The follow-up of patients with germ cell tumors (GCT)

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Follow-up of the adult male germ cell tumors (GCT)

- No firm guidelines can be given concerning the optimum follow-up strategy of GCT patients.

- Duration and intensity of the follow-up programs should consider histology of primary disease, prognostic category as well as sites of disease, administered therapies and the risk of recurrence/progression.

An ideal follow-up schedule identifies a recurrence early without causing harm by using unnecessary radiation
Risks of excess CT scans

- Typical chest CT has an associated radiation dose equivalent to 400 chest X-rays (8 vs 0.02 mSv). A chest X-ray is a low cost low-risk procedure, which is likely to pick up nodules of 1 cm or greater in the lung.
  (Royal College of Radiologists, 1998)

- Whole trunk CT produces dose of 10 to 30 mSv

- Typical whole trunk CT scan associated with a 1:1000 risk of cancer/leukaemia over the subsequent 40 years
Risks of excess CT scans

- Many follow-up recommendations that have been published most likely expose TGT survivors to unnecessary radiation, increasing the risk of a radiation-induced second cancer.

- Replacing CT by MRI scan would reduce this risk, but is not considered feasible for the majority of European countries and there is no definitive study at this time.

- However, effort should be made to reduce the frequency of CT scans and limit their overall number. PET-CT scanning has no role in the routine follow-up of TGT patients.
Why do we follow-up patients who have had germ cell tumors?

• To detect relapse: in the belief that earlier detection improves chance of cure
• To detect contralateral testicular cancers
• To manage acute and late toxicity
• To detect secondary neoplasms
• For reassurance, support and counselling with particular reference to issue such as employment and fertility
• To collect data
## Seminoma CSI Treatment options

<table>
<thead>
<tr>
<th>Surveillance</th>
<th>Adjuvant Radiotherapy</th>
<th>Adjuvant Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse rates 12-18%</td>
<td>Relapse rate &lt;5%</td>
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<tr>
<td><strong>Site of first detected relapse</strong>&lt;br&gt;92% infradiaphragmatic nodes</td>
<td>Site of first detected relapse after” dog-leg&quot; RT&lt;br&gt;78% chest or palpable lymph-nodes areas (supraclavicular fossa or inguinal regions)&lt;br&gt;After para-aortic nodal RT&lt;br&gt;59% infradiaphragmatic (mostly pelvic)</td>
<td>Site of first detected relapse after single dose&lt;br&gt;85% infradiaphragmatic nodes (primarily the para-aortic nodes) with half of rest in the chest</td>
</tr>
<tr>
<td><strong>Annual hazard rate for relapse</strong>&lt;br&gt;1- 2 yy &gt; 5%&lt;br&gt;3-4 yy 1 to 5%&lt;br&gt;5-10 yy &lt; 1%</td>
<td>Annual hazard rate for relapse&lt;br&gt;1- 3 yy 1 to 5%&lt;br&gt;4-10 yy &lt; 1%</td>
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<td>At relapse, ChT or RT according to previous treatment, clinical stage and site of disease</td>
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</tbody>
</table>
Stage I Seminoma

Adjuvant RT (PAS 20 Gy)
Adjuvant CBCDA (AUC 7)
Surveillance

 Proper staging
 • Abdominal CT scans
 • Reviewed histology
 • STM
 • Semen cryopreservation

 Equivalent outcomes
 • Cure approximates 100%
 • Different recurrence rates

 Age
 • Age-dependent toxicity
 • Higher risk for younger people

 Risk of recurrence
 • Low: 15-18%
 • Predictive factors not validated

 Consequences of Rx
 • Early side effects
 • Second cancers
 • CVD
 • Adherence to Follow-Up schedules

 Patient’s Empowerment for decision
Stage I Non-seminoma

Proper staging
- CT scans (no FDG-PET)
- Reviewed histology
- STM
- Semen cryo copreservation

Equivalent outcomes
- Cure approximates 100%
- Different recurrence rates

Patient’s Empowerment for decision

Risk of recurrence
- Roughly 30%
- Reliable predictive factors (VI)
  - 50% risk for VI +
  - 20% risk for VI -

Consequences of Rx
- Early side effects
- Second cancers
- CVD

Adjuvant PEB (1-2)
Surveillance
RPLND
Follow-up of the adult male germ cell tumors (GCT) (1)
(Testicular Cancer EAU 2014)

- Relapses in seminoma are rarer than in non-seminoma but tend to become evident in a longer period following the end of treatment.

- Following achievement of complete remission with chemotherapy for metastatic testicular cancer, relapse is very unlikely. It occurs in less than 10% of patients with good prognosis disease, but is more likely in patients with more advanced disease. In case of advanced intermediate or poor prognosis disease, an intensive surveillance aiming at an early detection of relapse is reasonable.

- Almost all recurrences will occur in the first 2 years, but further late relapses can occur; consequently surveillance should be intensive during the first 2 years, but follow-up should be pursued annually after 5 years.
Characteristics of relapse following therapy for germ cell tumour

Analysis of 96 relapses in 547 patients achieving remission

Median time to relapse 6 months (1-89), 85% within 18 months

Elevated markers 54%
Retro-peritoneal nodes 58%
Lung 26%
Liver 15%
CNS 8%

Flechon et al European Urology 48, 957-964: 2005
Relapses > 2 years after completion of primary chemotherapy for germ cell tumours

These patients have disease that is more chemotherapy resistant and immediate surgical resection of recurrent disease should be undertaken if feasible, irrespective of the level of tumour markers.

119 / 3704 (3.2%) Non-Seminoma

150 / 5880 (2.6%) Seminoma

10-year cause-specific survival

68% in all patients

50% in patients relapsing with vital malignant tumour

100% in those with teratoma/ necrosis before or after salvage chemotherapy.

# Localization of late relapses

*Oldenburg, Martin & Fossa J Clin Oncol 24: 5503-11, 2006*

<table>
<thead>
<tr>
<th>Site</th>
<th>Nonseminoma</th>
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<th>Seminoma</th>
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</thead>
<tbody>
<tr>
<td>Retroperitoneum</td>
<td>236 51%</td>
<td></td>
<td>34 55%</td>
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<tr>
<td>Mediastinum</td>
<td>43 9%</td>
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<td>17 27%</td>
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<tr>
<td>Lung/Pleura</td>
<td>77 17%</td>
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<td>2 3%</td>
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<tr>
<td>Neck/Supraclavicular</td>
<td>30 7%</td>
<td></td>
<td>9 15%</td>
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<tr>
<td>Pelvis</td>
<td>20 4%</td>
<td></td>
<td>1 2%</td>
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<tr>
<td>Other</td>
<td>53 12%</td>
<td></td>
<td>3 5%</td>
<td></td>
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<tr>
<td>AFP</td>
<td>207 49%</td>
<td></td>
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<tr>
<td>HCG</td>
<td>100 24%</td>
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</table>
Follow-up of the adult male germ cell tumors (GCT) (2)

( Testicular Cancer EAU 2014)

- After RPLND, relapse in the retroperitoneum is rare, and the chest is the most likely site of recurrence.

- CT of the chest has a higher predictive value than chest X-ray.

- Is demonstrated toxicity secondary to exposure to diagnostic X-rays. Therefore, the overall amount of exposure, in the absence of disease recurrence, should be kept within the 100 mSv (equivalent to about 5 CT thorax, abdomen and complete PET): the result is a recommendation to a limited use of surveys with higher administration of ionizing radiation (CT and PET), it does not extend after the first 3 years of observation.
Follow-up of the adult male germ cell tumors (GCT) (3)

(Testicular Cancer EAU 2014)

• With special expertise, US may be used as a method to screen the retroperitoneum during follow-up. However, the method is very much dependent on the investigator and can not be recommended as general method during follow-up.

• A contralateral testicular tumor is awaited in no more than 1.5% of patients in our country, nevertheless this risk should be monitored in all patients even after 5th year of follow-up

• Long-term side effects of treatment received great attention in the last years (second tumors, cardiovascular and renal diseases, hearing impairment, metabolic syndrome, and gonadal dysfunction); monitoring and preventing these specific long-term complications should currently be a part of the follow-up management
# Long-Term and Late Effects of GCT

<table>
<thead>
<tr>
<th>Long-Term and Late Effects of GCT</th>
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<tbody>
<tr>
<td>Secondary Malignant Neoplasms</td>
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<tr>
<td>Cardiovascular disease and Raynaud’s Phenomenon</td>
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<tr>
<td>Pulmonary Toxicity</td>
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<tr>
<td>Nephrotoxicity</td>
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<tr>
<td>Neurotoxicity and Ototoxicity</td>
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<tr>
<td>Avascular necrosis</td>
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<tr>
<td>Hypogonadism</td>
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<tr>
<td>Fertility and Sexuality</td>
</tr>
<tr>
<td>Psychosocial health and Impact of lifestyle factors</td>
</tr>
</tbody>
</table>
Trevis et Al. 2005
NIH Study

Patients treated for seminoma at the age of 35 yy have a 36% risk of developing a second cancer at the age of 75 yy.

For the general population the risk is 23%
Late Toxicity After GCT Treatment
Competing Risks: 2nd Cancers and Heart Disease

Cumulative risk of 2nd malignant neoplasm (SMN) or cardiovascular disease (CVD) by treatment among NSGCT survivors

1. **RPLND.**
   Both SMN and CVD in the absence of therapy.

2. **Chemo or RT:**
   Risk of SMN or CVD greater than after RPLND.

3. **RT+Chemo**
   Risk greater than either Chemo or RT.

van den Belt-Dusebout, JCO; 25:4370, 2007
Metabolic Syndrome
(20-30% of GCT long survivors)

NCEP definition
At least 3 of:
BP ≥ 130/85 or medication
Waist circum > 102
Fasting glucose ≥ 5.6 mmol/l
Triglycerides ≥ 1.7 mmol/l
HDL cholesterol ≤ 1.0 mmol/l

Norwegian definition
At least 2 of:
BP ≥ 140/90 or medication
BMI ≥ 30
Self reported diabetes /
Cholesterol ≥ 5.2 mmol/l or medication
Investigations to be performed at 2, 5 and 10 years to detect late effects of therapy for germ cell tumors

Blood pressure, height and weight
Creatinine + electrolytes
Fasting cholesterol, HDL, LDL, triglycerides and glucose
FSH, LH and testosterone
? Hip examination
? Osteoporosis screen

TGT Survivors need to be counselled on a healthy lifestyle (no smoking, regular physical exercise) and screened for other known risk factors such as hypertension, dyslipidaemia and excessive weight gain.
Gonadal dysfunction

- Semen cryopreservation should be considered in each patient. Compared with the general population the 10-year post-treatment paternity rate is significantly reduced, in part due to pre-existing fertility problems.

- Hypogonadism is present in 11%–35% of GCT survivors, depending on cut-off levels of testosterone used, age, cumulative cisplatin dose and follow-up duration.

- Therefore, determination of testosterone levels is recommended during follow-up, although it is not always clear when and at what testosterone level replacement should be offered.
Suggested follow-up protocol in GCT
(Fondazione IRCCS INT Milano)
### Stage I Seminoma

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<th>Surveillance</th>
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<th>Adjuvant carboplatin</th>
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<td>Determination of markers and physical examination at each visit</td>
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<tr>
<td>CT abdomen with m.d.c. (MRI if CT contra-indicated) at months 3, 9, 15, 21, 30 and 36</td>
<td>CT pelvis with m.d.c. (MRI if CT contra-indicated) (in patients receiving nodal RT para-aortic alone) at months 6, 18, 30</td>
<td>CT abdomen with m.d.c. (MRI if CT contra-indicated) at months 6, 12, 24</td>
</tr>
<tr>
<td>Abdominal ultrasound targeted to the retroperitoneum at months 6, 12, 18, 24, 42, 48, 54, 60</td>
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<td>Abdominal ultrasound targeted to the retroperitoneum once a year after the 5th year</td>
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<td>Chest X-ray once a year (up to 5 years)</td>
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<td>Surveillance</td>
<td>Adjuvant Chemotherapy</td>
<td>RPLND</td>
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<td>CT abdomen with m.d.c. (MRI if CT contra-indicated) at 6 months and 12</td>
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<td>Chest x-ray 4 times a year on the 1st and 2nd year, twice a year from the 3rd to the 5th year</td>
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<td>Chest x ray 4 times a year the first 2 years, twice a year from the 3rd to 5th year)</td>
<td>Chest x-ray 2 times a year to the 5th year</td>
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<td>Post radiotherapy for CSIIA/B</td>
<td>Postchemotherapy for CSII/Advanced</td>
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<td>Clinical evaluation: every 3-4 months for the first 2 years; every 6 months from the 3rd to 5th year; ≥ 1 year after the 5th year</td>
<td>If residual ≤ 3 cm: -&gt;surveillance</td>
<td></td>
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<tr>
<td>Determination of markers and physical examination at each visit</td>
<td>If residual&gt; 3 cm: with FDG/PET negative -&gt; surveillance</td>
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<tr>
<td>If post-treatment CT abdomen and pelvis scan is normal, no further routine CT scans. If post-treatment CT scan is abnormal, repeat the CT scan abdomen with m.d.c. (MRI if CT contra-indicated) at months 3, 6, 12, 24 but stop as soon as CT scan or MRI is normal or appearance is stable</td>
<td>In the case of surveillance: Clinical evaluation every 3 months for the first 2 years; every 6 months from the 3rd to 5th year; ≥ 1 year after the 5th year</td>
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<tr>
<td>Abdominal ultrasound targeted to the retroperitoneum every six months alternate to CT until months 54</td>
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### Advanced Non-Seminoma

<table>
<thead>
<tr>
<th>Disease in any venue: the absence of residual (Clinical remission or complete excision of residual carcinoma with criteria Fizazi ≤ 1)</th>
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<th>Metastatic disease in multiple sites</th>
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<tr>
<td>CT abdomen with m.d.c. and locations of previous disease (MRI if CT is contra=indicated) at months 3, 9, 18, 24</td>
<td>CT abdomen with m.d.c. and locations of previous disease (MRI if CT is contra-indicated) at months 6, 12 and 24</td>
<td>CT m.d.c. the sites of previous disease (MRI if CT is contra-indicated) with contrast medium at months 3, 6, 9, 12, 24</td>
</tr>
<tr>
<td>Abdominal ultrasound targeted to the retroperitoneum at months 6, 12, 15, 21, 30, 36, 42, 54</td>
<td>Abdominal ultrasound targeted to the retroperitoneum at months 9, 15, 21, 24, 30, 36, 42, 54</td>
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<tr>
<td>Abdominal ultrasound study with retroperitoneal once a year after the 5th year</td>
<td>Abdominal ultrasound study with retroperitoneal once a year after the 5th year</td>
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</tr>
<tr>
<td>Chest X Ray 4 times a year for the first 2 years; 2 times a year from the 3rd to the 5th year</td>
<td>Chest X Ray 4 times a year for the first 2 years; 2 times a year from the 3rd to the 5th year (CT of the chest instead of the chest X-ray in the case of pre-existing chest disease (the months of abdominal CT))</td>
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<tr>
<td>Ultrasound of the contralateral testis once per year</td>
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Conclusions

Managing patients with TGCT is a complex business requiring multidisciplinary teamwork and multiple clinical scenarios.

While evidence for best practice in terms of treatment is widely available and continuously evolving, the important issues regarding follow-up schedule are for the most part left to individual preference.

The standardising of follow-up would result in optimising risk/benefit ratios for individual patients, while ensuring economic use of resources.

Furthermore, this should enable future trials to address specific issues around follow-up giving meaningful and useful results.
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Thanks for the attention

www.tumorigerminali.it