Testicular Cancer: (Nearly) Everything To Know in 60 20 Minutes

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Relevant Disclosures

• Financial: None

• Potential Conflict: Vice Chair, AUA Testicular Cancer Guideline Panel
Outline

• Why You Should Pay Attention
• Epidemiology
• Diagnosis
• Management of Seminoma
• Management of Non-Seminoma
• Technique Matters
• Avoiding Common Errors
Why You Should Pay Attention
• 593 patients with GCT from USC, Johns Hopkins, and U of Chicago

• **Non-guideline directed care (NGDC) in 30%**

• Most commonly **inappropriate imaging (44%), overtreatment (40%), misdiagnosis (24%), undertreatment (16%)**

• NGDC was independently associated with disease relapse (HR 2.49, 95% CI: 1.61-3.85, p <0.01)

• Patients with NGDC had worse QOL and more financial difficulties

Ref: Wymer, J Urol, 2017; Saoud, Eur Urol Oncol, 2020
Epidemiology
International Incidence

REF: Znaor, Eur Urol, 2013
Incidence Rates Worldwide Are Increasing

Ref: Gurney et al, Eur Urol 2019
Incidence Rates in the United States Are Increasing
(Europe and US: most rapidly increasing in Hispanic/Spanish men)

Ref: Nigam et al, World J Urol 2015
Risk Factors for Developing GCT

- European, Scandinavian, or Caucasian

- Cryptorchidism
  - Between two and five-fold increased risk
  - Accounts for 5-10% of all GCT

- Subfertility
  - Up to twenty-fold increased risk

- Familial or genetic component (very rare)
  - Four-fold increase if father with GCT
  - Nine-fold increase if brother with GCT
  - KIT mutations
  - Y microdeletions

- Marijuana (??)

Diagnosis: Markers
AFP

• Can be elevated in: embryonal carcinoma, teratoma, yolk sac

• Never elevated in: seminoma or choriocarcinoma

• Half life: 5-7 days

• Can be elevated in: foregut tumors, EtOH abuse, liver abnormalities
Mildly Elevated AFP

- 705 consecutive patients at USC, Johns Hopkins, and U Chicago

- 10 (1.7%) with “elevated” AFP < 30 ng/ml and no evidence of cancer

- Do nothing for stable AFP < 30 ng/ml (except stage and check other testicle)

Ref: Wymer et. al, Annals Oncology, 2017
Beta Human Chorionic Gonadotropin (ß-HCG)

- Can be elevated: choriocarcinoma, embryonal, teratoma, seminoma (10-15%)

- Half life: ~24 hours

- Rarely elevated due to high LH; can do T stimulation test
Novel serum biomarker: microRNA 371a-3p

- Outperforms traditional serum tumor markers (AFP, HCG, LDH)
- Present in seminoma and non-seminoma
- Not present in teratoma
- PPV=97% (sensitivity=90%; specificity=94%)
- SWOG trial open

Ref: Dieckmann, JCO, 2019
AUA GUIDELINE STATEMENT:
For man with testis mass, AFP, HCG, LDH should be drawn and measured prior to any treatment, including orchiectomy.

Most folks don’t measure or make decisions based on LDH in isolation (eg IGCCCG risk stratification)

Ref: Stephenson et al, AUA Guidelines 2019
S-Staging based on POST-Orchiectomy Markers

- Wait for post-orchietomy marker nadir to finalize staging/plan
- Plenty of situations no need to wait (plan same regardless of nadir)
AUA Guideline Statement:
For borderline elevated AFP and HCG levels (within 3x upper limit of normal) post-orchiectomy, a rising trend should be confirmed before management decisions are made as false positive elevations may occur.

Stage IS (stage I with elevated markers): standard of care = chemotherapy

Elevated markers always equals chemotherapy......EXCEPT:
- desperation RPLND (exhausted all chemo options with surgically resectable disease)
- cystic retroperitoneal mass with mildly elevated STM
Diagnosis: Ultrasound
Look at Ultrasound

Picture courtesy of Joel Sheinfeld
AUA Guideline Statement:
Patients with normal serum tumor markers (HCG and AFP) and indeterminate findings on physical exam or testicular US should undergo repeat imaging in 6-8 weeks.

- Up to 50-80% of palpable mass < 2 cm are benign
  - benign tumors, cysts, infarcts, Leydig cell nodules

- Management options:
  - observation
  - inguinal orchiectomy
  - partial orchiectomy

Ref: Stephenson et al, AUA Guidelines 2019
Diagnosis: Abdominal CT Scans
AUA Guideline Statement

In patients with normal STM (HCG and AFP) and equivocal imaging findings for metastasis, clinicians may consider repeat imaging in 6-8 weeks.

Solitary lymph node < 15 mm should be approached cautiously, particularly if outside primary landing zone → consider repeat imaging in 4-8 weeks.
Stage IIb (little b) vs Stage IIB (big B)

- Proper definition of clinical stage IIB
  - largest node 2-5 cm
  - no more than 5 enlarged nodes
- IIb
  - solitary node < 3 cm
  - “landing zone”
- IIB
  - any node > 3 cm
  - multiple nodes
  - unexpected location

Implications

IIb: favor local therapy
- seminoma = RT (? RPLND)
- non-seminoma = RPLND

IIB: favor systemic therapy
- seminoma = chemo (BEPx3 or EPx4)
- non-seminoma = chemo (BEPx3 or EPx4)
Follow-Up CT Scans

• Consider abdomen only (no pelvis): unless risk factors for pelvic recurrence

• Consider single-phase (IV contrast not required)

• Following proper RPLND: get single scan at 1 yr (unless extenuating circumstances)

• Consider MRI (ongoing European trial vs CT)
Initial Management
Keys to Achieving Durable Cures

- All initial treatment decisions based on histology, serum tumor markers (AFTER ORCHIECTOMY), and CT scan staging

- Timely diagnosis, accurate staging, and IGCCCG risk stratification
### AJCC Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to testis</td>
</tr>
<tr>
<td>IS</td>
<td>Confined to testis with post-orchiectomy elevation of serum tumor markers</td>
</tr>
<tr>
<td>II</td>
<td>Retroperitoneal metastases</td>
</tr>
<tr>
<td>IIA</td>
<td>≤ 5 nodes, all &lt; 2 cm</td>
</tr>
<tr>
<td>IIB</td>
<td>&gt; 5 nodes, 2 – 5 cm</td>
</tr>
<tr>
<td>IIC</td>
<td>&gt; 5 cm</td>
</tr>
<tr>
<td>III</td>
<td>Supra-diaphragmatic or visceral metastases</td>
</tr>
</tbody>
</table>
Risk Stratification for Metastatic GCT: Know It or Know it Exists!!

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

IGCCCG Group, JCO, 1997

95% CURE
BEP x 3 or EP x 4

80% CURE
BEP x 4

50% CURE
BEP x 4
Management of Seminoma
Stage I Seminoma: Cure = 99%

Options

- adjuvant XRT (20 Gy)
- single dose carboplatin
  - observation
Stage I: Adjuvant Radiation

• Randomized trials (TE 10 and TE18):
  – standard of care is 20 Gy to para-aortic
  – recurrence-free survival at 3 years: ~96%
  – cancer-specific survival at 3 years: 99%

Ref: Fossa et al., JCO, 1999; Jones et al., JCO, 2005
Stage I: Chemotherapy (Single Dose Carboplatin) vs. Radiation

• TE19 Trial Results (n=1447):
  – Recurrence-free survival at 5 years: 96% vs 95%
  – Cancer-specific survival at 5 years: 99.9%

  – Chemotherapy:
    • Less moderate lethargy at 4 wk (7% vs 24%)
    • Less inability to work at 4 wk (19% vs 38%)
    • Lower risk of contralateral GCT at 5y (0.2% vs 1.2%)

Ref: Oliver et al., JCO, 2011
Stage I: Surveillance

• Pooled analysis
  – 638 men with median FU of 7 years
  – rete testis invasion and size > 4 cm predict recurrence (not validated)
  – relapse based on risk factors (0,1,or 2): 12%, 16%, 32%
  – 5-year cancer-specific survival: 99%

Ref: Warde et. al, JCO, 2002
Stage IIA and non-bulky IIb Seminoma

- Radiation therapy (standard of care)
  - 30-36 Gy (not 20 Gy)
  - Right: interaortocaval, precaval, paracaval and ipsilateral iliac
  - Left: para-aortic and ipsilateral iliac
Stage IIA Seminoma: RPLND??

- Phase II multicenter trial of 55 patients
- Pure seminoma with 1 or 2 RP lymph nodes, 1 – 3 cm in size
- **Primary endpoint:** 84% two-year recurrence-free survival

PI: Daneshmand, GU ASCO, 2021
Stage IIB-III Seminoma

Chemotherapy based on IGCCCG Risk Stratification
(poor-risk doesn’t exist)
Post-Chemo Seminoma Mass

If residual mass > 3 cm, consider a PET scan (highly debatable)

**look for reasons not to do an RPLND**

Consider RPLND only if SUV > 6, growing mass, or biopsy with cancer
Management of Non-Seminoma
Initial Non-Seminoma Management by Stage

• Stage I
  – surveillance for all patients
  – RPLND or chemotherapy as an option in high-risk patients

• Stage IS (elevated/rising markers)
  – chemotherapy (always IGCCCG good-risk)

• Stage IIA and non-bulky IIB (with normal STM)
  – solitary node < 3 cm: RPLND preferred
  – any node > 3 cm: chemotherapy preferred
  – other situations: RPLND vs chemotherapy

• Bulky IIB and Stage III
  – chemotherapy (regimen based on IGCCCG risk)
Non-Seminoma: Stage I

• Distinction between Stage I and II:
  - > 10 mm node in a sensible retroperitoneal region (no magic cutpoint)
  - if equivocal, repeat scans in 6-8 weeks common strategy
• **Risk factors** for recurrence drive management decisions:
  - > 40% embryonal carcinoma
  - lymphovascular invasion (LVI)
• All stage I patients: 30% of patients will relapse
  - no risk factors: 15% risk (surveillance)
  - one or both risk factors: 40-50% risk
Stage I: Surveillance

**Table 4 – Studies of surveillance in clinical stage I nonseminomatous germ cell tumors**

<table>
<thead>
<tr>
<th>Study (publication year)</th>
<th>No. of patients</th>
<th>Median follow-up, yr</th>
<th>No. of relapses (%)</th>
<th>Median time to relapse, mo (range)</th>
<th>No. of deaths (%)</th>
<th>Overall survival rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read (1992) [6]</td>
<td>373</td>
<td>5</td>
<td>100 (27)</td>
<td>NR</td>
<td>5 (2)</td>
<td>98</td>
</tr>
<tr>
<td>Daugaard (2003) [6]</td>
<td>301</td>
<td>5</td>
<td>86 (29)</td>
<td>5 (1-171)</td>
<td>0 (0)</td>
<td>98.6</td>
</tr>
<tr>
<td>Coils (1999) [6]</td>
<td>248</td>
<td>4.5</td>
<td>70 (28)</td>
<td>NR</td>
<td>3 (2)</td>
<td>97</td>
</tr>
<tr>
<td>Kollmannsberger (2010) [7]</td>
<td>223</td>
<td>4.3</td>
<td>59 (26)</td>
<td>4 (1-49)</td>
<td>0 (0)</td>
<td>100</td>
</tr>
<tr>
<td>Francis (2000) [6]</td>
<td>183</td>
<td>5.1</td>
<td>52 (28)</td>
<td>6 (1-122)</td>
<td>2 (1)</td>
<td>99</td>
</tr>
<tr>
<td>Roeleveld (2001) [6]</td>
<td>90</td>
<td>8</td>
<td>23 (26)</td>
<td>7 (3-44)</td>
<td>1 (1)</td>
<td>98.9</td>
</tr>
<tr>
<td>Nicolai (1995) [6]</td>
<td>85</td>
<td>11</td>
<td>25 (29)</td>
<td>7 (2-68)</td>
<td>3 (3.5)</td>
<td>96</td>
</tr>
</tbody>
</table>

NR = not recorded.

REF: Sturgeon and Jewett, Eur Urol, 2011
Stage I NSGCT: Surveillance vs BEP x 1

- 745 patients with CSI NSGCT in Sweden and Norway
- Observational cohort with median follow-up of 4.7 years

<table>
<thead>
<tr>
<th>No vascular invasion</th>
<th>86%</th>
<th>98%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular invasion</td>
<td>58%</td>
<td>96%</td>
</tr>
</tbody>
</table>

Five-year Relapse-Free Survival

Ref: Tandstad et al, JCO, 2009
Stage I NSGCT: RPLND

- RPLND
  - minimizes exposure to chemotherapy
  - minimizes radiation from future CT scans
  - risk of pain (100%), incision (100%), ejaculatory dysfunction (5%), and small bowel obstruction (1%)
• RPLND for clinical stage I – IIA NSGCT is a **diagnostic** and **therapeutic** procedure

• Approximately 20% - 30% of clinical stage I patients and 50% - 60% of clinical stage IIA harbor retroperitoneal disease

• **Open vs Robotic**: stay tuned........
Management after Primary RPLND

POSTSURGICAL MANAGEMENT

Stage IA, IB, IIA, IIB treated with nerve-sparing RPLND

- pN0:
  - Surveillance

- pN1:
  - Compliant
  - Noncompliant

- pN2:
  - Compliant
  - Noncompliant

- pN3
Management after Primary RPLND

85-90% cure with surveillance
Management after Primary RPLND

POSTSURGICAL MANAGEMENT

Surveillance

Surveillance (preferred) or Chemotherapy: GEP for 2 cycles or BEP for 2 cycles

Compliant

pN0

Noncompliant

Chemotherapy: EGP for 2 cycles or BEP for 2 cycles

Stage IA, IB, IIA, IIB treated with nerve-sparing RPLND

pN1

pN2

pN3
Management after Primary RPLND

50% cure with surveillance
Management after Primary RPLND

POSTSURGICAL MANAGEMENT

- pN0
  - Surveillance

- pN1
  - Compliant
  - Surveillance (preferred) or Chemotherapy: EP for 2 cycles or BEP for 2 cycles

- Noncompliant
  - Chemotherapy: EP for 2 cycles or BEP for 2 cycles

- pN2
  - Compliant
  - Chemotherapy (preferred): EP for 2 cycles or BEP for 2 cycles or Surveillance

- Noncompliant
  - Chemotherapy: EP for 2 cycles or BEP for 2 cycles

- pN3

Stage IA, IB, IIA, IIB treated with nerve-sparing RPLND
Management after Primary RPLND

POSTSURGICAL MANAGEMENT

- pN0
  - Surveillance
    - Surveillance (preferred)
      - or Chemotherapy:
        - EP for 2 cycles
        - or BEP for 2 cycles
  - Compliant
    - Chemotherapy:
      - EP for 2 cycles
      - or BEP for 2 cycles
  - pN1
    - Noncompliant
      - Chemotherapy (preferred):
        - EP for 2 cycles or BEP for 2 cycles
        - or Surveillance
  - Compliant
    - Chemotherapy:
      - EP for 2 cycles or BEP for 2 cycles
  - pN2
    - Noncompliant
      - Chemotherapy (preferred):
        - EP for 2 cycles or BEP for 2 cycles
  - pN3
    - Noncompliant
      - Chemotherapy (preferred):
        - EP for 4 cycles
        - or BEP for 3 cycles

EP = Etoposide/cisplatin
BEP = Bleomycin/etoposide/cisplatin
Between 1996-2005, 382 patients with CSI NSGCT
Randomized to unilateral RPLND versus one cycle BEP
Median follow-up of 4.7 years

Limitations:
- RPLND at 61 centers
- unilateral RPLND
- poor quality RPLND (9 local recurrences)
- intermediate-term follow-up
- unknown long-term toxicities

REF: Albers et al, JCO, 2008
Surveillance for All Stage 1 Non-Seminoma?

Reference: Nichols et al, JCO, 2013
Does RPLND have a role in CS IB NSGCT? Some, including one of us (G.J.B.), favor RPLND. The relapse rate after RPLND is approximately 5% to 10%\(^9\,10\) and the risk of retrograde ejaculation after a nerve-sparing RPLND is less than 5% in the hands of an expert surgeon.\(^11\) Because the operation is curative for the majority of patients with pathologic stage II disease, only 15% of patients receive chemotherapy after nerve-sparing bilateral RPLND,\(^12\) compared with 50% of patients who relapse during active surveillance, all of whom require three to four cycles of chemotherapy, and 100% of patients with CS IB disease, who receive one to two cycles of adjuvant chemotherapy. Hence, the chemotherapy risks are the least following RPLND. Informed decision-making by these patients is especially relevant since the threshold for preferring early definitive treatment over surveillance is precisely at the actual 50% risk cutoff for recurrence.\(^13\)

- **RPLND curative in 90-95%**
- **Rates of chemotherapy:**
  - Following RPLND, <10%
  - Surveillance: 30-50% (full course)
  - Adjuvant chemo: 100% (BEPx1-2)
- **Disease-specific survival: 99%**

Reference: de Wit and Bosl, JCO, 2013
Post-Chemotherapy Management of Non-Seminoma
Following Induction Chemotherapy for Metastatic GCT

Complete response = nothing > 1 cm on axial imaging
141 patients at Indiana University for metastatic NSGCT with complete response to chemotherapy, defined by residual masses less than 1 cm

Treated between 1984 – 2005

Median follow-up 15 years

15-year relapse-free survival: 90%
  - Good-risk: 95%
  - Intermediate/Poor-risk: 73%

15-year cancer-specific survival: 97%
  - Good-risk: 99%
  - Intermediate/Poor-risk: 91%

Reference: Ehrlich and Einhorn, et al, JCO, 2010
Post-Chemotherapy Non-Seminoma

• Full bilateral RPLND is **standard of care** for any RP mass > 1 cm
  - ~10-20% of the time, modified template may be reasonable
  - Criteria for modified template:
    - IGCCCG good-risk
    - left-sided primary
    - never had disease outside of para-aortic or left iliac

• Resection of all extra-gonadal residual masses (lung, liver, neck, etc)
Learn How to Do A Proper RPLND (Or Refer to Someone Who Does)

• US trainees: median RPLND’s 2
• NCDB: > 50% of US hospitals perform 2 or fewer RPLND’s
• Advanced disease → treatment at high-volume hospital is independent predictor of improved survival

AUA Guideline Statement
Among patients who are candidates for RPLND, consider referral to an experienced surgeon at a high-volume center
Technique Matters
RPLND: Technique Matters

• Removal of the gonadal vein and spermatic cord
  – paracolic recurrences can occur following incomplete excision

• Divide lumbar vessels and remove retrocaval and retroaortic nodes
  – putative etiology for recurrence

• Complete resection
  – re-operative RPLND has a higher morbidity rate and adversely impacts survival

• Nerve-sparing
  – essential to achieve antegrade ejaculation

REF: Kantzavelos, Urology, 2003; Donohue et al, Semin Urol Oncol, 1998; Chang, J Urol, 2002; McKiernan, Urology, 2003
Ejaculatory Neuroanatomy

• Non-nerve sparing full templates lead to retrograde ejaculation in > 95%

• Antegrade ejaculation requires:
  1) one sympathetic chain
  2) ≥ 1 post-sympathetic efferent nerve
  3) hypogastric plexus

• Two approaches to optimize antegrade ejaculation:
  – nerve-sparing
  – modified templates
No Nerve-Sparing Intent
No Nerve-Sparing Intent
Robotic Retroperitoneal Lymph Node Dissection

• **Open vs Robotic:** as long as it done well........

• Many groups showing equivalent short-term outcomes, less peri-operative morbidity

• Concerns for unique/aberrant recurrence patterns
  – 5 patient series from Indiana (Calaway Eur Urol 2019) with carcinomatosis, large volume liver lesions, colonic invasion, celiac nodes

  – Editorial from MSK (Sheinfeld et al), U Toronto (Nason et al) and others (Porter et al)

• **AUA Guideline Statement:** Surgeons with experience in the management of germ cell tumors and expertise in minimally invasive surgery may offer a minimally-invasive RPLND, acknowledging the lack of long-term data on oncologic outcomes
Avoiding Common Errors

• Young male with a retroperitoneal mass
  – Check STM and U/S testicle

• No PET scans for non-seminoma (fading for seminoma also)

• S-staging is based on post-orch markers (wait, if needed)

• Know your IGCCCG: EP4 vs BEP3 vs BEP4

• Non-seminoma post-chemotherapy residual mass > 1 cm: RPLND

• Presence (or lack) of teratoma in orchietomy correlates but does not accurately predict presence (or lack) in the retroperitoneum
With excellent cure rates for metastatic disease, long-term survivors are common and there is an increasing appreciation of long-term treatment effects.

**General**
- late relapse (1% - 6%)
- contralateral tumor (2% - 4%)
- infertility
- atypical nevi (37%)

**Chemotherapy**
- cardiovascular
- Raynoud’s phenomenon
- secondary cancers
- pulmonary toxicity
- ototoxicity
- renal impairment
- impaired spermatogenesis

**RPLND**
- anejaculation
- small bowel obstruction (1%)

**Radiotherapy**
- gastric ulcers
- cardiovascular morbidity
- secondary cancers
Conclusions

- Extremely gratifying to take care of men with testicular cancer
- Frequently mismanaged, there are ‘right’ and ‘wrong’ answers
- Know the algorithms or refer to someone who does
- Know/use NCCN, EAU, or AUA Guidelines