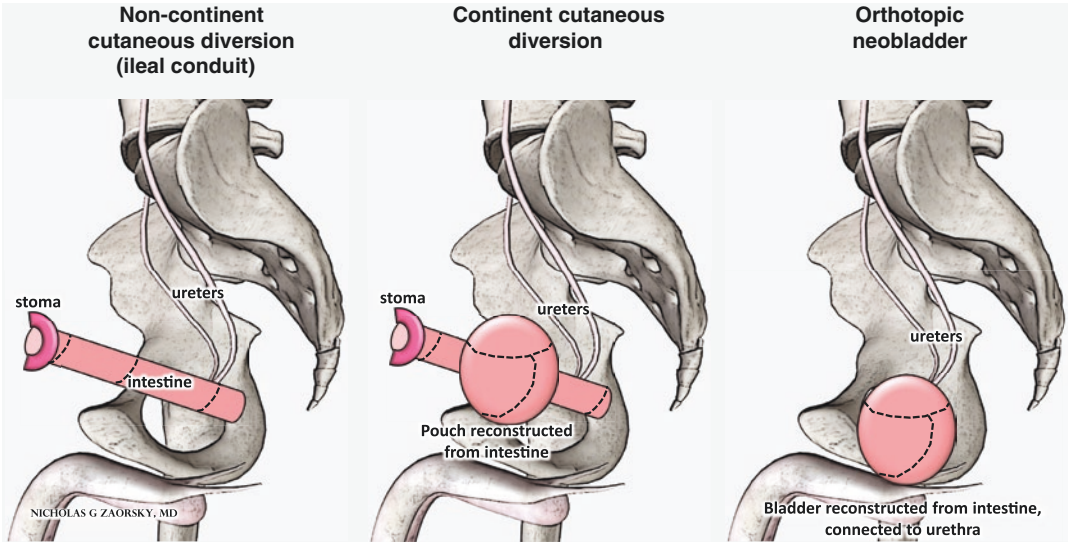
- Removal of bladder, urethra.
- Women: ant wall of vagina, uterus, fallopian tubes, ovaries, and surrounding fascia.

– Men: prostate, SVs, prox vas deferens, prox urethra, and margin of fat and peritoneum.
– PLND performed. pelvic LNs distal to common iliac bifurcation removed. Presacral LNs and common iliac LNs up to bifurcation removed.
– 42% upstaging and 6% downstaging following surgery.

Reconstructive Options Following Cystectomy

– Ileal conduit – conduit for urine to drain from kidneys, exteriorized via stoma through abdominal wall (continuous drainage of urine).
– Continent cutaneous diversion – Kock, Indiana, Miami pouch, low-pressure pouch from bowel segments connected to the skin require intermittent clean catheterization (no stoma needed).





– Orthotopic neobladders – internal reservoir connected to native urethra, rely on external sphincter for continence, constructed from the intestine, and anastomosed to urinary outflow tract.

Penn/SWOG post cystectomy risk groups for LRFS		
Stage	**Nodal Risk**	**5-yr LRFS**
Low	pT0 -2	8%
Intermed	pT3-4, R+ in soft tissue and 10+ LN dissected	20%
High	pT3-4, R+ in soft tissue and <10 LN dissected	>40%

Cystectomy Data

– Zehnder, 2011: USC + German pooled data. 5y RFS is 60% for pT2N0 dz.and 35% for pT3 dz.

Bladder Preservation Data

– NCIC Coppin 1996: T2–4: pre-op RT +/− cisplatin. Chemo ↓LRF but same OS.
– RTOG 8512: T2–4 N0–2: phase 2: RT 40/20 + cisplatin then restage and 24/12 for CR. 67% CR, 5 yr. OS 52%, LC 42%.
– RTOG 8903: 123 patients cT2–4aNx: RT 39.6/22 with cisplatin +/− neoadj MCV 2c. 25.2 Gy boost for CR (64.8 Gy). Stopped early (14% of MCV arm died). No change in CR, OS.
– RTOG 9506: 34 patients T2–4aNx: similar to prior. 3 yr. OS 83%, 66% intact bladder, 45% Tis failure.
– MGH Shipley 2002: same as RTOG 8903, 190 patients 5 yr. OS 54%, intact bladder 46%, hydronephrosis didn't matter.
– BC2001 (UK), James: phase 3 trial of concurrent chemo RT (5FU + mitomycin C) vs. RT alone. RT was 55 Gy/20 (40% of patients) or 64 Gy/32 (60% of patients) to bladder with margin. No ENI. However, adjacent LNs were likely in tx field given the technique. 5-FU was 500 mg/m2 CI fx 1–5 and 16–20; MMC was fx 1, 12 mg/m2. CRT improved LR DFS at 2 years (67% vs 54%), RFS 18% vs 32%, cystectomy rate 11% vs 17% ($p = 0.07$), trend to improve OS. Also 11% absolute improvement in DMs.
– RTOG 9906: same as others but BID RT and added paclitaxel concurrent and adjuvant gemcitabine. Same results.
– Mak, 2014: pooled analysis of 6 RCTs with bladder preservation, pCR was 69%.
– Advanced bladder cancer (ABC) meta-analysis, 2005: 11 RCTs with 3005 patients that compared NA chemo then local tx, vs local tx alone. Absolute OS benefit of 5% at 5 years (50% vs 45%).
– 5-year OS: T2 70%. T3–4 30%
– 5-year bladder preservation: T2 60%. T3–4 45%

Bladder Preservation Predictors of Poor Outcomes

– Hydronephrosis
– Tumor near ureteral orifice
– LNs near bifurcation
– Small bladder capacity
– >5 cm tumor
– Residual dz. post TURBT

NCCN

– **Tis**: bacillus Calmette-Guerin/BCG (alt: MMC, gem).
– **Ta**: observation or TURBT +/-BCG.
– **T1**: TURBT + BCG (upfront cystectomy for high grade). If residual, then BCG or cystectomy. Cysto Q3–6 months for first 2 yrs. CT if high grade.
– ***For Ta, T1, Tis, EBRT alone is rarely appropriate.***

– **Recurrence.**
– Repeat TURBT.

→ BCG x 6
→ if residual: cystectomy.
– Cytology only → mapping biopsies and ureteroscopy (could be UUT primary).

– **Stage II-III.**
  • Radical cystectomy (category I)
  • Partial cystectomy (small, dome, no CIS)
  • **Bladder preservation therapy (IIB)**
  • Chemo alone (MVAC or MCV)
– **T4b or N+:** chemo or CRT then surgery vs more RT.

Indications for Adjuvant RT
– R+ (primary)
– Positive soft tissue SMs
– N+

Relative Indications for Adjuvant RT
– Number LNs dissected (<10).
– pT3–4 (relative indication)

Failure Patterns Anatomic Regions
– If soft tissue R+: most likely in cystectomy bed and presacral region.
– If soft tissue R0: most likely pelvic sidewall.

Bladder Preservation Contraindications
– Tumor>5 cm, hydronephrosis, multifocal, poor bladder fx, carcinoma in situ (CIS), incomplete TURBT, non-TCC histology, M+ disease, near ureteral orifices

Bladder Preservation Technique
– Maximal TURBT (to negative margin)
– Bladder map from urologists, with biopsies from different parts of bladder to plan boost
– Review cystoscopy
– Pre-TURBT imaging
– Concurrent CRT or RT alone most successful if no hydronephrosis, no extensive CIS

Simulation
– Supine, arms on chest, in Alpha Cradle.
– CT sim with EMPTY bladder; second CT sim with FULL bladder.

3D-CRT (if Treating per MGH Regimen to Include Pelvic LNs)
– The minipelvis field will be treated with empty bladder, thus covering entire tumor/bladder. The comedown will treat just the tumor, avoid the bowel.
– Minipelvis (EMPTY bladder).
  • AP/PA: Sup = S1/S2; Inf = bottom of obturator foramen; Lats = 2 cm pelvic rim
  • Block medial border of femoral heads.
  • Laterals = 2 cm off anterior bladder/external iliacs (**front of PS**); 2 cm off post bladder/internal iliacs
  • Block small bowel, pubic skin, anal canal, posterior rectum
– CD (full bladder), try to treat with just laterals.
– CD = tumor bed +2 cm to field edge
– Minipelvis (4 field) to 39.6 + cisplatin (100 mg/m2) d 1 + 22 → rescope + urine cytology, if PR → cystectomy
– *"After completing 45 Gy minipelvis, I would request a restaging cystoscopy with directed and random biopsies. If invasive tumor anywhere or CIS at the original site, I would refer the patient for cystectomy. Otherwise, I would continue to 64.8 Gy using CD fields."*
– If CR → complete 45 Gy to whole pelvis
– CD (sim w/full bladder) to primary +2 cm margin to 64.8 Gy + additional cycle of cisplatin
– Cystoscopy w/ biopsies and cytology (75% CR)
– Boost to 60–65 Gy if no tumor remaining (T0 and neg cytology)

IMRT
– 60–66 Gy to whole bladder with IMRT using daily IGRT w/cisplatin 35-40 mg/m^2 weekly.
  • Note that treating bladder alone (no lymph nodes) is acceptable, per the UK MRC study.
– 55 Gy/20 fractions.

– **Adjuvant IMRT volumes:**
  • If treating LNs: hypogastric, o1bturator, intermediate/ext. iliac, perivesical, sacral,

presacral. For cLN+, the common iliac LNs are site of secondary involvement.
- If R+, all above, and cystectomy bed (i.e., everything below pubic symphysis).
- If N+, boost cN+ GTV to highest achievable dose.

Follow-Up

- Hx & PE, LFTs, Cr, lytes, chest imaging Q6–12 mo.
- Cystoscopy + urine cytology every 3–6 mo × 2 yrs., then increasing intervals
- Imaging of upper tracts, abdo and pelvis for recurrence every 3–6 mo × 2 yrs., then as clinically indicated

Late Effects

- Reduced bladder compliance (20%): chronic cystitis, hematuria (telangiectasia), contracted bladder
- Bowel urgency/rectal bleeding (25%)
- Impotence (50%)

Special Cases

- **N+ bladder cancer**. If N+ found at time of cystectomy, surgery is aborted! For cN+ disease, Gem/Cis → ChemoRT or surgery. 5y OS = 30%.
- **Hydronephrosis**. Surgery (or ChemoRT if not surgical candidate). 35% CR with bladder preservation (versus 70%).
- **Urachal:** Adenocarcinoma that involves the bladder and comes from enteric epithelium in embryonic tissue between dome of bladder and umbilicus. Treatment with surgery (cystectomy and take out the umbilicus). Post-op RT to bed to 60 Gy for positive margins. Adjuvant cisplatin/5-FU for positive LNs.

***Adjuvant* volumes**	**Components**	**Description from NRG-GU001**
CTV cystectomy bed Include if R+. Dose 54–60 Gy	**Sup**	2 cm above pubic symphysis
	Ant	Post of pubic rami/symphysis. Above and below, contour will stop at the planes defined by extending linesup and inf from the post aspect of symphysis
	Post	Abut the ant 1/3 of the external ano-rectal circumference w/o extending into anorectum. Above the level of rectum, stop posteriorly at plane defined by line going superior from ant border of rectum
	Lat	Medial border obturator internus muscles. Inferiorly, it is at the vaginal wall or prostate bed
	Inf	2-3 mm (1 axial CT slice) above the penile bulb for males, 1 cm below lower pole of obturator foramen for females.
CTV LNs		Trim LNs at pelvis, muscle, bone Do not trim at bowel bc risk of marginal miss LN CTV mirror high-risk prostate LN CTV
	Pelvic LNs: Always include (R0 or R+) R0: 45–50.4 R+: 54–60	**distal common iliac, internal iliac, external iliac, obturator** Sup at L5-S1 Externals iliacs extend inf to top of femoral heads Int iliacs extentinf until no longer visible, or exit through greater sciatic notch Expand by 7 mm in ant, post, lat dimensions
	Presacral LNs: Include if R+ 54–60 Gy	From L5-S1 to S2-3. Include 1-1.5 cm of tissue ant to sacrum and between vessels Sup at inf border of iliac contours Inf at top of pubic symphysis 1 cm width of tissue medial to obturator internus muscles, from ant border or ilium to post border or ilium
OARs	**ostomy bag**	for patients with non-continent diversions sim and treat with empty bag
	Bowel	entire bowel space, inc bowel, cecum, colon. sup at 3 cm above sup extent of LN CTV
	Rectum	from RS junction sup to level of iscial tuberosities inf
	Pelvic bones	Start 1 cm sup above nodal CTV and go 1 cm inf of CTV

Transitional Cell Carcinoma (TCC)/ Urothelial Cell Carcinoma (UCC) [76]

Ta: papillary, noninvasive
Tis
T1: subepithelial connective tissue
T2: muscularis
T3: into fat or renal parenchyma (for renal pelvis)
T4: adj organs
N0: none
N1: 1 regional LN, ≤ 2 cm
N2: 1 regional LN, 2 - ≤5 cm, or 2+ LNs all ≤5 cm
N3: 1 LN >5 cm

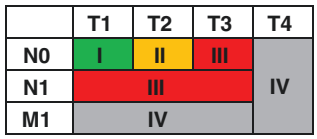
Stage I: T1
Stage II: T2
Stage III: T3
Stage IV: T4 or N+ or M+

Treatment

- Surgery.
- For pT2–4 or pN+, adjuvant chemo recommended.
- Primary indication for RT is R+.
- RT should include primary tumor bed and entire length of ureter.
- Ureter goes from renal fossa to the trigone to ipsi bladder.
- Dose is **45–50.4/1.8.**
- Boost GTV to **54–60 Gy**, if OAR constraints met.

Renal Cell Cancer (RCC) [8–12, 77–84]

- **T1** – ≤7 cm, kidney only.
  - T1a – ≤4 cm.
  - T1b – 4-7 cm.
- **T2** – >7 cm, kidney only.
  - T2a – 7-10 cm.
  - T2b – >10 cm.
- **T3** – into major veins or perinephric tissues.
  - T3a – into renal vein or perirenal fat.
  - T3b – into vena cava below diaphragm.
  - T3c – into vena cava above the diaphragm or wall of vena cava.
- **T4** – invades Gerota's fascia.
- **N1** – renal hilum, caval (para-/pre-/retrocaval), interaortocaval, aortic (para-/pre-/retroaortic).



Overview
- "RCC" refers to tumors arising within renal ctx, as opposed to renal medulla or pelvis
- 60 K/year, 13 K deaths/y in the USA.
- M > F.
- 5y OS: I = 81%, II = 74%, III = 53%, IV = 8%
- Genetic conditions: VHL (for clear cell RCC), Dirt-Hogg-Dube syndrome, tuberous sclerosis, met proto-oncogene.
- Sporadic RCC: mutation in the VHL tumor suppressor gene on 3p25.
- Classic triad: hematuria, flank pain, mass.
- Paraneoplastic syndromes (20%): ↑Ca, HTN, ↑LFTs.
- Pathologic subtypes: clear cell (70%), chromophilic, chromophobic, collecting duct.

Renal Neoplasms
- RCCs are 90% of primary renal neoplasms.
- Oncocytoma: benign, 5% of primary renal neoplasma.

RCC Subtypes
- Clear cell: 80%, typically 3p deletion, assoc. with VHL
- Papillary or chromophilic: 10%
- Chromophobe: 5%
- Collecting duct: <5%
- Renal medullary: rare, aggressive. Associated with sickle cell dz.

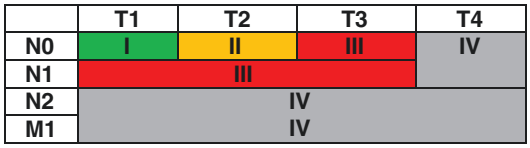
Workup
- H&P, CBC, CMP with corrected calcium, Cr, LFTs, CT chest/abd/pelv, urinalysis.
- If dye cannot be given or if there is IVC involvement, then abdominal MRI should be performed.
- No role for PET. Low sensitivity but high specificity.
- Cytology, cysto, ureteroscopy.
- CT or MRI brain only if suggested M+, sx.
- LDH in M+. LDH is prognostic and predictive.

Select Trials
- Four randomized trials show no benefit to PORT (Rotterdam, Sweden, Fugitt, Kjaer).
- Stein 1992: 147 patients, PORT vs obs: in T3 N0 patients, PORT won. LR 37% → 10%.
- Escudier/AVOREN: stage IV RCC given IFα +/− Avastin. Avastin doubled PFS (5 → 10 months).
- Escudier/TARGET: treatment-resistant RCC +/− sorafenib. Sorafenib doubled PFS (2.8 → 5.5 mo).
- Motzer, 2007: metastatic RCC: sunitinib vs IFα, sunitinib won.

NCCN
- **Local disease**: surgery (no radiation). If R0, then AS. CT or MRI in 6 m and then imaging q12m.
  - **PORT**: controversial. Consider for +SM, + LN
- **Metastatic disease**: surgery (palliative nephrectomy), sunitinib (multi-TKI), temsirolimus, bevacizumab and IFN, interleukin-2, sorafenib (Multi-TKI).

Urethral Cancer [8–12, 85–88]

- **Ta, Tis** – noninvasive papillary, polypoid, or verrucous carcinoma
- **T1** – subepithelial
- **T2** – spongiosum, prostate, periurethral muscle
- **T3** – cavernosum, EPE, ant vagina, bladder neck
- **T4** – adj organs (including bladder)
- **N1** – single, below common iliac
- **N2** – multiple below common iliac or a presacral node



Anatomy

– Epithelium transitions from squamous (outside) to pseudostratified to transitional cell
– Most common site in men: **bulbomembranous** (~60%)

Workup

– H&P, labs, *UA*, *alk phos*, *urine cytology.*
– Cystoscopy, biopsy.
– MRI pelvis, chest imaging.
– T2–3 is most common. 15% of all patients with DMs.

Male Early Stage

– Surgery: MSKCC (Dalbagni 1999): Tis-T1, 10 patients, surgery only 5-yr. DFS 83%
– RT: (Heysek 1985): 5 patients, LC in 4/5

Male Locally Advanced

– Surgery: MSKCC (Dalbagni 1999): T2-T4, 36 patients, surgery only 5-yr. DFS 45%.

Female

– After pelvic exenteration: 5-yr. OS 20%, LF 66%
– RT alone: 5-yr. OS 75% early stage, 34% advanced stage (Kreig 1999)
– RT alone approach: 50–60 Gy brachy alone or EBRT (45 Gy) + 20–25 Gy brachy

Concurrent Chemo

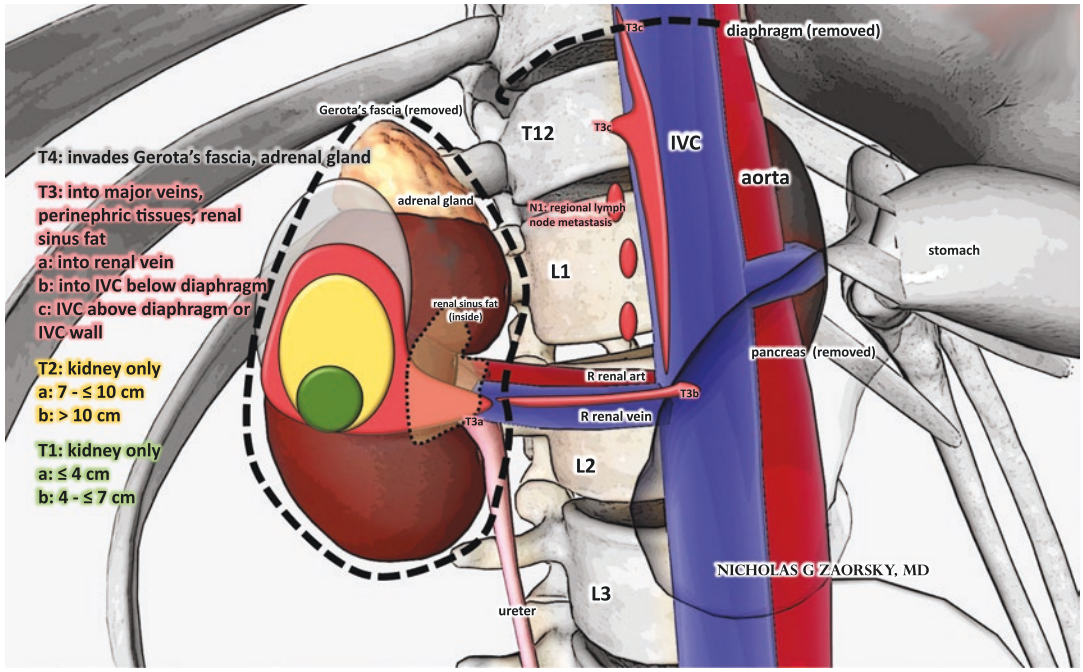
– Only case reports, consider 5FU/mitoC, 5FU/cisplatin, carbo/taxol (Eng 2003).

RT

– Prostatic only involvement: treat similar to prostate
– Non-prostatic: parallel opposed fields covering groin and pelvis with perineal and inguinal boost

NCCN

– Tis/Ta: TUR
– T1–2: surgery +/− PORT or chemoRT (66–70 Gy)
– T3-T4 or N+: chemoRT


T4: invades Gerota's fascia, adrenal gland
T3: into major veins, perinephric tissues, renal sinus fat
a: into renal vein
b: into IVC below diaphragm
c: IVC above diaphragm or IVC wall
T2: kidney only
a: 7 - ≤ 10 cm
b: > 10 cm
T1: kidney only
a: ≤ 4 cm
b: 4 - ≤ 7 cm
Gerota's fascia (removed)
adrenal gland
renal sinus fat (inside)
T12
L1
L2
L3
T3c
T3c
IVC
aorta
diaphragm (removed)
N1: regional lymph node metastasis
stomach
pancreas (removed)
R renal art
T3b
R renal vein
T3a
ureter
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Testicular Cancer/Seminoma (SGCT)/NSGCT [8–12, 89–108]

- **T1** – testis (including rete), epididymis, no LVSI, no vaginalis. AJCC8 has size breakdown: T1a is ≤3 cm. T1b is >3 cm.
- **T2** – T1 + LVSI or vaginalis (i.e., beyond albuginea).
- **T3** – spermatic cord.
- **T4** – scrotum.

– **N1** – N+, all ≤2 cm (no more than 5 total pN+).
– **N2** – N+, all 2 - ≤5 cm (or more than 5 pN+, or ECE) (this is "bulky" for NSGCT).
– **N3** – N+, >5 cm (this is "bulky" for SGCT).

- **M1a** – non-regional nodes or lung mets.
- **M1b** – distant.

- **S0** – normal serum markers (ALL POST ORCHIECTOMY).
- **S1** - LDH <1.5 ULN AND hCG <5000 AND AFP <1000.
- **S2** – LDH 1.5–10 ULN OR hCG 5000–50,000 OR AFP 1000–10,000.
- **S3** – LDH >10 ULN OR hCG >50,000 OR AFP >10,000.

Note no Stage IV for testicular cancer.

	T1	T2	T3	T4	10 yr
Any pT N0 M0 S1-3	IS				
N0	IA (S0)	IB (S0)			98% RFS
N1	IIA (S0-1)				92% RFS
N2	IIB (S0-1)				86% RFS
N3	IIC (S0-1)				70% RFS
M1a	IIIA (S0-1, any N)				90% OS
N+ S2	IIIB				
N+ S3	IIIC				80% OS
M1b					

S–Staging from International Germ Cell Consensus

Stage	normal	Half-life	S1	S2	S3	Units	Tumor	Can be elevated by
LDH	1		<1.5	1.5-10	>10	ULN		
hCG	<5	22–36h	<5K	5K–50K	>50K	mIU/mL	GCT > NSGCT	THC, reagent cross-reaction with LH
AFP	6	5–7d	<1K	1–10K	>10K	ng/mL	NSGCT. Never GCT.	HCC, cirrhosis, hepatitis
Need to have…			all	any	any			
Stage with N0			IS	IS	IS			
Stage with N+				IIIB	IIIC			
Needed for risk group			M0	M0	M1			
Risk group			Good (need all above)	Intermed (need all above)	Poor (need ANY above)			

Overview
- Lymph flows to PA nodes (left vein drains to renal vein).
- 95% GCTs (seminomas/NSGCTs).

DDx
- Benign: hydrocele, spermatocele, varicose veins, epididymitis
- Malignant: seminoma, NSGCT, lymphoma

Subtypes
- **Seminoma** (60%): beta-human chorionic gonadotropin (bHcG) can be ↑ (15%) but *NEVER AFP*
- **NSGCTs** (30%; ↑↑↑ aFP [produced by yolk sac], BHCG).
  - Mixed (60%)
  - Embryonal carcinoma (20%)
  - Yolk sac (↑AFP, Schiller Duval bodies)
  - Choriocarcinoma (↑↑↑bHcG)
  - Teratoma
- Others.
  - Sertoli cell: ↑estrogen
  - Leydig cell: ↑androgens
  - Lymphomas, sarcomas
- Mixed GCT/NSGCT

Seminoma	NSGCT
Solid	Cystic areas
Hypoechoic	Calcifications within tumor
Clear margins	Ill-defined margins
Homogeneous	Heterogeneous

Risk factors: cryptorchidism, first born, polyvinyl chloride, Downs, Klinefelter's, HIV

Workup: H&P, sperm banking?, Human chorionic gonadotropin (bHcG), alpha fetoprotein (AFP), lactate dehydrogenase (LDH), labs, CT abd/pelv +/− chest, +/-PET. Do not biopsy. Ask about prior pelvic surgeries bc of altered lymphatic drainage. Consult surgery for inguinal orchiectomy and high spermatic cord ligation. Type of surgery is a prognostic factor for relapse. Trans-scrotal orchiectomy not recommended due to possible seeding of scrotum and inguinal LNs.

Stage I Seminoma Observation Studies
- PMH (Warde 1995): Obs vs RT. stage I seminoma 1981–1991. $n = 364$. randomized to RT vs obs. Obs arm: 5 year *RFS 82%*. RT arm: 5 year RFS 95%. Only 1 patient died of seminoma, so CSS was 100%.
- Danish, Daugaard, 2003: 394 patients observed. 17% had relapses. Median time tor elapse 13 months. No deaths from seminoma.
- Kollmannsberger, 2010. Canada+Sweden. $N = 2483$ stage I on AS. Relapse in 19% of non-seminoma and 13% for seminoma patients. >90% of relapses in first 2 years.
- Third Spanish GC Group (Aparicio, 2011): $n = 227$. Patients with 0–1 RF observed. Patients with 2 RFs get 2c carbo. 10% of Group 1 had relapse vs 1% in carbo group. All but one of the relapses was in the RP LNs. 3-year DFS was 88% for surveillance vs 98% for carbo. 3-year OS 100%. Based on recent analyses, risk-adapted tx recommended. NCCN testicular panel discourages using 4 cm cutoff and rete testis invasion to guide management bc they have not been validated.

Stage I Seminoma Treatment Studies
- Norway MRC (Fossa 1999): RT field. stage I seminoma 30/15. Patients rando to PA only or PA + ipsi iliac (dogfield). Sup border was *T10/11*; inf border was mid obturator foramen. Ipsi margin was renal hilum down to *L5/S1*. Contra margin was transverse processes. 3-yr. RFS/OS same (~98%) and PA better tolerated for heme toxicity (leukopenia 42% vs 19%) and diarrhea (7% vs 14%). With DL, 92% had normal sperm count in 3y. Thus PA became SOC for stage I.
- Germany, Bruns, 2005. Where should we place sup border? No increased relapses when T11/12 used. Thus, it became SOC per NCCN.
- RT dose: MRC (Jones 2005): stage I seminoma, 20/10 vs 30/15. Mostly PA only. 5 yr. RFS same (~97%).
- MRC/EORTC TE 19 (Oliver 2005): 3:5, carbo vs RT. Carbo was AUC 7 × 1 c. RT was 20–30 Gy either PA (87%) or dog leg (13%). This was a non-inferiority trial. RFS same (~95%). Relapse location varied but chemo better tolerated. Rate of contra GCTs was reduced, $n = 2$ vs $n = 15$, $p = 0.03$.
- Pooled analysis of four RCTs for prognostic factors (Warde, 2002): stage I seminoma. (1)

Tumor size >4 cm and (3) rete testis invasion identified as risk factors.
– Chung, 2010: validation study of the 2 RFs: rete testes involvement did not predict relapse.

NCCN
– *All patients: radical transinguinal orchiectomy with high ligation of the spermatic cord (never biopsy), then repeat tumor markers. LNs not routinely dissected unless it is NSGCT.*
  • General options: surveillance (NCCN preferred); adjuvant RT (20 Gy to RP/PA LNs), adjuvant single agent chemo.
– Risk factors of recurrence: size >4 cm.
– **Surveillance**: At 15 yrs., 20% may relapse, <1% CSM.
– **Follow-up studies:**
  • **AFP, b-hCG, LDH** – q3–4 mo years 1–2, q6–12 mo years 3–4, then annually.
  • **CT abdo/pelvis** – q6 mo years 1–2, q6–12 mo year 3, annually yr. 4–5.
  • **CXR** as clinically indicated.
– High-risk features for recurrence: LVI+, size >4 cm, hCG >200 IU/L.

Counsel
– Fertility and sperm banking (per above)
– Surveillance (per above)
– Second malignancy: 36% vs 23% in general population. RR = ~2 for RT, chemo, or combination
– **Long-term effects of treatment:**
  – CV disease HR = 5.3 with CRT, HR = RT alone, HR = 1 for surgery alone.
  – Metabolic syndrome: 17% for CRT vs 10% for carbo or surg.
  – Duodenal ulcer: 5% risk if orchiectomy.
  – Bleo-induced pneumonitis in 10–20%, of those 10% die.
  – Non-fatherhood with RT: 18%.
  – Nephro-/neurotoxicity with cisplatin.
  – Risk of contralateral cancer: 0.1% per year.
  – Wait 1 year to have kid.
  – 50% have azoospermia at diagnosis
  – Only 30% can have kids.

Adjuvant Seminoma

– **I**: Obs* (13–16% LRF) or 20 Gy PA or carboplatin AUC 6. CSS is 99% for all! Previously, rete testis invasion and tumor size >4 cm were risk factors for relapse; since 2010, these are no longer used.
– For observation. HP q 3–6 m, CT at 3,6,12 m.

– **Stage I seminoma RT:**
– **PA field** is **T11/12** (note, lower than Fossa/MRC trial) to **L5/S1,** laterally through transverse process (~2 cm margin on nodes).
– For a right-sided tumor, includes paracaval, precaval, and interaortocaval LNs.
– For a left-sided tumor, include the above plus at least the latero-aortic and preaortic LNs.
– CTV = (IVC + 1.2 cm) + (aorta +1.9 cm).
– PTV = CTV + 0.5 cm. A 0.7 cm uniform margin around PTV to block edge accounts for penumbra.
– AP-PA, never IMRT
  • for a left-sided tumor, include the above plus *at least* the lateroaortic and preaortic LNs and include left renal hilum.

- **IIA**: 20 Gy* (dogleg+boost GTV to 30) or cis/etop x2c
  - Prior CTV for PA LNs for a stage I.
- Note modified dogleg I used for N+ seminoma.
- **IIB**: Cis/etop x2c is preferred OR 20 Gy (dogleg+boost GTV to 36) if LN is <3 cm.
- Contour the ipsi common, external, and proximal internal iliac veins and arteries down inferiorly to the upper border of the acetabulum.
- **Dogleg**: PA field but down to mid-obturator foramen (near top of acetabulum). 20/10, boost IIA nodes to 30 Gy, IIB nodes to 36 Gy.
- CTV = PA CTV + 1.2 cm vessel expansion, exclude bone and bowel.
- CTV boost = GTV + 0.8 cm, exclude bone and bowel.
- PTV = CTV + 0.7 cm to block edge
- D50 <8 Gy for each kidney.
- **IIC-III**: chemo (cis/etop +/− bleo) x 3 cycles.
- **Adjuvant NSGCT**: RT palliative only.
  - **I:** obs (30% LRF) vs RP-LND (30% path +) vs cis/etop/bleo x 3c (usually chemo not recommended).
  - **II:**
    - **pN1:** Surveillance preferred bc 60–90% of patients are cures with RPLND alone. If there is a low LN burned and the serum markers normalize after surgery, then observe; if not, then consider 2c EP or BEP.
    - **pN2:** 2c EP or BEP.
    - **pN3:** 3c EP or BEP.
  - **IIIB or IIIC:** BEP x 4 c.

Positive tumor markers after surgery → chemo

Technique, Other Considerations

- Supine, arms down, in Alpha Cradle.
- Position penis out of filed, place clamshell.
- Clamshell is a scrotal shield used to block the remaining testicle from internal + external scatter.
- CT sim WITH IV CONTRAST to delineate vessels.
- Start at 6 weeks after wound healed.
- **Use AP/PA, do not use IMRT bc there will be increased low dose spill with IMRT.**
- 2 cm margin on GTV nodes to block edge

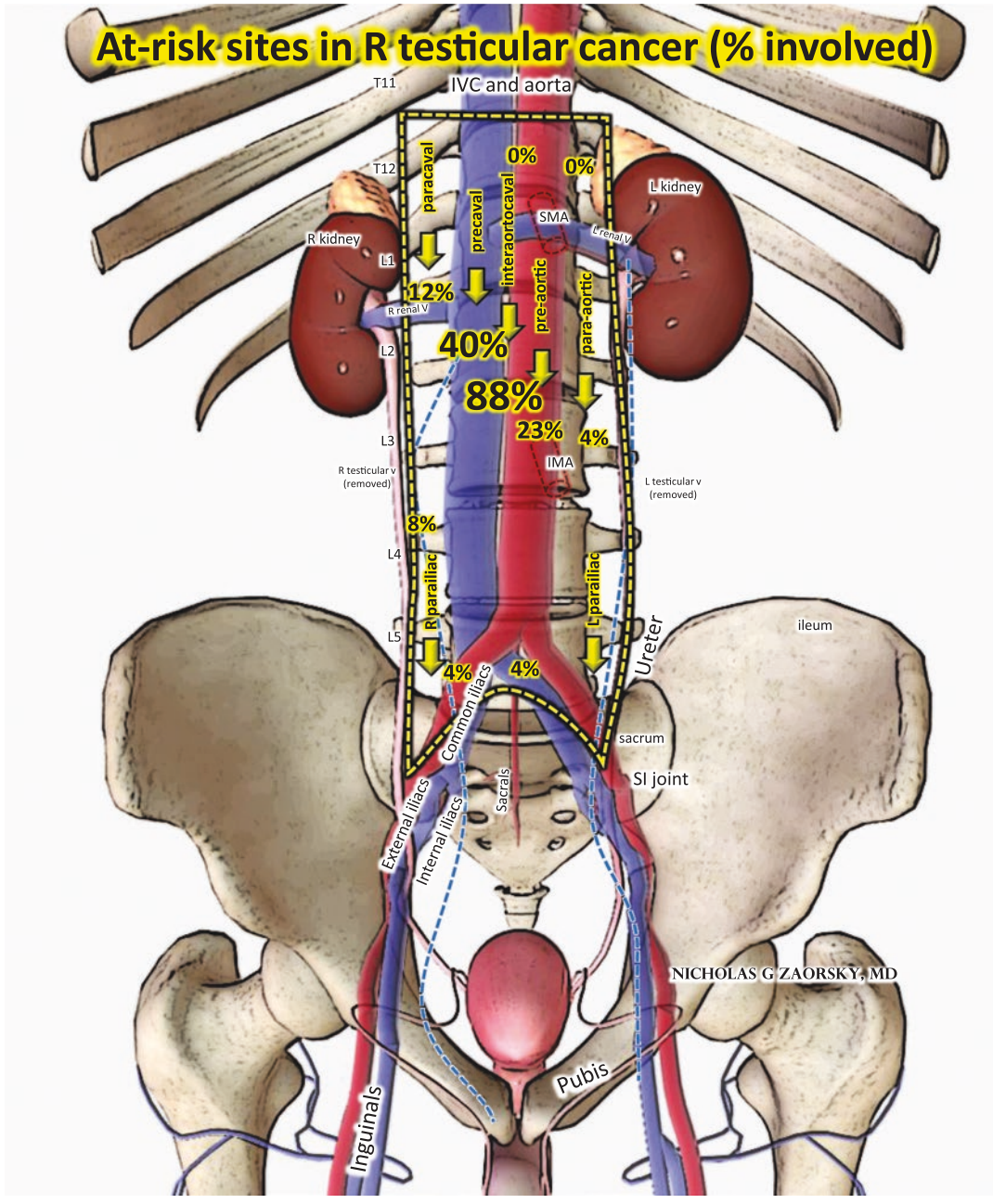
	Doses to remaining testicle	
Treating	without shield	with shield
PA	2 cGy/fx	0.7 cGy/fx
PA+ ipsi iliacs	4 cGy/fx	1.5 cGy/fx

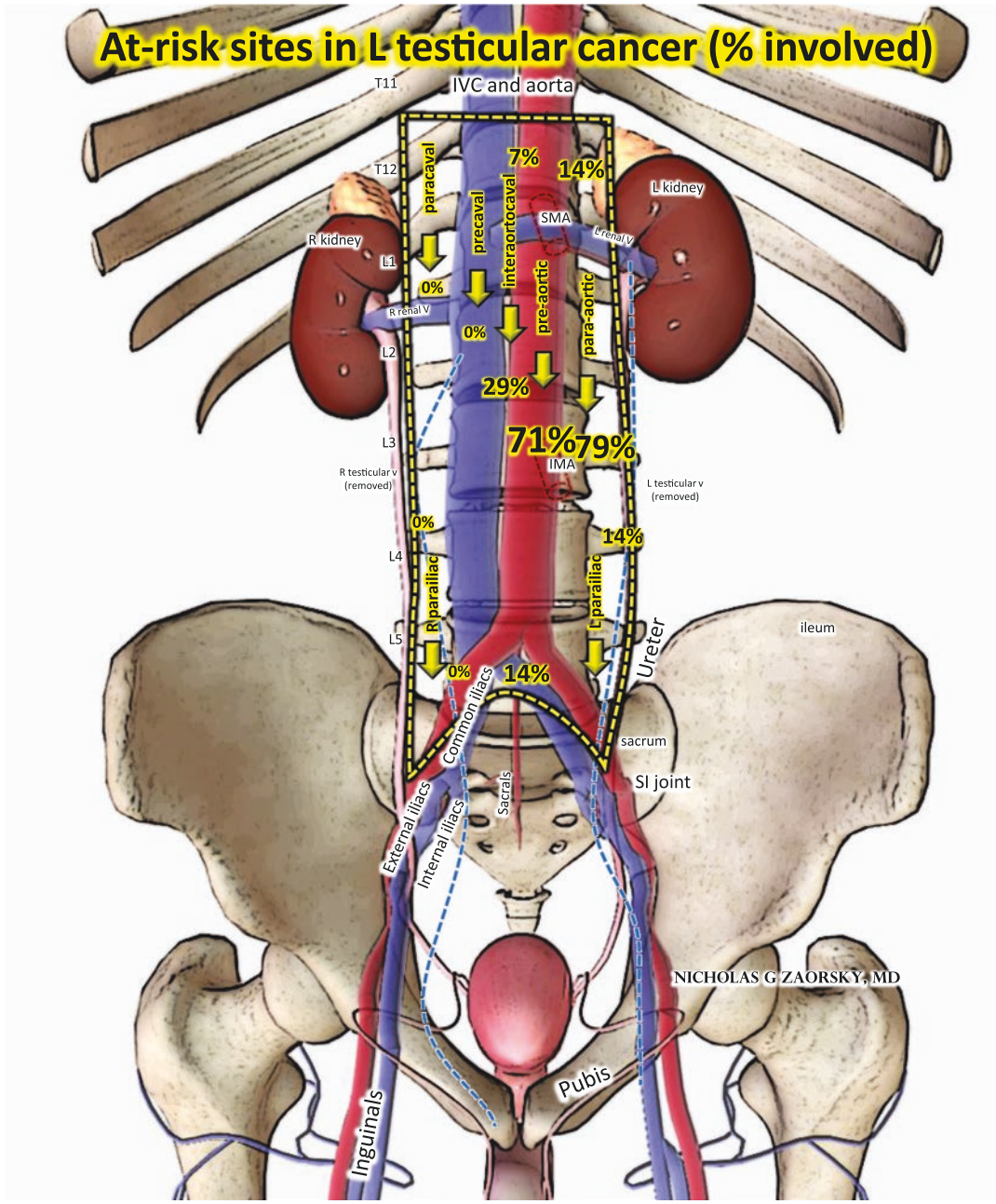
Contraindications to RT

- Horseshoe kidney – kidney overlaps with regional LNs targeted. RT would cause nephritis in 50% of cases. Further, standard RT fields may not cover sites of potential relapse. Recommendation for stage I dz. is surveillance. RPLND is an option if patient declines surveillance. For stage II, recommendation is BEP x3 of EP x4.
- IBD.
- Previous RT to abd or pelvis.

Dose Constraints

- 50 cGy: transient azoospermia
- 2 Gy causes sterilization
- 30% of patients are fertile after RT
- Kidneys: D50% <8 Gy.
- If only 1 kidney, D15% <20 Gy.


At-risk sites in R testicular cancer (% involved)
T11
IVC and aorta
T12
paracaval
precaval
interaortocaval
0%
0%
L kidney
SMA
L renal V
R kidney
L1
12%
R renal V
pre-aortic
para-aortic
40%
L2
88%
23%
4%
L3
IMA
R testicular v (removed)
L testicular v (removed)
8%
L4
R paraliliac
L paraliliac
L5
ileum
Ureter
4%
4%
Common iliacs
sacrum
SI joint
Sacrals
External iliacs
Internal iliacs
NICHOLAS G ZAORSKY, MD
Pubis
Inguinals


At-risk sites in L testicular cancer (% involved)
T11
IVC and aorta
T12
paracaval
precaval
interaortocaval
7%
14%
SMA
L renal V
L kidney
R kidney
L1
0%
R renal V
pre-aortic
para-aortic
0%
L2
29%
L3
71%
79%
IMA
R testicular v (removed)
L testicular v (removed)
0%
14%
L4
R paraaliac
L paraaliac
L5
Ureter
ileum
0%
14%
Common iliacs
sacrum
SI joint
Sacrals
External iliacs
Internal iliacs
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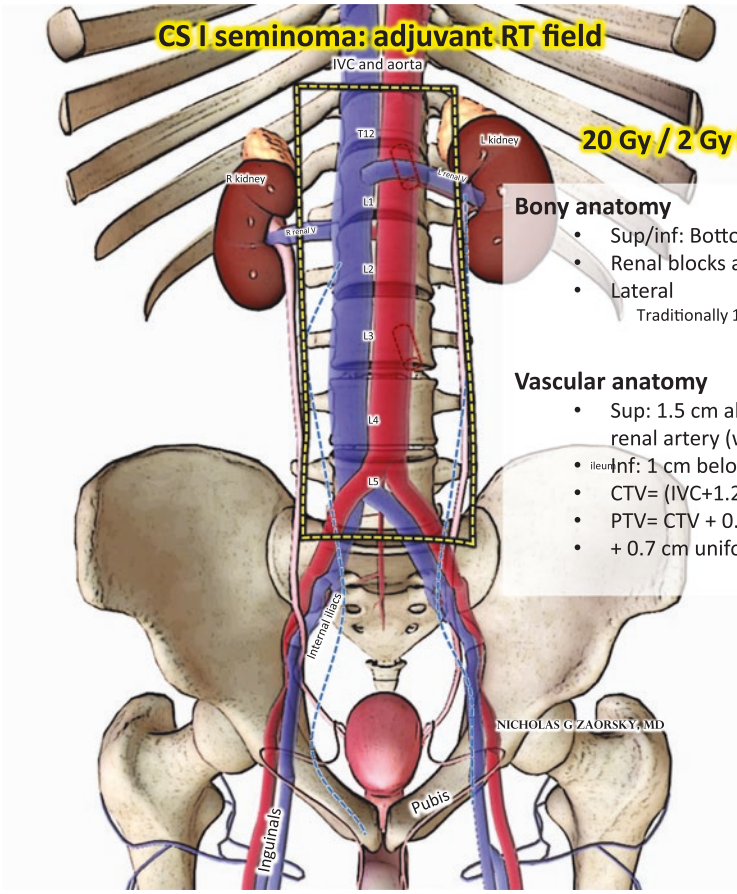


20 Gy / 2 Gy fractions, AP/PA

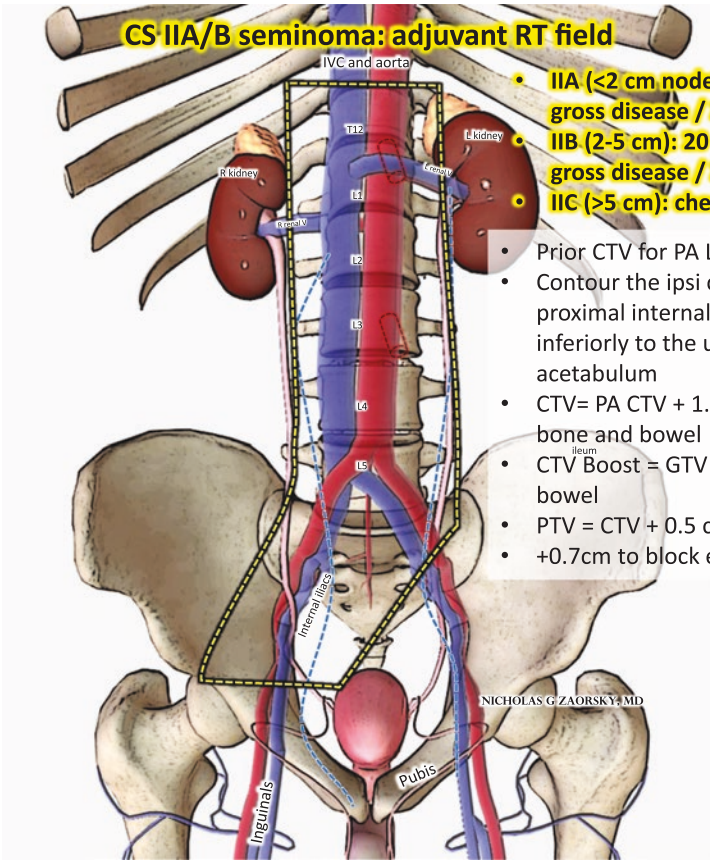
Bony anatomy

- Sup/inf: Bottom of T11 to bottom of L5
- Renal blocks at T12 (optional)
- Lateral
  - Traditionally 10cm wide including transverse processes

OR

Vascular anatomy

- Sup: 1.5 cm above L renal artery / 1 cm above R renal artery (whichever lower)
- Inf: 1 cm below aortic bifurcation
- CTV= (IVC+1.2cm) + (Ao + 1.9cm)
- PTV= CTV + 0.5 cm
- + 0.7 cm uniformly to block edge (for penumbra)



- **IIA (<2 cm node): 20 Gy DL field + 10 Gy boost to gross disease / 2 Gy fractions, AP/PA**
- **IIB (2-5 cm): 20 Gy DL field + 16 Gy boost to gross disease / 2 Gy fractions, AP/PA**
- **IIC (>5 cm): chemo**

- Prior CTV for PA LNs for a stage 1
- Contour the ipsi common, external and proximal internal iliac veins and arteries down inferiorly to the upper border of the acetabulum
- CTV= PA CTV + 1.2cm vessel expansion, exclude bone and bowel
- CTV Boost = GTV + 0.8cm, exclude bone and bowel
- PTV = CTV + 0.5 cm
- +0.7cm to block edge (for penumbra)

Extragonadal GCT and NGGCTs [108]

Overview

- For example, medistainum or retroperitoneum.
- In mediastinum, 30% of mediastinal GCTs are dxd incidentally with X-ray.
- Local sx include dyspnea (25%), chest pain (23%), cough, fever, weight loss.

Studies

- Bokemeyer, 2002: *n* = 524 extragonadal, either of mediastinum or RP, NSGCT. 5-year OS was 45% for mediastinal tumor and 62% for RP tumors.

Treatment Paradigm

- (1) Cis-based chemo. Chemo is usually BEP x3 or EP x 4
- (2) Surg for residual disease. +/− 40 Gy for residual dz.
  - objective response rate is 90%, with 2/3 of patients having CR.

Treatment per Stage

- **Stage IA:** observation (T1 N0).
- **Stage IB** (T2–4, N0):
  - 1. BEP x 2 c.
  - 2. RPLND
- **Stage IS** (persistently elevated markers).
  - Primary CTX: BEP x 3c
- **Stage II–III.**
  - BEP x 3 cycles. Post-chemo CT scan:
  - LN <1 cm: observe.
  - LN >1 cm → RPLND.

No role for RT except in patients who refuse chemo (then give ~40 Gy).

Penile Cancer [8–12, 109–117]

		Tis, Ta	T1a	T1b	T2	T3	T4
		Noninvasive verrucous	Subepithelial, no LVSI, no PNI, no G3-4	Subepithelial, +LVSI, +PNI, or G3-4	Spongiosum	Cavernosum	Other organ
N0		0	I	IIA		IIB	IV
N1	Unilat inguinal	-	IIIA				
N2	Mult, or bilat inguinal	-	IIIB				
N3	Fixed (ECE) or pelvic	IV					
M1							

- Tis, Ta: CIS, noninvasive verrucous.
- **T1**
  - T1a – subepithelial, no LVSI, no PNI, no G3–4.
  - T1b – subepithelial, +LVSI, +PNI, or G3–4.
- **T2** – spongiosum +/− urethra.
- **T3** – cavernosum +/− urethra.
- **T4** – adj structures (inc prostate).
- **N1** – unilateral inguinal.
- **N2** – multiple or bilateral inguinal.
- **N3** – fixed or pelvic (ECE).

Overview

– Located in glans 50%. foreskin 25%. both 9%. shaft in 2%.
– Risk factors: phimosis, poor hygiene, HPV 16, 18,
– HPV detected in 40–45%. HPV status should be documented. Unclear if HPV infection associated with prognosis.
– Workup: H&P, sperm banking? EUA if advanced, ultrasound or MRI, CT for nodes, CXR, biopsy.
– No randomized trials, mostly extracted from vulvar data.
– Need 5 cm for sexual intercourse.
– Need 3 cm to urinate standing.
– Overall, 45–80% are HPV related.

Precursor name	Histology	Subsequent Cancer	HPV relation
Erythroplasia of Queryat	PIN	Warty, basaloid	>80%
Bowen dz	SCC in situ		
Lichen sclerosis, condylomata, or SC hyperplasia		Keratinizing, verrucous	35%

LN

– cN0 → 20% pN+
– cN+ → 30–50% pN0
– Inguinal node borders:
  – Superior: inguinal ligament
  – Interior: fossa ovalis
  – Lateral: sartorious
  – Medially: adductor longus
– Male bulbomembranous and prostatic urethra: go to iliac, sacral, obturator LNs. Prepuce, shaft, etc. go to inguinals. Inguinal LNMs most common.

Early-Stage EBRT

– Grabstald & Kelly (1980): 10 patients, stage I-II: 90% LC.
– McLean 1993: 26 patients, stage I–II: mostly 50/20: 5 yr. DFS 50%.

Early-Stage Brachy

– Crook 2005: 49 patients, T1–3, Ir-192 to 55–65 Gy. 5 yr. LC 85%, OS 78%, penile preservation 86%.
– Mazeron 1984: T1–3 Ir-192 to ~65 Gy, LC 78%, penile preservation 74%.

Surgical Salvage

– Zouhair, 2001: 23 patients with LR, 80% salvage rate.
– PMH, Crook, 2002: 4/30 patients had LR. All salvaged.

Locally Advanced
- Krieg 1981: 17 patients stage I–IV, surgery+/-LND +/−RT, but 88% of patients without nodal treatment failed in nodes.
- Sarin 1997: 101 patients stage I–IV, mixed treatments, 10 yr. OS 39%, LC 55%, validated use of RT with surgical salvage. 2 patients attempted suicide after penectomy.

Inguinal LN Assessment (either LND or DSNB) if:
- LVI
- ≥pT1 G3
- T2 any G

Pelvic LND if: 2+ inguinal LNs, ECE, or seen on imaging.

Penile Preservation
- Best for T1–2 N0, primary <4 cm in maximum diameter, maximum DOI 1 cm.
- Traditionally, a 2 cm surgical margin was recommended; however, now **5–10 mm** SM recommended by NCCN, **3 mm** SM by EAU.
- In event of LR, surgical salvage in 80%.

NCCN
- In general, first do circumcision. Important if using RT to minimize toxicity.
- **Tis**: Resection, imiquimod, topical 5FU.
- **T1:** WLE or RT to GTV + 2 cm, 70 Gy.
- **T1–2 N0:**
  - Partial vs radical penectomy (need 1–2 cm margin)
    - Inguinal node dissection if T1b+
    - Pelvic dissection if ≥2 inguinal nodes
  - *Circumcision* with brachy (<4 cm)
    - 65 Gy HDR interstitial (preferred)
    - 60 Gy mold
  - *Circumcision* with 65–70 Gy with 2 cm margin
  - chemoRT (category 3),
- **PORT**: for multiple LNs + without ECE, adjuvant dose if 45–50 Gy. If ECE, then dose should be 60–70 Gy.

- **Locally advanced (T3 N+):**
  - Neoadj chemo for N2+, >4 cm nodes, T4.
    - Paclitaxel/ifosfamide/cisplatin.
  - ChemoRT: 50 Gy WPRT +10–20 Gy boost.
  - Radical penectomy + LND +/− post-op RT (same doses as head and neck).

Technique
- **Brachytherapy.**
- Brachytherapy mold (tube loaded with Ir-192), Paris system.
- Interstitial: 1 cm spacing, Ir-192.
- EBRT
- Ideally should be prone, with penis suspended in water bath.
- Otherwise, sim supine, foley, bolus, frog leg.
- Tape up if treating pelvis.
- GTV: visible disease.
- CTV: GTV + whole shaft of penis, +/−superficial and deep inguinal nodes, +/− pelvic nodes.
- PTV: CTV +1 cm.
- 50 Gy to a portion or entire penis.
- Cover pelvic nodes and bilateral inguinal nodes.
- 20 Gy CD to gross tumor +2 cm margin (total dose 70 Gy).
- Weekly cisplatin (40 mg/m2).
- Dose limits:
  - Urethra 60 Gy (stricture).
  - Testes 3 Gy (sterilization).

Male Urethral Cancer

Staging
- T1 Subepithelial connective tissue
- T2 Periurethral muscle, prostate, spongiosum
- T3 Bladder neck, prostate capsule, cavernosum
- T4 Adjacent organs
- N0.
- N+.

Background
- 20% cN+ versus penile 50% cN+
- But 90% of cN+ are pN+

Treatment
- **Prostatic urethra** = radical cystoprostatectomy + PLND
- **Bulbomembranous** = radical cystoprostatectomy + en bloc penectomy + PLND
- Penile **urethra** = treat like penile

Upper Urothelial Tract (UUT) Cancer

= Renal pelvis + ureter

Staging
- T1 Subepithelial connective tissue
- T2 Periurethral muscle, prostate, spongiosum
- T3 Bladder neck, prostate capsule, cavernosum
- T4 Adjacent organs

Background
- Renal pelvis 3–4x more common than ureter.
- UUT have worse stage-for-stage prognosis than bladder.
- 20% UUT tumors → synchronous/metachronous bladder cancer (only 1–4% vice versa).

Treatment

Radical nephroureterectomy: radical nephrectomy including ureter + part of bladder.

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Gynecologic Cancers

9

Daniel M. Trifiletti, Nicholas G. Zaorsky, and Surbhi Grover

Abstract

This chapter discusses the general management of patients with gynecologic system cancers, with special focus on principles that guide radiotherapy management. Several key components of trimodality care and brachytherapy are discussed.

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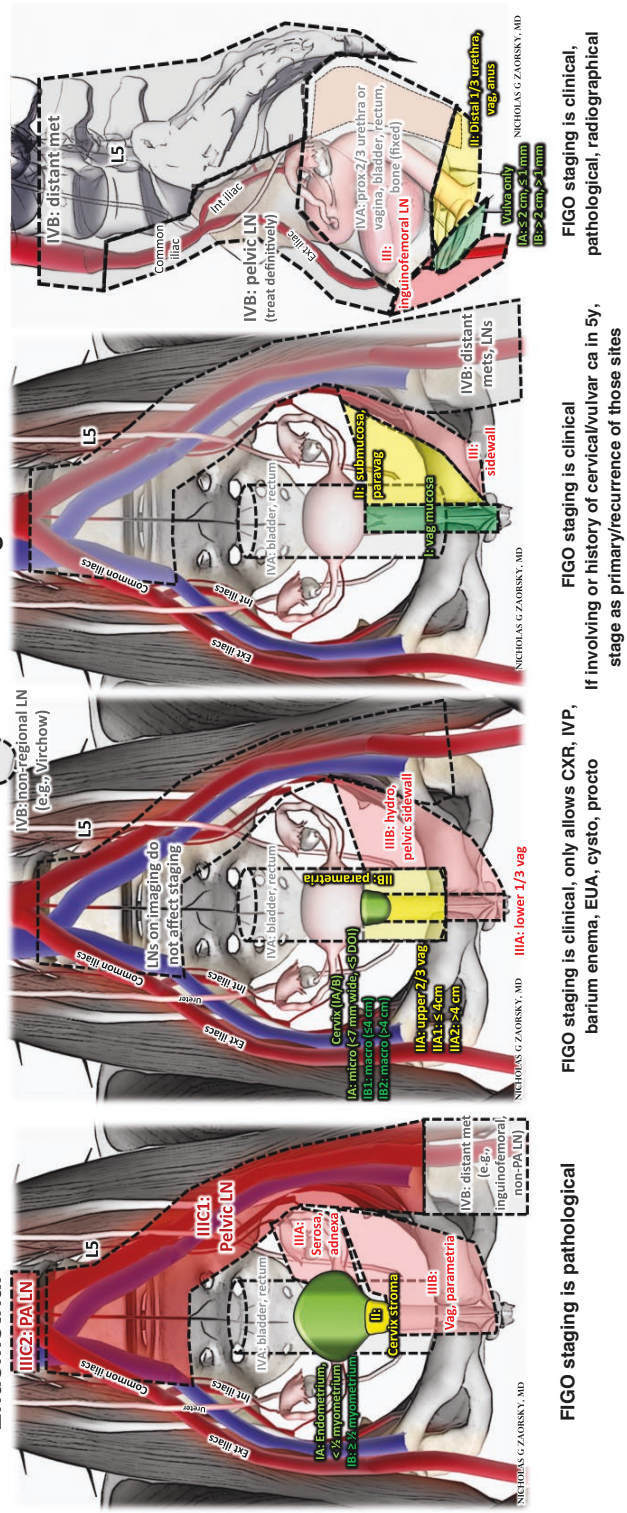
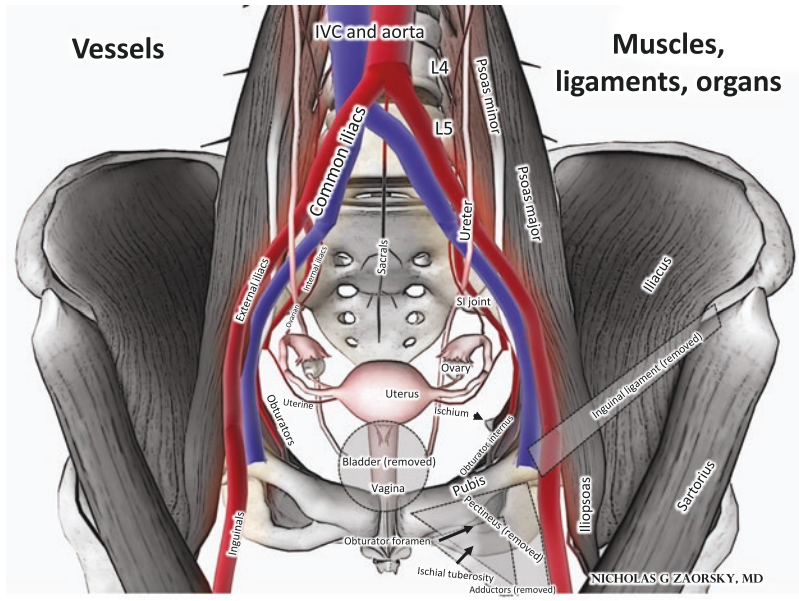
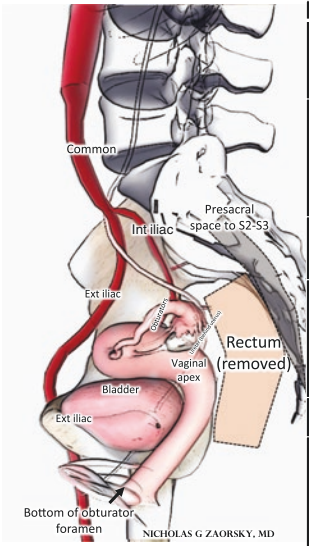

Endometrial
IIIC2: PALN
L5
Common iliac
Ext iliac
Int iliac
Ureter
IVA: bladder, rectum
IA: Endometrium, < ½ myometrium
IB: ≥ ½ myometrium
Ib
Cervix stroma
IIIC1: Pelvic LN
IIIA: Serosa, adnexa
IIIB: Vag, parametria
IVB: distant met (e.g., inguinofemoral, non-PA LN)
NICHOLAS G ZAORSKY, MD
FIGO staging is pathological
Cervical
IVB: non-regional LN (e.g., Virchow)
LNs on imaging do not affect staging
IIB: parametria
IIIB: hydro, pelvic sidewall
IA: micro (<7 mm wide, <5 DOI)
IB1: macro (≤4 cm)
IB2: macro (>4 cm)
IIA: upper 2/3 vag
IIA1: ≤ 4cm
IIA2: >4 cm
IIIA: lower 1/3 vag
FIGO staging is clinical, only allows CXR, IVP, barium enema, EUA, cysto, procto
Vaginal
IVB: distant mets, LNs
IIb: submucosa, paravag
Ivag mucosa
IIIb: sidewall
FIGO staging is clinical
If involving or history of cervical/vulvar ca in 5y, stage as primary/recurrence of those sites
Vulvar
IVB: distant met
IVB: pelvic LN (treat definitively)
IVA: prox 2/3 urethra or vagina, bladder, rectum, bone (fixed)
IIIb: inguinofemoral LN
IIb: distal 1/3 urethra, vag, anus
Vulva only
IA: ≤ 2 cm, ≤ 1 mm
IB: > 2 cm, > 1 mm
FIGO staging is clinical, pathological, radiographical

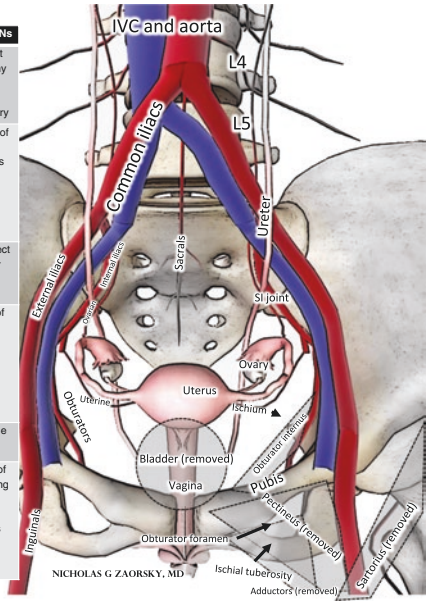
GYN LN Anatomy

	Interior iliac LNs	Obturator LNs	External iliac LNs	Inguinal LNs
Cranial	Bifurcation of common iliac artery	3–5 mm cranial to obturator canal	Bifurcation of common iliac artery	External iliac art leaves bony pelvis to become femoral artery
Caudal	Level of obturator canal; or where no space between obturator internus and midline organs	Obturator canal, where obturator artery exits pelvis	Roof of acetabulum and sup pubic rami	Lower edge of ischial tuberosities
Post	N/A	Interior iliac LNs	Interior iliac LNs	Medial aspect of anterior pectineal muscle
Ant	Obturator internus upper pelvis: 7 mm margin around internal iliac vessels	Ant extent of obturator internus	7 mm margin ant to ext. iliac vessels	Ant edge of sartorius muscle
Lateral	Medial edge of muscle or bone	Obturator internus	Iliopsoas muscle	Medial edge iliopsoas
Medial	Lower pelvis: mesorectum and presacral space upper pelvis: 7 mm around vessel	Bladder	Bladder or 7 mm margin around vessel	Lateral aspect of adductor long or medial aspect of pectineus



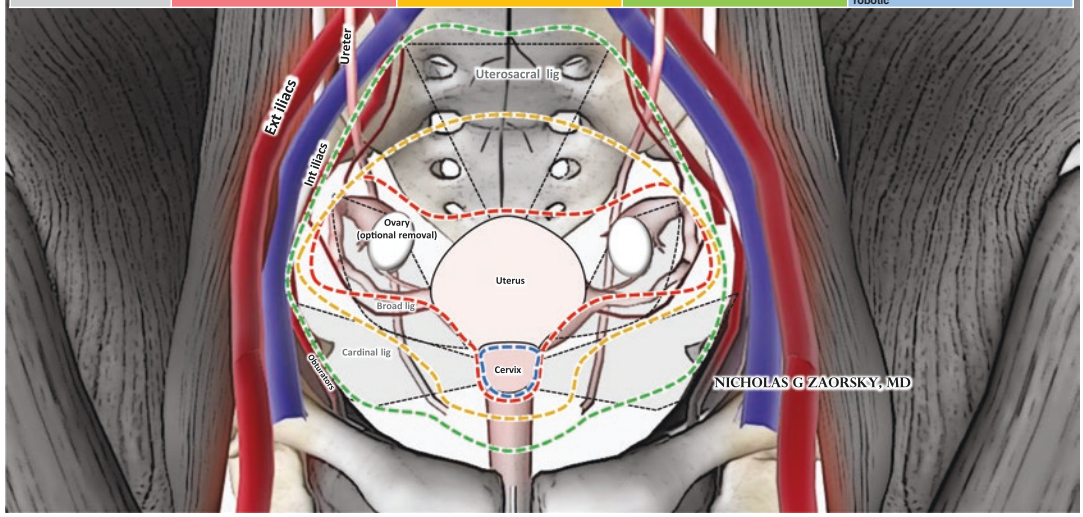


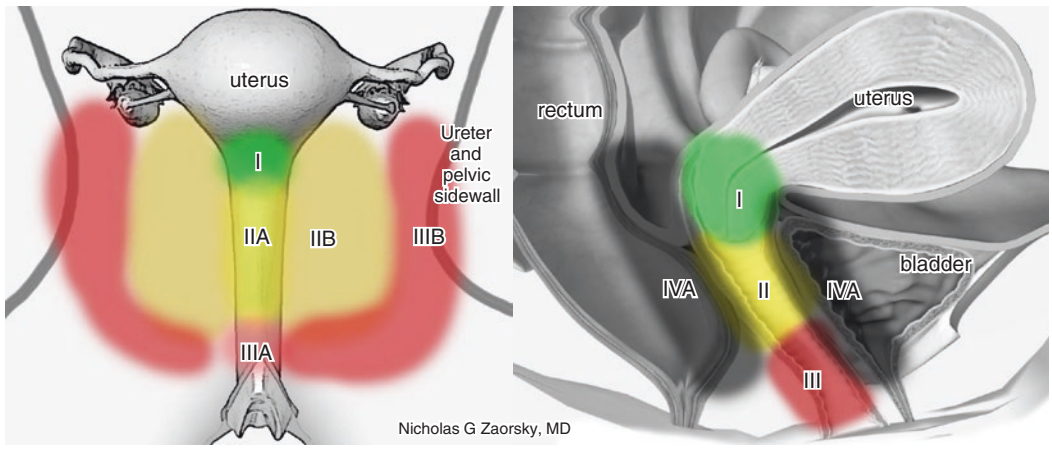
	int iliac LNs	obturator LNs	ext iliac LNs	inguinal LNs
cranial	bifurcation of common iliac artery	3-5 mm cranial to obturator canal	bifurcation of common iliac artery	ext iliac art leaves bony pelvis to become femoral artery
caudal	level of obturator canal; or where no space bw obturator internus and midline organs	obturator canal, where obt artery exits pelvis	roof of acetabulum and sup pubic rami	lower edge of ischial tuberosities
post	N/A	int iliac LNs	int iliac LNs	medial aspect of anterior pectineal muscle
ant	obturator internus upper pelvis: 7 mm margin around int iliac vessels	ant extent of obturator internus	7 mm margin ant to ext iliac vessels	ant edge of sartorius muscle
lateral	medial edge of muscle or bone	obturator internus	iliopsoas muscle	medial edge iliopsoas
medial	lower pelvis: mesorectum and presacral space upper pelvis: 7 mm around vessel	bladder	bladder or 7 mm margin around vessel	lat aspect of adductor long or medial aspect of pectineus



Cervical Cancer [1–18]

	Simple / Extrafascial hysterectomy (Type I)	Modified radical hysterectomy (Type II)	Radical hysterectomy (Type III)	Trachelectomy
Abbreviation	TAH	MRH	RH	
Indication (cervix, endometrial)	IA1 Endometrial ca (+BSO)	IA1 w LVSI; IA2 + Endometrial ca w cervix involved (+BSO)	IB1-2; IIA1	HSIL; IA1; IB1 < 2cm
Cervix	Removed	Removed	Removed	Removed
Uterus	Removed	Removed	Removed	Spared
Ovaries	Optional removal	Optional removal	Optional removal	Spared
Vaginal margin	1-2 mm	1-2 cm	Upper ~25-50%	None - upper ~25-50%
Ureters (tunnel through…)	N/A	Broad lig	Broad lig	N/A vs tunnel through broad lig
Bladder (mobilized to…)	Base of cervix	Upper vag	Middle vag	Peritoneal reflection
Rectum (mobilized to…)	N/A	Below cervix	Below mid vag	Peritoneal reflection
Uterine artery (ligate at…)	Uterus	Ureter	Internal iliacs	
Cardinal ligs	Resect at uterine/cervix border	Divided medial to ureters	Divide at pelvic sidewall	Resect at cervical border vs divide at pelvic sidewall
Uterosacral ligs	Divide at cervical border	Partially resected	Divided near sacral origin	Divide at cervical vs near sacral origin
Approach	Laparotomy vs laparoscopy	Laparotomy vs laparoscopy vs robotic	Laparotomy vs laparoscopy vs robotic	Vag vs laparotomy vs laparoscopy vs robotic





T1 cervix only
- T1a (*IA*) – micro
  - T1a1 (***IA1***) – <3 mm DOI, ≤7 mm wide
  - T1a2 (***IA2***) – 3–5 mm DOI, ≤7 mm wide
- T1b (*IB*) – macro
  - T1b1 (***IB1***) – ≤4 cm
  - T1b2 (***IB2***) – >4 cm

- **T2** outside cervix
  - T2a (IIA) – upper 2/3 vagina
    - T2a1 (***IIA1***) – ≤4 cm
    - T2a2 (***IIA2***) – >4 cm
  - T2b (***IIB***) – parametrium
- **T3**
  - T3a (***IIIA***) – lower 1/3 vagina
  - T3b (***IIIB***) – pelvic wall or hydronephrosis
- **T4** (***IVA***) – bladder or rectum involvement
- **N1** – regional (up to common iliac)
- **M1** (***IVB***) – distant including supraclavicular nodes

Anatomy
– Ligaments: broad (lateral from the uterus to pelvic sidewall), round (anterolateral from the uterus to pelvic sidewall, then through inguinal canal to connective tissue of labia majora), cardinal (lateral from the cervix to pelvic sidewall), uterosacral (posterior from the cervix to sacrum around S1–S3)
– Uterosacral ligament allows spread posteriorly into presacral space.

Screening
– 21–30 pap q3y if normal.
– 30–65 years, HPV testing plus Pap every 5 years or just Pap every 3 years (American Cancer Society)
– >65 yo: none.
– Pap smear: obtain good "scrapings," use small brush to obtain endocervical sample; no Pap smear if actively bleeding.
– ASCUS: repeat Pap 6 m. 2/3 resolve.
– ASCUS/LSIL → reflex HPV DNA; HPV DNA (−) → repeat Pap in 6 mo, HPV DNA (+) → colposcopy. 1/2 resolve.
– HGSIL: 1/3 resolve. Colposcopy and biopsy.

Directed Biopsy Results
– CIN1 → repeat Pap in 6 months.
– CIN2/3 → excision or ablation of transformation zone.

Vaccination
– 90% of HPV infections are cleared or suppressed by immunity in 1–2y of exposure
– Cervarix: 16,18
– Gardasil: 6, 11, 16, 18
– Gardasil 9: 6, 11, 16, 18, 31, 33, 45, 52, 58
– Boys and girls, age 11–12 → HPV vaccine (3 shots over 6 months)
– Does not prevent or speed clearance of an existing HPV infection.
– In vaccinated, decreases by 50% the development of high-grade disease.

Histology
- 80% of cervical cancer are SCC. Nearly all of these are HPV associated (in contrast to penile cancer, where it is ~80%).
- HPV types 16 and 18.
- Other histologies: adeno (15%), mucinous, endometrioid, serous, clear cell.

Workup
- History:
  - **Postcoital bleeding**: Vaginal bleeding relative to intercourse. Bleeding after menstruation, pain, dizziness.
  - Pap smear history, HPV vaccination, history of STDs, and HIV, pregnancy test.
  - Prior surgery, IBD, pelvic RT.
- Vital signs; CBC and CMP; transfuse if Hgb <10.
- **Pelvic exam, with EUA PRN.**
  - Patient in dorsal lithotomy position.
  - Inspect external genitalia, then eval cervix.
  - Pap smear: obtain good "scrapings," and use small brush to obtain endocervical sample; no Pap smear if actively bleeding.
  - **Vaginal** exam to assess vaginal extension, place right index and middle finger on either side of cervix, assessing size and rotating around to check fornices**.**
  - **Bimanual exam**: place index and middle within the vagina; place other hand suprapubic, putting pressure against the uterus and laterally to access adnexa. If cannot move, the mass = fixed.
  - **Rectovaginal exam** to assess for parametrial extension. Keep index finger in the vagina, place middle finger in the rectum, and sweep fingers side to side. If you cannot get your fingers around mass, possible pelvic sidewall.
  - Can't visualize lesion → colposcopy w/ cone biopsy.
  - Visualize lesion → cervical punch biopsy.
- Sigmoidoscopy/cystoscopy for IB2+. Edema on cysto does not change stage.
- Labs: especially hemoglobin and renal function tests, HIV test. Transfuse if Hgb <10.
- Smoking cessation.
- Imaging:
  - FIGO only allows CXR, IVP, EUA, cystoscopy, proctoscopy, and barium enema.
  - Not allowed in FIGO staging: CT, MRI, PET/CT, and exploratory surgery. However, these can be used to guide treatment. Patient with IB cancer with PET-avid nodes would be "IB, node positive."
  - Only one finding on imaging changes staging: hydronephrosis.
  - PET for IB1+.
  - MRI for bulky tumors.

Stage	Pelvic LN+	PA LN+	OS5
IA1	<1	0	98
IA2	6	3	95
IB1	15	10	85
IB2			
IIA	30	15	73
IIB	30	20	66
III	45	30	40
IVA	60	40	22
IVB			9

- LN risk (%) by stage: "rule of 15 s" = stage x 15
- Risk for PA LN involvement = 50% risk of pelvic LN involvement
- OS5 = rule of 15 s

Surgery: Preserves ovarian function, treatment done in less time, does not cause second malignancies (important in young women), takes only up to half of the vagina (preserves sexual function), does not cause stenosis, but is more invasive (risk of bleeding, infection), and some will require PORT

Pathology Report Components: Stromal invasion (and extent), LVSI, tumor size (esp. at 4 cm cut-off), parametrial invasion, margins, involved nodes

Surgery vs RT

- Italian, Landoni 1997: 343 pts. IB-IIA → RT vs RadHyst. RT was 47 Gy (range 40–53 Gy), delivered to WP using AP/PA or 4 fields, then LDR-BT to a total median dose of 76 Gy. For surgery, adjuvant RT 50.4 given for stage >IIA, <3 mm of uninvolved cervical stroma, cut through, LN+. Unchanged OS, DFS, but morbidity worse in surgery arm (28% vs 12%). Limitation: 65% of surgery pts. received adjuvant RT, and tox highest in combined tx. Thus, for IB2 and IIA2, CRT is recommended over surgery.

Post-op RT and Chemo

- **GOG 92** (Sedlis 1999/Rotman 2006): 277 pts. IB2 → RadHys +/− WPRT. Had to have 2 of (>4 cm, LVSI, middle/deep stroma invasion – note these are simplified). PORT ↓LF (21% vs 14%), ↓mets, ↑PFS (65 → 78%). OS borderlines better 80% vs 71%. Thus, if these factors are present, should recommend post-op WPRT.
- **INT 0107/SWOG 8797/RTOG 9112/GOG 109 (Peters, 2000)**: 243 pts. IA2, B-IIA RadHys, had to have either *(+margin, +LN, +parametrium [*i.e.*, pT2b])*. Then randomize → RT +/− cis/5FU. EBRT was whole pelvis 49.3/1.7, with 45 Gy to PA LNs if common iliacs +. No brachy. Chemo was *cis 70 mg/m^2 and 5FU 1000 mg/m^3* q3w x4c total, 2c concurrent, 2 cycles adj. CRT improved 4-yr. PFS (63 → 80%) and OS (71 → 81%). Identified the 3 Ps. Use of adjuvant chemo investigational; it is studied in RTOG 0724.
- **GOG 109 reanalysis** (Monk, 2005): tumor size <2 cm and 1 LN involved have no OS benefit of chemo.
- High-risk post-op (Peters RTOG 91–12): IA2–IIA (with positive margins, positive nodes, and/or parametrial invasion), RT (49.3Gy) vs cisplatin (70 mg/m^2) + 5FU (1000 mg/m^2) q 3wks x 4 + RT.
- **RTOG 0724:** early-stage, high-risk cervical ca, s/p rad hysterectomy. IA2, IB, and IIA, who have +LNs, +parametria, or + PA LNs. Stratify by BT, 3D vs IMRT, WPRT dose (45 vs 50.4). Rando to weekly cis (40 mg/m^2) + RT vs concurrent weekly cis + RT + adjuvant carbo (AUC 5) and paclitaxel (135 mg/m^2). For 3D WPRT, sup is L4/5. Inferior is bottom of obturator foramen. Lateral is 1–2 cm lateral of true pelvic diameter. If common iliac LNs+, then go up to L1/L2 sup. If PA LNs+, then go up to T11/T12. For lateral fields, ant border is 2 cm ant to the CB or 1 cm ant to contoured PA LNs. Post is 1–1.5 cm into the CB or >1 cm post to contoured PA LNs.

3D vs IMRT

- RTOG 1203 (TIME-C), Klopp, Yeung. 3D vs IMRT pelvis. Endometrial or cervical cancer s/p hysterectomy and have indication for adjuvant RT. ASTRO 2016: reduced acute GI/GU tox with IMRT. Sup border is L4–L5.

Pre-op Chemo vs Pre-op CRT

– GOG 123, Keys 1999 ("123 is P-R-E"). IB2. Rando to pre-op RT vs pre-op CRT. Note results of GOG 71 not yet available at that time. RT was WPRT 45 Gy then LDR BT, total point A dose of 75 Gy. Concurrent RT arm was cis 40 mg/m^2 qw x 6w. Wait 3–6w, then surgery was Class I extrafascial histo. CRT improved 5-year PFS 60% vs 71% and OS, 64% vs 78%. pCR increased from 41% to 52%. CRT increased acute heme and GI tox, but not late. Conclude that LC and OS improvement was from chemo, not the use of adjuvant hysterectomy.

Definitive RT and CRT

– **RTOG 90–01**, Morris MDACC, 1999; Eifel, 2004: 386 pts. IIB–IVA, >5 cm or LN+ → EFRT vs WPRT+cis (75 mg/m^2)/5FU(1000 mg/m^2) q 3w chemo. EFRT sup border for PA LNs was *L1/2*. For WPRT, sup border was *L4/5*. Inferior border was mid-pubis or 4 cm below lowest extent of dz. Lateral fields encompass S3. Both groups get 45 Gy EBRT +. All pts. got brachy, total 85 Gy to point A. CRT won. 8-yr. OS 41 → 67%, LRF 35 → 18%, DM 35 → 20%. More PA LN failures with WPRT+chemo (8 vs 4%), NSS. Thus, use CRT, and do not treat elective PA LNs. Note current PA LN border now goes to T12/L1 (level of renal hilum).
– NCIC, Pearcey, 2002: IB–IVA. *n* = 250. RT alone +/− chemo. RT was 45 Gy. Chemo was concurrent weekly cis 40 mg/m^2 x6c. No difference in 5-year OS, 62% vs 58%. Lack of surgery LN staging? More anemia in CRT arm? Underpowered?
– GOG 71, Keys 2003: 282 pts. IB2 → RT +/− adjuvant hysterectomy. No difference in OS, more LF in RT arm. Thus, conclude that should use definitive concurrent CRT for stage IB2. Results not available prior to starting GOG 123.
– Chemo for cervical cancer collaboration, 2008: for CRT v RT, 6% improvement in OS and HR of 0.81, favoring CRT.

CRT +/– Outback Chemo

– B9E-MC-JHQD (Duenas-Gonzalez, JCO, 2011): RCT of (1) concurrent CRT with cis 40 mg/m^2 + EBRT + BT to point A dose 85 Gy vs (2) concurrent CRT with cis 40 + gem 125, then adjuvant chemo with cis 50 + gem 1000 x 2c. *n* = 500, stage IIB–IVA. Cis and gem had improved PFS (65% vs 74%) and OS (69% vs 80%) but had worse G3–G4 tox (46% vs 86%) and had 2 tx-related deaths. Thus, currently cat 2b rec by NCCN.

RT + Different Chemos

– Both weekly cis and cis/5FU used in RCTs of CRT. No RCTs comparing the two. Most clinicians prefer weekly cis due to lower acute toxicity.
– GOG 85/SWOG 8695, Whitney, TJUH, 1999. IIB–IVA cervix. Concurrent CRT with either hydroxyurea or cis/5FU. Cis/5FU won for OS and tox.
– GOG 120, Rose 2007: IIB–IVA cervical cancer. 526 pts., IIB–IVA → RT with (cis vs cis/FU/hydroxyurea vs hydroxyurea). Cisplatin containing arms won. OS benefit, esp. for IIB and III patients.

Chemo + Different RTs

– NCIC: 353 pts. → CRT with LDR (35Gy) vs HDR (8x3). No difference in 5-yr. OS

Treatment

– "Primary therapy should avoid the routine use of both radical surgery and RT."
– **Dysplasia:**
  • LEEP is typically for CIN3.
  • Conization is typically for CIN3.
  • Cryotherapy.
– **IA1 R0 on biopsy/LEEP w/o LVSI:**
  • CKC (DOI <3 mm, no LVSI)
  • Radical trachelectomy (removal of cervix, parametria with cerclage placed, leaving uterus intact)
  • Extrafascial hysterectomy (i.e., a type I hysterectomy)

- **IA1 R+ on biopsy/LEEP or LVSI:**
  - CKC + PLND
  - If desiring fertility preservation, radical trachelectomy with LND
- **Incidental IA1 after TAH:**
  - No LVSI or 3Ps: observe.
  - +LVSI or 3Ps: completion RadHys or RT
- **IA2:**
  - Fertility-sparing = radical trachelectomy + LND.
  - MRH (type II) + PLND.
  - Assess need for adjuvant therapy (depending on risk factors*). Adjuvant RT: 45–50Gy pelvic EBRT +/− vaginal brachy.
  - RT alone: 45 pelvic EBRT + brachy (dose to Pt A = ***70–80 Gy***).
- **IB1:**
  - Type III radical hysterectomy + PLND.
  - Another option is EBRT + BT.
  - If desires fertility preservation, radical trachelectomy and PLND are possible.
- **IIA1**:
  - Type III radical hysterectomy + PLND.
  - For young healthy patients with small tumors, type II MRH is preferred to RT.

- **Post-op setting:**
- **Indications for RT alone, per modified Sedlis/GOG 92:** (need 2 of 3):
  - >1/3 stromal invasion
  - LVI
  - Tumor >4 cm

- **Indications for chemo-RT, per Peters/SWOG 8797/GOG 109:**
  - ***P***ositive margins (i.e., <3 mm)
  - ***P***ositive parametrial involvement
  - ***P***ositive LNs
    - 50.4 Gy.
    - Weekly cisplatin (40 mg/m^2)
    - + IVRT for (+)/close vaginal margin (5 Gy x3 to surface)

- **IB2, IIA2–IVA:**
  - Definitive chemo-RT
  - 45 Gy + 600 cGy x 5 HDR to point A (85 Gy)
  - Weekly cisplatin (40 mg/m^2)
  - II**B**/III**B**/IVA: **PM boost** to 54 Gy
  - Gross LN: boost to **59.4 Gy** (if LN >3 cm → surgery)

Adjuvant RT Technique

CT Simulation for EBRT:

- IV contrast helps visualize vessels for nodal contours.
- Instruct patient to arrive with full bladder to allow for both full and empty bladder CT scans.
- Fuse empty bladder scan for contouring and planning on full bladder scan (then treat on full bladder).
- Recommended: Place radiopaque marker at vaginal apex.
- If rectum distended, include anterior rectum in CTV, or consider re-sim if >3.5 cm rectal diameter.
- MRI: T2 is best to see cervix, tumor, and critical structures. T1 will be isointense.
- IMRT contours (per Consensus Guideline 2008 and RTOG 0418):

CTV Nodes:

- Common, external, and internal iliac (including obturator) nodes; ~7 mm margin from vessels excluding the bone, small bowel, and iliopsoas muscle.
- **Common iliacs**: posterolateral hugs vertebral bodies and psoas.
- **External iliac**: inferior border is top of femoral head (surrogate for inguinal ligament).
- **Internal iliac**: post border is piriform.
- **Obturator**: top of femoral head to top of pubic symphysis.
- Presacral space: including 1.5 cm anterior to S1–S3, not extending into foramina, stopping when piriform becomes visible.
- Include pertinent surgical clips.
- (+) pelvic LN → proximal PA (L1/L2)
- (+) PA nodes → T11/T12
- **CTV vagina/parametria:**
- ≥1.5 cm at midline (can include anterior rectum and posterior bladder)

- Inferior border ≥3 cm from vaginal apex or 1 cm above bottom of obturator foramen (whichever is lower)
- **ITV vagina/parametria:**
- Vaginal cuff = create vagina ITV, sum of vaginal contours full + empty bladder, include vaginal cuff and at least 3 cm of vagina inferior.
- PTV45–50.4 = (CTV nodes + ITV vagina/parametria) + 7 mm margin. Total PTV = 1.5–2.0 cm, including the ITV + SM.
- IMRT reduces acute and chronic GI toxicity (per Mundt et al.) and decreases neutropenia, improving ability to give concurrent chemo (per Brixey et al. IJROBP 2002).
- **Dose:** 50.4 Gy
- **Planning:** IMRT.
- **On treatment:** Daily CBCT and KV imaging.
- If bladder not full enough, re-instruct patient/drink more water.
- If gas, insert red rubber catheter.
- **Vaginal brachytherapy (VB)** "cuff" boost was *not* permitted on either GOG 92 or GOG 109. However, ABS Consensus Guideline 2012 specify it can be considered in patients at high risk of local relapse (e.g., R+).

Definitive RT Technique

(1) External Beam RT

Simulation:

- Full bladder (two cups an hour before) and empty rectum (have a BM before sim).
- Supine, arms on chest, Alpha Cradle.
- Place two gold seeds at the cervix.
- CT sim *with IV contrast*.
- Anatomy based: **traditional LN negative WPRT field is 4-field box:**
  - **Anterior/post**: 1 cm ant to pubic symphysis, covering the entire sacrum/sacral hollow.
  - **Superior**: bifurcation of the common iliacs (L4/5).
  - **Inferior**: obturator foramen or 3 cm below most inferior extent of vaginal involvement.
  - **Lateral**: 2 cm lateral to pelvic brim. Do not block femoral heads.
  - **Extended field:**
    - (+) Pelvic lymph nodes = L1/L2.
    - (+) PA nodes = T11/T12.
- **Parametrial boost**: boost sidewall 10 Gy for +parametria.
- **Sup** = bottom of SI joint.
- **Inferior** = same (bottom of obturator foramen); 5 cm midline block.
- LN boost: LN GTV + 2 cm.
- **Dose**: 45 Gy to large fields w/ sequential CD to 54 Gy PM boost, 59.4 Gy LN boost.
- First BT should be performed 4–6w after initiating EBRT to allow for tumor shrinkage.

Chemo:

- Cisplatin 40 mg/m^2 weekly, given Mon/Tues, before RT

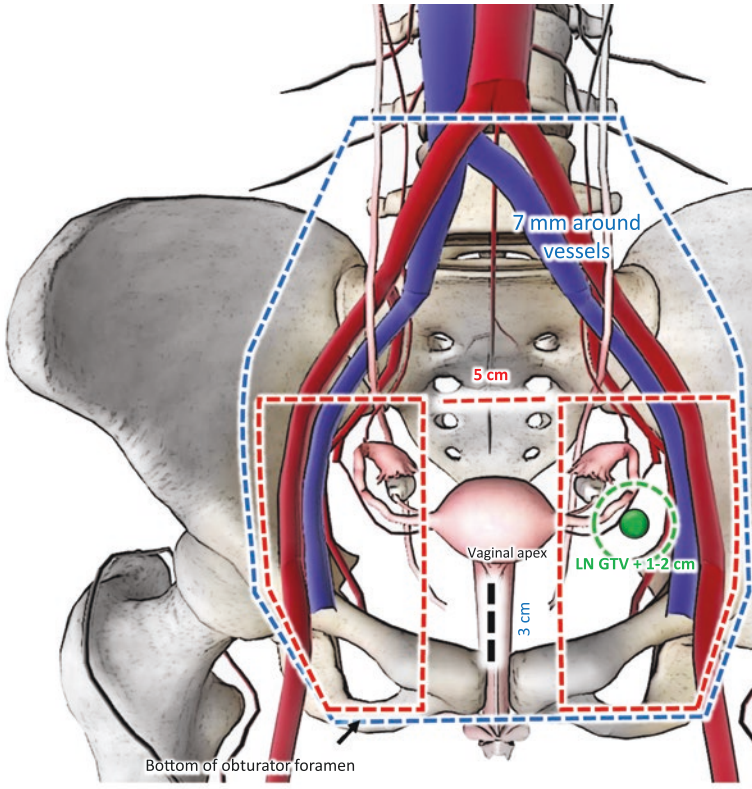
(2) Definitive Brachytherapy Technique

- General anesthesia.
- Patient in dorsal lithotomy.
- EUA, confirm less than 4 cm for good implant geometry.
- Prep, drape.
- Foley, inflate with 7 cc of 30% Renografin solution.
- +/− gold seeds into cervix at 12 + 6 o'clock.
- Sound the cervix. Grab with tenaculum to provide countertraction and advance until slight resistance and note depth.
- Dilate cervix using progressively larger dilators up to 16 French (6 mm). Note: 1 "French" or "Fr" = 0.33 mm = 0.013″.
- Insert Smit sleeve: Smit length = sound depth – 5 mm; suture in place.
- Insert tandem: curvature = uterus shape; length = sound depth – 5 mm.
- Place ovoids over the tandem and slide ovoids into the vagina. Use largest ovoids that comfortably fit. Why? Inverse square law: ↑ size, ↓ vaginal surface dose.
- Pack radio-opaque gauze posteriorly first, then anteriorly, using two separate packs.
- Ensure bladder is fully drained, clamp Foley, and inject 30–60 cc of dilute contrast.

- Take AP and lateral films to evaluate T&O placement.
- What to look for on orthogonals:
  - AP: tandem bisects ovoids, tandem not rotated, phalange close to cervical marker, ovoids high in fornix with 0.5–1 cm spacing, no packing above ovoids
  - Lateral: tandem bisects ovoids, midway between the sacrum and bladder, at least 3 cm away from sacral promontory, sufficient anterior, and post packing, Foley balloon pulled down
- **HDR-BT T&O:**
  - 5.5 Gy x 5, for patients with <4 cm residual dz. This gives EQD2 >85 Gy
  - 6 Gy in 5 fractions, for pts. with >4 cm residual dz. This has 35–45 EQD2
  - 5 Gy x 6
  - 7 Gy x 4
- **LDR-BT.** Dose rate is 0.4–0.6 Gy/hr. (e.g., with Cs-137). Lower dose rates prolong tx time and have reduced efficacy. Higher dose rates have more late toxicity.
- LDR-BT target dose to point A is ***80–90 Gy***. After 45 Gy EBRT, 35–45 Gy prescribed with LDR-BT.

- **ICRU 38 (1985) Guidelines**
  - "**Standard loading**" of LDR-BT. Tandem and Fletcher-Suit-Delclos ovoid. Using 137Cs. Per ABS, tandem is loaded 15-10-10 mgRaeq from cephalad to caudad. Tip loaded with more activity to provide adequate coverage in lower uterine segment. Small ovoids then loaded with 10-15 mgRaeq. Mini ovoid loaded with doses 5–7.5 mgRaeq because they lack internal shielding.
  - **Pt A**: 2 cm sup and 2 cm lateral from external os (parametria) – 85 Gy EQD2.
  - **Pt B**: 5 cm lateral from midline at the same level at point A, but in the plane of the patient/midline, and not from the tandem. The dose to point B should be ¼ to 1/3 the dose to point A. Represents obturator nodes, gets 25% pt. A dose – 55 Gy.
  - **Bladder pt**: defined w/ ***7 cc*** of contrast in balloon, perpendicular distance to surface of Foley catheter at the center in sup-inferior plane of Foley balloon and closest to applicator.
  - **Vaginal pt**: at midpoint of lateral surface of ovoid on AP film.
  - Rectal point is most anterior point along line that bisects the ovoids.
  - IIB/parametrial involvement: needs parametrial boost, 5.4–9 Gy.
  - PA LNs: tx only if involved or in pt. who cannot get chemo. Sup border is T12/L1 (higher than 90–01).

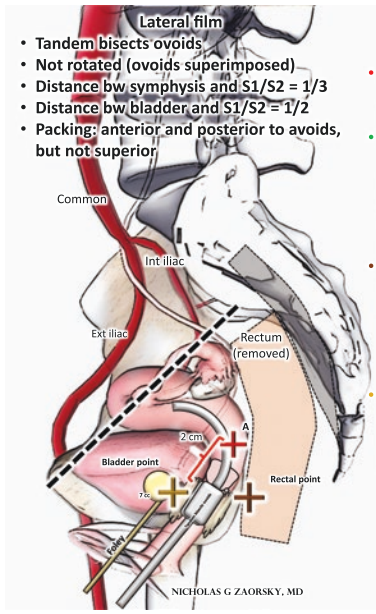
- Volume based:
  - **GTV_D** – macroscopic tumor seen clinically or on MR at *diagnosis.*
  - **GTV_{B1}, GTV_{B2}** – tumor seen clinically or on MR at *brachytherapy* insertion 1, 2, etc.
  - **HR CTV_{B1}**: High-risk CTV includes whole cervix and presumed extracervical extension (volume receiving total Rx dose). ~85Gy, D90 = 80–90 Gy.
  - **IR CTV_{B1}:** Intermediate risk corresponds to initial macroscopic disease ± margin; HR CTV + 5–15 mm margin (5 mm AP, 10 mm lateral/craniocaudal). ~60Gy.
  - Primary: PTV identical to CTV.
  - LN: CTV to PTV expansion for nodal treatment should be 7 mm.
  - Cumulative EQD2 maximums.
    - D2cc bladder ≤85 Gy.
    - D2cc rectum ≤75Gy.
    - D2cc sigmoid ≤75Gy.
- Total Tx time <7–8 wks, i.e., 56 days. 0.5–1.0% decrement in LC for each day delay after 8w, but no decrease in OS.



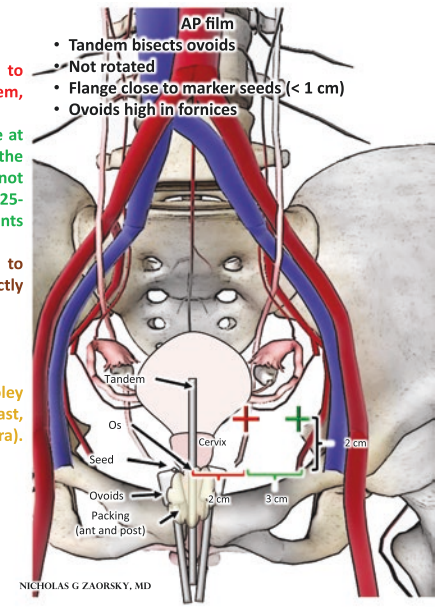
Cervical cancer whole pelvic field
traditional LN negative WPRT field is 4-field box:
ant: 1 cm ant to pubic symphysis, covering the entire sacrum / sacral hollow.
sup: bifurcation of the common iliacs (L4/5).
inf: obturator foramen or 3 cm below most inferior extent of vaginal involvement.
lateral: 2cm lat to pelvic brim. do not block femoral heads
Extended field
3D/IMRT: 7 mm around vessels
(+) Pelvic lymph nodes = L1/L2
(+) PA nodes = T11/T12
45 Gy in 25 fx

Parametrial boost
Sidewall +10 Gy for +parametria
Sup = bottom of SI joint;
Inf = same (bottom of obturator foramen); 5 cm midline block
Conedown to 54 Gy

LN boost
Boost gross nodes to 60 Gy with IMRT



- Point A = 2 cm sup and 2 cm lat to external os. Moves with tandem, always perpendicular,
- Point B = 5 cm lateral from midline at the same level at point A, but in the plane of the patient / midline, and not from tandem. Dose to point B = 25-33% the dose to point A. Represents obturator nodes.
- Rectal Point = 0.5 cm posterior to posterior vaginal wall, directly posterior to center of ovoids.
  - D2cc rectum ≤ 70 Gy
  - Rectal point ≤ 70 Gy
  - < 4.0 Gy/fx in 5 fx
- Bladder Point = AP: center of Foley balloon (inflated with 7 cc of contrast, pulled down against the urethra). Lateral: back of balloon.
  - D2cc bladder ≤ 90 Gy
  - Bladder point ≤ 75 Gy
  - <4.5 Gy/fx in 5 fx



Incomplete Definitive Therapy

- If <85 Gy given for CRT for stage IB2, "adjuvant" hysterectomy is recommended per NCCN.

Follow-Up

- PET/CT at 12 weeks posttreatment
- q3 mo x 1 year, q4 mo x 2 years, q6 mo for years 3, 4, and 5

Cervical Recurrence

- w/u = H&P, imaging (MR, PET/CT), and biopsy
- Central recurrence (prior RT) → surgery (radical hysterectomy or pelvic exenteration)
- Isolated PA nodal recurrence → CRT or surgery followed by CRT.
- CRT: match inferior border to previous treatment field (L4–L5), sup border = T11–T12.
- Dose = 54 Gy; then 59.4 Gy conedown.
- Outcomes = 25% salvage.

Chemo Toxicity

- Cis: myelosuppression, n/v, renal toxicity, neuropathy, hearing loss.
- ANC <500 for >7 days or febrile neutropenia: hold for a week and then repeat CBC.
- Cr >2.0 mg/dl: hold for 1w. Prevent with diuresis.

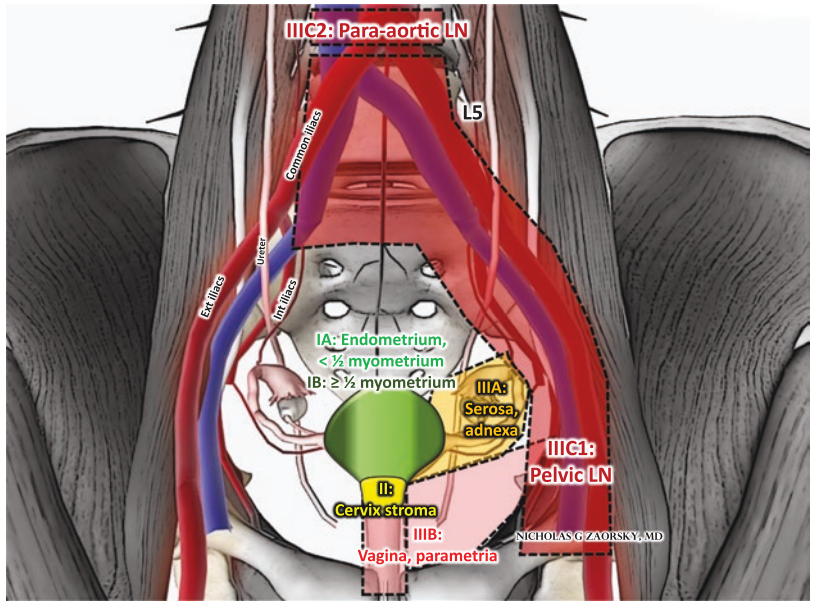
Acute RT Effects

- Fatigue, urinary frequency/urgency, diarrhea, epilation skin irritation
- Diarrhea = Imodium → Lomotil .

Late RT Effects

- Vaginal shortening, atrophy/dryness, stenosis
  - *Recommend dilator starting 1 month after treatment, 3x/w indefinitely.*
  - *Topical estrogen creams, lube, and moisturizers.*
- Vesicovaginal or rectovaginal fistula (<2%)
  - *If pt comes in with stool coming out of vagina → diverting colostomy.*
  - SBO/perforation (<5%), rectal bleeding.
  - *If pt comes with rectal bleed:*
  - *feel rectal anterior wall, hemorrhoids, and CBC.*
  - *If Hgb normal, f/u in 6 weeks w/ instructions to use stool softeners. If still low GI consult/colonoscopy, instruct to not bx, consider argon laser.*
- Pelvic insufficiency fracture = 5%; w/ osteoporosis = 15%
- Femoral neck fracture
- Ovarian failure

Uterine/Endometrial Cancer [1–4, 19–30]



- **T1**
- T1a (***IA***) – <½ myometrium
- T1b (***IB***) – ≥ ½ myometrium
- **T2** (***II***) – cervical stroma
- **T3**
- T3a (***IIIA***) – serosa/adnexa (*SAy it ain't so*)
- T3b (***IIIB***) – vagina/parametrium (***B*** *agina*, ***B*** *arametria*)
- **T4** (***IVA***) – bladder or rectum
- **N1** (***IIIC1***) – regional (pelvic/up to common iliac)
- **N2** (***IIIC2***) – para-aortic nodes
- **M1** (***IVB***) – distant

FIGO 1971 (Inoperable Endometrial Cancer Staging)

I. Confined to corpus
   IA. Length of uterine cavity 8 cm or less
   IB. Length of uterine cavity >8 cm
II. Involves corpus and cervix, but no extension beyond the uterus
III. Extends outside uterus but not outside the true pelvis
IV. Outside the true pelvis or involves the bladder or rectum
   IVA. Involves the bladder, rectum, sigmoid, or small bowel
   IVB. Distant mets

Pathology

– Simple hyperplasia→ cancer (<2%)
– Complex hyperplasia→ cancer (40%)
– **Subtypes:**
  - **Type I**. 80%. Endometrioid histology. Endometrial hyperplasia. G1–G2. Perimenopausal. ER driven. PI3K, PTEN, MSI. Less aggressive.
  - **Type II**. 20%. G3 Endometrioid. Non-endometrioid histology, e.g., clear cell, serous, and carcinosarcoma. Non-ER driven. Postmenopausal. Poor prognosis. p53.

Workup:

– H&P: *Postmenopausal bleeding*, ask about unopposed estrogen: nulliparity, obesity, tamoxifen, early menarche, late menopause, T2DM. Ask about IBD, pelvic RT.
– Labs: CBC, CMP, CA-125 (for trending in III/IV).
– US: Endometrial biopsy, imaging/scopes for symptoms. Normal endometrial stripe <5 mm. FNR is 10%. If negative and still symptomatic, do D/C.
– CXR + CT AP, MRI pelvis if suspected extrauterine involvement or not going to surgery.

- HNPCC (5%): <50 yo or FH colon or endometrial → genetic testing.
  - HNPCC = colonic + extracolonic (endometrial, other GI, ovarian).
  - Median age = 45; 80% colon, 60% endometrial.
  - Genetic testing = MLH1, MSH2, MSH6, PMS2.
- + pelvic nodes → 33% chance of + PA nodes.
- Creasman tables (uses AJCC 6 staging).

Risk pelvic LN+	G1	G2	G3
Endometrium only	0	3	0
Inner	3	5	9
Mid	0	9	4
Deep	11	19	34
Risk PA LN+ (2/3 risk of pelvic LN)	G1	G2	G3
Endometrium only	0	3	0
Inner	1	4	4
Mid	5	0	0
Deep	6	14	23

Surgical Procedure

- TAH-BSO + pelvic LND +/− PA sampling (if biopsy proven cervical ext.→ radical hysterectomy instead).
- Make midline incision.
- Inspect serosal, peritoneal, and diaphragmatic surfaces.
- Peritoneal washing (*does not affect staging*).
- Omental biopsy for serous, clear cell, and carcinosarcoma.
- Perform LND (in the U.S., not Europe) = common iliacs, external iliacs, internal iliacs, obturators + PA sampling.
- Sample PA for deeply invasive, high grade, serous, clear cell, and carcinosarcoma.
- Perform TAH, bivalve the uterus, and BSO.

Hysterectomy Types

- **Type I**: extrafascial hysterectomy. **Spares parametrium**; ureters not mobilized; ligate UA at the uterus. Takes 1–2 mm of vaginal cuff.
- Omental biopsy for uterine papillary serous carcinoma (UPSC) clear cell carcinoma (CCC). Use type I RH for most endometrial cancers.
- **Type II MRH**: Same as cervix above. Use this for endometrial cancers with cervical involvement.

Surgery +/– LND +/– RT

- **MRC ASTEC** trial 2009: stage I dz.: first randomization: TAH/BSO +/− LND. second randomization: intermed and high-risk pts. get obs vs adjuvant pelvic RT. No difference in OS for LND, 5-year OS 80%.
- NCIC EN.5 Study group.

	G1	G2	G3
I			
II			

- **ASTEC/EN.5** combination, 2009: Reported results of adjuvant RT. No difference in 5-year OS (84%) or DSS (~90%). WPRT reduced pelvic and vaginal recurrence, 6% vs 3%; however, had higher toxicity. Adverse risk factors identified: age >60, LVSI, tumor>2 cm, +cervical gland, ↑grade. These would later be used in PORTEC-1 and GOG 99.

	G1	G2	G3
I			
II			

Surgery +/− WPRT

- **GOG-99,** Keys 2004:
- Early-stage endometrial TAH/BSO + LND +/−50.4 Gy WPRT. No VCBT. LND was selective for any suspicious LNs. Initially enrolled *intermediate* risk (old stage I with any MI; occult II). Enrollment criteria revised while ongoing to only *high-intermediate* risk: (1) age >70 + 1 RF; (2) age >50 + 2 RF; (3) any age + 3 RFs. RFs are G2–3, LVSI, outer 1/3 MI.
- RT won. 4-yr. LRR 12 → 3% (SS), OS 86 → 92% (NSS). Mostly benefited high-risk patients. 72% recurrences in VC. Note difference for "high-intermed" risk for GOG-99 vs PORTEC-1.

	G1	G2	G3
I			
II			

– **PORTEC-1**:
Old IB (G2–3) + IC (G1–2): TAH/BSO w/o pelvic LND. Pts. with 50 + % MI specifically excluded. Randomized to +/−46 Gy WPRT, and possible VCBT boost if cervical involvement. RT won. LRR 14 → 4% between group 1 and group 2, 75% of failures in cuff. After vaginal recurrence, 2-year OS was 79% vs 21% if pelvic LN or DM. 15-yr rate of LRR: 16% (WPRT) vs 6% (VCBT), but no OS benefit (both ~85%). Defined "high-intermediate" risk features: (1) >60yo; (2) MI >50%; (3) G3 dz. If pt has two of these three RFs, then LR decreased from 24% to 4%. These pts. will be used to form cohort for PORTEC-2. Criticism was exclusion of pts. with >50% MI *and* G3, who would benefit most from WPRT. Among the points with two of these major risk factors, WPRT decreased LRR from 23% to 5%.

Adjuvant VCBT +/– WPRT
– **Norway**, Aalders 1980: old IB + IC: TAH/BSO + VC +/− 40 Gy WPRT (no LND). WPRT ↓LRR (7 → 2%). However DM slightly higher 5%, vs 10%, NSS. Unchanged OS. Subset analysis: >50% MI and G3 had improved CSM with WPRT, 28% vs 18%. LVSO and age >60 also identified as high-risk features.

Adjuvant WPRT vs VCBT
– **PORTEC-2**, Nout, 2010: old IB + IC + IIA. "High-intermediate dz": (1) >60 yo stage I, >50% MI or G3; (2) any age with endocervical glandular involvement, but not G3 with >50% MI. Randomize: 46 Gy WPRT vs VCBT. WPRT was to prox half of VC, parametrial, internal and exterior iliacs, and caudal part of common iliac chain. VC was LDR 30 Gy at 0.5–.7Gy/h, medium DR, 28 Gy at 1 Gy/h, or HDR, 21/3 – all to 5 mm from cylinder, 45–50 Gy equiv to mucosa. Similar results. Initial abstract, WPRT reduced pelvic failure (3y: 3.6 → 0.7%), however NSS by 5 years. VC recurrence similar between VCBT and WPRT: ~1.7%. 55% vs 13% had G1–2 GI toxicity. Tox resolved by 2y. Nout, 2009: update, WPRT has ↓QOL.

Adjuvant WPRT with IMRT
– RTCMIENDOMETRE, Barillot, 2014: IBG3, IC, or II endometrial cancer. Volumes per RTOG 041 study. 45Gy/25fx. CTCAE used at week 15. Toxicity was 27% had acute GI G2 toxicity. No G3+ toxicity. G1 tox in <20%.

Adjuvant RT +/– Chemo
– **PORTEC-3,** Creutzberg, de Boer, 2016. High-risk pts.: stage IAG3 + LVSI, IB G3, II, IIIA/B/C, I–III serous or clear cell. Randomize: Adjuvant WPRT + chemo vs WPRT alone in high-risk endometrial cancer. RT is 48.6/1.8 + 2 c concurrent cis 50 mg/m^2 in w1 and w4, then adjuvant carbo AUC5 and paclitaxel 175 mg/m^2 at 21 d intervals (adapted from RTOG 9708). In both arms, if cervical involvement, then VCBT. Primary outcome is 5y OS and FFS, currently no difference (ASCO, 2017). Worse QOL at 6 m for CRT, resolve by 1–2y.
– RTOG 9708: phase II: high risk early stage: WPRT + concurrent cisplatin, Q3wk. 4-yr. OS 85%, low failures.

Adjuvant RT vs Adjuvant Chemo
– GOG 122, Randall 2006: stage III/IV: debulking, then WART (30Gy/20fx, then pelvic LN boost of 15Gy/8 = total 45) vs chemo only (doxorubicin 60 mg/m^2 + cisplatin 50 mg/m^2 q3w x 7c, then 1c cis alone). For RT, if pelvic LNs were + and PA LNs not sampled, boost was to extended field covering all LNs. Fields AP/PA with PA kidney blocks, then 4-field box. Chemo won OS 42 → 55%, DFS 38 → 50%, but ↑toxicity. The only RCT where adjuvant RT loses? Criticisms: RT volume huge and doses inadequate for GTV. VCBT not used. Only 63% of pts. completed all planned chemo cycled due to toxicity. Reported survival sts adjusted for stage, which shouldn't be done for RCTs. There are no stats for unadjusted curves. This trial established SOC of chemo for III–IV endometrial cancer.
– GOG 249, presented ASTRO 2017: high risk stages I–II, serous, clear cell. Randomized between 45 Gy WPRT and cuff + carbo/Taxol. 3-year. OS 91% vs 88% (NSS). Acute toxicity worse with brachy/chemo, late toxicity similar.

Adjuvant Chemo +/– RT

– GOG 258, Matei ASCO 2017. Stage III/IVA endometrial cancer. Adjuvant RT + concurrent cis + 4c adjuvant carbo/Taxol vs 6c carbo/Taxol alone. *n* = 813. Similar G3+ tox, 58% CRT vs 63% CT. CRT reduced vaginal recurrence (3% vs 7%), pelvic+ PA LN recurrence (10% vs 21%). DMs more common with CRT (28% vs 21%).

Second Malignancy

– **PORTEC 1 + 2 + Dutch TME** pooled (2015): *n* = 2554. No increased risk of malignancy from RT: 26% in 15 years for both RT and non-RT arms.

Survival After Vaginal LR

– **Creutzberg/**PORTEC-1, 39 patients with isolated vaginal relapse, 87% txd with curative intent, either EBRT or BT. CR was 89%. At 3y, OS in salvage RT group 73%.5y OS 65% in control group vs 43% in RT group.

Treatment Paradigm

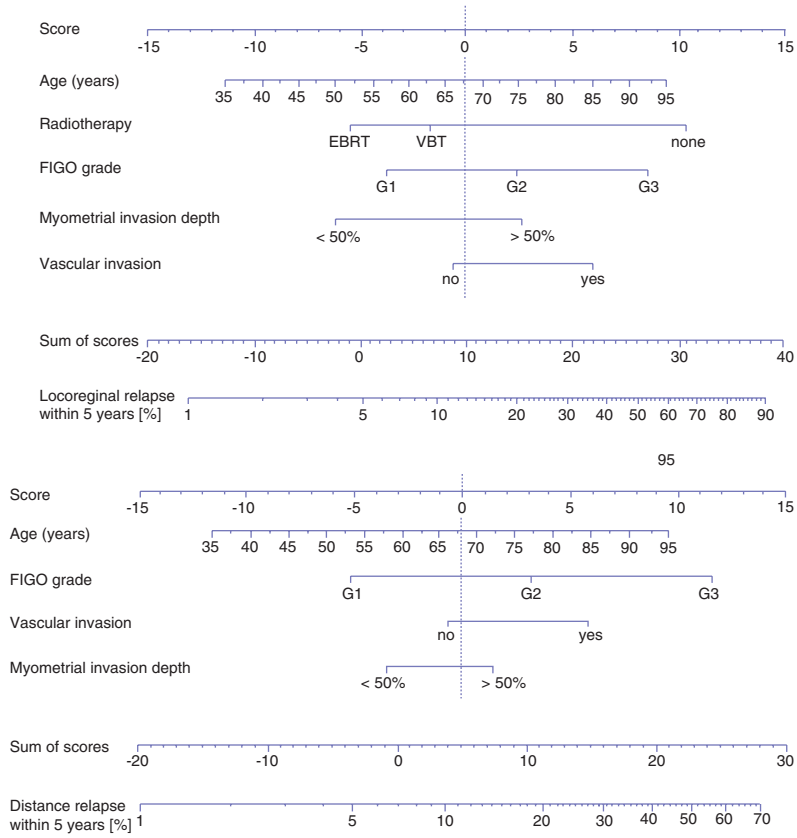
– All patients go for surgery if able: TAH/BSO, peritoneal inspection, fluid cytology, +/− LND (usually for grade 2/3), rad hysterectomy if cervical involvement.

	G1	G2	G3
IA	None HR: ± VCBT	None vs VCBT HR: ± VCBT	None vs VCBT HR: ± WPRT
IB	VCBT HR: ± WPRT	VCBT HR: ± WPRT	VCBT and/or WPRT
II	VCBT and/or WPRT	VCBT and/or WPRT	WPRT ± VCBT ± Chemo→Chemo
IIIA	WPRT ± VCBT + Chemo→Chemo *Chemo is carbo AUC5 , paclitaxel 175 x5c		
IIIB	Chemo and/or WPRT **+ VCBT**		
IIIC	Chemo and/or WPRT ± VCBT		
IV	Debulk to R0 -1. Then Chemo ± WPRT ± VCBT		

High Risk (HR) = >60 yo, LVSI, Cervical Segment Involvement
Indications for post-op RT with vaginal brachytherapy (VB) alone (per ASCO Consensus Guideline 2015):

- Recommended for FIGO IAG3, IBG1–2.
- Consider for FIGO IAG1–2 but high-risk features (+LVSI or >60yo).

Nomogram to predict local (A) and distant (B) recurrence (Creutzberg, 2015)



Endometrial general dosing

Setting	Treatment	Doses	EQD2 recommended
Post-op	VCBT alone to prox 3–4 cm vagina	**6 Gy × 5 to 0 mm** 4 Gy × 6 to 0 mm 5.5 Gy × 4 to 5 mm 7 Gy × 3 to 5 mm (increased tox)	**60 Gy** If prescribing to 5 mm, vaginal surface dose is 130%; rectal dose is 70%
	VCBT + WPRT	**6 Gy × 3 to 0 mm** + 45 Gy (0921) 6 Gy × 2 to 0 mm + 50.4 Gy (0418) "4–6 Gy × 2–3 to 0 mm + 45–50" (NCCN)	**70 Gy to vaginal mucosa**
Definitive	EBRT + Y-BT	"Individualized" (NCCN)	BT alone EQD2 D90 >48 Gy BT + EBRT EQD2 D90 >65 Gy If MRI used EQD2 **>80 Gy**

Techniques

VCBT CT Sim

- Wait 6–8 weeks after surgery, generally <12 weeks.
- +/− gold seed fiducial markers into vaginal cuff (exam room).
- Patient gets on CT simulation table, cylinder placed in vaginal canal, using largest diameter possible, and cylinder secured to treatment table.
- Take scout film to ensure cylinder is sup.
- Obtain CT simulation and transfer patient to stretcher while doing CT-based plan.
- Contour the bladder, rectum, and bowel.

VCBT Technique

- Cylinder allows treatment of entire length of the vagina, if needed. Cylinder diameter should be largest that will fit comfortably to minimize air pockets (3 cm average).
- Ovoids may improve lateral coverage if remnants of vaginal fornices present, but must still ensure adequate coverage at vaginal apex.
- Check for air gaps at the surface of the cylinder. If present, consider a larger diameter cylinder.
- When contouring the rectum, thickness of vaginal wall is ~5 mm, so rectal contour should not extend to <5 mm from cylinder.
- Length of the vagina treated predicts vaginal stenosis (Brachytherapy, Park et al. 2015).
- Volume is the cylinder itself, not the tissue.
- Treat proximal 3–5 cm of the vagina. Rarely, entire length of the vagina can be considered for serous/clear cell histology, grade 3, or extensive LVI, but should be used with caution (per ABS Consensus Guideline 2012).
- NOTE: "active length" must be converted to actual vaginal treatment length per institutional standards.

VCBT Alone Dose

- Dose is EQD2 ~60 Gy to vaginal mucosa.
- 7 Gy x 3 fractions (3x/week) to 0.5 cm depth (per PORTEC-2), though this has higher toxicity. Rx to 0.5 cm depth results in 130–170% dose at surface (10.5 Gy), rectal dose 70%.
- 6 Gy x 5 to vaginal mucosa.
- 4 Gy x 6 to vaginal mucosa.

WPRT Technique

- IMRT.
- Contour nodal CTV based upon RTOG guidelines.
- If (+) pelvic LN → proximal PA (L1/L2).
- If (+) PA nodes → T11/T12.
- Common iliac = artery/vein +7 mm, ensure posterolateral coverage hugging vertebral bodies/psoas.
- Presacral includes 2 cm of tissue anterior to S1, S2 [+S3 if cervix involved], should not extend into foramina, and should stop when piriform muscle becomes visible.
- External iliac = artery/vein +7 mm to top of femoral head (surrogate for inguinal ligament), ensure adequate anterior coverage.
- Internal iliac = artery/vein +7 mm, posteriorly bounded by piriform muscle.

- Obturator = top of femoral head to top of pubic symphysis, include 1.5 cm of soft tissue medial to pelvic sidewall.
- Vaginal cuff = create vagina ITV, sum of vaginal contours full + empty bladder, include vaginal cuff and at least 3 cm of vagina inferior.
- PTV = CTV + 5–7 mm.
- Contour bladder, rectum, bowel, cord.
- Dose = 50.4 Gy if WPRT alone. 45 Gy if VCBT boost.
- Boost gross nodes to 60 Gy with IMRT.

On Treatment

– Daily CBCT or KV imaging
  - If bladder not full enough, re-instruct patient/drink more water.
  - If gas, insert red rubber catheter.

WPRT+VCBT:

- ~70 Gy needed to vaginal mucosa.
- 45 Gy EBRT +6 Gy × 3 to vaginal mucosa (RTOG 0921 regimen).
- OR 50.4 Gy EBRT +6 Gy × 2 to vaginal mucosa (RTOG 0418 regimen).
- Boost: 6 Gy × 5 fractions (twice weekly) to vaginal surface (ASTRO Consensus Guideline 2014).
- Constraints w/ EBRT: D2cc rectum ≤70 Gy; D2cc bladder ≤90 Gy.
- If doing pre-op RT, dose is 75–80 Gy with BT + WPRT.

Medically Inoperable

– For stage I, should treat to EQD2 >48 Gy for BT alone, and >65 Gy for EBRT+BT **(Schwartz, 2015)**.
  - 45 Gy WPRT + Y-app (8.5 × 2) or just Y-app 8.5 × 4. Full list of doses for intrauterine sources below.

# HDR fx	HDR dose/fx (Gy at 2 cm)	Equiv dose for tumor (Gy)	Equiv dose late effects (Gy)
4	8.5	52	43
5	7.3	53	41
6	6.4	53	30
7	5.7	52	39

Stage III/IV

– Post-op chemo and RT. Most guidelines do not specify sequence. Study by Alvarez et al. compared order. Sandwich won.

Alvarez, stage III/IV chemo and RT order	3y PFS	3y OS
RT, then chemo	47	54
Chemo, then RT	52	57
Chemo, RT, chemo	69	88

Salvage

– WPRT + VC boost.
– Dose = 54 Gy; then: either IC (IVRT) (<5 mm) or IS (>5 mm) brachytherapy, 6 Gy x 5, or 59.4 Gy conedown.

Indications for Chemotherapy (Weekly Cis)

1. + LN
2. Bulky (>4 cm)
3. High-risk pathology

Fertility Preservation

– For PR+ tumors, Megace may be attempted with EBRT or TAHBSO in select cases. Pts. should have G1, endometrial histology, stage IA on MRI, limited comorbidity. CR in 50% of pts. Monitor q3-6 m with endometrial sampling.

Constraints

– Vagina.
  - Upper third: 120 Gy
  - Middle third: 80–90 Gy
  - Lower third: 60–70 Gy
– Sterilization occurs after 2–3 Gy.
– Ovarian failure occurs after 5–10 Gy.

Follow-Up

- Surveillance for stage I patients who don't get RT/follow-up
- q3 mo x 1 year, q4 mo x 2 years, q6 mo for years 3, 4, and 5
- Dilator at 2–4 wks post-RT → indefinitely

Toxicity

Acute RT Effects
- Fatigue, urinary frequency/urgency, diarrhea, epilation skin irritation
- Diarrhea = Imodium → Lomotil

Late RT Effects
- Vaginal shortening, atrophy/dryness, stenosis.
- Recommend dilator starting 1 month after treatment, 3x/w indefinitely.
- Topical estrogen creams, lube and moisturizers.
- Vesicovaginal or rectovaginal fistula (<2%).
  - **If pt comes in with stool coming out of vagina** → vitamin E, HBO, Trental, consider diverting colostomy.
    - SBO/perforation (<5%), rectal bleeding.
  - **If pt comes with rectal bleed:**
    - Feel rectal anterior wall, hemorrhoids, and CBC.
    - If Hgb normal, f/u in 6 weeks w/ instructions to use stool softeners. If still low GI consult/colonoscopy, instruct to not bx, and consider argon laser.
- Pelvic insufficiency fracture = 5%; if osteoporosis = 15%.
- Femoral neck fracture: refer to ortho.
- Ovarian failure.

Outcomes (OS5)
- I – 90
- II – 70
- III – 50

Uterine Serous Adenocarcinoma

Background
- Previously uterine papillary serous carcinoma, UPSC
- <10% of uterine cancers
- More aggressive than endometrial adeno
- Histologically like ovarian cancer
- G3 by definition
- UPSC classically fails *subdiaphragmatic*

Treatment
- Treatment is TAH-BSO.
- LN staging, peritoneal lavage with cytology, and omental/peritoneal biopsies.
- Then adjuvant chemo, with platinum/taxane-based agents. Then +/− tumor-directed RT. RT usually VCBT or pelvic/PA LN RT, depending on extend of PLND.
  - I – IVRT + chemo
  - II, III – pelvic + IVRT + chemo → chemo with Cis (40 mg/m^2) weekly, carbo/Taxol x 3
- WART not considered tumor-directed therapy and is no longer recommended.

Uterine Sarcoma [1–4, 31–34]

Leiomyosarcoma (LMS) and Endometrial Stromal Sarcoma (ESS)

- **T1**
  - T1a (***IA***) – ≤5 cm
  - T1b (***IB***) – >5 cm
- **T2**
  - T2a (***IIA***) – adnexa
  - T2b (***IIB***) – pelvic tissues
- **T3 –** invades abdominal tissues
  - T3a (***IIIA***) – one site
  - T3b (***IIIB***) – multiple sites
- **T4** (***IVA***) – bladder or rectum
- **N1** (***IIIC***) – nodes
- **M1** (***IVB***) – distant

Adenosarcoma

- **T1**.
  - T1a (***IA***) – endometrium only
  - T1b (***IB***) – ≤½ myometrium
  - T1c (***IC***) – >½ myometrium
- **T2**.
  - T2a (***IIA***) – adnexa
  - T2b (***IIB***) – pelvic tissues
- **T3 –** invades abdominal tissues
  - T3a (***IIIA***) – one site
  - T3b (***IIIB***) – multiple sites
- **T4** (***IVA***) – bladder or rectum
- **N1** (***IIIC***) – nodes
- **M1** (***IVB***) – distant

Tumor	Staging	Symptoms	Behavior	LNM incidence	Surg, LND	Adjuvant WPRT indications
Carcinosarcoma (MMMT) Malignant mixed mesodermal tumor/ malignant mixed Mullerian tumor	Treat and stage like regular high-grade endometrial cancer (FIGO staging)	Vaginal bleeding	Epithelial component dictates prognosis and treatment, not sarcomatous component Most have serous or G3 endometrioid histology and behave as their pure uterine cancer counterpart	20–38	PLND, PA-LND usually recommended	(Similar to endometrial): >60yo >50% MI II LN+ R+
Leiomyosarcoma (LMS)	IA/B: 5 cm cutoff IIA: adnexa IIB: pelvic tissues IIIA: 1 abdominal tissue site IIIB: >1 site IVA: bladder or rectum IV: DM	Uterine fibroid like symptoms		7–9	PLND, PA-LND usually not recommended unless extrauterine dz	R+
Endometrial stromal sarcoma (ESS)			Grade most important (vs LMS or MMMT) G1: hormone sensitive, indolent courseG3: aggressive, similar to LMS and MMMT Similar to undifferentiated sarcoma	10		R+
Adenosarcoma	Like AJCC 6th edition FIGO staging					R+

Overview
- 4% of uterine malignancies
- Higher rate of DM than regular uterine cancer
- Prognostic index for STS does not apply to uterine sarcomas

Genetics
- Hereditary leiomyomatosis and RCC (HLRCC) syndrome are rare, AD, caused by mutations in fumarate hydratase, a Krebs cycle enzyme.
- P53 mutation.
- ATRX mutations.
- MED2 mutation.

Trials
- EORTC 55874: stage I–II sarcomas (41% carcinoma) → surgery +/− WPRT 50.4/28. RT improved LC (40% vs 22%), but not OS. Benefit for carcinosarcoma, no benefit for LMS. 92 enrolled had carcinosarcoma, which is no longer classified as uterine sarcoma.
- Wright 2008: SEER database. Showed PORT improves OS for MMMT but not LMS.
- Mayo clinic: retrospective LMS. WPRT did not change OS but ↓LC.
- GOG 150: carcinosarcoma→ WART vs chemo. No difference but WART had ↑tox.

NCCN
- TAH/BSO initial treatment of choice.
- Limited randomized data after.
  - I – Observe.
  - ≥II – Gemcitabine/docetaxel
- WPRT fields are the same.
- Indications per table.

Vulvar Cancer [1–4, 35–44]

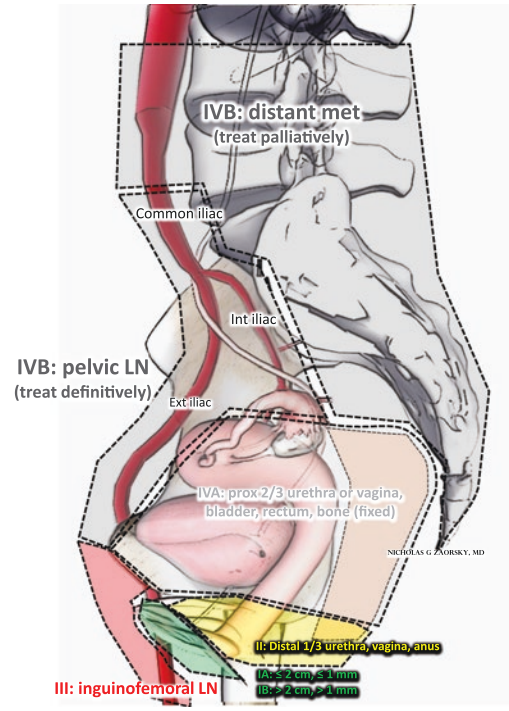
FIGO is combination of clinical, surgical, and path staging.

- Tis – CIS.
- **T1**.
  - T1a (***IA***) – ≤2 cm and ≤1 mm DOI.
  - T1b (***IB***) – >2 cm or >1 mm DOI.
  - **T2** (***II***) – ↓1/3 urethra, ↓1/3 vagina, or anus.
- **T3** (***IVA***) – ↑2/3 urethra, ↑2/3 vagina, adjuvant organs
- *Note no T4 for vulvar cancer.*

- **N1** (***IIIA***) – note all LNs are inguinal, not pelvic.
  - N1a – 1–2 LNs, each <5 mm.
  - N1b – 1 LN, ≥5 mm.
- **N2.**
  - N2a (***IIIB***) – 3+ LNs, each <5 mm.
  - N2b (***IIIB***) – 2+ LN ≥5 mm.
  - N2c (***IIIC***) – ECE.
- **N3** (***IVA***) – fixed/ulcerated LN.
- **M1** (***IVB***) – distant (pelvis LN is M1 disease. This will likely change in next AJCC manual.)

		T1a	T1b	T2	T3
		≤2cm + ≤1mm DOI	>2cm or >1mm DOI	↓1/3 Urethra, Vag; Anus	↑2/3 Urethra, Vag; Anus; *other organ*
N0		IA	IB	II (*UVA*)	IVA
N1a	1-2, <5mm	IIIA			
N1b	1, ≥5mm				
N2a	3+, <5mm	IIIB			
N2b	2+≥5mm				
N2c	ECE	IIIC			
N3	ulcer	IVA			
M1		IVB			

Stage	5-yr OS
I	90%
II	81%
III	68%
IV	20%



Overview
- 3500 dx/yr. in the U.S., 5% GYN malignant, 1% female malignant
- Subsites: labia majora/minora (70%), mons pubis, clitoris (10%), vestibule, perineal body (5%), posterior fourchette, Skene's glands = posterior to urethra, Bartholin's glands = posterior to introitus
- Workup: H&P, CBC, UA, HIV, EUA/PAP/DRE, PET-CT (strongly recommended, esp. for T2+) vs MRI based on size/stage
- Vulvar pruritus and pain
- Younger: VIN, Pap smear history, HPV vaccination, smoking history, HIV, pregnancy
  - <5% of patients w/ VIN → invasive cancer
  - Basaloid SCC (often p16 positive)
- Older: vulvar dystrophy, including lichen sclerosis, smoking, laundry facility worker
  - 5% of patients w/ LS → invasive cancer
  - Keratinizing SCC (p16 negative), 80% of cases

Physical
- Vaginal, rectal, inguinal LN exam
- Pelvic exam w/ Pap smear
- Bx primary and inguinal u/s (*highest sensitivity = u/s, >90%) w/ FNA of suspicious LN.
- MRI, PET/CT
- EUA
- Cystoscopy/proctoscopy for bladder/rectal involvement

Nodal Risk

- LN status is the most important prognostic factor for OS.
- LN spread: superficial inguinofemoral → deep inguinofemoral → exterior iliac. Exception: clitoris can bypass the superficial LNs and can spread straight to deep femoral LNs and pelvic LNs (obturator and external iliac).
  - Cloquet's node: most superior deep inguinal/femoral node. Can be mistaken for inguinal hernia.
- cN0 →
  - 25% inguinofemoral LN+
  - *if* IF LN (+) → 30% pelvic LN+, → 25% contralateral inguinal femorals LN+.

- **Size and nodal risk**
  - 2 cm tumor – 25%

- **DOI and nodal risk (for tumor ≤2 cm)**
- ≤1 mm – <1%
- 2 mm – 8%
- 3 mm – 10%
- 5 mm – 25%
- >5 mm – 40%
- lower UVA – >30%,

Surgery
- Lymphadenectomy for DOI >1 mm or G3 or LVSI (all stage IB+ pts).
- 2 cm margin is goal.
- PORT for +margin, close margin (***8 mm fixed, 1 cm frozen***), LVSI, DOI >5 mm.
- GROINSS-V:T1–T2 → SLNBx→no LND if neg. 3-yr. regional failure 2.3%. All isolated groin recurrences w/in 16 m. 10-yr. CSS 91% among SLNB- pts.; 65% if SLNB+. Lower tox for SLNB than LND.
- GOG 173, Levenback, 2012: SLNB, then completion inguinofemoral LND for T1–T2. 92% sensitivity of SLNB. FNR 2% if <4 cm; 7% if 4+ cm.
- **Role of SLNB**: Tumor <4 cm, >1 mm DOI, no palpable LNs, unifocal, no previous vulvar surgery, surgeon has performed >10 SLNBs prior.

Nodal RT

– Note: groin LN recurrences are almost never salvageable.
– GOG 37, Homesley, 1986; Kunos, 2009: *n* = 114. Rad vulvectomy with bilateral inguinal LND → PLND vs RT (pelvic +groin). RT was 6w post-op, 45–50/1.8–2, AP/PA. RT won, study closed early. 2-yr. LRR 24 → 5%, 2-yr OS 54 → 68%. Subset analysis: benefit limited to cN+ or matted LNs, 2+ LNs (similar to H&N sites), or ECE+. 6y OS NSS, but CSM was: 51% surgery vs 29% RT; as was groin failure 24% surgery, 5% RT. OS benefit also seen in RT with >20% ipsilateral LN+.
– GOG 88: cN0 with WLE → RT vs ILND+PORT. LR, PFS, and OS favored ILND+PORT.
  • Criticisms: no CT staging, 50 Gy mixed beam to 3 cm depth (inadequate dose and coverage for gross disease).
  • Koh 1993: mean inguinal depth 6.1 cm, failures in GOG88 <47Gy.
– Katz 2003: modern RT techniques; LC with RT ~90%.

Patterns of Failure

– GOG 74 + 88. Stehman, 1996. Stages I–III all had rad hemivulvectomy or vulvectomy. Most had inguinal LND. 92% of groin recurrences later died. Other vulvar recurrences, 32% died. Thus, thorough eval and tx of groin nodes key; although GOG 37 recommends RT for 2+ LNs, many would recommend for 1+.

Chemo

– Gill, 2015: NCDB. pLN+ vulvar cancer. CRT vs RT alone. Chemo reduced risk of death by 35%.

Neoadjuvant CRT for Unresectable Disease

– GOG 101: advanced primary or nodes→cisplatin/5FU + RT; 47.6 Gy BID; 97% were converted to resectable (31% pCR).
– GOG 205, Moore, 2012: phase II, T3–4 unresectable→inguinal LND → pre-op CRT (cisplatin 40 mg/m^2 qw + 57.6Gy/32fx). 45 Gy AP/PA pelvis, 12.6 Gy boost. Then resection or biopsy to confirm CR. 78% pCR, 64% cCR, 40% 2-yr. OS. Note the higher pCR rates vs GOG 101 – likely bc of higher dose, no break.

Treatment Paradigm/Pearls

– If resectable (can get 8+ mm margins w/o morbidity), then resect. If DOI >1 mm, then need Bx. Then assess for indications for post-op RT.
– No RCTs comparing chemo regimens.

Indications for Post-op RT:
to the primary (based on Heaps/UCLA data)

- R+: <1 cm clinical margin; <0.8 cm fixed margin. This was the strongest predictor in Heaps data, 48% vs 0%.
- LVSI.
- DOI >5 mm – 10 mm (continuous).
- >9.1 mm had 15% LR on Heaps.
- Size >4 cm.
- Infiltrative pattern.

RT to the Nodes:

- cLN+.
- >0–1 pLN+.
- ECE.

Indications to add chemo: T2–3, N+

Management

IA:
- Radical vulvectomy vs WLE (if well lateralized).
- No need to address nodes.

IB:
- Radical vulvectomy vs WLE (if well lateralized) + SLNBx, if (+) SLN → b/l IFLND.
- Only SLNBx if primary ≤4 cm, dual tracer (dye + radiotracer). If primary >4 cm need upfront bilateral IFLND.
- In GROINSS-V, if SLN (−), only 3% LR in untreated IFLN basin.
- Complications, SLNBx vs IFLND: ↓lymphedema (2% vs 25%), ↓wound breakdown/cellulitis

II (spread to lower 1/3 urethra, vagina, anus):

- Radical vulvectomy + unilateral or bilateral inguinal LND +/− post-op RT.

III-IVa – Radical vulvectomy+ bilateral ILND →Chemo RT

Post-op CRT
- 50.4 Gy to CTV (vulva and elective LN)
- 59.4 Gy to +SM or + LN
- 64.8 Gy to GRD
- Weekly cis (40 mg/m^2)

Unresectable = definitive CRT
- 50.4 Gy to CTV (vulva and elective LN)
- 59.4 Gy to +SM or + LN
- 64.8 Gy to GRD
- Weekly cis (40 mg/m^2)
- GOG 205: cis + RT (57.6 Gy) → incisional biopsy to assess response, if (+) → radical vulvectomy
- cCR = 65%, pCR = 50%

Technique

Simulation:
- Full bladder and empty rectum
- Supine, frog leg, Alpha Cradle
- Wire entire vulva, place additional fiducial markers around gross disease
- CT sim + IV contrast

Contours:
- GTV = Primary/gross residual
- CTV_Vulva = GTV + 1 cm and encompassing at least entire vulva
  - Anterior vulva includes at least 2 cm of the urethra to bladder neck.
  - Posterior vulva includes perineum between posterior fourchette and anal verge.
  - Vaginal extension: gross dz. + 3 cm. Consider entire vagina with creation of vaginal ITV (w/ full and empty bladder) + presacral LN.
  - Anal canal includes entire mesorectum and perirectal LN.
- PTV_Vulva = CTV_Vulva +1 cm
- CTV_LN = external iliacs, internal iliacs, obturators, inguinals (+ presacral LN for vaginal extension and + mesorectum/perirectal for anal canal). If posterior vaginal, then presacral nodes. In certain cases, lower common iliacs (L5/S1)
- Inguinal LN contours:

ASTRO consensus for inguinal LN coverage	Radial margin around femoral vessels (mm)
Anteromedial	≥35
Anterior	≥23
Anterolateral	≥25
Medial	≥22
Posterior	0
Lateral	0

- Sup = top of femoral heads
- Inferior = 2 cm below saphenofemoral junction
- Medial = beginning of adductor longus; lateral = iliopsoas
- Anterior = anterior border of sartorius; posterior = posterior border of pectineus
- PTV_nodes = CTV_LN + 7 mm
- PTV_LN_CD = GTV_LN + 1–2 cm

Doses (per ACR Consensus Guidelines):

- **Primary RT dosing.**
  - R0: 45–50.4 Gy
  - Close margin (<5 mm): 56–60 Gy
  - R1: 63–66 Gy
  - R2/gross residual: 64.8–70 Gy
- **LN RT dosing.**
  - 45 Gy to b/l groin nodes and pelvis. Boost involved LN (Viswanathan):
  - 1 LN: 50.4Gy
  - 2+ LN: 54–60Gy
  - ECE: 60–65Gy
  - Gross nodes (undissected): 64.8–70Gy

Planning:

- IMRT

On treatment:

- Bolus and OSLD with first fraction
- Daily KV imaging

Side Effects

- Cisplatin toxicity.
- Standard gynecologic pelvic toxicity.
- Moist desquamation by 3rd–5th week. If desquamation occurs earlier, then treat with fluconazole; if it worsens, then likely superinfection should be treated with Cipro.

Outcomes

5 yr	OS
I	**80**
II	**60**
III	**40**

Follow-Up

q3 mo × 1 year, q4 mo × 2 years, q6 mo for years 3, 4, and 5

Vaginal Cancer [1–4, 45–49]

AJCC 8 FIGO stage	Original FIGO	Description	Treatment	Lian 2008 5-yr DFS	Crevoisier 2007 5-yr DFS	Frank 2005, 5y values (%)		
						DFS	Pelvic control	CSS
CIS								
I	I	Vagina mucosa only	Surgery or VCBT If >5 mm deep, >2 cm or G3: add LND or WPRT	90%	83%	85	86	85
II	II	Paravaginal tissue/ submucosa	WPRT to 45 Gy + Cisplatin-based chemotherapy, rescan, then + VCBT to 75 Gy (6 Gy x3 HDR)	87%	76%	78	84	78
III	II (if just N1) III (if T3)	Pelvic wall (T3) or pelvic/inguinal LN up to common iliac (N1)		32%	52%	83	71	58
IV	IV	A: bladder or rectumB: DMs		26%	–			

Original FIGO Staging (Hacker, 2012) does not mention LN involvement. Thus, T2 N1 is FIGO II.

Overview
- Primary vaginal cancer is rare, only 1–2% of GYN malignancies. If the tumor extends to either cervix or the vulva, it is primary of those sites, not the vagina. If history of cervical or vulvar cancer in past 5 years, it is recurrence.
- Risk factors: CIS, HPV, irritation, ↑sex, DES.
- Risk of nodal involvement.
  - I: 5%
  - II: 25%
  - III: 75%
  - IV: 85%

Workup
- h/o prior cancer, HPV, VAIN/CIS, vaginal irritation, maternal DES exposure
- Physical, including inguinal LN exam, pelvic exam, and Pap
- EUA: necessary; in contrast EUA rarely necessary for cervical
- Bx primary w/ FNA of suspicious LN
- If adenocarcinoma → D&C to r/o endometrial
- MRI with aqueous gel in the vagina, PET/CT
- Cystoscopy/proctoscopy for anterior/posterior wall involvement, respectively

Pathology
- SCC
- Adenocarcinoma: most commonly mets; DES-related clear cell (mean age 26); non-DES-related clear cell (mean age 70)
- Melanoma
- Sarcoma
- LMS most common

Poor Prognostic Features
- Stage
- Age >60
- Low hemoglobin
- >4 cm
- Middle/lower 1/3

Post-op RT Alone
- Frank 2005. 5-year pelvic control 86% for stage I, 84% stage II, and 71% for stages III–IVA. 20% got concurrent cis-based chemo. 5-year DSS 86% stage I, 84% stage II, and 71% stages III–IVA. Predominant relapse was LRR, 68% for Stage I-II, 83% for III-IVA. Major complications: 4% Stage I, 21% Stage III-VIA. Tumors >4 cm had worse CSS, 60% vs 82%. Predominant failure for SCC was locoregional, while clear cell more likely to have DMs.
- Note there are no RCTs to show benefit of concurrent CRT for vaginal cancer; still stages II–IV dz. treated with definitive CRT, usually with weekly cis.

Neoadjuvant CRT for Unresectable Disease

– GOG 101 advanced primary or nodes→cisplatin/5FU + RT; 47.6 Gy BID; 97% were converted to resectable (31% pCR).

Treatment

– **VAIN 1**: observation
– **VAIN 2/3**: WLE, laser, 5FU, Vcuff.
– **I**: surgery or VCBT to 6 Gy x 5.
  • If >5 mm deep, >2 cm or G3: add LND or WPRT.

– **II**:
– **(Option 1**) WPRT to 45 Gy + BT to 75 Gy (6 Gy x 3 HDR) + cisplatin-based chemotherapy (40 mg/m^2 weekly)
– Same simulation/fields as vulva (L5/S1)
– If involves lower 1/3 vagina, include inguinal LN.
– Reevaluate patient at 40 Gy for whether <5 mm or ≥ 5 mm.
– BT when possible:
  • IC BT is for superficial lesions <0.5 cm from surface.
  • IS BT is for deep tumors >0.5 cm from surface.
  • Apex = template. Lateral and distal = freehand.

(Option 2): Radical vulvovaginectomy + pelvic LND + IFLND for distal 1/3

– **III/IVA:**
– Definitive CRT with cisplatin (40 mg/m^2 weekly)
– WPRT (45 Gy) + IS brachytherapy or IMRT boost

Technique

– Sim frog leg.
– Vaginal marker.
– Fields: pelvic, R/L inguinal.
– Sup border at L5–S1. Inferior is 2 cm below vag introitus. Lateral is 2 cm lateral to pelvic brim.
– If disease involves the rectovaginal septum (e.g., near pouch of Douglas) or bladder, then include the perirectal LNs, do not BT because of high risk of fistula, and use IMRT boost.
– **Vagina Tolerance**
  • Upper vagina = 120 Gy
  • Middle vagina = 100 Gy
  • Lower vagina = 80 Gy

ABS/UPMC/MDACC Recommendations

Based on Location:

Apex: and <0.5 cm, use ICRT. If >0.5 cm, EBRT or interstitial.

Mid-vagina: interstitial therapy for anterior or lateral. If posterior or massive, use EBRT boost.

Distal: confined lesions gevt interstitial. Massive tumors need EBRT boost.

Who should get vaginal cylinder alone? Superficial (<0.5 cm thickness).

Who should get interstitial brachy? Apical tumor, well defined, mobile, and >0.5 cm thick.

Who gets chemo? Stage III+, high-risk dz.

Ovarian Cancer and Fallopian Tube Cancer [1–4, 47, 50–55]

AJCC 8th Edition

- **T1**.
  - T1a (***IA***) – one ovary, capsule intact
  - T1b (***IB***) – both ovaries, capsule intact
  - T1c (***IC***) – capsule ruptured or + washings
- **T2** – pelvic extension.
  - T2a (***IIA***) – implants on uterus/tube, −wash
  - T2b (***IIB***) – implants in pelvis, −wash
  - T2c (***IIC***) – implants with +wash
- **T3.**
  - T3a (***IIIA2***) – micro-peritoneal implants
  - T3b (***IIIB***) – macro-peritoneal implants <2 cm
  - T3c (***IIIC***) – macro-peritoneal implants ≥2 cm
- **N1** (***IIIA1***) – intra-abdominal/inguinal nodes
- **M1** (***IV***) – distant

AJCC 7th Edition (Changes in stage III dz):

- **T3**
  - T3a (***IIIA***) – micro-peritoneal implants
  - T3b (***IIIB***) – macro-peritoneal implants <2 cm
  - T3c (***IIIC***) – macro-peritoneal implants ≥2 cm
- **N1** (***IIIC***) – intra-abdominal/inguinal nodes

Overview

– BRCA1: 45% risk, BRCA2 25% risk (also HNPCC).
– Epithelial 65%, germ cell 25%, sex cord stromal 5%, mets 5%.
– Workup: H&P, gyn exam, labs, CA125, AFP/bHcG.
– US, CT C/A/P.
– Surgical staging and debulking.
– Similar to fallopian tube, presents at advanced stage.
– Domchek, 2010; Finch, 2014: For BRCA+ women, a BSO decreases risk of ovarian ca development by 70–80% and additionally appears to decrease risk of breast cancer and all-cause mortality.

Trials

– GOG 111: cis/paclitxel improved OS
– GOG 158: carb/paclitxel less toxic
– GOG 172: intraperitoneal chemo toxic but effective
– Smith 1975: WART vs old chemo. Same results but more tox with WART (WART is 30 Gy at 1.5/fx)

NCCN

– Tx = Symptoms/debulking → chemotherapy
– Pt refuses chemo → WART 30 Gy at 1.5 Gy fractions + pelvis and PA LN boost to 45 Gy
  - Block kidneys at 15 Gy, liver at 25 Gy
– RT generally only for local recurrence or palliation

Fallopian Tube

– Made mostly of epithelial cells.
  - Serous carcinomas are 75% of cancers, endometrioid and mucinous are 10%.

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Hematologic Cancers

10

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Abstract

This chapter discusses the general management of patients with hematologic cancers, with special focus on principles that guide radiotherapy management. Several key components of trimodality care and radiotherapy field design are discussed.

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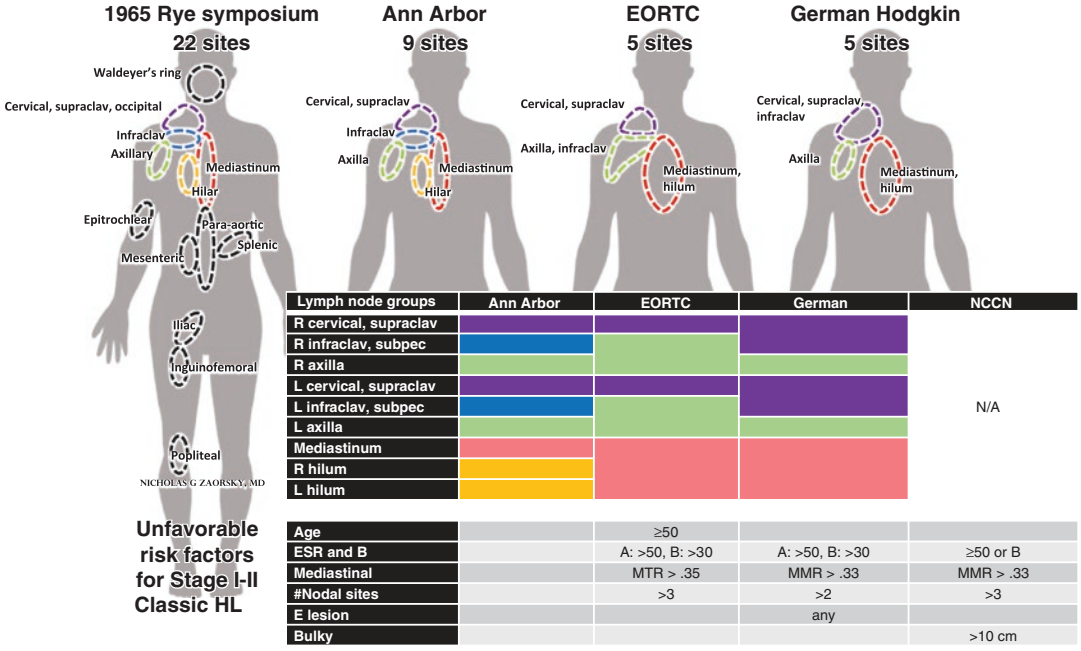
Uptake	No uptake		Mediastinum		Liver		New site
Deauville	1	2		3		4	5a 5b
Interpretation	Negative			Equivocal		Positive	



Lymph node groups	Ann Arbor	EORTC	German	NCCN
R cervical, supraclav				
R infraclav, subpec				
R axilla				
L cervical, supraclav				N/A
L infraclav, subpec				
L axilla				
Mediastinum				
R hilum				
L hilum				

Unfavorable risk factors for Stage I-II Classic HL

Age		≥50		
ESR and B		A: >50, B: >30	A: >50, B: >30	≥50 or B
Mediastinal		MTR > .35	MMR > .33	MMR > .33
#Nodal sites		>3	>2	>3
E lesion			any	
Bulky				>10 cm

Hematologic Pearls [1–3]

General Workup

- **History**:
  - **B-sx:** fever >38°, drenching night sweats, weight loss >10% over 6 months.
  - **Also ask about** pruritus/pain with EtOH.
- **Physical**: examine all nodal stations (spleen, liver, Waldeyer's ring); slit lamp, ophtho exam if ocular involvement.
- Fertility preservation: sperm/egg bank, oophoropexy.
- Core or excisional bx (not FNA because need architecture), with CD markers and relevant translocations.
- Labs: CBC, CMP w/ diff, ESR, LFTs, albumin, LDH, HCG, HIV, beta-2 microglobulin for NHL, HepB/HepC for rituximab because of HBV reactivation from CHOP.
- Smoking cessation.
- PFTs for bleomycin.
- MUGA for adriamycin.
- Vaccines if splenic RT: pneumococcal, H flu, meningococcal.
- BM Bx:
  - **For HL,** previously if B-sx, stage III/IV, cytopenias with negative PET, recurrence. Now only if cytopenias with negative PET-CT.
  - **Get it for all NHL.**
  - Not needed for MALT.
- Always consider referral for protons, especially in young.
- Follow-up: cardiac, lung tox, second cancer, TSH q6-12 m if treating neck, annual MRI and mammo for women 8–10 y after RT or age 10–30 yo.

Risk Factors for CNS Mets

- Burkitt's lymphoma
- Lymphoblastic
- Immunocompromised
- BM+
- Parameningeal
- Testicular relapse

Syndromes

- Wiskott-Aldrich: X-linked recessive. Eczema, thrombocytopenia, and immune deficiency. High risk for leukemia and lymphoma.
- Ataxia-telangiectasia. ATM mutation, which produces protein for DNA DSB repair. Pts have ataxia, telangiectasia, involuntary movements, immune deficiency, leukemia, and lymphoma.

Treatment Planning

Technique (mostly for HL): IFRT, ISRT, and INRT

- **TLI/STLI**: 1970s+; 30–45 Gy; TLI – mantle followed by inverted Y + spleen (usually 2-3w break). STLI: mantle + upper abdominal (w/o pelvic).
- **EFRT**: 1980s+ – usually mantle or inverted Y; covers involved region + uninvolved region.
  - **Inverted Y** = PA + pelvic fields.
  - **Mantle**:
    - Base of mandible to diaphragm, from 2–3 cm above tip of mastoid to ~4 cm above xiphoid.
    - Submandibular, cervical, supraclav, infraclav, axillary, mediastinal, and hilar nodes.
    - Blocks placed over humeral heads, occiput, and mouth AP/PA.
    - HVL block over larynx anteriorly, cervical cord posteriorly.
    - If high cervical nodes are involved, extend field to include preauricular nodes.

- **IFRT** (*do not use this anymore!*) – 1995+; 20–30 Gy; site of clinically involved LN, Kaplan/Rye group (per below); LN grouping not clearly defined; depends on bony anatomy; 2D. SOC since HD8.
  - **Cervical/supraclav**: extends from base of the skull to clavicles. Patient positioned in mark. Oral cavity block placed if tumor coverage not compromised.
  - **Axilla**: C5/6, tip of scapula or 2 cm below LNs, ipsi transverse process, flash axilla.
  - **Mediastinum**:
    - **Upper border** should be at *C5–6*. If sclav is involved, then upper border should be top of the larynx.
    - **Lower border** is 5 cm below carina or 2 cm below inf extent of pre-chemo dz.
    - **Lat borders** are 1.5 cm margin on post-chemo volume.
  - **PA field**:
    - Top of T11 or 2 cm above pre-chemo volume to aortic bifurcation (bottom L4) or 2 cm below pre-chemo volume.
    - Encompass lateral transverse processed of L-spine and 2 cm from post-chemo volume.
- **Pelvic field:**
  - Includes external iliac, inguinal, femoral nodes, middle SI joint to 5 cm below lesser trochanter; lateral border includes greater trochanter, medial border at obturator foramen, including 2 cm beyond involved nodes
  - **ISRT**: 3D; 2008+; pre-chemo GTV determines CTV (carve out bone, lung); becoming the SOC.
    - Supine, head extended, alpha cradle, arms akimbo.
    - **Pure ISRT:** routine in the USA; optimal pre-tx imaging not available. Not possible to reduce CTV to same extent as INRT. GTV + ~1 cm = CTV. CTV + 1 cm = PTV.
    - **INRT**: subtype of ISRT where pre-chemo imaging available, no margin for imaging limitations; upfront PET-CT mandatory in tx position; typically, pregnant women not eligible because CT and PET are avoided.
      - INRT alone acceptable for NLPHL, though CTV is more generous (~3–5 cm along vessel).
      - INRT is the SOC for early-stage fav HL per ILROG, if pre-treatment imaging in the treatment position is available.
- **INRT contours (Specht, *IJROBP*, 2014)**
  (A) Prechemotherapy GTV_{CT} on prechemotherapy CT scan.
  (B) Prechemotherapy GTV_{PET} on prechemotherapy CT scan.
  (C) Postchemotherapy GTV_{CT} on postchemotherapy CT scan.
  (D) Postchemotherapy GTV_{PET} on postchemotherapy CT scan.
  (E) Clinical target volume, created by modifying GTV_{CT} and GTV_{PET}, on the postchemotherapy CT scan.
- Take into account tumor shrinkage, anatomic changes.
- CTV encompasses all initial lymphoma volume while still respecting normal structures (e.g., lungs, CW, muscles).
- ITV – CTV + margin, create by using 4D CT or fluoro to account for motion.
- ITV + setup error margin = PTV. Use DIBH if involving mediastinum.
- Commence 3–4w after completing chemo,

Total Body Irradiation (TBI)

– Dose of RT alone to achieve immunosuppression is too high and would cause toxicity. Combine with chemo. RT targets all anatomic compartments, while chemo is unable to penetrate sanctuary sites (e.g., brain, testes).
– Lymphocytes are both sensitive to RT and chemo; however, some may be present in areas of low blood supply or sanctuary sites where chemo is not effective, but RT is.

Indications
– Bulk >5 cm at time of recurrence
– PR to salvage chemo or persistent disease posttransplant

Pretransplant Preferred
– Irradiating large volume of BM.
– LC will affect the transplant.
– Suboptimal response to chemo.
– Residual dz. pretransplant such as FDG-avid tumor or >2 cm tumor.

Posttransplant Preferred
– Large radiation exposure to the lung
– Delay in transplant undesirable
– Maximal cytoreduction desired for RT planning
– Recurrence localized

Peri-ASCT Studies
– Hoppe, 2008: refractory DLCL receiving IFRT. 1.5 Gy BID to 30 Gy. 5 yr PFS 53%, 5 yr OS 58%. Minimal tx-related mortality and morbidity.
– **Common regimens**:
  • **2 Gy x 1 fraction.** Non-myeloablative.
  • **2 Gy, BID**, for 3 days, to a total dose of 12 Gy.
  • If not giving etoposide for conditioning, some protocols call for 13.8 Gy in 1.65 Gy fx, BID.
– Technique: 18 MV preferred over lower E beams to improve homogeneity.
– AP/PA or opposed laterals with lung blocks.
– Use beam spoiler to increase surface dose.

TBI Studies
– Hartman, 1998: meta-analysis. Busulfan/cyclophos vs TBI. TBI won because it had less VOD. Other endpoints, OS, DFS, acute GVHD, chronic GVHD, pneumonitis, were similar.
– Clift, 1990; Clift, 1991: 16 Gy vs 12 Gy in pts. with relapsed AML or CML. 16 Gy arms had lower relapses but more tox, so 12 Gy was chosen.

Planning
– Typically 400 cm SSD.
– Large SSD reduces the % change in PDD due to ISL.
– 40 × 40 cm tx field becomes 160 × 60 cm at 4 m SSD
– Dose per MU is 1/16 of the dose at 100 cm SSD.

Benefits Over Chemo
– No "sanctuary" sites (e.g., testes, brain).
– Dose delivered independent of blood supply.
– Dose delivered independent of renal, hepatic function.
– No cross-resistance with chemo.
– Dose can be homogenous.
– Dose tailored to boost areas at risk and spare sensitive organs (e.g., lungs w/ lung blocks).

Toxicities of TBI
– Nausea, parotitis, fatigue, and erythema are most common.
– Radiation pneumonitis and RT-induced malignancies are relatively uncommon.

Pediatric Hodgkin's Lymphoma

COG risk group	Definition	Treatment	Outcomes
Low (favorable)	Stage I or II; not B, X, E	**ABVE** x 2 cycles→ If CR →ABVE x 2 (no RT) If PR →ABVE x 2 →**ISRT 21 Gy / 1.5 Gy fxs**	EFS5 90%
Intermediate (unfavorable)	Everyone else: unfavorable stage I/II, or stage IIIA	ABVE-**PC** x2. (1) If rapid early response (RER), ABVE-PC x2. If CR, then no RT. If < CR, then IFRT. (2) If slow early response (SERs), then randomize (2a) augmented chemo w DECAx2 +ABVE-PCx2 + 21 Gy/1.5 IFRT vs (2b) ABVD-PC x2 + 21 Gy/1.5	EFS5 85%
High	Stage IIIB or IVB	ABVD x6 → **IFRT**	EFS5 80%

Workup

- Ask about B symptoms.
- Complete nodal exam and examination of spleen and liver.
- Labs: CBC, CMP, ESR, LDH, albumin, pregnancy test.
- PET with diagnostic CT w/ or w/o contrast.
- BM bx if stage III/IV or B-sx.

Chemos

- ABVE-PC = adriamycin, bleomycin, vincristine, **etoposide**, prednisone, cyclophosphamide

Peds HL, Low and Intermediate Risk

- COG AHOD 0431: low-risk peds HL AVPC x3c, then IFRT vs obs. IFRT is 21 Gy/1.5 Gy.
- HOD99, Donaldson, 2007: VAMP chemo and low-dose 15 Gy IFRT. 10y EFS 89%.
- HD95, Dorfell, 2013: early-stage pts. rando to IFRT vs omission. Had similar 10y PFS 97% vs 93%. Int risk pts., including IIB, rando to RT vs no RT. RT won, w/ 10y PFS 91% vs 68%.
- CCG 5942, Nachman, 2002; Wolden 2012: all risk groups w/ CR rando to IFRT vs no RT. Closed early due to worse EFS, even in low-risk group I pts. 32/34 relapses in previously involved dz. 10y EFS 91% vs 83%. OS was similar ~96%. Majority of deaths due to PD or toxicity of salvage.

Peds HL, Intermediate-High Risk

- AHOD 0031 Friedman, JCO: Peds lymphoma. Int risk HL pts., excludes I-IIA and IIIB-IVB. Pts get doxo, bleomycin vcr, etoposide, prednisone, cyclophosphamide (ABVE-PC) x2.
  - (1) If rapid early response (RER), ABVE-PC x2. If CR, then (1a) 21 Gy IFRT (standard arm) vs (1b) no IFRT. (1c) If < CR, then IFRT.
  - (2) If slow early response (SERs), then randomize (2a) augmented chemo w/ DECAx2 + ABVE-PCx2 + 21 Gy/1.5 IFRT vs (2b) ABVD-PC x2 + 21 Gy/1.5. *For RER*, definition is >60% response on interval CT. *For CR in RER* group, definition is 80 + % reduction in perpendicular diameters on CT, return to normal size for lesions, no residual extramediastinal LN mass >2 cm, no dz. in nonmeasurable sites, negative gallium or FDG-PET. No difference in outcomes w/ RT.
  - (3) IF PD, then off-protocol tx.
    - Results: RER better than SER: 4y EFS 87% vs 77% and OS 99% vs 95%. RERs w/ CR by PET had no benefit w/ IFRT: 4y EFS 87% vs 87%. SERs w/ PET+ dz. had improved EFS w/ DECA vs ABVE 71% vs 55%. Thus, if RER after 2c of chemo and CR after 4c chemo, then do not need RT. If pts. had recurrence, it was rarely in a new site.

Hodgkin's Lymphoma (HL) [4–37]

I	II	III	IV	-A	-E	-X *Dropped in AJCC8*	**-B**
Single LN region, or 1 organ	2+ LN regions on 1 side of diaphragm; or 1 organ + regional LN	Both sides of diaphragm	Multifocal organ (e.g., liver, BM, lung)+/– LNs	no B-sx	extralymphatic site	Bulky dz.: >1/3 mid-thoracic diameter (~T5/6 on PA CXR), or >10 cm on CT Trials: cutoff of 5 cm or 10 cm MSKCC: >7 cm Lugano: >10 cm or MTR >1/3	B-sx Temp >38 °C within prev month; unexplained >10% weight loss in last 6 m; drenching night sweats

Stage III-IV HL IPS, Hasenclever, 1998 ("*ALL SHAM*")

25 centers, 5K pts, all txd w chemo+/-RT

Age >/= 45	Risk factors	FFP
Leukocytosis >15	0	84
Lymphocytopenia <8% or <0.6	1	77
Stage IV	2	67
Hgb <10.5	3	60
Albumin <4.0	4	51
Male	5+	42

Subtypes

- **Classical: CD 15+, 30+,** 45–, 20–. EBV + in 50%. T > B cells. Reed-Sternberg cells pathognomonic, large, *both mono-/multi*nucleated and lobulated. Divided into stage I–II F, stage I–II UF, stage III–IV. A single risk factor makes pt. UF. Among risk groups, extranodal dz. rare.
  - **Nodular sclerosing (NSHL):** >70% of HL in the USA, young adults.
  - **Mixed cellularity** (MCCHL): bimodal: childhood/older adults, abdominal, splenic involvement, EBV+.
  - **Lymphocyte depleted** (LDCHL): <1% of cases, HIV+.
  - **Lymphocyte rich** (LRCHL): usually limited dz., no systemic sx, males, older age.
- **Nonclassical/nodular lymphocyte predominant HL (NLPHL):** CD 15-, 30-, **20+, 45+, 79a+, 57+**. EBV neg. B > T cells. Small, *mono*nucleated, *multi*-lobulated. L&H/"popcorn" cells – small variants of RS cells w/ very lobulated nuclei. 5% of cases. Indolent, peripheral LNs, usually stage I–II, late relapse, excellent OS, need follow-up more than classic HL, high death from non-HL dz. highest propensity to become DLBCL.
  - For NLPHL, RT is mainstay of treatment.

Overview

- 8200 cases/yr. in the USA, 1300 deaths
- **Common sx:** asx LAD (70%) in neck, (70%, mediastinum (60%), PAs (35%), RP (25%), axilla (25%); B-sx (30%); EtOH-induced pain at LAD site; pruritus (poor prognostic if severe).

Workup

- LN exam.
- **Kaplan / Rye LN groups** (1966): includes 14 sites total. Some LNs are within one group:
  - Waldeyer's ring: palatine, pharyngeal, lingual tonsils
  - Cervical/supraclav/occipital/preauricular
  - Epitrochlear/brachial
  - Inguinal/femoral
- Smoking cessation.
- Fertility preservation: sperm/egg bank; oophoropexy if pelvic RT anticipated.
- Excisional bx (to preserve LN architecture) w/ IHC. Tumor cells are <1% of tissue. If in HN area and concern for SCC, could try FNA first.
- CBC w/diff, CMP, ESR, LDH, LFTs, albumin, HepB/HepC, HIV, BHcG.
- diagnostic CT, PET-CT.
- PFTs (bleomycin), echocardiogram/MUGA (adriamycin).

– BM Bx: previously if B-sympx, stage III/IV, cytopenias with negative PET, recurrence. Now only if cytopenias with negative PET-CT.

Unfavorable risk factors	GHSG [38]	NCCN [38]
ESR & B symptoms (*normal ESR <20 mm/hr)	>50 if A; >30 if B	>50 or B
Mediastinal mass	MMR >0.33	MMR >0.33
# of nodal sites	>2	>3
E lesion	any	
Bulky		>10 cm

– International prognostic score (IPS) for HL: age >45; male sex; stage IV; Hgb <10.5; albumin <4.0; WBC >15; lymphocytopenia <0.6 of 8% of WBCs. May influence chemo; should be used in stage III–IV dz.
– Gene assay for CD68+, CD163+ macrophages: presence of cells is a poor prognostic factor.
– Staging laparotomy not needed with STNI or chemo (EORTC H6F).
– Note: GHSG/EORTC unfav has different nodal grouping: mediastinum and hilum are one site; EORTC IF/SP with axilla; GHSG IF/SP with cervical LN.
– **Favorable vs unfavorable**: single risk factor makes one unfavorable.
– **Advanced HL (stage III/IV) IPS** (NEJM, 1998): age 45+, leukocytosis >15, lymphopenia, stage IV, Hgb <10.5, albumin <4, male ("ALLSHAM"). Each risk factor decreases FFPD by 8%.
– van Nimwegen, 2016: 2617 HL survivors, 1965–1995 in the Netherlands. Median interval bw dx and CAD dx is 19y. Risk of CAD increased linearly w/ increasing mean heart dose, ERR of 7.4%/Gy, which resulted in a 2.5-fold increased risk of CAD w/ mean heart dose of 20 Gy.

	Ann Arbor 9 sites	EORTC 5 sites	GHSG 5 sites
R cervical			
R infraclav			
R axilla			
L cervical			
L infraclav			
L axilla			
mediastinum			
R hilum			
L hilum			

Chemotherapy

– **ABVD**:
• 28-day cycle:
  • Doxorubicin 25 mg/m2 IV, days 1 and 15. Tox is cardiomyopathy, max dose is 400–500 mg/m2 in life.
  • Bleomycin 10 units/m2, days 1 and 15. Tox is pulmonary fibrosis. Check PET-CT and CT sim.
  • Vinblastine 6 mg/m2 IV, days 1 and 15. Tox is neuropathy, cytopenias, and hair loss.
  • Dacarbazine, 375 mg/m2, days 1 and 15. Tox is infertility, sterility, birth defects, N/V.
  • HD13 found that dacarbazine is crucial.
– **Stanford V**: mechlorethamine, Oncovin (vincristine), prednisone, etoposide, adriamycin, bleomycin, vinblastine (MOPE-ABV). Always needs RT.
  • **Stanford V** is 3 months; **ABVD** is 4 months; Stanford V omits procarbazine, has lower dose of bleomycin (5 vs 10) and less overall cumulative dose of doxorubicin.
– **AVPC**: adriamycin, vincristine, prednisone, cyclophosphamide.
– **MOPP**: mechlorethamine, vincristine, procarbazine, prednisone.
– **BEACOPP**: bleomycin, etoposide, adriamycin, cyclophosphamide, Oncovin, procarbazine, prednisone. Usually use in UF. Hesitancy to use esc-BEACOPP in US because acute tox, inc risk leukemia w/ agents, toxic for elderly.

Large Volume and Staging

– EORTC H6 (Carde, 1993): stages I–II.
  • H6F patients randomized to clinical staging + STNI vs staging lap, then mantle RT or chemo as indicated. There were no OS differences, lap abandoned.
  • H6U patients all receive mantle RT. Then randomize to ABVD vs MOPP. 6-year FFP 88% vs 76%, favor ABVD. OS was 93% vs 89% (NSS) mainly from lap-related death. Less heme, gonad toxicity w/ ABVD. Increased pulm tox w/ bleomycin.

RT vs CRT

– Four trials showed improvement with CRT, one with OS improvement (H8F):
  • EORTC H7F, H8F, German HD7, SWOG S9133.
– **EORTC H7F**, Noordijk, 2006. Parallel to H8. Goal to reduce toxicity. *n* = 333 fav risk pts. Rando: EBVP x 6c, then IFRT 36–40 Gy vs STNI 40. CRT improved 10y EFS 88% vs 78%, but not OS, 92%.
– **EORTC 7 U**: 389 U risk pts. randomized to (1) EBVP x 6c, then IFRT 36–40 Gy vs; (2) MOPP/ABV x 6c, then IFRT 36–40 Gy. After 10 y EFS 68% vs 88%, favoring MOPP/ABV, prompting early closure. 10y OS was also better 79% vs 87%.
– **EORTC H8F**. *n* = 542. Rando to MOPP/ABV x3c + IFRT 36–40 Gy vs STNI 36–40 Gy alone. CMT improved EFS and OS. Thus, chemo and IFRT are preferred.
– **EORTC H8-U**, Ferme, 2007. *n* = 996. Rando to MOPP/ABV x6c + IFRT 36–40 Gy vs MOPP/ABV x 4c + IFRT 36–40 Gy vs MOPP/ABV x 4c + STNI 36–40 Gy. No difference in 5y EFS (~85%) or OS (~86%). Thus 4c CMT + IFRT sufficient.
– Milan, Bonadonna, 2004. early HL, F and UF. ABVDx4c, then STNI 30.6–40 vs IFRT 36–40. No difference in RFS or OS. Shows IFRT sufficient.
– HD7, Engert, 2007. 650 fav HL. EFRT 30–40 vs ABVDx2c, then EFRT. 7y FFTF 67% vs 88%, favoring CMT. No difference in OS, 93%, mostly because chemo salvage still available.

Chemo vs RT

– NCIC/ECOG HD.6, Meyer, 2012: unfav/fav I-II, nonbulky.
– : ABVD x4-6c vs STNI +/− ABVDx2 (depending on risk): 5 yr. PFS initially favored CRT (88 → 95%), same OS; 12 yr. f/u showed ↓OS in chemoRT arm (94% vs 87%). For good risk pts., STNI had better outcomes than ABVDx4-6c. For high-risk pts., STNI arm only got 2c chemo. Concluded ABVD superior to STNI alone. Criticisms: STNI w/o chemo not SOC. Dose too high. RT alone group had many pts. >40 yo. 5/24 deaths in RT arm not from RT.

Chemo +/– RT

– Laskar: very mixed group: 6c ABVD with CR → IFRT vs obs. RT won: 8 yr. EFS 76 → 88%, OS 89 → 100%.
– Cochrane meta-analysis: Five trials (CALGB 7751, EORTC-GELA H9-F, GATLA 9-H-77, Mexico B2H031, MSK 90–44): HR for OS and PFS was 0.4, in favor for chemo + RT. H9-F closed early because so many failures.

Intermediate-High Risk

– HD11: I-II U, then rando to ABVDx4 or BEACOPP x4; then secondary rando IFRT 30 Gy vs 20 Gy. *n* = 1395. No PETs. No diff in outcomes for chemo. Similar outcomes for BEACOPP+ 20 or 30 Gy and ABVD +30 Gy. Suggestion for worse outcomes w/ 20 Gy, but not powered to detect difference. Worse tox w/ BEACOPP. Thus, ABVD x4, then IFRT 30 Gy is SOC.
– HD14, von Tresckow, 2012: early stage, UF. Follows HD11; will further intensification help? Rando: ABVD x4 + 30 Gy IFRT vs BEACOPPesc x2 + ABVD x2 + 30 Gy IFRT (intensified arm). 5-year FFTF was 88% vs 95%, favoring intensification. OS 97% both. No difference in CR, both at 95%. G3–4 tox worse 87% vs 51%. Thus, although PFS + FFTF better, ABVDx4 remains SOC. If X dz., some recommend x6–8.
– EORTC H10: what is role of interim PET? Two cohort patients, F and UF. Interim PET was valid prognosticator.
  • H10F cohort got ABVD x 3c, then INRT 30 Gy, despite interim PET after 2c. Experimental arm got ABVD x 2 followed by PET. If negative interim PET, 2 cycles ABVD and if positive, BEACOPPesc x 2c + INRT 30 Gy Decreased PFS in ABVD alone arm, stopped this arm.
  • H10U cohort got ABVD x4c + INRT 30 Gy as SOC. Experimental arm got ABVD x 2c then PET. If neg, then ABVD x4c. (This no-RT arm closed due to inc failures.) If pos, then BEACOPesc + INRT 30 Gy.

Advanced-Stage Chemo

- Aleman/SWOG: III –IV → 4–6c MOPP-ABV w/ CR → IFRT vs obs. Same EFS and OS.
- ECOG 2496: Stanford V better than ABVD for IPS 3–7.
- HD9 BEACOPP x 8 vs esc BEACOPP x8 vs COPP-ABVD x 8 (though not all got ABVD). Esc BEACOPP had best FFP and OS, but more G4 tox, more AML/MDS.
- EORTC 20012: esc BEACOPP x4 vs ABVD x 8, no RT. Similar outcomes.

Advanced-Stage Consolidative RT

- EORTC 20884, Aleman 2003: Advanced HL, II–IV, not IIB. ABV/MOPP x 6c. If CR, IFRT 30 Gy vs obs. If PR, 30 Gy IFRT. No PETs, only CTs. No diff in OS or RFS among the pts. w/ CR. Thus, no need for RT if there is CR after ABV/MOPP x 6c. Among the pts. w/ PR to chemo, outcomes not different from those w/ CR after chemo. Thus, 30 Gy IFRT after PR improves prognosis. However, pts. w/ X dz. more likely to have PR than CR. No differences in second malignancy rates for pts. w/ CR vs PR and then RT. There was more leukemia in the CR-RT arm, cause unknown. Criticism is use of MOPP/ABV, highly toxic; in the USA, ABVD is used, no known superiority.
- SWOG 7808: no benefit with IFRT after chemo if CR.
- Laskar, Tata Memorial, 2004. Mostly MC HL, a better prognosis subtype. ABVD x6c. If CR, rando to obs vs IFRT 21 Gy + 10 Gy boost to X. EFS 88% vs 76% favoring RT. OS 100% vs 89% favoring RT. 15% pts. did receive EFRT and 115 got inverted Y. 50% pts. <15 yo and half stages I–II.
- German, HD15, Engert, 2012. Eval different chemo. Only residual dz. >2.5 cm and PET+ txd w/ 30 Gy IFRT.

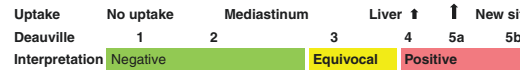
↓Field Size, ↓Dose, ↓Chemo

- GPMC, German HD8, Milan, EORTC H8U all ↓ FS.
- German HD8, Engert, 2010. Early unfav. COPPx2 and ABVDx2, then rando to 30 Gy EFRT vs 30 Gy IFRT. X dz. boost +10 Gy. 5-y OS 91%, and FFTF 85% (NSS). EFRT had more toxicity. IFRT was winner.
- German HD10, Engert, 2010: stages I–II favorable (GHSG fav criteria): 2x2 design (2-4c ABVD and 20–30 IFRT): 5 yr. DFS and OS were same in all arms.
- UK RAPID (Radford, 2015): IA/IIA HL. Pts get 3c ABVD, then rando: IFRT 30 Gy vs obs. Non-inferiority. 3-year PFS was 95% vs 91%; however, 4% absolute diff 95%CI was above the 7% non-inferiority margin, so treatments were not deemed non-inferior. Still, authors conclude omission possible given excellent prognosis.

NLPHL

- Chen, JCO, 2011: stages I–II. *N* = 93 receiving RT alone. 13 got CMT. 7 got chemo alone. 10-yr. PFS 85% and 61% for stages I and II, resp. OS >90%. No PFS or OS differences bw EFRT vs regional RT vs limited field RT; but more second malignancy, CV deaths with EFRT. 6/7 chemo pts. had early relapses.
- BCCA / Al-Mansour, 2010: *n* = 95. 7% risk to become DLBCL at 10y; 30% at 20y.

PETs and Deauville PET Criteria



- 1: No uptake
- 2: Uptake ≤ mediastinum
- 3: Mediastinum < uptake ≤ *liver*
- 4: ↑Moderately compared to *liver*
- 5a: ↑Markedly compared to *liver*
- 5b: New FDG avid site
- 1–2 are neg; 4–5 are positive; 3 can be either, depending on goal of study (e.g., esc vs de-esc). Usually negative.
- Restaging PET/CT is 2 weeks after day 15 of last cycle of ABVD. If Deauville 4 on interim PET-CT, the ast PET-CT is 6–8 wk. after chemo or 8–12 wk. after RT.
- Do not perform 7-10d after chemo to avoid false positive from inflammation.
- Interim PET is + in 14% F and 24% UF patients.

Treatment Paradigm

HL, Classical (i.e., NSHL, CD 15/30+), I–IIF
- NCCN (very favorable, meeting GHSG HD10 criteria): ABVD x 2 → restage w/ PET →:
  - Deauville 1–3 → ISRT **20 Gy.**
  - Deauville 4 → Consider another ABVD x2c then ISRT **20 Gy.**
- UK RAPID trial approach is ABVD x3 cycles (intent for chemo alone), then PET:
  - Deauville 1–2, then observe vs fourth c ABVD.
  - Deauville 3–4, then fourth c ABVD +**30 Gy** ISRT.
  - Deauville 5, biopsy.
- Stanford V × 8 weeks +30 Gy ISRT.
- Cannot omit RT even PET-neg after chemo (EORTC H10F, H10U, RAPID).

Classic HL, I–IIU
- NCCN:
  - ABVD x 4 → restage w/ PET →.
  - Deauville 1–3 = ISRT **30 Gy** vs (2 more cycles and no RT). All X should get RT.
  - Deauville 4 → ABVD x 2 → restage w/ PET → Deauville 1–3 → ISRT **30 Gy**
  - Persistent Deauville 4 or 5 needs bx → if (+) it is refractory.
- HD11: ABVD x 2; then PET; then two more cycles, IFRT 30 Gy.
- Esc BEACOPP x2, ABVDx2 then 30 Gy ISRT.
- Stanford V x 12 w, then 30–36 Gy ISRT.
- Cannot omit RT even PET-neg after chemo (EORTC H10F, H10U, RAPID).

Classic HL, III–IV
- Calculate the advanced IPS score: male, age ≥45, stage IV, Hgb <10.5, Alb <4, leukocytosis >15 k, lymphocytopenia <0.6 k/mL (or <8%).
- NCCN:
  - ABVD x 2 PET →.
    - if CR (Deauville 1–3), 4 cycles (6 total), **no RT**. May consider ISRT to sites of initial bulk, 30–36 Gy (controversial, no benefit in Aleman or SWOG).
    - if PR (Deauville 4–5), esc BEACOPP or ABVD x 4 cycles, **30–36 Gy** ISRT to initially bulky or PET+ sites.
- Stanford V x 12 weeks + ISRT to initial sites >5 cm, involved spleen, 30–36 Gy.
- Esc BEACOPP x 6 cycles, then 30–36 Gy for residual PET+ sites >2.5 cm.

Bulky Dz: 30–36 Gy w/ ABVD, 36 Gy w/ Stanford V

Relapsed/Refractory
- Chemo: ICE or BEAM → Transplant and stem cell rescue.
- Consider ISRT to persistent disease or initially bulky sites.

HL, Nonclassical (i.e., NLPHL, CD20+)
- ***RT mainstay of tx***
- IA-IIA: ISRT w/ 30 Gy (preferred vs obs) → PET/CT →
  - CR = observe
  - PR = refer to medonc for R-CHOP or ABVD.
- IB-IIB or IAX/IIAX: chemo + rituximab +ISRT (30 Gy; 36 for bulk, ABVD+/−R or R-CHOP).
- IIIA, IVA: chemo + rituximab +/− ISRT OR rituximab alone OR local RT palliation for symptomatic dz.
- IIIB, IV: chemo + rituximab +/− ISRT.
- All pts. should be followed because relapses occur up to 15 y post-tx.
- RT: CTV + 2–5 cm. For CD, can use 1 cm.

Pregnant Women: HL more common because immune-suppressed; some avoid CT and PET staging and use US; if asx, tx may be delayed til after delivery; avoid RT; can use ABVD in 2nd/3rd trimester**.**

Treatment
- GTV = Post-chemo disease if present.
- CTV = Prechemotherapy PET-CT. Adjusted to exclude uninvolved normal tissues (lung after chemo shrinkage).
- ITV = CTV + motion (4D-CT).
- PTV = CTV + 5 mm.
- Use DIBH if in mediastinum.

Protons: best for mediastinum, spleen, PA LNs.

Constraints (per ILROG):
- Lung: V20 <20%; mean lung <12 Gy.
- Heart: mean <15 Gy.
- Bone growth affected at 8 Gy.
- Breast tissue growth affected at 5–10 Gy.
- Thyroid: >15 Gy assoc. w/ 30% risk insufficiency.
- TD 5/5:
  - Testes: 2 Gy (permanent sterility), 0.5 Gy (temporary azoospermia).
  - Oocytes. Sterilization by 2 Gy. Failure by 6–10 Gy (single fx), 12–15 Gy fractionated in age <40.

Follow-Up
- Need one PET-CT to confirm response after RT; otherwise, no role for routine PET-CT in follow-up.
- q3 mo x 2y, q6 mo x3y, then annually with H&P, labs including TSH.
- CXR or CT q6 mo x5y (alternate PET-CT with CT yearly).

Toxicity
- Dermatitis, post scalp hair loss, xerostomia, dental caries (fluoride x 2 years after RT), esophagitis, thyroid dysfunction, Lhermitte's, herpes zoster, pneumonitis, and pericarditis.
- **Lhermitte's:** 20% in HL, likely from chemo. No correlation w/ dose. Should resolve w/ time.
- Adriamycin: cardiomyopathy (limit is 450 mg w/ RT, 550 w/o RT).
- Bleomycin: pulmonary fibrosis.
- Vinblastine: neuropathy and hair loss.

Late Effects Monitoring (After 5 Years)
- Optimize cardiovascular health, baseline echo, and stress test q10y, especially if cardiac RT.
- Carotid ultrasound at 10 y if neck RT.
- If splenic RT → pneumo, meningo, flu vaccines q5y.
- Chest XR/CT qyr if at risk for lung ca.
- **Female age >25:** Start breast mammo 10 years after treatment or at 40, whichever earlier if chest or axillary RT.Get annual breast MRI at age 40 or 10 yrs. after RT.
  - Cumulative risk of breast cancer in 30y after treatment for HL 19% (~0.7% per year) and 26% for women <21 yo.

Outcomes
- Early stage favorable/unfavorable and NLPHL: 10-yr. OS = 90% – 10-yr. EFS = 85%.
- Advanced stage:
  - 10-yr. OS = 80% – 10-yr. EFS = 75%

Non-Hodgkin's Lymphoma (NHL) [4–8, 39–48]

Overview
- NHL (vs HL): more LN+, more E-LN dz., less contiguous, rare to have stage I NHL (only 10%).
- Incidence rose in 1970s–1980s, as did death rates; both plateaued in the 1990s and 2000s. Rituximab was approved in 1997.

Categories
- Low-grade NHL: follicular (G1, G2, G3A), SLL/CLL, MALT, MF
- Intermediate-grade NHL: follicular (G3B), mantle cell, DLBCL, T/NK cell, peripheral T cell, anaplastic large cell (100% CD30+, >90% ALK rearrangement)
- High-grade NHL: Burkitt's lymphoma, lymphoblastic

History
- Painless lymphadenopathy ~2/3; B symptoms ~40%
- Indolent lymphomas: Slow-growing, waxing/waning LAD, hepatomegaly, splenomegaly, or cytopenias
- Aggressive lymphomas: Fulminant symptoms relating to rapidly enlarging mass

Genetics
- Germinal center B cell (GCB): hypermutations, REL amp, bcl-2 translocation. OS5 = 64%.
- Primary mediastinal B-Cell (PMBCL): similar to NSHL. OS5 = 60%.
- Activated B-cell (ABC): NFKB activated. OS5 = 30%.
- **Follicular**: t(14,18) → ↑bcl-2, an anti-apoptosis gene.
- **Mantle cell**: t(11,14) → ↑bcl-1.
- **MALT**: t(11,18), tri3. If translocation present, then resistant to abx.
- **Burkitt's lymphoma**: t(8,14) → ↑c-myc, a proto-oncogene.
- **SLL/CLL**: del13, t(14,19), tri12.
- **Richter syndrome**: SLL/CLL → DLBCL transformation (5%): ↑bcl-2; t(14,18); others
  - DLBCL is most common lymphoid neoplasm; AIDS-defining illness.
- "Double hit": bcl-2 OR 6, AND c-myc translocation
- "Triple hit": bcl-2 AND 6 AND c-myc translocation
- Translocation more common than overexpression (i.e., gene amplification); "double-expressor" lymphomas have similar poor prognosis.

CD Markers:
- B cell: CD19, 20, and 21.
- T cell: CD2, 3, 7, 8.
- Anaplastic large cell lymphoma CD 30+ (ki-1 antigen).
- Natural killer T-cell lymphoma CD 56+.

Workup
- CBC w/diff, CMP, LDH, B2micro, SPEP, HIV.
- HepB, HepC: Need to check because rituximab may react to hepatitis B.
- Excisional bx (not FNA).
- BM biopsy for all DLBCL, T cell, and FL! The only exception is gastric MALT
  - NCCN says b/l or unilateral core biopsy (as long as biopsy is >1.6 cm).
- Any area of DLBCL in FL of any grade = treat as DLBCL.
- PET-CT.

Special Case Workup
- Check CSF with LP if HIV+, testicular, epidural, or paranasal sinus involvement, double-expressor lymphoma, bone marrow with large cell lymphoma, or four to six risk factors (>1 extranodal site, elevated LDH, age >60, PS >1, stage III or IV, kidney/adrenal gland involvement, 2+ E sites).
- MRI if getting LP.
- Echo if getting anthracyclines.
- For mantle cell early stage → EGD and colonoscopy.

Staging

- Same as for Hodgkin's lymphoma.
- Bulky = >7.5 cm.
- Practical staging: Limited, I–II whether bulky is limited or advanced depends on histology. Advanced, III–IV.

Chemotherapy

- R-CHOP is q 3 weeks.
- Rituximab. Anti-CD20. May reactivate HBV.
- Cyclophosphamide 750 mg/m^2 d1. DNA alykator, N-mustard.
- Adriamycin 50 mg/m^2 d1. inhibits nucleic acid production. Heart limit is ~400 w/ RT, ~500 w/ RT.
- Oncovin (vincristine) 1.4 mg/m^2 d1. Inhibits microtubule formation, arrests cells in metaphase.
- Prednisone 100 mg/d PO d 1–4. Unclear mechanism, synergistic?

Intermediate-High-Grade Lymphoma NHL/DLBCL [51–55]

International Prognostic Index (IPI) (*APLES or LAKES*)				Revised IPI (ritux adds 10%)
Age >60 ECOG ≥2/ KPS <70 LDH >ULN >1 extranodal Stage III/IV	Risk group	#	5 yr. OS	5 yr. OS
	Low risk	0–1	73%	94%
	Low/int risk	2	51%	79%
	Int/high risk	3	43%	55%
	High risk	4–5	26%	

Age-adjusted IPI for pts <60 yo, Schipp, 1993 (“*APLES* w/o the vowels”)		
ECOG ≥2 LDH > ULN Stage III/IV	Risk group	#
	Low risk	0–1
	Int risk	2
	Int/high risk	3

Stage-adjusted IPI from SWOG 8736 (Miller, 1998) (*PALS*) Excludes E dz. and stage III/IV. Use only for stage I/II			
Age >60 ECOG ≥2 LDH > ULN Stage II	Risk group	#	5 yr. PFS
	Low risk	0–1	77%
	Low/int risk	2	60%
	Int/high risk	3	34%
	High risk	4	0%

The 4 RCTs	Patients	Arms	Outcomes	Criticisms	Any local relapse	Isolated local relapse	Distant relapse
GELA LNH93–4 (elderly) Bonnet, 2007	>60 y/o, low risk, age-adjusted IPI 0, stages I–II. 8% X.56% E	CHOP 4c +/− 40 Gy IFRT	5 yr. EFS and OS (~70%) same	RT started >5w after chemo in 50% pts. Only 88% pts. in CMT arm got RT. In field recurrence 34%, which is >10% than the other GELA study and >15% than the two US studies. This was a very specific population	63% vs 34% Criticized for this hi value	47% vs 21%	53% vs 79%
GELA LNH93–1 (young) Reyes, 2005	≤ 60 yo, low risk (IPI 0) stages I–II (E or X allowed)	AVCBP x3c + consolidation (e.g. MTX, leucovorin, etoposide, ifos, cytarabine) vs CHOP x3c + 40 Gy IFRT	AVCBP w/o RT won. 5y EFS 82% vs 74%. OS 90% vs 81%	Effect of RT difficult to interpret given the different chemos + consolidation. AVCBP is toxic (150% intensity of CHOP; needs hospitalization, hi rate of AML, lung ca)	62% (AVCBP) vs 28%	41% vs 23%	59% vs 77%
ECOG 1484Horning, 2004	I–IIE, int grade NHL	CHOP 8c If CR, then 30 Gy vs obsIf PR, 40 Gy for all pts	For the pts. w/ CR, RT won over obs. Primary endpoint was DFS. 6 yr. DFS 56 → 73%, OS numerically better but NSS. Conversion from PR → CR did not influence DFS	More X pts. on RT arm; not powered for OS	48% (15/31) vs 17% (3/17)		52% (16/31) vs 82% (14/17)
SWOG 8736, Miller, 1998	I–IIE int grade NHL	CHOP 8c vs CHOP 3c + 40–55 IFRT	5 yr. results favored CRT, but 8 yr. overlapped. In-field LRR 0%. Inc. rates of cardio tox in 8c of chemo vs 3 c + IFRT. As advanced stage is factor in original IPI, investigators modified index to make "***stage-adjusted IPI***" to exclude >1 E sites and stages III–IV. IFRT felt to compensate for reduction in chemo	(1) Differing # chemos; (2) Stage adjusted IPI = 0 in 90% of pts., low risk of failure. (3) Relapses not reported in primary pub or abstracts. Anecdotal reports state excess late relapses out of field	0% with RT	Relapses not reported in primary publication or abstracts. Note that DLBCL I-II IPI 2–4 pts. felt to drive the late out-of-field recurrences; thus, felt to benefit from more chemo	

Intermediate-Grade Trials for DLBCL

Pre-rituximab Era

- For the four main RCTs, 45% of relapses in the chemo alone arms were in initial dz. sites. RT improved LC by ~70%. LC may improve OS w/ longer dz. control from rituximab.
- Mexico, Aviles, 2005: NHL, got chemo, had residual. Rando to 30/1.5 vs obs. RT improved PFS and OS. Main RCT to suggest this approach before RICOVER-60.

Post-rituximab Era (Approved 1997)

- SWOG 0014, Persky, 2008: Single arm. RCHOP x3c + IFRT (40–46 Gy). PFS improved vs 8736 (historic control).
- MInT: II-IV or IX, IPA 0–1. CHOP-like x 6 +/− ritux. Ritux won. 6 yr. EFS 56 → 74%. Not an RT trial, but RT to all sites initial bulk/ ENI.
- MDACC: *n* = 469; I-IV; DLBCL; 30% received consolidative RT. On MVA, RT improved PFS (HR, 0.19), and OS.
- Unfolder: four arms: R-CHOP 21 x 6 or RCHOP 14 x 6 +/− RT (bulky >7.5 cm or ENI). All must have PR+. The no-RT arms were closed because of hi relapse.
- MDACC retrospective (Phan, 2010): Consolidative RT after RCHOP improves OS and PFS for *early and late* stage dz.

Rituximab Era, Elderly

- Rationale for RT is that pts. cannot tolerate 6c R-CHOP.
- RICOVER-60, Pfreudschun, 2008. Any dz. stage or IPI previously untxd aggressive B-cell NHL, 61–80 yo. Four arms: CHOP x6c or 8c +/− Rit. IFRT 36 Gy to X dz. or ENI. 6c RCHOP arm declared superior over CHOP. Investigators tried to omit RT in this arm.
- RICOVER-noRTh, Held, 2014: Amendment to RICOVER-60 to compare pts. receiving RT 36 Gy to cohort receiving same immuno-chemo but no RT (RICOVER-noRTh). In ITT and as treated analyses, RT benefits elderly pts. w/ X. Trend toward worse PFS and OS w/o RT. In per-protocol analysis, EFS, PFS, and OS all improved w/ RT.

Relapse

- MSKCC, Hoppe, 2008: IFRT prior to high-dose ASCR as salvage for 164 pts. w/ relapse or refractory NHL. RT 30 Gy IFRT in 1.5 Gy BID. Many received TBI. 2y OS 67%, 5 y OS 58%.

RT vs Chemo

Pugh, 2010, SEER: RT has cardioprotective effect for NHL, supposedly because there are a reduced number of CHOP cycles w/ adriamycin.

Treatment

DLBCL, General

- **I-II (non-X, i.e., <7.5 cm):**
  - **For IPI 0–1**, RCHOP x 3c preferred. Then PET-CT. Then ISRT **30–36 Gy**. Boost FDG-avid residual dz. to **40–46 Gy**.
  - Reduces risk of relapse by 50–60%.
  - Alternative (cat 2b) is R-CHOP x 6c and no further treatment.
  - **For IPI 2–4**, RCHOP x6c.
  - Then ISRT **30–36 Gy**.
  - If unable to tolerate chemo, then **36–45 Gy** ISRT (depending on response to chemo).
  - Boost FDG-avid residual dz. after chemo to **40–46 Gy**.
- **I-II (X, i.e., >7.5 cm):** RCHOP x6c +/− ISRT **30–36 Gy**. X dz. (RICOVER-noRTh)

- **III/IV:**
  - If high IPI, clinical trial for high-dose chemo with autologous stem cell rescue.
  - R-CHOP x 4 → restage w/ PET.
  - CR→ R-CHOP x 2 → observe. Consider ISRT only to initial bulk (**36 Gy**), per German group.
  - PR → R-CHOP x 2→ restage w/ PET.
  - If PET negative: ISRT only to initial bulk (**36 Gy**).
  - If PET positive: refractory, go to transplant.

- **Aggressive histology (e.g., double/triple hit, Burkitt's lymphoma):**
  - da-R-EPOCH or R-CHOP x 6c, then PET-CT, then 30 Gy ISRT for PR.

Gastric DLBCL

- Same treatment as above [R-CHOP x **3** → ISRT (**30** Gy)].

Testicular DLBCL

- Orchiectomy→ R-CHOP x 6 w/ IT-MTX → scrotal RT to 30 Gy (high contralateral relapse rate w/o RT).
- RT technique:
  - Tape penis up.
  - Measure scrotum separation.
  - Use en face electrons (flash lat and inf.); 9–12 MeV.
  - No bolus.
  - Want ≥80% of dose from 0.5 cm depth to 0.5 cm from posterior.

DLBCL of Bone (See Separate Section)

- R-CHOP x three cycles + RT 45 G to GTV +2–3 cmy. Cover larger volume of bone.
- Using less chemo but more RT as local therapy.

DLBCL of the Breast

- R-CHOP x six cycles + RT 36 Gy to whole breast (use tangents).
- Using more chemo but less RT to minimize dose to breast.

Mantle Cell

- Most often advanced stage. Median OS 3–4 years.
- I–II: chemo+RT.
  - RT for stages I–II: 30–36 Gy at 1.5 Gy/fx.
- III+: chemo.
- Palliation: 2 Gy x 2 fx ("Boom boom"), can repeat PRN.

Primary Cutaneous B-Cell Lymphoma, Leg Type

- Complete skin exam; labs w/ LDH, HBV, CT CAP and or PET, BM bx.
- Leg type has poor prognosis.
- NCCN: R-CHOP and local RT 30 Gy.
- Palliation: 2 Gy × 2.

Which DLBCLs Need CSF Chemoprophylaxis?

- Testicular, paranasal sinus, epidural, BM involvement.
- Give 4–8c of IT MTX.

Primary Mediastinal B-Cell Lymphoma (PMBCL) [48]

Overview

- Note this is different from DLBCL (not "diffuse"!).
- Arises in B-cell clones in thymus, and not in nodal B-cells. CD 19/20+, CD3-, consistent w/ B-cell immunophenotype. May be CD30+ or CD45+. Mostly younger women; thus, aim to avoid RT. Invasive in pleura, pericardium. 2/3 present w/ mass >10 cm. 30–40% w/ SVC obstruction.
- Females in 30s.
- Present with early-stage, X disease.

Workup

Same as NHL: LDH, CBC, urate, PET CT, BM biopsy, get IPI, HBV, echo or MUGA, pregnancy testing.

Studies

- Dunleavy, 2013: NCI regimen of DA-EPOCH-R. *n* = 51. No RT. Untreated. At 5-y, EFS is 93%, OS 97%. CR rate is 96%.
  - These outcomes are unprecedented in a phase II study.

Treatment

- Tx w/ DA-EPOCH-R x 6c (Dunleavy, 2013). Chemo requires inpt stay for 1 w.
- Then PET-CT.
- No RT unless persistent focal disease.
- Less preferred: R-CHOP x6 w/ ISRT 30 Gy; or R-CHOP x4, then ICE x3c, +/− ISRT 30 Gy.

Mediastinal Gray Zone Lymphoma

Overview

- B-cell lymphoma, unclassifiable, males, 20–40
- Male version of PMBCL

Treatment

- R-da-EPOCH vs R-CHOP.
- Consolidate all early-stage patients regardless of PET.
- 30 Gy ISRT. Boost 10–15 Gy for PR.

Primary Lymphoma of Bone [56, 57]

Overview

- <2% adult lymphoma
- >90% occur over 30 yo
- Most are DLBCLs and can have B-sx.
- TROG/ALLG, Christie, 2010: 3c CHOP, then shrinking RT field of 45 Gy/1.8: first entire involved bone txd to 36 Gy, w/ final 5 fx to 2 cm margins. LC was 72%. OS 90% at 5 y. Closed early due to poor accrual and new availability of rituximab.
- Bologna, Pellegrini, 2011: chemo w/ R-MACOP-B vs R-CHOP21 x 6c. rituximab gave 95% CR and 8 year OS 95%, PFS 100%. 11/21 pts. got RT.
- Held, JCO 2013: RT after chemo improves PFS.

Treatment

- Chemo then remains SOC.
- R-CHOP x3–6c, then shrinking RT field, similar to DLBCL: 30–36 Gy for CR and 40–45 Gy for PR. Spare joint space if not involved. CTV = GTV + 1 cm.
- Alternative: 6c R-CHOP 36 Gy to the GTV (based on pre-chemo dz., PET, MRI) + 1 cm.
- MRI planning is helpful to delineate full extent of involvement.

Low-Grade Indolent NHL (Non-MALT) [49, 50]

FL International Prognostic Index (FLIPI): ("*NoooooLASH*")				
Nodal Sites: ≥ 5 **LDH > ULN** **Age ≥60** **Stage III/IV** **Hgb <12**	Risk group	# factors	5y OS %	10yr OS %
	Low risk	0-1	91	71
	Int risk	2	78	50
	High risk	3-5	53	36

FLIPI-2 ("*B-BLAH*")			
B2micro > ULN **BM involvement** **Largest LN >6 cm** **Age ≥60** **Hgb <12**	Risk group	# factors	10yr OS
	Low risk	0-1	80%
	Int risk	2	51%
	High risk	3-5	19%

Subtypes: Follicular lymphoma (FL), Marginal zone lymphoma (MZL), SLL, lymphoplasmacytic.

FL subtypes: typical, FL with 1p36 translocation, duodenal FL, large B-cell lymphoma with IRF-4 translocation, pediatric-like FL.

FL Natural History and Outcomes:
- EFS5 = 65%
- OS5 = 85%
- EFS15 = 30%
- OS15 = 60%
- FL fails distantly
- 30–65% transform to DLBCL
- 80% present as stage III/IV
- 50% of FL patients have + BM (vs 15% of DLBCL)

FL Genetics:
- t(14;18) seen in 90% of FLs. This results in overexpression of anti-apoptotic Bcl-2.

FL Frading:
- Demonstrates mix of centrocytes (small, cleaved cells) and centroblasts (large, non-cleaved cells),
- Grade correlates to density of *centroblasts*:
- G1: <5 centroblasts/hpf.
- G2: 5–15/hpf.
- G3: >15/hpf. Treat like DLBCL.

GELF Criteria:
- Criteria for treating follicular lymphoma
- ≥3 nodal sites (each >3 cm), mass ≥7 cm, B-sympx, splenomegaly, effusion/ascites, cytopenia, leukemia

Stages I–II, Staging Studies:
- FLIPI-2, Federico, 2009: prospective data collection to make better prognostic index. See in staging.

Stages I–II, Observation:
- Stanford/Advani, 2004, 63% of pts. avoided tx in 86 months. Freedom from treatment 56% at 10y. OS 97% at 5y, 85% at 10y, and 22% at 20y

Stages I–II, RT Alone:
- With RT: 50% without progression at 10 y.
- National LymphoCare Study: Stage I pts., only 27% of patients receiving RT up front. 17% observe; others get chemo, PFS better with chemo.
- MacManus, 1996: $n = 43$ FL Stage 1–2. IFRT, EFRT, and TLI. Dose 35–50 Gy. RT to both sides of diaphragm was associated w/ better 10y FFR, 67% vs 36%.

FL stages I–II, Adjuvant Chemo:
- Five RCTs failed to show benefit of RT + adjuvant chemo w/ CVP or CHOP.

Dose, Fractionation:
- UK British Nat Lymphoma investigation (Lowry, 2011): indolent NHL (mostly FL, MZL): 40–45/2 vs 24/2. Non-inferiority. Response similar, 93%. No diff in in-field progression.

– "Boom boom"/the Netherlands. Salvage for previously-irradiated recurrent indolent lymphoma. Tx 2 Gy x 2 fx. Response rate 92%. CR 61%, PR 31%, SD 5%, PD 2%. Median time to progression 14 m.
– Follicular Radiotherapy Trial, FORT, Hoskin, 2014: any stage. Recurrent or definitive MZL or FL. 4 Gy / 2 vs 24 Gy /12 measure response in 12 w. CR 68% vs 50% in favor or 24 Gy. primary endpoint LC w/ ITT. OS unchanged.

RIT:

– SWOG S0016, Press, 2013: RCT of advanced-stage FL, RCHOP x6c vs CHOP RIT w/ Bexxar (I-131 tositumomab, a CD-20 radiotherapeutic Ig). No difference in 2y PFS (~78%) or OS (~95%). Bexxar now off market.

Treatment Paradigm Follicular Lymphoma

– Grade determines management for FL. G1–2 is indolent (G3A often considered indolent). G3 is aggressive, treated like DLBCL.

Stages I–II, G1–2 FL:

– ISRT alone results in 50% DFS.
– **24 Gy / 2 Gy fractions**. Or 4 Gy / 2.
  • CTV = GTV + 5 cm prox and distal, 1.5 cm radially. The CC margin is not specified for pelvis/extremity.
  • If excised entirely, observation is an option.
  • Provide generous coverage of nodal region.
  • Cutaneous FL/MZL = 24 Gy to lesion +1–1.5 cm.
  • If CR or PR, then observe.
  • If SD or PD, then treat like stage III/IV.
  • ALCL = 30 Gy
– Consider immunotherapy+/− chemotherapy if bulky or non-contiguous LN regions involved.

Stages I–II, G3 FL:

– Treat like DLBCL.
– R-CHOP 3c if IPI 0–1, 6 otherwise, then ISRT 30 Gy for CR.

Stages III–IV, FL:

– No treatment considered curative.
– Several RCTs show that tx can be deferred without reducing survival.
– Observation is an option if no indication for treatment.
– Immunotherapy + chemotherapy.
  – R + bendamustine (BR)
  – RCHOP
  – RCVP
  – R
– Palliative RT, 2 Gy x 2. 90% response rate. 60% CR.

Indications for Treatment of Stages III–IV, FL:

– Candidate for RCT
– Symptomatic dz.
– End-organ dysfunction
– Cytopenias
– X
– Dz. progression
– Clinical trial
– Pt preference

Surveillance:

– H&P with labs q6m x 5 years
– CT C/A/P annually x 2 years, then clinically indicated

Relapse:

– Biopsy to r/o transformation to high grade
– Chemo/Zevalin (CD20 Y-90)/Bexxar (CD20 I-131). Zevalin (ibritumomab tiuxetan) is a CD20-specific mAb that is conjugated to Y-90
– Contraindications: plts <100 k, <15% marrow cellularity, >25 marrow involved, pregnancy, nursing mother
– Pre-tx biodistribution scan 1 wk. before tx
– **I-131 Bexaar (I-tositumomab)**
  • Beta/gamma
  • 0.4 mCi/kg
  • 75% cytopenia in 6–8 wks, 5% hypothyroid
– **Y-90 Zevalin (Y-ibritumomab)**
  • pure beta
  • 75 cGy
  • 75% cytopenia (thrombo/neutro) in 6–8 wks

Marginal Zone Lymphoma (MZL) [58]

- Three subtypes: splenic; nodal; extranodal (includes MALT).
- Most common stage is **IAE.**
- Consider surgery for certain sites: e.g., lung, breast, thyroid, bowel.
- Typical treatment is 24–30 Gy to whole organ.
- LC >95%. OS is excellent.
- Failure pattern is outside of the RT field.
- Disease for paired organs (e.g. orbit, parotid, skin) has higher distant relapse rate.

Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma [4–8, 58, 59]

Lugano staging A, no B-sx; B, has B-sx		
IE1	Confined to GI tract	Mucosa/submucosa
IE2		Into muscularis/serosa
IIE1	Outside GI tract	Perigastric LNs
IIE2		Distant abd LNs
IIIE		Into adventitia
IVE		Across diaphragm/distant mets

Overview

- Arises from Peyer's patches, marginal zone.
- Etiology is chronic inflammation from infection or autoimmune disorder.
- Most commonly (80–90%) in stomach, followed by lung (12%), orbit (<10%), skin (<10%).
- Low-grade B-cell lymphoma: t(11:18), t(14;18),tri3, CD 20+, 35+, 5−, 10−.
- Use FLIPI (HASSL).
- Ann Arbor or Lugano staging. For Ann Arbor, 80% are **IAE**, B-sx rare.

Workup

- H&P. Detailed exam of other MALT sites (eyes, skin, thyroid, parotids).
- Labs: CBC w/diff, CMP, LDH.
- Imaging: CT C/A/P,
- EGD/EUS if gastric. *H. pylori* test on histopathology. If negative, perform rapid urease test (RUT) and blood antibody.
- BM Bx generally not indicated, only for advanced (unlike for FL).
- Fertility counseling: 2–4 Gy for sperm, 8 Gy for eggs.

MALT Site-Specific Recommendations

Gastric MALT

- Commonly caused by *H. pylori*. High-grade MALT likely to be DLBCL and likely would not be affected. Can initially check serum anti-*H. pylori* IgG, but this will remain positive even if dz. treated.
- MSKCC, Schecter, 1998: 17 pts. who failed abx. After FU of 27 m, 100% biopsy-confirmed pCR and 100% EFS after IFRT 30/20.
- Tx strategy
  - Rapid urease test.
  - **Quadruple therapy:** "Mmm BLT!" (**b**ismuth 30 mg QID; **l**ansoprazole 300 mg BID; **t**etracycline 500 mg QID; **m**etronidazole 500 mg TID for 14 d) is superior to **triple therapy** (**c**larithromycin 500 mg BID; **a**moxicillin 1 g BID or metronidazole 500 mg BID for PCN allrg; **o**meprazole).
  - Urea breath test 1 m after abx. Urea is hydrolyzed by *H. pylori* to make CO2 and ammonia. A labeled nonradioactive carbon isotope (13C) is given PO and then detected. Positive UBT indicates *H. pylori* is present.
  - EGD w/ bx Q3m.
  - Secondary abx if still *H. pylori* positive +/− persistent dz.
  - ISRT (chemo if XRT contraindicated) for persistence/progression.
- Note: DLBCL of stomach → RCHOP x3–6 (depends on IPI) + ISRT.
- **RT indications**
  - *H. Pylori* negative.
  - t(11,18) → (<5% respond to abx)
  - Invasion past submucosa
  - Progression on abx
  - Failure after two courses of abx. Note, lag of CR may be 28 months
  - Rapid/symptomatic progression

- **Technique**
  - RT most common for IAE or IIAE *H. pylori*-negative patients, t(11;18), or deeply invasive lesions.
  - Sim fasting for 3 h with small volume PO contrast, 4D with breath-hold.
  - ISRT with 3D or IMRT For 3D use half beam block to avoid liver, obliques to avoid kidney.
  - CTV: Cover *whole stomach* + perigastric nodes ITV = CTV + margin for motion, 1–2 cm.
  - PTV = ITV + 1 cm.
  - **30 Gy in 20 fx**, i.e. 1.5 Gy fractions. Boost residual to **36 Gy.** Shechter (MSKCC, 1998): response rate to 30/20 is *100%*.
  - Prophylactic antiemetics and H2 blocker or PPI.
  - Kidney mean <20 Gy, liver V25 <50%.

Orbital MALT
- Detailed ophthalmologic exam.
- MRI orbits.
- 90% caused by *Chlamydia psittaci*.
- Abx: doxycycline for *Chlamydia psittaci*. 60% ORR.
- RT commonly **24 Gy / 12** or 16 fractions to entire orbit.
- If arising from extraocular muscles, then cover whole orbit, with bolus, which limits the dose to Meibomian gland and conjunctiva and limits risk of dry eyes.
- Pts develop dry eyes because of dose to Meibomian glands and not lacrimal gland.
- 95% local control (↑distant failure)
- If conjunctival MALT, cover just conjunctiva with single anterior electron field, 6 MeV + 2 cm margin with lens shield. Also can try 25–30 Gy in 10–20fx (can dose reduce for low grade to 19.5–24 Gy).

Lacrimal MALT
- Detailed ophthalmologic exam
- MRI orbits
- 24 Gy / 12 fractions to entire gland

Conjunctival MALT
- Chlamydia psittaci
- 24 Gy / 12 fractions to entire gland with electrons or superficial x-rays
- Eye shield

Salivary MALT
- Commonly caused by Sjogren's syndrome
- Treat whole gland
- 24–30 Gy in 12–20 fx
- Cervical nodes if involved

Small bowel MALT
- Associated with *Campylobacter jejuni*
- Surg. If R0, observe. Else, consider RT 24 Gy/12 fx

Thyroid MALT
- Associated with Hashimoto's.
- Surg. If R0, observe. Else, consider RT 24 Gy/12 fx.

Breast MALT
- Surg. If R0, observe. Else, consider RT 24 Gy/12 fx, WBI w/ tangents.

Skin MALT
- Commonly caused by *Borrelia burgdorferi* (abx: doxycycline)
- Surgery vs electrons
- 24–30 Gy in 12–20 fx

Lung MALT
- Early stage → surgery with PORT for +margin or mediastinal nodes
- Advanced stage → chemo +/− IFRT

Solitary Plasmacytoma (SP, SEP and SBP) [4–8, 60, 61]

Overview

- 15,000 cases/yr. in UA.
- Workup: H&P, CBC w/ diff, CMP, *LDH, Ca/albumin, B2micro (tells how bulky tumor is), SPEP with immunofixation, UPEP with immunofixation, 24 hr urine for total protein, serum-free light-chain assay,* ***skeletal survey*** *(not bone scan) biopsy lesion AND unilateral BMbx; bone marrow MRI upstages 30%.*
- PET-CT can be helpful but no bone scan (lytic lesions).
- M-protein: a "monoclonal protein," aka paraprotein, aka M-component. It is not IgM.
  - Note: Compared to MM, "solitary" plasmacytoma RT dose different; plasmacytoma (bone met) tx in setting of MM is palliative; SPs are not staged.
  - SBP 40% more common than SEP.

Tumor	Dx criteria for SPs, all required	Location (usually)	LN+	Progress to MM at 10y	DDx	Treatment	RT technique	LC	Follow-up
SEP	**SEP/SBP lesion by skeletal survey (negative on bone scan!) Plasmacytoma by biopsy,** <5% plasma cells **No end-organ damage (CRAB - calcium, renal, anemia, bone)**	HN	30–40%	25%	NHL, MALToma	RT or surgery	Mass + primary LNs. Head and neck: consider treating first echelon LN **GTV + 2–3 cm to 50.4 Gy, ENI to 40 Gy.** Keep GTV ≥45 Gy	LC = 88–100%. Tsang, 2001: mostly SBP, some SEP. 8y LC 83%, OS 65%, DFS 44%	q3–6 m: CBC CMP SPEP UPEP FLC PRN: LDH B2 micro BM Bx Body MRI, CT, PET Skel surv (or q1y)
SBP		Axial skeleton	Rare	75%	Mets, MM	RT or surgery	Bone GTV + *2-3 cm* Spine: whole VB Standard tx is RT, **40–50 Gy**. **No ENI.** In cases of surgical resection, adjuvant RT still recommended		

	Plasma Cell Neoplasm	M-Spike	M Protein < 3 g/dL	BM Plasma Cells >10%	End Organ Damage (CRAB)
SBP/SEP	+	+/-	-	-	-
MGUS	+/-	+	-	-	-
Smoldering MM	+	+	+	+	-
MM	+	+	+	+	+

Multiple Myeloma (MM) [62–65]

International Staging System (ISS) for MM, Greipp, 2005		Stage I	Stage II	Stage III
MST		62m	44m	29m
B2-microglobulin		<3.5 mg/L	–	≥ 5.5 mg/L
Albumin		≥ 3.5 g/dL	-	any
		*Subclassification: A = Cr <2.0 mg/dL; B= Cr ≥ 2.0 mg/dL		
Revised ISS		**Stage I**	**Stage II**	**Stage III**
ISS		I (and both of below)		III (and either of below)
chromosomal abnormalities by FISH		standard risk	-	high risk
Serum LDH		≤ULN	-	>ULN
		Durie Salmon criteria staging for MM		
	Smoldering myeloma	Stage I	Stage II	Stage III
Hgb (>12 or 13.5 is WNL)	No end organ damage, so all should be WNL	>10 g/dL		<8.5 g/dL
Serum Ca (8.5-10.2 is WNL)		≤12 mg/dL		>12 mg/dL
Bone xray		WNL, or SBP only		Advanced lesions
M protein production		Low IgG <5 g/dL IgA <3 g/dL Light chain loss < 4g/24h		High IgG >7 g/dL IgA >5 g/dL Light chain loss > 12g/24h
SPEP M-spike	≥ 3 g/dL OR BJ protein ≥ 500 mg/24h	≥ 3 g/dL or free light chain (FLC)ratio > 100		
BM plasma cells	≥10% -60%	≥10%		

POEMS Syndrome:
- Polyneuropathy, organomegaly, endocrinopathy, M-spike, skin changes.
- Variant of MM w/ solitary or limited sclerotic bone lesions,
- Elevated VEGF.
- POEMS patients respond well to RT.

Dx Criteria for MM (All Required)
- A. Clonal plasma cells (≥10% BM bx) or biopsy + SBP/SEP.
- B. M-spike (>3 g/L) on SPEP or UPEP.
- C. End-organ damage: "CRAB."
  - Ca >11.5 mg/dL
  - Cr >2 mg/dL
  - Hgb <10 g/dL (anemia)
  - Bone lesions (on skeletal survey; not BS because lesions are lytic/osteopenic, not blastic)
  - Others used as evidence for organ damage but not diagnostic of MM
    - Frequent severe infections
  - Amyloidosis
  - Hyperviscosity syndrome
- Note: No clinical features / only a + b is **"smoldering MM/smoldering myeloma (SM)."** Most SMs are detected because of MGUS.

Prognosticators of poor OS
- Plasma cell labeling index >1%
- Low albumin (<3.5 g/dL)
- High beta2 microglobulin

MM Treatment Paradigm
1. Myeloma chemotherapy (bortezomib/lenalidomide/dexa) followed by HDCT + autologous SCT. The preferred approach for anyone eligible for transplant. For txp, melphalan commonly used for conditioning (not usually TBI)
2. Primary chemotherapy (bortezomib/lenalidomide/dexamethasone). Preferred in high-risk pts. not candidates for transplant
3. Bisphosphonates
4. Palliative RT, 30 Gy /10 fractions

Bone Marrow Transplant (ASCT)

- Primary treatment after myeloma-based chemotherapy.
- Condition with high-dose melphalan.
- PARMA (NEJM 1995): compared HDC +/− BMT. IFRT given for >5 cm disease in both arms. BMT improved OS at 5 yrs. – 32% vs 53%. IFRT reduced relapses in BMT arm (35% vs 55%).

Bisphosphonates (Skeletal Events 41 → 24%)

Chemotherapy (Lots of Options)

- Bortezomib/lenalidomide/dexamethasone. Note bortezomib has increased incidence of HZV reactivation.
- Maintenance with lenalidomide or bortezomib.

Palliative RT

- Dose: **20–37.5 Gy @ 1.5–2.5 Gy/fx,** e.g. 20 Gy / 10 fraction; can also do 8 Gy / 1 fraction. If non-weight-bearing bone, then do **20 Gy/10 fractions**.
- If uncontrolled pain, weight-bearing bone, impending fx, or spinal cord compression: can go up to **30–37.5 Gy in 10–15 fx**. For spinal cord compression, this leads to improvement in motor deficits in 50% (Rades, 2006).

Mycosis Fungoides (MF)/Cutaneous T-cell Lymphoma (CTCL)/Sezary Syndrome [66, 67]

AJCC 8th Stage, Olsen, 2007.

	Incidence (%)	Progression (%):
T1 < 10% BSA T1a patch T1b plaque +/- patch	28	0
T2 ≥10% BSA T2a patch T2b plaque +/- patch	36	10
T3 *tumors*, ≥1cm diameter	20	36
T4 generalized, >80% BSA	16	41
N0 **N1** Dutch G1 or NCI LN0-2 **N2** Dutch G2 or NCI LN3 **N3** Dutch G3-4 or NCI LN4		
M0 **M1** Visceral involvement		
B0 No Sezary cells, <5% circulating of lymphocytes		
B1 Sezary cells, >5%; or neither B0 or B2	8	
B2 ≥ 1000 Sezary cells/uL		

IA **T1** N0M0 B0-1. 10y OS 93%
IB **T2** N0M0 B0-1. 10y OS 93%
IIA T1-2 **N1-2** M0 B0-1
IIB **T3** N0-2 M0 B0-1
IIIA **T4** N0-2 M0 B0. 10 y OS 50%
IIIB **T4** N0-2 M0 **B1**
IVA1:T1-4 N0-2 M0 **B2**. 10y OS 24%
IVA2:T1-4 **N3** M0 B0-2
IVB: T1-4 N0-3 **M1** B0-2

Primary cutaneous lymphoma type	Cell	Behavior	Incidence (%)
MF	T	Indolent	50
Anaplastic large cell (ALCL) (CD30+)	T	Indolent	8
Lymphomatoid papulosis	T	Indolent	12
CD4+ pleomorphic	T	Indolent	2
Sezary	T	Aggressive	3
NK/T	T	Aggressive	<3
Primary MZL	B	Indolent	7
Primary FCL, t(14;18) neg	B	Indolent	11
Primary DLBCL, leg type	B	Aggressive	4

Background
- 5–10% of patients w/ CTCL present w/ Sezary syndrome
- Sezary cells are enlarged atypical lymphocytes w/ convoluted nuclei and are found in skin, nodes, and peripheral blood.
- Sezary syndrome: presence of Sezary cells in peripheral blood, >1 K cells/uL + diffuse erythroderma.
- 17% of primary CTCL present w/ generalized erythroderma, and 50% of those cases have diagnosis of Sezary syndrome.

Workup
- Skin biopsy: Immunophenotype commonly CD2+, 3+, 4+, 5+, CD 8-, 30-, PCR for T-cell receptor gene rearrangement
- Biopsy only cLN+, those that are firm, irregular, clustered, fixed, or >1.5 cm diameter
- If palpable but biopsy negative, still N1
- CBC with Sezary screen, CMP, LDH
- Flow cytometry, PCR for T-cell receptor gene rearrangement
- PET/CT for stage IB+

CD30+ Lymphoproliferative Disorders

- **Lymphomatoid papulosis**: indolent, chronic, recurrent, self-healing. Disappears in 3–12 weeks. Histologically indistinguishable from cutaneous ALCL,
- **ALCL**: cutaneous lymphoma. Persistent and progressive. ISRT 30–40 Gy. 99% CR to RT, but 40% relapse. If multifocal, consider MTX, systemic retinoids, brentuximab, pralatrexate, observation if asymptomatic. If cutaneous ALCL within regional LNs, then MTX +/− RT, pralatrexate+/− RT, brentuximab +/− RT, CHOP +/− RT.

Treatment for CTCL

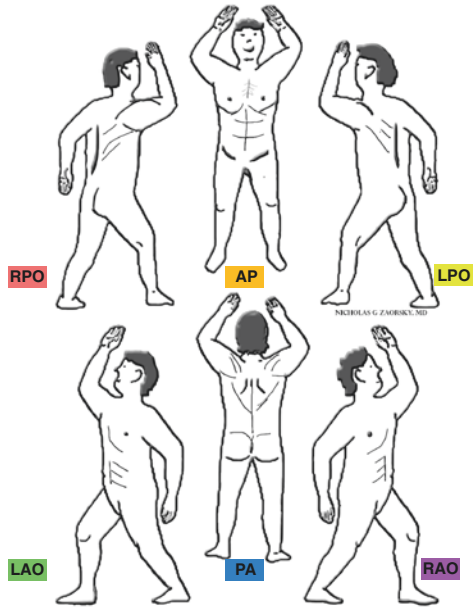
Limited Patch/Plaque (T1–3):

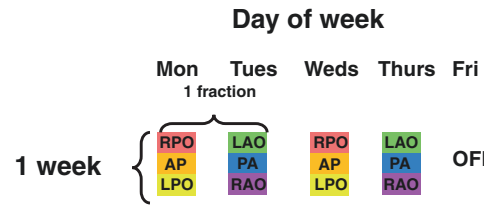
- Topical corticosteroids, chemotherapy, retinoids
- Local XRT, palliation: **8–12 Gy**, unilesional: 20–30 Gy

Stage III:

- TSEBT: **12–24 Gy** in 2 Gy fractions to total skin, **20–30 Gy** boost to scalp, perineum, soles.
- Prescribed to skin surface such that 80% IDL covers 4 mm depth.
- Use 1 Gy per day, 4 days per week.
- Gantry angles 12–23° to point above pts. head and below feet to allow for photon contamination from gantry head to avoid striking the pt. (<1% per dual field).
- 6 pt. positions (AP/LPO/RPO d1, PA/LAO/RAO d2) tx 3 positions/day, 4d/wk., for 9 wks to 36 Gy.
- Extended SSD of ~3.5–4 m used and pt. rotated through series of 6 different positions.
- Large acrylic sheet is placed 20 cm from pt. surface to scatter the electron beam.
- 6 MeV w/ beam spoiler to make 4 MeV
- **Measure** OSLDs at skin surface. Most common dose verification sites are vertex of scalp, axillae, inframammary folds, perineum, intergluteal cleft, medial thigh, soles of feet, palms.
- **Shielding**: Eyes and nail beds often shielded throughout therapy as are tops of feet to avoid edema. Toes and finger nails are shielded after 9 Gy.
- **Boost**: soles, perineum, scalp.

Complications Desquamation, hair loss, lymphedema, nail loss, loss of perspiration, second CA, and parotiditis





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Soft Tissue Cancers

11

Nicholas G. Zaorsky, Daniel M. Trifiletti, and Heath B. Mackley

Abstract

This chapter discusses the general management of patients with sarcomas, particularly soft tissue sarcomas, with special focus on principles that guide radiotherapy management. Several key components of trimodality care and radiation field design are discussed.

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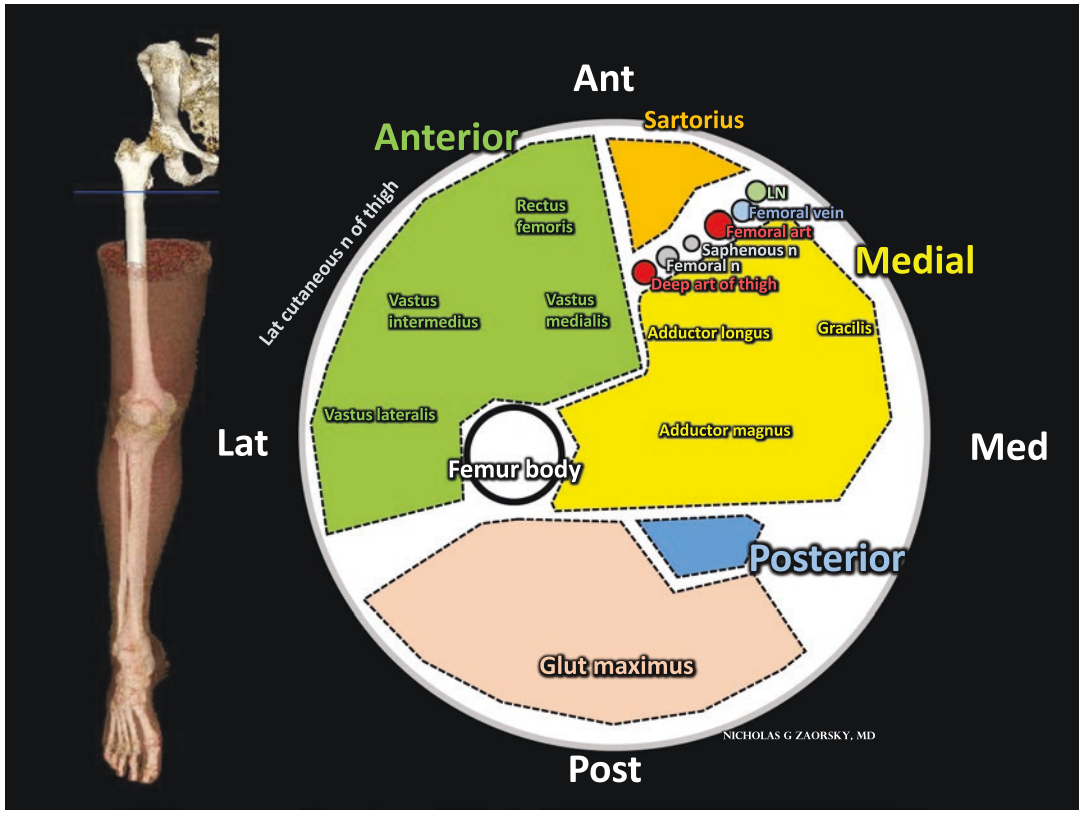
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NICHOLAS G ZAORSKY, MD
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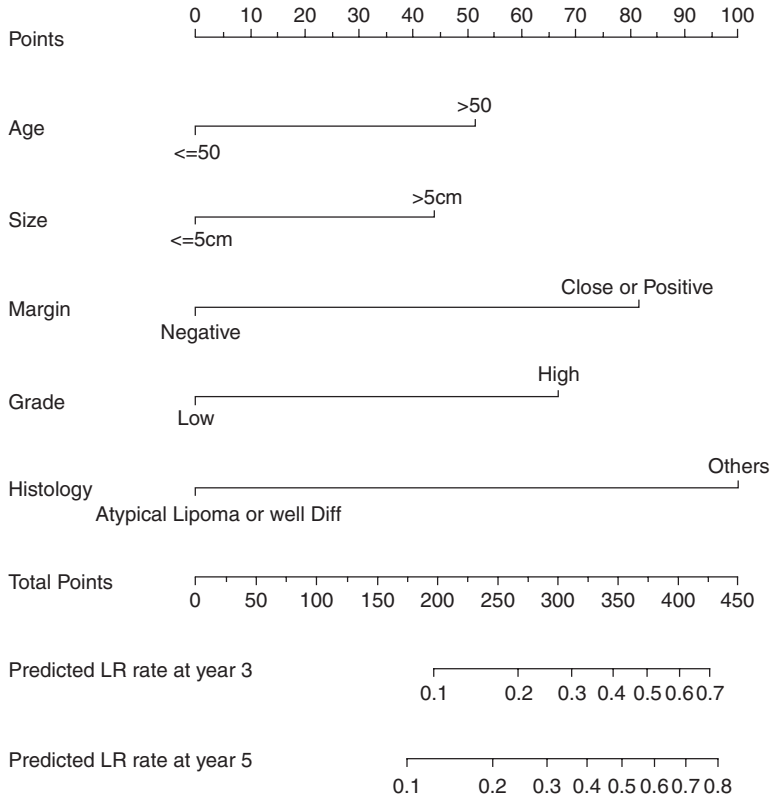
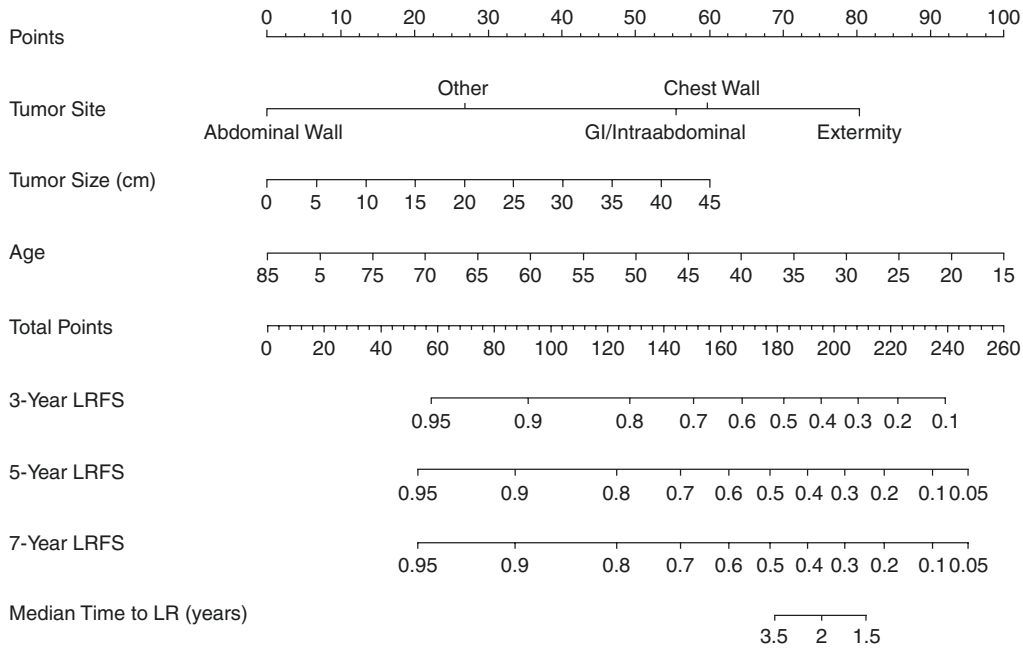


Nomogram to predict the rate of local recurrence of extremity soft tissue sarcoma, after resection, without radiation therapy. Adapted from [1]



Nomogram to predict the rate of local recurrence of desmoid after surgery, without adjuvant therapy. Adapted from [2]

Osteosarcoma [3–16]

AJCC 7	T1	T2	T3
N0	IA (G1,2,X)	IB (G1,2,X)	IB (G1,2,X)
	IIA (G3,4)	IIB (G3,4)	III (G3)
N1	IVB		
M1a	IVA		
M1b	IVB		

AJCC 8	T1	T2	T3
N0	IA (G1)	IB (G1)	IB (G1)
	IIA (G3)	IIB (G2)	III (G3)
N1	IVB		
M1a	IVA		
M1b	IVB		

- **T1** – ≤8 cm
- **T2** – >8 cm
- **T3** – discontinuous tumors
- **N1** – nodes
- **M1a** – lung
- **M1b** – others

Overview

– Prevalence: osteosarcoma (56% of peds bone tumors) > chondrosarcoma > Ewing (36% of peds bone tumors) > MFH.
– 800 cases/year, 2× more common than Ewing sarcoma.
– Bimodal distribution: 15 yo and >65 yo (usually associated with Paget disease and fibrous dysplasia).
– If pt. w RB loss and retinoblastoma, later as risk for osteosarcoma.
– High rate of bone production and turnover are risk factors.
– Boys > girls.
– 90% have localized dz. If treated w NA-chemo and surg, OS is 65%.
– 90% of pts. w localized dz develop mets w/o chemo, usually to the lung. OS is 20%.
– MDR1 gene (multidrug resistance gene) makes p-glycoprotein, removes doxo from cells, and increases mortality.

Subtypes

– **Classic**: 75% of cases, presents in areas of rapidly proliferating intramedullary bone.
– **Juxtacortical**: rare, arises adjacent to outer surface of cortical bone. Usually G1 (parosteal) or G2 (periosteal). G1 has low DM rate and is curable w surgery alone. G2 has 20% DM rate, and role of chemo is controversial.

Anatomy

– Bone has diaphysis (shaft), epiphysis (end), and metaphysis (joining the parts).
– Osteosarcoma most frequently arises in appendicular skeleton at metaphyses of the femur, tibia, and humerus.

Presentation

– Localized bone pain and soft tissue mass
– "Growing pains"

Workup

– H&P, labs, Alk Phos, ESR, plain films, CT primary+chest, MRI primary, and bone scan.
– Biopsy after images. Need to excise biopsy site.
– Bx should be performed at same institution doing surgery.
– Bx should avoid contamination of other areas.
– Bx should not increase the extent of subsequent surgery.

Imaging for Osteosarcoma

– Sunburst periosteal reaction.
– Sclerotic, metaphysis.
– Codman's triangle.
– In contrast, Ewing sarcoma usually lytic, at diaphysis, has onion skin.

Studies

– Neoadj and adj chemo ↓LF (Link 1986, Eilber 1987).
– Ozaki 2003: retrospec. RT improved OS for R1 or R2.
– Machak, Mayo, 2003: 5-year OS for unresectable osteosarc receiving NACT, RT, and adj chemo is 60%.
– Souhami, 1997: doublet chemo w doxorubicin and cis better tolerated. No difference in OS.
– DeLaney: retrospective. Doses >55 Gy have better LC.

Treatment Paradigm

- Treatment paradigm is pre-op chemo with MAP (methotrexate, adria, cisplatin), surg, then adj chemo for 4 m. Long-term survival is 60% w CMT vs 20% for surgery alone.
- In rare cases of resectable tumors, then go straight to surgery. If R0, then observe. If R+, then adjuvant chemo.

Role of RT

- If unresectable (e.g., pelvis, sacrum, spine), then neoadjuvant chemo, then RT to **60–70 Gy** +/− sensitizers, and adj chemo (cat 1).
- If R1 resection where re-resection difficult (e.g., jaw). R1 PORT to 60 Gy.
- If R2 after surgery: dose is **>55 Gy w boost to 64–68 Gy** to areas.
- Inoperable: 70 Gy.
- Palliation as needed
- Sm-153 being investigated.

Chondrosarcoma [17]

AJCC 8	T1	T2	T3
N0	IA (G1)	IB (G1)	IB (G1)
	IIA (G3)	IIB (G2)	III (G3)
N1	IVB		
M1a	IVA		
M1b	IVB		

Background
- 30% of primary bone tumors, behind osteosarcoma, MM.
- 75% arise in the proximal femur, pelvis, and proximal humerus.
- In skull base they arise from petroclival bone and spheno-occipital junction and are locally aggressive.
- Skull base chondrosarcoma has better 5-year LC vs chordomas: 85–95%. 10-year OS 80%.

Subtypes
- Conventional: 85% of tumors
  - G1: atypical cartilaginous tumor/chondrosarcoma G1 (**ACT/CS1**)
  - G2–3: malignant, due to DM potential
- Other types: Dedifferentiated, mesenchymal, and clear cell.

Workup
- Plain radiographs, MRI, and CT.
- CT CAP for DMs, esp. for G3.
- On plain film, mineralization of matrix may produce punctate or ring-and-arc pattern of calcification.
- Core needle or open biopsy. FNA not recommended.
- Neuro-ophtho and endocrine workup for BOS chondrosarcoma.

Studies
- Rosenberg, 1999. Surg and adj RT yields >90% LC is BOS, superior to chordoma.

Treatment Paradigm
- WLE first.
- For ACT/CS1 intracompartmental chondrosarcomas, intralesional curettage and adjuvant cryosurgery can be used as alternative.
- RT if unresectable. Dose >60 Gy for R+. In BOS, dose should be >65 Gy.
- No chemo generally. Consider for mesenchymal type.

Follow-Up
- Imaging locally and chest q6-12 m for 2 years and then q12m for 10 + years.

AJCC 7	T1	T2	T3
N0	IA (G1,2,X)	IB (G1,2,X)	IB (G1,2,X)
	IIA (G3,4)	IIB (G3,4)	III (G3)
N1	IVB		
M1a	IVA		
M1b	IVB		

Chordoma [13, 18–23]

Background

- Originates from midline notochord remnant, which extend from the sella turcica to the sacrococcygeal bone in the fetus. Chordomas can rise anywhere along this tract but are most frequent in the BOS or sacrococcygeal bones.
- Typically at BOS; thus, resection is difficult.
- DMs in 5%.
- Poor prognostic factors: recurrence, BOS, female, tumor necrosis in pre-tx biopsy, and >70 cc.

Location: sacrococcygeal (50%), spheno-occipital (35%), and vertebral column (15%)

DDx of Sacral Bone Lesion: Mets, MM. Chordoma is the most frequent primary malignant bone tumor of sacrum and mobile spine. Other lesions: chondrosarcoma, Ewing sarcoma, osteosarcoma, PNET, Paget, and benign tumors (e.g., giant-cell tumor, hemangioma)

Symptoms: Depend on site of origin. Usually pain of gradual onset

Subtypes

- Classic (no cartilaginous or mesenchymal components)
- Dedifferentiated
- Chondroid, 30% of cranial region chondrosarcomas

Natural History: 95% of patients will have LR; 40% will have LR and DMs after tx. DM most likely to the lung and bone

Workup

- Do not perform transrectal biopsy due to propensity to seed along tracts in the rectum. All biopsy tracts should be marked and removed in subsequent surgery.
- MRI: T1 intermediate–low. T2 high.

Pathology

- Physaliferous cells
- Express cytokeratin and epithelial membrane antigen
- S-100+

Studies

- UF/UPMC, 2014: 5-year LC w RT is 30–60%. LC approximates CSM. RT dose required is >60 Gy. UF treats to 75/1.8, going past dose constraints to get LC.
- UPMC: SRS is tx option.
- Carpentier, 2002: pts. managed w surgery +RT have improved recurrence vs salvage RT. 5-year OS 80% vs 50%. 10-year OS 65% vs 0%.
- Delaney, 2014: phase II of pre- or post-op RT. 11% LR. Favors dose of 77.4 Gy RBE for primary tumors, 70 Gy for adjuvant.
- Catton, 1996: retrospective for BOS chordomas. 50 Gy photons. 85% pts. had pain palliation, but LC was 27%, 5-year PFS 23%, and MST 62 m.
- Yamada, 2013: SRS. 24 Gy in 1 fraction. 95% LC rate at 24 m.
- Hug, 1999, Loma Linda: 58 pts., 33 chordomas, 25 chondrosarcoma. LC 76% for chordoma, 92% chondrosarcoma. 5-year OS chordoma 79% vs 100% chondrosarcoma. High volume of residual (>25 cc) worse.
- Fagundes, 1995: recurrence. Surg + RT vs BSC. 2-year OS 63% vs 21%. However, 5-year OS was only 6%.

Chemo

- Not shown to be effective
- Imatinib: some activity if PDGF-beta overexpression

Treatment Paradigm

- Maximal safe resection w adjuvant RT..
- For surgery, SOC is **en bloc spondylectomy**.
  - Low = sacrifice S4 and below.
  - Mid = sacrifice S3 and below.
  - High = sacrifice S2 and below.
  - Total = sacrifice S1 and below.
- Consider protons or SRS for chordoma at BoS.
- Otherwise RT, aim for dose escalation **>60 Gy,** conventional fractionation. Another option is SRS, **24 Gy/ 1fx**. Chordomas are radioresistant.

Technique for Chondrosarcoma and Chordoma

- Spare 2 cm of skin.
- CTV is surgical bed + scar +2 cm.
- In the brain, they can be treated by 72 Gy at 1.8 Gy fractions.

Recurrence

Can try surgery and RT again

Toxicity

- 26% of BOS chordomas will have endocrine abnormalities.
- 10% will have vision loss, brainstem injury, and temporal lobe injury in 5 years.
- Risk of sacral neuropathy increases if >77 Gy.

Chloroma/Granulocytic Sarcoma or Myeloid Sarcoma

Background

- Extramedullary manifestation of AML, a solid collection of leukemic cells occurring outside of the bone marrow
- Sometimes associated w AML but can also be present w myeloproliferative disorders.
- Usually an ominous sign, possibly preceding blast crisis or conversion to AML.
- Green is from myeloperoxidase on path specimen. Name derived from "chloros."
- Most are in craniofacial bones or orbit.
- Radiosensitive.

Studies

- Bakst, MSKCC, 2012: symptom relief in 95%, 37% relief during RT

Treatment

- 24 Gy/2 Gy fractions adequate
- GTV + 2–3 cm
- 80% LC

Extremity Soft Tissue Sarcoma (eSTS) [3–7, 24–53]

AJCC 8th edition (deep/superficial not important)

- **T1** – ≤5 cm
- **T2–** 5–10 cm.
- **T3**– 10–15 cm
- **T4** – >15 cm
- **N1** – nodes.
- AJCC 7th edition (deep/superficial important)
- **T1** – ≤5 cm
  - T1a – superficial
  - T1b – deep (inc all RP)
- **T2** – >5 cm
  - T2a – superficial
  - T2b – deep
- **N1** – nodes

AJCC8	TNM	G	AJCC7	TNM	G	Paradigm
IA	T1	1	IA	T1	1	Surg alone w good margins
IB	T2-4	1	IB	T2	1	Surg alone w good margins,RT (cat 1)
II	T1	2/3	IIA	T1	2/3	Pre-op RT (cat 1) then surg, then +/- RT boost +/- chemo
			IIB	T2	2	Surg (cat 2a), then RT (cat 1) +/- chemo
IIIA	T2	2/3	III	T2 or	3	Preop chemo +/-RT (cat 2b), then surg,+/- RT boost +/- chemo
IIIB	T3-4	2/3		N1	-	*If unresectable: RT+/- chemo, then reconsider surg
IV	N1 or M1	-	IV	M1	-	Oligo: treat curatively Disseminated: chemo, RT, surg, ablate, embolize

Grading

– AJCC recommends a 3-tier system.
– FNCLCC (French Federation of Cancer Centers) is preferred.
– Three parameters: differentiation, mitotic activity, and extent of necrosis.

Overview

– 11,000 cases/year, 4400 deaths/year
– Median age 45–55 yo.
– Histology:
  - **Unclassified (or undifferentiated) pleomorphic sarcoma**, aka **malignant fibrous histiocytoma** (**MFH**). 25% of cases. 26% of RT-induced histology.
  - **Liposarcoma** 15%, 12q amplification involving MDM2 and CDK4.
    - **Subtypes:**
    - **Myxoid/round cell liposarcoma** t(12;16)
    - **Pleomorphic liposarcoma**
    - **Well differentiated/dedifferentiated**
  - **Leiomyosarcoma** 10%
  - **Synovial sarcoma** 5% [t(x,18)], SYX-SSX
  - **Malignant peripheral nerve sheath tumor** (MPNST) (5%)
  - **Clear cell** <5% [t(12,22)]
  - **Angiosarcoma**. 21% of RT-induced sarcomas
  - **Ewing/PNET**: t(11,22), EWSR-FLI1
  - >50 other subtypes
– STS arises from primitive mesenchyme of mesoderm.
– Risk factors: RT, chemo, genetics, viral, chronic edema, thorotrast, chlorophenols, vinyl chloride, arsenic, and herbicides.
– Anatomic location (per ACS): 46% in LE (75% of these above knee), 18% trunk, 13% UE, 12% RP, 9% HN, and 1% mediastinum.
– Finnish database: RT as risk factor, 0.03% at 10 years.

Syndromes

– Stewart-Treves syndrome and lymphangiosarcoma from lymphedema, e.g., from breast cancer tx. Usually angiosarcoma
– Li-Fraumeni, AD, and "sarcoma, breast, leukemia, and adrenal gland cancer syndrome."

↑LN+: "CARE"

– Clear cell, 28%
– Angio, 11%
– Rhabdo, 15%
– Epithelioid, 20%
– Synovial no longer thought to have high LN involvement (thus, no more "SCARE")

Workup

- H&P:
  - Ask about kinetics of growth and neuro sx.
  - Extremity exam regarding ROM and lymphedema
  - Neuro exam for re-strength and sensation
  - LN exam for CARE tumors
- Xray, CT, MRI, CXR (<5 cm), or CT chest (>5 cm)
- Fertility preservation.
- **Incisional biopsy:** longitudinal, placed along future resection axis, preferably by the surgeon who will later do resection.
- **Excisional biopsy contaminates surrounding tissue.**
- Genetic testing (Li-Fraumeni, h/o early breast ca, bone sarcoma, brain tumors) DM, lung (RP sarcoma→ liver).
- PET best for prognostication, grading, determine response to chemo.
  - CT A/P: myxoid/round cell liposarcoma, epithelioid, angiosarcoma, and leiomyosarcoma.
  - MRI spine: myxoid and round cell.
  - MRI brain: **alveolar** soft part sarcoma (ASPS) or angiosarcoma.
  - For surg, goal is 1 cm SMs in all directions.

DDx: Primary or metastatic carcinoma, lymphoma, desmoid tumors, and benign lesions (lipoma, lymphangioma, leiomyoma, neuroma, schwannoma)

Recurrence After Surgery Alone

- Simple excision: 90%
- WLE: 40%
- Soft part excision: 25%
- Amputation: 15%

Prognostic Factors

- Toulmonde analyzed 719 pts. from the FSG alive and event free for >5 years after dz 9% had a late LR 6% had DM+.
- Pisters analyzed 1041 pts. from MSKCC, 1982–1994.
- MSKCC [1] nomogram for LR after LSS for STS of extremities.

Pisters, 1996	Toulmonde, 2014
Any LR	**Late LR**
Age >50, R+, prev recurrence, histologic subtypes (fibrosarcoma, MPNST)	Internal trunk location (25% of pts) and tumor size >10 cm (14% of pts)
Any DM	**Late DM**
Large tumor size, G3, deep location, recurrent dz, histologic subtypes (leiomyosarcoma)	G2–3

Angiosarcoma

- 2% of STS
- Elderly white males on scalp and face
- 50% cutaneous in HN
- Very poor prognosis due to field cancerization
- Presents as "spreading bruise" that is red/blue

Surgery Alone

- MDACC, Pisters, 2007: n = 88 w T1, any G, all get LSS alone if R0. 10-year LR 11%, and most recurrences in high grade

RT Alone

- Lingberg, 1972: 2-year LR 66% and 2-year DFS 17%

Chemo

- Limited data.
- SMAC, Pervaiz 2008: meta-analysis for chemo (doxorubicin based). Chemo improved LC 4% (HR 0.73) and OS 6% (HR 0.77). NNT was 17 to prevent 1 death. Doxo + ifos better than doxo alone.
- MGH (Delaney, 2003): retrospective 48 pts. with neoadj CRT (MAID +44/22 split course) with boost post-op if R1. At 5 years LC 92% and OS 87%. Compared to historical control, there was improved 5-year DMs (75% vs 44%), DFS (70% vs 42%), and OS (87% vs 58%). Trend toward improved LC in CRT group vs historical control (92% vs 86%).
- RTOG 9514: used Harvard neoadj CRT, more intense chemo, with 64 pts. showing similar results (OS 71%), but toxic. 5% tx-related deaths, mostly AML. 84% had G4 toxicity.
- EORTC STBSG 62871, Gortzak, 2001: RCT STS 8+ cm, G2–3. Rando to surg alone vs NA

doxo/ifos. PORT for marginal surg, R+, LR. No difference in 5-year DFS (~54%) or OS (~65%), but not powered for this.

Post-op RT

- NCIC / Yang 1998: WLE w 1–2 cm margin R0 +/-EBRT (45 Gy wide field +18 Gy boost to bed = 63 Gy). *n* = 91. G3 tumors got chemo. RT improved LC for all grades (70% vs 100%), but no change in OS or DMFS (similar to MSKCC). For G1 patients, LC favored RT arm, 95% vs 67%, NSS. RT worsened joint motion and edema.
- Pisters 1996: 1982–1994. WLE+/−brachy (45 Gy LDR Ir-192). Tx volume was 2 cm sup/inf and 1.5–2 cm med/lat. Brachy →↑LC for G3 (89% vs 66% at 5 years), but not for G1–2.
  - Subset analysis on 20% of pts.: BT improved LC if R0 but not if R2.
- Higher LR if age >50, recurrent at presentation, R+, fibrosarcoma or malignant peripheral nerve tumor. Higher DM if large tumor, G3, deep location, recurrent dz, and leiomyosarcoma.
- MGH (Delaney, 2007): *n* = 154. Retrospective. All R+. At 5 years, LC 76%, DFS 48%, and OS 65%. LC highest if dose >64 Gy (85% vs 66%).

Amputation Versus LSS

- NCI, Rosenberg 1982: STS, G3 → amputation vs WLE + RT (boost to 60–70 Gy). Randomization favored LSS, 2:1. No difference in OS (83% at 5 years). Increased LR w LSS, 20% vs 0%. No difference in 5-year DFS 88% vs 83% (NSS)

Pre-op Versus Post-op RT

- Pollack 1998: pre-op (50 Gy) vs post-op (60–66 Gy). Same LC (81%).
- O'Sullivan 2002: pre-op (50 Gy) vs post-op (66–70 Gy). If +margin, pre-op got 16 Gy boost, and 10/88 pts. received this boost. PTV1 expansion was *5 cm* prox and distal to GTV; PTV2 was reduced to *2 cm* around target. Primary endpoint, more temporary wound healing problems with pre-op (35 vs 15%) but more late fibrosis with post-op. Trial closed early because of higher rates of wound complications w pre-op, esp. in ant thigh (45% vs 38%).
  - Secondary endpoints: Same LC (93%) and DM (25%). Pre-op had slight benefit for OS (85% vs 72%) but washed out after 5 years, and it was underpowered. Pre-op RT had higher acute wound complications (35% vs 17%), but lower rate of G2+ fibrosis (32% vs 48%), edema (15% vs 23%), and joint stiffness (18% vs 23%). Overall, supports use of pre-op RT in STS.
- CAN-NCIC-SRS (Davis, 2005): compared late RT morbidity from O'Sullivan study, more detailed metrics.

Pre-op RT +/– Boost

- Toronto, Al Yami, 2010. *N* = 216. All treated w pre-op RT and have R+. Retrospective review. 50/25 for 52 pts.; 41 pts. received 16 Gy boost. No difference in OS 11.5% w/o boost, 22% w boost. 5-year LC 90% vs 74% (NSS).
- MGH, Pan, 2014. *N* = 67. Similar to above. No difference in LC for boost. Thus, do not boost.

Hyperthermia

- EORTC 62961, Issels, ASCO 2007. 341 pts. w 5+ cm G2–3, deep and extracompartmental STS get NA EIA +/− regional hyperthermia. Hyperthermia won, improved LRC 3.8 years vs 2 years and median DFS 2.6 years vs 1.4 years.

Toxicity

- MGH (Baldini, 2013): *n* = 103. STS of extremity or trunk pre-op RT median dose 50 Gy. Twenty-three had BT boost, median 18 Gy in 2–4 Gy fractions BID. 90% LC. Major wound complications (MWC) rate 35%, and 25% of these required reoperation. MWC higher if diabetes, size >10 cm, proximity to the skin <3 mm, use of vascular flap or STSG closure. Authors conclude they favor pre-op RT, but 35% MWC rate is concerning.

– Toronto (Griffin, 2015): *n* = 798. 30% had WCs. No difference for IMRT vs 3D. Trend for more WCs if surg after 6 w

EBRT Versus BT
– MSKCC (Alektiar, 2011): IMRT vs LDR-BT, retrospective. IMRT was 50 Gy pre-op; 63 Gy post-op. LDR-BT was 45 Gy, ~950 cGy/day. On MVA, IMRT associated w improved LC.

IMRT Versus 3D-CRT
– Folkert. JCO 2014. *n* = 319. 5-year LR 8% vs 15%, (54% relative reduction) favoring IMRT. Factors associated w LR included lesion size (< vs >10 cm; age <50 vs >50).
– PMH (O'Sullivan, 2013): *n* = 70. Phase 2 of pre-op IGRT IMRT. 5-year LC 88%. IGRT/IMRT decreased need for tissue transfer.

IMRT
– Alektiar, 2008. 41 pts. extremity STS w LSS and IMRT. 51% had close or R+. IMRT used in pre-op in 7 pts. and post-op in 21. At 5 years LC 94%, DMFS 61%, and OS 64%

IGRT
– RTOG 0630 (Wang, JCO, 2015). Multi-institutional assessing late tox of STS of extremity w pre-op IGRT. In pts. with G3 tumors ≥8 cm, the CTV = GTV + 3 cm longitudinal and 1.5 cm radial. For G1 tumors or tumors <8 cm, CTV = GTV + 2 cm longitudinal and 1 cm radial. 50 Gy/25 to 95% of PTV. Primary endpoint was toxicity, plan to test 20% abs improvement in G2+ tox at 2 years from 37% in the pre-op RT arm of CAN-NCIC-SRT2 study. G2 late tox (subQ fibrosis, joint stiffness, edema) was 10.5% vs 37% in CAN-NCIC-SR2. Fibrosis 5.4% vs 31%. Joint stiffness 3.5% vs 18%. Edema 15% vs 5.3%. 2-year LC was 94%, all failures in CTV.

Treatment Paradigm

– **Stage I**: surgery alone, aim for >1 cm SMs, consider RT for +margin (cat 2b) or close SMs
– **Stage II–III:**
  • Surgery + PORT
  • Pre-op RT + surgery
  • Pre-op chemo cat 2b
– **Angiosarcoma**: WLE + post-op to primary and regional LNs

Pre-op eSTS Technique
Simulation
– Supine (upper inner thigh) vs prone (buttock/posterior thigh)
– Rigid immobilization
– CT sim without contrast

Contours
– Fuse T1 post + T2 MRI with planning CT
– GTV = T1 post-MRI volume
– CTV = 1.5 cm radial, 4 cm longitudinal
– *ensure this covers the T2 edema.
  • [CTV_50 = operative bed +1.5 cm radial, 4 cm longitudinal]
  • [CTV_66 = operative bed +1.5 cm radial, 2 cm longitudinal]
– PTV = CTV + 5 mm

Dose
– 50 Gy in 25 fractions

Planning
– IMRT or 3D.
– 6 MV beam energy
– Daily KV imaging

Technique (for Both Pre- and Post-op)
– Spare >1 cm of limb cross section to decrease lymphedema risk.
– Treat ½ bone circumference if possible.
– Minimize joint treated.
– >60 Gy to femur – risk of osteonecrosis.
– When to treat scar:
  • Traditionally, it was always covered.
  • Haas IJROBP, 2012 review recommendations: (1) CTV large (>5 cm); (2) G2–3; (3) R1.
    • In low-risk pts. (G1, wide R0), coverage to drain sites can be omitted. Tx will increase risk of late morbidity.

- Drain site should be marked w BB.
- Treat scar to full dose, using bolus if necessary.

Constraints
(RTOG 0630)
– Joints V50 <50%
– Bone, weight-bearing V50 <50%
– Skin + subq tissue, longitudinal V20 <50%
– Anus V30 <50%
– Femoral head: V60% <5%
– Kidney V14 <50%
– Lungs V20 <20%

Additional Constraints, to Prevent Bone Fracture, Pre-op (Dickie, 2009)
– Bone V40 <64%
– Mean bone dose <37 Gy
– Max bone dose <59 Gy

Pathologic Fracture Risk Factors
– Bone V40 >64%
– Bone mean >37 Gy
– Bone Dmax >59 Gy
– Female
– >55 yo

Others
– Epiphysis <20 Gy (prevent premature closure).

Brachytherapy
– CTV: Tumor bed plus 2–3 cm sup/inf & 1–1.5 cm circumferentially.
– Afterloading catheters placed 1 cm apart.
– Catheters loaded with iridium-192 loaded after POD 7–14 to permit wound healing.
– Time >7 days can lead to higher infection risk.
– **Dose**:
  – 15–25 Gy at 40–50 cGy/hr. given as boost tx plus 45–50 Gy with EBRT
  – 45 Gy over 4–6 days, which is equivalent to 60 Gy EBRT, can be given for definitive post-op tx or for tx of recurrent disease
  – HDR-BT: 3.4 Gy BID × 10 fx over 5 days

Retroperitoneal Sarcoma (RPS) [54–58]

Background

- Incidence 2.7 per 1 M.
- 10–15% of all STSs.
- Mendenhall 2005: review of lit. GTR in ~50%, but close margins. Most fail locally. At 5 years LC 50% and OS 50%.
- Failure pattern mostly local, unlike extremity STS.
- Most likely metastasize to the liver.
- Most likely histology liposarcoma (30–60%) and leiomyosarcoma (20–30%).
- DDx: sarcoma, GIST, lymphoma, GCT, DT, lipoma, PNST.
- CT: usually homogenous, fat density,
- Biopsy remains controversial for patients receiving surgery first. If CT suggestive, no further dx tests are needed. NCCN rec CT-guided core bx before pre-op chemo and/or RT. Goal is to avoid inappropriate tx of non-malignant tumor.

Organs in RP Space: The pancreas, kidneys, adrenals, ureters, and ascending/descending colon

Histology: Liposarcoma and leiomyosarcoma most likely; in children, RMS most likely

Pre-op

- Alabama, Tzeng, 2006: pre-op RT (45/25) w selective dose escalation (to 57.5) to margin at risk. 2-year LR 20%
- Koshy, 2003: IMRT vs 3D-CRT retrospective at Emory. 50.4 to PTV. IMRT decreased dose to small bowel 36 Gy to 27 Gy. Max and min doses delivered to PTV significantly increased by 6 and 22%, respectively. V95 improved from 95% to 99%. No difference in LR
- Toronto/MDACC, Pawlik, 2006: G2–3 RPS treated w pre-op RT (median 45 Gy) w concurrent low-dose doxorubicin. *N* = 72. 57 (89%) pts. had laparotomy, 95% w R0–1. Recurrence rate 52% if R0. At 5 years, LRFS 60%, DFS 46%, and OS 61%. Favorable vs historic controls

Post-op

- Bates, 2015, SEER. *n* = 114. Adj RT associated w improved median OS in high-grade RPS, 36 m vs 27 m, HR 0.79. Absolute OS benefit 21%. On MVA, RT, male sex, age >65, stage, all associated w survival

Pre-op Versus Post-op

- Bolla, 2007: worse toxicity w PORT vs pre-op, 23% vs 0%

IORT/PORT Versus PORT

- NCI, Sindelar, 1993: IORT + PORT vs PORT alone. 35 pts. randomized. IORT is 20 Gy and PORT is 35–40 Gy. PORT alone is 50–55 Gy. Both get doxo, cyclophos, and MTX. No difference in OS at 5 years. MST ~4 years. With IORT, there was a decrease in LR, 80% vs 40%; dec in RT enteritis, 50% vs 13%; dec in peripheral neuropathy, 80% vs 60%.
- MGH, Gieschen, 2001: 29 pts. 16 get IORT, 10–20 Gy w intraop electrons, and 13 get no IORT. All get 45 Gy EBRT. LC improved w IORT, 83% vs 61%.
- Stucky, JSO, 2014: 1996–2011. pre-op RT, surg, then IOERT. EBRT 45–50 Gy/1.8–2. Then, surg, and IOERT to any close or high-risk SM, dose 10–20 Gy. 5-year LC 89% for surg+RT vs 46% for surg alone.

Surg Versus Pre-op RT Then Surg

- ACOSOG Z9031 (Pisters). Surg alone vs pre-op RT then surg. Closed due to poor accrual.
- EORTC 62092–22,092: Surg alone vs pre-op RT then surg. Ongoing. Primary endpt is difference in RFS. Secondary endpts are DMFS, rumor response, and toxicity. Using 3D or IMRT, 50.4/28.

Growth Rate

- PMH (Wong, 2014) *n* = 39 w 118 CBCT. GTV increase in volume mean 7% during first 2w of RT, then by 4% by the end of pre-op RT. Breathing motion correlated w more sup tumors, supporting use of 4D.

Treatment Paradigm

- Pre-op RT, then surgery. Tumor displaces normal bowel and areas at high risk for toxicity. Further, LR is 50–95% after surgery. Dose escalates areas at risk for R+ (e.g., vessels) w dose painting. Avoid post-op because bowel will be near R+ site, and vascular supply limits BEDs.
- RT is 50.4/1.8 (MDACC regimen), or 45/25 with SIB to 57.5 (Alabama regimen).

Absolute Contraindications to Resection

- Spinal cord involvement
- Distant metastases
- Peritoneal implants
- Involvement of superior mesenteric vessels
- Extensive vascular involvement (e.g., aorta)

Relative Contraindications to Resection

- Involvement of IVC and iliac veins (as they can be ligated or grafted)

Pre-op Versus Post-op for Sarcoma [50, 61]

	Extremity STS		RPS
	Pre-op preferred for Stage II-III	Post-op, as needed for Stage IB	Pre-op preferredfor M0
vs. amputation		Comparable outcomes with LSS +RT vs. amputation (Rosenberg, Ann Surg, 1982)	N/A
Indications	Preferred over post-op for G2-3 at MGH Amputation, NV bundle sacrifice, Unavoidable + margin	G1-3 with R+ LR s/p prior surgery alone Location not amenable to salvage surgery	Preferred over post-op, as <70% amenable to R0. Pre-op will give smaller field, less chance to have to escalate near bowel
Timing	3-6 weeks. >6 w assoc w > late fibrosis.	3-8 weeks	3-6 weeks
Pros/cons (O'Sullivan, Lancet, 2002)	Smaller field, lower dose (50 Gy), ↑ acute wound comps (35 vs 17%), ↓-stage; reduced surgical seeding; improved tumor oxygenation (?); may improve resectability and chance for R0; <15% LR toxicities are *temporary*	Bigger fields (~330 cm^2 vs. ~420 cm^2), higher dose (60-66 Gy), ↓ acute wound comps, ↑ long-term fibrosis, ↓ ROM; <15% LR; scar bolus; possible hypoxia in tumor bed toxicities are *permanent*	N/A
Volumes (Haas, IJROBP, 2012; White, 2005; Wang, 2011; Bahig, 2013; Wang, 2015) [59,60]	GTV = MR T1 post-gadolinium CTV = GTV + T2 peri-tumoral edema + *4 cm* prox/distal, *+1.5 cm* radial, edited at bone (White). Reasonable to decrease to 3 cm prox/distal (Wang). PTV = CTV + 5-10 mm (depending on IGRT use) PTV = 50 Gy RTOG 0630 volume (Wang): G2/3 tumor AND≥8 cm, CTV sup/inf margins *3 cm*, radial *1.5 cm*. Also cover edema on T2 MR ALL OTHERS, CTV sup/inf margins *2 cm*, radial *1 cm*. Also cover edema on T2 MR	GTV = MR T1 post-gadolinium (if present) CTV = GTV post op bed *+ 4 cm* prox/distal, *+1.5 cm* radial, edited at bone, scar Haas IJROBP drain site coverage recommendations: (1) CTV large (>5 cm); (2) G2-3; (3) R1. PTV = CTV + 5-10 mm PTV1 = 50 Gy PTV2 (cone down to GTV) = 16-20 Gy 60-66Gy for R0 66-68Gy for R1 70-76Gy for R2	(per IEP) CTV = iGTV + *1.5 cm* symmetric margins. 4DCT for sim w some form of respiratory control if tumor >1 cm. Trim from uninvolved bone, kidney, liver, bowel/air cavity, extension below uninvolved skin, expansion beyond RP compartment. If 4D unavailable for upper abd tumor, then CTV is 2-2.5 cm cephalon-caudal, and 1.5-2.0 cm radially. (per RTOG S-0124) CTV= 5 cm circumferential margin, trim at OARs down to 3 cm. Consider SIB PTV 57.5 Gy @ 2.3 Gy/fx
	If R+, consider boost: 10-16 Gy IORT 12-20 Gy BT 10-14 or 16-20 or 20-26 Gy EBRT		
Outcomes	Likely no difference in outcomes, esp. when control for SM status: LC (O'Sullivan, Lancet, 2002; Pollack, IJROBP, 1998); OS (O'Sullivan, ASCO, 2004) LC, DFS, LNM, DM rates (Zagars, IJROBP, 2003). Trend toward improved OS, LC on meta-analysis (Al-Absi, *Ann Surg Onc*, 2010)		
Toxicities G2+(O'Sullivan, Lancet, 2002)	Fibrosis 23% Edema 15% Joint stiffness 18%	Fibrosis 48% Edema 23% Joint stiffness 23%	
Pt QOL	No difference in 3-year QOL; QOL is likely dependent on tumor characteristics (Davis, JCO, 2002)		

Kaposi Sarcoma [62, 63]

Overview
- Limited data
- Treatment not recommended unless cosmetic or functional impairment, not responding to HAART.

Kaposi Sarcoma
- Four types:
  - AIDS assoc
  - Iatrogenic, from immune suppression
  - Endemic to sub-Saharan Africa
  - Classic – in elderly men w Mediterranean or East European heritage
- HHV8 infection

Studies
- Kirova 1998: 30 Gy (15–10 for face/groins). 92% response
- Stelzer (IJROBP 27,;1993). PRT. *Arms:* 8 Gy / 1 vs 20 Gy / 10f x vs 40 Gy / 20 fx. *Results:* Greater dose a/w higher response rate, lower incidence of residual pigmentation, longer duration of tumor control
- **South Africa** (Radiother Oncol, 2008;88:211). PRT, $n = 60$. *Inclusion criteria*, epidemic KS. *Arms*, 20/5 vs 24/12. *Results*, arms equivalent

Treatment
- **Good life expectancy:** 40 Gy / 20 fractions, 30 Gy/15 fx.
- **Poor life expectancy:** Palliate 20 Gy /5 fractions, 8–12 Gy/1fx.
- **Other considerations:**
  - **15 Gy** for oral lesions.
  - **20 Gy** for the eyelids, conjunctiva, and genitals.
  - TSEB given in 4 Gy fractions weekly for 6–8 weeks has also been used.

Desmoid Tumor (DT)/Aggressive Fibromatosis [3–7, 64–69]

Cleveland Clinic for *FAP-Associated* Intra-abdominal Tumors
- I asymptomatic, <10 cm, not growing
- II mildly symptomatic, <10 cm, not growing
- III moderately symptomatic (restrictive, but not hospitalized), 10–20 cm, or slow grow
- IV severely symptomatic, septic complications (e.g., fistula, abscess), >20 cm, or rapid growth

Overview
- 900 cases/year
- Don't metastasize
- Eval for Gardner's syndrome or FAP, caused by APC gene mutation
- Locations:
  (1) Abd wall is most common.
  (2) Trunk or extremity.
  (3) Intra-abdominal.
    - More common in women (abdominal wall)

Workup
- H&P, MRI, and bx to rule out STS. Do not need systemic imaging since no DM potential.
- **Incisional biopsy** is preferred because it provides greater amount of tissue for pathologic review and allows more accurate delineation between benign and malignant process.
- **Imaging**: no characteristics to distinguish desmoid from malignancy.

Risk Factors
- Trauma
- High estrogen states, e.g., pregnancy

Manifestation
- Benign, fibroblastic neoplasms, slow growing
- If in the abdomen, typically presents w intestinal obstruction and bowel ischemia. Most are associated w Gardner syndrome. Usually high M/M

Studies
- Quintini 2012: OS for FAP associated tumors 76%.
- Crago, 2013: *n* = 495. 1982–2011. 5-year LC 69%. Adj RT not associated w LC or RFS. MVA factors associated w recurrence: extremity location, young age, large tumor size. Abd wall had best outcomes, w 5-year RFS 91%. Nomogram provided.
- Keus, 2013: inoperable, recurrent, or R+ desmoids received 56 Gy/28. At 3 years LC 82%, CR 14%, PR 36%, SD 41%, and PD 7%. Acute G3 toxicity limited to skin and membranes and pain.
- Ballo, 1998: surgery alone. LR 13% for R0. 52% for R1.
- Nuyttens 2000: dose >50 Gy (50–56) for GTV and post-op 50 Gy. 22% LR.

Surgery
- Goal is 2 cm margin
- R0: 15% LR
- R1: 26% LR
- Crago 2013: R1 resection → observed. Did well

Medical Options
- Tamoxifen, NSAIDs, MTX, and imatinib

NCCN
- **Observe**
- **Resect**
  - R0: observe
  - R1: observe (Crago 2013) or reresect
  - R2: reresect + RT (50 Gy per NCCN; some say to 56 Gy)
- **Unresectable**: RT (54–58 Gy) or systemic therapy. Unresectable usually in extremity, superficial trunk, HN; GENERALLY NOT retroperitoneal. RT alone has 80% LC.

- Dose response at ≥55 Gy a/w better LC in RR (Pediatr Blood Cancer, 2011).
- MDACC recommends 56 Gy based on their experience (IJROBP 2008) because higher doses have more toxicity.
- **Nonsurgical approaches:**
  - Hormone ablation, e.g., w tam
  - NSAIDs, e.g., sulindac
  - Low-dose cytotoxic chemo, e.g., MTX and doxo
  - Targeted tx, e.g., imatinib

Treatment Planning

- CTV = GTV + 3–5 cm longitudinal and 2 cm in all other directions

Paraganglioma (Previously Glomus Tumor, Chemodectoma, Nonchromaffin Paraganglioma) [70–73]

Glasscock-Jackson Staging

I	Jugular bulb, middle ear, or mastoid
II	Under IAC +/− intracranial
III	To petrous apex +/− intracranial
IV	Clivus or infratemporal fossa

Overview

- 2% of soft tissue tumors.
- 40–60 yos.
- Arise from glomus cells (chemoreceptors along blood vessels) that originate from neural crest and regulate BP and flow.
- 75% of sympathetic paragangliomas arise in the abdomen, usually at confluence of L renal vain and the vena cava or inf to mesenteric artery near aortic bifurcation (organ of Zuckerkandl).
- May be associated w tympanic branch of glossopharyngeal nerve (nerve of Jacobson) or the auricular branch of the vagus nerve (nerve of Arnold).

Nail

- Arises from glomus body under the nail, in the fingertip or foot.
- "Glomus tumor" is antiquated and refers to nail bed tumors.

Ear

- Glomus tympanicum: arises from Jacobson nerve at cochlear promontory. Presents w pulsatile tinnitus, otalgia, and conductive hearing loss.
- Majority are benign and may be malignant.
- Paragangliomas of the middle ear/jugulotympanic paragangliomas (glomus tympanicum)/ chemodectomas /nonchromaffin paragangliomas, vascular, benign tumors, arising from paraganglia in the middle ear. Pathognomonic finding is blushing tympanic membrane w pulsatile tinnitus.
- 5% of HN paragangliomas produce catecholamines.
- MRI: "salt and pepper appearance."
- Vagal N typically must be removed during surgery.

Studies

- Suarez, 2012, systematic review for vagal paraganglioma. SRS, CFRT, surgery compared. For CFRT, LC 89%; for SRS LC 94% (NSS). Reduction in tumor size unknown. 3.2% of pts. died from dz progression. In 14 SRS studies w 261 patients, 32% of tumors decreased in size, 61% unchanged, 6% grew during treatment, and 0% had CR of tumor. <5% of pts. maintain vagal function after surgery.
- Combs, 2014: $n = 39$. CTV is GTV as seen on T1 MRI + 1–5 mm. PTV = CTV + 1–2 mm. LC 97%.
- Guss, IJROBP, 2011: meta-analysis. For linac-based cases, most common marginal dose was 15 Gy, and range was 15–20 Gy. In Gamma Knife treatment, most common average marginal dose was 15 Gy, and range was 12–18 Gy.

Glomus Tumor Treatment

- **Surgery**. For jugular foramen tumors, this is indicated if tumor secretes catecholamines (as RT has not been shown to decrease levels); facial CN palsy suitable for repair w nerve graft; intracranial extension and mass effect; young pts. w minimal risk of CN damage.
- **RT** to ***45 Gy*** is most acceptable. > dose does not improve LC. CTV is GTV as seen on T1 MRI + 1–5 mm. PTV = CTV + 1–2 mm. LC is 89%.
- **SRS**: ***15–20 Gy*** on LINAC or 12–18 Gy on GK.
- Embolization sometimes used to stabilize or shrink tumor and used as adjunct to RT.

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Bone/Spine Cancers

12

Daniel M. Trifiletti, Nicholas G. Zaorsky, and Daniel E. Spratt

Abstract

This chapter discusses the general management of patients with bone and spine tumors, with special focus on principles that guide radiotherapy and radiosurgery management. Several key components of trimodality care and palliative care are discussed.

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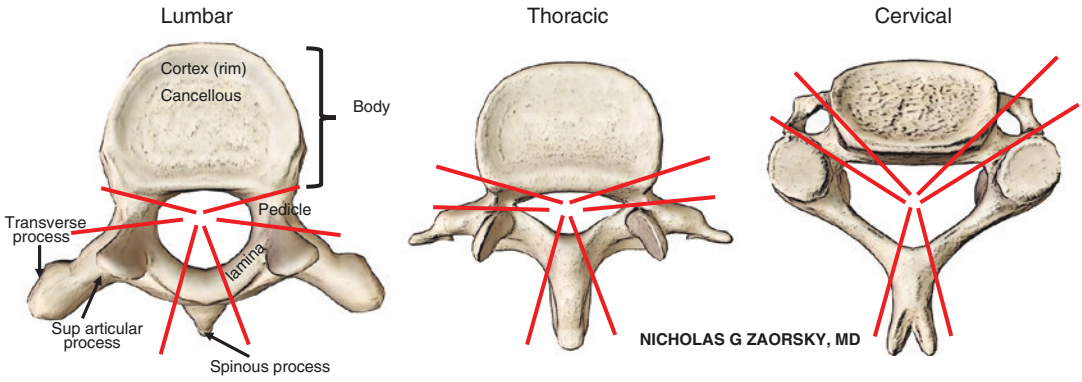

Lumbar
Thoracic
Cervical
Cortex (rim)
Cancellous
Body
Pedicle
Transverse process
lamina
Sup articular process
Spinous process
NICHOLAS G ZAORSKY, MD

Malignant Spinal Cord Compression (MSCC) [1–20]

Goals of Care
1. Preserve/restore neurologic function
2. Reduce pain
3. Provide local control

Epidemiology
- 300,000 patients have osseous metastatic disease/year in the USA.
- The spine is the most common location of bone metastases (60% spine).
- 10% of patients with spine metastases will develop MSCC (~20,000 per year).
- Usually in >50-year-olds.
- Most common cancers causing MSCC are lung cancer, prostate cancer, multiple myeloma, breast cancer, and lymphoma.
- 20% of MSCC cases lack history of cancer – usually from non-Hodgkin lymphoma, myeloma, and small-cell lung cancer.

Anatomy
- Most commonly arises from the vertebral body (80%)
- Most commonly in the thoracic spine (60%)

Presentation
- Most common: Pain (70–95%)
- Also common: Sensory deficit (45–90%), weakness (61–91%), and autonomic dysfunction (40–57%)

Pain Types
- Biologic pain: cancer-related pain and night and morning pain. Non-positional. Inflammatory. Steroids often help.
- Mechanical: from mechanical strain, not necessary cancer-related, positional pain.
- Radicular: radiating pain from osseous or cancer compressing neural foramen, often positional.
- Funicular: radiating pain from compression of the cord itself, non-positional.

Workup
- H&P, full neuro exam assessing for sensation, motor, bowel/bladder, and gait/proprioception
- Steroids (dexamethasone 10 mg IV × 1 and then 4–6 mg Q6H). Careful if no cancer diagnosis is known (e.g., lymphoma)
- Surgical consult for stability, decompression, fixation
- MRI total spine (20% have additional tumors), emergent bx if needed if no cancer diagnosis
- CT myelogram if MRI contraindicated
- Surgery = 360 degree decompression with stabilization (not laminectomy)
- CT appearance:
  - Lytic: hypodense. Lung, breast, GI, thyroid, melanoma, myeloma, renal cell, urothelial, and ovarian
  - Blastic: hyperdense. Lung, breast, GI, prostate, and nasopharynx

MSCC Compression Grading Scale (Bilsky Scale)

0. No compression
1. Indenting epidural space, obscuring some CSF, no cord contact
2. Abutment of the spinal cord
3. Frank compression and displacement of spinal cord

Steroids

- Vecht 1989: loading dose 10 mg IV vs 100 mg IV. Both went on to 16 mg daily. No difference.
- Sorenson, 1994: Randomize to (1) 96 mg IV × 1, then 24 mg QID ×3, then taper over 10 d vs (2) no dex. Gait function following tx: 81% vs 63%. Ambulatory at 6 m: 59% vs 33%.

SINS Score (Spine Oncology Study Group, 2010)

Component scores		**Score**
Spine location		
Junctional		3
Mobile spine (other C- and L-spine)		2
Semirigid (other T-spine)		1
Rigid (other sacrum)		0
Pain relief with recumbence and/or pain with movement/loading of the spine		
Yes		3
No (occasional pain but not mechanical)		1
Pain-free lesion		0
Bone lesion quality		
Lytic		2
Mixed		1
Blastic		0
Radiographic spinal alignment		
Subluxation/translation		4
De novo deformity (kyphosis/scoliosis)		2
Normal alignment		0
Vertebral body collapse		
>50% collapse		3
<50% collapse		2
No collapse with >50% body involved		1
None of the above		0
Posterolateral involvement of spinal elements		
Bilateral		3
Unilateral		1
None of the above		0
The SINS score = sum all six component scores (range 0–18)		
Score	**Classification**	**Action**
0 to 6	Stable	Stabilization not indicated
7 to 12	Potentially stable	Stabilization may be indicated
13 to 18	Instability	Stabilization indicated

Surgery +/− PORT

- Patchell, Lancet, 2005: *n* = 100. 30 Gy vs surgery +30Gy. All received steroids, one lesion, no cauda equina, >3 m life expectancy, paralyzed<48 hrs, and not radiosensitive. Primary endpoint was ability to walk.
- Stopped early. Surgery + RT winner. Regained ambulation 19 → 62%, sustained ambulation 13 → 122 days, and OS 100 → 126 days. Also improved continence, mental ambulation, and narc use.

Duration of sx and Neurologic Improvement

- Rades 2002. 1998–2000. *n* = 98. MSCC. Prospective analysis.
  - Favorable predictors of ambulation: time-to-develop motor deficit (slower better), type of tumor (favorable = myeloma, lymphoma, SCLC, testicular better), and pretreatment ambulation (ambulation better).

RT: Short Versus Long Course

- Rades 2009: nonrandomized. 1–5 fx vs 10–20 fx. Long course won. 1 yr LC 61 → 81%.
- Rades 2011: short course (8/1 and 20/5) vs long course (30/10 and 50/20) RT for MSCC. *n* = 265. 1-year LC 61% vs 81% (favored long course). 1-year OR 23% vs 30% (NSS). Unchanged motor functional improvement. Thus, pts. w favorable survival should receive long-course RT.
- RTOG 97–14 (Howell, 2013) subgroup analysis of painful vertebral body bone mets, treated with single fraction vs multifraction (SFRT vs MFRT): Similar pain relief 62–70%. Lower acute tox with SFRT (20% vs 10%). Higher 3-month re-tx rate w SFRT (5% vs 15%).
- SCORE-2. Non-inf RCT 30/10 vs 20/5 for MSCC. Poor performance patients (~50% died within 2 months). Only 10% fit enough for surgery. No difference in any endpoint.
- SCORAD-3. Presented, not published as of December 2017. 8/1 vs 20/5. MSCC. Very poor performance status patients, too sick for surgery. 1/3 of cohort did not even live to 8-week f/u. No differences in any endpoint.

NCCN

- Dexamethasone 8–10 mg dexamethasone bolus, then 4 mg Q6H minimum
- Debulking/fixation if solitary site with >3 m life expectancy, paraplegia <24 hrs, not hematologic cancer, or if unstable
- Post-op RT 1–3 weeks post-op
- Chemo for hematologic cancers
- SBRT not for MSCC
- OAR: thecal sac or cord PRV + 1.5 mm

Surgery Versus RT Paradigm

- Surgery if there are no histologic proof of cancer, mechanical instability, radioresistance, and previously irradiated site. Always follow with post-op RT if possible.
- All other cases → conventional EBRT (cEBRT).

SBRT Versus cEBRT Paradigm

- SBRT never for MSCC with grade 2–3 disease. Possible to use for select grade 1. Grade 0 is no compression so this is simply a bone, only spine metastasis.
- SBRT for MSCC is for radioresistant tumors postoperatively after the epidural space has been reconstituted and decompressed.

Radioresponsiveness			
	Intermediate		
Very	Favorable	Unfavorable	Resistant
Lymphoma	Prostate	HPV-squamous cell	Melanoma
Multiple myeloma	Breast	NSCLC	Sarcoma
Germinoma	HPV+ squamous cell		Renal cell

cEBRT Sim/Planning

- Cervical spine: laterals, pull shoulders down.
- Thoracic/lumbar: Usually AP/PA. Make sure spine is straight.
- Add +/− 1 vertebral body.
- 30/10, 20/5, and 8/1.

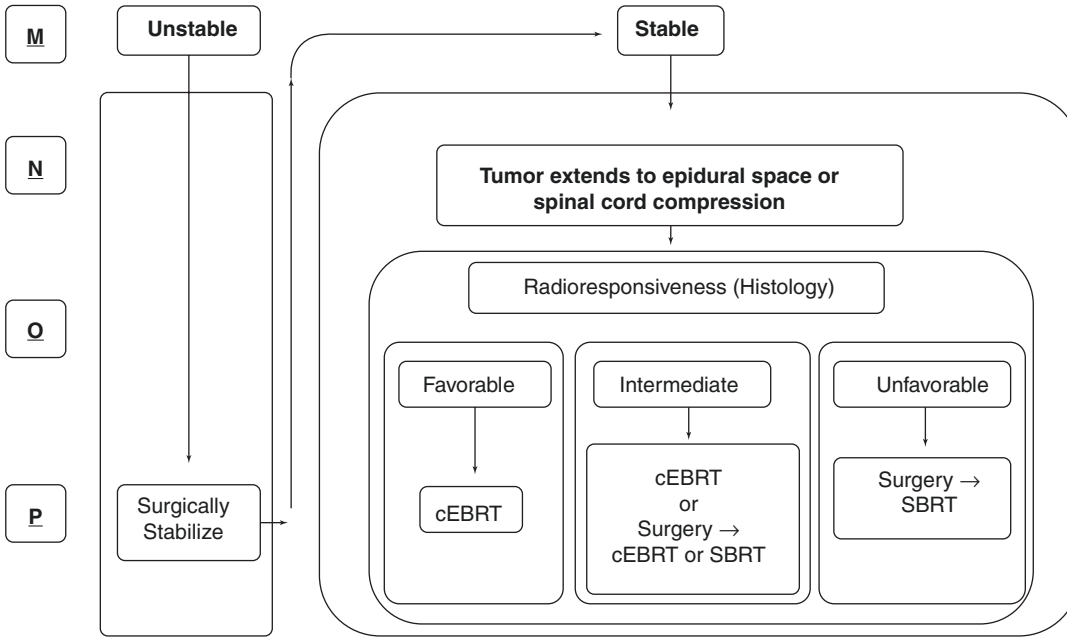
Spine SBRT Sim/Planning

- Below T4: total body immobilization (e.g., BodyFix)
- Above T4: 5-point mask
- Myelogram simulation preferred, however MRI registration acceptable to define cord

Spine SBRT Dose Constraints

Serial tissue	Volume	Volume max (Gy)
Spinal cord	D0.35 cc	10 Gy
	D10%	10 Gy
	D0.03 cc	14 Gy
Cauda equina	<0.03 cc <5 cc	16 Gy 14 Gy
Sacral plexus	<0.03 cc <5 cc	18 Gy 14.4 Gy
Esophagus	<0.03 cc <5 cc	16 Gy 11.9 Gy

MNOP Algorithm for Patient with MSCC (Spratt DE et al. Lancet Onc 2017)



Simplified

	Radiosensitive	Radioresistant
Low-grade MSCC	cEBRT	SBRT
High-grade MSCC	cEBRT	Surgery, then SBRT

Bone Metastases [1–5, 21–33]

Overview
– Sites: spine > pelvis > ribs > femur > skull

Fracture Risk
– Femur: 65%; subtrochanteric > fem neck > peritrochanteric
– Acetabulum: 9%
– Tibia: 8%
– Humerus: 17%
– Forearm: 2%

Surgery
– Mirels 1989: scoring system for fracture from mets to long bones. Mean score 7 in nonfracture group. >8 should get surgical *evaluation* for prophylactic internal fixation prior to RT.

Mirels points	1	2	3
Site	UE	LE	Peritroch
Pain	Mild	Mod	Mechanical
Radiograph	Blastic	Mix	Lytic
% of shaft	<33%	34–67%	>68%

Mirels score	*n*	Fracture rate, %
<7	11	0
7	19	5
8	12	33
9	7	57
10–12	18	100

– VanderLinden 2004: femur cortical involvement >30 mm and/or circumferential >50% predict for fx

Algorithm
– (1) Fracture: surgery and then post-op RT.
– (2) No fracture: if painless, observe; if painful, then assess for impending fracture. If no impending fracture, then RT. If yes, then surgery.

EBRT
– RTOG 97–14 (Harstell 2005): breast and prostate bone mets → 8 × 1 vs 30/10. Overall response 66%. Pain CR same: 15–18%. At 3 mos, 33% no longer required narcotics. More G2+ tox with 30/10 (17% vs 10% G2-4 tox). More retreatment with 8 × 1 (9 vs 18%).

– TROG 96.05: 1996–2002, RCT of 8 Gy x 1 vs 20 Gy x 5. 8 × 1 not effective as 20/5, but not SS worse.
– Bone pain trial working party: 8 × 1 vs 20/5 vs 30/10. Same effectiveness. More reRT with 8 × 1 (23 vs 10%).
– Chow 2007: meta-analysis. No differences except 2.5× increase in retreatment if 8 × 1.
– ASTRO guidelines: Essentially 8 Gy x 1 for everything.

Radiopharmaceuticals
- Strontium-89 (β): Sciuto 2002 and Porter 1993
- Samarium-153 (β and γ): Sartor 2004 and Oosterhof 2003
- Radium-223 (α):
  - ALSYMPCA: Ra223 improved OS (11 → 14.9 m) over placebo for symptomatic mCRPC patients

PORT
- Townsend 1994: PORT reduced need for 2nd surgery (15 → 2%) and improved function

PORT Pain Flares
- Hird, IJROBP, 2009: 8 Gy x1 or 20 Gy/5. 40% pain flare in 10 d after RT.
- Loblaw, 2006: RCT of 8 Gy x1 vs 20 Gy/5. Monitor for 7 d. Pain flare has 2 pt increase in intensity w/o change in analgesics. Overall rate 34%. Higher in 8 Gy x1: 43% vs 24%.
- Bomez, 2015: Most had w/ 20 Gy/5 (61%), some 8 Gy/1 (31%). Pain flare incidence 38%. Usually on d1-5, lasting 3d.

Steroids for Pain Flare
- Chow, Lancet Onc, 2015: *n* = 298. Randomize to dexamethasone ***8 mg*** taken >1 h prior to RT w/ ***8 Gy x1***, then 8 mg QD for 4d after tx (total 40 mg over 5 d); vs placebo. Decrease in acute pain flare *26%* vs *35%* (~**8–**9% absolute difference). Largest difference in 0–5 d post RT. No difference in 6–10 days post-RT.

SRS/SBRT

General concept – SRS/SBRT often used for radioresistant histologies (sarcoma, melanoma, RCC) and oligometastatic disease. However, for simple pain control, ASTRO recommends 8 Gy x 1.

- Gerstzen 2007: Retrospective, median 20Gy x1. Improved pain in 86%, LC 90%. More durable than historical series of 8 Gy x 1 or 30 Gy in 10 fx.

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Physics and Radiobiology

13

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Abstract

This chapter discusses the basics of clinical radiation physics and radiation biology. Special emphasis is placed on the key aspects of physics and radiobiology that guide clinical management and preparation for board exams and maintenance of certification exams.

Radiation Physics

This chapter discusses the basics of clinical radiation physics and radiation biology. Special emphasis is placed on the key aspects of physics and radiobiology that guide clinical management and preparation for board exams and maintenance of certification exams.

Units

Measurement	Common units	Official (SI) unit
Energy	Joules (J), mega-electron volts (MeV)	Joules (J)
Activity: disintegrations per unit time	Curie (Ci)	Becquerel (Bq)
Exposure: ionization	Roentgen (R)	Coulombs/kg (C/kg)
Absorbed dose: energy deposited in tissue	Rad	Gray (Gy) 1 Gy = 1 J/kg
Dose equivalent: biological effect	Rem	Sievert (Sv)

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Useful Constants

- Planck's constant: 6.62×10^{-34} (J*sec)
- Speed of light in a vacuum = $3e^8$ (m/sec)
- Electron volt: 1 eV = 1 V * 1.6×10^{-19} C = 1.6×10^{-19} J
- Rest mass of electron: 0.511 MeV
- Rest mass of proton: 938.2 MeV
- Rest mass of neutron: 939.6 MeV
- 1 amu = 931 MeV
- 1 Ci = 3.7×10^{10} disintegrations/sec = 3.7×10^{10} Bq = 37 GBq
- Avogadro's number: 6.02×10^{23} atoms per gram atomic weight
- 1 roentgen = 2.58×10^{-4} C/kg
- 100 rad = 1 Gy

Decay Equations and Calculations

$$A_{(t)} = A_0 e^{-\lambda t} = A_{(0)} e^{(-0.693t)/(t1/2)}$$

- Unit: Bq = 1 decay/second. Older unit = 1 Ci = 3.7×10^{10} Bq
- Given at time 0, need to find activity at later time:

$$\lambda = (0.693) / t_{1/2} = \ln(2) / t_{1/2}$$

- λ = "lambda" is the inverse of the mean lifetime, aka decay rate, or how much decays in a given amount of time. Units is disintegrations / (time period you are using).

$$A_0 = A_{(t)} e^{+\lambda t} = A_{(t)} e^{(0.693t)/(t1/2)}$$

Given at activity new time, need to find original activity:

$$t_{1/2} = -.693^* t / \left(\ln\left(A_{(t)} / A_0\right)\right)$$

Given activities, need to find the half-life:

$$\text{Mean Life} = 1/\lambda = 1.44 \bullet t_{1/2}$$

Photon Attenuation Equations

$$I_x = I_0 e^{-\mu x}$$

- Photon beam intensity.
- μ is the linear attenuation coefficient in cm^{-1}.

- x is the distance traveled in cm.

$$\text{HVL} = \ln(2)/\quad = 0.693/$$

$$\text{TVL} = \ln(10)/\quad = 3.32^{*}\text{HVL}$$

Mean free path = $1/\mu$ = average distance a photon travels between collisions

Dose Ratios

- **SSD: Source to surface distance**
- **SAD: Source axis distance (distance from source to isocenter)**

$$\text{Percent Depth Dose } (\text{PDD}) = D_{\text{depth}} / D_{d0}$$

- D_{depth} = dose at some depth
- D_{d0} = dose at depth at some fixed reference depth. For orthovoltage $d0$ = surface. For megavoltage, $d0$ = depth of dose maximum
- For PDD, the distance from the source to the detector changes (i.e., water level remains constant, detector moves)

$$\text{Tissue Phantom Ratio}(\text{TPR}) = D_{\text{depth}} / D_{\text{dref}}$$

- D_{depth} = dose at some depth.
- D_{dref} = dose at some reference depth.
- For TPR, the distance from source todetector is fixed (i.e., water level changes, detector remains stationary).

$$\text{Tissue Maximum Ratio}(\text{TMR}) = D_{\text{depth}} / D_{\text{max}}$$

- D_{depth} = dose at some depth.
- D_{dmax} = dose at depth of dose maximum.
- TMR is the TPR where d_{ref} is thedepth of dose maximum.

$$\text{Tissue Air Ratio}(\text{TAR}) = D_{\text{depth}} / D_{\text{freespace}}$$

- D_{depth} = dose at some depth
- $D_{\text{freesoace}}$ = dose “in air” (with a miniphantom forbuildup) as the same source to detector distance as D_{depth}

Basic Hand Calculations [1]

$$\text{Equivalent square field} = 2^{*}\left(A^{*}B\right)/\left(A+B\right)$$

For Photon SSD Setups

$$D = \mathrm{MU}^{*} K_{\mathrm{ref}}{}^{*} \left(S_c{}^{*} S_p{}^{*} \mathrm{PDD}/100^{*} \mathrm{INV}^2 \right)$$

$$\mathrm{INV2} = \left[\left(\mathrm{SSD}_{\mathrm{ref}} + d_{\mathrm{ref}} \right) / \left(\mathrm{SSD} + d_{\mathrm{ref}} \right) \right]^2$$

- K_{ref} = calibrated dose rate (usually 1 cGy/MU, 10 × 10 cm field at surface, $d_{\mathrm{ref}} = d_{\mathrm{max}}$)
- S_{c} field size = collimator opening
- S_{p} field size = field size at surface

For Photon SAD Setups

$$D = \mathrm{MU}^{*} K_{\mathrm{ref}}{}^{*} \left(S_c{}^{*} S_p{}^{*} \mathrm{TMR}^{*} \mathrm{INV}^2 \right)$$

$$\mathrm{INV2} = \left[\mathrm{SAD}_{\mathrm{ref}} / \mathrm{SAD}_p \right]^2$$

- K_{ref} = calibrated dose rate (usually 1 cGy/MU, 10 × 10cm field at $\mathrm{SAD}_{\mathrm{ref}}$, $d_{\mathrm{ref}} = d_{\mathrm{max}}$)
- S_{c} field size = collimator opening
- S_{p} field size = fields size at depth of calc point *p*

For Electron Beams (Always SSD Setup)

$$D = \mathrm{MU}^{*} K_{\mathrm{ref}}{}^{*} \left(\mathrm{CF}^{*} \mathrm{PDD}/100^{*} \mathrm{INV}^2 \right)$$

- K_{ref} = calibrated dose rate
- CF = cone factor

$$\text{Mayneord F factor} = \left[\left(\mathrm{SSD}_2 + d_{\mathrm{max}} \right) / \left(\mathrm{SSD}_1 + d_{\mathrm{max}} \right)^2 \right] \times \left[\left(\mathrm{SSD}_1 + d \right) / \left(\mathrm{SSD}_2 + d \right) \right]^2$$

Optimum Relationship Between Wedge Angle and Hinge Angle

$$\theta = 90^{\circ} - \varphi / 2$$

Θ = wedge angle, φ = hinge angle

Field-Matching Problems

To Eliminate Divergence of Parallel–Opposed Fields

$$\theta = \arctan \left(0.5^{*} \mathrm{FW} / \mathrm{SAD} \right)$$

Additional requiredrotation = 2* Θ

Linear Accelerator Calibration (AAPM TG-51) [2]

For MV Photon Beams

$$D^{Q}_{w} = M^{*}k_{Q*}N^{60Co}_{D,w}$$

- D^{Q}_{w} = dose to water for your beam quality (Q)
- M = corrected ion chamber reading
- k_{Q} = beam quality correction factor from reference ^{60}Co beam to your beam quality
- $N^{60Co}_{D,w}$ = calibration factor for absorbed dose to water for reference ^{60}Co beam

For MV ElectronBeams

$$D^{Q}_{w} = M^{*}\mathrm{P}_{gr}{}^{Q*}k'_{R50}{}^{*}k_{ecal}{}^{*}N^{60Co}_{D,w}$$

- D^{Q}_{w} = dose to water for your beam quality (Q)
- M = corrected ion chamber reading
- $P_{gr}{}^{Q}$ = gradient correction factor
- k'_{R50} = electron quality conversion factor
- k_{ecal} = photon-electron conversion factor
- $N^{60Co}_{D,w}$ = calibration factor for absorbed dose to water for reference ^{60}Co beam

Corrected Ion Chamber Reading

$$M = M_{\mathrm{raw}}{}^{*}C_{t,p}{}^{*}p_{\mathrm{ion}}{}^{*}p_{\mathrm{pol}}$$

- M_{raw} = raw electrometer reading

Temperature and Pressure Correction ($C_{t,p}$)

- $[(273 + T_{\mathrm{celsius}})/(273 + 22)] \times [760/P]$
- STP is 22 C and 760 mm Hg
- The reading will:
  - Decrease with increasing temperature (i.e., it is inversely proportional to T).
  - Increase with increasing pressure (i.e., it is directly proportional to P).

Ion Recombination Correction (p_{ion})

$$p_{\mathrm{ion}} = \left[\left(1 - V_{\mathrm{H}}/V_{\mathrm{L}}\right)/\left(M_{\mathrm{H}}/M_{\mathrm{L}} - V_{\mathrm{H}}/V_{\mathrm{L}}\right)\right]$$

- V_{H} = high bias voltage (usually 300 V), M_{L} = low bias voltage (usually 150 V)
- M_{H} = measurement under high bias, M_{L} = measurement under low voltage
- Pion >1 since M_{H} should be greater than M_{L}

Polarity Correction (p_{pol})

$$P_{pol} = \left| \left(M +_{raw} - M -_{raw} \right) / 2M_{raw} \right|$$

- $M+$ = measurement under positive bias (usually 300 V)
- $M-$ = measurement under negative bias (usually -300 V)
- M = measurement under clinically used bias

Film Analysis

Optical density = log (I_o/I_t).

Radiation Safety and Dose Limits

Equivalent dose (H) = $W_R{}^*D$, units Sv

- Adjusts absorbed dose for the biological effectiveness of the type of radiation
- D = absorbed dose (Gy)
- W_R = radiation weighting factor

Radiation Weighting Factors [3]

Radiation type	W_R
Photons/electrons	1
Neutrons	5–20 (energy dependent. Peak value of 20 at ~ 1 MeV)
Protons	2
Alpha particles	20

$$\text{Effective dose}\left(E\right) = \sum_{T} \left(W_T{}^* H_T \right)$$

- Adjusts absorbed dose to account for the sensitivity of each organ to each type of radiation
- T = organ
- W_T = weighting factor for organ
- H_T = equivalent dose for organ T
- $\sum_T {}^*W_T = 1$

Organ Weighting Factors [3, 4]

Organ	W_T
Gonads	0.2
Red bone marrow	0.12
Colon	0.12
Lung	0.12
Stomach	0.12
Bladder	0.05
Breast	0.05
Liver	0.05
Esophagus	0.05
Thyroid	0.05
Skin	0.01
Bone surfaces	0.01
Remaining organs	0.05

Whole body dose limits (1 rem = 0.01 mSv) [3]		
	Per year	**Per hr**
Occupational	50 mSv	0.02 mSv
Fetus	0.5 mSv/**month**	
Public cont. exposure	1 mSv	
Public intermittent exposure	5 mSv	
Total effective dose per individual in the U.S. from background sources: 3.1 mSv/yr. [5]		

Acute total body exposures [6]	
<2 Gy	Observe
2–5 Gy	Prodrome, latency, cytopenias?
5–10 Gy	Hospitalize, hypotension?
10–20 Gy	GI syndrome, fatal
>50 Gy	Cerebrovascular syndrome, fatal

Typical External Beam Parameters (Assume a 10 × 10 Field) [7]

Beam	Superficial	Orthovoltage	Co-60	4 MV	6 MV	10 MV	18 MV	25MV
D_{max}	0	0	0.5	1	1.5	2.5	3.5	5

Radiation Linear Energy Transfer and Weighting Factors [3]

Radiation	LET (keV/μm)
2.5 MeV α	150
1 GeV Fe ions	150
14 MeV neutrons	100
250 kV Xrays	2
150 MeV protons	0.5
^{60}Co γ	0.2

Brachytherapy

Brachytherapy Sources [8, 9]

Isotope	τ	Energy	Decay mechanism	Use
^{103}Pd	17 days	21 keV photons (avg)	Electron capture	Prostate LDR
^{125}I	60 days	28 keV photons (avg)	Electron capture	Prostate LDR, eye plaque
^{131}Cs	9.7 days	30 keV photons (avg)	Electron capture	Prostate LDR
^{99m}Tc	6 hrs	140 keV photons	Isometric transition	SPECT, bone scan
^{131}I	8 days	364 keV photons (avg)	Beta −/gamma	Thyroid ablation
^{192}Ir	74 days	380 keV photons (avg)	Beta −	HDR or LDR
^{198}Au	2.7 days	412 keV photons	Beta −	Prostate LDR, eye plaque (historical)
^{90}Sr	28 yrs	546 keV β (max, mean ~ 1/3)	Beta −	Source of ^{90}Y, ophthalmic applicator, intravascular
^{18}F	110 min	633 keV positrons	Beta +	PET, annihilation 511 keV photons × 2
^{137}Cs	30 yrs	660 keV photons	Beta −	GYN Brachy, LDR
^{226}Ra	1622 yrs	830 keV photons (avg)	Alpha	GYN Brachy, LDR (historical)
^{223}Ra	11.4 days	5.8 MeV α	Alpha	Xofigo
^{222}Rn	3.8 days	830 keV photons (avg) 5.5 MeV alpha	Alpha	Environmental hazard, radium daughter
^{60}Co	5.3 yrs	1.25 MeV photons (avg)	Beta −	Teletherapy, radiosurgery
^{40}K	10^9 yrs	1.3 MeV β (max, mean ~ 1/3)	Beta −	Small amts. commonly found in nature, animals, bananas, etc.
^{89}Sr	50 days	1.5 MeV β (max, mean ~ 1/3)	Beta −	IV tx of bone mets
^{32}P	14.3 days	1.7 MeV β (max, mean ~ 1/3)	Beta −	IV tx of bone mets, polycythemia vera, intravascular
^{90}Y	2.7 days	2.3 MeV β (max, mean ~ 1/3)	Beta −	TheraSpheres, SIR-Spheres

Brachytherapy Patient Release Regulations [10]

	Release with instructions if activity <	Release with instructions if dose rate at 1 m <	Release without instructions if activity <	Release without instructions if dose rate at 1 m <
^{125}I	9 mCi	0.01 mSv/h	2 mCi	0.002 mSv/h
^{103}Pd	40 mCi	0.03 mSv/h	8 mCi	0.007 mSv/h
^{192}Ir	2 mCi	0.008 mSv/h	0.3 mCi	0.002 mSv/h
^{131}I	33 mCi	0.07 mSv/h	–	–

Radiotherapy Structural Shielding Equations [11]

Workload (W): How often radiation source is used.
Use factor (U): Fraction of time beam is aimed in particular direction.
Occupancy factor (T): Howoften adjacent area is occupied.
Distance (d): Distance from area of interest to source.
Design goals: 0.1 mSv / week (controlled areas), 0.02 mSv/week (uncontrolled areas), 0.02 mSv/h [CITE NCRP]

Primary Barrier

$$B = Pd^2 / \mathrm{WUT}$$

requiredTVLs = $n = -\log(B)$
Required barrier thickness = $X = \mathrm{TVL}_1 + (n-1)\mathrm{TVL}_e$

Type of area	Occupancy factor (T)
Office, lab, reception, nursing station, etc.	1
Patient exam room and treatment room	0.5
Corridors, lounges, staff rest rooms, patient rooms	0.2
Corridor doors to treatment/imaging rooms	0.125
Public restrooms, storage rooms, holding areas	0.05
Unattended outdoor areas, stairways	0.025

Radiobiology

Dose/Fractionation Calculations [6]
- Early responding tissues: $\alpha/\beta = 10$
- Early responding tissues: $\alpha/\beta = 3$

$$\mathrm{BED} = \text{total dose}^{*}\text{relative effectiveness} = nd^{*}\left[1 + d/\left(\alpha/\beta\right)\right]$$

- n = number of fractions
- d = dose per fraction
- α/β = alpha/beta ratio for target

To Compare Fractionation Schemes

$$\left(nd/n_1d_1\right) = \left(\alpha/\beta + d_1\right)/\left(\alpha/\beta + d\right)$$

- n = standard # fractions
- n_1 = equivalent # fractions needed for altered schedule
- d = standard dose / fraction
- d_1 = desired dose / fraction

$$\mathrm{EQD}_2 = \left[\mathrm{BED}/\left(1 + 2/\left(\alpha/\beta\right)\right)\right]$$

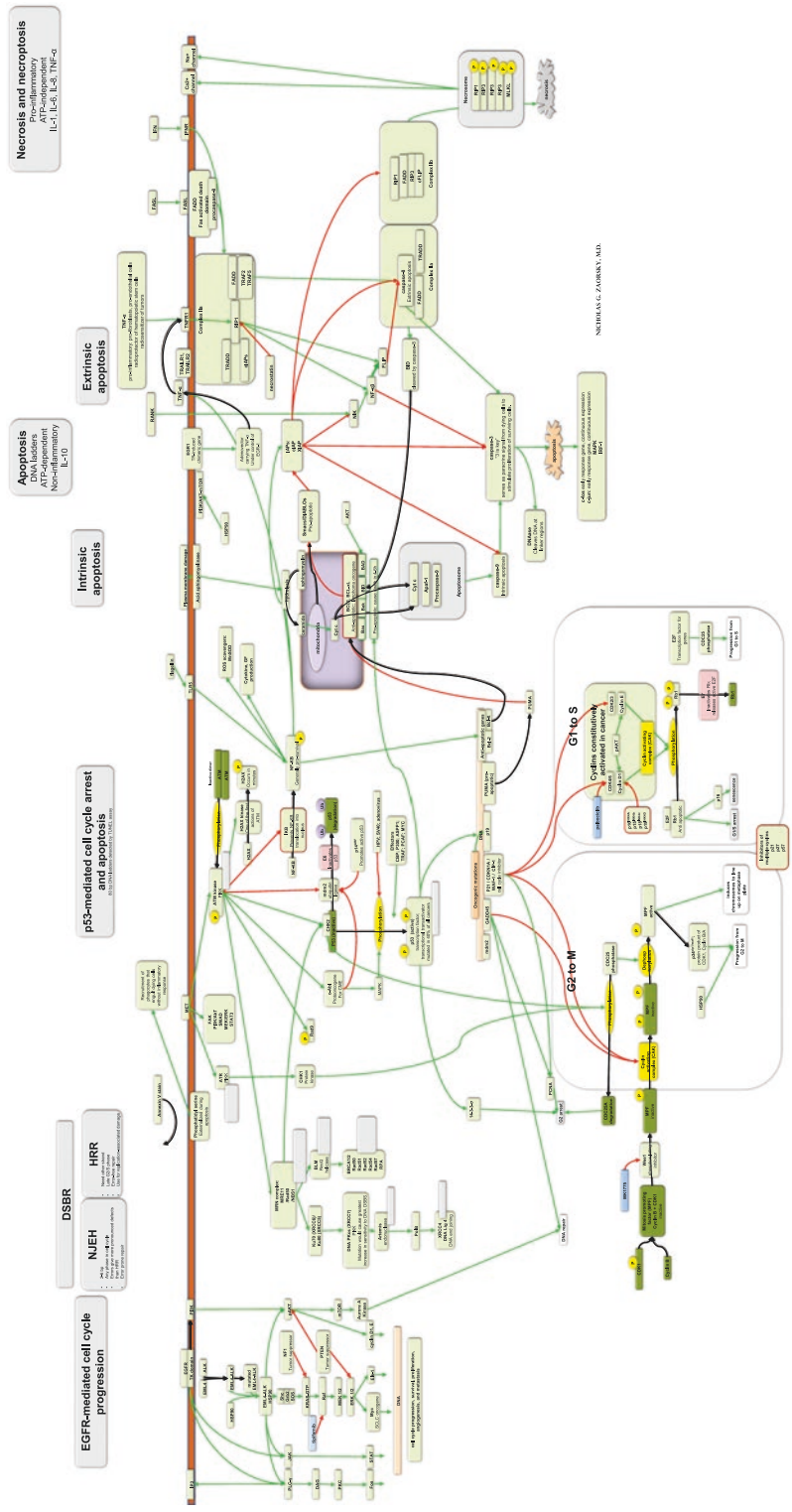
- EQD_2 is the equivalent total dose in 2 Gy fractions.

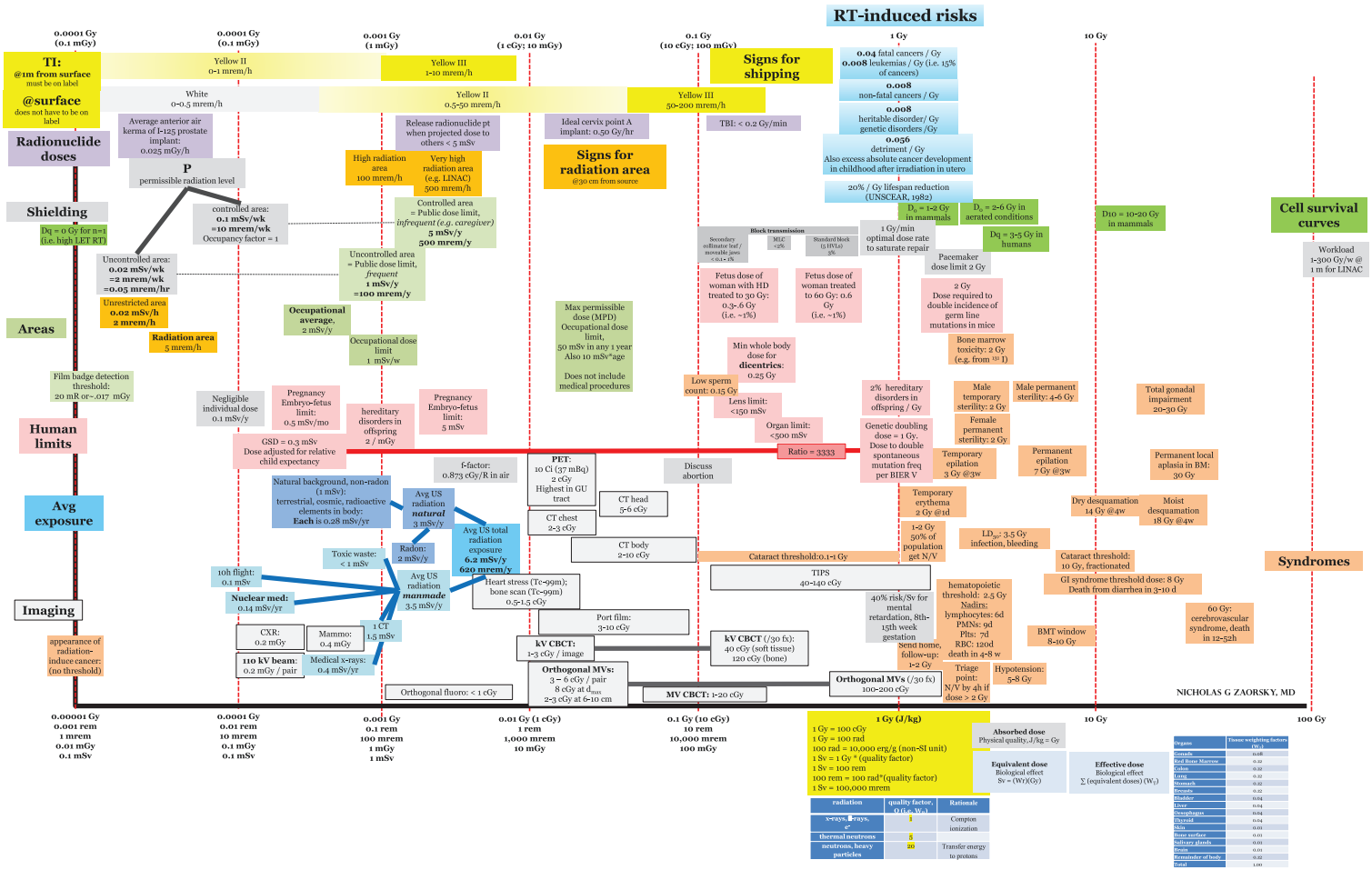
Important Tumor Markers

Marker	Classic association	Also seen in
AFP	HCC, NSGCTs	GI, pregnancy, cirrhosis
β2microglob	Myeloma	B cell, lung, breast, bone dz
CA-125	Ovarian	GYN, breast, lung, abdominal
CA 15–3	Breast	Ovary, lung prostate
CA 19–9	Pancreas, bile duct	Abdominal
CA 50	HCC	GI
CA 27.29	Breast	Various
Calcitonin	Medullary thyroid	Various
CEA	Colorectal	Various
Neuron-enolase (NSE)	Neuroblastoma, SCLC	Wilms, melanoma, thyroid, testicle, Merkel cell
PSA	Prostate	Benign GU
Thyroglobulin	Thyroid (non-MTC)	Benign thyroid
Desmin	Sarcoma, colorectal	Intermediate filaments in skeletal muscle tissue, smooth muscle, cardiac muscle
βHcG	NSGCTs, choriocarcinomas	Pregnancy
S100	Melanoma, schwannoma, neurofibroma, MNST, paraganglioma, clear cell sarcoma	
BCR-ABL	t(9:22), usually in CML	

Translocation	Cancer
t(2:13) and t(1:13)	Alveolar rhabdomyosarcoma
t(8:14) and t(8:22)	Burkitt's, B-cell All
t(11:14)	Mantle cell (BCL1, cyclin D1)
t(11:22)	Ewings, PNET
t(12:22)	Clear cell sarcoma
t(14:18)	Follicular, DLBCL (BCL2)
t(14:19)	CLL (BCL3)
t(X:18)	Synovial cell sarcoma

Cancer	CD testing
All lymphoid	45+
B cells	19+, 20+, 22+
T cells	2+, 3+, 5+, 7+, 4 + (helper), 8+ (cytotoxic)
NK cells	16+, 56+, 57+
Follicular	5-, 10+, 43-
Mantle cell	5+, 23−, 43+
MALT	5−, 10−, 23−
Hodgkin	15+, 30+


Necrosis and necroptosis
Pro-inflammatory
ATP-independent
IL-1, IL-6, IL-8, TNF-α
Apoptosis
DNA ladders
ATP-dependent
Non-inflammatory
IL-10
Extrinsic apoptosis
Intrinsic apoptosis
p53-mediated cell cycle arrest and apoptosis
EGFR-mediated cell cycle progression
DSBR
NJEH
HRR
G1-to-S
G2-to-M
NICHOLAS C. ZACHIOS, M.D.


RT-induced risks
0.0001 Gy (0.1 mGy)
0.0001 Gy (0.1 mGy)
0.001 Gy (1 mGy)
0.01 Gy (1 cGy; 10 mGy)
0.1 Gy (10 cGy; 100 mGy)
1 Gy
10 Gy
100 Gy
TI:
@1m from surface
must be on label
@surface
does not have to be on label
Yellow II
0-1 mrem/h
Yellow III
1-10 mrem/h
White
0-0.5 mrem/h
Yellow II
0.5-50 mrem/h
Yellow III
50-200 mrem/h
Signs for shipping
0.04 fatal cancers / Gy
0.008 leukemias / Gy (i.e. 15% of cancers)
0.008 non-fatal cancers / Gy
0.008 heritable disorder/ Gy
genetic disorders /Gy
0.056 detriment / Gy
Also excess absolute cancer development in childhood after irradiation in utero
20% / Gy lifespan reduction (UNSCEAR, 1982)
Radionuclide doses
Average anterior air kerma of I-125 prostate implant: 0.025 mGy/h
Release radionuclide pt when projected dose to others < 5 mSv
Ideal cervix point A implant: 0.50 Gy/hr
TBI: < 0.2 Gy/min
Signs for radiation area
@30 cm from source
High radiation area 100 mrem/h
Very high radiation area (e.g. LINAC) 500 mrem/h
P
permissible radiation level
Shielding
Dq = 0 Gy for n=1 (i.e. high LET RT)
controlled area: 0.1 mSv/wk =10 mrem/wk Occupancy factor = 1
Controlled area = Public dose limit, infrequent (e.g. caregiver) 5 mSv/y 500 mrem/y
Uncontrolled area: 0.02 mSv/wk =2 mrem/wk =0.05 mrem/hr
Uncontrolled area = Public dose limit, frequent 1 mSv/y =100 mrem/y
Unrestricted area 0.02 mSv/h 2 mrem/h
Areas
Occupational average, 2 mSv/y
Occupational dose limit 1 mSv/w
Radiation area 5 mrem/h
Max permissible dose (MPD) Occupational dose limit, 50 mSv in any 1 year Also 10 mSv*age
Does not include medical procedures
Human limits
Film badge detection threshold: 20 mR or ~.017 mGy
Negligible individual dose 0.1 mSv/y
Pregnancy Embryo-fetus limit: 0.5 mSv/mo
hereditary disorders in offspring 2 / mGy
Pregnancy Embryo-fetus limit: 5 mSv
GSD = 0.3 mSv Dose adjusted for relative child expectancy
Ratio = 3333
Avg exposure
Natural background, non-radon (1 mSv): terrestrial, cosmic, radioactive elements in body: Each is 0.28 mSv/yr
Avg US radiation natural 3 mSv/y
Avg US total radiation exposure 6.2 mSv/y 620 mrem/y
Radon: 2 mSv/y
Toxic waste: < 1 mSv
Avg US radiation mammade 3.5 mSv/y
10h flight: 0.1 mSv
Nuclear med: 0.14 mSv/yr
Imaging
appearance of radiation-induce cancer: (no threshold)
CXR: 0.2 mGy
Mammo: 0.4 mGy
110 kV beam: 0.2 mGy / pair
1 CT 1.5 mSv
Medical x-rays: 0.4 mSv/yr
f-factor: 0.873 cGy/R in air
PET: 10 Ci (37 mBq) 2 cGy Highest in GU tract
CT chest 2-3 cGy
CT head 5-6 cGy
CT body 2-10 cGy
Heart stress (Tc-99m); bone scan (Tc-99m) 0.5-1.5 cGy
Port film: 3-10 cGy
kV CBCT: 1-3 cGy / image
Orthogonal MVs: 3 – 6 cGy / pair 8 cGy at dmax 2-3 cGy at 6-10 cm
Orthogonal fluoro: < 1 cGy
MV CBCT: 1-20 cGy
kV CBCT (/30 fx): 40 cGy (soft tissue) 120 cGy (bone)
Orthogonal MVs (/30 fx) 100-200 cGy
Discuss abortion
Low sperm count: 0.15 Gy
Min whole body dose for dicentrics: 0.25 Gy
Lens limit: <150 mSv
Organ limit: <500 mSv
Cataract threshold:0.1-1 Gy
TIPS 40-140 cGy
40% risk/Sv for mental retardation, 8th-15th week gestation
Fetus dose of woman with HD treated to 30 Gy: 0.3-.6 Gy (i.e. ~1%)
Fetus dose of woman treated to 60 Gy: 0.6 Gy (i.e. ~1%)
Block transmission
Secondary collimator leaf / movable jaws <0.1-1%
MLC <2%
Standard block (5 HVLs) 5%
1 Gy/min optimal dose rate to saturate repair
Pacemaker dose limit 2 Gy
2 Gy Dose required to double incidence of germ line mutations in mice
Bone marrow toxicity: 2 Gy (e.g. from 131 I)
D0 = 1-2 Gy in mammals
D0 = 2-6 Gy in aerated conditions
Dq = 3-5 Gy in humans
D10 = 10-20 Gy in mammals
Cell survival curves
Workload 1-300 Gy/w @ 1 m for LINAC
2% hereditary disorders in offspring / Gy
Genetic doubling dose = 1 Gy. Dose to double spontaneous mutation freq per BIER V
Male temporary sterility: 2 Gy
Male permanent sterility: 4-6 Gy
Female permanent sterility: 2 Gy
Total gonadal impairment 20-30 Gy
Temporary epilation 3 Gy @3w
Permanent epilation 7 Gy @3w
Permanent local aplasia in BM: 30 Gy
Temporary erythema 2 Gy @1d
Dry desquamation 14 Gy @4w
Moist desquamation 18 Gy @4w
1-2 Gy 50% of population get N/V
LD50: 3.5 Gy infection, bleeding
Cataract threshold: 10 Gy, fractionated
GI syndrome threshold dose: 8 Gy Death from diarrhea in 3-10 d
Syndromes
hematopoietic threshold: 2.5 Gy Nadirs: lymphocytes: 6d PMNs: 9d Plts: 7d RBC: 120d death in 4-8 w
BMT window 8-10 Gy
60 Gy: cerebrovascular syndrome, death in 12-52h
send home, follow-up: 1-2 Gy
Triage point: N/V by 4h if dose > 2 Gy
Hypotension: 5-8 Gy
NICHOLAS G ZAORSKY, MD
0.00001 Gy 0.001 rem 1 mrem 0.01 mGy 0.1 mSv
0.0001 Gy 0.01 rem 10 mrem 0.1 mGy 0.1 mSv
0.001 Gy 0.1 rem 100 mrem 1 mGy 1 mSv
0.01 Gy (1 cGy) 1 rem 1,000 mrem 10 mGy
0.1 Gy (10 cGy) 10 rem 10,000 mrem 100 mGy
1 Gy (J/kg)
1 Gy = 100 cGy
1 Gy = 100 rad
100 rad = 10,000 erg/g (non-SI unit)
1 Sv = 1 Gy * (quality factor)
1 Sv = 100 rem
100 rem = 100 rad*(quality factor)
1 Sv = 100,000 mrem
Absorbed dose Physical quality, J/kg = Gy
Equivalent dose Biological effect Sv = (WR)(Gy)
Effective dose Biological effect ∑ (equivalent doses) (WT)
radiation
quality factor, Dose, WR
Rationale
x-rays, γ-rays, e-
1
Compton ionization
thermal neutrons
5
neutrons, heavy particles
20
Transfer energy to protons
Organs
Tissue weighting factors WT
Gonads 0.08
Red Bone Marrow 0.12
Colon 0.12
Lung 0.12
Stomach 0.12
Breasts 0.12
Bladder 0.04
Liver 0.04
Oesophagus 0.04
Thyroid 0.04
Skin 0.01
Bone surface 0.01
Salivary glands 0.01
Brain 0.01
Remainder of body 0.12
Total 1.00

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