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

<table>
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<tr>
<th>Design</th>
<th>Advantages</th>
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<td>Cancer Registries</td>
<td>Large N</td>
<td>Limited treatment data</td>
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<td>Long-term follow-up</td>
<td>Potential confounding bias</td>
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<td>Single Institutions</td>
<td>Detailed treatment</td>
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<td>Completeness of follow-up?</td>
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<td>Dose-response case-control studies</td>
<td>Detailed treatment Quantify risk per unit dose</td>
<td>Expensive &amp; time consuming</td>
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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 (IROBP, 2013)
Radiotherapy & 2nd Cancers
Impact of Cell Killing & Fractionation

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

Berrington de Gonzalez et al (IJROBP, 2013)
Second Brain Cancer After Childhood Radiotherapy

Berrington de Gonzalez et al. (IJROBP, 2013)

Second Sarcoma After Childhood Radiotherapy

Berrington de Gonzalez et al. (IJROBP, 2013)

Second Thyroid Cancer After Childhood Radiotherapy

Berrington de Gonzalez et al. (IJROBP, 2013)
Summary of Dose-Response Curves from US CCSS

Risks Generally Highest for Youngest Children: e.g. Glioma after Childhood Cancer Radiotherapy

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 (JROBP, 2013)
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?

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

Cumulative Number of Patients Treated Worldwide with Protons

Number of Proton Therapy Centers
1954-2009: 24
2010-2017: 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

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
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?


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Pediatric Proton Consortium Registry: 12 US Centers

PI: Torunn York MGH

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COMMENTSARY

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

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Torunn Y. York, MD, and Ruth A. Kleinerman, PhD
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

QUESTIONS?
THANK YOU.