PARTICULAR NEEDS FOR PEDIATRIC RADIOTHERAPY

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DISCLOSURES

NONE

INTRODUCTION

• Special thanks to Dr. Bruce Thomadsen and the AAPM

• AAPM 2018 - “BEYOND THE FUTURE”

• COG AND AAPM - “BEYOND THE FUTURE IN PEDIATRIC RADIATION THERAPY”
LEARNING OBJECTIVES

a) To describe the particular needs for pediatric radiotherapy planning, delivery and quality assurance and the important role for radiation physicists in this context.

b) To highlight the opportunities for radiation physicists to conduct clinical and basic research in pediatric radiation oncology in the Children’s Oncology Group.

c) To describe the advantages of becoming a member of the Children’s Oncology Group

d) To promote a long-term collaboration between the COG and AAPM to improve the quality of pediatric radiation therapy and the clinical outcomes of children stricken with cancer.

PARTICULAR NEEDS FOR RT IN CHILDREN

- Both tumor and normal tissues are growing
- Normal tissues vulnerable to lifelong RT injury
- IGRT – Imaging modalities add to risk of late effects
- Proton therapy – Pros and Cons
- Anesthesia - Immobilization
- Organ motion
- Tissue density changes (craniopharyngioma, sinuses, Lungs especially for protons)
- Patient anatomy (bladder, rectum, GI – adaptive RT)
- Organ maturity and target volumes (bone, brain)
Importance of both Cure and Late Toxicity

COG
- The world's largest organization devoted exclusively to childhood and adolescent cancer research
- > 10,000 experts in childhood cancer > 200 leading hospitals across North America, Australia, New Zealand, and Europe
- 220 sites and about 250 RT facilities accrue patients
- 249 sites have IMRT credentialing
- 21 proton centers, 10-15 new proton centers are expected to open in the next few years

Challenges and Opportunities
Research Opportunities: RT Physics

- Develop novel RT techniques in pediatric cancer
- Improve current strategies for normal tissue and target definition
- Provide consensus recommendations for proton therapy planning and delivery
- Explore strategies to limit RT exposure during IGRT
- Improve techniques currently used for TBI
- Application for novel physics research techniques - deep machine learning, phantom dosimetry, QA, RT Compliance (COG database, IROC archive, COG Research Platform, NIH Grants)

CARDIAC-SPARING WHOLE LUNG IMRT IN CHILDREN AND YOUNG ADULTS WITH LUNG METASTASES: A FEASIBILITY STUDY

R21CA159547 Kalapurakal (Completed), (06/01/11 - 05/31/14)

- John A. Kalapurakal MD Radiation Oncology; David Walterhouse MD Pediatric Oncology; Cynthia Rigby MD, Diagnostic Radiology; TJ Fitzgerald MD, GARC; Mahesh Gopalakrishnan BS, Radiation Physics (Northwestern University); David Fowlowill Ph.D Radiology Physics Center, Houston TX; Fred Rademaker PhD (Statistics, Northwestern)

Northwestern University; Boston Children’s hospital; Emory University; Memorial Sloan Kettering Cancer Center; MD Anderson Cancer Center
The target 20 patients (1-25 yrs, 11 males) were accrued from 5 centers in 2 years
- Pediatric sarcomas (14), Wilms tumor (5), hepatoblastoma (1)
- CS-IMRT WLI technique was feasible in all 20 patients
- Median RT dose was 150y using a mean of 9 fields
- Pre-treatment central review resulted in target contour changes in 7, re-planning in 3 and minor deviations in 2 patients. There were no major deviations
- Mean whole heart and cardiac volume doses $V_{95}$, $V_{83}$, $V_{67}$ and $V_{50}$ for AP-WLI was 96-100%
- Mean Whole Heart 39% (p<0.0001), 65% (p<0.0001), 85% (p<0.0001) and 96% (0.0083);
- Mean Left Ventricle 33% (p<0.0001), 61% (p<0.0001), 82% (p<0.0001) and 95% (0.006);
  (similar data myocardium, atria, coronaries)
- 4D lung volumes were significantly larger than 3D volumes (p<0.0001)
- AP-WLI technique significantly underdosed 4D lung volumes (0.008)
- CS-IMRT was well tolerated with no AE, CT changes consolidation or fibrosis (minimum 2 yr. FU for all patients)
- 18 were in CR and 2 had progressive disease in lungs before IMRT
- 2.43 year OS 90%; 90% lung metastasis PFS 65%; 52%

Conclusions
- This trial has demonstrated the feasibility of CS-IMRT
- Confirmed the reported advantages of CS-IMRT including: superior cardiac protection and superior dose coverage of 4D lung volumes
- CS-IMRT was well tolerated. One patient had reduced LVEF at 5 years
- CS-IMRT resulted in good survival outcomes
- CS-IMRT targeting 4D lung volumes with iROC QA pre-review will be used in the next generation of COG renal tumor protocols
Accuracy of A Computational Human Phantom Model for Retrospective Target-Organ Dosimetry of Patients treated with Radiation Therapy on National Wilms Tumor Study Protocols


1 Department of Radiation Oncology, Northwestern University, Chicago, IL, 2Northwestern Memorial Hospital, Chicago, IL, 3East Carolina University, Greenville, NC, 4Fred Hutchinson Cancer Center, Seattle, WA, 5Quality Assurance Review Center, Lincoln, RI, 6Lurie Childrens Hospital, Chicago, IL, 7University of Massachusetts Medical Center, Worcester, MA, 8National Cancer Institute, National Institutes of Health, Rockville, MD.
Introduction

- NWTS late effect study: correlation with late effects was analyzed by Prescribed RT fields/doses and not target organ dosimetry.
- Childhood Cancer Survivor Study (CCSS): used a mathematical phantom model and point doses to ascertain organ dosimetry (this model lacked both CT accuracy and 3D organ anatomy data and thus led to the inability to accurately co-relate RT-late effects to 3D organ dosimetry).
- UF/NCI Computational Human Phantoms (CHP’s) model: patient dependent phantoms that preserve the anatomic position of organs and they are scaled based on Age, Sex, Height and Weight.

R01CA159547 (Kalapurakal) RETROSPECTIVE NCI PHANTOM-MONTE CARLO DOSIMETRY FOR LATE EFFECTS IN WILMS TUMOR 08/01/17 - 07/31/22

- AIM 1 - Estimate RT doses (mean dose, D30, D70) to specific organs of 5000 irradiated NWTS Subjects using the 3D NCI Phantom and TPS-MC dosimetry model
- AIM 2 - Study the association between RT dose (mean dose, D30 and D70) estimated using the 3D NCI Phantom and TPS-MC dosimetry model and NWTS late effects.
- We will study the five 5 targeted late effects: CHF (Total heart, ventricles, myocardium); ESRD (Solitary or partial kidneys); Restrictive Pulmonary Disease (Lungs and chest wall); Adverse Pregnancy Outcomes (Ovaries, uterus and pelvis); Second Malignant Neoplasms (breast, thyroid, stomach, colon, liver, kidney) and reproductive impairment in males (testes) and females (ovaries, uterus, pelvis)
PROTON THERAPY – OPPORTUNITY AND CHALLENGES

Caution – clinical application of protons

• More sensitive to organ motion, set up errors that can lead to anatomic changes in tumor or tissue density in the path of the beam
• Re-simulation and re-planning: Normal tissue (NT) density change (sinuses, anatomic cavities), edema, hydrocephalus, WI loss; Tr. Size - Under/over ranging can affect tumor/NT dose
• RBE protons 1.1(10% less dose for isoeffect) meta-analysis of photon/proton in-vivo-vitro data
• Entrance to mid SOBP DNA damage response similar low LET x-rays (1.1-1.15), distal end → complex DNA damage, slow repair kinetics (1LET) and higher RBE(~1.36 distal edge, ~1.7 distal fall-off at 2Gy/fr
• Thus dose extends 1-2mm beyond distal fall-off in NT (not estimated TPS) “biologic range extension”
• RBE: physical (dose/fr, LET) biologic factors (tissue type, cell cycle, end point, oxygenation, sensitizers)
Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy

Daniel J. Indelicato, Stella Flamourakis, Robyn L. Botson, Julie A. Bradley, Christopher G. Morris, Philip R. Alansky, Eric Sandler, & Nancy P. Mendelsohn

Abstract

Background. Proton therapy offers superior low- and intermediate-energy dose distribution compared with photon-based radiation for brain and skull base tumors, yet issues related to the target volume may invoke a comparable radiation dose. We investigated the tolerance of the pediatric brainstem to proton therapy and identified prognostic variables.

Methods. All patients < 18 years old with tumors of the brain or skull base treated from 2007 to 2013 were reviewed. 313 who received > 5000 cGy to the brainstem were included in the study. Brainstem toxicity was graded according to the NCIC Common Terminology Criteria for Adverse Events v.4.

Results. The three most common toxicities were palsy, stroke, and neuropathy, and low-grade glioma. Median follow-up was 4.2 years with a range of 0.1–10.4 years. The Cox proportional hazards model was used to evaluate for factors that adversely affected the risk of brainstem toxicity. The two-year cumulative incidence of toxicity was 5.2%. The two-year cumulative incidence of grade ≥ 3 toxicity was 2.7%. Univariate analysis identified age > 4 years, posterior fossa tumor location, and specific dosimetric parameters as factors associated with an increased risk of toxicity.

Conclusions. Utilization of current national brainstem dose guidelines is associated with a low risk of brainstem toxicity in pediatric patients. For young patients with posterior fossa tumors, particularly those who undergo aggressive surgery, one data suggest more conservative dosimetric guidelines should be considered.

Table II: Clinical and dosimetric variables potentially associated with brainstem toxicity

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<th>Variable</th>
<th>Factor</th>
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<td>Age (y)</td>
<td>&lt;4</td>
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<td>Gender</td>
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<td>Location</td>
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<td>Dose (cGy)</td>
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<td>Treatment duration</td>
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<td>Follow-up</td>
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Critical Review

National Cancer Institute Workshop on Proton Therapy for Children: Considerations Regarding Brainstem Injury

**Imaging and Radiation Oncology Core**

**Houston QA Center Activities**

David Followill, Ph.D., and Thomas J. Fitzgerald MD

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**Brainstem – Proton Therapy**
- D50% ≤ 5240cGy and D0.1cc ≤ 5660cGy – Goal
- D50% ≤ 5400cGy and D0.1cc ≤ 5800cGy – Maximum

**Brainstem – Photon Therapy**
- D50% ≤ 6150cGy and D10% ≤ 6300cGy – Goal
- D50% ≤ 6200cGy and D10% ≤ 6400cGy – Maximum
### Research Resource

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<tr>
<th>Committee</th>
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1. Chair’s Report. John Kalapurakal MD (5 min)

DISEASE COMMITTEE REPORTS

1. Rhabdomyosarcoma. Sarah Donaldson MD (10 min)
2. NCI grants, Medulloblastoma. Jeff Buchsbaum MD (10 min)
3. CNS Tumors. Daphne Haas Kogan MD (10 min)
4. Neuroblastoma. Daphne Haas Kogan (10 min)
5. Leukemia. Natia Esiashvili MD (10 min)
6. Renal Tumors. Arnold Paulino MD (10 min)
7. Ewing Sarcoma. Nadia Laack, Ralph Valtner, Thomas Cash, Richard Gorlick (10 min)
8. Hodgkin Lymphoma. David Hodgson MD (10 min)
9. Rare Tumors. Matthew Krasin (5 min)

QA REPORTS

1. IROC Houston. David Followill PhD (10 min)
2. IROC Rhode Island. TJ Fitzgerald MD/Fran Laurie (10 min)

WORKING GROUP REPORTS

1. Proton Committee. Anita Mahajan/T Yock MD (10 min)
2. Education Committee. John Breneman/Ken Roberts MD (10 min)
3. Late Effects/Publications Committee. Louis Conatine MD (10 min)
4. Physics Committee. Chia-Ho PhD (10 min)
5. PROS/SIOP update. Karen Marcus MD (5 min)
6. International Outreach. Natia Esiashvili MD (5 min)
7. Membership Committee. Paul Chuba MD (5 min)
8. IPMC Report. Arthur Liu MD (5 min)
9. Young Investigators. Erin Murphy MD (5 min)
10. Cancer Control (CCL) Committee. Anita Mahajan (5 min)

NIH Funding Opportunities for (Radiation) Scientists with a Focus on Pediatrics

Jeff Buchsbaum
Radiation Research Program
Division of Cancer Treatment & Diagnosis
National Cancer Institute, National Institutes of Health

CONCLUSIONS: Physicists and YIs

- ✔ COG WELCOMES YOU TO JOIN OUR TEAM!
- ✔ Develop novel RT techniques in pediatric cancer
- ✔ Improve current strategies for normal tissue and target definition
- ✔ Provide consensus recommendations for proton therapy planning and delivery
- ✔ Explore strategies to limit RT exposure during IGRT
- ✔ Improve techniques currently used for TBI
- ✔ Application for novel physics research techniques - deep machine learning, phantom dosimetry, QA, RT Compliance, (COG database, IROC archive, COG Research Platform, NIH Grants)
THANK YOU

• j-kalapurakal@northwestern.edu