Curing Children with Cancer, But At What Cost? PENTEC: Pediatric Normal Tissue Effects in the Clinic, emphasizing radiation therapy

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Director, Judy DiMarzo Cancer Survivorship Program
Vice Chair, Department of Radiation Oncology

No conflicts of interest
What is PENTEC?

A group of physicians (radiation and pediatric oncologists, subspecialists), physicists (clinical and modelers), epidemiologists who intend to critically synthesize existing data to:

• Develop quantitative evidence-based dose/volume guidelines to inform RT planning and improve outcomes

• Describe relevant physics issues specific to pediatric radiotherapy

• Propose dose-volume-outcome reporting standards to inform future RT guidelines
PENTEC session content

• How organ development complicates normal tissue radiation response in children/adolescents

• Scope of problem: normal tissue toxicity in children

• Epidemiologic considerations in understanding and synthesizing evidence

• Methodologic complexities in analyzing data: age, developmental status, dose, volume, chemotherapy interactions, on and on and on and on
Follow-up of children who survive cancer
Should be individually tailored but may not be necessary for all

Young Survivors in a Deadly War

More and more young people are beating cancer, but many find that getting well is only half the battle.

Medical surveillance of long-term survivors of cancer

Kevin C. Oeffinger, MD
Leslie L. Robison, PhD

Leslie L. Robison\textsuperscript{a,b}, Melissa M. Hudson\textsuperscript{b}

\textsuperscript{a}Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, 332 N. Lauderdale
\textsuperscript{b}Division of Survivorship, St. Jude Children's Research Hospital, 332 N. Lauderdale Street, Memphis, TN.

JAMA, June 27, 2007—Vol 297, No. 24 (Reprinted)
• Over 250,000 childhood cancer survivors in the US
• 1 in 1,000 is a childhood cancer survivor
• 1 in 570 is a childhood cancer survivor (ages 20 to 34 yr.)
Cumulative Cause-Specific Mortality

Years since diagnosis

Cumulative probability of cause-specific mortality [%]

Recurrence/Original

SMN

Other

External

Cardiac

Pulmonary

Mertens JCO, 2001. 19:3163-72
Incidence of Health Conditions in 10,397 Adults in Children’s Cancer Survivor Study

- 73% with 1 or more late effects
- 42% with moderate, severe, life-threatening late effect

Oeffinger, NEJM, 2006
Spectrum of Treatment Effects

Life-Threatening  Life-Altering

- Cardiomyopathy
- Pulmonary fibrosis
- High grade second cancers

- Obesity
- Immunodeficiency
- Chronic hepatitis
- Endocrinopathy
- Asplenia

- Infertility
- Neurocognitive deficits

- Seizure disorder
- Low grade second cancers
- Hearing/vision loss
- Amputation
- Chronic pain
- Short stature

- Short stature
As we know, there are known knowns. There are things we know we know. We also know there are known unknowns.

» Donald Rumsfeld
<table>
<thead>
<tr>
<th>Risk</th>
<th>Levels of Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>No difference</td>
<td>Strong</td>
</tr>
<tr>
<td>Cataracts</td>
<td>More</td>
<td>Weak</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>More</td>
<td>Moderate</td>
</tr>
<tr>
<td>Heart</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td>Breast hypoplasia</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td>Lung</td>
<td>Less</td>
<td>Weak</td>
</tr>
<tr>
<td>Thyroid hypofunction</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td>Thyroid nodules</td>
<td>More</td>
<td>Moderate</td>
</tr>
<tr>
<td>Thyroid autoimmune</td>
<td>No data</td>
<td>Weak</td>
</tr>
<tr>
<td>Kidney</td>
<td>same</td>
<td>weak</td>
</tr>
<tr>
<td>Bladder</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td>Testes</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td>Ovaries</td>
<td>Less</td>
<td>Strong</td>
</tr>
<tr>
<td>Uterus</td>
<td>More</td>
<td>Moderate</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td>Immune</td>
<td>No data</td>
<td>Strong</td>
</tr>
<tr>
<td>Marrow whole body</td>
<td>Less</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Comparative Risks after Radiotherapy: Children vs. Adults

UN Scientific Committee: Constine, Mettler 2013
Why the difference?

**Children**
- Impairment of growth
- Hypoplasia and impairment of maturation

**Adults**
- Inability to repair damage secondary to cell attrition, senescence and comorbid illness
- Fibrotic and inflammatory changes
Risk-Based Survivor Care

Host Factors
- Age
- Gender
- Race

Premorbid conditions

Genetic
- BRCA, ATM, p53 polymorphisms

Tumor Factors
- Histology
- Site
- Biology
- Response

Health Behaviors
- Tobacco
- Diet
- Alcohol
- Exercise
- Sun

Aging

Treatment Events
- Surgery
- Chemotherapy
- Radiation therapy

Treatment Factors
- Surgery
- Chemotherapy
- Radiation therapy
# Tolerance Radiation Doses

**Single Dose (Gy) $T_{5/5} - T_{5/50}$**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Single Dose</th>
<th>Tissue</th>
<th>Single Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td>2-10</td>
<td>Heart</td>
<td>18-20</td>
</tr>
<tr>
<td>Lens</td>
<td>2-10</td>
<td>Liver</td>
<td>15-20</td>
</tr>
<tr>
<td>Lung</td>
<td>7-10</td>
<td>Mucosa</td>
<td>15-20</td>
</tr>
<tr>
<td>Thyroid</td>
<td>7.5</td>
<td>Skin</td>
<td>12-20</td>
</tr>
<tr>
<td>GI tract</td>
<td>10-20</td>
<td>Testes</td>
<td>&gt; 20</td>
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<tr>
<td>Kidney</td>
<td>10-20</td>
<td>Spinal Cord</td>
<td>20-25</td>
</tr>
<tr>
<td>Ovary</td>
<td>&gt; 20-40</td>
<td>Brain</td>
<td>20-30</td>
</tr>
</tbody>
</table>

**Fractionated dose (Gy) $T_{5/5} - T_{5/50}$**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Fractionated Dose</th>
<th>Tissue</th>
<th>Fractionated Dose</th>
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<tbody>
<tr>
<td>Testes</td>
<td>1.5-2.5</td>
<td>Liver</td>
<td>35-40</td>
</tr>
<tr>
<td>Ovary</td>
<td>5-15</td>
<td>Mucosa</td>
<td>30-40</td>
</tr>
<tr>
<td>Lens</td>
<td>6-20</td>
<td>Skin</td>
<td>30-40</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>15-30</td>
<td>Heart</td>
<td>40-50</td>
</tr>
<tr>
<td>Kidney</td>
<td>23-28</td>
<td>GI tract</td>
<td>45-50</td>
</tr>
<tr>
<td>Lung</td>
<td>25-30</td>
<td>Spinal Cord</td>
<td>50-60</td>
</tr>
<tr>
<td>Thyroid</td>
<td>30-40</td>
<td>Brain</td>
<td>60-70</td>
</tr>
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</table>
Risk of late toxicity as a function of dose and volume of radiation exposure

<table>
<thead>
<tr>
<th>Volume</th>
<th>0-20%</th>
<th>20-40%</th>
<th>40-60%</th>
<th>60-80%</th>
<th>80-100%</th>
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<tbody>
<tr>
<td>Spinal cord</td>
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<tr>
<td>Dose (Gy)</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>70</td>
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<tr>
<td>0-20%</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
<td>10-50%</td>
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</tbody>
</table>

Rubin, Constine, et al
LENT scoring
IJROBP 1995
Constine, Dhakal
SAM Q1: Which is not true about the risk of late effects after radiation therapy for children compared with adults?

1. Children have an increased risk due to cell hypertrophy and hyperplasia
2. Children have a decreased risk in some normal tissues (e.g. lung) due to superior repair capacities or less base-line injury
3. Children are more sensitive than adults for most late effects with the exception of ovarian failure and bone marrow suppression
4. Children have a lower likelihood of developing second cancers because of their superior ability to repair mutations
The correct answer is:

4. Children have a lower likelihood of developing second cancers because of their superior ability to repair mutations

Ref: Constine, LS (ed) Cancer Genesis, Treatment, and Late Effects Across the Age Spectrum.
Sem Rad Onc 20(1) 2010: 78 pp
Fig. 7. Litter 9. Irradiated femora (○) and control femora (■) of litter 9. This shows the quantitative effects of 750, 1,000, and 1,500 r administered at one month (arrow).
Fig. 11. Gross Appearance of Stunted Femora. Photograph of dissected femora from 4 animals. Rats No. 69, 73, 70, and No. 51 illustrate the curvature mentioned in the text. All the right femora shown here are stunted by the irradiation administered six to ten months before necropsy.
Growth Impairment

Risk factors

- Younger age (prepubertal)
- Higher dose (> 20 Gy)
- Higher daily fraction (≥ 2 Gy)
- Larger treatment field
- Epiphysis in treatment field
2 yr old girl treated with high dose RT to hemi-abdomen for Wilms
Scoliosis in Neuroblastoma

Paulino et al. IJROBP. Volume 61, Number 3, 2005
Height loss as function of age/dose after RT to lumbar spine for Wilms tumor

Hogeboom CJ et al. Medical and Pediatric Oncology 2001;36:295-304
An example of the model for expected stature loss after radiation therapy to the spine during childhood in a hypothetical male patient treated from T10-11 to L4-5 - his Ideal Adult Stature was 176.8 cm.

Silber JH, Littman PS, Meadows AT: J Clin Oncol 8:304-312, 1990
Radiation Cardiac Injury

Manifestations
- Restrictive cardiomyopathy
- Premature CAD
- Myocardial infarction
- Valvular disease
- Autonomic dysfunction
- Conduction defects

Risk Factors
- Younger age (< 5 y)
- Higher dose (> 35 Gy)
- Higher daily fraction (≥ 2 Gy)
- Larger volume of heart in field
- Anteriorly weighted field
- Subcarinal shielding
- Longer time from RT
- Use of cardiotoxic chemoRx

Mantle Field
Incidence of CVD vs RT Dose to Heart (Childhood Cancer Survivors)

Adapted from Mulrooney, BMJ 2009
CHF Risk by Dose < 15 Gy

Role of TBI and Fractionation on CHF risk

<table>
<thead>
<tr>
<th>TBI fractionation schedule</th>
<th>Physical dose (Gy)</th>
<th>EQD&lt;sub&gt;2&lt;/sub&gt; (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 8.0 Gy</td>
<td>8.0</td>
<td>17.6</td>
</tr>
<tr>
<td>1 x 7.5 Gy</td>
<td>7.5</td>
<td>15.75</td>
</tr>
<tr>
<td>2 x 6.0 Gy</td>
<td>12.0</td>
<td>21.6</td>
</tr>
<tr>
<td>2 x 5.0 Gy</td>
<td>10.0</td>
<td>16.0</td>
</tr>
<tr>
<td>2 x 4.5 Gy</td>
<td>9.0</td>
<td>13.5</td>
</tr>
</tbody>
</table>

As EQD2

Pulmonary Dysfunction

- Paramediastinal fibrosis
- Pulmonary fibrosis
- Restrictive lung disease
- Pneumothorax
Dental Abnormalities After RT

- Tooth/root agenesis
- Adontia
- Microdontia
- Root thinning or shortening
- Enamel dysplasia

Dose thresholds are age/endpoint dependent: 10-20 Gy
Dental Abnormalities After Radiation

- Salivary gland dysfunction
- Xerostomia
- Dental caries
- Periodontal disease

Dose thresholds relate to salivary gland dysfunction: 20-40 Gy dependent on volume, bilateral v unilateral
Hypothyroidism

Risk Factors

- Female sex
- Older age (> 15 y)
- Higher radiation dose
  - 30% if 35-44 Gy
  - 50% if > 45 Gy
- Time < 5 y from Dx

Sklar et al, JCEM 2000
Peak Growth Hormone according to hypothalamic mean dose and time from irradiation

Merchant et al, JCO 29:4776, 2011
Female Gonadal Dysfunction

Manifestations:
- Delayed/arrested puberty
- Infertility/early menopause

Risk factors:
- Older age
- High doses of alkylators
- > 6-10 Gy radiation to pelvis (permanent if > 20 Gy)
- Gonadal radiation combined with alkylators

Age & Risk of Ovarian Failure
## Effect of Fractionated Testicular Radiation on Sperm Count

<table>
<thead>
<tr>
<th>Rounded Dose (Gy)</th>
<th>Effect post-RT</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 – 0.3</td>
<td>Temporary oligospermia</td>
<td></td>
</tr>
<tr>
<td>0.3 – 0.5</td>
<td>Temporary aspermia at 4-12 months</td>
<td>Full recovery by 48 months</td>
</tr>
<tr>
<td>0.5 – 1.0</td>
<td>100% temporary aspermia from 3 – 17 months</td>
<td>Recovery begins at 8–38 months</td>
</tr>
<tr>
<td>1.0 – 2.0</td>
<td>100% temporary aspermia from 2 – 15 months</td>
<td>Recovery begins at 9–20 months</td>
</tr>
<tr>
<td>2.0 – 3.0</td>
<td>100% temporary aspermia beginning at 1-2 months</td>
<td>Recovery begins in some cases at 12–14 years</td>
</tr>
<tr>
<td></td>
<td>(a certain percentage will suffer permanent aspermia)—large daily fractions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100% aspermia beginning at about 2 months</td>
<td>No recovery observed up to 40 months</td>
</tr>
<tr>
<td></td>
<td>——small daily fractions</td>
<td></td>
</tr>
</tbody>
</table>

Ash P; Brit J Radiol; 53:271; 1980
Abnormal Testosterone Value vs Radiation Dose to Testicles

Izard M, Rad & Onc; 34:1 (1995)
Bilateral Whole Kidney RT – non TBI

Correlation of Dose with Symptomatic Radiation Nephropathy

- Thompson, et al.
- Luxton
- Dewit, et al.
- LeBourgeois; Dewit; Kim
- Avioli, et al.
- Kim, et al.

% Incidence vs Dose (cGy)
IQ After Conformal RT for Low Grade Glioma

- n = 78
- 54 Gy
- 10mm margin

Merchant TE, J Clin Oncol 2009; 27:3691
Hearing loss

- 78 children, 155 ears after RT for BT: 14% hearing loss at 3-5 yrs

Table 1. Incidence of hearing loss for 155 ears of 78 pediatric patients with brain tumor

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Mean cochlear dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤30</td>
</tr>
<tr>
<td>High (6,000 and 8,000 Hz)</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate (2,000, 3,000, and 4,000 Hz)</td>
<td>0</td>
</tr>
<tr>
<td>Low (250, 500, and 1,000 Hz)</td>
<td>0</td>
</tr>
</tbody>
</table>

Incidence of hearing loss expressed as percent.
* Linearly extrapolated to 60 Gy.

HUA et al. IJROBP 72:892, 2008
Secondary Acute Myeloid Leukemia

- Brief latency: 3 to 10 years
- Risk related to chemotherapy
  - Alkylating agents
  - Epipodophyllotoxins
- No additional risk after radiation
CHILDHOOD CANCER SURVIVOR STUDY (CCSS)
Second and Subsequent Malignancies
Cumulative incidence by exposure to radiotherapy
Breast cancer risk, dose and volume, Childhood cancer survivors


Dose-response Relations Between RT Dose and Relative Risk (RR) of Second Neoplasms


Dose (Gy)

Relative Risk

A

Observed RR Meningioma
Fitted Line Meningioma
Observed RR Glioma
Fitted Line Glioma

CNS SMNs

B

Linear
Linear exponential
Recorded ORs

Thyroid SMNs

Neglia
JNCI 98:1528, 2006

Ronckers
Rad Res, 166:618, 2006

SAM Q2 Which is true about SMNs in children following radiation therapy

1. SMNs increase in incidence for the first 20 years after RT, and then taper

2. SMNs increase according to radiation dose in all tissues except for the breast

3. The radiation volume is not relevant to the incidence of SMNs, since dose is the dominant factor

4. Acute leukemias are more likely due to radiotherapy than to chemotherapy
The correct answer is:

4. Acute leukemias are more likely due to radiotherapy than to chemotherapy

Make everything as simple as possible, but not simpler.

Or

Make everything as simple as possible, if not simpler.

»Albert Einstein