What we have learned from epidemiological studies of pediatric radiotherapy patients and remaining questions

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Epidemiologic Studies of 2nd Cancers after Radiotherapy

Design	Advantages	Disadvantages
Cancer Registries	Large N Long-term follow-up Highly complete	Limited treatment data Potential confounding bias
Single Institutions	Detailed treatment	Small N Completeness of follow-up?
Dose-response case-control studies	Detailed treatment Quantify risk per unit dose	Expensive & time consuming

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Second Cancer Radiation Dose-Response Studies

- 28 published matched case-control studies
  - 18 Childhood cancer studies
- 3400 Patients with 2nd cancers
- Matched to Controls without 2nd cancer

- Individual dose reconstruction to location of 2nd cancer
  - Requires detailed radiotherapy records
  - & Medical physicists!

Berrington de Gonzalez et al (IJROBP, 2013)

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Table 1 Study characteristics for the 28 eligible epidemiologic studies of high-dose fractionated radiation therapy, dose-response relationships and comparison with BEIR VII estimates of the ERR/Gy for lower-dose radiation exposure

Ref no.	Reference	2nd cancer	1st cancer	Cases	Controls
10	Travis et al, 2003*	Breast	Hodgkin disease	105	266
11	Guibout et al, 2005	Breast	Childhood	16	NA
12	Inskip et al, 2009	Breast	Childhood	107	389
13	Neglia et al, 2006	Glioma	Childhood	35	123
14	Taylor et al, 2010	Glioma/PNET	Childhood	68	68
13	Neglia et al, 2006	Meningioma	Childhood	58	196
14	Taylor et al, 2010	Meningioma	Childhood	109	109
15	Little et al, 1998	Brain	Childhood	22	282
16	Inskip et al, 1994	Lung	Breast	61	120
17	Gilbert et al, 2003	Lung	Hodgkin disease	227	455
18	Tucker et al, 1991	Thyroid	Childhood	22	82
19	de Vathaire et al, 1999	Thyroid	Childhood	14	NA
20	Bhatti et al, 2010[1]	Thyroid	Childhood	115	NA
21	Tucker et al, 1987	Bone sarcoma	Childhood	64	204
22	Boice et al, 1988	Bone sarcoma	Cervix	15	155
23	Hawkins et al, 1996	Bone sarcoma	Childhood	59	220
24	Le Vu et al, 1998	Bone sarcoma	Childhood	32	160
22	Boice et al, 1988	Soft tissue sarcoma	Cervix	46	598
25	Wong et al, 1997	Soft tissue sarcoma	Retinoblastoma	31	89
26	Menu-Branthomme et al, 2004	Soft tissue sarcoma	Childhood	23	113
27	Rubino et al, 2005	Sarcoma	Breast	14	98
28	Henderson et al	Sarcoma	Childhood	105	422
29	Morton et al	Esophagus	Breast	252	488
30	van den Belt-Dusebout 2009	Stomach	Testes & Hodgkin disease	42	126
22	Boice et al, 1988	Colon	Cervix	409	759
22	Boice et al, 1988	Rectum	Cervix	488	901
22	Boice et al, 1988	Uterine corpus	Cervix	313	469
22	Boice et al, 1988	Ovary	Cervix	309	560
22	Boice et al, 1988	Bladder	Cervix	273	520

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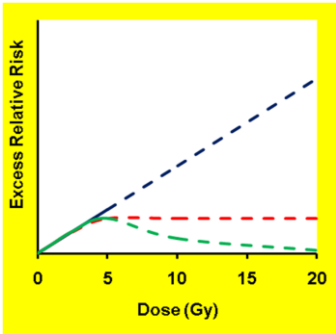
Radiotherapy & 2nd Cancers
Impact of Cell Killing & Fractionation



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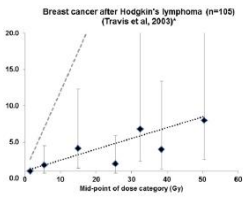
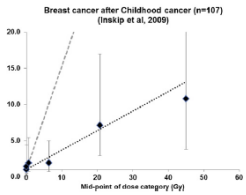
Second Breast Cancer After Childhood Radiotherapy:– Linear dose-response





ERR/Gy = 0.15
Japanese A-bomb = 1.10
Ratio = 7.3

ERR/Gy = 0.27
Japanese A-bomb = 1.43
Ratio = 5.3

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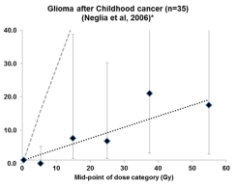
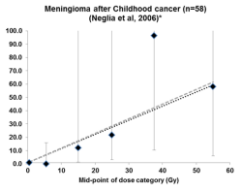
Second Brain Cancer After Childhood Radiotherapy





Berrington de Gonzalez et al (IJROBP, 2013)

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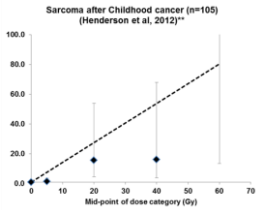
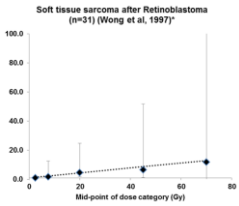
Second Sarcoma After Childhood Radiotherapy





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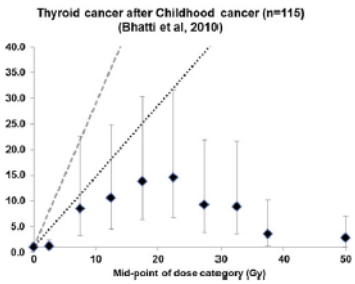
Second Thyroid Cancer After Childhood Radiotherapy



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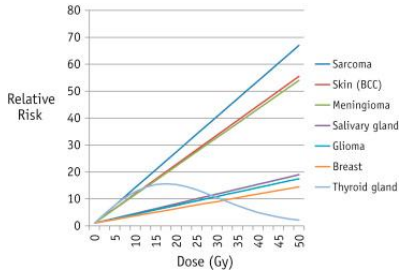
Summary of Dose-Response Curves from US CCSS



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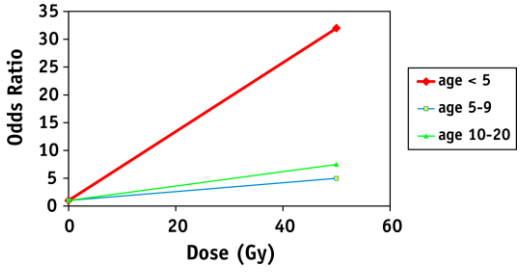
Risks Generally Highest for Youngest Children:- eg Glioma after Childhood Cancer Radiotherapy



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Second Cancer Radiation Dose-Response Studies:- Summary of Findings

- **Linear dose-response**
  - **Exception 2nd thyroid cancer**
- **2nd Cancer risks highest for youngest children**
- **5-10 years before radiation-related cancers occur**
- **Excess risk persists throughout lifetime**
- **Excess risks lower than from acute exposure**

Berrington de Gonzalez et al (IJROBP, 2013)

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Remaining Questions

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By definition we cannot observe the late effects of current treatments.

What's the impact of changes in treatment practice and modality on 2nd cancer risks?

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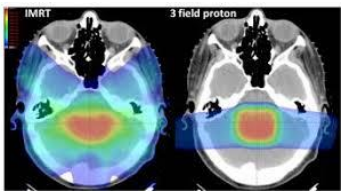
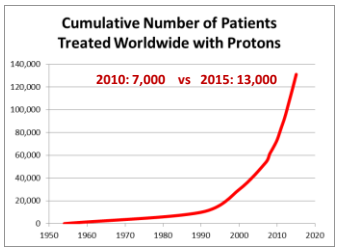
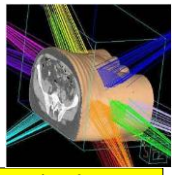
Impact of New Technologies on 2nd Cancer Risks?

- **Aim to Reduce High-dose Exposure to Normal Tissue**
  - **Reduce acute toxicities**
- **But, could Increase Low-dose Exposure & Possible Neutron dose (passive scattering protons)**
  - **Net risk-benefit for 2nd cancers uncertain**



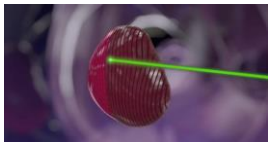
Rapid Adoption of Emerging Radiotherapy Technologies



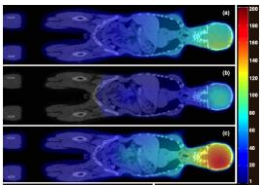


Number of Proton Therapy Centers
1954-2009 - 24
2010-17 - 40 new
2017 - 39 development

Scanning Beam vs Passive Scattering: Neutrons RBE 10-20?



US registry data: 70% of pediatric patients treated with passive scattering



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RBE for Protons = 1.1 ?

- **Dose decreases, RBE increases**
- **Fractionation increases RBE**
- **Variability with Tissue**
- **Energy increases, RBE increases up to 100mEv**
- **Quantification difficult and uncertain…**
- **RBE for tumor control vs normal tissue effects**
- **Proton dose distributions more heterogeneous**

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Brain Necrosis after Pediatric Proton Therapy

- Higher rates but difficult to compare with other case series
  - Florida case series n=313
  - 2yr cumulative incidence of toxicity = 2.8%
  - Posterior fossa tumors age <5 = 12.5%
  - St Jude's photon case series = 3.7% after 5 yrs
  - MRI change protons vs photons 43% vs 17% IMRT
    - Age <3 associated with higher risks
- Reduction in prescribed dose?
- Could this impact tumor control?

Indelicato et al (2014); Bishop et al (2012); Murphy et al (2012)

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COMMENTARY

A Clarion Call for Large-Scale Collaborative Studies of Pediatric Proton Therapy

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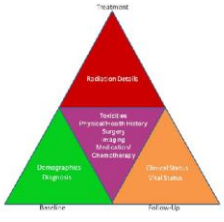
Pediatric Proton Consortium Registry:- 12 US Centers



PPCR
Pediatric Proton Consortium Registry

PI: Torunn Yock MGH

Summary:-

- ***Second cancers rare but serious late-effect of RT***
- ***Risk generally increases with organ dose***
- ***Risks from emerging technologies uncertain***
- ***Other changes in practice need monitoring***
- ***Well-designed comparative studies essential***

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QUESTIONS?

THANK YOU.

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