Pediatric oncology and infertility: Risks and options

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Cancer in children is the leading cause of death by disease past infancy in the U.S.

It is estimated that 15,780 children and adolescents will be diagnosed with cancer this year.

- Leukemia,
- Brain and other CNS tumors,
- Lymphoma,
- Rhabdomyosarcoma,
- Neuroblastoma,
- Wilms’ tumor,
- Bone cancers: Osteosarcoma, Ewing sarcoma
- Germ cell tumors
* Childhood Cancer

* Overall outlook for children with cancer has improved greatly over last 50 years.

* In 1975, just over 50% of children diagnosed with cancer survived at 5 years.

* Now more than 85% survive their cancer.
*5-Year Survival Rate, Age 0-19*

- **Overall**: 83.9%
- **Acute Lymphoblastic Leukemia**: 90%
- **Acute Myeloid Leukemia**: 65.7%
- **Hodgkin Lymphoma**: 97.2%
- **Non-Hodgkin Lymphoma**: 85.9%
- **Bone and Joint**: 74.6%
- **Brain and CNS**: 74.4%
- **Neuroblastoma**: 74.1%
- **Soft Tissue**: 77.9%
- **Wilms Tumor**: 93.1%

Surveillance, Epidemiology, and End Results (SEER) Program. Seer.cancer.gov
Cure rates for childhood cancer now approach 85%, with >379,000 childhood cancer survivors living in the USA.

Currently, one of every 640 young adults is a survivor of cancer in childhood or adolescence.

As treatment regimens for pediatric malignancies have improved, many survivors are entering their reproductive years.

Maintenance of fertility is extremely important with regard to the long-term quality of life for these survivors.
Male Gonadotoxicity

* Gonadal damage is a common consequence of the treatments used to cure pediatric cancer.

* The extent of cytotoxic germ cell damage depends on the specific agents used (Alkylators) and the cumulative doses received.

* Alkylating agents are the most common class of drugs known to effect gonadal function, and their impact has been studied extensively.

* Additionally, the testes have a very low threshold for radiation exposure, and even small doses are known to be gonadotoxic.

* There is no protection for the prepubertal testes.
Male Gonadotoxicity

* Cancer therapy is more likely to affect a male’s ability to produce sperm.

* Cancer therapy is less likely to affect ability to develop secondary sexual characteristics and less likely to affect sexual function.

* **Sperm-producing cells** are more sensitive to toxic effects of therapy than Leydig cells.

* For most survivors, sexual function and pubertal development are preserved, but fertility may be affected.
**Gonadotoxic Chemotherapeutic Agents: Male**

<table>
<thead>
<tr>
<th>Gonadotoxic Agents</th>
<th>Cumulative doses</th>
</tr>
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<tbody>
<tr>
<td>Cyclophosphamide*</td>
<td>7-9 g/m²</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>42-60 g/m²</td>
</tr>
<tr>
<td>Nitrosureas, e.g. BCNU and CCNU</td>
<td>1 g/m² and 500 mg/m²</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>1.4 g/m²</td>
</tr>
<tr>
<td>Melphalan</td>
<td>140 mg/m²</td>
</tr>
<tr>
<td>Busulfan</td>
<td>600 mg/m²</td>
</tr>
<tr>
<td>Procarbazine*</td>
<td>4 g/m²</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>500-600 mg/m²</td>
</tr>
</tbody>
</table>

- The **total dose of chemotherapy** drug is an important determinant of potential damage.
- The higher the total dose, the more potential for damage to the sperm forming cells.
- **Combinations** of drugs may result in infertility at lower total doses.
* **Radiation and Male Infertility**

*Sperm-forming cells are *extremely sensitive* to the effects of radiation therapy.

*Effects of radiation are dictated by *dosage and radiation field*.

*Doses as low as 600cGy cause irreversible damage to sperm-forming cells.*
## Impairment of Spermatogenesis with XRT

<table>
<thead>
<tr>
<th>Testicular dose (cGy)</th>
<th>Effect on spermatogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>No effect</td>
</tr>
<tr>
<td>10-30</td>
<td>Temporary oligospermia</td>
</tr>
<tr>
<td>30-50</td>
<td>Temporary azoospermia at 4-12 mo. after radiation. 100% recovery by 48 mo.</td>
</tr>
<tr>
<td>50-100</td>
<td>100% temporary azoospermia for 3-17 mo. after radiation. Recovery begins at 8-26mo.</td>
</tr>
<tr>
<td>100-200</td>
<td>100% azoospermia from 2 months to at least 9 mo. Recovery begins at 11-20 mo.</td>
</tr>
<tr>
<td>200-300</td>
<td>100% azoospermia beginning at 1-2 mo. May lead to permanent azoospermia. If recovery takes place, it may take years.</td>
</tr>
<tr>
<td>1200</td>
<td>Permanent azoospermia</td>
</tr>
<tr>
<td>2400</td>
<td>Permanent azoospermia</td>
</tr>
</tbody>
</table>
Recent report confirms in over 6,000 male survivors of pediatric cancer when compared with siblings, survivors are approximately half as likely to sire a pregnancy 5 years or more after diagnosis.
* Pubertal Boys

* Pubertal males can produce a semen sample prior to starting gonadotoxic therapy and cryopreserve sperm for future use.

* Because intracytoplasmic sperm injection can achieve fertilization with as few as one motile sperm, this method has proven to be successful even when the number of cryopreserved sperm is small.

* Pregnancy can occur using frozen semen samples even after decades of storage.

* Boys as young as 12-13 can produce a specimen to be saved.
* Viable sperm can be collected from adolescent boys who are newly diagnosed with cancer.

* Younger age at diagnosis should not be considered a limiting factor, need to be tanner stage III.

* Effect of Chemotherapy on Semen Quality

  * Semen quality was reduced with one course of gonadotoxic therapy.

  * Sperm banking prior to initiation of therapy is feasible and necessary to ensure the possibility of preserved fertility.

* Patients and Families

* Parents and teens want information regarding sperm cryopreservation early. Providers should offer it as soon as possible to reduce treatment delays.

* **Parents** play an important role in the decision to sperm bank.

* Finances, ethics, religion are not important considerations.

* Sperm banking should be offered to all eligible adolescents regardless of the gonadotoxicity of the planned chemo.
Semen analysis in adolescent cancer patients prior to bone marrow transplantation: When is it too late for fertility preservation?

DFCI reviewed charts of male cancer patients who underwent BMT at age > 13 years from 2003-2010.

Their goal was to determine number of fertility preservation attempts prior to initial treatment and/or BMT and the outcomes of those sperm banking attempts.

68 patients who had a BMT were included in this analysis.

Yu, RN. Pediatr Blood Cancer. 2013 Jan;60(1):129-32
Semen analysis in adolescent cancer patients prior to bone marrow transplantation

Fig. 1. Decision to bank sperm.

Yu, RN. Pediatr Blood Cancer. 2013 Jan;60(1):129-32
* Key Points of Practice

* 416 patients have been approached about banking and 353 have agreed (85%). Of those 353, 79% have been successful

* Designated team to counsel teens and families.
  * Consent teens and explain the process
  * Facilitate appointments for family
  * Receive results and share these with our patients
Prepubertal Boys

* Prepubertal males pose a particular challenge for fertility preservation.

* Prepubertal boys cannot produce semen for cryopreservation and they do not have mature spermatozoa.

* A recent and encouraging approach is the use of cryopreserved testicular tissue.

* Use of testicular tissue cryopreservation in humans remains experimental.
Fig. 1. Male germline stem cell preservation. Before treatment for cancer by chemotherapy or irradiation, a boy could undergo a testicular biopsy to recover stem cells. The stem cells could be cryopreserved or, after development of the necessary techniques, could be cultured. After treatment, the stem cells would be transplanted to the patient’s testes for the production of spermatozoa.
In rodents, autotransplantation has resulted in restored spermatogenesis and mice have reproduced *in vivo*.

Brinster RL. PNAS 1994;91:11303-7; Brinster RL. Science 2002;296:2174
While steady progress has been made in animal research with SSCs, hurdles remain for translating this fertility-based science into the clinical setting for prepubertal boys newly diagnosed with cancer.

One major challenge is that germ cells yield a low number of SSCs, as 10,000 germ cells may contain only 2 stem cells.

Methods are needed to isolate and increase the number of SSCs available to be cultured and subsequently matured in vitro or autotransplanted.
A multidisciplinary team was assembled to provide this to our patients within the context of a research protocol.

Partnered with a leader in Veterinary Research, Urology, Reproductive Endocrinology, Andrology, and Nursing.

Goal: To develop a translational research protocol that would allow us to preserve a portion of the testicular tissue for the patient’s potential clinical use while providing human prepubertal testicular tissue to researchers.
Patients and Methods

The consent process carefully details that the use of cryopreserved testicular tissue in humans to restore fertility is **experimental**.

In those cases where the parent grants consent for the biopsy, an open testicular biopsy is performed during a procedure when the patient is under general anesthesia for another purpose. i.e. CVL placement, bone marrow aspirates/biopsy

A separate operative procedure for the testicular biopsy alone is **not allowed** per the protocol.
* Patients and Methods

* The procedure always occurs **before** any therapy is initiated.

* Size of biopsy is approximately 80 mm$^3$ ($\frac{1}{2}$ size of an eraser head on a pencil). Varies depending on age and size of testes.

* This is the size of a normal testis biopsy done for clinical reasons such as evaluation for cancer.

* Distribution of tissue: $\frac{1}{2}$ for patient, $\frac{1}{2}$ for research
* **Testicular Tissue Cryopreservation**

* Testicular Tissue Cryopreservation study for patients at very high risk of infertility

* Since 2008, 108 patients eligible since beginning this study, 87 families have agreed (80% acceptability)

* Laboratory scientists including Dr. R. Brinster and Dr. S. Ryeom

* MSKCC and Seattle Children’s Hospital

Female Gonadotoxicity

Cancer treatments accelerate ovarian aging. Females are at higher risk for premature ovarian failure rather than acute ovarian failure.

Risk of premature ovarian failure depends on:

- Age of patient
- Type chemotherapy – alkylation agents, cumulative dose
- Site and dose of radiotherapy - Recent study showed that around 200 cGy can destroy 50% of immature oocytes

* Stem cell transplant
* Female gonadotoxicity and chemotherapy

*Dose

* Increased incidence of ovarian failure with higher doses of gonadotoxic drugs
* The exact dose of chemotherapy associated with gonadal failure is not always predictable.

* High risk with alkylator therapy: cytoxan, ifosfamide, busulfan, melphalan, procarbazine
Acute ovarian failure vs Premature menopause
* 5,149 female survivors, and 1,441 female siblings

* When analysis was adjusted, the relative risk (RR) of a survivor ever being pregnant was 0.81, compared with the sibling cohort.

* A dose-response relationship was present for decreased risk of pregnancy with increasing dose of ovarian/uterine radiation.

* Increasing alkylation score was also significantly associated with the risk of not having been pregnant.
* Female gonadotoxicity and radiotherapy

* Abdominal-pelvic and total body irradiation cause a dose dependent reduction in the ovarian follicular pool.

* The magnitude of the reduction is age-dependent

* A recent study showed that around 200 cGy can destroy 50% of immature oocytes

* Ovarian Ovarian transposition/Proton therapy
**Ovarian Transposition**

<table>
<thead>
<tr>
<th></th>
<th>Mean total (cGy)</th>
<th>Median total (cGy)</th>
<th>Maximum total (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ovary</td>
<td>983</td>
<td>1053</td>
<td>1624</td>
</tr>
<tr>
<td>Left transposed ovary</td>
<td>68</td>
<td>70</td>
<td>84</td>
</tr>
<tr>
<td>Right ovary</td>
<td>166</td>
<td>129</td>
<td>723</td>
</tr>
<tr>
<td>Right transposed ovary</td>
<td>87</td>
<td>87</td>
<td>103</td>
</tr>
</tbody>
</table>

Fig. 2. CT treatment-planning axial slices demonstrating the radiation isodose distribution to the ovaries before (A, B) and after (C) lateral transposition.
Proton Therapy: Optimal method of delivering fertility-sparing CSI

Lester-Coll N.H., J Adolesc Young Adult Oncol. 3(2):96-9, 2014.
* Fertility Preservation Options for Females: Embryo and Egg Cryopreservation

* Pediatric Concerns
  * Delay in treatment (2-6 weeks)
  * Random-start protocol, in which ovarian stimulation is initiated regardless of menstrual cycle phase
  * Risk from ovarian stimulation

* Not an option for some patients
  * No partner and unwilling to use donor sperm
  * Religious/ethical objections to embryo freezing
  * Prepubertal patient
* Fertility Preservation Options for Females: Embryo and Egg Cryopreservation

* Difficult to accomplish in Pediatrics
  * Only possible in girls who have gone through puberty
  * Patients facing bone marrow transplantation
  * Survivors at risk for premature menopause

* At CHOP
  * 14 patients have cryopreserved eggs
  * Random start protocols - increase number of patients who can choose this option
* Patient is stimulated on presentation regardless of where they are in menstrual cycle.

* Random start controlled ovarian stimulation is as effective as conventional start ovarian stimulation.

* Potential use in our patient population where delays in therapy are of concern.
* Fertility Preservation Options for Females: Investigational Approaches

* Ovarian tissue cryopreservation - similar to testicular tissue cryopreservation, uses laparoscopy

* Collaborate with Oncofertility Consortium

* Open study at CHOP for patients over 1 year of age
Ovarian Tissue Cryopreservation

Worldwide there have been over 60 live births using ovarian tissue transplantation.

Theoretically two ways to proceed:
- Reimplant tissue when ready to conceive
- Mature follicle containing egg outside of the body and use this egg with IVF

Second option better if there is a concern over transplanting cancer cells.

Donnez et al. Fertil Steril. 2013
* Ovarian Tissue Cryopreservation

* 53 patients at CHOP, ages 3-20
* 7 patients with sarcoma- aggressive alkylator therapy
* 2 patients with medulloblastoma- CSXRT tagged with oophecy
* 10 patients due to receive high dose abdominal radiation
* 34 patients pre-SCT
* No infections or excessive bleeding No delays in beginning therapy
* No excessive complaints pain

Retrospective cohort analysis of 4,699 children of 1,128 male and 1,627 female childhood cancer survivors.

Neither ovarian radiation nor testicular radiation was related to risk of congenital anomalies.

Treatment with alkylating agents also was not significantly associated with anomalies in children of male or female survivors.

Strong evidence that children of cancer survivors are not at increased risk for congenital anomalies stemming from treatment.
* Points specific to pediatrics

* Males at greater risk for infertility than females since age is protective in females.

* Female pediatric patients more at risk for premature ovarian failure rather than acute ovarian failure.

* Timing is critical factor in pediatric oncology.

* Different patient population, different approach.

* Families interested in experimental options, interested in moving the science forward/
*Key Points of Practice*

*Team: REIs should partner with pediatric oncologists who will help champion fertility counseling and preservation.*

*Meet face to face to identify and explain varying needs of this patient population.*

*Time sensitivity  
Flexible scheduling  
Options for patients who are too sick to leave hospital  
Developmental considerations of patients  
Families  
Hold regular meetings to provide feedback and identify areas for improvement.*
* Key Points of Practice

* Identify a team of clinicians to develop expertise and lead the initiative within your center

* Disseminate information - Tumor board/JC

* Insert reminders or prompts into standard processes or workflows. Embed a field within electronic documents

* Changing a culture
* Clinical service – 2 weeks

* Three teenage boys sperm banked
* 10yo female from NY with sickle cell had ovarian tissue frozen
* 3yo with Wilms’ tumor had ovarian tissue frozen from Dupont
* 10yo female with AML had ovarian tissue frozen
* 9yo boy with Ewing sarcoma had testicular tissue frozen
* 14yo female with aplastic anemia from NY counseled on freezing eggs prior to transplant
* 2yo male with germ cell tumor- counseled on phone regarding infertility risk (from Canada)
### Acknowledgements

**Cancer Survivorship Team**
- Claire Carlson, RN, BSN
- Sue Ogle, MSN, CRNP
- Wendy Hobbie, MSN, CRNP

**CHOP Surgery**
- Tom Kolon, MD (Urology)
- Pete Mattei, MD (General Surgery)

**Collaborators**
- Michael Glassner, MD (Mainline Fertility)
- Margarett Schnorhavorian, MD (Seattle Children’s)
- John Mulhall, MD (MSKCC)

*Funding* NICHD, St. Baldrick’s Foundation, Alex’s Lemonade Stand Foundation