Renal Cancer

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Kidney Anatomy

- Paired retroperitoneal organ
- ~ 3 vertebral bodies long
- Centered at L1 and L2
- Between **T12-L3**
- Right lower than left
- Liver pushes right one down
- Gerotia's fascia encompasses:
  - Kidney
  - Adrenal gland
  - Perirenal fat
- Para Aortic lymph node drainage
- Adjacent to many vital organs

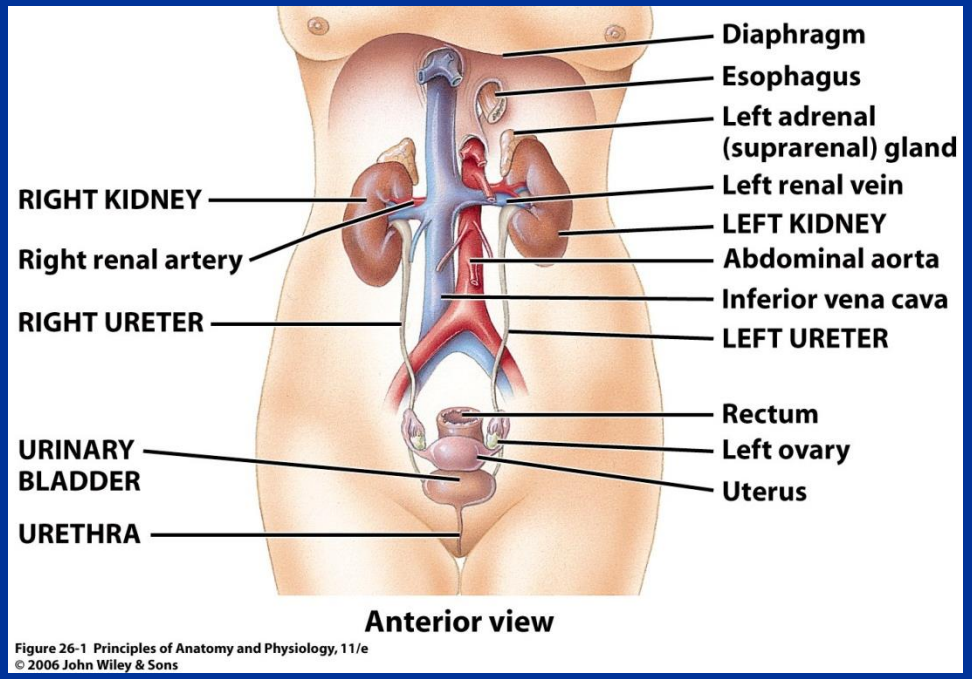


Figure 26-1 Principles of Anatomy and Physiology, 11/e
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Epidemiology

- 2% all new US cancers
- 2007: 51,000 new cases, 13,000 deaths (BOTH INCREASING)

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Epidemiology

- 2% all new US cancers
- 2026 estimates:
  - 80,450 new cases - increased 1990-2000s partly due to newer imaging and thus more incidental findings. Leveling off more recently
  - 15,160 deaths (falling slightly)
- Peak incidence **55-74** years old. Avg age 65
- M:F = 2:1
- Race
  - Highest incidence –African Americans, American Indians, Alaska Natives
  - Lowest incidence – Californian Asian/Pacific Islanders

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Acquired Risk Factors

- Smoking
- Obesity
- Family History
- Diabetes
- Hypertension
- Exposures:
  - Leather tanning
    - Asbestos
    - Cadmium
    - Trichloroethylene
  - Automotive gasoline fumes, diesel exhaust
  - Pain killers (phenacetin, acetaminophen)
  - Not alcohol

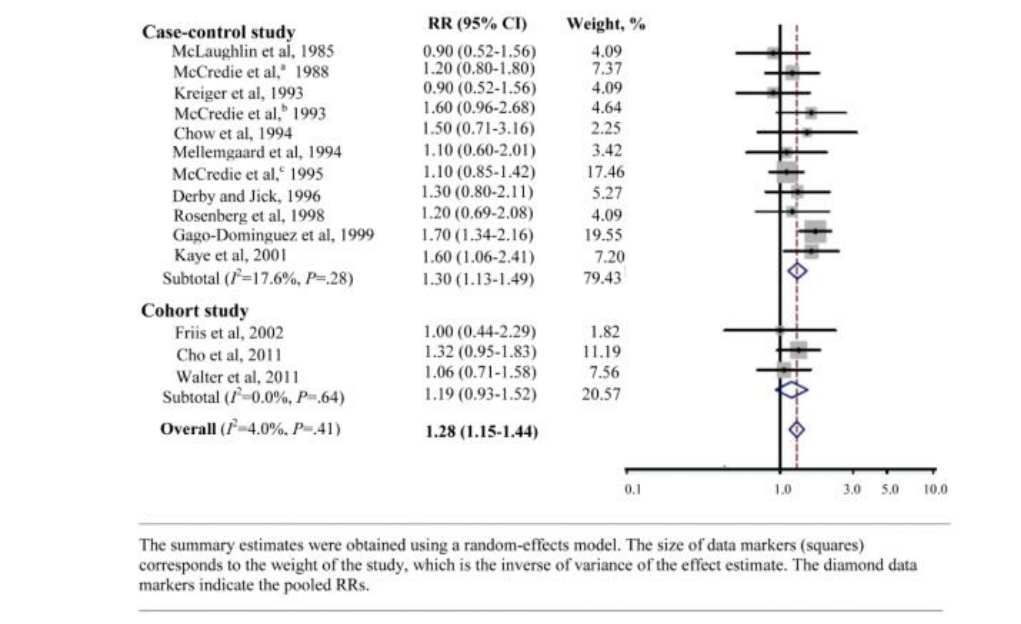


Figure 1.
Adjusted Relative Risks (RRs) of Kidney Cancer Associated with Acetaminophen Use

Choueiri *Int J Cancer* 2014

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Genetic Risk Factors (Family History)

- Von Hippel Lindau disease (VHL gene)
- Familial Renal Cancer (SDHB and SDHD genes)
- Hereditary papillary renal carcinoma (MET gene)
- Birt-Hogg-Dube (BHD) syndrome (FLCN gene)
- Cowden syndrome (PTEN gene)
- Tuberous sclerosis (TSC1 and TSC2 genes)
- BAP1 tumor predisposition syndrome (BAP1 gene)

Possible role for screening CT in high risk patients. Not for average risk.

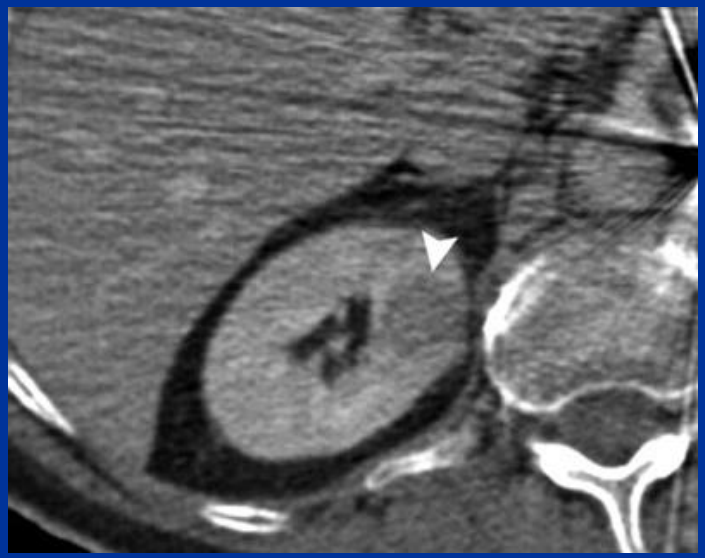
Clinical Presentation

- **"Classic" Triad** (only 10% with all 3)
  - Hematuria (bloody or dark/rusty/brown urine) 60%
  - Flank Pain 45%
  - Abdominal Mass 40%
- Fever
- Weight loss
- High blood pressure
- High blood calcium
- Ruddy or pale complexion (anemia vs. erythrocytosis)
- Metastatic symptoms
  - Bony pain, cough, headache, neurologic symptoms
- Increased incidence of incidental finding on imaging
  - Found earlier, better prognosis

Differential Diagnosis of Solid Renal Lesions

- Renal cell carcinoma (#1, 85%)
  - 70% Clear cell histology
  - 20% Papillary
  - 5% Chromophobe

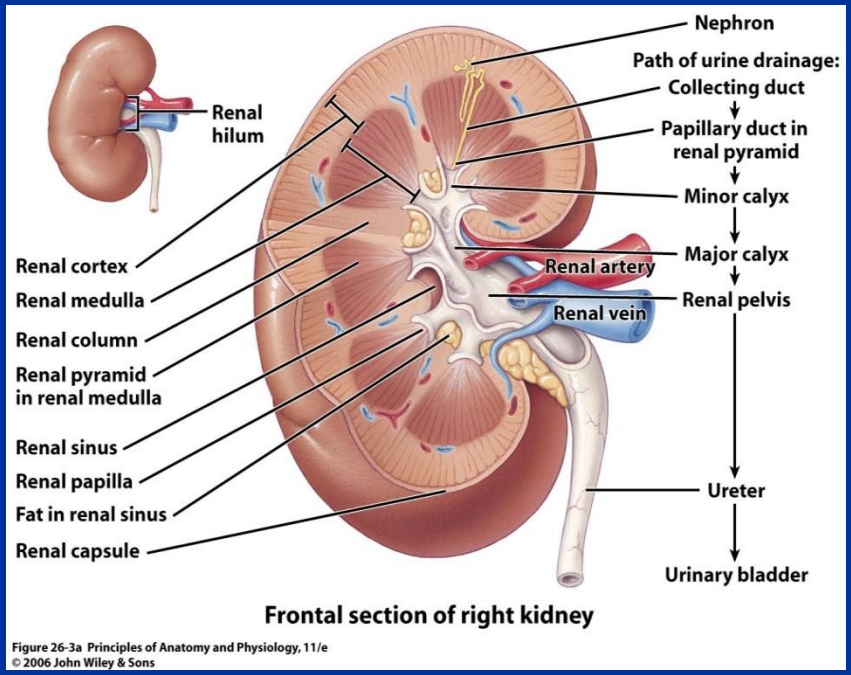
  } Smaller with better prognosis
- Metastasis
- Lymphoma
- Benign tumors:
  - Angiomyolipoma
  - Oncocytoma
- Wilm's Tumor or neuroblastoma (pediatric)
- Rare subtypes



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Transitional Cell Cancer

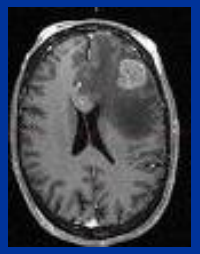
- Cancer of the urinary passage
- **Behaves like bladder cancer**
- Treat like bladder cancer



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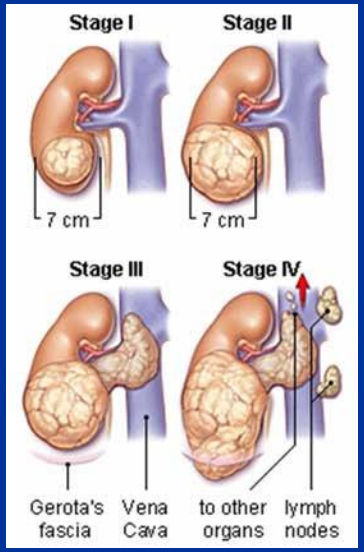
Routes of Spread

- Direct local extension
  - Into renal vein or IVC
  - Extension through kidney/fascia
- Lymph node involvement
  - Periaortic → pelvis, mediastinum, SCV
- Hematogenous (most common)
  - Lung #1 (50-75% of metastatic patients)
  - Liver
  - Bone
  - Distant LN
  - Adrenal
  - Brain
  - Contralateral kidney
  - Soft tissue





AJCC Staging 8th ed, 2017



T1 tumor ≤ 7 cm in greatest dimension limited to the kidney
T1a ≤ 4 cm
T1b > 4 cm

T2 tumor > 7 cm in greatest dimension limited to the kidney
T2a tumor > 7 cm <10 cm
T2b tumor > 10 cm

T3 tumor extends into major veins/adrenal gland/perinephric tissue but not thru Gerota's fascia
T3a tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b tumor grossly extends into the vena cava below the diaphragm
T3c tumor grossly extends into the vena cava above the diaphragm or invades wall of VC

T4 tumor invades beyond Gerota's fascia (including contiguous extension into ipsilateral adrenal gland

N1 mets in regional lymph nodes (renal hilar, paracaval, paraaortic)

M1 distant mets (bone, liver, lung, brain, distant lymph nodes)

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AJCC Staging

Stage I	**T1**	N0	M0
Stage II	**T2**	N0	M0
Stage III	T1-T2	**N1**	M0
	T3	N0-N1	M0
Stage IV	**T4**	Any N	M0
	any T	any N	**M1**

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Prognostic Factors at diagnosis

- Perinepheric or renal vein extension
- Nodal disease
- DM
- Tumor grade
- Histological type

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Prognostic Systems

RISK MODELS TO DIRECT TREATMENT

Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model[1]

Prognostic Factors
- Interval from diagnosis to treatment of <1 year
- Karnofsky PS <80%
- Serum lactate dehydrogenase (LDH) >1.5 times the upper limit of normal (ULN)
- Corrected serum calcium greater than the ULN
- Serum hemoglobin less than the lower limit of normal (LLN)

Prognostic Risk Groups
- Low-risk group: no prognostic factors
- Intermediate-risk group: 1 or 2 prognostic factors
- Poor-risk group: ≥3 prognostic factors

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria[2]

Prognostic Factors
- <1 year from time of diagnosis to systemic therapy
- PS <80% (Karnofsky)
- Hemoglobin less than the LLN (Normal: 120 g/L or 12 g/dL)
- Calcium greater than the ULN (Normal: 8.5–10.2 mg/dL)
- Neutrophil greater than the ULN (Normal: 2.0–7.0×10^9/L)
- Platelets greater than the ULN (Normal: 150,000–400,000)

Prognostic Risk Groups
- Favorable-risk group: no prognostic factors
- Intermediate-risk group: 1 or 2 prognostic factors
- Poor-risk group: 3–6 prognostic factors

General Treatment Principles

- Surgery mainstay of treatment
- Metastases is the overwhelming problem
- Standard chemotherapy with poor response rate
- Biologic therapies
- Role of Radiation
  - No standard role for RT to the renal bed (increasing interest in modern studies to re-eval)
  - Palliation of metastases
  - Definitive therapy for oligomet
    - increasing role with improvements in systemic Rx
  - Growing role of SBRT to primary (unresectable, nephron-sparing)

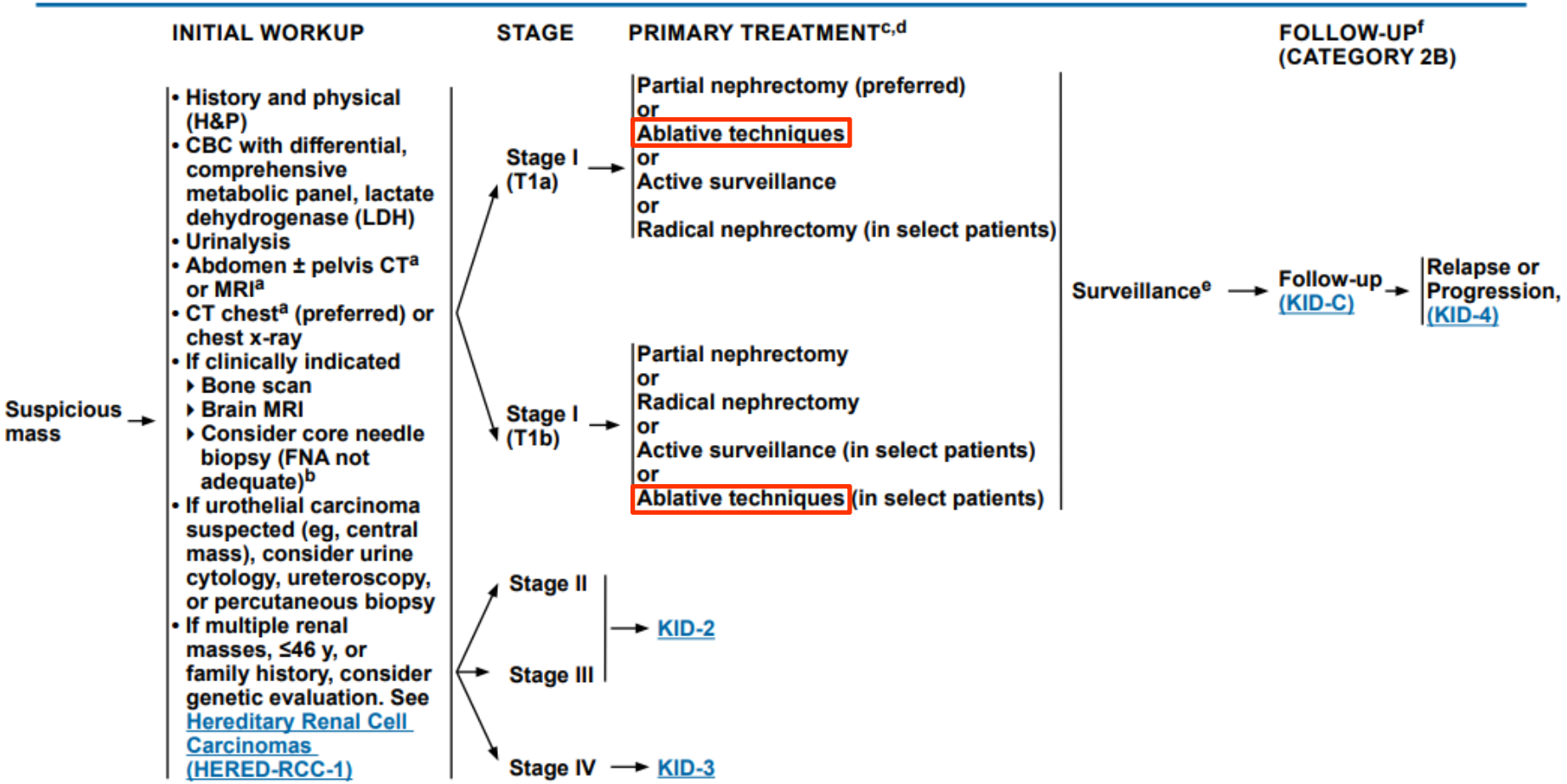
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NCCN Guidelines Version 3.2025
Kidney Cancer

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Discussion



[a] Imaging with and without contrast is strongly preferred, such as a renal protocol for abdomen.
[b] Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance or ablative techniques, cryosurgery, and radiofrequency ablation strategies.
[c] General Principles of Management for Renal Cell Carcinoma (KID-A).
[d] Stereotactic body radiation therapy (SBRT) may be considered for non-optimal surgical candidates with stage I kidney cancer (category 2B) or with stage II/III kidney cancer (both category 3). See Principles of Radiation Therapy (KID-B).
[e] Follow-up (KID-C).
[f] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

Note: All recommendations are category 2A unless otherwise indicated.

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NCCN Guidelines Version 1.2026
Kidney Cancer

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INITIAL WORKUP[a]

- History and physical (H&P)
- Complete blood count (CBC) with differential, comprehensive metabolic panel
- Urinalysis
- Abdomen ± pelvis CT[b] or MRI[b]
- CT chest[b] (preferred) or chest x-ray
- If clinically indicated
  - Bone scan
  - Brain MRI
  - Consider core needle biopsy (fine-needle aspiration [FNA] not adequate)[c]
- If urothelial carcinoma suspected (eg, central mass), consider urine cytology, ureteroscopy, or percutaneous biopsy
- If multiple renal masses, ≤46 y, or family history, consider genetic evaluation. See Hereditary Renal Cell Carcinomas (HERED-RCC-1)

Suspicious mass →

STAGE

Stage I (T1a) →
PRIMARY TREATMENT[d,e]
Partial nephrectomy (preferred)
or
Percutaneous ablation
or
Stereotactic body radiation therapy (SBRT)
or
Active surveillance
or
Radical nephrectomy (in select patients)

Stage I (T1b) →
PRIMARY TREATMENT[d,e]
Partial nephrectomy
or
Radical nephrectomy
or
Active surveillance (in select patients)
or
Percutaneous ablation (category 2B) (in select patients)
or
SBRT (in select patients)

Stage II
Stage III
→ KID-2

Stage IV → KID-3

FOLLOW-UP[g] (CATEGORY 2B)

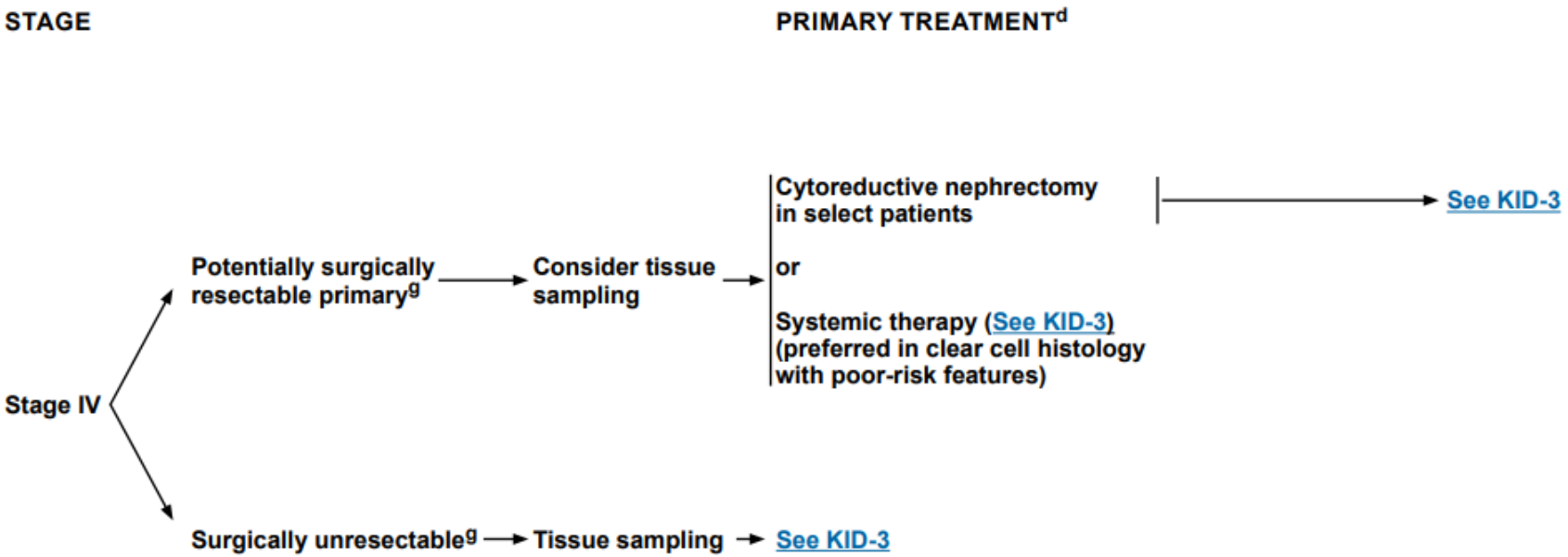
Surveillance[f] → Follow-up (KID-C) → Relapse or Progression (KID-4)

[a] Refer to the NCCN Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).
[b] Imaging with and without contrast is strongly preferred, such as a renal protocol for abdomen.
[c] Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide decisions on surveillance, percutaneous ablation, and/or surgery.
[d] General Principles of Management for Renal Cell Carcinoma (KID-A).
[e] SBRT is an option for patients considered non-optimal for either surgery or percutaneous ablation for clinical stage T1a kidney cancer (category 2A). SBRT is an option for non-optimal surgical candidates for clinical stage T1b kidney cancer (category 2A). SBRT may be considered for non-optimal surgical candidates with stage II (category 2B) or III (category 3) kidney cancer. See Principles of Radiation Therapy (KID-B).
[f] Follow-up (KID-C).
[g] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

Note: All recommendations are category 2A unless otherwise indicated.

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[d] See Principles of Surgery (KID-A).
[g] Individualize treatment based on symptoms and extent of metastatic disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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PRINCIPLES OF RADIATION THERAPY

General Treatment Information:

- **Consider radiation therapy (RT) in the following situations:**
  - **Modalities: SBRT should be considered as the primary radiation modality in all situations unless precluded by anatomic site, proximity to organs at risk (OAR), or past treatments.**

Primary Disease:

- **Definitive therapy[1,2]**
  - **Definitive radiation using SBRT may be considered as a treatment option for non-optimal surgical candidates. Consider referral to a high-volume center with specialized expertise.**
  - **Patient selection: SBRT can be considered for patients with T1 and T2a tumors (≤10 cm in diameter). There are insufficient data to pursue SBRT in tumors >7 cm. When delivering SBRT to tumors abutting bowel, consideration should be given to the use of a 5-fraction schedule, with strict adherence (eg, priority 1) to bowel constraints, with target coverage designated as priority 2. Volumetric image guidance with motion management is required. When available, strong consideration should be given to on-table adaptive technology—such as CT-guided or MR-guided adaptive techniques. In the absence of online adaptation, planning volume (PRV) constraints must be applied. To further mitigate risk of gastrointestinal toxicity, an every-other-day schedule may be considered.**
  - **Dosing regimens: SBRT should be delivered using over 1–5 fractions. Conventional fractionation is discouraged. Dose and fractionation options should attempt to keep the biologically effective dose (BED) to ≥80 Gy assuming an alpha/beta ratio of 10 due to association with improved local control. Established dosing regimens include:**
    - **25–26 Gy in 1 fraction[a]**
    - **39–48 Gy in 3 fractions**
    - **48 Gy in 4 fractions**
    - **40–50 Gy in 5 fractions[b]**
  - **For multi-fraction dosing, treatment can be delivered on consecutive or non-consecutive days.**
  - **Treatment technique:**
    - **For simulation and treatment planning four-dimensional (4D)-CT and fusion with a renal protocol CT and/or renal MRI is strongly encouraged.**
    - **Motion management is essential, with method dependent upon treatment platform and institutional practice. An internal target volume (ITV) should be utilized pending method of motion management.**
    - **When available, on-table adaptive technology such as CT-guided or MR-guided adaptive techniques should be utilized in the planning of tumors abutting bowel.**
    - **Use of daily pretreatment imaging including MRI if available or cone-beam CT is recommended. Volumetric image guidance is required when treating tumors abutting bowel.**
    - **OAR should be contoured to include a 3-mm PRV and to account for motion on 4D-CT.[c] Bowel PRV of 5 mm should be used when planning tumor abutting bowel.**
    - **OAR constraints for SBRT 1- and 3-fraction regimens per FASTRACK II protocol.[3] OAR constraints for SBRT 5-fraction regimen per UK Consensus guidelines.[4]**

[a] The use of single-fraction regimens has been largely limited to small (≤4 cm) tumors.
[b] The regimen of 40 Gy in 5 fractions has a lower BED than others listed; its use is favored only in settings where dose-volume criteria for OAR cannot be met with higher BED regimens (eg, larger tumors or those with unfavorable anatomic relationships).
[c] For specific representative OAR dose constraints, see TROG 15.03 FASTRACK II Protocol: Siva S, et al. Lancet Oncol 2024;25:308-316.

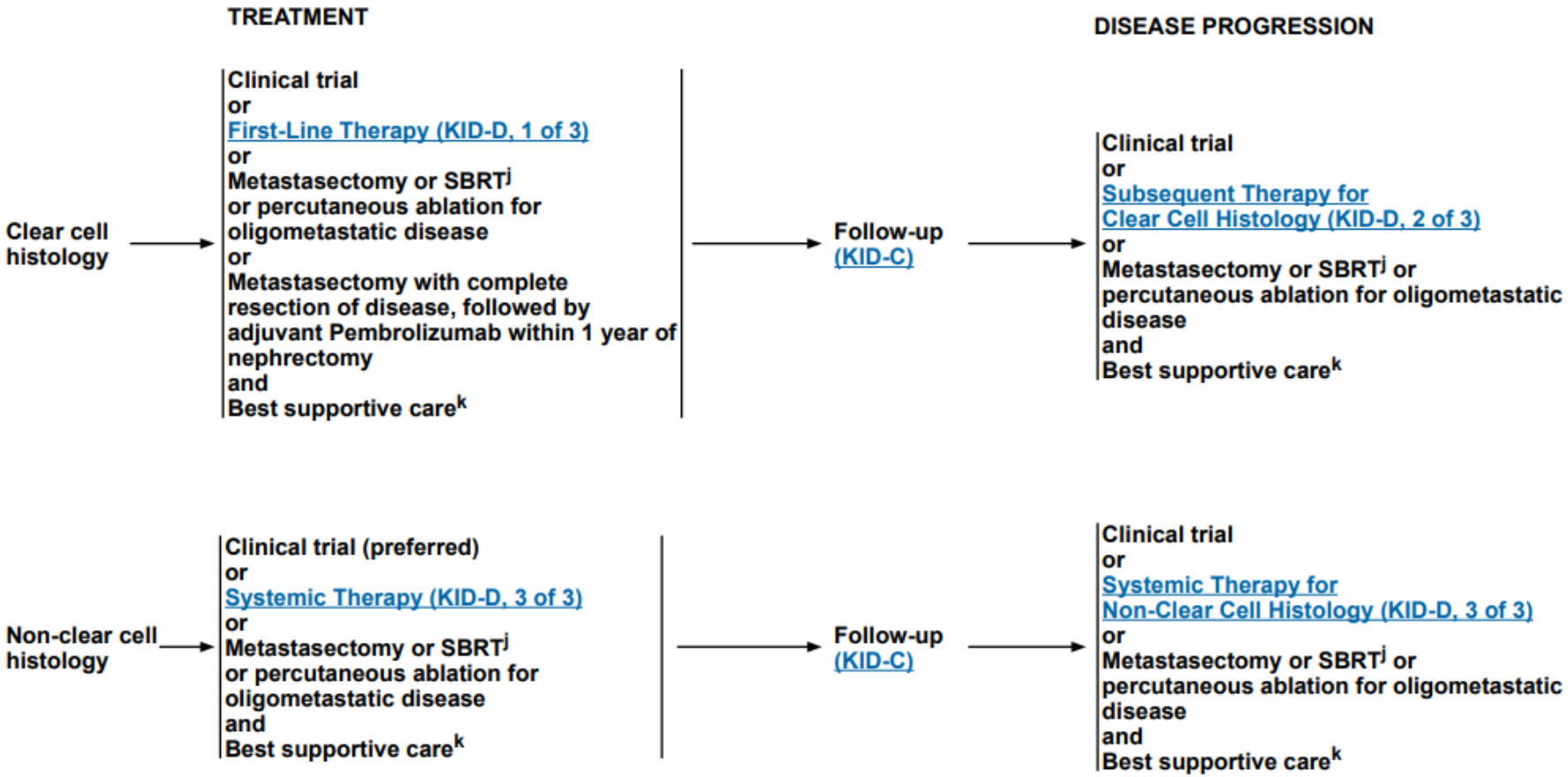
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References

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STAGE IV OR RELAPSED DISEASE



[j] Principles of Radiation Therapy (KID-B).

[k] Best supportive care can include radiation therapy (RT) where SBRT is the preferred approach, bisphosphonates, or receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors for bony metastases. An FDA-approved biosimilar is an appropriate substitute for denosumab.

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Role of Surgery – Radical Nephrectomy

- **Radical Nephrectomy**
  - Remove Gerotia's fascia with kidney, adrenal, and perinephric fat
  - Remove RV and IVC involvement (1/2 with long term survival)
  - Adrenal glad sparing if small, lower pole tumors
- **Nephrectomy standard in Stages I-III**
- **Nephrectomy beneficial in Stage IV**
  - Cytoreductive nephrectomy improves survival
  - Nephrectomy and surgical metastasectomy if resectable monometastatic disease
  - Palliative nephrectomy even none of above apply
- **Medically or surgically inoperable – systemic therapy only**
- **Partial Nephrectomy**:
  - "Nephron-sparing" surgery
  - Preferred for early stage T1a and other selected



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Role of Chemotherapy

- Not a part of standard treatment strategies
- Traditional chemotherapy response rates 6-7%

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0) OR RELAPSED DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)			
Risk	**Preferred**	**Other Recommended**	**Useful in Certain Circumstances**
Favorable[a]	• Axitinib + Pembrolizumab[b] (category 1) • Cabozantinib + Nivolumab[b,c] (category 1) • Ipilimumab + Nivolumab[b,d] (category 1) • Lenvatinib + Pembrolizumab[b] (category 1)	• Axitinib + Avelumab[b] • Pazopanib • Sunitinib • Cabozantinib (category 2B)	• Active surveillance[1,2,3] • Axitinib (category 2B)
Poor/ intermediate[a]	• Axitinib + Pembrolizumab[b] (category 1) • Cabozantinib + Nivolumab[b,c] (category 1) • Ipilimumab + Nivolumab[b,d] (category 1) • Lenvatinib + Pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + Avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B)

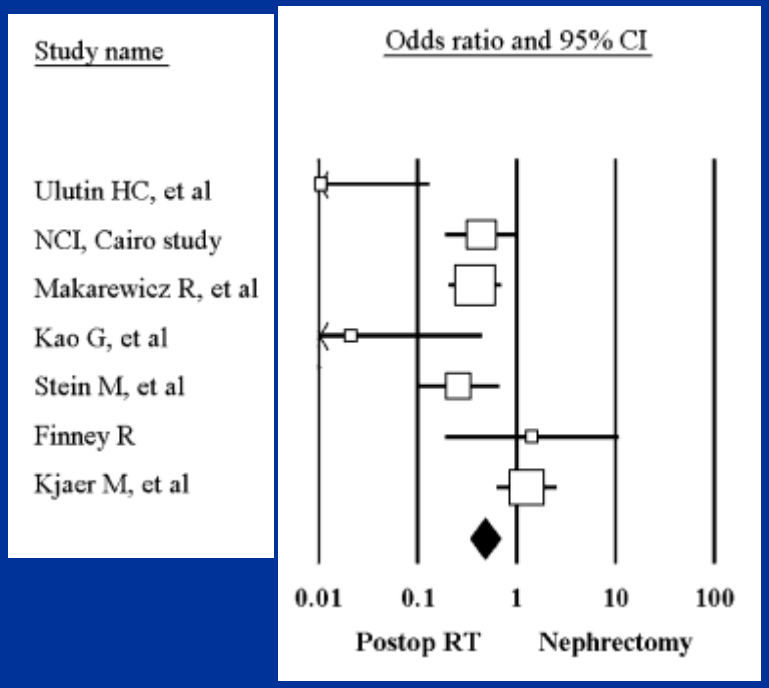
SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)			
Immuno-oncology (IO) Therapy History Status	**Preferred**	**Other Recommended**	**Useful in Certain Circumstances**
IO Therapy Naïve	• None	• Axitinib + Pembrolizumab[b] • Cabozantinib • Cabozantinib + Nivolumab[b,c] • Everolimus/Lenvatinib • Ipilimumab + Nivolumab[b,d] • Lenvatinib + Pembrolizumab[b] • Nivolumab[b,c]	• Axitinib • Everolimus • Lenvatinib • Pazopanib • Sunitinib • Tivozanib • Belzutifan (category 2B) • Bevacizumab[f] (category 2B)
Prior IO Therapy	• None	• Axitinib • Belzutifan[e] • Cabozantinib • Everolimus/Lenvatinib • Tivozanib	• Everolimus • Ipilimumab + Nivolumab[b,d] • Lenvatinib • Pazopanib • Sunitinib • Axitinib + Pembrolizumab[b] (category 2B) • Bevacizumab[f] (category 2B) • Cabozantinib + Nivolumab[b,c] (category 2B) • Lenvatinib + Pembrolizumab[b] (category 2B)

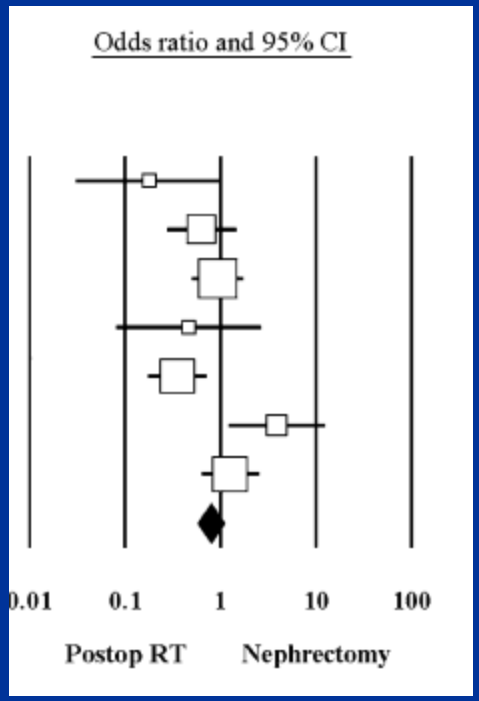
Role for adjuvant Radiation Therapy?

- Older trials suggested no role for adjuvant radiation after nephrectomy
  - No benefit and damages adjacent normal tissues
  - Including nodal involvement or incomplete resection
- More recent metanalysis suggests local control benefit
- Modern trials may be warranted

Metanalysis of adjuvant RT after nephrectomy

- Locoregional control
- Overall survival



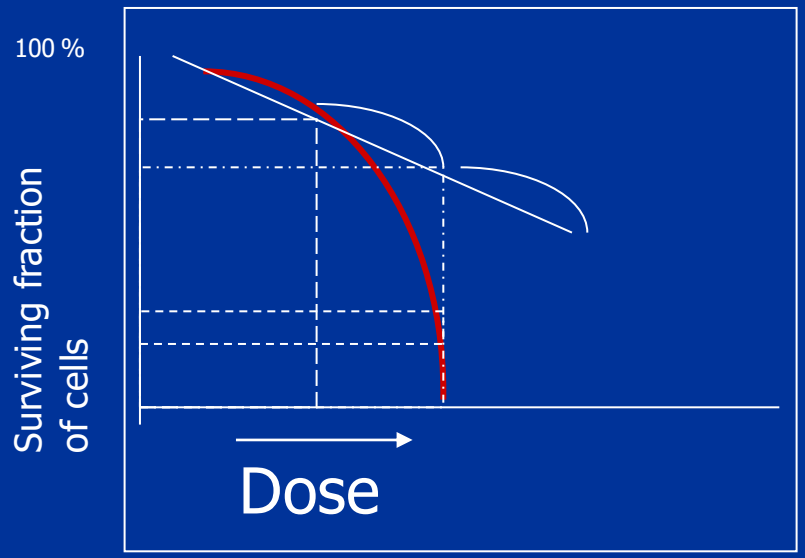


Tunio et al *Ann Onc* 2010

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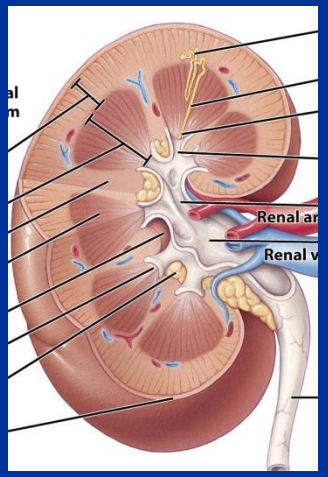
Radiobiology - Single Fraction

- Large single doses:
  - 20 Gy x 1 = 50 Gy fractionated (α/β = 10)
  - Overcomes radioresistant large "shoulder"
    - Melanoma, renal cell carcinoma, sarcoma
    - Benign lesions: meningiomas, schwannomas, AVM

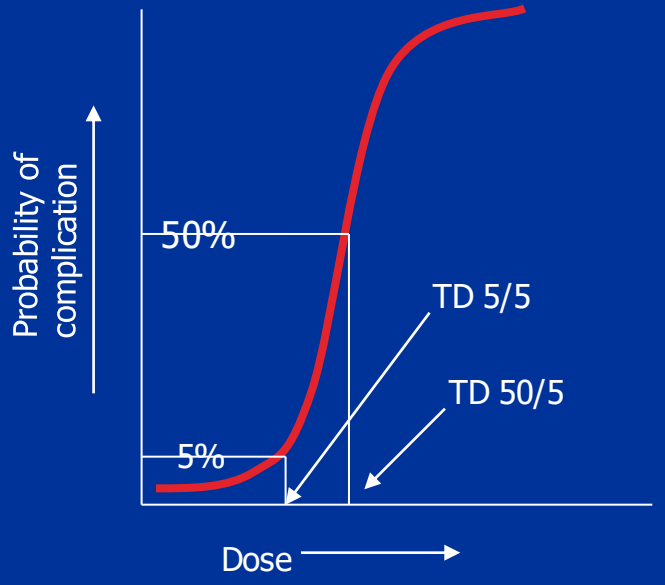


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Radiation Tolerance



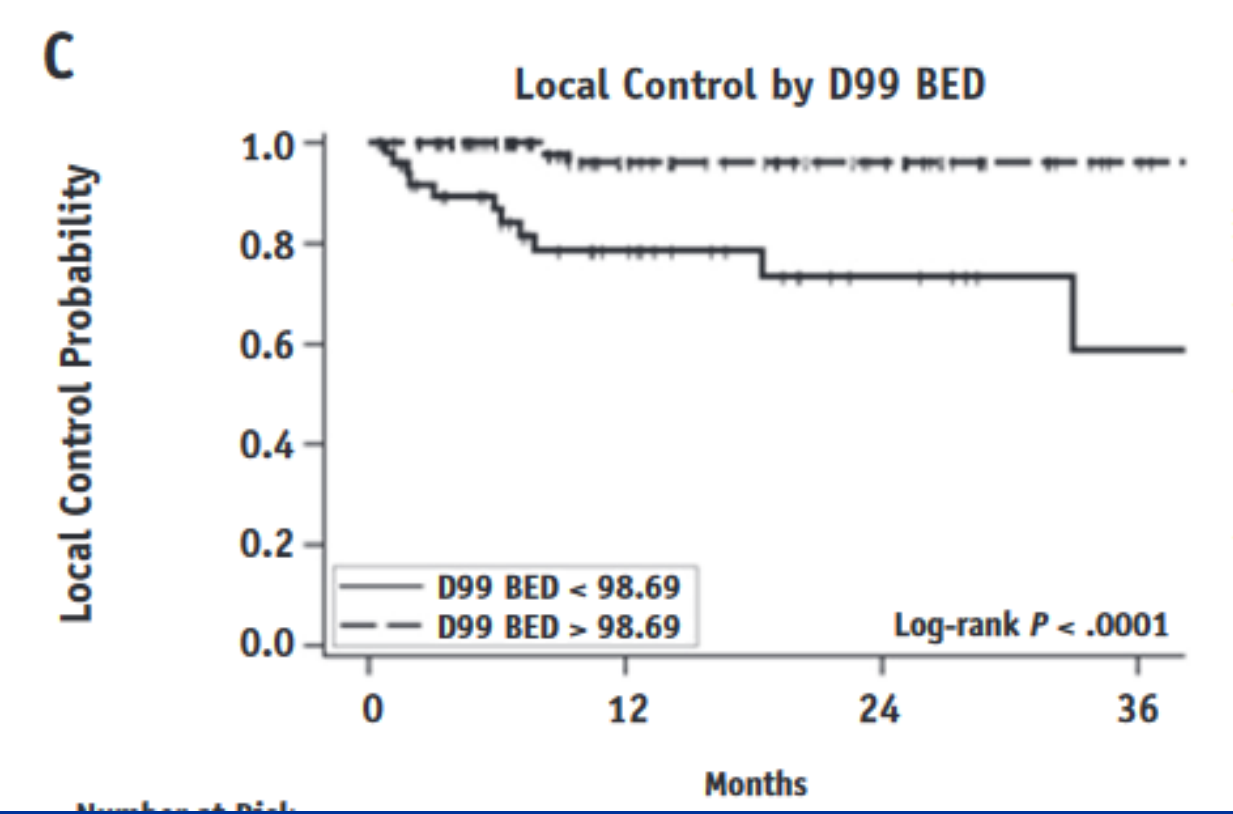
- Bilateral nephritis is fatal
- Kidney is a parallel organ
- Dose-Volume Tolerance:
  - TD 5/5 (5% complications at 5 years):
    - 1/3 to 50 Gy
    - 2/3 to 30 Gy
    - **Whole organ 23 Gy**
  - T/D 50/5 (50% complications at 5 years):
    - 1/3 to 2/3 to 40 Gy
    - Whole organ to 28 Gy



MSK tolerance table: GI

Rx	Kidneys
3-4 fractions	Each: V15 Gy <67% (Guideline) Both: V10 Gy <50% **(LIMIT)** *Single fuctioning kidney*: V10Gy<33% **(LIMIT)**
25-29 fractions	Each: V20 Gy < 33% (Guideline) Both: V20 Gy < 50% **(LIMIT)** Single functioning kidney: V20Gy<33% **(LIMIT)**

Safety and Efficacy of Stereotactic Ablative Radiation Therapy for Renal Cell Carcinoma Extracranial Metastases

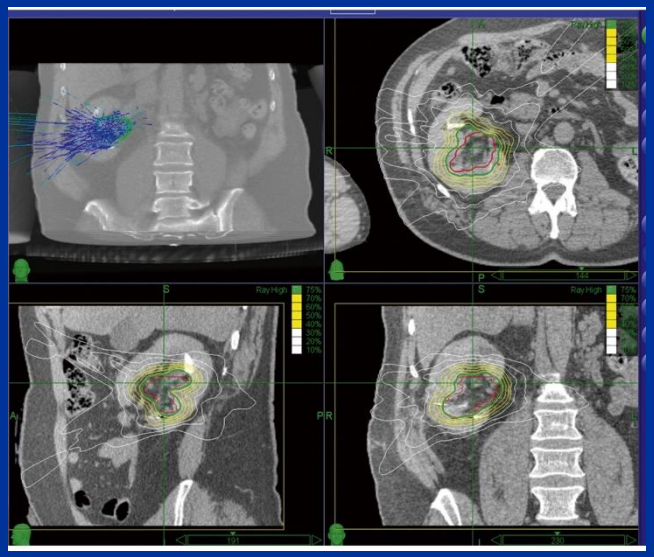


Wang IJROBP 2017

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SBRT for renal tumors

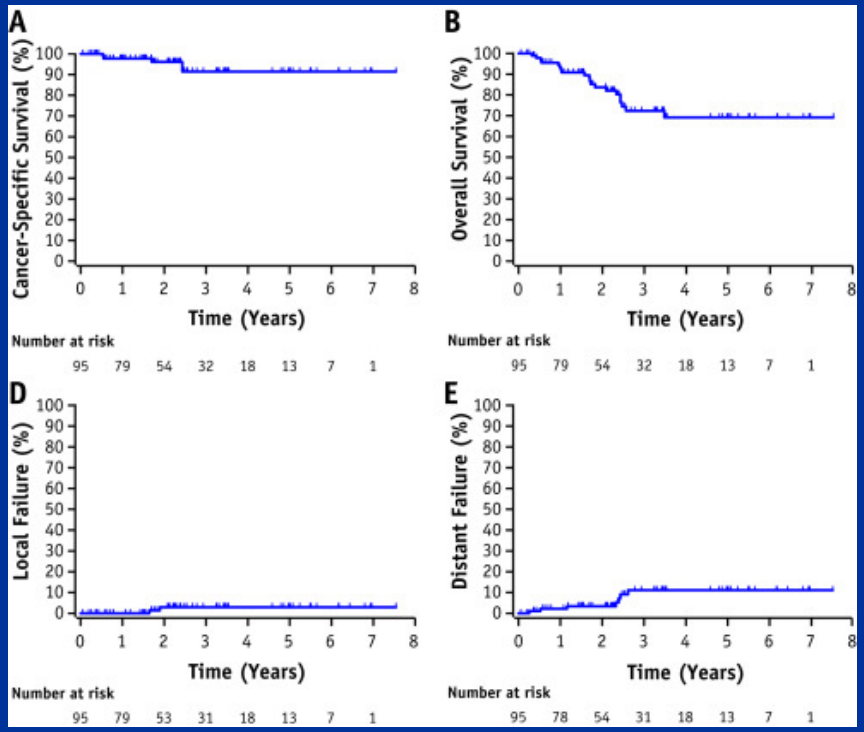
- Surgery is the standard of care for treatment of localized RCC
- Patients ineligible for surgery are being managed with ablative therapies
- SBRT (SABR) is gaining in popularity as a treatment option for such patients.
- IROCK (International Radiosurgery Oncology Consortium for Kidney) is a group of 9 institutions located around the world who report on pooled data for SBRT kidney



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Stereotactic Ablative Radiotherapy for ≥T1b Primary Renal Cell Carcinoma: A Report From the International Radiosurgery Oncology Consortium for Kidney (IROCK)

- Pooled data on SBRT for larger RCC (<4cm), largely medically inoperable
- 4 year CSS/LF 91%/3%
- No grade 3+ tox
- Result compare favorably with other nephron-sparing approaches



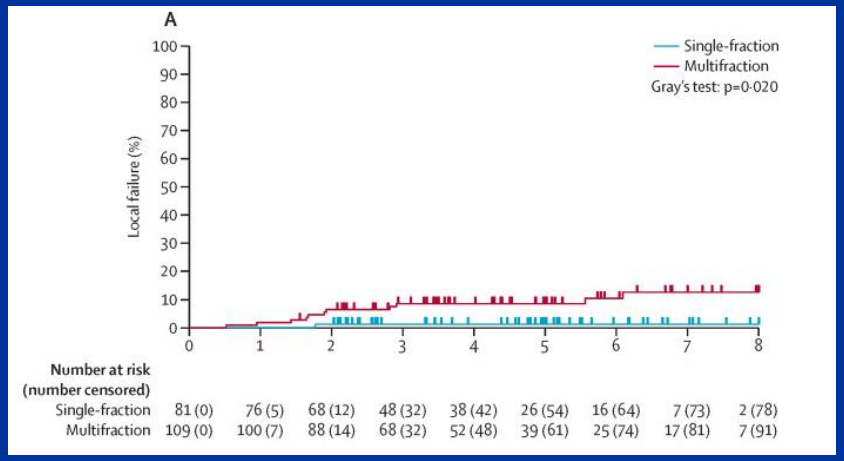
Siva S, et al, IJROBP 2020

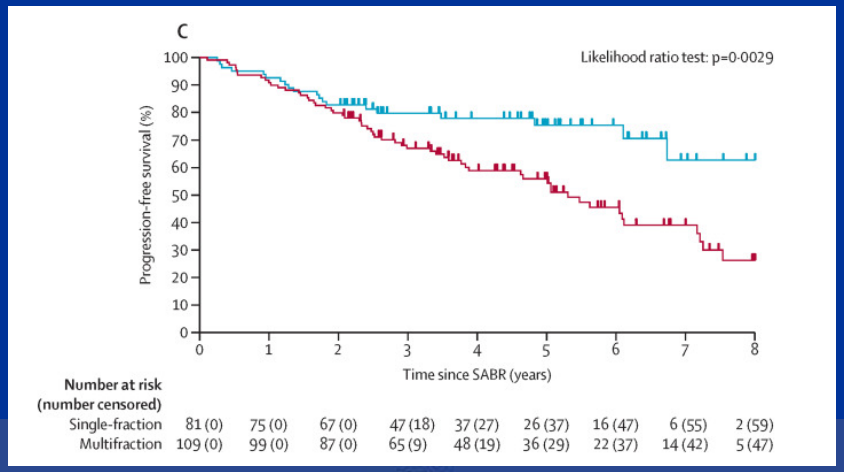
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SABR Dose/fractionation

(IROCK metanalysis Siva et al *Lancet Oncology* 2022)

- "Single-fraction SABR might yield less local failure than multifraction, but further evidence from randomised trials is needed to elucidate optimal treatment schedules."

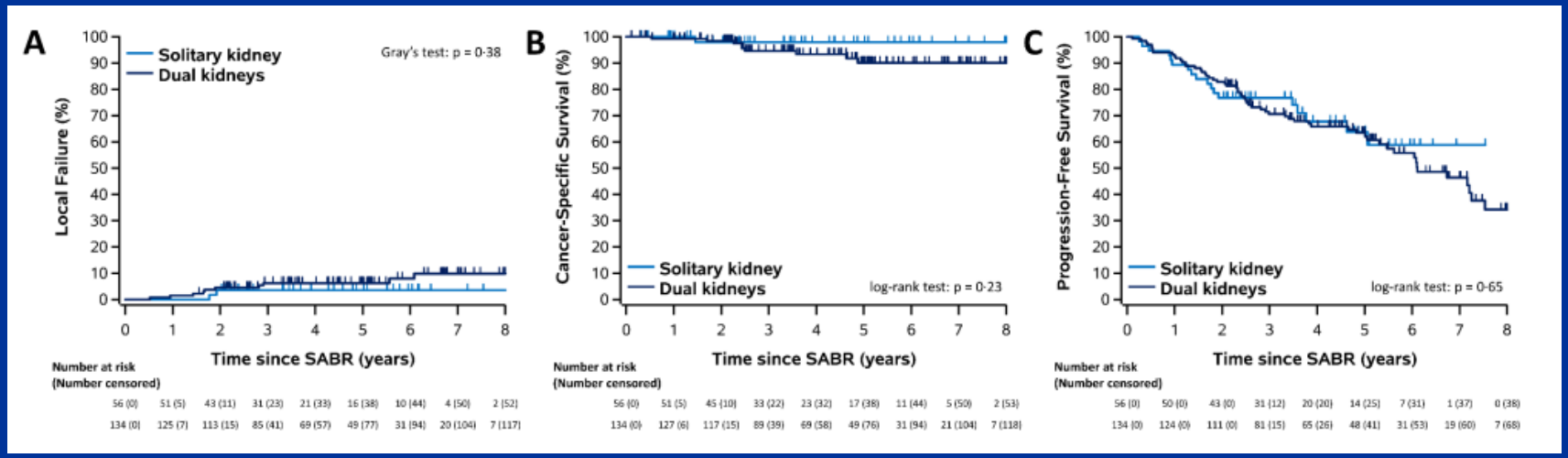




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Solitary vs Two Kidneys

(IROCK metanalysis Siva et al *Lancet Oncology* 2022)



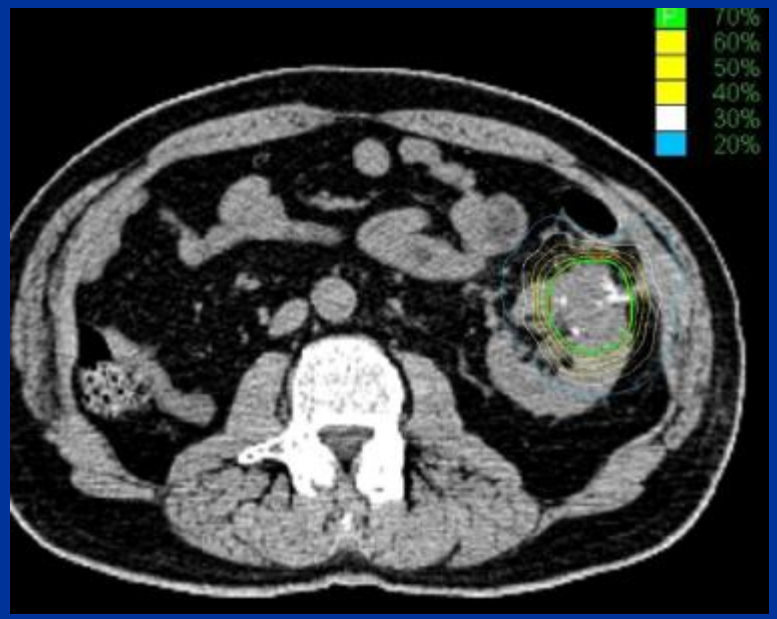
- Median FU 5 y; no diff in LF, CSS, PFS

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SBRT for renal cell carcinoma in patients with impaired renal function: Berlin, Germany

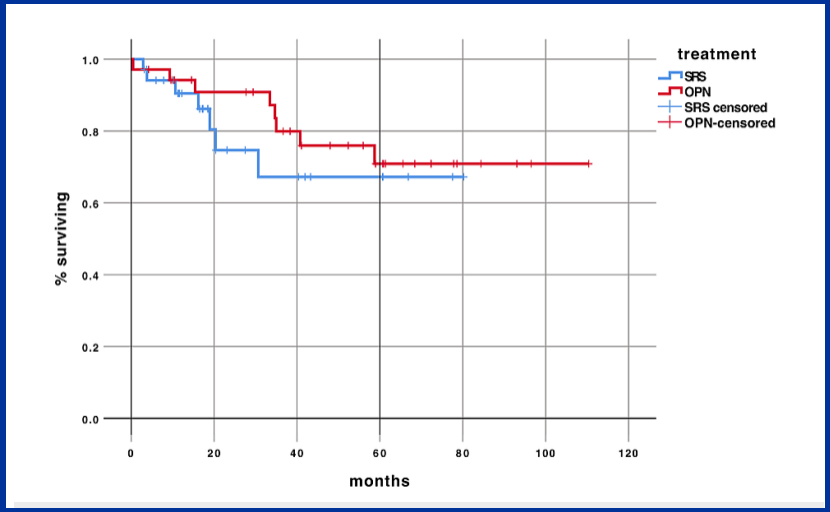
Senger BMC Urology 2019

- Retrospective, n=10 pts (13 lesions), at increased risk for ESRD
- Cyberknife, fiducial marker, resp motion tracking
- Single fraction 24-25 Gy or 36 Gy/3 fractions
- PTV margin GTV+ 3mm
- Local control 92.3% (27 mo)
- Toxicity:
  - stable renal function
  - Grade 1 GI = 2



Partial nephrectomy vs SBRT

- Retrospective matched pair analysis
- N= 571 PN vs 99 SBRT
- Matched for ECOG, age,stage, size
- Median diameter 2.8 cm (SBRT) vs 3.5 cm (PN) p=0.104
- LC 98% in both grps; no diff OS
- 3 gold fiducials placed next
- to the tumor under local anesthesia and ultrasound guidance



Staehler et al. Cureus 2022 (Munich)

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SBRT vs other ablative

- Meta-analysis of ablative therapies for primary treatment of RCC
- Despite SBRT patients being older with larger less favorable tumors, the treatment compared favorably to other more invasive therapies in terms of safety and efficacy

Huang et al Lancet Oncology 2025

	SBRT (N=612)	Radiofrequency ablation (N=2503)	Microwave ablation (N=2069)	Cryoablation (N=3726)	p value
Age, years	73·5 (8·0)	65·6 (8·0)	66·7 (6·9)	68·6 (4·4)	<0·0001
Sex					
Female	172/591 (29·1%)	702/2157 (32·5%)	573/1999 (28·7%)	1071/3271 (32·7%)	..
Male	419/591 (70·9%)	1455/2157 (67·5%)	1426/1999 (71·3%)	2200/3271 (67·3%)	0·77
Tumour size, cm	3·9 (0·9)	2·8 (0·7)	3·0 (0·8)	2·9 (0·8)	<0·0001
eGFR, mL/min per 1·73 m²	63·9 (14·2)	68·3 (17·6)	71·9 (9·9)	65·9 (8·8)	0·57
Histology					
Clear cell carcinoma	312 (51·0%)	1156 (46·2%)	1481 (71·6%)	2236 (60·0%)	0·028
Papillary cell carcinoma	39 (6·4%)	283 (11·3%)	275 (13·3%)	511 (13·7%)	0·037
Chromophobe	3 (0·5%)	86 (3·4%)	50 (2·4%)	174 (4·7%)	0·031
Other or unknown	258 (42·2%)	978 (39·1%)	263 (12·7%)	805 (21·6%)	..
Follow-up, months	27·8 (22·0–43·0)	34·2 (23·9–48·8)	24·5 (17·8–36·1)	28·7 (24·3–42·5)	0·018

Data are n (%), n/N (%), mean (SD), or median (IQR). eGFR=estimated glomerular filtration rate. SBRT=stereotactic body radiotherapy.

Table 1: **Summary of baseline patient characteristics and duration of follow-up, by treatment type**

	SBRT (N=612)	Radiofrequency ablation (N=2503)	Microwave ablation (N=2069)	Cryoablation (N=3726)
Local control (primary endpoint)				
Overall				
1 year	99% (97–100; I^2=6%)	96% (94–98; I^2=73%)	97% (95–99; I^2=74%)	95% (93–96; I^2=61%)
2 years	97% (95–99; I^2=0%)	95% (92–98; I^2=77%)	95% (92–98; I^2=77%)	94% (91–96; I^2=69%)
5 years	95% (89–98; I^2=42%)	92% (88–96; I^2=78%)	86% (75–94; I^2=66%)	90% (87–93; I^2=74%)
Tumour size <4 cm				
1 year	98% (93–100; I^2=0%)	97% (94–98; I^2=74%)	97% (95–99; I^2=77%)	96% (95–97; I^2=48%)
2 years	95% (90–99; I^2=0%)	96% (93–98; I^2=77%)	96% (93–98; I^2=79%)	95% (93–97; I^2=62%)
5 years	98% (91–100; I^2=0%)	95% (91–97; I^2=65%)	92% (72–100; I^2=61%)	91% (88–94; I^2=75%)
Tumour size ≥4 cm				
1 year	99% (97–100; I^2=26%)	91% (86–95; I^2=0%)	94% (91–97; I^2=0%)	88% (82–94; I^2=59%)
2 years	98% (96–99; I^2=0%)	88% (83–93; I^2=0%)	92% (87–96; I^2=15%)	86% (80–92; I^2=52%)
5 years	93% (85–98; I^2=59%)	79% (64–91; I^2=83%)	82% (65–94; I^2=78%)	85% (76–93; I^2=60%)

Huang et al Lancet Oncology 2025

Cancer Center

FASTRACK II Trial

- Multicenter prospective trial
- Biopsy proven
- SABR 1 or 3 fractions

- Eligibility:
  - Medically inoperable
  - Adequate kidney function
  - Not abutting bowel
  - < 10 cm tumor size

Siva et al Lancet Oncology 2024

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FASTRACK II Trial

- Median FU 43 mo
- Local control 100%
- 5y FFDF: 97%
- CSS: 100%
- Kidney function loss: -14.6

Siva et al Lancet Oncology 2024

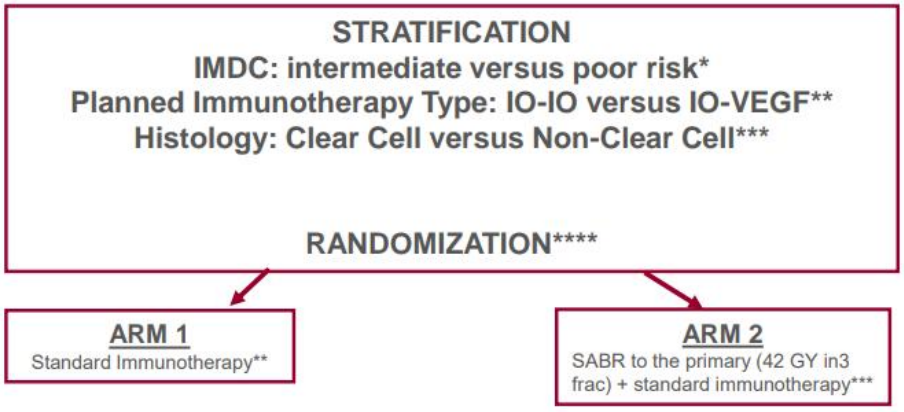
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Currently open at MSK:

NRG-GU012

RANDOMIZED PHASE II **S**TEREOTACTIC **A**BLATIVE RADIATION THERAPY (SABR) FOR **M**ETASTATIC **U**NRESECTED **R**ENAL CELL C**A**RCINOMA (RCC) RECEIVING **I**MMUNOTHERAPY (**SAMURAI**)

Study Schema



**International Metastatic RCC database consortium (IMDC): Intermediate risk is 1-2 risk factors and poor risk is 3 or more risk factors (See Section 3.1.3).*
*** Standard immunotherapy includes the following combinations: IO-IO (Immuno-Oncology): defined as receipt of nivolumab + ipilimumab; Immuno-Oncology-vascular endothelial growth factor) (IO-VEGF): defined as receipt of pembrolizumab + axitinib, avelumab + axitinib, nivolumab + cabozantinib, or pembrolizumab + lenvatinib*
**** Maximum accrual of non-clear cell is 48 patients.*
*****Randomization is 2:1 favoring the experimental arm (Arm 2).*

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Seminoma

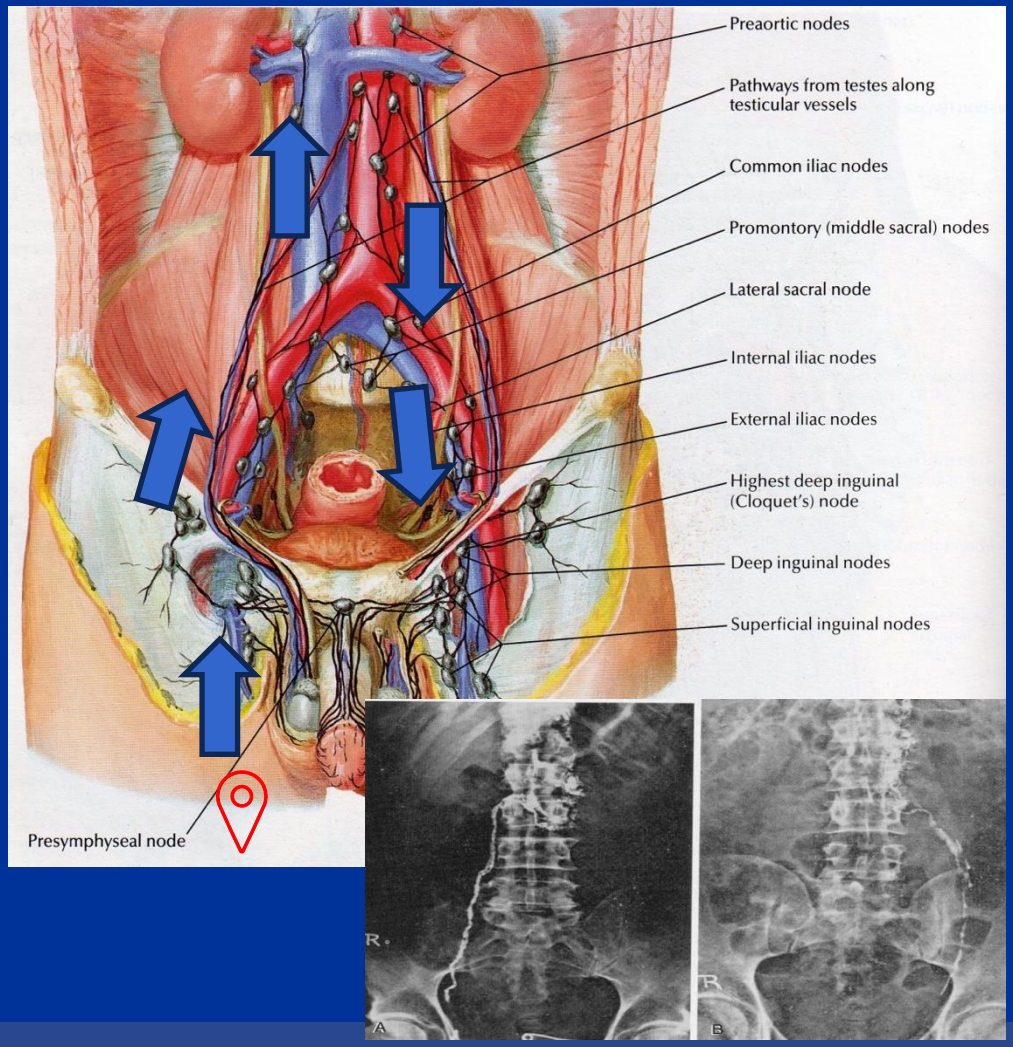
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Testicular Cancer Epidemiology

- Incidence of testicular cancer has been increasing for several decades (mainly seminoma). Rate is slowing.
- #1 solid tumor in men 15-34 years old
- 2% of all human cancers
- 2026 projected: 9,810 new cases, 630 deaths
- Trimodal incidence
  - Infancy
  - 20-40 years
  - >65 year
- Mean Age at presentation
  - Seminoma: 35 years (older people)
  - Non-seminoma: 25 years (kids and young people)

Lymphatic Drainage

- Originate near rete testes in **testicular hilum**
- Passes with spermatic cord through inguinal ring
- Courses with testicular veins to **retroperitoneal lymph nodes**
- R testicular vein joins IVC a few cm below where renal vein joins IVC
- L testicular vein enters L renal vein
- Subsequent **spread from PAs:**
  - **Common Iliac → Extrnal Iliac**
  - Mediastinal
  - Left SCV (thoracic duct)
- Spermatic cord invasion → obturator, external iliac
- **Scrotal invasion→ inguinal**



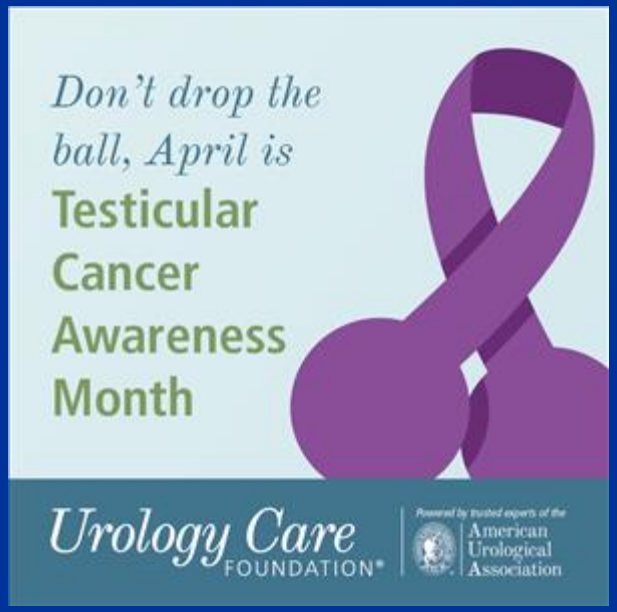
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Risk Factors

- Male Sex
- Age 14-34
- Cryptorchidism: undescended testicle
  - Increased for all histologies
  - 5-20% risk in BOTH testes (RR = 40)
  - Risk may be reduced with gonadoplexy prior to puberty
- Prior testicular cancer/CIS (2.5% contralateral)
- Family hx
- White : Black = 5 : 1
- HIV+ (seminoma)
- First-born son (in utero estrog)
- Advanced maternal age
- Prenatal estrogen exposure
- PVC exposure
- Testicular Trauma (?)
- Height (higher risk in taller men)
- Genetic Syndromes:
  - Dysplastic Nevus Syndrome
  - Klinefelter's Syndrome - 47 XXY
  - Down's Syndrome
  - Chromosome 1 and 12 abnormalities

AUA recommendation

"The best way to increase the chances we can cure someone of testicular cancer is to catch it early. Men in their late teens and older should get in the habit of performing self-exams on a monthly basis"



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Screening

- US Preventive Task Force: (2011) recommends against screening based on the lack of evidence demonstrating that screening for testicular cancer leads to a meaningful reduction in mortality or improved health outcomes.

- American Cancer Society:
  - Testicular exam recommended as part of a routine MD checkup.
  - Advises men to be aware of testicular cancer and to see a doctor right away if they find a lump in a testicle.
  - Because regular testicular self-exams have not been studied enough to show they reduce the death rate from this cancer, the ACS does not have a recommendation on regular testicular self-exams for all men.
  - However, some doctors recommend that all men examine their testicles monthly after puberty.

- American Urologic Association: patients who were previously cryptorchid should perform monthly testicular self-examination after puberty to potentially help find cancer early

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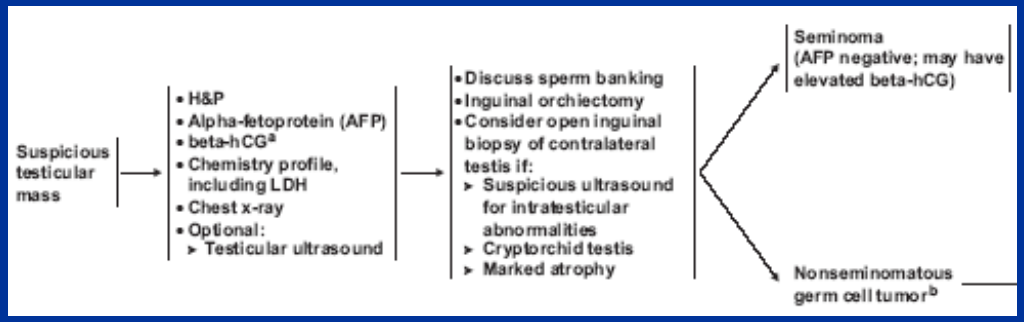
Clinical Presentation

- Testicular mass #1 (classically painless)
  - Tumor until proven otherwise (> 95%)
  - Differential: hernia, epididymitis, orchitis, hyrdocele, varicocele, spermatocele
  - Solid testicular mass in male > 60 → lymphoma #1
- Testicular enlargement
- Testicular heaviness / pain
- Gynecomastia / breast tenderness (2%)
  - 2º/2 β–HCG causing increased estradiol
- Metastatic presentations
  - Neck mass, SOB, back pain, abdominal complaints
- Up to 10% found on routine imaging



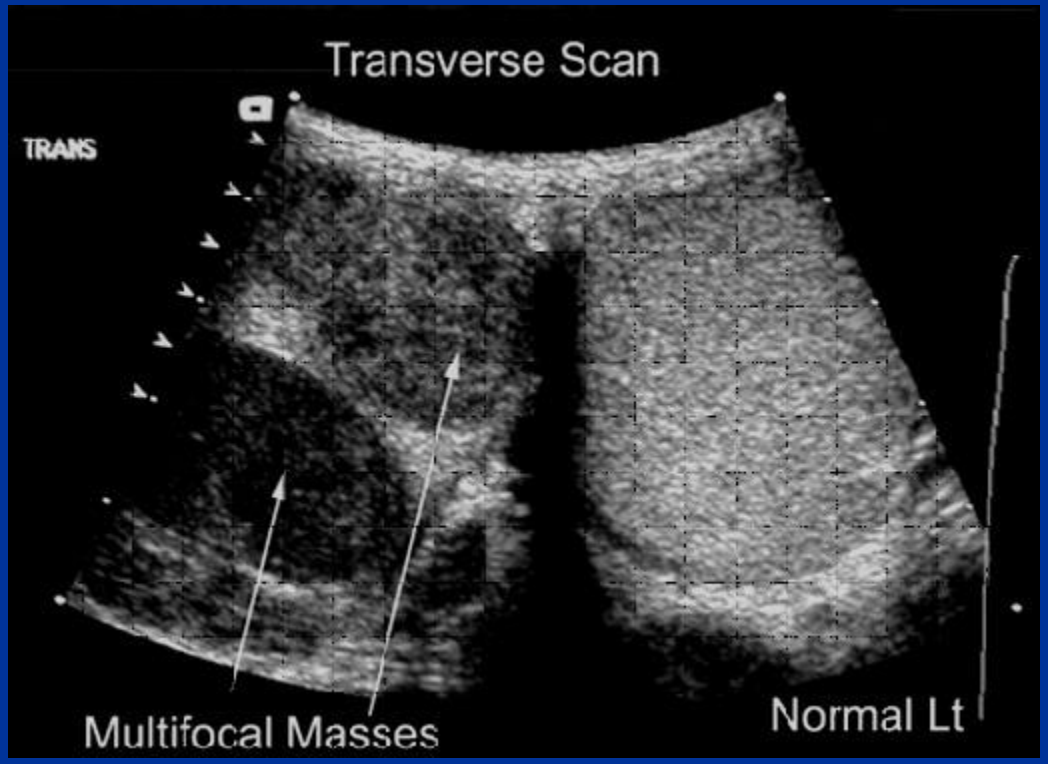
Work-up

- Full H&P
  - Sexual hx, family hx, surgical hx, RF's, B symptoms, abdominal exam, breast exam, bilateral testicular exam with transillumination, nodal exam including SCV and inguinals
- CBC, Chem-7, LFT's
- Serum Markers prior to surgery
- Trans-scrotal ultrasound (MRI if inconclusive)
- Fertility counseling and discuss sperm banking
- CXR



NCCN guidelines – www.nccn.org

Trans-scrotal Ultrasound



Radical Inguinal Orchiectomy

- Indicated if high clinical suspicion of cancer (diagnostic and therapeutic)
- High inguinal incision
- Mobilize testicular vessels and vas deferens
- Non-crushing clamp over spermatic cord contents to prevent spread through manipulation
- Testicle delivered through wound to avoid scrotal incision



- NO ROLE FOR BIOPSY (seeding)
- NO ROLE FOR SCROTAL INCISION (lymphatic pattern disruption)
- Testis sparing surgery: small masses, bilateral; low suspicion for cancer
  - Gentile *J Urol* 2020

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Serum Markers

- β–HCG
  - Half-life 1-2 days*
- AFP
  - Half-life 4-6 days* (A**F**P – **Five days**)
  - Never elevated in pure seminoma
- LDH
  - Marker for general burden of disease
  - Prognostic for patients with metastatic disease

**After 5 half-lives a previously elevated serum marker should return to normal limits if all tumor cells have been removed*

Serum Marker Frequency of Elevation

Histology	AFP (%)	β-HCG
Seminoma	0	9
Teratoma	38	25
Embryonal	70	60
Choriocarcinoma	0	100
Yolk Sac Tumor*	75	25

* most common histology in childhood GCT

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General Testicular Pathology

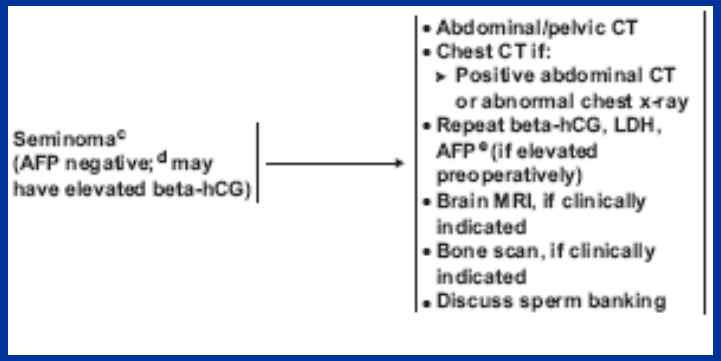
- 95% are GCTs (seminoma + NSGCTs)
- Seminoma most common single histology 45%
- NSGCT's together are more common

- Pure Seminoma **(45%)**
  - Classic (85%, +PLAP)
  - (Anaplastic: no longer used)
  - (Spermatocytic tumor: distinct entity, favorable)
- Non-seminoma **(55%)**
  - Embryonal: component of 85% of all mixed GCTs (pure: usu no AFP)
  - Yolk Sac (AFP, Schiller Duval Bodies):
    - high AFP
  - Teratoma
  - Choriocarcinoma (β–HCG; no AFP): most aggressive
  - Mixed **(15% total)**
- Other 1^{o}
  - Lymphoma
  - Sertoli cell (estrogen, gynecomastia)
  - Leydig cell (androgens & estrogen, early puberty & gynecomastia)
  - Embryonal Rhabdomyosarcoma
- Metastases (rare)
  - Prostate
  - Lung
  - Kidney
  - Melanoma

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Work-up: after surgery

- CT C/A/P
- Serum markers after surgery
- Further imaging if clinically indicated
- Discuss sperm banking again before adjuvant treatment



NCCN guidelines – www.nccn.org

Retroperitoneal LAN



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AJCC Staging 8th Edition (2017)

Primary Tumor

pTis Germ cell neoplasia in situ

pT1 Tumor limited to testis (including rete testis invasion) without lymphovascular invasion

pT1a* Tumor smaller than 3 cm in size

pT1b* Tumor 3 cm or larger in size

pT2 Tumor limited to testis (including rete testis invasion) with lymphovascular invasion

OR

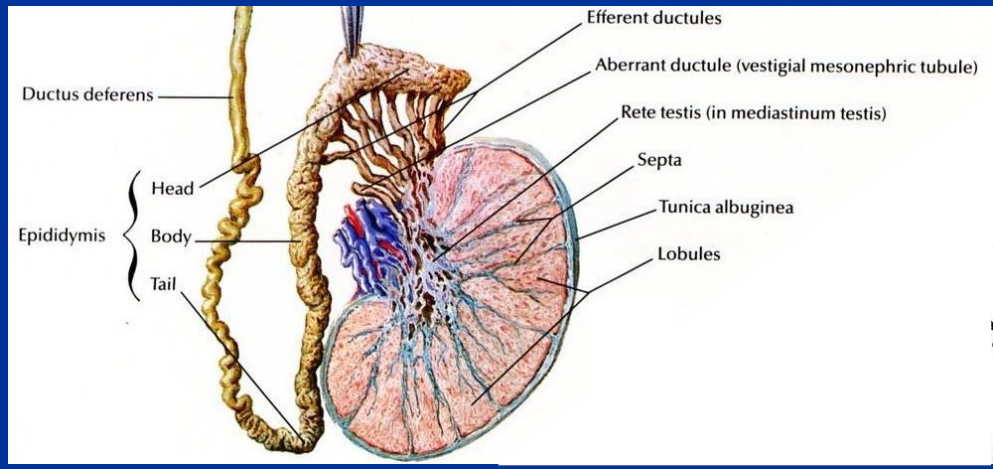
Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer

covering the external surface of tunica albuginea with or without lymphovascular invasion

pT3 Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion

pT4 Tumor invades scrotum with or without lymphovascular invasion

*Subclassification of pT1 applies to only pure seminoma



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AJCC Staging 8th Edition (2107) continued

Clinical nodal status (exam, CT scans, LAG)

- **cN1** Metastasis with a lymph node mass 2 cm or smaller in greatest dimension
  OR
  Multiple lymph nodes, none larger than 2 cm in greatest dimension
- **cN2** ≥ 1 regional lymph node, with at least one > 2 cm but ≤ 5 cm in greatest dimension
- **cN3** Any regional lymph node > 5 cm in greatest dimension

Pathological nodal status (retroperitoneal node dissection)

- **pN1** Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to ve nodes positive, none larger than 2 cm in greatest dimension
- **pN2** Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than five nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumor
- **pN3** Any positive node > 5 cm in greatest dimension

Metastatic Sites

- **M1a** Nonregional lymph node or pulmonary mets (most common site = lymph nodes)
- **M1b** Other distant mets (liver, bone, …)

Serum Markers

Sx	Serum tumor markers not available					
S0	Normal values					
S1	LDH < 1.5 x normal	&	hCG < 5,000 mIu/ml	&	AFP < 1,000 ng/ml	
S2	LDH 1.5-10 x normal	or	hCG 5,000-50,000 mIu/ml	or	AFP 1,000-10,000 ng/ml	
S3	LDH > 10 x normal	or	hCG > 50,000 mIu/ml	or	AFP > 10,000 ng/ml	

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AJCC Stage Groupings

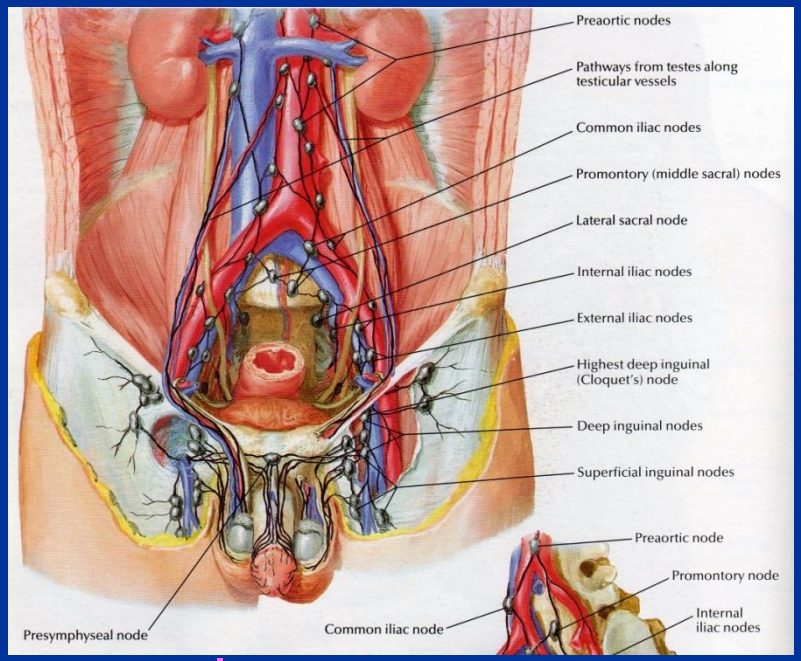
Stage	**0**	**pTis**	N0	M0	S0
Stage	**IA**	pT1	**N0**	M0	S0
	IB	pT2-T4	**N0**	M0	S0
	IS	any T	**N0**	M0	S1-S3
Stage	**IIA**	any T	**N1**	M0	S0-S1
	IIB	any T	**N2**	M0	S0-S1
	IIC	any T	**N3**	M0	S0-S1
Stage	**IIIA**	any T	any N	**M1a**	S0-S1
	IIIB	any T	N+	M0	**S2**
		any T	any N	M1a	**S2**
	IIIC	any T	N+	M0	**S3**
		any T	any N	M1a	**S3**
		any T	any N	**M1b**	any S

85% stage I at presentation

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Regional Nodes

- Interaortocaval
- Periaortic
- Paracaval
- Preaortic
- Precaval
- Retroarotic
- Retrocaval
- Nodes along spermatic vein
- If prior scrotal or inguinal surgery, also:
  - Intrapelvic
  - External iliac
  - Inguinal



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Metastatic Sites

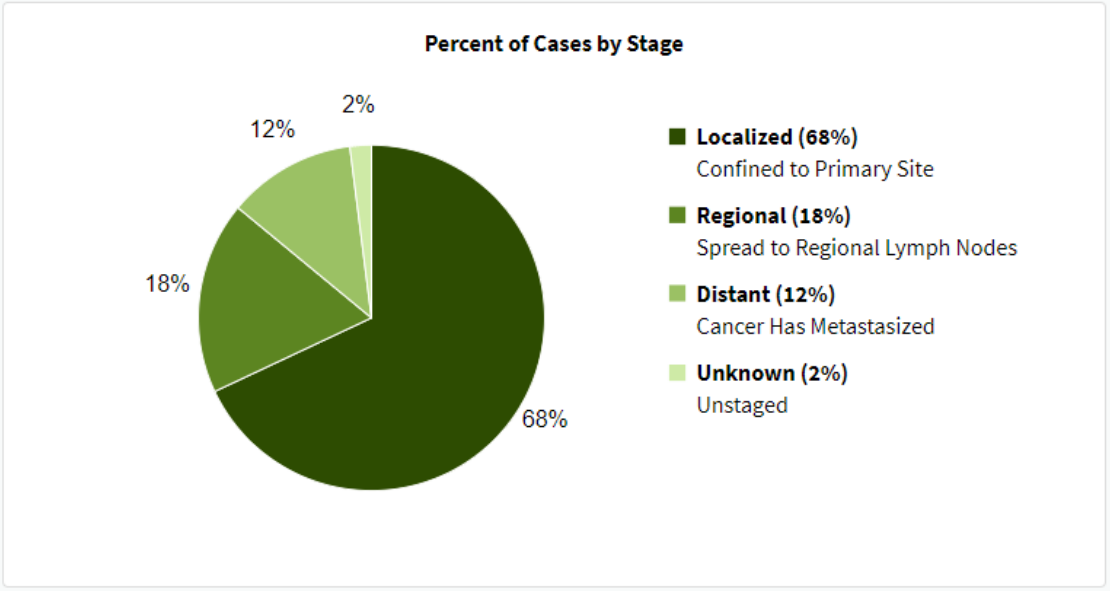
- Lymph Nodes (#1)
- Lung
- Liver
- Bone
- Other visceral sites

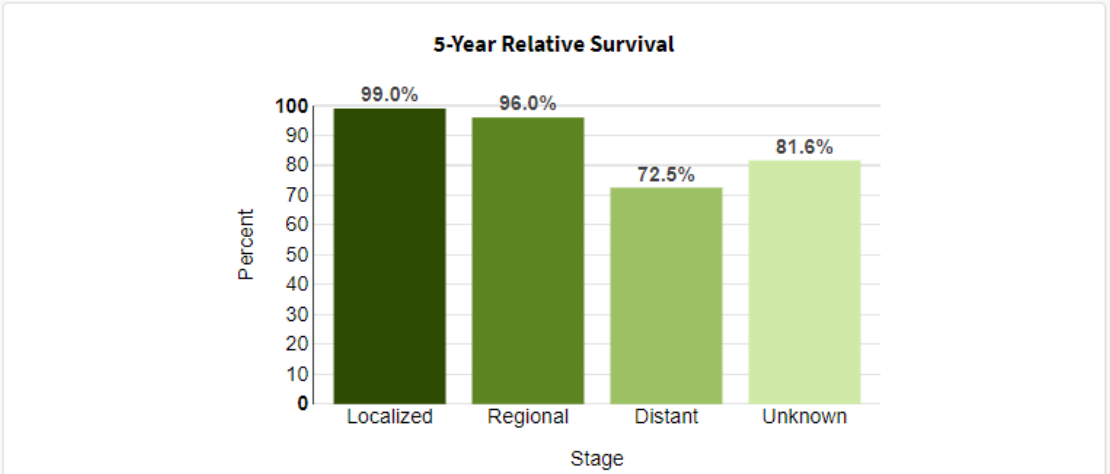
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Seminoma General Treatment Principles

- Confirm histology, work-up, and staging
- Cure rates approach 100%
- Late toxicities increasingly appreciated with aging of population treated with contemporary treatments
- Interest in observation or chemotherapy to avoid late radiation effects

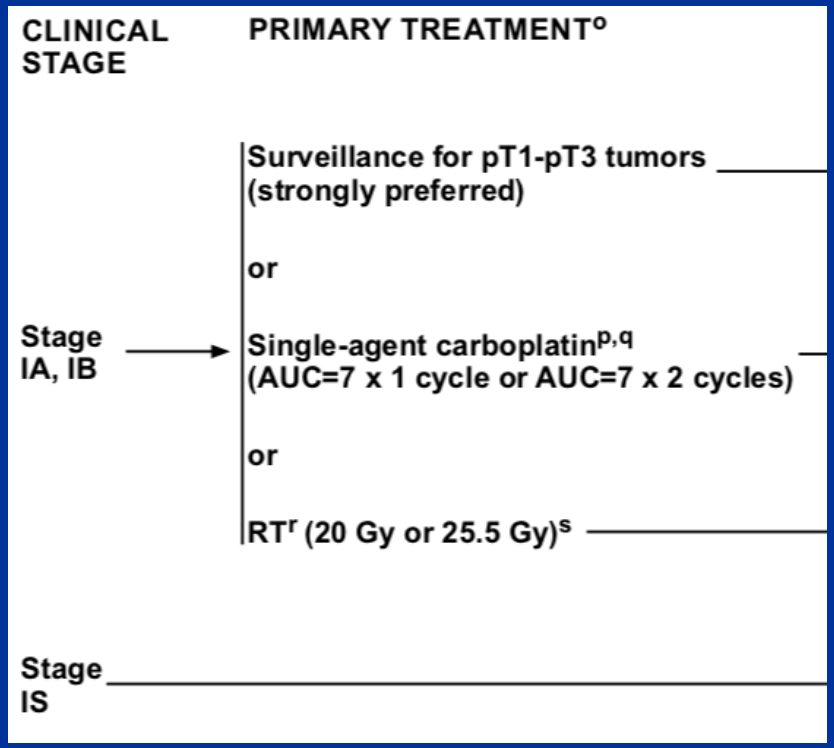
Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Testicular Cancer

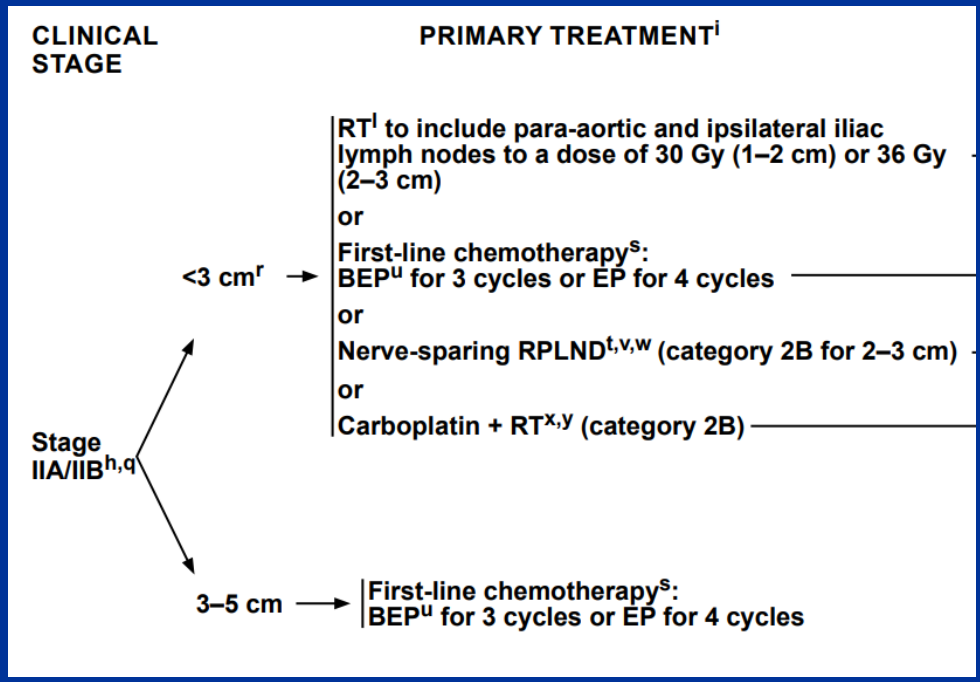




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Seminoma Treatment Options





NCCN guidelines – www.nccn.org

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PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

General Principles

- Modern radiotherapy involves smaller fields and lower doses than were used in the past. References are provided to support current recommended management.
- The mean dose (Dmean) and dose delivered to 50% of the volume (D50%) of the kidneys, liver, and bowel are lower with CT-based anteroposterior-posteroanterior (AP-PA) three-dimensional conformal RT (3D-CRT) than intensity-modulated RT (IMRT).[1] As a result, the risk of second cancers arising in the kidneys, liver, or bowel may be lower with 3D-CRT than IMRT, and IMRT is not necessary.[2] Proton therapy can also be considered. See Discussion.
- Timing of Radiotherapy:
  - Radiotherapy should start once the orchiectomy wound has fully healed.
  - Patients should be treated 5 days per week.
  - Patients who miss a fraction should be treated with the same total dose and with the same fraction size, extending the overall treatment time slightly.
- Antiemetic medication significantly improves nausea. See NCCN Guidelines for Antiemesis. Antiemetic prophylaxis is encouraged at least 2 hours prior to each treatment, and some cases may require more frequent dosing.

Preparation for Radiotherapy

- A discussion of semen analysis and sperm banking prior to post-orchiectomy treatment is recommended if clinically indicated.[3,4]
- If sperm banking is desired, it should be performed prior to the delivery of adjuvant therapy.

General Treatment Information

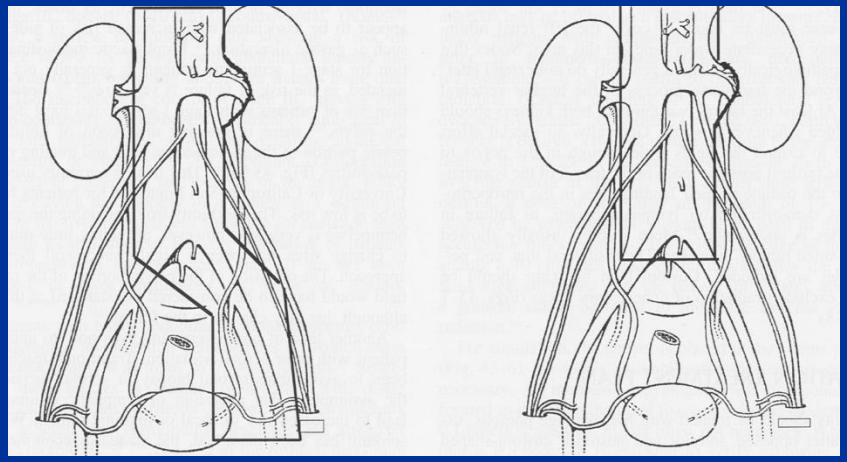
- Treatment Planning Principles
  - A non-contrast CT simulation should be performed with the patient supine, arms at the patient's sides, in the treatment position.
    - ◊ Immobilization with a cast may be used to improve the reproducibility of patient setup.
    - ◊ All patients, with the exception of those who have undergone bilateral orchiectomy, should be treated with a scrotal shield.

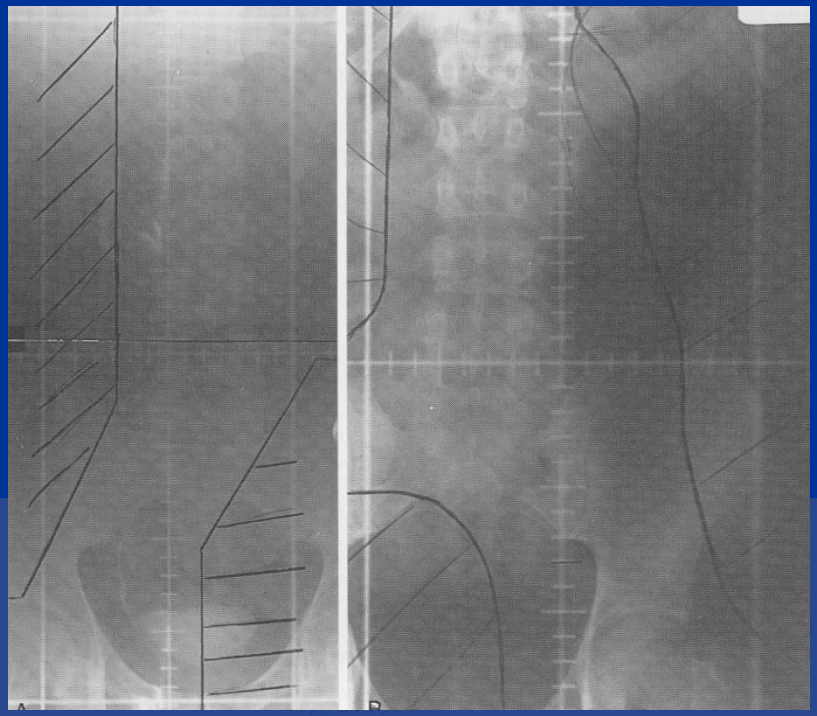
Radiation Simulation

- Sperm banking prior to simulation
- Supine
- Immobilization devices: +/- mold
- CT simulation
- Clamshell for contralateral testis
- Penis out of field

Radiation Fields

- AP/PA beams
- DL or PA field for Stage I
- Borders
  - Superior – T10-11 interspace
  - Inferior – Top obturator foramen (L5-S1 for PA)
  - Lateral – 2 cm on nodes (10-12 cm wide)
    - Include left renal hilum for left sided tumors
    - Remember R → L crossover
- Boost gross nodes with 2 cm margin
- No need to cover inguinal orchiectomy scar
- No need to cover scrotum if violated
- No role prophylactic mediastinal radiation for Stage I or II patients – $\leq$ 2% relapse in mediastinum with standard fields

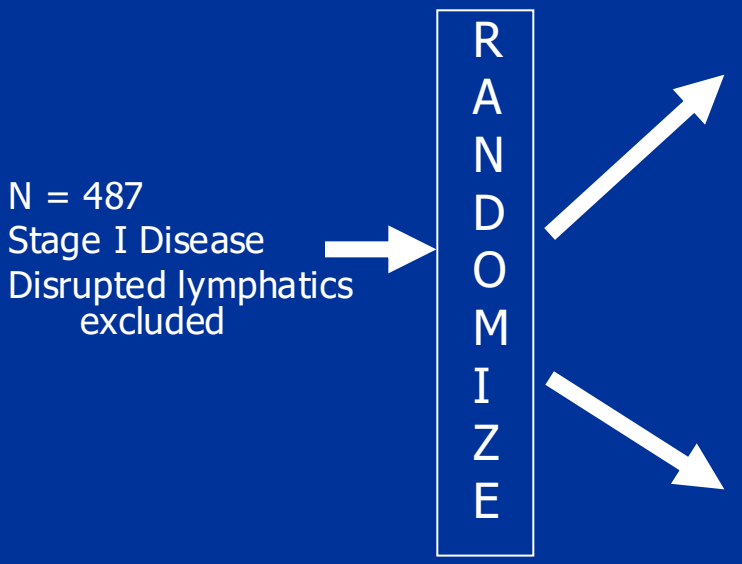




Dogleg vs. PA Field ?

- Background
  - ≤ 15% of patients with stage I have pelvic disease
- Rationale
  - Can the pelvic nodes be safely omitted from field?

Evidence – DL vs. PA fields



	% RFS_3	% OS_3	% Pelvic $Relapse_3$
DL	**96**	**97**	**0**
PA	**99** (NS)	**100** (NS)	**2** (p=.04)

XRT 30 Gy/15 fractions

PA with
- Less N/V
- Lower azoospermia (35 vs 11%)
- More rapid recovery of sperm count (20 vs 13 mo)

Fossa, SD el al. Optimal planning target volume for stage I testicular seminoma: A MRC randomized trial. JCO 1999; 17: 1146-54.

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Radiation Dose

- Stage I: 20- 25.5 Gy
- Stage IIA: 30 Gy
- Stage IIB: 36 Gy

Radiation fields (adapted from NCCN)

PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

Treatment Modalities

- **Linear accelerators with >6 MV photons should be used when possible.**

Target Volumes by Stage (or location)

Figure 1:
Stage I RT Field

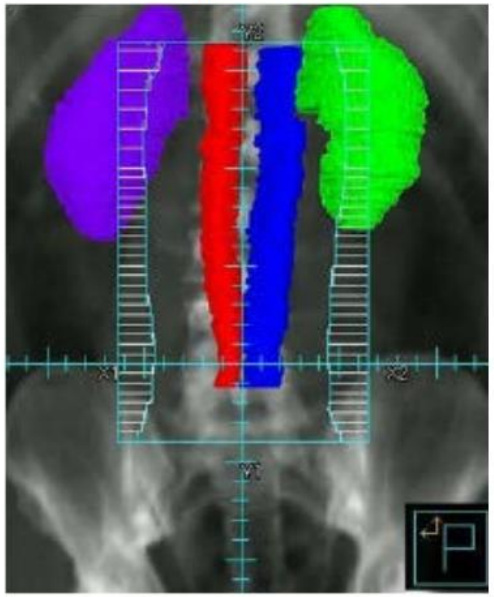


Figure 2:
Stage II RT Large Field

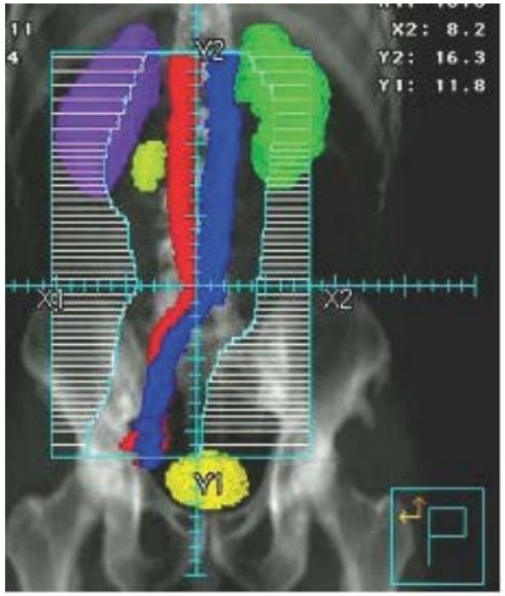
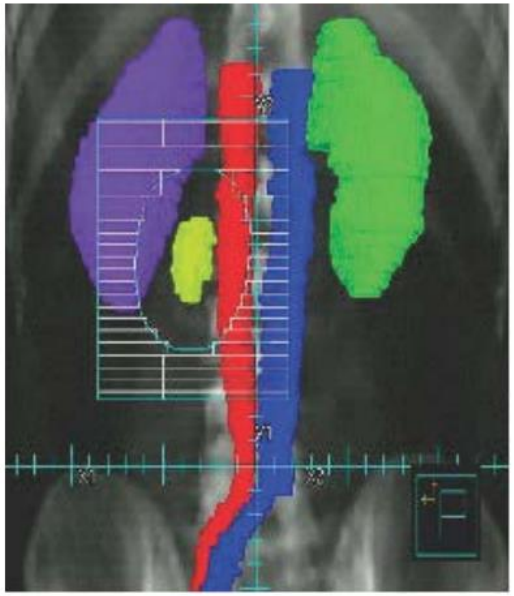
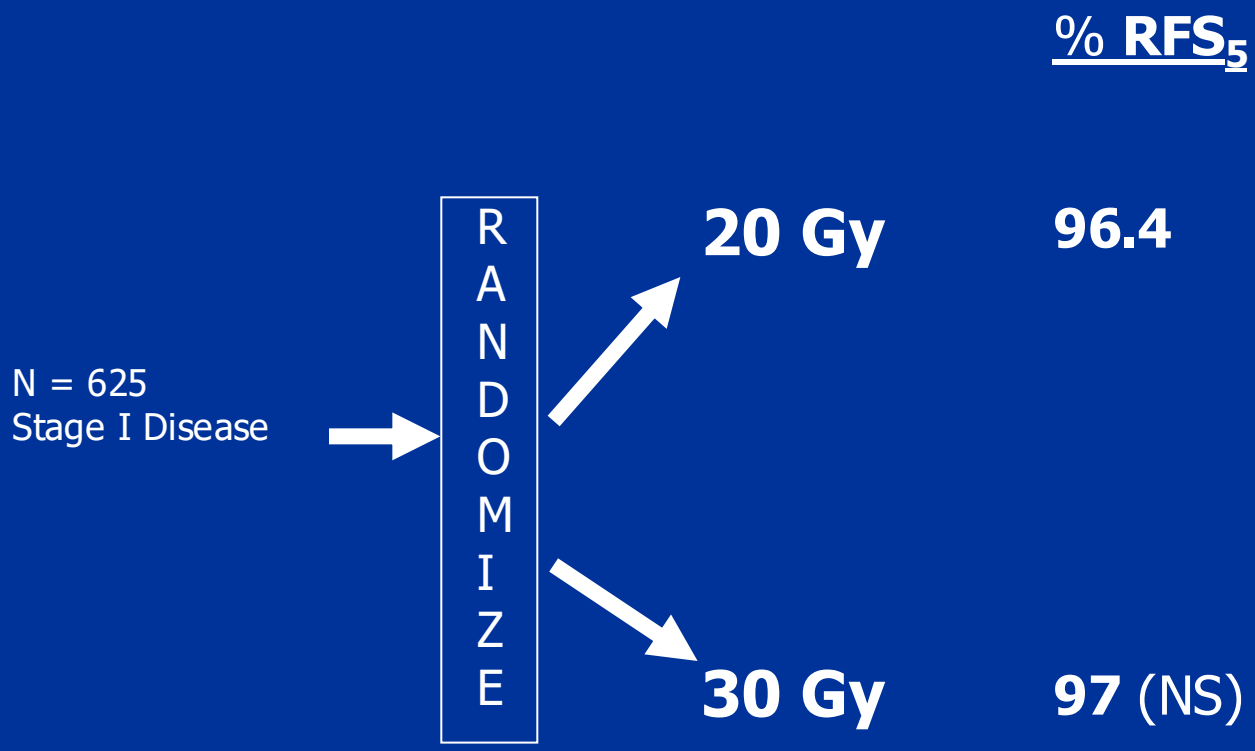


Figure 3:
Stage II Cone-Down Field



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Evidence – Radiation Dose



XRT : **2 Gy/fraction**
PA fields
DL if prior inguinal sx

20 Gy with:
- Decreased lethargy
- Less missed work time

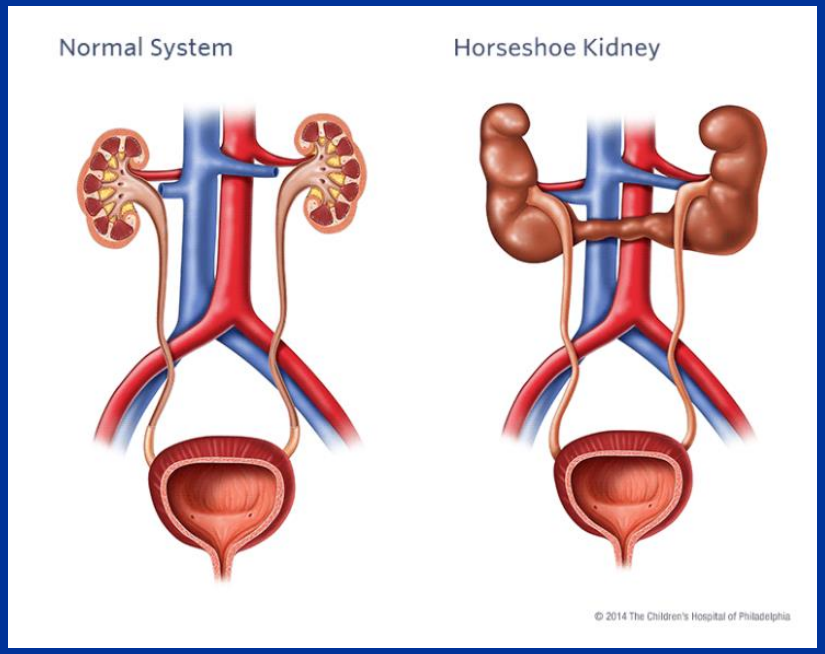
Jones, WG et al. Randomized Trial of 30 Gy vs. 20 Gy in the adjuvant treatment of Stage I testicular seminoma: a report on the MRC Trial TE18, EORTC trial 30942. JCO 2005; 23: 1200-8

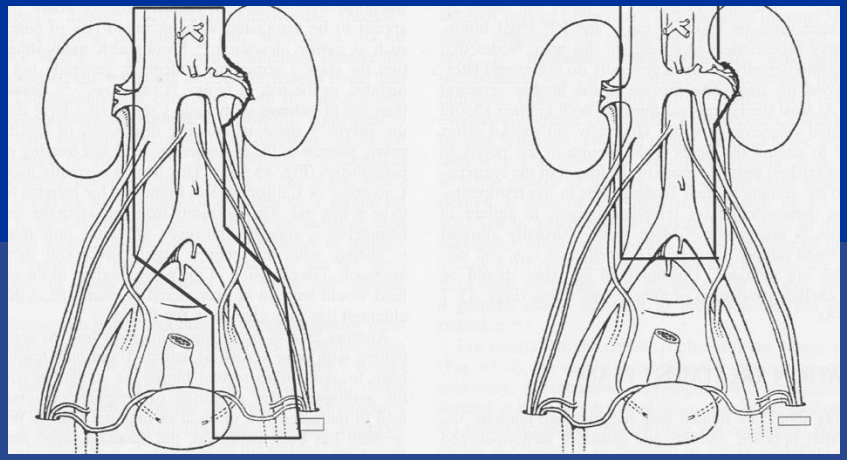
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"Contraindications" to Adjuvant Radiotherapy

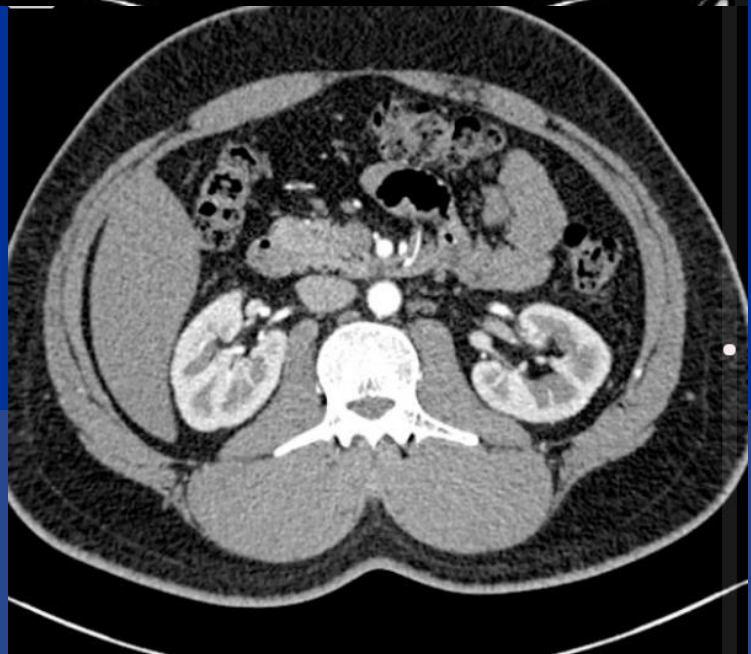
- Inflammatory Bowel Disease
- Horseshoe kidney
- Prior abdominopelvic radiation
  - If second primary after standard management for first, consider re-irradiation with carefully calculated kidney doses
- For these patients, consider surveillance or adjuvant chemotherapy

Horseshoe Kidney







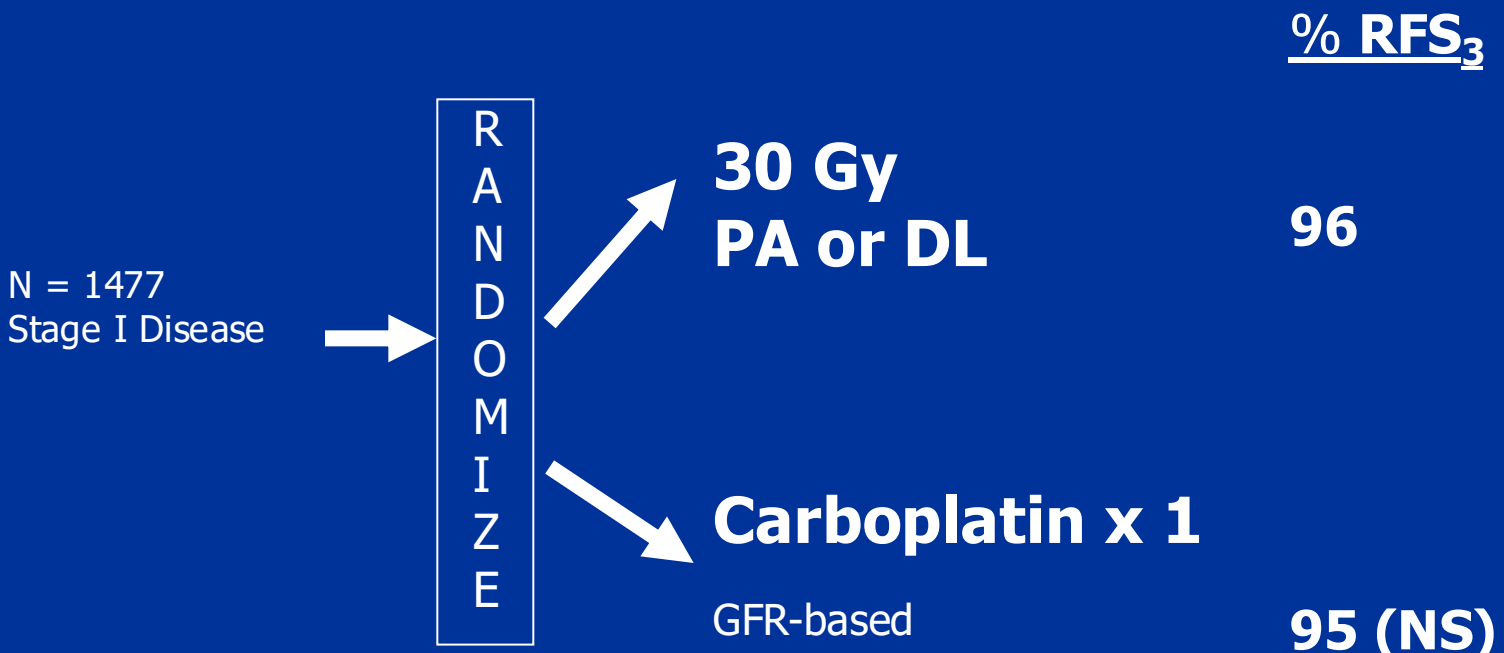


Chemotherapy ?

- Seminomas are very sensitive to platinum chemotherapy
- Is adjuvant chemotherapy equivalent to XRT in stage I patients?

Radiation vs. Chemotherapy

MRC TE19/EORTC 30982



Median f/u – 4 years

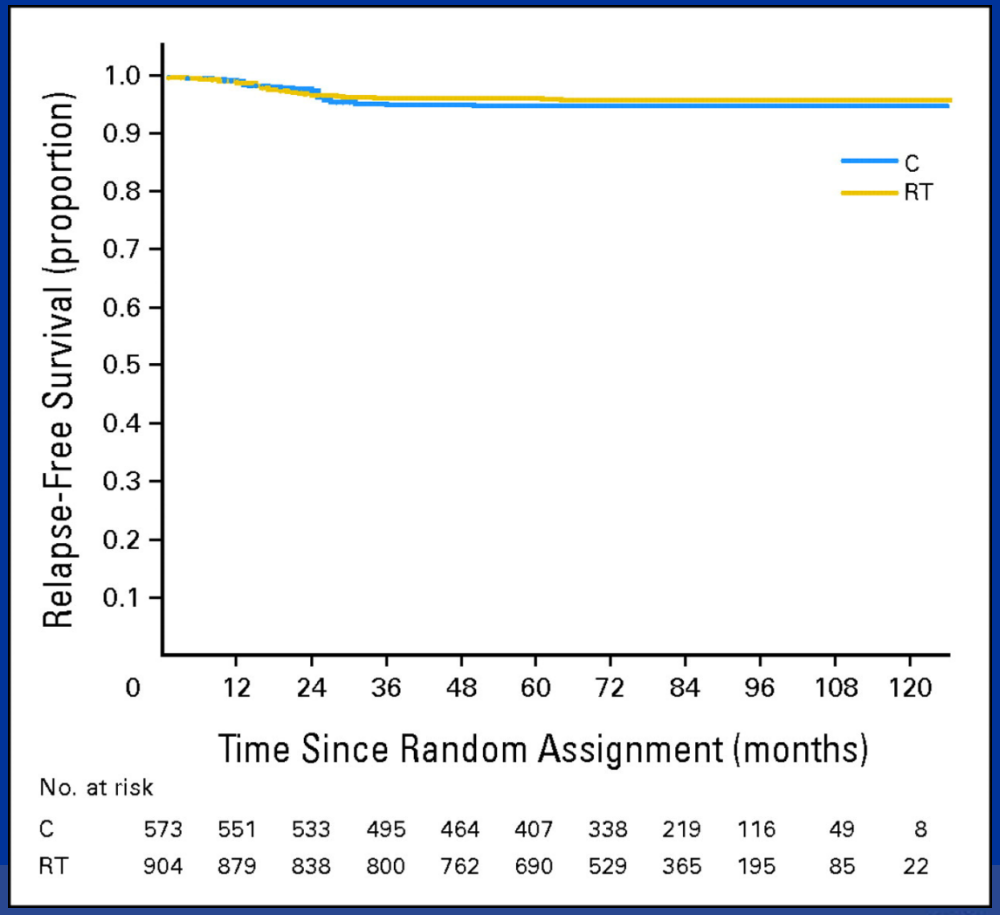
Second testicular primaries – 10 RT arm, 2 chemo arm

1 seminoma death in RT arm

Oliver, RT et al. Radiotherapy vs. single dose carboplatin in adjuvant treatment of stage I seminoma: a randomized trial. Lancet 2005; 366: 293-300.

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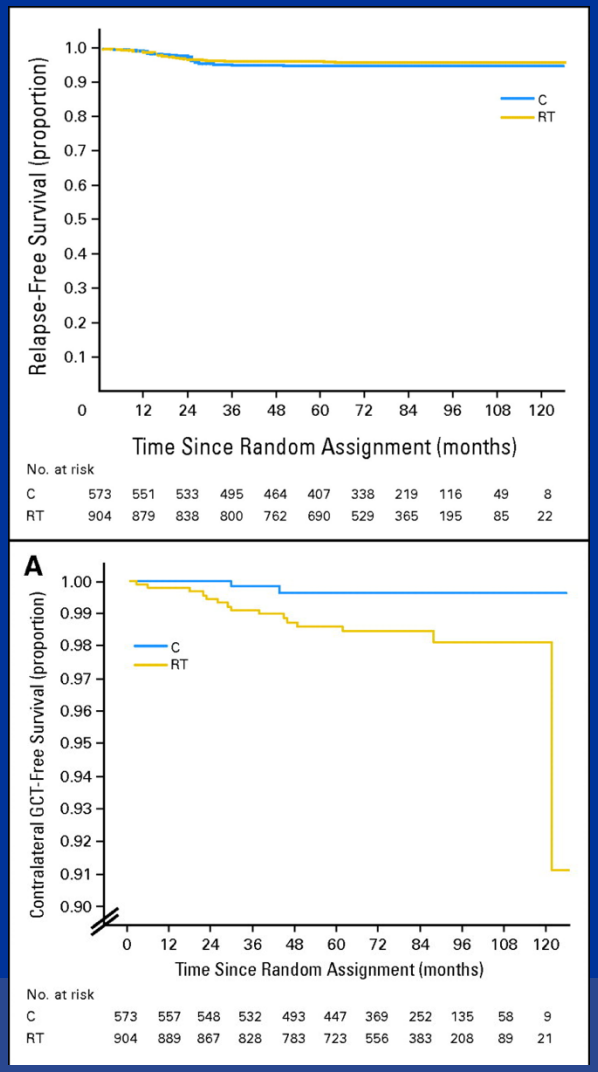
Carbo vs RT: Update with 6.5 y followup



Oliver RT, J Clin Oncol 2011

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Chemo vs RT vs Surveillance



- Subsequent studies have shown higher rates of heart and cerebrovasc disease after carboplatin
- Longer term studies failed to confirm reduced contralat cancers

Oliver RT, J Clin Oncol 2011

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Surveillance

- Cause Specific Survival ~ 100% for Stage I seminoma
  - Successful salvage if recurs
- Recurrence rates 15-20% untreated Stage I

  (= proportion of patients benefitting from adjuvant therapy)
- 85% of patients relapse in PA nodes (most within 2 years)
- Main factors to help with selection
  - Main factors – size > 4 cm and rete testis invasion
  - Minor risk factors – LVSI and age

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Surveillance

- 80-85% stage I patients are over-treated and unnecessarily exposed to chemotherapy/radiation
- But surveillance period is long – 10 years, 21 CT scans, and salvage toxicities need to be considered
- *Both* treatment and surveillance cost $ and time
- **In general, surveillance offers advantages in well-selected and compliant patients**

Seminoma: Acute Radiation Effects

- Nausea & vomiting
  - Start anti-emetic at first treatment
- Loose stools & diarrhea
- Oligospermia
- Transient myelosuppression

Late radiation effects

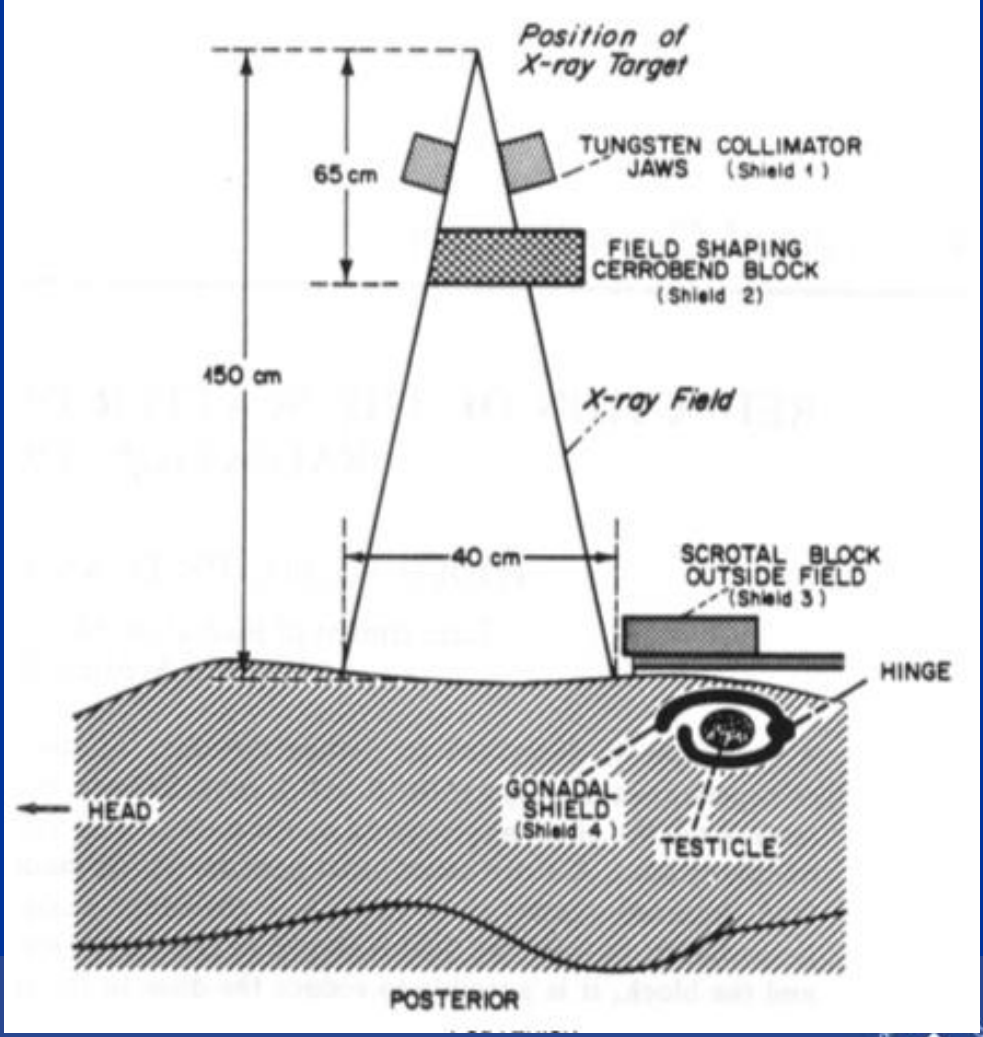
- SBO, chronic diarrhea, PUD (<2% if $\leq$ 35Gy)
- Oligospermia for 1 year
- Infertility
- Cardiotoxicity -- less common with current techniques i.e. no mediastinal RT
- Second cancers
- Immunosuppression

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Testicular Dose

- PA decreases testicle dose by 50% vs. DL
- With clamshell, contralateral testis reduced
  - By 2-3x
  - 1-2% of primary dose
  - ~ 25 cGy
- Mostly from internal scatter
- Use diodes or TLD (OSL) to confirm testicular dose

Testicular shield



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Testicular shield

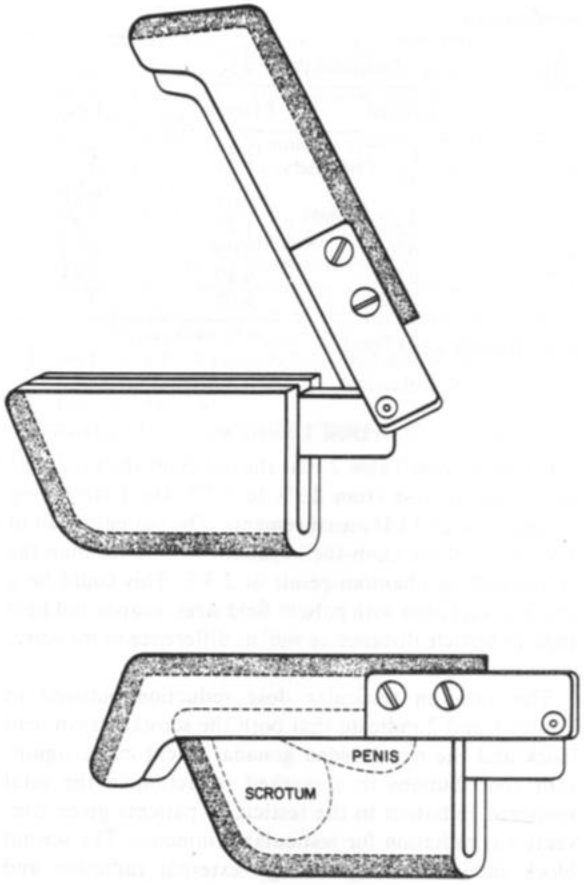


Fig. 3. Two gonadal shields, one closed and the other open. Dotted line illustrates the location of the front wall of the shield which separates the testicle from the radiation field.

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Radiation and the Testes

- 10 cGy — Reduction in spermatozoa
- 15 cGy — Temporary sterility
- 2 Gy — Azoospermia lasting for several years
- 6-8 Gy (fractionated) — Permanent azoospermia
- Leydig cells (make testosterone) are fairly resistant, so libido and hormonal function retained

Hall & Giaccia – Radiobiology for the radiologist, 6th Ed – LWW 2006

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Late effects - Fertility

- Most have diminished fertility prior to treatment
  - 50% sub-fertile counts at presentation or post-sx
- Contribution from surgery, radiation, or coexisting testicular abnormality unknown
- Lower testicular dose associated with more rapid recovery or sperm counts at 1 year
- Wait 6-12 months before insemination due to concerns of potentially damaged genetic material; However:
  - **Senturia *(Lancet 5:766, 1985)***
    - » Studied children of testicular cancer patients
    - » DOES NOT appear to be an increase in birth defects
- Counsel patient and partner about risks and options if pregnancy occurs in this time period.
- 30% can have children after radiation therapy

Onco-testicular Sperm Extraction (TESE)

- Ex vivo extraction of testis tissue at the time of radical orchiectomy
- Tissue extraction is meticulously targeted in areas distant from the tumor site to enhance the likelihood of healthy tissue retrieval.
- Performing onco-TESE on the healthy contralateral testicle is avoided to minimize surgical trauma

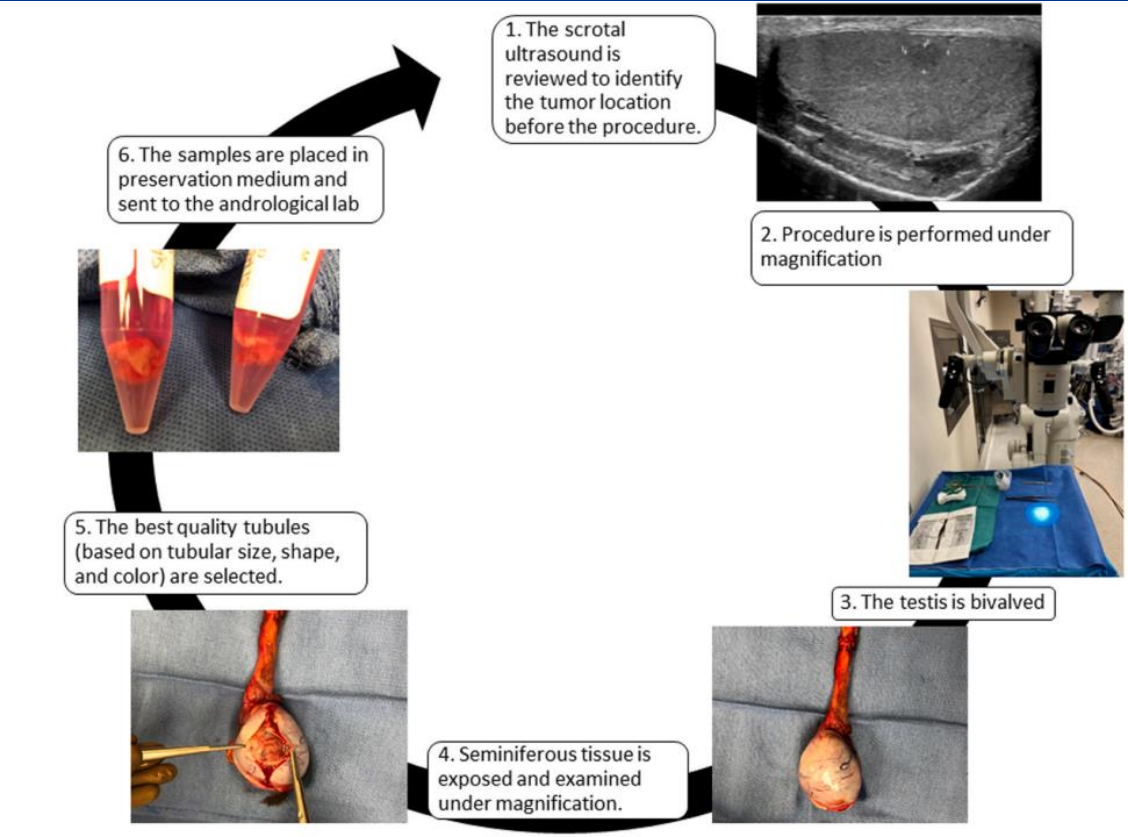


Figure 1. Onco-testicular sperm extraction steps. Illustration of the steps followed for onco-testicular sperm extraction at our institution.

Flores et al (MSK) *Urology* 2024

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Late radiation effects – Secondary Malignancies

- Testicular cancer patients have higher rates of second tumors compared to age-matched controls
- Hard to determine the incidence due to radiation
- Confounding genetic variables
- Correlated with increased cancer rates in:
  - Bladder
  - Kidney
  - Stomach
  - Colon
  - Pancreas
  - Skin
  - Leukemia
  - Sarcomas

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Evidence – SMN and CV Disease

N = 2707
Any stage or treatment
Retrospective
Looked at SMN and CVD
Compared to general population
Median f/u 17.6 years

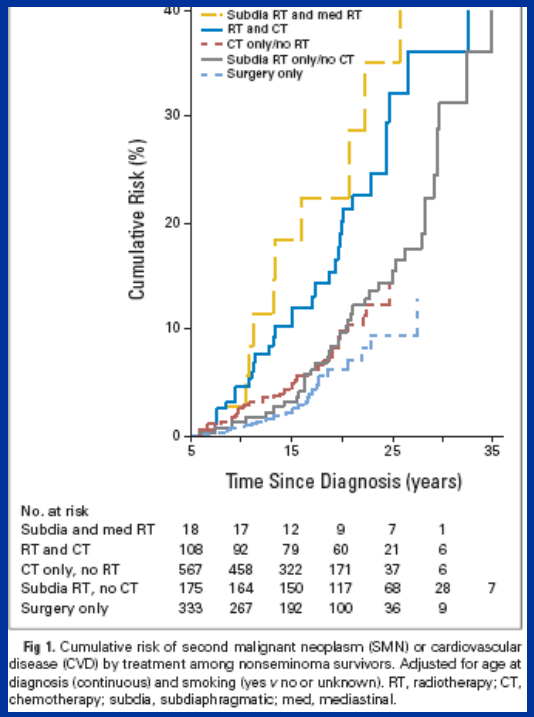


Fig 1. Cumulative risk of second malignant neoplasm (SMN) or cardiovascular disease (CVD) by treatment among nonseminoma survivors. Adjusted for age at diagnosis (continuous) and smoking (yes *v* no or unknown). RT, radiotherapy; CT, chemotherapy; subdia, subdiaphragmatic; med, mediastinal.

SMN risks compared to surgery only
2.6x increase with XRT
2.1x increase with chemotherapy

CVD risk compared to surgery only
NO increase with subdiaphragmatic radiation
3.0x increase with mediastinal radiation
1.7x increase with chemotherapy

SMN or CVD risk relative to surgery only
1.8x with XRT
1.9x with chemotherapy
1.7x with smoking

- **CT increases the risk of developing a major late complication to a similar extent as subdiaphragmatic irradiation**
- **Subdiaphragmatic RT increases risk of SMN**
- **CT increases risk of SMN and CVD**

Van den Belt-Dusebout et al. Treatment-specific Risks of Second Malignancies and Cardiovascular Disease in 5-Year Survivors of Testicular Cancer. JCO 2007; 25(28):4370-78.

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