Clinical Radiation Oncology Review

Daniel M. Trifiletti
University of Virginia

Disclaimer: The following is meant to serve as a brief review of information in preparation for board examinations in Radiation Oncology and allow for an open-access, printable, updatable resource for trainees. Recommendations are briefly summarized, vary by institution, and there may be errors. NCCN guidelines are taken from 2014 and may be out-dated. This should be taken into consideration when reading.

Table of Contents

Stage I	Stage II	Stage III	Stage IV
IA	IIA	IIIA	IVA
IB	IIB	IIIB	IVB
IC	IIC	IIIC	IVC

Acknowledgements: To Neil Shah, BS for aiding in the preparation of this review.

Pediatrics

Rhabdomyosarcoma[1-11]

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

	Sites	TNM	5 yr OS
Stage 1	*Fav*: Orbit, H&N, GU, biliary	Any T, Any N	90%
Stage 2	*Unfav*: Parameningeal, Bladder/Prostate, Extremity, Other	≤5cm and N0	85%
Stage 3	Same as II	>5cm or N1	70%
Stage 4	-	M1	30%

	Stage	Group
Low risk	EMB 1 (fav site) EMB 2-3 (unfav site)	I-III I-II (R1, LN)
Intermediate risk	EMB 2-3 ALV	III any
High risk	4	IV

	Surgery
Group I	R0, localized
Group IIA	R1
Group IIB	+LN
Group IIC	+M and +LN
Group III	Gross disease
Group IV	M1

Parameningeal Sites (25%): Infratemporal fossa, Middle ear, Mastoid region, Nasal cavity, Nasopharynx, Paranasal sinus, Pterygopalatine fossa, Parapharyngeal region (IMMNNPPP) [not orbital]

Overview
- ~3% of childhood cancers
- Hyperdiploid does better
- Embryonal assoc with LOH 11p15.5
- Alveolar assoc with t(2:13) and t(1:13). This is FKHR, PAX3, PAX7
- VAC: vincristine/actinomycinD/cyclophosphamide
- Workup: H&P, labs, CT/MRI, CT chest/abd, BMBx
- If parameningeal: LP with cytology +/- neuraxis MRI

Histology	Freq	Locations	OS
Embryonal	60%	H&N or GU	66%
Alveolar	25%	Trunk or abd	54%
Botyroid	10%	GU, nasophar, biliary	95%
Undiff	5%		40%
Spindle cell	<5%	paratesticular	88%

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. 5 yr OS 55%
- IRS II: LC improved for >40Gy (93% LC). RT was tumor +5cm. 5 yr OS 63%
- IRS III: RT was tumor+2cm. bladder/vagina/uterus doesn't need RT after CR to chemo. 5 yr OS 73%
- IRS IV: no benefit to VAC-IE or BID RT.
- COG D9803: int 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.

Technique
- Orbit: biopsy only→45Gy to tumor+2cm
- Otherwise CTV = GTV+1cm
- Include entire LN chain if N+
- If >1 lung met→ whole lung RT (15 Gy in 10 fx)
- Dose limits
  - Kidney <14.4 Gy
  - Liver < 23.4 Gy mean
  - Lungs <15 Gy at 1.5/fx
  - Whole abd < 24 Gy at 1.5/fx

RT doses	
R0, N0	36Gy
R1 or N1	41.4Gy
R2	50.4Gy
Orbits	45Gy

General Guidelines
- Provides site-specific reccs
  - can move and replant gonads
  - LND required for paratesticular, pelvic, extremities (>20% LN+ rate)
  - cCR after chemo in bladder/vagina/uterus doesn't need RT
- Low Risk
  - Stage 1-3, Group I: surgery→chemo (VA or VAC). No RT
  - Stage 1, Group II: surgery→chemo(VA) +RT at week 3 (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 3 (36Gy)
  - Stage 3, Group II: surgery→VAC→RT at wk 3 (36Gy for N0, 41.4 for N1)
- Int Risk
  - Surgery→chemo→(repeat surgery if possible)→RT(50.4Gy)
- High Risk
  - Chemo (VCPT→VAC). RT to primary and metastatic sites (45-50.4Gy)

- (same as bone sarcoma, not commonly used)
- **T1** - ≤8cm
- **T2** - >8cm
- **T3** – discontinuous tumors

- **N1** – nodes

- **M1a** - lung
- **M1b** - other

Overview
- 200 cases/yr
- Ewing's family: Ewing's sarcoma (87%), Extraosseous Ewing's (8%), PNET (5%), Askin's tumor
- t(11:22): involves the EWS gene on ch22
- ↑c-myc activity (↑n-myc in neuroblastoma)
- CD99+, vimentin+, NSE- (PNETs are CD99+, vimentin+, NSE+)
- Workup: H&P, labs, plain film (onion skinning)
- CT/MRI, bone scan, CT chest
- Bx, BMBx?

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. 5yr 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: chemo→surgery or RT. RT was randomized whole bone+boost vs 4cm margin +boost. No difference in LC or RFS
- 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

Technique
- 45 Gy to CTV (initial GTV+1-1.5cm) with PTV margin
- Boost postchemo volume with same margin to 55.8Gy
- "consider boosting to 59.4 for chemo response <50%"
- Paraspinal tumors stop at 45Gy
- Lung primary (Askin's): hemithorax RT (15-20 Gy at 1.5/fx) followed by boost of primary
- Lung mets: whole lung RT
  - <14 yo: 15 Gy at 1.5/fx (current COG study says 12 Gy for <6 yo)
  - >14 yo: 18 Gy at 1.5/fx

NCCN
- Induction VAC-IE x12wks→local treatment (surgery or RT) with VAC→ adj chemo
- Consider preop RT if marginally resectable (36-45Gy)
- Postop RT (adequate margin is >1cm)
  - R0 with poor chemo response: 45 Gy
  - R1: 45 Gy
  - R2/bx: 45 Gy + boost to 55.8Gy

Wilms Tumor[1-5,18-22]

Stage I	R0, Limited to kidney, capsule intact, LN neg
Stage II	R0, capsule broken, into vessels
Stage III	R1, R2, LN+, into peritoneum, spillage, piecemeal
Stage IV	Distant mets or LN outside abd/pelv
Stage V	Bilateral tumors

Overview
- 450 cases/yr usually 3-4 year olds
- Unfavorable histology: anaplastic, sarcomatous, clear cell, rhabdoid
- Del ch22q, LOH 1p and LOH 16q have poorer RFS and OS
- Clear cell and Rhabdoid are not actually Wilm's tumors
- 10% of Wilms is assoc with congential abn:
  - WAGR syndrome (del 11p13, WT1)
  - Denys-drash syndrome (WT1 mutation)
  - Beckwith-Wiedemann syn (WT2 mut, 11p15.5)
- Workup: H&P, u/s, labs, CT/MRI, CT chest, NO Bx
- Clear cell: add bone scan, MRI brain, BMBx
- Rhabdoid: MRI (15% have brain tumor)

Trials
- NWTS 1: showed no RT needed for group 1, <2 yo if given chemo. RT should start <9 days after surgery
- NWTS 2: showed RT not needed for all group 1. adding Adriamycin improved OS
- NWTS 3: showed RT not needed for stage II if chemo given. 10 Gy for stage III if Adriamycin used
- NWTS 4: showed pulse-intensive chemo less toxic than standard
- NWTS 5:stage I, FH and <550g 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

Technique
- Start by day 9 postop
- Flank RT: usually AP/PA, 1.8Gy/fx. Preop GTV+1cm
  - Treat entire vertebral body
  - Stage I-II, FH: no RT
  - Stage III or UF: 10.8Gy
  - Diffuse anaplasia or rhabdoid: 19.8Gy
  - 10.8Gy for infants
  - Boost R2 another 10 Gy
  - Opposite kidney ≤14.4 Gy
- WLI: 12 Gy in 8 fx (add PO Bactrim)
- Brain mets
  - <16 yo: 21.6 Gy with 10.8Gy boost
  - >16 yo: 30.6 Gy in 17fx
- Liver mets: 19.8 Gy in 11fx
- Bone mets
  - 25.2 Gy in 14 fx (3cm margin)
  - 30.6 Gy is >16 yo

Risk class	Meaning	Tx after nephrectomy
Very low risk FH	• <2 yo, tumor <550g	• Obs
Low risk FH	• ≥2 yo, tumor ≥550g, no LOH (1p, 16q)	• VA (no RT)
Std risk FH	• I-II with LOH • III with no LOH • IV, no LOH, with rapid response to chemo	• VAD (no RT) • RT→VAD • RT→VAD (no lung RT)
High risk FH	• III with LOH • IV with LOH or slow responder to chemo	• RT→VAD/C/E • RT→VAD/C/E (include whole lung)
High risk UF	• Any focal anaplasia • Stage I diffuse anaplasia • I-III clear cell	• RT→VAD • RT→VDC/CE
Highest risk	• II-IV diffuse • IV clear cell • I-IV rhabdoid	• RT→chemo→ RT to mets

Neuroblastoma[1-5,23-28]

INRGSS Staging (preop)

Stage L1	Localized tumor
Stage L2	Locally invasive by defined criteria
Stage M	Metastatic disease except MS
Stage MS	Metastatic to only skin/liver/marrow and <18m

INSS Staging (postop)

Stage 1	R0, R1, Localized tumor, LN -
Stage 2A	Stage I but R2
Stage 2B	Stage 2B but ipsi LN+
Stage 3	Midline/contralateral primary or LNs
Stage 4	Mets except 4S
Stage 4S	Stage 1-2B w/ mets only to skin/liver/marrow & <1yr

COG RISK GROUPINGS		
Low Risk	*Intermediate Risk*	*High Risk*
Any stage 1	<1 yo, stage 3, no MYCN	Any MYCN
<1 yo, stage 2	>1 yo, stage 3, no MYCN, fav hist	>18 months, stage 3, unfav hist
Stage 2, no MYCN	<1 yo, 4S, no MYCN	>18 months, stage 4
<1 yo, 4S, fav hist, hyperdip and no MYCN	<1 yo, 4S, no MYCN, non-hyperdip and/or unfav hist	

Overview
- 650 cases/yr
- Median dx is 17m (wilms is 3-4 yo)
- Primitive neural crest cells (usually calcified, wilms isn't)
- Homer-Wright pseudorosettes
- Stains NSE+, synaptophysin+, neurofilament+
- Shimada classification: based on stroma, age, diff, mitoses, nodular/diffuse (SAD MiNd)
- Poorer prognosis: ↑stage, ↑age, n-myc amp, diploid, Shimada (SANDS)
- Also poorer prognosis: LOH 1p or 11q,↑telomerase
- Tumors can spontaneously regress, so screening not helpful
- Blueberry muffin sign, raccoon eyes, opsoclonus-myoclonus-trucal ataxia
- Chemos: carboplatin, etoposide, cyclophosphamide, doxorubicin, ifosfamide
- Workup: H&P, labs, *urine catecholamines (VMA, HVA), BMBx*
- CT/MRI, *MIBG scan*, CT chest

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
- CCG 3891: phase III, 539 pts→chemo x5m→surgery (+10Gy if STR) → bone marrow transplant +/- TBI. Then randomized to +/- cis-retinoic acid. TBI improved and cis-retinoic acid improved 5 yr OS.
- Matthay 2007: phase II of refractory NB. Showed a 36% reponse rate with I-131 MIBG

Technique
- Usually cover tumor +2cm
- 24Gy for int risk (controversial +/- RT)
- 21.6 Gy for high risk (1.8/fx)
  - Target postchemo, preop tumor bed and boost gross residual to 36Gy
  - No ENI
- 4S liver involvement 4.5Gy @ 1.5/fx to whole liver
- For cord compression
  - <3 yo: 9 Gy @1.8
  - ≥3 yo: 21.6 Gy @1.8
- Dose contraints
  - Contralateral kidney <15 Gy
  - Lung V15 < 66%
  - Liver V15 < 66%

Guidelines
- Low risk
  - surgery
    - obs if GTR
    - STR or recur→chemo
  - RT (24Gy) if cord compression, etc
  - Can obs if clinically stable 4S low risk
- Int risk
  - surgery→chemo (RT for residual disease)
- High risk
  - High dose chemo→surgery→high dose chemo
  - All patients get RT (21.6Gy at 1.8/fx).
  - Then cis-retinoic acid

Retinoblastoma[1-5,29]

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

Overview
- 250 cases/yr
- RB1 tumor suppressor on ch13→defect in G1/S checkpoint
- Flexner-Wintersteiner rosettes
- Trilateral RB: bilateraleral RB + midline CNS PNET: uniformly fatal
- Pts are prone to osteosarcomas
- Workup: H&P, optho exam, labs, genetic counseling?
- Bilateral ultrasound, MRI
- If extraocular: bone scan, LP
- Biopsy not required

Trials
- Shields 1997: retrospective of chemo +/- local therapy. Local treatment reduced LC from ~70→0%

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

Guidelines
- 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
  - 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 eyes, chemo, CSI? (MS is 11m)

Medulloblastoma[1-5,29-34]

- **T1** - <3cm
- **T2** - ≥3cm
- **T3**
  - T3a - >3cm into aqueduct or foramen Luschka
  - T3b - >3cm invading brainstem
- **T4** - >3cm past foramen magnum
- **M1** – CSF+
- **M2** – nodules in cranium
- **M3** – nodules in spine
- **M4** - outside CSF

	Age	Residual	M	5 yr EFS
Std Risk	>3 yr	<1.5 cm^2	0	80%
High Risk	<3 yr	>1.5 cm^2	+, or PNET	50%

General

1. 500 cases/yr US
2. Bimodal (7 y/o and 25 y/o)
3. Assoc with Gorlin syndrome (PTCH1) and Turcot syndrome (APC)
4. Cell of origin is neuroectodermal cells from the germinal matrix of the cerebellum
5. Medullo has an intact INI1 (loss of INI1 is an ATRT)
6. Homer-wright rossettes (same as all blastomas but retinoblastoma)
7. Variants
    a. Classic
    b. Nodular/desmoplastic: good prog (LOH 9q)
    c. Large cell/anaplastic: poor prog
    d. Four genetic subgroups
        i. WNT group: CTNNB1 mut, assoc with Turcot (10%, good prog)
        ii. SHH group: PTCH1, GLI3, MYCN mut, usually desmoplastic(30%, int prog)
        iii. Group 3: MYC amp , usually large cell (poor prog)
        iv. Group 4: MYCN, CDK6 amp (int prog)

Workup

1. H&P, labs, fundoscopic exam, audiometry, IQ
2. Preop MRI brain/spine
3. *MRI brain 24-48 hours postop*
4. *MRI spine 10-14 days postop*
5. *CSF cytology 10-14 days postop*

Trials

1. POG 8631: std risk → 36 vs 23.4 Gy (no chemo. No diff
2. CCG 9892: std risk → 23.4 with vincristine→55.8 Gy PF boost→adj chemo. Favorable EFS (phase II)
3. Baby POG: <3 yo treated with chemo alone until 3 yo. 5 yr OS was 40%
4. German BTSG: similar to baby POG (58% 5 yr OS)
5. Retrospective series show low failures outside tumor bed (ANCS0331 is studying this)

Simulation/Planning

1. Prone, neck extended, mask, protons?
2. CSI technique
    a. Cranial iso behind the lenses
    b. Place spine fields first
    c. Inferior spine border is S2-3
    d. Lateral spine border is 1cm past pedicles, wider lower
    e. Rotate head colimator to arctan (½ length of thorax field/SSD)
    f. Kick couch for head fields arctan(½ length of cranial field/SAD) toward beam
    g. Skin gap = ([0.5 x length1 x d]/SSD1) + ([0.5 x length2 x d]/SSD2)
    h. Feather: move the junction superiorly 0.5cm on 7^{th} and 13^{th} fraction
3. Dose constraints
    a. Cochlea: V30<50%, max 35 Gy

COG approach

1. Standard risk over 3 y/o
    a. Resection
    b. RT with vincristine
        i. CSI to 23.4 Gy
        ii. Post fossa to 54 Gy (36 Gy?)
        iii. Cavity/residual to 54-55.8 Gy
    c. Adj cisplatin/CCNU/vincristine
        i. 8 cycles, Q6wks
2. High risk over 3 y/o
    a. Resection
    b. RT with vincristine
        i. CSI to 36 Gy
        ii. Cavity/residual 54-55.8 Gy
        iii. Brain/thecal mets 54-55.8 Gy
        iv. Spinal mets 45 Gy
        v. Diffuse spinal disease 39.6 Gy
    c. Adj cisplatin/CCNU/vincristine
        i. 8 cycles, Q6wks
3. Under 3 y/o
    a. Resection
    b. Adj chemo until 3 yo
    c. Then consider CSI/chemo

Ependymoma[1-5,35-37]

General

1. Bimodal (5 yo and 35 yo)
2. Cell of origin is the ependymal cell
3. Assoc with NF2 (ch 22)
4. WHO classification
    a. Grade I: myxopapillary and subependymoma
    b. Grade II: classic
    c. Grade III: anaplastic
    d. Grade IV: ependymoblastoma
5. Perivascular pseudorosettes
6. Poor prognosis
    a. erbB-2/erbB-4 overexpression
    b. age <4 yo
    c. supratentorial location

Workup

1. H&P, labs, fundoscopic exam, audiometry, IQ
2. Preop MRI brain/spine
3. *MRI spine 10-14 days postop*
4. *CSF cytology 10-14 days postop*

Trials

1. Rogers 2005: posterior fossa ependymomas, retrospective. 10 yr LC improved with RT (50%→100%)
2. Merhant 2009 and Koshy 2011 suggest RT → ↑OS in children under 3yo
3. Retrospective series show no benefit to CSI

Simulation/Planning

1. Preop GTV + 1-2cm to 54-59.4 Gy

COG approach

1. If supratentorial, grade I-II and GTR: can observe
2. If infratentorial
    a. Over 3 yo: Resection and adj RT (~54Gy)
    b. Under 3 yo: Resection and adj chemo (cisplatin/cyclophos/etoposide)
        i. Can give 2 cycles then re-resection vs RT
3. If Spinal: RT for incomplete resection or anaplastic histology
    a. 2 vertebral bodies above/below to 45 Gy
    b. Boost to 50.4-59.4 Gy if no cord in field
4. Ependymoblastoma
    a. Treat like high risk medulloblastoma (CSI to 36Gy)
5. Follow up
    a. for >10 yrs, late recurrences happen
    b. craniospinal MRI Q3-6m then Q1yr

Germ cell and Non-Germ cell tumors, Pineal Tumors[1-5,38,39]

General

1. Histology
    a. Germinomas (more common)
        i. AFP ≤10nl/mL (always)
        ii. Usually bHcG<50
        iii. Stains with placental alkaline phosphatase
    b. NGGCT
        i. Endodermal sinus tumor (yolk sac)
            1. ↑AFP
        ii. Teratoma
        iii. Embryonal
            1. ↑bHcG and ↑AFP
        iv. Mixed
2. Usually arise from proximal 3rd ventricle (pineal or suprasellar)
3. Parinaud syndrome: poor upward gaze, accomodates but abnl light response (caused by pressure on the superior colliculus)

Workup

1. H&P, labs, *bHcG, AFP,*
2. MRI brain/spine
3. *CSF cytology with AFP and bHcG*

Trials

1. SIOP CNS GCT96: M0 → CSI 24 Gy + 16 Gy boost vs chemo+IFRT 40 Gy. All CRT failures were in the ventricles
2. Rogers 2008: lit review with similar results

COG approach

1. Localized germinoma: RT only
    a. WVRT to 21-24 Gy
    b. Boost primary to 40-45 Gy
    c. Protocols evaluationg neoadj chemo
2. +CSF germinoma (like low risk medullo)
    a. CSI to 24 Gy
    b. Boost to 45 Gy
3. NGGCT: all get chemo
    a. chemoRT
        i. Induction platinum-based chemo
        ii. Then CSI 30-36 Gy
        iii. Then boost 50.4-54 Gy
    b. Surgery + chemo
        i. Resection
        ii. Adj platinum-based chemo
        iii. Restage
        iv. CSI (36→50.4) vs IFRT
4. Pineoblastoma:Treat like a high risk medullo (CSI to 36, boost to 54 Gy)
5. Pineocytoma: treat like low grade glioma (delayed RT)

Craniopharyngioma[1-5,40]

General
1. Rathke's pouch origin
2. Bimodal (10 yo and 50 yo)

Workup
1. H&P, labs, *endocrine labs*
2. MRI brain
3. *CSF cytology with AFP and bHcG*

Trials
1. Stripp 2004: 10 yr LC with surgery worse than surgery+RT (42%→84%), but if RT used as salvage 10 yr LC was unchanged

COG approach
1. Max safe resection (usually STR) then RT (or can observe)
2. 50.4-54 Gy to GTV + 5-10mm (no CTV)
    a. Watch for welling
3. Can use intracystic bleomycin
4. Can use β-emitters (Y90, P32, Rh186). Rx is 200-250 Gy to cyst wall
    a. P32 is 0.7MeV, t1/2 14 days, effective depth is 4mm

Brainstem Glioma[1-5,40-46]

General
1. 2 classes
    a. Focal: upper midbrain/lower medulla
    b. Diffuse: pons and upper medulla

Workup
1. H&P, labs
2. MRI brain/spine
3. No biopsy

Trials
1. Cohen 2011: no benefit to concurrent/adj TMZ
2. POG/CCG trials showed no benefit to hyperfrac or dose escalation
3. Janssens 2013: hypofractioned treatment has same OS and PFS

COG approach
1. Steroids and 54Gy

Notes

Central Nervous System

Low Grade Glioma[1-5,47-51]

General

Tumor Type	MS (m)
Oligodendroglioma	120
Mixed Oligoastrocytoma	>60
Astrocytoma	60
Anaplastic oligodendroglioma	<60
Anaplstic Astrocytoma	36
Glioblastoma	12

1. 20% of gliomas
2. 70% present with seizures (better prognosis)
3. Juvenile Pilocytic Astrocytoma (JPA)
    a. Rosenthal fibers histologically
    b. WHO I: treat with surgery, consider PORT if STR
    c. Pilomyxoid astrocytoma is an atypical JPA, more aggressive
4. Subependymal giant cell tumor
    a. Associated with tuberus sclerosis (ch9)
    b. WHO I
5. LGGs commonly do not enhance, but usually show T2 signal and mass effect
6. 75% will progress to high grade glioma
7. Postop MRI indicated within 72 hrs of surgery
8. 4 features of glioma grading (AMEN): atypia, mitosis, endothelial proliferation, and necrosis
9. Gemistocytic subtype is more aggressive (could consider it a grade III)

Workup

1. H&P, neuro exam
2. MRI w/wo gadolinium
3. Hearing/optho eval?
4. Surgery eval for maximum safe resection. No biopsy unless unresectable

Trials

1. Smith 2008: retrospective, 216 pts, resection >90% correlated with 5yr OS (97% vs 76%)
2. EORTC 22845 (nonbelievers): 311 pts, WHO I-II. Surgery (42% GTR) → obs vs 54 Gy. OS was the same (~66%), but RT had better median PFS (5.3 vs 3.4 yr). 65% of obs arm got RT at progression
3. EORTC 22844 (believers): 343 pts, WHO I-II. Surgery (30% GTR) → 45 Gy vs 59.4 Gy. Same OS (59%), PFS (49%). Determined that <40 yo, oligo histology, GTR and good KPS were prognostic
4. INT/NCCTG (Shaw): 203 pts, WHO I-II. Surgery (14% GTR) → 50.4Gy vs 64.8Gy. Same 5 yr OS (~70%), 92% of failures in in field
5. RTOG 9802: pending (high risk pts get RT +/- PCV). Early results show that PCV improves PFS but not OS
6. RTOG 0424: pending (high risk pts get RT +/- TMZ)

Simulation/Planning

NCCN high risk of ≥3 of	
Astrocytoma	≥6cm tumor
≥40 yo	Crossing midline
Increased perfusion	Significant preop neuro sympx
KPS <70	Non 1p19q codel
	Non IDH1/2 mut

1. Supine, aquaplast, fuse MRI
2. GTV = T1 enhancing + FLAIR
3. CTV = GTV + 1-2cm

NCCN

1. Surgical resection then postop MRI within 72 hours, Testing for 1p/19q, IDH1/2
    a. If low risk and GTR: observe with RT if progression
    b. If low risk and STR: RT (cat 2a) or chemo (cat 2b, TMZ or PCV)
    c. If high risk regardless of resection: PORT (cat 2a) or chemo (cat 2b, TMZ or PCV)
2. Follow up MRI Q6m for 5 yrs then annually

High Grade Glioma[1-5,52-60]

General

1. Most common primary malignant brain tumor
2. MGMT repairs DNA damage
    a. Removes alkyl group from O6 guanine
    b. Hypermethylated promoter silences MGMT
3. Pseudoprogression: up to 50% of patients, more common if MGMT hypermeth
4. Primary GBM: EGFR/MDM2 amp, LOH 10,/p16 loss
5. Secondary GBM: p53 mut, LOH 19q, LOH10/p16 loss
6. RTOG RPA: age +/-50, histology, KPS +/-70, MS changes, Sx+/-3m
7. Additional prognostic factors: MGMT, extent of resection

Brain Pathology	
Pseudopalasading necrosis	GBM
Rosenthal fibers	JPA
Psamomma bodies	Meningioma
Verocay body	Schwannoma
Schiller Duval bodies	Yolk sac
Fried egg	Oligodendroglioma
Pseudorossettes	Ependymoma
Homer-Wright Rossettes	Medulloblastoma, neuroblastoma, PNET, +/- pineoblastoma
Flexner-wintersteiner rosettes	Retinoblastoma, +/- pineoblastoma

Workup

1. H&P, neuro exam
2. +/- dex, +/- keppra
3. MRI w/wo gadolinium
4. Hearing/optho eval?
5. Surgery eval for maximum safe resection. No biopsy unless unresectable
6. MR spectroscopy?
    a. NAA: neuronal marker
    b. Choline: cellular integrity
    c. Creatine: cellular energy
    d. Lactate: anaerobic metabolism

Surgery +/- RT

1. Keime-Guibert 2007: 81 pts, elderly GBM, >70 yo, KPS >70. Surgery +/- 50.4Gy. Stopped early, RT won. MS 4.3 →7.3m, independent of extent of resection
2. Bauman 1994: 29 pts, elderly GBM, >65 yo. 30/10 WBRT improved MS over observation (10m vs 1m)
3. Walker 1978, 1979: RT ~doubles MS after surgery

RT dose/fractionation

1. Roa 2004: 100 pts, 60/30 vs 40/15. No difference in MS
2. RTOG 7401: No benefit to 70 Gy over 60 Gy
3. Chan 2002: no benefit to 90 Gy
4. MRC 1991: 474 pts. 45/20 vs 60/30. 60 Gy improved MS (9m vs 12m)
5. RTOG 9305: 203 pts, surgery + 60 Gy + BCNU +/- SRS. No differences
6. RTOG 0023: phase 2 trial of fractionated SRS. No differences

ChemoRT

1. Stupp 2009: 573 pts, GBM, RT +/- TMZ. TMZ was concurent (75mg/m2/day) and adjuvant (150-200mg/m2/day x5days Q4wks x6months). TMZ won. MS 12.1→14.6m. 5 yr OS 1.9→9.8%. MGMT hypermeth pts did the best
2. Walker 1980: 476 pts. RT alone vs RT+MeCCNU vs RT+BCNU. No differences
3. RTOG 0525: tested dose dense TMZ, no benefit, long term results pending
4. RTOG 9402: 289 pts grade III tumors. Surgery +/- adj PCV 4c, then RT. All pts got RT. RT went to 59.4Gy (50.4+9). MS same, but PFS improved with PCV (1.7→2.6yrs). 1p19q codel had better prognosis and had the only benefit from PCV
5. EORTC 26951: 368 pts, grade III tumors. Surgery → RT → +/-PCVx6c. RT went to 59.4 Gy (45+14.4). MS same, PFS improved with PCV (13→23m). 1p19q codel pts did better, but PCV benefited everyone
6. NOA-04: grade III tumors, RT vs PCV (or TMZ). PFS and OS same between groups,

Simulation/Planning

1. Supine, aquaplast, fuse MRI
2. CTV1 = (T1+g + T2) + 2cm
3. CTV2 = (T1+g) + 1-2cm

NCCN

1. Surgical resection +/- carmustine wafer
    a. then postop MRI within 72 hours, Testing for MGMT, IDH1/2
    b. oligo 1p19q codel
        i. RT + adj or neoadj PCV (cat 1, adj preferred)
        ii. RT +TMZ
        iii. TMA or PCV alone (cat 2b)
    c. AA or 1p19q non-codel
        i. RT alone (cat 1)
        ii. RT +TMZ
        iii. TMA or PCV alone
    d. GBM
        i. 60 Gy with TMZ and adjuvant TMZ
        ii. RT alone?
        iii. TMZ alone?
        iv. Supportive care?
2. Recurrent disease: 25/5 vs chemo vs pall care
3. Follow up MRI at 6wk then Q2m for 3 yrs

Primary CNS Lymphoma[1-5,61-65]

General

1. 1000 cases/yr, 4% of primary brain tumors
2. Associated with immunodeciency (AIDS), EBV, DLBCL
3. Gain of chr12→ ↑MDM2→↓p53
4. NHL assoc with CNS spread: Burkitt, lymphoblastic, immunocompromised, BM+, parameningeal, testicular relapse
5. All are stage IE (extranodal NHL)

Workup

1. H&P, labs, *HIV, LDH, bHcG, EBV, toxoplasmosis titer*
2. CSF cytology
3. Slit lamp exam
4. Testicular ultrasound? PETCT?
5. MRI +/-spine
6. CT CAP
7. SPECT if immunocompromised
8. Delay steroids and bx

RT dose/omission

1. RTOG 8315: WBRT (40Gy) → boost to 60Gy. 80% failed in boost field
2. RTOG 9310: 45 Gy (1.8/fx) vs 36 Gy (1.2/fx BID). Same OS and DFS, but worse neurotoxicity with BID (4%→23%)
3. Abrey 2000 (MSKCC): 52 pts, chemo+WBRT+chemo. Not all got RT, but it improved DFS. OS was not better with RT
4. NABTT 9607: HD MTX Q2wks until CR (or 8 cycles). Then more MTX. Not RT. MS was 22.8 (comparatively favorable)

Ocular Lymphoma

1. Usually DLBCL
2. 75% will go on to develop CNS lymphoma
3. Dx by vitrectomy
4. Tx is 36 Gy to orbit or intraocular chemo
5. Mean OS is 6-18m (uniformly fatal)

Simulation/Planning

1. helmet field (to C2, include orbits): 36 Gy
2. cone down to WBRT: 45 Gy
3. if leptomeningeal: CSI to 36 Gy +/- boost to 45
4. If CR: 24-36Gy WBRT, or obs
5. If PR: 36-45 Gy

NCCN

1. KPS > 40: high dose MTX
    a. If CR: observe or 24-36 Gy WBRT
    b. If not: 36 Gy WBRT + boost to 45 Gy
2. KPS < 40: steroids
    a. If ↑KPS: RT

Meningioma[1-5,66]

General

1. Risk factors: prior RT, NF2 (ch22, Merlin gene), HRT
2. Psammoma bodies and calcifications
3. Grading
    a. Grade I: benign
    b. Grade II: atypical (clear cell, choroid)
    c. Grade III: analplastic (rhabdoid, papillary)
4. Dural tails are not thought to have tumor cells
5. Simpson grading
    a. I: GTR including dura/bone
    b. II: GTR and coagulate dura
    c. III: GTR without coagulation
    d. IV: STR
    e. V: decompression alone

Workup

1. H&P, labs, MRI

Trials

1. Goldsmith 1994: improved PFS with dose ↑52 Gy

NCCN

1. Observation
2. Surgery with RT if STR, grade II-III, or recurrent
    a. 54 Gy is benign
    b. 60 Gy if malignant
    c. 12-16 Gy SRS (50% isodose)

Pituitary Tumors[1-5,67]

General

1. 75% functional, 25% nonfunctional
2. Assoc with MEN-1 (auto dominant, 3 P's)
3. Derives from Rathke's pouch or 3rd ventricle
4. Presents as ↑hormone or bitemp hemianopsia
5. Subtypes
    a. Prolactinoma (30%): nl prolactin 2-25
        i. Bromocriptine or
    b. GH (25%): nl GH <10
        i. Somatostatin, octreotide
    c. ACTH (15%)
        i. Ketoconazole, cyproheptadine, RU-486
    d. TSH (<1%)
6. Macroadenoma (≥1cm) vs microadenoma (<1cm)
7. Can take years (5-10) to correct horomones
8. 95% LC afer transsphenoidal resection overall
    a. Risk for ↓LC: ↑age, >2cm, TSH-secreting
    b. RT along LC is ~90%

Workup

1. H&P, labs, hormone levels MRI

Trials

1. McCollough 1991: 10 yr LC was 95%, better if >45 Gy

Simulation/Planning

1. 45-50.4Gy for no GTV
2. 50-54 Gy if gross disease
3. SRS for microadenomas
    a. 20 Gy if functioning
    b. 14-18 Gy if nonfunctioning
    c. Optic nerve max 8 Gy

Notes

Head and Neck

Ocular Melanoma[1-5,68-73]

COMS

	Apical Height	Basal Diameter	10yr OS
Small	<3mm	5-16mm	80%
Medium	3-10mm	5-16mm	60%
Large	>10mm	>16mm	40%
Diffuse	Thickness <20% basal		
Metastatic	N1, M1		<7m

Overview
- 2,000 cases/yr (1/3 asymptomatic)
- 98% caucasians
- Usually arises from choroid
- Usually mets to liver (90%)
- BAP1 inactivation found in most ocular melanoma
- Workup: H&P, eye exam, slit lamp, B-scan u/s, LFTs, liver u/s, *no bx*

Trials
- COMS 1997: obs small tumors. 5 yr OS 94%, 33% progressed
- COMS 28: (COMS medium)→enucleation vs eye plaque. Same 12 yr OS (~60%), 13% of plaque pts ended up getting enucleations 2/2 tumor or pain
- Quivey 1993: retrospective I-125. 13% local failure

Plaque Technique
- I-125 seeds
- 85 Gy to apex (if less then 5mm apex→Rx to 5mm)
- 2mm around tumor

Treatment
- COMS small: observation or local therapy. 33% progress with obx
- COMS medium: enucleation, plaque, SRS(25-40Gy to 50% isodose), or protons (56cGyE)
- COMS large: enucleation or protons

Nasopharyngeal Cancer[1-5,74-81]

- **T1** – NP, OP, or nasal cavity
- **T2** – parapharyngeal space extension
- **T3** – bony structures or paranasal sinuses
- **T4** – intracranial, CNs, infratemporal fossa, hypopharynx, orbit, masticator space

- **N1** – unilateral ≤6cm (RP LNs can be bilateral)
- **N2** – bilateral, ≤6cm
- **N3a** – >6cm
- **N3b** – supraclav (defined by Ho)

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

Pathology
- WHO grade
  - I: keratinizing SCC (smokers, USA)
  - II: nonkert SCC (EBV assoc)
  - III: undiff (lympoepithelioma, EBV assoc)
- EBV: titers >1500 copies/ml→ ↓OS. Persistent EBV after tx → ↓OS (Lin et al)
- 70% cN+, 90% pN+, 50% BL N+

Anatomy
- Borders
  - Ant: choanae
  - Post: clivus, C1, C2
  - Sup: sphenoid sinus
  - Inf: soft palate
  - Lat: Eustachian tube, torus tubarius, fossa of Rosenmueller (deep is parapharyngeal space)
- Villaret/Jugular foramen syndrome: parapharyngeal space invasion (CN IX-XII, sympathetic nerve palsy)
- Rotundum: V2
- Ovale: V3
- Lacerum: carotid→cavernous sinus→cranial fossa (Jacod syndrome)
- Cavernous sinus: carotid, III, IV, V2, V3, VI
- Triangle of Ho: superior clavicle, point where neck meets shoulder

Workup
- H&P, FNL, otoscopy, CN exam, labs (EBV IgA/DNA)
- MRI + CT, CT chest, +/- PET

RT +/- chemo
- Al Sarraf, Int 0099 (mostly WHO I) stage III/IV:70/35 +- HD cis and adj cis/5FU: CRT won; 3 yr OS 47→78%, PFS 24→65%
- Wee, 2005: confirmed Int 0999 for WHO III: 2 yr OS 78 →85%
- Chen, 2005: RT +/- LD cis: 59→70%, lower toxicity
- Baujet: metaanalysis, chemo improved OS when given concurrent
- Chen 2012: CRT +/-adj cis/5FU: no benefit to added chemo, long term data pending

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: 70 Gy @2.12 w/ cis + adj cis/5FU: 2 yr LRC 91%, OS 79%

Sim/planning (based on Nancy Lee's recs)
- Dental eval, aquaplast, supine, 33 fx IMRT, MRI fusion
- CTV70: @2.12 = GTV
- CTV59.4 @ 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)
- CTV 54 @ 1.64: RS space, BL Ib-V, supraclav for N+
- Dose limits:
  - 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%

NCCN
- I: RT alone (70/35 or 66/30)
- II-IVB: CRT with cis (70 Gy) + adj cis/5FU
- Surgery for residual disease

Maxillary Sinus Cancer[1-5,82-84]

- **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

- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6cm
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

Histology
- SCC most common, also Adenoid cystic, plasmacytoma, lymphoma, SNUC, etc

Anatomy
- Subsites: septum, floor, lateral wall, vestibule
- 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, II

Workup
- H&P, FNL, CN exam, biopsy
- CT/MRI, CT chest, +/- PET

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

Maxillary Sinus
- 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

Nasal Cavity and Ethmoid Sinus Cancer[1-5,82-84]

- **T1** – one subsite, no bony invasion
- **T2** – two subsites, +/- bony invasion
- **T3** – maxillary sinus, orbital wall, palate, cribriform plate
- **T4** -
  - T4a – anterior orbit, skin, pterygoid plates, cranial fossa, sphenoid/frontal sinuses
  - T4b – orbital apex, dura, brain, middle cranial fossa, CNs other than V2, nasopharynx, clivus

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

Chemo?
- Sinus cancers not included in postop CRT trials, but usually extrapolated for SCC histology

Sim/planning (based on Nancy Lee's recs)
- Dentistry, supine, mask, eyes straight, bite block
- Brachytherapy for nasal cavity?
- Esthesios: here we do chemo 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
- Unresectable: chemoRT to 70 Gy, cisplatin
- Consider alt fractionation for tissue sparing
  - Accelerated: BID once per week (6 fx/wk)
  - Concomitant boost: BID last 2 wks
  - Hyperfractionation: BID throughout
- IMRT preferred for normal tissue sparing
- Preop RT or CRT to 50 Gy accepted

Oral Cavity Cancer[1-5,85-98]

- **T1** – ≤2cm
- **T2** – 2-4cm
- **T3** - >4cm
- **T4** -
  - T4a – cortical bone, deep muscles of tongue (genio, hyo, stylo, palatoglossus)
  - T4b – masticator space, pterygoid plates, skull base, encases carotid

- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6cm
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

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

Pathology
- Tobacco, ETOH, poor hygiene, betel/acreca nuts
- Oral leukoplakia (10% risk)
- Erythroplakia (30% risk)

Anatomy
- Subsites: lips, gingivobuccal sulcus, buccal mucosa, gingival, retromolar trigone, hard palate, FOM, ant 2/3 tongue
- CN XII: motor, CN V: sensory, CN VII: taste (BOT CN IX taste)
- Ear pain? Auriculotemporal nerve (CN V3)
- Oral Tongue requiring LND: >3mm DOI, grade 3, +LVSI, recurrence
- Adequate margin in OC SCC: 1cm (1.5cm for tongue)
- Extrinsic tongue muscles: Genioglossus, Styloglossus, Palatoglossus, Hyoglossus

Workup
- H&P, palpation, FNL, CN exam, bx, labs
- MRI + CT, CT chest, +/- PET
- Dentistry

Lip
- Commisure involvement→↑nodal risk
- Surgery preferred unless concern for postop function
- T1/2: electrons (+bolus), orthovoltage, brachy (50/25 + boost of 10-16 Gy), no neck tx
- T3: 50/25 + boost of 20 Gy, treat neck levels I/II
- T4 or N+: same as T3 but treat neck I-IV

Brachytherapy
- can use LDR (Granenbauer 2001), PDR (Melzner 2007) or HDR (Martinex-Monge 2009)
- can be alone or as EBRT boost (~50 Gy EBRT)

Altered fractionation (no chemo)
- RTOG 9003: advanced H&N SCC→ 70/35 (std) vs 81.6 @1.2 BID (hyperfrac) vs 67.2 @1.6 BID split (split) vs 72 w/ last 12fx BID (conboost). Hyperfrac and Conboost won (LRC 54%, DFS 39%, OS 53%). ↑toxicity
- MARCH metaanalysis: 6,515 pts. 3.4% OS benefit at 5 years for altered fractionation, mostly for young pts

ChemoRT
- MACH-NC metaanalysis: 17,346 pts: 4.5% OS benefit with any CRT, greater with concurrent (6.5%). Platinum-monotherapy is gold standard, no benefit if age >71

Postop RT, CRT
- Ang 2001: OC SCC: +margin, PNI, ECE had ↑failure without postop RT
- EORTC 22931: operable stage III/IV H&N SCC of OC, OP, larynx, hypopharnx: postop 66/33 +/- concurrent cisplatin (100mg/m2 Q3wks): CRT won: 5yr 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 (100mg/m2 Q3wks): CRT won: 2 yr DFS 43→54%, LRC 72→82%, trend for OS. ↑toxicity
- Metaanalysis: CRT improved OS, DFS and LRC for ECE or +margins. Trend for stage III/IV, PNI, LVSI, low neck nodes

Sim/planning
- Dental eval, PEG?, aquaplast, supine, bite block
- Dose limits:
  - Cord < 45 Gy max
  - Parotid mean < 26Gy
  - Larynx mean <43.5 Gy
  - Mandible <70 Gy max

NCCN
- I-II: RT alone (70/35 or 66/30) or surgery alone
  - Postop RT for T3+, N2+, PNI, LVSI (6wks postop)
  - Postop CRT for +margin, +ECE
- III-IVB: CRT with cis (70 Gy), 100mg/m2 Q3wks
  - Alt frac if no chemo given
  - Induction chemo (category 3)
- Surgery for residual disease

Oropharyngeal Cancer[1-5,85-98]

- **T1** – ≤2cm
- **T2** – 2-4 cm
- **T3** – >4cm or lingual surface of epiglottis
- **T4** -
  - T4a – larynx, deep tongue muscles, medial pterygoid, hard palate, mandible
  - T4b – lateral pterygoid, pterygoid plates, lateral nasopharynx, skull base, carotid

- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

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

HPV-Associated SCC
- Younger, nonsmokers (~60% of new cancers)
- subtypes 16(80%), 18: ↑nodes, ↑mets
- E6→↓p53; E7→↓Rb→↑p16
- RTOG 0129: better 3 yr OS for HPV+ (57→82%)

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: auriculotoemporal nerve (CN V)
  - BOT: Jacobson's nerve (CN IX)
  - Larynx/HPX: Arnold's nerve (CN X)

Workup
- H&P, palpation, FNL, CN exam, biopsy (p16)
- MRI + CT, CT chest, +/- PET, dentistry

Preop vs Postop RT
- RTOG 7303: advanced H&N SCC→50 Gy preop vs 60 Gy postop→postop improved LRC 48→65% overall and OS for oropharynx (26→38%)

Altered fractionation (no chemo)
- RTOG 0022: T1-2N0-1 OP SCC: 66 Gy in 30 fx (@2.2): 91% 2 yr LRC (N staging clinical only)
- RTOG 9003: advanced H&N SCC→ 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%). No difference in OS 53%. ↑toxicity
- EORTC 22791: T2/3 oropharynx 70/35 vs 80.5 @1.15 BID. Hyperfrac ↑LRC 40→59%, OS 31→47%. No BOT in this trial
- MARCH metaanalysis: 6,515 pts. 3.4% OS benefit at 5 yrs for altered fractionation, mostly in young pts

ChemoRT
- GORTEC 9401: stage III/IV oropharynx: 70/35 +/- carbo/5FU. CRT improved LC 25→48%, DFS 15→27%, OS 16→23%
- Adelstein 2003: stage III/IV H&N SCC: RT +/- cisplatin (100mg/m2 Q3wks): CRT won. 3 yr OS 23→37%, DFS 33→51%.
- Bonner 2006: advanced OP, larynx, hypopharynx: RT vs CRT (cetuximab). CRT won. 3 yr LRC 34→47%, OS 45→55%. Rash with cetuximab
- GORTEC 9902: advanced H&N SCC: carbo/5FU+RT. RT was 70/35 vs 70/30 vs 64.8/18 (no chemo). Similar outcomes except ↑toxicity in 64.8/18 arm
- MACH-NC metaanalysis: 17,346 pts: 4.5% OS benefit with any CRT, greater with concurrent (6.5%). Platinum-monotherapy is gold standard, no benefit if age >71

Postop RT +/- chemo
- EORTC 22931: operable stage III/IV H&N SCC of OC, OP, larynx, hypopharynx (ECE, +margin, PNI, LVSI, level IV/V nodes): postop 66/33 +/- concurrent cisplatin (100mg/m2 Q3wks): CRT won: 5yr 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 (100mg/m2 Q3wks): CRT won: 2 yr DFS 43→54%, LRC 72→82%, trend for OS. ↑toxicity
- Metaanalysis: CRT improved OS, DFS and LRC for ECE or +margins. Trend for stage III/IV, PNI, LVSI, low neck nodes

Induction chemo
- TAX323: unresectable H&N SCC: TPF vs PF induction →RT alone. TPF increased MS 16→19months
- TAX 324: Posner: unresectable H&N SCC: TPF vs PF induction →CRT with carboplatin. Induction CRT won. 3 yr OS 48→62%. 25% of patients never made it to RT (progressed, died, withdrew)
- DeCIDE trial: locally advanced H&N SCC: CRT with docetaxol, 5FU, hyroxyurea, BID fx vs TPF induction then same CRT: no OS advantage, underpowered
- PARADIGM trial: TPF induction + CRT with docetaxol or carboplatin vs CRT with cisplatin: no difference (3 yr OS 73% induction; 78% CRT))

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

NCCN
- I-II: RT alone (70/35 or 66/30) or surgery alone
  - Postop RT for T3+, N2+, PNI, LVSI,
  - Postop CRT for +margin, +ECE
- III-IVB: CRT with cis (70 Gy), 100mg/m2 Q3wks
  - Alt frac if no chemo given
  - Induction chemo (category 3)
- Surgery for residual disease

Salivary Gland Cancer[1-5,99-105]

- **T1** - ≤2cm w/o extraparenchymal extension
- **T2** – 2-4cm w/o extraparenchymal extension
- **T3** - >4cm or extraparenchymal extension
- **T4**
  - T4a – skin, mandible, ear, CN VII
  - T4b – skull base, pterygoid plates, carotid

- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

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

Histology
- Benign most common: usually pleomorphic adenoma (consider postop RT for multifocal, PNI, residual, recurrent)
- Most common malignant: mucoepidermoid carcinoma
- Also ACC, Acinic cell,
- ACC, ductal, undifferentiated → ↑DM (lung, bone, liver)

Anatomy
- Parotid: facial nerve, Stensen's duct, most common, malignant less common (20%)
- 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 glands: most likely malignant (90%)
- Frey's syndrome, auriculotemporal nerve syndrome, gustatory sweating (CN VII damage)

Workup
- H&P, bimanual palpation, FNL, CN exam, biopsy (FNA)
- MRI + CT, CT chest, +/- PET, dentistry

Postop 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
- 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

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

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

NCCN
- Operable: surgery with END for G3, T4
  - Postop RT for T3+, N+,, +margin, close margin, PNI, LVSI, G2-3, ACC, recurrent
  - No defined role for chemo if M0 (RTOG 1002 pending)
- Inoperable: RT +/- chemo, consider neutrons

Laryngeal and Hypopharyngeal Cancer[1-5,106-115]

	Supraglottis	Glottis	Subglottis	Hypopharynx
T1	**1 subsite*, normal VCs**	**Normal VC movement (T1a one cord, T1b both)**	**Subglottis only**	**One subsite**, ≤2cm**
T2	**2+ subsites or glottis**	**Supra/subglottis or impaired VC**	**To VCs**	**2+ subsites, 2-4cm**
T3	**Fixed cord, paraglottic space, inner cartilage, pre-epiglottic space**	**Fixed cord, paraglottic space, inner cartilage, post-cricoid area**	**Fixed cord**	**>4cm, fixed VC, esophagus**
T4a	**Through cartilage, beyond larynx**	**Through cartilage, beyond larynx**	**Cricoid invasion, ANY cartilage invasion, outside larynx**	**Thyroid/cricoids cartilage, hyoid, central compartment**
T4b	**Prevertebral space, carotid, mediastinum**			

*Supraglottic subsites: false cords, arytenoids, suprahyoid epiglottis, infrahyoid epiglottis, aryepiglotic folds
** Hypopharynx subsites: pyriform sinus, Hypopharyngeal wall, postcricoid region

- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6cm
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

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

Anatomy
- Larynx Subsites
  - Supraglottis: epiglottis, AE folds, arytenoids, false cords, ventricle
  - Glottis: TVCs, ant/post commisures
  - Subglottis: 5mm below glottis to inferior cricoid
- Hypopharynx: Superior Hyoid to inferior cricoids
  - Subsites: Pyriform sinus, hypopharngeal walls, post cricoids area
- Ear pain?
  - Oral tongue: auriculotoemporal nerve (CN V)
  - BOT: Jacobson's nerve (CN IX)
  - Larynx/HPX: Arnold's nerve (CN X)

Workup
- H&P, FNL, biopsy
- CT +/- MRI, CT chest, +/- PET, dentistry

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. 5 yr LC 77→92%, CSS & toxicity unchanged
- RTOG 95-12: T2 glottis: 70/35 vs 79.2 BID (1.2 Gy). No change, trend for ↑LC (70→79%, p>0.11)
- RTOG 90-03 included larynx/hypopharynx primaries

Larynx Preservation
- VA Larynx Trial: III/IV larynx: surgery+PORT vs cis/5FU x3c then RT. PR or CR required before RT. 64% larynx preservation at 2 yrs, OS unchanged (68%), LC lower for CRT (98→88%). Non-chemo responders got surgery.
- RTOG 91-11: III/IV larynx: RT alone vs chemo→RT vs CRT. Induction chemo was cis/5FU. All cN2 patients got planned neck dissection after RT. Concurrent CRT won. 5 yr larynx preservation 84→71→66%, LRC 69→55→51%. Chemo reduced DMs (13 vs 22%). OS unchanged.
- TAX 324 (Posner): unresectable head & neck (33% larynx/hypopharynx): induction TPF vs PF x3 cycles, then 70 Gy. TPF won. 3 yr OS 48→62%, 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%

ChemoRT
- See oropharynx (RTOG 9501, EORTC 22931)

Sim/planning
- Mask, shoulders down
- T1 glottis: 5x5cm opposed laterals (top of thyroid cartilage through cricoid, flash to anterior vert body
- T2 glottis: same by 6x6cm down to 1st tracheal ring
- Hypopharynx: always treat nodes II-V and RPNs
- Boost stoma for emergent trach, subglottic extension, or anterior soft tissue extension

NCCN Larynx
- Tis: *cord stripping (laser/CO2)* or RT
- T1a: RT or cordectomy
  - 63Gy @2.25 to 66Gy @2.0
- T1b: RT or hemilaryngectomy
  - 65.25Gy @2.25 to 70Gy @2.0
- T3 or N+: chemoRT (surgery salvage) or induction chemo or laryngectomy
  - After induction: surgery for residual, RT for CR, consider chemoRT for PR
- T4: laryngectomy or chemoRT

NCCN Hypopharynx
- T1-2: RT or organ sparing surgery if able
- T2-3: induction chemo or surgery or chemoRT
  - After induction: surgery for residual, RT for CR or PR (consider chemoRT)
- T4a: *surgery* or induction or CRT
- T4: laryngectomy or chemoRT

Thyroid Cancer[1-5,116-124]

- **T1** -
  - T1a - ≤1cm
  - T1b – 1-2 cm
- **T2** – 2-4 cm, capsule intact
- **T3** - >4cm, minimal extrathyroid extension
- **T4** -
  - T4a – subQ, larynx, trachea, esophagus, recurrent laryngeal, or any anaplastic
  - T4b – prevertebral fascia, carotid, mediastinum (anaplastic out of thyroid)

- **N1a** – level VI
- **N1b –** head and neck LNs I-VII or RPs

Papillary/Follicular		Papillary/Follicular		MTC		Anaplastic	
<45 years old		>45 years old					
TxNxM0	I	T1	I	T1	I		
M1	II	T2	II	T2-3	II		
		T3 or N1a	III	N1a	III		
		T4a or N1b	IVA	T4a or N1b	IVA	T4a	IVA
		T4b	IVB	T4b	IVB	T4b	IVB
		M1	IVC	M1	IVC	M1	IVC

Pathology

- Papillary carcinoma (Follicular cells)
  - Has a 'follicular variant'
  - Good prognosis except diffuse sclerosing, tall cell, columnar cell
  - Takes up RAI
- Follicular carcinoma (Follicular cells)
  - Looks like follicular adenoma but invasive
  - Takes up RAI
- Hurthle Cell (oncocytic carcinoma)
  - Can be benign or malignant
  - Takes up RAI
- Medullary carcinoma (parafollicular/C cells)
  - Excrete calcitonin (↓serum calcium)
  - 25% associated w/ MEN syndrome(RET, Ch 10)
    - MEN2A: pheochromocytoma, parathyroid, MTC
    - MEN2B: marfanoid, ganglioneuromas, pheochromocytoma, MTC
  - Don't take up RAI, but can use by bystander affect
- Anaplastic carcinoma
  - ↑age, mets, does not take up RAI

Workup

- H&P, ultrasound, FNA, TSH, T3, T4
- CT (no iodine), +/-CT chest, +/- RAI scan
- For MTC: calcitonin, CEA, catecholamines, RET

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 Carcinoma

- SEER (Chen): EBRT improved OS for patients with >1m 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)

Radioactive Iodine

- Use in PTC, FTC, HTC, and some MTC
- Avoid iodine contrast 4-6 months prior to treatment
- ^{131}I: 8d half life, 364keV, 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 1,000 mCi

NCCN

- Contains criteria for biopsy (anything >2cm)
- Surgery if feasible
- Neck dissection if <15 y/o, >45 y/o, RT history, T3+, N+
- RAI indications: ETE, >4cm, postop Thyroglobulin>5ng/mL (consider for N+, >1cm, LVSI, anti Tg antibodies, poorly differentiated)
- EBRT: no defined role, consider for:
  - Unresectable disease that doesn't take RAI
  - Postop locally invasive MTC (50/25)
  - Consider in anaplastic carcinoma
  - Bulky mets after RAI
  - Doses similar to SCC (50→70Gy)

Unknown Primary[1-5,125-129]

- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

	T0
N1	III
N2	IVA
N3	IVB
M1	IVC

General

- 45% tonsil, 40% BOT, 10% pyriform sinus
- 25% of N1 will fail at primary site if neck alone is treated
- "neck violation": incisional/excisional biopsy of node
- PET scan PPV 90%, NPV 75%
- Waldeyer's ring: palatine, tubal, pharyngeal, and lingual tonsils

Workup

- H&P, skin exam, FNL, FNA, labs, CT neck/chest, +/-MRI, +/- PET (before biopsy)
- Test for EBV, HPV
- Direct laryngoscopy detects 50% of cases. Biopsy:
  - Nasopharynx
  - Tonsils (or tonsillectomies)
  - Base of tongue
  - Pyriform sinuses
  - Triple endoscopy if levels IV-V

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. 5 yr OS 71%, DFS 85%. All nodal failures had bulky disease.

Technique

- Standard head & neck, IMRT
- Target nasopharynx, oropharynx, RPNs, bilateral IB-IV
- Conventional: opposed laterals matched to AP yoke w/ larynx block
  - Match-line based on nodal disease (don't bisect a positive node)

NCCN

- Surgery +/-PORT preferred for N1
  - RT alone for N1 category 2B
- ChemoRT for ≥N2 with surgery if residual disease after treatment
  - 70 Gy to GTV
  - 50-66 Gy to "mucosa"
  - 44-50 (@2Gy) or 54-63 (@1.8Gy) to low risk

UVA IMRT Technique (Shoushtari 2011)

- N1/N2a without ECE: RT alone then neck dissection
  - 56 Gy to GTV then planned neck dissection
  - 50-56 Gy to pharyngeal axis
  - 504 Gy to bilateral necks
- N2b-N3 or any +ECE: chemoRT then neck dissection
  - Chemo
  - 56-70 Gy to GTV then neck dissection
  - 50-56 Gy to pharyngeal axis
  - 50.4 Gy to bilateral neck

Melanoma[1-5,130-140]

- **T1** - ≤1mm thick
  - T1a – nonulcerated, mitotic rate <1/mm^2
  - T1b – ulcerated or mitotic rate ≥1/mm^2
- **T2** – 1.01-2mm thick
  - T2a - nonulcerated
  - T2b - ulcerated
- **T3** – 2.01-4mm thick
  - T3a - nonulcerated
  - T3b – ulcerated
- **T4** - >4mm thick
  - T4a - nonulcerated
  - T4b – ulcerated

- **N1** – 1 node
  - N1a – micro
  - N1b – macro
- **N2** – 2-3 nodes or in-transit met
  - N2a – micro
  - N2b – macro
  - N3 – in-transit met w/o node
- **N3** – ≥4 nodes or matted or in-transit+node

- **M1a** – skin, subQ, distant nodes
- **M1b** - lung
- **M1c** – other, or any met with ↑LDH

	T1a	T1b/T2a	T2b/T3a	T3b/T4a	T4b
N0	**IA**	**IB**	**IIA**	**IIB**	**IIC**
cN+	**III**				
M1	**IV**				
pIIIA	TXa, N1a/N2a				
pIIIB	TXa, N1b/N2b/N2c or TXb, N1a/N2a				
pIIIC	TXb, N1b/N2b/N2c or N3				

Tumor Thickness	Recommended Clinical Margins[2]
In situ[1]	0.5-1.0 cm
≤1.0 mm	1.0 cm (category 1)
1.01-2 mm	1-2 cm (category 1)
2.01-4 mm	2.0 cm (category 1)
>4 mm	2.0 cm (category 1)

General

- Subtypes: superficial spreading (65%), nodular (25%) lentigo maligna, acral lentiginous
- 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+,

Workup

- WLE with SLN
- <1mm: nothing special
- >1mm, labs, CXR, consider CT for nodes
- LN+: PET-CT, MRI

Adjuvant Therapy

- Interferon alpha (ECOG 1684/1690/1694): IFN-alpha for T4 or N+ pts provided ↑ 10 % RFS
- Ang 1994: phase II, 79 pts WLE + 30/5 twice weekly (some patients got LND). 5 yr LRC 88%, OS 47%
- 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%
- Ballo et al: multiple reports from MDACC on 30/5 adjuvant
- TROG 0201: phase III, 250 pts. Observation vs 48/20. Had to have palpable LN disease and high risk. RT ↑LRC (60→80%) but did not affect OS

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%)
-

Metastatic disease

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

Technique

- Primary RT: (Overgaard) 50 Gy in 20 fx with 100-250 kv, 1.5cm margin and hyperthermia. Consider in lentigo maligna of the face
- Cord max: 24 Gy in 4 fractions

NCCN

- Surgery for everyone
- Stage I/II: observation
- Stage III: obs or IFN-alpha and/or RT (RT is cat 2B)
- Stage IV:
- Adjuvant RT if
  - LDH < 1.5 ULN AND
  - ECE and/or
  - Any parotid node, 2+ cervical LNs, 2+ axillary LNs, 3+ inguinal LNs

Squamous Cell and Basal Cell Carcinoma of the Skin[1-5,141-145]

- **T1** - ≤2cm, ≤1 high risk feature
- **T2** - >2cm; or ≥2 high risk features
- **T3** – into maxilla, orbit, temporal bone
- **T4** – skeleton or PNI to skull base

*high risk features:
DOI>2mm, Clark level≥IV, +PNI
Ear, hair-bearing lip
G3 or G4

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

- **N1** – single, ≤3cm
- **N2**
  - N2a – single ipsi, 3-6
  - N2b – multiple ipsi, ≤6cm
  - N2c – contralateral, ≤6cm
- **N3** – >6cm

General
- Associated conditions: albino, xeroderma pigmentosum, Turcot syndrome, Fanconi Anemia, Gorlin syndrome
- Marjolin's ulcer: SCC from chronic inflammation

Workup
- H&P, exam, biopsy

Retrospective Reports
- Rogers & Coldiron 2009: showed that RT was most expensive treatment of available optiosn
- 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% to 0% neck failure)

Common Fractionation
- 0-42 Gy/ 5-7 fractions 2-3 times per week
- 45-57 Gy/ 10-19 fractions 2-5 times per week
- 66-72 Gy/ 33-35 fractions for large T4 unresectable cancers or when pathologic nodes are being treated
- 12-20 Gy/ 1 fraction for symptomatic management of large bleeding tumors of very ill/ nursing home type patient

NCCN
- Surgery with PORT for high risk features (T3/4, parotid gland, +margin)
- Topical 5FU/imiquimod for low risk superficial BCC
- RT for nonsurgical candidates
- Neck treatment same as other H&N cancer

Primary Tumor[1]	Dose Time Fractionation Schedule
Tumor Diameter	Dose Fractionation and Treatment Duration
< 2 cm	64 Gy in 32 fractions over 6-6.4 weeks 55 Gy in 20 fractions over 4 weeks 50 Gy in 15 fractions over 3 weeks 35 Gy in 5 fractions over 5 days
≥ 2 cm	66 Gy in 33 fractions over 6 - 6.6 weeks 55 Gy in 20 fractions over 4 weeks
Postoperative adjuvant	50 Gy in 20 fractions over 4 weeks 60 Gy in 30 fractions over 6 weeks
Regional Disease--all doses at 2 Gy per fraction using shrinking field technique	
• After Lymph node dissection	
▸ Head and neck; with ECE:	60-66 Gy over 6 - 6.6 weeks
▸ Head and neck; without ECE:	56 Gy over 5.6 weeks
▸ Axilla, groin; with ECE:	60 Gy over 6 weeks
▸ Axilla, groin; without ECE:	54 Gy over 5.4 weeks
• No lymph node dissection	
▸ Clinically (-) but at risk for subclinical disease:	50 Gy over 5 weeks
▸ Clinically evident adenopathy: head and neck:	66-70 Gy over 6.6 - 7 weeks
▸ Clinically evident adenopathy: axilla, groin:	66 Gy over 6.6 weeks

ECE= Extracapsular extension

Merkel Cell Carcinoma[1-5,146-148]

- **T1** - ≤2cm
- **T2** – 2-5cm
- **T3** - >5cm
- **T4** – into bone, muscle, fascia, cartilage

- **N1** –
  - N1a – micro
  - N1b – macro
- **N2** – in-transit mets

- **M1a** – skin, subQ, distant nodes
- **M1b** – lung
- **M1c** – other

	T1	T2	T3	T4
pN0	IA	IIA		IIC
cN0	IB	IIB		
N1a	IIIA			
N1b	IIIB			
N2				
M1	IV			

General
- Arises from Merkel cells (tactile receptors, maybe neural crest derived)
- 80% caused by Merkel cell Polymyxoma virus
- S-100 neg, leukocyte antigen neg, Enolase +,

Workup
- Same as melanoma
- Use of SLNBx debated as drainage can be erratic

Retrospective Reports
- Mojica 2007: SEER analysis, 1665 pts, surgery +/- PORT. RT improved mean survival for all size tumors
- TROG 96.07: phase II, high risk disease: 50/25 with concurrent carbo/etop. 3 yr OS 76%, increased toxicity
-

Technique
- NCCN doses in table
- 5cm margins on primary

NCCN
- Surgery for everyone
- Primary RT for everyone
- Nodal RT if N+ or high risk

Dose recommendations for radiation therapy:

• Primary Site:	
▸ Negative resection margins	50-56 Gy
▸ Microscopic (+) resection margins	56-60 Gy
▸ Gross (+) resection margins or unresectable	60-66 Gy
• Nodal Bed:	
▸ No SLNB or LN dissection	
◊ Clinically (-) but at risk for subclinical disease	46-50 Gy
◊ Clinically evident lymphadenopathy	60-66 Gy[1,2]
▸ After SLNB without LN Dissection	
◊ Negative SLN biopsy: axilla or groin	Radiation not indicated[3]
◊ Negative SLN biopsy: head and neck, if at risk for false-negative biopsy	46-50 Gy[3]
◊ Microscopic N+ on SLNB: axilla or groin	50 Gy[4]
◊ Microscopic N+ on SLNB: head and neck	50-56 Gy[4]
▸ After LN Dissection	
◊ Lymph node dissection: axilla or groin	50-54 Gy[5]
◊ Lymph node dissection: head and neck	50-60 Gy

Notes

Thorax

Early Stage Non-Small Cell Lung Cancer[1-5,149-158]

- **T1** - ≤3cm
  - T1a - ≤2cm
  - T1b – 2-3cm
- **T2** – 3-7cm
  - T2a – 3-5cm; or mainstem bronchus (>2cm from carina), visceral pleura, atelectasis
  - T2b – 5-7cm
- **T3** - >7cm; or parietal pleura, chest wall, diaphragm, phrenic nerve, pericardium, bronchus <2cm from carina, whole lung atelectasis, tumor in same lobe
- **T4** – mediastinum, heart, great vessels, trachea, recurrent laryngeal, esophagus, vertebrae, carina, tumor in same lung

- **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** – disant mets

	T1	T2a	T2b	T3	T4
N0	IA	IB	IIA	IIB	IIIA
N1	IIA		IIB	IIIA	
N2	IIIA				IIIB
N3	IIIB				
M1	IV				

Overview
- Lung ca: 228,200 cases/yr, 160,000 deaths
- Risk factors: smoking, asbestos, radon
- 5 lobes, 5 segments/lobe (except RUL-3 and RML-2)
- 50% adeno, 35% SCC, 15% large cell
- 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 T790M mutation[149,159-176]
- Kras and ↑ERCC1 don't respond well to platinums
- Workup: H&P, labs, CT chest, PETCT, MRI for stage II-IV, bx
- Medically inop: FEV1<40% or (<1.2L for lobe, <2L for pneumonectomy), DLCO <60%, FVC <70%
- *Smoking cessation*
- USPSTF screening: current or recent smokers, 55-79 yo, more than 30 pack/yrs→ low dose CT annually

Surgery
- Cervical mediastinoscopy: evals 1-4R
- Ant Mediastinoscopy (chamberlain): adds 4L-7
- LCSG 821: T1N0→ lobe vs wedge. Wedge ↑LF (6→18%)

Conventional RT alone
- Dosoretz 1996: T1-3N0 med inop review. Dose >64 Gy improved PFS
- Sibley 1998: T1-2N0 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%

SBRT
- Timmerman 2006: T1-3N0→60-66 Gy in 3 fx. LC 88%, OS 43%, 9% regional failure
- Onishi 2004: 245 pts, BED ≥100Gy improved LF (26→8%) and 3 yr OS (69→88%)
- RTOG 0236: T1-3N0 peripheral→20Gy x 3 fx. 2 yr LC 94%, OS 72%
- RTOG 0618: operable SBRT. 33 pts, 18x3 SBRT. 2 yr LF 19.2%, OS 84.4%

Postop therapy
- LACE meta-analysis: 5% improvement at 5 yrs for stage I-II after resection. Most benefit in N1 pts
- Pre vs postop chemo: no difference (EORTC 08012, CHEST trial, NATCH spanish trial)
- Italian study: 104 pts, pN0→ PORT vs obs. 50.4 Gy. PORT improved LF (23→2%) and 5 yrs OS (58→67%)

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal Cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	105% of PTV prescription^
Brachial Plexus	17.5 Gy	24 Gy (8 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32 Gy (6.4 Gy/fx)
Heart/ Pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	105% of PTV prescription^
Great Vessels	37 Gy	NS	49 Gy (12.25 Gy/fx)	105% of PTV prescription^
Trachea & Proximal Bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription^
Rib	30 Gy	30 Gy (10 Gy/fx)	40 Gy (10 Gy/fx)	NS
Skin	26 Gy	24 Gy (8 Gy/fx)	36 Gy (9 Gy/fx)	32 Gy (6.4 Gy/fx)
Stomach	12.4 Gy	NS	27.2 Gy (6.8 Gy/fx)	NS

*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).
^for central tumor location. NS = not specified

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25–34 Gy	1	Peripheral, small (<2 cm) tumors, esp. >1 cm from chest wall
45–60 Gy	3	Peripheral tumors and >1 cm from chest wall
48–50 Gy	4	Central or peripheral tumors <4–5 cm, especially <1 cm from chest wall
50–55 Gy	5	Central or peripheral tumors, especially <1 cm from chest wall
60–70 Gy	8–10	Central tumors

Technique
- Supine, arms up +/-contrast, 4D?
- SBRT: ITV +5mm radial 8mm sup/inf
- PORT
  - CTV: bronchial stump + nodal stations
  - 50-54 Gy

NCCN
- T1-3N0-1
  - mediastinal sampling/dissection and resection
  - R0 and N0: observe
  - pN1: chemo
  - pN2: CRT (50-54 Gy)
  - R1: reresect or sequential CRT
  - R2: concurrent CRT
  - Med inop: SABR (if N1→conventional CRT)

1	High mediastinal	8	Paraesoph ↓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

Induction Chemo
- MDACC (1998): surgery +/- neoadj cis/etop/cyclophos. Chemo ↑MS (14→21m)
- Madrid (1999): same as MDACC but cis/ifos/mitoC. MS 10→22m.
- Spanish Trial 9901: phase II. N2 or T4→ cis/gem/docetaxel x3c→surgery. pCR 13%. MS 16m
- EORTC 08941: IIIA→chemo→ surgery vs RT. PORT permitted. Same OS. Pts did worse after pneumonectomy
- See Dillman regemin

Neoadj CRT
- German LCCGT: stage IIIA-B→induction cis/etop x3c→surgery. Randomized to preop CRT or postop RT. pCR improved with preop CRT (20→60%), but same OS. Worse OS if pneumonectomy.
- INT-0139: IIIA→ CRT (45Gy) + surgery vs CRT alone (61Gy). Both got post cis/etop. Surgery improved LF (22→10%), but same OS. OS worse if pneumonectomy.
- SWOG 9416: superior sulcus phase II of induction CRT to 45 Gy with cis/etop. Then surgery and postop chemo. 94% R0 resection, 56% pCR, 5 yr OS 44%.

Adjuvant PORT
- LCSG 773: T3 or N2 → obs vs PORT (50Gy). PORT improved LR (41→3%) but same OS
- PORT metaanalysis trial: 10 trials. PORT→↓OS, mostly in stage I-II
- No benefit to CRT over PORT alone (INT 0115, RTOG 9105)
- PCI: RTOG 0214: PCI reduced brain failure, but same OS

Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

Treatment Type	Total Dose	Fraction Size	Treatment Duration
Definitive RT with or without chemotherapy	60–70 Gy	2 Gy	6–7 weeks
Preoperative RT	45–50 Gy	1.8–2 Gy	5 weeks
Postoperative RT			
• Negative margins	50–54 Gy	1.8–2 Gy	5–6 weeks
• Extracapsular nodal extension or microscopic positive margins	54–60 Gy	1.8–2 Gy	6 weeks
• Gross residual tumor	60–70 Gy	2 Gy	6–7 weeks
Palliative RT			
• Obstructive disease (SVC syndrome or obstructive pneumonia)	30–45 Gy	3 Gy	2–3 weeks
• Bone metastases with soft tissue mass	20–30 Gy	4–3 Gy	1–2 weeks
• Bone metastases without soft tissue mass	8–30 Gy	8–3 Gy	1 day–2 weeks
• Brain metastases	CNS GLs*	CNS GLs*	CNS GLs*
• Symptomatic chest disease in patients with poor PS	17 Gy	8.5 Gy	1–2 weeks
• Any metastasis in patients with poor PS	8–20 Gy	8–4 Gy	1 day–1 week

Definitive CRT

↑Dose
- RTOG 7301: dose escalation. 40→60Gy. 60Gy won
- RTOG 8311: dose escalation BID. 1.2/fx→ 69.6Gy won
- RTOG 9311: dose escalation with chemo. 70→90Gy. 83.8 Gy won
- RTOG 0617: 60 vs 74 Gy and +/- Cetuximab. Closed early. 74Gy more toxic, worse OS. +/- cetux had same OS
- CHART: 54 Gy at 1.5Gy TID (x12 consec days) vs 60/30. TID improved 3 yr OS by 10% but ↑tox. Mostly SCC

+Chemo
- CALGB 8433 (Dillman): IIIA→60/30 vs cis/vinblast+60/30 (sequential). CRT improved ↑MS (10→14m). 5 yr OS (7→19%)
- RTOG 8808: II-IIIB→ 60/30 vs 69.6BID vs cis/vinblast+60/30(dillman). CRT improved MS (11.4→12→13.2m)
- RTOG 9410: 3 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→15.6m). more tox with chemo
- Cis/etop and cis/vinblast can be given full dose with RT
- Carbo/taxol, gem, vinorelbine require dose reduction

Induction chemo
- LAMP trial: 3 arms: Dillman (chemo→RT) vs (chemo→CRT) vs (CRT→chemo). Chemo was carbo/taxol. CRT→chemo improved MS (13→16.3→12.7m)
- CALGB 39801: CRT +/- induction chemo (carbo/taxol). Same OS

Technique
- PTV = GTV + 1-1.5cm

NCCN
- Superior Sulcus Tumor (T3-4N0-1): preop CRT (45-50 Gy)
- T4NX: definitive CRT
- N2-3M0: definitive CRT (cat 1) or neoadj chemo +/- RT (45Gy)
- Contralateral nodules: treat as 2 primary tumors if curable
- Dose: 60-70 Gy (2/fx)

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT

OAR	Constraints in 30–35 Fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%; V5 ≤65%; MLD ≤20 Gy
Heart	V40 ≤80%; V45 ≤60%; V60 ≤30%; Mean ≤35 Gy
Esophagus	Mean ≤34 Gy; Max ≤105% of prescription dose
Brachial plexus	Max ≤66 Gy

Vxx = % of the whole OAR receiving ≥xx Gy.

Small Cell Lung Cancer[1-5,178-186]

Overview
- 15% of lung cancer
- 1/3 pts present with limited stage dz
- Paraneoplastic syndromes: SIADH, ACTH production, Lambert-Eaton syndrome
- Markers: S100, synaptophysin, chromogranin, neurotensin, EGFR-
- Del3p, amplification of bcl2 and c-myc family
- Workup: H&P, labs, biopsy, PET-CT, MRI brain, BM bx if ↑LDH

Limited stage: ~24 month OS
- Pignon 1992: metaanalysis (2140 pts) of chemo +/- thoracic RT. RT improved 3 yr OS (8.9→14.3%)
- Fried 2004: metanalysis of early vs delayed RT. Early improved 2yr OS by 5.2%
- Takada 2002: concurrent vs sequential CRT. Concurrent improved 5 yr OS (20→30%).
- INT 0096 (Turrisi): 417 pts→cis/etop with RT (45/25 vs 45 Gy at 1.5/fx BID). BID ↓LF (52→36%) and ↑5yr OS (15→26%). BID ↑ grade 3 esophagitis (11→27%). Cord max 36 Gy.
- 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 vs 70/35 (CALGB 8837). This trial includes ENI

PCI
- Auperin 1999: metaanalysis 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
- Slotman 2007: ES with response to chemo→ +/- PCI. PCI improved 1 yr OS (13→27%). No routine MRIs done.

Extensive stage: ~9 month OS
- Jeremic 1999: PR or CR after chemo→ chest RT vs more chemo. RT improved 5 yr OS (3.7→9.1%)
- Slotman 2014:ES with PR or CR→ +/- thoracic RT (30/10). RT improved 2 yr OS (+/- thoracic RT (30/10). RT improved 2 yr OS (3→13%).

Technique
- High dose = GTV+1cm
- Lung V20<30%
- Esophagus V60<50%
- Heart V40<50%

NCCN
- T1-2N0: mediastinal sampling. If neg→lobectomy and node dissection
  - Postop chemo, postop CRT for N+
- Above T1-2N0: chemoRT, usually cis/etop
  - 45 Gy BID or 60-70Gy
  - +/- ENI
  - then PCI for PR or CR
- M1: chemo +/-RT

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT

OAR	Constraints in 30–35 Fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%; V5 ≤65%; MLD ≤20 Gy
Heart	V40 ≤80%; V45 ≤60%; V60 ≤30%; Mean ≤35 Gy
Esophagus	Mean ≤34 Gy; Max ≤105% of prescription dose
Brachial plexus	Max ≤66 Gy

Vxx = % of the whole OAR receiving ≥xx Gy.

Thymoma and Thymic Carcinoma[1-5,187-191]

Masaoka Staging

- **T1** - encapsulated
- **T2** - through capsule
  - T2a – microscopic invasion
  - T2b – adhesion to fat/pleura
- **T3** – into organs
  - T3a – into adj organs
  - T3b – into great vessels
- **T4** – pleural/pericardial invasion
- **N1** – ant mediastinal nodes
- **N2** –intrathoracic nodes
- **N3** – supraclav

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

Overview
- Anterior mediastinal mass
- Assoc with MG, red cell aplasia, hypogammaglobulinemia
- 50% of thymomas have MG, 15% of MGs have thymoma
- WHO grading (A, AB, B1-3, C)
- Thymic carcinoid/carcinoma (30% N+)
- Workup: same as NSCLC, rule out germ cell tumor

PORT
- Forquer 2009: SEER database. PORT improved 5 yr OS for stage 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, not prognositic
- Wright 2008: phase II. cis/etop x2c neoadj had good results.

Technique
- PTV = CTV + 1.5-2cm
- PORT: 45-54 Gy
- Inoperable: 60-70Gy
- No ENI

NCCN
- Operable: resect
  - Stage I, R0: obs
  - Stage II-IV, R0: consider PORT (cat2b) (45-50Gy)
  - R1 or R2: PORT +/-chemo (R1=54Gy, R2=60Gy)
- Inoperable: CRT (60-70Gy)

Pleural Mesothelioma[1-5,192-194]

- **T1** -
  - T1a – ipsi parietal pleura, no visceral
  - T1b – ipsi parietal pleura, +visceral
- **T2** – into diaphragm or pulmonary parenchyma
- **T3** –endothoracic fascia, mediastinal fat, chestwall, outer pericardium
- **T4** - multifocal, into peritoneum, contralateral pleura, mediastinal organ, spine, internal pericardium
- **N1** – ipsi hilar
- **N2** –ipsi mediastinal/IM
- **N3** – contra mediastinal/IM, supraclav

	T1a	T1b	T2	T3	T4
N0	IA	IB	II	III	IV
N1	III				
N2					
N3	IV				
M1					

Overview
- 2500 cases/yr
- 80% involve asbestos
- Stains for calretinin, vimentin WT1, cytokeratin
- Workup: same as NSCLC

Surgery
- Extrapleural pneumonectomy (EPP) removes parietal/visceral pleura, lung, mediastinal nodes, pericardium, ipsi diaphragm (~20% mortality)
- Pleurectomy/decortication: more like debulking

Adj RT
- Rusch 2001: phase II→ EPP and hemithoracic 54 Gy. MS 34m for Stage I-II, 10m for stage III-IV
- Flores 2006: induction gem/cis→EPP→54Gy. MS 33m

Chemotherapy
- Vogelzag 2003: metastatic→cis +/-pemetrexed. Pem imrpvoed MS 9→12m

Technique
- Hemithoracic RT 4-8 wks postop to 54 Gy
- Contralateral lung V20<7%, V5<50%, mean <8.5Gy
- Heart V40Gy<50%

Hanson and Roach guidelines
- Stage I-II: extrapleural pneumonectomy (EPP)
  - With PORT (54 Gy)
  - Inoperable: neoadj chemo to shrink
- Stage III-IV: same

Breast

Ductal and Lobular Carcinoma In-situ[1-5,195-200]

General

- DCIS
  - 15-20% of all breast cancer
  - 1/3 progress to IDC at 10yrs
  - ~10% risk of IBTR for lump only
  - E-cadherin +
- LCIS
  - 25% risk of invasive cancer in either breast
  - Mammographically occult
  - E-cadherin – (indian file)
- Molecular subtypes (invasive disease)
  - Luminal A: +/+/--
  - Luminal B: +/+/+
  - Basal: --/--/--
  - Her2u: --/--/+

Workup

- H&P (GYN/cardiac history), breast exam, LN exam
- Bilateral diagnostic mammo, u/s, biopsy (hormone/Her2 staining), labs, CXR
- Breast MRI controversial (consider for young or BRCA+)
- T4, N2+ or symptoms: Bone scan & CT chest/abd/pelv, +/- PET, +/- MRI

Lumpectomy +/- RT

- NSABP B-17: lump +/- 50 Gy. At 12 yrs RT reduced LF 32→16%, same DM and OS
- EORTC 10853: lump +/- 50 Gy. At 10 yr RT reduced LRF 26→15%, same DM and OS
- Swedish: lump+/- 50 Gy. At 5 yr RT reduced LF 22→7%, same DM and OS
- UKCCR: lump then (50Gy, tamox, neither, both). All breast events 8, 18, 22, 6% respectively
- Metaanalysis of above: BCS +/-RT: HR 0.49, all subgroups benefit from RT without significant long-term toxicity

Tamoxifen

- NSABP B-24: lump +50Gy +/- Tamox(5yrs). 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 above

Technique

- Absolute contraindications to BCT (NCCN): pregnant, diffuse microcalcs, poor cosmesis expected, +margin
- Relative contraindications to BCT (NCCN): prior RT, connective tissue disease (scleroderma/lupus), tumors >5cm, focally +margin, BRCA+
- Supine, arms up, head turned slightly, vac lok
- Wire scar/drain and 2cm beyond breast tissue (medial midline)
- Iso at midpoint between med & lat wires
- Half-beam block at deep edge
- High tangents: top border 2cm below humerus
- Dose constraints for APBI
  - Contralateral Dmax ≤3 Gy
  - Ipsi lung V20<15%, V5 < 50%
  - Contra lung V5%<15%
  - Heart V20<5%, mean < 4 Gy
- NCCN dose guidelines
  - WBRT: 45-50 at 1.8-2/fx or 42.5 at 2.66/fx
  - WBRT boost recommended if <50 yo and G3 (10-16 Gy at 2Gy/fx)
  - 3field: 50-50.4 at 1.8-2/fx (+/- 10Gy boost)
  - APBI (experimental): 34/10 with brachy or 38.5/10 BID with photons

NCCN

- LCIS: surgical resection, then cancer risk reduction, no RT indicated
- DCIS
  - Lumpectomy (no ALND) + WBRT (cat 1)
    - Consider boost for margins <1mm
  - TM +/- SLNBx +/- reconstruction (altered lymph flow after TM)
  - Lumpectomy (no ALND) without WBRT (cat 2B)
  - (Tamoxifen x5 yrs if ER+)
- Exam and mammo annually x5 years

Early Stage Breast Cancer[1-5,200-216]

- **T1** - ≤ 2cm
  - T1mi - ≤ 0.1cm
  - T1a – > 0.1 and ≤ 0.5cm
  - T1b - > 0.5 and ≤ 1cm
  - T1c - > 1.0 and ≤ 2cm
- **T2** - > 2.0 and ≤ 5cm
-
- **T3** - > 5cm
- **T4** -
  - T4a – chest wall (not pec)
  - T4b – skin edema, ulceration
  - T4c – 4a + 4b
  - T4d - inflammatory

cN0	No nodes	**pN0**	No nodes
cN1	Mobile axillary 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
cN2b	IM nodes only	**pN2b**	Clinical IM nodes only
cN3a	Infraclav nodes (ax level III)	**pN3a**	10+ axillary or any infraclav
cN3b	IM + axillary nodes	**pN3b**	IM + axillary nodes
cN3c	Supraclav	**pN3c**	Supraclav

	T1	**T2**	**T3**	**T4**
N0	**IA** **T1N1mi = IB**	**IIA**	**IIB**	**IIIB**
N1	**IIA**	**IIB**	**IIIA**	
N2	**IIIA**			
N3	**IIIC**			
M1	**IV**			

General
- Extensive intraductal component: ≥25% DCIS
- Tubular & Mucinous histologies are favorable

Surgery
- Lumpectomy > WLE > quadrantectomy (quad) > total (simple) mastectomy (TM) > MRM > Rad Mast (RM)
- NSABP B-**04**: If cN0: RM vs TM+RT vs MRM if pN+. If cN+: RM vs TM+RT. At 25 yr f/u, no difference in DFS or OS. Nodal treatment (by RT or LND) reduced LRF from 19% to **4%**
- SLNBx
  - NSABP B-32: ALND vs SLNBx (ALND if pos). SLNBx accuracy 97%, 9.8% false neg, NPV 96%
  - Kim 2006: metaanalysis of SLNBx. False neg rate 7.3%
  - Unaffected by neoadj chemo? (Buchholz 2008)

Mastectomy vs BCS
- NSABP B-06: stage I/II, <4cm, neg margins: TM vs lump vs lump+50Gy. At 20 yrs, same DFS, OS, and DMFS. RT decreased LF from 39→14%.
- EORTC 10801: stage I/II: MRM vs lump+50Gy+boost. At 10 yrs MRM reduced LF (20→12%) but same OS (65%). 48% in lumpectomy group had pos margins
- Milan I: T1N0, 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, ≤2.5cm. quad+ALND +/- 60Gy. At 10 yrs RT reduced LF (23.5→8%), same OS. All patients received systemic therapy
- Swedish Trial: ≤3cm. 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, pT1N0, ER+. Tamox +/- RT. RT improved 8yr LF (7→1%), but OS same
- NSABP B-21: pN0, ≤1cm. three arms (tamox vs RT vs both). At 8 yr LF 16.5%, 9.3% and 2.8% respectively, same OS

Timing
- JCRT Sequencing: stage I/II. chemoRT vs RTchemo. At 11 yrs, same OS, DM etc. For close margins (<1mm) 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: <3cm. lump+ALND+50Gy +/- 10Gy boost. At 3 yrs boost improved LF 4.5→3.6%. cosmesis unchanged

Hypofractionation
- Whelan (Canadian): 50/25 vs 42.5/16. No boost, no >25cm separation.10 yr LR unchanged (~6.4%), cosmesis good
- 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. Same findings as START A. Less adverse effects with hypofrac.
- RMH/GO3: similar doses to START A. showed that 42.9/13 had lowest IBTR

NCCN
- ≤T3, ≤N1
  - Lumpectomy with aSLNBx
    - chemo 1st if (>1cm, pN+)
    - (pN0) WBRT +/-boost
    - (pN+) 3field +/- boost
    - (pT1N0, 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

ASTRO APBI Criteria (2009)[2,217]			
	"suitable"	**"cautionary"**	**"unsuitable"**
Age	≥60 y	50-59 y	<50 y
BRCA1/2	Not present		Present
Tumor size	≤2 cm	2.1-3.0 cm	>3 cm
T stage	T1	T0 or T2	T3 or T4
Margins	Negative by ≥2 mm	Close (<2 mm)	Positive
Grade	Any		
LVSI	No	Limited/focal	Extensive
ER status	Positive	Negative	
Multicentricity	Unicentric only		Multicentric
Multifocality	Clinically unifocal, total size ≤2.0 cm Microscopic multifocality allowed, provided the lesion is clinically unifocal (by PE and MMG/US) and total lesion size (including intervening normal breast parenchyma) is ≤2.0 cm	Clinically unifocal, total size 2.1-3.0 cm Microscopic multifocality allowed, provided the lesion is clinically unifocal and total lesion size is 2.1-3.0 cm cm	Clinically multifocal or microscopically multifocal >3 cm in total size
Histology	Invasive ductal or other favorable subtypes	Invasive lobular	
Pure DCIS	Not allowed	≤3 cm	>3 cm
EIC	Not allowed	≤3 cm	>3 cm
Associated LCIS	Allowed		
N stage	pN0(i^-,i^+)		pN1, pN2, pN3
Nodal surgery	SN Bx or ALND		None performed
Neoadjuvant therapy	Not allowed		If used

Locally Advanced Breast Cancer[1-5,218-230]

General
- Inflammatory: rapid erythema, warmth, edema
- Risk of IMN+
  - 5% of tumors have IMN as sentinel node
  - 10% if Ax node neg
  - 20-50% if Ax node pos

Workup
- Staging above
- See above, include bone scan, CT chest/abd/pelv, +/-PET-CT, MRI brain

Chemotherapy
- Agents
  - CMF: cyclophosphamide, methotrexate, 5FU
  - FAC: 5FU, Adriamycin, cyclophosphamide
  - AC: Adriamycin, cyclophosphamide
  - ACT: AC then paclitaxel
  - TAC: docetaxel (taxotere), Adriamycin, cyclophosphamide
  - FEC: 5FU, epirubicin, cyclophosphamide
  - TC: docetaxel (taxotere), cyclophosphamide
  - Trastuzumab: monocolonal antibody for HER2/neu
  - Tamoxifen: SERM, hot flashes, ↑thromboembolic dz, ↑uterine cancer
  - Anastrozole, letrozole: Aromatase inhibitors, postmenopausal pts only
- EBCTCG chemo/HT: metaanalysis, 6m 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)
- NSABP B-28: LN+ pts randomized to AC vs ACT. Taxane improved 5 yr DFS 72→76%
- CALGB 9741: showed that dose dense ACT improved 4 yr DFS 75→82%
- NSABP B-18: preop vs postop AC x4c. 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%)
- NSABP B-31: HER2+ pts: ACT vs ACT+H. Herceptin improved 3 yr DFS (75→87%) and OS (92→94%)
- NSABP B-14: ER+ pts: Tamox x5 yrs vs placebo. Tamox improved 15 yr DFS and OS
- ATAC Trial: ER+/- postmen pts: anastrozole, tamox, or both. AI improved DFS over tamox (89 vs 87%), both was 87%, but only for ER+ pts

Post-Mastectomy RT
- Danish 82b: premenopausal. MRM+CMF +/- RT. At 10 yrs PMRT improved LRF (32→9%), DFS (34→48%), and OS (45→54%). Improvements regardless of tumor size of #LNs. (mean 7 LNs excised). +IMN RT
- Danish 82c: postmenopausal. MRM+tamox +/- RT. At 10 yrs PMRT improved LRF (35→8%), DFS (24→36%), and OS (36→45%). No benefit for N0 patients. +IMN RT
- British Columbia trail: premenopausal. MRM+CMF +/-RT. At 20 yrs PMRT improved LRF (26→10%) and OS (37→47%). (mean 11 LNs excised). +IMN RT
- EBCTCG metaanalysis: 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

Axillary dissection
- ACOSOG Z0011:T1-2, cN0, SLNBx+ (1 or 2 SLN by H&E). lumpectomy with neg margins +/- ALND. All got PORT (tangents). 97% got systemic therapy (HT or chemo). 5 yr regional control same (99+%), OS same (92%). Radiation field design varied widely (some included nodal RT).

Technique
- Iso at midaxillary line, 4cm deep
- Half beam block deep and superior borders
- If long breasted, kick couch away on tangents
- 15° oblique off cord on supraclav field
- Bolus?

NCCN
- T4+, N2+
  - Neoadj chemo → MRM → 3f RT
  - Consider for Herceptin/HT
- Inflammatory breast cancer
  - same

Gastrointestinal

Esophageal Cancer[1-5,231-241]

- **T1**
  - T1a – into lamina propria or muscular mucosae
  - T1b – into submucosa
- **T2** – muscularis propria
- **T3** - adventitia
- **T4** – adj structures
  - T4a – pleura, pericardium, diaphragm
  - T4b – aorta, vertebrae, trachea

- **N1** – 1-2 nodes
- **N2** – 3-6 nodes
- **N3** – 7+ nodes

Overview
- 16,500 cases/yr, 14,200 deaths/yr
- Risk factors: tobacco, ETOH, nitrosamines, Plummer Vinson syndrome, achalasia, GERD
- Anatomy
  - Cervical: cricoid to thoracic inlet (15-18cm)
  - Upper thoracic: to carina (18-24cm)
  - Midthoracic: to GE junction (24-32cm)
  - Low thoracic: GE junction (32-40cm)
- Workup: H&P, supraclav, labs, EGD, EUS, bronch, PFTs, PET-CT

Surgical Techniques
- Endoscopic mucosal resection
  - No ulceration, T1N0, no LVSI, <2cm, G1-2
  - 98% OS (Ell 2007)
- Transhiatal esophagectomy: no thoracotomy, pull up. Difficult LN dissection but better tolerated
- Ivor-Lewis (right thoracotomy): good exposure, risk mediastinitis
- Left thoracotomy: good for lower 3rd resections
- Optimum # nodes = 23 (Peyre 2008)
- Surgery alone ~20% three year OS

Preop Chemo
- RTOG 8911: T1-2Nx → surgery +/- preop cis5FU. Same OS, 2.5% pCR
- MAGIC trial: T1-3N0-1 gastric/GE/loweresophagus→ surgery +/- periop epirubicin, cisplatin, 5FU. Chemo improved 5 yr OS (23→36%)

Preop CRT
- Gebski 2007: metanalysis with 1209 pts. Preop CRT improves OS compared to surgery alone
- EORTC (Bosset): T1-3N0 or T1-2N1, SCC only→ surgery +/- preopCRT (cis x2c with 37/10 split course). pCR 26%, same OS (18m)
- CALGB 9781 (Tepper): T1-3N1→surgery +/-preop CRT (cis5FU with 50.4Gy). CRT ↑5yr OS (16→39%). 40% pCR
- Burmeister 2006: T1-2N0-1→surgery +/-preop CRT (cis5FU with 35/15). Same DFS and OS (35%). 13% pCR
- Stahl 2009: T3-4NX adeno→ neoadj chemo +/- RT (30/15). All got surgery. Closed early but CRT had better pCR (2→15.6%), and trended better OS (28→47%)
- CROSS: 368 pts (75% adeno)→surgery +/-preop CRT. 41.4 Gy in 23 fx with carbo/taxol. CRT ↑OS (24m→49.4m).
  - ↑R0 resection with CRT (69→92%)
  - pCRT 23% adeno and 49% SCC

Definitive CRT
- RTOG 8501: T1-3N0-1→RT (64 Gy) vs CRT (cis5FU with 50 Gy). CRT improved 5 yr OS (0→27%)
- INT0123 (RTOG 9405): T1-4N0-1→CRT to 50 Gy vs 65 Gy. Stopped early because of ↑death (2→10%)
- Stahl 2008: T3-4N0-1 SCC→ chemo x 3c → RT alone (64/32) vs RT+surgery (40/20). Surgery improved LC but CRT had less treatment related mortality (13→4%)

Technique
- Generally Sim supine, arms up, PO contrast
  - Cervical eso: supraclav, neck nodes
  - Upper thoracic: include SCV and mediastinal nodes
  - Mid thoracic: paraesophageal nodes
  - Low thoracic: consider gastric nodes, celiac axis
- CTV: tumor +3-4cm up/down and 1cm radially
- Boost same but 2cm up/down
- Dose limitations
  - cord, liver, kidneys,
  - Lung V5<50%, V10<40%, V20<20%
  - Heart V40<30%

NCCN
- Tis-T1a: EMR vs esophagectomy
- T1bN0: esophagectomy (postop CRT if R1, R2, or N+)
- T2-T4a or N+
  - Preop CRT (41.4-50.4)
  - Defin CRT if cervical or decline surg (50-50.4)
    - then PET/EGD. Can observe if cCR and SCC
  - Esophagectomy (if low risk tumor)
- T4b: defin CRT (50-50.4)

Gastric Cancer[1-5,234,242-250]

- **T1**
  - T1a – into lamina propria or muscular mucosae
  - T1b – into submucosa
- **T2** – muscularis propria
- **T3** – subserosa
- **T4**
  - T4a – serosa
  - T4b – adj structures

	T1	T2	T3	T4a	T4b
N0	IA	IB	IIA	IIB	IIIB
N1	IB	IIA	IIB	IIIA	
N2	IIA	IIB	IIIA	IIIB	IIIC
N3	IIB	IIIA	IIIB	IIIC	IIIC
M1	IV				

- **N1** – 1-2 nodes
- **N2** – 3-6 nodes
- **N3** – 7+ nodes
  - N3a – 7-15 nodes
  - N3b – 16+ nodes

Overview
- 22,700 cases/yr, 12,000 deaths/yr
- Risk factors: salt, nitrates, H pylori, pernicious anemia
- 22.1% HER2 positive
- Anatomy
  - GEJ, fundus: 35%, diffuse
  - Body: 25%
  - Antrum: 40%, intestinal
  - LN groups: perigastric, gastroduodenal, Pas, celiac, portahepatic, suprapancreatic, splenic, +/- paraesophageal
- Workup: H&P, nodal eval, labs, CEA, Hpylori
- EGD, EUS, bx, PET
- PEG tube?

Surgery
- Aim for >3cm margins, ≥15 LNs
- D0: no nodes
- D1: perigastric nodes
- D2: D1+ left gastric, hepatic, celiac and splenic nodes
- D3: D2 + hepatoduodenal, peripancreatic, portocaval, PA nodes, middle colic
- Gouzi 1989: subtotal vs total gastrectomy: no difference
- Dutch trial: D1 vs D2. D2 had more complications/deaths. Same 11 yr OS, but the 15 yr data showed D2 ↑CSS (37→48%)
- MRC trial: D1 vs D2. Same 5 yr OS, more tox with D2
- JCOG trial: D2 vs D2+Pas. Same as Dutch
- Taiwanese trial: D1 vs D3. D3 improved 5 yr OS (54→60%). No adj chemo or RT

Preop Chemo and RT
- MAGIC Trial: mostly stomach, but some GEJ/eso→ surgery +/- pre/postop chemo (ECF). pCR rate 0%. Chemo improved downstaging, R0, OS (23→36%)
- RTOG 9904: phase II: preop CRT (45 Gy with 5FU+taxol). pCR 26%,

Postop CRT
- Macdonald 2009 (INT 0116): 556 pts, surgery +/- CRT. 54% D0 resection. Chemo was 5FU, leucovorin. RT was 45/25. CRT improved DFS and OS (HR 1.32).
- Kim 2005: retrospective. 990 pts with D2 +/-CRT. 5 yr OS improved with CRT (51→57%)
- CALGB 80101: surgery→ (5FU + 45 Gy) vs (ECF +45 Gy). Given as chemo→CRT→chemo sandwhich. 3 yr data show similar outcomes.

Metastatic
- ToGA trial: metastatic gastric, cis/5FU +/- trastuzumab. Improved median OS (11→13.5m)

Technique
- Fast for 3 hrs before sim
- Supine, arms up, IV contrast, oral contrast, 4D?
- CTVp: residual dz + remaining stomach + anastomosis, 3-5cm margin
- CTVn
  - Always: perigastrics
  - T4 or N+: celiac, suprapancreatic, portahepatic, splenic
  - Consider paraesophagealand splenic for high tumors
- Heart V40<30%
- Liver V30<60% mean <25Gy
- At least 2/3 one kidney <20 Gy

NCCN
- Tis-1aN0: endoscopic resection or gastrectomy alone
- T1b: surgery alone
- T2+ or N+
  - preop chemo +/-RT
  - surgery then CRT (sandwhich C→CRT→C)
    - could obs pT2N0 with R0 resection
    - could chemo only after D2
    - Dose is 45-50.4 Gy (1.8/fx)
- Unresectable: 5FU based CRT

Pancreatic Cancer[1-5,251-266]

- **T1** - ≤2cm
- **T2** - >2cm
- **T3** - beyond pancreas
- **T4** – involves SMA or celiac
- **N1** – nodes

	T1	T2	T3	T4
N0	IA	IB	IIA	III
N1	IIB			
M1	IV			

CRITERIA DEFINING RESECTABILITY STATUS[1]

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis, SMA, or common hepatic artery).	No tumor contact with the SMV or PV or ≤180° contact without vein contour irregularity
Borderline Resectable[2]	Pancreatic head /uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Presence of variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery [some members prefer this criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the IVC
Unresectable[2]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

Overview
- 45,000 cases/yr, 35,000 deaths/yr in US
- Risk factors: tobacco, dietary fat, RT, chemo
- 1st echelon LNs: pancreaticoduodenal, suprapancreatic, pyloric, pancreaticosplenic
- 50% are M1 at diagnosis
- Workup: H&P, jaundice, DRE, LFTs, CA19-9
- EGD, EUS, ERCP, bx, stent?, CT C/A/P, +/-MRI

Surgery
- For head lesions: pancreaticoduodenectomy (classic or pylorus-sparing): ~4% mortality (Pancreaticojejunostomy, Choledochojejunostomy, Gastrojejunostomy)
- No benefit to extended LND (Riall 2005)

Pro-Postop RT
- GITSG 9173: 43 pts. Surgery → CRT (5FU + 40 Gy split). CRT improved OS (5→14%).
- Mayo Clinic (2008): retrospective, 472 pts. T1-3N0-1 with R0 resection. Patients who got 5FU+50.4 Gy did better than observation (MS 19→25m)
- Johns Hopkins (2008): same as mayo clinic
- Hazard 2007: SEER analysis. RT→ ↑OS (12→17m MS). No benefit for T1-2N0
- RTOG 9704: 451 pts→GTR→CRT sandwich. Gem/5FU/Gem vs 5FU/5FU/5FU. RT was 50.4 Gy. Gem was Qwk. Gem arm trended toward 3 yr ↑OS (22→31%). ~75% of pts failed distantly first
- EORTC 40891: surgery +/- CRT (5FU + 40Gy split). Same 10 yr OS (18%). Included periampullary. For pancreatic tumors OS was improved (10→20%)

Anti-Postop RT
- ESPAC-1: surgery→2x2 (+/-5FU, +/-40Gy split). Chemo ↑OS (14→19m), but CRT worsened 5 yr OS (20→10%). Included periampullary cancers
- Stocken 2005: metaanalysis, 875 pts, chemo improved MS (14→19m), but not CRT (~15m). RT improved outcomes for positive margins

Chemo trials
- CONKO-001: 368pts→R0 or R1 +/- gemcitabine x6c. Gem → ↑DFS (6.9→13.4m) but not OS (~21m). No RT
- ESPAC-3: 5FU vs gem. No RT. Same MS (~23m)
- Krishnan 2007: retrospective. Induction chemo → CRT had longer MS then upfront CRT (8→12m)
- Conroy 2011: FOLFIRINOX > gem
- VonHoff 2013: gem+abraxane > gem

Unresectable
- GITSG: 40Gy+5FU vs 60Gy+5FU vs 60Gy. First two were split course but CRT improved MS (22→42m)
- RTOG 9812: phase II: 50.4Gy + paclitaxel. MS was 11m
- Tempero 2003: big bolus vs small bolus gemcitabine. Slow infusion ↑OS (5→8m)
- French FFCD: phase III. gem +/- RT with 5FU. CRT had worse survival (13→8.6m)
- ECOG 4201: close early. 71 pts→ gem +/- RT. CRT improved 2yr OS (4→12%), but more toxicity
- LAP-07: gem +/- erlotinib. If response then chemo vs CRT (54Gy with xeloda). CRT provided no OS benefit (OS ~15m)

Technique
- Sim supine, arms up, +IV and PO contrast
- Intact
  - GTV + 2-3cm
  - cover pancreaticoduodenal, suprapancreatic, celiac, porta hepatis, duodenal loop (splenic for tail tumors)
- Postop
  - Peripancreatic nodes, anastomoses, tumor bed
  - Postop nodal beds +1cm
- Tolerances
  - Kidney V18 <50%
  - Bowel/stomach max 55 Gy, V50<10%
  - Liver mean <30 Gy

NCCN
- Resectable
  - resection→ gem or 5FU or sandwich with RT
  - 45-46 Gy (1.8-2/fx) + 5-9 Gy boost
- Borderline
  - Neoadj chemo(FOLFIRINOX or gem/abraxane) +/-RT
  - Resection (cat 2b) follow above
- Unresectable
  - FOLFIRINOX or gem+/-abraxane or 5FU
    - RT after "adequate course of chemo"
    - 45-54 Gy (1.8-2.5/fx) or 36 Gy (2.4/fx)

Hepatocellular Carcinoma[1-5,267-275]

- **T1** – single tumor, no vascular invasion
- **T2** – single + vascular invasion or multiple tumors
- **T3**
  - T3a – >5cm
  - T3b – into portal/hepatic vein
- **T4** – adj organs or visceral peritoneum

- **N1** – nodes

	T1	T2	T3a	T3b	T4
N0	**I**	**II**	**IIIA**	**IIIB**	**IIIC**
N1	**IVA**				
M1	**IVB**				

Overview
- 22,000 cases/yr, 17,000 deaths/yr
- Assoc with cirrhosis, hepB, hepC, aflatoxin B
- Cirrhosis or HepB+ → annual screening u/s and AFP
- Workup: labs, LFTs, AFP, hep panels, ultrasound
- Triphasic liver CT or MRI, chest CT
- No need to biopsy if >1cm and classic on 2 modalities

Surgery
- Partial hepatectomy: 5 yr OS ~40%
- Transplant: 5 yr OS ~70%
- Lau 2008: surgery + 131I- lipiodol→↑OS

IR procedures
- RFA: better for deep tumors <3cm
- Cryoablation: can treat up to 6cm (not in US)
- ETOH injection (not in US)
- TACE: 50% response but no ↑OS

Sorafenib
- TKI against c-rad and PDGF-α
- Llovet 2008: advanced HCC→ sorafenib vs placebo. Sorafenib ↑OS (7.9→10.7m)

SBRT
- Traditionally was 50+ Gy (2 Gy/fx) 3D or IMRT
- Tse 2008: 41 pts median 36 Gy in 6 fx. Median OS 11.7m
- Rusthoven 2009: 60Gy in 3 fx. 2 yr LC 92%, OS 30%. Maintained 700cc liver <15 Gy
- Bujold 2013: 102 pts, median 36/6, OS 17m, LC 87%, 30% grade 3+ tox
- Dawson 2012: phase I suggests sorafenib ↑RT tox
- Technique:
  - Gated sim with contrast
  - CTV: GTV+1cm

Whole Liver RT
- Russell 1993: 1.5 Gy BID dose escalation. Recommended dose of 30Gy
- Hanson recommends 21 Gy in 7 fx
- Soliman 2013: phase II of 8 Gy x1 to whole liver, improved QOL, 48% had ↓symptoms at 1month
- Technique:
  - Gated sim with contrast
  - CTV: GTV+1cm

Radioembolization
- Y90: 50-80% response

NCCN
- Resect if feasible
- If not: ablation or TACE (SBRT is cat 2B)
- UNOS criteria for transplant: one tumor <5cm or 2-3 tumors <3cm each, no vascular involvement, N0M0
- Avoid Y90 if bili < 2mg/dL or CP class C

Colorectal Cancer[1-5,276-286]

- **T1** - submucosa
- **T2** – muscularis propria
- **T3** – pericolorectal tissues
- **T4** -
  - T4a – visceral peritoneum
  - T4b – adj organs

- **N1**
  - N1a – 1 node
  - N1b – 2-3 nodes
  - N1c – tumor deposits
- **N2**
  - N2a – 4-6 nodes
  - N2b – 7+ nodes

- **M1a** – one organ
- **M1b** – multiple organs

	T1	T2	T3	T4a	T4b
N0	I		IIA	IIB	IIC
N1	IIIA		IIIB		IIIC
N2a	IIIA	IIIB		IIIC	
N2b	IIIB		IIIC		
M1	IV				

Overview
- 110,000 colon cancer/yr, 41,000 rectal cancer/yr
- Screening: ≥50 yr colonoscopy Q10yrs
- FAP: APC gene, HNPCC: DNA mismatch
- Rectum: rectosigmoid (S3) to 2cm prox to dentate line
- Workup: H&P, DRE, pelvic, labs (CEA), colonoscopy, bx
- CT C/A/P, Ultrasound +/- MRI

Transanal Excision
- Criteria: T1, within 8cm from anal verge, mobile, <30% circumference, <3cm tumor, >3mm margin, grade 1-2, N0, no LVSI, no PNI, reliable pt
  - Data supporting this approach: CALGB 89-84: 10yr LF 8%.....RTOG 89-02: 5yr LF 4%
- Adj CRT or completion APR/LAR if doesn't meet criteria

Adj Chemo
- NSABP R-01: Dukes B&C pts→ obs vs MOF chemo vs 46 Gy. Chemo improved DFS and OS, RT → ↑LRC
- GITSG 7175: surgery→ obs vs chemo vs RT vs CRT (2x2). CRT improved OS 10 yrs (45 vs 27%) and LRR
- Intergroup/NCCTG 794751: stage II-III postop→ RT alone vs CRT. CRT improved OS (55 vs 45%), DM, and LR, but had worse toxicity

Preop RT
- Swedish: surgery +/- preop 25/5. RT ↑OS (38 vs 30%), CSS and LRR (9 vs 26%). TME was not used
- Dutch TME trial: TME +/- preop 25/5. No OS benefit, but RT ↓LRR (5.6 vs 10.9%). No chemo

Preop CRT
- Swedish Uppsala: 25/5 preop vs 60 Gy postop (split course). No OS difference, but preop ↓LR (13 vs 22%)
- German: T3+ or N+→ preop 50.4+5FU (1000mg x2c) vs postop 55.8+5FU (1000mg x2c). All pts got postop 5FU (500mg/m2/day x 4c). Preop CRT won, but only 54% of adj pts got full dose
  - Same 5 yr OS (~75%)
  - LR: 13→6%, pCR: 8%
  - Sphincter-preservation: 19→39%
  - Acute tox: 40→27%, Late tox: 24→14%
  - 18% overtreated
- NSABP R-03: T3+ or N+. same design as GRCT, but poor accrual. Trend toward ↑OS with neoadj. pCR in 15%
- French 9203: preop RT vs preop CRT (5FU). CRT had worse tox, but ↓5yr LR (16.5→8.1%) and →pCR (3.6→11.4%). Same OS
- EORTC 22921:+/-chemo, +/-RT. Showed that CRT improves LC but not OS compared to RT alone
- NSABP R-04: 5FU vs capectiabine: no difference. Adding oxaliplatin only worsened tox

Colon Cancer
- Intergroup 0130: T4 or T3N1-2 of colon→ adj chemo or adj CRT. No difference in 5 yr OS or DFS and tox worse. Only accrued 222/700 pts

Technique
- Prone, bellow board, PO contrast, full bladder, (wire scar and include if postop)
- 3-4 fields
  - Sup: L5/S1
  - Inf: 3cm below tumor of below obturator foramen
  - Lateral: 2cm outside pelvic brim
  - Post: entire sacrum and presacral space
  - Ant: T3 (post to pub symph), T4 (ant to pub symph, but ensure 3cm margin on tumor)
- Boost GTV +2-3cm
- 45 Gy WPRT + 5.4 Gy boost if preop
- Up to 54 if postop

NCCN
- Colon
  - consider pre or postop RT for T4 or pos margins
  - 45-50 Gy with 5FU
- Rectal
  - T1N0: transanal vs APR/LAR
    - If high risk, then TME and postop CRT if T3+ or N+
    - High risk: T2, +margin, LVSI, G3
  - T3+ or N+: neoadj CRT, then TME, then adj chemo
    - 50.4 Gy with xeloda

Anal Cancer[1-5,287-297]

- **T1** - ≤2cm
- **T2** – 2-5cm
- **T3** - >5cm
- **T4** – adj organ

- **N1** – perirectal nodes
- **N2** – unilat internal iliac, unilat inguinal
- **N3** – perirectal+inguinal, BL internal iliac, BL inguinal

	T1	T2	T3	T4
N0	**I**	**II**		**IIIA**
N1	**IIIA**			**IIIB**
N2	**IIIB**			
N3				
M1	**IV**			

Overview
- 7000 cases/year
- HPV associated (16, 18), AIDS assoc
- 33% are N+, but only 50% of cN+ are pN+
- Anatomy: anal canal is 3-4cm long, from anal verge to anorectal ring. Dentate line divides histology
- Anal margin: 5cm ring around anus, treat like skin cancer
- Above dentate drains to rectal nodes. Below drains to inguinals
- Workup: H&P, GYN exam, DRE, labs, HIV, PET-CT, +/- MRI, anoscopy
- Mitomycin C: hypoxic cell radiosensitizer
- 5FU: 1000mg/m2/day continuous infusion
- mitoC: 10mg/m2 bolus on days 1 and 29
- capecitabine: 825mg/m2 BID mon-fri

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 T1N0, 100% LC

RT vs CRT
- Nigro 1974: 30/15 + 5FU+mitoC then surgery for some. 71% pCR. Same control with or without APR (~80%)
- ACT I: 45Gy+boost +/- 5FU+mitoC. Split course RT. CRT improved LC (36→59%) but not OS.
- ACT II: 50.4Gy with 5FU + mitoC vs cisplatin. No difference
- EORTC trial: same as ACT I
- RTOG 8704: 45Gy with 5FU +/- mitoC. MitoC improved CR rate (85→92%), and ↓colostomy rate, but same OS
- CALGB 9281: neoadj chemo trial, no clear benefit. Showed 70% OS and 70% sphincter preservation
- RTOG 9811: 5FU + cis with induction vs 5FU + mitoC without induction.5 yr OS with mitoC better (71→78%). Same toxicity
- Gylnne-Jones 2008: phase II data of capecitabine instead of 5FU. Good results

RT technique
- Salama 2007: 53 pts s/p chemoIMRT. Favorable results
- RTOG 0529: phase II of dose painted IMRT. Less heme, GI, and derm toxicity
  - T2N0
    - PTVA (primary): 50.4/28
    - PTV42 (all nodal regions): 42/28
  - T3-4N0
    - PTVA: 54/30
    - PTV45: 45/30
  - N+
    - PTVA: 54/30
    - PTV54 (nodes >3cm): 54/30
    - PTV50 (nodes <3cm): 50.4/30
    - PTV45: 45/30

Technique
- IMRT to cover primary, inguinals, internal/external iliacs (from L5/S1 to inf border of lesser trochanter)
- 3cm margin on primary, 1-2cm margin on nodes
- Doses below
- Constraints
  - Small bowel max 54 Gy, V30<200cc
  - Vulva/penis: 25 Gy max, V20<50%
- Counsel vaginal dilator
- No benefit to routine posttreatment biopsy (Cummings 1991). Continues to regress for up to 12 months

NCCN
- RT + 5FU/MitoC for any M0 disease. Or can use xeloda
  - 30.6 Gy/17fx then 14.4 Gy boost to the field below the SI joints (can treat cN0 nodes to 36 Gy)
  - Min dose of 45 Gy to primary, at least 2.5cm margin
  - T3/4 or N+ needs 54-59 Gy total dose
  - Include inguinals, anus, perineum from L5/S1
- Anal margin: can excise, skin cancer reccomendations

Genitourinary

Low Risk Prostate Cancer[1-5,298-304]

- **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: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

- **N1** – pelvic, hypogastric, obturator, iliac (internal, external), sacral

- **M1a** - non-regional lymph nodes
- **M1b** - bone
- **M1c** - other sites

Group	I	IIA	IIB	III	IV
T	1-2a	2b	2c	3	4
GS	<7	7	>7	-	-
PSA	<10	10-20	≥20	-	-
N,M	-	-	-	-	N1, M1
10yr bPFS	90%	85%	60%	30-50%	<20%

Overview
- 230,000 cases, 27,000 deaths annually
- Zones: Peripheral (2/3 cancers), Transitional (BPH), Central, Anterior fibromuscular stroma
- PSA velocity: ≥2ng/ml/yr →↑GS7
- PSA density (PSA/gland volume): >7% → ↑risk
- Free PSA <25% → ↑cancer
- Screening: 50 y/o, DRE & PSA, debated
  - 1,400 screened→ 48 cancers → 1 death prevented
- Work up: DRE, PSA, Alk Phos, CBC, BMP, LFTs,
- Active Surveillance: biannual DRE/PSA, annual Bx (25% will end up getting treated)

EBRT
- 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% 5yr FFS (51% if <72Gy)

Dose escalation trials: (↑ bPFS ~20%, no change in OS)
- PROG 9509: low risk; 50.4 then proton boost to 70.2 vs 79.2 GyE; 10yr bFail: 32→17%
- MDACC: mixed risk; 70 vs 78 Gy; 8yr FFF 59→78%; CSS (97%) and OS (78%) unchanged
- Netherlands: 68 vs 78 Gy; 7yr bPFS 45→56%
- MRC: 64 vs 74 Gy, 5yr bPFS 60→71%
- GETUG: 70 vs 80 Gy; 5yr PSA failure 31→24%

EBRT Dose constraints

Rectum		Bladder	
V75	15%	V80	15%
V70	20%	V75	25%
V65	30%	V70	35%
V50	50%	V65	50%
Bowel V45<195cc		Femur V50<5%	

Brachytherapy
- ^{103}Pd: 17d, 21keV, EC, 125 Gy mono, 100 Gy w/ EBRT
- ^{125}I: 60d, 28keV, EC, 145 Gy mono, 110 w/ EBRT
- ^{192}Ir: 74d, 3.8MeV (~13.5 Gy x2 or 10.5 Gy x3 mono, 15 Gy x1 or 9.5 Gy x2 w/ EBRT)
- Relative contraindications: Prev RT or TURP, int/high risk, SVI, pub arch interference, median lobe, >60cc gland, AUA>15, DM (add EBRT for T2c, GS7 or PSA>10)
- GS 7 can get LDR monotherapy if all this: 3+4, PSA<10, ≤4/12 cores, ≤T2a, ≤50% each core, between 20-65cc gland
- 5mm TRUS slices, 5mm PTV expansion (3mm ant, 0mm post)

LDR PTV		Urethra	
D90	**>105%**		
V100	>95%	V125	<50%
V150	<70%	V150	0%
V200	<40%	V200	0%
Rectum V100%<1cc			

- Post implant dosimetry
- Post-brachy obstruction risk ≈ AUA score (%)

Toxicity
- RP: ED, incontinence, stricture (50% potent, 75% continent)
- RT: urinary freq, proctitis (50% potent, ≤1% late GI/GU)

NCCN Guidelines
- 75.6-79.2 Gy @ 2/fx (up to 81 Gy for int/high risk)
- No nodes/ADT for low risk

Intermediate/High Risk Prostate Cancer[1-5,303,305-317]

- Consider CT abd/pelv, bone scan, +/- pelvic MRI

- **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%

- **ADT +/- RT**
  - Scandanavian (SPCG-7): int/high risk; 3m ADT +/- 70 Gy; 10yr OS 61→70%, CSS 76→88%

- **Int risk RT +/- ADT: most improve OS 5-10%**
  - RTOG 8610: high risk; 70 Gy +/- 4m ADT; 10 yr CSS 64→77%, ↓DM, ↑OS trend
  - RTOG 9408: int risk; 68 Gy +/- 4m ADT; 12 yr OS 51→56%
  - D-Amico: mostly int risk; 70 Gy +/- 6m ADT; 8 yr OS 61→74%
  - TTROG 96.01: mostly high risk; 66 Gy +/- ADT (0m, 3m, 6m); DFS 32→49→52%, ↑OS with ADT
  - Crook: mixed risk: 66 Gy + ADT (3m vs 6m); no differences (longer better for high risk)
  - RTOG 9413: int/high risk, 2x2 (+/- WP, neoadj/adj ADT): mixed data, no clear result

- **High risk RT +/- ADT: improves OS**
  - RTOG 8531: WP RT; 70 Gy +/- indefinite goserelin; 10yr OS 39→49%
  - EORTC 22863: WP RT; 70 Gy +/- 3yr goserelin; 10yr OS 32→42%
  - Duration of ADT
    - RTOG 9202: WP RT; ~70Gy + 2m vs 2yr ADT; OS 32→45%
    - EORTC 22961: WP RT; 70 Gy + 6m vs 3yr ADT; 5 yr OS 81→85%

- **Types of ADT**
  - Castration
  - GnRH agonists
    - Goserelin (Zoladex)
    - Leuprolide (Lupron)
    - Triptorelin (Trelstar)
  - Antiandrogens: bicalutamide (Casodex)
  - Non-steroidal antiandrogen: Flutamide
  - Estrogens
  - Ketoconazole: blocks P450
  - Degarelix: GnRH antagonist, no initial flare

- **Whole Pelvis RT?**
  - All failed to show a clear subgroup with benefit
  - RTOG 7706
  - RTOG 9413
  - GETUG-01

- **NCCN**
  - Up to 81 Gy permitted
  - +/- nodes
  - +/- 4-6 m ADT int risk
  - +/- 2-3 yrs ADT high risk
  - If brachy then +/- EBRT/ADT

Adjuvant/Salvage and Metastatic Prostate Cancer[1-5,313,318-323]

- **Adjuvant vs Salvage RT**
  - SWOG 8794: pT3N0 or +M; obs with salv RT vs adj RT; 15yr OS 37→47%, LF 22→8%
  - EORTC 22911: pT3N0 or +M; obs with salv RT vs adj RT; 5yr bPFS 53→74%, OS same
  - German ARO 9602: pT3N0 or +M; obs with salv RT vs adj RT; bPFS 54→72%, OS same
- **NCCN**
  - Postop dosing: 64-70 Gy @ 2Gy/fx
- **PSA Failure**
  - After RP: ≥0.2 ng/mL
  - 1996 ASTRO definition: 3 consecutive rises, then back-dated
  - 2005 Phoenix definition: rise of 2 ng/mL over nadir
  - PSA bounce: ↑2ng/mL ~12m out (~20% risk)
- **Salvage ADT?**
  - King (2004): Salvage RT +/- ADT; 5 yr OS 87→100%, bPFS 31→57%

- **Node Positive**
  - Messing Trial: pN+; RP +/- ADT; 12yr MS 11.3→13.0yrs
  - RTOG 8531: cN+; RT +/- ADT; 9yr OS 38→62%
  - Zangers trial: N+; ADT +/- 70 Gy; 10yr OS 46→67%

- **Metastatic**
  - 1st line: ADT
  - 2nd line: Docetaxel/Prednisone
    - SWOG 9916
    - TAX 327
  - ^{223}Ra (Alpharadin): bone only mets
    - 11.4d, alpha emitter, 5.8 MeV avg
    - 1000kBq/ml, Rx is 50kBq/kg Q4wks x 6 treatments
    - Requires
      - ANC ≥ 1.5 x10^9/L
      - PLT ≥ 100x10^9/L
      - Hgb ≥ 10 g/dL

Bladder Cancer[1-5,324-330]

- **Tis, Ta** – CIS, non-invasive, 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** - single LN below common iliac
- **N2** - multiple LNs below common iliac
- **N3** - common iliac LN

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%

	Ta,Tis	T1	T2	T3	T4a	T4b
N0	0a,0is	I	II	III	III	IV
N+	IV					

Overview
- Risk factors: smoking, dyes, irritation (foley)
- 93% TCC (5% SCC, 2% adenocarcinoma)
- 75% Ta, Tis, T1 at presentation
- Cystectomy: en block removal of bladder, perivesicular tissue, urethra, prostate (or uterus)

Workup
- H&P, labs, *UA, alk phos, urine cytology*
- Cystoscopy, biopsy, bladder mapping, EUA, TURBT
- Superficial: CT pelv + IVP
- Muscle invasive: CT chest/abd/pelv +/- MRI

Neoadjuvant chemo and RT
- Chemo metaanalysis 2003: 5% OS advantage at 5 yrs with multiagent cisplatin
- Cole 1995: MDACC: preop 50/25 vs no preop therapy 5 yr LC improved 72→91%, but nothing else

Bladder Preservation Data
- NCIC Coppin 1996: T2-4: preop RT +/- cisplatin. Chemo ↓LRF, but same OS
- RTOG 8512: T2-4N0-2: phase II: RT 40/20 +cisplatin then restage and 24/12 for CR. 67% CR, 5 yr OS 52%, LC 42%
- RTOG 8903: 123 pts 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 pts T2-4aNx: similar to prior. 3 yr OS 83%, 66% intact bladder, 45% Tis failure
- MGH Shipley 2002: same as RTOG 8903, 190 pts. 5 yr OS 54%, intact bladder 46%, hydronephrosis didn't matter
- RTOG 9906: same as others but BID RT and added paclitaxel concurrent and adjuvant gemcitabine. Same results.

Bladder Preservation Technique
- Maximal TURBT (to negative margin)
- Sim bladder empty
- 45 Gy to whole bladder + nodes with concurrent cisplatin or 5FU/mitomycinC
- Cystoscopy w/ biopsies and cytology (75% CR)
- Boost to 60-65 Gy if no tumor remaining (T0 and neg cytology)

NCCN
- Tis: BCG
- Ta: observation or TURBT +/-BCG
- T1: TURBT + BCG (upfront cystectomy for high grade)
- Stage II-III
  - Neoadjuvant chemo + radical cystectomy +/- adj chemo for pT3-4 or N+ (postop RT for +margin or pT3-4)
  - Bladder preservation as above (cat 2B)
    - Consider cystectomy if multifocal, cT3b-4, component of Tis, hydronephrosis, subtotal TURBT
- T4b or N+: chemo or CRT then surgery vs more RT

Renal Cell Cancer[1-5,331-335]

- **T1** - ≤ 7cm, 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)

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

Overview
- Genetic conditions: VHL, 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

Workup
- H&P, labs CT chest/abd/pelv +/- MRI

Select trials
- 4 randomized trials show no benefit to PORT (Rotterdam, Sweden, Fugitt, Kjaer)
- Stein 1992: 147 pts, PORT vs obs: in T3N0 pts, PORT won. LR 37%→10%.
- Escudier/AVOREN: stage IV RCC given IFα +/- Avastin. Avastin doubled PFS (5→10months)
- Escudier/TARGET: treatment resistant RCC +/- sorafenib. Sorafenib doubled PFS (2.8→5.5mo)
- Motzer, 2007: metastatic RCC: sunitinib vs IFα, sunitinib won

NCCN
- Local disease: surgery (no radiation)
- Metastatic disease: surgery (palliative nephrectomy), sunitinib (multi-TKI), temsirolimus, bevacizumab & IFN, interleukin-2, sorafenib (Multi-TKI)

Urethral Cancer[1-5,336-339]

- **Ta, Tis** - non-invasive papillary, polypoid, or verrucous carcinoma
- **T1** – supepithelial
- **T2** – spongiosum, prostate, periurethral muscle
- **T3** - cavernosum, EPE, ant vagina, bladder neck
- **T4** - adj organs (including bladder)

- **N1** – single, ≤2cm
- **N2** – >2cm or multiple

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

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

Male Early stage
- Surgery: MSKCC (Dalbagni 1999): Tis-T1, 10 pts, surgery only 5 yr DFS 83%
- RT: (Heysek 1985): 5 pts, LC in 4/5

Male Locally Advanced
- Surgery: MSKCC (Dalbagni 1999): T2-T4, 36 pts, 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: 50-60Gy brachy alone or EBRT (45Gy) + 20-25 Gy brachy

Concurrent chemo
- Only case reports, consider 5FU/mitoC, 5FU/cisplatin, carbo/taxol (Eng 2003)

NCCN
- Tis/Ta: TUR
- T1-2: surgery +/- PORT or chemoRT (66-70 Gy)
- T3-T4 or N+: chemoRT

Testicular Cancer[1-5,340-342]

- **T1** – testis, epididymis, no LVSI, no vaginalis
- **T2** – T1 + LVSI or vaginalis
- **T3** – spermatic cord
- **T4** – scrotum

- **N1** – N+, all ≤2cm (path ≤5 nodes)
- **N2** – N+, all 2-5cm (path >5 nodes or ECE)
- **N3** – N+, >5cm

- **M1a** – nonregional nodes or lung mets
- **M1b** – distant

	T1	T2	T3	T4	10 yr RFS
N0	**IA (S0)**	**IB (S0)**			98%
N1	**IIA (S0-1)**				92%
N2	**IIB (S0-1)**				86%
N3	**IIC (S0-1)**				70%
M1a	**IIIA (S0-1, any N)**				90% OS
S2	**IIIB**				
S3	**IIIC**				80% OS
M1b					
IS - Any T N0 M0 S1-3					

- **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

Overview
- Lymph flows to PA nodes (left vein drains to renal vein)
- 95% GCTs (seminomas/ NSGCTs)
- Seminoma: bHcG can be ↑ (15%) but NEVER AFP
- NSGCTs
  - embryonal carcinoma (most common)
  - yolk sac (↑AFP, Schiller Duval bodies)
  - choriocarcinoma (↑bHcG)
  - teratoma
  - mixed (60%)
- others
  - sertoli cell: ↑estrogen
  - leydig cell: ↑androgens
  - lymphomas, sarcomas
- Risk factors: cryptorchidism, first born, polyvinyl chloride, Downs, Klinefelter's, HIV
- bHcG half life: 24 hrs
- AFP half life: 5 days
- Workup: H&P, sperm banking?, bHcG, AFP, LDH, labs, CT abd/pelv +/- chest, +/-PET. Do not biopsy.

Stage I Seminoma
- RT field: MRC (Fossa 1999): stage I seminoma comparing dogleg vs PA only. 3 yr RFS/OS same (~98%) and PA better tolerated
- RT dose: MRC (Jones 2005): stage I seminoma, 20 /10 vs 30/15. Mostly PA only.5 yr RFS same (~97%)
- Chemo: MRC (Oliver 2005): carbo x 1c vs RT. RFS same (~95%). Relapse location varied but chemo better tolerated

Technique
- Sperm bank?
- Supine, clamshell other testicle, move penis
- PA: T11/12 to L5/S1, laterally through transverse process (2cm margin on nodes). For left sided tumors include left renal hilum)
- Dogleg: PA field but down to top of acetabulum
- 20/10, boost IIA nodes to 30 Gy, IIB nodes to 36 Gy
- Do not use IMRT
- 2cm margin on GTV nodes to block edge
- Dose limits
  - 50 cGy: transient azospermia
  - 2 Gy causes sterilization
  - 30% of patients are fertile after RT
  - Kidneys: D50%< 8 Gy

NCCN
- *All patients: radical transinguinal orchiectomy with high ligation of the spermatic cord (never biopsy), then repeat tumor markers*
- Adjuvant Seminoma
  - I: obs* (16% LRF) or 20 Gy PA or carboplatin
  - IIA: 20 Gy* (dogleg+boost GTV to 30) or cis/etop x4c
  - IIB: cis/etop* x4c or 20 Gy (dogleg+boost GTV to 36)
  - IIC-III: chemo (cis/etop +/- bleo)
- Adjuvant NSGCT: RT palliative only
  - I: obs (30% LRF) vs RP-LND (30% path +) vs cis/etop/bleo
  - Positive tumor markers after surgery → chemo
- Follow up depends on tx, but generally labs/CT Q3m for 2 years then Q6m for 2 years, then Qyear

Penile Cancer[1-5,343-348]

- Tis, Ta: CIS, noninvasive verrucous
- **T1**
  - T1a – subepithelial, no LVSI, no G3-4
  - T1b – subepithelial, +LVSI or G3-4
- **T2** – spongiosum or cavernosum
- **T3** – urethra
- **T4** – adj structures (inc prostate)

- **N1** – unilateral inguinal
- **N2** – multiple or bilateral inguinal
- **N3** – fixed or pelvic (ECE)

	Tis, Ta	T1a	T1b	T2	T3	T4
N0	**0**	**I**	**II**			**IV**
N1	**-**	**IIIA**				
N2	**-**	**IIIB**				
N3	**IV**					
M1						

Risk Group	Stage & Grade	LN (+)
Low	T1 G1	0%
Intermediate	T1 G2-3, T2 G1	33%
High	T2 G2-3, T3 G1-3	83%

Overview
- cN0→ 20% pN+
- cN+ → 30-50% pN0
- risk factors: uncircumcised, phimosis, poor hygiene, HPV 16, 18
- inguinal node borders:
  - superior: inguinal ligament
  - interior: fossa ovalis
  - lateral: sartorious
  - medially: adductor longus
- 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 5cm for sexual intercourse
- Need 3 cm to urinate standing

Early Stage EBRT
- Grabstald & Kelly (1980): 10 pts, stage I-II: 90 % LC
- McLean 1993: 26 pts, stage I-II: mostly 50/20: 5 yr DFS 50%

Early stage Brachy
- Crook 2005: 49 pts, T1-3, Ir-192 to 55-65 Gy. 5 yr LC 85%, OS 78%, penile preservation 86%
- Mazeron 1984: T1-3 Ir-192 to ~65Gy, LC 78%, penile preservation 74%

Locally Advanced
- Krieg 1981: 17 pts stage I-IV, surgery+/-LND +/-RT, but 88% of pts without nodal treatment failed in nodes
- Sarin 1997: 101 pts stage I-IV, mixed treatments, 10 yr OS 39%, LC 55%, validated use of RT with surgical salvage. 2 pts attempted suicide after penectomy

Technique
- Sim supine, foley, suspend penis, bolus, frog leg
- Tape up if treating pelvis
- Brachytherapy mold (tube loaded with Ir-192)
- Interstitial: 1cm spacing, Ir-192
- Dose limits:
  - Urethra 60 Gy
  - Testes 3 Gy

NCCN
- Tis: resection, imiquimod, topical 5FU
- T1-2:
  - partial vs radical penectomy (need 1-2cm margin)
    - inguinal node dissection if T1b+
    - pelvic dissection if ≥2 inguinal nodes
  - *Circumcision* with brachy (<4cm)
    - 65 Gy HDR interstitial (preferred)
    - 60 Gy mold
  - *Circumcision* with 65-70 Gy with 2cm margin
  - chemoRT (category 3)
- Locally advanced:
  - Neoadj chemo for N2+, >4cm 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)

Notes

Gynecologic

Cervical Cancer[1-5,349-355]

- **T1**
  - T1a (*IA*) – micro
    - T1a1 (***IA1***) – <3mm DOI, ≤7mm wide
    - T1a2 (***IA2***) – 3-5mm DOI, ≤7mm wide
  - T1b (*IB*) – macro
    - T1b1 (***IB1***) – ≤4cm
    - T1b2 (***IB2***) – >4cm
- **T2**
  - T2a (II) – upper 2/3 vagina
    - T2a1 (***IIA1***) – ≤4cm
    - T2a2 (***IIA2***) – >4cm
  - T2b (***IIB***) – parametium
- **T3**
  - T3a (***IIIA***) – lower 1/3 vagina
  - T3b (***IIIB***) – pelvic wall or hydro
- **T4** (***IVA***) – bladder or rectum

- **N1** – regional (up to common iliac)

- **M1** (***IVB***) - distant

Overview
- HPV types 16 and 18
- ASCUS: 2/3 resolve, repeat pap 6m
- LGSIL: 1/2 resolve, repeat pap 6m
- HGSIL: 1/3 resolve, colposcopy & biopsy
- Workup: history, EUA, pap smear, colposcopy? Sigmoidoscopy?, labs, PETCT, MRI

Surgery
- Class I: extrafascial TAH
- Class II: modified radical hysterectomy (extended to ureters)
- Class III: radical abdominal hysterectomy (to sidewall)
- Class IV: extended radical hysterectomy (bladder + excision)

Postop RT and Chemo
- GOG 92 (Sedlis): 277 pts IB2 → RadHys +/- WPRT. Had to have 2 of (>4cm, LVSI, middle/deep stroma invasion). PORT ↓LF, ↓mets, ↑PFS (65→78%)
- GOG 109 (Peters): 243 pts IB-IIA → RadHys, RT +/- cis/5FU. Had to have either (+margin, +LN, +parametrium). CRT improved 4 yr PFS (63→80%) and OS (71→81%)

Definitive RT and CRT
- Landoni 1997: 343 pts IB-IIA → RT vs RadHyst. Adjuvant RT given for stage >IIA. Unchanged OS, DFS, but morbidity worse in surgery arm (28 vs 12%)
- RTOG 90-01: 386 pts IIB-IVA, >5cm or LN+ → EFRT vs WPRT+cis/5FU. All pts got brachy. CRT won. 8yr OS 41→67%, LRF 35→18%, DM 35→20%.
- GOG 120: 526 pts, IIB-IVA → RT with (cis vs cis/FU/hydroxyurea vs hydroxyurea). Cisplatin containing arms won
- NCIC: 353 pts → CRT with LDR (35Gy) vs HDR (8x3). No difference in 5 yr OS
- GOG 71: 282 pts IB2 → RT +/- adjuvant hysterectomy. No difference in OS, more LF in RT arm

Technique
- WPRT borders: L5/S1→obtruator canal, 2cm lateral to pelvic brim, public symphysis to sacral hollow. 45 Gy in 25 fx
- Boost gross nodes to 60 Gy with IMRT
- Boost sidewall 10 Gy for +parametria
- T&O: 6 Gy in 5 fractions
- Dose constraints (EQD2)
  - Vagina: 120 Gy
  - Rectum: 75 Gy
  - Bladder: 85 Gy

NCCN
- IA1, IA2, IB1, IIA1: Surgery +/- PORT +/- chemo
- Incidental IA1 after TAH
  - No LVSI or 3Ps: observe
  - +LVSI or 3Ps: completion RadHys or RT
- IB1: definitive RT
- IB2-IVA: chemoRT

Endometrial Cancer[1-5,356-361]

- **T1**
  - T1a (***IA***) – < ½ myometrium
  - T1b (***IB***) – ≥ ½ myometrium
- **T2** (***II***) – cervical stroma
- **T3**
  - T3a (***IIIA***) – serosa/adenexa
  - T3b (***IIIB***) – vagina/parametrium
- **T4** (***IVA***) – bladder or rectum
- **N1** (***IIIC1***) – regional (up to common iliac)
- **N2** (***IIIC2***) – paraaortic 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 true pelvis

IV - Outside the true pelvis or involves bladder or rectum
- IVA - Involves bladder, rectum, sigmoid, or small bowel
- IVB - Distant mets

Overview
- Risk factors: esotrogen, nulliparity, obesity, tamoxifen
- Simple hyperplasia→cancer (<2%)
- Complex hyperplasia→cancer (40%)
- Pathology: endometrioid adenocarcinoma, UPSC, clear cell, mucinous, sarcomas
- Lynch Syndrome: microsat instability, uterine + colon ca
- + pelvic nodes → 33% chance of + PA nodes
- Workup: H&P, labs, CA-125 (for trending in III/IV), Endometrial biopsy, imaging/scopes for symptoms

Surgery
- All patients go for surgery if able: TAH/BSO, peritoneal inspection, fluid cytology, +/- LND (usually for grade 2/3), rad hys if cervical involvement
- ASTEC trial 2009: stage I dz: TAH/BSO +/- LND: no difference, but some high risk patients got WPRT

Adjuvant RT
- GOG 99: old IB+IC+IIA: TAH/BSO+LND +/-50.4 Gy WPRT: RT won. LRR 12→3%, OS 86→92% NSS. Mostly benefited high risk patients
- PORTEC-1: old IB+IC: TAH/BSO +/-46 Gy WPRT (no LND required). RT won. LRR 14→4%, 75% of failures in cuff. OS unchanged (~85%). Better for high risk pts.
- Aalders 1980: old IB+IC: TAH/BSO + VC +/- 40 Gy WPRT (no LND). WPRT ↓LRR (7→2%), unchanged OS
- PORTEC-2: old IB+IC+IIA: 46 Gy WPRT vs 21/3 VC. Similar results except that WPRT reduced pelvic failure (3.6→0.7%) and ↓QOL

Adjuvant Chemo
- RTOG 9708: phase II: high risk early stage: WPRT + concurrent cisplatin, Q3wk. 4 yr OS 85%, low failures
- GOG 122: stage III/IV: debulking, then WART+boost vs chemo only (doxorubicin+cisplatin). Chemo won. OS 42→55%, DFS 38→50%, but ↑toxicity

Technique
- WPRT borders: L5/S1→obtruator canal, 2cm lateral to pelvic brim, public symphysis to split sacrum (include sacral hollow for stage II+). 45 Gy in 25 fx
- Boost gross nodes to 60 Gy with IMRT
- VC: target usually upper 2/3 vagina, to 5mm depth. 21 Gy in fx HDR (eval for vaginal extension).
- If WPRT+VC: lower VC dose to 4-6 Gy in 2-3 fx
- Y-app: 21/3 to uterine serosa (~2cm)

NCCN/ASTRO guidelines (Klopp 2014)
- Surgery if able with RT as below within 12 wks, LND for high risk
- Stage III/IV: postop chemoRT
- Fertility-sparing options as appropriate
- Inoperable: 45 Gy WPRT + Y-app (8.5 x2) or just Y-app 8.5x4
- Dilator at 2-4 wks post-RT→ indefinitely
- Risk factors: age>60, LVSI, tumor>2cm, +cervical gland, ↑grade

		G1	G2	G3
Surgically staged:Stage I[d]	Stage IA (<50% myometrial invasion), Adverse risk factors not present	Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
	Stage IA (<50% myometrial invasion), Adverse risk factors present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or pelvic RT (category 2B for pelvic RT)	Observe or Vaginal brachytherapy and/or Pelvic RT
	Stage IB (≥50% myometrial invasion), Adverse risk factors not present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Vaginal brachytherapy and/or Pelvic RT or Observe (category 2B for observation)
	Stage IB (≥50% myometrial invasion), Adverse risk factors present	Observe or Vaginal brachytherapy and/or Pelvic RT	Observe or Vaginal brachytherapy and/or Pelvic RT	Pelvic RT and/or Vaginal brachytherapy ± chemotherapy[g,n] (category 2B for chemotherapy)
Surgically staged:[d] Stage II[o,p]		Vaginal brachytherapy and/or pelvic RT	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy ± chemotherapy[n] (category 2B for chemotherapy)
Surgically staged:[d] Stage IIIA		Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy

Uterine Sarcoma Cancer[1-5,362-365]

Leiomyosarcoma and Endometrial Stromal Sarcoma

- **T1**
  - T1a (***IA***) – ≤5cm
  - T1b (***IB***) – >5cm
- **T2**
  - T2a (***IIA***) – adenexa
  - 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

Overview
- 4% of uterine malignancies
- Carcinosarcoma (MMMT) staged like plain EndoCa
- ESS is less aggressive, can respond to hormone therapy

Trials
- EORTC 55874: stage I-II sarcomas (41% carcino)→surgery +/- WPRT. RT improved LC, but not OS. No benefit for LMS.

Adenosarcoma

- **T1**
  - T1a (***IA***) – endometrium only
  - T1b (***IB***) – ≤ ½ myometrium
  - T1c (***IC***) – > ½ myometrium
- **T2**
  - T2a (***IIA***) – adenexa
  - 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

- 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: carcinocarcoma→ WART vs chemo. No difference but WART had ↑tox

NCCN
- Basically the same as endometrial cancer

Vulvar Cancer[1-5,366-370]

- Tis – CIS
- **T1**
  - T1a (***IA***) – ≤2cm and ≤1mm DOI
  - T1b (***IB***) – >2cm or >1mm DOI
- **T2** (***II***) – ↓1/3 urethra, ↓1/3 vagina, or anus

- **N1** (***IIIA***)
  - N1a – 1-2 LNs, each <5mm
  - N1b – 1 LN, ≥5mm
- **N2**
  - N2a (***IIIB***) – 3+ LNs, each <5mm
  - N2b (***IIIB***) – 2+ LN ≥5mm
  - N2c (***IIIC***) – ECE
- **N3** (***IVA***) – fixed/ulcerated LN

Stage	5 yr OS
I	90%
II	81%
III	68%
IV	20%

- **T3** (***IVA***) – ↑2/3 urethra, ↑2/3 vagina, adj organs

- **M1** (***IVB***) – distant (including pelvic nodes)

Overview
- 3,500 dx/yr in US, 5% GYN malig, 1% female malig
- Risk factors: ↑age, HPV (# 6, 16, 18, 33), VIN, Bowens/Pagets, vaginitis, smoking laundry facilities
- Subsites: labia majora/minora, mons pubis, clitoris, vestibule, perineal body, posterior forchette, Barotholins
- LN spread: superficial inguinofemoral → deep inguinofemoral → ext iliac (clitoris can spread straight to deep)
  - Cloquet's node: superior deep femoral node
- Workup: H&P, CBC, UA, HIV, EUA/PAP/DRE, CT C/A/P vs PET vs MRI based on size/stage

Surgery
- Lymphadenctomy for DOI>1mm or G3 or LVSI (all stage IB+ pts)
- 2cm margin is goal
- PORT for +margin, close margin (8mm fixed, 1cm frozen), LVSI, DOI>5mm
- GROINSS-V:T1-T2→SLNBx→no LND if neg. 3yr regional failure 2.3%.

Nodal RT
- GOG 37: WLE with ILND → PLND vs RT (pelv +groin); RT won; 2 yr LRR 24→5%, OS 54→68%
  - No benefit for only 1 node (similar to H&N sites)
- 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 3cm depth (inadeq dose and coverage for gross disease)
  - Koh 1993: mean inguinal depth 6.1cm, failures in GOG88 <47Gy
- Katz 2003: modern RT techniques; LC with RT ~90%

Neoadj 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: phase II, T3-4 unresectable→inguinal LND→ preop CRT (cisplatin + 57.6Gy/32fx). 45 Gy AP/PA pelvis, 12.6 Gy boost. 50% pCR, 40% 2yr OS.
  - Improved results compared to GOG101

Technique
- Sim Frog-leg +/- bolus
- 3D-CRT: "pair of paints"
  - 1 PA beam: pelvis only
  - 3 AP fields: 'pelvic, R/L inguinal

ACR Consensus Guidelines (no NCCN)
- Chemos: cisplatin +/- 5FU, mitomycin C
- RT alone: 45-50.4 Gy @ 1.8 + 14-24 Gy boost (brachy vs EBRT)
- Neoadj CRT: 57.6 Gy @ 1.8 (GOG205)
- Definitive CRT: no dose given (~60 Gy?)
- Vulva + BL nodes if cN0

Vaginal Cancer[1-5,371-374]

- **Tis** – CIS
- **T1** (***I***) – vagina only
- **T2** (***II***) – paravaginal tissue
- **T3** (***III***) – pelvic wall
- **T4** (***IVA***) – bladder or rectum

- **N1** (***III***) – pelvic/inguinal (up to common iliac)

- **M1** (***IVB***) - distant

Stage	Lian 2008 5 yr DFS	Crevoisier 2007 5 yr DFS	Frank 2005 5 yr DFS
I	90%	83%	85%
II	87%	76%	78%
III	32%	52%	
IV	26%	-	83%

Overview
- Risk factors: CIS, HPV, irritation, ↑sex, DES
- Prognostic factors: >60 yo, lower location size, anemia
- Workup: exam, biopsy, labs, CT/MRI, +/- PET
- Risk of nodal involvement
  - I: 5%
  - II: 25%
  - III: 75%
  - IV: 85%

Nodal RT
- RT techniques; LC with RT ~90%

Neoadj CRT for unresectable disease
- GOG 101: aresults compared to GOG101

Technique
- Sim Frog- fields: 'pelvic, R/L inguinal

Hanson and Roach Guidelines
- CIS: WLE, laser, 5FU, Vcuff
- I: surgery or cuff to 65Gy
  - If >5mm deep, >2cm or G3: add LND or WPRT
- II+: WPRT to 45 Gy + brachy to 75 Gy (6x3 HDR)

Ovarian Cancer and Fallopian Tube Cancer[1-5,375-378]

- **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 (***IIIA***) – micro peritoneal implants
  - T3b (***IIIB***) – macro peritoneal implants <2cm
  - T3c (***IIIC***) – macro peritoneal implants ≥2cm

- **N1** (***IIIC***) – intraabd/inguinal nodes

- **M1** (***IV***) - distant

Overview
- BRCA1: 45% risk, BRCA2 25% risk (also HNPCC)
- Epithelial 65%, germcell 25%, sex cord stromal 5%, mets 5%
- Workup: H&P, gyn exam, labs, CA125, AFP/bHcG
- Ultrasound, CT C/A/P
- Surgical staging and debulking

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
- RT only for local recurrence of palliation

Notes

Hematologic

Hodgkin's Disease[1-5,379-387]

Overview
- 8,200 cases/USyr, 1,300 deaths
- Classical: CD 15+, 30+, 45-, 20-
  - Nodular sclerosing
  - Mixed cellularity
  - Lymphocyte depleted
  - Lymphocyte rich
- Nonclassical: CD 15-, 30-, 45+, 20+
  - Nodular lymphocyte predominant HL
- B-symptoms
  - Temp > 38°C
  - > 10% weight loss in last 6m
  - Drenching night sweats
- Bulky disease
  - >1/3 mid-thoracic diameter (~T5/6 on PA CXR)
  - 5cm or 10cm (depends on trial)
- Workup
  - CBC w/diff, CMP, *ESR, LDH, albumin, alk phos, Hep B, BHcG*
  - PET-CT, PFTs (bleo), echocardiogram (adria)
  - BM Bx if: B-sympx, Stage III/IV, bulky, >2 sites, recurrence
  - Staging laparotomy not needed with STNI or chemo (EORTC H6F)
  - Grouped nodes:
    - Waldeyer's: Palantine, pharyngeal, lingual tonsils
    - Cervical/supraclav/occipital/preauricular
    - Epitrochlear/brachial
    - Inguinal/femoral
    - German unfav has different nodal grouping

- **Chemotherapy**
  - ABVD: adriamycin, bleomycin, vinblastine, dacarbazine
  - Stanford V: mechlorethamine, oncovorin, prednisone, etoposide, adriamycin, bleomycin, vinblastine (MOPE-ABV, needs RT)
  - BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, oncovorine, procarbazine, prednisone

International Prognostic Score (IPI: WALSHAM)	
WBC > 15k	Stage IV
Alb <4	Hgb <10.5
Lymph <600	Age>45, male

RT vs CRT
- 4 trials showed improvement with CRT, one with OS improvement (H8F): EORTC H7F, H8F, German HD7, SWOG S9133

Chemo +/- RT
- NCI: unfav I-II, nonbulky: ABVD x4-6c vs ABVD x2c + STNI: 5 yr PFS initially favored CRT (88→95%), same OS; 12 yr f/u showed ↓OS in chemoRT arm (94% vs 87%) (RT and nonRT related deaths in RT arm)
- Laskar: very mixed group: 6c ABVD with CR→ IFRT vs obs. RT won: 8yr EFS 76→88%, OS 89→100%
- Aleman: III-IV→ 4-6c MOPP-ABV w/ CR→ IFRT v sobs. Same EFS and OS

↓Field size, ↓dose, ↓chemo
- GPMC, German HD8, Milan, EORTC H8U all ↓ FS
- German HD10: stage I-II favorable (German fav criteria): 2x2 design (2-4c ABVD and 20-30 IFRT): 5 yr DFS and OS were same in all arms

Technique
- Mantle: inf border at T10/11
- TLI: mantle + inv-Y + spleen
- STLI: TLI –inv-Y
- Block larynx ≤ 20 Gy
- Block heart ≤ 30 Gy

Deauville PET criteria
- 1: no uptake
- 2: uptake < mediastinum
- 3: medistinum < uptake < liver
- 4: ↑moderately compared to liver
- 5a: ↑markedly compared to liver
- 5b: new FDG avid site

- **NCCN**
- Classical
- IA-IIA: ISRT 30 Gy (20 Gy if qual for HD10)
- IB-IIB: chemo then RT (30 Gy; 36 for bulk)
- Nonclassical
- IA-IIA: ISRT: 30 Gy, 25-30 to adjacent nodes
- IB-IIB: chemo then RT (30 Gy; 36 for bulk, ABVD or R-CHOP)
- III-IV: chemo +/- RT

Examples of Unfavorable Risk Factors for Stage I-II Hodgkin Disease

Risk Factor	GHSG	EORTC	NCIC	NCCN
Age		≥50	≥40	
Histology			MC or LD	
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	>50 or any B sx	>50 or any B sx
Mediastinal mass	MMR > .33	MTR > .35	MMR > .33 or > 10 cm	MMR > .33
# Nodal sites	>2*	>3**	>3	>3
E lesion	any			
Bulky				>10 cm

Non-Hodgkin's Lymphoma[1-5,388-390]

a. Overview

i. Categories
1. Low grade NHL: follicular (G1,G2), CLL, MALT, mucosis fungoides
2. Intermediate grade NHL: follicular (G3), mantle cell, DLBCL, T/NK cell, peripheral T cell, anaplastic large cell
3. High grade NHL: Burkitt's, lymphoblastic

ii. Genetics
1. Follicular: t(11,18)→ ↑bcl-2
2. SLL/CLL: del13, t(14,19), tri12
3. MALT: t(11,18), tri3
4. Richter syndrome: SLL/CLL → DLBCL transformation (5%)

iii. Workup
1. CBC w/diff, CMP, *LDH, B2micro, SPE, HIV, HepB, HepC*
2. BM Bx for most
3. LP for CNS, testicular, paranasal sinus, immunodeficient
4. PET-CT for all, MRI if getting LP

iv. GELF-Criteria
1. ≥3 nodal sites (each >3cm), mass ≥7cm, B-sympx, splenomegaly, effusion/ascites, cytopenia, leukemia

b. Chemotherapy

International prognostic Index (IPI) (APLES)				Revised IPI (ritux)
Age >60 ECOG ≥2 LDH > ULN >1 extranodal Stage III/IV			5yr OS	5yr OS
	Low risk	0-1	73%	94%
	Low/int risk	2	51%	79%
	Int/high risk	3	43%	55%
	High risk	4-5	26%	

FL International prognostic Index (FLIPI) (HASSL): separate nodal groups			
Hgb < 12 Age ≥60 Stage III/IV ≥5 extranodal LDH > ULN			10yr OS
	Low risk	0-1	71%
	Int risk	2	50%
	High risk	3-5	36%

i. R-CHOP: rituximab, cyclophosphamide, hydroxydaunomycin (adria), oncovorin (vincristine), prednisone

c. Intermediate Grade Trials

i. SWOG 8736: 1-IIE int grade NHL: CHOPx8c vs CHOP x3c +IFRT (40-55 Gy): 5 yr results favored CRT, but 7 yr results overlapped

ii. ECOG E1484: 1-IIE, int grade NHL: CHOPx8c with CR→IFRT vs obs: RT won. 6 yr DFS 56→73%, OS same

iii. GELA LNH-93-4: >60 y/o, low risk: CHOPx4c vs CHOPx4c + IFRT (40Gy): 5 yr EFS and OS same

d. NCCN

i. Follicular Lymphoma
1. Low grade localized FL: 24-30 Gy only
2. III/IV: palliative (>20 Gy or 2x2 Gy)

ii. DLBCL
1. I-II: RCHOP x3-6c +/- RT (40-50 Gy for PR)
2. III/IV: palliative
3. Testicle: 25-30 Gy

iii. Mantle cell: I-II: chemo +/-RT

iv. SLL: palliation

v. Marginal zone: palliation

General Dose Guidelines:
- Localized CLL/SLL: 24-30 Gy
- Follicular lymphoma: 24-30 Gy
- Marginal zone lymphoma:
  - Gastric: 30 Gy
  - Other extranodal sites: 24-30 Gy
  - Nodal MZL: 24-30 Gy
- Early-stage mantle cell lymphoma: 30-36 Gy
- Mini-dose RT (2 Gy x 2 may be repeated) for palliation/local control of SLL, FL, MZL, MCL
- Diffuse large cell lymphoma or PTCL
  - Consolidation after chemotherapy CR: 30-36 Gy
  - Complimentary after PR: 40-50 Gy
  - RT as primary treatment for refractory or noncandidates for chemotherapy: 45-55 Gy
  - Salvage pre- or post-stem cell transplantation: 30-40 Gy
- Primary cutaneous anaplastic large cell lymphoma: 30-36 Gy

MALT Lymphoma[1-5]

1. Overview
a. Arises from Peyer's patches, marginal zone
b. t(11:18), tri3, CD 20+, 35+. 5-, 10-
c. Workup: T&P, CBC w/diff, CMP, LDH CXR, CT A/P, EGD/EUS, BM Bx for advanced
d. Use FLIPI (HASSL)
e. Ann Arbor or Lugano staging

2. RT indications
a. H. Pylori negative
b. t(11,18) → (<5% respond to abx)
c. invasion past submucosa
d. progression on abx
e. failure after 2 courses of abx
f. rapid/symptomatic progression

Lugano Staging	
IE1	Mucosa/submucosa
IE2	Into muscularis/seroa
IIE1	Perigastric LNs
IIE2	Distant abd LNs
IIIE	Into adventitia
IVE	Across diaphragm

3. Site Specific recommendations
a. Gastric MALT
   i. Commonly caused by H. pylori (abx: triple therapy)
   ii. Tx strategy
      1. Rapid urease test on biopsy
      2. Triple therapy (clarithromycin/flagyl/PPI)
      3. Urea breath test 1m after abx
      4. EGD w/ bx Q3m
      5. Secondary abx if persistent dz
      6. IFRT vs chemo for persistence/progression
   iii. Note: DLBCL of stomach → RCHOP +IFRT
   iv. Technique
      1. Sim fasting with PO contrast, 4D
      2. Cover whole stomach + perigastric nodes +/- celiac
      3. 2cm margin
      4. 4-field to 30 Gy in 20 fx (boost residual to 36 Gy)
      5. Kidney mean <20 Gy, liver V25<50%
   v. 10 yr LC 95%, DFS 50%

b. Orbital MALT
   i. Commonly caused by Chlamydia psittaci (abx: doxycycline)
   ii. Treat whole orbit
   iii. 25-30 Gy in 10-20fx (can dose reduce for low grade to 19.5-24 Gy)
   iv. 95% local control (↑distant failure)

c. Salivary MALT
   i. Commonly caused by Sjogeren's syndrome
   ii. (Thyroid caused by Hashimoto thyroiditis)
   iii. Treat whole gland
   iv. 30 Gy in 20 fx
   v. Cervical nodes if involved

d. Skin MALT
   i. Commonly caused by Borrelia burgdorferi (abx: doxycycline)
   ii. Surgery vs electrons
   iii. 30 Gy in 20 fx

e. Lung MALT
   i. Early stage → surgery with PORT for +margin or mediastinal nodes
   ii. Advanced stage → chemo +/- IFRT

Plasmacytoma/Multiple Myeloma[1-5,391,392]

1. **Overview**
   a. 15,000 cases/yr in UA
   b. Solitary extramedullary plasmacytoma (SEP)→MM (25% @10yrs)
   c. Solitary bone plasmacytoma (SBP)→MM (75% @10yrs)
   d. CRAB: ↑calcium, renal failure, anemia, bone lesions
   e. POEMS: Polyneuropathy, organomegaly, endocrinopathy, M-spike, skin changes (POEMS patients respond well to RT)
   f. Workup: H&P, CBC w/ diff, CMP, *LDH, Ca/albumin, B2micro, SPEP, UPEP, skeletal survey, unilateral BMbx*
   g. PET-CT can be helpful but no bone scan (lytic lesions)

International Staging System (ISS)			
	Stage I	**Stage II**	**Stage III**
B2-micro	<3.5 mg/L	-	≥5.5 mg/L
Albumin	≥3.5 g/dL	-	any
MS	62m	44m	29m
Note: also Durie-Salmon criteria staging (more involved)			

2. **Dx Criteria for MGUS (all required)**
   a. SPEP M-spike < 3g/dL
   b. BM plasma cells < 10%
   c. No end organ damage
3. **Dx Criteria for Solitary Plasmacytoma (all required)**
   a. Single bone/extraosseus lesion by skeletal survey
   b. Plasmacytoma by biopsy
   c. <5% plasma cells by BM bx
   d. No end organ damage

4. **Dx Criteria for MM (all required)**
   a. Clonal plasma cells (≥10% BM bx)
   b. M-spike on SPEP or UPEP
   c. End organ damage: CRAB
      i. Ca >11.5 mg/dL
      ii. Cr >2mg/dL
      iii. Hgb <10g/dL
      iv. Bone lesions
   d. Note: only a+b is "smoldering MM"
   e. Treatment
      i. Bisphosphonates (skeletal events 41→24%)
      ii. Chemotherapy (lots of options)
         1. Boprtezomib/dexamethasone
         2. Add melphan if no transplant planned
         3. Maintenance with bortezomib or thalidomide
      iii. Bone marrow transplant
         1. Condition with high dose melphalan
      iv. Palliative RT
         1. 20-36 Gy @ 1.5-2 Gy/fx

5. **SEP**
   a. Tournier-Rangeard, 2006: SEP retrospective
      i. 5 yr LC: 100% if ≥45 Gy, 50% if <45 Gy
      ii. 5 yr DFS: 81% among all doses
   b. Technique
      i. Mass + primary LNs
      ii. ≥45 Gy
      iii. Then restage

6. **SBP**
   a. Tsang, 2001: mostly SBP (also some SEP)
      i. 8 yr LC: 83%
      ii. 8 yr OS: 65%
      iii. 8 yr DFS 44%
      iv. Freedom from MM: 50%
   b. Technique
      i. Bone with 2-3cm margin
      ii. Spine: 2 above and 2 below
      iii. ≥45 Gy
      iv. Then restage

STAGING SYSTEMS FOR MULTIPLE MYELOMA

Stage	Durie-Salmon Criteria[1]	ISS Criteria[2]
I	All of the following: • Hemoglobin value >10 g/dL • Serum calcium value normal or ≤12 mg/dL • Bone x-ray, normal bone structure or solitary bone plasmacytoma only • Low M-component production rate ▸ IgG value <5 g/dL; ▸ IgA value <3 g/dL ▸ Bence Jones protein <4 g/24 h	Serum beta-2 microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: • Hemoglobin value <8.5 g/dL • Serum calcium value >12 mg/dL • Advanced lytic bone lesions • High M-component production rate ▸ IgG value >7 g/dL; ▸ IgA value >5 g/dL ▸ Bence Jones protein >12 g/24 h	Serum beta-2 microglobulin ≥5.5 mg/L
Subclassification Criteria A Normal renal function (serum creatinine level <2.0 mg/dL) B Abnormal renal function (serum creatinine level ≥2.0 mg/dL)		

Sarcoma

Osteosarcoma, Chondrosarcoma, Chordoma[1-5,393-395]

- **T1** - ≤8cm
- **T2** - >8cm
- **T3** – discontinuous tumors

- **N1** – nodes

- **M1a** - lung
- **M1b** - other

	T1	T2	T3
N0	**IA** (G1) **IIA** (G3)	**IB** (G1) **IIB** (G2)	**IB** (G1) **III** (G3)
N1	**IVB**		
M1a	**IVA**		
M1b	**IVB**		

Overview
- Prevalence: osteosarcoma>chondrosarcoma>ewings>MFH
- Physaliferous cell: chordoma
- Onion skin: ewings (lytic, diaphysis)
- Sunburst: osteosarcoma (sclerotic, metaphysis)
- Workup: H&P, labs, alkphos, ESR, plain films, CT primary+chest, bone scan
- Biopsy after images. Need to excise biopsy site

Osteosarcoma
- Neoadj and adj chemo ↓LF (Link 1986, Eilber 1987)
- Ozaki 2003: retrospec. RT improved OS for R1 or R2

Technique
- Spare 2cm skin
- CTV is surgical bed + scar + 2cm

NCCN
- Resect if possible otherwise RT
- Osteosarcoma needs neoadj and adj chemo (cat 1)

CHONDROSARCOMA
- **Base of Skull Tumors**
  - **Postoperative therapy or RT for unresectable disease: >70 Gy with specialized techniques**
- **Extracranial Sites**
  - **Preoperative RT (19.8 to 50.4 Gy) may be considered (if positive margins are likely) followed by individualized postoperative RT with final target doses of 70 Gy (R1 resection)[1] and 72 to 78 Gy (R2 resection).[1]**
  - **Postoperative RT (60 to 70 Gy) may be considered, especially for high-grade/dedifferentiated/mesenchymal subtypes with close or positive margins.**
  - **Consider high-dose therapy with specialized techniques for unresectable disease.**

CHORDOMA
- **Base of Skull**
  - **Postoperative RT (R1 and R2 resection)[1] or RT for unresectable disease 70 Gy or higher (total dose will depend on normal tissue tolerance)**
  - **Consider postoperative RT for R0 resections**
- **Mobile Spine**
  - **Consider preoperative RT (19.8 to 50.4 Gy) and postoperative RT to total dose of 70 Gy (depending upon normal tissue tolerances)**

GIANT CELL TUMOR OF BONE

Treatment of Metastatic Disease
- **Consider RT (50 to 60 Gy) for unresectable/progressive/recurrent disease that has not responded to serial embolizations, denosumab, IFN, or PEG IFN.**
- **An increased risk of malignant transformation following RT has been noted in some studies.**

OSTEOSARCOMA

Treatment of Primary Tumor
- **RT should be considered for patients with positive margins of resection, subtotal resections, or unresectable disease**
  - **Postoperative RT (R1 and R2 resections):[1] 55 Gy with 9 to 13 Gy boost to microscopic or gross disease (total dose to high risk sites 64 to 68 Gy)**
  - **Unresectable disease: 60 to 70 Gy (total dose will depend on normal tissue tolerance)**

Treatment of Metastatic Disease
- **Consider use of ^{153}Sm-EDTMP**
- **Consider use of stereotactic radiosurgery, especially for oligometastases**

Soft Tissue Sarcoma[1-5,396-405]

- **T1** - ≤5cm
  - T1a - superficial
  - T1b - deep
- **T2** - >5cm
  - T2a - superficial
  - T2b - deep

- **N1** – nodes

	TNM	G
IA	T1	1
IB	T2	1
IIA	T1	2/3
IIB	T2	2
III	T2 or N1	3 -
IV	M1	-

Overview
- 11,000 cases/yr, 4,400 deaths/yr
- Histology
  - Undiff pleomorphic sarcoma (MFH) 25%
  - Liposarcoma 15%
  - Leiomyosarcoma 10%
  - Synovial sarcoma 5% [t(x,18)]
  - MPNST (5%)
  - Clear cell <5% [t(11,22)]
- Grade based on diff, necrosis, mitosis
- Stewart-Treves syndrome: lymphangiosarcoma from lymphedema
- ↑LN+: SCARE [synovial, clear cell, angio, rhabdo, epitheliod]
- Workup: H&P, Xray, CT, MRI, CT chest, bx
- Biopsy incision should be excised

Karposi Sarcoma
- AIDS assoc and non-AIDS assoc
- HHV8 infection
- Kirova 1998: 30 Gy (15-10 for face/groins). 92% response

Surgery & Chemo
- Goal is >1cm in all directions
- Pervaiz 2008: metaanalysis for chemo (doxorubicin-based). Chemo improved LC 4% and OS 6%
- Harvard study: retrospective 48 pts with neoadj CRT (MAID +44/22 split course) with boost postop if R1. 5 yr LC 92%, OS 87%.
- RTOG 9514: used Harvard neoadj CRT with 64 pts. showed similar results (OS 71%), but toxic

Postop RT
- Rosenberg 1982: G3→ amputation vs WLE+RT (boost to 60-70Gy). No difference in LC or OS.
- Pisters 1996: WLW+/-brachy (45Gy LDR).
  Brachy →↑LC for G3, but not for G1-2
- Yang 1998: WLE +/-EBRT (63Gy). G3 tumors got chemo. RT improved LC for all grades, but no change in OS.

Preop vs Postop RT
- Pollack 1998: preop (50Gy) vs postop (60-66Gy). Same LC (81%)
- O'sullivan 2002: preop (50Gy) vs postop (66Gy). If +margin, preop got 16Gy boost. Same LC (93%) and DM(25%). No difference in OS. More temporary wound healing problems with preop (35 vs 15%), but more late fibrosis with postop.

Retropeitoneal sarcoma
- Mendenhall 2005: review of lit. GRT in ~50%, but close margins. Most faily locally. 5 yr LC 50%, OS 50%.

Technique
- Postop (3-8wks postop)
  - CTV is tumor bed, edema, and scar (3-6cm longitudinally and 2cm radially) to 50 Gy
  - Boost tumor bed +2cm
    - 60-66Gy for R0
    - 66-68Gy for R1
    - 70-76Gy for R2
- Preop (3-6 weeks preop)
  - 50 Gy to large volume
  - 16-18 Gy PORT for R1
  - 20-26 Gy PORT for R2
- Unresectable disease to 75Gy
- No ENI

NCCN
- Stage I: surgery alone, consider RT for +margin (cat 2b)
- Stage II-III:
  - Surgery + PORT
  - PreopRT + surgery
  - Preopchemo cat 2b
- Retroperitoneal sarcoma: surgery+PORT (cat 2b for preopRT), same doses

Desmoid Tumor[1-5,406,407]

Overview
- 900 cases/yr
- Benign, fibroblastic neoplasms
- Don't metastasize
- Assoc with APC gene mutation
- More common in women, abdominal wall
- Workup: H&P, MRI, bx to rule out STS
- Eval for Gardner's syndrome or FAP

Surgery
- Goal is 2cm margin
- R0: 15% LR
- R1: 26% LR
- Crago 2013: R1 resection → observed. Did well.

RT dose
- RT alone: 22% LR (Nuyttens 2000)
- Nuyttens 2000: dose >50Gy (50-56) for GTV, post op50 Gy
- Margin similar to STS

Medical options
- Tamoxifen, NSAIDs, MTX, imatinib

NCCN
- Observe
- Resect
  - R0: observe
  - R1: observe (Crago 2013) or reresect
  - R2: reresect or RT (50 Gy) or obs
- RT (56-58Gy) or systemic therapy

Notes

Palliative

Brain Metastases[1-5,408-416]

- **Background**
  - Most common brain tumor (30% of cancer pts)
  - Solitary vs single
  - Lung>breast>melanoma>others
  - Hemorrhagic: RCC, choriocarcinoma, melanoma

- **Workup**
  - H&P, MRI, rule out infection, steroids for neuro sympx (4mg Q6H)
  - Only anticonvulsants if seizure (Glantz 2000 guidelines)
  - Identify primary (CT C/A/P), KPS

- **WBRT+Surgery?**
  - Patchell #1 (1990): solitary brain mets: 36/12 WBRT +/- preRT surgery. Surgery+RT won. ↑survival, ↑LC, ↓neurologic death, ↑functional status. 6 out of 60 patients were excluded (noncancerous tumor)
  - Patchell #2 (1998): solitary brain mets: surgery +/- 50.4/28 WBRT: postop RT won. ↑LRC, ↓new mets, ↓neurologic death. OS unchanged
  - EORTC 22952: surgery or SRS +/- 30/10 WBRT: similar findings to Patchell #2

- **WBRT+SRS?**
  - Andrews 2004: 1-3 mets, KPS>70: 37.5/15 WBRT +/- SRS (15-24 Gy): same findings as Patchell #1 (↑survival, ↑KPS, ↑LC)
  - RTOG 9508: 1-3 mets, <4cm: WBRT +/- SRS boost: SRS ↑ OS (4.9→6.5m) for single met, but not for >1 met

- **SRS alone**
  - JROSG 99-1: 1-4 mets, KPS>70: SRS +/- 30/10 WBRT: same findings as Patchell #2
  - Chang 2009: 1-3 mets, KPS>70, STS +/- 30/12 WBRT: whole brain ↑LRC, but ↓neurocognitive and ↓OS (15.2→5.7 months)

- **Fractionation**
  - RTOG whole brain fractionation papers (6901, 7361): outcomes were the same for 30-40/20-15, worse for 10/1 and 15/2
  - RTOG 7606, 9104: WBRT escalation to ~50 Gy provided no benefit
  - NCCN WBRT: 30-45 Gy in 1.8-3 Gy/fx (20/5 for ↓KPS)
  - WBRT reirradiation: 20/5
  - SRS fractionation: RTOG 9005 (Shaw):
    - ≤20mm → 24 Gy
    - 21-30mm → 18 Gy
    - 31-40mm → 15 Gy

- **Sim/planning**
  - Supine, short mask, opposed laterals, flash skin
  - Block: orbits, nasal cavity, C2 (include temporal fossa)
  - 5% risk of symptomatic necrosis with SRS
  - 50% of neurocognitive dysfunction with WBRT by formal testing

- **NCCN**
  - 1-3 mets:
    - Surgery +WBRT (category 1, can do SRS if single met)
    - Surgery + SRS boost
    - SRS +/- WBRT (category 2b)
    - WBRT alone for ↓KPS for disseminated systemic disease
  - 4+ mets:
    - WBRT +/- SRS
    - SRS +/- WBRT for ↑KPS

Cord Compression[1-5,417-421]

- **Background**
  - Usually lung, breast, prostate, RCC, lymphoma, myeloma
  - Batson venous plexus: drains from pelvis directly into spine
  - Epidural vs intradural vs intramedullary

- **Workup**
  - H&P, sensation, motor, bowel/bladder, gait
  - Steroids (dexamethasone 10mg IVx1 then 4-6mg Q6H)
  - Surgical consult for stability, possible debulking/fixation
  - MRI C/T/L spine (20% have additional tumors), bx if needed
  - CT if concern for bony retropulsion
  - CT myelogram if MRI contraindicated
  - Surgery = 360 degree decompression with stabilization (not laminectomy)

- **Steroids**
  - Vecht 1989: loading dose 10mg IV vs 100mg IV. Both went on to 16mg daily. No difference

- **Trials**
  - Patchell 2005: 30Gy vs surgery + 30Gy. All +steroids, one lesion, no cauda equine, >3m life expectancy, paralyzed<48 hrs, not radiosensitive. Stopped early, surgery won. Regained ambulation 19→62%, sustained ambulation 13→122 days, OS 100→126 days
  - Rades 2005: retrospective. 8/1 vs 30/10 (no surgery). No differences in motor fxn or stability. 34% regained ambulation
  - Rades 2009: nonrandomized. 1-5 fx vs 10-20 fx. Long course won. 1 yr LC 61→81%. Motor function and OS unchanged overall, but improved for ↑KPS, ↓disease
  - Rades 2008: retrospective: reirradiation for cord compression: no myelopathy if BED<100Gy total

- **SBRT for vertebral body mets (not cord compression)**
  - Gerzsten: 12.5-25Gy x1. Mostly reirradiations. 86% improvement in pain, LC 90%

- **Sim/planning**
  - Cervical: laterals. Others: usually AP/PA
  - +/- 1 vertebral body
  - 30/10, 20/5, 8/1

- **NCCN**
  - Dexamethasone 4mg Q6H minimum
  - Debulking/fixation if solitary site with >3m life expectancy, paraplegia < 24 hrs, not hematologic cancer, or if unstable
  - Postop RT 1-3 weeks postop
  - Chemo for hematologic cancers
  - Consider SBRT if no cord compression

Bone Metastases[1-5,422-428]

Overview
- Sites: spine > pelvis > ribs > femur > skull

Surgery
- Mirels 1989: scoring system for fx
- VanderLinden 2004: femur cortical involvement >30mm and/or circumerfential >50% predict for fx

EBRT
- RTOG 9714: breast and prostate bone mets → 8x1 vs 30/10. Pain CR/PR same (15%/50%). More tox with 30/10, more retreatment with 8x1 (9 vs 18%)
- Bone pain trial working party: 8x1 vs 20/5 vs 30/10. Same effectiveness. More reRT with 8x1 (23 vs 10%)
- Chow 2007: metaanalysis. No differences except 2.5x increase in retreatment if 8x1

Radiopharmaceuticals
- Strontium-89 (β): Sciuto 2002, Porter 1993
- Samarium-153 (β and γ): sartor 2004, Oosterhof 2003
- Radium-223 (α):
  - ALSYMPCA: Ra223 improved OS (11→14.9m) over placebo

PORT
- Townsend 1994: PORT reduced need for 2nd surgery (15→2%) and improved faster

SRS
- Gerstzen 2007: retrospective, median 20Gy x1. Improved pain in 86%, LC 90%

Physics and Radiobiology

Brachytherapy Sources[2,4]

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	Gamma	SPECT, Bone scan
^{131}I	8 days	364 keV photons (avg)	Beta -	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 , Opthalmic applicator, Intravascular
^{18}F	110 min	633 keV positrons	Beta +	PET, annihilation 511 keV photons x 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
^{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

	Release with instructions if activity <	Release with instructions if dose rate at 1m <	Release without instructions if activity <	Release without instructions if dose rate at 1m <
^{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	--	--

Radiobiology[2,4]

Marker	Classic association	Also seen in
AFP	HCC, NSGCTs	GI, pregnancy, cirrhosis
β2microglob	Myeloma	Bcell, 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 27.29	Breast	Various
Calcitonin	Medullary thyroid	Various
CEA	Colorectal	Various
Neuron-enolase	Neuroblastoma, SCLC	Wilms, melanoma, thyroid, testicle, Merkel cell
PSA	Prostate	Benign GU
Thyroglobulin	Thyroid (non-MTC)	Benign thyroid
βHcG	NSGCTs	pregnancy

Dose Limits (1rem = 0.01mSv)		
	Per year	**Per hr**
Occupational	50 mSv	0.02mSv
Fetus	0.5 mSv/**month**	
Public cont exposure	1 mSv	
Public intermittent exposure	5 mSv	
Background radiation: 2.5 mSv/yr		

Acute TBI	
<2 Gy	Observe
2-5 Gy	Prodrome, latency, cytopenias?
5-10 Gy	Hospitalize, hypotension?
10-20 Gy	GI syndrome, FATAL
>50 Gy	Cerebrovasc syndrome, FATAL

Translocation	**Cancer**
t(2:13) and t(1:13)	Alveolar Rhabdo
t(8:14) and t(8:22)	Burkitts, Bcell ALL
t(11:14)	Mantle cell (BCL1, cyclin D1)
t(11:22)	Ewings, PPNET
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-
Hodgkins	15+, 30+

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

Statistics

References

1. MacDonald SM, Taghian AG. Is it time to use protons for breast cancer? *Cancer journal (Sudbury, Mass.).* 2007;13(2):84-86.
2. Cook B DT. Wikibooks Radiation Oncology. https://en.wikibooks.org/wiki/Radiation_Oncology, 2015.
3. Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. *AJCC cancer staging manual.* Vol 7th. New York, NY: Springer; 2010.
4. Hansen E RM. *Handbook of Evidence-Based Radiation Oncology Second Edition.* Springer; 2010.
5. Hristov B LS, Christodouleas JP. *Radiation Oncology - A Question Based Review 2nd Edition.* LWW; 2014.
6. Arndt CA, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(31):5182-5188.
7. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1995;13(3):610-630.
8. Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2001;19(12):3091-3102.
9. Maurer HM, Beltangady M, Gehan EA, et al. The Intergroup Rhabdomyosarcoma Study-I. A final report. *Cancer.* 1988;61(2):209-220.
10. Maurer HM, Gehan EA, Beltangady M, et al. The Intergroup Rhabdomyosarcoma Study-II. *Cancer.* 1993;71(5):1904-1922.
11. Nesbit ME, Jr., Gehan EA, Burgert EO, Jr., et al. Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long-term follow-up of the First Intergroup study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1990;8(10):1664-1674.
12. Burgert EO, Jr., Nesbit ME, Garnsey LA, et al. Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: intergroup study IESS-II. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1990;8(9):1514-1524.
13. Donaldson SS, Torrey M, Link MP, et al. A multidisciplinary study investigating radiotherapy in Ewing's sarcoma: end results of POG #8346. Pediatric Oncology Group. *International journal of radiation oncology, biology, physics.* 1998;42(1):125-135.
14. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med.* 2003;348(8):694-701.
15. Heyn RM, Holland R, Newton WA, Jr., Tefft M, Breslow N, Hartmann JR. The role of combined chemotherapy in the treatment of rhabdomyosarcoma in children. *Cancer.* 1974;34(6):2128-2142.
16. Schuck A, Ahrens S, Paulussen M, et al. Local therapy in localized Ewing tumors: results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. *International journal of radiation oncology, biology, physics.* 2003;55(1):168-177.
17. Schuck A, Rube C, Konemann S, et al. Postoperative radiotherapy in the treatment of Ewing tumors: influence of the interval between surgery and radiotherapy. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al].* 2002;178(1):25-31.
18. D'Angio GJ, Breslow N, Beckwith JB, et al. Treatment of Wilms' tumor. Results of the Third National Wilms' Tumor Study. *Cancer.* 1989;64(2):349-360.
19. D'Angio GJ, Evans A, Breslow N, et al. The treatment of Wilms' tumor: results of the Second National Wilms' Tumor Study. *Cancer.* 1981;47(9):2302-2311.
20. D'Angio GJ, Evans AE, Breslow N, et al. The treatment of Wilms' tumor: Results of the national Wilms' tumor study. *Cancer.* 1976;38(2):633-646.
21. Green DM, Breslow NE, Beckwith JB, et al. Comparison between single-dose and divided-dose administration of dactinomycin and doxorubicin for patients with Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol.* 1998;16(1):237-245.
22. Grundy PE, Breslow NE, Li S, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol.* 2005;23(29):7312-7321.
23. Castleberry RP, Kun LE, Shuster JJ, et al. Radiotherapy improves the outlook for patients older than 1 year with Pediatric Oncology Group stage C neuroblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1991;9(5):789-795.
24. London WB, Castleberry RP, Matthay KK, et al. Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(27):6459-6465.
25. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. *N Engl J Med.* 1999;341(16):1165-1173.
26. Matthay KK, Yanik G, Messina J, et al. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(9):1054-1060.
27. Nitschke R, Smith EI, Shochat S, et al. Localized neuroblastoma treated by surgery: a Pediatric Oncology Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1988;6(8):1271-1279.
28. Strother D, van Hoff J, Rao PV, et al. Event-free survival of children with biologically favourable neuroblastoma based on the degree of initial tumour resection: results from the Pediatric Oncology Group. *European journal of cancer (Oxford, England : 1990).* 1997;33(12):2121-2125.
29. Shields CL, Shields JA, Needle M, et al. Combined chemoreduction and adjuvant treatment for intraocular retinoblastoma. *Ophthalmology.* 1997;104(12):2101-2111.
30. Duffner PK, Horowitz ME, Krischer JP, et al. The treatment of malignant brain tumors in infants and very young children: an update of the Pediatric Oncology Group experience. *Neuro-oncology.* 1999;1(2):152-161.
31. Packer RJ, Goldwein J, Nicholson HS, et al. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1999;17(7):2127-2136.
32. Rutkowski S, Bode U, Deinlein F, et al. Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. *N Engl J Med.* 2005;352(10):978-986.
33. Thomas PR, Deutsch M, Kepner JL, et al. Low-stage medulloblastoma: final analysis of trial comparing standard-dose with reduced-dose neuraxis irradiation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2000;18(16):3004-3011.
34. Zeltzer PM, Boyett JM, Finlay JL, et al. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1999;17(3):832-845.
35. Koshy M, Rich S, Merchant TE, Mahmood U, Regine WF, Kwok Y. Post-operative radiation improves survival in children younger than 3 years with intracranial ependymoma. *Journal of neuro-oncology.* 2011;105(3):583-590.
36. Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. *The Lancet. Oncology.* 2009;10(3):258-266.
37. Rogers L, Pueschel J, Spetzler R, et al. Is gross-total resection sufficient treatment for posterior fossa ependymomas? *Journal of neurosurgery.* 2005;102(4):629-636.
38. Calaminus G, Kortmann R, Worch J, et al. SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. *Neuro-oncology.* 2013;15(6):788-796.

39. Rogers SJ, Mosleh-Shirazi MA, Saran FH. Radiotherapy of localised intracranial germinoma: time to sever historical ties? *The Lancet. Oncology.* 2005;6(7):509-519.
40. Stripp DC, Maity A, Janss AJ, et al. Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. *International journal of radiation oncology, biology, physics.* 2004;58(3):714-720.
41. Cohen KJ, Heideman RL, Zhou T, et al. Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children's Oncology Group. *Neuro-oncology.* 2011;13(4):410-416.
42. Edwards MS, Wara WM, Urtasun RC, et al. Hyperfractionated radiation therapy for brain-stem glioma: a phase I-II trial. *Journal of neurosurgery.* 1989;70(5):691-700.
43. Greenberg ML, Fisher PG, Freeman C, et al. Etoposide, vincristine, and cyclosporin A with standard-dose radiation therapy in newly diagnosed diffuse intrinsic brainstem gliomas: a pediatric oncology group phase I study. *Pediatric blood & cancer.* 2005;45(5):644-648.
44. Jalali R, Raut N, Arora B, et al. Prospective evaluation of radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma. *International journal of radiation oncology, biology, physics.* 2010;77(1):113-118.
45. Janssens GO, Jansen MH, Lauwers SJ, et al. Hypofractionation vs conventional radiation therapy for newly diagnosed diffuse intrinsic pontine glioma: a matched-cohort analysis. *International journal of radiation oncology, biology, physics.* 2013;85(2):315-320.
46. Skowronska-Gardas A. A literature review of the recent radiotherapy clinical trials in pediatric brain tumors. *Rev Recent Clin Trials.* 2009;4(1):42-55.
47. Karim AB, Maat B, Hatlevoll R, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. *International journal of radiation oncology, biology, physics.* 1996;36(3):549-556.
48. Pignatti F, van den Bent M, Curran D, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2002;20(8):2076-2084.
49. Shaw E, Arusell R, Scheithauer B, et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2002;20(9):2267-2276.
50. Shaw EG, Wang M, Coons SW, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012;30(25):3065-3070.
51. van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet.* 2005;366(9490):985-990.
52. Cairncross G, Berkey B, Shaw E, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(18):2707-2714.
53. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(3):337-343.
54. DeAngelis LM. Anaplastic glioma: how to prognosticate outcome and choose a treatment strategy. [corrected]. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(35):5861-5862.
55. Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2004;22(9):1583-1588.
56. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *The Lancet. Oncology.* 2009;10(5):459-466.
57. van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(18):2715-2722.
58. Walker MD, Alexander E, Jr., Hunt WE, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. *Journal of neurosurgery.* 1978;49(3):333-343.
59. Wick W, Hartmann C, Engel C, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(35):5874-5880.
60. Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *The Lancet. Oncology.* 2012;13(7):707-715.
61. Abrey LE, Ben-Porat L, Panageas KS, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(36):5711-5715.
62. DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2002;20(24):4643-4648.
63. Laack NN, Ballman KV, Brown PB, O'Neill BP. Whole-brain radiotherapy and high-dose methylprednisolone for elderly patients with primary central nervous system lymphoma: Results of North Central Cancer Treatment Group (NCCTG) 96-73-51. *International journal of radiation oncology, biology, physics.* 2006;65(5):1429-1439.
64. Nelson DF, Martz KL, Bonner H, et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. *International journal of radiation oncology, biology, physics.* 1992;23(1):9-17.
65. Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *The Lancet. Oncology.* 2010;11(11):1036-1047.
66. Goldsmith BJ, Wara WM, Wilson CB, Larson DA. Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1967 to 1990. *Journal of neurosurgery.* 1994;80(2):195-201.
67. McCollough WM, Marcus RB, Jr., Rhoton AL, Jr., Ballinger WE, Million RR. Long-term follow-up of radiotherapy for pituitary adenoma: the absence of late recurrence after greater than or equal to 4500 cGy. *International journal of radiation oncology, biology, physics.* 1991;21(3):607-614.
68. Mortality in patients with small choroidal melanoma. COMS report no. 4. The Collaborative Ocular Melanoma Study Group. *Arch Ophthalmol.* 1997;115(7):886-893.
69. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. *Arch Ophthalmol.* 2006;124(12):1684-1693.
70. Diener-West M, Hawkins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma. II. A meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. *Arch Ophthalmol.* 1992;110(2):245-250.
71. Hawkins BS. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma: IV. Ten-year mortality findings and prognostic factors. COMS report number 24. *Am J Ophthalmol.* 2004;138(6):936-951.
72. Nag S, Quivey JM, Earle JD, Followill D, Fontanesi J, Finger PT. The American Brachytherapy Society recommendations for brachytherapy of uveal melanomas. *International journal of radiation oncology, biology, physics.* 2003;56(2):544-555.

73. Straatsma BR, Diener-West M, Caldwell R, Engstrom RE. Mortality after deferral of treatment or no treatment for choroidal melanoma. *Am J Ophthalmol.* 2003;136(1):47-54.
74. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1998;16(4):1310-1317.
75. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *International journal of radiation oncology, biology, physics.* 2006;64(1):47-56.
76. Chen QY, Wen YF, Guo L, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. *J Natl Cancer Inst.* 2011;103(23):1761-1770.
77. Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(28):6966-6975.
78. Lee AW, Tung SY, Chan AT, et al. Preliminary results of a randomized study (NPC-9902 Trial) on therapeutic gain by concurrent chemotherapy and/or accelerated fractionation for locally advanced nasopharyngeal carcinoma. *International journal of radiation oncology, biology, physics.* 2006;66(1):142-151.
79. Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(22):3684-3690.
80. Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *International journal of radiation oncology, biology, physics.* 2002;53(1):12-22.
81. Sultanem K, Shu HK, Xia P, et al. Three-dimensional intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: the University of California-San Francisco experience. *International journal of radiation oncology, biology, physics.* 2000;48(3):711-722.
82. Bristol IJ, Ahamad A, Garden AS, et al. Postoperative radiotherapy for maxillary sinus cancer: long-term outcomes and toxicities of treatment. *International journal of radiation oncology, biology, physics.* 2007;68(3):719-730.
83. Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer.* 2001;92(12):3012-3029.
84. Le QT, Fu KK, Kaplan MJ, Terris DJ, Fee WE, Goffinet DR. Lymph node metastasis in maxillary sinus carcinoma. *International journal of radiation oncology, biology, physics.* 2000;46(3):541-549.
85. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med.* 2010;363(1):24-35.
86. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *International journal of radiation oncology, biology, physics.* 2001;51(3):571-578.
87. Beitler JJ, Zhang Q, Fu KK, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *International journal of radiation oncology, biology, physics.* 2014;89(1):13-20.
88. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck.* 2005;27(10):843-850.
89. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350(19):1945-1952.
90. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst.* 1999;91(24):2081-2086.
91. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350(19):1937-1944.
92. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). *International journal of radiation oncology, biology, physics.* 2010;76(5):1333-1338.
93. Grabenbauer GG, Rodel C, Brunner T, et al. Interstitial brachytherapy with Ir-192 low-dose-rate in the treatment of primary and recurrent cancer of the oral cavity and oropharynx. Review of 318 patients treated between 1985 and 1997. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al].* 2001;177(7):338-344.
94. Marcial VA, Pajak TF, Kramer S, et al. Radiation Therapy Oncology Group (RTOG) studies in head and neck cancer. *Semin Oncol.* 1988;15(1):39-60.
95. Martinez-Monge R, Gomez-Iturriaga A, Cambeiro M, et al. Phase I-II trial of perioperative high-dose-rate brachytherapy in oral cavity and oropharyngeal cancer. *Brachytherapy.* 2009;8(1):26-33.
96. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2009;92(1):4-14.
97. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med.* 2007;357(17):1705-1715.
98. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med.* 2007;357(17):1695-1704.
99. Chen AM, Bucci MK, Quivey JM, Garcia J, Eisele DW, Fu KK. Long-term outcome of patients treated by radiation therapy alone for salivary gland carcinomas. *International journal of radiation oncology, biology, physics.* 2006;66(4):1044-1050.
100. Chen AM, Bucci MK, Weinberg V, et al. Adenoid cystic carcinoma of the head and neck treated by surgery with or without postoperative radiation therapy: prognostic features of recurrence. *International journal of radiation oncology, biology, physics.* 2006;66(1):152-159.
101. Chen AM, Garcia J, Lee NY, Bucci MK, Eisele DW. Patterns of nodal relapse after surgery and postoperative radiation therapy for carcinomas of the major and minor salivary glands: what is the role of elective neck irradiation? *International journal of radiation oncology, biology, physics.* 2007;67(4):988-994.
102. Laramore GE, Krall JM, Griffin TW, et al. Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. Radiation Therapy Oncology Group. Medical Research Council. *International journal of radiation oncology, biology, physics.* 1993;27(2):235-240.
103. Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Hinerman RW, Villaret DB. Radiotherapy alone or combined with surgery for adenoid cystic carcinoma of the head and neck. *Head Neck.* 2004;26(2):154-162.
104. Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Villaret DB. Radiotherapy alone or combined with surgery for salivary gland carcinoma. *Cancer.* 2005;103(12):2544-2550.
105. Terhaard CH, Lubsen H, Rasch CR, et al. The role of radiotherapy in the treatment of malignant salivary gland tumors. *International journal of radiation oncology, biology, physics.* 2005;61(1):103-111.
106. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med.* 1991;324(24):1685-1690.
107. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* 2003;349(22):2091-2098.
108. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(7):845-852.

109. Lefebvre JL, Andry G, Chevalier D, et al. Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. *Ann Oncol.* 2012;23(10):2708-2714.
110. Lefebvre JL, Rolland F, Tesselaar M, et al. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. *J Natl Cancer Inst.* 2009;101(3):142-152.
111. Olsen KD. Reexamining the treatment of advanced laryngeal cancer. *Head Neck.* 2010;32(1):1-7.
112. Richard JM, Sancho-Garnier H, Pessey JJ, et al. Randomized trial of induction chemotherapy in larynx carcinoma. *Oral Oncol.* 1998;34(3):224-228.
113. Trotti A, 3rd, Zhang Q, Bentzen SM, et al. Randomized trial of hyperfractionation versus conventional fractionation in T2 squamous cell carcinoma of the vocal cord (RTOG 9512). *International journal of radiation oncology, biology, physics.* 2014;89(5):958-963.
114. Weber RS, Berkey BA, Forastiere A, et al. Outcome of salvage total laryngectomy following organ preservation therapy: the Radiation Therapy Oncology Group trial 91-11. *Arch Otolaryngol Head Neck Surg.* 2003;129(1):44-49.
115. Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *International journal of radiation oncology, biology, physics.* 2006;64(1):77-82.
116. Brierley JD, Panzarella T, Tsang RW, Gospodarowicz MK, O'Sullivan B. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. *Cancer.* 1997;79(12):2414-2423.
117. Chen J, Tward JD, Shrieve DC, Hitchcock YJ. Surgery and radiotherapy improves survival in patients with anaplastic thyroid carcinoma: analysis of the surveillance, epidemiology, and end results 1983-2002. *Am J Clin Oncol.* 2008;31(5):460-464.
118. De Crevoisier R, Baudin E, Bachelot A, et al. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy. *International journal of radiation oncology, biology, physics.* 2004;60(4):1137-1143.
119. Haigh PI, Ituarte PH, Wu HS, et al. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. *Cancer.* 2001;91(12):2335-2342.
120. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer.* 2005;103(7):1330-1335.
121. Robbins RJ, Schlumberger MJ. The evolving role of (131)I for the treatment of differentiated thyroid carcinoma. *J Nucl Med.* 2005;46 Suppl 1:28S-37S.
122. Rosenbluth BD, Serrano V, Happersett L, et al. Intensity-modulated radiation therapy for the treatment of nonanaplastic thyroid cancer. *International journal of radiation oncology, biology, physics.* 2005;63(5):1419-1426.
123. Tennvall J, Lundell G, Hallquist A, Wahlberg P, Wallin G, Tibblin S. Combined doxorubicin, hyperfractionated radiotherapy, and surgery in anaplastic thyroid carcinoma. Report on two protocols. The Swedish Anaplastic Thyroid Cancer Group. *Cancer.* 1994;74(4):1348-1354.
124. Tsang RW, Brierley JD, Simpson WJ, Panzarella T, Gospodarowicz MK, Sutcliffe SB. The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. *Cancer.* 1998;82(2):375-388.
125. Barker CA, Morris CG, Mendenhall WM. Larynx-sparing radiotherapy for squamous cell carcinoma from an unknown head and neck primary site. *Am J Clin Oncol.* 2005;28(5):445-448.
126. Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. *International journal of radiation oncology, biology, physics.* 2001;50(1):55-63.
127. McQuone SJ, Eisele DW, Lee DJ, Westra WH, Koch WM. Occult tonsillar carcinoma in the unknown primary. *Laryngoscope.* 1998;108(11 Pt 1):1605-1610.
128. Reddy SP, Marks JE. Metastatic carcinoma in the cervical lymph nodes from an unknown primary site: results of bilateral neck plus mucosal irradiation vs. ipsilateral neck irradiation. *International journal of radiation oncology, biology, physics.* 1997;37(4):797-802.
129. Shoushtari A, Saylor D, Kerr KL, et al. Outcomes of patients with head-and-neck cancer of unknown primary origin treated with intensity-modulated radiotherapy. *International journal of radiation oncology, biology, physics.* 2011;81(3):e83-91.
130. Ang KK, Peters LJ, Weber RS, et al. Postoperative radiotherapy for cutaneous melanoma of the head and neck region. *International journal of radiation oncology, biology, physics.* 1994;30(4):795-798.
131. Ballo MT, Bonnen MD, Garden AS, et al. Adjuvant irradiation for cervical lymph node metastases from melanoma. *Cancer.* 2003;97(7):1789-1796.
132. Ballo MT, Garden AS, Myers JN, et al. Melanoma metastatic to cervical lymph nodes: Can radiotherapy replace formal dissection after local excision of nodal disease? *Head Neck.* 2005;27(8):718-721.
133. Ballo MT, Strom EA, Zagars GK, et al. Adjuvant irradiation for axillary metastases from malignant melanoma. *International journal of radiation oncology, biology, physics.* 2002;52(4):964-972.
134. Beadle BM, Guadagnolo BA, Ballo MT, et al. Radiation therapy field extent for adjuvant treatment of axillary metastases from malignant melanoma. *International journal of radiation oncology, biology, physics.* 2009;73(5):1376-1382.
135. Bonnen MD, Ballo MT, Myers JN, et al. Elective radiotherapy provides regional control for patients with cutaneous melanoma of the head and neck. *Cancer.* 2004;100(2):383-389.
136. Burmeister BH, Mark Smithers B, Burmeister E, et al. A prospective phase II study of adjuvant postoperative radiation therapy following nodal surgery in malignant melanoma-Trans Tasman Radiation Oncology Group (TROG) Study 96.06. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2006;81(2):136-142.
137. Chang DT, Amdur RJ, Morris CG, Mendenhall WM. Adjuvant radiotherapy for cutaneous melanoma: comparing hypofractionation to conventional fractionation. *International journal of radiation oncology, biology, physics.* 2006;66(4):1051-1055.
138. Overgaard J. The role of radiotherapy in recurrent and metastatic malignant melanoma: a clinical radiobiological study. *International journal of radiation oncology, biology, physics.* 1986;12(6):867-872.
139. Overgaard J, Gonzalez Gonzalez D, Hulshof MC, et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. European Society for Hyperthermic Oncology. *Lancet.* 1995;345(8949):540-543.
140. Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. *International journal of radiation oncology, biology, physics.* 1991;20(3):429-432.
141. Avril MF, Auperin A, Margulis A, et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. *British journal of cancer.* 1997;76(1):100-106.
142. Balamucki CJ, Mancuso AA, Amdur RJ, et al. Skin carcinoma of the head and neck with perineural invasion. *Am J Otolaryngol.* 2012;33(4):447-454.
143. Garcia-Serra A, Hinerman RW, Mendenhall WM, et al. Carcinoma of the skin with perineural invasion. *Head Neck.* 2003;25(12):1027-1033.
144. Mendenhall WM, Parsons JT, Mendenhall NP, Million RR. T2-T4 carcinoma of the skin of the head and neck treated with radical irradiation. *International journal of radiation oncology, biology, physics.* 1987;13(7):975-981.
145. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol.* 2010;146(3):283-287.
146. Mendenhall WM, Kirwan JM, Morris CG, Amdur RJ, Werning JW, Mendenhall NP. Cutaneous Merkel cell carcinoma. *Am J Otolaryngol.* 2012;33(1):88-92.
147. Mojica P, Smith D, Ellenhorn JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(9):1043-1047.

148. Poulsen M, Rischin D, Walpole E, et al. High-risk Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: a Trans-Tasman Radiation Oncology Group Study--TROG 96:07. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2003;21(23):4371-4376.
149. Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *International journal of radiation oncology, biology, physics.* 2005;61(2):318-328.
150. Dosoretz DE, Katin MJ, Blitzer PH, et al. Medically Inoperable Lung Carcinoma: The Role of Radiation Therapy. *Semin Radiat Oncol.* 1996;6(2):98-104.
151. Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet.* 2007;369(9577):1929-1937.
152. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg.* 1995;60(3):615-622; discussion 622-613.
153. Moiseenko V, Liu M, Bergman AM, et al. Monte Carlo calculation of dose distribution in early stage NSCLC patients planned for accelerated hypofractionated radiation therapy in the NCIC-BR25 protocol. *Physics in medicine and biology.* 2010;55(3):723-733.
154. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer.* 2004;101(7):1623-1631.
155. Sibley GS, Jamieson TA, Marks LB, Anscher MS, Prosnitz LR. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. *International journal of radiation oncology, biology, physics.* 1998;40(1):149-154.
156. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(30):4833-4839.
157. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *Jama.* 2010;303(11):1070-1076.
158. Trodella L, Granone P, Valente S, et al. Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2002;62(1):11-19.
159. Postoperative radiotherapy for non-small cell lung cancer. *The Cochrane database of systematic reviews.* 2005(2):CD002142.
160. PL03.05 An intergroup randomized phase III comparison of standard-dose (60 Gy) vs high-dose (74 Gy) chemoradiotherapy (CRT) +/- cetuximab (cetux) for stage III non-small cell lung cancer (NSCLC): results on cetux from RTOG 0617. *Clin Adv Hematol Oncol.* 2014;12(1 Suppl 1):2-4.
161. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet.* 2009;374(9687):379-386.
162. Ball D, Bishop J, Smith J, et al. A randomised phase III study of accelerated or standard fraction radiotherapy with or without concurrent carboplatin in inoperable non-small cell lung cancer: final report of an Australian multi-centre trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 1999;52(2):129-136.
163. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(25):5883-5891.
164. Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF. A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1990;8(9):1543-1555.
165. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med.* 1990;323(14):940-945.
166. Gore EM, Bae K, Wong SJ, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(3):272-278.
167. Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. *N Engl J Med.* 2000;343(17):1217-1222.
168. Perez CA, Stanley K, Rubin P, et al. Patterns of tumor recurrence after definitive irradiation for inoperable non-oat cell carcinoma of the lung. *International journal of radiation oncology, biology, physics.* 1980;6(8):987-994.
169. Rosell R, Gomez-Codina J, Camps C, et al. Preresectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial. *Lung Cancer.* 1999;26(1):7-14.
170. Roth JA, Atkinson EN, Fossella F, et al. Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *Lung Cancer.* 1998;21(1):1-6.
171. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: Initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Thorac Cardiovasc Surg.* 2001;121(3):472-483.
172. Sause W, Kolesar P, Taylor SI, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest.* 2000;117(2):358-364.
173. Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *The Lancet. Oncology.* 2008;9(7):636-648.
174. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst.* 2007;99(6):442-450.
175. Weisenburger TH. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. LCSG 773. *Chest.* 1994;106(6 Suppl):297S-301S.
176. Werner-Wasik M, Paulus R, Curran WJ, Jr., Byhardt R. Acute esophagitis and late lung toxicity in concurrent chemoradiotherapy trials in patients with locally advanced non-small-cell lung cancer: analysis of the radiation therapy oncology group (RTOG) database. *Clin Lung Cancer.* 2011;12(4):245-251.
177. Stinchcombe TE, Hodgson L, Herndon JE, et al. "Treatment outcomes of different prognostic groups of patients on Cancer and Leukemia Group B trial 39801: Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for unresectable stage III non-small cell lung cancer". *J Thorac Oncol.* 2009;4(9):1117-1125.
178. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med.* 1999;341(7):476-484.
179. Choi NC, Herndon JE, 2nd, Rosenman J, et al. Phase I study to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1998;16(11):3528-3536.
180. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1999;17(7):2092-2099.
181. Le Pechoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *The Lancet. Oncology.* 2009;10(5):467-474.

182. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med.* 1992;327(23):1618-1624.
183. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med.* 2007;357(7):664-672.
184. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet.* 2015;385(9962):36-42.
185. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2002;20(14):3054-3060.
186. Turrisi AT, 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med.* 1999;340(4):265-271.
187. Forquer JA, Rong N, Fakiris AJ, Loehrer PJ, Sr., Johnstone PA. Postoperative radiotherapy after surgical resection of thymoma: differing roles in localized and regional disease. *International journal of radiation oncology, biology, physics.* 2010;76(2):440-445.
188. Haniuda M, Miyazawa M, Yoshida K, et al. Is postoperative radiotherapy for thymoma effective? *Annals of surgery.* 1996;224(2):219-224.
189. Mangi AA, Wright CD, Allan JS, et al. Adjuvant radiation therapy for stage II thymoma. *Ann Thorac Surg.* 2002;74(4):1033-1037.
190. Mornex F, Resbeut M, Richaud P, et al. Radiotherapy and chemotherapy for invasive thymomas: a multicentric retrospective review of 90 cases. The FNCLCC trialists. Federation Nationale des Centres de Lutte Contre le Cancer. *International journal of radiation oncology, biology, physics.* 1995;32(3):651-659.
191. Wright CD. Management of thymomas. *Critical reviews in oncology/hematology.* 2008;65(2):109-120.
192. Flores RM, Krug LM, Rosenzweig KE, et al. Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma: a phase II trial. *J Thorac Oncol.* 2006;1(4):289-295.
193. Rusch VW, Rosenzweig K, Venkatraman E, et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg.* 2001;122(4):788-795.
194. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2003;21(14):2636-2644.
195. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(21):3381-3387.
196. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet.* 1999;353(9169):1993-2000.
197. Holmberg L, Garmo H, Granstrand B, et al. Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(8):1247-1252.
198. Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. *Lancet.* 2003;362(9378):95-102.
199. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst.* 2011;103(6):478-488.
200. Dunne C, Burke JP, Morrow M, Kell MR. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(10):1615-1620.
201. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(22):3259-3265.
202. Bellon JR, Come SE, Gelman RS, et al. Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: updated results of a prospective randomized trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(9):1934-1940.
203. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *The Lancet. Oncology.* 2008;9(4):331-341.
204. Buchholz TA, Lehman CD, Harris JR, et al. Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: a National Cancer Institute conference. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(5):791-797.
205. Cascinelli N, Greco M, Bufalino R, et al. Prognosis of breast cancer with axillary node metastases after surgical treatment only. *Eur J Cancer Clin Oncol.* 1987;23(6):795-799.
206. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347(16):1233-1241.
207. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2002;20(20):4141-4149.
208. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med.* 2002;347(8):567-575.
209. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *The Lancet. Oncology.* 2013;14(11):1086-1094.
210. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med.* 2004;351(10):971-977.
211. Krag DN, Anderson SJ, Julian TB, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *The Lancet. Oncology.* 2007;8(10):881-888.
212. Romestaing P, Lehingue Y, Carrie C, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1997;15(3):963-968.
213. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst.* 2000;92(14):1143-1150.
214. Vernon CC, Hand JW, Field SB, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. International Collaborative Hyperthermia Group. *International journal of radiation oncology, biology, physics.* 1996;35(4):731-744.
215. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347(16):1227-1232.
216. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* 2010;362(6):513-520.
217. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *International journal of radiation oncology, biology, physics.* 2009;74(4):987-1001.
218. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2003;21(8):1431-1439.

219. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;366(9503):2087-2106.
220. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst.* 2001;93(9):684-690.
221. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. *J Natl Cancer Inst.* 1997;89(22):1673-1682.
222. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet.* 2005;365(9453):60-62.
223. Mamounas EP, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(16):3686-3696.
224. McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet.* 2014;383(9935):2127-2135.
225. Olson JA, Jr., McCall LM, Beitsch P, et al. Impact of immediate versus delayed axillary node dissection on surgical outcomes in breast cancer patients with positive sentinel nodes: results from American College of Surgeons Oncology Group Trials Z0010 and Z0011. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(21):3530-3535.
226. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med.* 1997;337(14):949-955.
227. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet.* 1999;353(9165):1641-1648.
228. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 2005;353(16):1673-1684.
229. Truong PT, Olivotto IA, Kader HA, Panades M, Speers CH, Berthelet E. Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. *International journal of radiation oncology, biology, physics.* 2005;61(5):1337-1347.
230. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *Journal of the National Cancer Institute. Monographs.* 2001(30):96-102.
231. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med.* 1997;337(3):161-167.
232. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *The Lancet. Oncology.* 2005;6(9):659-668.
233. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *Jama.* 1999;281(17):1623-1627.
234. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355(1):11-20.
235. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *The Lancet. Oncology.* 2007;8(3):226-234.
236. Kelsen DP, Winter KA, Gunderson LL, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(24):3719-3725.
237. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2002;20(5):1167-1174.
238. Peyre CG, Hagen JA, DeMeester SR, et al. Predicting systemic disease in patients with esophageal cancer after esophagectomy: a multinational study on the significance of the number of involved lymph nodes. *Annals of surgery.* 2008;248(6):979-985.
239. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(6):851-856.
240. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(7):1086-1092.
241. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* 2012;366(22):2074-2084.
242. Ajani JA, Winter K, Okawara GS, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(24):3953-3958.
243. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* 2010;376(9742):687-697.
244. Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. *N Engl J Med.* 1999;340(12):908-914.
245. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *British journal of cancer.* 1999;79(9-10):1522-1530.
246. Gouzi JL, Huguier M, Fagniez PL, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. *Annals of surgery.* 1989;209(2):162-166.
247. Hartgrink HH, van de Velde CJ, Putter H, et al. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 2004;30(6):643-649.
248. Kim HH, Hyung WJ, Cho GS, et al. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report--a phase III multicenter, prospective, randomized Trial (KLASS Trial). *Annals of surgery.* 2010;251(3):417-420.
249. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med.* 2001;345(10):725-730.
250. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med.* 2008;359(5):453-462.
251. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol.* 2008;19(9):1592-1599.
252. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011;364(19):1817-1825.

253. Corsini MM, Miller RC, Haddock MG, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975-2005). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(21):3511-3516.
254. Hazard L, Tward JD, Szabo A, Shrieve DC. Radiation therapy is associated with improved survival in patients with pancreatic adenocarcinoma: results of a study from the Surveillance, Epidemiology, and End Results (SEER) registry data. *Cancer.* 2007;110(10):2191-2201.
255. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(21):3503-3510.
256. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg.* 1985;120(8):899-903.
257. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer.* 2007;110(1):47-55.
258. Loehrer PJ, Sr., Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(31):4105-4112.
259. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet.* 2001;358(9293):1576-1585.
260. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *Jama.* 2007;297(3):267-277.
261. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *Jama.* 2008;299(9):1019-1026.
262. Rich T, Harris J, Abrams R, et al. Phase II study of external irradiation and weekly paclitaxel for nonmetastatic, unresectable pancreatic cancer: RTOG-98-12. *Am J Clin Oncol.* 2004;27(1):51-56.
263. Smeenk HG, van Eijck CH, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. *Annals of surgery.* 2007;246(5):734-740.
264. Stocken DD, Buchler MW, Dervenis C, et al. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. *British journal of cancer.* 2005;92(8):1372-1381.
265. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(6):504-512.
266. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013;369(18):1691-1703.
267. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(13):1631-1639.
268. Dawson LA, Hashem S, Bujold A. Stereotactic body radiation therapy for hepatocellular carcinoma. *Am Soc Clin Oncol Educ Book.* 2012:261-264.
269. Lau WY, Lai EC. Treatment of unresectable hepatocellular carcinoma with transarterial radioembolization: iodine-131-lipiodol. *ANZ J Surg.* 2008;78(5):331-332.
270. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359(4):378-390.
271. Meng MB, Cui YL, Lu Y, et al. Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2009;92(2):184-194.
272. Russell AH, Clyde C, Wasserman TH, Turner SS, Rotman M. Accelerated hyperfractionated hepatic irradiation in the management of patients with liver metastases: results of the RTOG dose escalating protocol. *International journal of radiation oncology, biology, physics.* 1993;27(1):117-123.
273. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(10):1572-1578.
274. Soliman H, Ringash J, Jiang H, et al. Phase II trial of palliative radiotherapy for hepatocellular carcinoma and liver metastases. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(31):3980-3986.
275. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(4):657-664.
276. Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(28):4379-4386.
277. Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst.* 1988;80(1):21-29.
278. Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum.* 1993;36(6):564-572.
279. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(28):4620-4625.
280. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med.* 1991;324(11):709-715.
281. Martenson JA, Jr., Willett CG, Sargent DJ, et al. Phase III study of adjuvant chemotherapy and radiation therapy compared with chemotherapy alone in the surgical adjuvant treatment of colon cancer: results of intergroup protocol 0130. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2004;22(16):3277-3283.
282. Pahlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. *Annals of surgery.* 1990;211(2):187-195.
283. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Annals of surgery.* 2007;246(5):693-701.
284. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(31):5124-5130.
285. Russell AH, Harris J, Rosenberg PJ, et al. Anal sphincter conservation for patients with adenocarcinoma of the distal rectum: long-term results of radiation therapy oncology group protocol 89-02. *International journal of radiation oncology, biology, physics.* 2000;46(2):313-322.
286. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004;351(17):1731-1740.
287. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *Jama.* 2008;299(16):1914-1921.
288. Bartelink H, Roelofsen F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1997;15(5):2040-2049.
289. Boman BM, Moertel CG, O'Connell MJ, et al. Carcinoma of the anal canal. A clinical and pathologic study of 188 cases. *Cancer.* 1984;54(1):114-125.

290. Deniaud-Alexandre E, Touboul E, Tiret E, et al. [Epidermoid carcinomas of the anal canal treated with definitive radiation therapy in a series of 305 patients]. *Cancer Radiother.* 2003;7(4):237-253.
291. Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1996;14(9):2527-2539.
292. Glynne-Jones R, Meadows H, Wan S, et al. EXTRA--a multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. *International journal of radiation oncology, biology, physics.* 2008;72(1):119-126.
293. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 x 2 factorial trial. *The Lancet. Oncology.* 2013;14(6):516-524.
294. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *International journal of radiation oncology, biology, physics.* 2013;86(1):27-33.
295. Nigro ND, Vaitkevicius VK, Considine B, Jr. Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum.* 1974;17(3):354-356.
296. Northover J, Glynne-Jones R, Sebag-Montefiore D, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). *British journal of cancer.* 2010;102(7):1123-1128.
297. Salama JK, Mell LK, Schomas DA, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(29):4581-4586.
298. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med.* 2005;352(19):1977-1984.
299. Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *The Lancet. Oncology.* 2007;8(6):475-487.
300. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *International journal of radiation oncology, biology, physics.* 2008;70(1):67-74.
301. Kupelian PA, Elshaikh M, Reddy CA, Zippe C, Klein EA. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2002;20(16):3376-3385.
302. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(13):1990-1996.
303. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(34):5366-5373.
304. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(7):1106-1111.
305. Asbell SO, Krall JM, Pilepich MV, et al. Elective pelvic irradiation in stage A2, B carcinoma of the prostate: analysis of RTOG 77-06. *International journal of radiation oncology, biology, physics.* 1988;15(6):1307-1316.
306. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet.* 2002;360(9327):103-106.
307. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med.* 2009;360(24):2516-2527.
308. Crook J, Patil N, Wallace K, et al. A phase III randomized trial of the timing of meloxicam with iodine-125 prostate brachytherapy. *International journal of radiation oncology, biology, physics.* 2010;77(2):496-501.
309. Denham JW, Steigler A, Lamb DS, et al. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial. *The Lancet. Oncology.* 2005;6(11):841-850.
310. Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(15):2497-2504.
311. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med.* 2011;365(2):107-118.
312. Lawton CA, DeSilvio M, Roach M, 3rd, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *International journal of radiation oncology, biology, physics.* 2007;69(3):646-655.
313. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. *International journal of radiation oncology, biology, physics.* 2005;61(5):1285-1290.
314. Roach M, 3rd, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(4):585-591.
315. Steigler A, Denham JW, Lamb DS, et al. Risk Stratification after Biochemical Failure following Curative Treatment of Locally Advanced Prostate Cancer: Data from the TROG 96.01 Trial. *Prostate Cancer.* 2012;2012:814724.
316. Stephenson AJ, Kattan MW, Eastham JA, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(26):4300-4305.
317. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet.* 2009;373(9660):301-308.
318. Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet.* 2005;366(9485):572-578.
319. King CR, Presti JC, Jr., Gill H, Brooks J, Hancock SL. Radiotherapy after radical prostatectomy: does transient androgen suppression improve outcomes? *International journal of radiation oncology, biology, physics.* 2004;59(2):341-347.
320. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *The Lancet. Oncology.* 2006;7(6):472-479.
321. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol.* 2009;181(3):956-962.
322. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(18):2924-2930.
323. Zagars GK, Pollack A, von Eschenbach AC. Addition of radiation therapy to androgen ablation improves outcome for subclinically node-positive prostate cancer. *Urology.* 2001;58(2):233-239.

324. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet.* 2003;361(9373):1927-1934.
325. Cole CJ, Pollack A, Zagars GK, Dinney CP, Swanson DA, von Eschenbach AC. Local control of muscle-invasive bladder cancer: preoperative radiotherapy and cystectomy versus cystectomy alone. *International journal of radiation oncology, biology, physics.* 1995;32(2):331-340.
326. Coppin CM, Gospodarowicz MK, James K, et al. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1996;14(11):2901-2907.
327. Kaufman DS, Winter KA, Shipley WU, et al. The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. *Oncologist.* 2000;5(6):471-476.
328. Kaufman DS, Winter KA, Shipley WU, et al. Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology.* 2009;73(4):833-837.
329. Shipley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1998;16(11):3576-3583.
330. Tester W, Porter A, Asbell S, et al. Combined modality program with possible organ preservation for invasive bladder carcinoma: results of RTOG protocol 85-12. *International journal of radiation oncology, biology, physics.* 1993;25(5):783-790.
331. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(13):2144-2150.
332. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007;356(2):125-134.
333. Kjaer M, Iversen P, Hvidt V, et al. A randomized trial of postoperative radiotherapy versus observation in stage II and III renal adenocarcinoma. A study by the Copenhagen Renal Cancer Study Group. *Scand J Urol Nephrol.* 1987;21(4):285-289.
334. Motzer RJ, Basch E. Targeted drugs for metastatic renal cell carcinoma. *Lancet.* 2007;370(9605):2071-2073.
335. Stein M, Kuten A, Halpern J, Coachman NM, Cohen Y, Robinson E. The value of postoperative irradiation in renal cell cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 1992;24(1):41-44.
336. Dalbagni G, Zhang ZF, Lacombe L, Herr HW. Male urethral carcinoma: analysis of treatment outcome. *Urology.* 1999;53(6):1126-1132.
337. Eng TY, Naguib M, Galang T, Fuller CD. Retrospective study of the treatment of urethral cancer. *Am J Clin Oncol.* 2003;26(6):558-562.
338. Heysek RV, Parsons JT, Drylie DM, Million RR. Carcinoma of the male urethra. *J Urol.* 1985;134(4):753-755.
339. Krieg R, Hoffman R. Current management of unusual genitourinary cancers. Part 2: Urethral cancer. *Oncology (Williston Park, N.Y.).* 1999;13(11):1511-1517, 1520; discussion 1523-1514.
340. Fossa SD, Horwich A, Russell JM, et al. Optimal planning target volume for stage I testicular seminoma: A Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1999;17(4):1146.
341. Jones WG, Fossa SD, Mead GM, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I Testicular Seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(6):1200-1208.
342. Oliver RT, Mason MD, Mead GM, et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. *Lancet.* 2005;366(9482):293-300.
343. Crook JM, Jezioranski J, Grimard L, Esche B, Pond G. Penile brachytherapy: results for 49 patients. *International journal of radiation oncology, biology, physics.* 2005;62(2):460-467.
344. Grabstald H, Kelley CD. Radiation therapy of penile cancer: six to ten-year follow-up. *Urology.* 1980;15(6):575-576.
345. Krieg RM, Luk KH. Carcinoma of penis. Review of cases treated by surgery and radiation therapy 1960-1977. *Urology.* 1981;18(2):149-154.
346. Mazeron JJ, Langlois D, Lobo PA, et al. Interstitial radiation therapy for carcinoma of the penis using iridium 192 wires: the Henri Mondor experience (1970-1979). *International journal of radiation oncology, biology, physics.* 1984;10(10):1891-1895.
347. McLean M, Akl AM, Warde P, Bissett R, Panzarella T, Gospodarowicz M. The results of primary radiation therapy in the management of squamous cell carcinoma of the penis. *International journal of radiation oncology, biology, physics.* 1993;25(4):623-628.
348. Sarin R, Norman AR, Steel GG, Horwich A. Treatment results and prognostic factors in 101 men treated for squamous carcinoma of the penis. *International journal of radiation oncology, biology, physics.* 1997;38(4):713-722.
349. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2004;22(5):872-880.
350. Keys HM, Bundy BN, Stehman FB, et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. *Gynecol Oncol.* 2003;89(3):343-353.
351. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet.* 1997;350(9077):535-540.
352. Pearcey R, Brundage M, Drouin P, et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2002;20(4):966-972.
353. Peters WA, 3rd, Liu PY, Barrett RJ, 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2000;18(8):1606-1613.
354. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med.* 1999;340(15):1144-1153.
355. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecol Oncol.* 1999;73(2):177-183.
356. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstetrics and gynecology.* 1980;56(4):419-427.
357. Greven K, Winter K, Underhill K, Fontenesci J, Cooper J, Burke T. Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. *Gynecol Oncol.* 2006;103(1):155-159.
358. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2004;92(3):744-751.
359. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet.* 2010;375(9717):816-823.

360. Nout RA, van de Poll-Franse LV, Lybeert ML, et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(13):1692-1700.
361. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(1):36-44.
362. Giuntoli RL, 2nd, Metzinger DS, DiMarco CS, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. *Gynecol Oncol.* 2003;89(3):460-469.
363. Reed NS, Mangioni C, Malmstrom H, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). *European journal of cancer (Oxford, England : 1990).* 2008;44(6):808-818.
364. Wolfson AH, Brady MF, Rocereto T, et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. *Gynecol Oncol.* 2007;107(2):177-185.
365. Wright JD, Seshan VE, Shah M, et al. The role of radiation in improving survival for early-stage carcinosarcoma and leiomyosarcoma. *Am J Obstet Gynecol.* 2008;199(5):536 e531-538.
366. Katz A, Eifel PJ, Jhingran A, Levenback CF. The role of radiation therapy in preventing regional recurrences of invasive squamous cell carcinoma of the vulva. *International journal of radiation oncology, biology, physics.* 2003;57(2):409-418.
367. Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. *Obstetrics and gynecology.* 2009;114(3):537-546.
368. Moore DH, Ali S, Koh WJ, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. *Gynecol Oncol.* 2012;124(3):529-533.
369. Moore DH, Thomas GM, Montana GS, Saxer A, Gallup DG, Olt G. Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group. *International journal of radiation oncology, biology, physics.* 1998;42(1):79-85.
370. Stehman FB, Bundy BN, Thomas G, et al. Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group study. *International journal of radiation oncology, biology, physics.* 1992;24(2):389-396.
371. Montana GS, Thomas GM, Moore DH, et al. Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a gynecologic oncology group study. *International journal of radiation oncology, biology, physics.* 2000;48(4):1007-1013.
372. de Crevoisier R, Sanfilippo N, Gerbaulet A, et al. Exclusive radiotherapy for primary squamous cell carcinoma of the vagina. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2007;85(3):362-370.
373. Frank SJ, Jhingran A, Levenback C, Eifel PJ. Definitive radiation therapy for squamous cell carcinoma of the vagina. *International journal of radiation oncology, biology, physics.* 2005;62(1):138-147.
374. Lian J, Dundas G, Carlone M, Ghosh S, Pearcey R. Twenty-year review of radiotherapy for vaginal cancer: an institutional experience. *Gynecol Oncol.* 2008;111(2):298-306.
375. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin versus paclitaxel and cisplatin: a phase III randomized trial in patients with suboptimal stage III/IV ovarian cancer (from the Gynecologic Oncology Group). *Semin Oncol.* 1996;23(5 Suppl 12):40-47.
376. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2003;21(17):3194-3200.
377. Smith JP, Rutledge FN, Delclos L. Postoperative treatment of early cancer of the ovary: a random trial between postoperative irradiation and chemotherapy. *Natl Cancer Inst Monogr.* 1975;42:149-153.
378. Wenzel LB, Huang HQ, Armstrong DK, Walker JL, Cella D. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(4):437-443.
379. Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med.* 2003;348(24):2396-2406.
380. Engert A, Franklin J, Eich HT, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(23):3495-3502.
381. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med.* 2010;363(7):640-652.
382. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2003;21(19):3601-3608.
383. Ferme C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med.* 2007;357(19):1916-1927.
384. Laskar S, Gupta T, Vimal S, et al. Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2004;22(1):62-68.
385. Longo DL, Glatstein E, Duffey PL, et al. Radiation therapy versus combination chemotherapy in the treatment of early-stage Hodgkin's disease: seven-year results of a prospective randomized trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1991;9(6):906-917.
386. Noordijk EM, Carde P, Dupouy N, et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(19):3128-3135.
387. Press OW, LeBlanc M, Lichter AS, et al. Phase III randomized intergroup trial of subtotal lymphoid irradiation versus doxorubicin, vinblastine, and subtotal lymphoid irradiation for stage IA to IIA Hodgkin's disease. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2001;19(22):4238-4244.
388. Bonnet C, Fillet G, Mounier N, et al. CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(7):787-792.
389. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2004;22(15):3032-3038.
390. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med.* 1998;339(1):21-26.
391. Tournier-Rangeard L, Lapeyre M, Graff-Caillaud P, et al. Radiotherapy for solitary extramedullary plasmacytoma in the head-and-neck region: A dose greater than 45 Gy to the target volume improves the local control. *International journal of radiation oncology, biology, physics.* 2006;64(4):1013-1017.

392. Tsang RW, Gospodarowicz MK, Pintilie M, et al. Solitary plasmacytoma treated with radiotherapy: impact of tumor size on outcome. *International journal of radiation oncology, biology, physics.* 2001;50(1):113-120.
393. Eilber F, Giuliano A, Eckardt J, Patterson K, Moseley S, Goodnight J. Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1987;5(1):21-26.
394. Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J Med.* 1986;314(25):1600-1606.
395. Ozaki T, Flege S, Kevric M, et al. Osteosarcoma of the pelvis: experience of the Cooperative Osteosarcoma Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2003;21(2):334-341.
396. DeLaney TF, Spiro IJ, Suit HD, et al. Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. *International journal of radiation oncology, biology, physics.* 2003;56(4):1117-1127.
397. Kirova YM, Belembaogo E, Frikha H, et al. Radiotherapy in the management of epidemic Kaposi's sarcoma: a retrospective study of 643 cases. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 1998;46(1):19-22.
398. Kraybill WG, Harris J, Spiro IJ, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(4):619-625.
399. Mendenhall WM, Zlotecki RA, Hochwald SN, Hemming AW, Grobmyer SR, Cance WG. Retroperitoneal soft tissue sarcoma. *Cancer.* 2005;104(4):669-675.
400. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet.* 2002;359(9325):2235-2241.
401. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer.* 2008;113(3):573-581.
402. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1996;14(3):859-868.
403. Pollack A, Zagars GK, Goswitz MS, Pollock RA, Feig BW, Pisters PW. Preoperative vs. postoperative radiotherapy in the treatment of soft tissue sarcomas: a matter of presentation. *International journal of radiation oncology, biology, physics.* 1998;42(3):563-572.
404. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Annals of surgery.* 1982;196(3):305-315.
405. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1998;16(1):197-203.
406. Crago AM, Denton B, Salas S, et al. A prognostic nomogram for prediction of recurrence in desmoid fibromatosis. *Annals of surgery.* 2013;258(2):347-353.
407. Nuyttens JJ, Rust PF, Thomas CR, Jr., Turrisi AT, 3rd. Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors: A comparative review of 22 articles. *Cancer.* 2000;88(7):1517-1523.
408. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet.* 2004;363(9422):1665-1672.
409. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *Jama.* 2006;295(21):2483-2491.
410. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *The Lancet. Oncology.* 2009;10(11):1037-1044.
411. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *International journal of radiation oncology, biology, physics.* 1997;37(4):745-751.
412. Gelber RD, Larson M, Borgelt BB, Kramer S. Equivalence of radiation schedules for the palliative treatment of brain metastases in patients with favorable prognosis. *Cancer.* 1981;48(8):1749-1753.
413. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(2):134-141.
414. Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favorable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group. *International journal of radiation oncology, biology, physics.* 1981;7(7):891-895.
415. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *Jama.* 1998;280(17):1485-1489.
416. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990;322(8):494-500.
417. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet.* 2005;366(9486):643-648.
418. Rades D, Lange M, Veninga T, et al. Preliminary results of spinal cord compression recurrence evaluation (score-1) study comparing short-course versus long-course radiotherapy for local control of malignant epidural spinal cord compression. *International journal of radiation oncology, biology, physics.* 2009;73(1):228-234.
419. Rades D, Rudat V, Veninga T, Stalpers LJ, Hoskin PJ, Schild SE. Prognostic factors for functional outcome and survival after reirradiation for in-field recurrences of metastatic spinal cord compression. *Cancer.* 2008;113(5):1090-1096.
420. Rades D, Stalpers LJ, Veninga T, et al. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(15):3366-3375.
421. Vecht CJ, Haaxma-Reiche H, van Putten WL, de Visser M, Vries EP, Twijnstra A. Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. *Neurology.* 1989;39(9):1255-1257.
422. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 1999;52(2):111-121.
423. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(11):1423-1436.
424. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. *Spine (Phila Pa 1976).* 2007;32(2):193-199.
425. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst.* 2005;97(11):798-804.
426. Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res.* 1989(249):256-264.

427. Townsend PW, Rosenthal HG, Smalley SR, Cozad SC, Hassanein RE. Impact of postoperative radiation therapy and other perioperative factors on outcome after orthopedic stabilization of impending or pathologic fractures due to metastatic disease. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1994;12(11):2345-2350.
428. Van der Linden YM, Dijkstra PD, Kroon HM, et al. Comparative analysis of risk factors for pathological fracture with femoral metastases. *J Bone Joint Surg Br*. 2004;86(4):566-573.