Testis Cancer Overview

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Testis Cancer- Distinguishing Features

- Occurs in young men (ages 15-35)
- Metastatic pattern of spread consistent
- Chemosensitive
- “Surgery sensitive” after metastasis has occurred in low and high stage disease
  - Chemotherapy failures can be salvaged with surgery, surgery failures can be salvaged with chemotherapy

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Testis Cancer

- Most common solid tumor in men ages 15-35
- Incidence Highest in northern Europe and North America

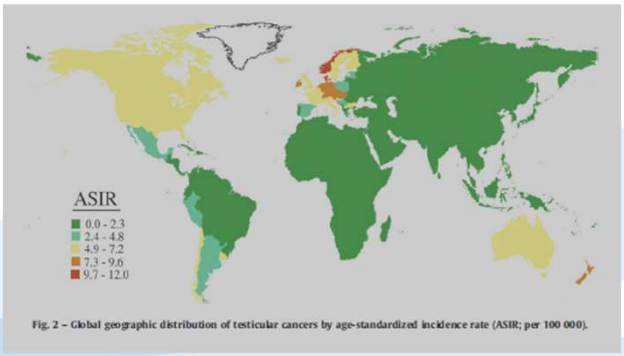

Fig. 2 – Global geographic distribution of testicular cancers by age-standardized incidence rate (ASIR; per 100 000).

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Testis Cancer: 30-year trends in US

- Incidence increasing over time

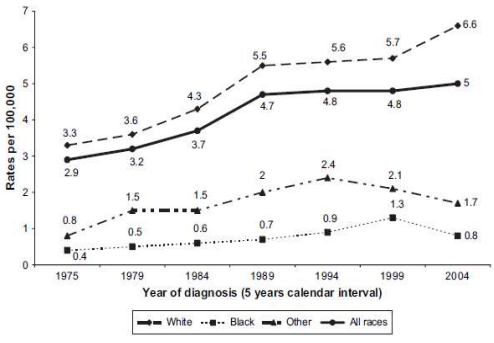

Figure 1 Three decades (1975–2004) testicular cancer incidence rates among US males, aged 15–49 years by race/ethnicity.

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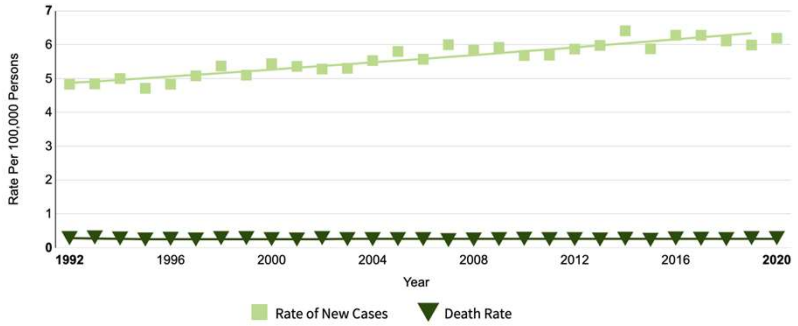
…Last 30 Years



- Greatest demographic changes (AAPC)
  - Asian/Pacific Islanders (2.47)
  - Hispanics (2.10)
  - American Indian/Alaska Natives (1.71)
  - Non-Hispanic Blacks (1.28)
  - Non-Hispanic Whites (0.41)

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Risk Factors

- ITGCN- 50% will develop GCT
- Microlithiasis- not a risk factor
- Contralateral testis cancer- 2-3% will develop a second primary GCT
- Cryptorchidism
  - Delayed Orchiopexy (> 10 yrs)
  - 10% of testis tumors are associated with UDT
    - 25% of these occur in the contralateral testis
- Pre-/Peri-natal Risk Factors
  - DES exposure/high levels of maternal estrogen
  - Maternal & Paternal Endocrine Disrupting Chemical (EDC) exposure
    - (Chromium VI/Toluene/Nickel exposure; OR 2.0)
- Genetic Syndromes (Trisomy 21, Androgen Insensitivity, Klinefelters)
- Gonadal Dysgenesis
- Marijuana (OR 1.7) & Tobacco (OR 1.2)
- Family History/Hereditary GCT…

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Lacson, JC et al. Cancer, 2012 Nov 1;118(21):5374-83.
Trabert B et al. Cancer, 2011 Feb 15;117(4):848-53.
Daling JR, Cancer. 2009 Feb 9
Pettersson A, N Engl J Med. 2007. 3;356(18):1835-1841
Walsh TJ, J Urol. 2007;178(4 Pt 1):1440-1446

Familial/Hereditary Testis Cancer

GCT-susceptible families:

- 1-2% have an affected family member
  - Higher risk among siblings
    (or step brothers) 😂
  - 4 to 8-fold increased risk
- Early onset
- Bilateral tumors are more common (8%-14%)
- Autosomal Recessive
- Seminoma = Nonseminomas
- Genetic, Lifestyle, and Environmental Factors likely contribute

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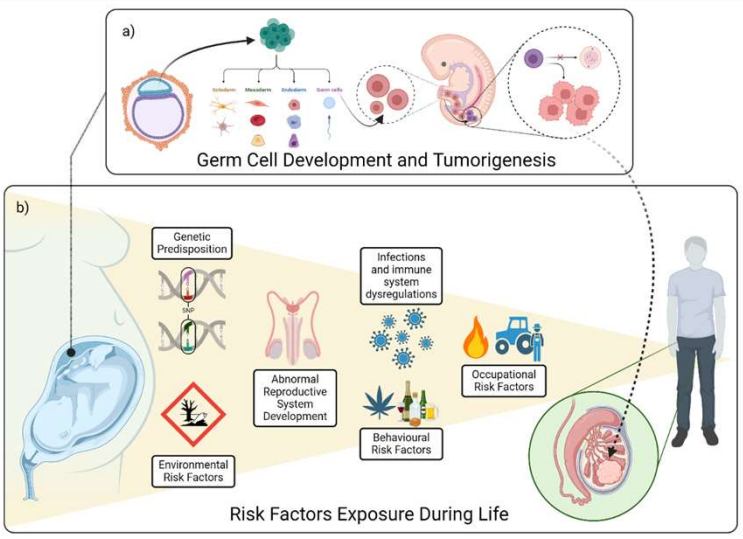
Pathogenesis



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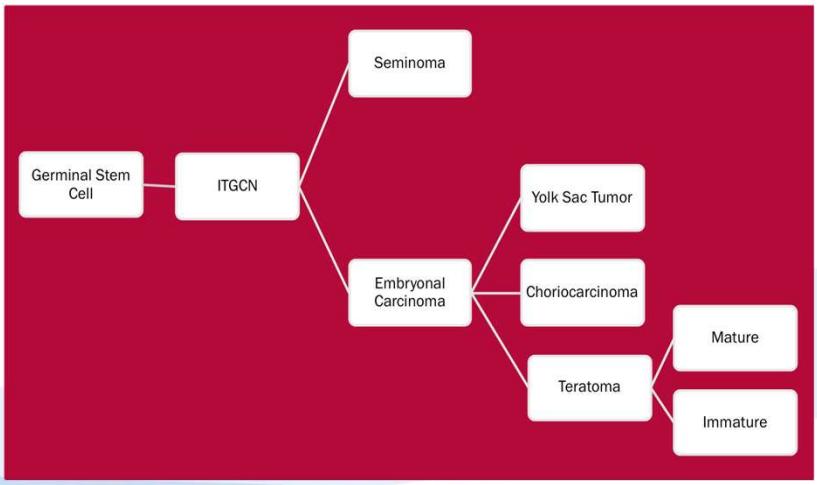
A Disease Of Differentiation



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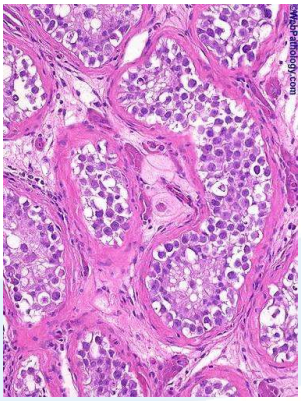
Histopathologic Aspects of ITGCN

Courtesy of Wade Sexton

- Usually post pubertal
- Normal appearing sertoli cells
- Variable involvement of seminiferous tubules
- Adjacent to germ cell tumors
- Not present in:
  - *spermatocytic seminoma*
  - *pediatric teratoma*
  - *pediatric yolk sac*



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Genetic differentiation

Histology	Age	Ploidy	Chromosomes
Teratoma/ YST	Infantile	diploid aneuploid	-1p, -6q
Seminoma/NS/ ITGCN	Postpubertal	CIS: hypertriploid	i(12p) or +12
		SEM: hypertriploid	i(12p)
		NS: hypotriploid	i(12p)
Spermatocytic Seminoma	Older	diploid or tetraploid	+9

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Oosterhuis et al. APMIS 111:280,2003.

Prevalence of Testicular ITGCN

Courtesy of Wade Sexton

- Cryptorchidism - 5%
- Extragonadal germ cell tumor - 40%
- Intersex - 25% to 100%
- Contralateral testis - 6%

Giwercman, J Urol, 145:77, 1991
Giwercman, Scand J Urol Nephrol, 148:1, 1992
von der Masse, BMJ, 293:1398, 1986
Muller, Int J Androl 10:543, 1987

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Bilateral Testis Tumors

- 2-3% testis tumors bilateral
  - 70% metachronous
  - 30% synchronous
- Median time between tumors ~ 5 years
- Long-term survival >90%
- Seminoma most common histology in the second primary

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Fossa SD et al, J NCI 97(14):1056-66, 2005
Hentrich et al, Acta Oncol. 44(6):523-5, 2005
Holzbeierlein et al, J Urol. 169(6):2122-5, 2003
Zequi Sde C et al, BJU Int. 2012 Oct;110(8):1102-9

Presentation

- Presentation with a solid tumor
- Delay in diagnosis common
  - Results in more advanced stage at presentation
  - Increases the burden of therapy
  - Secondary decrease in survival
- 30-40% are treated initially for epididymitis
- Ultrasound is very sensitive for detection of intratesticular lesions

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Symptoms

- Local
  - Mass
  - Pain +/-
  - Swelling
- Systemic
  - Back pain
  - Neck mass
  - Cough
  - GI symptoms
  - CNS symptoms
  - LE swelling
  - Gynecomastia
    (5-10% of patients)

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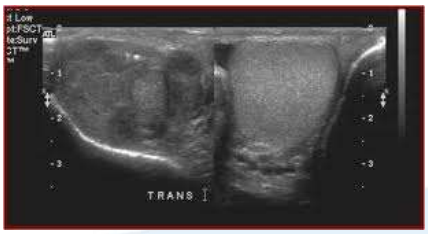
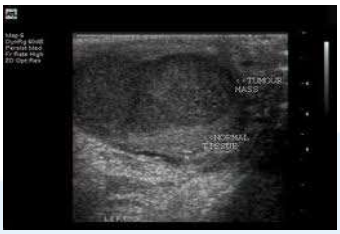
Evaluation and work-up of a testis mass

- Physical Exam
- Scrotal Ultrasound





- Serum Tumor Markers (STM)

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Serum Tumor Markers (STM)

- Use in staging unique to testis cancers
- 50-70% of patients will have elevated values
- Useful for
  - Diagnosis
  - Assessment of risk strata
  - Monitoring of response to treatment
  - Surveillance for recurrence or relapse
- If cancer cells are eradicated by treatment, then STM should decline according to their respective half-lives

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Serum Tumor Markers

- B-HCG
  - Produced by syncytiotrophoblasts
  - Elevated in
    - Choriocarcinomas (100%)
    - Embryonal Carcinoma (40-60%)
    - Seminoma (15%)
  - T1/2 18-36 hrs
  - False +
    - X-reactivity with LH
    - Hypogonadism
    - Pituitary overproduction of HCG
    - Marijuana abuse
- AFP
  - Seen in Embryonal and YST
  - T1/2 5-7 days
  - **Presence excludes seminoma**
  - False +
    - Liver, pancreatic stomach and lung cancer
    - Hepatic regeneration
    - Chemo induced liver damage

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Lactate Dehydrogenase (LDH)

- Is a non-specific marker of disease
  - LDH >200 U/dl - usually a reliable marker in representing tumor burden
- Produced by muscle, liver, numerous organs
- May be elevated in all types of GCTs
- Clinical utility in question

  -We do NOT routinely obtain this STM 

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AUA Guidelines

Statement 2: Serum AFP, HCG, and LDH should be measured prior to any treatment, including orchiectomy, in patient with suspected GCT (Moderate Recommendation; Evidence Level C)

- AFP, HCG and LDH are essential for characterization and risk stratification
  - Pure seminoma does not produce AFP
  - IGCCCG risk classification based upon post-orchiectomy levels
- Baseline serum tumor marker levels are important for post-orchiectomy interpretation
  - AFP, HCG, LDH levels that are declining according to $T_{1/2}$ or rising relative to pre-orchiectomy values may impact treatment decision

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STM

- If markers do not fall according to expected $T_{1/2}$, evidence then exists that germ cell elements remains present and viable.
- Converse, normalization of STM does NOT guarantee complete eradication of all cancer cells
- This is a unique feature to testis cancer that allows us to follow and monitor treatment effect

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Radical Orchiectomy

- High Ligation with Inguinal Approach
  - Rationale
    - Lower chance of cutting into tumor
      - If spillage occurs, another lymphatic region of lymphatic spread can occur
    - Removal of lymphatics draining primary (i.e. spermatic cord)
      - Facilitates retrieval of remnant cord at time of RPLND

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Scrotal Violation

- Meta-analysis of 206 patients
  - Scrotal violation increased risk of local recurrence from 0.4% to 2.9%
  - No difference in distant recurrence or survival
- Single institution series (IU) – 78 patients
  - 6.4% local recurrence
  - No recurrence in patients who received chemotherapy

Add photo here
June 2020

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Capelouto et al, J Urol, 153:981, 1995
Leibovitch I, et al., J Urol. 1995 Sep;154(3):935-9

Scrotal Violation

- Low-stage Seminoma & NSGCT
  - Surveillance
  - Include ipsilateral groin/scrotum if receiving adjuvant XRT (*Seminoma only*)
  - Excise scrotal scar/cord remnant at RPLND
- Post-Chemotherapy for Advanced-Stage GCT
  - Residual Disease
    - Excise cord remnant at RPLND
    - Formal hemiscrotectomy and ILND not recommended
  - Complete Response
    - Local recurrence following systemic chemo rare

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Aki et al, Urology 2000, 459-62

Partial Orchiectomy

- Candidates
  - Suspicion of a benign tumor
  - Synchronous/Bilateral tumors
  - Solitary testis
  - Criteria
    - Solitary better
    - Size <2 cm
    - Polar location
    - Patients must have normal LH and Testosterone
- Rationale
  - Does NOT preserve fertility
  - Maintain androgen function

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De Stefani S et al. Urol. 79 (4), 2012.
Lawrentschuk N et al. J Urol. 2011 Feb;185(2):508-13.
Dieckmann KP et al. Ann Oncol. 2013 Jan 4
Powell TM and Tarter TH. J Urol. 2006;176(1):96-98.
Heidenreich A, et al. J Urol. 2001;166(6):2161-2165.
Carmignani L, et al. J Urol. 2003;170(5):1783-1786.
Connolly SS, et al. BJU Int. 2006;98(5):1005-1007

Partial Orchiectomy

- Follow principals of radical orchiectomy
  - Inguinal incision
  - Drape field to prevent contamination
  - Intraoperative testicular ultrasound
  - Cold ischemia during tumor excision?
  - Intraoperative frozen and margin assessment
  - Adjacent tissue biopsies to assess for ITGCN
- Pathological findings
  - 50% to 90% of small lesions (< 10 mm) have benign histology
  - Seminoma - most common germ cell tumor
- Adjuvant XRT (15-20 Gy) for CIS found on biopsies
- Strict surveillance with markers, exam, U/S

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Lawrentschuk N et al. J Urol. 2011 Feb;185(2):508-13.
Dieckmann KP et al. Ann Oncol. 2013 Jan 4
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Connolly SS, et al. BJU Int. 2006;98(5):1005-1007

Orchiectomy Results

- 96% are of germ cell origin
  - Seminoma (~50%)
  - Non-seminoma (~50%)
    - Embryonal
    - Yolk Sac Tumor
    - Teratoma
    - Choriocarcinoma
- 3-5% are non-germinal/stromal
  - Leydig cell tumor (1-2%)
  - Sertoli cell tumor (1-2%)
  - Other (<1%)
    - Adenocarcinoma of the rete testis
    - Carcinoid tumors
    - Mesotheliomas
    - Leukemia/Lymphoma
  - Benign tumors
    - Adenomatoid tumors
    - Adrenal Rest tumors
    - Cystadenomas
    - Epidermoid cyst

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Mostofi FK. Cancer 1973, 32:1186
Eble J.N., Sauter G, Epstein J.I., Sesterhenn I.A (Eds.): IARC Press: Lyon 2004.

Germ Cell Tumors

- Seminoma
  - 10-20% produce HCG by syncytiotrophoblasts
  - Chemotherapy and radiation sensitive tumors
- Non-Seminoma
  - Embryonal Carcinoma
    - Ability to differentiate/de-differentiate
  - Teratoma
    - Chemotherapy resistant tumor
    - Late relapse
    - Surgery is only treatment
    - Tendancy to dedifferentiate
  - Yolk Sac Tumor
    - Produces AFP
    - Commonly seen in late relapse
  - Choriocarcinoma
    - Produces HCG
    - Hematogenous metastasis early in course
    - Choriocarcinoma syndrome

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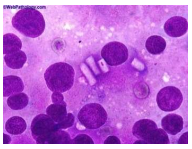
Sex Cord Stromal Tumors

- Leydig Cell
  - Most common non-germ-cell tumor
  - Intracytoplasmic Reinke's crystals



- Sertoli Cell
  - 1% of testicular tumors
  - Diagnosis usually before age 20
  - 1/3rd with gynecomastia

- 10% malignancy rate
  - Size > 5 cm, LVI, High mitotic index, Cord invasion, infiltrative margins, and necrosis
  - However, histology is not predictive of malignancy
- Virilization and gynecomastia should increase clinical suspicion

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Dilworth J. Urology 1991; 37:399-412.
Conkey DS, Clin Oncol 2005;17:322-27.
Featherstone JM, J Urol 2009;181:2090-2096

Sex Cord Stromal Tumors

- Management:
  - Radical orchiectomy
  - Radiographic staging
  - CSI tumors (*controversial*)
    - Surveillance
      - Recommended in patients with no malignant features
    - Primary RPLND for those with 1 or more risk features
      - Surgery only chance for cure
  - Metastatic and/or malignant tumors:
    - Role of RPLND unclear
    - Response to chemo/XRT limited
    - Incurable in most circumstances

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Featherstone JM, J Urol 2009;181:2090-2096
Calaway et al, J Urol 2017

Rhabdomyosarcoma

- CSI patients need RPLND to further stage
- Pathologic findings will dictate type of chemotherapy given
- Advanced stage, initial chemotherapy followed by PC-RPLND
- XRT rarely used

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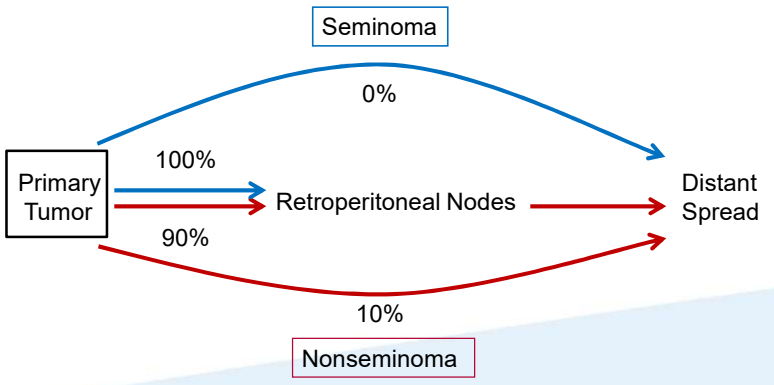
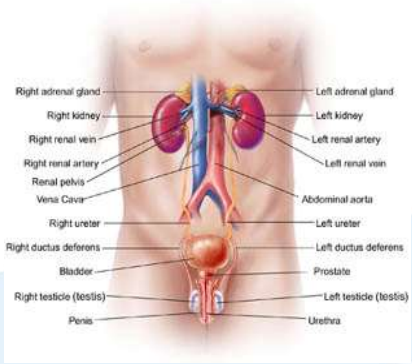
Germ Cell Tumor

Natural History





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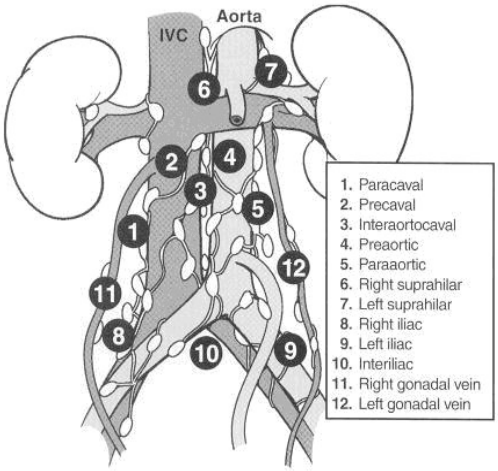
RP spread

- Predictable Metastatic Spread of Testicular GCT in greater than 90% of cases
- L sided primary tumors:
  - Para-aortic, pre-aortic, interaortocaval nodes
- R sided primary tumors:
  - Para-caval, pre-caval, interaortocaval nodes



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Clinical Staging

- Determination of serum markers
- CT scans of abdomen and chest
- Physical examination with special attention to other lymphatic drainage areas: cervical nodes, axillary nodes, etc.
- Staging especially important in testis cancer since different stages are treated differently

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Imaging for metastasis

- CT - (not perfect)
  - Unable to detect micrometastases
  - 70-85% accurate (with path correlation)
- MRI
  - Vascular involvement
  - Increasing role in surveillance
- PET
  - Poorly differentiates teratoma from fibrosis
  - No defined role in clinical stage I
  - Used for post-chemotherapy seminoma residual mass (6-8 weeks after chemo)
    - Recent data reveals false (+) rate of 68-77%
- Brain MRI, Bone Scan
  - If clinically indicated

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Testis Cancer - TNMS Staging System

AJCC/UICC

- Primary Tumor
  - pTx primary tumor cannot be assessed
  - pT0 No evidence of primary (e.g., scar)
  - pTis intratubular germ cell neoplasia
  - pT1 limited to testis/rete testis; no L/V invasion
    - T1a in seminoma if <3cm
    - T1b if >3cm
  - pT2 limited, but + L/V invasion, or hilar/epididymis invasion
  - pT3 direct cord invasion +/- L/V invasion
  - pT4 direct scrotal invasion +/- L/V invasion

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Testis Cancer - TNMS Staging System
AJCC/UICC

- Regional lymph nodes (N) - clinical
  - Nx RLN's cannot be assessed
  - N0 no regional LN mets
  - N1 LN mass, single or multiple nodes, ≤ 2cm
  - N2 LN mass, single or multiple nodes, > 2-5 cm
  - N3 LN mass > 5cm

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Testis Cancer - TNMS Staging System
AJCC/UICC

- Regional lymph nodes (pN)- pathologic
  - pNx RLN's cannot be assessed
  - pN0 no regional lymph node mets
  - pN1 mass ≤ 2cm; or ≤ 5 pos. nodes, none > 2cm
  - pN2 mass 2-5 cm; or > 5 nodes pos., none > 5cm; or (+) extra-nodal extension
  - pN3 LN mass > 5cm

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Testis Cancer - TNMS Staging System
AJCC/UICC

- Distant Metastasis (M)
  - Mx Distant mets cannot be assessed
  - M0 No distant mets
  - M1 Distant mets
    - M1a: non-regional nodal or pulmonary mets
    - M1b: distant mets other than nonregional nodal or pulmonary

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Testis Cancer - TNMS Staging System
AJCC/UICC

- Serum Tumor Markers (S) (*Post-Orchiectomy)
  - Sx markers not available or performed
  - S0 markers WNL
  - S1

LDH	<1.5 x nl AND
hCG (mIU/ml)	<5000 AND
AFP (ng/ml)	<1,000

  - S2

LDH	1.5 - 10 x nl or
hCG (mIU/ml)	5,000 - 50,000 or
AFP (ng/ml)	1,000 - 10,000

  - S3

LDH	>10 x nl or
hCG (mIU/ml)	>50,000 or
AFP (ng/ml)	>10,000

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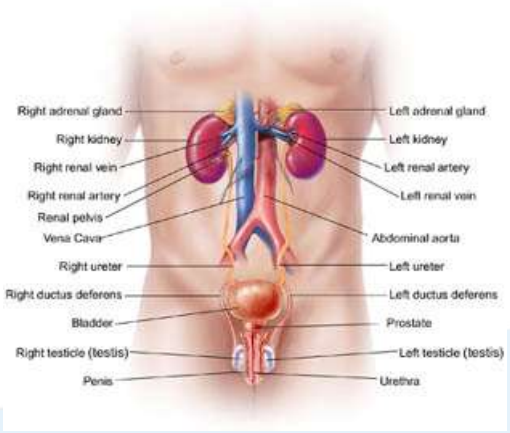
AJCC Staging System Groupings



Clinical Stage	Description
CS I	Tumor confined to the testis, no clinical metastases
CS Is	Tumor confined to the testis with persistently elevated STM
CS II	Regional retroperitoneal lymph node metastases
CS III	Non-regional nodal or visceral metastases

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Stage	T	N	M	S
Stage I	pT1-4	N0	M0	SX
IA	pT1	N0	M0	S0
IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
IS	Any pT	N0	M0	S1-3
Stage II	Any pT	N1 - 3	M0	SX
IIA	Any pT	N1	M0	S0 - 1
IIB	Any pT	N2	M0	S0 - 1
IIC	Any pT	N3	M0	S0 - 1
Stage III	Any pT	Any N	M1	SX
IIIA	Any pT	Any N	M1a	S0 - 1
IIIB	Any pT	N1 - 3	M0	S2
	Any pT	Any N	M1a	S2
IIIC	Any pT	N1 - 3	M0	S3
	Any pT	Any N	M1a	S3
	Any pT	Any N	M1b	Any S

AFP-alpha-fetoprotein, hCG-human chorionic gonadotropin, LDH-lactate dehydrogenase | From AJCC Cancer Staging=

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IGCCCG Risk Classification

RISK CLASSIFICATION FOR ADVANCED DISEASE (post-orchiectomy)[1]

Risk Status	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy markers- all of: AFP < 1,000 ng/mL hCG < 5,000 iu/L LDH < 1.5 x upper limit of normal	Any primary site and No nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Intermediate Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy markers- any of: AFP 1,000-10,000 ng/mL hCG 5,000-50,000 iu/L LDH 1.5-10 x upper limit of normal	Any primary site and Nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Poor Risk	Mediastinal primary tumor or Nonpulmonary visceral metastases or Post-orchiectomy markers- any of: AFP > 10,000 ng/mL hCG > 50,000 iu/L LDH > 10 x upper limit of normal	No patients classified as poor prognosis

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Selection of therapy

- Choice of therapy is contingent upon clinical staging and histology of the primary
- Therefore, therapy will be discussed for each clinical stage (I, II, or III) for both seminoma and nonseminoma

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Seminoma

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Clinical Stage I: Seminoma

- CT of abdomen and chest are normal
- In this circumstance we know that approximately 15% will have occult metastasis, usually to the retroperitoneal lymphatics
- Risk stratification based upon size >4cm and rete testis invasion of limited value!
  - High risk (30% relapse)
  - Low risk (5% relapse)

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Clinical Stage I
seminoma

- 3 management options:
  - Adjuvant radiotherapy to eradicate retroperitoneal metastases, with chemotherapy for the small number who recur
  - Adjuvant Carboplatin, with salvage chemotherapy/radiation/surgery for those who relapse
  - Close observation with frequent CT scans, CXR, exams. The 15-20% with metastasis will become evident and can be treated with chemotherapy (BEPx3 or EPx4), radiation, or RPLND!

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Adjuvant Radiotherapy

- Two phase III studies have verified the following in CS I seminoma:
  - No "dog leg" extension of the radiation template along ipsilateral iliacs is necessary
  - Dose of radiation has been reduced to 20 Gy
  - Long-term risk of secondary malignancy limits utility

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Adjuvant Chemotherapy

- Alternative approach to clinical stage I seminoma is to administer 1 cycle of carboplatin chemotherapy to all patients
- Rationale: seminoma is sensitive to carboplatin, and carboplatin has low morbidity and is easy to administer
- Whether this approach will be as effective as the other 2 strategies is unknown
- A phase III study showed equivalence of radiation and carboplatin but was a noninferiority design
- Limited by long-term risks, severity unknown?

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Surveillance

- Seminoma can have an indolent natural history
- Risk factors for RP metastasis are size of primary > 4cm and rete testis invasion
- Risk factors really not that important, in my opinion
- Surveillance must be continued for 5 years because of the fact that some grow slowly

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Clinical stage I
seminoma

- Any option ultimately yields a chance for cure of 96-98%
- Choice of radiotherapy, chemotherapy or close observation (also called “surveillance”) is driven by patient and physician choice, availability of medical care, etc.
- Secondary cancers induced by therapeutic radiation/chemotherapy has become more of an issue

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AUA Guidelines

Statement 26: Clinicians should recommend surveillance after orchiectomy for patients with stage I seminoma. Adjuvant radiotherapy and carboplatin-based chemotherapy are less preferred alternatives. (Strong Recommendation, Evidence Level B)

- Surveillance, carboplatin, PA radiotherapy → 100% survival
- Surveillance → relapse 15-20% → no “high-risk” category
- Surveillance recommended as it affords patient best opportunity to avoid treatment without compromising survival
- Carboplatin, PA radiotherapy: ↓ relapse 15-20% → 4-5%
  - Secondary cancers & long-term morbidities induced by therapeutic radiation/chemotherapy has become more of an issue

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AUA Guidelines

Statement 38: For a patient with CSI seminoma choosing surveillance, clinicians should obtain a history and physical examination and perform cross-sectional imaging of the abdomen with or without the pelvis, every 4-6 months for the first 2 years, and then every 6-12 months in years 3-5. Routine surveillance imaging of the chest and serum tumor marker assessment can be obtained as clinically indicated. (Moderate Recommendation; Evidence Level: Grade B)

Clinical Stage I Seminoma- Active Surveillance Follow-Up			
	Years 1-2	Years 3-5	> Year 5
History and Physical CT abdomen +/-pelvis	Every 4-6 months	Every 6-12 months	If clinically indicated

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Clinical stage II
seminoma

- Evidence of retroperitoneal metastasis only
- Substratified by "nonbulky" (<3cm diameter node, CSIIa/b) and bulky (>3cm, CSIIb/c)
- Nonbulky traditionally treated with radiotherapy (30-36 Gy).
  - Cure with radiotherapy alone is 85-90%.
  - Relapsers are treated with chemotherapy.
  - Overall cure is 95-99%.
  - **Caution**: XRT failures treated with chemotherapy have a 4-6 times greater risk of developing acute leukemia
- Surgery with RPLND !?!
  - SEMS, PrimeTest, CoTrims, IU, MSKCC trials ~81% DFS at 2 years
  - Relapse treated with chemotherapy

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Clinical stage II
seminoma

- Bulky (CSIIb/c) disease has a higher probability of occult metastasis outside the retroperitoneum
- Therefore, chemotherapy is given since it is considered a systemic disease. BEPx3 or EPx4 are given, and are generally considered therapeutically equal
- Overall cure is 90-95%

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AUA Guidelines

Statement 27a. For patients with stage IIA or IIB seminoma with a lymph node ≤3cm, clinicians should recommend RT or multi-agent cisplatin-based chemotherapy based on shared decision-making. *(Moderate Recommendation; Evidence Level: Grade B)*

Statement 27b. For patients with stage IIA or IIB seminoma with a lymph node ≤3cm *who wish to avoid the long-term toxicities associated with chemotherapy or radiation therapy,* RPLND may be offered as an appropriate and effective treatment option. *(Moderate Recommendation; Evidence Level: Grade B)*

- BEPx3/EPx4 chemotherapy and dog-leg radiotherapy (30 Gy) associated with cancer-specific survival rates > 97%
  - No proven differences in long-term survival between treatments
- RPLND for CS II seminoma < 3 cm becoming new standard of care???

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Clinical Stage IIc/III

seminoma

- Disseminated seminoma is treated with either BEPx3 or EPx4 for good risk disease.
  - Intermediate (presence of non- pulmonary visceral mets) BEP x 4
  - No poor risk patients
- Overall cure is 93-98%
- If evidence of residual tumor is seen on CT scans after chemotherapy, most would observe these masses since there is a very high probability that they contain necrosis only

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Chemotherapy Toxicity

- Secondary Malignancy (SM)
  - Increase in RR (1.8 to 2.1) vs. surgery
- Cardiovascular (CVD) Side Effects
  - Increase in RR (2.5 to 7) vs. surgery
  - Cumulative risks similar to smoking!!
- No known “safe” lower limit of exposure
- Limited long-term data with BEP x 1-2

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Meinardi et al, JCO 2000, 18:1725; Huddart et al, JCO 2003, 21:1513; Bohlen et al, JU 2001, 165:441; Travis LB, JNCI, 2005, 1354-65; van den Belt-Dusebout AW, JCO 2007, 25:4370, Abouassaly 2011.

Chemotherapy Toxicity

- Cisplatin
  - Renal insufficiency
  - Neuropathy
  - Nausea and vomiting
  - Myelosuppression
  - Ototoxicity
  - Vascular
  - Alopecia
  - Infertility

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Chemotherapy Toxicity

- Etoposide
  - Secondary malignancy (leukemia)
  - Myelosuppression
  - Alopecia
  - Nausea and vomiting
  - Mucositis

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Chemotherapy Toxicity

- Bleomycin
  - Pulmonary fibrosis (risk goes up specifically with 4 or more cycles)
  - Raynaud's phenomenon
  - Vascular
  - Skin desquamation

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Postchemotherapy Seminoma

Value of PET imaging?

- Some argued to resect residual masses if > 3 cm
  - 20% will harbor residual viable seminoma
  - ~100% necrosis present at time of PC-RPLND if <3cm
- A European study (SEMPET) suggested strongly that PET scans were highly predictive of residual seminoma versus fibrosis
  - IGCCCG analysis of PET: ~77% false (+) rate*
- Use of PET scans done selectively
  - After 6 weeks from completion of chemotherapy
  - Tumor size >3cm
  - Serial use of imaging to assess change over time

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*Cathomas et al, JCO

Nonseminoma (NSGCT)

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Clinical stage I
Nonseminoma

- AFP and/or HCG are elevated in 60-80%
- These must normalize or be decaying according to half-life to be considered stage I
- CT scans of abdomen and chest are normal
- Overall chance for cure is 98-99%
- 3 available options for management

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Clinical Stage Is
Nonseminoma

- If CT scans are normal but AFP and/or HCG do not decline appropriately after radical orchiectomy, the patient is designated CS Is
- These patients have systemic disease beyond the retroperitoneum and systemic chemotherapy is the appropriate therapy

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AUA Guidelines

Statement 28: Clinicians should recommend risk-appropriate, multi-agent chemotherapy for patients with NSGCT with elevated and rising post-orchiectomy serum AFP or beta-hCG (i.e. stage TanyN1-2S1). (Strong Recommendation; Evidence Level: Grade B)

- Elevated post-orchiectomy AFP, HCG in CSIs NSGCT are markers of occult systemic disease
- Clinical stage IS NSGCT → high rates of systemic relapse after RPLND alone → primary chemotherapy (BEPx3 or EPx4) recommended

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CSI NSGCT: Risk Stratification

- Low Risk
  - 15% risk of relapse
  - Surveillance preferred
- High Risk
  - *Lymphovascular invasion (LVI+) & Embryonal Predominance* identifies pts at higher risk → 45-55%
  - Surveillance, RPLND or BEP x 1-2 cycles are acceptable options
  - Shared decision-making recommended
- RPLND is recommended for those with secondary somatic-type malignancy in the testis
  - Neither GCT-specific nor histology-specific chemotherapy has demonstrated efficacy for these tumors
  - PNET, Sarcoma, Adenocarcinoma, etc.

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AUA Guidelines

Statement 29: Surveillance recommended for CS IA NSGCT. RPLND or BEPx1 chemotherapy are appropriate alternatives for those who decline surveillance (Moderate Recommendation; Evidence Level: Grade B)

Statement 30: For patients with CS IB NSGCT, clinicians should recommend *surveillance, RPLND, or BEPx1/BEPx2* based on shared decision-making. (Strong Recommendation; Evidence Level: Grade B)

Statement 31: Patients with stage I NSGCT and any secondary somatic malignancy (also known as teratoma with malignant transformation) in the primary tumor at orchiectomy should undergo RPLND. (Expert Opinion)

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Clinical stage I
Nonseminoma

- First option: nerve sparing RPLND
  - Benefits:
    - 1) staging of retroperitoneum
    - 2) surgical resection of lymphatic metastasis curative at the 50-75% level
    - 3) lower necessity of giving chemotherapy
  - Disadvantages:
    - 1) patients with no metastatic tumor derive no therapeutic benefit
    - 2) patients with occult tumor outside the retropertoneum will require chemotherapy after surgery
  - Preferred option if evidence of somatic transformation of teratoma present in the primary tumor

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NS-RPLND

- What is “nerve sparing”?
- It is the preservation of sympathetic fibers in the retroperitoneum which control emission and ejaculation
- Since testis cancer occurs in young men, preservation of fertility is important to some
- Hence NS RPLND is the removal of lymphatics with preservation of sympathetics
- Omission of nerve sparing results in Anejaculation

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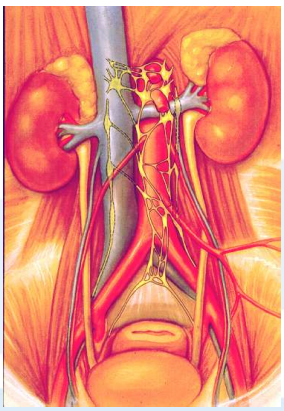
Why save nerves?

Emission/ejaculation rates

- Full bilateral w/o nerve-sparing 0%
- Modified 75-90%
- Modified w/nerve sparing 99%



- Nerves affect fertility
- No effect on sexual function

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NS-RPLND vs. Surveillance
High-Risk Patients

- If the patient is compliant and has access to adequate medical care, he is presented his options and makes a choice
- Major reasons for choosing NS-RPLND:
  - 1) getting along with therapy
  - 2) avoiding chemotherapy
  - 3) easier follow-up with no CT scans required if pN0
- Reasons for surveillance: 50% chance of cure with orchiectomy alone
- Individual life circumstance of the patient usually determines chosen therapy (shared decision-making)

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Testis cancer chemotherapy
Limitations in CSI NSGCT management

- Nausea, vomiting, neutropenia better managed
- Impaired spermatogenesis 20-50%; probably less effect with lower doses
- Cardiovascular: O/E ratio of 7.1 compared to general population; also elevated lipids, hypertension
- Numbness/tingling real and persistent Reynaud's
- Effects on Leydig cell function low T
- Subclinical effects on kidney (microalbuminuria)
- More insulin resistant
- Secondary leukemias

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Clinical stage II
Nonseminoma

- Evidence of retroperitoneal metastasis on CT imaging
- Higher volume metastasis (>5cm, CSIIc) treated with chemotherapy because of the relatively high likelihood (>50%) of occult disease outside the retroperitoneum
- Smaller volume metastasis can be treated with either chemotherapy or RPLND

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AUA Guidelines

Statement 32: Clinicians should recommend RPLND or chemotherapy for patients with stage IIA NSGCT with normal post-orchiectomy serum (S0) AFP and beta-HCG. (Moderate Recommendation; Evidence Level: Grade B)

- Excellent prognosis associated with chemotherapy and RPLND
- RPLND advantages:
  - pN0 up to 25%, removes teratoma, ↓ chemotherapy, ↓ CT imaging
  - Most will have pN1 disease → cure 80-90% with RPLND alone
  - 10-18% will require chemotherapy for relapse
- Chemotherapy BEPx3 or EPx4 → 30% will require RPLND for residual disease
- Specific considerations may favor one treatment over the other

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AUA Guidelines

Statement 33. In patients with clinical stage IIB NSGCT and normal post-orchiectomy serum AFP and hCG, clinicians should recommend risk-appropriate, multi-agent chemotherapy. (Moderate Recommendation; Evidence Level: Grade B). Clinicians may offer RPLND as an alternative to chemotherapy to select patients with clinical stage IIB NSGCT with normal post-orchiectomy serum AFP and hCG. *(Conditional Recommendation; Evidence Level: Grade C)*

For exam purposes…

- Chemotherapy favored over RPLND for most CS IIB NSGCT
- Most will have pN2-3 disease → relapse rate 15-20% after RPLND alone → some patients will require adjuvant chemotherapy
- RPLND may be primarily considered in select pts with teratoma in primary tumor and/or unifocal masses up to 3-5 cm

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AUA Guidelines

Statement 37: After primary RPLND, clinicians should recommend surveillance or adjuvant chemotherapy in patients with NSGCT who have pathological stage II disease that is not pure teratoma.

For patients with pN1 and/or pN1-3 pure teratoma, surveillance is preferred.

For patients with pN2-3 at RPLND, multi-agent cisplatin based chemotherapy is preferred. (Moderate Recommendation; Evidence Level: Grade B)

For exam purposes...

- Randomized trial showed ↓ relapse with adjuvant chemotherapy but no difference in overall survival (benefit greatest in pN3 disease)
- Observation preferred → pN1 and/or pure teratoma → < 20% relapse
- Chemotherapy preferred → pN2-3 →↓relapse from 50-70% with RPLND alone to 1-4%
  - In reality, relapse is 15% for pN2 disease without EC, 20% with EC
  - For pN3 disease, relapse is 30% without EC, 50% with EC.

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Tachibana el al, EurUrol 2023

Clinical stage III
nonseminoma

- These patients have evidence of metastasis outside the retroperitoneum, and are treated with systemic chemotherapy
- They are classified into risk categories according to IGCCCG parameters

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IGCCCG Risk Classification

RISK CLASSIFICATION FOR ADVANCED DISEASE (post-orchiectomy)[1]

Risk Status	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy markers- all of: AFP < 1,000 ng/mL hCG < 5,000 iu/L LDH < 1.5 x upper limit of normal	Any primary site and No nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Intermediate Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy markers- any of: AFP 1,000-10,000 ng/mL hCG 5,000-50,000 iu/L LDH 1.5-10 x upper limit of normal	Any primary site and Nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Poor Risk	Mediastinal primary tumor or Nonpulmonary visceral metastases or Post-orchiectomy markers- any of: AFP > 10,000 ng/mL hCG > 50,000 iu/L LDH > 10 x upper limit of normal	No patients classified as poor prognosis

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Disseminated nonseminoma

- Good risk: BEPx3 or EPx4; overall cure rate is 92-98%
- Intermediate: BEPx4; cure rate ~85%
- Poor risk: BEPx4 or VIPx4 (vinblastine, ifosfamide, cisplatin), with the overall cure only about 50-70%

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Side Effects of Chemotherapy

- Bleomycin
  - Pulmonary fibrosis, mucositis
- Cisplatin
  - Neurotoxicity, ototoxicity, nephrotoxicity
- Etoposide
  - Myelosuppresion, alopecia

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Post-Chemotherapy Management for NSGCT

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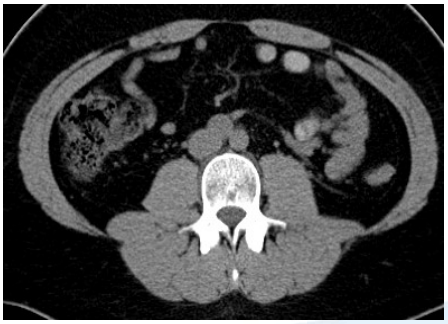
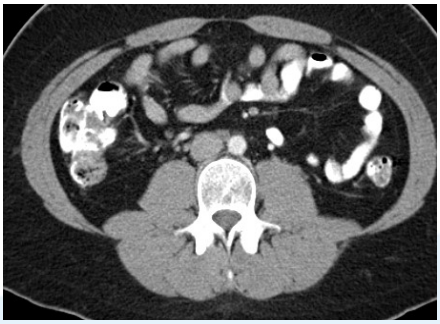
Complete Response After Chemo





Observe or RPLND?

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Complete Response After Chemo

- CR following chemotherapy:
  - normalization of tumor markers
  - No residual mass, or residual mass < 1 cm
  - Experienced by ~ 70% of patients with mets receiving 1st line chemo
  - Only 5% will recur
- Some centers recommend PC-RPLND for all patients regardless of complete response (CR)
  - Teratoma in ~20% patients with CR?**
  - Controversial
  - Many centers observe CR patients, <5% recur

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***Oldenburg J et al. J Clin Oncol 2003, 12:3310-17*
***Carver BS, JCO 2007, 25:4367*

PC-RPLND

- Rationale
  - In the setting of residual disease in the RP, unresected teratoma and/or viable malignancy is present in 50-90% of patients
  - predispose the patient to disease progression and even death
  - No valid predictive ability to identify preoperatively those patients with necrosis
- Indications
  - Performed after completion of systemic chemotherapy in the setting of residual RP mass and normal STM's.
  - Can be considered in circumstances of a complete clinical response to chemotherapy

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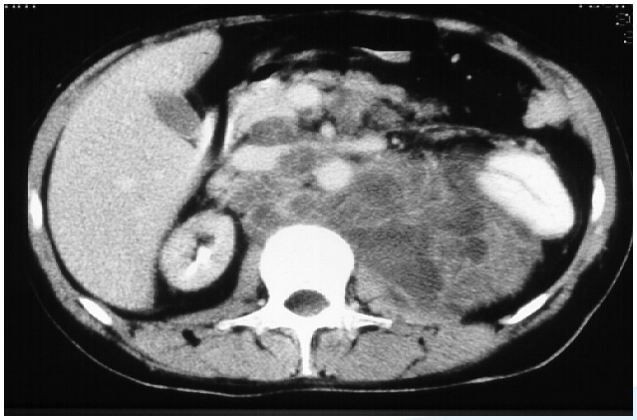

Post chemotherapy retroperitoneal resection may be a difficult surgical challenge but is clinically necessary

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Extent of Surgery

- Rationale for bilateral RPLND – *"Best test answer"*
  - Variable distribution of mets (outside boundaries of modified dissection following chemotherapy)
  - Inability to differentiate tumor from necrosis intraoperatively
- *Modified dissection in select patients
  - Small residual mass (or no palpable disease)
  - Location of disease in primary landing zone pre and post chemo

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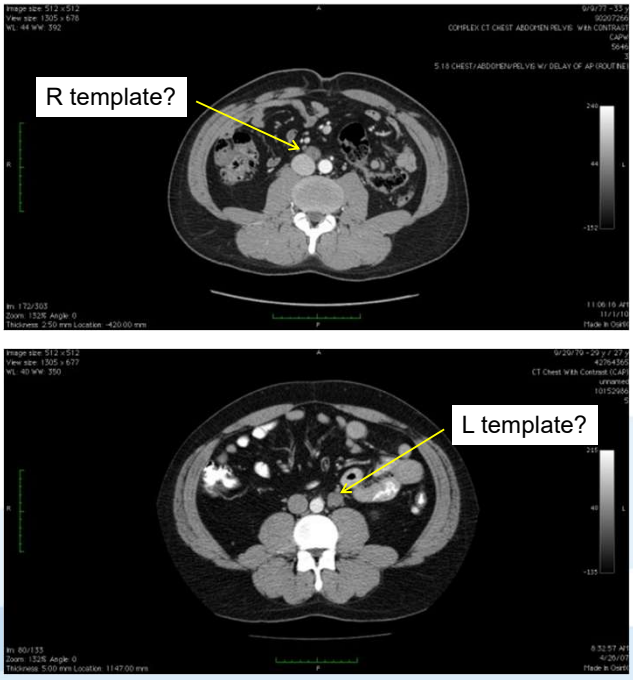
Carver BS, JCO 2007, 25:4365
Kakiashvili D, et al, J Urol 181(4):911a, 2009
**Beck SD et al, Cancer 2007, 100:1235-40*
**Heidenreich A et al, Eur Urol 2009, 55:217-26*



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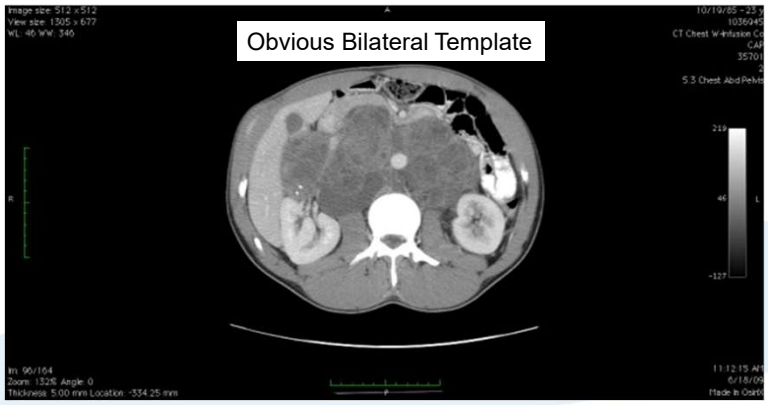

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Metastatic Testicular Cancer

Principles of Complete Resection

May require additional procedures

• Pulmonary/mediastinal resection	20%
• Retrocrural dissection	10%
• Hepatic resection	6%
• Vascular resection ± graft	6%
• GI Resection	5%
• Renovascular injury nephrectomy	5%-15%

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Winter C et al, Eur Urol 2012;61:403–9.
Johnston, P et al, The Journal of Urology® (2013), doi: 10.1016/j.juro.2013.03.039.
Cary KC et al, J Urol. 2013 Mar;189(3):812-7.

Histology of Residual Mass

- Histology of residual mass following induction chemotherapy
  - 5-15% viable GCT → 70-75% cured
  - 45-50% teratoma → 95% cured
  - 40-45% fibrosis → 97% cured
- 2 courses post-op chemo recommended if viable germ cell tumor demonstrated
  - *May be omitted for good risk NSGCT if resection complete and < 10% viable GCT

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*Fizazi K et al. J Clin Oncol 2001, 19:2647-57.

RPLND terminology

- Salvage RPLND
  - Performed after completion of both induction and salvage (standard TIP or high-dose carboplatin) chemotherapy
  - *Desperation RPLND*
    - Performed despite STM elevation
- Resection of Late Relapse
  - Performed for recurrent RP disease >24 months after CR to primary therapy

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Management of Residual Mass
Salvage Chemo

- Histology following salvage chemotherapy (historical)
  - 50% viable GCT
  - 40% teratoma
  - 10% fibrosis
- Histology following Taxane-based salvage chemotherapy
  - 14% viable GCT
  - 31% Teratoma
  - 63% fibrosis

•Complete resection critical
•Post-op chemotherapy ineffective if viable tumor demonstrated

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Fox et al, JCO 11:1294, 1993
Eggener SE, Cancer, 109(3):528 , 2007

Marker Elevation Post-Chemotherapy

- Controversial Management
  - 2nd line chemo vs. desperation RPLND
  - Multidisciplinary discussion and management
  - Cystic teratoma might cause stable marker leak
  - Select patients cured with surgery
  - Poor prognostic factors:
    - Elevated AFP
    - Rising beta-HCG
    - Redo RPLND
    - Viable non-teratomatous germ cell elements

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Beck SD et al, Urol Clin North Am 2007, 34(2):219-225.
Sexton et al, J Urol, 169:1353, 2003

Desperation Surgery

- Elevated markers after 2nd or 3rd line chemo
- Disease limited to one site (i.e. RP nodes) consider surgery en lieu of 3rd line chemo despite marker levels
- Overall long-term survival 50%
  - 30% five-year survival for active GCT
  - Adjuvant chemo ineffective

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Beck SD et al, Urol Oncol 2005;23:423–30.

Late Relapse of Testis Cancer

- Relapse > 2 years from initial successful management
  - Seminoma ~ 1.4% - Nonseminoma ~ 3.2%
- May occur at any time
  - Median 7 years (2-32)
  - Most always within 10 years
- Characteristics:
  - Elevated AFP
  - Yolk sac and teratoma most common
  - Not chemosensitive (unless chemo-naive)
- Primary management is surgical

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Baniel et al, J Clin Oncol, 13:1170, 1995
George et al, JCO 21:113, 2003
Oldenburg J et al, J Clin Oncol 2006;24:5503–11.

Extragonadal GCT

- Primary mediastinal GCT – poor prognosis
- Primary retroperitoneal GCT
  - Prognosis equivalent to tumor stage for testicular primary GCT
  - Consider spontaneous regression of testicular tumor
  - Consider orchiectomy:
    - Laterality of metastatic pattern in retroperitoneum
    - Ipsilateral testis atrophy (normal contralateral)
    - U/S evidence - scar, atrophy, Ca^{2+}, hyper/hypoechoic foci
    - ~ 50% risk of CIS or tumor foci

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Angulo JC et. al., J Urol, 182:2303, 2009

Testicular Cancer

- The high cure rates attained in this disease are due to advances in medical and surgical therapy
- Oncologists and urologists work together in a collegial atmosphere to attain the highest chance for cure
- As such, the advances in testis cancer serve as a model for the multidisciplinary treatment of other cancers

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Question #1

- Which one of these is not considered a risk factor for developing testicular germ cell tumor?
  - A. Gonadal Dysgenesis
  - B. Cryptorchidism
  - C. Testicular Microlithiasis
  - D. Marijuana Use
  - E. Maternal Diethylstilbestrol (DES) exposure

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Question #2

- 4-month-old male presents with painless mass in the the right testicle. Orchiectomy reveals a 1.4cm yolk sac tumor. Next steps:

A. CT Chest, Abdomen and Pelvis
B. STM assessment
C. Adjuvant chemotherapy
D. RPLND
E. Observation

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Question #3

- How do you evaluate for a falsely elevated HCG?

A. Confirm with presence of elevated serum LH
B. Testosterone suppression test
C. Draw early morning, fasting HCG
D. 24-hour urine HCG collection

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Question # 4

- Prior to orchiectomy for nonseminoma, a patient is found to have an AFP of 100 and the HCG is 30. Ten days after orchiectomy the HCG is normal and the AFP is 41. CT scans of CAP are normal.

Next step in evaluation & management?

A. RPLND
B. Induction chemotherapy
C. Radiation
D. PET scan
E. Trend markers for normalization

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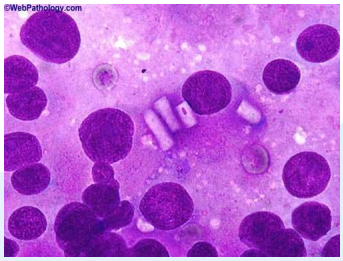
Question #5

- 32-year-old male presents with an incidentally discovered testis mass. Orchiectomy performed, H&E histopathologic assessment reveals the follow. Which blood test is most likely to be abnormal?

A. HCG
B. LDH
C. AFP
D. Both AFP and HCG
E. None of the above



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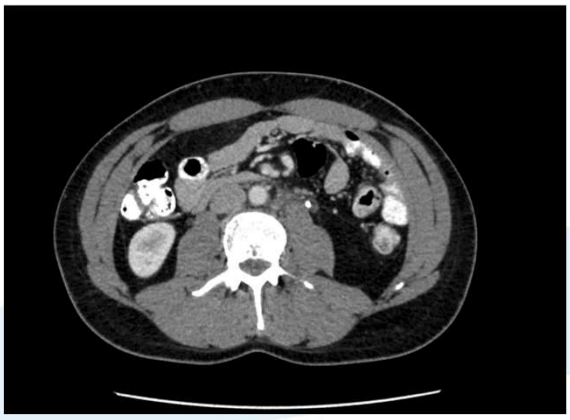
Question #6

- 44 yo male with back pain. CT reveals bulky lymphadenopathy in para-aortic region. HCG and AFP normal. LDH = 1200. Orchiectomy reveals right pT2 4 cm classic seminoma. Treated with BEP x 3. Markers normalize. Post-chemotherapy CT reveals:

Next step in evaluation & management?
A. RPLND
B. Salvage chemotherapy
C. Salvage radiation
D. PET scan
E. Observation



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QUESTIONS?

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