Management of Testicular Cancer

Christian Kollmannsberger MD FRCPC

Clinical Professor
Div. of Medical Oncology
BC Cancer - Vancouver Cancer Centre
Dept. of Medicine, University of British Columbia

Associate Member
Dept. of Urologic Science, University of British Columbia
Vancouver, Canada
In compliance with accreditation, we require the following disclosures to the session audience:

<table>
<thead>
<tr>
<th>Disclosures</th>
<th>Details</th>
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<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>N/A</td>
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<td>Employee</td>
<td>N/A</td>
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<tr>
<td>Consultant</td>
<td>Pfizer, Novartis, Sanofi, Astellas, BMS, Ipsen, Eisai</td>
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<td>Major Stockholder</td>
<td>N/A</td>
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<td>Speakers Bureau</td>
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<td>Honoraria for presentations</td>
<td>Pfizer, Ipsen, Eisai, BMS</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>Pfizer, Novartis, Ipsen, Eisai, Sanofi, Astellas, BMS</td>
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None of these is related to testicular cancer, because in testis cancer the drugs are old and cheap.
Agenda

The “old”:
- TKIs Sunitinib and Pazopanib
- Active Surveillance

The “new”
Immunotherapy:
- Immunotherapy/Immunotherapy combination: Nivolumab / Ipilimumab
- Immunotherapy/TKI combination:
  - Avelumab/Axitinib
  - Pembrolizumab/Axitinib
- Immunotherapy/VEGF Inhibitor combination: Atezolizumab/Bevacizumab
Background

Then

1970

Metastatic ds.: < 10% cured
Regional ds.: 40-50% cured
Local ds.: adj. RT

Now

2018

Metastatic ds.: < 95% cured
Regional ds.: > 99% cured
Local ds.: no adj. RT
most pts just surgery

Barnett Rosenberg
Background

“A Milestone in Oncology”

THE SIXTY-SEVENTH
annual meeting of
the American Association
for Cancer Research

PROCEEDINGS
TWELFTH
annual meeting of
the American Society of
Clinical Oncology
MAY 4-8, 1976
Toronto, Ontario, Canada

Volume 17, March 1976

ASCO Abstracts, 1976

C-13combination chemotherapy of disseminated
testicular carcinoma with cis-platinum,
diammine dichloride (CPDD), vinblastine (VLB),
and bleomycin (Bleo). Lawrence H. Einhorn,
Becky E. Furnas, and Nancy Powell. Indiana Uni-
versity Medical Center, Indianapolis, IdN 46202
(Introduced by Robert J. Rohn)

Twenty-one patients with disseminated
testicular carcinoma were treated with CPDD
20 mg/m² IV for five consecutive days q 3 weeks
(total of 3 courses), VLB 0.2 mg/kg IV for 2
consecutive days q 3 weeks, and Bleo 30 units
IV weekly for 12 consecutive weeks. VLB was
given on day 2 of each course 6 hours prior to
Bleo. Maintenance therapy consisted of VLB
0.3 mg/kg IV q 4 weeks. BCG by scarification
was added at this point to all patients
achieving a complete remission (c.R.)

Seven patients had received prior che-
motherapy for disseminated disease and two had
received prior radiotherapy prophylactically
following retroperitoneal dissection. All
twenty-one patients had pulmonary metastases.
One patient died after just 5 days of therapy.
Significant toxicity consisted of nausea,
vomiting, alopecia, stomatitis, weight loss,
nephrotoxicity, and leukopenia with 3 episodes
of gram negative sepsis.

There were 15 complete (75%) and 5
partial remissions in the 20 evaluable patients.
Also, 2 of the 5 partial remissions are dis-
ease-free following surgical removal of resid-
ual disease. Thus far, 13 of 15 C.R.'s remain
alive and disease-free from 6 to 18 months
with a median of 9 months.

The basis of modern testis cancer management

Einhorn and Donohue Arch Int Med 1977
Background

1% of all malignant diseases in men

but:

- most common malignancy in men 15-35 years of age
- increasing incidence in the past 4 decades

Robert-Koch-Institute 2002

McGlynn Cancer 2003
The Changing Incidence of Testicular Cancer

- 1% of all malignant diseases in men
- most common malignancy in men aged 15-40

Increase in stage I disease

Increase in stage I seminoma
Risk Factors

Known risk factors:

- Previous testis cancer
  (Incidence 3-5% contralateral tumors)

- Testicular Dysgenesis Syndrome
  Cryptorchism
  Testicular atrophy
  Mumps orchitis

- Familial Risk (first-degree relatives)

Risk 2-13x elevated
Location and Type of Germ Cell Tumors

Gonadal (Testicular) Primary: 95 – 97%

Extragonadal Primary: 3-5%
- Cranial
- Mediastinal
- Retroperitoneal

Testicular Cancer Subtypes:

- Seminoma: 60%
- Nonseminoma: 40%
  - (“mixed germ cell tumor”)
- Embryonal
- Choriocarcinoma
- Teratoma
- Yolk Sac
- Seminoma
Histology of Germ Cell Tumors

- Chorioncarcinoma
- Seminoma
- Embryonal carcinoma
- Yolk sac tumor
Differences between Seminoma and Nonseminoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seminoma</th>
<th>Nonseminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Peak (years)</td>
<td>30-40</td>
<td>20-30</td>
</tr>
<tr>
<td>Tumor markers</td>
<td>Rare (if at all only HCG)</td>
<td>AFP/HCG in up to 70%</td>
</tr>
<tr>
<td>Growth biology</td>
<td>Slow</td>
<td>Aggressive</td>
</tr>
<tr>
<td>Organ metastases</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Outstanding</td>
<td>Excellent</td>
</tr>
<tr>
<td>Pathology</td>
<td>Pure</td>
<td>Mixed</td>
</tr>
<tr>
<td>Treatment</td>
<td>RT / Chemo sensitive</td>
<td>Chemo sensitive</td>
</tr>
<tr>
<td>Residual lesions after chemotherapy</td>
<td>Watch</td>
<td>Resect</td>
</tr>
</tbody>
</table>
Tumor Markers in Germ Cell Cancer

- **AFP** = Alpha – Fetoprotein
  - Yolk sac and teratocarcinoma
- **β-HCG** = human Choriogonadotropin
  - Chorioncarcinoma and embryonal carcinoma
- **[LDH]** = Lactatdehydrogenase

- Elevated in 60-80% of nonseminomas
- HCG occasionally elevated in seminoma (low level elevation)
- LDH can be elevated in both seminomas and nonseminomas
Tumor Markers in Germ Cell Cancer

- Tumor marker level correlates with tumor size and rate of progression

- Marker for treatment response (decrease and normalize)

- Very high levels (AFP > 1,000, β-HCG > 50,000) and high LDH-level (> 10 x normal) indicate a poor prognosis
# Symptoms at Initial Diagnosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>74%</td>
<td>Other neoplasms</td>
</tr>
<tr>
<td>Pain</td>
<td>30%</td>
<td>Inflammation, torsion</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>10%</td>
<td>Drugs, liver disease</td>
</tr>
<tr>
<td>Infertility</td>
<td>5%</td>
<td>Primary infertility</td>
</tr>
<tr>
<td>Organ manifestations</td>
<td>&lt;5%</td>
<td>Stroke, low back pain, SOB</td>
</tr>
</tbody>
</table>

Any testicular mass is considered malignant until proven otherwise
Staging Procedures

**Radiology:**
- Testicular US
- CT Abdomen with contrast
- Chest X-ray or CT chest
- Head CT and bone scan only if symptoms or poor prognosis features

**Laboratory**
- CBC, creatinine, LDH, AFP, HCG, electrolytes, magnesium, albumin
- TSH, T3/T4 if HCG high
- Testosterone, LH, FSH, semen analysis if fertility is an issue
- Audiogram, if pre-existing hearing issues
- Pulmonary function test, if pre-existing lung issues and bleomycin planned or if 4 cycles of BEP given
Diagnostic Ultrasound and Orchiectomy

There is NO biopsy
Staging Procedures

**Radiology:**
- Testicular US
- CT Abdomen with contrast
- Chest X-ray or CT chest
- Head CT and bone scan only if symptoms or poor prognosis features

**Laboratory**
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- TSH, T3/4, if HCG high
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Stage I Testis Cancer

- Most common presentation of testicular cancer:
  - 80% of seminomas
  - 60% of nonseminomas

- What constitutes “stage I”:
  - Normalization of tumor markers after orchiectomy
  - Negative CT abdomen/pelvis
  - Negative chest X-ray/CT chest

Imaging should be current – within 4 weeks prior or after orchiectomy
Overriding Principles in CSI GCT

- Several management options exist: adjuvant chemotherapy, active surveillance and adjuvant radiation or RPLND for CSI-S and CSI-NS, respectively.
- CSI is very favorable stage, cure rate 99 – 100% irrespective of management modality employed.
- Highly effective chemotherapy provides a safety net.
- Death from stage I disease is extremely rare.
- Short AND long-term QoL is the driver of CSI treatment decisions.

We should minimize toxicity in particular in patients who are already cured!
Risk Factors for Relapse in CSI NS GCT

• Lymphovascular invasion
• Embryonal predominant disease
• Absence of yolk sac elements
• Presence of undifferentiated tumor
• MIB-1 score

• Lymphovascular invasion
• LVI neg: 14-22% relapses
• LVI pos: 50% relapses

MRC Prospective Surveillance Study 1984 - 1987
Relapse-free Rate by vascular invasion

No VI  (n=199)
VI     (n=192)

VERY modest discriminative power
(50% false positive)

Read JCO 1992
Risk Factors for Relapse in CSI S GCT

Validation attempt: 685 pts with CSI seminoma managed with active surveillance

Only tumor size validated !!!!

Poor discrimination of “high risk”, 74% of all pts with an 8 cm primary are cured by orchiectomy alone and need **NO** further treatment

Chung P et al Cancer Medicine 2015
Patterns of Relapse

Median time to relapse in Nonseminoma is short!
Most relapses occur in the first 2-3 years of F/U

Kollmannsberger, Tandstad et al JCO 2014
Treatment options in clinical stage I GCT

Clinical stage I disease

Normalization of tumor markers after orchiectomy
Negative CT abdomen/pelvis and chest X-ray/CT chest

CSI Nonseminoma
- Primary retroperitoneal lymph node dissection (RPLND)
- Adjuvant chemotherapy with 1 cycle of BEP
- Active surveillance

CSI seminoma
- Adjuvant Radiation of paraaortic nodes
- Adjuvant chemotherapy with 1 cycle of carboplatin
- Active surveillance

Cure rate 99 – 100% irrespective of treatment modality employed
Management Options in CSI Disease

The ideal approach:

- Maintains the excellent cure rates
- is easily delivered
- avoids any therapy for those who are cured by orchiectomy
- minimizes number of patients who require additional (beyond orchiectomy) and in particular dual therapy to achieve cure
**Surveillance schedule in Stage I GCT**

<table>
<thead>
<tr>
<th>Seminoma / low risk nonseminoma</th>
<th>High risk Nonseminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td><strong>Time</strong></td>
</tr>
<tr>
<td>Year 1 @ 6, 12, months</td>
<td>Year 1 @ 3, 6,12, months</td>
</tr>
<tr>
<td>Every 2-3 months @ 6,12 months</td>
<td>Every 2 months @ 3,6,12 months</td>
</tr>
<tr>
<td>Year 2 @ 18, 24 months</td>
<td>Year 2 @ 18, 24 months</td>
</tr>
<tr>
<td>Every 3 months @ 18,24 months</td>
<td>Every 3 months @ 18,24 months</td>
</tr>
<tr>
<td>Year 3 @ 30, 36 months</td>
<td>Year 3 @ 36 months</td>
</tr>
<tr>
<td>Every 6 months @ 30, 36 months</td>
<td>Every 6 months @ 36 months</td>
</tr>
<tr>
<td>Year 4 -</td>
<td>Year 4 -</td>
</tr>
<tr>
<td>Every 6 months -</td>
<td>Every 6 months -</td>
</tr>
<tr>
<td>Year 5 -</td>
<td>Year 5 -</td>
</tr>
<tr>
<td>Every 6 months -</td>
<td>Every 6 months -</td>
</tr>
</tbody>
</table>

“Late” relapses on active surveillance have the same prognosis as de-novo metastatic tumors

Kollmannsberger, Tandstad et al JCO 2014
Compliance required for any treatment strategy since no adjuvant modality completely eliminates recurrences

No evidence that lack of compliance reduces survival in patients

**Compliance is no issue in the vast majority of patients**

**Overall survival approaches 100%**

- Almost all patients with recurrence / advanced disease are cured (97-100%)
- Large population-based series of surveillance show death rates in CSI testis cancer are vanishingly low
Treatment of metastatic GCT
If in doubt
CALL A FRIEND !!!!
Evolution of chemotherapy

*Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer*

- 47 evaluable patients
- 74% CR rate, additional 5 pts rendered disease-free with post-chemotherapy surgery (85% NED)
- 30/47 (60%) long term survivors

• Einhorn and Donohue Arch Int Med 1977
Metastatic Testicular Cancer Staging and Classification

Stage I

Stage 1A
Is in the testicle/epididymis / may have spread to the inner layer of the membrane that surrounds the testicle (tunica albuginea). Tumour markers normal.

Stage 1B
Is in the testicle/epididymis and has spread to the testis blood vessels or lymph vessels grown into the outer layer of the membrane that surrounds the testicle (tunica vaginalis). grown into the spermatic cord or the scrotum and may have spread to the blood vessels or lymph vessels in the testicle. All tumour marker levels are normal.
**Stage II**

**Stage 2A**
The cancer has spread to 1 or more lymph nodes in the groin, and they are **not larger than 2 cm**. Tumour marker levels may be slightly higher than normal.

**Stage 2B**
The cancer has spread to 1 or more lymph nodes in the groin, and they are **between 2 and 5 cm**. Tumour marker levels may be slightly higher than normal.

**Stage 2C**
The cancer has spread to 1 or more lymph nodes in the groin, and they are **larger than 5 cm**. Tumour marker levels may be slightly higher than normal.
# Prognostic factors in metastatic testicular cancer – IGCCCG classification

## Good Prognosis

<table>
<thead>
<tr>
<th>NON-SEMINOMA</th>
<th>SEMINOMA</th>
</tr>
</thead>
</table>
| Testis / Retroperitoneal primary **and**
No non-pulmonary visceral metas. **and**
good markers |
| Any primary site **and**
No non-pulmonary visceral metas. **and**
Normal markers |
| 56% of non-seminomas |
| 90% of seminomas |

## Intermediate Prognosis

<table>
<thead>
<tr>
<th>NON-SEMINOMA</th>
<th>SEMINOMA</th>
</tr>
</thead>
</table>
| Testis / Retroperitoneal primary **and**
No non-pulmonary visceral metas. **and**
intermediate markers |
| Any primary site **and**
Non-pulmonary visceral metas. **and**
Normal markers |
| 28% of non-seminomas |
| 10% of seminomas |

## Poor Prognosis

<table>
<thead>
<tr>
<th>NON-SEMINOMA</th>
<th>SEMINOMA</th>
</tr>
</thead>
</table>
| Mediastinal primary site **or**
Non-pulmonary visceral metastases **or**
poor markers |
| No patient classified as poor prognosis |
| 16% of non-seminomas |

**Graph:**
- **IGCCCG**
- P<0.0005
- Follow-up (years)
- Proportion surviving (%)
Standard Chemotherapy Regimen in Testis Cancer

“BEP”

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>d 1-5</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m²</td>
<td>d 1-5</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>30 IU</td>
<td>d 1, 8, 15 q 3 weeks</td>
</tr>
</tbody>
</table>

Postpone only in case of granulocytopenia and fever or thrombocytopenia < 100 000/µl

Primary prophylactic application of G-CSF recommended in intermediate and poor risk
Secondary prophylactic application of G-CSF recommended in good risk
Influence of cisplatin-based combination regimens on survival of patients with malignant germ cell cancer

Overall Treatment Strategy in Non-Seminomatous Testis Cancer

Orchiectomy

3 - 4 cycles of Cisplatin - based Chemotherapy

- no residual tumor
  - M - observation

- Residual tumor
  - M -
  - Secondary resection

- 50 - 60 % necrosis
- 10 - 20 % vital carcinoma
- 30 % Teratoma

* in 30% divergent histologies if multiple resections

Hartmann/Bokemeyer 1997
Overall Treatment Strategy in Seminomatous Testis Cancer

1. **Orchiectomy**
2. 3 - 4 cycles of Cisplatin-based Chemotherapy
   - **No residual tumor** M - → observation
   - **Residual tumor** M - → observation

**Baseline**

β-HCG
## Treatment of Advanced Disease based on the IGCCCG Classification Risk Group

<table>
<thead>
<tr>
<th>Patient group</th>
<th>5 Y-OS</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>“good prognosis”</td>
<td>95-98%</td>
<td>3 x PEB</td>
</tr>
<tr>
<td>Seminoma or nonseminoma</td>
<td></td>
<td>[*or 4 x EP]</td>
</tr>
<tr>
<td>“intermediate prognosis”</td>
<td>85-90%</td>
<td>4 x PEB</td>
</tr>
<tr>
<td>Seminoma and nonseminoma</td>
<td></td>
<td>[*or 4 x VIP]</td>
</tr>
<tr>
<td>“poor prognosis”</td>
<td>55-65%</td>
<td>4 x PEB</td>
</tr>
<tr>
<td>nonseminoma</td>
<td></td>
<td>[*or 4 x VIP]</td>
</tr>
</tbody>
</table>

*if contraindications for bleomycin

References:
- Wood et al. CUAJ 2010
- NCCN 2010
Treatment Management in Testis Cancer

Tumor markers prior to each cycle

Two cycles, then restaging (imaging / tumor markers)
→ Continue treatment if CR / PR / SD and M↓

If progression on imaging (growing teratoma) and M↓
→ Resection after Ctx, immediately only in extreme emergency

if M↑ after 2 cycles change to (HD-)Salvage Ctx

Marker plateau [ß-HCG < 50] after end of Ctx
→ wait and see whether normalization
→ Salvage Ctx only if unequivocal marker progression
# Acute Toxicity of Cisplatin-based Chemotherapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Toxicity</th>
<th>Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Nausea / Vomiting</td>
<td><strong>Hydration</strong></td>
</tr>
<tr>
<td></td>
<td>Thromboembolic events</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal toxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ototoxicity</td>
<td>Triple antiemesis</td>
</tr>
<tr>
<td></td>
<td>Tinnitus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infertility</td>
<td>LMWH (particularly if large retroperitoneal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphadenopathy (&lt; 3 cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>NO</strong> port, no permanent venous access device</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sperm-banking</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Mucositis</td>
<td>Mouthwash</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infertility</td>
<td>G-CSF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sperm-banking</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Lung toxicity</td>
<td><strong>Careful monitoring:</strong></td>
</tr>
<tr>
<td></td>
<td>Vascular Damage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PFTS if 4 cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOB on exertion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fine rales, crackles, decreased breath sounds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or pleural friction rubs</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Stop bleomycin</strong> if suspected toxicity</td>
</tr>
</tbody>
</table>
Risk of bleomycin induced pulmonary injury

N = 835 Pts 1982 – 1999 Royal Marsden Hospital

- 6.8% pulmonary toxicity (Symptoms – X-ray)
- 8 (1%) deaths
- median interval to toxicity 4.2 months [1-8 months]

Risk factors:

- Age > 40 years (A)
- advanced disease Stadium (B)
- poor renal function (C)
- > 300 mg of bleomycin (D)

Sullivan et al Ann Oncol 2003
Management of residual lesions in Seminoma

• Present in 30-80% of patients
  - Peckham, Br J Cancer 1985
  - Fossà, J Clin Oncol 1987
  - Motzer, J Clin Oncol 1987
  - Puc, J Clin Oncol 1996
  - Herr, J Urol 1997
  - Horwich, Ann Oncol 1997
  - Horwich, Br J Cancer 2000

• Lesions > 3cm: viable tumor present in 11-37%
• Lesions < 3 cm: viable tumor present in < 10%
  - Herr, J Urol 1997
  - Ravi, BJU Int 1999
  - Ganjoo, J Clin Oncol 1999
  - De Santis, J Clin Oncol 2004
  - Heidenreich, Eur Urol 2008

• Resection technically demanding, often incomplete, increased morbidity, if done at all requires an expert centre
  - Friedman, J Clin Oncol 1985
  - Fossà, J Clin Oncol 1987
  - Schultz, J Clin Oncol 1989
  - Ravi, BJU Int 1999
  - Flechon, J Urol 2002
  - Mosharafa, J Urol 2003
  - Herr, J Urol 1997
  - Horwich, Ann Oncol 1997
  - Horwich, Br J Cancer 2000

• No risk of teratoma
CNS-Metastases in testis cancer

- Prior to the introduction of cisplatin-based chemotherapy brain metastases were found in 20 – 40 % on autopsy

- Incidence of CNS-metastases is estimated to be 2-5 %, is however 10 % in patients with advanced metastatic disease (poor risk)

- Patients with brain metastases at diagnosis have a 30-40% survival probability

- Despite unfavorable prognosis, selected patients achieve long-term survival even with relapse in the brain

- The optimal management of brain metastases is not defined, individual decision in each patient
False Positive Stage IIA Disease?

- Not all small volume CT changes represent disease
- Memorial Sloan Kettering series in CSIIA non-seminoma (negative markers)
  - 11/23 patients CSIIA patients were PSI at the time of primary RPLND
    
    Stephenson et al JCO 2007

- Differentiation between inflammatory LN and metastatic LN difficult
- Benefit from PET for detection of occult metastases in stage I seminoma modest
  
  Loriot et al GU ASCO 2010

Particularly in seminoma where the risk of relapse is lower, small volume radiographic changes (< 2 cm) should be confirmed by follow-up CT in 2-4 months

Primary RPLND as alternative in carefully selected patients
Significance of the Treating Center
Compliance with Guidelines – French Experience

N=82 pts referred to high volume centre for salvage therapy

Treated in first-line in compliance with the guidelines: 50% (!)

- Type of chemotherapy
- Dose – number of cycles
- Schedule – dose delays
- Indication and schedule for post-chemotherapy surgery for residual lesions

Only independent predictive factor for compliance with guidelines:

**Treatment center**

Thibault et al Eur J Cancer 2014
Significance of the Treating Center
Results from the German second-opinion network for testicular cancer

“Virtual tumor board” by a group of experts providing second opinions

N= 1284 second opinions

Discrepancies between proposed first-line treatment plan and second opinion: 40% (!)

- Over-treatment 28%
- Under-treatment 16%
- Approx. every 6th second opinion recommended a relevant treatment change
- In 31% of cases the second opinion recommendation was not implemented

Zengerling et al Onc Rep 2014
Significance of the Treating Center
Results from the German second-opinion network for testicular cancer

Over-treatment:
- increased acute morbidity
- Increased long-term toxicity
- Impact on overall cure rate
- Increased cost

Under-treatment:
- Decreased cure rates
- Increased need for salvage therapy
- Increased total burden of therapy
“If there was a new drug that improved overall survival ....by 15-20% , everyone would prescribe it.

Pursuing this goal [of expert care for each patient] ought to be as much a priority for our field as developing the next new agent”

Modified according to Halm et al JCO 2017
Influence of the institution’s experience

Institutions with <5, 5-9, 10-19, >19 patients/year

(P=0.01)

Overall survival

Collette JNCI 1999
Treatment of relapsed disease

Send patient to an expert center
Cure rates between 25-50% with standard dose chemotherapy or high dose chemotherapy + autologous stem cell support
Treatment of refractory disease

Send patient to an expert center
Prognosis of Refractory Disease

Definition of “refractory”:

“Cisplatin-refractory”:
   Relapse within 4-6 weeks after cisplatin based chemotherapy

“Absolutely cisplatin refractory”:
   Progression while being ON cisplatin based chemotherapy

“Refractory”:
   relapse after multiple lines of cisplatin based chemotherapy or
   after salvage high dose chemotherapy

Cure rates between 0-25% with
Chemotherapy + surgery
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Late Toxicity

- Young patients
- Excellent prognosis
- Normal life expectancy after curative treatment

risk - benefit analysis for current and future treatment strategies necessary
Late Toxicity

Affected organs and extent of toxicity depending on:

- Cytostatic agent used
- Dose
- Application schedule
- Pre-existing diseases or injuries
# Late Toxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Nephrotoxicity, Ototoxicity, Neuropathy, Gonadal toxicity, Induction of leukemias, Cardiovascular Toxicity</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Induction of leukemias, Gonadal toxicity</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Pulmonary toxicity, Vascular damage, Gonadal toxicity</td>
</tr>
<tr>
<td>(Ifosfamide)</td>
<td>Induction of secondary neoplasias, Gonadal toxicity</td>
</tr>
<tr>
<td>BEP / VIP</td>
<td>Secondary solid malignancies</td>
</tr>
</tbody>
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Agent and Dose dependent
Late Toxicity

There is no official survivorship program for testis cancer survivors:

My “personal” program for patients who received chemotherapy:

As of year 3:

**Investigations:**
- Testosterone 1-2x / year
- Fasting lipid profile 1-2x / year
- Fasting glucose 1-2x / year
- Blood pressure
- CBC, Creatinine 1-2x / year

**Life style changes:**
- No smoking
- Regular exercise
- (halfway) healthy diet
Bilateral Testicular Cancer

Risk to develop a contralateral testicular cancer in testis cancer patients:

2-4%
Conclusions

- Raising incidence
- Highly curable malignancy
- Minimizing toxicity is important
- Many patients are still treated sub-optimal
- Treatment is aggressive but short
- Consideration of long-term toxicity
- Survivorship is an important issue