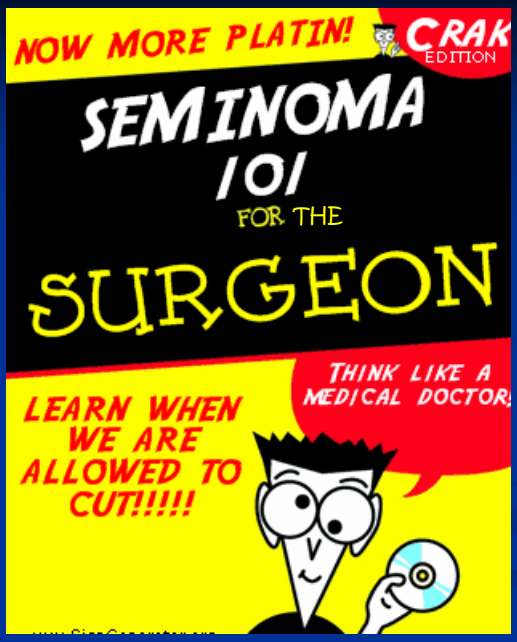
Seminoma 101

Jeff McCracken

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)

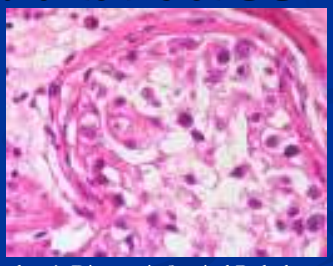
Clinical Stage	Description
I	Any T stage, N0, M0
IIA	Any T stage, Lymph node(s) < 2cm (N1), M0
IIB	Any T stage, Lymph node(s) 2-5 cm (N2), M0
IIC	Any T stage, Lymph node(s) >5 cm (N3), M0
IIIA	Any T stage, any N stage, non-regional nodal or pulmonary metastases (M1a)
IIIB	Any T stage, any N stage, non-visceral pulmonary mets (M1b)

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

Pathogenesis

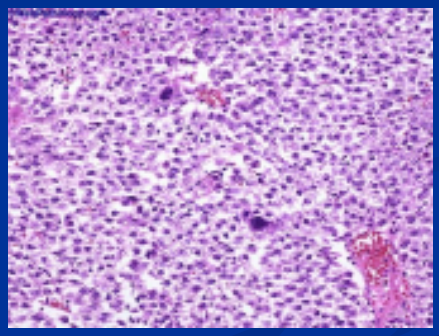
- Arises from intratubular germ cell neoplasia (ITGCN)
- Considered precursor for other forms of GCT
  - Embryonal carcinoma
  - Yolk sac tumor
  - Choriocarcinoma
  - Teratoma



- Ulbright TM: Testicular and paratesticular tumors. Sternberg's Diagnostic Surgical Pathology, 4th Edition. SE Mills, JK Greenson, HA Oberman et al. 2004: p. 2168

Pathogenesis

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

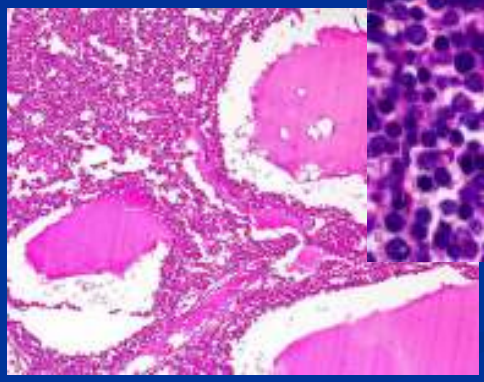


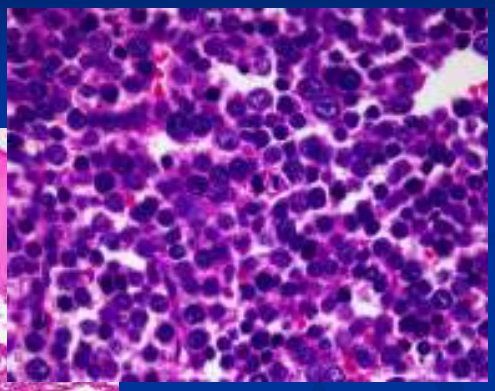
Pathology

- 3 histologic subtypes
  - Spermatocytic
  - Anaplastic
  - Classic

Spermatocytic

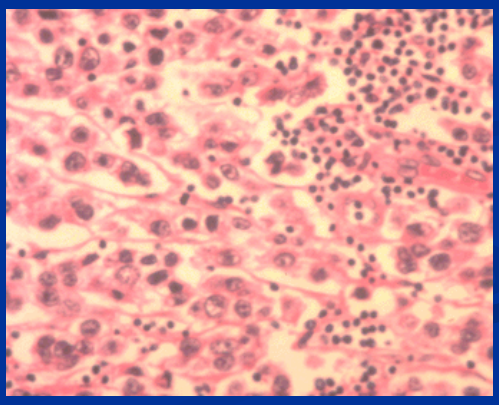
- Rare – 1-2% of cases





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

- **International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group.** J Clin Oncol. 1997 Feb;15(2):594-603

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

- **International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group.** J Clin Oncol. 1997 Feb;15(2):594-603

Career Pathways '06

Management Overview

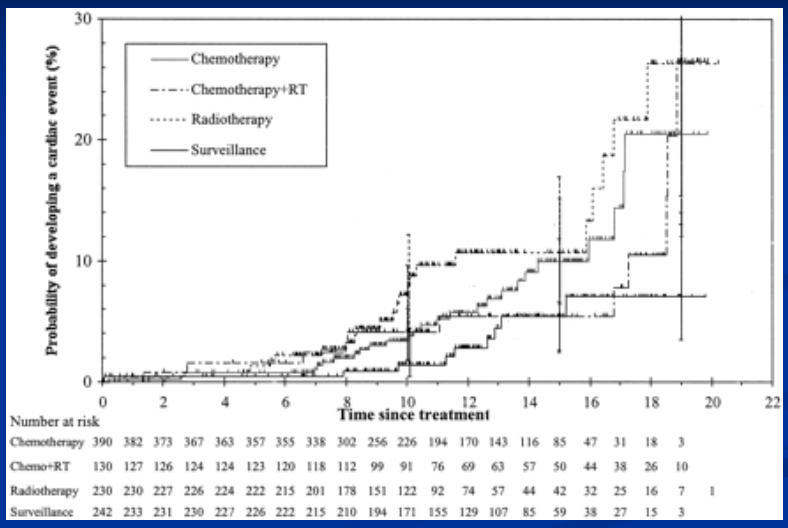
- Decrease morbidity
- >30 years of life expectancy

Side effects

Treatment

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

- 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
- Bajorin DF Et Al, Acute nonlymphocytic leukemia in germ cell tumor patients treated with etoposide-containing chemotherapy. J Natl Cancer Inst. 1993 Jan 6;85(1):60-2



Late Toxicity Following Curative Treatment of Testicular Cancer

CHRISTIAN KOLLMANNSBERGER, MD,[1] MARKUS KUZCYK, MD,[2] F. MAYER, MD,[1] JÖRG T. HARTMANN, MD,[1] LOTHAR KANZ, MD,[1] AND CARSTEN BOKEMEYER, MD[1]*
[1]Department of Medicine, Division of Hematology/Oncology/Immunology/Rheumatology, University of Tübingen, Tübingen, Germany
[2]Department of Urology, Hannover University Medical School, Hannover, Germany

- In 20-30% standard chemotherapy:
  - Long-term renal dysfunction
  - Sensory peripheral neuropathy
  - Hearing loss
  - Reynaud's phenomenon

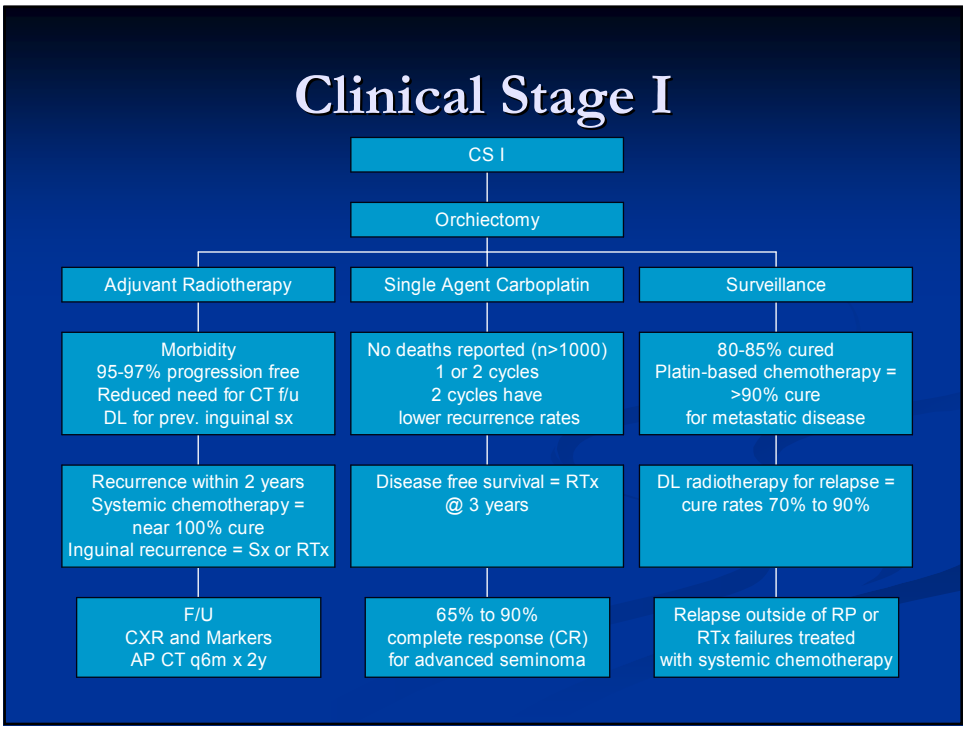
- Christian Kollmannsberger, Markus Kuzcyk, F. Mayer, Jörg T. Hartmann, Lothar Kanz, Carsten Bokemeyer. **Late toxicity following curative treatment of testicular cancer** Seminars in Surgical Oncology. Volume 17, Issue 4, 1999. Pages 275-281

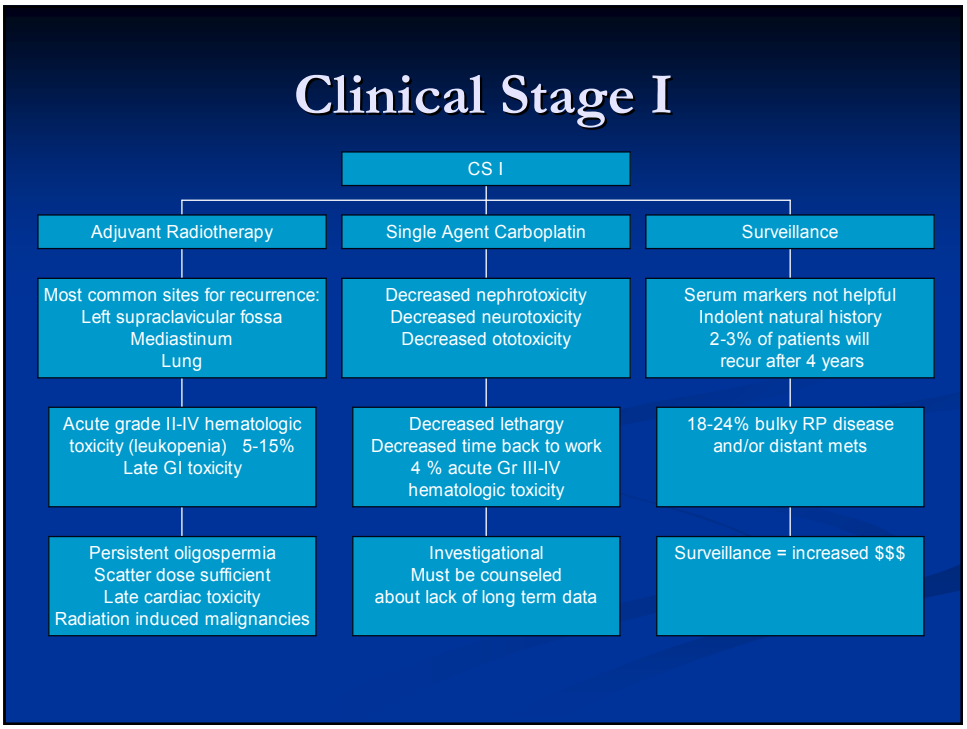
Infradiaphragmatic radiotherapy

- 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

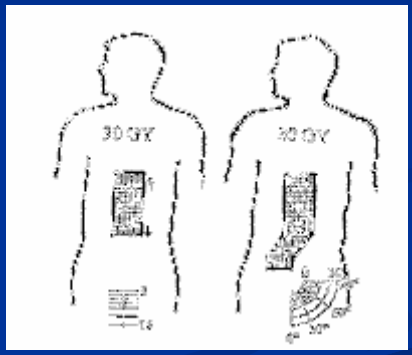
- 80 % of presenters
- 15-20% have occult RP
- = 80-85% cured by orchiectomy

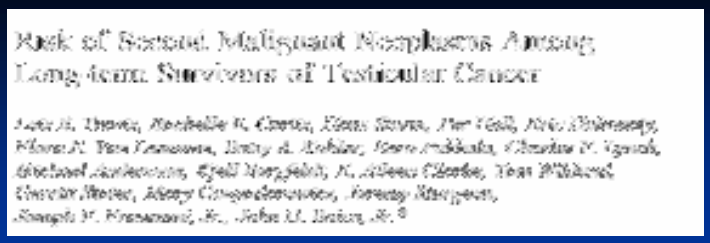

Clinical Stage I
CS I
Orchiectomy
Adjuvant Radiotherapy
Single Agent Carboplatin
Surveillance
Morbidity
95-97% progression free
Reduced need for CT f/u
DL for prev. inguinal sx
No deaths reported (n>1000)
1 or 2 cycles
2 cycles have
lower recurrence rates
80-85% cured
Platin-based chemotherapy =
>90% cure
for metastatic disease
Recurrence within 2 years
Systemic chemotherapy =
near 100% cure
Inguinal recurrence = Sx or RTx
Disease free survival = RTx
@ 3 years
DL radiotherapy for relapse =
cure rates 70% to 90%
F/U
CXR and Markers
AP CT q6m x 2y
65% to 90%
complete response (CR)
for advanced seminoma
Relapse outside of RP or
RTx failures treated
with systemic chemotherapy


Clinical Stage I
CS I
Adjuvant Radiotherapy
Single Agent Carboplatin
Surveillance
Most common sites for recurrence:
Left supraclavicular fossa
Mediastinum
Lung
Decreased nephrotoxicity
Decreased neurotoxicity
Decreased ototoxicity
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 lethargy
Decreased time back to work
4 % acute Gr III-IV
hematologic toxicity
18-24% bulky RP disease
and/or distant mets
Persistent oligospermia
Scatter dose sufficient
Late cardiac toxicity
Radiation induced malignancies
Investigational
Must be counseled
about lack of long term data
Surveillance = increased $$$

McLoughlin MG, Jackson SM, Olivotto I, Coy P.
Radiation therapy for seminoma of the testis: results in British Columbia.
Can Med Assoc J. 1980 Sep 20;123(6):507-12.

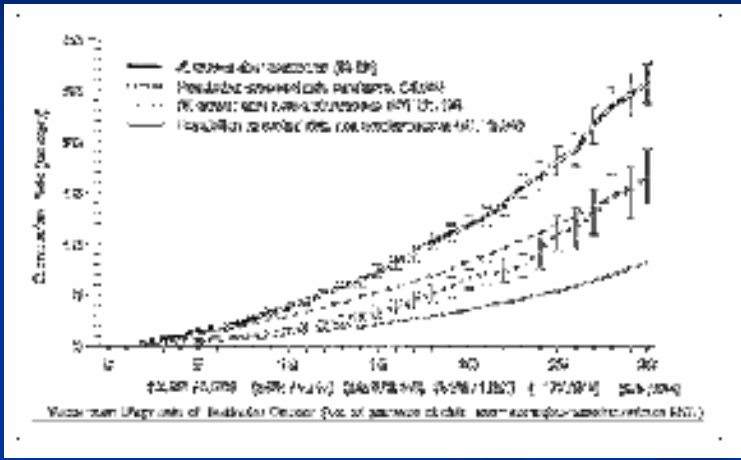
- 1942 -1978
- N=362
- 5-year survival rates were 87% overall
- 96% for those with a T1 or T2
- 62% for the 24 with palpable or distant metastases at the time of clinical presentation
- 28 patients in whom the disease recurred 15 were successfully treated
- The incidence of other cancers was not increased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

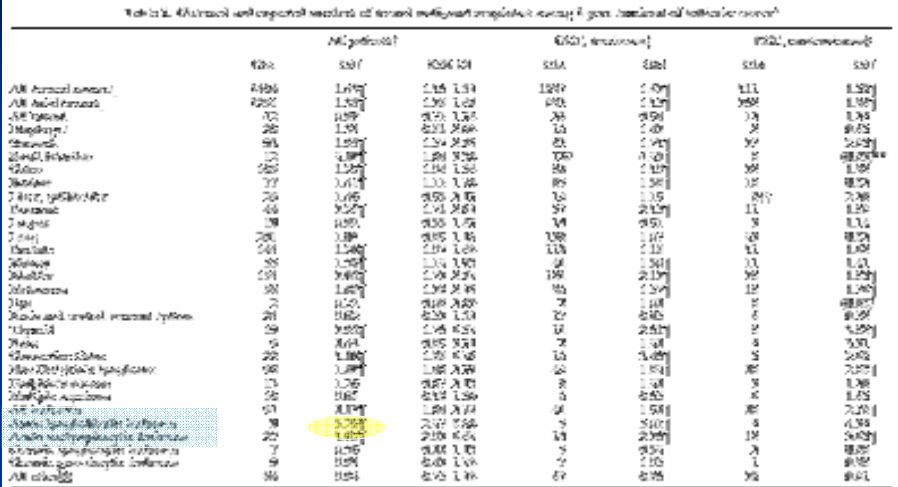



Risk of Second Malignant Neoplasms Among Long-term Survivors of Testicular Cancer

- 28,000 patients with testis cancer
- 15,000 seminoma
- 16 population based registries worldwide
- 1.43 X expected
- Chance of 2º malignancy was 18% at 25 years
  - Leukemia
  - Upper GI tumours
  - Bladder
  - Possibly pancreas
- J Natl Cancer Inst 1997; 89:1429.

Cumulative risk





Multiple myeloma	10	0.81	0.39–1.50
All leukemia	64	2.13¶	1.64–2.72
Acute lymphoblastic leukemia	9	5.20¶	2.37–9.86
Acute nonlymphocytic leukemia	27	3.07¶	2.02–4.47
Chronic lymphocytic leukemia	7	0.56	0.22–1.15
Chronic granulocytic leukemia	9	0.93	0.42–1.76

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 3years)

20 Gy vs. 30 Gy PARTx

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

Prognostic Factors for Relapse in Stage I Seminoma Managed by Surveillance: A Pooled Analysis

- 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

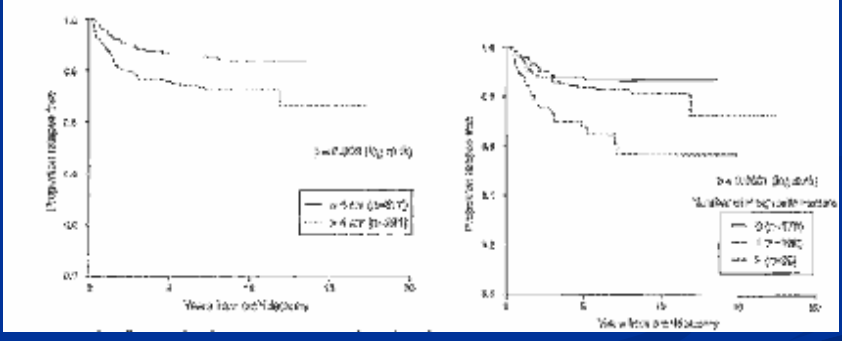
Prognostic Factors for Relapse in Stage I Seminoma Managed by Surveillance: A Pooled Analysis

- 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

Tumor Size	Rete Testis Involvement	
	No	Yes
≤ 4 cm	n = 176 87.8% ± 2.5%* HR = 1.0†	n = 75 85.6% ± 4.3%* HR = 1.7† 95% CI, 1.1-2.6‡
> 4 cm	n = 107 83.0% ± 3.7%* HR = 2.0† 95% CI, 1.3-3.2	n = 95 68.5% ± 4.9%* HR = 3.4† 95% CI, 2.0-6.1

Prognostic Factors for Relapse in Stage I Seminoma Managed by Surveillance: A Pooled Analysis



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

- Oliver RT et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial: Urologic Oncology: Seminars and Original Investigations, Volume 24, Issue 2, March-April 2006, Page 175

Single Agent Carboplatin

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

Single Agent Carboplatin *

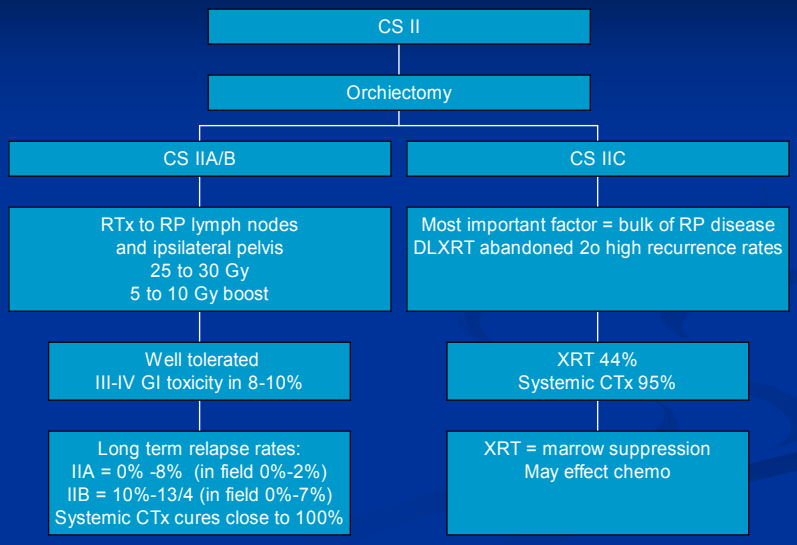
- CS I seminoma and not candidate for surveillance adjuvant RTx considered standard of care
- Must be counseled about lack of long term data

Career Pathways '06

Staging (AJCC/UICC)

Clinical Stage	Description
I	Any T stage, N0, M0
IIA	Any T stage, Lymph node < 2cm (N1), M0
IIB	Any T stage, Lymph node 2-5 cm (N2), M0
IIC	Any T stage, Lymph node >5 cm (N3), M0
IIIA	Any T stage, any N stage, non-regional nodal or pulmonary metastases (M1a)
IIIB	Ant T stage, any N stage, non-visceral pulmonary mets (M1b)

CLINICAL STAGE II SEMINOMA



CLINICAL STAGE IIC

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

- Chung PW, Gospodarowicz MK, Panzarella T, Jewett MA, Sturgeon JF, Tew-George B, Bayley AJ, Catton CN, Milosevic MF, Moore M, Warde PR. Stage II testicular seminoma: patterns of recurrence and outcome of treatment. Eur Urol. 2004 Jun;45(6):754-59; discussion 759-60.

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

- Bokemeyer C, Kollmannsberger C, Stenning S, Hartmann JT, Horwich A, Clemm C, Gerl A, Meisner C, Ruckerl CP, Schmoll HJ, Kanz L, Oliver T. Metastatic seminoma treated with either single agent carboplatin or cisplatin-based combination chemotherapy: a pooled analysis of two randomised trials. Br J Cancer. 2004 Aug 16;91(4):683-7.

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

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

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

Management of Post Chemo Masses

- 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

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

Imaging

Imaging

- Fluorodeoxyglucose-positron emission tomography (FDG-PET)
  - Prospective randomized trial
  - Viable seminoma in PCTx residual masses

2-^{18}fluoro-deoxy-D-glucose Positron Emission Tomography Is a Reliable Predictor for Viable Tumor in Postchemotherapy Seminoma: An Update of the Prospective Multicentric SEMPET Trial

Maria De Santis, Alexander Becherer, Carsten Bokemeyer, Franz Stoiber, Karin Oechsle, Franz Sellner, Alois Lang, Kurt Kletter, Bernhard M. Dohmen, Christian Dittrich, and Jörg Pont

- Positive scan = more predictive for viable tumour than using CT 3cm cutoff
- Specificity = 100%
- Sensitivity = 80%

FDG-PET

- 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.

J Urol. 1997 Mar;157(3):860-2.

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

Herr HW Et al, Surgery for a post-chemotherapy residual mass in seminoma. J Urol. 1997 Mar;157(3):860-2.

- 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

Late Recurrence

- 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

- Dieckmann, KP. Late relapse of testicular germ cell neoplasms: a descriptive analysis of 122 cases. J Urol. 2005 Mar;173(3):824-9.

Results

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

- Dieckmann, KP. Late relapse of testicular germ cell neoplasms: a descriptive analysis of 122 cases. J Urol. 2005 Mar;173(3):824-9.

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

- Bredael JJ et al Autopsy findings in 154 patients with germ cell tumors of the testis. Cancer. 1982 Aug 1;50(3):548-51.

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