Testicular cancer: Treatment strategies and fertility preservation

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International variation in estimates of national age-standardised testicular cancer (a) incidence rates and (b) mortality rates, all ages.

Relative risk of testicular cancer is related to the prenatal environment

- **The first generation** of Finnish immigrants to Sweden (born in FIN, but raised in S) had the risk of TC equal to that in FIN (low)*
- **The second generation** (born in S) had the same risk as the Swedish population (higher than in FIN)*

Histologic classification

I. Germ cell neoplasms (90–95%)

II. Sex cord-stromal neoplasms (4%)
   A. Leydig cell tumour (3%)
   B. Sertoli cell tumour (1%)
   C. Sertoli-Leydig cell tumour (rare)
   D. Granulosa cell tumours (<1%)
   E. Tumours in the fibroma/thecoma group (rare)
   F. Mixed and indeterminant (unclassified) sex cord-stromal tumours (<1%)

III. Mixed germ cell-sex cord-stromal neoplasms (<1%)
   A. Gonadoblastoma (0.5%)
   B. Other mixed germ cell-sex cord-stromal tumours (rare)

IV. Lymphoid and Haematopoietic tumours (<1%)
   A. Lymphoma (? 1% as true primary neoplasm)
   B. Plasmacytoma (rare) and multiple myeloma
   C. Granulocytic sarcoma and leukemic infiltrates (rare)
   D. Miscellaneous others, including metastatic tumours (1–2 %)
Development of testicular germ cell tumours

The hypothetical development of the testicular germ cell tumors according to Ulbricht et al. The direct descendant of IGCNU is probably the seminoma (S). Embryonal carcinomas (EC) develop from seminomas. EC can undergo a somatic transformation to teratoma (T) or an extra embryonic one to yolk sac (YST) tumor and choriocarcinoma (CC). Somatic type tumors develop from teratoma. Deviations from this sequence are purportedly possible but infrequent. It = intratubular; SS = spermatocytic seminoma; STGC = syncytiotrophoblastic cells; P = pediatric.
Germ cell tumours

GONADAL
95-98%

EXTRAGONADAL
2-5%

MEDIASTINAL (ant. mediastinum)
RETROPERITONEAL
PINEAL, SACRO-COCIGEAL, ETC.
STAGE 1 (disease confined to the testis)

**Work up:** CT scan thorax and abdomen, LDH, alfa-fetoprotein, beta-HCG
scrotal US
PET/CT is never recommended
CLINICAL STAGE 1 SEMINOMA
(70-75% of all seminoma)

Prognostic factors: tumour size > 4 cm, vascular invasion, beta HCG > 200
Moertensen ASCO 2013

*Less used in the present days
Relapse rate in Stage 1 seminoma: Active surveillance in 1822 patients

- **No. of relapses**: 355 / 1822 (19.5%)

  - **Time to relapse**:
    - < 2 years: 257 (72.4%) patients
    - 2–5 years: 72 (20.3%) patients
    - > 5 years: 26 (7.3%) patients

  - **Median time to relapse**: 13.7 months (range 1.2-173.3 months)

CLINICAL STAGE 1 NON-SEMINOMA

- Active surveillance*
- 1-2 courses of BEP
- RPLND nerve sparing**

*In some countries (i.e. Denmark, Canada is the main option)
** When chemotherapy or surveillance is not accepted
Lymphatic spread is rather easy to be defined

Thoracic duct
Cisterna chyli
Lumbar trunks (of cisterna chyli)
Right lumbar (retro-caval) nodes
Aorto-caval nodes

Celiac nodes
Superior mesenteric nodes
Intestinal trunk (of cisterna chyli)
Lumbar (para-aortic) nodes
Inferior mesenteric nodes
Common iliac nodes
External iliac nodes
Internal iliac (hypogastric) nodes
The lymphatic way continues

- Lumbar ducts
- Cisterna chyli
- Thoracic duct
- Posterior mediastinum
- Left supraclavicular area
**Tumour markers in germ cell testicular neoplasms**

**Tumour markers**
- Alfa-fetoprotein: Never in seminoma
- Beta-HCG
- LDH (marker of masses)

**False tumour markers**
- Hepatitis, liver damage, week-end drinkers, rare familiar cases for alfa
- Marijuana abuse, LH elevation for beta
Stage II disease (retroperitoneal disease)

Stage IIA: Nodal involvement up to 2 cm
Stage IIB: Nodal involvement 2-5 cm
Stage IIC: Nodal involvement > 5 cm

- If seminoma Stage IIA RT or chemotherapy. In higher stages: chemotherapy
- If non seminoma any stage II: chemotherapy. In stage II non seminoma with marker negative disease, surgery or even short time follow-up may be considered
Relationship IGCCCG → prognosis

Good @ 5 years
- PFS 89%
- OS 92%

Intermediate @ 5 years
- PFS 75%
- OS 80%

NS

Poor @ 5 years
- PFS 41%
- OS 48%

Sem.

Intermediate @ 5 years
- PFS 67%
- OS 72%

Practical criteria for first-line treatment decision

Seminoma + elevated beta-HCG and/or LDH = **SEMINOMA**
Seminoma + elevated AFP = **NON-SEMINOMA**
Seminoma + Mature teratoma = **NON-SEMINOMA**

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Primary mediastinal = **POOR PROGNOSIS**
Metastases to the mediastinum = **GOOD PROGNOSIS**

----------------------------------------

CNS metastases = **POOR PROGNOSIS NON SEM**
**INTERMEDIATE PROGNOSIS SEM**
Primary CNS = **GOOD PROGNOSIS (???)**

(No data from IGCCCG)
BEP was, is and probably will be the standard

What to do in second-line

- Second line schedules include cisplatin
- VeIP, VIP, PEI, TIP; no data regarding a possible “best combination”
- Overall 25-40% of relapsed patients achieve cure (including also surgery)
- Interesting results have been obtained with High-Dose Chemotherapy (HDCT)
## HDCT as second-line for relapsed/refractory GCTs

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>OS (%)</th>
<th>PFS (%)</th>
<th>mFU (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodenhuis et al. [34]</td>
<td>Prospective, phase II</td>
<td>35</td>
<td>Conventional induction chemotherapy followed by two cycles of HD-CTC</td>
<td>Not reported</td>
<td>54</td>
<td>37</td>
</tr>
<tr>
<td>Bhatia et al. [33]</td>
<td>Prospective, phase II</td>
<td>65</td>
<td>One to two cycles of conventional VeIP followed by two cycles of HD-CE</td>
<td>Not reported</td>
<td>57</td>
<td>39</td>
</tr>
<tr>
<td>Motzer et al. 2000 [32]</td>
<td>Prospective, phase II</td>
<td>37</td>
<td>Two cycles of TI followed by three cycles of HD-CE</td>
<td>54</td>
<td>49</td>
<td>31</td>
</tr>
<tr>
<td>Rick et al. 2001 [41]</td>
<td>Prospective, phase II</td>
<td>62</td>
<td>Three cycles of standard TIP followed by one cycle of HD-CE</td>
<td>30 (at 3 years)</td>
<td>25 (at 3 years)</td>
<td>36</td>
</tr>
<tr>
<td>Pico et al. [38]</td>
<td>Prospective, randomized, phase III</td>
<td>128 (SDCT) versus 135 (HDCT)</td>
<td>Four cycles of conventional VeIP or VIP versus three cycles of conventional VeIP or VIP followed by one cycle of HD-CE</td>
<td>53 versus 53 (at 3 years)</td>
<td>35 versus 42 (at 3 years)</td>
<td>45</td>
</tr>
<tr>
<td>Einhorn et al. [36]</td>
<td>Retrospective</td>
<td>135</td>
<td>Two cycles of HD-CE</td>
<td>Not reported</td>
<td>70</td>
<td>48</td>
</tr>
<tr>
<td>Lorch et al. [40]</td>
<td>Prospective, randomized, phase II</td>
<td>111 (sequential HDCT) versus 105 (single HDCT)</td>
<td>VIP + three cycles HD-CE versus three cycles of VIP + one cycle of HD-CE</td>
<td>47 versus 45 (at 5 years)</td>
<td>49 versus 39 (at 5 years), $P = 0.057$</td>
<td>90</td>
</tr>
<tr>
<td>Feldman et al. [37]</td>
<td>Prospective, phase I–II</td>
<td>107</td>
<td>Two cycles of TI followed by three cycles of HD-CE</td>
<td>52 (at 5 years)</td>
<td>48 (at 5 years)</td>
<td>61</td>
</tr>
</tbody>
</table>

Unless specified, OS and PFS rates refer to mFU.

Conventional-Dose Versus High-Dose Chemotherapy As First Salvage Treatment in Male Patients With Metastatic Germ Cell Tumors: Evidence From a Large International Database

After first-line...

Not all relapses look alike!
# How to identify the prognostic score: IGCCCG-2

<table>
<thead>
<tr>
<th>SCORE POINTS</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary site</strong></td>
<td>Gonadal</td>
<td>Extraparotid</td>
<td>-</td>
<td>Mediastinal Nonseminoma</td>
<td></td>
</tr>
<tr>
<td><strong>Prior Response</strong></td>
<td>CR/PRm-</td>
<td>PRm+/SD</td>
<td>PD</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>PFI</strong></td>
<td>&gt; 3 months</td>
<td>≤ 3 months</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>AFP salvage</strong></td>
<td>Normal</td>
<td>≤ 1000</td>
<td>&gt; 1000</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>HCG salvage</strong></td>
<td>≤ 1000</td>
<td>&gt; 1000</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>LBB</strong></td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

**Step 1:** Calculate score sum (values from 0 to 10)

**Step 2:** Form temporary category from score sum (0)=0; (1 or 2)=1; (3 or 4)=2; (5 or more)=3

**Step 3:** Correct temporary category for histology

- "pure seminoma = -1"
- "non-seminoma or mixed histologies = 0"

**Step 4:**

-1=Very low risk; 0=Low risk; 1=Intermediate risk; 2=High risk; 3=Very high risk

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

Different risk groups, different outcomes

Surgery of residual disease

Advanced germ cell tumours often after chemotherapy show residual mass(es). The residual disease may contain:

- Fibrosis
- Necrosis
- Viable cells
- Teratoma*  

*Teratoma is extremely rare in seminoma
Surgery post-chemotherapy in non seminoma

NSGCTs

Any residual mass > 1 cm diameter and normalised serum tumour markers
Any residual mass > 1 cm in diameter and plateauing serum tumour markers
Residual masses < 1 cm in diameter and mature teratoma in the primary orchiectomy specimen
Marker-negative in-field recurrence after prior RPLND
Residual marker-negative or plateauing markers after salvage chemotherapy
Desperation RPLND in patients with chemoresistant and completely respectable masses

Teratoma: its role in residual disease

ECA + T

Chemotherapy

ECA + T

Teratoma Growing Syndrome

Courtesy of Dr G Rosti
Long-term clinical outcome after post chemotherapy retroperitoneal lymph node dissection in men with residual teratoma

It is not just a question of teratoma!

TWIT
The most frequently reported somatic type malignancies developed in teratoma

- Rhabdomyosarcoma
- PNET
- Chondrosarcoma
- Osteosarcoma
- Malignant Schwannoma
- Nephroblastoma (Wilms tumor)
- Carcinoid
- Adenocarcinoma
- Squamous carcinoma
- Neuroendocrine carcinoma

Courtesy of Dr G Rosti
Surgery post chemotherapy

Courtesy of Dr G Rosti
The role of PET/TC in the evaluation of residual disease

No indication in non seminoma cases

Mandatory in seminoma
## SEMINOMA

- Overall PET and CT (discrimination of residual tumour size, < or ≥ 3 cm) results

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mode</th>
<th>TN n (%)</th>
<th>FN n (%)</th>
<th>TP n (%)</th>
<th>FP n (%)</th>
<th>SENS (95% CI)</th>
<th>SPEC (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PPV (95% CI)</th>
<th>ACC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All lesion sizes</td>
<td>127</td>
<td>PET</td>
<td>87 (69)</td>
<td>7 (6)</td>
<td>14 (11)</td>
<td>19 (15)</td>
<td>67% (45–83)</td>
<td>82% (74–88)</td>
<td>93% (85–96)</td>
<td>42% (27–59)</td>
<td>80% (72–86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT</td>
<td>47 (37)</td>
<td>7 (6)</td>
<td>14 (11)</td>
<td>59 (46)</td>
<td>67% (45–83)</td>
<td>44% (35–54)</td>
<td>87% (76–94)</td>
<td>19% (12–30)</td>
<td>48% (40–57)</td>
</tr>
<tr>
<td>Lesions &lt;3 cm</td>
<td>54</td>
<td>PET</td>
<td>39 (72)</td>
<td>4 (7)</td>
<td>3 (6)</td>
<td>8 (15)</td>
<td>43% (16–75)</td>
<td>83% (70–91)</td>
<td>91% (78–96)</td>
<td>27% (10–57)</td>
<td>78% (65–87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT</td>
<td>47 (87)</td>
<td>7 (13)</td>
<td>0a</td>
<td>0a</td>
<td>0%a</td>
<td>100%a</td>
<td>87% (76–94)</td>
<td>— (NA)</td>
<td>87% (76–94)</td>
</tr>
<tr>
<td>Lesions ≥3 cm</td>
<td>73</td>
<td>PET</td>
<td>48 (66)</td>
<td>3 (4)</td>
<td>11 (15)</td>
<td>11 (15)</td>
<td>79% (52–92)</td>
<td>81% (70–89)</td>
<td>94% (84–98)</td>
<td>50% (31–69)</td>
<td>81% (70–88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT</td>
<td>0a</td>
<td>0a</td>
<td>14 (19)</td>
<td>59 (81)</td>
<td>100%a</td>
<td>0%a</td>
<td>— (NA)</td>
<td>19% (12–30)</td>
<td>19% (12–30)</td>
</tr>
</tbody>
</table>

aPer definition

PET, positron emission tomography; CT, computed tomography; TN, true negative; FN, false negative; TP, true positive; FP, false positive; SENS, sensitivity; SPEC, specificity; NPV, negative predictive value; PPV, positive predictive value; ACC, accuracy; CI, confidence interval; NA: not applicable.

Testicular cancer: Fertility preservation
Scenario

- Testicular cancer is the most common cancer in young men in Western populations

- Its incidence is increasing in many countries worldwide

- Mortality rates are declining and most men are cured

- An understanding of the risks and long-term side effects of treatment are important in managing men with this disease (particularly those at fertility age)

Fertility Preservation: Agenda

- Who is candidate for?
- Why to do it?
- When to preserve fertility?
- How to preserve?
Who is candidate for?

- More than 18,000 young males/year aged between 15 and 40 years (reproductive age) develop a testicular cancer

### Fertility preservation

Semen may be obtained and stored before a man undergoes a procedure or exposure that might prevent or impair his fertility, such as:

- vasectomy (in case of a future change in marital situation or desire for more children);
- treatment with cytotoxic agents or radiotherapy, which is likely to impair spermatogenesis permanently (Meseguer et al., 2006; Schmidt et al., 2004);
- active duty in a dangerous occupation, e.g. in military forces, in countries where posthumous procreation is acceptable.

- severe oligozoospermia or intermittent presence of motile spermatozoa in the semen (as backup for ICSI) (Bourne et al., 1995);
- treatment of infertility that may not persist, such as surgery for genital tract obstruction or gonadotrophin treatment for hypohalamic-pituitary hypogonadism;
- the need for special collection, such as assisted ejaculation for patients with spinal cord injury, spermatozoa from retrograde ejaculation in urine, or surgical collection from the genital tract;
- men who are unable to provide fresh semen on the day of an ART procedure.

### Minimizing infectious disease transmission

For men with HIV controlled by antiretroviral therapy, samples with an undetectable viral load may be stored for IUI, IVF or ICSI, to attempt conception while reducing the risk of transmission of HIV to the female partner.
Why to preserve?

- Because it is strongly suggested by WHO guidelines

- Because 3/4 of cancer patients aged below 35 years have thought about the future and are interested in research treatments to help preserve fertility

- Because 81% of adolescents with cancer and 93% of their parents are interested in options to help preserve fertility during cancer treatments, but they are not willing to postpone treatment for this purpose

In patients diagnosed with testicular cancer, pre-treatment sperm DNA fragmentation levels are not significantly different from that of proven fertile controls. However, after chemotherapy DNA fragmentation results significantly higher than pre-treatment values.

Smit et al., Hum Reprod 2010; 25: 1877-83
Testicular irradiation >2.5 Gy in adult men and > 6 Gy in pre-pubertal boys is associated with prolonged azoospermia.

In patients with testicular cancer, sperm DNA fragmentation is significantly higher in patients who are treated with radiotherapy compared with that in patients treated with chemotherapy alone.

Smit et al., Hum Reprod 2010; 25: 1877-83

Testicular irradiation >2.5 Gy in adult men and > 6 Gy in pre-pubertal boys is associated with prolonged azoospermia.

Modified from Dohle GR et al. Int J Urol 2010;17(4):327-331
# Classes of chemotherapy and their mechanisms of action

<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Name of drugs</th>
<th>Mechanism</th>
<th>Cell cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>Cyclophosphamide, nitrogen mustard, chloroethyl nitrosurea, busulfan, chlorambucil, melphalan, thiotepa</td>
<td>Cross-link DNA strand, interrupt RNA and protein synthesis</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Cisplatin and analogues</td>
<td>Cisplatin, carboplatin</td>
<td>Interferes with DNA synthesis without affecting normal RNA and protein synthesis</td>
<td>Possibly specific (G2 arrest)</td>
</tr>
<tr>
<td>Vinca alkaloids (aneuploidy inducers)</td>
<td>Vincristine, vinblastine</td>
<td>Bind tubulin and cause dissociation of the microtubule apparatus</td>
<td>Specific: G1 and S phase</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Methotrexate, aminopterin, 5-fluorouracil, cytarabine</td>
<td>Inhibit cellular metabolites by acting as false substrates for reactions required in DNA or RNA synthesis</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Topoisomerase interactive agents</td>
<td>Bleomycin, actinomycin, doxorubicin, daunorubicin</td>
<td>Interact with enzyme-DNA complex. Prevents rescaling of the top I-mediated DNA single strand breaks</td>
<td>Specific: G2 arrest/ S-phase apoptosis</td>
</tr>
</tbody>
</table>
Molecular Karyotyping of Human Single Sperm by Array-Comparative Genomic Hybridization

- Normozoospermic men, (n: 3)
  - 100 single sperm

- Severe oligozoospermic (<5 mil/mL) (n: 3)
  - 100 single sperm

- After chemotherapy (6 months after the end of treatments) (n: 3)
  - 100 single sperm

### Why to preserve?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Altered karyotype (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normozoospermia</td>
<td>7.8%</td>
</tr>
<tr>
<td>Severe oligozoospermia</td>
<td>16.3%</td>
</tr>
<tr>
<td>Chemiotherapy</td>
<td>23.8%</td>
</tr>
</tbody>
</table>

Because of elevated aneuploidy frequencies prior to and up to 24 months from the start of chemotherapy, patients should receive **genetic counselling** about the potentially increased risk of an aneuploid conceptus from sperm cryopreserved prior to chemotherapy, and for conceptions **up to 2 years** after the initiation of treatment.
When to preserve?

- Before orchiectomy
- Before performing RPLND and before any surgical treatment at urogenital level
- Before any chemotherapy and/or after two years from the end of treatments
- Before radiotherapy at genital level
“Cryopreservation of semen before cancer treatment starts is currently the only established method able to preserve future male fertility”

Dohle GR. Int J Urol 2010;17(4):327-331
As part of education and informed consent before cancer therapy, medical oncologists should address the possibility of infertility with patients treated during their reproductive years (or with parents) and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists.

- 91% oncologists recognize the importance of discussing infertility risks
- Only 61% of them discuss fertility preservation routinely with patients
- Before treatments, just 10% oncologists refer patients to fertility specialists for sperm banking

Children suffering from cancer may become azoospermic or oligozoospermic after chemotherapy.

How to preserve?

Testicular tissue harvesting

- Stored germ cells could be re-implanted into the patient’s own testes
  - GERM CELL TRANSPLANTATION –

- Transplantation into a host to complete spermatogenesis
  - SPERMATOGENESIS EX-SITU -

- Stored stem cells could be maturated in vitro
  - IN VITRO SPERMATOGENESIS –

Spermatogenesis from stem cells
BIOLOGICAL PROBLEMS

TECHNICAL DIFFICULTIES

GENETIC and ETHICAL CONCERNS

Modified by Brinster RL. Science 2007;316(5823):404-405
Thank you!