Cancer and Fertility

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Advances in cancer treatment have led to improvements in survival

Survival rates

<table>
<thead>
<tr>
<th></th>
<th>0–9</th>
<th>10–19</th>
<th>20–29</th>
<th>30–39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18,499</td>
<td>43,137</td>
<td>74,785</td>
<td>134,634</td>
</tr>
<tr>
<td>Female</td>
<td>8,636</td>
<td>36,912</td>
<td>105,114</td>
<td>250,921</td>
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~13.7 million cancer survivors in the US
5% are younger than 40 years of age

Siegel 2012, De Moor 2013
Cancer treatments affect fertility

Surgery
- If reproductive structures removed/altered

Radiation Therapy
- Based on field of treatment and dose

Chemotherapy and Hormonal Therapy
- Based on agent and dose
Patient factors also affect fertility

- Age (females)
- Diagnosis
- Obesity
- Tobacco smoking, alcohol, drugs
- Pre-treatment fertility
Fertility is an important issue for cancer survivors

Many young cancer patients...

- Have not yet started or completed their families at the time of diagnosis
- Want to be parents after treatment
- Do not recall being told of risk of infertility
- Are distressed or concerned about possibility of infertility

Clinicians don’t always discuss fertility with their patients

- Believe this is important
- Inadequate knowledge
- Barriers
  - Lack of time
  - Lack of resources
  - Concern about cost
  - Don’t know where to refer

There is national recognition of the need to address fertility concerns.
There is professional recognition of the need to address fertility concerns

Health care providers have a responsibility to

• Inform patients about the risks that their cancer treatment will permanently impair fertility

• Discuss options for fertility preservation and parenting after cancer

• Refer to appropriate specialists

American Society of Clinical Oncology (Loren et al, 2013)
American Medical Association (2013)
NCCN AYA Adolescent and Young Adult Clinical Oncology Guidelines (NCCN, 2012)
European Society for Medical Oncology (Pentheroudakis et al, 2010)
American Academy of Pediatrics (Fallat et al, 2008)
American Society of Reproductive Medicine (ASRM, 2005)
Outline

- Basics of reproductive biology
- Effects of treatment on fertility
- Options for fertility preservation
- Resources at MSKCC to help you discuss fertility with your patients
MALES

Basics of Reproductive Biology
Effects of Treatment on Fertility
Options for Fertility Preservation
Spermatogenesis and Ejaculation

- Stem spermatogonia
- Differentiating spermatogonia
- Spermatocyte
- Spermatid
- Testicular Sperm
- Ejaculated Sperm

27 days
24 days
22 days
12 days

Normal
Fertility Effects of Treatment

Impaired sperm production
- Depletion of stem cells and developing sperm
  Recovery – Oligospermia – Azoospermia

Impaired sperm transport
- Injury to pelvic ducts/blood vessels/nerves → erectile/ejaculatory dysfunction

Pituitary gland dysfunction
- Disruption of hypothalamic-pituitary-gonadal axis
Evaluation of Male Fertility

It is impossible to predict with certainty who will be affected permanently

- **Semen analysis (WHO criteria, 2010)**
  - Volume: 1.5 (1.4–1.7) ml
  - Sperm concentration: 15 (12–16) million/ml
  - Progressive motility: 32 (31–34)%
  - Vitality: 58 (55–63)%

  *DNA integrity testing not included*

- **Hormonal analysis**
  - FSH, LH, Testosterone
Males
Fertility Preservation Options

Cryopreservation of Gametes or Gonadal Tissue

Post-Pubertal

Sperm Cryopreservation

Sperm Banking
Electroejaculation
Testicular Sperm Extraction

Pre-Pubertal

Testicular Tissue Cryopreservation

Reduction of Gonadal Toxicity

Gonadal Shielding
John

19 year old male

- Diagnosis: Testicular cancer
- Treatment plan: Orchiectomy followed by chemotherapy with BEP (bleomycin, etoposide, cisplatin)
- Social: single college student, no children

What is available for this patient?
Sperm Cryopreservation (Banking)

Semen collected, analyzed, placed in vials, frozen, and stored for possible future use

**Sperm Bank Collection**
- Manual stimulation
- 3 collections
- Abstain 2-5 days

**Electroejaculation (EEJ)**
- If patient is unable to collect manually

**Testicular Sperm Extraction (TESE)**
- If patient is azoospermic
Peter

8 year old male

- Diagnosis: Rhabdomyosarcoma
- Treatment plan: Chemotherapy with VAC (vincristine, doxorubicin, cyclophosphamide)
- Social: school-aged child

What is available for this patient?
Testicular Tissue Cryopreservation

- Tissue biopsied, frozen, and stored for potential future use
  - Tissue reimplantation – no live births to date
    - Concern about re-implanting cancer cells
  - In vitro maturation – no live births to date

- Investigational
38 year old male

- Diagnosis: Rectal cancer
- Treatment plan: Pelvic RT with CI fluorouracil followed by surgical resection and adjuvant chemotherapy with FOLFOX (fluorouracil and oxaliplatin)
- Social: married with 3 year old son
Gonadal Shielding

During pelvic/inguinal field radiation

- With IMRT to minimize testicular dose
- Also recommend sperm banking before treatment
Males

Fertility Preservation Options

- Cryopreservation of Gametes or Gonadal Tissue
  - Post-Pubertal
    - Sperm Cryopreservation
      - Sperm Banking
      - Electro-ejaculation
      - Testicular Sperm Extraction
  - Pre-Pubertal
    - Testicular Tissue Cryopreservation
    - Gonadal Shielding
  - Reduction of Gonadal Toxicity
FEMALES

Basics of Reproductive Biology
Effects of Treatment on Fertility
Options for Fertility Preservation
Ovarian Reserve = number and quality of eggs
Effect of Age on Ovarian Reserve

Loss of follicles \(\rightarrow\) Infertility, Menopause

- Optimal fertility
- Declining fertility
- End of fertility
- Menopause

- Loss of follicles leads to infertility and menopause.
Females
Fertility Effects of Treatment

Depletion of ovarian follicle pool (oocytes)
- Premature ovarian failure $\rightarrow$ infertility, menopause
  May have narrowed window of reproductive opportunity

Pituitary gland dysfunction
- Disruption of hypothalamic-pituitary-gonadal axis

Uterine damage
- Vascular changes, endometrial injury $\rightarrow$ inability to support embryo implantation
- Myometrial fibrosis $\rightarrow$ inability to accommodate a growing fetus
Evaluation of Female Fertility

It is impossible to predict with certainty who will be affected permanently.

- Transvaginal ultrasound
  - Ovarian antral follicle count
- Hormonal analysis
  - Anti-Mullerian Hormone (AMH)
  - Follicle Stimulating Hormone (FSH)
  - Estradiol
Females
Fertility Preservation Options

Cryopreservation of Gametes or Gonadal Tissue

- Post-Pubertal
  - Oocytes
  - Embryos
  - Ovarian Tissue

- Pre-Pubertal
  - Ovarian Transposition
  - Ovarian Suppression
  - Alternative Treatment

Reduction of Gonadal Toxicity
Susan

33 year old female

- Diagnosis: Breast cancer
- Treatment plan: Mastectomy with immediate reconstruction followed by AC-T (doxorubicin, cyclophosphamide, paclitaxel) → tamoxifen
- Social: married, 1 child

What is available for this patient?
Embryo Cryopreservation

Ovarian Stimulation

Daily hormone injections
Starts day 2 of menses
Continues for ~10 days

With anesthesia

Oocyte Retrieval
Kelly

18 year old female

- Diagnosis: Relapsed Hodgkin Lymphoma
- Prior treatment: ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) 2 years ago
- Treatment plan: BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)
- Social: single college student, no children

What is available for this patient?
Oocyte Cryopreservation

In Vitro Fertilization

Cryo-preservation
Embryo/Oocyte Cryopreservation

- Concerns about delay in treatment
  - Generally requires about 3 weeks of time
  - Expedited referrals
  - Downregulation of pituitary with GnRHa

- Concerns about ↑ estrogen
  - No evidence about effect on recurrence/survival
  - Aromatase inhibitor (eg, letrozole) can lower estrogen levels
Embryo/Oocyte Cryopreservation

Concerns about specific medical risks
• Bleeding if thrombocytopenic or liver dysfunction
• Infection if neutropenic
• History of DVT/VTE
• Anesthesia complications because of disease in the chest
## Embryo Transfer

### Success Rates with Thawed Embryos From Non-Donor Oocytes

<table>
<thead>
<tr>
<th>Percentage Range</th>
<th>Success Rate</th>
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<tbody>
<tr>
<td>&lt;35</td>
<td>39.3%</td>
</tr>
<tr>
<td>35-37</td>
<td>35.7%</td>
</tr>
<tr>
<td>38-40</td>
<td>30.3%</td>
</tr>
<tr>
<td>41-42</td>
<td>24.5%</td>
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</tbody>
</table>

SART 2011
18 year old female

- Diagnosis: Non-Hodgkin Lymphoma
- Treatment plan: BEAM (BCNU, etoposide, cytarabine, melphalan), must start within 5 days
- Social: single college student, no children

What is available for this patient?
Ovarian Tissue Cryopreservation

- Ovary resected, cortex dissected, frozen, and stored for potential future use
  - Tissue reimplantation – ~20 live births to date
    Concern about re-implanting cancer cells
  - In vitro maturation – no live births to date
- Investigational
Ovarian Suppression

GnRH agonist (leuprolide)

- To prevent recruitment of follicles, potentially protecting them from effects of chemotherapy
- Initiated 2-4 weeks before starting chemotherapy, continued monthly throughout treatment
- Investigational - studied primarily in breast cancer and lymphoma with conflicting results
Barbara

3 year old female

- Diagnosis: Neuroblastoma
- Treatment plan: RT and multiagent chemotherapy
- Social: pre-school child

What is available for this patient?
Ovarian Tissue Cryopreservation

- Ovary resected, cortex dissected, frozen, and stored for potential future use
  - Tissue reimplantation – no live births to date
    - Concern about re-implanting cancer cells
  - In vitro maturation – no live births to date
- Investigational
Ellen

28 year old female

- Diagnosis: Leiomyosarcoma of bladder
- Treatment plan: Pelvic RT with gemcitabine, followed by partial cystectomy
- Social: married, 2 year old daughter

What is available for this patient?
Ovarian Transposition

Prior to pelvic/inguinal field radiation

- With IMRT to minimize ovarian & uterine dose
- Also consider embryo/oocyte cryopreservation
- If IVF needed in the future patient will need transabdominal retrieval
- Does not protect the uterus
Alternative Treatment For Select Patients

- Early stage cervical cancer
  - Radical Trachelectomy
- Rectal cancer
  - No pelvic radiation
- Non-gonadotoxic chemotherapy regimen
Females
Fertility Preservation Options

Cryopreservation of Gametes or Gonadal Tissue

Post-Pubertal

Oocytes

Embryos

Pre-Pubertal

Ovarian Tissue

Ovarian Transposition

Ovarian Suppression

Reduction of Gonadal Toxicity

Alternative Treatment
What does this mean for you?

Recognize that despite your personal assumptions about which patients may be interested in fertility preservation, the following factors may NOT be significant from the patient’s perspective:

- Age
- Previous children
- Religious and ethical beliefs
- Advanced disease
- Limited financial resources
What does this mean for you?

- Initiate the discussion in those at risk
  - Inform patient of risk of infertility
  - Assess interest in future parenting
  - Explain options for fertility preservation

- Refer patients interested in learning more or who want to pursue fertility preservation

The goal is to ensure patients have the opportunity to participate in the decision-making – to avoid regret in the future