Treatment Options for the Infertile Male with Cancer:
Sperm Banking, Sperm Procurement and Assisted Reproduction

Alexander W. Pastuszak, MD, PhD
Assistant Professor
Division of Urology
Department of Surgery
University of Utah School of Medicine
Disclosures

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• **Antares Pharmaceuticals** – author

• **Woven Health** – founder and leadership role
Objectives

• Present the relationship between cancer and male fertility

• Understand the impact of cancer treatment on male fertility potential

• Discuss methods of fertility preservation in men with a history of cancer
Foundational Concepts

- Detrimental effect of cancer on male fertility is multifactorial
- Cancer itself may impair sperm production
  - Hormonal derangements (e.g. hCG secretion)
  - Direct testicular involvement by tumor
  - Genetic influences between cancer and male fertility
- Therapeutic interventions are harmful
  - Chemotherapy
  - Biologics?
  - Radiotherapy
  - Surgical therapy
Fertility is a spectrum
• “Normal” sperm counts not essential for fertility

Measures to improve fertility must not diminish cancer cure rates

Primary goal to preserve natural fertility, using assisted reproduction techniques (ART) only when necessary
Safety of Fathering a Child After Cancer Treatment

• Sperm production takes ~3 months
• No standard guidelines
  • General recommendation is to wait 1-2 years
  • Varies based on drug – chemo vs. biologics
• Considerations
  • Health status
  • Post-treatment period
  • Drugs used
Potential for Recovery of Spermatogenesis After Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Good</th>
<th>Moderate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin</td>
<td>Vincristine</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>(B)EP</td>
<td>Chlorambucil</td>
</tr>
<tr>
<td>Prednisone</td>
<td>ABVD</td>
<td>Mechlorethamine</td>
</tr>
<tr>
<td>Estrogens</td>
<td></td>
<td>Procarbazine</td>
</tr>
<tr>
<td>Androgens</td>
<td></td>
<td>CHOP</td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thioguanine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(B)EP and CHOP used for testis cancer and lymphoma
Iatrogenic Testicular Injury

- Radiotherapy (XRT)
- Chemotherapy / Biologics
- Surgical therapy
Surgery: Retroperitoneal Lymph Node Dissection (RPLND)

Indications in testicular cancer:
- Primary low stage non-semimomatous disease
- Post-chemotherapy

Damage to sympathetic function possible → retrograde or anejaculation
- Incompetent bladder neck
- Decreased or absent vasal contraction
RPLND: Treatment of Ejaculatory Failure

- Sympathomimetic medications (10-14 d)
  - **Sudafed** (60 mg QID) → adrenergic stimulant
  - **Imipramine** (25 mg QID) → inhibits NE reuptake

- May improve both retrograde and/or anejaculation
  - Promotes bladder neck closure / vasa contraction
Transrectal Electroejaculation (EEJ)
- General anesthesia required
- Virtually 100% successful
- Semen quality always impaired
  - IUI possible → 8-10% success/month
  - IVF/ICSI success comparable to normal couples
- EEJ can be used prior to therapy in men or boys incapable of producing sample for banking

RPLND: Treatment of Ejaculatory Failure

Probe-accessory sex gland interface

Preventive/Protective Measures

• Sperm banking
• Pre-treatment testicular sperm extraction (TESE)
• Hormonal suppression of spermatogenesis
  • GnRH agonists
  • Exogenous testosterone
• Post-treatment sperm extraction (onco-TESE)
Sperm Banking

No limit below which sperm banking is denied, except **azoospermia**
- ICSI → only one sperm per egg

**Sample Options**
- Ejaculated / stimulated (PVS vs. EEJ) sample
- Pre-treatment testicular sperm extraction (TESE)
- Onco-TESE
Access to Sperm Banking

• Sperm banks in Kenya and East Africa

• **Discuss sperm banking PRIOR to cancer treatment!!**
  • Uncertain results after treatment…
  • Pediatrics → promise of spermatogonial stem cell repopulation

• Banking can usually be done **same day → NO DELAY IN CANCER TREATMENT**
Testicular Sperm Extraction (TESE)

1. In-office (vs. OR) procedure
2. Cord block usually used
3. ? IV sedation

Focal Mature Sperm
# TESE in Azoospermic Men Prior to Chemotherapy for Testis Cancer

## Clinical Stage (Testis Cancer) Table

<table>
<thead>
<tr>
<th>Clinical Stage (Testis Cancer)</th>
<th># of Patients</th>
<th>Successful Sperm Retrieval</th>
<th>Maturation Arrest</th>
<th>Sertoli Cell Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>100% (2/2)</td>
<td>0% (0/2)</td>
<td>0% (0/2)</td>
</tr>
<tr>
<td>IIA-IIB</td>
<td>8</td>
<td>38% (3/8)</td>
<td>38% (3/8)</td>
<td>25% (2/8)</td>
</tr>
<tr>
<td>≥ IIC</td>
<td>4</td>
<td>25% (1/4)</td>
<td>0% (0/4)</td>
<td>75% (3/4)</td>
</tr>
</tbody>
</table>

### TESE in Azoospermic Men Prior to Chemotherapy for Lymphoma

<table>
<thead>
<tr>
<th>Disease</th>
<th># of Patients</th>
<th>Successful Sperm Retrieval</th>
<th>Maturation Arrest</th>
<th>Sertoli Cell Only</th>
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</thead>
<tbody>
<tr>
<td>Hodgkin's</td>
<td>7</td>
<td>43% (3/7)</td>
<td>29% (2/7)</td>
<td>29% (2/7)</td>
</tr>
<tr>
<td>Non-Hodgkin's</td>
<td>10</td>
<td>50% (5/10)</td>
<td>30% (3/10)</td>
<td>20% (2/10)</td>
</tr>
</tbody>
</table>
Post-Treatment Azoospermia - Options

- Use of sperm from concentrated pellet
  - 21% of NOA, 9% of OA men have sperm in pellet

- Microscopic Epididymal Sperm Aspiration (MESA)
  - Prostate Cancer after RRP
  - Non responsive anejaculatory patient (RPLND)

- Testicular Sperm Extraction (TESE / microTESE)
  - Post-treatment azoospermia
  - Anejaculatory treatment failure

- Therapeutic Donor Insemination (TDI)

Shin et al. 2016:
- 66 men with post-chemo azoospermia
- Underwent microTESE / ICSI → sperm retrieval, pregnancy, birth rates

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Sperm retrieval</th>
<th>SRR (%)</th>
<th>No. of pregnancies</th>
<th>PR (%)</th>
<th>No. of deliveries</th>
<th>LBR (%)</th>
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</thead>
<tbody>
<tr>
<td>Testicular cancer</td>
<td>Yes</td>
<td>11</td>
<td>52</td>
<td>7</td>
<td>33</td>
<td>29</td>
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<tr>
<td></td>
<td>No</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ALL</td>
<td></td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>22</td>
<td>11</td>
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<tr>
<td>Hodgkin’s lymphoma</td>
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<td>6</td>
<td>3</td>
<td>5</td>
<td>56</td>
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<td>AML</td>
<td></td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>43</td>
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<tr>
<td>Non-Hodgkin’s lymphoma</td>
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<td>3</td>
<td>4</td>
<td>3</td>
<td>43</td>
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<td>Rhabdomyosarcoma</td>
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<td>4</td>
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<td>14</td>
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<td>Bladder cancer</td>
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<td>2</td>
<td>1</td>
<td>33</td>
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<td>Osteosarcoma</td>
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<td>1</td>
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<td>50</td>
<td>50</td>
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<tr>
<td>Anaplastic anemia</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Total</td>
<td></td>
<td>31</td>
<td>35</td>
<td>47</td>
<td>23</td>
<td>18</td>
</tr>
</tbody>
</table>

Sperm Retrieval Rate → 40%
Clinical Pregnancy Rate → 35%
Live Birth Rate → 27%

No significant difference in SRR, clinical pregnancy, or live birth rates between any cancers; no predictors of mTESE success by MVA
Onco-TESE – Sperm Extraction After Orchietomy

• Sperm harvesting from the testicle of men with testicular cancer after / during orchietomy
Onco-TESE – Likelihood of Finding Sperm

Shoshany et al. 2016
• Histologic slides reviewed from 214 radical orchiectomy specimens

58% (7 of 12 men) with azoospermia or cryptozoospermia had mature sperm
Onco-TESE Outcomes

• **Sperm Retrieval**: 16 of 27 (59%) oncoTESE cases → successful sperm retrieval

• **Pregnancy**: 4 of 6 men → initiated pregnancy with IVF/ICSI.

• **Live births**: 2

_Sperm retrieval rates are similar to microTESE for testicular failure_
Summary

- Patients with cancer often have impaired spermatogenesis
- Superimposed on this baseline defect are iatrogenic effects of treatment: XRT, CT and surgery
- **Sperm banking is the best pre-treatment insurance for ultimate chance of fertility**
- Post-therapy, patients can benefit from interventions: EEJ, TESE, Onco-TESE