Pediatric Radiotherapy in the 21st Century

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Disclosures
• Senior Editor for pediatrics and sarcomas for the International Journal of Radiation Oncology Biology Physics (compensated)
• Chair of Peds/CNS written exam committee for the American Board of Radiology (non-compensated)
• Vice-chair of Radiation Oncology for the Children’s Oncology Group (non-compensated)

Outline
• Overview of radiotherapy in the treatment of pediatric cancer
• Strategies and examples of pediatric radiotherapy in the 21st century
  – Risk-adapted radiotherapy
  – Combined radiotherapy and systemic agents
  – Radiotherapy for metastatic disease
  – Protons
Cancer is the second most common cause of death among children and adolescents in the United States, surpassed only by accidents.

- Approximately 16,000 children and adolescents are diagnosed with cancer each year in the U.S.
- 2000 will die from their disease.

Between 1975 and 2004, 5 year mortality from pediatric cancers decreased from 42% to 20%.

The Role of Radiotherapy

- Although its use has declined over time, radiotherapy plays a significant role in the treatment of many of the common pediatric cancers:
  - CNS tumors
  - Sarcomas
  - Neuroblastoma
  - Wilms tumor
  - Hodgkin lymphoma
  - TBI for transplants

About 1/3 of children with cancer get radiotherapy.
But…

- Radiotherapy is a significant contributor to the morbidity of cancer treatment in children

- 18 Gy to the left hemi-thorax at age 11 for Ewing sarcoma

- 55 Gy to left lower leg at age 8 for Ewing sarcoma

*Courtesy of Lynn Million, MD*
Not all radiation late effects are visible

- Neurocognition
- Neuroendocrine
- Functional
  - Pulmonary
  - Cardiac
  - Reproductive
- Risk of radiation-induced malignancy

Pediatric Radiotherapy Treatment and Research in the 21st Century

- Maximize efficacy
- Minimize side effects

  Risk-adapted radiotherapy

  Combined radiotherapy and systemic agents

  Radiotherapy for metastatic disease

  Protons

Risk-adapted Radiotherapy

- Modifying radiotherapy based upon specific prognostic factors, or response to other anti-neoplastic therapy
Medulloblastoma

- **Old Classification**
  - Classic
  - Desmoplastic
  - Large Cell
  - Anaplastic

“Average Risk” (23.4 Gy CSI) vs. “High Risk” (36-39.6 Gy CSI)

All Get CSI

Risk Adaptation Based on Prognostic Factors

Response-adapted therapy

40 Gy is not sufficient radiotherapy dose for Group III orbital adenoid cystic carcinoma after less than complete response to 12 weeks of ABMT0031 chemotherapy.

A report from the Soft Tissue Sarcoma Committee of the Children’s Oncology Group.
Combined radiotherapy and systemic agents

• Radiosensitizers
• Biologic agents
• Immunotherapy

• Radiosensitizers
  – Chemical agents that are synergistic with radiation, increasing tumor cell kill
  – Most are cytotoxic chemotherapy drugs (poisons) that act on DNA causing damage and inhibiting DNA repair
  – The interaction/synergism between most cytotoxic agents and ionizing radiation has been well characterized

= Improved Survival
Biologic Agents (targeted therapy)

- Everolimus
- Dabrafenib
- Pazopanib
- etc

The interactions between ionizing radiotherapy and most biologic agents have **NOT** been well characterized.

**Immunotherapy**

**Abscopal Response of Un-irradiated Tumor**

Prior to irradiation of an extra-thoracic soft tissue sarcoma

6 weeks following radiotherapy plus an immune checkpoint inhibitor
Radiotherapy for metastatic disease

- Traditionally, treatment of metastatic disease has been almost entirely in the realm of chemotherapy
- Some exceptions
  - TBI for leukemia
  - Whole lung RT for Wilms tumor, Ewing sarcoma
- Radiotherapy for metastases is limited by toxicity

Risk of cardiac events increases non-linearly with increasing radiation dose

5 Gy Exposure to the Heart Doubles the Risk of Cardio-vascular Disease

Van der Pal et al, JCO, 2012

5 Gy Exposure to the Heart

5 Gy Exposure to the Heart

Cumulative Radiotherapy Dose (Gray)
Radiotherapy for metastatic disease

Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

• Stereotactic Body Radiotherapy (SBRT)

Protons
• About 70% of children requiring radiotherapy would benefit from protons
  – Most brain tumors
  – Most sarcomas
  – Hodgkin lymphoma
  – Probably neuroblastoma
  – Possibly Wilms tumor
**Brain stem injury**

![Brain stem image](image)

**Dose vs LET/RBE**

![Dose vs LET/RBE graph](image)

**Cells Respond Differently to Proton/Carbon Particle Therapy vs X-ray/Photon Beams**

![Cell response graphs](image)
So.....

• Pediatric radiotherapy in the 21st century will
  
  – **Increase efficacy** through combination with systemic agents, identifying high risk patients requiring RT, and new indications for RT such as oligometastases
  
  – **Decrease side effects** by better understanding of the biologic responses to RT (especially protons), identifying patients requiring less or no radiotherapy, and improving technology for radiotherapy targeting and delivery
New Developments for Pediatric Radiotherapy – A Clinician’s Wish List for Physics

- LET and RBE based treatment planning for protons
- FLASH radiotherapy
- More “gentle” IGRT
- Standardized TBI
- “On the fly” adaptive treatment planning
- Improved algorithms/artificial intelligence to optimize treatment plans

On behalf of All the Children, thank you for your expertise and the role it plays in providing cures