UPDATE ON TESTICULAR TUMORS

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TESTICULAR TUMORS
clinically - intrascrotal mass

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germ cell tumors</td>
<td>85-90 %</td>
</tr>
<tr>
<td><strong>Seminomas</strong></td>
<td>40-50%</td>
</tr>
<tr>
<td><strong>Non seminomatous GCT</strong></td>
<td>10-20%</td>
</tr>
<tr>
<td><em>of one histological type</em></td>
<td></td>
</tr>
<tr>
<td><em>mixed types</em></td>
<td>30-50%</td>
</tr>
<tr>
<td>Gonadal stroma tumors</td>
<td>3-5%</td>
</tr>
<tr>
<td>Malignant lymphomas</td>
<td>3-5%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2%</td>
</tr>
</tbody>
</table>
GCT INCIDENCE

- remarkable race dependent geographical variation
- white men, Western countries highest (8-10/100,000)
- black men, Africa lowest incidence of GCT (< 2/100,000)
- incidence Europe and worldwide steadily ↑
- almost doubled in the last 30 years
INCIDENCE OF TESTICULAR TUMORS IN THE EC 2002

Table 1. Histopathologic types of testicular tumors observed at IP-MF from 2000 to 2012. Percentages, listed in brackets, refer to the total number of cases in a given year.

<table>
<thead>
<tr>
<th>Year</th>
<th>All</th>
<th>Seminoma</th>
<th>MGT</th>
<th>Teratoma</th>
<th>EC</th>
<th>DLBL</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>45</td>
<td>24 (53.3%)</td>
<td>14</td>
<td>1 (2.2%)</td>
<td>1</td>
<td>1 (2.2%)</td>
<td>4 (8.9%)</td>
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<tr>
<td>2001</td>
<td>44</td>
<td>23 (52.3%)</td>
<td>9</td>
<td>6 (13.6%)</td>
<td>4</td>
<td>0 (0.0%)</td>
<td>2 (4.5%)</td>
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<tr>
<td>2002</td>
<td>47</td>
<td>20 (42.6%)</td>
<td>19</td>
<td>2 (4.3%)</td>
<td>3</td>
<td>1 (2.1%)</td>
<td>2 (4.3%)</td>
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<tr>
<td>2003</td>
<td>51</td>
<td>24 (47.1%)</td>
<td>19</td>
<td>5 (9.8%)</td>
<td>1</td>
<td>0 (0.0%)</td>
<td>2 (3.9%)</td>
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<tr>
<td>2004</td>
<td>58</td>
<td>33 (56.9%)</td>
<td>16</td>
<td>2 (3.4%)</td>
<td>3</td>
<td>0 (0.0%)</td>
<td>4 (6.9%)</td>
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<tr>
<td>2005</td>
<td>48</td>
<td>18 (37.5%)</td>
<td>24</td>
<td>2 (4.2%)</td>
<td>1</td>
<td>1 (2.1%)</td>
<td>2 (4.2%)</td>
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<tr>
<td>2006</td>
<td>69</td>
<td>32 (46.4%)</td>
<td>24</td>
<td>0 (0.0%)</td>
<td>9</td>
<td>1 (1.4%)</td>
<td>4 (4.4%)</td>
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<tr>
<td>2007</td>
<td>50</td>
<td>21 (42.0%)</td>
<td>18</td>
<td>4 (8.0%)</td>
<td>4</td>
<td>1 (2.0%)</td>
<td>2 (4.0%)</td>
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<tr>
<td>2008</td>
<td>65</td>
<td>30 (46.2%)</td>
<td>23</td>
<td>2 (3.1%)</td>
<td>4</td>
<td>1 (1.5%)</td>
<td>5 (7.7%)</td>
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<tr>
<td>2009</td>
<td>54</td>
<td>29 (53.7%)</td>
<td>11</td>
<td>2 (3.7%)</td>
<td>4</td>
<td>4 (7.4%)</td>
<td>4 (7.4%)</td>
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<tr>
<td>2010</td>
<td>57</td>
<td>26 (45.6%)</td>
<td>16</td>
<td>2 (3.5%)</td>
<td>6</td>
<td>2 (3.5%)</td>
<td>5 (8.8%)</td>
</tr>
<tr>
<td>2011</td>
<td>68</td>
<td>39 (57.4%)</td>
<td>20</td>
<td>2 (2.9%)</td>
<td>2</td>
<td>2 (2.9%)</td>
<td>3 (4.4%)</td>
</tr>
<tr>
<td>2012</td>
<td>60</td>
<td>32 (53.3%)</td>
<td>15</td>
<td>5 (8.3%)</td>
<td>3</td>
<td>0 (0.0%)</td>
<td>5 (8.3%)</td>
</tr>
</tbody>
</table>

| All  | 716 | 351 (49.0%)| 228 (31.8%)| 35 (4.9%)| 45 (6.3%)| 14 (2.0%)| 43 (6.0%) |

MGT - mixed germ cell tumor; EC - embryonal carcinoma, DLBL - diffuse large B-cell lymphoma

SLO - in 2006-2010 testicular tumors 1,6% cancers in men (14th place) crude incidence 10,1/100.000

ETIOLOGIC FACTORS/ASSOCIATED CONDITIONS
TESTICULAR GTC

most important etiol factors (3.5 – 15x (50x) \( \uparrow \) estimated risk):

1. Cryptorchidism \( 3.5-5 \) fold
2. Prior testicular GCT (in contra-lateral testis) \( 5-10 \) fold
3. Family history of GCT \( 5.5 \) fold
4. Disorders of sex development (gonadal dysgenesis, androgen insensitivity syndrome-15X) - intersex syndromes (\textit{with Y Chromosome*}) \( 50 \) fold

\*mainly Gonadoblastoma
Seminoma - pivotal role as a precursor of most (adult type) GCT
INTRATUBULAR GERM CELL NEOPLASIA, UNCLASSIFIED (ICGN-U)

• precursor of most GCT
• adjacent to most invasive GCT
  - MI: tubules: reduced diameter, thickened wall, loss of normal germ cells (sometimes pagetoid spread in tubules with spermatogenesis)
  - cells: larger than normal spermatogonia, clear vacuolated cytoplasm (PAS+)
  - may be present in rete testis
• DD: intratubular growth of GCT (seminoma, embryonal carcinoma...)
  - microinvasive disease (seminoma)

PLAP ICGNU intratubular seminoma
GERM CELL TUMORS

Precursor lesion
Intratubular germ cell neoplasia, unclassified (ICGNU) (Cis)

Other types

Tumors of one histologic type (pure forms)

- Seminoma
  - Var: Seminoma with syncytiotrophoblastic cells
- Spermatocytic Seminoma
  - Var: Spermatocytic seminoma with sarcoma
- Embryonal carcinoma
- Yolk sac tumor (Endodermal sinus tumor)
- Choriocarcinoma (and other trophoblastic tumors)
  - Monophasic choriocarcinoma
  - Placental site trophoblastic tumor
- Teratoma
  - (Mature teratoma; Immature teratoma)
  - Teratoma with somatic type malignancies (-with secondary mal. comp.)
  - Monodermal teratoma (Monodermal variants:)
    - Dermoid cyst/Epidermoid cyst
    - Carcinoid (pure and with teratomatous elements)
    - Primitive neuroectodermal tumor

Tumors of more than one histologic type

Mixed germ cell tumors
- Var: polyembryoma and diffuse embryoma
SEMINOMA

- most frequent pure GCT (<50%)
- **presentation:**
  - painless mass (dull, aching sensation)
  - to 11% normal-sized or atrophic testes
  - 2 - 3% patients present with symptoms of meta (back pain-retroperit. invoiv.)
  - gynecomastia, ↑ serum hCG (syncytiotrophoblast c.)
- **MA:**
  - cream to tan and often multinodular
  - occasional yellow foci of necrosis (extensive necrosis infrequent)
- **MI:**
  - usually: diffuse, sheetlike pattern, fibrous septa with inflam. inf. (lymphoc, plasma c, granulomas)
  - some: cordlike arrangement, intertubular growth (**DD: lymphoma**), coag. necrosis
  - cells clear to lightly eosinophilic (15 to 25 μm), cytoplasm abundant (**PAS**+)
  - cell borders well defined
  - nuclei uniform, round to oval, usually central
  - finely granular chromatin, 1-2 prominent nucleoli

- **IHC:** PLAP+, CD117+, OCT3/4+, SALL4+, NANOG+, CK7/8/18+, podoplanin+, CD30-, SOX17+, AFP-, SOX2-, Glypican-3-..
Prominent fibrosis

Granulomatous stromal reaction

Tubular pattern

Intra / peritubular growth-colarretes
Cord-like pattern

Plasmacytoid seminoma

Signet ring seminoma

Intertubular growth

Microcystic pattern
Seminoma with syncytiotrophoblastic giant cells
SPERMATOCYTIC SEMINOMA (SS)

- **age > 50 years;** 1-4.5% of GCT; 5% bilateral; tumor marker negative

- **MA:** mucoid gelatinous appearance

- **MI:** 3 cell types, no stroma, no lymphocytes

- **IHC:** PLAP (neg/ + rarely), CK 18/CAM 5.2 (-/ + dot like), CD 117 (pos in 80%)

- **GEN:** amplification of a locus on chr. 9
  - mutations in genes previously linked to paternal-age-effect disorders

- **TH:** surgery (orchiectomy) alone (+surveillance)

- **PROGN:**
  - indolent course, recurrence extremely rare
  - metastases very rare (nearly only when sarcomatous transformation)

- **DD:** classical seminoma, pure EC and testicular lymphoma
SPERMATOCYTIC SEMINOMA (SS)

- small 6-8µm
- large 15-20µm
- giant 50-150µm
macro/microcystic appearance
(intercellular oedema)
- **SS with sarcoma**-rare (16 cases)
- most rhabdomyosarcomas
- poor prognosis

- **Anaplastic SS** (7 cases):
  - prominent nucleoli
  - one (large) type of cells (no small, no giant cells!)
  - good prognosis (similar to SS)
  - 1 case metastasized (Mikuz et al 2013)
EMBRYONAL CARCINOMA (EC)

- **very common in mixed GCTs** (87% of non-seminomatous GCT)
- pure only 2.3% of cases, ↓ (↑ recognition of foci of YST) → categorization as mixed GTC
- Symptoms: painless swelling, gynecomastia
  10% symptoms from metastases
- Serum: PLAP, βhCG, α-fetoprotein (AFP)
- **MA:** usually poorly circumscribed, gray-white, prominent areas of hemorrhage, necrosis
- **MI:** 3 major patterns, cohesive groups of primitive, anaplastic epithelial cells
  - **solid pattern** (cells are arranged in diffuse sheets)
  - **tubular** or **glandular pattern** (well-defined, glandlike or tubule-like structures), cuboidal to columnar epithelium
  - EC with syncitiotrophoblastic giant cells

**IHC:** PLAP+, CK8/18+, CD30+, OCT3/4+, SALL4+, SOX2+, SOX17-, AFP-, EMA-, CD117-, Glypican-3-
EC

- solid and glandular pattern

EC with seminoma-like cells

- papillary pattern
• **Def:** tumour characterized by numerous patterns that recapitulate the yolk sac, allantois and extra embryonic mesenchyme.

• Pure form only 2.4% of all GCTs

• **Yolk sac elements** in ~ 44% of all non seminom GCTs (mixed GCT)
  
  82% of GCTs in children (no assoc. with cryptorchidism, incid. stable rate)

• **Symptoms:** painless swelling
• Serum: AFP 100 – 1000 ng/ml

• **MA:**
  
  *children*
  
  - solid, gray or white to tan,
  - relatively homogeneous nodules with myxoid or gelatinous cut surfaces; sometimes cystic change

  *adults*
  
  - heterogeneous appearance
  - areas of hemorrhage, necrosis, and cystic change frequent

• **MI:** numerous patterns (hybrid, incomplete and transitional forms common)
DIFFERENT HISTOLOGICAL PATTERNS IN YST
PATTERN OF NO PROGNOSTIC OR THERAPEUTIC IMPORTANCE!

- microcystic / honeycomb / reticular / vacuolated
- macrocystic
- endodermal sinus (perivasc)
  Schiller- Duval bodies
- papillary
- solid
- glandular / alveolar
- myxomatous
- sarcomatoid
- macrocystic
- polyvesicular vitelline
- hepatoid
- parietal
Microcystic pattern

Papillary pattern

Pseudorosette formation-Schiller Duval body
Polyembryoma / diffuse embryoma
double layer pattern of EC (mixed EC+YST)

Embryoid body

CD30
Endodermal sinus pattern (+hyaline globules)

Labryrinthine pattern

Glandular pattern
CHORIOCARCINOMA

• Incidence: 0.8/100,000/year (pure form < 1%, 8% mixed GCT)

• Symptoms:
  • Hemorrhage from metastases "Choriocarcinoma syndrome" (lung, CNS, GIT, anemia)
  • Gynecomastia
  • βHCG > 100,000 mIU/ml
  • Rarely hyperthyroidism (cross reaction HCG/TSH)

• MA: usually hemorrhagic/necrotic nodule, may be normal (regression/scar)

• MI: small basophilic cuboidal cells (cytotrophoblast) covered with large multinucleated eosinophilic syncytial cells (syncytiotrophoblast); background hemorrhage, necrosis

• IHC: β-HCG

• Monophasic choriocarcinoma (biphasic pattern absent; instead atypical trophoblastic cells of varying size)

• Placental site trophoblastic tumor (intermediate trophoblastic cells) (PLAP+)
βHCG
Table 17-6 Immunohistochemistry in Intratubular Germ Cell Neoplasia, Unspecified Type, and Germ Cell Tumor

<table>
<thead>
<tr>
<th>Marker</th>
<th>IGCNU</th>
<th>Classic Seminoma</th>
<th>Spermatocytic Seminoma</th>
<th>Embryonal Carcinoma</th>
<th>YST</th>
<th>Choriocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-kit (CD117)</td>
<td>+</td>
<td>+</td>
<td></td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>OCT3/4</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>PLAP</td>
<td>+</td>
<td>+</td>
<td>S</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>AE1/AE3</td>
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<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD30</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
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<td>−</td>
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<tr>
<td>SALL4</td>
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<td>+</td>
<td>S</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Glypican-3</td>
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<td>−</td>
<td>+</td>
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<td>hCG</td>
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<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>

Reactivity: +, positive; S, sometimes positive; −, negative.
Bostwick, Cheng 2014
TERATOMA

- **Def:** Tumour composed of several types of tissue representing different germinal layers (endoderm, mesoderm and ecto-derm). They may be composed exclusively of well differentiated, mature tissues or have immature, fetal-like tissues. It has been recommended to consider these morphologies as a single entity based on genetics.
- 2nd most frequent GCT in *childhood* (after YST); 15-18% of all testicular tumors
  - Average age = 20 Mo
  - MI: organized, well differentiated, mature tissue types; *organoid structures*
  - keratinizing and non-keratinizing squamous epithelium, neural and glandular tissues
- **Behaviour of testicular teratoma different from ovarial!**
  - distinction mature vs. immature not important
  - depending whether pre or postpubertal
- **Before puberty absolutely benign / After puberty can metastasize**

- **PURE POSTPUBERTAL TERATOMA 20-40ys**
  - malignant tumors *(origin: malignant germ cel (ICGNU)→nonteratomatous GCT→differentiation into teratomatous elements)*
  - complex cytogenetic abnormalities including 12p amplification-often in form of i(12p); when mixed-similar anomalies to other components
  - **MA:** predominantly solid
  - **MI:** *disordered arrangement*, cytological atypia, mitoses
  - ICGNU in adjacent tubules (90%), atrophy, impaired spermatogenesis
Variants of teratoma: DERMOID CYST (≤ 20 cases)
Variants of teratoma: EPIDERMOID CYST (1 % of GCT)
Variants of teratoma: TERATOMA WITH SOMATIC TYPE MALIGNANCIES

Rare in primary tumors – in metastases after chemotherapy

We diagnose such neoplasms when they form a pure nodule of “substantial size” – in order of half to a whole field viewed with a 4x objective.

Table 6.16 The most frequent somatic malignancies developed in teratomas

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

Testicular teratoma with somatic type malignancy

Figure 1. B: Prima

Figure 3: stasis. Si

Figure 4. A: 2nd metastasis. Cords and trabeculae of small round to oval cells with slightly eccentric nuclei and finely stippled chromatin were the hallmark of 2nd metastasis (HE, 200x). B: 2nd metastasis. Positivity for synaptophysin in small cells (synaptophysin, 200x).

SPONTANEOUS REGRESSION OF TESTICULAR GCT

• patient presenting with metastatic disease

• „In 30-80% of the so called „extragonadal germ cell tumors“ in adults one of the testes contains a scar with or without IGCNU or tumor residuals."

• clin. inapparent primary t.- „ghost evidence“ of preexisting t. on histology of testis:
  • dense, often hyaline scarring
  • intratubular calcifications
  • sometimes ICGNU in adjacent tubules
  • lymphoplasmacytic infiltrate
  • hemosiderin laden macrophages
  • testicular atrophy
  • rarely small residual focus of invasive (seminoma)

• most prone to spontaneous regression choriocarcinoma (rarest)
• most cases seminoma (greater frequency)
• may also appear in embryonal carcinoma
Burnt out tumor

Fibrous scar

Intratubular calcifications
No spermatogenesis
Partially regressed seminoma / Burnt out tumor

Residual focus of invasive seminoma
STAGING AND PROGNOSTIC MARKERS

- most testicular cancers: localized at presentation (qualify as clinical stage I)
- further refinement - postorchiectomy levels of serum markers (LDH, βHCG, AFP)
- most difficult therapeutical choices for clinicians: in localized tumors →

  - **Seminoma** - most important factors guiding clinicians (should be included in a biopsy report!)
    - tumor diameter (> 4 cm) and
    - invasion of the rete testis
  - **Non-seminomatous GCT** (identification of VI is not problematic!)
    - presence of VI
    - amount of EC
Seminoma cells easily smear across tissue or embedded block!
Seminoma: - diameter ≥ 4 cm  
- rete testis invasion:

CK w.sp.

a. discontinuous pagetoid spread within tubules  
b. inter-tubular spread within the parenchyma
PRIMARY TESTICULAR LYMPHOMA (PTL)

- most common testicular tumors, men >60 (60-80) years
- **majority of PTL are diffuse large B-cell lymphomas (DLBCL)**
- Adults: 80% DLBCL
- plasmocytoma less frequent
- MALT, follicular ly, T cell ly exceptional
- Children: Burkit and lymphoblastic ly
- **PTL unique and aggressive extranodal non-Hodgkin ly**
- high risk of extranodal recurrences
- **predilection for dissemination to extranodal and atypical sites:**
  - central nervous system (CNS)
  - Waldeyer’s ring
  - lung
  - skin
  - contralateral testis

→ **careful evaluation of especially CNS**

No cases of Hodgkin lymphoma of the testis!
CONCLUSION

• testicular tumors - relatively rare, complex
• surgical procedure – simple → every pathologist can be challenged
• to avoid diagnostic errors → inappropriate treatment
• awareness of relevant areas necessary in testicular GCT (classification-special types of GTC, prognostic factors..)

Think of other tumor types!
Acknowledgments

prof. Gregor Mikuz

some Figs form Bostwick, Cheng 2014