Neutrons and the Risk of Second Malignancies Following Proton vs. Photon Radiation Therapies

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Background

- Radiation increases risk of second malignant neoplasms (SMN)

- Increasing concern about SMN
  - Escalation therapeutic dose
  - Earlier detection/intervention of first cancer
  - Increasing life expectancies
  - Evolution of radiotherapy treatments
Incidence of Second Malignant Neoplasms and Non-malignant Skin Cancer (CCSS)

Proton Therapy: the Problem?

“Does it make any sense to spend over $100 million on a proton facility, with the aim to reduce doses to normal tissues, and then to bathe the patient with a total body dose of neutrons …”

Hall, Technol in Ca Res Treat 2007;6:31-34
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)
Monte Carlo Simulation of Proton Treatment

Ratio of Relative Risk

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

Baseline RRR, LNT, ICRP-92

Uncertainties: Fontenot et al, in preparation
Results: Fontenot et al, IJROBP 74 616-622 (2009)
Dependence on Neutron $w_R$ for Carcinogenesis

Prospective Randomized Clinical Trial of SMN Following Proton Therapy vs IMRT

- 2000 pts/y for 5 y

- 80% power to detect an \( \text{RRR} \) of 0.67 for developing SMN with 2-sided t-test at significance level of 0.05

- Obstacles
  - Duration of study: 12.1 years
  - Ethical issues associated with equipoise
Retrospective Clinical Trial of SMN following proton therapy vs IMRT

- 11,000 patients treated from 1995-2005
- Average follow-up of 8.8 years
- Complete follow-up on every patient through 2009
- 80% power to detect an RRR of 0.67 for developing SMN with 2-sided t-test (p=0.05)

Obstacles
- Selection bias: Retrospective approach does not allow randomization
- Follow-up data may not be complete
Comparative Risk for SMN Following Photon CRT and IMRT versus Proton Therapy for Craniospinal Irradiation

Photon CRT (6 MV, 1 field)
Risk: 55%
Rel. risk: 12

Photon IMRT (15 MV, 9 field)
Risk: 31%
Rel. risk: 7

Protons (SOBP, 1 field)
Risk: 4-5%
Rel. risk: 1

From Newhauser et al, PMB, 2009; Miralbell et al., IJROBP 2002
Methods Include Supercomputing Monte Carlo Dose Calculations

Figure 1. Monte Carlo simulation of particle fluences for the three craniospinal treatment fields. The upper plots represent the logarithm of the proton fluence, including primary protons and secondary protons generated via (n, xp) reactions in the treatment unit and in the phantom. The corresponding lower plots represent the logarithm of neutron fluence, including neutrons generated internally and externally to the phantom. Note that the fluence in each plot was scaled to maximize the visibility of the shape of the distributions, not their magnitude. (A), (B) Cranial field. (C), (D) Superior spinal field. (E), (F) Inferior spinal field.

Newhauser et al, PMB, 54 2277-2291 (2009)
Prospective Randomized Clinical Trial of SMN Following CSI with Proton Therapy vI MRT

- 200 pts/y for 4 y

- 80% power to detect an RRR of 0.14 for developing SMN with 2-sided t-test at significance level of 0.05

Obstacles

- Duration of study: 8.5 years
- Ethical issues associated with equipoise
Is Passive Scattering a Problem?

“Protons are a major step forward for radiotherapy, but neutrons are bad news and must be minimized by the use of spot scanning techniques.”

Hall, Technol in Ca Res Treat 2007;6:31-34
$$RRR = \frac{RR_{proton}}{RR_{IMRT}}$$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( RRR ) (Scattered)</th>
<th>( RRR ) (Scanned)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>0.66</td>
<td>0.56</td>
</tr>
<tr>
<td>CSI</td>
<td>0.16</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Based on data from Newhauser et al PMB 2009 and Fontenot et al IJROBP 2009
Conclusions on 2\textsuperscript{nd} Cancer Risk

RCT data unavailable for advanced RT modalities

\textit{In-silico} RCTs can provide rigorous evidence for selecting treatment modality

\textit{In-silico} case studies revealed lower risk following proton $\nu$ photon therapies
End