Stadium I testis carcinoom …
en dan…
Gevorderd stadium….
En dan…

Martijn Kerst
Dutch registry

- 24% of all tumors in male 15-44 yr

- Rising incidence
  - 1989  336
  - 2011  725

- 55% seminoma
- 45 % non-seminoma

- 2/3 presenting in clinical stage I

iKNL 2013
Diagnosis and Clinical Staging

- **Histology**: WHO classification
- **Lab**: including AFP, ßHCG and LDH
- **CT scanning**: Abdomen & Chest
- **Ultrasound**: contra-lateral testis
- **MRI**: CNS *on indication*
- **Skeletal scan**: *on indication*
- **PET scan**: *not indicated*
Seminoma testis

☼ Prognostic factors
☼ Therapy
Active Surveillance / Radio-Th- / Chemo-Th

Non-Seminoma testis

☼ Prognostic factors
☼ Therapy
Active Surveillance / RPLND / Chemo-Th
Seminoma

Prognostic factors/Surveillance

• Profylactic radiotherapy
  Standard for several decades

• Surveillance
  Pooled analysis (638 patients 4 centers Europe&Canada) :
  2 factors independently associated with relapse
  - Tumor size > 4 cm (Rel.Risk 2.0)
  - Tumor-invasion in rete testis (RR 1.7)

  - Median FU 7 years:
    • 0 factors; 5 year Rel.Rate 12%
    • 1 factor 16%
    • 2 factors 31%

• Additional factors:
  - Age < 30 and elevated HCG….

Warde. JCO 2002; Aparicio. JCO 2005
Seminoma
Profylactic radiotherapy

• Two multi-center phase III trials:
  – Reduced field: "dog leg" → Para-Aortal
  – Reduced dose: 30 gy → 20 Gy

• Positive
  – Low relapse rate (overall Relapse-Rate <5%)
  – Salvage safe & effective (cure rate 98-99%)
  – Risk of chemotherapy minimized

• Negative
  – 80% unnecessary treated
  – Early and late toxicity

Fossa JCO 1999; Jones JCO 2005
Randomized trial of carboplatin versus radiotherapy for stage I seminoma:

Mature results on relapse and contra-lateral testis cancer rates

1° endpoint. Non-inferiority (to exclude absolute difference in 2 yr RR of more than 3%)

MRC TE19/EORTC 30982

Oliver. Lancet 2005; JCO 2011
Flowchart

1996-2001
Carboplatin AUC 7

Patients randomly assigned
(N = 1,477)

Allocated to carboplatin (n = 573)
- Mean (SD) age, years (n = 38.2; 9.0)
- Raised HCG pre-orchiectomy (n = 88; 15%)
- Previous ipsilateral operation (n = 56; 10%)
- Median (IQR) days from orchiectomy to treatment (n = 45; 33-56%)

Allocated to radiotherapy (n = 904)
- Mean (SD) age, years (n = 38.5; 9.8)
- Raised HCG pre-orchiectomy (n = 121; 13%)
- Previous ipsilateral operation (n = 86; 10%)
- Median (IQR) days from orchiectomy to treatment (n = 57; 46-70%)

Randomly assigned with respect to radiotherapy dose?

YES (n = 583)
- Allocated 20 Gy (n = 289)
- Allocated 30 Gy (n = 294)

NO (n = 321)
- Received center's standard RT schedule

Carboplatin received (n = 561)
- Not received (n = 12)

Radiotherapy received (n = 887)
- Not received (n = 17)

Analyzed (n = 573)
- Excluded from analysis
  - ITT analysis (n = 0)
  - PPA (n = 12)

Analyzed (n = 904)
- Excluded from analysis
  - ITT analysis (n = 0)
  - PPA (n = 17)

Oliver R T D et al. JCO 2011;29:957-962
Relapse-free survival by allocated treatment. Carbo non-inferior to RT

5 year RFS:
94.7% Carbo
96.0% RT
HR 1.25
(90% ci 0.83-1.89)

Oliver R T D et al. JCO 2011;29:957-962
**Contra-lateral GCT free survival**

- **RT** 98.8%
- **C** 99.8%
- **HR** 0.22

(95% ci 0.05-0.95)

**Contra-lateral GCT rates by allocated treatment**

**Carboplatin: A significant risk-reduction**

Oliver R T D et al. JCO 2011;29:957-962
Seminoma Adjuvant chemotherapy
Conclusions MRC/EORTC trial

• In the adjuvant setting for stage I seminoma testis is carboplatin AUC 7 non-inferior to adjuvant radiotherapy

• Carboplatin results in a significant reduction in the medium term of risk of second GCT

Carboplatin should be dosed at AUC 7 according to GFR measuring EDTA or comparable isotope technique (or a urinary 24 hour creatinine clearance)

Oliver JCO 2011
Risk-adapted treatment in seminoma stage I

The Third Spanish Germ Cell Cancer Group Study
Aparicio et al JCO 2005; JCO 2011

2004-2008
N=227
No or One Risk Factor: Active Surveillance
Two Risk Factors: 2 cycles of carboplatin

Median Follow-up 34 months
Risk-adapted treatment in stage I seminoma testis

Flowchart

Patients registered (N = 241)

Excluded from analysis (protocol deviations) (n = 14; 5.8%)

Study population (n = 227)

0-1 risk factors (n = 11)
- Synchronous NSGCT
- Received carboplatin
- No risk factors (n = 1)
- Tumor size > 4 cm (n = 7)
- Rete testis invasion (n = 2)

Follow-up ≤ 12 months (n = 3)
- No relapse, ongoing follow-up > 12 months (n = 8)

Two risk factors (received surveillance) (n = 3)

No relapse, ongoing follow-up > 12 months (n = 3)

0-1 risk factors (received surveillance) (n = 153)
- Follow-up ≤ 12 months (n = 16)
- Lost to follow-up at 15-45 months (n = 7)
- Relapse at 3-31 months (n = 15)
- No relapse, ongoing follow-up > 12 months (n = 115)

2 risk factors (received carboplatin) (n = 74)
- Follow-up ≤ 12 months (n = 7)
- Lost to follow-up at 18-26 months (n = 4)
- Relapse at 25 months (n = 1)
- No relapse, ongoing follow-up > 12 months (n = 62)

Aparicio J et al. JCO 2011;29:4677-4681
Disease-free survival for 153 patients undergoing active surveillance according to risk factor.

- No risk factor-84: Relapse Rate 4.8%
- Tumor>4 cm-44: Relapse Rate 13.6%
- Rete testis inv-25: Relapse Rate 20%

Aparicio J et al. JCO 2011;29:4677-4681
Disease-free survival for the entire study population:
Adjuvant carboplatin versus Surveillance

Median FU 34m
Active Surveillance (n=153) RR 9.9%
Adj Carboplatin (n=74) RR 1.4%

Aparicio J et al. JCO 2011;29:4677-4681
Seminoma  Adjuvant chemotherapy
Conclusions Spanish trial

With the limitations of the short follow-up and the small numbers, the study shows that a risk-adaptive approach is effective for stage I seminoma

- The presence of a risk factor is related with higher recurrence rate ($p=0.048$)
- 3 yr DFS  88% (surveillance) vs 98% (carboplatin)
- 3 yr OS 100% (effective salvage)
Clinical practice guideline

• Surveillance is considered the preferred strategy

• The risk-adapted approach is controversial
  – Risk-factors not validated in an independent set of patients
  – One or Two cycles carboplatin
  – Short follow-up
  – Some concern about late toxicity
    • N=199; median FU 9 years; no mortality/death (Powles JCO 2008)

• Adjuvant carboplatin is as effective as adjuvant RT and less toxic (limited follow-up)

Oldenburg Ann Oncol 2013
Non-Seminoma stage I
Non-Seminoma
Prognostic factors

- **Lympho-vascular invasion (LVI)** is the main independent prognostic factor for relapse
  
  *(ECC inconsistent in multifactorial analysis)*

  - 3 year Relapse-Rate
    - LVI Neg / Low-Risk 15-20%
    - LVI Pos / High-Risk 40-50%

- Immunohistochemical parameters not usefull

Vergouwe JCO 2003
Non-Seminoma
Active surveillance

• Several studies (> 2000 patients).
  – 95% of relapses within 2 years
  – 99% of relapses within 3-4 years
  – Virtually all relapses are low-volume and good-prognosis disease
  – Overall survival 98-99%

• Advantage
  – Best means to avoid overtreatment
  – Excellent survival

• Disadvantage
  – Access to dedicated hospital (and staff)
  – Patients compliance
  – May require post-chemotherapy surgery

De Wit & Fizazi JCO 2006
Non-Seminoma

Retroperitoneal Lymph node dissection

• RPLND is technically demanding (complications…)

• Published series on RPLND reveal..
  – RPLND is no definitive treatment
  – 30-50% of deemed clinical stage I harbor occult metastatic disease

  – In case of pathologic stage 1:
    • 10% occult metastatic disease…
    • Follow-up ! BEP 3x at relapse

  – In case of pathologic stage 2:
    • Follow-up
    • Adjuvant 2xBEP in case of
      – a) six or more T+ Lnn
      – b) node size > 2 cm
      – c) extra-nodal spread

De Wit & Fizazi JCO 2006
Non-Seminoma
Retroperitoneal Lymph node dissection

• Advantage
  – Pathological staging
  – Reduces the need for chemotherapy
  – Eradicates mature teratoma

• Disadvantage
  – Overtreatment
  – Surgical complications
  – Not a definite treatment

De Wit & Fizazi JCO 2006
Non-Seminoma

Adjuvant chemotherapy

• Several studies* with 1-2 cycles of adjuvant BEP (like) chemotherapy result in relapse-rates around 2-5%

• ASCO 2013: Tandstad et al. SWENOTECA group
  – 1998-2010 Clinical stage I; median FU 8 year.
  – One course of BEP
    – 247 LVI Pos  3,4% relapse
    – 239 LVI Neg  1,3% relapse
  – 5 and 10 year OS: 98,9 and 96,8%
  – 5 and 10 year disease specific survival: 100 and 99,6%

Non-Seminoma

Adjuvant chemotherapy

• Advantage
  – Reduction of the risk of recurrence to <5%

• Disadvantage
  – Overtreatment….
  – Not a definitive treatment…
  – No very long-term follow-up data
  – Concern about Acute and Late toxicity….

De Wit & Fizazi JCO 2006
Clinical practice guideline

• **Low-Risk**
  – Surveillance is the standard
  – If not feasible: adjuvant chemotherapy (1-2 cycles)
  – If not suitable for Surveillance and Chemotherapy: RPLND

• **High Risk: Two standards**
  – 1. Active surveillance; BEP at relapse
  – 2. Adjuvant chemotherapy (1-2 cycles BEP)

  – RPLND in case of contra-indications to standards
Sentinel node biopsy in germ cell tumours

Prof. dr Simon Horenblas
Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital
Amsterdam
The Netherlands
Adagium

Law no XIII:

*The delivery of medical care is to do as much nothing as possible*
Gevorderd stadium...
Klinische stadiëring

IIa: regionale LN < 2cm
IIb: regionale LN > 2cm and < 5 cm
IIc: regionale LN > 5cm

IIIA: niet-regionale LN en/of pulmonale metastasen (=M1a) (en bij non-seminoom lage markers)
IIIB: niet-regionale LN en/of pulmonale metastasen (=M1a)(en bij non-seminoom intermediaire markers)
IIIC: metastasen buiten de long (=M1b)/primair mediastinaal (of bij non-seminoom M1a met hoge markers)
# Prognosis definition of advanced germ cell tumors (stadium IIbc-III)

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Patients (n)</th>
<th>5-y Survival Rate (%)</th>
<th>Nonseminoma</th>
<th>Seminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>90% S 56% NS</td>
<td>91%</td>
<td>Testicular/retroperitoneal primary with &quot;low marker&quot; and no visceral metastases (except lung)</td>
<td>Any primary localization and/or any marker level (but normal AFP) and no visceral metastases (except lung)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&quot;Low marker&quot;</td>
<td>&quot;Low marker&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AFP &lt;1000 ng/mL</td>
<td>AFP normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HCG &lt;1000 ng/mL (&lt;5000 mIU/mL)</td>
<td>HCG &lt;1000 ng/mL (&lt;5000 mIU/mL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LDH &lt;1.5 × normal</td>
<td>LDH &lt;1.5 × normal</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10% S 28% NS</td>
<td>79%</td>
<td>Testicular/primary retroperitoneal tumor and &quot;intermediate marker&quot; and no visceral metastases (except lung)</td>
<td>Any primary localization and any marker level and nonpulmonary visceral metastases (liver, bone, CNS) ± lung</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&quot;Intermediate marker&quot;</td>
<td>AFP normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AFP 1000-10 000 ng/mL</td>
<td>HCG 1000-10 000 ng/mL (5000-50 000 mIU/mL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LDH 1.5-10 × normal</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>16% NS</td>
<td>48%</td>
<td>Primary mediastinal NS germ cell tumor or testicular/retroperitoneal primary with nonpulmonary visceral metastases (liver, bone, CNS, intestine) ± lung and/or &quot;high marker&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High marker</td>
<td>No group with poor prognosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AFP &gt;10 000 ng/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HCG &gt;10 000 ng/mL (&gt;50 000 mIU/mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LDH &gt;10 × normal</td>
<td></td>
</tr>
</tbody>
</table>
Bleomycine-Etoposide-cisPlatin
### Good prognosis group

**Standard of care:** 3xBEP

#### Table 2. Randomized trials of first-line chemotherapy regimens in patients with good-prognosis metastatic germ cell tumors

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Patients (n)</th>
<th>Regimen</th>
<th>Cycles (n)</th>
<th>P Value</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosl et al(^{44})</td>
<td>164</td>
<td>VAB-6 EP</td>
<td>3</td>
<td>NS</td>
<td>4×EP equal efficacy, less toxic</td>
</tr>
<tr>
<td>Einhorn et al(^{10})</td>
<td>184</td>
<td>BEP</td>
<td>4</td>
<td>NR</td>
<td>3×BEP equal efficacy, less toxic</td>
</tr>
<tr>
<td>Levi et al(^{45})</td>
<td>218</td>
<td>PVB EP</td>
<td>4</td>
<td>NR</td>
<td>4×PVB more effective</td>
</tr>
<tr>
<td>Bajorin et al(^{16})</td>
<td>265</td>
<td>EP</td>
<td>4</td>
<td>0.02</td>
<td>4×EP more effective</td>
</tr>
<tr>
<td>Loehrer et al(^{1})</td>
<td>166</td>
<td>BEP</td>
<td>3</td>
<td>0.01</td>
<td>3×BEP more effective</td>
</tr>
<tr>
<td>Bokemeyer et al(^{17})</td>
<td>54</td>
<td>BEP</td>
<td>3</td>
<td>0.02</td>
<td>3×BEP more effective</td>
</tr>
<tr>
<td>de Wit et al(^{10})</td>
<td>395</td>
<td>BE(_{360})C</td>
<td>4</td>
<td>NR</td>
<td>4×BE(_{360})P more effective</td>
</tr>
<tr>
<td>Horwich et al(^{18})</td>
<td>598</td>
<td>rdBEP</td>
<td>4</td>
<td>&lt;.001</td>
<td>4×BEP more effective</td>
</tr>
<tr>
<td>Clemm et al(^{12})</td>
<td>130</td>
<td>CEB</td>
<td>4</td>
<td>0.21</td>
<td>4×EP more effective</td>
</tr>
<tr>
<td>Horwich et al(^{19}) (only seminoma)</td>
<td>130</td>
<td>EP</td>
<td>4</td>
<td>0.21</td>
<td>4×EP more effective</td>
</tr>
<tr>
<td>de Wit et al(^{14})</td>
<td>792</td>
<td>BEP + EP</td>
<td>3 + 1</td>
<td>.02(^{a})</td>
<td>3×BEP and 3-d vs 5-d protocol equivalent</td>
</tr>
<tr>
<td>Toner et al(^{46})</td>
<td>166</td>
<td>BEP</td>
<td>3</td>
<td>0.08</td>
<td>3×BEP equal efficacy but less toxicity</td>
</tr>
<tr>
<td>Culin et al(^{11})</td>
<td>270</td>
<td>rdBEP</td>
<td>3</td>
<td>0.14</td>
<td>3×BEP and 4×EP equivalent efficacy and toxicity</td>
</tr>
</tbody>
</table>
Intermediate/Poor prognosis: standard of care: 4xBEP*

* Williams, NEJM 1987

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Patients (n)</th>
<th>Regimen</th>
<th>Cycles (n)</th>
<th>Response (%)</th>
<th>P Value</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>de Wit et al(^{22})</td>
<td>84</td>
<td>BEP</td>
<td>4</td>
<td>82</td>
<td>0.72</td>
<td>4xBEP equal efficacy, less toxic</td>
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<tr>
<td></td>
<td></td>
<td>VIP</td>
<td>4</td>
<td>80</td>
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<tr>
<td>Poor</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Williams et al(^{47})</td>
<td>72</td>
<td>BEP</td>
<td>4</td>
<td>63</td>
<td>NS</td>
<td>4xBEP more effective, less toxic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PVB</td>
<td>4</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nichols et al(^{24})</td>
<td>153</td>
<td>BEP</td>
<td>4</td>
<td>73</td>
<td>0.9</td>
<td>4xBEP equal efficacy, less toxic</td>
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<tr>
<td></td>
<td></td>
<td>BEP(^{200})</td>
<td>4</td>
<td>68</td>
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</tr>
<tr>
<td>de Wit et al(^{25})</td>
<td>208</td>
<td>BEP(^{200})</td>
<td>4</td>
<td>72</td>
<td>NS</td>
<td>4xBEP equal efficacy, less toxic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PVB/BEP</td>
<td>4</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaye et al(^{48})</td>
<td>371</td>
<td>BEP + EP</td>
<td>4 + 2</td>
<td>65</td>
<td>NS</td>
<td>4xBEP + 2xEP equal efficacy, less toxic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOP + VIP-B</td>
<td>3 + 3</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nichols et al(^{49})</td>
<td>286</td>
<td>BEP</td>
<td>4</td>
<td>60(^{b})</td>
<td>0.29</td>
<td>4xBEP equal efficacy, less toxic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VIP</td>
<td>4</td>
<td>63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{22}\) Reference not provided.
\(^{200}\) BEP\(^{200}\) regimen as per de Wit et al\(^{25}\).
\(^{25}\) BEP\(^{200}\) regimen as per de Wit et al\(^{25}\).
\(^{47}\) Reference not provided.
\(^{48}\) Reference not provided.
\(^{49}\) Reference not provided.
Carboplatin-Etop-Bleo in seminoma

- Retrospective cohort study NKI-AvL
- 18 pts with stage IIa-IIIc seminoma, treated with CEB
- 5 yr PFS 86.6%, 10 yr OS 85.7%
- No grade III-IV neuropathy, ototoxicity or nefrotoxicity

Giesen et al, Urologic Oncology 2013
Bleomycine

- 1966
Hamao Umezawa vond antikankeractiviteit tijdens screening van cultuurfiltraat van Streptomyces verticullus

- 1969
Launched in Japan

- 1973
Goedkeuring FDA
Toxiciteit

- Na infusie griepachtige verschijnselen
- Met name longtoxiciteit (‘pneumonitis’)
- Huidtoxiciteit
- Raynaud’s syndroom
- Vaatschade
- *Niet* hematotoxisch!
Toxiciteit: long

- Let op respiratoire klachten
- Laagdrempelig diagnostiek
  - X-Th respectievelijk CT-scan
  - longfunctie
  - BAL
- Tijdig stoppen en tijdig starten steroïden
Cumulatieve dosering

• Risicofactoren:
  – leeftijd
  – cumulatieve dosis
  – roken
  – gebruik G-CSF

• Testiscarcinoom
  – good prognosis: 3 x BEP (270 IU)
  – interm/poor prognosis: 4 x BEP (360 IU)
Toxiciteit: huid

- Van tevoren inlichten
Toxiciteit cisplatin

- Nefro-toxisch
- Oto-toxisch
- Neuro-toxisch
Late toxiciteit

- Raynaud
- Gehoorsverlies
- Sensorische neuropathie

Sub-klinisch hypogonadisme
Salvage chemotherapie

Conventionele chemotherapie

- TIP
  - Taxol / Ifos / cisPlatin

Hoge dosis chemotherapie

- TIGER
  - Remissie-inductie
  - Consolidatie met hoge dosis chemotherapie en stamcel-transplantatie
Prognostische indeling voor salvage CT

Table 4. Prognostic Score for Patients With Nonseminoma and Seminoma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score Points</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Score</th>
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<tbody>
<tr>
<td>Primary site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonadal</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Extragonadal</td>
<td>1</td>
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</tr>
<tr>
<td>Mediastinal</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>nonseminoma</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Prior response</td>
<td>CR/PRm−</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PRm+/SD</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PD</td>
<td>3</td>
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</tr>
<tr>
<td>PFI, months</td>
<td>&gt; 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤ 3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AFP salvage</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤ 1,000</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1,000</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCG salvage</td>
<td>≤ 1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1,000</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBB</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score sum (values from 0 to 10)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Add histology score points: pure seminoma = −1; nonseminoma or mixed tumors = 0</td>
<td></td>
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</tr>
<tr>
<td>Final prognostic score (−1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)</td>
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</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; PRm−, partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease; PD, progressive disease; PFI, progression-free interval; AFP, alpha fetoprotein; HCG, human chorionic gonadotrophin; LBB, liver, bone, brain metastases.

Table 5. Survival Rates According to Prognostic Categories (validation set plus patients with seminoma)

<table>
<thead>
<tr>
<th>Prognostic Category (n = 664)</th>
<th>Score</th>
<th>No. of Patients</th>
<th>%</th>
<th>HR</th>
<th>95% CI</th>
<th>2-Year PFS</th>
<th>3-Year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>−1</td>
<td>76</td>
<td>13.0</td>
<td>1</td>
<td></td>
<td>75.1</td>
<td>77.0</td>
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<tr>
<td>Low</td>
<td>0</td>
<td>132</td>
<td>22.6</td>
<td>1.17</td>
<td>1.32 to 3.58</td>
<td>51.0</td>
<td>55.6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1</td>
<td>219</td>
<td>37.4</td>
<td>3.20</td>
<td>2.00 to 5.11</td>
<td>40.1</td>
<td>58.3</td>
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<tr>
<td>High</td>
<td>2</td>
<td>122</td>
<td>20.9</td>
<td>4.85</td>
<td>2.98 to 7.89</td>
<td>25.9</td>
<td>27.1</td>
</tr>
<tr>
<td>Very high</td>
<td>3</td>
<td>36</td>
<td>6.1</td>
<td>11.70</td>
<td>6.70 to 20.45</td>
<td>5.8</td>
<td>6.1</td>
</tr>
<tr>
<td>No unequivocal classification</td>
<td>69</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

Lorch 2010
Salvage CT: Retrospectieve analysis of CDCT vs HDCT

Lorch 2011
Tiger Trial

Eligibility
- Histologically-confirmed GCT
- PD following 1st-line CT
- Prior treatment included ≥3 but ≤5 cycles of cisplatin-based CT
- Adequate organ function for HDCT
- Any primary site
- No prior TIP or HDCT

Stratification
- Primary site
- ECOG ≤3 months
- > PR-neg to 1st-line CT
- Liver, bone, or brain metastases
- HCG ≥1000 mIU/mL
- AFP ≥1000 mIU/mL
- Pure seminoma histology

Randomization 1:1

Primary Endpoint:
- Disease-Free Survival (DFS) at 2 years

Secondary Endpoints:
- Overall Survival (OS) at 3 years
- Favorable Response Rate (CR + PR-neg markers)
- Toxicity
- Prospective Evaluation of the IGCCCG-2 Prognostic Score