Dosimetry for Epidemiology Cohorts Who Receive Radiation Therapy

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Introduction

- About 1 in 2 men and women born today will be diagnosed with some form of cancer in their lifetime (Howlader et al., SEER, 2012).

- Almost 2/3 of all cancer patients receive some form of radiation therapy during the course of treatment (Physician Characteristics and Distribution in the U.S., 2010).

- The vast majority of these treatments will be with photon therapy (DeVita et al., 2008).
High Incidence of Second Malignant Neoplasms and Non-malignant Skin Cancer

**Incidence and Mortality of Second Cancers**

- CCSS: Mortality of primary ca is decreasing, with increases in rates of mortality attributable to subsequent neoplasms, cardiac death, and pulmonary death largely due to treatment-related causes. (Armstrong et al 2009, JCO)

- For some types of cancers and in some pediatric cancers, second cancers can cause more deaths than the primary cancers. (Tubiana M 2009, Radiother Oncol)

- Second cancers account for 6~10% of all cancers and are the fourth or fifth most common cancer in USA. (Neugut A.I. 1999, Multiple Primary Cancers)

See also review of 2nd solid Ca after RT: Berrington de Gonzalez, IJROBP 86 224-233 (2013)
What Causes Second Cancers? **Radiation** is a Treatment-Related Risk Factor.

**Table 3.** Host and Treatment Factors Increasing Risk of Selected Subsequent Neoplasms After Childhood Cancer

<table>
<thead>
<tr>
<th>Subsequent Cancer</th>
<th>Host Factor</th>
<th>Treatment Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any subsequent malignancy histology&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Female sex, young age at diagnosis; primary diagnosis Hodgkin's disease or soft tissue sarcoma</td>
<td>Alkylating agents; epipodophyllotoxins; anthracyclines</td>
</tr>
<tr>
<td>Breast&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Female sex; primary diagnosis of bone tumor or soft tissue sarcoma</td>
<td>Chest radiation</td>
</tr>
<tr>
<td>Thyroid&lt;sup&gt;9,45&lt;/sup&gt;</td>
<td>Younger age at diagnosis</td>
<td>Thyroid radiation (20 to 40 Gy)</td>
</tr>
<tr>
<td>CNS&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Young age at initial therapy (glioma); ≥ age 5 at initial therapy (meningioma)</td>
<td>CNS radiation</td>
</tr>
<tr>
<td>Sarcoma&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Primary diagnosis of soft tissue sarcoma; history of other subsequent neoplasm; family history of cancer</td>
<td>Radiation therapy; higher anthracycline dose (&gt; 100 mg/m^2); higher alkylating agent dose (alkylators score ≥ 2)</td>
</tr>
<tr>
<td>Nonmelanoma skin cancer&lt;sup&gt;43&lt;/sup&gt;</td>
<td>White race; older attained age; primary diagnosis of HD; family history of skin cancer</td>
<td>Radiation therapy</td>
</tr>
</tbody>
</table>

Where Do Second Cancers Develop?

12% in PTV

66% surrounding PTV

22% at distance >5cm

Improving Outcomes for Ca Survivors

Approach to Reduce Late Effects: Start By Reducing Physical Dose to Normal tissues

Protons
NAS BEIR VII (2006): “A large number of studies involving ionizing radiation ... have increased our general knowledge of risk... Many studies lack the sample size and high-quality dosimetry that are necessary for the precise estimate of risk as a junction of dose ...”

IOM (2009): 100 initial top priorities for comparative effectiveness research: “... strategies for localized prostate cancer (... proton beam and IMRT) on survival, recurrence, side effects ...”
Radiation Exposure
Radiation: Therapeutic, Scatter, Leakage

Current Photon Dose Models

From Jagetic et al (in preparation)
**Methods: New Physics Model**

Sources (primary and scatter)

Photon Fluence in air

Attenuation in head, phantom

Scattering in head, phantom

Convert fluence to dose

Combine doses

\[ D_T = D_P + D_L + D_S \]

Jagetic L and Newhauser WD, A simple and fast analytical method to calculate doses to the whole body from external beam, megavoltage x-ray therapy. Phys Med Biol. 60 (2015) 4753–4775
Methods: Physical Model Predictions

6 MV, in-water, cross-plane, 5x5 cm², d=1.5 cm


Comparison of Various Models and Measurements

Jagetic et al, in preparation

- Measured (Kaderka et al., 2012)
- Measured (Stovall et al., 1995)
- Analytical Model (Jagetic and Newhauser, 2015)
- Pinnacle TPS (Jagetic and Newhauser, 2015)
- Eclipse TPS (Jagetic and Newhauser, 2015)

$D / [D_{max} (CA)]$ (mGy/Gy)

Position (cm)

- 3.3 mGy/Gy
- 1.5 mGy/Gy
A simple, descriptive, and broadly applicable model of therapeutic and stray absorbed dose from 6 MV to 25 MV photon beams

Christopher Schneider¹,², Wayne D Newhauser¹,², Lydia Jagetic¹, Uwe Schneider³,⁴, Robert Kaderka⁵, Saveta Miljanić⁶, Željka Knežević⁶, Liliana Stolarczyk⁷, Marco Durante⁵,⁸, and Roger Harrison⁹

Figure 5– Measured and calculated relative absorbed doses for 6, 12, and 20 MV beams at 10 cm and 25 cm depths in water from EURADOS data set.
Figure 6 – Points represent doses measured in anthropomorphic phantom for various treatment machines and techniques. Lines represent analytical model calculation from model as trained on KGU and EURADOS data sets, respectively.
Neutron Leakage Exposure From Proton RT

Proton Therapy: New Model of Neutron Leakage

\[
\left(\frac{H}{D}\right)_p = \left(\frac{H}{D}\right)_{E,iso} \left(\frac{d}{d_{iso}}\right)^{-q} \sum_{i=1}^{4} C_i(E) \exp\left[-\alpha_i(d' - d'_{iso})\right] \exp\left[-\frac{(x^2 + y^2)d_{iso}^2}{2\sigma_i^2 z^2}\right]
\]

- Divergence
- Attenuation in Phantom
- Relative Lateral Intensity
- Shape of neutron energy distribution

Neutron Leakage Exposure From Proton RT

Routine Prospective Calculation of Stray Neutron Dose to is Feasible

Sagittal equivalent dose planes overlaying a thoracic CT image of the HL patient showing (a) proton equivalent dose and (b) combined proton and neutron equivalent dose. Equivalent dose values are percentages of the prescribed target equivalent dose, i.e., 36 Sv. The mediastinal tumor and healthy thyroid are contoured in black.

Eley, Newhauser, Homann, Howell, Schneider, Durante Bert. Cancers 2015, 7, 427-438
# Current Capabilities of Analytical Dose Models

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Photon Therapy</th>
<th>Proton Therapy</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic</td>
<td>★★★</td>
<td>★★★★</td>
<td>Excellent</td>
</tr>
<tr>
<td>Patient Scatter</td>
<td>★★★</td>
<td>★</td>
<td>Poor</td>
</tr>
<tr>
<td>Leakage</td>
<td>★★★</td>
<td>★★★</td>
<td>Fair</td>
</tr>
<tr>
<td>Head Scatter</td>
<td>★</td>
<td>N/A</td>
<td>Poor</td>
</tr>
<tr>
<td>Photoneutrons</td>
<td></td>
<td>N/A</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Radiation RISK
Risk Assessment Methods

\[ \text{Risk} = r_T \cdot H_T \]

Organ-Specific Risk Models

\[ H_T = w_{R,T} D_T \]

Organ or tissue dose

- Therapeutic (from tx plan)
  - +
  - Leakage (from MC)
  - +
  - Scatter (from MC)
Risk Quantities

Incidence rate: number of newly diagnosed cases of disease X per population over a period of time

\[ R_e = \text{rate in individuals exposed to radiation} \]
\[ R_u = \text{rate in individuals unexposed to radiation} \]
Relative Risk Quantities

Relative Risk

\[ RR = \frac{R_e}{R_u} \]

Excess Relative Risk

\[ ERR = RR - 1 \]

Ratio of Relative Risk

\[ RRR = \frac{R_{e, \text{proton}} / R_u}{R_{e, \text{IMRT}} / R_u} = \frac{R_{e, \text{proton}}}{R_{e, \text{IMRT}}} \]
Risk Models: Governing Factors

- Increases with dose
- Varies with organ or tissue
- Risk decreases with age at exposure
- Risk decreases with attained age
- Sex, genetics, and many other host factors
- Varies with type of radiation
- Competing causes of death

Uncertainties: Deviations from Linear Non-threshold Risk Model

Hall (2006)
Comparative Risk for SMN Following Proton RT v IMRT for Prostate Cancer

Passively scattered protons

6-MV IMRT with photons

Fontenot et al, IJROBP 74 616-622 (2009)
Ratio of Relative Risk

$$RRR = \frac{RR_{PSPT}}{RR_{IMRT}}$$ (Includes Neutrons)

Uncertainties: Fontenot et al, PMB (in review)
Results: Fontenot et al, IJROBP 74 616-622 (2009)
Visualize Spatial Distribution of Risk:

*Endpoint matters*

From Newhauser and Durante (Nature Rev Ca, 2011)
Second cancers are a major public health issue.

Need capability to calculate dose and risk.

Need to epidemiologic risk data to minimize risk of 2nd cancer.
End