Advances in Pediatric Radiation Oncology

Is Proton Therapy Fertility Sparing?

2019 Oncofertility Conference
Jeffrey Gross, MD MS
November 12, 2019
Our mission is for the patients of tomorrow to receive better treatments, and have fewer complications of treatment, than today.
Goals and objectives

1. Describe history of radiation therapy for pelvic tumors, and recent advances

2. Review the physics and radiobiology of x-rays and protons, impact on ovarian tissues

3. Describe a method for monitoring fertility and early surrogate endpoints in research and clinical practice

4. Describe how proton therapy may preserve ovarian function and reserve when treating targets near the ovaries
Survivors who pass the 5-year milestone are now living longer.

THANKS TO:
- Improved treatments with less toxicity for low-risk patients*
- Better screening for health issues related to cancer treatment
- Better medical care for late effects of therapy.

Results were from 34,033 survivors in the Childhood Cancer Survivor Study.

"This study shows that research is resulting in better treatment approaches, allowing survivors to live longer and healthier lives."

-Greg Armstrong, MD
Principal Investigator, Childhood Cancer Survivor Study

Cumulative incidence of grade 3–5 chronic health conditions in 5-year survivors of childhood cancer by diagnosis decade and siblings

Temporal pattern in the risk of chronic health conditions from the Childhood Cancer Survivor Study cohort

Cumulative incidence of grade 3–5 chronic health conditions by organ system at 15 years after primary cancer diagnosis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>5.9% (5.3–6.4)</td>
<td>3.6% (3.2–3.9)</td>
<td>2.8% (2.5–3.2)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0033</td>
</tr>
<tr>
<td>Thyroid nodules requiring surgery</td>
<td>1.9% (1.6–2.3)</td>
<td>1.2% (0.9–1.4)</td>
<td>0.9% (0.7–1.1)</td>
<td>0.00017</td>
<td>&lt;0.0001</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Gonadal dysfunction</strong></td>
<td><strong>3.5% (3.1–4.0)</strong></td>
<td><strong>1.8% (1.5–2.1)</strong></td>
<td><strong>0.9% (0.7–1.0)</strong></td>
<td><strong>&lt;0.0001</strong></td>
<td><strong>&lt;0.0001</strong></td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td>Diabetes mellitus requiring insulin</td>
<td>0.4% (0.2–0.5)</td>
<td>0.5% (0.3–0.6)</td>
<td>0.9% (0.7–1.0)</td>
<td>0.35</td>
<td>0.00014</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

**Boys**
- Testicular hypofunction
- Azoospermia

**Girls**
- Post-ablative ovarian failure
- Premature menopause, onset <40 years of age
- Female infertility

Historical context: RT alone for HL

Early curative treatments for many cancers prior to the development of effective chemotherapies primarily involved irradiation.

Radiation treatments were crude compared to what is possible today.

Doses 35-45 Gy prescribed to the nodal targets, high rates of ovarian failure.
Historical context: Improvements in RT delivery

Axial

Coronal

Sagittal

2 Beams

4 Beams

6 Beams, intensity modulation

Depth Dose Curve of High Energy X-Rays

High Energy X-Rays

Relative Dose

Depth in Tissue (cm)
Ovarian primordial follicles are exquisitely sensitive to radiation damage

High doses cause ovarian failure in up to 97.5% of patients

Doses as low as 2 Gy, might not cause acute ovarian failure, but destroy 50% of the immature oocytes in the human ovary leading to early menopause

Comparison of X-rays and other possible modalities

Radiation modalities differ in:

1. Quality of dose distribution

Protons > X-rays
Proton interactions with matter

Speed = Energy = Potential Range
Depth-dose curve for protons

**Graph Description:**
- **X-axis:** Depth in Tissue (cm)
- **Y-axis:** Relative Dose

**Key Elements:**
- **Bragg peak:** A sharp increase in dose at a specific depth, indicating the end of the dose delivery.
- **Protons:** A line representing the dose distribution for protons.

**Inset Image:**
- Various cellular and tissue structures labeled, including different organs and tissues.

**Legend:**
- High energy X-rays and protons shown for comparison.

**Note:** The depth-dose curve is crucial for understanding how proton therapy delivers a high dose of radiation to a specific region while minimizing the dose to surrounding healthy tissues.
Building a clinical proton beam

“Spread-Out Bragg Peak”
Comparison of x-ray techniques and proton therapy

Comparison of X-rays and other possible modalities

Radiation modalities differ in:

1. Quality of dose distribution
   - Protons > X-rays

2. LET, RBE
   - Protons = X-rays?
Linear Energy Transfer (LET)

LET = Energy transferred per unit path length (keV/µm)

- X-rays are low LET throughout
- Protons start as low LET, but LET peaks at SOBP
Relative Biological Effectiveness (RBE)

RBE increases with LET, as the space in between ionizations approaches the distance between DNA strands.

Maximum cell kill around LET = 100 keV/µm.
Proton radiotherapy to preserve fertility and endocrine function: a translational investigation

A study to assess the feasibility and efficacy of proton therapy to spare ovarian function and primordial follicle reserve by comparing Anti-Müllerian Hormone (AMH) levels and primordial follicle counts following x-ray and proton therapy in mice

Proton beam appears to spare the ovaries
Experimental design: subjects, endpoints

- 124 prepubertal female mice, post-natal day 21
- AMH, biomarker for ovarian function
  - Baseline, 1w, 3w, 8w post-treatment
- Primordial follicle count, ovarian reserve
  - 8w post-treatment
Experimental design: study groups, conditions

- Sham control (n=30)

- X-ray beam directed at ovaries
  - 0.2 Gy, single dose (n=14)
  - 1.8 Gy, single dose (n=13)

Hypothesize that low dose (0.2 Gy) will selectively eliminate PFs and cause decreased AMH over time

High dose (1.8 Gy) will ablate all follicles and cause immediate AMH decline
Experimental design: study groups, conditions

- Proton beam directed at ovaries
  - 0.2 Gy, single dose
    • Center of SOBP (n=13)
    • Distal SOBP (n=12)
  - 1.8 Gy, single dose
    • Center of SOBP (n=13)
    • Beyond SOBP (n=29)

Hypothesize same effect as x-rays
Hypothesize sparing relative to x-rays vs. increased RBE effects
Hypothesize no effect
Results: primordial follicle count 8 weeks post-treatment

XRT or PRT, Center of SOBP Plateau
1.8 Gy

Tukey corrections applied, *p<0.01, **p<0.001
Results: primordial follicle count 8 weeks post-treatment

XRT or PRT, Center of SOBP Plateau 0.2 Gy

Tukey corrections applied, *p<0.01, **p<0.001
Results: primordial follicle count 8 weeks post-treatment

Tukey corrections applied, *p<0.01, **p<0.001
Results: primordial follicle count 8 weeks post-treatment

Tukey corrections applied, *p<0.01, **p<0.001

- Primordial follicle count (number per animal)
- 1.8 Gy XRT (n=13)
- 1.8 Gy PRT center of SOBP (n=13)
- 0.2 Gy XRT (n=14)
- 0.2 Gy PRT center of SOBP (n=13)
- 0.2 Gy PRT within distal SOBP (n=12)
- 1.8 Gy PRT beyond distal SOBP (n=29)
- Control (n=30)
Results: AMH level at 8 weeks post treatment

Tukey corrections applied, *p<0.01, **p<0.001
Results: AMH level at 8 weeks post treatment

Tukey corrections applied, *p<0.01, **p<0.001
Results: AMH level at 8 weeks post treatment

Tukey corrections applied, *p<0.01, **p<0.001
Results: AMH level at 8 weeks post treatment

Tukey corrections applied, *p<0.01, **p<0.001


Tukey corrections applied, *p<0.01, **p<0.001
Ex-vivo whole ovary irradiation apparatus
Confirmatory study: experimental design

- Sham control (n=10)
- 0.2 Gy X-rays (n=9)
- P1 Protons, 0.2 Gy (n=9)
- P2 Protons, 0.15 Gy (n=9)
- P3 Protons, 0.08 Gy (n=9)
- P4 Protons, ~0 Gy (n=9)

Hypothesize same effect as x-rays

Hypothesize sparing of primordial follicles relative to x-rays
Primordial follicle count 48 hours post treatment in ex vivo ovaries

Tukey corrections applied, *p<0.01, **p<0.001
Primordial follicle count 48 hours post treatment in ex vivo ovaries

Central developing follicles spared, peripheral primordial follicles absent

All follicles included peripheral primordial follicles spared
Take-aways: proton therapy can be fertility sparing

1. Ovarian primordial follicles are very sensitive to radiation damage, and thus reliable for analyzing the effects of small differences in radiation dose

2. AMH is a useful tool for assessing ovarian function following pelvic radiation therapy

3. All radiation exposures are potentially mutagenic, specific effects of protons requires further study

4. Agents to block or strategies to mitigate the gonadotoxic effects of chemotherapy are greatly needed
THANK YOU!

Team members, collaborators:

Teresa Woodruff and entire Woodruff Lab
Sarah Wagner
So-Youn Kim
Alison Grover
Vinai Gondi
Mark Pankuch and NM Chicago Proton Center
Gayle Woloschak
Mandy Kozlowski and the NU IACUC

and of course, my family!

This research was supported in part by the National Institutes of Health’s National Center for Advancing Translational Sciences, Grant Number UL1TR001422.

2019 Oncofertility Conference
Jeffrey Gross, MD MS
November 12, 2019