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)

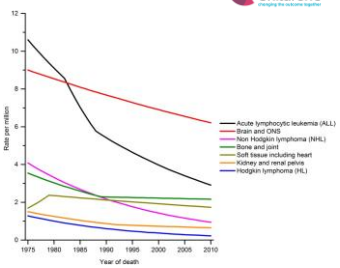
Outline

- 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**

CA: A Cancer Journal for Clinicians
Volume 63, Issue 1, Article first published online: 17 Jan 2013

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



The Role of Radiotherapy

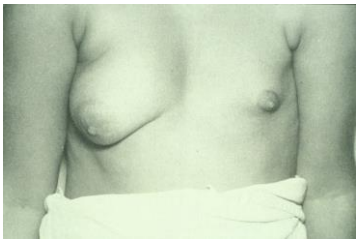
- Although its use has declined over time, radiotherapy plays a significant role in the treatment of many of the common pediatric cancers
  - CNS tumors
  - Sarcomas
  - Neuroblastoma
  - Wilms tumor
  - Hodgkin lymphoma
  - TBI for transplants

About 1/3 of children with cancer get radiotherapy

But…

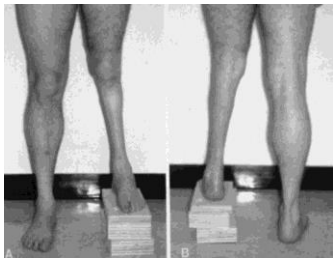
- Radiotherapy is a significant contributor to the morbidity of cancer treatment in children

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



Courtesy of Lynn Million, MD

- 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

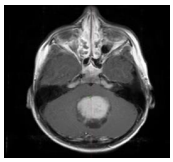
Risk-adapted Radiotherapy

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

Risk Adaptation Based on Prognostic Factors

Medulloblastoma

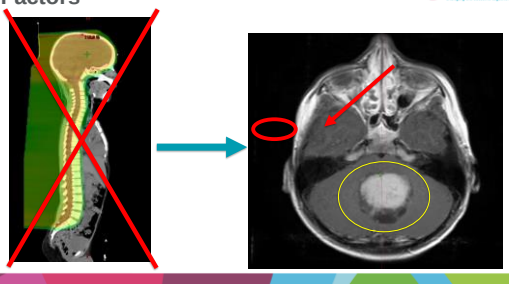
- Old Classification
  - Classic
  - Desmoplastic
  - Large Cell Anaplastic



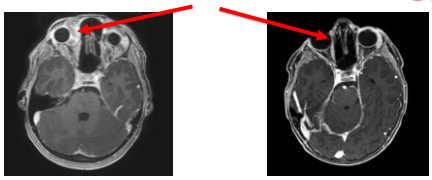
"Average Risk"
(23.4 Gy CSI)
vs
"High Risk"
(36-39.6 Gy CSI)

All Get CSI

Risk Adaptation Based on Prognostic Factors



Response-adapted therapy



RESEARCH ARTICLE

WILEY aspho

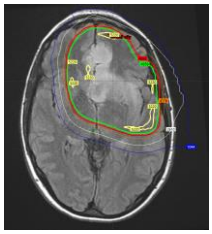
45 Gy is not sufficient radiotherapy dose for Group III orbital embryonal rhabdomyosarcoma after less than complete response to 12 weeks of ARST0331 chemotherapy

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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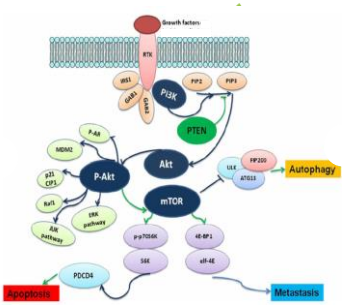
Improved Survival

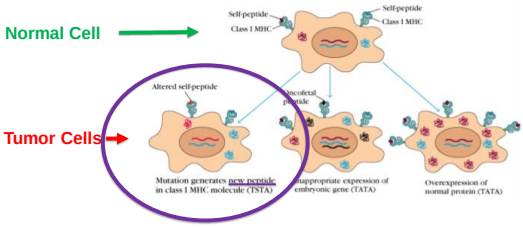
Biologic Agents (targeted therapy)

- Everolimus
- Dabrafenib
- Pazopanib
- etc

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

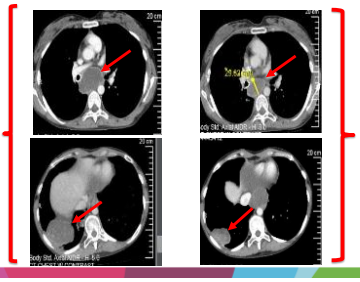


Immunotherapy



Abscopal Response of Un-irradiated Tumor

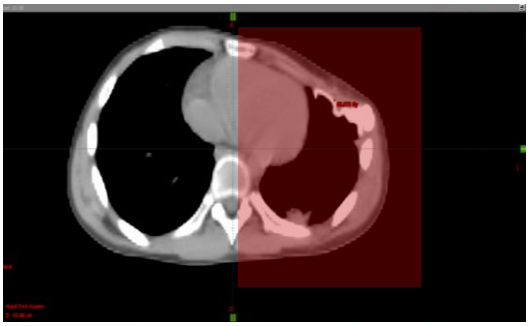
Prior to irradiation of an extra-thoracic soft tissue sarcoma



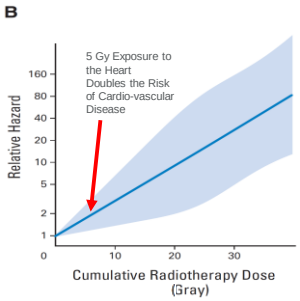
6 weeks following radiotherapy plus an immune checkpoint inhibitor

Radiotherapy for metastatic disease

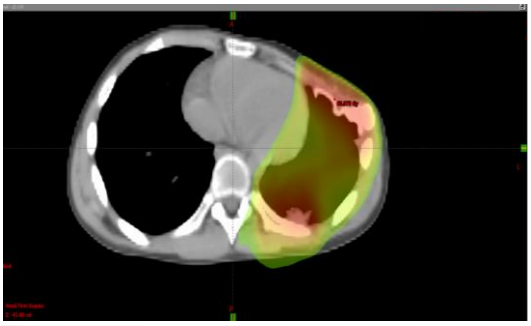
- Traditionally, treatment of metastatic disease has been almost entirely in the realm of chemotherapy
- Some exceptions
  - TBI for leukemia
  - Whole lung RT for Wilms tumor, Ewing sarcoma
- Radiotherapy for metastases is limited by toxicity

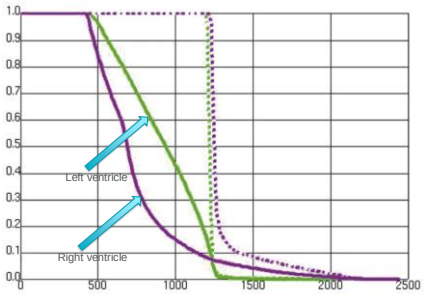


Risk of cardiac events increases non-linearly with increasing radiation dose



Van der Pal et al, ICO, 2012





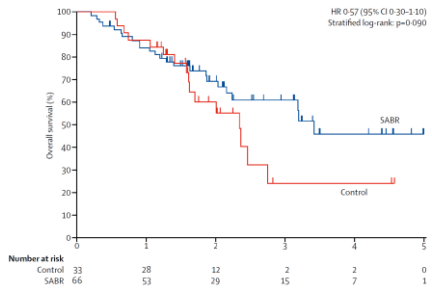
Kobpunakul et al. IJROBP 2017

Radiotherapy for metastatic disease

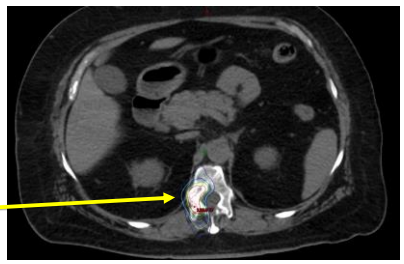
Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

David A Palma, Robert Olson, Stephen Harrow, Stewart Gaede, Alexander V Louie, Cornelis Haasbeek, Liam Mulroy, Michael Lock, George B Rodrigues, Brian P Yaremko, Devin Schellenberg, Belal Ahmad, Gwendolyn Griffioen, Sashendra Senthi, Anand Swaminath, Neil Kopek, Mitchell Liu, Karen Moore, Suzanne Currie, Glenn S Bauman, Andrew Warner, Suresh Senan

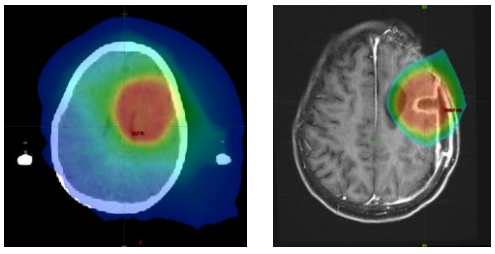
Lancet, 2019



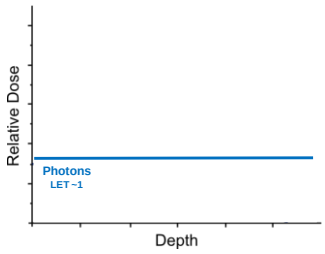
- Stereotactic Body Radiotherapy (SBRT)

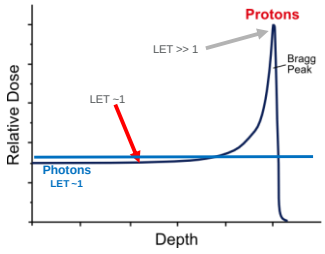


Protons



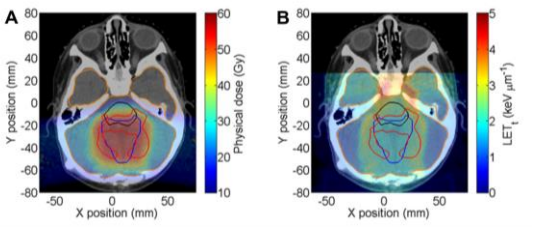
- About 70% of children requiring radiotherapy would benefit from protons
  - Most brain tumors
  - Most sarcomas
  - Hodgkin lymphoma
  - Probably neuroblastoma
  - Possibly Wilms tumor





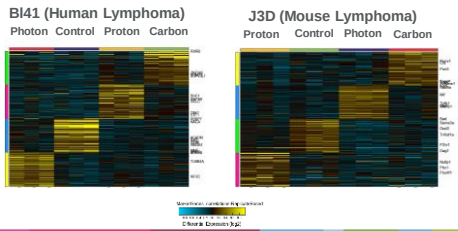
Brain stem injury

Dose vs LET/RBE



Peeler et al, 2016

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



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