Second Cancers After Photon and Proton Radiotherapies

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Acknowledgments & Disclosure

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- Colleagues and trainees too numerous to mention individually
- I do not have any conflicts of interest
Objectives of Lecture

- Review basics of radiogenic second cancers
- Current state of knowledge
- Gaps in knowledge
- Comparative risk assessment
- Methods of dose and risk assessment
- Future directions in research & clinical practice
Review: Deterministic Effects

- **Severity increases with dose**, above a threshold
- Effect usually occurs after large doses
- Occurs hours, days, months or years after exposure
- **Examples**
  - Reduction in fertility
  - Cataracts

National Eye Institute
Review: Stochastic Effects

- Probability increases with dose
- Severity independent of dose (all or nothing)
- Principal effect after exposure to low doses

Examples
- Lung Cancer
- Genetic effects
Review: Goals of “Radiation Protection”

- Prevent occurrence of serious radiation-induced conditions in exposed persons. These include acute and chronic deterministic effects.

- Reduce stochastic effects in exposed persons to a degree that is acceptable in relation to the benefits to the individual and society from the activities that generate such exposure.
Objectives of Lecture

- Review basics of radiogenic second cancers
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Long Term Trends

Good news!

Declining due to investment in cancer research, screening, intervention, and prevention.

From Jemal et al, CA Cancer J Clin, 59 (2009)
Data from Surveillance, Epidemiology, and End Results (SEER) program
Trends in 5-Year Relative **Survival** Rates (%) for **Children** Younger than Age 15 Years (United States, 1975-2004)

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<tbody>
<tr>
<td>All sites</td>
<td><strong>58</strong></td>
<td>63</td>
<td>67</td>
<td>68</td>
<td>71</td>
<td>76</td>
<td>77</td>
<td><strong>80†</strong></td>
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<tr>
<td>Acute lymphocytic leukemia</td>
<td>58</td>
<td>66</td>
<td>71</td>
<td>73</td>
<td>78</td>
<td>83</td>
<td>84</td>
<td><strong>88†</strong></td>
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<tr>
<td>Acute myeloid leukemia</td>
<td>19</td>
<td>26</td>
<td>27†</td>
<td>31†</td>
<td>37†</td>
<td>41</td>
<td>42†</td>
<td>55†</td>
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<tr>
<td>Bone and joint</td>
<td>51†</td>
<td>49</td>
<td>57†</td>
<td>58†</td>
<td>67†</td>
<td>67</td>
<td>74</td>
<td><strong>71†</strong></td>
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<tr>
<td>Brain and other nervous system</td>
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<td>62</td>
<td>64</td>
<td>64</td>
<td>70</td>
<td>74†</td>
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<tr>
<td>Hodgkin lymphoma</td>
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<td>88</td>
<td>91</td>
<td>87</td>
<td>97</td>
<td>95</td>
<td><strong>96†</strong></td>
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<tr>
<td>Neuroblastoma</td>
<td>52</td>
<td>57</td>
<td>55</td>
<td>52</td>
<td>62</td>
<td>76</td>
<td>67</td>
<td><strong>70†</strong></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>43</td>
<td>53</td>
<td>67</td>
<td>70</td>
<td>71</td>
<td>76</td>
<td>81</td>
<td><strong>86†</strong></td>
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<tr>
<td>Soft tissue</td>
<td>61</td>
<td>75</td>
<td>69</td>
<td>73</td>
<td>65</td>
<td>80</td>
<td>77</td>
<td><strong>74†</strong></td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>73</td>
<td>79</td>
<td>87</td>
<td>91</td>
<td>92</td>
<td>92</td>
<td>92</td>
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</table>

Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

*Survival rates are adjusted for normal life expectancy and are based on follow-up of patients through 2005.

†Difference in rates between 1975 to 1977 and 1996 to 2004 is statistically significant (P<.05).

Source: Ries LAG, Melbert D, Krapcho M, et al.\(^3\)

Medulloblastoma 5-y Survival (SEER 9 Registries)

Smith et al, J Clin Oncol, 2010
Cancer Survivors in the United States

- **Large Population of Survivors**
  - > 10,000,000 (~3.5% of total population)
  - > 250,000 diagnosed before age 21
  - 2nd primary ca in survivors make up 16% of all ca incidence

- **Childhood Cancer Survivor Study**
  - 10,397 survivors (1970-1986), mean age: 27 y
  - 28% had a severe or life-threatening condition
  - 62% had at least one chronic condition
  - 73% had chronic condition at 30 y
  - Late effects: Second cancer, cardiovascular disease, kidney disease, musculoskeletal conditions, and endocrine abnormalities

Incidence of Second Malignant Neoplasms and Non-Melanoma Skin Cancer (CCSS)

Meadows et al, J Clin Oncol (2009)

Cumulative Incidence (%) vs Time Since Diagnosis (years)

- SMN: 9.3%
- NMSC: 6.9%
**Radiation is a Treatment-Related Risk Factor For Development of Second Cancers**

### 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</td>
<td>Female sex, young age at diagnosis; primary diagnosis Hodgkin’s disease or soft tissue sarcoma</td>
<td>Alkylation agents; epipodophyllotoxins; anthracyclines</td>
</tr>
<tr>
<td>Breast</td>
<td>Female sex; primary diagnosis of bone tumor or soft tissue sarcoma</td>
<td>Chest radiation</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Younger age at diagnosis</td>
<td>Thyroid radiation (20 to 40 Gy)</td>
</tr>
<tr>
<td>CNS</td>
<td>Young age at initial therapy (glioma); ≥ age 5 at initial therapy (meningioma)</td>
<td>CNS radiation</td>
</tr>
<tr>
<td>Sarcoma</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/m²); higher alkylating agent dose (alkylators score ≥ 2)</td>
</tr>
<tr>
<td>Nonmelanoma skin cancer</td>
<td>White race; older attained age; primary diagnosis of HD; family history of skin cancer</td>
<td>Radiation therapy</td>
</tr>
</tbody>
</table>

Knowledge: **Extensive** Evidence on Late Effects Caused by Treatments

**Overview**

**Pediatric Cancer Survivorship: The Childhood Cancer Survivor Study—Editor’s Foreword**
Patricia A. Ganz

**Review Articles**

**The Childhood Cancer Survivor Study: A National Cancer Institute–Supported Resource for Outcome and Intervention Research**

**Second Neoplasms in Survivors of Childhood Cancer: Findings From the Childhood Cancer Survivor Study Cohort**
Anna T. Meadows, Debra L. Friedman, Joseph P. Neglia, Ann C. Mertens, Sarah S. Donaldson, Marilyn Stovall, Sue Hammond, Yutaka Yasui, and Peter D. Inskip
Knowledge: Essentially Complete Understanding of Therapeutic Radiation Physics
Aside: A Bit on Proton Therapy

Big, expensive, difficult, rare, effective

Photo: www.tka-architects.com/proton.swf
MDACC Proton Center: Side View

- Accelerator Vault
- Gantry Rooms
- Fixed Beam Treatment Room
- Experimental Room
Big, Expensive, Challenging

NCC Korea, Photo Courtesy J Kim
Proton Accelerator

70-250 MeV
8 \(10^{10}\) p/spill
2 - 6.7 s rep
0.5-5 s/spill
Stable beam properties (no feedback)
High reliability

University of Tsukuba
Proton Gantry

13 m diameter
220 tons
SAD $\geq$ 2.7 m
Objectives of Lecture

- Review basics of radiogenic second cancers
- Current state of knowledge
- **Gaps in knowledge**
- Comparative risk assessment
- Methods of dose and risk assessment
- Future directions in research & clinical practice
Limitations of Knowledge: Dosimetry of Therapeutic Exposures

- 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 function of dose …”

- Concept of integral dose irrelevant in assessing risk of SMN (Nguyen et al. IJ ROBP 2008). Instead, one needs high-quality, high-resolution dosimetry (cf. Newhauser et al. PMB 2009 and refs therein).
Limitations of Knowledge: Dosimetry of Out-of-Field Exposures

Commercial treatment planning systems for EBRT lack capability to predict doses from stray, leakage, and scatter radiation (cf. Newhauser et al, PMB 2009; Howell et al, PMB, in review).

Exposures are “reconstructed” using calculation and measurement methods (cf. Stovall et al, Rad Res 2006). Bias and uncertainties from methods not fully known.

Reconstruction for advanced RTs (e.g., IMRT) is more complex pre-IMRT EBRT (cf. AAPM TG 36, 1995). Required level of realism not yet known.
Limitations in Knowledge: Outcomes of Childhood Cancers

Limitations in Knowledge: Evidence-based Selection of RT

“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 Ca Res Treat, 6:31-34 (2007)
Objectives of Lecture

- Review basics of radiogenic second cancers
- Current state of knowledge
- Gaps in knowledge
- Comparative risk assessment: pedi CSI, prostate
- Methods of dose and risk assessment
- Future directions in research & clinical practice
Therapeutic Proton CSI

Unwanted Neutron “Bath”

Taddei et al., Phys Med Biol (in press)
Comparison of Risk of SMN Following CRT, IMRT and 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

Newhauser et al, PMB, 2009; Miralbell et al, IJROBP 2002
Prospective Randomized Clinical Trial of SMN Following CSI with Proton Therapy vs. 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
Comparative Risk for SMN
Following Proton RT vs. 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

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

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

Uncertainties: Fontenot et al, PMB (in review)
Alternative to *In-silico* Study: Prospective Randomized Clinical Trial of SMN Following Proton Therapy vs. 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
Objectives of Lecture

- Review basics of radiogenic second cancers
- Current state of knowledge
- Gaps in knowledge
- Comparative risk assessment for pediatric CSI
- Methods of dose and risk assessment
- Future directions in research & clinical practice
Risk Assessment Methods

\[ Risk = r_T \cdot H_T \]

Organ-Specific Risk Models
eg, BEIR VII (2006)

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

Organ or tissue dose

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

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

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

Excess Absolute Risk \((EAR)\)

\[ EAR = R_e - R_u \]
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

Dose Reconstruction Model:
Monte Carlo Simulation of Proton Nozzle
Monte Carlo Simulation Model

Range Modulator Wheel

From Y. Zheng, UTMDACC
Also see Zheng et al, PMB (2008)
Geometry Model + MC Simulation

CSI – Superior Spinal Field

Logarithm of proton fluence (arb units)  Logarithm of neutron fluence (arb units)

Newhauser et al, PMB, 54 2277-2291 (2009)
Monte Carlo Dose Calculations

Newhauser et al, PMB, 54 2277-2291 (2009)
Monte Carlo Reconstruction of Neutron Dose From CSI

Supercomputer

- 1072 processor computer cluster
  - Linux (Red Hat derivative)
  - 268 nodes
  - Node: 2 Dual-Core AMD Opterons
  - 10 TB data storage
  - Infiniband interconnect: sustained bandwidth of 625 GB/s

- Time to perform CSI dose reconstruction: ~3 weeks!
Uncertainties:
Radiation weighting factors for neutrons

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

Uncertainties: Deviations from Linear Non-threshold Risk Model

Hall (2006)
Sensitivity Tests: Cell Sterilization

Fontenot et al. IJ ROBP, 2009
Predicted risk for using various cell sterilization models

Fontenot et al, PMB (in review)
Objectives of Lecture

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Future: Dose Reconstructions

- Reduce **dosimetric uncertainties** for protons, IMRT
  - Validate predictions of $H/D$ against measurements
  - Biomarkers of dose and or risk (Durante and Loeffler 2010)

- Compare with other advanced RTs
  - C12 (Bert et al. Radiat Oncol 2010; Yonai et al. Radiother Oncol 2010)
  - Tomotherapy (CSI: Parker et al. IJ ROBP 2010)
  - Cyberknife, GK, Protons (Ocular: Zytokovicz et al. PMB 2007)

- First/additional studies for various primary cancers
  - Liver, breast, thorax, GI, GU, CNS, HD, …
Future: Improve Risk Modeling

- Take into account genetic variations in individual susceptibility and sensitivity to SMN (cf Travis et al JNCI 2006).

- **TP53** gene and 5-y survival after tx for medulloblastoma
  (Hawkins et al, J CO, 2010)
  - Mutated TP53: ↓ 0%
  - Normal TP53: 74%

- **Rb1** gene and SMN risk after Tx for retinoblastoma
  - SMN develop in tx field and are hard to treat (Marees et al Euro J Ca, 2009).
  - Rb1: ↑ risk to 21% at 50 y (Kleinerman et al. 2005)
  - Rb1 + RT: ↑ risk to 38% at 50 y (Kleinerman et al. 2005)
  - Rb1: Neglecting Rb1 sensitivity leads to underprediction of risk
    (Randeniya et al PMB, in review)
Summary

- Feasible to reconstruct dose and predict risk for developing SMN
- Rapid progress in last few years, still many gaps in knowledge
- Few available comparative studies thus far suggest SMN risk lower after proton vs photon therapies
- Future clinical practice will include risk assessment and lifelong follow-up plan
End
Extra Materials
Selected Recent/Forthcoming Studies
On Predicted Risk of SMN


- **CNS**: Athar *et al.*, PMB (2010)

- **Retinoblastoma**: Randeniya *et al.*, PMB (in review)

- **Liver**: Taddei *et al.*, Proc CAARI, AIP (2009); Taddei *et al.*, PMB (in review), Howell *et al.*, (in preparation)

- **Prostate**: Fontenot *et al.*, Nucl Technol (2009); Fontenot *et al.*, IJ ROBP (2010); Bednarz *et al.*, Med Phys (2010); Classie *et al.*, Med Phys (2010); Fontenot *et al.*, PMB (in review)
Question: Is scanning necessary?

“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
Answer: No.  

Scattering also provides low risk.

Recall: $\text{RRR} = \frac{\text{RR}_{\text{proton}}}{\text{RR}_{\text{IMRT}}}$

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

Based on data from Newhauser et al PMB 2009 and Fontenot et al IJROBP 2009
Future: Improving Healthcare

- **Delphi panel** (Mertens et al. Health Policy, 2004)

- **Barriers to enhancing care for survivors of childhood cancer**
  - Plan for followup care not provided by oncologist
  - Few organized programs providing specialized FU care
  - Lack of funding for late effects research initiatives

- **Recommended initiatives**
  - Survivor education initiatives
  - Establish cancer survivor management teams and comprehensive late effects clinics
  - Provide tx summary and lifelong FU outline
  - Develop evidence-based best-practice guidelines