Treatment of Germ Cell Tumors

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# Germ-cell tumors: Prognosis

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localized</strong></td>
<td>99%</td>
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</table>
Stage 1: multi-national retrospective study

- $n = 2483$ pts
  - 1139 NS  Relapse: 19%
  - 1344 Seminoma  Relapse: 13%

- **Time to relapse:**
  - 4 months (NS, vascular invasion)
  - 8 months (NS, no vascular invasion)
  - 14 months (Seminoma)

- **Detection of relapse:**
  - 50% Tumor markers, 50% CT scan

Kollmansberger C, J Clin Oncol 2015
## Surveillance modalities in clinical stage I GCTs

**Table 4.** Authors’ Recommendations for Surveillance Schedules Based on the Observed Patterns of Relapse and the Authors’ Expert Opinion

<table>
<thead>
<tr>
<th>Year</th>
<th>Physical Examination</th>
<th>Tumor Marker*</th>
<th>Chest X-Ray</th>
<th>CT/MRI Abdomen†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSI-NONSEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>2</td>
<td>2</td>
<td>4, 8, 12</td>
<td>4, 8, 12</td>
</tr>
<tr>
<td>Year 2</td>
<td>3</td>
<td>3</td>
<td>18, 24</td>
<td>18, 24</td>
</tr>
<tr>
<td>Year 3</td>
<td>6</td>
<td>6</td>
<td>—</td>
<td>36‡</td>
</tr>
<tr>
<td>Year 4</td>
<td>6</td>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Year 5</td>
<td>6</td>
<td>6</td>
<td>—</td>
<td>60‡</td>
</tr>
<tr>
<td>CSI-SEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>3</td>
<td>3</td>
<td>6, 12</td>
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</tr>
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<td>6</td>
<td>6</td>
<td>18, 24</td>
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</tr>
<tr>
<td>Year 3</td>
<td>6</td>
<td>6</td>
<td>—</td>
<td>30, 36</td>
</tr>
<tr>
<td>Year 4</td>
<td>6</td>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Year 5</td>
<td>6</td>
<td>6</td>
<td>—</td>
<td>60‡</td>
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</table>

Abbreviations: CSI-NONSEM, clinical stage I nonseminoma; CSI-SEM, clinical stage I seminoma; CT, computed tomography; MRI, magnetic resonance imaging.

*Alpha fetoprotein/human chorionic gonadotropin (lactate dehydrogenase is of questionable benefit in stage I).‡
†MRI only in experienced centers.
‡Proposed by several authors.
Relapse-free survival after **1 BEP** for stage 1 NSGCT

n=517 pts

(A) patients without lymphovascular invasion; (B) patients with lymphovascular invasion.

Tumeur germinale non séminomateuse de stade 1

Evaluation du risque individuel de rechute

- Soit intervention. « curage ganglionnaire lombo-aortique »
  - Avantages:
    - Meilleure évaluation du stade
  - Inconvénients:
    - 2e intervention
    - Risque de trouble de l’éjaculation (5-10%)
    - En cas d’atteinte, le plus souvent chimiothérapie

- Soit chimiothérapie « 1-2 cycles de BEP »
  - Avantages:
    - Diminution du risque de rechute (2%)
  - Inconvénients:
    - perte des cheveux transitoire
    - Nausées
    - Baisse des globules blancs

- Soit surveillance et traitement en cas de rechute
  - Avantages:
    - Pas de traitement systématique (et donc pas d’effets secondaires)
  - Inconvénients:
    - Traitement (et effets secondaires) si rechute

Chances de guérison ≥ 99%
Testicule opéré
Marqueurs sanguins normaux
Scanner de l’abdomen, du pelvis et du thorax normal

Séminome pur de stade 1

Evaluation du risque individuel de rechute

Soit radiothérapie sur les ganglions du ventre « lombo-aortiques »
Soit chimiothérapie « 1 cycle de carboplatine »
Soit surveillance et traitement en cas de rechute

Avantages:
- Diminution du risque de rechute (3%)

Inconvénients:
- immédiats modérés (nausées, diarrhée, douleur abdominale)
- Retardés: très rarement, secondes tumeurs

- Diminution du risque de rechute (3%)
- Nausées
- Baisse des globules blancs

Pas de traitement systématique (et donc pas d’effets secondaires)

Traitement (et effets secondaires) si rechute

Chances de guérison ≥ 99%
Metastatic GCT: Prognosis (IGCCC)

- **Good prognosis**
  - Non-Seminoma:
    - Testis/retroperitoneal primary and no non-pulmonary visceral metastases and good markers - all of AFP ≤ 1000 ng/ml and hCG < 5000 IU/L (1000 ng/ml) and LDH < 1.5 x upper limit of normal
    - 58% of non-semionomas: 5 year PFS 89% 5 year Survival 92%
  - Seminoma:
    - Any primary site and no non-pulmonary visceral metastases and normal AFP, any hCG, any LDH
    - 96% of semionomas: 5 year PFS 82% 5 year Survival 88%

- **Intermediate prognosis**
  - Non-Seminoma:
    - Testis/retroperitoneal primary and no non-pulmonary visceral metastases and intermediate markers - any of: AFP ≥ 1000 and ≤ 10,000 ng/mL or hCG ≥ 5000 IU/L and ≤ 50,000 IU/L or LDH ≥ 1.5 x N and ≤ 10 x N
    - 28% of non-semionomas: 5 year PFS 75% 5 year Survival 89%
  - Seminoma:
    - Any primary site and non-pulmonary visceral metastases and normal AFP, any hCG, any LDH
    - 10% of semionomas: 5 year PFS 67% 5 year Survival 72%

- **Poor prognosis**
  - Non-Seminoma:
    - Mediastinal primary or non-pulmonary visceral metastases and poor markers - any of: AFP > 10,000 ng/ml or hCG > 50,000 IU/L (1000 ng/ml) or LDH > 10 x upper limit of normal
    - 16% of non-semionomas: 5 year PFS 41% 5 year Survival 48%
  - Seminoma:
    - No patients classified as poor prognosis

J Clin Oncol 1997, 15: 594-603

Fig 4. Definition of the Germ Cell Consensus Classification.
Germ-cell tumors: Prognosis

Localized

Survival: 99%

Metastatic (IGCCCG)

- Good prognosis: 95%
- Intermediate prognosis: 80%
- Poor prognosis: 50%
Stage II seminoma

- **Stage IIa:**
  - Consider repeating CT scan (or PET): false+?
  - Radiotherapy Iliac + para-aortic field
  - 36 Gy

- **Stage IIb:**
  - RXT or CT (debated)
  - CT favored by most experts

- **Stage IIc:**
  - Chemotherapy (high relapse rate with RXT)
  - 4 EP (or 3 BEP)
Metastatic seminoma: S99 trial

Progression-free survival:
3-year PFS: **91%** (84-95)

Overall survival:
3-year OS: **96%** (91-99)

n= 130 pts
4 EP
or 4 VIP + G-CSF

Causes of death (n= 9):
- Seminoma: 2
- Toxicity: 1
- Toxicity of salvage chemotherapy: 1
- Other: 5

Fizazi K, Eur Urol 2014; 65: 381-6
Metastatic seminoma: The SEMITEP trial
Residual masses post-chemotherapy for advanced seminoma

Pet scan? (De Santis, JCO 2004, 22: 1034-1039)

51 pts: Specificity: 100%, Sensitivity: 80%

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>TP</th>
<th>TN</th>
<th>FN</th>
<th>FP</th>
</tr>
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<tbody>
<tr>
<td>T&gt; 3 cm</td>
<td>19</td>
<td>7</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T&lt; 3 cm</td>
<td>37</td>
<td>1</td>
<td>34</td>
<td>2</td>
<td>0</td>
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Mistakes = 2/51 (4%) 

Confirmation at a larger scale: 6% FN, 15% FP
(Bachner M, Ann Oncol 2012; 23: 59-64)
Good prognosis metastatic NSGCT

• Definition:
  – Primary tumor site: Testis/RP
  – Extra-pulmonary visceral mets: No
  – Tumor marker before chemo:
    • hCG: < 5000
    • AFP: < 1000
    • LDH: < 1.5 x norm

• 60% of metastatic NSGCT

• Cure rate >95%

J Clin Oncol 1997, 15: 594-603
Good prognosis metastatic NSGCT

- **3 BEP** established as standard treatment: no difference with 4 BEP (Einhorn 1989)
- **Cisplatin > Carboplatin** (relapse):
  - Phase III EP vs EC (Bosl 1994)
  - Phase III BEP vs BEC (Bokemeyer 1996)
- **Role of bleomycin debated**
  - Most specialists would support bleomycin use
  - Also recommended in the European consensus
GETUG T93 trial: 3 BEP vs 4 EP

n = 251 Good-risk NSGCT

Event-Free Survival

Logrank p = 0.06

4EP; 84% at 4 years
3BEP; 90% at 4 years

Culine et al., Ann Oncol 2007
GETUG T93 trial: 3 BEP vs 4 EP

Overall Survival

Logrank p=0.14

BEP: 5 deaths
EP: 12 deaths

Median follow-up = 51 months

Culine et al., Ann Oncol 2007
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4 BEP vs 4 T-BEP in Intermediate-prognosis metastatic GCT: EORTC Phase III trial

n= 337/498 planned

Intent to treat  p=0.15

Eligible population  p=0.03

Per protocol

PFS

OS (NS)

de Wit R et al. JCO 2012;30:792-799
## Germ-cell tumors: Prognosis

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3 ways to be a poor-risk Non seminoma GCT patient

• Very high tumor markers
  – hCG > 50 000
  – AFP > 10 000
  – LDH > 10 x N

• Visceral metastases

• Primary mediastinal site

IGCCCG, J Clin Oncol 1997, 15: 594-603
Poor-risk GCT: A standard established in 1987…

- 4 BEP > 4 PVB:
  - DFS ($p<0.05$) and OS ($p<0.05$)
  - Better tolerance (neurotoxicity)

**4 BEP = standard**
Poor-risk GCT:
25 years of negative phase 3 trials

CISCA/VB: Culine, J Clin Oncol 2007;26:421-7

Background: Survival according to tumor marker decline

Fizazi, J Clin Oncol 2004, 22: 3868-76

http://www.gustaveroussy.fr/calculation-tumor/NSGCT.html

App!
GETUG 13 Phase III design

Median follow-up: 4.1 years (0.3; 8.8 years)

- Poor-risk GCT (IGCCCG)
- Registration 1st BEP
- Day 21: Tumor marker
  - Favorable decline → 4 BEP (total)
  - Unfavorable decline R
    - Dose-dense regimen
      n=105
    - 4 BEP (total)
      n=98

n=263 → n=254 → n=51 → n=203 → n=203
GETUG 13: Dose-dense regimen

Dose-dense regimen
= 6 drugs instead of 3
in almost the same amount of time

Cisplatin, Ifosfamide, Bleomycin
+ G-CSF
/ 3 weeks × 2 cycles

Cisplatin 100 mg/m² d1
Ifosfamide 2g/m² d10,12,14
Mesnum
Bleomycin 25 U/d d10-14
(continuous IV)
G-CSF as above

Presented by: Karim Fizazi
Primary endpoint: PFS in randomized patients with an unfavorable decline

HR: 0.66 [0.44-1.00]  
p=0.05

3-year PFS: 59% vs 48%

cNED: 63 vs 46 pts

Fizazi K, Lancet Oncol 2014; 15: 1442-50
Outcome according to tumor marker decline

Fav-BEP vs Unfav-BEP:
3-year PFS: 70% vs 48%
HR=0.66  (0.49 ; 0.88), p=0.01

Fav-BEP vs Unfav-BEP:
3-year OS: 84% vs 65%
HR=0.65  (0.45 ; 0.95), p=0.024

Fizazi K, Lancet Oncol 2014; 15: 1442-50
Results (2016): PFS in patients with an unfavorable tumor marker decline (Primary endpoint)

5-year PFS: 60% vs 47%  
HR: 0.65 [0.43-0.97]  
p=0.037
Results (2016): OS in patients with an unfavorable tumor marker decline (Secondary endpoint)

5-year OS: 70.4% vs 60.8%
HR: 0.69 [0.43-1.11]
p=0.12

75 vs 59 pts alive at last follow-up

Presented by: Karim Fizazi (ASCO 2016)
## Main toxicities and outcome

<table>
<thead>
<tr>
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<th>Dose-dense</th>
<th>BEP</th>
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<tbody>
<tr>
<td>Neutropenic fever</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Neurotoxicity ≥ grade 2</td>
<td>23%</td>
<td>4%</td>
</tr>
<tr>
<td>(mostly reversible at 2y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic deaths</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Second cancers</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Salvage HDC + transplant</td>
<td>6%</td>
<td>16%</td>
</tr>
<tr>
<td>p=0.015</td>
<td></td>
<td></td>
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Long-term Results (2016):
Reversible neurotoxicity

Presented by: Karim Fizazi
Impact of the treating institution on the outcome of poor risk metastatic germ-cell cancer

EORTC/MRC trial

Survival probability

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%


p < 0.018

years after randomisation

5-9 Pat.
10-19 Pat.
> 19 Pat.
< 5 Pat.
Germ-cell tumors: Prognosis

Localized
Survival 99%

Metastatic (IGCCCG)
- Good prognosis 95%
- Intermediate prognosis 80%
- Poor prognosis 50%

Salvage setting 40%
Prognostic classification: metastatic GCT + failure to first-line cisplatin-based chemotherapy

n= 1984 pts

Prognostic factors:
- Histology: NS vs Seminoma
- Tumor site: Testis/Extra/Med
- Visceral metastases
- Previous response
- Progression-free interval (3m)
- hCG (1000)
- AFP (1000)

Prognostic score

PFS

J Clin Oncol 2010, 28: 4906-11
Conventional vs High-dose salvage chemotherapy
IT94 Phase 3 trial: OS

Conclusion: No benefit to single intensification

Pico et al., Ann Oncol 2005, 16: 1152-1159
Single vs Sequential HD chemotherapy for salvage

n = 230 pts

1 VIP + 3 HD CE
3 VIP + 1 HD CEC

4% vs 16% toxic death rate

OS borderline better for sequential
Sequential CT better tolerated

Lorch A et al., J Clin Oncol 2007, 25: 2778-84
Lorch A et al., J Clin Oncol 2012; 30: 800-5
Salvage chemotherapy for GCTs

- Only 1 previous line?
- Complete response?
- Testis primary?

Yes

Good prognosis

Triplet conventional dose + G-CSF

No

Poor prognosis

High-dose chemo + transplant
Conclusion: Treatment of GCT

- Patient centralisation for a better quality of care +++
- Rigorous use of validated treatments
  - Not 5, 6, or 7 cycles of BEP!
  - Expertise for surgery
- If well applied, things usually go well!