Radiation Therapy for Testicular Cancer

Steven W. Davis, MD
Case

• 41 y.o. male presents with a 6 week history of painful right testicle
• Other sx’s: decreased libido
• PMHx: Eczema, seasonal allergies
• PSHx: Vasectomy
• Medications: Rhinocort
• Allergies: NKDA
Case

- Family Hx: No history of cancer
- Social Hx: Married with 3 children
- ROS: negative
- Exam: scrotum without lesion, TTP of right testicle but no palpable mass
- Labs: serum AFP, LDH, and HCG: WNL
Case

• Ultrasound Scrotum:
  – Multiple nodules in right testicle
  – Given multifocality, may represent non-seminomatous tumor
  – Right hydrocele

• CT: Abdomen/Pelvis
  – No evidence of metastatic disease

• CXR:
  – No evidence of disease
Case

• Right radical orchiectomy

• Pathology
  – Testicle, right, radical orchiectomy:
    • Spermatocytic seminoma
    • Multifocal, 1.0, 0.5 cm
    • Limited to testes, margins negative, no LVI
    • pT1 NX S0, Stage IA
    • IHC: -OCT3/4

• Referred to radiation oncology for evaluation for adjuvant therapy
Testicular Cancer

- Only 1-2% of malignant tumors in men
- Most common malignant tumor in men ages 15-35
- World (2008): 52,000 cases with 9000 deaths
- US: 8480 cases with 350 deaths

- Isochrome 12p in 80% of germ cell tumors
  - DDX1, KRAS, c-KIT (ligand KITGL)
  - ITGCN and invasive tumors

Loss of one arm and duplication of the other
Classification of Testicular Tumors

- Germ Cell Tumors (95%)
  - Seminomatous (35%)
    - Seminoma
    - Spermatocytic Seminoma
  - Non-seminomatous (5-10%)
    - Embryonal
    - Yolk Sac
    - Choriocarcinoma
    - Teratoma
  - Mixed (50-60%)
Classification of Testicular Tumors

• Sex Cord Stromal Tumors
  – Leydig Cell Tumors
  – Sertoli Cell Tumors

• Others
  – Lymphoma (most common in age >65)
  – Sarcomas
Germ Cell Tumors

• 10% occur outside of Testes
  – Most common locations: retroperitoneum and anterior mediastinum
  – Dysgerminoma of Ovary/mediastinum

• Seminomas: 4\textsuperscript{th} Decade
• Non-seminomas: 3\textsuperscript{rd} Decade

• European Decent: 6.36/100,000
• African Decent: 1.30/100,000
Seminoma

• Most common single tumor type (35%)
• 85% present in stage I
• Risk Factors
  – Cryptorchidism
  – Klinefelter’s Syndrome
  – Diethylstibestrol (DES) exposure
  – Immunosuppression
Spermatocytic Seminoma

• Older age 50-60
• Rarely metastasize (1 of >200 cases in literature)
• More likely bilateral: 8-10% vs 2-4%
• Treatment:
  – Most urologists recommend orchiectomy with surveillance
  – No great data available
### Stage TNM system

**TX** Unknown status of testis  
**T0** No apparent primary (includes scars)  
**Tis** Intratubular tumor, no invasion  
**T1** Testis and epididymis only; no vascular invasion or penetration of tunica albuginea  
**T2** Testis and epididymis with vascular invasion or through tunica albuginea to involve tunica vaginalis  
**T3** Spermatic cord  
**T4** Scrotum

**N0** No regional node involvement  
**N1** Node mass or single nodes ≤2 cm; ≤5 nodes involved; no node >2 cm  
**N2** Node mass >2 but ≤5 cm; or >5 nodes involved, none >5 cm; or extranodal tumor  
**N3** Node mass > 5 cm

**MX** Unknown status of distant metastases  
**M0** No distant metastases  
**M1a** Non-regional nodal or lung metastases  
**M1b** Distant metastasis other than non-regional nodal or lung  
**SX** No marker studies available  
**S0** All marker studies normal

### Grouping

- **Stage 0** – Tis, N0, M0, S0  
- **Stage IA** – T1, N0, M0, S0  
- **Stage IB** – T2-T4, N0, M0, S0  
- **Stage IS** – any T, N0, M0, S1-S3  
- **Stage IIA** – any T, N1, M0, S0-S1  
- **Stage IIB** – any T, N2, M0, S0-S1  
- **Stage IIC** – any T, N3, M0, S0-S1  
- **Stage IIIA** – any T, any N, M1a, S0-S1  
- **Stage IIIB** – any T, any N, M0-M1a, S2  
- **Stage IIIC** – any T, any N, M0-M1a, S3 any T, any N, M1b, any S

### LDH*: hCG (mIU/mL) | AFP (ng/mL)
---|---|---
S1 | <1.5 × N & | <5000 & | <1000
S2 | 1.5–10 × N or | 5000–50 000 or | 1000–10 000
S3 | >10 × N or | >50 000 or | >10 000

*LDH levels expressed as elevations above upper limit of normal (N).
Serum Tumor Markers

- **HCG**
  - Elevated in choriocarcinoma
  - 15% of seminoma patients
- **AFP**
  - Elevated in yolk sac tumor
  - If elevated, not pure seminoma
- **LDH**
  - Elevated in 60% of GCT
  - Acute phase reactant
- **Measurement before/after orchiectomy can help monitor treatment response, disease remission**
Survival

• Seminomas 5-yr OS
  – Stage I: virtually 100%
  – Stage II: 97%
  – Stage III: 85%

• Non-seminomatous Germ Cell Tumors 5-yr OS
  – Stage I: 99%
  – Stage II: 98%
  – Stage III: 86-50%
Stage III Risk Stratification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Seminoma</th>
<th>Nonseminoma</th>
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<tbody>
<tr>
<td>Good risk</td>
<td>Any primary site <em>and</em> No nonpulmonary visceral metastases <em>and</em> Normal AFP, any HCG, any LDH</td>
<td>Gonadal or retroperitoneal primary tumor No pulmonary or visceral metastases Good tumor markers (all): ( \text{AFP} &lt; 1,000 \text{ ng/mL} ), ( \text{HCG} &lt; 5,000 \text{ IU/L} ), ( \text{LDH} &lt; 1.5 \times \text{ULN} )</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Any primary site <em>and</em> Nonpulmonary visceral metastases <em>and</em> Normal AFP, any HCG, any LDH</td>
<td>Gonadal or retroperitoneal primary tumor No pulmonary visceral metastases Intermediate tumor markers (any): ( \text{AFP} 1,000-10,000 \text{ ng/mL} ), ( \text{HCG} 5,000-50,000 \text{ IU/L} ), ( \text{LDH} 1.5 \times \text{ULN} )</td>
</tr>
<tr>
<td>Poor risk</td>
<td>NA</td>
<td>Mediastinal primary tumor <em>or</em> Nonpulmonary visceral metastases <em>or</em> Poor tumor markers (any): ( \text{AFP} &gt; 10,000 \text{ ng/mL} ), ( \text{HCG} &gt; 50,000 \text{ IU/L} ), ( \text{LDH} &gt; 10 \times \text{ULN} )</td>
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*Source: Reference 11.*
Treatment Decisions

• Surgery: Radical inguinal orchiectomy with high ligation of spermatic cord
  – Only deferred for high-burden metastatic disease when chemotherapy may be offered first

• Seminoma vs. NSGCT/Mixed Tumor

• Stage at Presentation
  – Stage I, Stage II or Stage III
NSGCT Stage I

• Surveillance
  – 21% recurrence rate
  – Usually in first 12 months (after 24 months rare)
  – Usually to retroperitoneal LNs (60%)
  – Chemotherapy for salvage: >98% cure

• RPLND with nerve sparing
  – 10% recurrence rate

• Single cycle adjuvant BEP
  – Cisplatin, Etoposide, Bleomycin
1996-2005: 286 patients randomized to RPLND or 1 Cycle of BEP
Relapse rate of 10% vs 3% recurrence (HR 7.9 at 24 months)
NSGCT Stage II and III

• Stage II
  – IIA – observation vs. RPLND vs. 2 cycles of BEP
    • Teratoma may favor surgery
  – IIB/C – chemotherapy BEP x2

• Stage III
  – Chemotherapy BEP x3 - 4
  – Good prognosis 5-yr OS 80%, Poor 50%
  – Increased survival at specialty centers
Seminoma Stage I

• Historically patients got radiation:
  – 30 Gy/15 fractions in “dog leg” configuration—
    paraaortics with ipsilateral inguinals
  – MRC trial TE 10, 1999, PA vs. “dog leg”
    • Fields: PA (sup T10/T11, inf L5/S1, lat inclusion of ipsilateral renal hilum); 
      Dog-Leg (sup T10/T11; inf mid-obturator foramen; ipsilateral inclusion of renal hilum 
      vertically down to L5/S1, then diagonal to lateral edge of acetabulum, then vertically 
      down to mid-obturator foramen; contralateral transverse process vertically to L5/S1, 
      then diagonal parallel with ipsilateral and vertically down to mid-obturator foramen)
    • 478 Men, same relapse rate, lower toxicity and better sperm counts with PA
  – MRC trial TE 18, 2005, 30 Gy/15 vs 20 Gy/10
    • 628 men, same relapse rate
    • return to work sooner (relatively similar toxicity at 12 wks, 
      less lethargy at 4 weeks)
MRC trial TE 19/ EORTC 30982

• 1447 patients in 14 countries
  – 1 cycle carboplatin vs. radiation therapy (30/15 or 20/10)
  – 2005
    • 3-yr RFS carbo 95% vs RT 96%
    • Toxicity: reported less fatigue with carbo
    • Decreased 2\textsuperscript{nd} testicular tumors with carbo 10 vs 2
  – 2011
    • 5-yr RFS carbo 94.7% vs RT 96%
    • Contralateral GCT carbo 2 RT 15 HR 0.22, P=0.03
Risk of Secondary Malignancy

• 2005, Scandanavian Study
• >40,000 testicular tumors
• Showed lifetime risk of 36% vs 23% for solid visceral cancers
  – Stomach, Bowel, Pancreas, and Liver
• 10 patients
• Planned with protons and traditional photons
• Predicted 6.94 excess bladder, large bowel, pancreas and stomach cancers with photons
Seminoma Stage IIA/IIB

- EBRT – 20 Gy/10 fractions to paraaortics and pelvic lymph nodes
- Boost dose (+10 Gy for IIA and +16 Gy for IIB) for gross lymph node disease
- Prior inguinal surgery disrupts lymphatics and may require contralateral node coverage
Seminoma IIC and III

• Chemotherapy
  – EP x4 vs BEP x3 (BEP x4 for intermediates)
  – Either good or intermediate IGCCCG prognostic group
Case

• Chose surveillance

• Follow-up
  – Follow up visit, CT abdomen and pelvis and Labs
    • every 3-4 months x 3 years
    • then q6 months x4 years
    • Then q 1 year until 10 years
References

• Gunderson and Tepper. Clinical Radiation oncology. 2011. Elsevier and Sanders
• Hansen, EK and Roach M. Handbook of Evidence-Based Radiation Oncology. 2nd edition. 2011 Springer Press