ESTIMATING THE RISK FOR DEVELOPING SECOND CANCERS AFTER RADIATION THERAPY

NorthEast AAPM Chapter

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Disclosure

I have no conflicts of interest to disclose

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“Secondary Cancer Risk Assessment for (Pediatric) Radiation Oncology Patients”

Acknowledgements

Harald Paganetti, Christina Zacharatou Jarslkog, Bryan Bednarz, Torunn Yock, and Judy Adams
Scattered/Secondary dose as a function of lateral distance

Monte Carlo
- Poff et al
- Zheng et al
- Zacharatou Jarlskog et al

Experimental
- IMRT (10 x 10 field): Klein et al
- Yan et al
- Wroe et al
- Mesoloras et al

H [mSv/Gy]

0 10 20 30 40 50 60 70 80 90 100

Lateral distance to the field edge [cm]

Facility (treatment head dependent)
Beam energy
Air gap
Distance to the field edge
Aperture / Field size
Treatment volume
Secondary Neutron

Paganetti et al. Accurate Monte Carlo for nozzle design, commissioning, and quality assurance in proton therapy Med. Phys. 2004

Secondary Neutron


Paganetti et al. Accurate Monte Carlo for nozzle design, commissioning, and quality assurance in proton therapy Med. Phys. 2004
Secondary Neutron


Paganetti et al. Accurate Monte Carlo for nozzle design, commissioning, and quality assurance in proton therapy Med. Phys. 2004
Neutrons generated in the treatment head decrease with increasing aperture size.

- ~20% of the beam treats
- ~80% of the beam produces neutrons
- ~60% of the beam treats
- ~40% of the beam produce neutrons

External Neutrons
Neutrons generated in the patient increase with increasing treatment volume

Internal Neutrons

For large treatment field interaction region is large
IMRT: Scattered Photon Doses

- Treatment head shielding
- Beam energy
- Distance to the field edge
- Aperture / Field size / # of segments
- More MUs imply more MLC transmission and head leakage
Scattered Photon

Bednarz et al. PMB 54 43-57 (2009)

Varian Linac 2100 Clinac C
Scattered Photon

Patient scatter

Varian Linac 2100 Clinac C
Scattered Photon

Varian Linac 2100 Clinac C

Bednarz et al. PMB 54 43-57 (2009)

MLC leakage

Patient scatter
Scattered Photon

Bednarz et al. PMB 54 43-57 (2009)

Varian Linac 2100 Clinac C
Now we know our secondary and scattered component.

How to get accurate dose estimates?
Epidemiologic studies... should be based on **accurate**, individual dose estimates, preferably to the **organ of interest**...
Estimating Organ Doses

- Get accurate organ doses is through simulations.
- Score individual energy deposition event.
- Track particle type and assign an appropriate weight.
Patient Representation

Stylized
- Organs analytically defined

Voxelized
- Large voxels
- Limited resolution

Hybrid
- Organs are defined by surfaces.
- Voxelized as needed

Patient CT
- CT is performed on a region of interest

accuracy
Simulations Performed at MGH

Voxelized Phantoms
Treatment Fields in Proton Therapy & IMRT

<table>
<thead>
<tr>
<th>Field</th>
<th>Aperture diameter [cm]</th>
<th>Beam Energy [MeV]</th>
<th>SOBP range [cm]</th>
<th>SOBP Modulation width [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>169.2</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>169.2</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>169.2</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>178.3</td>
<td>15</td>
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<tr>
<td>5</td>
<td>6</td>
<td>178.3</td>
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<td>9</td>
<td>178.3</td>
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<td>10</td>
</tr>
</tbody>
</table>

IMRT fields were matched to proton therapy fields. We normalized the dose at the depth equal to the center of SOBP of the corresponding proton field.
Small Range

Large Range

Absorbed Doses
Scenarios for brain & spine fields

Brain

T12

Spine
Radiation Weighting Factor

For protons RBE is assumed 1.1 in the SOBP region.

For photons the weighting factor is 1.0.

Energy dependent neutron weighting factor

From: *Annals of the ICRP; ICRP 92*
IMRT vs. Proton Therapy
Out-of-field organs

Doses averaged over 6 fields assuming a 8-year old female patient
IMRT vs. Proton Therapy
Out-of-field organs

Doses averaged over 6 fields assuming a 8-year old female patient
Equivalent dose as a function of field size

**Absorbed Doses (mSv/Gy)**

- Passive Proton
- IMRT
- Proton scanning

**Field Index**

1. Passive Proton
2. IMRT
3. Proton scanning
Equivalent dose as a function of patient’s age (averaged over several brain fields)

Geometrical effect

$H_{\text{tot}} = \text{External} + \text{Internal neutron equivalent doses}$
Out-of-Field
Second Cancer Risks
Risk Estimation From Organ Doses

- 0.05-2.5Sv gold standard based on atomic bomb survivors.
- Out-of-field organs in RT get low doses of radiation.
- No data for low doses - models are questionable???
ICRP & NCRP recommend linear risk-dose relationship

- 0.05-2.5Sv gold standard based on atomic bomb survivors.
- Out-of-field organs in RT get low doses of radiation.
- No data for low doses - models are questionable???
Out-of-field RISK

Risk Models

☐ BEIR V (NCR 1990)
☐ ICRP (1991)
☐ NCRP (1993)
☐ EPA (1994, 1999)
☐ UNSEAR (2000)
☑ BEIR VII (2006)

All these models are for low doses of radiation
Recommendation of dose-response relationships to allow risk assessment

- function of dose
- function of organ
- function of patient’s age at exposure
- function of gender
- attained age
BIER VII - Risk Models

EAR - Excess Absolute Risk - difference
ERR - Excess Relative Risk - ratio

\[ EAR \text{ or } ERR(s, a, e^*, D) = \rho(D) \cdot \beta_s \cdot e^{re^*} \cdot (a/60)^\eta \]

\( \rho(D) \) is a linear function of dose for solid tumors
\( e^* = (e-30)/10 \) (equals 0 for \( e>30 \)) - age at exposure
\( \gamma, \beta, \eta = \text{organ/gender/model dependent} \)
\( a = \text{attained age} \)

Although ERR and EAR have the same form but values and interpretation of parameters are different.
Lifetime Attributable Risks - LARs

\[
LAR(D,e) = \frac{\int_{a=e+L}^{100} M(D,e,a)S(a)/S(e)da}{a=e+L}
\]

\[
M(D,e,a) = EAR(D,e,a) \quad M(D,e,a) = ERR(D,e,a) \cdot \lambda(a)
\]

\[
S(a)/S(e) = \text{probability of surviving from age } e \text{ to } a \text{ age.}
\]

\[
L \text{ latent period (5 years) for solid cancer induction.}
\]

\[
\lambda(a) = \text{the unexposed baseline risk.}
\]

Dose and Dose Rate Effective Factor - DDREF

Risk models are based on atomic bomb survivors with single acute exposure. Need a correction factor in fractionated RT.

BIER VII: 1.0 for neutrons and 1.5 for photons
 Pediatric Patients

☐ Have a long post treatment lives.
☐ More sensitive to radiation induced cancer compared to adults by a factor of at least 10. \textit{ICRP Pub. 60 1990}
☐ Scattered radiation in a small body is more significant.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{chart.png}
\caption{Out-of-field RISK}
\end{figure}

\textit{BEIR, Health risks from exposure to low levels of ionizing radiation, BEIR VII, Phase 2. National Research Council, National Academy of Science, 2006}
Excess relative risk (ERR) for thyroid cancer per treatment Gy assuming a 4-year old female patient

Internal Neutrons

External Neutrons

(a) 0.008

(b) 0.04

ERR / Gy

Out-of-field RISK

Field Index

1,4  2,5  3,6

1,4  2,5  3,6
Excess relative risk (ERR) for thyroid cancer per treatment Gy assuming a 4-year old female patient.

Internal Neutrons

External Neutrons

Field Index
How do IMRT, Passively Scattered, and Scanning Proton Therapy compare?

Assuming idealized scanning no neutron contamination from treatment head.
Lifetime Attributable Risk(%) for the out-of-field organs from field #6 for a 54 Gy treatment assuming lifespan to age 100 years

<table>
<thead>
<tr>
<th>8-year old female</th>
<th>14-year old male</th>
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<tbody>
<tr>
<td>Bladder Wall</td>
<td>Scanning Proton</td>
</tr>
<tr>
<td>Ovaries</td>
<td>6-MV IMRT</td>
</tr>
<tr>
<td>Uterus</td>
<td>PassiveProton</td>
</tr>
<tr>
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<td>Larynx</td>
<td></td>
</tr>
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Out-of-field RISK

ISO

LAR[\%]

0.0  0.5  1.0  1.5

(a)

(b)
Lifetime Attributable Risk(%) for the out-of-field organs from field #6 for a 54 Gy treatment assuming lifespan to age 100 years

8-year old female

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<td>0.0</td>
</tr>
<tr>
<td>Breasts ERR</td>
<td></td>
<td>0.24%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Breasts EAR</td>
<td></td>
<td>0.13%</td>
<td>0.0%</td>
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<td>Bronchi</td>
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<td>0.0</td>
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<tr>
<td>Testes</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.0</td>
<td>0.0</td>
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8-year old female:
- Bladder Wall: 0.0%
- Ovaries: 0.0%
- Uterus: 0.0%
- Kidneys: 0.0%
- Pancreas: 0.0%
- Liver: 0.0%
- Esophagus: 0.0%
- Lungs: 0.0%
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- Bronchi: 0.0%
- Thyroid: 1.14%
- Larynx: 0.15%

14-year old male:
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- Testes: 0.0%
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- Kidneys: 0.0%
- Pancreas: 0.0%
- Liver: 0.0%
- Esophagus: 0.0%
- Lungs: 0.0%
- Breasts ERR: 0.0%
- Breasts EAR: 0.0%
- Bronchi: 0.0%
- Thyroid: 0.0%
- Larynx: 0.0%

Out-of-field RISK

ISO

LAR[%]:
- Bladder Wall: 0.0%
- Ovaries: 0.0%
- Uterus: 0.0%
- Kidneys: 0.0%
- Pancreas: 0.0%
- Liver: 0.0%
- Esophagus: 0.0%
- Lungs: 0.0%
- Breasts ERR: 0.24%
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- Thyroid: 1.14%
- Larynx: 0.15%

ISO

LAR [%]:
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- Thyroid: 0.0%
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Lifetime Attributable Risk(%) for the out-of-field organs from field #6 for a 54 Gy treatment assuming lifespan to age 100 years.

8-year old female

- Bladder Wall
- Ovaries
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- Kidneys
- Pancreas
- Liver
- Esophagus
- Lungs
- Breasts ERR
- Breasts EAR
- Bronchi
- Thyroid
- Larynx

\[
\frac{LAR_{IMRT}}{LAR_{Proton}} \approx 2 - 4
\]

\[
\frac{LAR_{IMRT}}{LAR_{Proton}} \approx 0.5
\]

14-year old male

- Bladder Wall
- Testes
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\frac{LAR_{IMRT}}{LAR_{Proton}} \approx 2 - 4
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<tr>
<td>Larynx</td>
<td>1.25%</td>
<td>0.15%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.42%</td>
<td>0.61%</td>
</tr>
<tr>
<td>Bronchi</td>
<td>2.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.02%</td>
<td>0.75%</td>
</tr>
<tr>
<td>Lungs</td>
<td>1.24%</td>
<td>0.38%</td>
</tr>
<tr>
<td>Breasts ERR</td>
<td>0.41%</td>
<td>16.01%</td>
</tr>
<tr>
<td>Breasts EAR</td>
<td>6.67%</td>
<td>7.76%</td>
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<tr>
<td>Kidneys</td>
<td>1.02%</td>
<td>1.69%</td>
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<tr>
<td>Pancreas</td>
<td>1.25%</td>
<td>1.25%</td>
</tr>
<tr>
<td>Liver</td>
<td>0.24%</td>
<td>0.90%</td>
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<tr>
<td>Esophagus</td>
<td>6.67%</td>
<td>0.75%</td>
</tr>
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</table>

Out-of-field RISK

ISO
Comparison with other groups
Comparison of equivalent doses for different structures using proton therapy and IMRT. Assumed 100 GyE for spine field. MGH and ISO data shown.
Similarities:
- Green band - $D_{\text{Neutron}} > D_{\text{IMRT}}$
- Photon doses look similar and at large distances plateau out.

Differences:
- At large distances neutron doses differ - owing to different treatment head.
## Excess Relative Risk (ERR)

### MD Anderson - Prostate Field

<table>
<thead>
<tr>
<th>Organs</th>
<th>Medium T2a adenocarcinoma separation</th>
<th>Proton</th>
<th>IMRT</th>
</tr>
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<tbody>
<tr>
<td><strong>Colon</strong></td>
<td>2.25</td>
<td></td>
<td>2.73</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>0.05</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td>0.04</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
<td><strong>3.99</strong></td>
<td></td>
<td><strong>6.92</strong></td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>0.07</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Thyroid</strong></td>
<td>0.01</td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Bone Marrow</strong></td>
<td>0.63</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Remainder</strong></td>
<td>0.11</td>
<td></td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Fontenot et al. IJROBP 74, 616-622 (2009)*
## Excess Relative Risk (ERR)

### MD Anderson - Prostate Field

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**In-Field Comparison**

- **Colon**: Proton 2.25 vs. IMRT 2.73
- **Bladder**: Proton 3.99 vs. IMRT 6.92

Fontenot et al. *IJROBP* 74, 616-622 (2009)
In-Field Secondary Cancer Induction
In Field Second Cancer Risk

- It has been predicted that 6-10% of all cancer diagnosed in the USA are secondary cancer... malignancies which develop after first cancer ... histologically different from the primary disease.


- Preliminary data suggests that SPMs (Second Primary Malignancies) are mainly observed in tissues having absorbed doses above 2 Gy and their incidence increases with the dose.

  *Tubiana Rad. and Onc. 91 4-15 (2009)*
In-Field Organs

IMRT Treatment

Proton Treatment

Integral dose from IMRT is 2 to 3 times higher
In-Field Doses

- In-Field organ-at-risk (OARs) get large doses in 10s of Gy.
  Small portion of OAR sometimes get the full target dose.

- Dose gradient in these OARs is sharp.

- It is meaningless to talk about mean dose.

- Organ Equivalent Dose (OED) is a useful quantity.

- Any dose distribution in an organ is equivalent and corresponds to the same OED if it causes the same radiation induced cancer. Schneider et al.; Int. J. Radiat. Biol. Phys. 61, 2005

How does high dose translate into Second Cancer Risk?
High dose region: > 5 Gy

Scarce data at high doses.

Balance between cell kill and repopulation.

- Bell shaped
- Plateau
- Linear - unlikely
In-Field RISKS

Linear?
Plateau?
Bell shaped?

High dose region: > 5 Gy
Scarce data at high doses.
Balance between cell kill and repopulation.

- Bell shaped
- Plateau
- Linear - unlikely
Risk Models: High Dose

- Not many in the market.

Lindsay Schneider Davis

- Recently Schneider came up with a **Mechanistic model** for second cancer “carcinoma” induction.

\[
EAR_C = \mu \frac{e^{\alpha' D}}{\alpha'/R} \left( 1 - 2R + R^2 e^{\alpha' D} - (1 - R)^2 e^{\frac{\alpha'R}{1+R^D}} \right)
\]

**OED**

- \(R\) = Repopulation factor 0 - 1
- \(\alpha' = \alpha + \beta d_F\): \(\alpha\) and \(\beta\) are the usual parameters from the linear-quadratic model; \(d_F\) fractionated dose.
- \(\mu\) is risk co-efficient
In-Field RISks

Small dose - linear
Small R - bell shaped
Large R - plateau shaped
In-Field Studies at MGH

- Currently we are also looking into “In-Field” doses and associated second cancer induction in pediatric patients based on Schneider’s model.

- Make clinically relevant plans.

- Obtain In-Field doses from the TPS.

- Assess Risks with different Repopulation rate.

- Glioma and Ewing’s Sarcoma.
Optic Glioma: In-Field Organs

4-year old female

14-year old male

\[ \frac{LAR_{IMRT}}{LAR_{Proton}} = 3.0 \]

\[ \frac{LAR_{IMRT}}{LAR_{Proton}} = 4.7 \]
Optic Glioma: In-Field Organs

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\[
\frac{LAR_{\text{IMRT}}}{LAR_{\text{Proton}}} = 3.0
\]

\[
\frac{LAR_{\text{IMRT}}}{LAR_{\text{Proton}}} = 4.7
\]

BASELINE_{\text{ORAL CAVITY}} = 0.68%

BASELINE_{\text{BRAIN}} = 0.56%

BASELINE_{\text{ORAL CAVITY}} = 1.41%

BASELINE_{\text{BRAIN}} = 0.65%
Combining in-field & out-of-field risks
What can we learn?
Combining in-field & out-of-field risks
What can we learn?

\[
\frac{LAR_{IMRT}}{LAR_{Proton}} \approx 3.0
\]

\[
\frac{LAR_{IMRT}}{LAR_{Proton}} \approx 0.5
\]

\[
\frac{LAR_{IMRT}}{LAR_{Proton}} \approx 2 - 4
\]

Large photon integral dose
Neutron doses > IMRT doses
DDREF lowers the photon risks
Secondary neutron doses become much smaller

Neutron doses are facility dependent.
LAR_{Proton} may change.
Young patients are subject to greater risks because of geometrical differences and age.

Most out-of-field lifetime risks are <1%.

Out-of-field neutron doses in proton therapy depend on the treatment model.

Risks in Scanning Proton Beam are much lower compared to other modalities.
In-Field IMRT second cancer risks are higher compared to proton therapy.

IMRT has an advantage for out-of-field organs near the field edge.

Proton therapy shows an advantage over IMRT beyond ~30 to 40 cm from the field edge.
Thank You