Patients with Differences of Sex Development and the Development of Gonadal Malignancy: Risk Stratification and Long-Term Outcomes

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Some patients with DSD are known to be at increased risk for pre-malignant GCNIS/Gb and invasive GCTs

Current management often involves early gonadectomy
- Guaranteed infertility and hypogonadism
- Prevention of potential future gonadal GCT

Natural history of timing of these events is unknown
Long-term oncologic outcomes are unknown
Objectives

1. To validate a previously described malignancy risk stratification system
2. To determine likelihood of finding Gb or GCT at the time of gonadal surgery
3. To describe long-term oncologic outcomes for patients with DSD and Gb or invasive GCT

¹Cools et al., 2006, Looijenga et. al. 2007
Methods

- Systematic PubMed review to identify patients (PRISMA)
  - Included patients with DSD diagnosis + gonadal surgery + pathology reported

- Recorded information on:
  - DSD diagnosis, karyotype, age at surgery, pathologic diagnosis, treatment, follow up, recurrence, survival

- Grouped patients and report trends using descriptive non-parametric methods:
  - Risk class\(^1\)
  - Pathologic diagnosis

- Evaluated the rates of finding Gb or GCT at gonadal surgery and compared RFS and OS using the Kaplan-Meier method and log-rank testing

\(^1\)Cools et al., 2006, Looijenga et. al. 2007
# Risk Classification System

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Disorder</th>
<th>Malignancy risk (%)</th>
<th>Recommended action</th>
<th>Studies (n)</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>GD* (+Y)* intra-abdominal</td>
<td>15–35</td>
<td>Gonadectomy(^c)</td>
<td>12</td>
<td>&gt;350</td>
</tr>
<tr>
<td></td>
<td>PAIS non-scrotal</td>
<td>50</td>
<td>Gonadectomy(^c)</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Frasier</td>
<td>60</td>
<td>Gonadectomy(^c)</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Denys–Drash (+Y)</td>
<td>40</td>
<td>Gonadectomy(^c)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Turner (+Y)</td>
<td>12</td>
<td>Gonadectomy(^c)</td>
<td>11</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>17(\beta)-HSD</td>
<td>28</td>
<td>Monitor</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>GD (+Y)(^c)</td>
<td>Unknown</td>
<td>Biopsy(^d) and irradiation?</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PAIS scrotal gonad</td>
<td>Unknown</td>
<td>Biopsy(^d) and irradiation?</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>CAIS</td>
<td>2</td>
<td>Biopsy(^d) and ???</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Ovotestis DSD</td>
<td>3</td>
<td>Testis tissue removal?</td>
<td>3</td>
<td>426</td>
</tr>
<tr>
<td></td>
<td>Turner (− Y)</td>
<td>1</td>
<td>None</td>
<td>11</td>
<td>557</td>
</tr>
<tr>
<td>No (?)</td>
<td>5(\alpha)-reductase</td>
<td>0</td>
<td>Unresolved</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Leydig cell hypoplasia</td>
<td>0</td>
<td>Unresolved</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

CAIS, complete androgen insensitivity syndrome; 17\(\beta\)-HSD, 17\(\beta\)-hydroxysteroid dehydrogenase deficiency; PAIS, partial androgen insensitivity syndrome.

\(^a\) Gonadal dysgenesis (including not further specified, 46XY, 46X/46X\(\alpha\), mixed, partial, complete).

\(^b\) GBY region positive, including the TSPY gene.

\(^c\) At time of diagnosis.

\(^d\) At puberty, allowing investigation of at least 30 seminiferous tubules, with diagnosis preferably based on OCT3/4 immunohistochemistry.

\(^1\) Looijenga et al., 2007
### Results

- 386 articles, 2037 patients (range 1951-2017)
- Median age at surgery 17 y (IQR 11-20 y)
- Median follow up 60 mos (IQR 30-68.1 mos)

<table>
<thead>
<tr>
<th>Risk class</th>
<th>n (%)</th>
<th>No Gb/GCT</th>
<th>Gb</th>
<th>GCT</th>
<th>Median age at surgery (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2037 (100%)</td>
<td>61%</td>
<td>18.1%</td>
<td>11.9%</td>
<td>17 y (11-20 y)</td>
</tr>
<tr>
<td>High/intermediate</td>
<td>1175 (58%)</td>
<td>54.6%</td>
<td>23.8%</td>
<td>21.6%</td>
<td>16 y (7-19.9 y)</td>
</tr>
<tr>
<td>Low</td>
<td>580 (28%)</td>
<td>81.6%</td>
<td>8.1%</td>
<td>10.3%</td>
<td>16 y (14-21.7 y)</td>
</tr>
<tr>
<td>No*</td>
<td>4 (&lt;1%)</td>
<td>75%</td>
<td>0%</td>
<td>25%</td>
<td>13.6 y (9-40.8 y)</td>
</tr>
<tr>
<td>Unknown</td>
<td>278 (14%)</td>
<td>41.1%</td>
<td>20.4%</td>
<td>38.5%</td>
<td>18.9 y (14-24 y)</td>
</tr>
</tbody>
</table>

*Not further analyzed due to only 4 patients*
Gb/GCT-free and GCT-free Survival by Age at Gonadal Surgery

*p<0.001
RFS and OS by Risk Category

Recurrence-free survival by DSD risk category

DSD risk class
- high/intermediate risk
- low risk
- no risk
- unknown risk

5 y RFS:
High/intermediate – 95.9%
Low – 98.1%
Unknown – 88.8%

Overall survival by DSD risk category

DSD risk class
- high/intermediate risk
- low risk
- no risk
- unknown risk

5 y OS:
High/intermediate – 96.4%
Low – 97%
Unknown – 90.1%

*p<0.001
RFS and OS by Pathology

Recurrence-free survival by pathologic diagnosis

5 y RFS:
No Gb/GCT – 99.6%
Gb – 98.4%
GCT – 83.3%

Overall survival by pathologic diagnosis

5 y OS:
No Gb/GCT – 99.6%
Gb – 96.7%
GCT – 86.6%

*p<0.001
Limitations

- Classification and accuracy of DSD diagnoses has changed significantly over time
- Reporting/publication bias
- Large studies had mean/medians used for individual patients
- Risk classification was limited based on data reported
Conclusions

- Previously reported malignancy risk classification system appears to work well
  - Some DSD diagnoses are missing
- Risk of finding Gb or GCT at surgery increases with age, regardless of risk
- 5 y RFS/OS equivalent for Gb and no Gb/GCT, worse for GCT
- This information can be useful when counseling families:
  - If/when to perform gonadectomy
  - Outcomes if any gonadal pathology is found