Seminoma 101

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Grand Rounds May 31st, 2006

Objectives

- Pathogenesis
- Clinical stage for stage management
- Probability of treatment success
- Short and long term morbidity
- Indications for post-chemotherapy surgery in patients with advanced seminoma
- Imaging modalities in clinical staging
Introduction

- Incidence: 8000 cases/year of testicular cancer in US
- 25-40% pure seminoma
Introduction

- Limited role of RPLND = Urologist not as likely to be involved in care

- Significant changes over past 20 years in every stage

- Most significant in Clinical Stage I (CS I)

Staging (AJCC/UICC)

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Pathogenesis

- Arises from intratubular germ cell neoplasia (ITGCN)
- Considered precursor for other forms of GCT
  - Embryonal carcinoma
  - Yolk sac tumor
  - Choriocarcinoma
  - Teratoma

Pathogenesis

- 15% contain syncytiotrophoblasts cells which produce human chorionic gonadotropin (HCG)
- HCG >1000 suspicious for NSGCT
- Seminoma does not produce AFP

Pathology

- 3 histologic subtypes
  - Spermatocytic
  - Anaplastic
  - Classic
Spermatocytic

- Rare – 1-2% of cases

Anaplastic

- Increased mitotic activity
- Nuclear pleomorphism
- Cellular anaplasia
Anaplastic

- Presents as:
  - More advanced stage than classic
  - Prognosis stage for stage is similar

What is the difference in presentation between seminoma and NSGCT?

**Seminoma vs. NSGCT**

- 70-80% clinical stage I
- <5% have distant mets
- CS I 15-20% RP mets
- Diagnosis equally divided among stages I, II, III
- CS I 30-40% RP mets

**Seminoma vs. NSGCT**

- **Systemic Relapse**
  - CS I = 1%
  - CS IIA/B = 10%

- **Systemic relapse**
  - CS I = 10%
  - CS IIA/B = 40%

**Seminoma vs. NSGCT** *

- **No poor prognosis category**
- 90% metastatic cases classified as good risk (5YS = >90%)

- **Metastatic = poor prognosis category**
- 56% cases good prognosis

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Career Pathways ‘06

Management Overview

- Decrease morbidity
- >30 years of life expectancy
Side effects

- Cis-platin based chemotherapy
  - ~5 x increased risk of major cardiovascular events within 10 years of treatment
- Etoposide doses of 2g/m² or less = 0.5% risk of secondary leukemias

Treatment

- R.A. Huddart Et Al, Cardiovascular Disease as a Long-Term Complication of Treatment for Testicular Cancer, JCO Vol 21, Issue 8 (April), 2003: 1513-1523
In 20-30% standard chemotherapy:
- Long-term renal dysfunction
- Sensory peripheral neuropathy
- Hearing loss
- Reynaud’s phenomenon

Christian Kollmannsberger, Markus Kuzcyk, F. Mayer, Jörg T. Hartmann, Lothar Kanz, Carsten Bokemeyer. Late toxicity following curative treatment of testicular cancer
Infradiaphragmatic radiotherapy

- At 15 years post XRT
- Standardized mortality ratio (SMR) of 1.55
  - SMR cardiac 1.8
  - SMR non-GCT cancer deaths 1.79

CLINICAL STAGE I

- 80% of presenters
- 15-20% have occult RP
- = 80-85% cured by orchiectomy
Clinical Stage I

- **Orchiectomy**
- **Adjuvant Radiotherapy**
  - Morbidity: 95-97% progression free
  - Reduced need for CT f/u DL for prev. inguinal sx
  - Recurrence within 2 years
    - Systemic chemotherapy = near 100% cure
    - Inguinal recurrence = Sx or RTx
  - F/U: CXR and Markers AP CT q6m x 2y
- **Single Agent Carboplatin**
  - Dose: 1 or 2 cycles
  - 2 cycles have lower recurrence rates
  - Disease free survival = RTx @ 3 years
  - 65% to 90% complete response (CR) for advanced seminoma
- **Surveillance**
  - Relapse outside of RP or RTx failures treated with systemic chemotherapy
  - DL radiotherapy for relapse = cure rates 70% to 90%

**Morbidity**
- 95-97% progression free
- Reduced need for CT f/u DL for prev. inguinal sx

**Recurrence within 2 years**
- Systemic chemotherapy = near 100% cure
- Inguinal recurrence = Sx or RTx

**F/U**
- CXR and Markers
- AP CT q6m x 2y

**Disease free survival = RTx @ 3 years**
- 65% to 90% complete response (CR) for advanced seminoma

**DL radiotherapy for relapse = cure rates 70% to 90%**

**Platin-based chemotherapy = >90% cure for metastatic disease**

**Surveillance**
- Increased $$$

**Investigational**
- Must be counseled about lack of long term data

**Serum markers not helpful**
- Indolent natural history
- 2-3% of patients will recur after 4 years

**Acute grade II-IV hematologic toxicity (leukopenia) 5-15%**
- Late GI toxicity

**Decreased nephrotoxicity**
- Decreased neurotoxicity
- Decreased ototoxicity

**Decreased lethargy**
- Decreased time back to work
- 4% acute GI III/IV hematologic toxicity

**18-24% bulky RP disease and/or distant mets**

**Persistent oligospermia**
- Scatter dose sufficient
- Late cardiac toxicity
- Radiation induced malignancies

**Decreased Decline**
- Decreased lethargy
- Decreased time back to work
- 4% acute GI III/IV hematologic toxicity

**Surveillance**
- Increased $$$
McLoughlin MG, Jackson SM, Olivotto I, Coy P.
Radiation therapy for seminoma of the testis: results in British Colombia.

- 1942-1978
- N=362
- 5-year survival rates were 87% overall
- 96% for those with a T1 or T2
- 62% for the 24 with palpable or distant metastases at the time of clinical presentation
- 28 patients in whom the disease recurred 15 were successfully treated
- The incidence of other cancers was not increased over the expected rate in the general male population of the same age.

- 28,000 patients with testis cancer
- 15,000 seminoma
- 16 population based registries worldwide
- 1.43 X expected
- Chance of 2° malignancy was 18% at 25 years
  - Leukemia
  - Upper GI tumours
  - Bladder
  - Possibly pancreas
Cumulative risk
DL XRT vs. Para-aortic

- Small significant increase in pelvic recurrence at 3 years (2% vs. 0% p=0.04)
- Routine pelvic CT need to look for pelvic recurrence
- Overall survival 99% vs 100%
- Improved recovery of spermatogenesis at 18 months (no difference at 3 years)
20 Gy vs. 30 Gy PARTx

- Randomized
- 5 year relapse free survival 96% vs 97%
- Overall survival 99.6% vs 100%

- 638 patients median f/u 7 years
- Univariate analysis
  - tumor size >4cm (p=0.003)
  - rete testis invasion (p=0.003)
  - lymphovascular invasion (0.038)
  - anaplastic vs classic (p=0.056)
- = all significant predictors
Multivariate analysis only:

- rete testis invasion
- tumor >4cm significant predictors of relapse

### Table 3. Five-Year Relapse-Free Rates Based on Tumor Size and Rete Testis Invasion

<table>
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<tr>
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<th>Rete Testis Involvement</th>
<th>Rate Testis Involvement</th>
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<tr>
<td>n ≤ 4 cm</td>
<td>n = 176</td>
<td>n = 75</td>
</tr>
<tr>
<td></td>
<td>87.8% ± 2.5%*</td>
<td>85.6% ± 4.3%*</td>
</tr>
<tr>
<td></td>
<td>HR = 1.0†</td>
<td>HR = 1.7†</td>
</tr>
<tr>
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<td>95% CI, 1.1-2.6†</td>
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<tr>
<td>n &gt; 4 cm</td>
<td>n = 107</td>
<td>n = 95</td>
</tr>
<tr>
<td></td>
<td>83.0% ± 3.7%*</td>
<td>68.5% ± 4.2%*</td>
</tr>
<tr>
<td></td>
<td>HR = 2.0†</td>
<td>HR = 3.4†</td>
</tr>
<tr>
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<td>95% CI, 1.3-3.2</td>
<td>95% CI, 2.0-6.1</td>
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Who to treat?

- 21% of patients have both risk factors = optimal candidate for RTx
- 80% appropriate candidates for surveillance
- 70% overall avoid unnecessary therapy

Single Agent Carboplatin

- MRC study
- 1477 randomized
- 1 cycle carboplatin vs 20-30 Gy para-aortic XRT
- Median f/u 4yrs

Single Agent Carboplatin

- 3 year relapse free survival 96% vs 95% for RTx
- 1 death in RTx group

Single Agent Carboplatin *

- CS I seminoma and not candidate for surveillance adjuvant RTx considered standard of care
- Must be counseled about lack of long term data
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CLINICAL STAGE II SEMINOMA

CS II

Orchectomy

CS IIA/B

RTx to RP lymph nodes and ipsilateral pelvis
25 to 30 Gy
5 to 10 Gy boost

Well tolerated
III-IV GI toxicity in 8-10%

Long term relapse rates:
IIA = 0%-4% (in field 0%-2%)
IIB = 10%-13/4 (in field 0%-7%)
Systemic CTx cures close to 100%

CS IIC

Most important factor = bulk of RP disease
DLXRT abandoned 2o high recurrence rates

XRT 44%
Systemic CTx 95%

XRT = marrow suppression
May effect chemo

CLINICAL STAGE IIC

- XRT suited for solitary masses <3cm
- Multiple masses, or >3cm, or symptoms = Induction chemotherapy

Systemic chemo IIA/B?

- Consider if clinical stage IIA-B with lateral masses
  - O/W radiating large volume of 1 or 2 kidneys and/or liver

ADVANCED SEMINOMA (CS III)

- <5% presentation
- 90% Stage III considered “good risk”
  - IGCCCG
- 5 yr overall survival 91% with 85% progression free
- Remaining 10% “intermediate risk”
ADVANCED SEMINOMA
(CS III)

- Non-pulmonary visceral mets
  - 5yrs overall survival 79% with 75% progression free
  - IGCCCG only recognizes NPVM as prognostic

CS III Treatment

- Good Risk (IIIA)
  - 4 cycles EP or 3 cycles BEP

- Non-pulmonary visceral mets (IIIB)
  - Induction of 4 cycles BEP

- Single agent carboplatin = worse survival

CS III Relapse

- 10% to 15% relapse after induction CTx
- 10% relapse after CR
- Confers poor prognosis
- Long term survival 20% to 50%
- Salvage chemotherapy rare
  - difficult to develop novel approach

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Post Chemo Residual Masses

- After 1st line chemotherapy
  - 58%-80% of patients have detectable masses radiologically
- In NSGCT acceptable for surgical resection
  - 5%-20% incidence of viable GC malignancy
  - 30%-40% incidence of teratoma

Management of Post Chemo Masses

- Seminoma = controversial
  - 1) masses contain viable cancer in 10% to 20% of cases overall
  - 2) surgical resection is technically difficult and often not feasible 2nd to desmoplastic reaction after chemo and increased morbidity
  - 3) teratoma is rarely observed
Management of Post Chemo Masses

- Treatment options:
  - 1) Observation
  - 2) Resection
  - 3) Salvage chemotherapy = evidence of relapse

Post-chemotherapy radiotherapy has no role in the management of residual masses

- G. M. Duchesne, S. P. et al. Radiotherapy after chemotherapy for metastatic seminoma—a diminishing role
  European Journal of Cancer, Volume 33, Issue 6, May 1997, Pages 829-835
Observation

- Pros
  - Surgery morbid
  - Up to 90% necrosis with no viable GCT elements

Observation

- Spontaneous resolution reported in 50%-60%
  - Median 13-18 months
- Protracted time course = change in size not useful tool to predict need for additional tx
Size matters

- >3cm cutoff
  - 27%-38% progression
- <3cm cutoff
  - 0% to 4% progression

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Fluorodeoxyglucose-positron emission tomography (FDG-PET)
- Prospective randomized trial
- Viable seminoma in PCTx residual masses
Positive scan = more predictive for viable tumour than using CT 3cm cutoff

- Specificity = 100%
- Sensitivity = 80%

2 of 44 patients with negative scan were later found to have viable seminoma

- Both <3cm masses

CONCLUSION:

FDG-PET appears to be useful tool to characterize PCTx masses
FDG-PET

- Positive scan suggests surgical resection indicated - if feasible
- Observation justified in patients with negative scan (after primary CTx)
  - More so if size <3 cm

FDG-PET

- No role in NSGCT
  - Does not exclude teratoma (present in ~40% post chemo RPLND specimens)
Resection vs. Surveillance with Salvage CTx

- No evidence
- Complete excision rates
  - 58% to 74%

Herr HW Et al, Surgery for a post-chemotherapy residual mass in seminoma.

- 55 PCTx masses
  - Of 27 with >3cm resected or bx = 30% tumour
    - 6 seminoma
    - 2 teratoma
  - Of 28 with < 3cm all necrotic

- Of 8 with viable tumour 6 masses well defined and completely resected = alive @ 4 yrs

- Of 8 with viable tumour 2 masses poorly defined, not complete resected and died

- Of 26 patients with a complete resection of necrotic mass 3 had relapse at distant sites and died

Conclusions (pre PET era)

- Residual mass smaller than 3 cm
  - = No benefit from surgery

- Residual mass >=3 cm surgery preferred:
  - define response
  - resect viable tumor when possible
  - direct further treatment
SEMINOMA SUMMARY

- Indolent natural history
- Radiation sensitivity
- Platin-based CTx sensitivity
- DL radiotherapy = standard of care
  - Stages I, IIA, and IIB
- Overall survival rates approach 100%
SUMMARY

- Surveillance acceptable alternative in CS I

- Single agent carboplatin for CS I promising
  - Further follow-up necessary to determine long-term efficacy

SUMMARY

- Bulky retroperitoneal disease and or distant mets
  - Induction chemotherapy

- Overall survival rates of >90% for metastatic seminoma expected
SUMMARY

- Many residual masses >3cm should be resected
  - FDG-PET positive
  - Technically feasible
- Salvage chemotherapy = diminished survival
- Residual Masses safely observed if <3cm
  - FDG-PET negative

Testes: a privilege?
Principles of XRT

- Superior aspect of T10-11 vertebral body to inguinal ligament
- 8-10 cm wide
- Ipsilateral renal hilum
- High rate of recurrence if margin extended only to transverse vertebral process
Late Recurrence

- Late recurrence (>2 years)
  - insensitivity to cisplatin-based chemotherapy
- Poor prognosis
  - cancer control rate <50% with salvage CTx and surgery

122 patients with late recurrence
- 41% pure seminoma at diagnosis
- 6% prior exposure to prior cisplatin-based chemotherapy
- Majority tx with either single agent carboplatin or radiation therapy

Results

- Long-term cancer control in 88%
- Late relapse of seminoma favorable if no prior exposure to cisplatin


Pathogenesis

- Transition into GCT is important for treatment options
- 10-15% of patients have NSGCT recurrence after definitive therapy
- 30% of deaths from pure seminoma have NSGCT elements in mets on autopsy

Adjuvant radiotherapy

Follow up (Post DLXRT)

- CXR and serum tumor markers
  - q3months X 2 years then
  - q6months for years 3 to 5
  - then annually

- CT Abdo/pelvis q6months x 2years then annually