Childhood Cancer Data Initiative Webinar Series

Comparing Proton and Photon Therapy: Insights from an NCI Pediatric Study

Pediatric Proton and Photon Therapy Comparison Cohort

Cari Kitahara, Ph.D. and Choonsik Lee, Ph.D.

NIH NATIONAL CANCER INSTITUTE

October 8, 2024

Agenda

1. *Rationale and Objectives*
2. *Study Design*
3. *Current Status of Enrollment*
4. *Dosimetry Methods*
5. *Q&A*

Today's Speakers from the National Cancer Institute (NCI)

Cari Kitahara, Ph.D.

Lead Principal Investigator
Radiation Epidemiology Branch
Division of Cancer Epidemiology and Genetics
NCI

Choonsik Lee, Ph.D.

Dosimetry Unit Head and Senior Investigator
Radiation Epidemiology Branch
Division of Cancer Epidemiology and Genetics
NCI

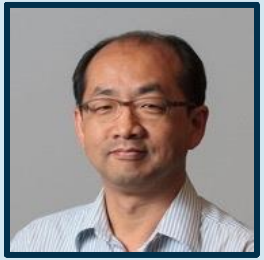
NCI Study Team

Epidemiologists

Cari Kitahara, Ph.D.
Lead Investigator

Todd Gibson, Ph.D.
Staff Scientist

Medical Physicists (Dosimetrists)



Choonsik Lee, Ph.D.
Lead

Jungwook Shin, Ph.D.

Matthew Mille, Ph.D.

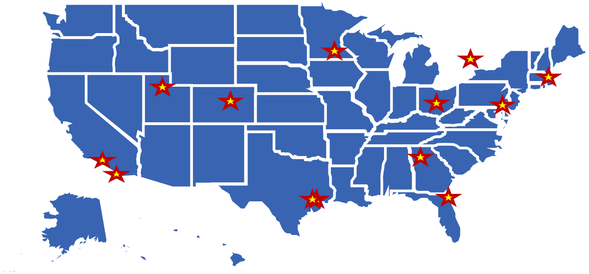
Keith Griffin, Ph.D.

Sergio Morato Rafet, Ph.D.

Study Team Outside of NCI

Amy Berrington, D.Phil.
Institute for Cancer Research, London

Torunn Yock, M.D. and team
Massachusetts General Hospital

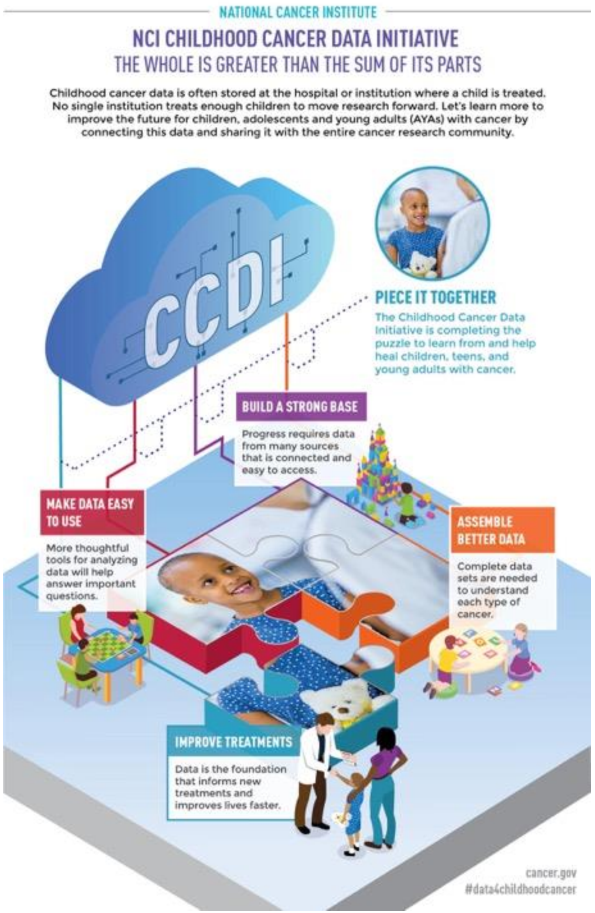


Investigators at participating treatment centers

Study Funding

Funding for data collection provided by the NCI Childhood Cancer Data Initiative (CCDI)

CCDI goals include improving data sharing to accelerate pediatric cancer treatment and survivorship



Rationale and Objectives

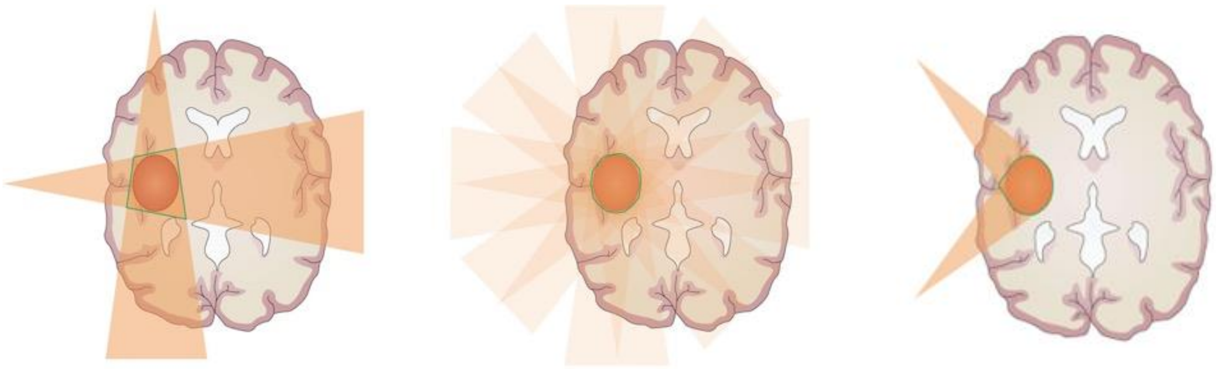
Cari Kitahara, Ph.D.

Advances in Cancer Radiotherapy

- Radiotherapy is an essential tool in the treatment of many cancers
- Conventional radiotherapy associated with late effects (subsequent malignancies)
- Pediatric patients particularly radiosensitive

Goal of emerging radiotherapy techniques:
Reduce radiation exposure to normal (“healthy”) tissues

Focus on Reduction in Normal Tissue Dose



Conventional photon radiotherapy

Intensity modulated radiation therapy

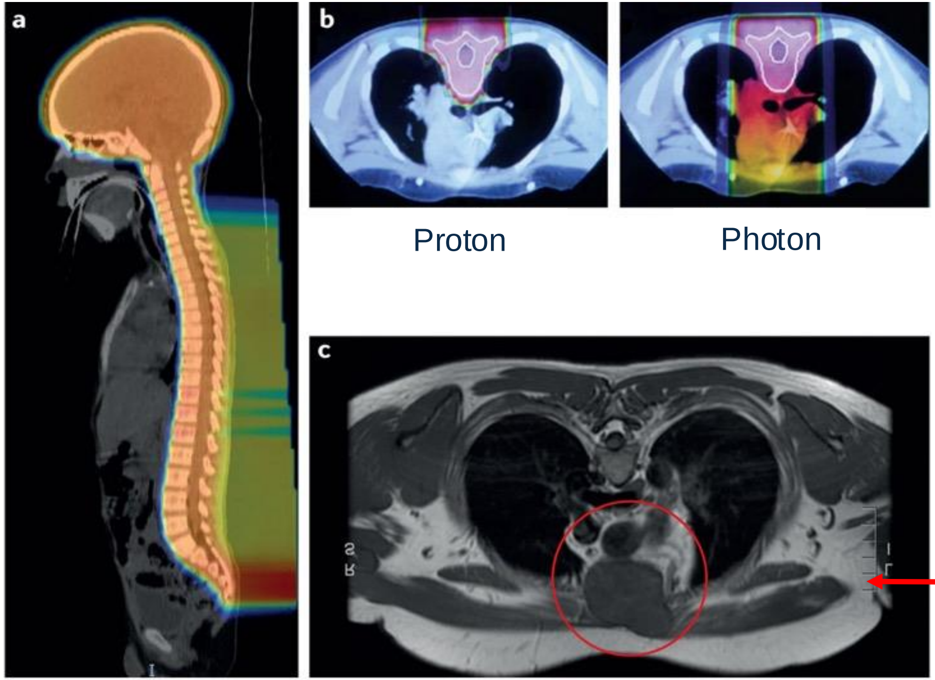
Proton therapy

Passive scattering

Pencil beam scanning

Gondi V, et al. *Nat Rev Neurol* 2016

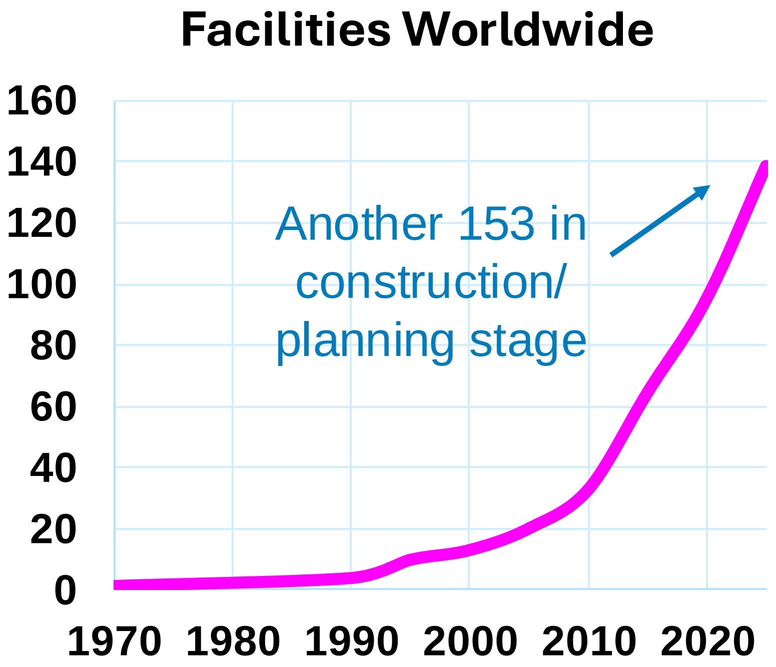
Craniospinal Irradiation in Proton Therapy (Medulloblastoma)

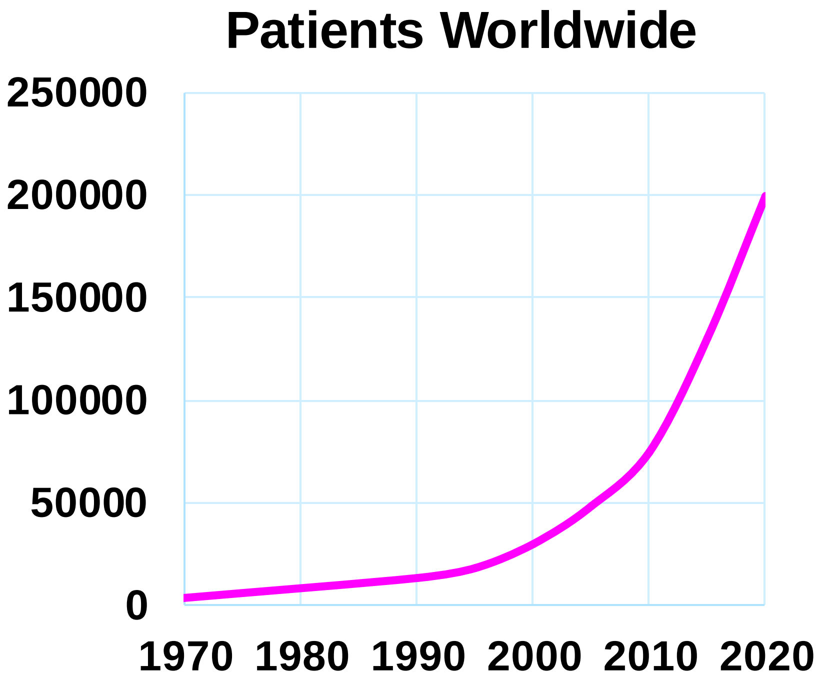


Radiation-induced second cancer (sarcoma)

Gondi V, et al. *Nat Rev Neurol* 2016

Rapid Expansion in Proton Therapy





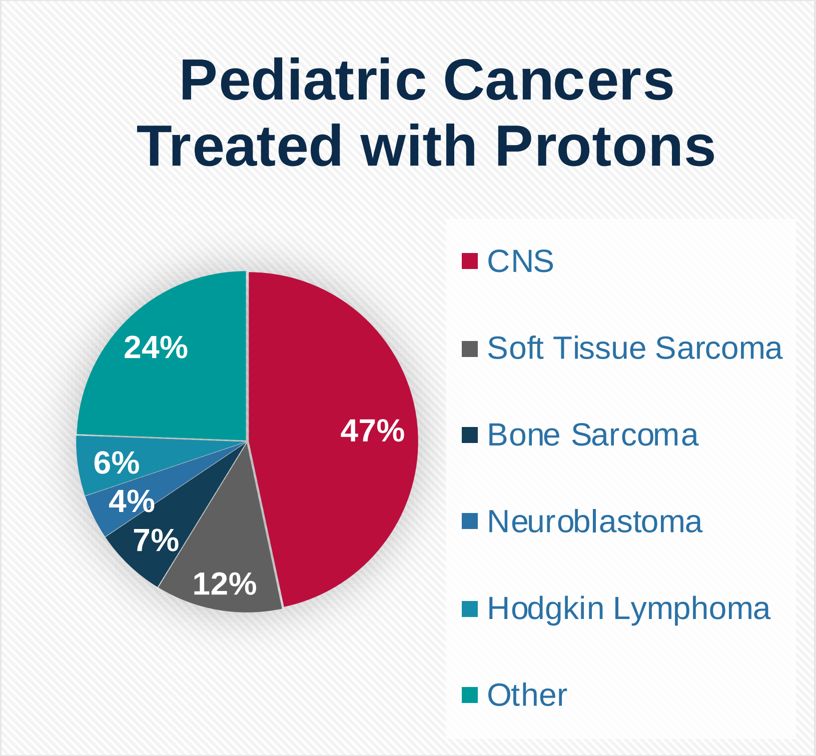
Particle Therapy Co-Operative Group (https://PTCOG.site)

U.S. Pediatric Radiotherapy Patients: Patterns of Care Survey

Pediatric proton patients doubled from 2012 to 2016

Proton centers increased from 9 to 23

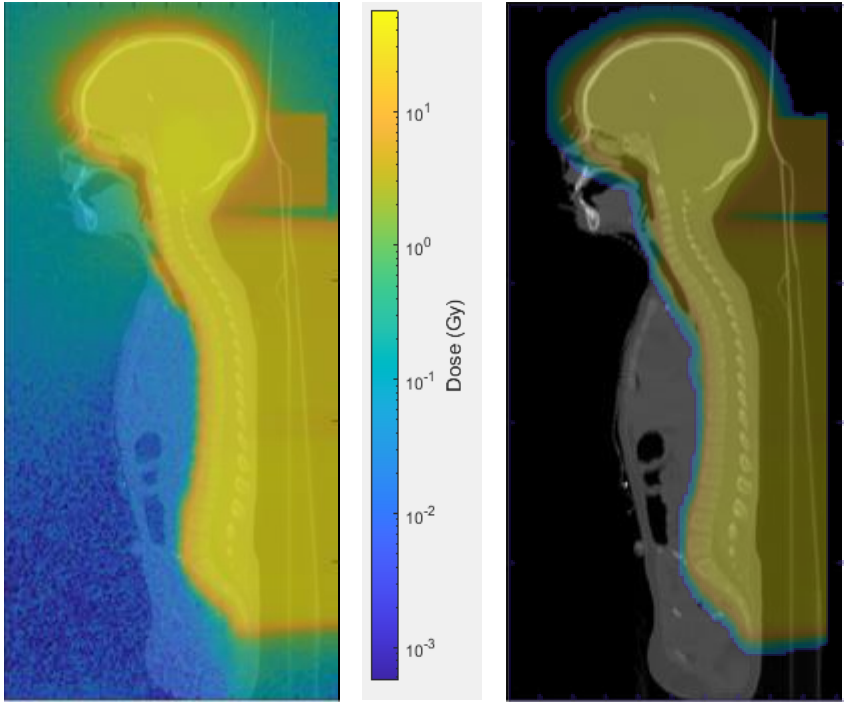
15% of pediatric U.S. radiotherapy patients



Journy N, et al. *Radiother Oncol* 2019

Scattered (Out of Field) Neutron Doses

- Passive scattering *versus* pencil beam proton therapy – more neutron scatter
- Neutron doses more carcinogenic than photons
- Neutron doses and associated cancer risks from proton therapy remain unclear



Proton and neutron dose

Proton only dose

*Are risks of second cancers **lower** in pediatric cancer patients treated with **proton therapy** versus **photon therapy**?*

We do not know yet.

Studies Examining Late Effects of Proton Therapy

- **No randomized trials of pediatric patients** – considered unethical due to dosimetric advantages of protons
- **Reliance on single-center observational and modeling studies**
  - Small sample sizes
  - Lack of formal comparison group
  - Short or likely incomplete follow-up
- **Large-scale observational studies required**

Commentary

International Journal of
Radiation Oncology
biology • physics

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COMMENTARY

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

CrossMark

Amy Berrington de Gonzalez, DPhil,* Bhadrasian Vikram, MD,[†]
Jeffrey C. Buchsbaum, MD,[†] Florent de Vathaire, PhD,[‡]
Wolfgang Dörr, MD,[§] Daphne Hass-Kogan, MD,[||]
Johannes A. Langendijk, MD,[¶] Anita Mahajan, MD,[#]
Wayne Newhauser, PhD,** Andrea Ottolenghi, PhD,[††]
Cecile Ronckers, PhD,[‡‡] Reinhard Schulte, MD,[§§] Linda Walsh, ScD,[||||]
Torunn I. Yock, MD,[¶¶] and Ruth A. Kleinerman, PhD*

Berrington de González A, Vikram B, Buchsbaum JC, et al. A Clarion Call for Large-Scale Collaborative Studies of Pediatric Proton Therapy. *Int J Radiat Oncol Biol Phys.* 2017 August 1. doi: 10.1016/j.ijrobp.2017.03.033.

Study Design

Cari Kitahara, Ph.D.

Scientific Article

Advances in Radiation Oncology (2023) 8, 101273

advances in radiation oncology

www.advancesradonc.org

Scientific Article

The Pediatric Proton and Photon Therapy Comparison Cohort: Study Design for a Multicenter Retrospective Cohort to Investigate Subsequent Cancers After Pediatric Radiation Therapy

Check for updates

Amy Berrington de González, DPhil,[a,*] Todd M. Gibson, PhD,[a] Choonsik Lee, PhD,[a] Paul S. Albert, PhD,[a] Keith T. Griffin, MS,[a] Cari Meinhold Kitahara, PhD,[a] Danping Liu, PhD,[a] Matthew M. Mille, PhD,[a] Jungwook Shin, PhD,[a] Benjamin V.M. Bajaj, MPH,[b] Tristin E. Flood, MS,[b] Sara L. Gallotto, MS,[b] Harald Paganetti, PhD,[b] Safia K. Ahmed, MD,[c] Bree R. Eaton, MD,[d] Daniel J. Indelicato, MD,[e] Sarah A. Milgrom, MD,[f] Joshua D. Palmer, MD,[g] Sujith Baliga, MD,[g] Matthew M. Poppe, MD,[h] Derek S. Tsang, MD,[i] Kenneth Wong, MD,[j,k] and Torunn I. Yock, MD[b]

[a]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland;* [b]*Department of Radiation*

Berrington de González A, Gibson TM, Lee C, et al. The Pediatric Proton and Photon Therapy Comparison Cohort: Study design for a multicenter retrospective cohort to investigate subsequent cancers after pediatric radiation therapy. *Advances in Radiation Oncology.* 2023 May 21. doi: 10.1016/j.adro.2023.101273.

NCI Pediatric Proton and Photon Therapy Comparison Cohort

- **Primary aim →** Examine risks of second cancers
  - Proton (passive scattering, pencil beam) versus photon therapy
  - Dose-response
  - Dose-volume effects
- **Secondary aim →** Examine differences in in-field and out-of-field doses by radiotherapy modality

Berrington de González A, Gibson TM, Lee C, et al. The Pediatric Proton and Photon Therapy Comparison Cohort: Study design for a multicenter retrospective cohort to investigate subsequent cancers after pediatric radiation therapy. *Advances in Radiation Oncology.* 2023 May 21. doi: 10.1016/j.adro.2023.101273.

Building Upon Infrastructure of an Existing Registry

- **Pediatric Proton Consortium Registry (PPCR)**
  - Eligible: Treated in U.S. or Canada from 2015-present
  - 25 participating proton or photon centers → 4,800 patients
  - Active enrollment (patient consent required)
  - Primary outcomes: Acute adverse effects
- **NCI Pediatric Proton and Photon Therapy Comparison Cohort**
  - Eligible: Treated in U.S. or Canada from 2007-2023; selected first primary cancers
  - Proton or photon centers with >500 eligible patients: targeting 20,000 total patients
  - Passive enrollment (patient consent not required)
  - Primary outcomes: Radiation-associated second cancers

PPCR
Pediatric Proton/Photon Consortium Registry

NCI Pediatric Proton and Photon Therapy Comparison Cohort

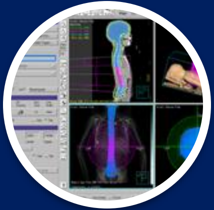
Radiotherapy Centers

10,000 proton and 10,000 photon therapy patients

(2007-2023)

Electronic Medical Records

First tumor characteristics, chemotherapy, surgery



Electronic Radiotherapy Records

Digital Imaging and Communications in Medicine (DICOM®) data

Registry Linkages

Second cancers and death

(2007-future)

Retrospective Record Linkage Study with Prospective Follow-up

Berrington de Gonzalez A, et al. *Adv Radiat Oncol* 2023

Strengths of Study Design

- **Pediatric patients treated with radiotherapy** in the modern era
  - Older (3D-CRT, IMRT, passive scattering) and newer (VMAT, pencil beam) modalities
- **No active consent required** → more inclusive, less selection bias
- **Cancer registry linkages** → more complete, systematic, long-term follow-up
- **Detailed covariate data**
  - Age, stage, treatments, insurance status, known cancer predispositions
- **Comprehensive dosimetry**
  - Organ doses, particle type (photon, proton, neutron), dose-volume

Importance of Study Findings

- **Inform treatment decisions** for current and future patients
- **Inform long-term surveillance strategies**

Current Status of Enrollment

Cari Kitahara, Ph.D.

NCI Pediatric Proton and Photon Therapy Comparison Study

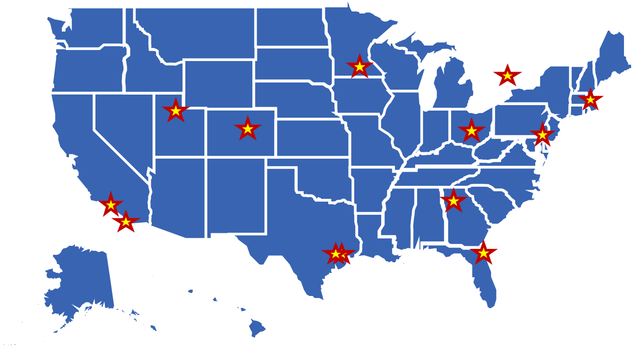
13 Study Centers (as of 9/24)

2020
1. University of Colorado, Denver
2. Children’s Hospital Los Angeles
3. University Health Network Toronto

2021
4. Massachusetts General Hospital
5. University of Florida
6. Mayo Clinic - Rochester
7. Emory University
8. The Ohio State University
9. University of Utah

2023
10. University of Pennsylvania/Children’s Hospital of Philadelphia
11. University of Texas/MD Anderson Cancer Center
12. California Protons Cancer Therapy Center
13. Baylor University

Funding for data collection by CCDI



NCI Pediatric Proton and Photon Therapy Comparison Study

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1. University of Colorado, Denver
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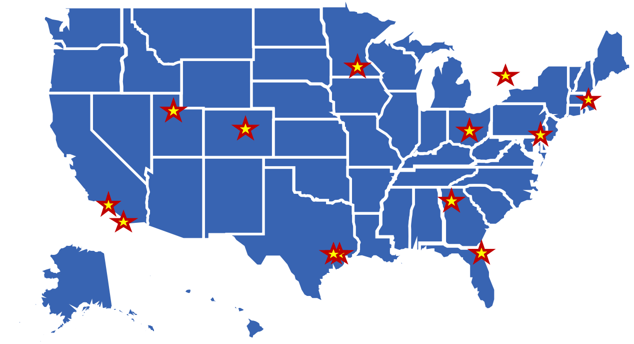
5. University of Florida
6. Mayo Clinic - Rochester
7. Emory University
8. The Ohio State University
9. University of Utah

2023
10. University of Pennsylvania/Children's Hospital of Philadelphia
11. University of Texas/MD Anderson Cancer Center
12. California Protons Cancer Therapy Center
13. Baylor University

Funding for data collection by CCDI



2024: 3-5 new centers expected

Current Status of Enrollment (October 8, 2024)

Primary Modality Per Patient	Enrolled Patients (%)*
	Total (n=7,301)
Proton therapy	43%
Photon therapy	53%
Both	2%
Unknown	2%

*Transfer of patient data in process

Current Status of Enrollment (October 8, 2024) Cont.

	Enrolled (%)
Year of diagnosis	
Before 2010	22%
2010-2014	35%
2015-2019	36%
2020-2023	8%
Age at diagnosis	
<5	26%
5-9	23%
10-14	23%
15-21	27%

Current Status of Enrollment (October 8, 2024) Cont.

	Enrolled (%)
First cancer diagnosis	
Central nervous system tumors	57%
Hodgkin's lymphoma	10%
Neuroblastoma	6%
Rhabdomyosarcoma	11%
Bone sarcoma	9%
Soft tissue sarcoma	6%

Dosimetry Methods

Choonsik Lee, Ph.D.

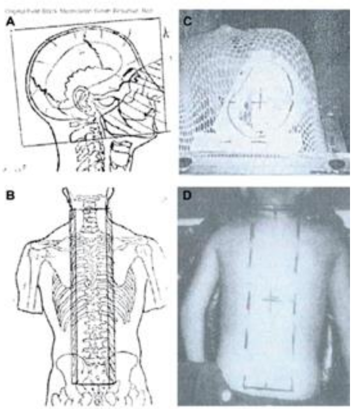
Dosimetry Methods Agenda

1. *Background*
2. *Method Development*
   - *Anatomy extension*
   - *Automatic segmentation*
   - *Monte Carlo simulation*
3. *Publications*

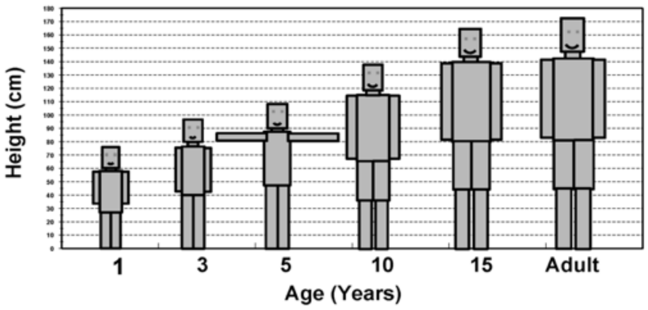
Dosimetry Study Goal

Estimate individualized, whole-body organ doses for 10,000 photon and 10,000 proton therapy patients

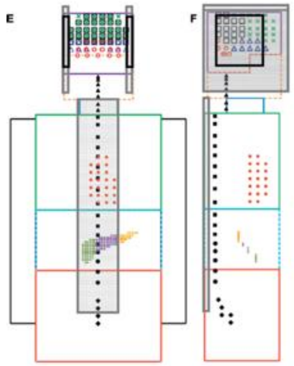
Historical Methods for Organ Dose Estimation



Extract parameters from paper radiotherapy records



Measurements of dose in water and simplified anatomy phantoms



Mean dose or point dose to a few organs

Stovall et al. MP 1989, Diallo et al. RO 1996

Dosimetry Study Goal

- **Estimate individualized, whole-body organ doses for 10,000 photon and 10,000 proton therapy patients**

  - **Individualized**: collect electronic radiotherapy records (DICOM-RT)
  - **Whole-body**: extend anatomy to whole body for out-of-field dose
  - **Organ dose**: automatic segmentation methods
  - **Photon and proton**: develop Monte Carlo radiation transport methods

Data Flow for Pediatric Proton and Photon Therapy Comparison Study

DICOM-RT:

- DICOM CT
- RT STRUCTURE
- RT DOSE
- RT PLAN

MIMcloud

REDCap

Patient and treatment data

DICOM-RT automatically mirrored

U.S./Canada proton and photon centers

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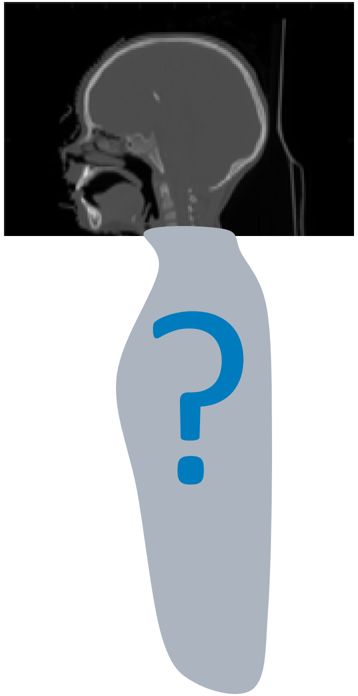
Amazon Web Services

Dose calculations

DICOM-RT	ISSUES
DICOM CT	
RT STRUCTURE	
RT DOSE	
RT PLAN	

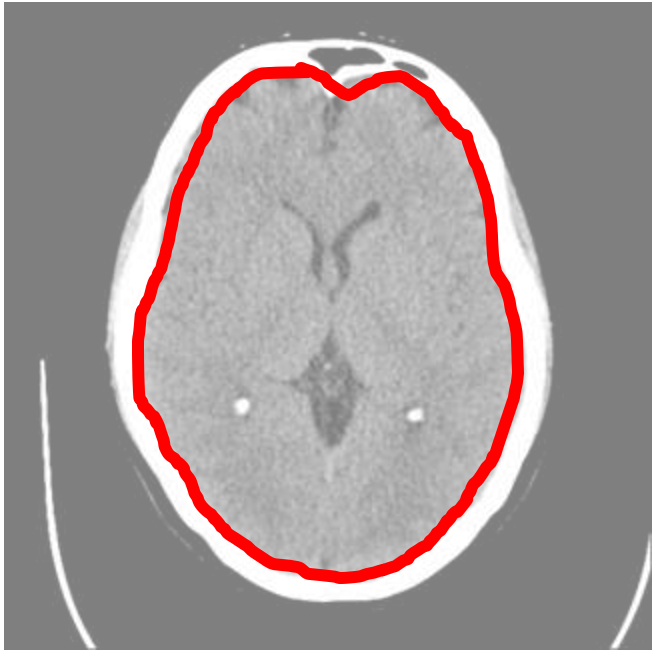
DICOM-RT	ISSUES
DICOM CT	Missing anatomy
RT STRUCTURE	
RT DOSE	
RT PLAN	



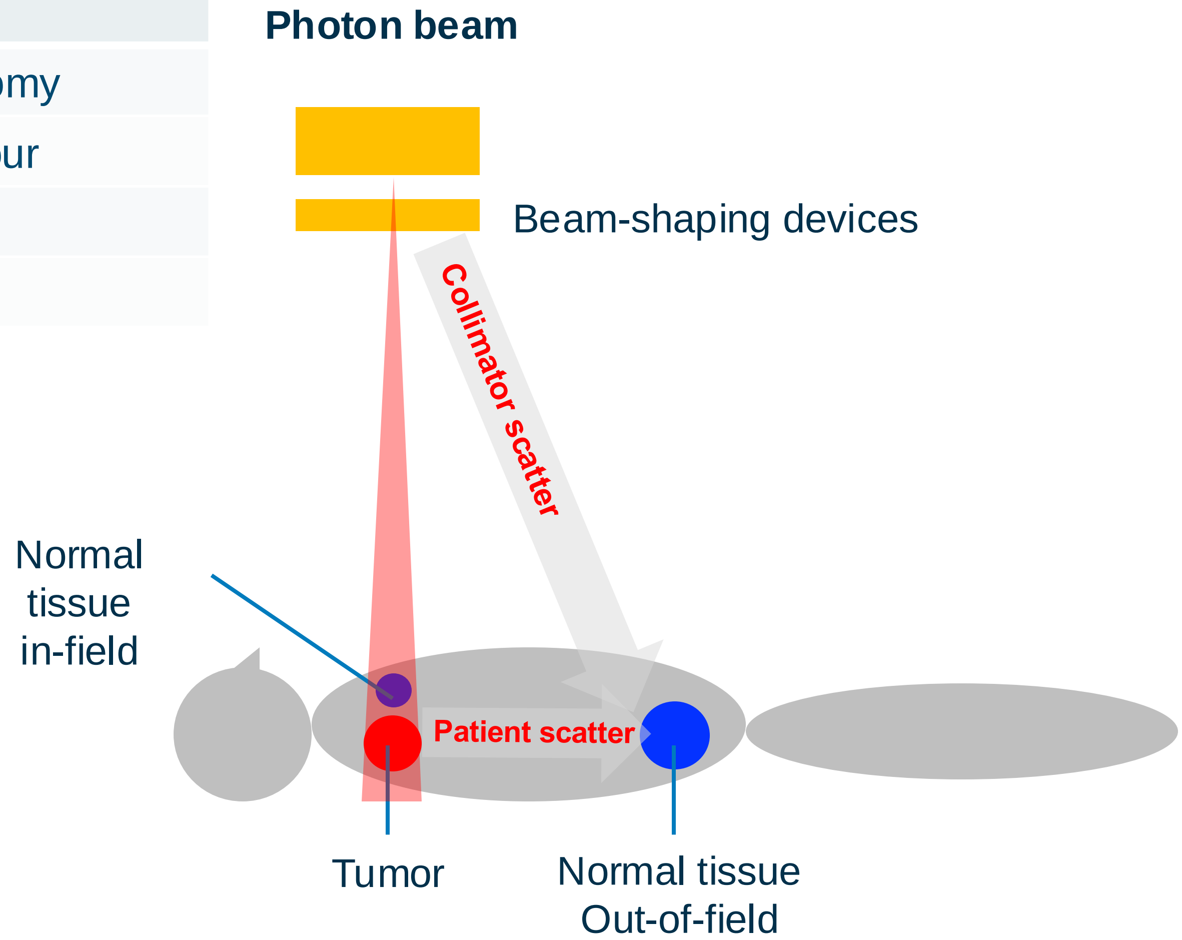
DICOM-RT	ISSUES
DICOM CT	Missing anatomy
RT STRUCTURE	Missing contour
RT DOSE	
RT PLAN	

DICOM CT +
RT STRUCTURE

Brain sub-structures?

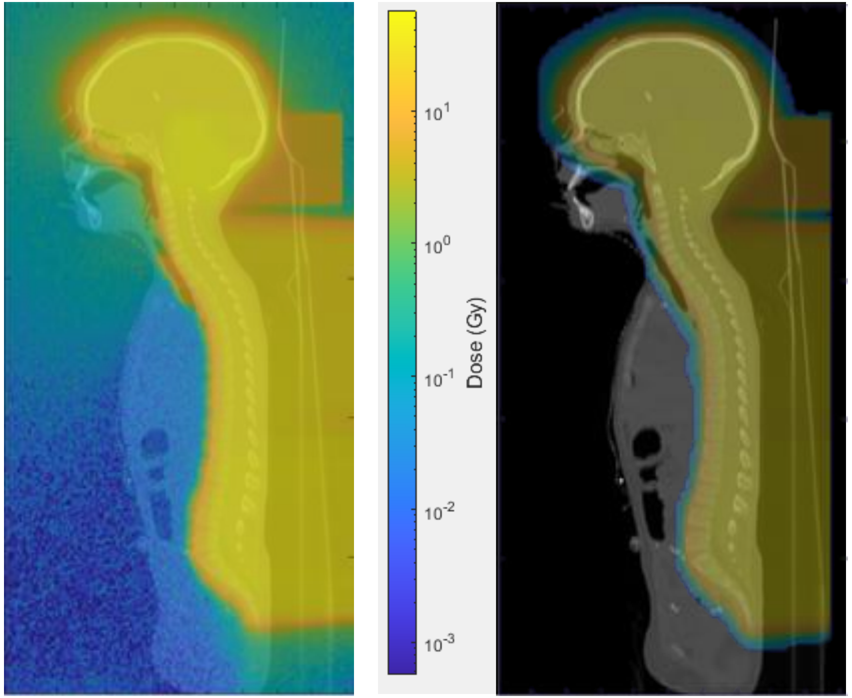


DICOM-RT	ISSUES
DICOM CT	Missing anatomy
RT STRUCTURE	Missing contour
RT DOSE	Missing dose
RT PLAN	



DICOM-RT	ISSUES
DICOM CT	Missing anatomy
RT STRUCTURE	Missing contour
RT DOSE	Missing dose
RT PLAN	

Monte Carlo (gold standard)	**RT DOSE**
Main proton, scattered proton, neutron	Main proton only

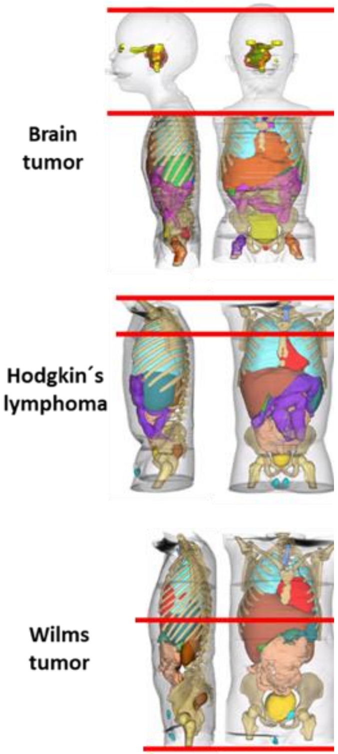


Dosimetry Methods

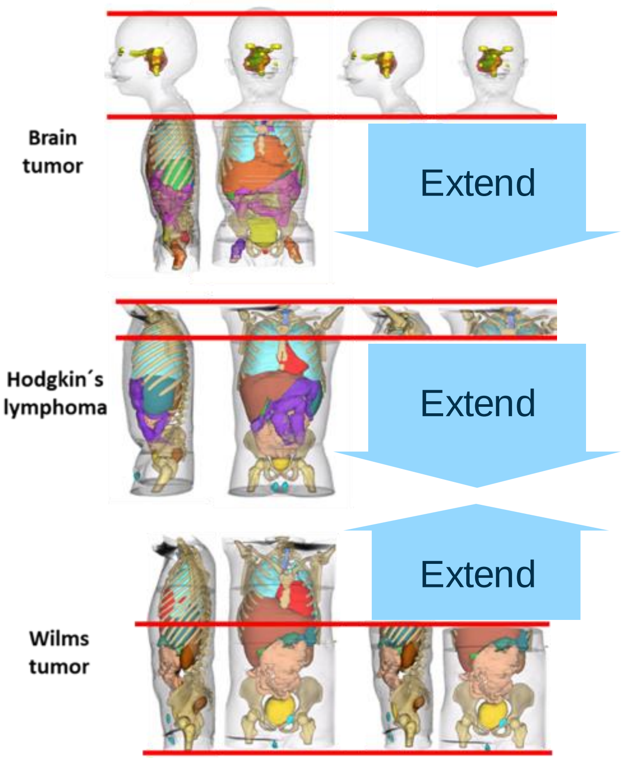
Solution to missing anatomy:
CT anatomy extension

CT Anatomy Extension

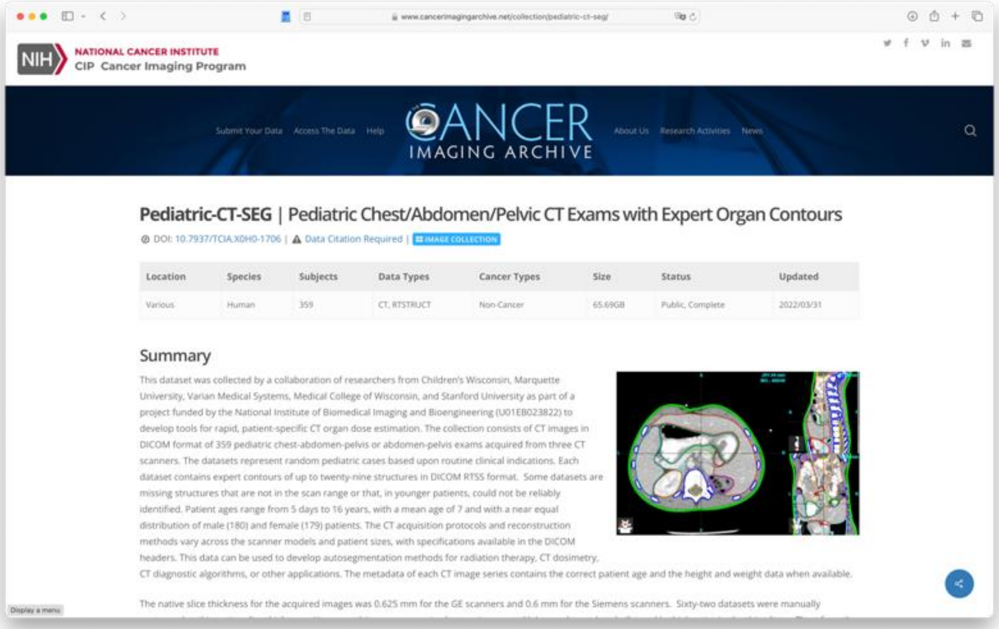
Original CT



CT Anatomy Extension Cont.



Pediatric CTs: 180 males and 179 females



Pediatric-CT-SEG | Pediatric Chest/Abdomen/Pelvic CT Exams with Expert Organ Contours

DOI: 10.7937/TCIA.X0H0-1706 | Data Citation Required | IMAGE COLLECTION

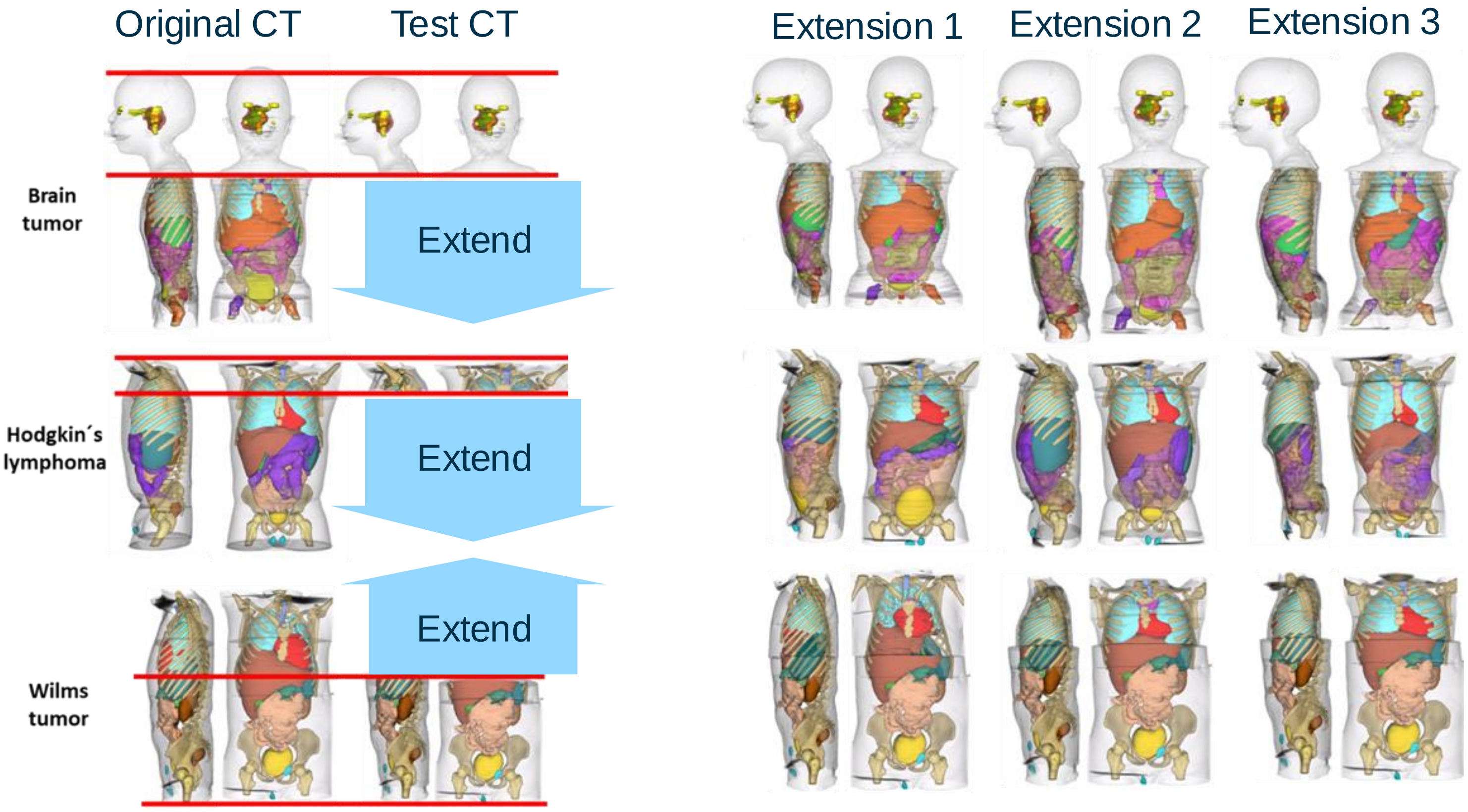
Location	Species	Subjects	Data Types	Cancer Types	Size	Status	Updated
Various	Human	359	CT, RTSTRUCT	Non-Cancer	65.69GB	Public, Complete	2022/03/31

Summary

This dataset was collected by a collaboration of researchers from Children's Wisconsin, Marquette University, Varian Medical Systems, Medical College of Wisconsin, and Stanford University as part of a project funded by the National Institute of Biomedical Imaging and Bioengineering (U01EB023822) to develop tools for rapid, patient-specific CT organ dose estimation. The collection consists of CT images in DICOM format of 359 pediatric chest-abdomen-pelvis or abdomen-pelvis exams acquired from three CT scanners. The datasets represent random pediatric cases based upon routine clinical indications. Each dataset contains expert contours of up to twenty-nine structures in DICOM RTSS format. Some datasets are missing structures that are not in the scan range or that, in younger patients, could not be reliably identified. Patient ages range from 5 days to 16 years, with a mean age of 7 and with a near equal distribution of male (180) and female (179) patients. The CT acquisition protocols and reconstruction methods vary across the scanner models and patient sizes, with specifications available in the DICOM headers. This data can be used to develop autosegmentation methods for radiation therapy, CT dosimetry, CT diagnostic algorithms, or other applications. The metadata of each CT image series contains the correct patient age and the height and weight data when available.

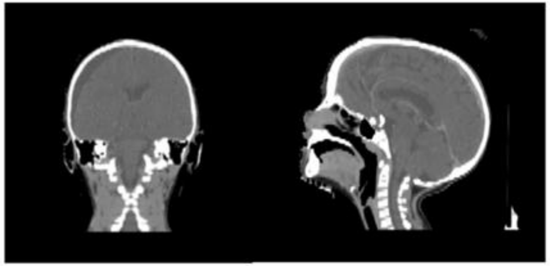
The native slice thickness for the acquired images was 0.625 mm for the GE scanners and 0.6 mm for the Siemens scanners. Sixty-two datasets were manually

CT Anatomy Extension Cont.

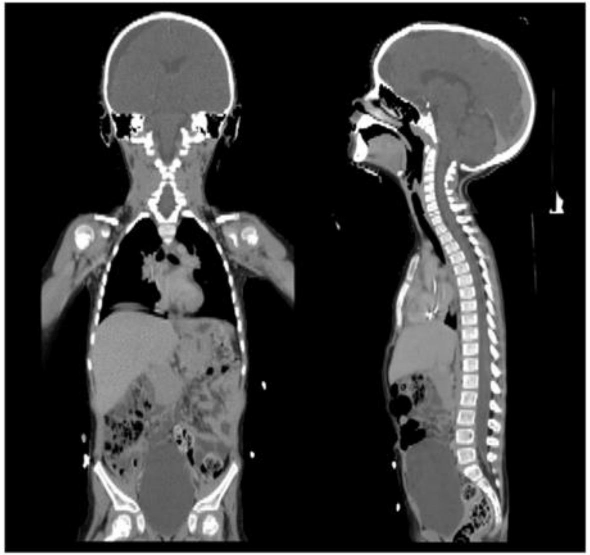


CT Anatomy Extension: Examples

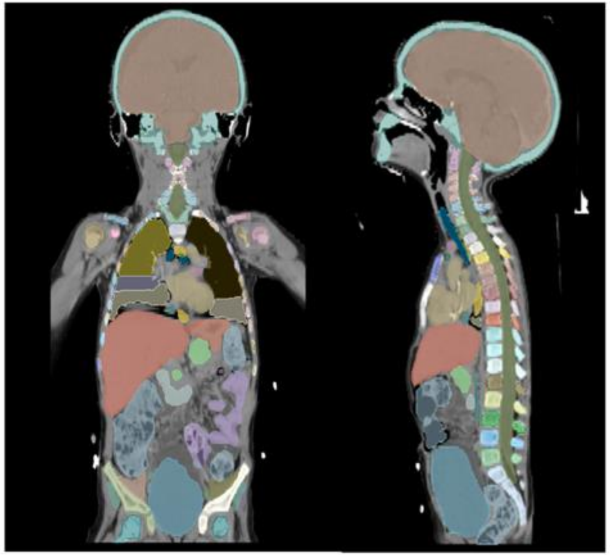
Original head CT



Torso-extended CT



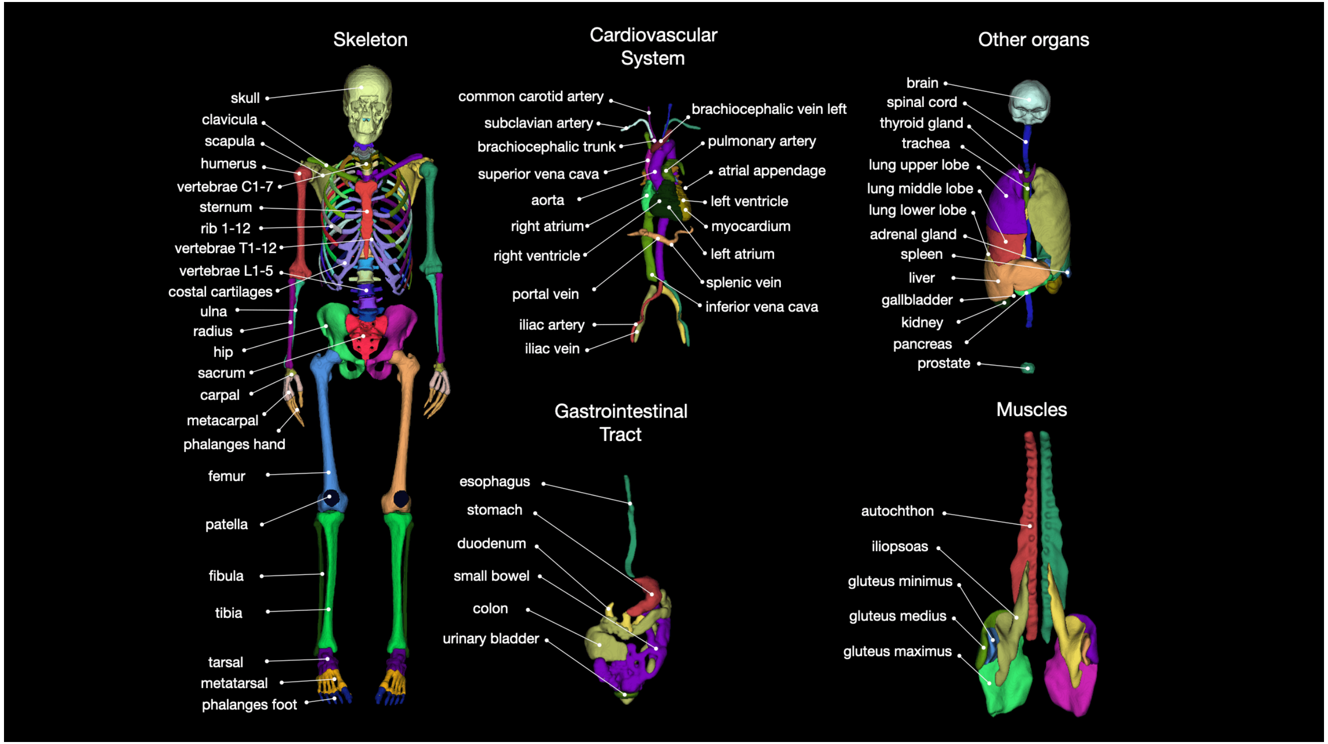
Torso-extended CT with contours



Dosimetry Methods

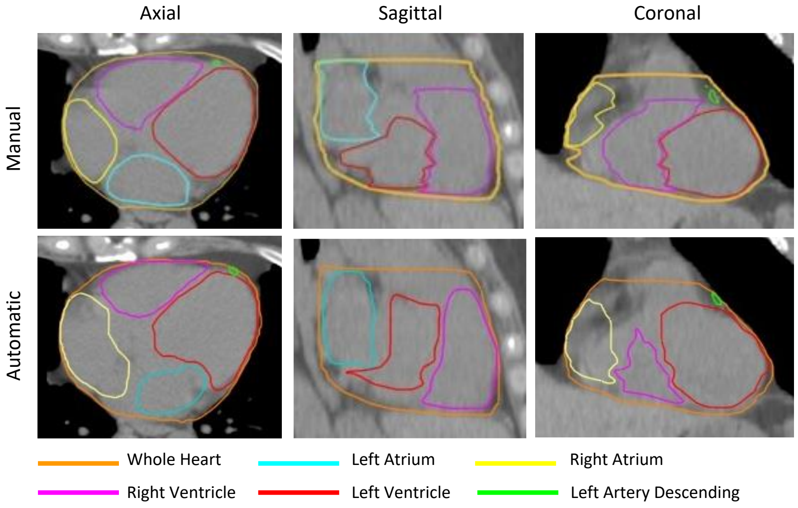
Solution to missing contour:
Automatic organ segmentation

Centralized Segmentation: TotalSegmentator

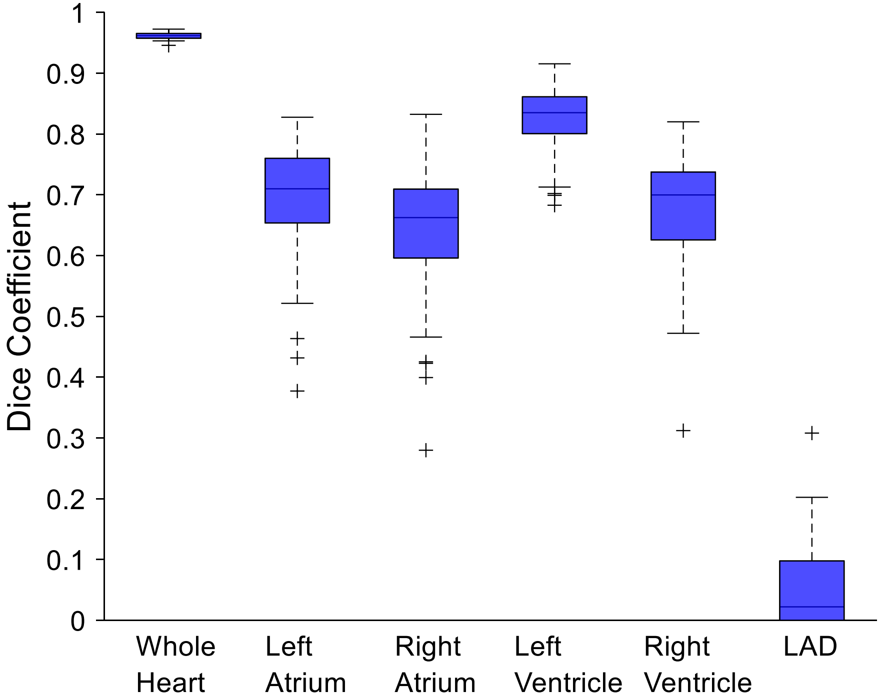


Missing organs: thyroid, testes, ovaries, breast, substructures of the brain and heart

Atlas-based Heart Segmentation Methods[1,2]



Geometric evaluation for RadComp[3] breast radiotherapy cohort



[1]Jung ... Lee phiRO 2019
[2]Jung ... Lee phiRO 2021
[3]Radiotherapy Comparative Effectiveness

In-house Deep Learning-based Segmentation Methods

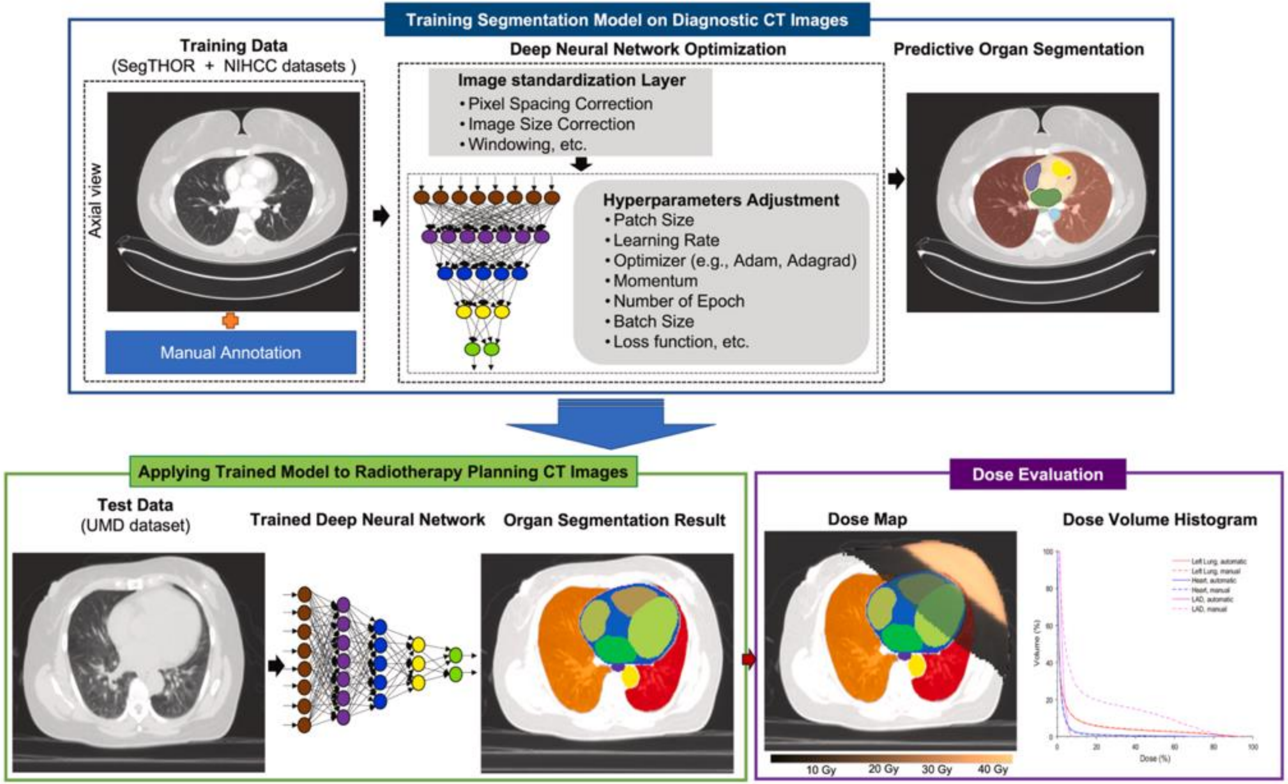
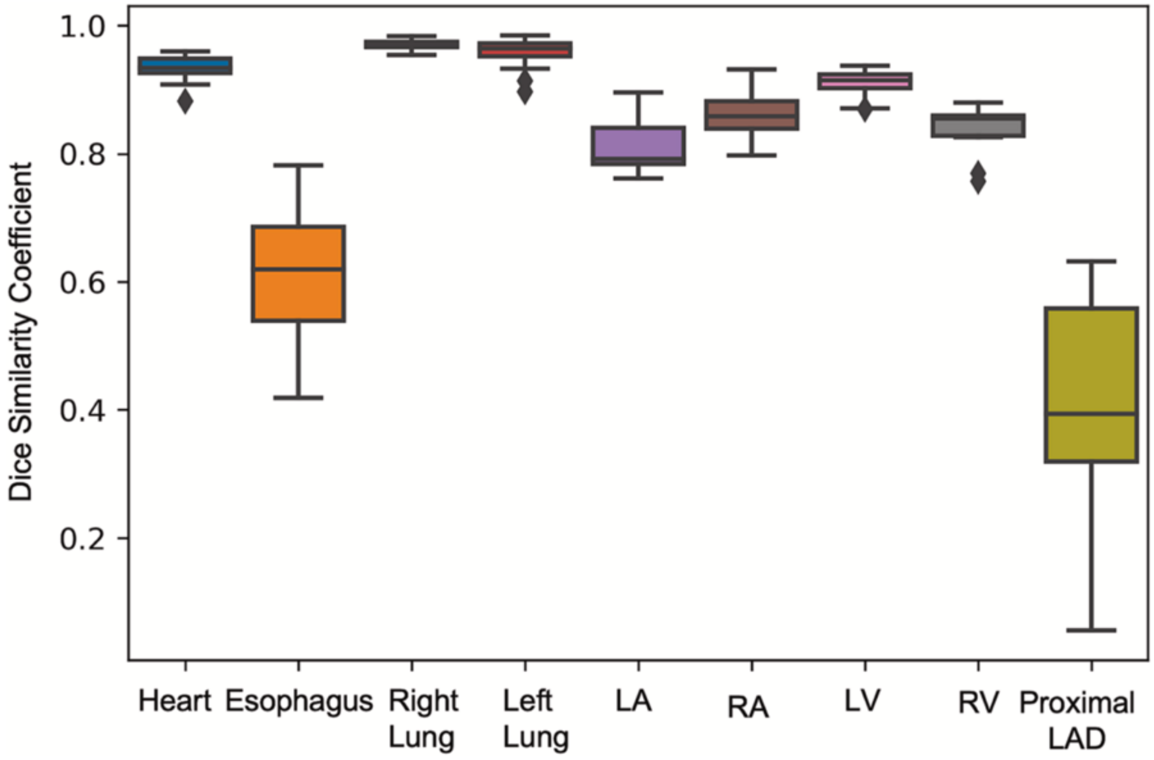


Fig. 1. Workflow diagram of the deep learning segmentation method used in this study.

Saha... Mille PhiRO 2023

In-house Deep Learning-based Segmentation Methods Cont.

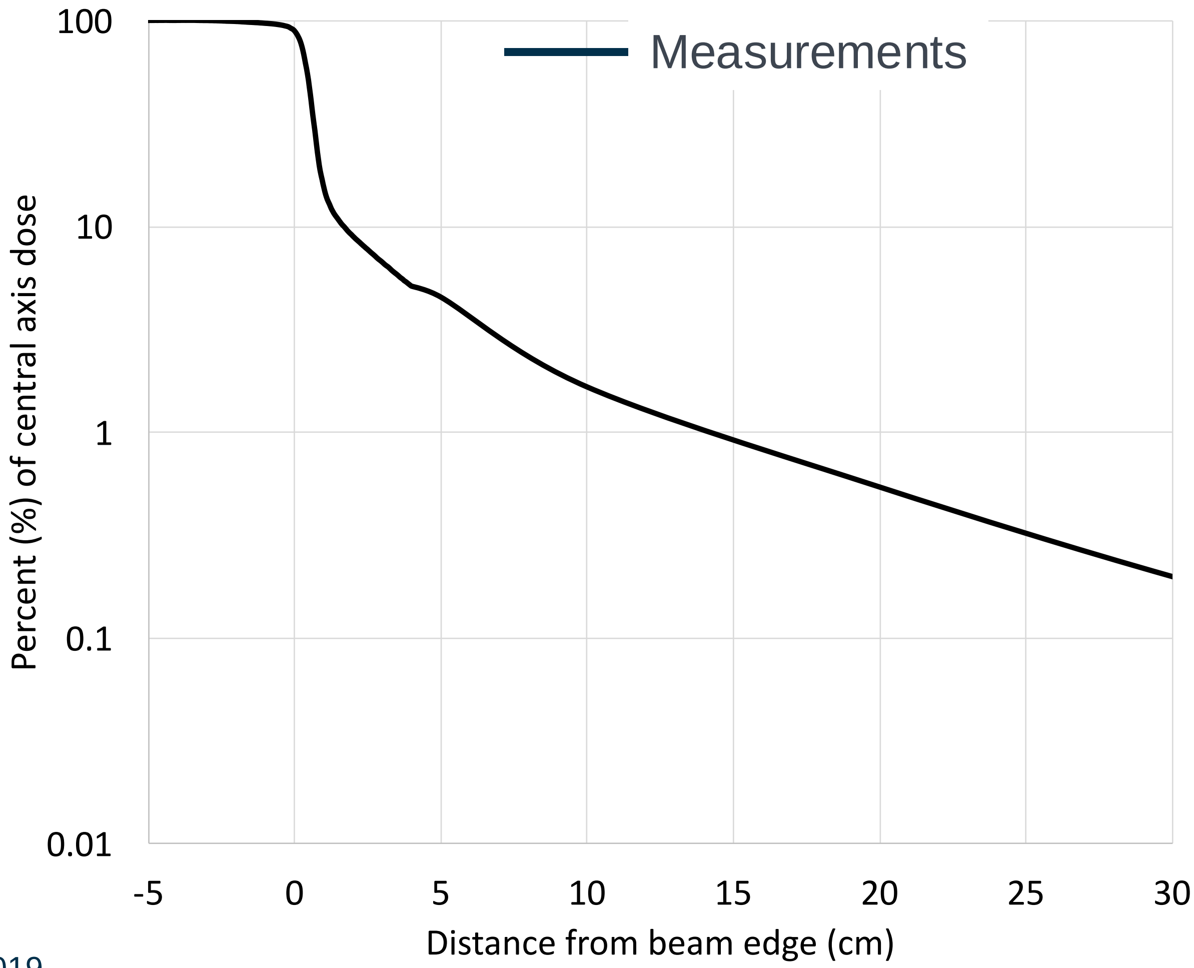


Saha... Mille PhiRO 2023

Dosimetry Methods

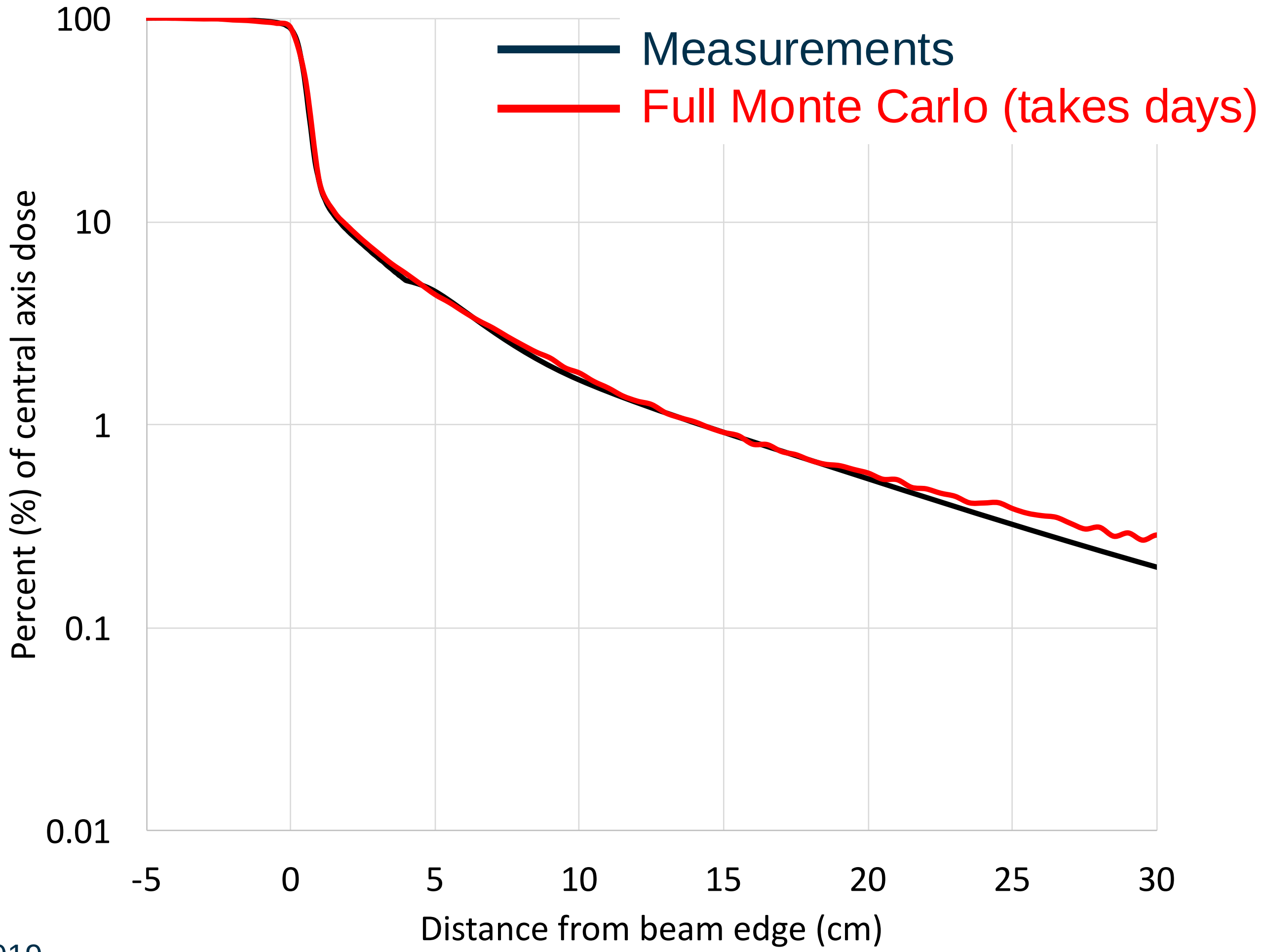
Solution to missing dose:
Monte Carlo simulations

Monte Carlo Simulation: Photon Therapy



Lee ... Lee PMB 2015
Kalapurakal ... Lee PBC 2018
Mille ... Lee JRP 2018
Griffin ... Lee Phys Med Biol 2019

Monte Carlo Simulation: Photon Therapy Cont.



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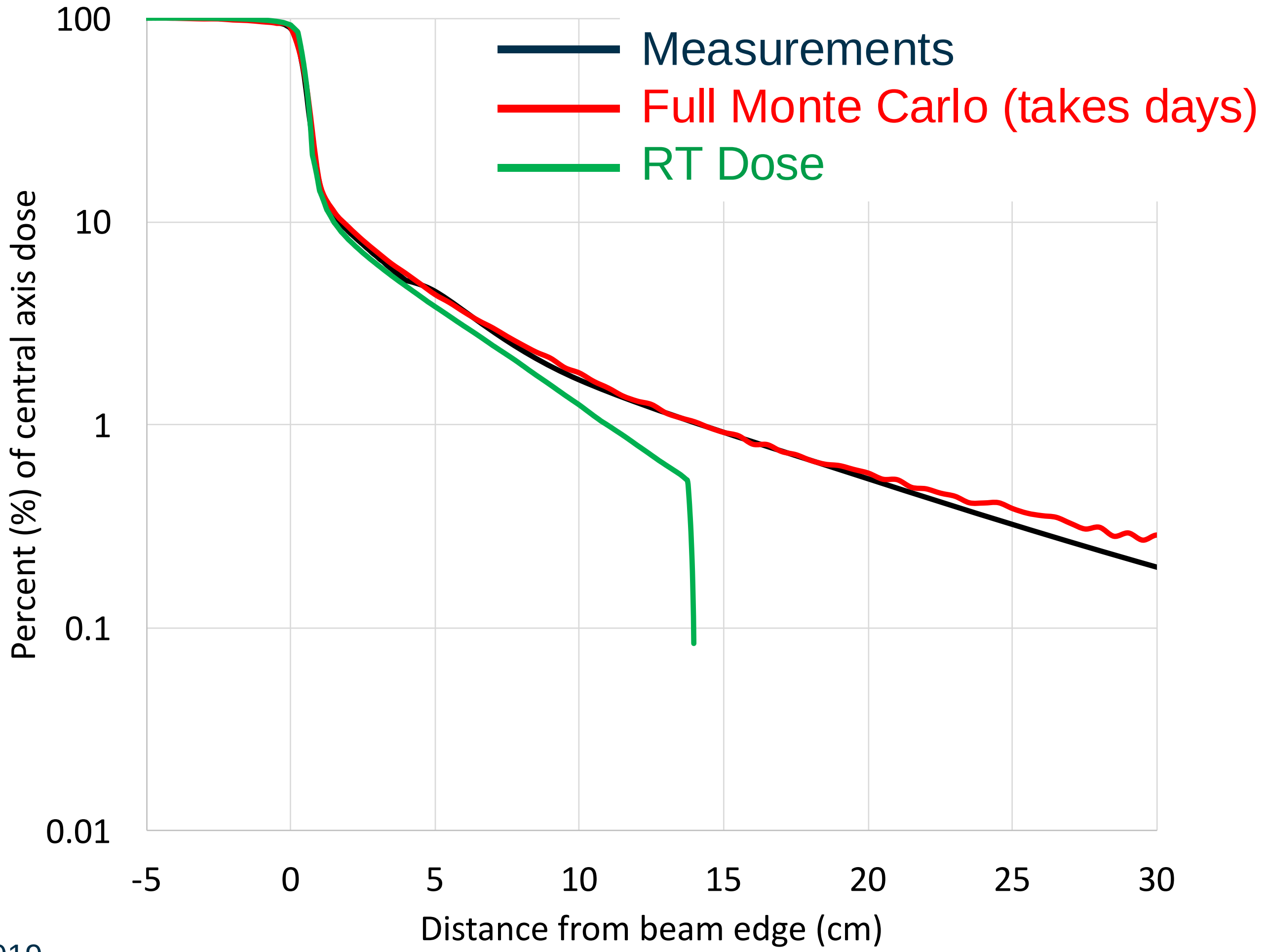

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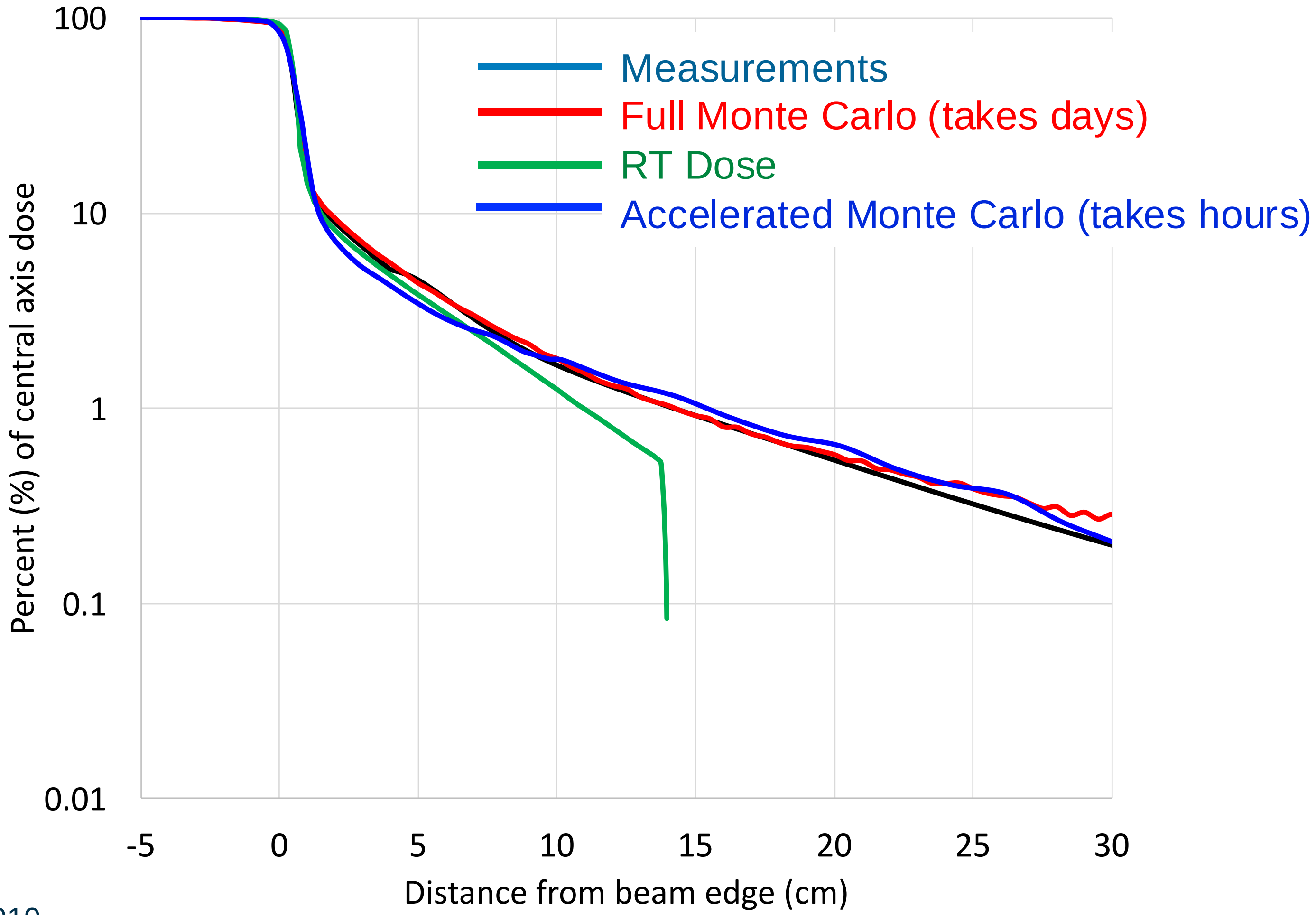

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Griffin ... Lee Phys Med Biol 2019

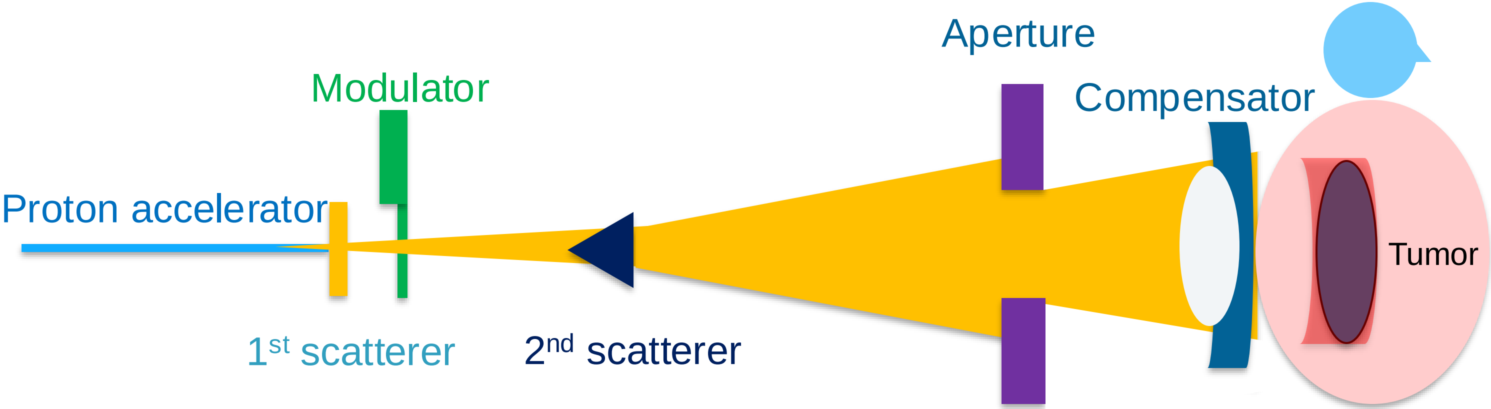
Compatibility Tested for Multiple TPS and Techniques

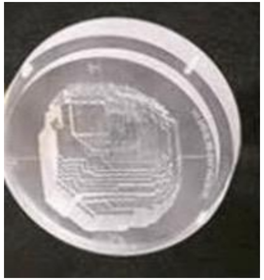
- **Eclipse MLC**[1]: Univ. Michigan breast therapy patients (n=120)
- **Pinnacle block**: National Wilms Tumor Study patients (n=5000)
- **Eclipse EDW**[2]: Univ. Maryland breast therapy patients (n=50)
- **RayStation EDW**[2]: MDACC breast therapy patients (n=20)

[1]Multi-Leaf Collimator
[2]Enhanced Dynamic Wedge

Proton Therapy: Passive Scattering

Massachusetts General Hospital
Founding Member, Mass General Brigham

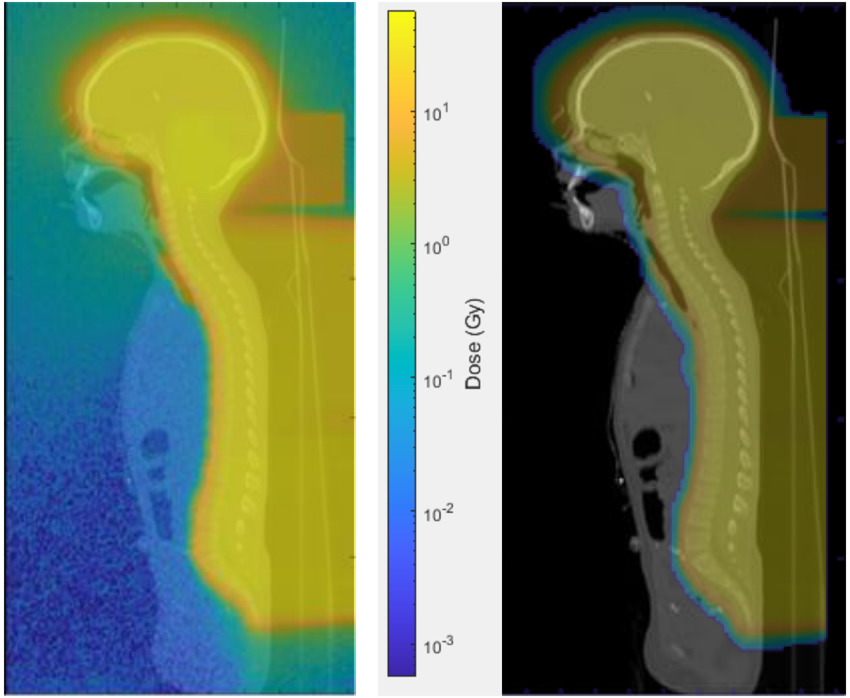




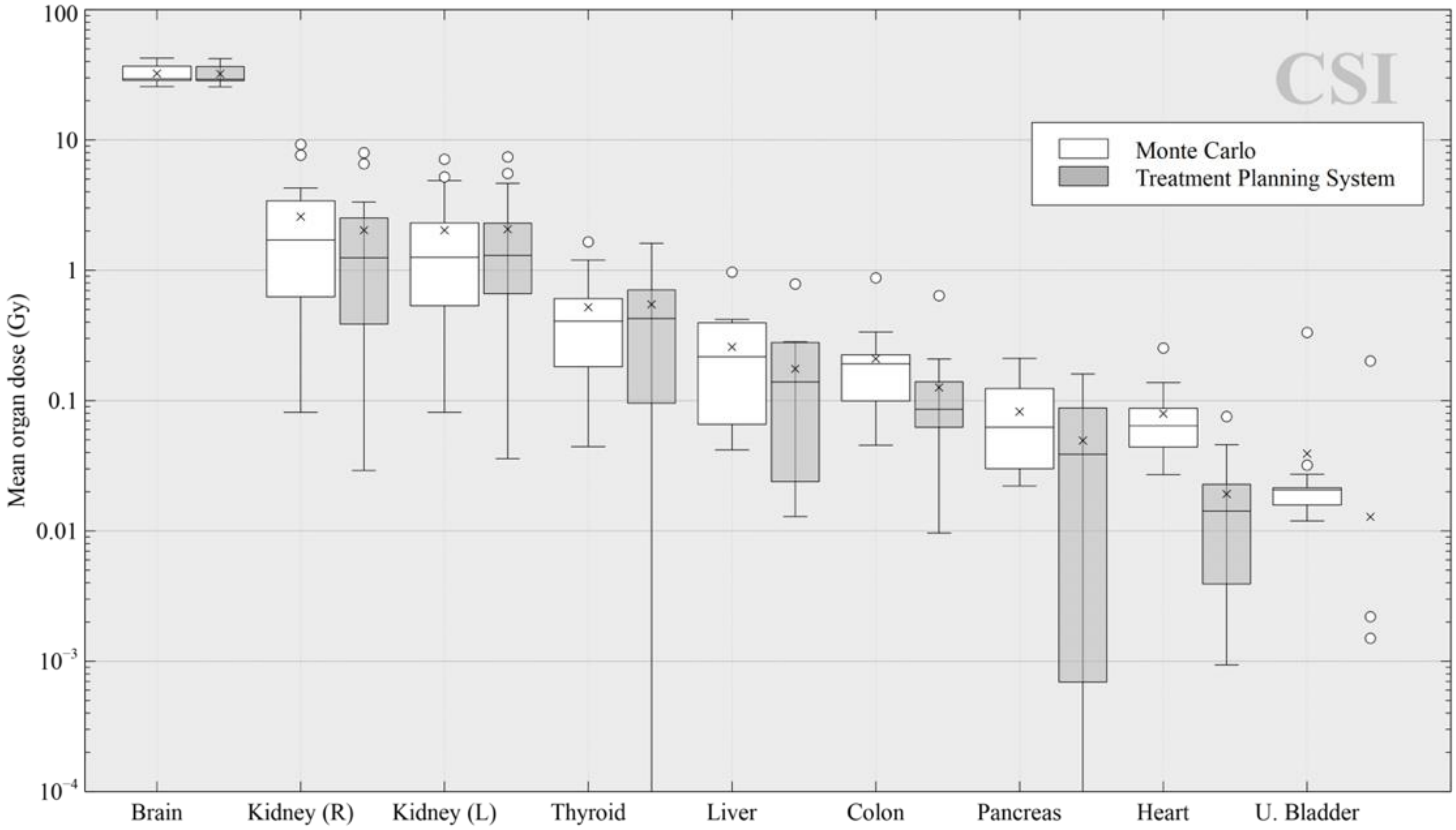
Monte Carlo Dose Calculation for 30 Craniospinal Patients

Monte Carlo
Main proton, scattered proton, neutron

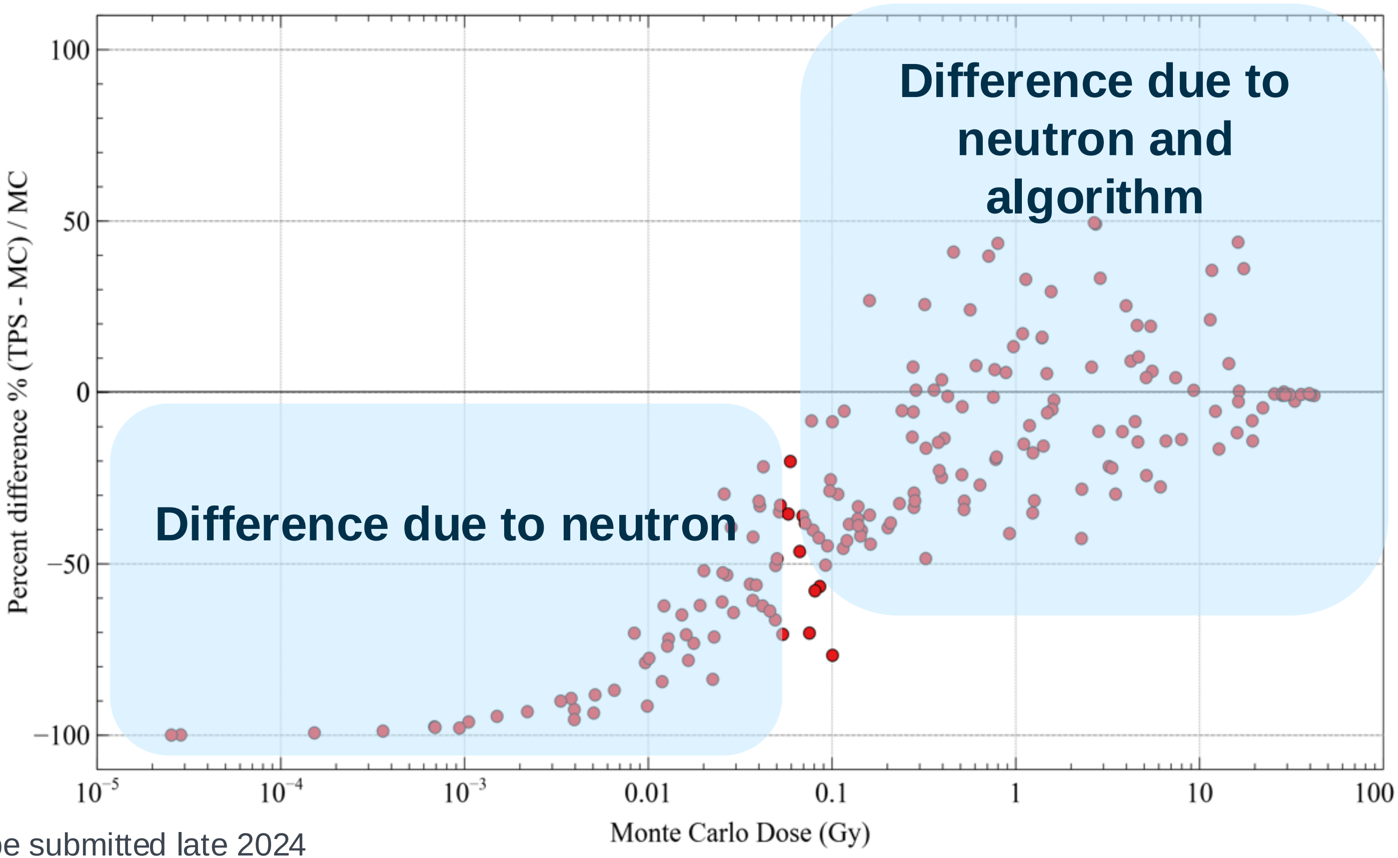
RT Dose
Main proton only



Monte Carlo vs. RT Dose for Craniospinal Passive Scattering

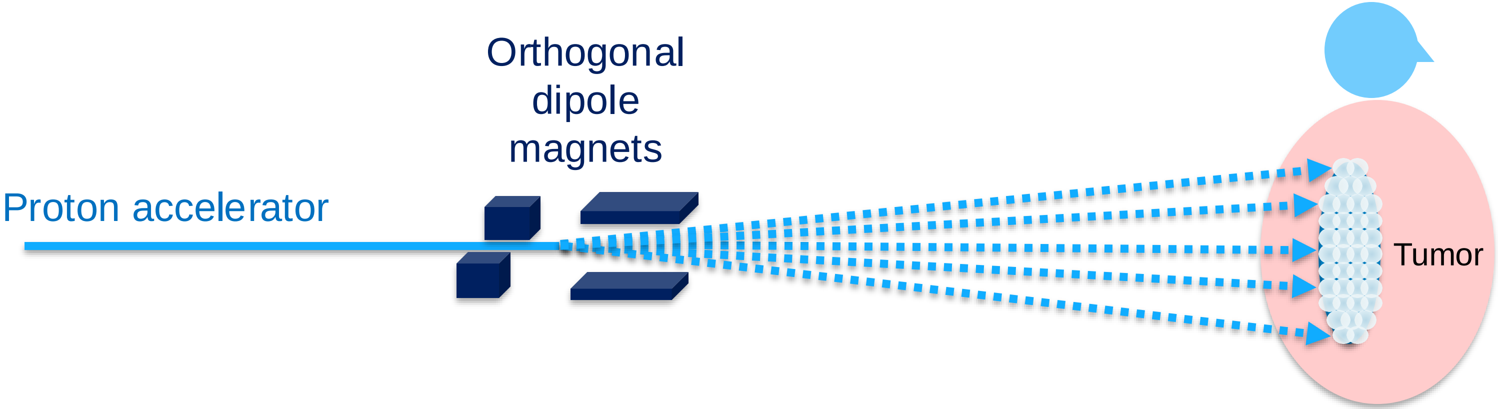


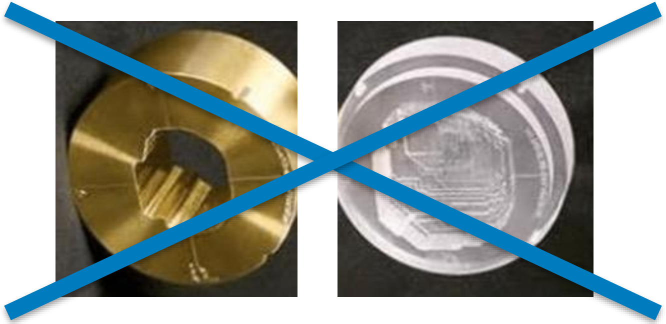
Monte Carlo vs. RT Dose for Craniospinal Passive Scattering



Griffin et al. to be submitted late 2024

Proton Therapy: Pencil Beam Scanning (PBS)



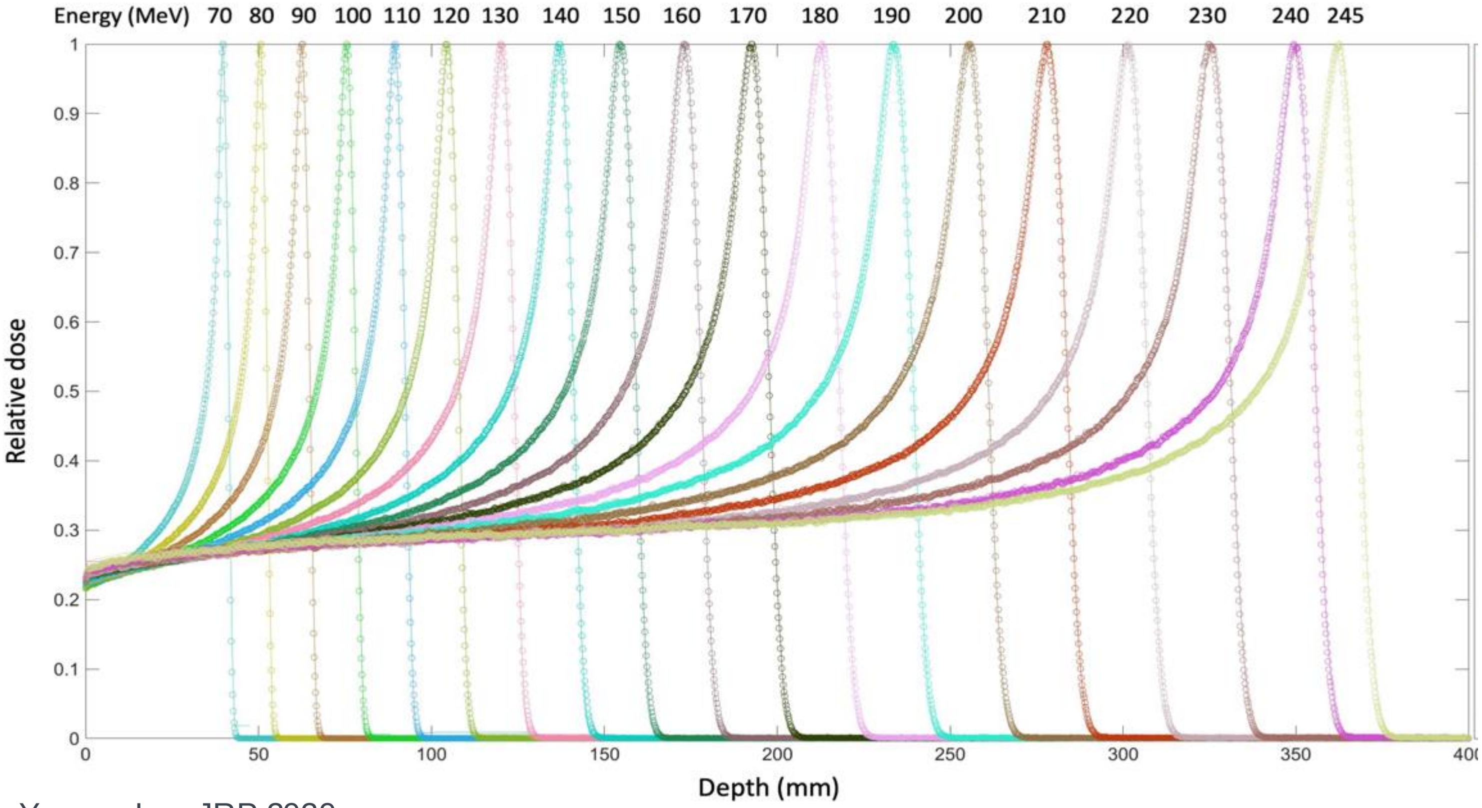


Collaboration to Develop PBS Dose Calculation Methods

Maryland Proton Treatment Center
Affiliated with University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center

TOol for PArticle Simulation (TOPAS)

Validation of Computer Simulation Model of PBS



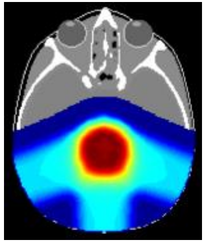
Measurement (solid)

Simulation (line)

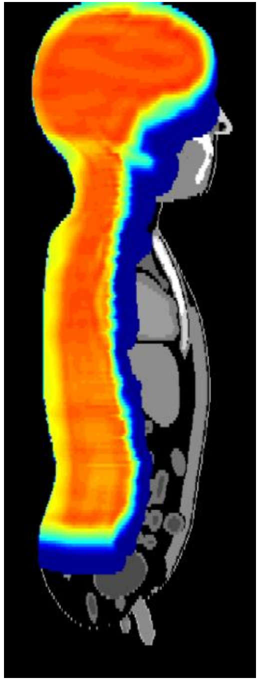
Yeom... Lee JRP 2020

Organ Dose for PBS Patients: Monte Carlo Calculations

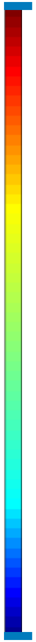
Intracranial



Craniospinal



Dose per prescribed dose (Gy/Gy)



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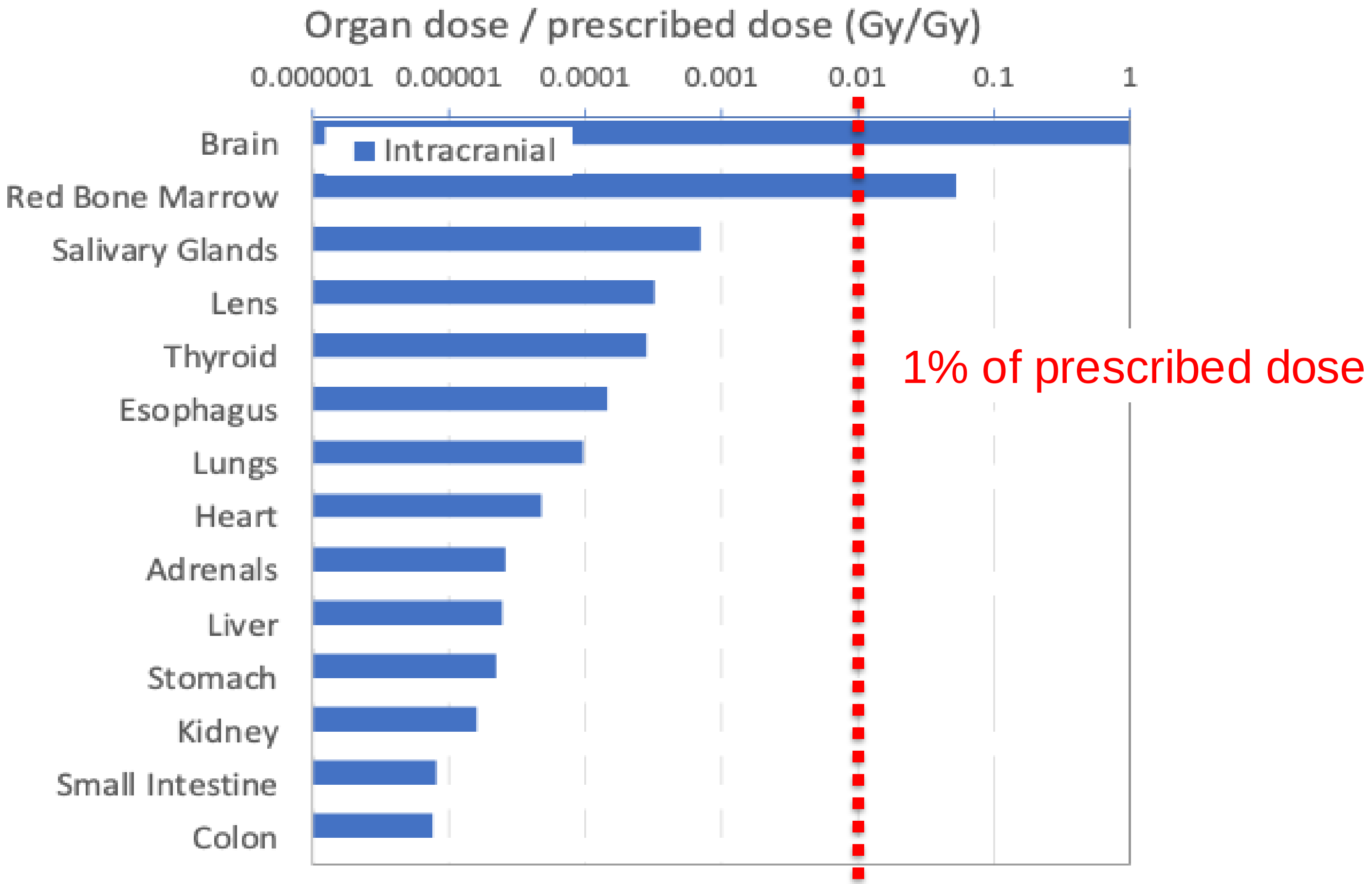
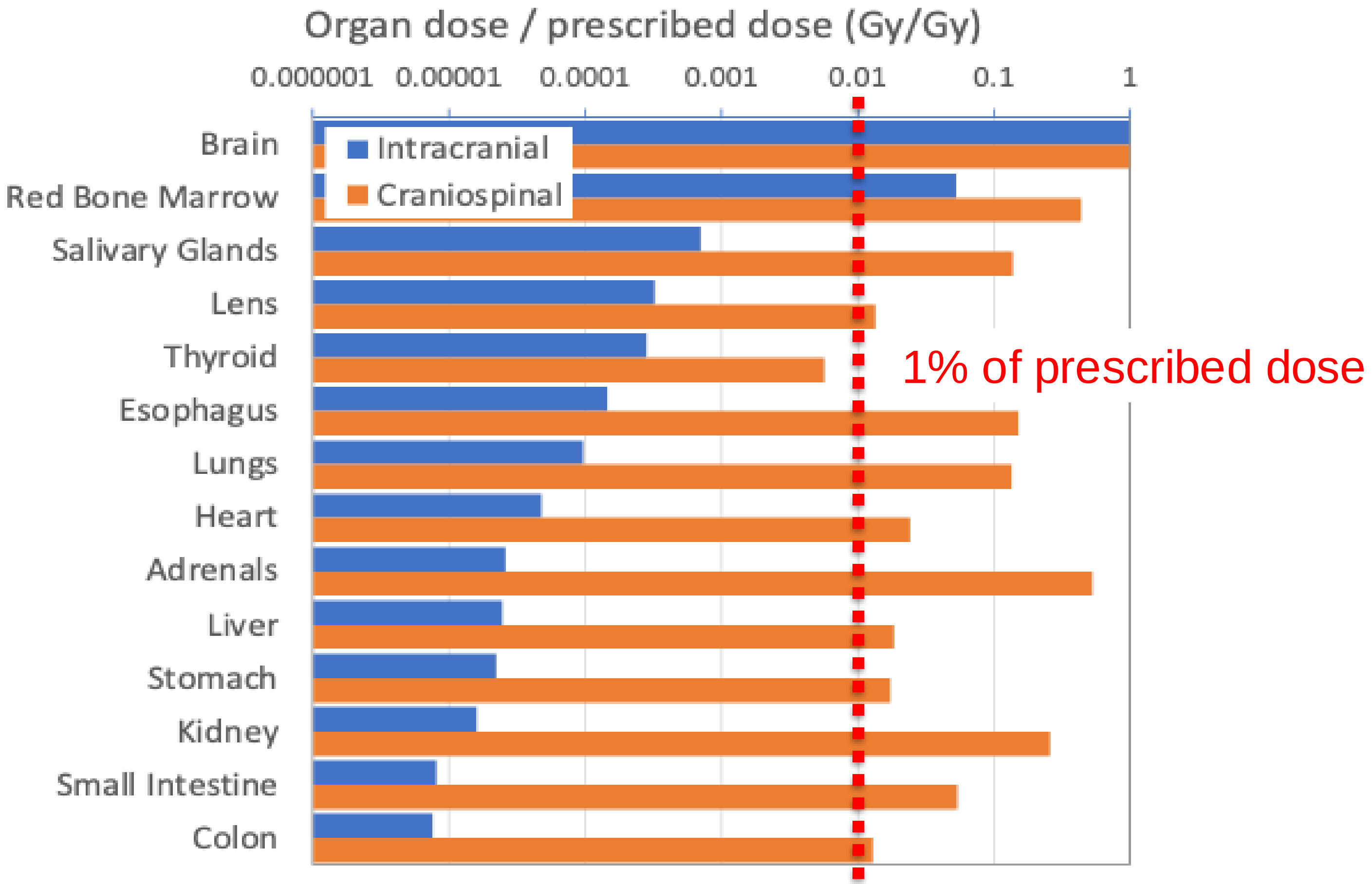
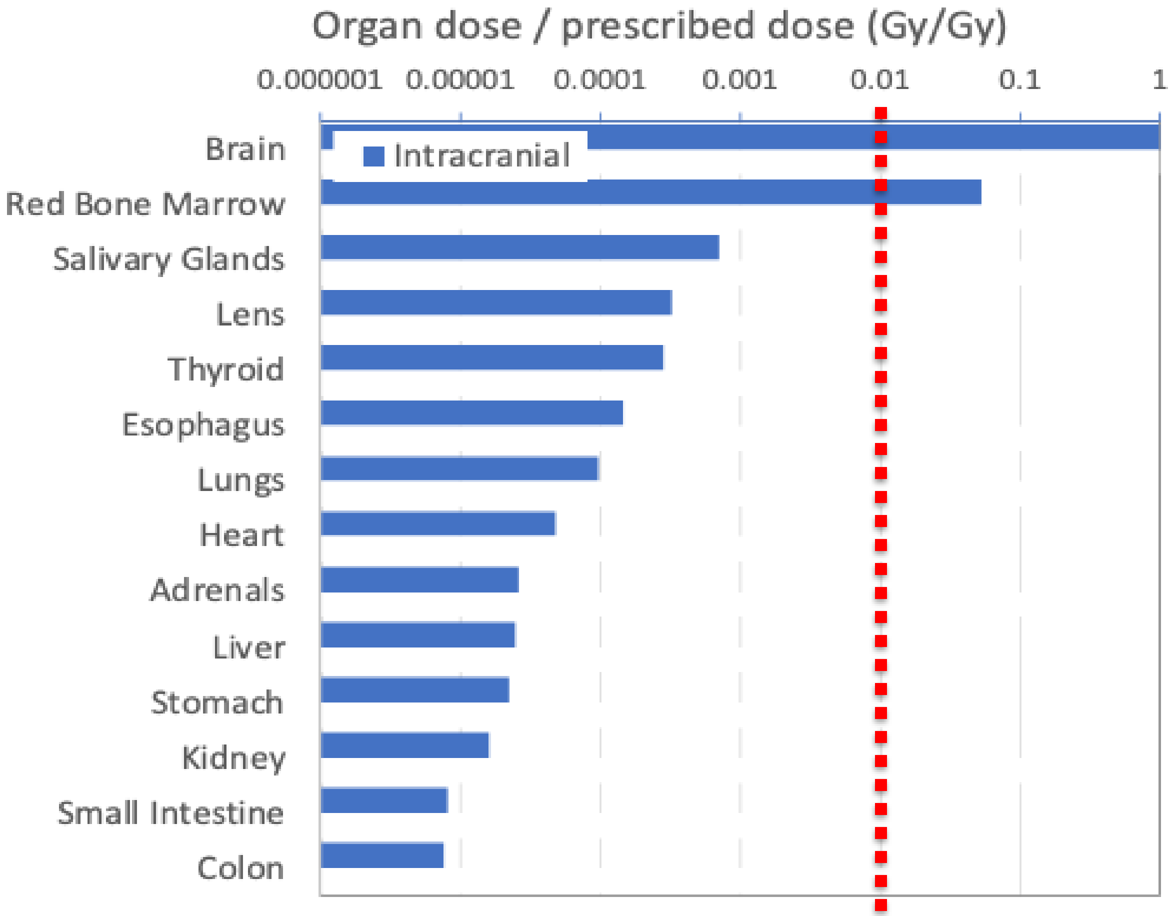
Organ Dose for PBS Patients: Monte Carlo Calculations

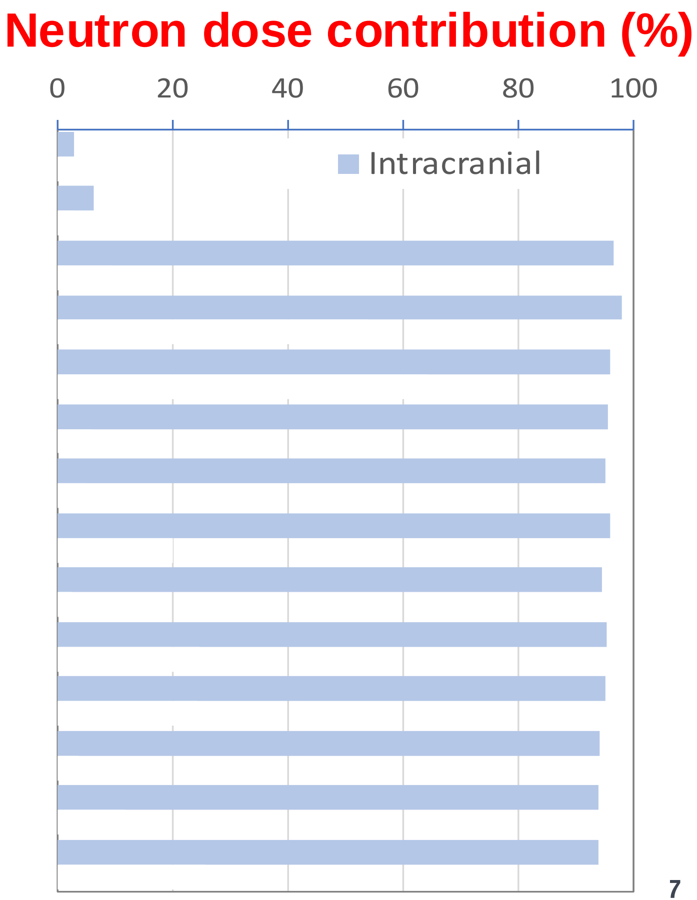


Organ Dose for PBS Patients: Monte Carlo Calculations Cont.

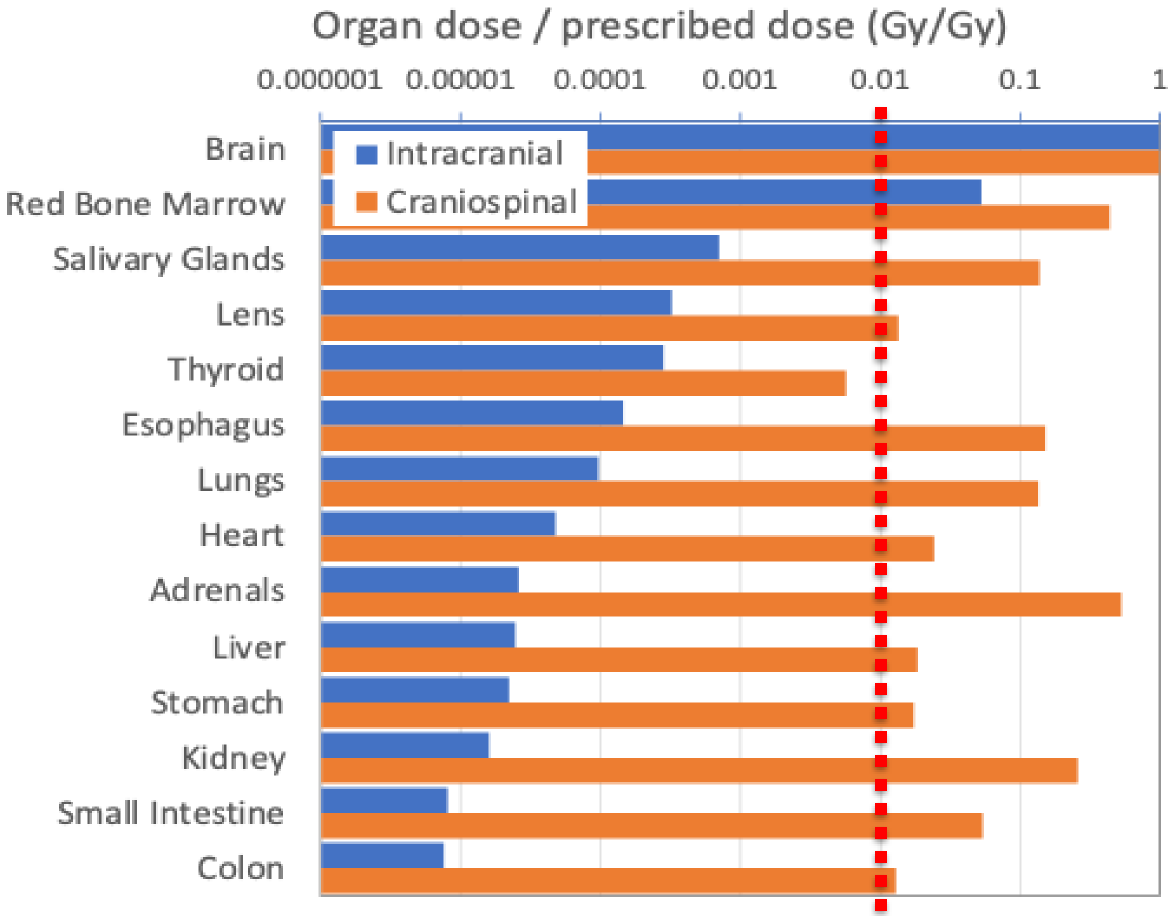


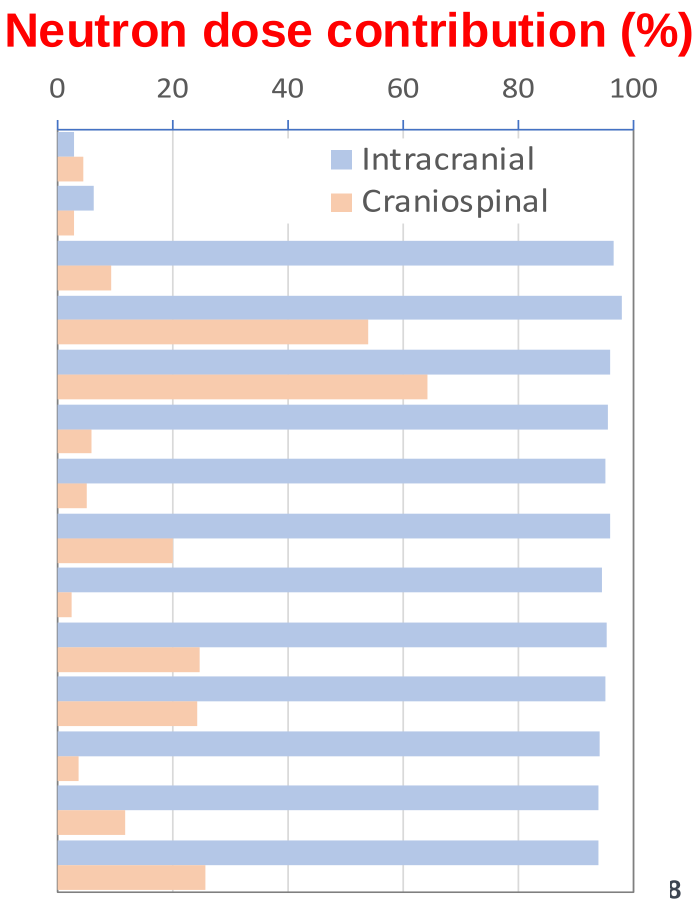
Organ Dose for PBS Patients: Monte Carlo Calculations Cont.





Organ Dose for PBS Patients: Monte Carlo Calculations Cont.





Method Papers Published to Date

- **Solution to missing anatomy**
  - Morato Rafet et al. Realistic extension of partial-body pediatric CT for whole-body organ dose estimation in radiotherapy patients, RPC (in press)
- **Solution to missing contour**
  - Jung JW, Lee C, Mosher EG, et al. Automatic segmentation of cardiac structures for breast cancer radiotherapy. *Phys Imaging Radiat Oncol.* 2019 Dec 5. doi: 10.1016/j.phro.2019.11.007.
  - Jung JW, Mille MM, Ky B, et al. Application of an automatic segmentation method for evaluating cardiac structure doses received by breast radiotherapy patients. *Phys Imaging Radiat Oncol.* 2021 Aug 23. doi: 10.1016/j.phro.2021.08.005.
  - Saha M, Jung JW, Lee SW, et al. A deep learning segmentation method to assess dose to organs at risk during breast radiotherapy. *Phys Imaging Radiat Oncol.* 2023 Nov 21. doi: 10.1016/j.phro.2023.100520.

Method Papers Published to Date Cont.

- **Solution to missing dose**
  - Mille MM, Jung JW, Lee C, et al. Comparison of normal tissue dose calculation methods for epidemiological studies of radiotherapy patients. *J Radiol Prot.* 2018 Jun. doi: 10.1088/1361-6498/aabd4f.
  - Yeom YS, Kuzmin G, Griffin K, et al. A Monte Carlo model for organ dose reconstruction of patients in pencil beam scanning (PBS) proton therapy for epidemiologic studies of late effects. *J Radiol Prot.* 2020 Mar. doi: 10.1088/1361-6498/ab437d.
  - Yeom YS, Griffin K, Mille M, et al. A dose voxel kernel method for rapid reconstruction of out-of-field neutron dose of patients in pencil beam scanning (PBS) proton therapy. *Phys Med Biol.* 2020 Aug 27. doi: 10.1088/1361-6560/abaa5f.

Publication Plan

- **Method papers**
  - Use of natural language processing for centralizing organ contour naming
  - Comparison of organ contours manual vs. automatic segmentation
  - Dose comparison TPS vs. Monte Carlo for photon and proton patients
- **Application papers**
  - Dose comparison for specific cancer types photon vs. proton therapy

Q&A

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