

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

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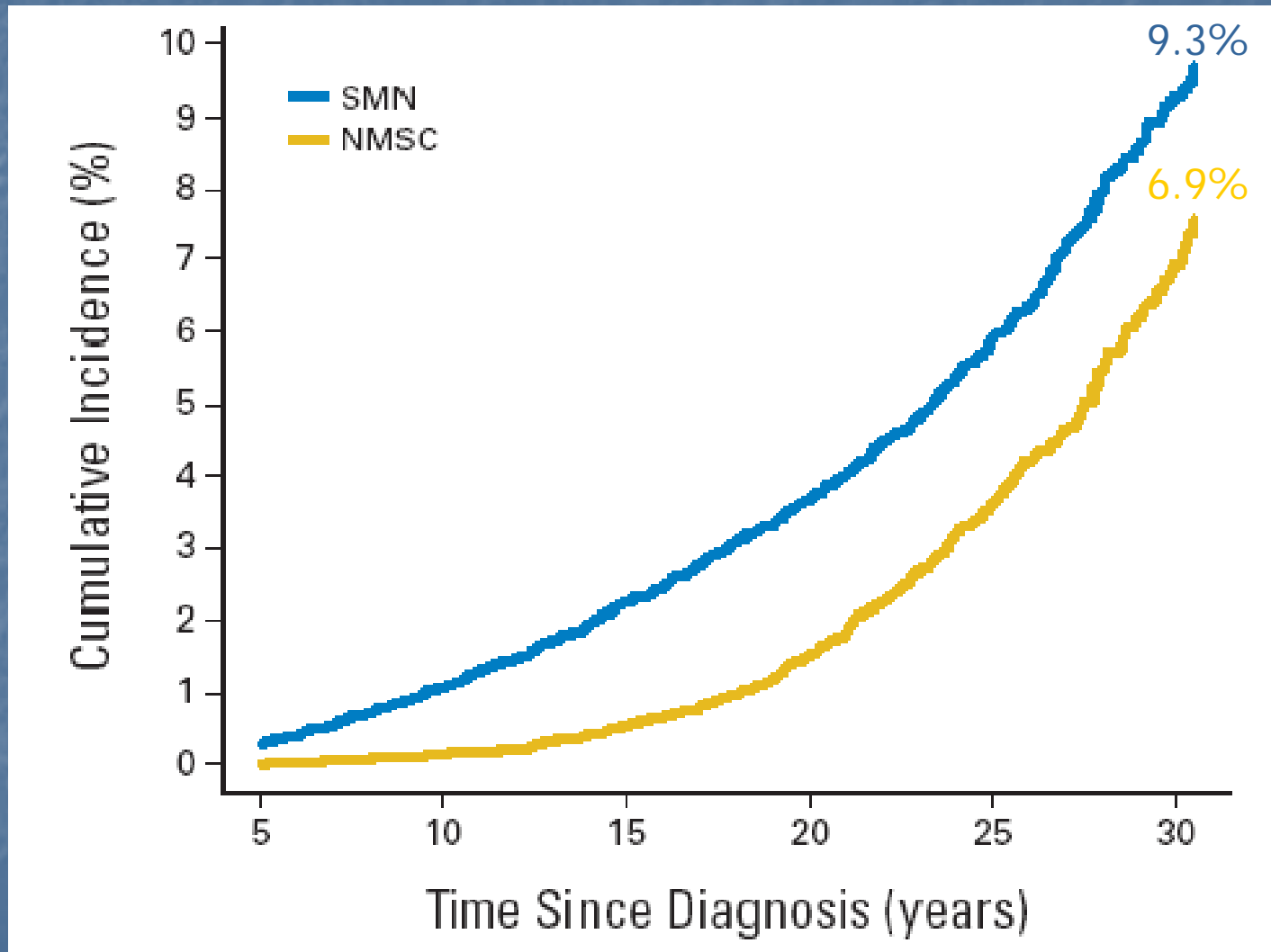
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- Northern Illinois University through a subcontract of Department of Defense contract W81XWH-08-1-0205
- I do not have any conflicts of interest

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)



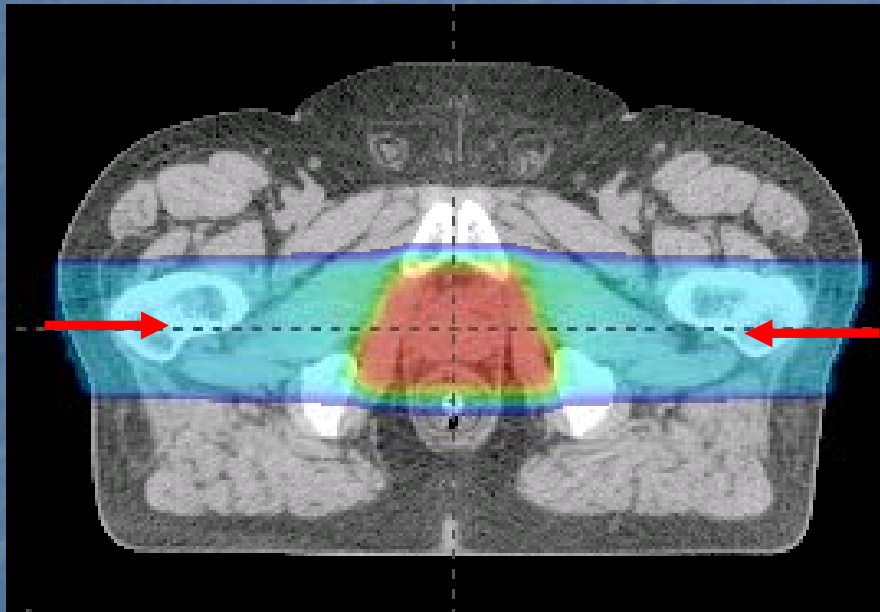
Meadows et al. J Clin Oncol (eprint ahead of print, 2009)

Proton Therapy: the Problem?

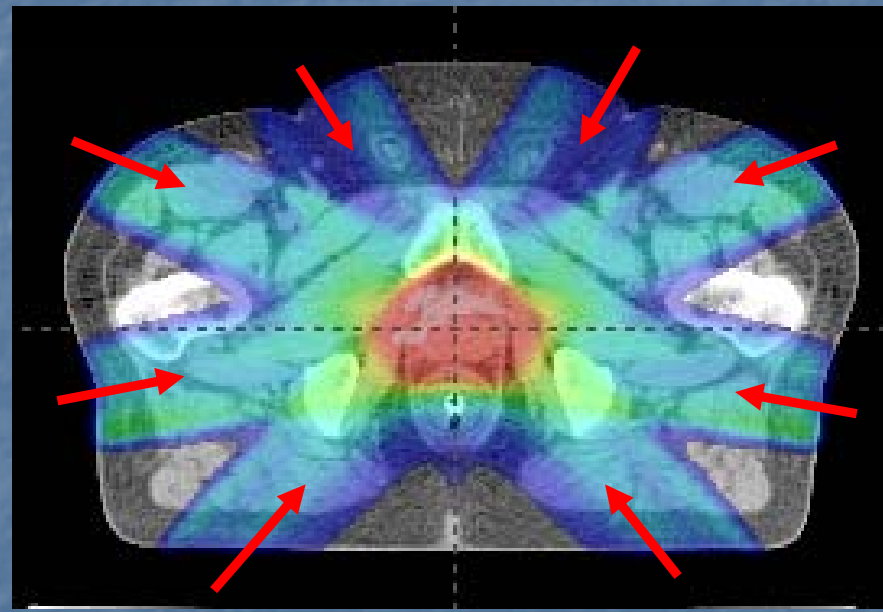
“Does it make any sense to spend over \$100 million on a proton facility, with the aim to reduce doses to normal tissues, and then to bathe the patient with a total body dose of neutrons ...”

Hall, Technol in Ca Res Treat 2007;6:31-34

Comparative Risk for SMN Following Proton RT v IMRT for Prostate Cancer

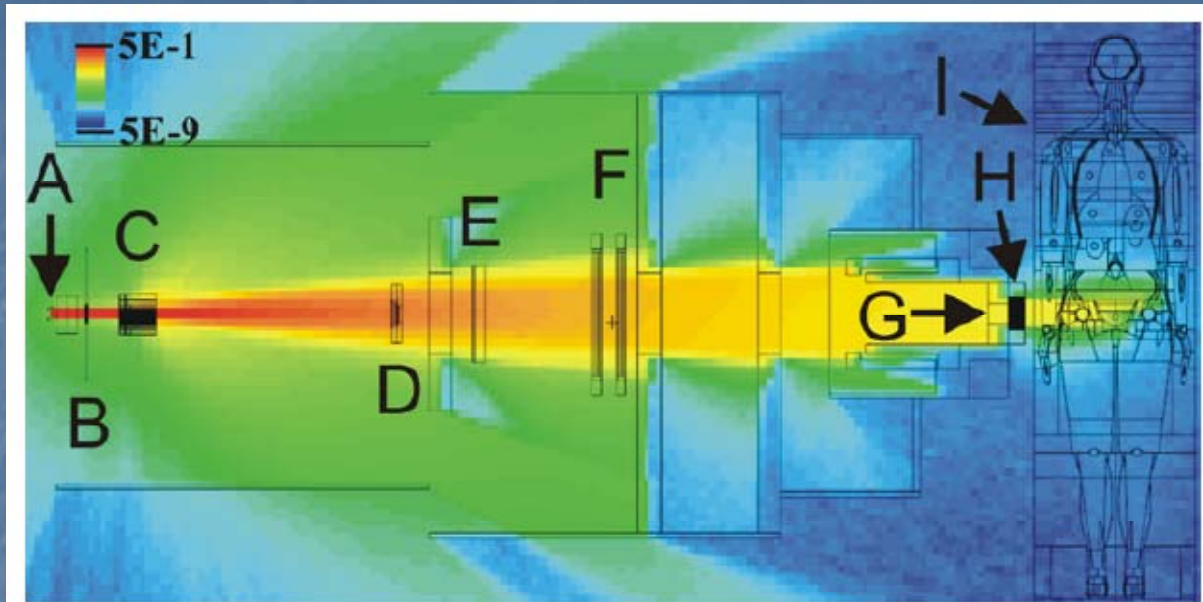


Passively scattered protons

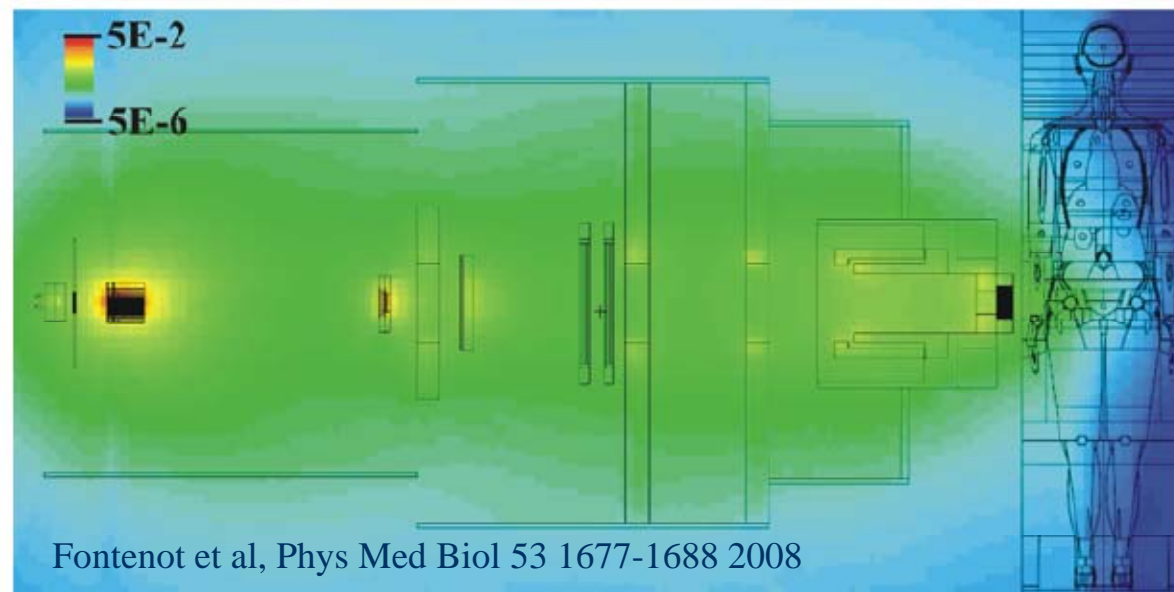


6-MV IMRT with photons

Monte Carlo Simulation of Proton Treatment



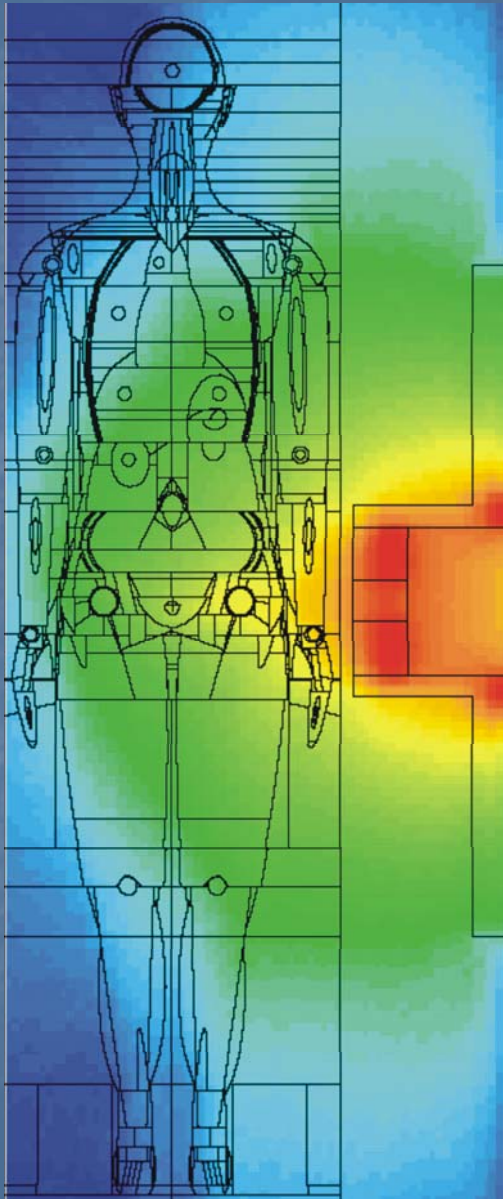
Log
Proton
Fluence



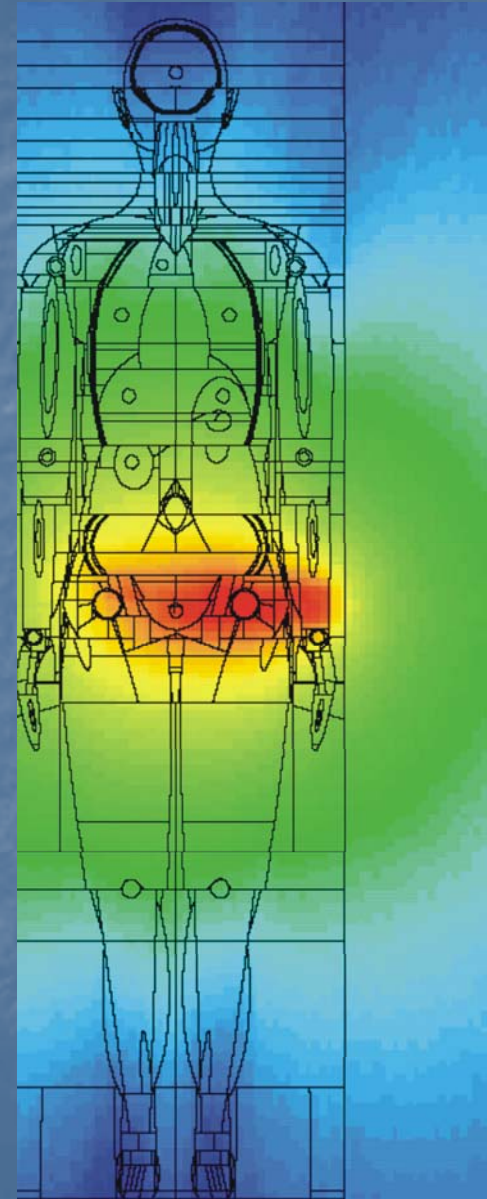
Log
Neutron
Fluence

Fontenot et al, Phys Med Biol 53 1677-1688 2008

Neutron Fluence Passive Scattering

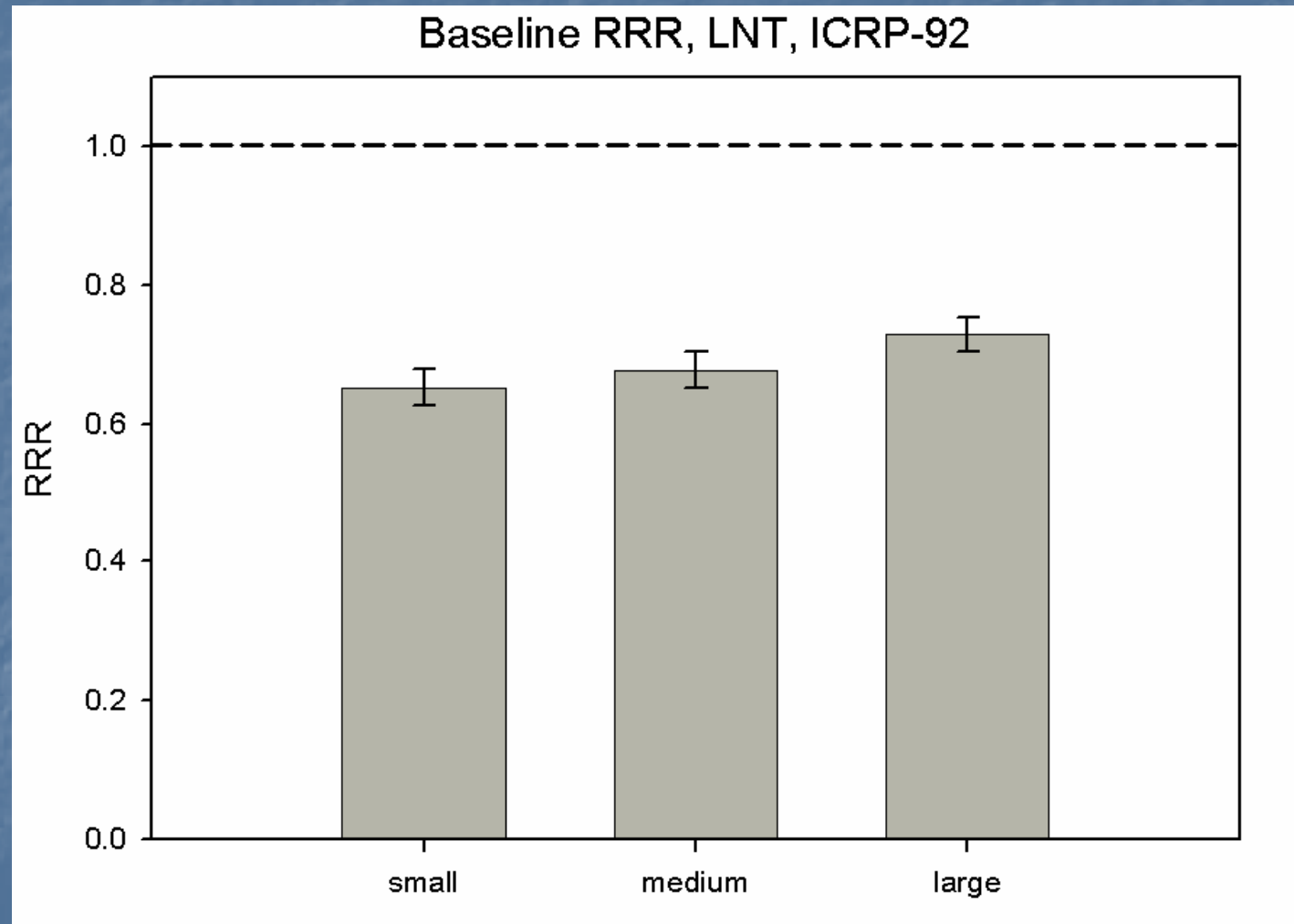
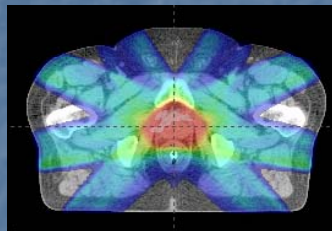
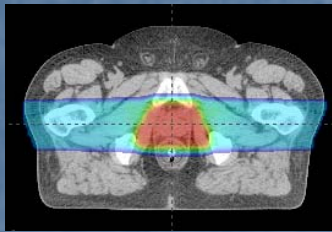


Neutron Fluence Spot Scanning



Ratio of Relative Risk

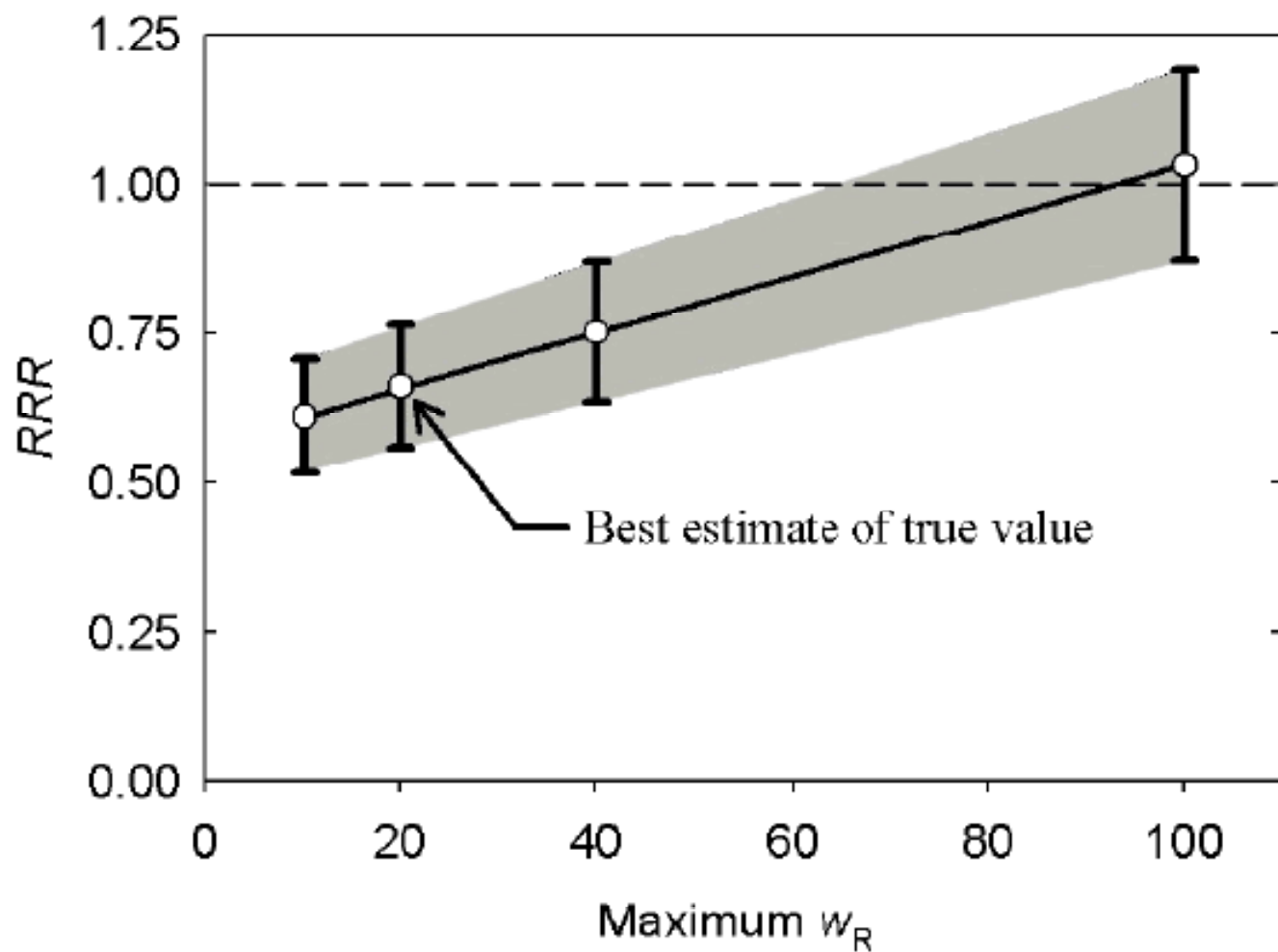
$$RRR = RR_{PSPT} / RR_{IMRT} \text{ (Includes Neutrons)}$$



Uncertainties: Fontenot et al, in preparation

Results: Fontenot et al, IJROBP 74 616-622 (2009)

RRR Dependence on Neutron w_R for Carcinogenesis



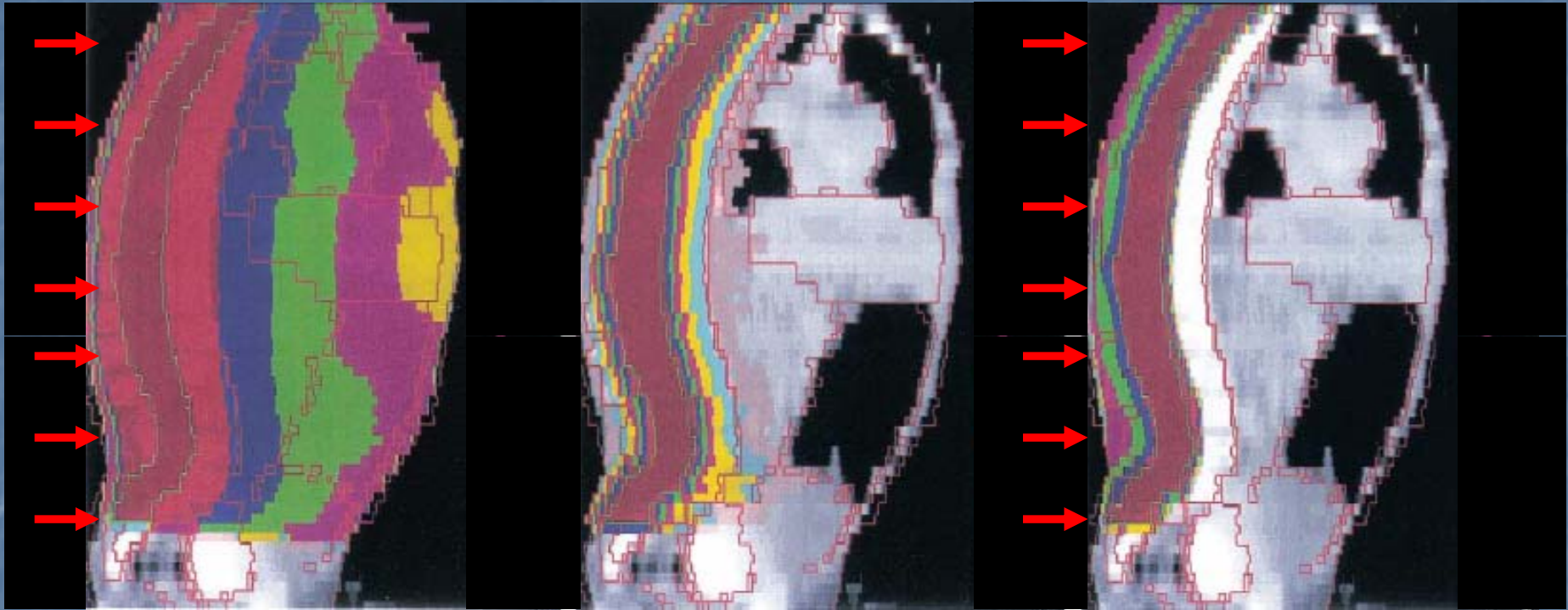
Prospective Randomized Clinical Trial of SMN Following Proton Therapy v IMRT

- 2000 pts/y for 5 y
- 80% power to detect an *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 v 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)

31%

7

Protons
(SOBP, 1 field)

4-5%

1

From Newhauser et al, PMB, 2009; Miralbell et al., IJROBP 2002

Methods Include Supercomputing Monte Carlo Dose Calculations

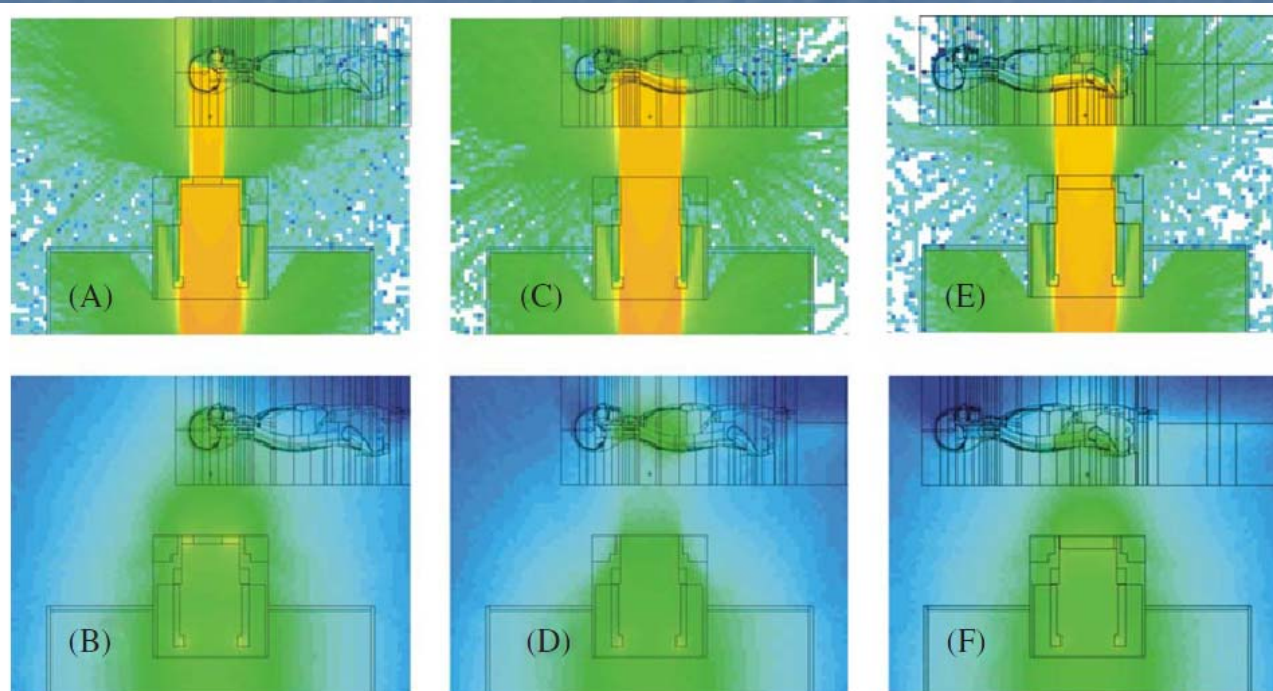


Figure 1. Monte Carlo simulation of particle fluences for the three craniospinal treatment fields. The upper plots represent the logarithm of the proton fluence, including primary protons and secondary protons generated via (n, xp) reactions in the treatment unit and in the phantom. The corresponding 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)

Newhauser et al, Trans Am Nucl Soc 99 63-64 (2008)

Prospective Randomized Clinical Trial of SMN Following CSI with Proton Therapy *v* IMRT

- 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

$$RRR = RR_{\text{proton}} / RR_{\text{IMRT}}$$

Treatment	<i>RRR</i> (Scattered)	<i>RRR</i> (Scanned)
Prostate	0.66	0.56
CSI	0.16	0.14

Based on data from Newhauser et al PMB 2009 and Fontenot et al IJROBP 2009

Conclusions on 2nd Cancer Risk

RCT data unavailable for advanced RT modalities

In-silico RCTs can provide rigorous evidence for selecting treatment modality

In-silico case studies revealed lower risk following proton ν photon therapies

End