Testicular Cancer

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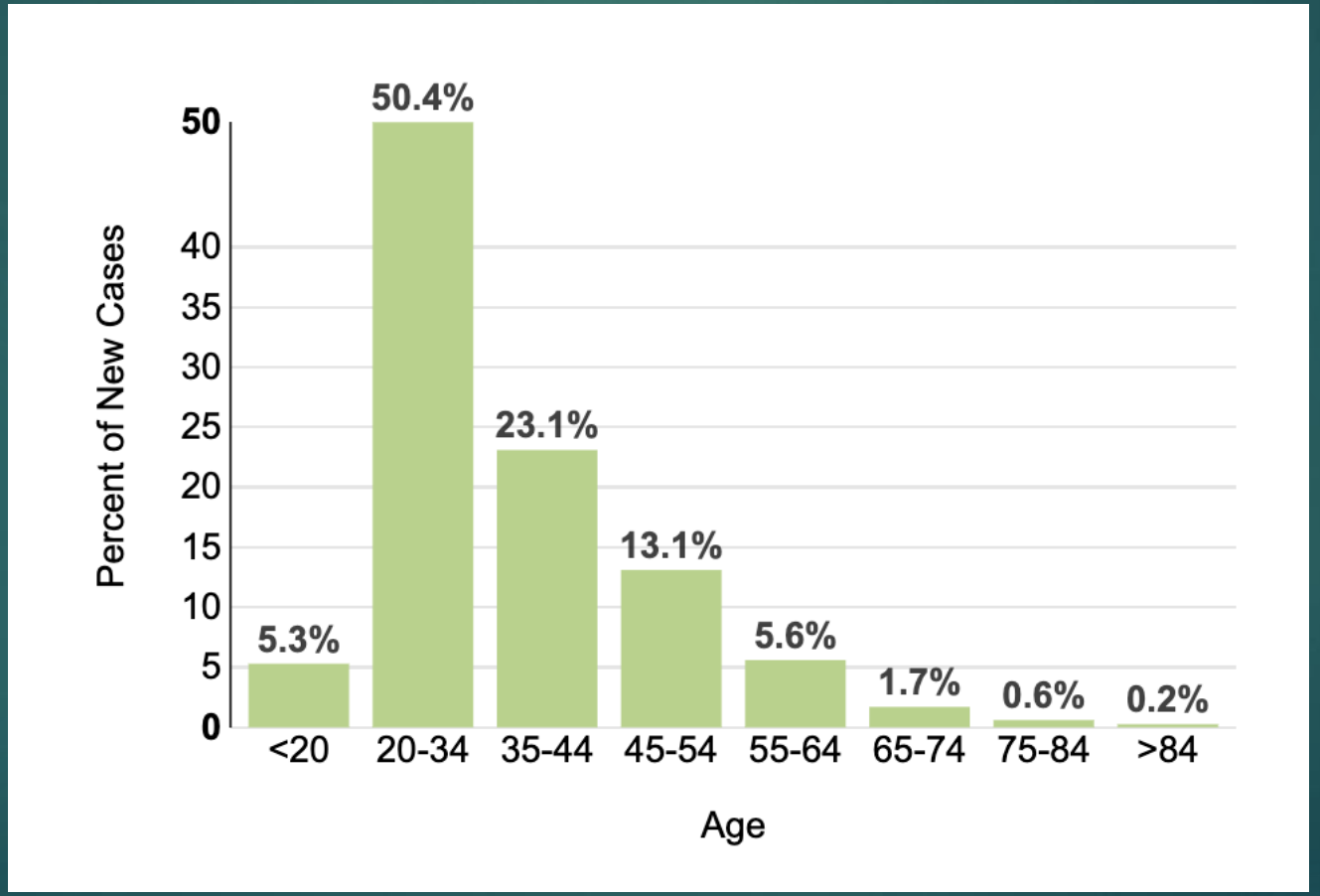
9/23/24

Disclosures

- None

Epidemiology

- Mainly affects young males



Epidemiology

- In 2024, estimated 9,760 new diagnoses[1]
  - 500 deaths from testicular cancer
- Increasing incidence over last several decades
  - Particularly in Hispanic Americans

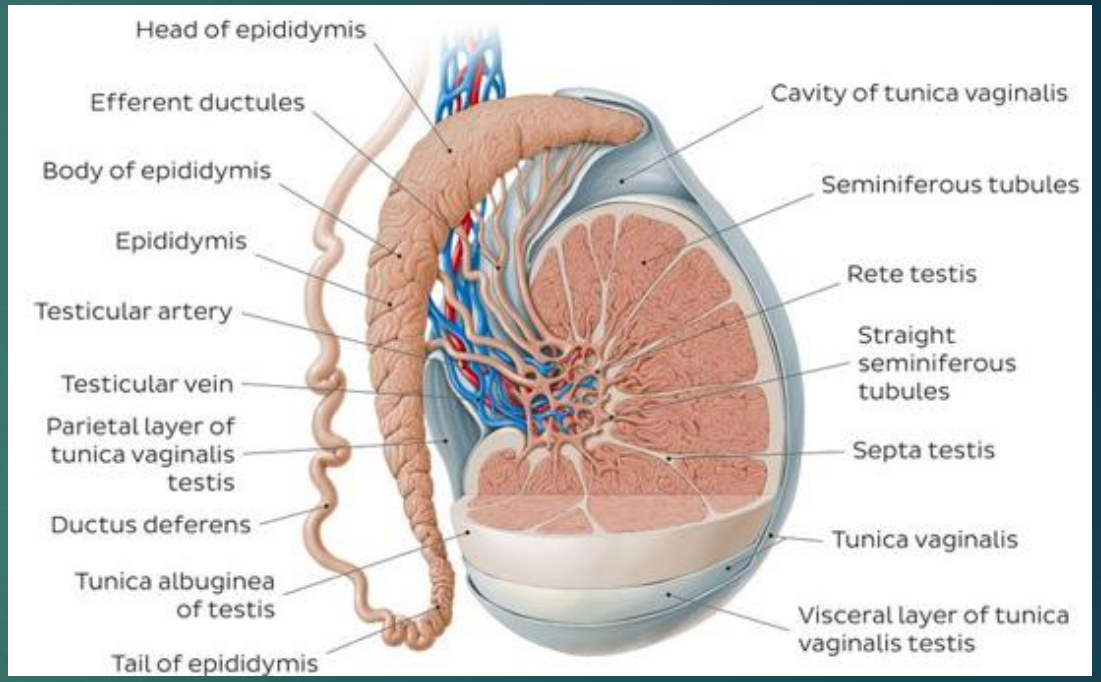
1. www.cancer.org

Epidemiology

- Risk Factors
  - Cryptorchidism (RR=10-15, Absolute risk 2-3%)
  - Klinefelter's Syndrome
  - Personal history (2-3% risk of contralateral second primary)
  - Infertility
  - Family history (Brother RR=8-10, Father RR=4)
    - Germline CHEK2 mutations

Pathology

- Seminoma
- Non-seminoma
  - Embryonal – worse prognosis for stage I
  - Choriocarcinoma
  - Yolk sac tumor – better prognosis for Stage I
  - Teratoma
- If any histology other than seminoma → non-seminoma
- If alpha-fetoprotein is elevated → non-seminoma
- Other rare histologies – lymphoma (>70yr), sex cord/stromal



Pathology

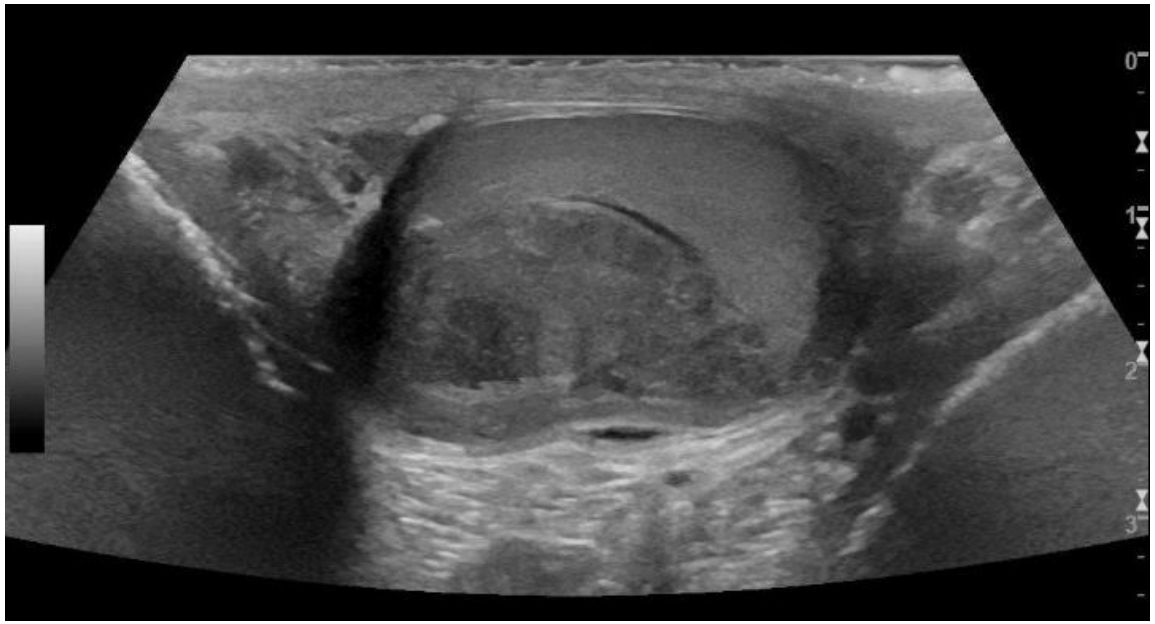
- Teratoma
  - Higher malignant potential in men than women or children
- Isochromosome 12p
  - Occurs in approximately 50% of germ cell tumors (GCT)
  - Excess copies of 12p can help identify some poorly differentiated carcinomas as GCT through FISH/cytogenetics

Presentation

- Painless testicular mass is pathognomonic
- Testicular pain or discomfort
- Testicular swelling
- Testicular tenderness
- Growth or shrinkage of testicle
- Abdominal pain/mass
- Back pain
- Gynecomastia and/or gynecodynia
- Supraclavicular and/or cervical lymphadenopathy
- Renal failure
- Lower limb edema
- Infertility

Evaluation

- H&P
- Scrotal ultrasound
- Tumor markers
  - B-HCG, AFP, LDH
- Chemistry panel
- Radical inguinal orchiectomy
- Consider sperm banking



Evaluation

- Pure seminoma
  - CT AP
  - CXR
    - CT chest if RP LAD or abnormal CXR
  - Repeat tumor markers
    - Staging is based off post-orchiectomy values
  - Brain MRI
    - HCG >5,000
    - Extensive lung mets
    - Symptoms
- Non-seminoma
  - CT CAP
  - Repeat tumor markers
    - Staging is based off post-orchiectomy values
  - Brain MRI
    - HCG >5,000, AFP >10,000
    - Choriocarcinoma
    - Extensive lung mets
    - Liver mets
    - Symptoms

AFP

- Half-life 5-7 days
- Not produced by seminoma
- Can be associated with numerous cancer, but mostly hepatocellular carcinoma and non-seminomatous germ cell tumor
- AFP levels <20 ng/mL can be non-specific and treatment decisions should not be based on this alone
- Can be produced by teratoma at low levels
- May be elevated due to liver disease or hepatotoxicity (any liver regenerative state)

β HCG

- Half-life 1-3 days
- Can be made by any type of germ cell tumor
- Extremely high levels suggest choriocarcinoma
- False positives
  - Cross reactivity with luteinizing hormone
    - Can test for this by administering exogenous testosterone
  - Pituitary production in hypogonadal men
  - Marijuana consumption may lead to elevated B-HCG

Lactate Dehydrogenase

- Many conditions can elevate LDH
- Useful only for staging of disseminated disease
- The only important LDH is the level on day 1 of the first cycle of first-line chemotherapy for disseminated disease
- Treatment decisions should never be made on elevated LDH alone

Serum Tumor Markers

	Good (S1)	Intermediate (S2)	Poor (S3)
AFP (ng/mL)	<1,000	1,000-10,000	>10,000
BHCG (IU/L)	<5,000	5,000-50,000	>50,000
LDH*	<1.5x ULN	1.5-10x ULN	>10x ULN

* In practice, cutoff of >3x ULN is generally used

Staging

Stage I

Stage I

- Limited to testis, scrotum, and spermatic cord

Stage II

Stage II

- Metastases to retroperitoneal lymph nodes only
- Tumor markers normal (S0) or S1

Stage III

Stage III

- Distant metastases (including pelvic nodes)
- RP nodal mets only and S2/S3

Risk Stratification for advanced disease

	Good	Intermediate	Poor
Seminoma	Primary Site: Any Mets to nodes and/or lung	Non-pulmonary visceral mets	None
Non-seminoma	Primary Site: testis or RP Mets to nodes and/or lungs S0-1	Primary Site: testis or RP Mets to nodes and/or lungs S2	Primary site: Mediastinum Non-pulmonary visceral mets S3

Survival Based on Risk Categories for Advanced Disease

Risk Group	Percent of Patients	5 year survival
Good risk	60%	95%
Intermediate risk	26%	89%
High risk	14%	67%

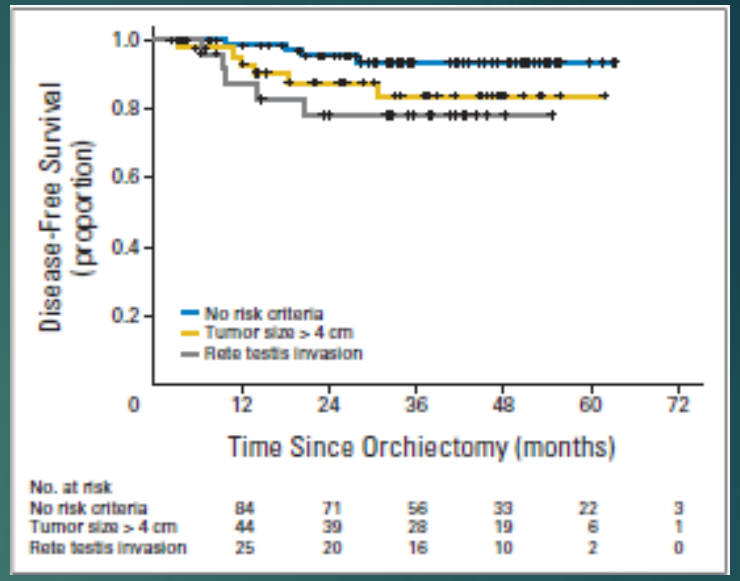
International Germ Cell Cancer Collaborative Group updates. J Clin Oncol. May 2021..

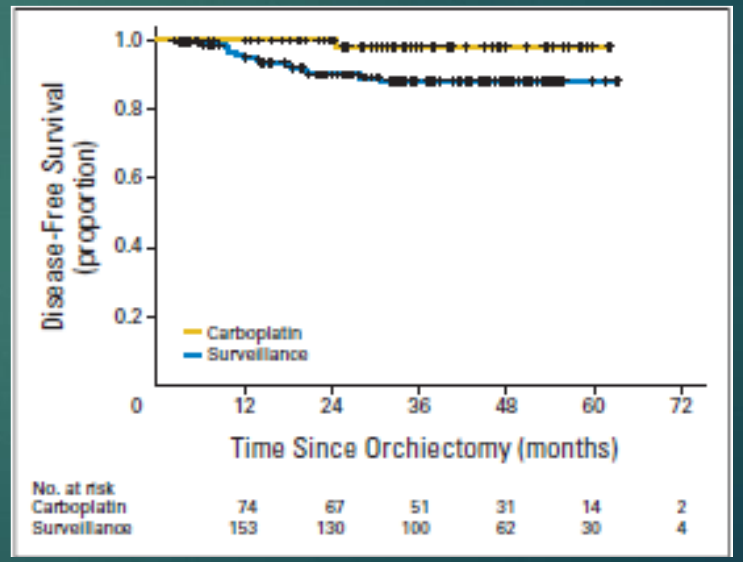
Important Considerations

- Testis masses necessitate urgent workup
- Do not biopsy the testis
- Radical inguinal orchiectomy is the standard since transcrotal orchiectomy can lead to seeding of disease and increased local recurrence rates
- Discuss sperm banking prior to surgery, radiation, or chemotherapy (20-30% risk of infertility)
- The testis is a sanctuary site
  - Even in patients with metastatic disease at diagnosis, radical inguinal orchiectomy should be performed, either before or after chemotherapy

Stage I Seminoma

- Active Surveillance - preferred
  - Risk of relapse~5-15%
  - Tumor size >4cm and rete testis involvement are risk factors for recurrence
- Adjuvant chemotherapy
  - 1-2 doses carboplatin AUC 7
    - 2 is generally preferred as risk of relapse is lower
  - ~2% recurrence rate
  - May decrease risk of contralateral primary



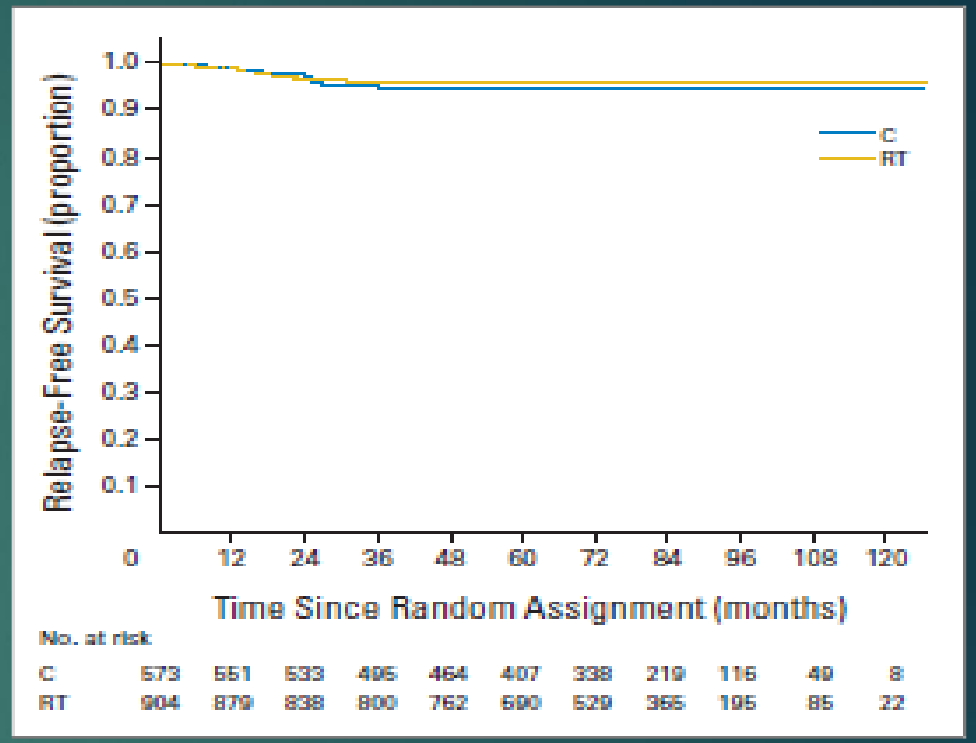


Solberg et al, Ann Onc 2016;27(7):1299-1304

Aparicio et al, JCO 2011;29:4677-4681

Stage I Seminoma

- Adjuvant radiation therapy
  - 25-30 Gy to infradiaphragmatic LNs
  - ~4% relapse rate
  - Risk of secondary cancer, GI complications, cardiovascular disease
  - In current use, improvements in radiation field have limited incidence of secondary malignancy



RT (20 Gy in 10 fractions or 30 Gy in 15) vs. carboplatin AUC 7 x1

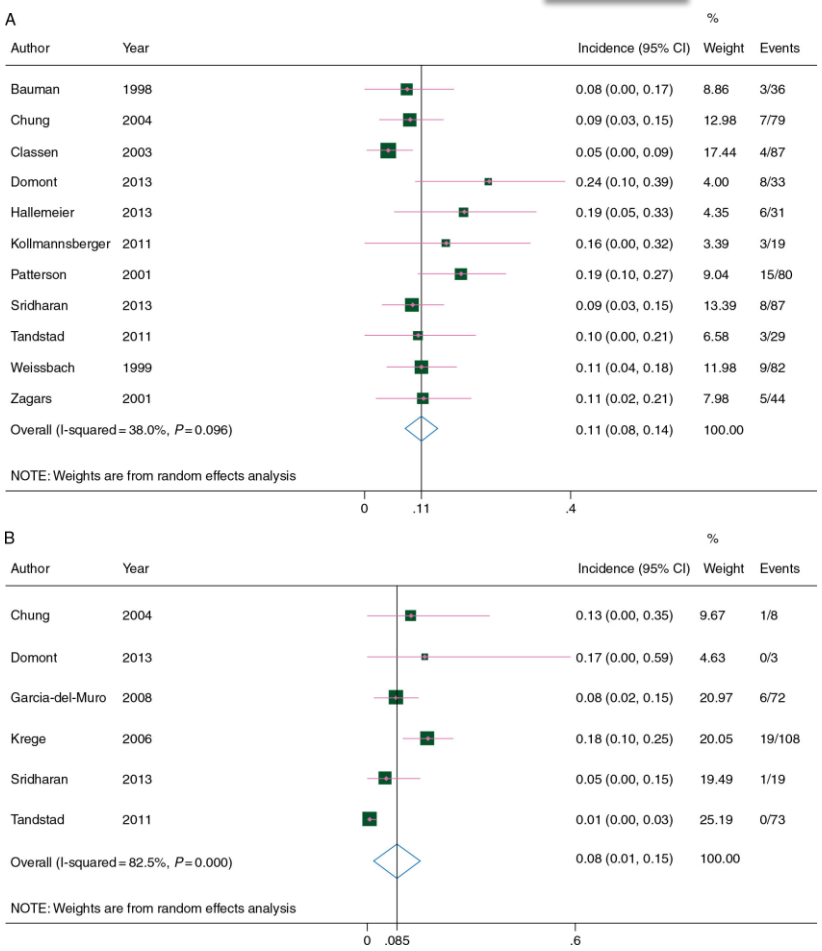
Oliver et al. JCO 2011;29(8):957-962

Stage I Seminoma

- With any option, survival ~100%
- Relapse with tumor markers or measurable disease is treated as the stage at recurrence
- Caution with Stage IS
  - Generally portends occult disease
  - Consider false positive BHCG

Stage II Seminoma

- Nodes <3cm (IIA/IIB)
  - Radiation therapy or chemotherapy (BEPx3 or EPx4)
    - BEP – Bleomycin, etoposide, cisplatin; EP – etoposide, cisplatin
  - Up to 3cm in largest diameter
  - RPLND is now in guidelines
    - Recurrence rate 20-25%
- Nodes >3cm (IIB/IIC)
  - Chemotherapy BEPx3 or EPx4
- No randomized trials



A: Relapse rate of radiotherapy studies
B: Relapse rate of chemotherapy studies

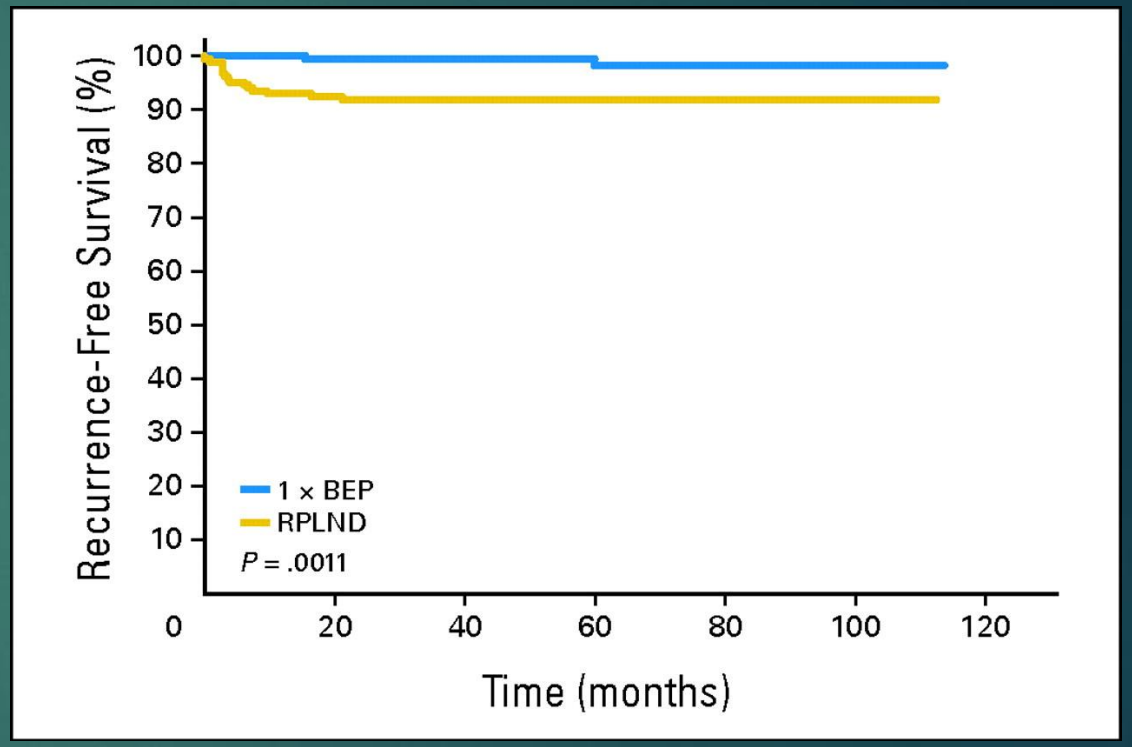
Giannatempo et al, Annals Onc 2015;26(4):657-668
Matulewicz et al. J Urol 2024;211(1):80-89
Daneshmand et al. JCO 2023;41(16):3009-3018

Stage I Non-seminoma

- Surveillance, RPLND, and BEP x1 are all options
- Surveillance
  - 20-30% relapse rate for all patients
  - LVI and high % embryonal histology predictive of relapse, ~50%
    - More likely to consider adjuvant treatment
- Stage IS – treat as advanced disease with chemotherapy
  - Mild elevation of AFP (<20) or HCG may be due to benign causes
  - Markers typically rise if due to metastatic disease

Stage I Non-seminoma

- Retroperitoneal lymph node dissection
  - 20% likelihood of finding residual disease
    - Unclear who benefits from adjuvant chemo – typically given for >5 nodes or >2cm in size
  - 11% risk of relapse
  - 10-20% of patient get chemotherapy
  - 10% risk of retrograde ejaculation
- Chemotherapy
  - 1 cycle BEP
  - 2% risk of relapse



Albers et al, JCO 2008;26(18):2966-2972

Stage II Non-seminoma

- IIA with normal markers
  - RPLND
    - 30% will be benign
    - Use of adjuvant chemo based on amount/size of nodes
  - BEP x3 or EP x4
  - If borderline LAD, consider short interval repeat imaging

- IIA with S1, IIB/IIC
  - BEP x3 or EP x4

Good Risk Disease

- BEP x3
  - Equivalent to BEP x4
  - Less cisplatin – anorexia, nausea, vomiting, neurotoxicity, ototoxicity, infertility
  - Less risk of etoposide-induced leukemia
    - Dose-dependent
- EP x4
  - EP x4 superior to EP x3
  - Bleomycin can cause pulmonary fibrosis
  - Post-chemo RPLND is more difficult after bleomycin
  - Consider in >50yr, renal insufficiency, pre-existing lung disease

De Wit et al, JCO 2001;19(6):1629-1640
Culine et al, Ann Onc 2007;18(5):917-924

BEP x3 vs EP x4

GETUG T93BP – 257 patient, 1:1 randomization

	BEP x3 (127)	EP x4 (124)	P-value
G3-4 Neutropenia	47%	62%	<0.001
G1-3 Neurotoxicity	2	7	<0.001
Adverse Events*	13%	22%	0.05
PFS	91%	86%	0.135
4yr OS	96%	92%	0.096

* Residual cancer at resection, incomplete response, recurrence

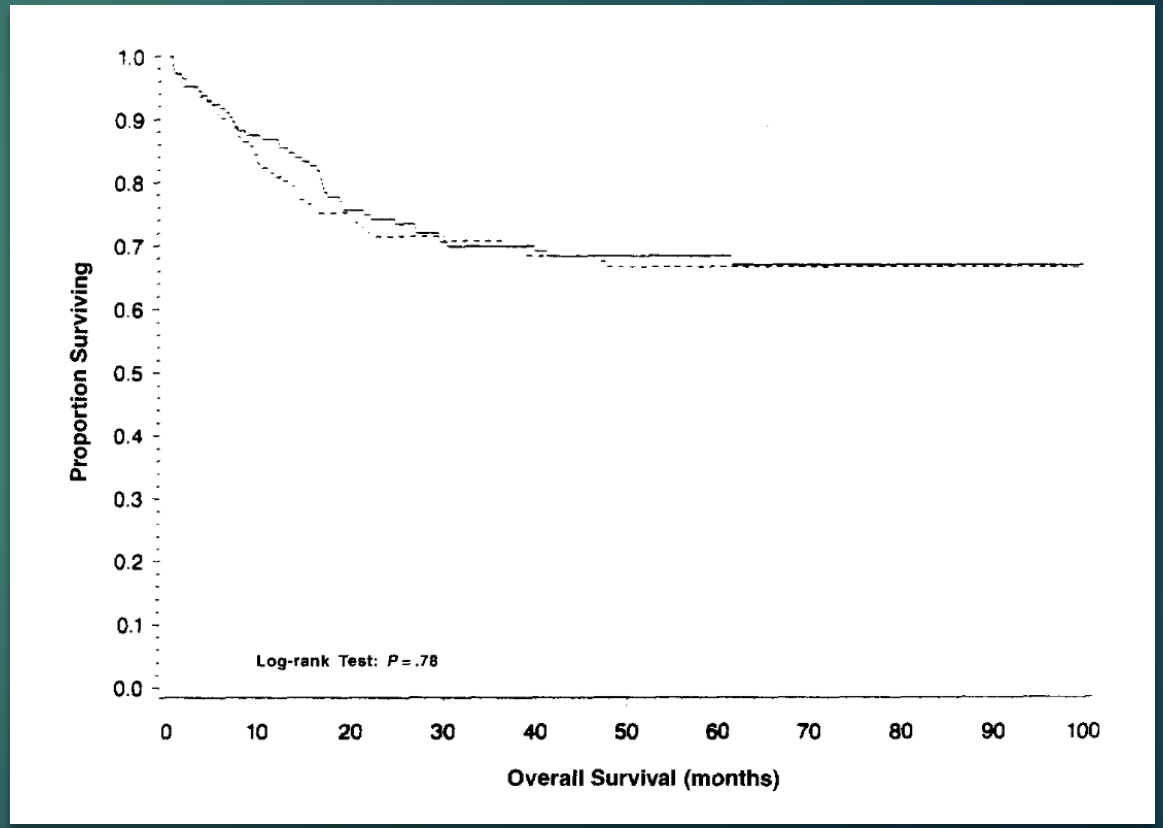
Indiana University Testis Cancer Database – 223 patients

	BEP x3 (178)	EP x4 (45)	P-value
10yr OS	98%	91%	<0.01
Adjusted risk of death		3.1	<0.10

Culine et al, Ann Onc 2007;18(5):917-924
Cary et al, Clin GU Cancer 2018;16(2)e307-e313

Intermediate and Poor Risk Disease

- BEP x4 or VIP x4
  - VP-16 (etoposide), ifosfamide, cisplatin
  - VIP for patients with concern for bleomycin pulmonary toxicity
  - Increased hematologic toxicity with VIP
    - Need to use GCSF



Nichols et al, JCO 1998;16(4)1287-1293

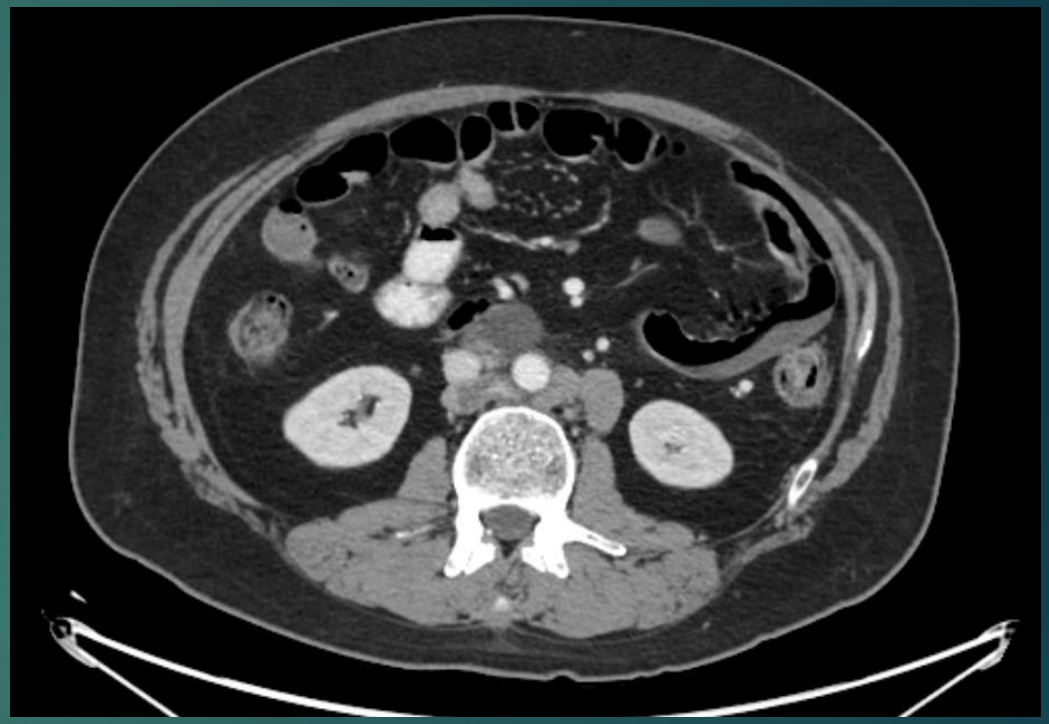
Post-chemotherapy management

- Seminoma
  - Most residual masses are benign
    - <3cm – 3% carcinoma (path+ or relapse)
    - >3cm – 30% carcinoma

  - Observe
  - Observe masses <3cm, resect/biopsy if >3cm
  - **Observe <3cm, PET if >3cm--resect/biopsy if PET+**
    - Generally wait until at least 6-8 weeks post-chemo for PET
      - Improved sensitivity and specificity

Post-chemotherapy management

- Non-seminoma
  - Resect residual masses when possible
  - Residual mass histology
    - Viable carcinoma: 10%
    - Teratoma: 40%
    - Fibrosis/necrosis: 50%
  - Teratoma needs to be removed
    - Growing teratoma syndrome
    - Malignant transformation
    - Chemo resistant
    - Low level of AFP production can cloud the diagnosis of residual NSGCT



Recurrent/Relapsed Disease

- For Stage I surveillance and Stage I/II treated with RPLND or RT, treat based on stage at time of recurrence

- Post-chemo recurrence
  - Most often <2 yrs for NSGCT, <3yr for seminoma
  - Salvage chemotherapy
    - VIP x4
    - VeIP x4 (vinblastine, ifosfamide, cisplatin)
    - TIP x4 (paclitaxel, ifosfamide, cisplatin)
    - High-dose chemotherapy with autologous stem cell rescue

HDC with Autologous Stem Cell Rescue

- No benefit over standard chemotherapy for 1st line treatment
- No high-quality studies comparing HDC to standard salvage chemotherapy
- Retrospective analysis from Indiana University
  - Tandem transplant with carboplatin 700mg/m2 and etoposide 750mg/m2 qd x3
  - 364 patients
  - 2yr OS 66%
  - 2nd line – 2yr PFS 63%; 3rd line – 2yr PFS 49%
- TIGER Trial – salvage chemo for HCD with TI-CE

Adra et al, JCO 2017;35(10):1096-1102

Late Relapse

- Often can be cured
- Resection is integral to the plan
- At risk for subsequent relapse

Chemotherapy Regimen Summary

Seminoma Stage I	NSGCT Stage I	Pathological stage II*	Good-risk disease	Intermediate- or poor-risk disease
Carboplatin 1 or 2 doses	BEP x 1 or BEP x 2	BEP x 2 or EP x 2	BEP X 3 or EP X 4	BEP X 4 or VIP X 4

	Relapsed after first-line chemotherapy
Salvage Treatment	VeIP x 4 or TIP x 4 or HDCT x 2

*Pathological stage II refers to patients who had positive nodes with GCT after undergoing primary RPLND for Stage I/II disease.

Surveillance

- Clinic visit, tumor markers, imaging
  - Decrease frequency over time away from treatment
- Less intense follow-up for patient who have had systemic therapy
- Trend to using less imaging due to concern over radiation exposure
  - MRI can be used in place of CT
- Consult NCCN guidelines as recommendations change frequently

Survivorship

- Cardiovascular disease risk increases ~2X
- Metabolic syndrome up to 10X risk
- Infertility
- Hypogonadism
- Erectile dysfunction – often with normal testosterone levels and may be a neuropathy
- Secondary malignancy risk increases 1.5-2X
- Contralateral primary testicular cancer – 2-3%
  - Testicular self-exam, exam at clinic visits

Survivorship

- Restrictive pulmonary disease - may be more related to cisplatin than bleomycin
- Hearing loss, tinnitus
- Peripheral neuropathy
- Renal dysfunction
- Raynaud's phenomenon

Mortality	Total cohort	Surgery	Platinum-based CT	Radiotherapy	Combination
	SMR (95% CI)	**SMR (95% CI)**	**SMR (95% CI)**	**SMR (95% CI)**	**SMR (95% CI)**
Total	**1.23 (1.14-1.33)**	0.95 (0.79-1.14)	**1.23 (1.07-1.43)**	**1.28 (1.15-1.43)**	**2.04 (1.54-2.70)**
Second cancers	**1.53 (1.35-1.73)**	1.13 (0.83-1.55)	**1.43 (1.12-1.83)**	**1.59 (1.34-1.89)**	**3.24 (2.17-4.83)**
Non-cancer	**1.15 (1.04-1.27)**	0.92 (0.71-1.16)	**1.23 (1.03-1.47)**	**1.17 (1.01-1.34)**	**1.55 (1.05-2.30)**

Hellesnes, ASCO 2021

Key Points

- Affects young men and is highly curable, even with advanced disease
- Tumor markers are critical for diagnosis, staging, prognosis, treatment response, and surveillance
- For Stage I, surveillance is preferred
- Chemo-sensitive: don't dose reduce or delay!
- High-dose chemotherapy with autologous stem cell rescue can be curative
- Patients can have significant long-term side effects from treatment

Things to Remember for the Boards

- Diagnosis
  - Seminoma vs non-seminoma
  - Staging
  - Risk stratification for Stage III disease
- Use of serum tumor markers for staging, prognosis, treatment response, and surveillance
  - Know the half-lives of AFP (5-7 days) and BHCG (1-3 days) and causes of false positives
- Treatment options by stage and risk

Things to Remember for the Boards

- Management of residual masses
  - PET for seminoma >3cm
  - Resection for NSGCT >1cm
    - Risk of teratoma and persistent disease
- Complications and toxicity of treatment