Radiation Physics for Pediatric Tumors

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On behalf of Radiation Oncology Discipline Committee of Children's Oncology Group, last updated in December 2024

Disclosure

No conflict of interest.

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This educational slide set is divided into pediatric photon therapy physics and pediatric proton therapy physics, each with its own outline.

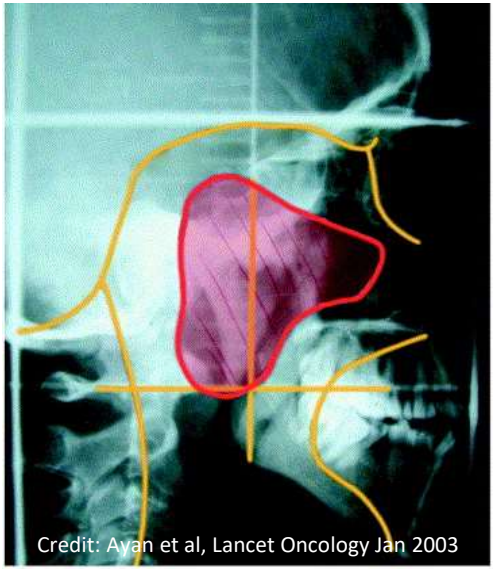
Pediatric Photon Therapy Physics

Outline for Pediatric Photon Therapy

1. Radiation therapy techniques and contemporary delivery
2. Pediatric CT simulation – anesthesia, radiation exposure, respiratory motion
3. Pediatric MRI for RT planning
4. Pediatric RT planning – tradeoff and clinical trial guidelines
5. Image guidance for children receiving radiation therapy
6. Craniospinal Irradiation (CSI), Total Body Irradiation (TBI), and pediatric brachytherapy
7. VMAT for pediatric patients
8. Summary

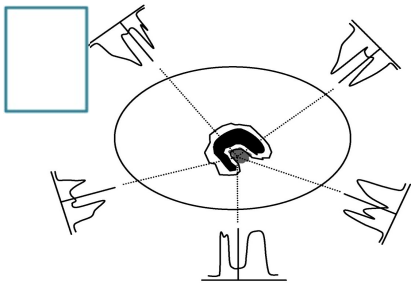
Radiation Therapy Techniques

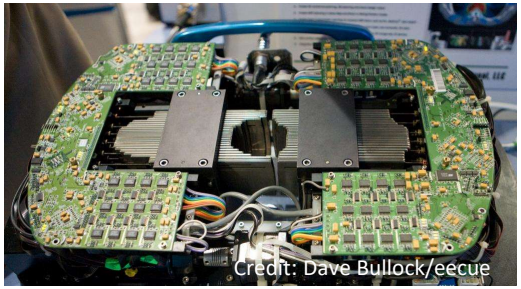
2D radiation therapy



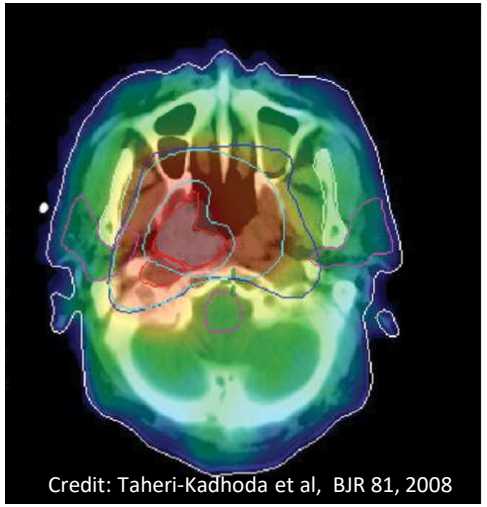
Credit: Ayan et al, Lancet Oncology Jan 2003

IMRT (Intensity Modulated) since early 2000



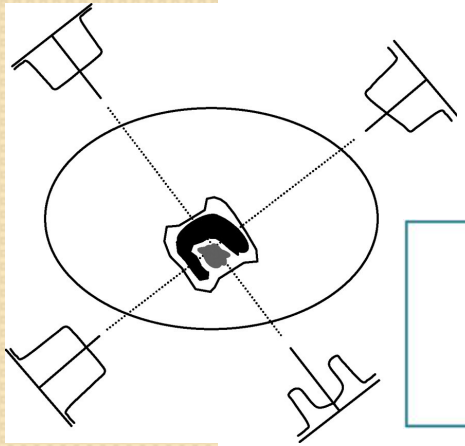


Credit: Dave Bullock/eecue

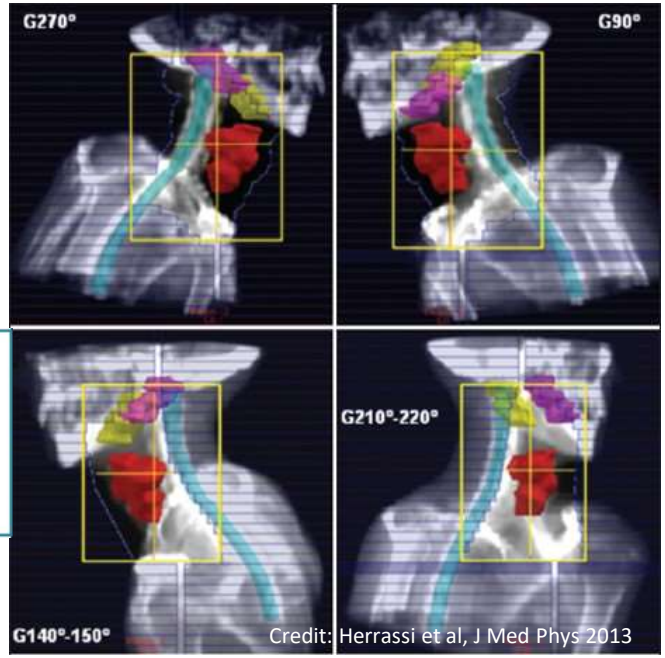


Credit: Taheri-Kadhoda et al, BJR 81, 2008

3D conformal since 1990's

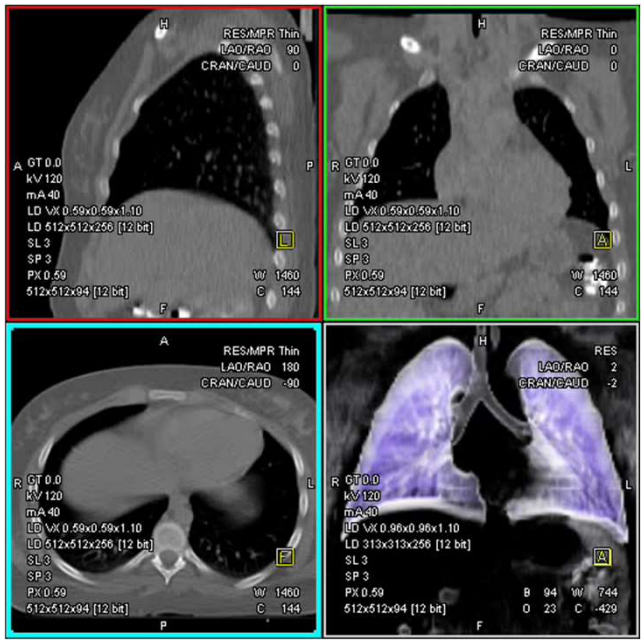


Credit: Journal of ICRU

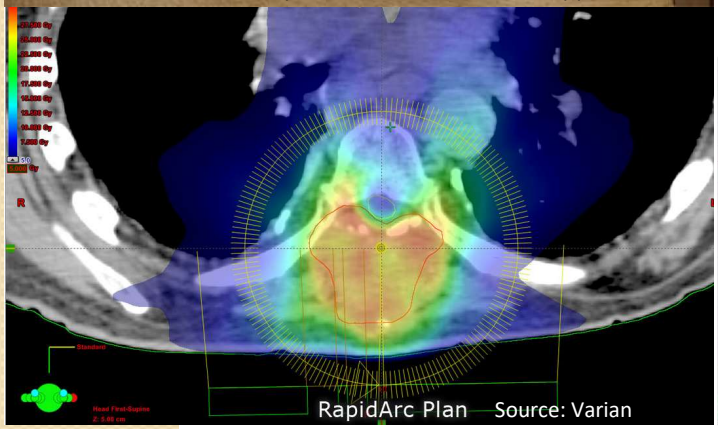


Credit: Herrassi et al, J Med Phys 2013

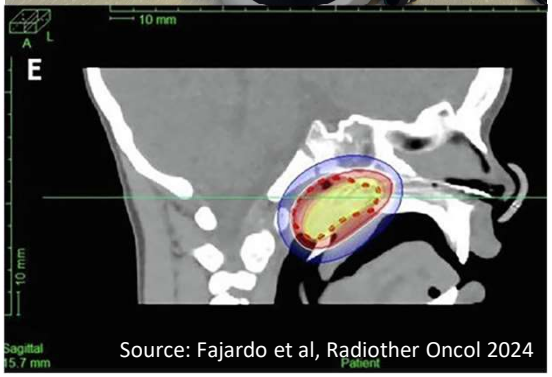
4D radiation therapy since 2000's



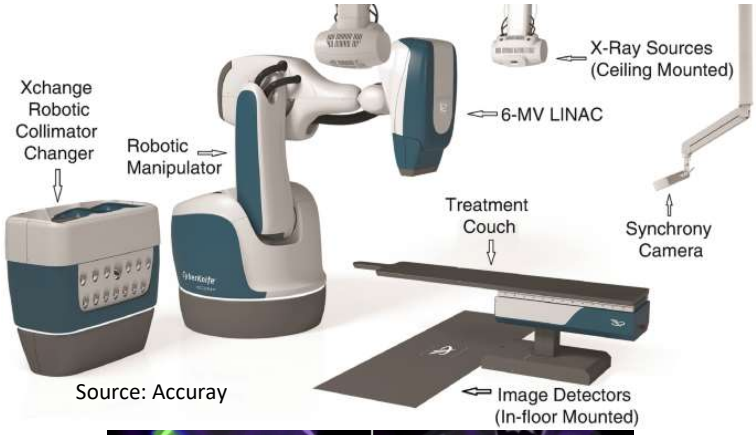
Contemporary Radiation Therapy Delivery (I)

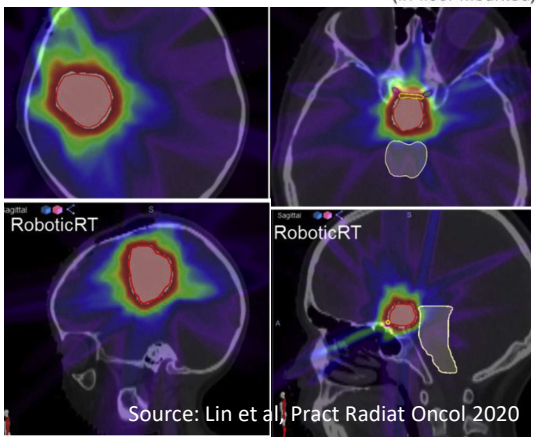


External beam arc therapy



Brachytherapy





Robotic radiotherapy

Stereotactic radiosurgery

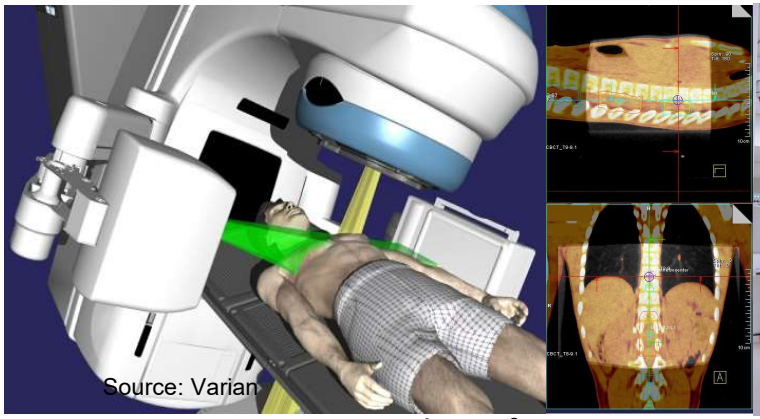
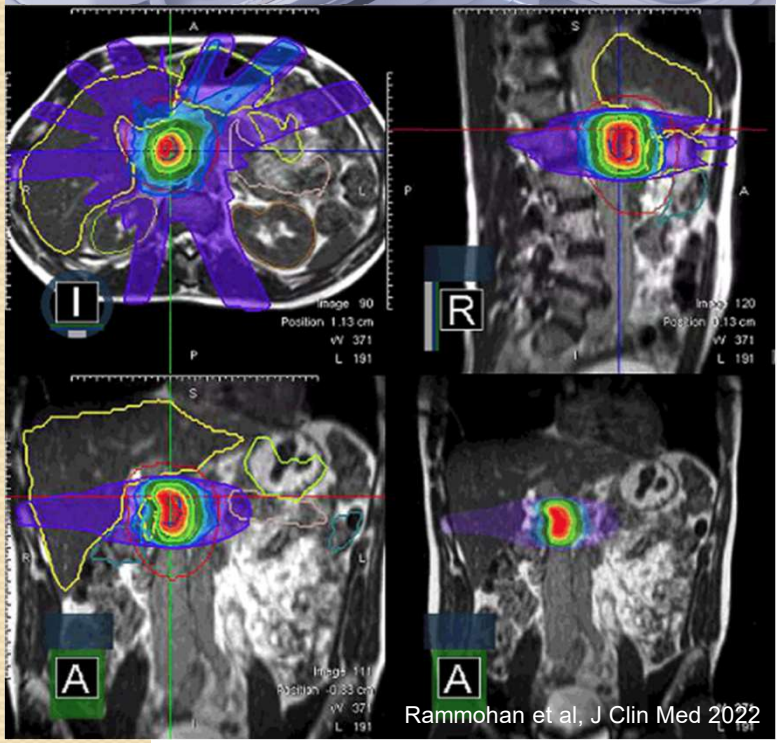


Image-guidance for patient setup and motion monitoring

Contemporary Radiation Therapy Delivery (II)

MR-Linac

Source: Elekta Medical



Rammohan et al, J Clin Med 2022

PET/CT Linac

Source: RefleXion Medical

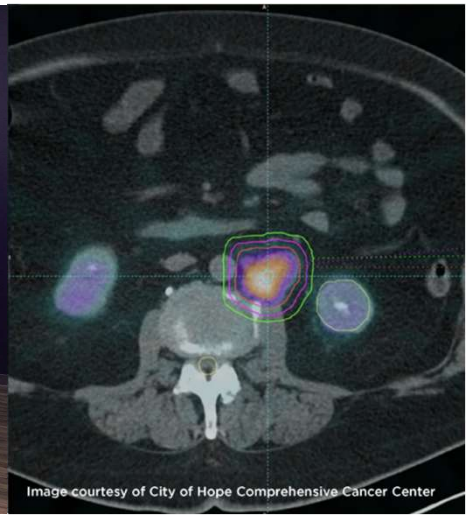
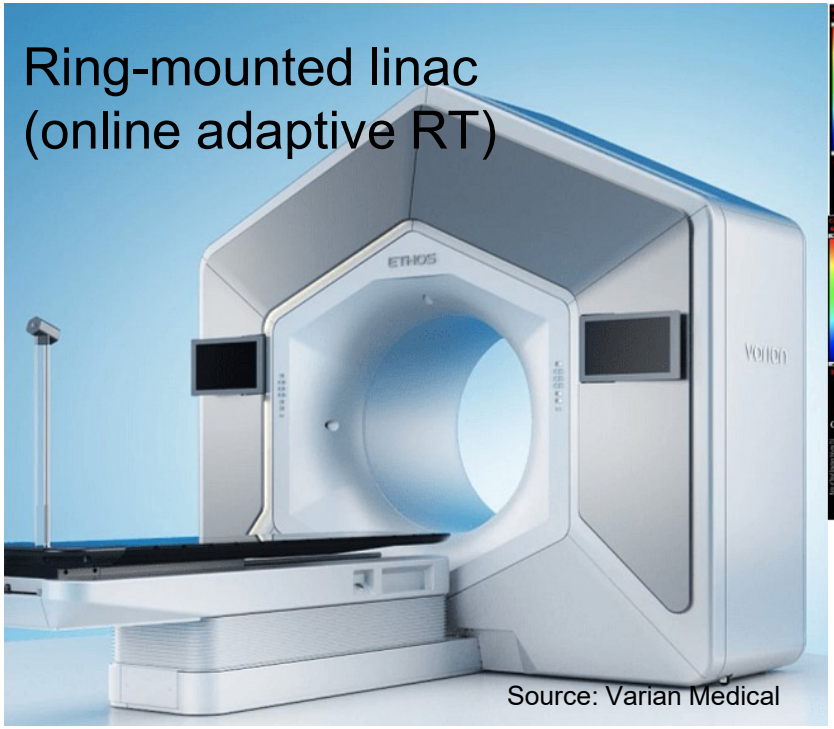
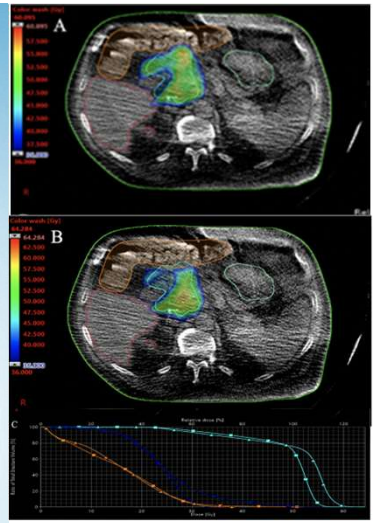


Image courtesy of City of Hope Comprehensive Cancer Center

Ring-mounted linac
(online adaptive RT)



Source: Varian Medical

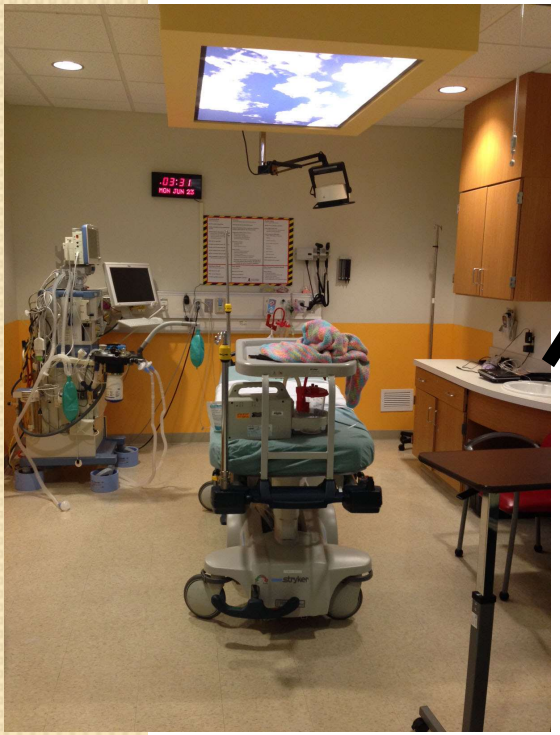


Schiff et al, IJROBP 2022

Pediatric Simulation: Anesthesia

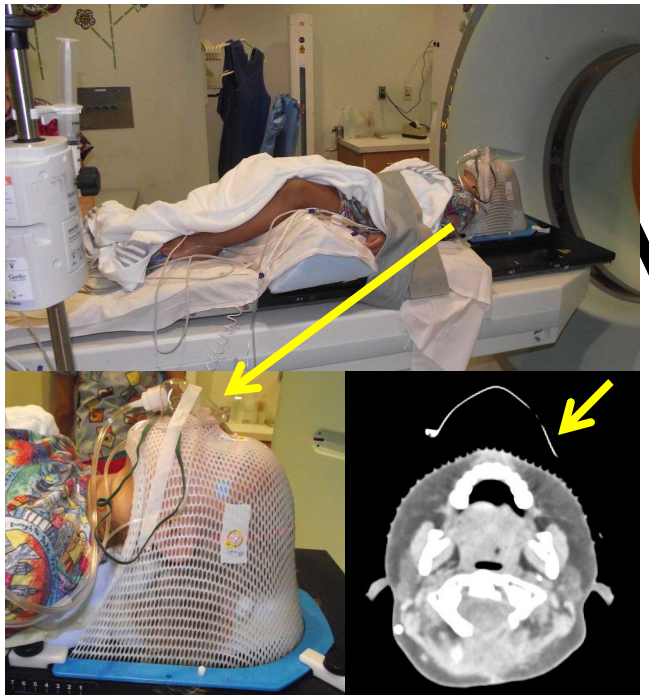
- General anesthesia with intravenous propofol to <7 years old and uncooperative older children at St. Jude Children's Research Hospital (~40% of treated children).
- Relevant publications – Anghelescu IJROBP 2008, Owusu-Agyemang Radiother Oncol 2014
- Longer simulation time (1-1.5 hr) and treatment time (30 min-1 hr), even when anesthetized outside.

Anesthesia induction room



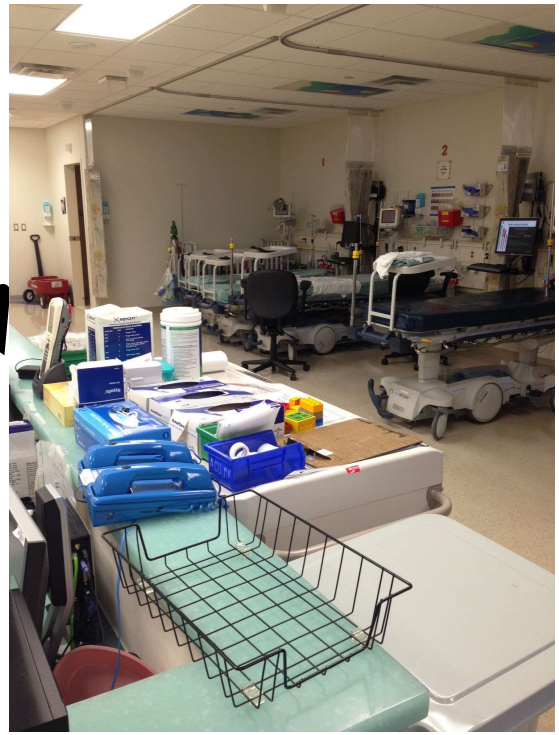
with parents/guardians present

CT sim



Supplemental oxygen is provided by face mask. Oxygen tubing is used for patients in prone position and for proton patients. In case of rare upper airway obstruction, oral airway or laryngeal mask airway are used, often affecting neck curvature.

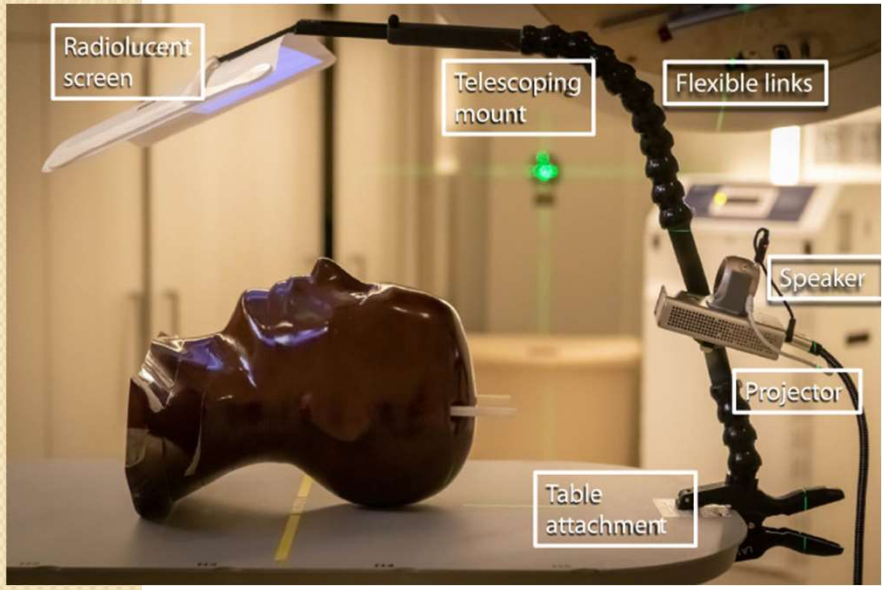
Central anesthesia recovery



Pediatric Simulation: Anesthesia Alternative for Older Children

- Audio-visual assisted devices have been tested in selected institutions as an alternative to anesthesia for children undergoing radiation therapy

Avatar video distraction (Stanford)



Anesthesia avoidance was observed in 54.5% patients aged 3 to 4, 80.6% patients aged 5 to 7, and 84.8% patients aged 8 to 10.

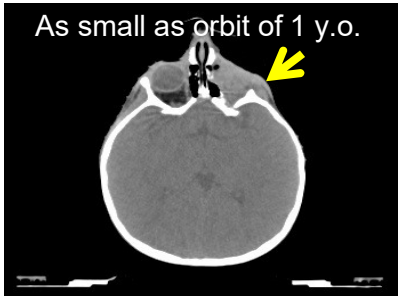
Gutkin et al, IJROBP 2023

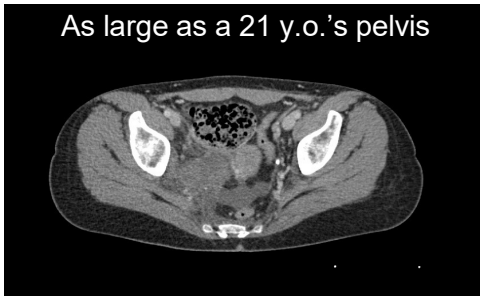
PROMISE (UT Southwestern)

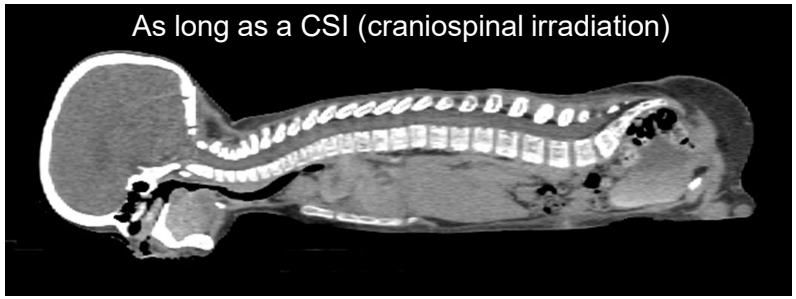
An interactive incentive-based movie system is integrated with a commercial video surveillance gating module to be used in lieu of sedation. The team reported a 30% absolute reduction in general anesthesia use for children ages 3-7.

https://clinicaltrials.gov/study/NCT05148078
https://www.sciencedirect.com/science/article/pii/S0360301621010877

Pediatric Simulation: CT Sim



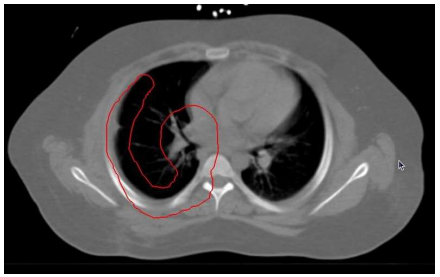




- **Methods to reduce radiation exposure from CT scans for pediatric patients**
  - ❑ Select an appropriate scan protocol based on anatomic sites
  - ❑ Limit the body scanned to the smallest necessary area but cover enough to allow the use of non-coplanar beams
  - ❑ Use automatic exposure control such as tube current modulation (e.g. Siemens CARE Dose4D and Philips Dose-Right)
  - ❑ Statistical iterative reconstruction already commercially available
  - ❑ Be careful with changing kVp – affecting energy spectrum and calibration curve
- Consider tradeoff between radiation exposure and image quality for treatment planning. Having to repeat scans due to insufficient quality defeats the purpose.
- **Image gently** by The Alliance for Radiation Safety in Pediatric Imaging: What can I do as a physicist? http://www.imagegently.org/Roles-What-can-I-do/Physicist

Pediatric Simulation: Respiratory Motion

- Relevant to neuroblastoma, thoracic tumors and pulmonary mets
- Unlike high image contrast of adult pulmonary lesions, pediatric tumors often need surrogates (fiducials, OARs) to determine target motion.
- Adults 8-16 breaths/min, younger children 15-20 breaths/min, and infants much higher. Teenagers approach adult respiration rates and motion extent.
- Example: Adolescents showed a larger kidney motion in S/I than children but in general <10 mm.



chest wall tumor

neuroblastoma

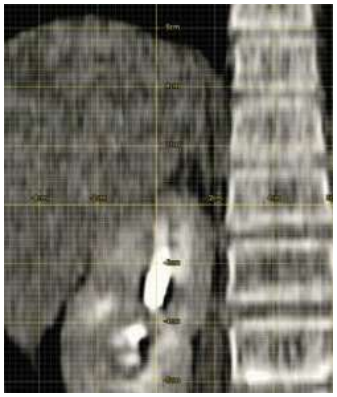


Table 1. Descriptive statistics of renal motion in pediatric patients grouped by age

Patient group	*n*	Variable	Mean	SD	Med	Min	Max	Lower 95% CI*	Upper 95% CI*
Young (2–8 years)	11	Age (years)	4.08	2.11	3.00	2.00	8.00	2.74	5.42
		Height (cm)	101.91	20.52	97.00	79.00	152.10	88.87	114.94
		Movement (mm)							
		Diaphragm	5.08	1.88	4.50	3.00	10.00	3.89	6.28
		R kidney ML	0.69	0.23	0.70	0.40	1.20	0.54	0.85
		L kidney ML	0.67	0.30	0.60	0.30	1.40	0.47	0.87
		R kidney AP	0.70	0.39	0.50	0.30	1.70	0.44	0.96
		L kidney AP	0.92	0.30	0.80	0.50	1.40	0.72	1.12
		R kidney SI	1.91	0.93	2.00	0.60	3.70	1.28	2.54
		L kidney SI	1.72	0.81	1.60	0.70	3.40	1.17	2.26
Old (9–18 years)	9	Age (years)	12.33	3.35	12.00	9.00	18.00	9.76	14.91
		Height (cm)	151.20	14.11	149.00	132.10	175.50	140.36	162.04
		Movement (mm)							
		Diaphragm	9.56	3.57	8.00	7.00	17.00	6.81	12.30
		R kidney ML	1.14	0.52	1.10	0.60	2.20	0.74	1.55
		L kidney ML	0.86	0.48	0.70	0.50	2.10	0.49	1.22
		R kidney AP	1.36	0.44	1.40	0.90	2.30	1.02	1.69
		L kidney AP	0.94	0.43	0.90	0.40	1.70	0.62	1.27
		R kidney SI	3.90	1.71	3.60	1.50	6.30	2.59	5.21
		L kidney SI	3.07	1.24	3.40	0.80	4.60	2.11	4.02

Abbreviations: AP = anteroposterior; CI = confidence interval; L = left; ML = mediolateral; Max = maximum; Med = median; Min = minimum; R = right; SD = standard deviation; SI = superoinferior.
* Lower and upper limits of the 95% confidence interval are shown.

Pai-Panandiker et al, IJROBP 2012:82:1771-1776

Pediatric Simulation: Respiratory Motion

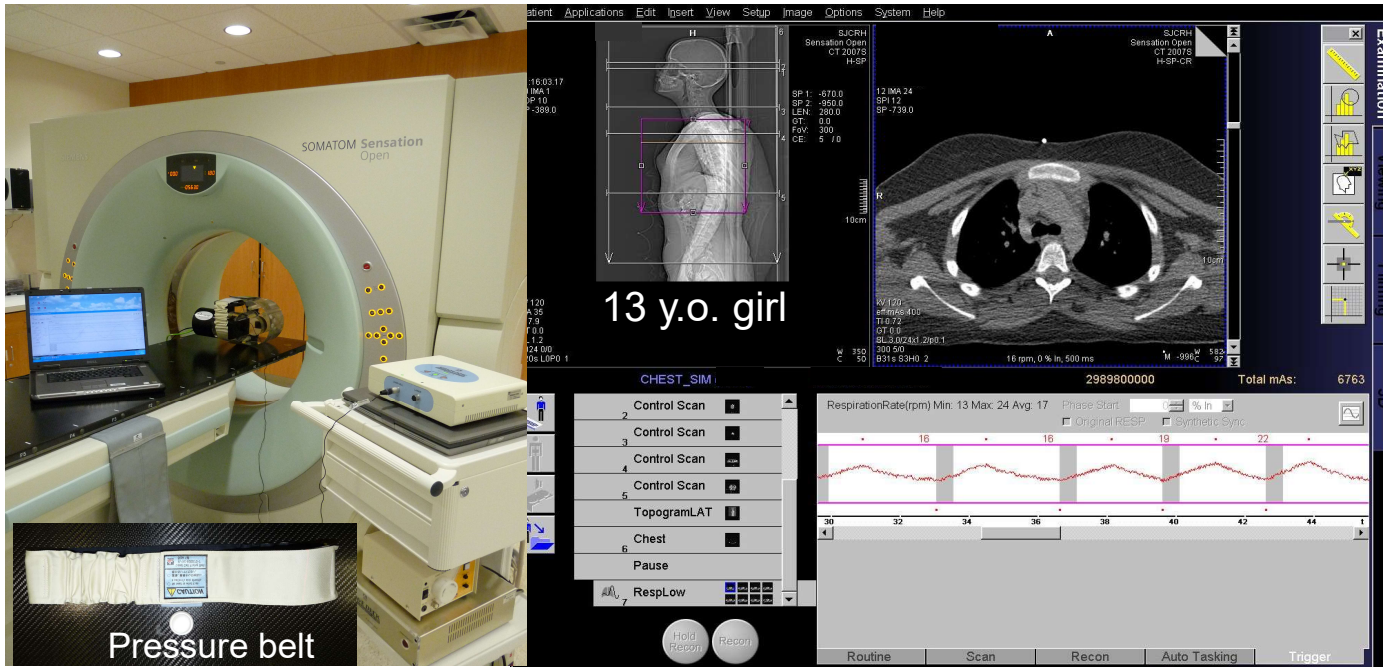
- St Jude 4DCT protocol: measured CTDI of 33 mGy (32cm diameter plastic body phantom).

  120 KV, 400 effective mAs,

  0.5-1s rotation

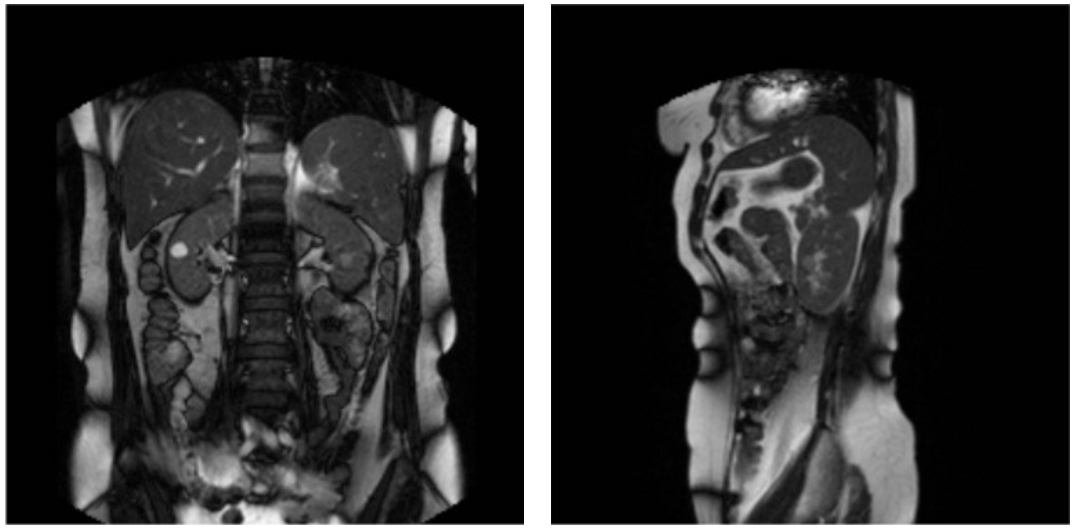
  0.1 pitch, 3mm slice,

  1.2 mm collimation



Hua et al, Med Phys 2009:36:2726

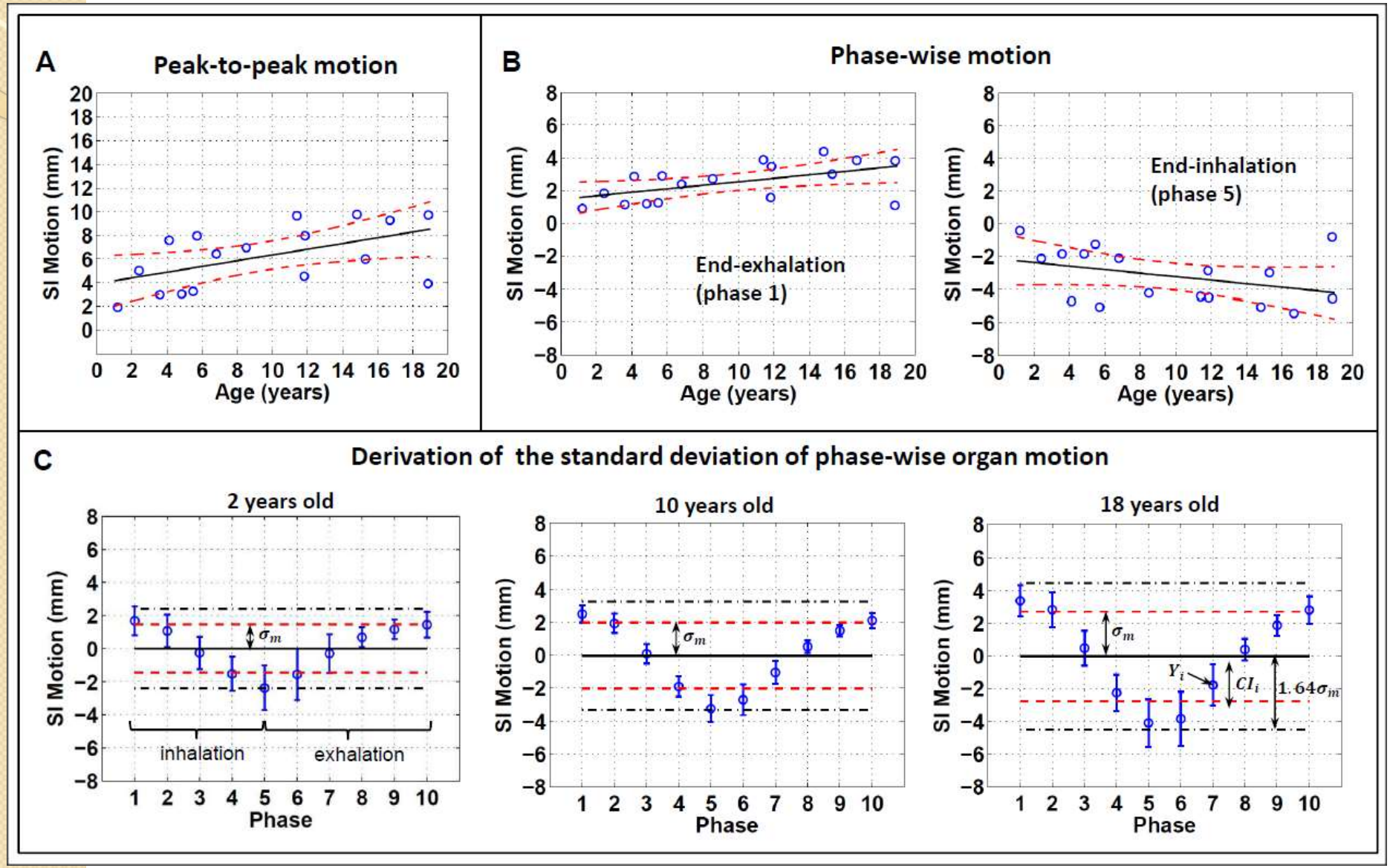
- 2D cine MRI or 4D MRI may be a good alternative for assessing the motion extent due to no radiation exposure to children and better soft tissue contrast. But motion could be out of 2D plane and pixel resolution is often lower than CT.



Stam et al, Phys Med Biol 2013:58:2235-2245

Pediatric Organ Motion Measured with 4D MRI

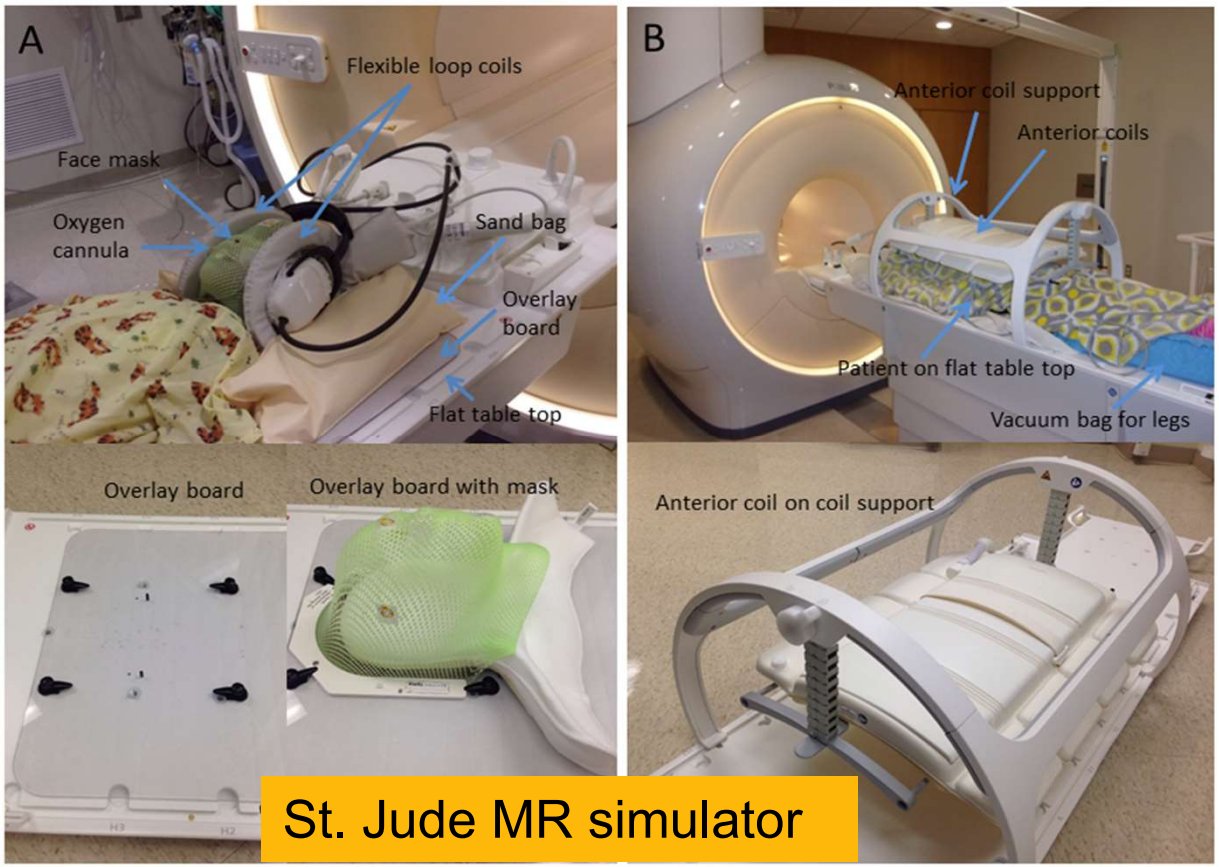
Liver dome (diaphragm) motion



Uh, Krasin, Li, Li, Tinkle, Lucas, Merchant, Hua. Quantification of pediatric abdominal organ motion with a 4-dimensional magnetic resonance imaging method. Int J Radiat Oncol Biol Phys 99(1):227-237, 2017.

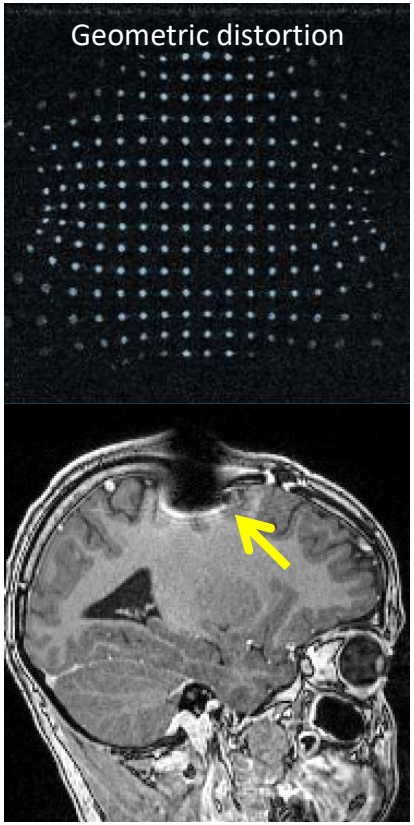
Pediatric MRI for RT

- MRI is essential for delineating CNS tumors and the majority of solid tumors.
- MRI is helpful for critical organ delineation in children (e.g., ovary, chiasm, thyroid).
- MRI in treatment position is preferable for registration.
- More RO departments now have dedicated MR scanners with lasers and flat tabletop.
- Vendors offer radiation oncology configurations with RF coils to accommodate immobilization devices although not specifically designed for children.



Hua et al, J Med Imag Radiat Sci 2018

Pediatric MRI for RT



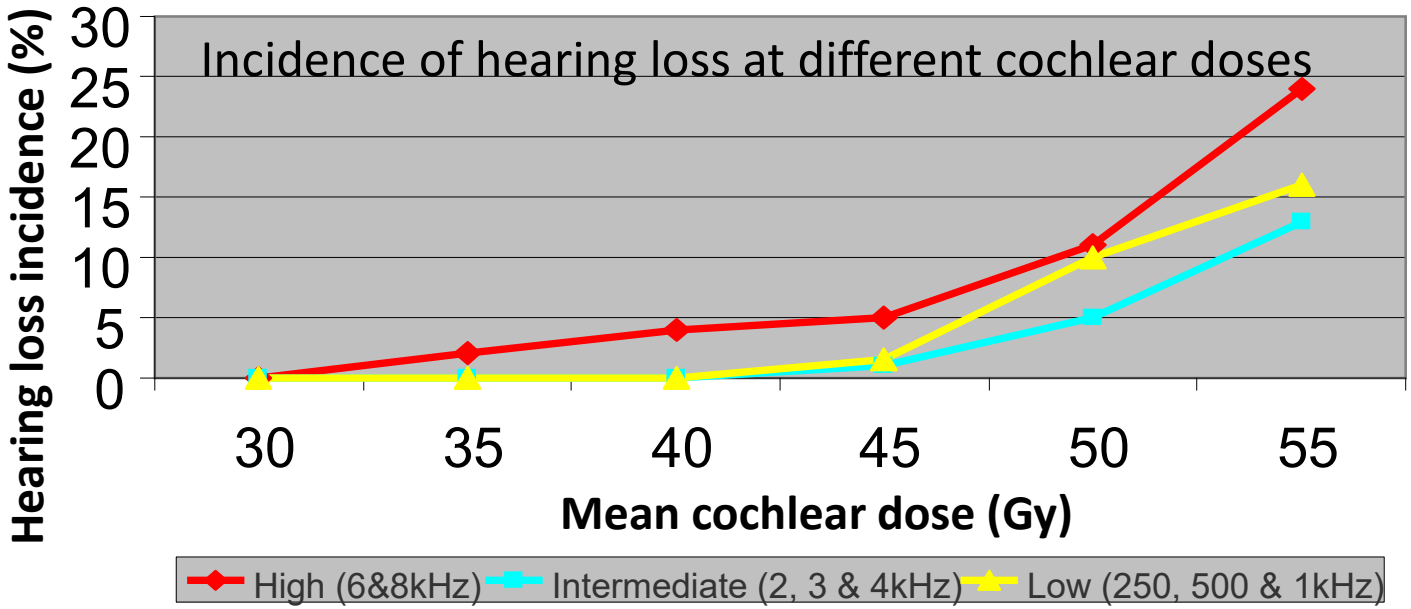
- **Watch out for spatial distortion**
  - ❑ Position target within the high homogeneity region of the magnet (important for tumors in extremity, shoulder, skin surface)
  - ❑ Paramagnetic objects causing local distortion (orthodontic braces, CSF shunts – common in children)
  - ❑ Focus on target region when registering MRI to CT
  - ❑ Monitor the spatial distortion regularly with QA

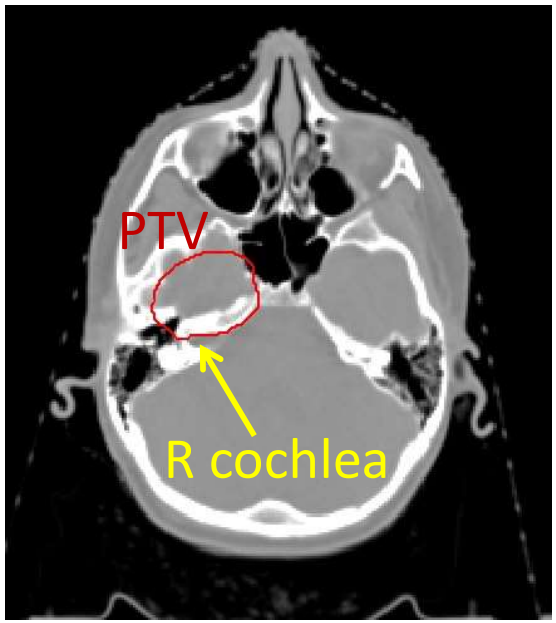
- **MRI pulse sequences for pediatric MR sim**
  - ❑ Perform important sequences first and keep them short in case un-sedated children becoming agitated after a few minutes
  - ❑ Isotropic high resolution 3D imaging (e.g. 1mm T1W MPRAGE) good for reformatting
  - ❑ Fast sequences to minimize motion artifacts in thorax and abdomen (e.g. BLADE)
  - ❑ Sequences to reduce artifacts from blood vessel and CSF pulsations often seen in children (e.g. in posterior fossa region of the brain)
  - ❑ Close monitoring for increased heating from high SAR sequences in young children

RT Planning: Normal Tissue Sparing Vs. Tumor Coverage

Normal tissue sparing is important but don't over protect at the expense of tumor coverage.

Example: Currently a conservative planning constraint of Dmean to cochlea <35Gy is often recommended for preserving hearing after RT.



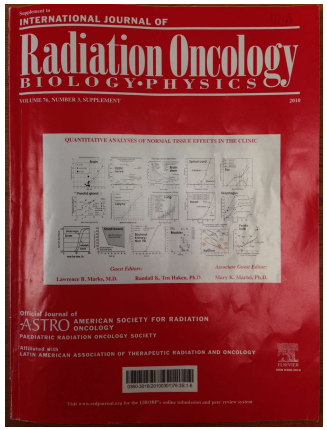


Hua et al, IJROBP vol 72, p892-899, 2008

RT Planning: PENTEC Reports

Adults

QUANTEC (QUantitative Analysis of Normal Tissue Effects in the Clinic) reports, published in 2010, reviewed dose-volume-outcome data of normal tissues in adults and recommended dose/volume constraints for treatment planning.



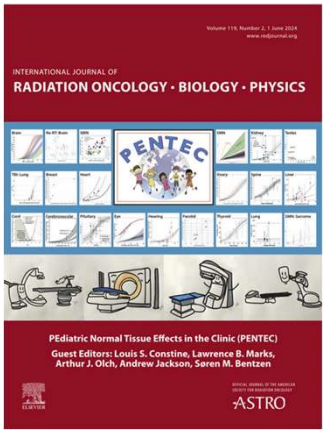
Children and Adolescents

PENTEC (PEdiatric Normal Tissue Effects in the Clinic) reports have been published in 2024 in the special issue of red journal.

There are total 35 clinical end points in 19 organ specific reports. Also published are 6 introductory papers and 3 visionary papers.

Also see 2024 AAPM scientific symposium on PENTEC.

https://aapm.confex.com/aapm/2024am/meetingapp.cgi/Session/2443

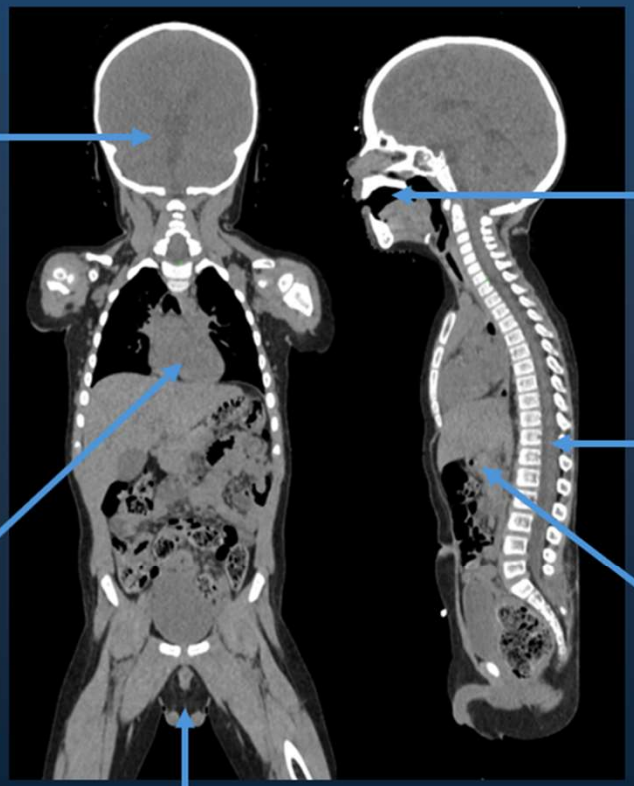


RT Planning: PENTEC Reports

19 PENTEC Organ-Specific Reports

Neurocognitive effects and necrosis (brain)
Brain and brainstem necrosis after re-irradiation (brain)
Cerebrovascular effects (cerebral vasculature)
Central endocrine complications (hypothalamic-pituitary axis)

Cardiac diseases (heart)
Breast hypoplasia & decreased lactation (breast)
Pulmonary effects (lungs)
Idiopathic pneumonitis syndrome after TBI (lungs)



Retinopathy, optic neuropathy, and cataract (eyes)
Hearing loss (cochlea)
Salivary and dental complications (parotid, teeth)
Primary hypothyroidism (thyroid)

Radiation myelopathy (spinal cord)
Spinal abnormalities and growth impairment (spine)

Liver late effects (liver)
Kidney diseases (kidneys)

Subsequent neoplasms after RT (CNS, sarcoma, and lung cancer)

Male testicular dysfunction (testes) Female reproductive dysfunction (ovary, uterus)

RT Planning: Clinical Trial Guidelines

- Many pediatric patients are enrolled on clinical trials (COG, PBTC, other consortia, institutional trials) and treated per guidelines. The best resource is in the section of radiation therapy guidelines of the protocol.
- Different trials may have different RT guidelines (allowed treatment techniques, target definition and dose, OAR constraints, data reporting) due to principal investigator's preference and difference in treatment regimens.

e.g. ARAR0331 for childhood nasopharyngeal carcinoma (61.2-66.6 Gy)

High priority

Spinal cord	max dose 45 Gy or 1 cc can not exceed 50 Gy
Mandible/TM joint	no more than 1 cc exceeding 77 Gy
Temporal lobes	max dose 65 Gy, no more than 1 cc exceeding 60 Gy
Brainstem	max dose 60 Gy, no more than 1 cc exceeding 54 Gy
Optic nerve and chiasm	max dose 60 Gy, no more than 1 cc exceeding 54 Gy

Low priority

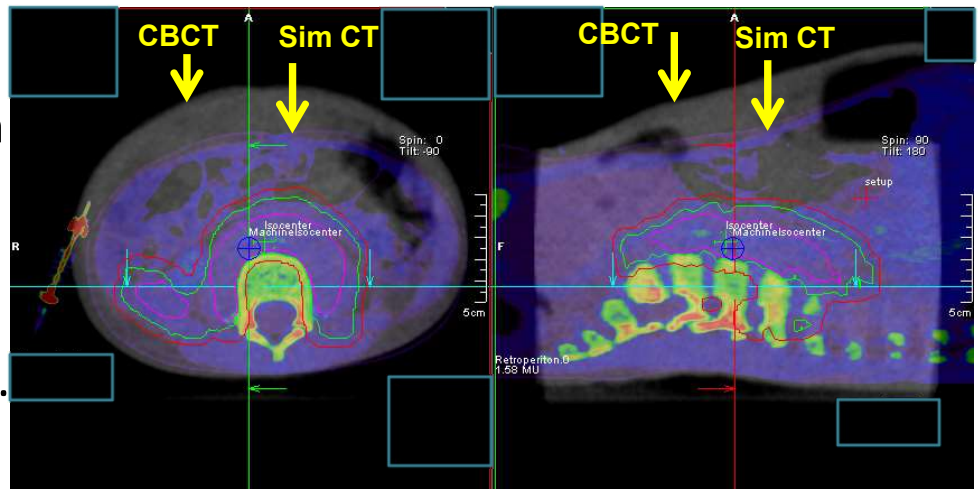
Parotid	mean dose ≤ 26 Gy to at least one gland
Oral cavity	mean dose ≤ 40 Gy, no more than 1 cc exceeding 70 Gy
Cochlea	mean dose < 40 Gy

and glottic larynx, eyes, lens, pituitary, unspecified tissues

Image Guidance: Approaches and Imaging Frequency

- Pediatric IGRT approaches – implanted fiducials, EPID/2D orthogonal X-rays, CBCT, CT on rail, optical tracking/surface imaging, and MRI.

- **IGRT practice for children**
  - ❑ Survey of 80 COG member institutions in 2004 – 88% performed portal imaging once per week (Olch et al IJROBP 2004).
  - ❑ Survey of 9 international institutions with dedicated pediatric expertise – IGRT was used daily in 45% and weekly in 35% of pediatric patients. >50% CNS patients had daily IGRT. All photon institutions equip kV CBCT (Alcorn et al PROS 2014).
  - ❑ St. Jude performs daily CBCT for all patients except TBI, TLI and CSI (3mm PTV margin for brain cases, 3-5 mm for body). Higher imaging dose than weekly but allow tighter margins and occasionally detect anatomy changes.



2017 Children Oncology Group IGRT Practice Survey

Received: 5 July 2020 | Revised: 16 June 2020 | Accepted: 19 July 2020

DOI: 10.1002/pbc.28629

Pediatric Blood & Cancer | aspho | WILEY

CLINICAL PRACTICE GUIDELINES

Practice patterns and recommendations for pediatric image-guided radiotherapy: A Children's Oncology Group report

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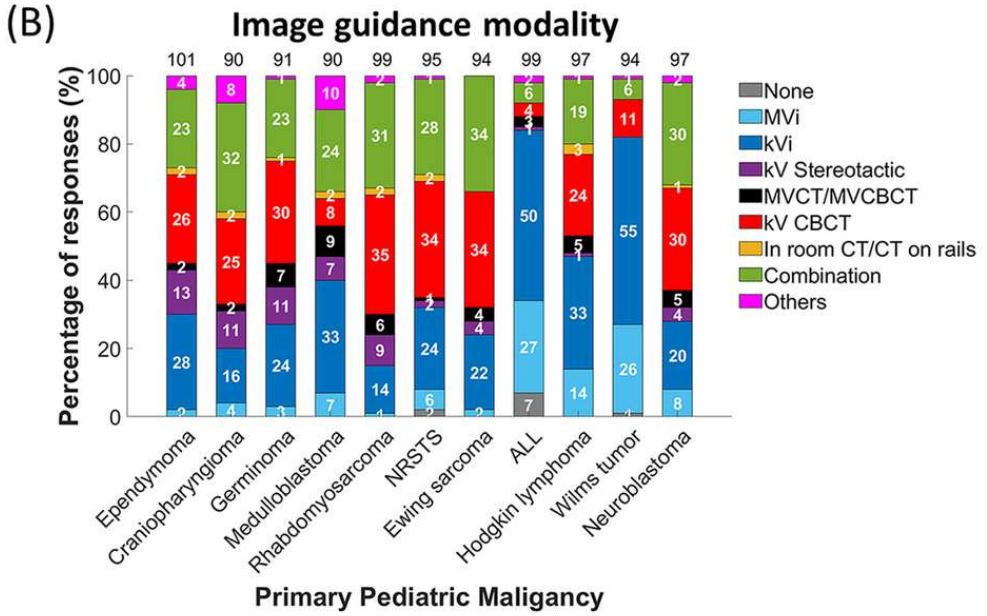
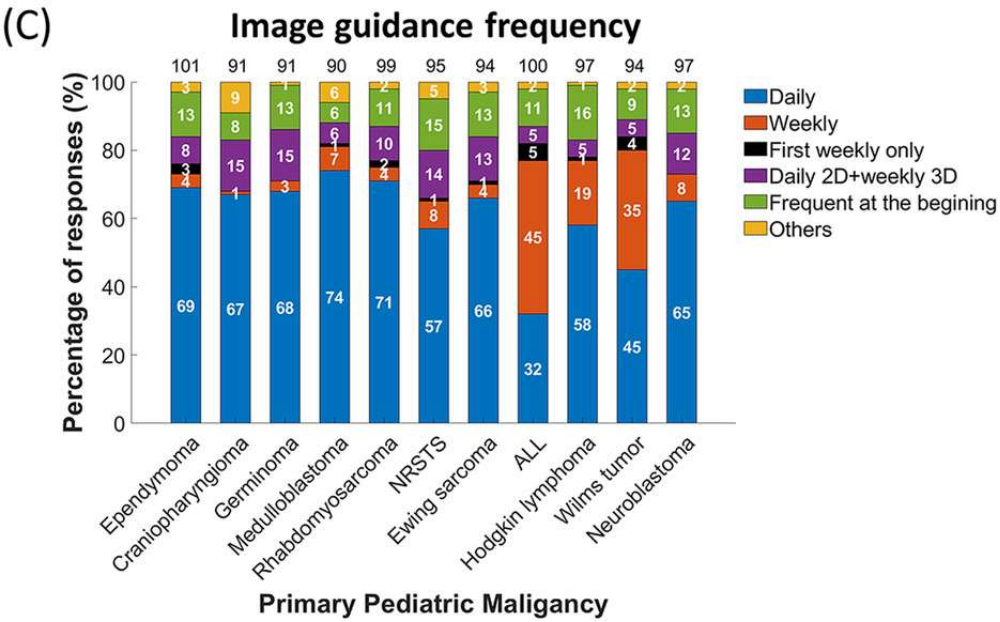




- Survey conducted in 2017
- 168 responses from radiation oncologists or medical physicists
- Daily image guidance is now the majority with CBCT or 2D X-ray

https://pmc.ncbi.nlm.nih.gov/articles/PMC7774502/

2017 Children Oncology Group IGRT Practice Survey

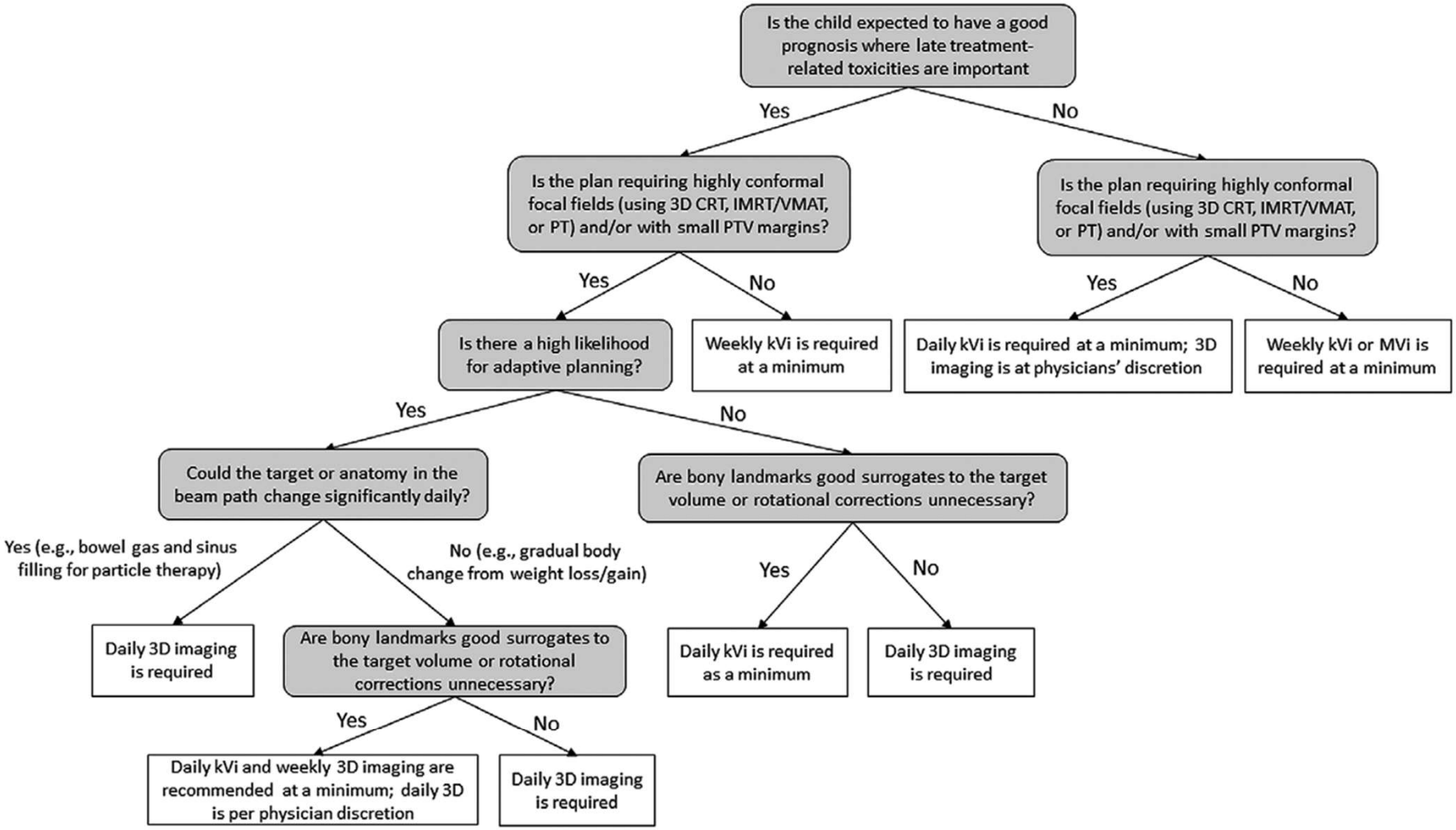


FIGURE 2 Recommended image guidance decision tree for pediatric IGRT

Abbreviations: CRT, conformal radiotherapy; IMRT/VMAT, intensity-modulated radiotherapy/volumetric modulated arc therapy; kVi, kilovoltage imaging; MVi, megavoltage imaging; PT, proton therapy; PTV, planning target volume; 3D, three-dimensional

2017 Children Oncology Group IGRT Practice Survey

TABLE 6 Choose wisely recommendations for pediatric IGRT practice

The following recommendations for wise selection of pediatric IGRT are based on the community practice revealed by the COG survey results, existing evidence, and COG member consensus.

Image guidance modality

- Guiding 2D treatments with 2D kV imaging is generally sufficient without 3D imaging and normally gives a lower imaging dose. These treatments may include whole-brain irradiation for acute lymphocytic/lymphoblastic leukemia, nodal irradiation fields for lymphoma, or flank/whole-abdomen radiotherapy for Wilms tumor.
- 3D imaging is recommended when bony landmarks are not reliable surrogates for tumor positions, when margins are small, or when rotational corrections are needed without the guidance of implanted fiducials.Consider 3D imaging to reduce margins before prioritizing 2D imaging to reduce imaging dose.
- Do not use MV imaging for more than verifying the field shape on the first fraction unless the low-dose setting is adopted. Consider an alternative method of using the light field projection on field shape diagram in advance.
- Be cautious about electron therapy and light field verification without image guidance for superficial tumors such as chest wall sarcoma. The majority of pediatric radiation oncologists favor conformal treatment with image guidance.

Imaging frequency

- Do not rely solely on weekly imaging at the start of 3D CRT, including CSI beam placement. Such practice is uncommon. Consider reducing imaging frequency to weekly only after daily imaging has confirmed stable anatomy.
- Do not reduce the imaging frequency solely in an effort to reduce the imaging dose. The benefits of accurate tumor targeting with reduced margins may outweigh the risk from the imaging dose.
- Minimize repeated imaging in a session to adjust the patient position. Improve patient setup procedures and immobilization devices to minimize multiple exposures.

Imaging dose reduction

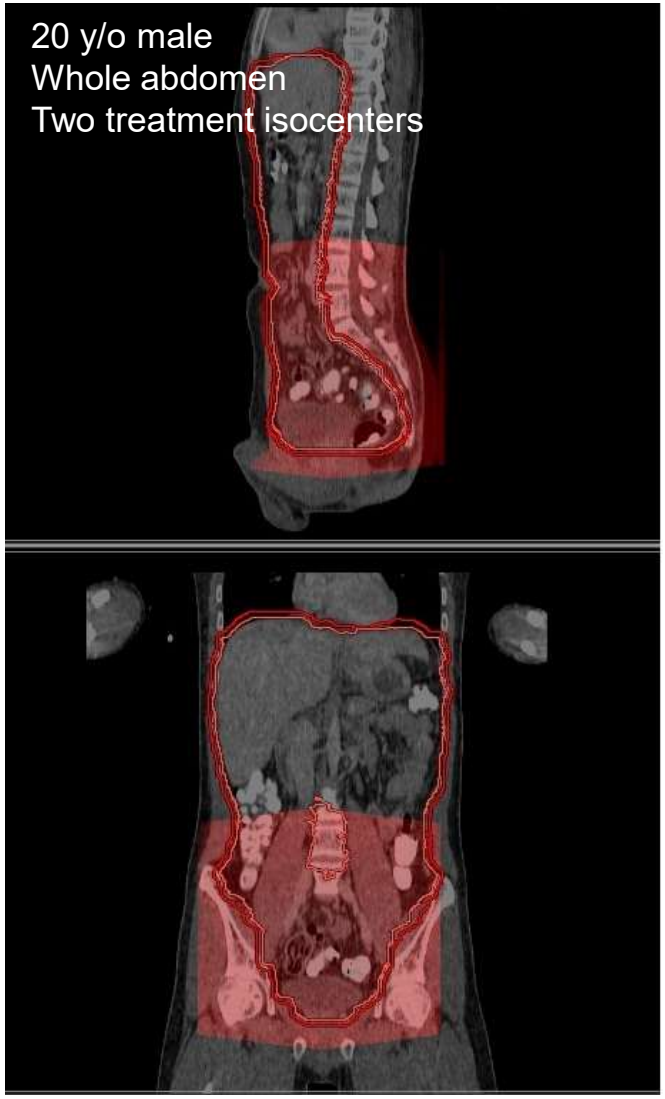
- When both MV and kV imaging are available on the same treatment delivery system, choose kV to reduce imaging dose to patients.
- Use field-limiting devices (e.g., blades, collimators, cassettes) to block radiation-sensitive organs (e.g., lens, thyroid, gonads) if target verification is not compromised.
- When volumetric image guidance is preferred in situations where only bony anatomy is used for registration (e.g., for rotational correction), utilize institutional 3D low-dose image-acquisition techniques. Superior guidance can still be provided without exposing patients to a significantly higher dose than that with 2D X-rays.
- Do not directly apply imaging guidance techniques designed for adults to young children without modifications. If it is not possible to modify technique parameters such as mAs, consider using the vendor's low-dose techniques.
- Consider using non-ionizing position verification methods (e.g., surface imaging or MRI guidance) to replace or supplement ionizing radiation methods whenever possible.

Abbreviations: CNS, central nervous system; COG, Children's Oncology Group; CRT, conformal radiotherapy; CBCT, cone-beam computed tomography; CSI, craniospinal irradiation; IGRT, image-guided radiotherapy; kV, kilovoltage; mAs, milliampere second; MRI, magnetic resonance imaging; MV, megavoltage; RO, radiation oncologist; RT, radiotherapy; 2D, two-dimensional; 3D, three-dimensional.

Image Guidance: Variation in Target Volume and Location

St. Jude example CBCT cases (w Siemens in-line KView CBCT)

As large as whole abdomen



As small as a finger

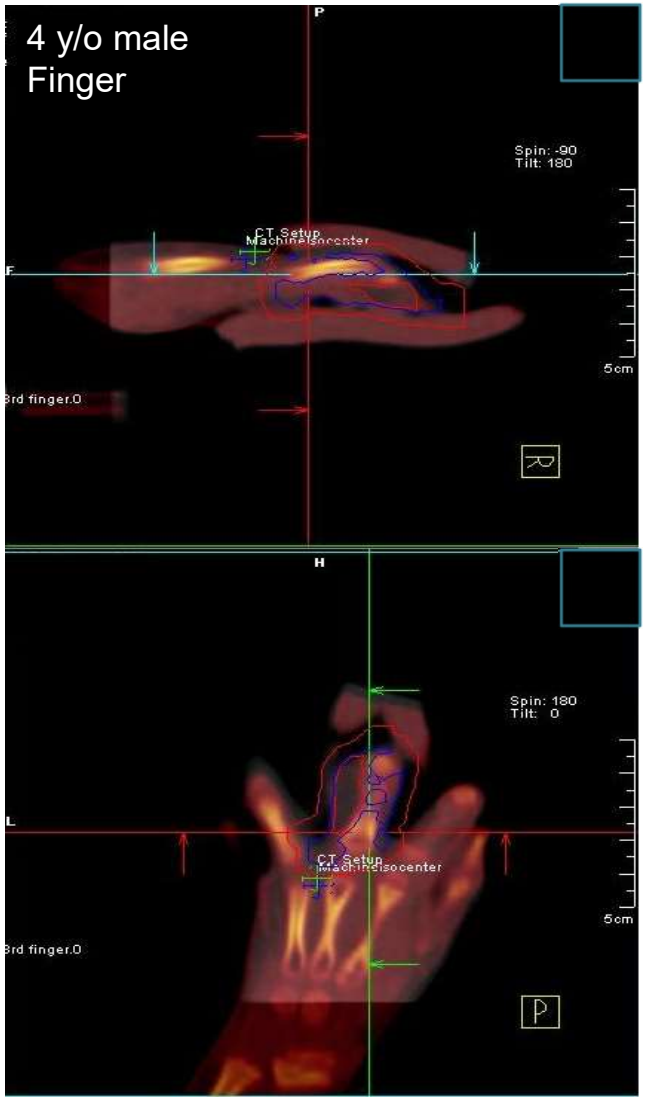


Image Guidance: CBCT Dose Reduction

Dose Reduction Strategies

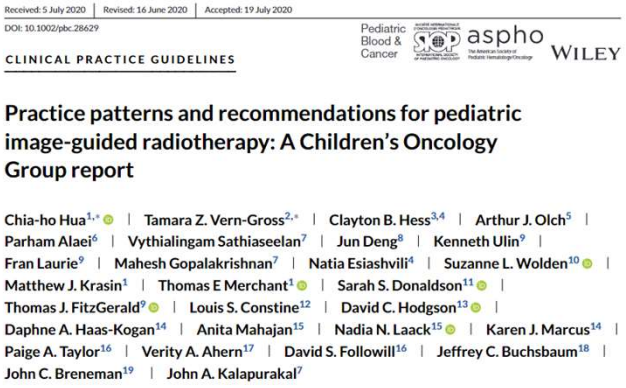
- Reducing the cranio-caudal length of the patient being scanned by adjusting the collimator blades for each individual patient
- Using the X-ray technique that best matches the clinical task – reducing beam current and exposure time per projection for smaller patients
- Selecting the appropriate range of the CBCT projection (e.g., posterior arc) to avoid sensitive structures such as lens
- Low-dose protocols (lower kVp, lower mAs) may be sufficient for verification purposes
- 2D X-ray radiograph may be sufficient for localization in brain tumor patients (e.g., take posterior-anterior X-ray instead of anterior-posterior to reduce doses to lens)

Useful resources

https://aapm.onlinelibrary.wiley.com/doi/epdf/10.1002/mp.12824

2018 AAPM Summer School
Video recording including image guidance overview and guidelines; managing and calculating imaging dose

https://www.aapm.org/education/vl/default.asp?t=byE&e=SS&y=2018

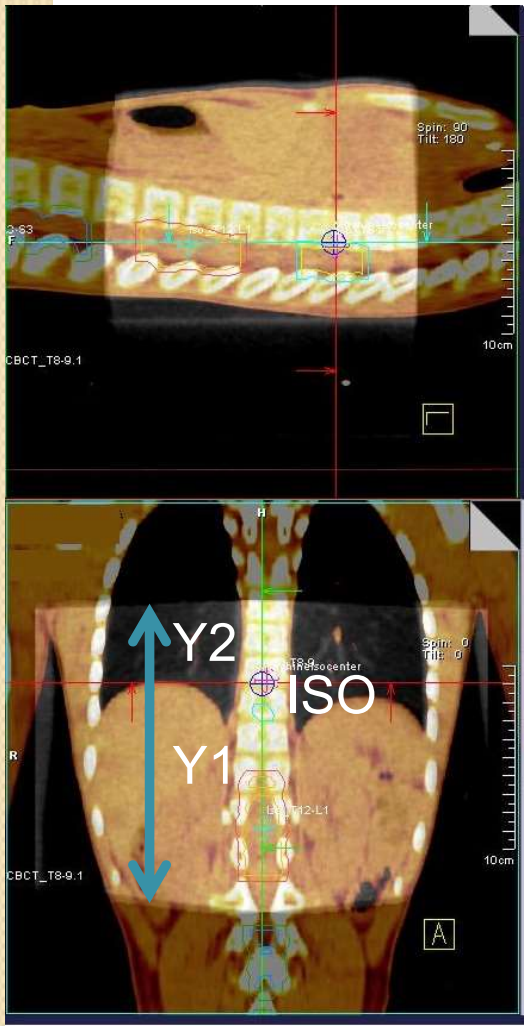


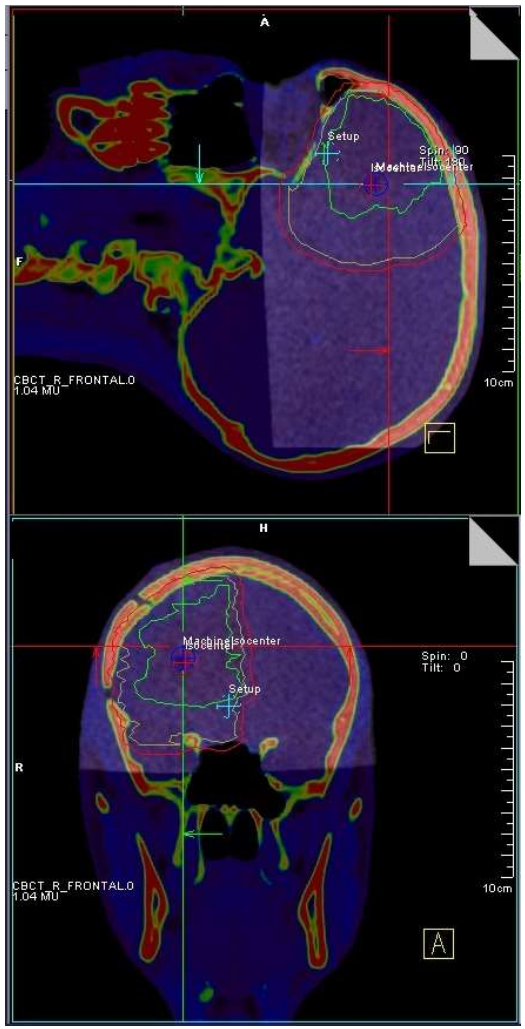
https://pmc.ncbi.nlm.nih.gov/articles/PMC7774502/

Image Guidance: Collimation to Reduce Scan Length and Dose

Longitudinal asymmetric collimation is needed for pediatric CBCT

- To minimize exposure to thyroid, lens, testes, heart, and previously irradiated spinal cord
- To include additional anatomic landmarks (orbit, vertebral body) for improved image registration
- To cover two neighboring targets with one CBCT while using one treatment isocenter as the imaging isocenter





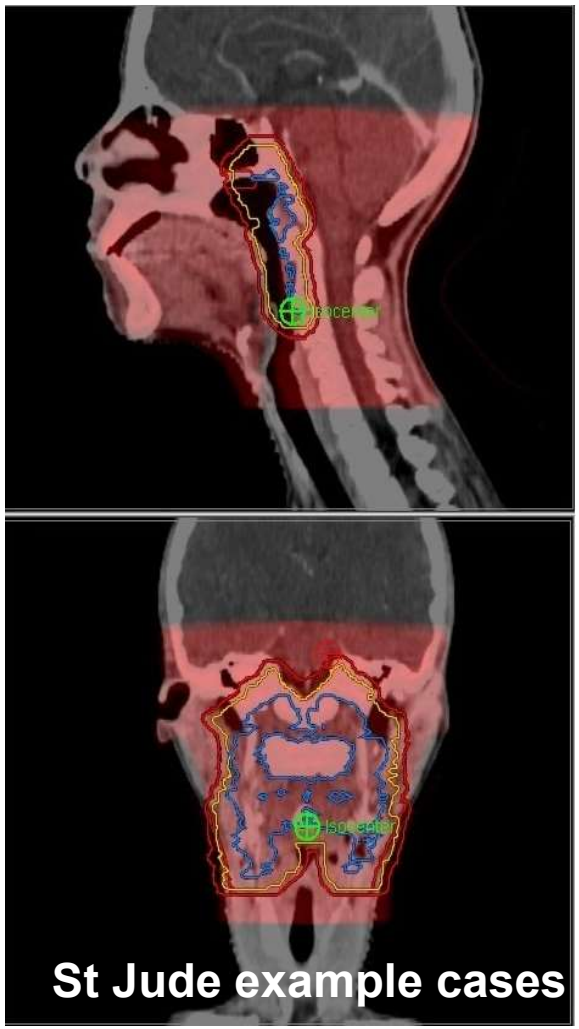
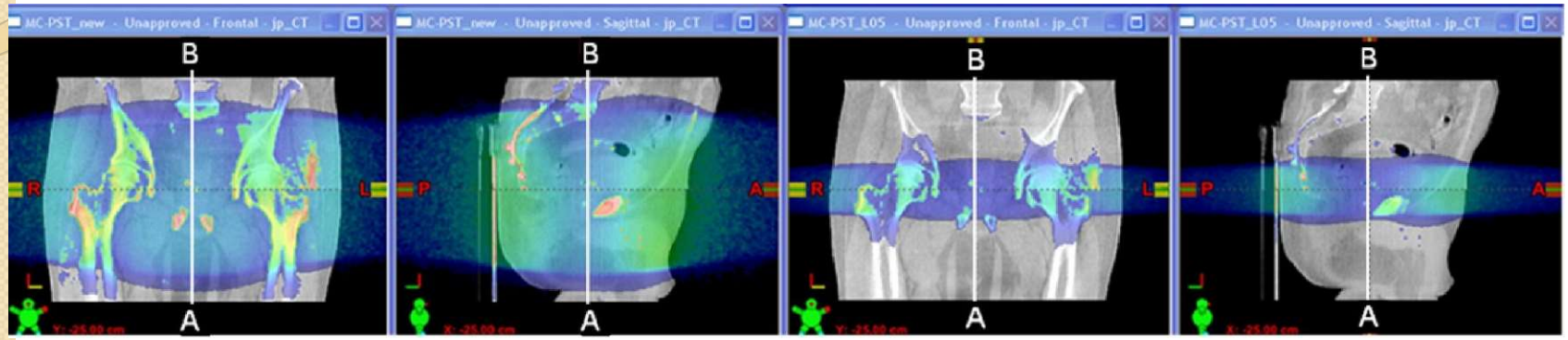
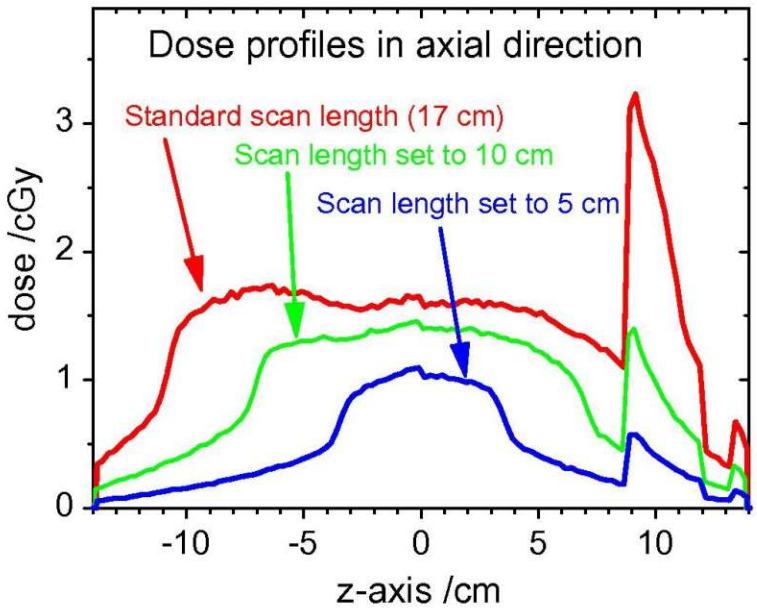


Image Guidance: Collimation to Reduce Scan Length and Dose

Length=16cm

Length=5cm





Ding et al, Radiotherapy and Oncology 2010

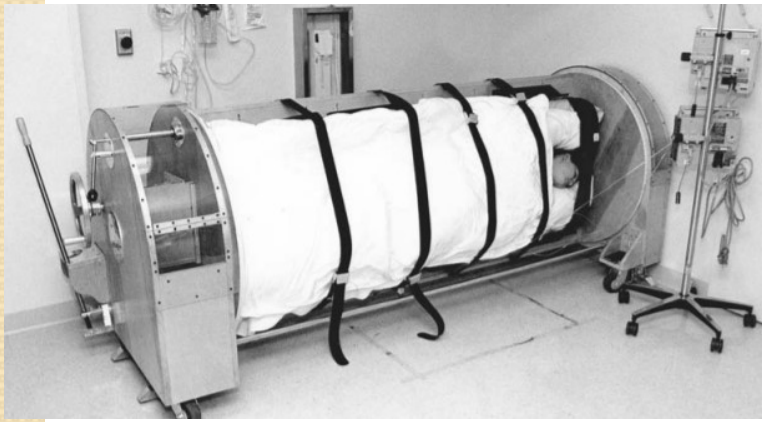
Craniospinal Irradiation (CSI)

- CSI typically consists of irradiating the whole brain and the entire spine in multiple fields with the patient in either supine or prone position. Prone was preferred for direct visualization of light field but supine is becoming the mainstream due to easy airway access, patient comfort, and the advent of image guidance.
- CSI of 18-39.6Gy is mostly delivered to patients with medulloblastoma and selected brain tumors. Coverage of cribriform plate region and sparing of optical lens are important in treatment planning.
- Traditionally CSI was delivered with 3D CRT but VMAT and Tomotherapy have become popular as well as proton therapy. Descriptions and comparisons of different techniques (photon vs. electron, VMAT, Tomotherapy) can be found in these articles and slides.

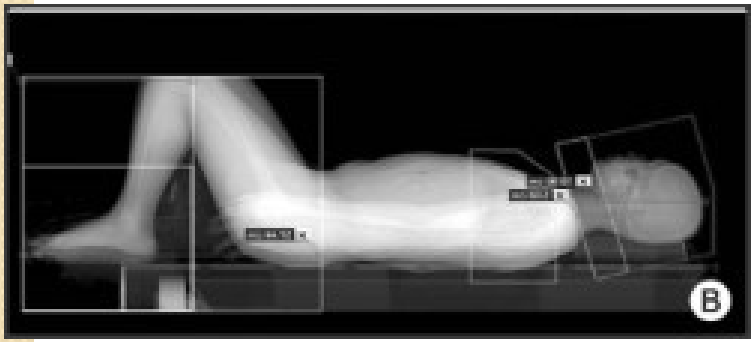
Verma et al (supine vs. prone, MDACC) Prac Radiat Oncol 2015,
Chojnacka et al (electron vs. photon) Rep Pract Oncol Radiother 2010,
Burkeen et al (Johns Hopkins review) ASTRO & ARRO education slides 2014 at https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/MedulloblastomaAJW.pdf
Landry et al (VMAT) medical dosimetry http://pubs.medicaldosimetry.org/pub/2570d6bd-de0a-46fc-9e24-0bac2d38f55e
Myers et al (3D CRT, VMAT, Tomotherapy) Technol Cancer Res Treat 2015
Barra et al (3D CRT vs. Tomotherapy) Tumori 2016
Mesbah et al (Tomotherapy for pediatric RT) Radiat Oncol 2011
Bedford et al (helical VMAT) Int J Radiat Oncol Biol Phys 2012
Hansen et al (noncoplanar IMRT vs. VMAT) Med Dosim 2015

Total Body Irradiation (TBI)

- TBI is mostly given to patients with acute lymphoblastic leukemia (ALL) before stem cell (bone marrow) transplant.
- TBI can be given with patients either standing or lying down on the floor or table. Radiation can be delivered in AP/PA or opposed lateral beams.
- Lungs are the sensitive organs, may or may not be protected with partial transmission blocks.



Rotating TBI bed, St Jude Children's Research Hospital



Park et al. Radiatation Oncology Journal 2014

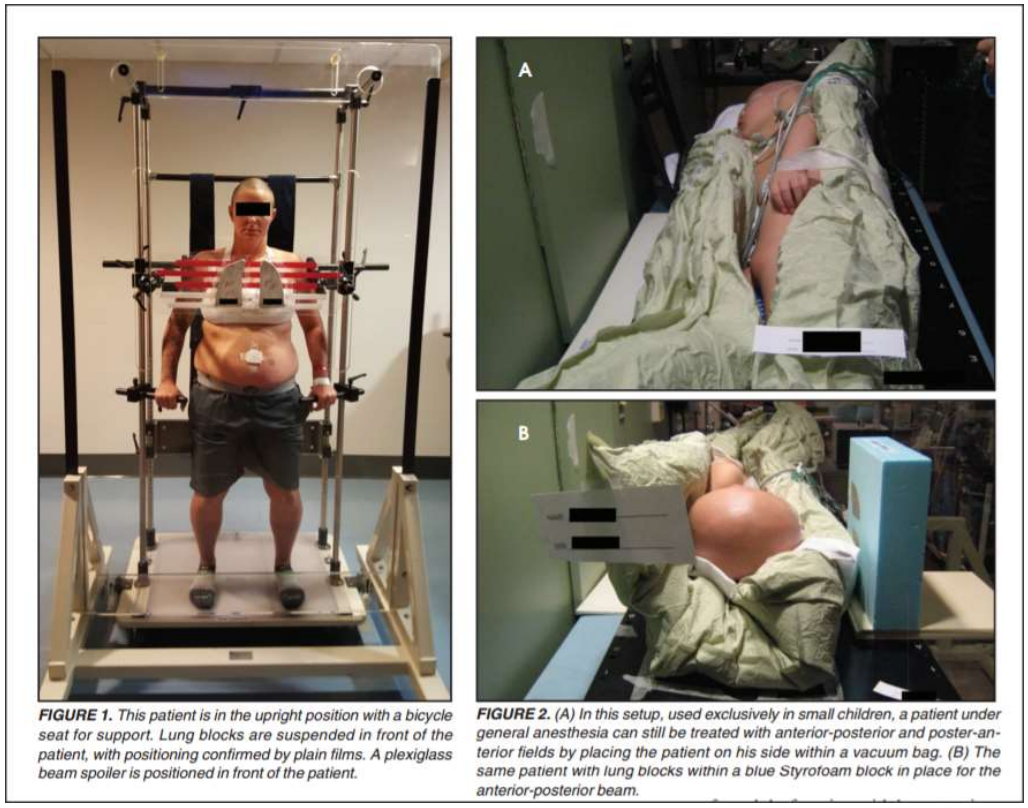


FIGURE 1. *This patient is in the upright position with a bicycle seat for support. Lung blocks are suspended in front of the patient, with positioning confirmed by plain films. A plexiglass beam spoiler is positioned in front of the patient.*

FIGURE 2. *(A) In this setup, used exclusively in small children, a patient under general anesthesia can still be treated with anterior-posterior and poster-anterior fields by placing the patient on his side within a vacuum bag. (B) The same patient with lung blocks within a blue Styrofoam block in place for the anterior-posterior beam.*

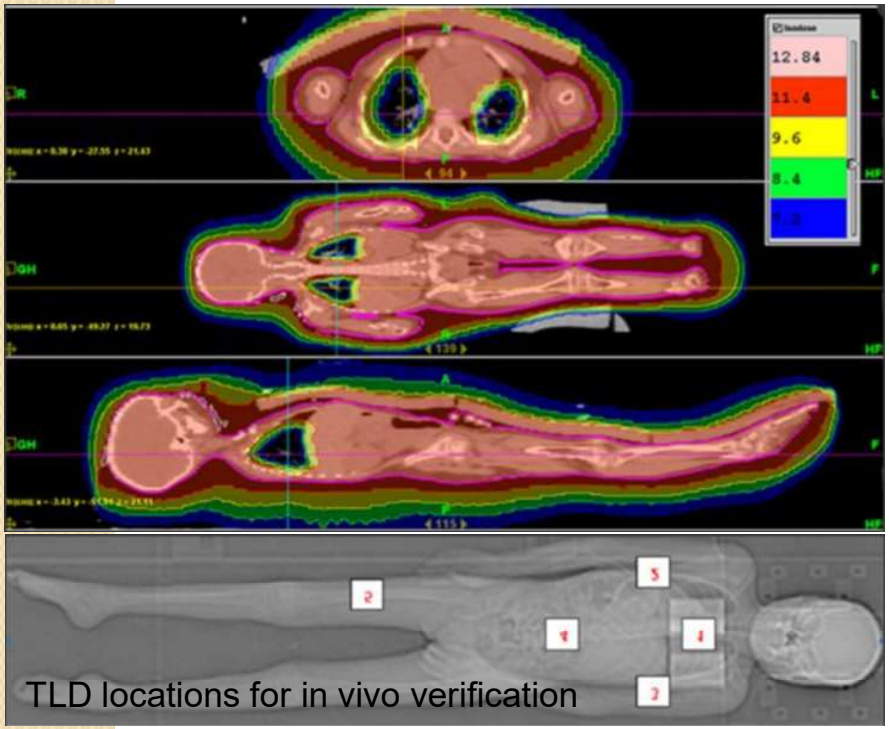
Wills et al, Applied Radiation Oncology, 2016

Total Body Irradiation (Tomo-TBI)

Although TBI has been traditionally delivered in children and young adults with linacs, Tomotherapy (helical mode or static mode) or VMAT is another viable option.

Helical Tomotherapy

Supine position, head support and vacuum cradle
CT head-toe, planning structures of reduced body and lung volumes
Constraints: 95% PTV by 95% of prescribed dose (12Gy)
Constraints: mean lung dose <10Gy and Dmin=8Gy
Ion chamber and TLD measurements for QA
Pre-treatment MVCTs for image guidance

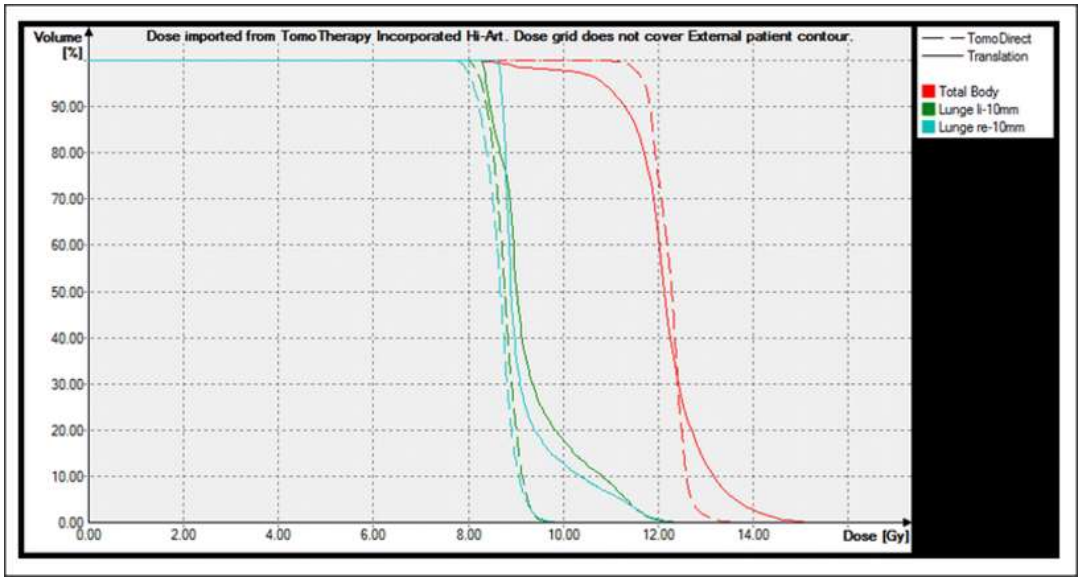


TLD locations for in vivo verification

Gruen et al. Radiat Oncol, 2013:8:92

Static Tomotherapy (TomoDirect)

Supine position, vacuum cushion
CT planning
PTV=body without 5mm skin
If having to split treatment into two parts, an overlap region is created with a gradual dose gradient
Constraints: median lung dose <9Gy and V8Gy>90%
TLD and Delta4 phantom measurements for QA
Pre-treatment MVCTs for image guidance



Higher homogeneity in target and lower max dose in lungs when compared to conventional translational methods with lung blocks.

Salz et al. Radiat Oncol, 2015:10:58

Total Body Irradiation (VMAT-TBI)

UT Southwestern field arrangement and planning objectives

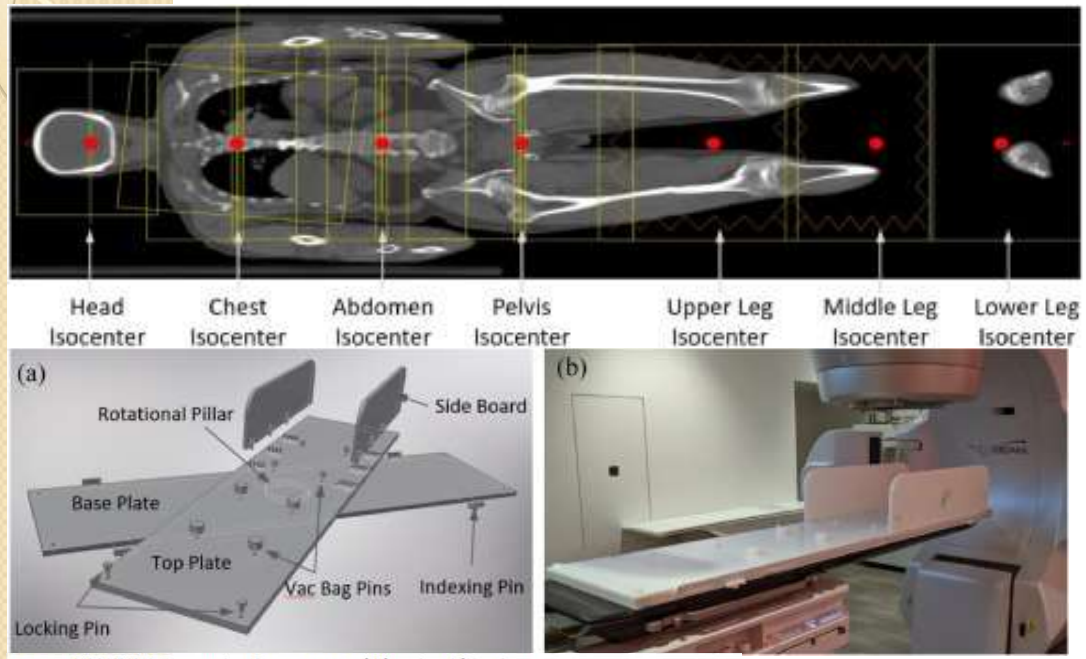
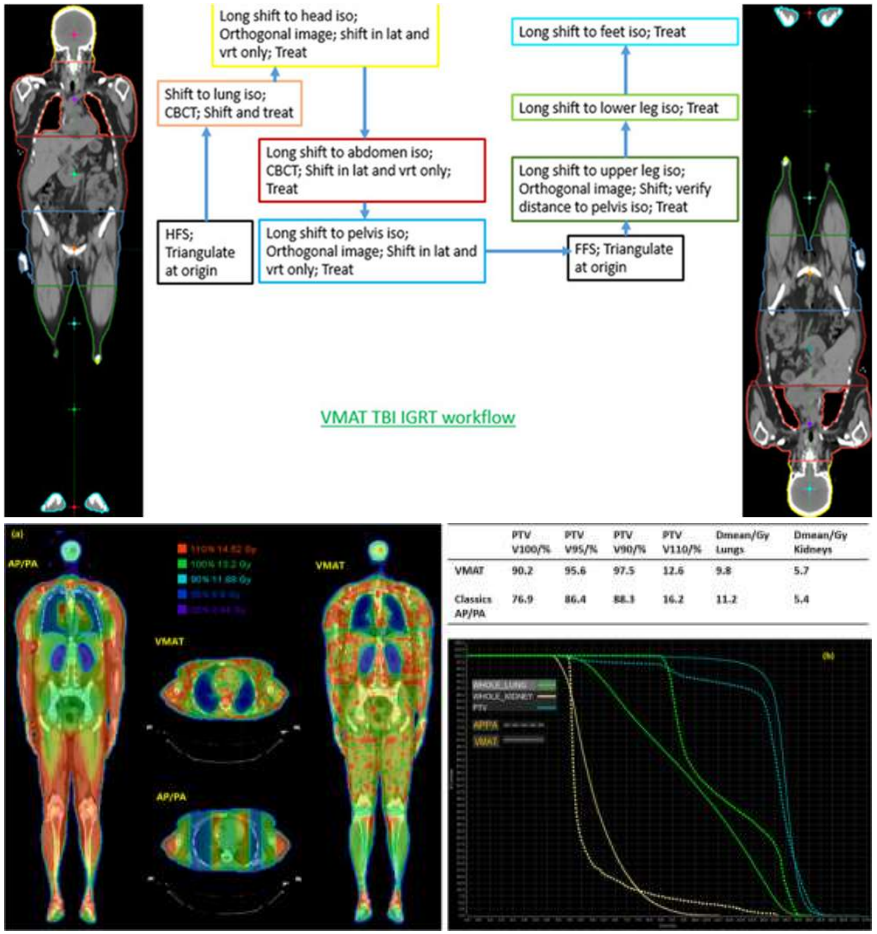


Table 2. VMAT-TBI Contouring Structures and Planning Objectives

Structure	DVH metric	Objective	Notes
PTV	V_{Rx}	> 90%	PTV is defined as the body with a 5mm contraction and the lungs subtracted
Lungs	Mean	75% Rx (low-dose cohort) 75%-50% Rx (standard–dose cohort)	Lungs is defined as 1 cm contraction from the lungs. Standard-dose cohort started with 75% Rx in first three years and gradually lowered to 67-50% Rx in later years.
Spinal Cord	D_{max}	< 125% Rx	As homogenous as possible
Bowel	D_{max}	< 125% Rx	
Kidney (individual)	Mean	< 108% Rx	
Oral Cavity	D_{max}	< 125% Rx	
Whole Brain	D_{max}	< 125% Rx	

Zhang-Velten et al. Transplant Cell Ther, 2022:28(2):e1-113

Cleveland Clinic workflow and dosimetry



- VMAT for the body and AP/PA for legs/feet
- Treatment time ~1 hr/fraction
- VMAT-TBI improves target coverage and reduces lung dose

Guo et al. JACMP, 2021:22(10):169-177

Technical Variations in Pediatric TBI within 88 US institutions

COG Radiation Oncology Discipline conducted pediatric TBI practice survey in 2020; 88 of 152 COG member institutions responded; large variations in technical practice was found

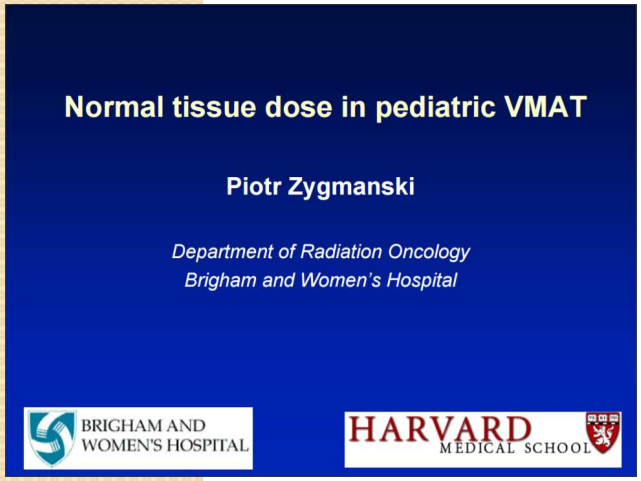
Key findings:

	AP/PA	Lateral
Energy, MV	6 (79%), 10 (15%), 15 (13%)	6 (51%), 10 (12%), 15 (23%)
Positioning	supine+prone 42%, decubitus 40%	Supine only 67%, sitting up 31%
Technique	AP/PA 56%, lateral 50%, VMAT/Tomo 16%	
Treatment distance, cm	401-500 (39%), 201-300 (20%)	401-500 (47%), 301-400 (33%)
Dose rate, cGy/min	Mostly 6-10 followed by 11-15	
Spoiler thickness, cm	0.6-1 (47%), 1.1-1.5 (24%)	0.1-1.0 (39%), 1.1-1.5 (27%)
Lung block frequency	Every fraction 56%	No lung blocks 77%
Compensator	None, H&N, legs, and/or chest	Legs, H&N, chest, and/or arms
Measurements	Caliper >> CT	
MU calculation	Hand calc or spread sheet >> TPS	
Lung dose determination	Rx × percentage transmission or chest CT to calculate mid/mean lung dose	
Dose verification	Head, neck, lung, umbilicus, hip, and/or leg	
Verification detector	OSLD > diose > MOSFET > TLD	
Lung block verification	DR > film > CR	CR > film > DR

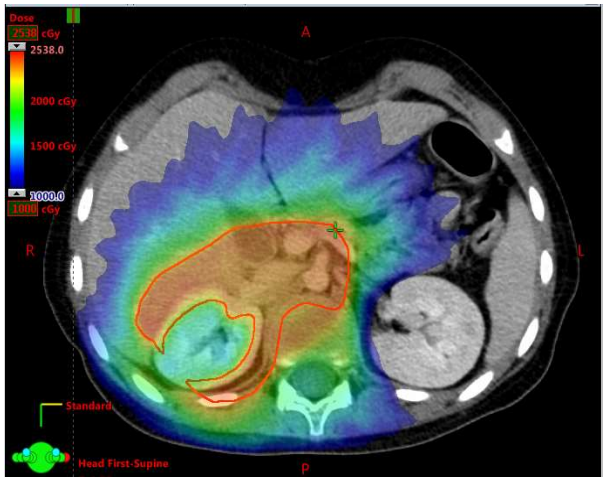
New COG protocols with a TBI component require participating institutions to be TBI credentialed (including irradiation of IROC pediatric TBI phantom). https://irochouston.mdanderson.org/

VMAT for Pediatric Patients

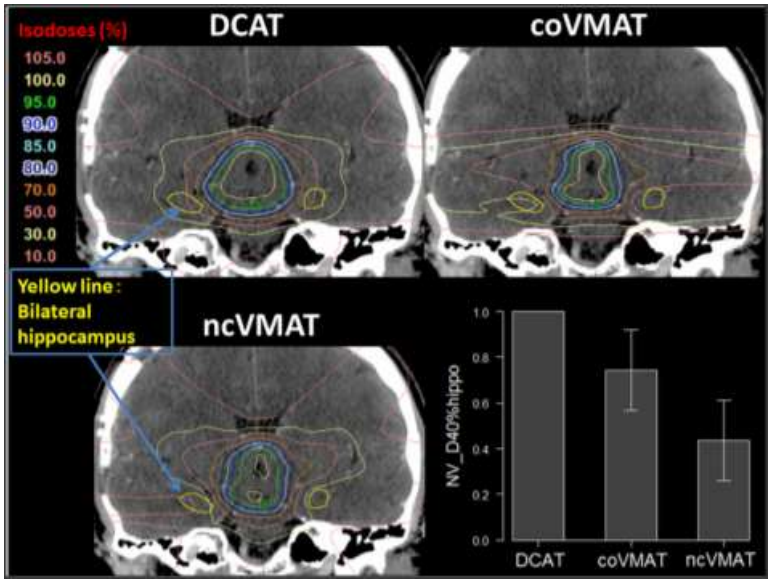
- VMAT (rotational therapy) is a variant of IMRT.
- Non-rotational IMRT and VMAT have been routinely used to treat complex pediatric tumors.
- Reported advantages of VMAT are the reduced treatment MU and time when compared to IMRT delivered with multi-fields with MLC. Long-term effect of low dose bath is often the concern in pediatric patients.
- VMAT has been applied to many pediatric tumors, including tumors in CNS, thorax, extremity, total marrow irradiation, and CSI.



http://chapter.aapm.org/NE/DOCUMENTS/Presentations/2010WinterMeeting/VMAT_NEAAPM_2010.pdf



Example kidney-sparing neuroblastoma RT with VMAT, <25% of kidney receiving >18Gy, courtesy of Dr. Olch at CHLA



Noncoplanar VMAT can achieve better bilateral hippocampal sparing than coplanar VMAT and dynamic conformal arc. Uto et al, Radiat Oncol 2016

Second Cancer Risk with IMRT and VMAT

JAMA Oncology | Brief Report

Comparing Risk for Second Primary Cancers After Intensity-Modulated vs 3-Dimensional Conformal Radiation Therapy for Prostate Cancer, 2002-2015

Kishan J. Pithadia, BS; Pragati G. Advani, MD, DrPH; Deborah E. Citrin, MD; Justin E. Bekelman, MD; Diana R. Withrow, PhD; Amy Berrington de Gonzalez, DPhil; Lindsay M. Morton, PhD; Sara J. Schonfeld, PhD

(Survivor outcomes) IMRT for prostate cancer is not associated with an increased risk of second primary cancers, either solid or hematologic, when compared to 3D CRT, based on SEER data of cancer survivors.

Clinical and Translational Oncology (2023) 25:1368–1377
https://doi.org/10.1007/s12094-022-03034-z

RESEARCH ARTICLE

Predicted cardiac and second cancer risks for patients undergoing VMAT for mediastinal Hodgkin lymphoma

Orla A. Houlihan[1,8] · Georgios Ntentas[2,3,4] · David J. Cutter[2,5] · Patricia Daly[1,6,7] · Charles Gillham[1,6,7] · Orla McArdle[1] · Frances K. Duane[1,6,7]

Received: 6 October 2022 / Accepted: 29 November 2022 / Published online: 31 December 2022

(Estimation from 44 HL treatment plans using prior survivorship models) For patients with mediastinal lymphoma excess mortality risks from cardiovascular disease and second cancers remain clinically significant despite contemporary chemotherapy and photon-RT. Efforts to reduce the toxicity of combined modality treatment should be continued to further reduce potentially fatal treatment effects.

Cancer
An International Interdisciplinary Journal of the American Cancer Society

Original Article | Free Access

Second cancer risk after primary cancer treatment with three-dimensional conformal, intensity-modulated, or proton beam radiation therapy

Michael Xiang MD, PhD, Daniel T. Chang MD, Erqi L. Pollom MD, MS

First published: 19 May 2020 | https://doi.org/10.1002/cncr.32938 | Citations: 111

(National Cancer database) The risk of a second cancer diagnosis was similar after IMRT versus 3DCRT for 9 tumor types, whereas PBRT was associated with a lower risk.

MEDICAL PHYSICS
The International Journal of Medical Physics Research and Practice

RESEARCH ARTICLE | Full Access

Out-of-field doses in pediatric craniospinal irradiations with 3D-CRT, VMAT, and scanning proton radiotherapy: A phantom study

Marija Majer, Iva Ambrožová, Marie Davídková, Marijke De Saint-Hubert, Mladen Kasabašić, Željka Knežević, Renata Kopeć, Dawid Krzempek, Katarzyna Krzempek ... See all authors

First published: 28 January 2022 | https://doi.org/10.1002/mp.15493 | Citations: 8

PBS is the most promising technique for out-of-field dose reduction in comparison to photon techniques. Among photon techniques, VMAT is a preferred choice for most of out-of-field organs and especially for the thyroid, while doses for eyes, breasts, and lungs are lower for 3D-CRT.

Second Cancer Risk with IMRT and VMAT

Asian Pac J Cancer Prev. 2017;18(7):1897–1903. doi: 10.22034/APJCP.2017.18.7.1897

Radiation-Induced Second Cancer Risk from External Beam Photon Radiotherapy for Head and Neck Cancer: Impact on in-Field and Out-of-Field Organs

Vasanthan Sakthivel [1,3,*], Ganesh Kadirampatti Mani [1,2], Sunil Mani [3], Raghavendiran Boopathy [3]

(Estimated risk using LAR model) VMAT provides better OAR sparing than 7-9 field IMRT. Organ-specific lifetime attribute risk (LAR) is lower with VMAT except for skin and soft tissues. Excess absolute risk (EAR) based on all organs: 10MV IMRT > 6MV VMAT > 6MV IMRT.

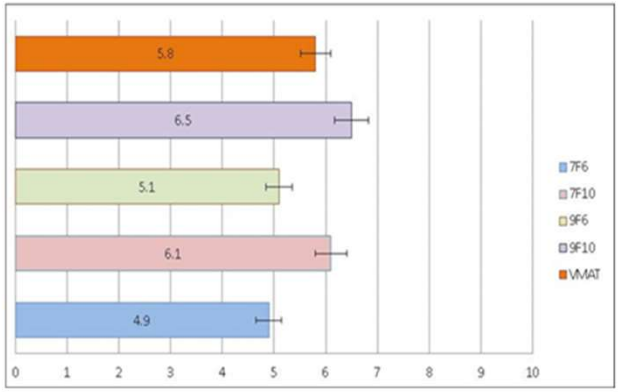


Figure 3. EAR Based on All Organs Studied (per 10,000 person-Year)

Average LAR as a Function of Organ and Age at Exposure (Yr) for the Five Patients Considered

	Organ	7F6	7F10	9F6	9F10	VMAT
LAR (%/MU)	Brain	2.21E-05	2.61E-05	2.45E-05	2.81E-05	1.81E-05
	Brainstem	2.62E-05	3.18E-05	2.87E-05	4.02E-05	1.92E-05
	Soft tissue	1.74E-05	2.75E-05	1.90E-05	2.71E-05	2.74E-05
	Skin	1.85E-05	1.94E-05	2.15E-05	2.15E-05	2.85E-05
	Cord	2.18E-05	2.21E-05	2.70E-05	2.78E-05	1.78E-05
	Bone	2.32E-05	2.41E-05	2.49E-05	2.60E-05	1.82E-05
	Mandible	2.72E-05	3.12E-05	3.87E-05	4.02E-05	2.82E-05
	Esophagus	1.72E-05	3.07E-05	1.51E-05	3.12E-05	1.62E-05
	Lungs	6.20E-06	5.10E-06	6.11E-06	7.20E-06	4.20E-06
	Stomach	5.21E-06	4.51E-06	4.21E-06	6.51E-06	3.21E-06
	Bowel	2.02E-07	1.72E-07	2.77E-07	3.92E-07	3.02E-07
	Bladder	1.02E-07	2.14E-07	1.11E-07	2.17E-07	2.06E-07

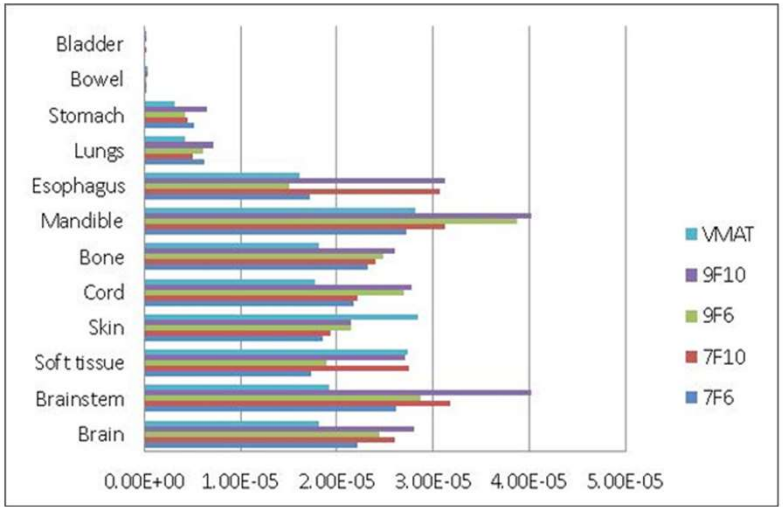


Figure 4. Estimates of LARs of Cancer Incidence (%)

Second Cancer Risk with IMRT and VMAT

Australasian Physical & Engineering Sciences in Medicine (2019) 42:201–209
https://doi.org/10.1007/s13246-019-00731-y

SCIENTIFIC PAPER

Second malignant neoplasm risk after craniospinal irradiation in X-ray-based techniques compared to proton therapy

Vasanthan Sakthivel[1,2] · Kadirampatti M. Ganesh[2,3] · Craig McKenzie[4,5] · Raghavendiran Boopathy[1] · Jothybasu Selvaraj[6,7]

Received: 11 July 2018 / Accepted: 24 January 2019 / Published online: 6 February 2019

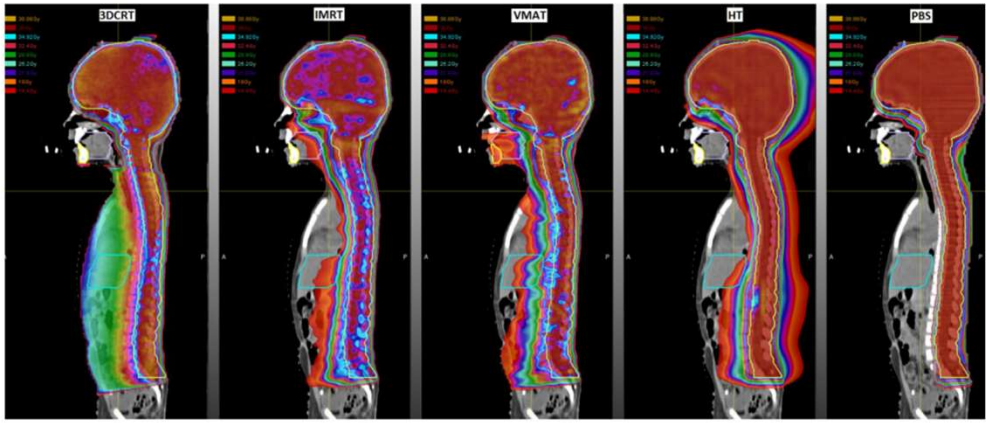
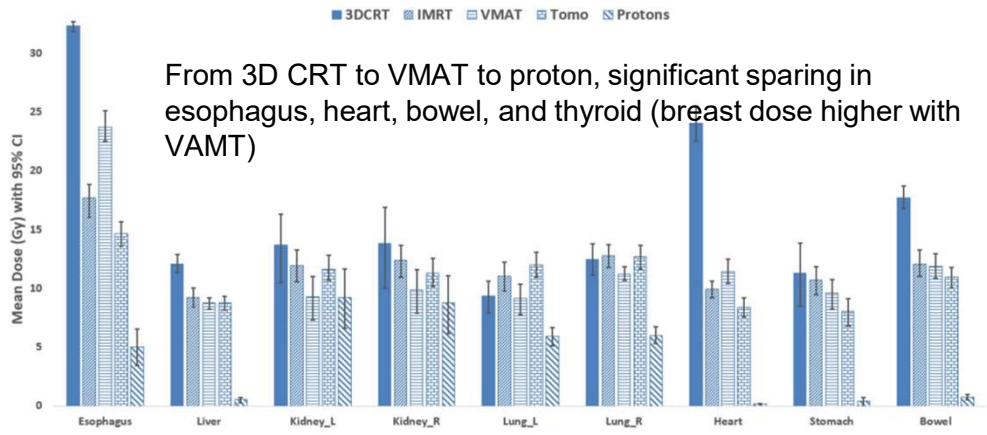


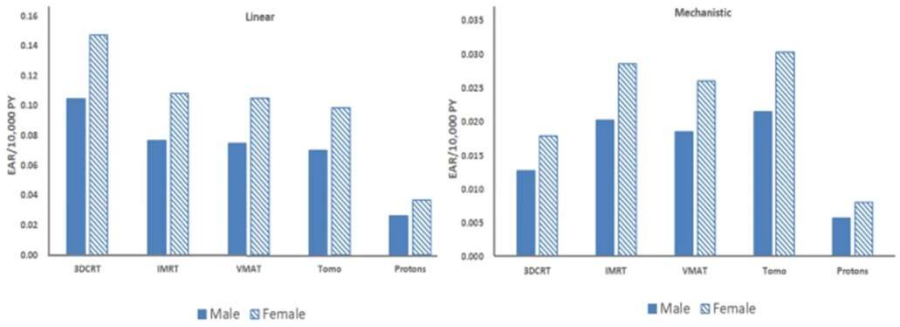
Fig. 1 Dose wash comparison of 3DCRT, IMRT, VMAT, HT and pencil beam scanning PBT. Color wash shown above 50% of the prescription dose (irradiated volume)



From 3D CRT to VMAT to proton, significant sparing in esophagus, heart, bowel, and thyroid (breast dose higher with VAMT)

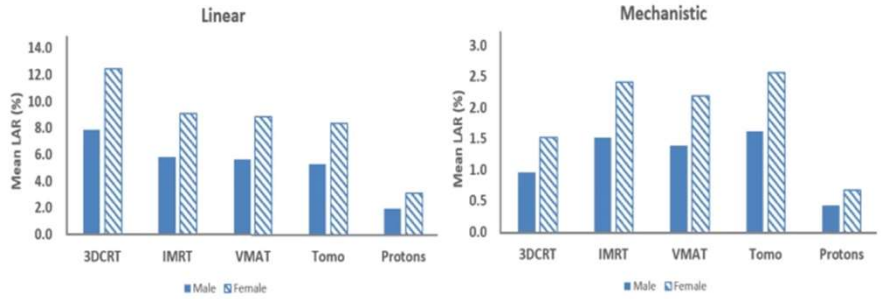
Fig. 3 Mean doses and 95% confidence intervals calculated for organs-at-risk for cranio-spinal irradiation treatment plans planned with 3DCRT, IMRT, VMAT, Tomotherapy and Proton beam therapy

Fig. 5



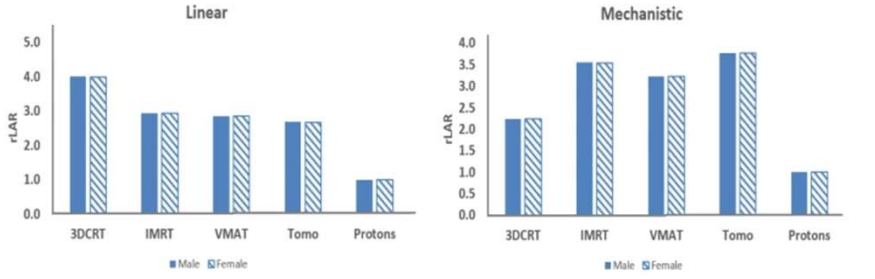
Mean EAR for male and female patients for the linear and mechanistic model

Fig. 6



The mean LAR for various techniques with the linear and the mechanistic model

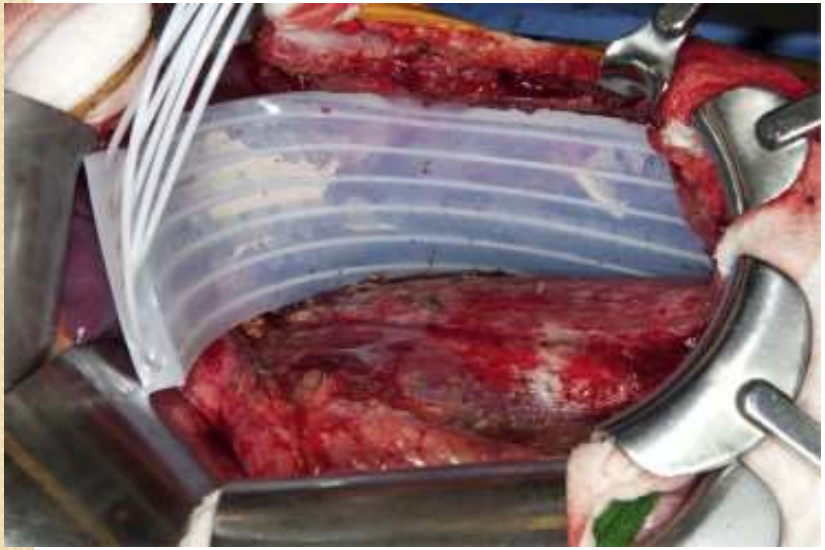
Fig. 7



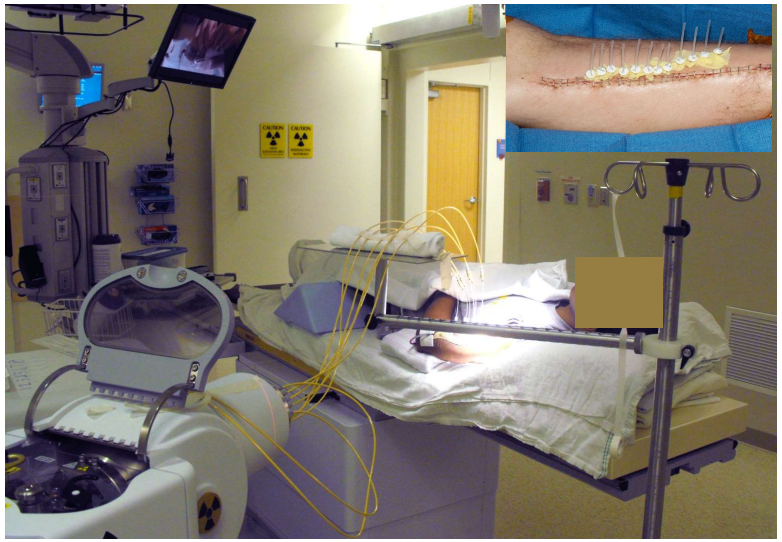
Relative LAR (rLAR) for various techniques with the linear and the mechanistic model

Pediatric Brachytherapy

- Soft tissue sarcoma – HDR with interstitial catheters (multiple fractions) or IORT with HAM applicator on tumor bed after surgical resection (single fraction)
- Retinoblastoma – episcleral plaque brachytherapy with I-125 or Pd-103
- Neuroblastoma – EBRT is mainstay but HDR-IORT has been performed
- Brain tumors – EBRT is mainstay but intracavitary brachytherapy with P-32 has been performed for craniopharyngioma and I-125 for low grade glioma



MSKCC HDR+HAM applicator, Folkert et al, IJROBP, 2014



St Jude sarcoma HDR treatment setup with interstitial catheters

Relevant publications: HDR-IORT techniques and planning for pediatric sarcoma – please see Folkert et al, IJROBP 2014
ABS consensus guidelines for retinoblastoma plaque brachytherapy – Brachytherapy 13(1), 2014
RT for retinoblastoma MDACC experience – Agarwal et al, IJPT, March 2016
Chapter of pediatric brachytherapy in the book "Brachytherapy, 2nd edition, applications and techniques"

Summary for Pediatric Photon Therapy

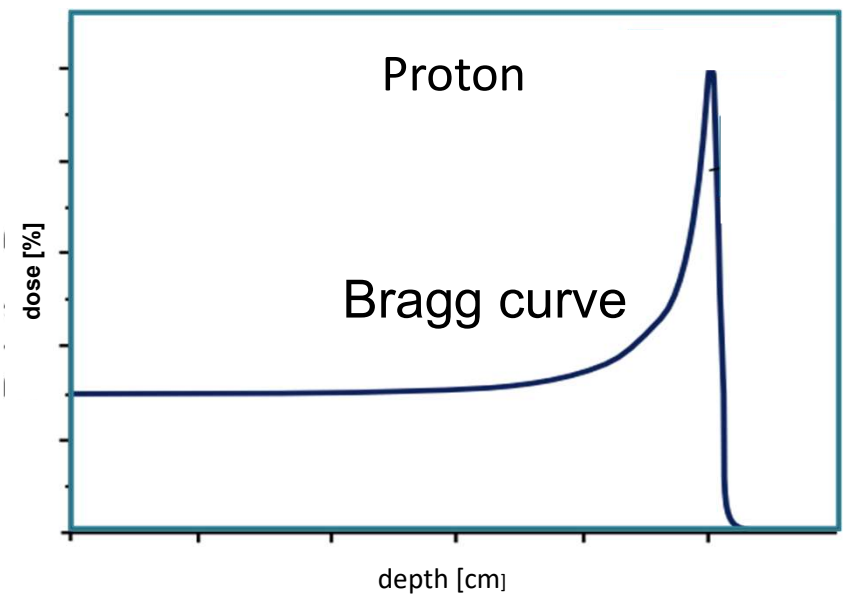
- CT and MR simulation for pediatric patients should tailor CT scan protocols and MR pulse sequences to different anatomical sites and patient size.
- Efforts to reduce radiation exposure from CT Sim and CBCT imaging should be made.
- Daily image guidance is a common practice for most pediatric radiotherapy.
- Radiotherapy guidelines in clinical trials are currently the best resources for setting normal tissue planning constraints for children enrolled in those trials. PENTEC reports were published in Int J Radiat Oncol Phys in 2024 for guidance on normal tissue protection in pediatric radiotherapy planning.
- New delivery techniques have been applied for pediatric malignancies with complex shapes, such as Tomotherapy and VMAT for craniospinal irradiation and total body irradiation.

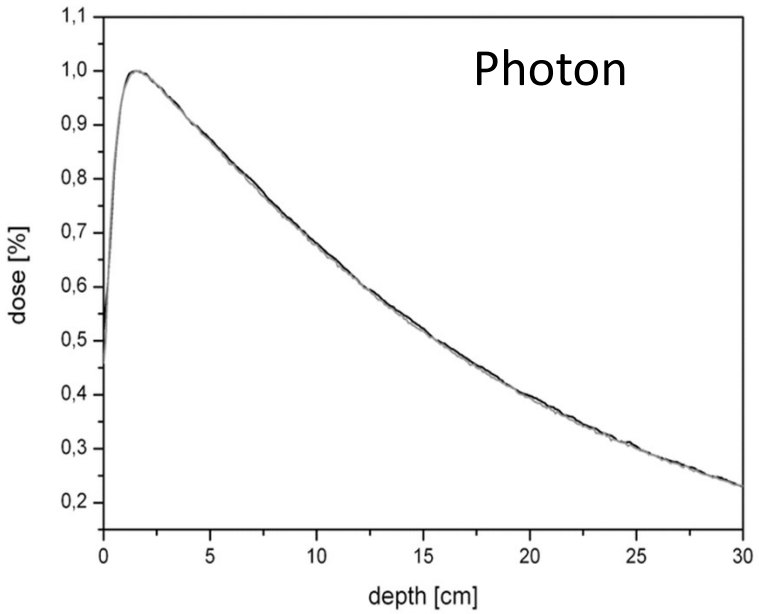
Pediatric Proton Therapy Physics

Outline for Pediatric Proton Therapy

1. General proton therapy physics
2. Scanning beams vs. scatter beams
3. Proton therapy facilities
4. Volumetric image guidance for proton therapy
5. Pediatric proton therapy: patterns of care
6. Proton dosimetric advantages and predictions of radiation necrosis and second cancer risk
7. Challenges in pediatric proton therapy
8. Proton techniques for pediatric CSI
9. Proton techniques for pediatric Hodgkin lymphoma
10. Controversy on brainstem necrosis in children
11. Bowel gas, metal artifact, beam hardening
12. Summary

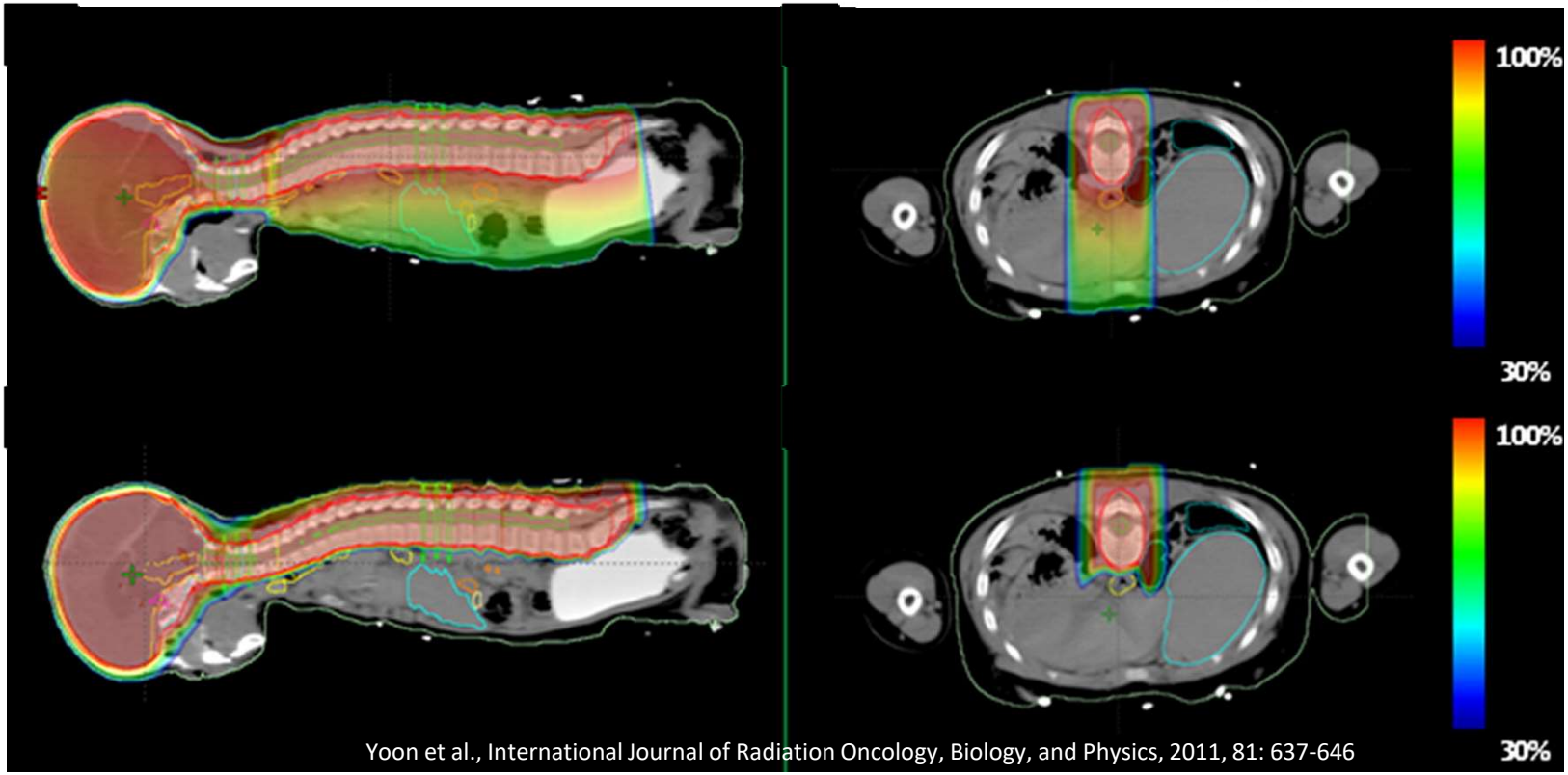
General Proton Therapy Physics





Photon

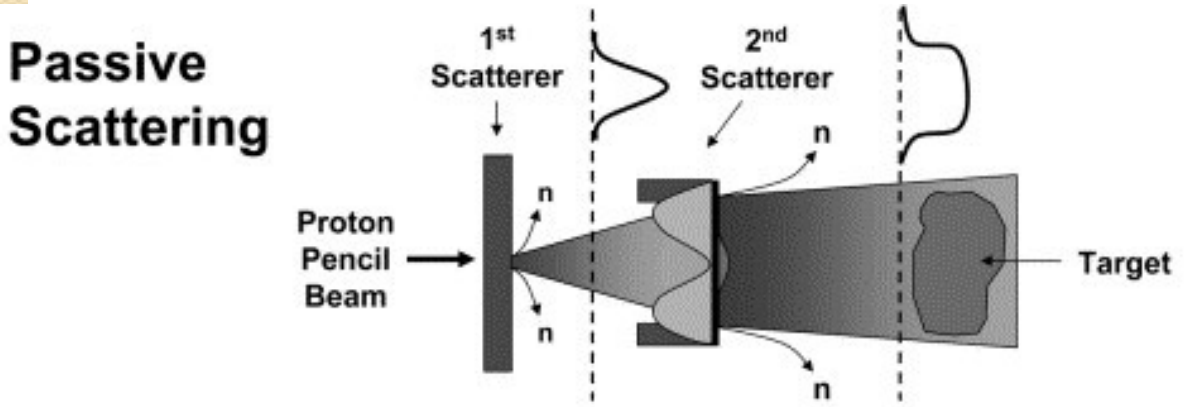
Proton



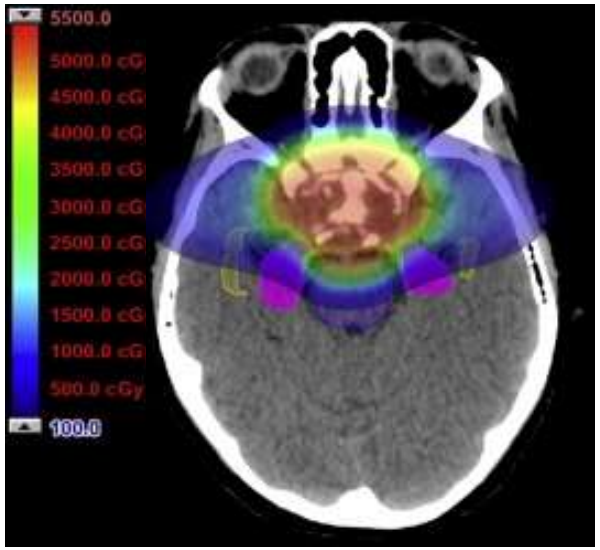
Yoon et al., International Journal of Radiation Oncology, Biology, and Physics, 2011, 81: 637-646

Two Types of Proton Beam Delivery Nozzles (Scattering vs. Scanning)

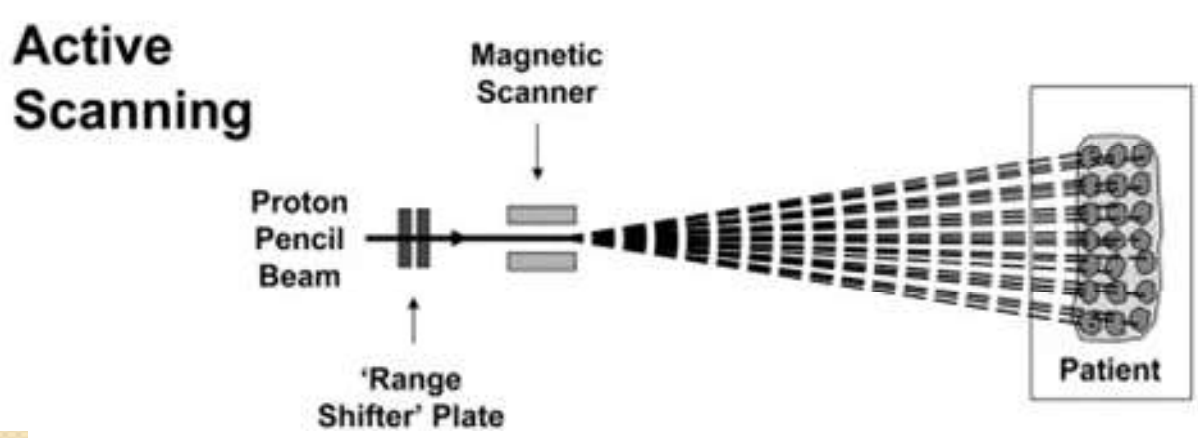
Passive scattering is the traditional technology.



3D conformal proton plan



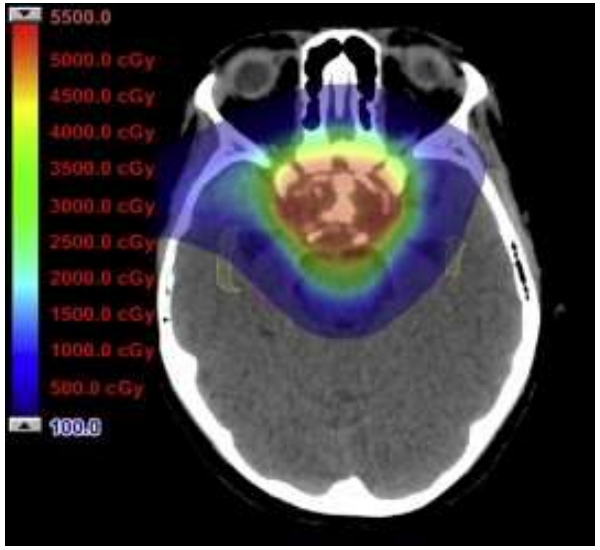
State of the art technology is scanning beam.



Source: Hall, IJROBP 2006 vol 65

(a.k.a. pencil beam scanning, spot scanning)

Intensity modulated proton plan



Source: Boehling et al, IJROBP 2012 vol 82

Proton Therapy Facilities

HITACHI

National Cancer Center Japan, MD Anderson,
Nagoya City Hospital, Hokkaido University,
Mayo Clinic, St. Jude Children's Research Hospital ,
Johns Hopkins, etc

IBA

MGH, U Florida, Procure, U Penn, Indiana, Hampton U,
Korean NCC, Wanjie, WPE, PTC Czech, Apollo PTC, etc

Varian (former ACCEL)

California Protons Cancer Therapy Center,
PSI (by ACCEL), Maryland PTC, Emory Univ,
New York Proton Center, etc

Sumitomo

National Cancer Center Japan
Aizawa hospital Japan, Chang Gung hospital Taiwan
Sansung medical center Korea

Optivus

Mevion

MITSUBISHI

ProTom

ProNova

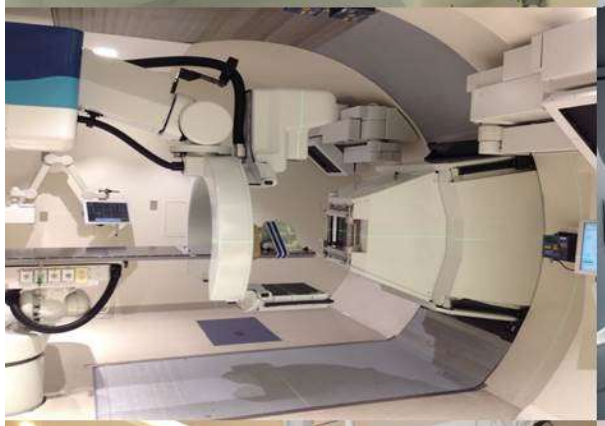
Volumetric image guidance for proton therapy

Used to rely on 2D orthogonal imaging for verifying patient positions. But the era of volumetric image guidance with CBCT and CT-on-rails has arrived.

Gantry mounted CBCT

Nozzle mounted CBCT

C-arm mounted CBCT



In-room CT on rails

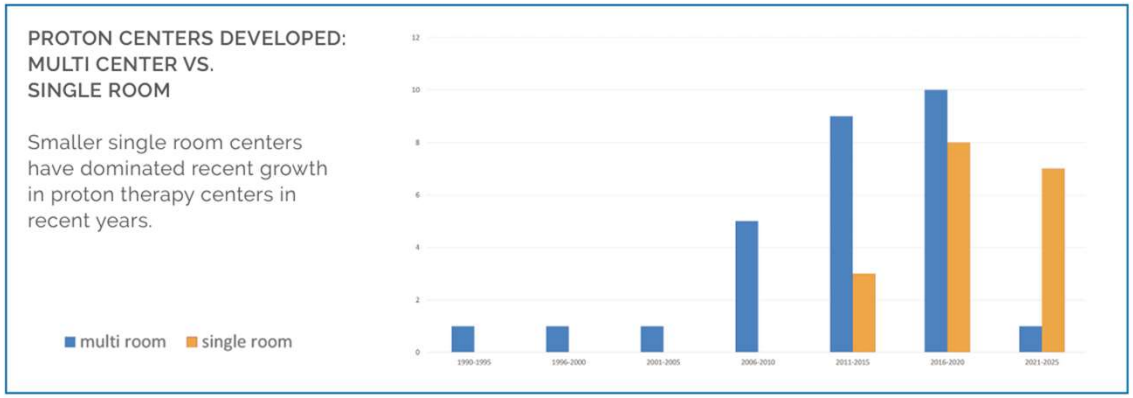
In-room CT on rails

Couch mounted CBCT

Landry and Hua. Med Phys. 45(11):e1086-e1095, 2018

Pediatric Proton Therapy: Patterns of Care

- Estimated 15,700 children/adolescents are diagnosed with cancer each year in US (~10,000 excluding leukemias) (CureSearch website). Approximately 3000 require RT as part of frontline management (Siegel 2012 CA).
- # of proton centers in US ↑from 6 in 2006 to 45 in 2024.
- NAPT Member Survey in 2023 shows pencil beam scanning is now the dominant form of treatment.
- Multi-room centers were the only option in the past but single room facilities have dominated recent growth in proton therapy centers (2023 NAPT data)

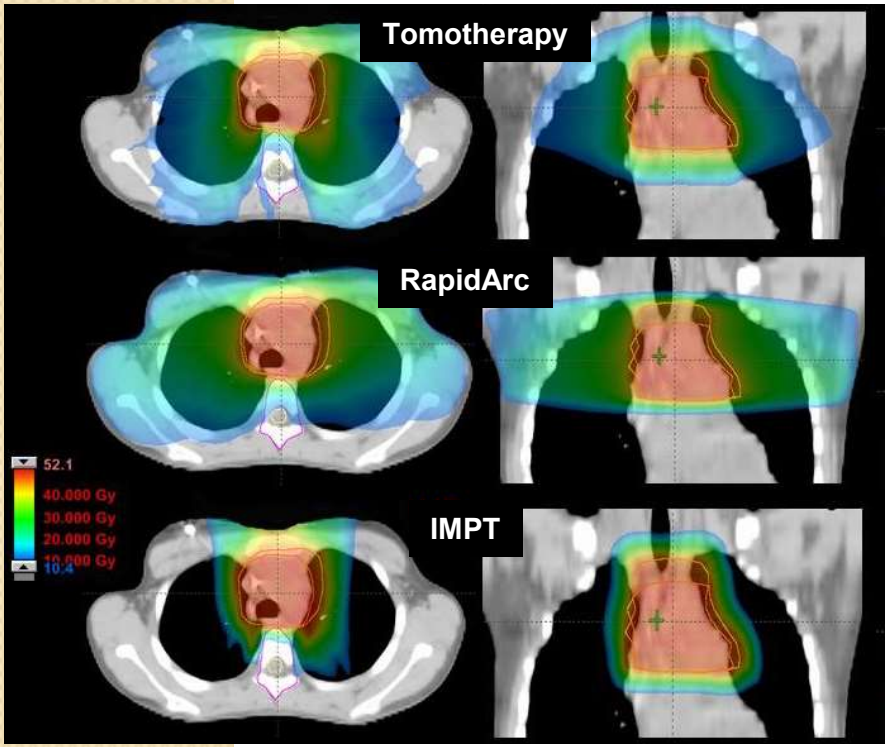


https://proton-therapy.org/

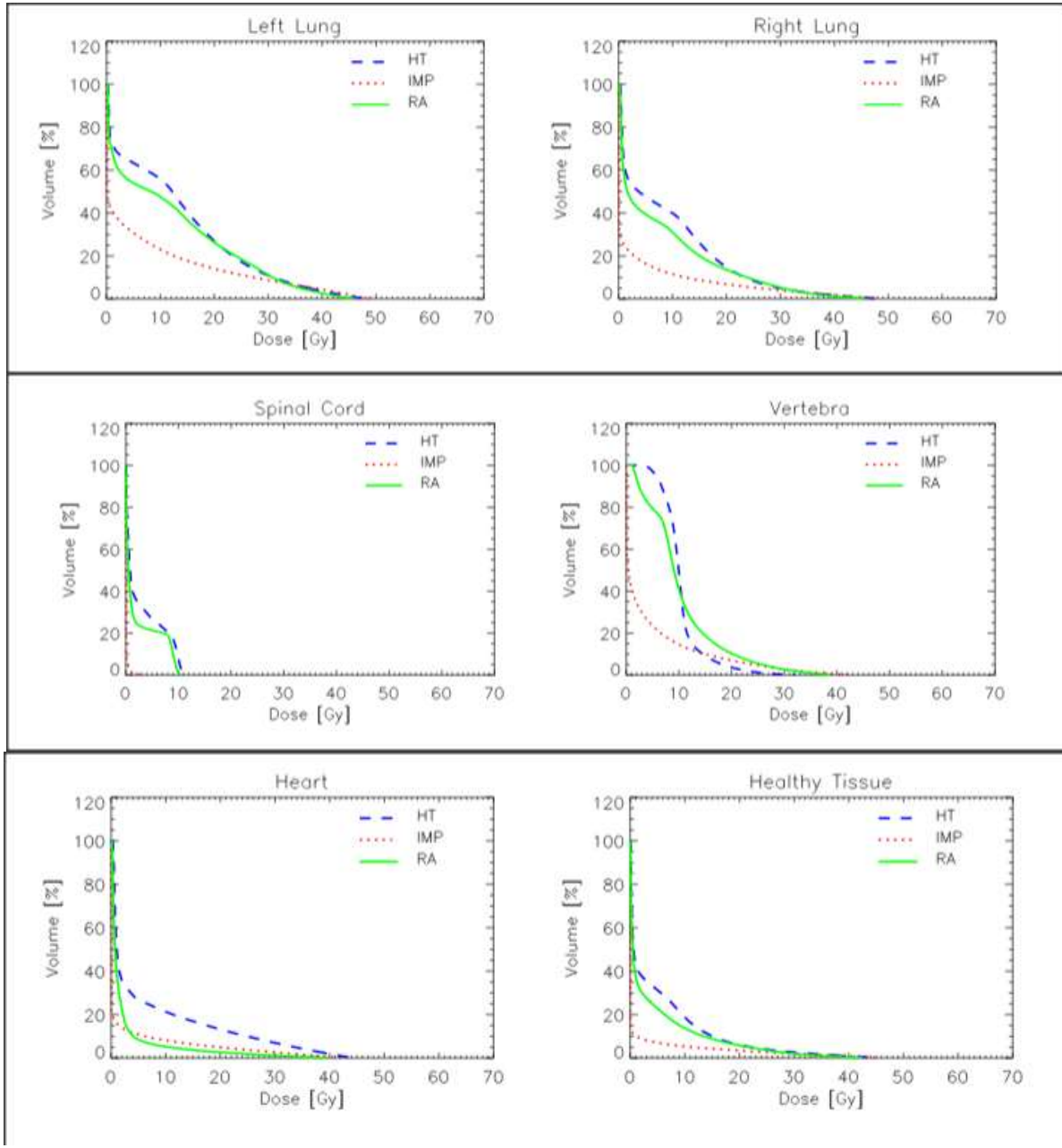
Pediatric Proton Therapy: Dosimetric Advantages in Critical Organs

IMPT produced the best healthy tissue sparing and the lowest integral dose compared to helical Tomotherapy and RapidArc although all techniques were satisfactory.

Rhabdomyosarcoma in mediastinum

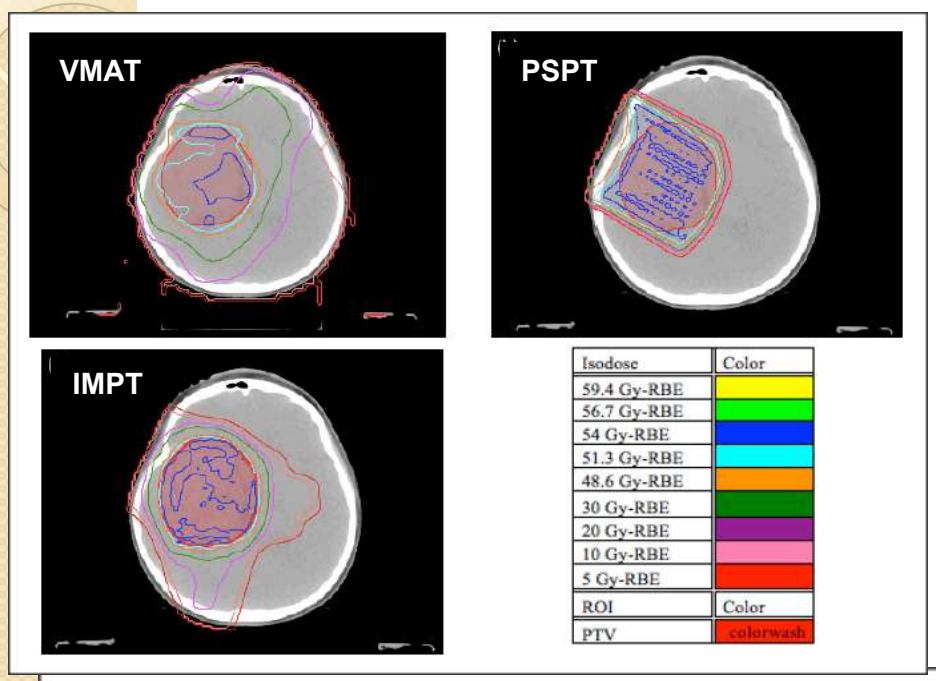


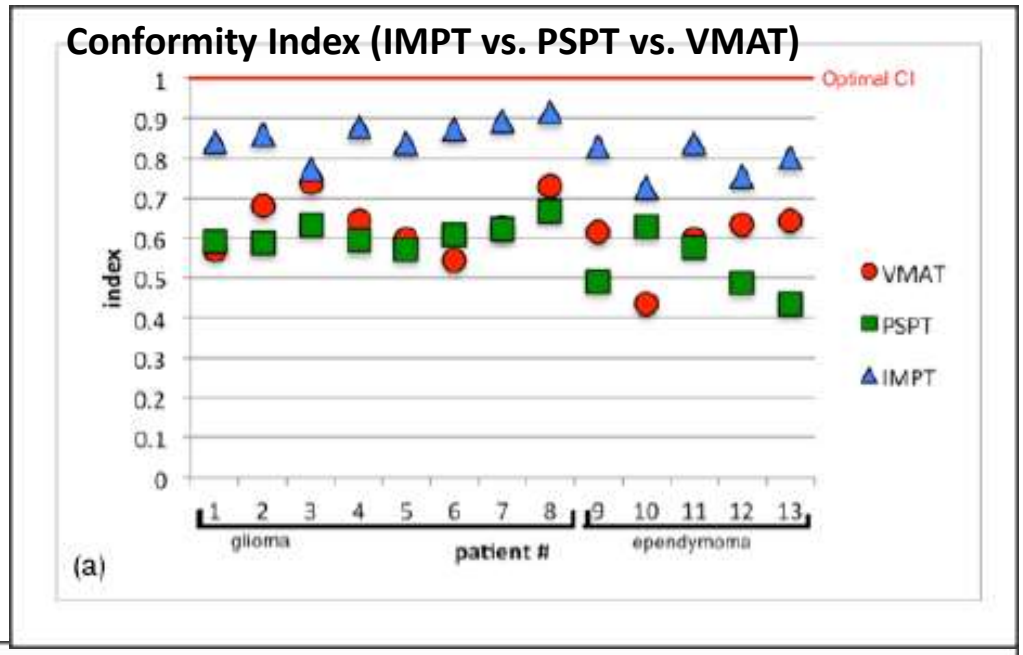
Fogliata et al, Radiotherapy and Oncology 2009:4:2

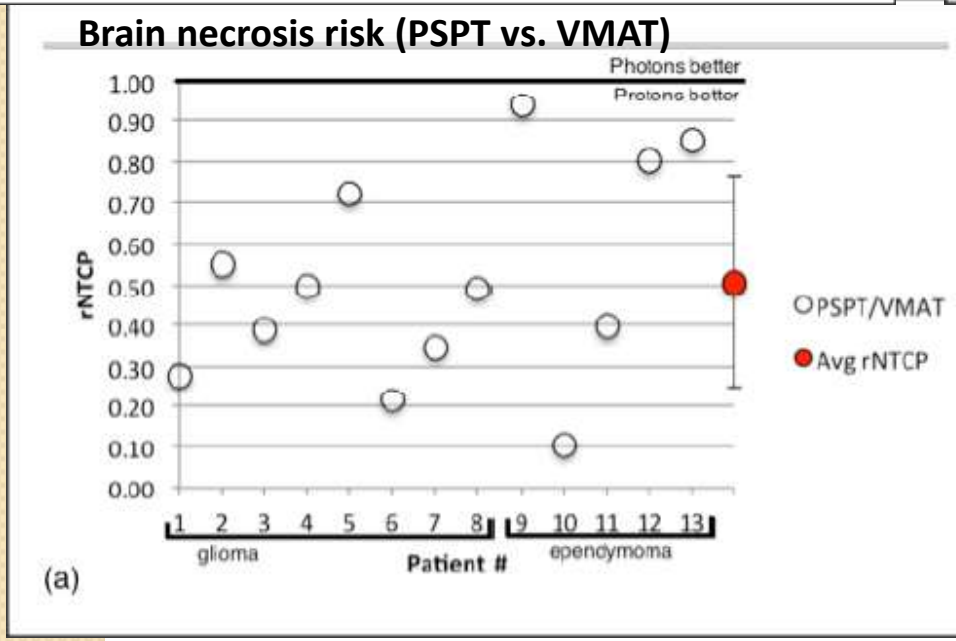


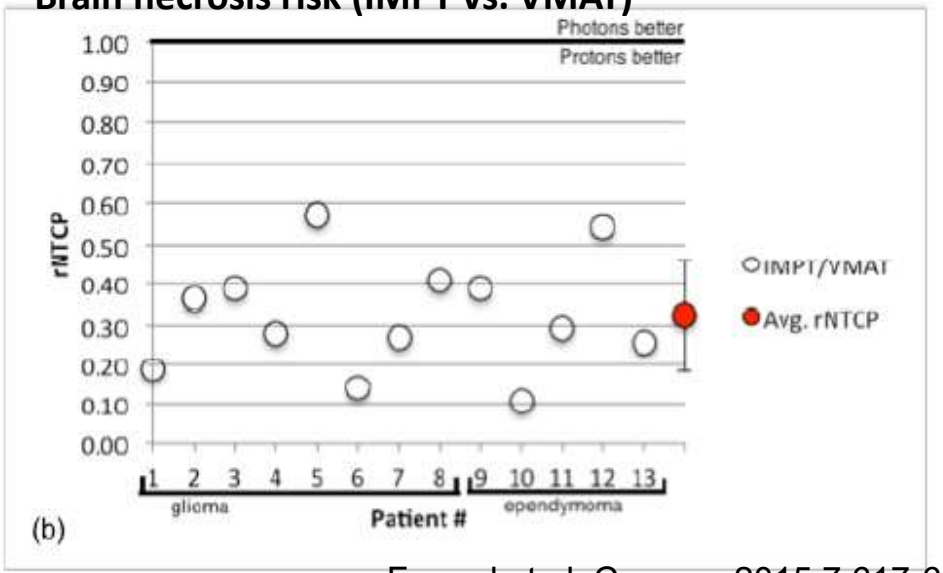
Pediatric Proton Therapy: Necrosis Risk

IMPT and PSPT plans resulted in a significant lower predicted risk of necrosis than VMAT plans.







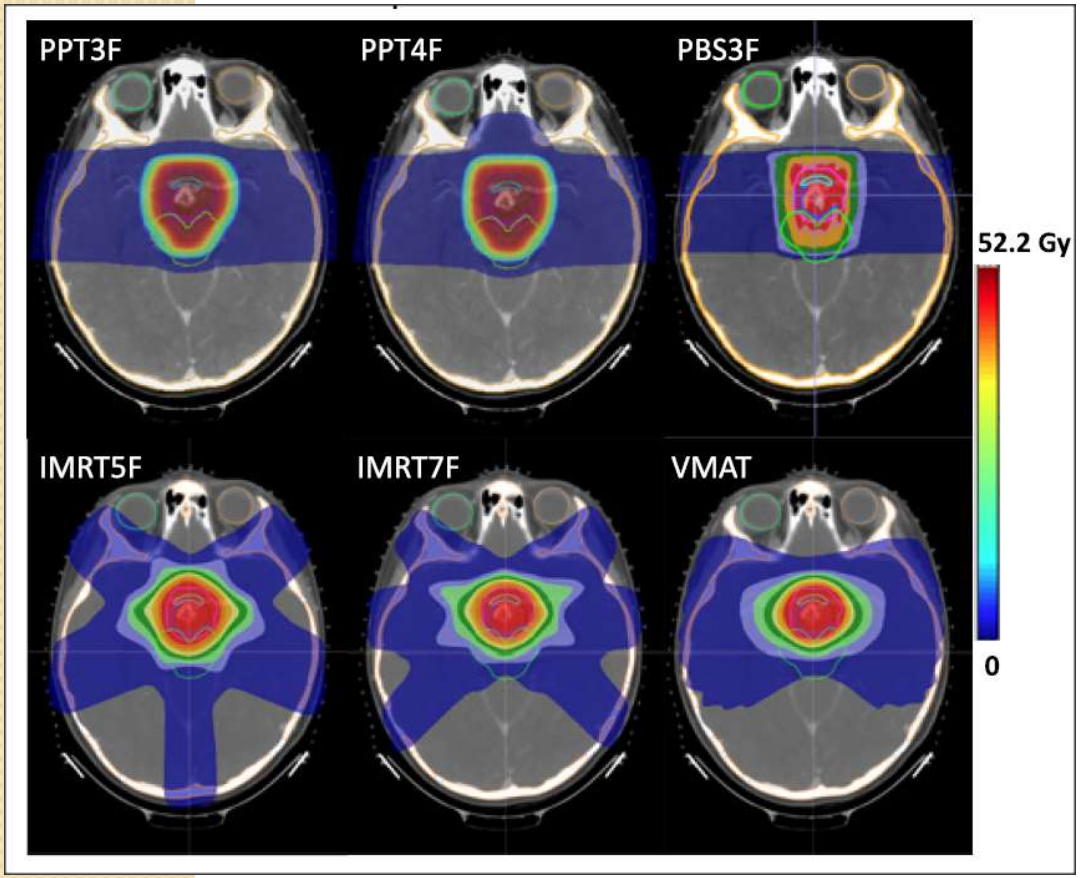


Freund et al, Cancers 2015:7:617-630

Pediatric Proton Therapy: Second Cancer Risk Prediction

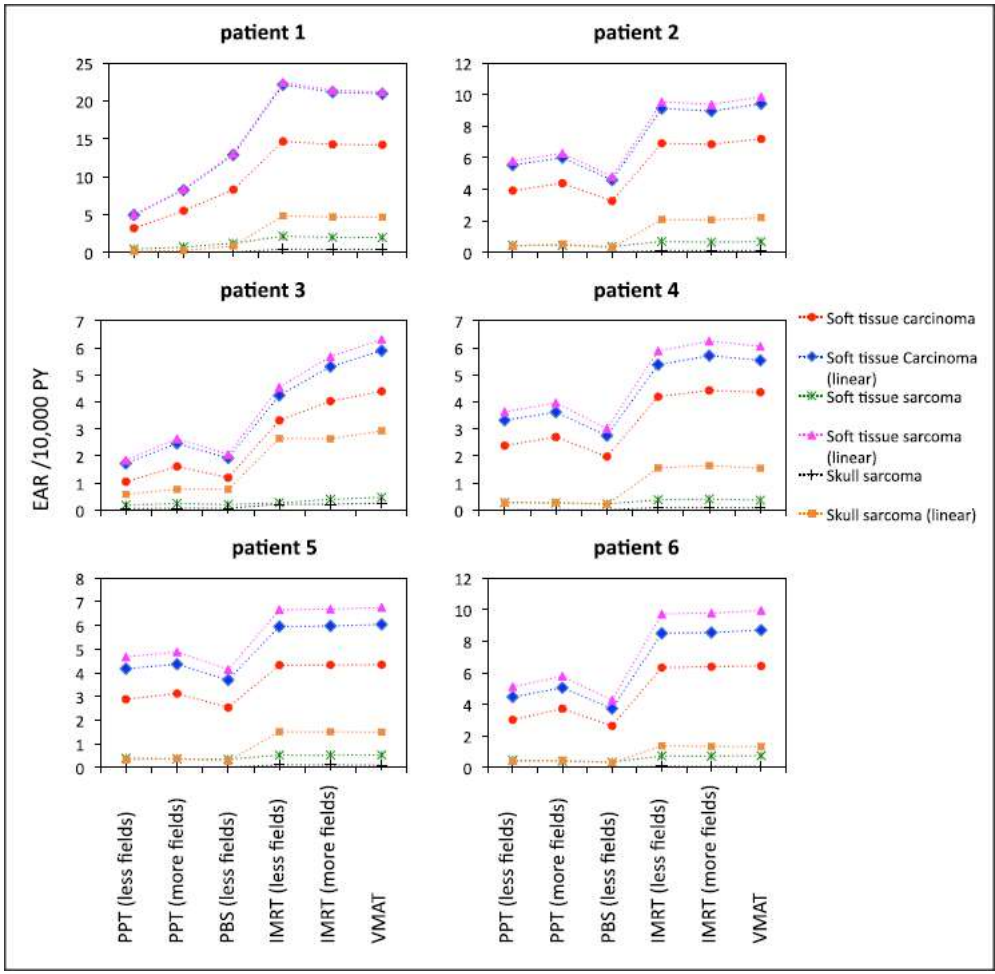
In general, protons irradiated smaller volumes of healthy tissue than IMRT and VMAT. Proton therapy was particularly superior at the lower-dose end of the DVH curves.

IMRT and VMAT lead to higher risk of developing second malignancies compared to PPT and PBS for pediatric patients with brain/head and neck tumors.



Moteabbed et al, PMB 2014:59:2883-2899

Excess absolute risk of proton vs. photon



Pediatric Proton Therapy: Challenges

Biology and clinical

- Limited knowledge on in-vivo biological effect. Uncertain RBE effect at distal edge
- Concerns about brain and brainstem necrosis in treatment of posterior fossa tumors
- Limited data on clinical outcomes and normal tissue tolerance. Demonstrate clinical significance.

Physics and technical

- Range uncertainty (e.g. requiring margin of 3.5% ×tumor depth)
- Larger spot sizes at lower energies (conformity of shallow target in small children)
- Limited options for beam angle (avoid going through bowel gas and high heterogeneous tissues)
- Motion interplay effects with proton scanning (mitigation strategies were proposed)

Workflow and application

- Longer wait for beam ready after patient setup (motion while beam switching from room to room)
- Longer delivery time (dose rate, layer switching, longer scanning with larger volume, SBRT-type?)
- Is proton (especially scanning beams) better for SIB or reirradiation?
- Fiscal challenges (referral, more staff and room time, affordability, financial burden on centers)

Proton Craniospinal Irradiation for Children

- Dose reduction in mandible, parotid gland, thyroid gland, lung, kidney, heart, ovary, uterine, and other non-target intracranial structures (St Clair 2004 IJROBP, Lee 2005 IJROBP, Howell 2012 IJROBP).
- IMPT achieves better OAR sparing than passive scattered beams while maintaining cribriform plate coverage (Dinh 2013 RO).

Table 4 Organs at risk 36Gy(RBE) prescribed CSI dose, Passive Scatter vs. IMPT

Index	PSW (Gy(RBE))	PSWO (Gy(RBE))	IMPT (Gy(RBE))
Left cochlea (mean)	36.4 ± 1.3	36.7 ± 1.0	28.6 ± 3.3†
Right cochlea (mean)	36.4 ± 1.4	36.7 ± 0.9	27.4 ± 1.5†
Left lens (max)	22.2 ± 5.5	24.8 ± 6.1*	12.5 ± 4.0†
Right lens (max)	22.8 ± 5.2	25.2 ± 5.9*	12.9 ± 5.0†
Brainstem (max)	39.3 ± 2.0	38.8 ± 2.0*	38.4 ± 0.5

Abbreviations: PSW passive scatter with compensator; *PSWO* passive scatter without compensator; *IMPT* intensity modulated proton therapy; Data presented as mean ± standard deviation; *significant vs. PSW, †significant vs. PSW or PWO, ($p < 0.05$), Student's t-test with Bonferroni correction for multiple comparisons.

Dinh et al, Radiat Oncol 2013:8:289

- **Models predict lower risk** of second cancer, lower rate of pneumonitis, cardiac failure, xerostomia, blindness, hypothyroidism, and ototoxicity (Mirabell 2002 IJROBP, Newhauser 2009 PMB, Thaddei 2010 PMB, Brodin 2011 Acta Oncol, Zhang 2013 PMB).

23.4 Gy(RBE) CSI to 4 y.o. → predicted life time risk of second cancer is 24.6% for passive scatter proton CSI risk for photon CSI is 5.6 times higher (Zhang 2013 PMB)

Proton Craniospinal Irradiation for Children

Current clinical techniques:

- Supine position is common. Many centers require all fields to be set up and filmed prior to treatment of the first field.
- More common to treat with scattered beams but will change with the advent of scanning beams.
- Two posterior oblique beams for whole brain are common for lens sparing (Cochran 2008 IJROBP, Mahajan 2014 IJPT). Single PA spot scanning beam for uniform dose to the whole brain is feasible. Use one or more PA beams to cover spinal targets.
- Compensator use for passive scattered beams increased heterogeneity within the brain (Jin 2011 JACMP, Dinh 2013 RO). Many do not use compensators for whole brain.

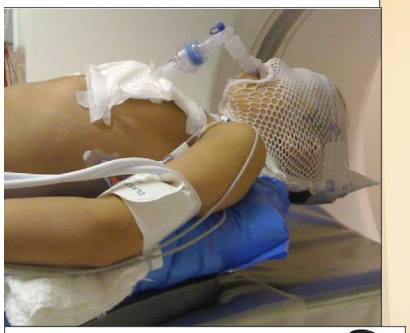
Clinical outcomes

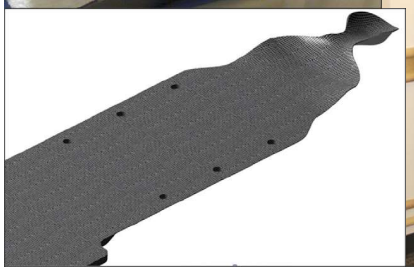
- No published data yet on long term effects of proton CSI
- Acute toxicity is mild – 40% experienced nausea requiring antiemetic for nausea prophylaxis and most patients experienced some degree of alopecia and dry skin (Mahajan 2014 IJPT).

Proton CSI setup

Indiana University Setup (no longer open)

- In house short and long CSI carbon fiber boards
- Indexed, homogeneous, torso-length
- No sharp thickness changes

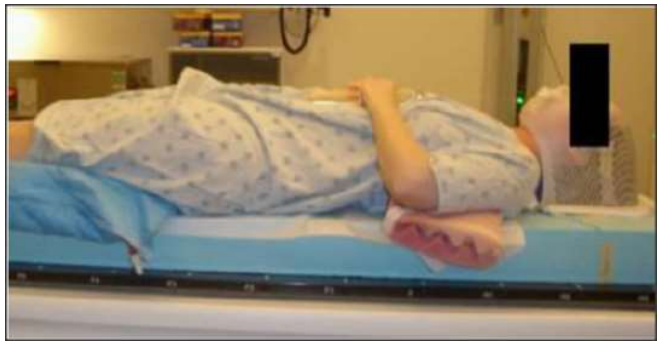




Buchsbaum et al, Med Dosim 2013:38:70-76

MDACC Setup

- Neutral head position and straight cervical spine/back
- 10cm thick styrofoam to elevate patient to prevent the posterior oblique whole brain fields from intersecting the couch edges.



Giebeler et al, Radiat Oncol 2013:8:32

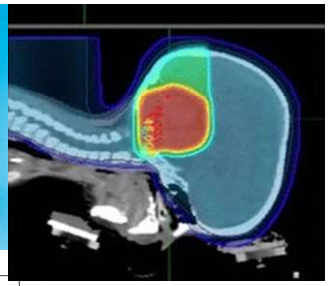
Mass General Hospital Setup

- Prone head holder with chin and forehead pads
- Anterior face mask

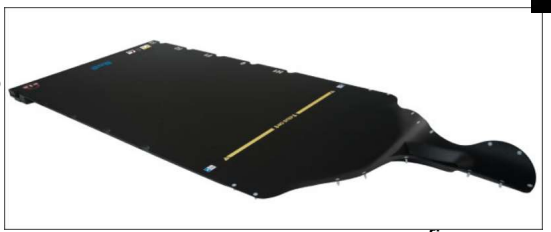
Commercial BOS (base of skull) couch inserts

- Allow aperture to get close to patient to minimize penumbra
- No flat base so more freedom to choose beam angles

www.civco.com



Min et al, Radiat Oncol 2014:9:220

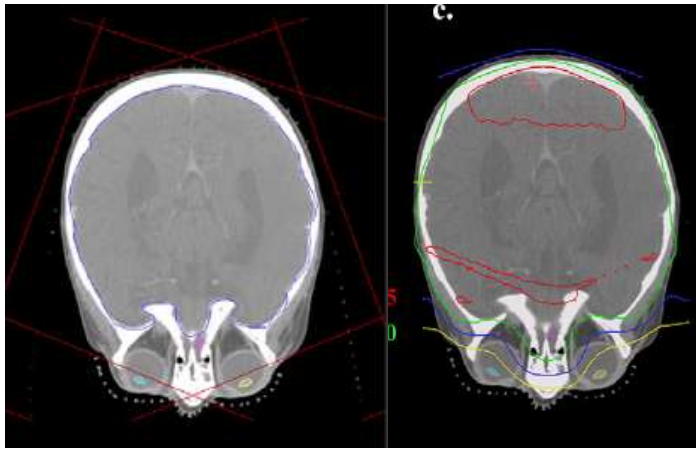


www.qfix.com

Proton CSI: Whole Brain Techniques

MGH patient treatment (Cochran 2008 IJROBP)

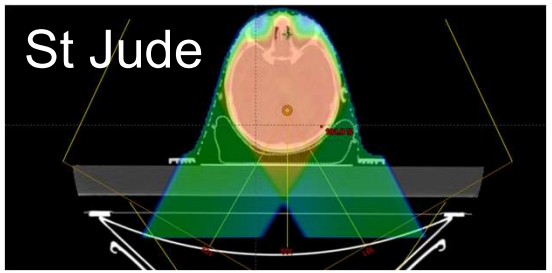
Posterior oblique beams (20° in the posterior direction) spare lens more than opposed laterals for **passive scattered** beams.



Cochran et al, Int J Radiat Oncol Biol Phys 2008:70:1336-1342

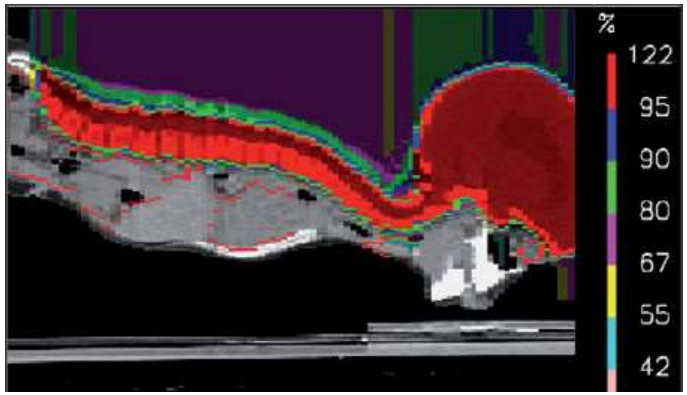
St Jude **IMPT** patient treatment

2 cranial fields-mirrored **posterior oblique** beams, angled 30° away from midplane



PSI and Scripps (now California Protons) patient treatment (Timmermann 2007 Strahlenther Onkol, Chang PTCOG meeting 2015)

A **single PA** beam of **spot scanning** for whole brain and spinal axis. Allow for a precise individual conformation of dose to the frontal subarachnoid space (Timmermann 2007 Strahlenther Onkol).



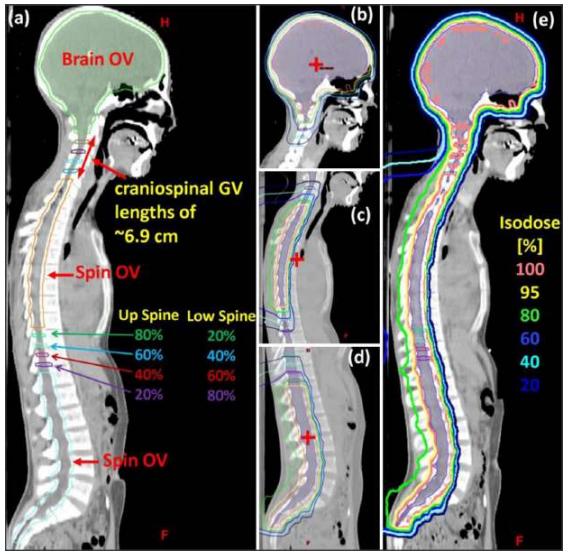
Timmermann et al, Strahlenther Onkol 2007:12:685-688

NYPC paper study (Hu 2024 Med Dosi) investigated the feasibility of changing from 2 posterior obliques to a single PA field.

Proton CSI: Low Gradients Across Spine Field Junction to Remove Junction Changes

U Penn patient treatment (Lin 2014 IJROBP)

- ❑ No junction change. 5-8 cm overlap region between fields
- ❑ 4 equally spaced "gradient volumes" optimized to achieve low dose-gradient junctions



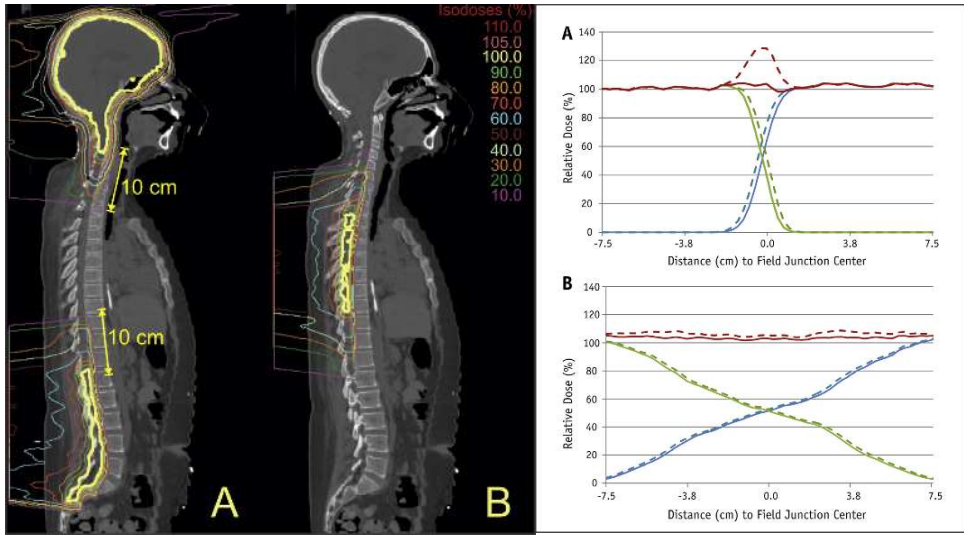
Lin et al, Int J Radiat Oncol Biol Phys 2014:90:71-78

Scripps (now California Protons) treatment (Chang 2015 PTCOG meeting)

- ❑ Two isocenters for entire CSI and two fields overlap 5-6 cm
- ❑ Overlaps in high thoracic region to avoid thyroid & esophagus
- ❑ Commercial IMPT TPS to create 2%/mm smooth dose gradients

MDACC paper study (Stoker 2014 IJROBP):

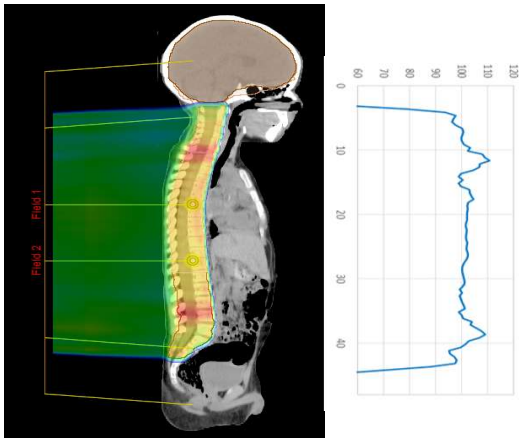
- ❑ 10-cm overlap region between fields
- ❑ Target divided along the cranio-caudal axis into 4 to 10 equally sized tapering segments
- ❑ 3 staged IMPT optimization
- ❑ OAR sparing as good or better than passive scattered plans



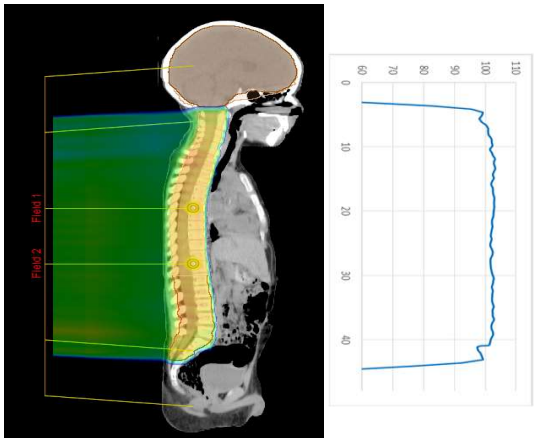
Stoker et al, Int J Radiat Oncol Biol Phys 2014:90:637-644

Pediatric Proton CSI without Junction Changes Via Robust Optimization

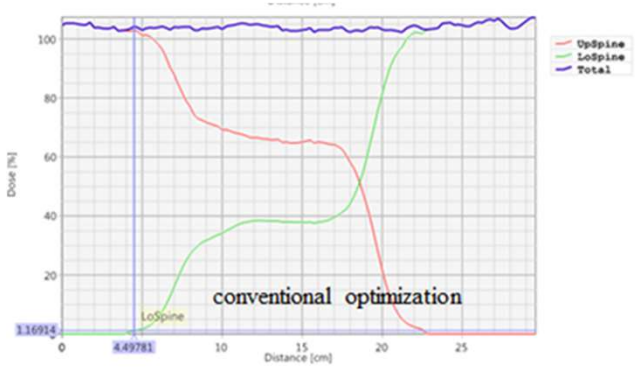
- Robust optimized IMPT plan can achieve a low dose gradient in overlapped junctions, is less sensitive to junction mismatch, and may eliminate the need for junction shifts.
- 10 cm overlap is needed to achieve max 5% dose variations applying a 3mm shift.

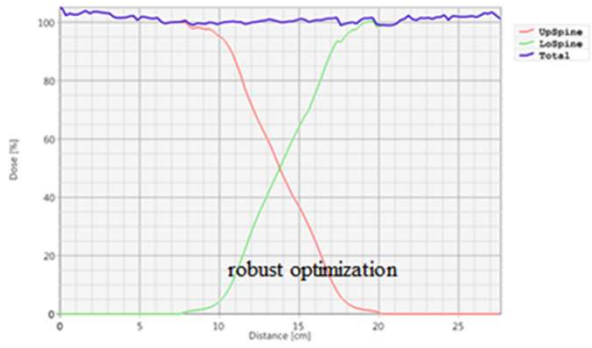


Conventional MFO optimization applying 3mm intra-fractional junction shift



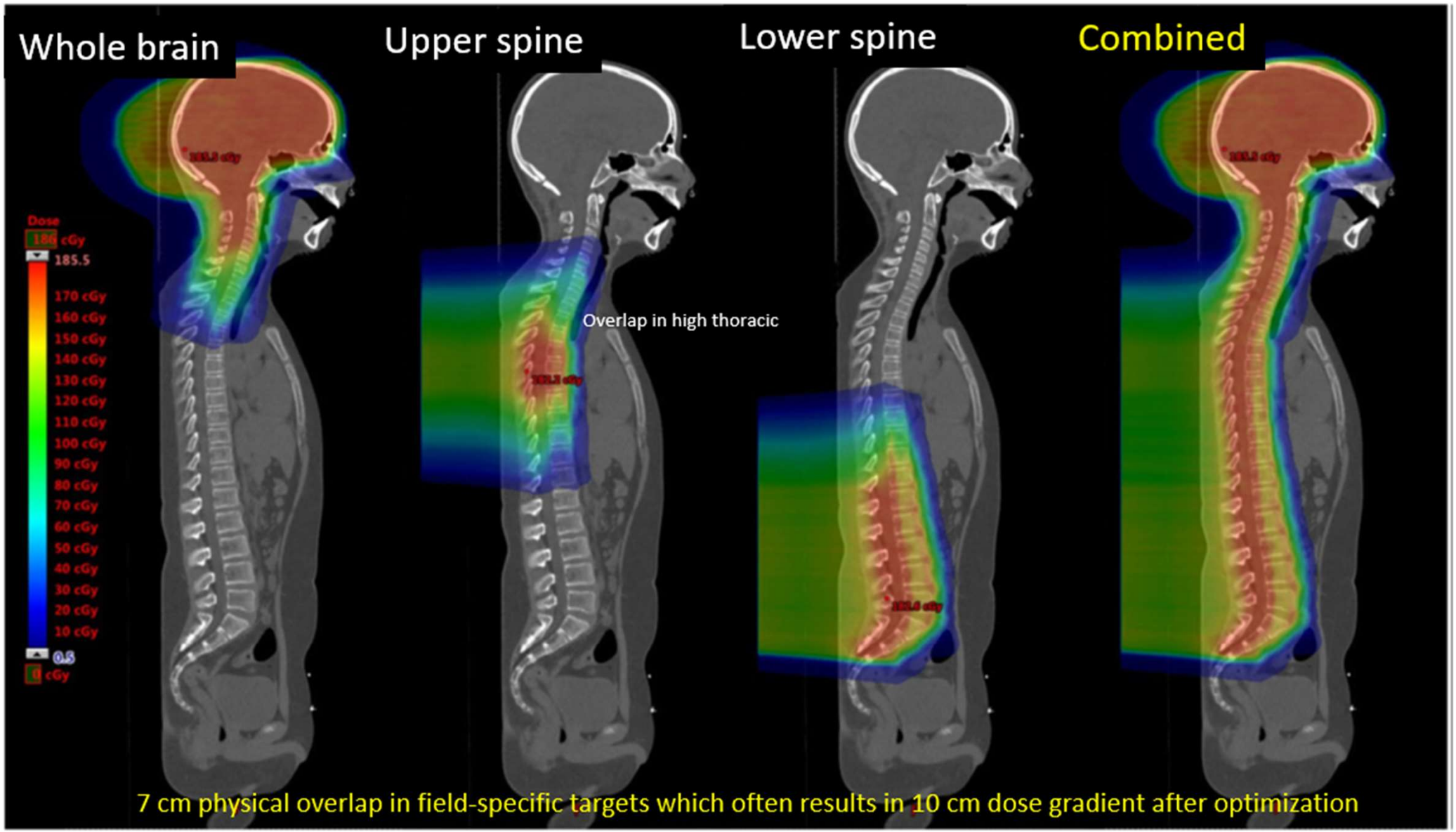
Robust optimization applying 3mm intra-fractional junction





Courtesy of Xiaodong Zhang. Liao et al. AAPM 2014 meeting TH-C-BRD-12

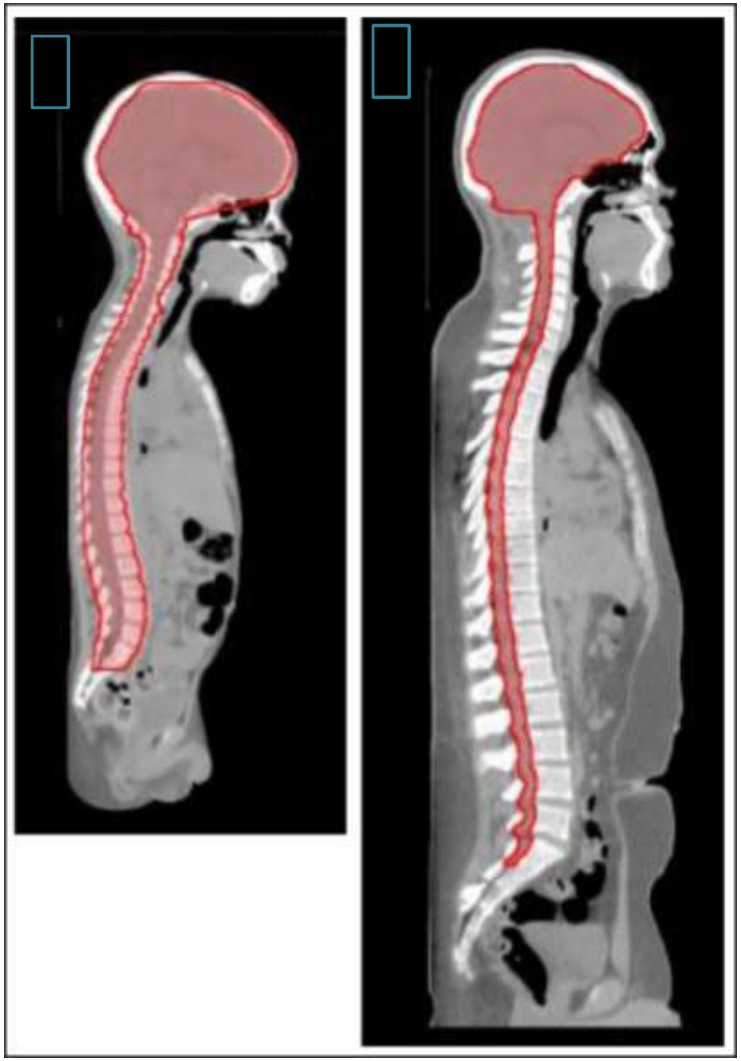
Pediatric Proton CSI without Junction Changes Via Robust Optimization



Hua et al. Ped Blood Cancer 68:e28344 2021

Pediatric Proton CSI: Vertebral Body Inclusion (Symmetric Bone Growth Vs. Bone Marrow Sparing)

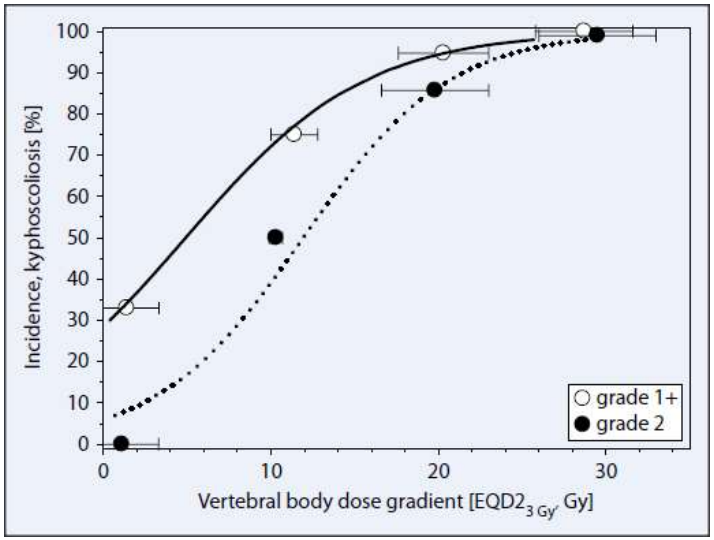
- Common practice is to include the entire vertebral body for irradiation for younger children (**prepubertal**, not yet reaching the skeletal maturity, often <15 y.o.) to prevent differential growth of the spine (Krejcarek 2007 IJROBP, Giebeler 2013 Radiat Oncol, Lin 2014 IJROBP). But spare esophagus and thyroid.
- For older children (**postpubertal**), spare the vertebral body and the bone marrow inside. Allow for better tolerance of chemotherapy. Typically only the spinal canal is included with a few mm extension into the vertebral bodies to account for distal range uncertainty (Krejcarek 2007 IJROBP, Giebeler 2013 Radiat Oncol).
- May decide based on evidence of wrist epiphyseal closure on plain film (McMullen 2013 Pract Radiat Oncol)



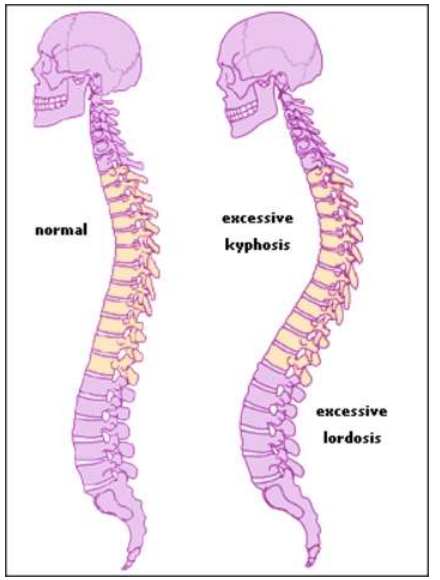
Giebeler et al. Radiat Oncol 2013:8:32

Pediatric Proton CSI: Vertebral Body Inclusion (Bone Tolerance Dose)

- The exact proton tolerance for pediatric growing bone is yet to be determined.
- For photon, **20 Gy tolerance** in children < 6 y.o. and **35 Gy** for older children (scoliosis, kyphosis, bony hypoplasia). Recommended a homogeneous dose profile within the vertebral bodies in younger children (Dorr 2013 Strahlenther Onkol).
- Lower CSI dose (18-23.4Gy) creates a dilemma regarding vertebral body coverage.
- St Jude photon data showed **lumbar spine** (L1-L5) was more affected by radiation than cervical or thoracic spine. Radiation insult to the more rapidly growing posterior components of the lumbar spine could contribute to greater lumbar lordosis (Hartley 2008 IJROBP).



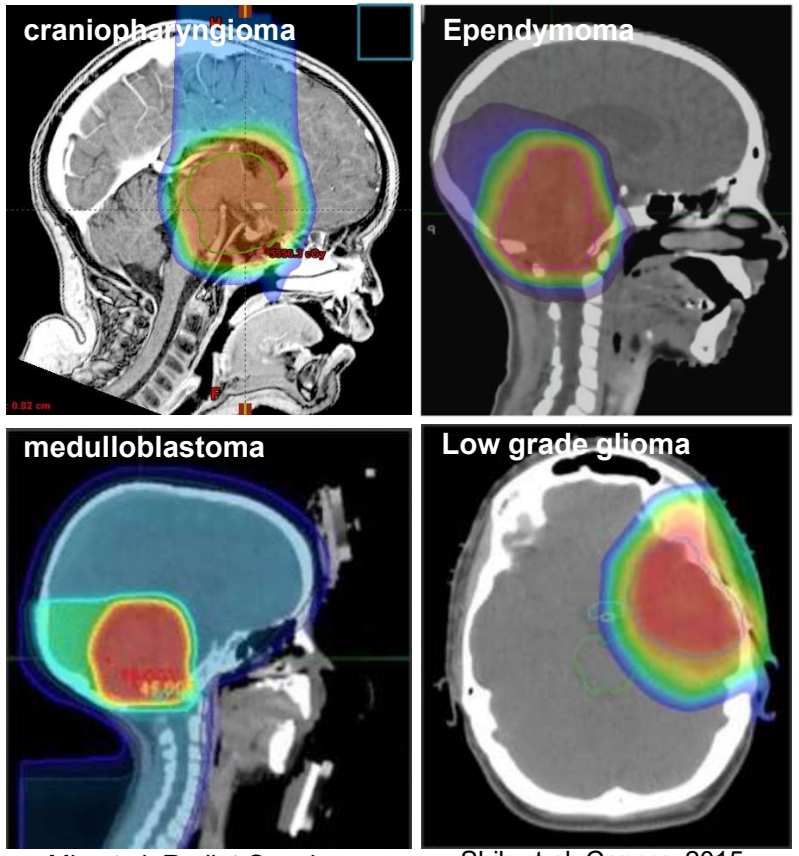
Dorr et al, Strahlenther Onkol 2013:189:529-534



Source: http://ww.spinalstenosis.org

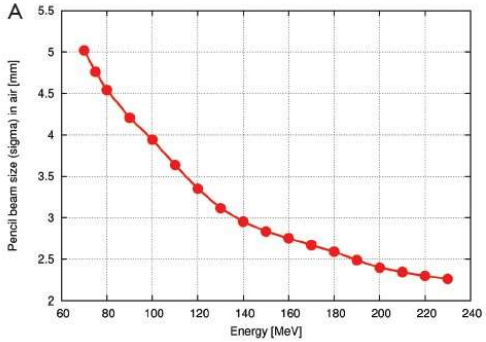
Proton Therapy for Pediatric Brain Tumors

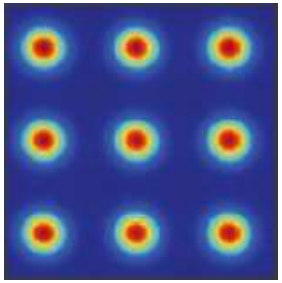
- Commonly – medullo/PNET, ependymoma, craniopharyngioma, and low grade glioma.
- RT late effects – vision (chiasm, lens, optic nerve), hearing (cochlea, auditory nerve), endocrine (hypothalamus, pituitary), neurocognition (brain, medial temporal lobe).
- IMPT with MFO produces better target conformity and OAR sparing than SFUD (SFO) and passively scattered plans (Yeung 2014 Pediatr Blood Cancer)
- For IMPT, smaller spot sizes result in better plan quality. But pediatric brain tumors, typically 5-10cm deep, require lower beam energies which have larger spot sizes. The use of range shifter to treat <4cm deep tumors further degrade the spot sizes.



Min et al, Radiat Oncol, 2014:9:220

Shih et al, Cancer, 2015: 121:1712-1719





Safai et al, Transl Cancer Res, 2012:1:196-206

Proton Therapy for Pediatric Brain Tumors

- Common planning rules
  - Avoid beams passing bony anatomy that could drastically change WEPL with a small rotation setup error, e.g. sinus cavities
  - Avoid partially clipping couch corners or small high density setup devices
  - Avoid stopping all distal edges within OAR
  - Be aware of device inhomogeneity and stability over time (e.g. head cushion, head rest)
- Be aware of skin dose for single proton beam (permanent alopecia reported with concurrent chemo)
- Be aware of anatomy and tumor changes during proton course – steroid use, tumor growth, early response, cyst changes, CSF shunting. Repeat MRI/CT may be needed for surveillance and replanning.

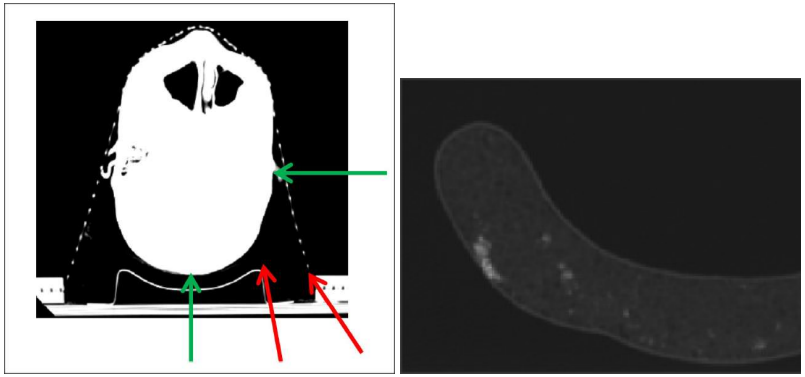
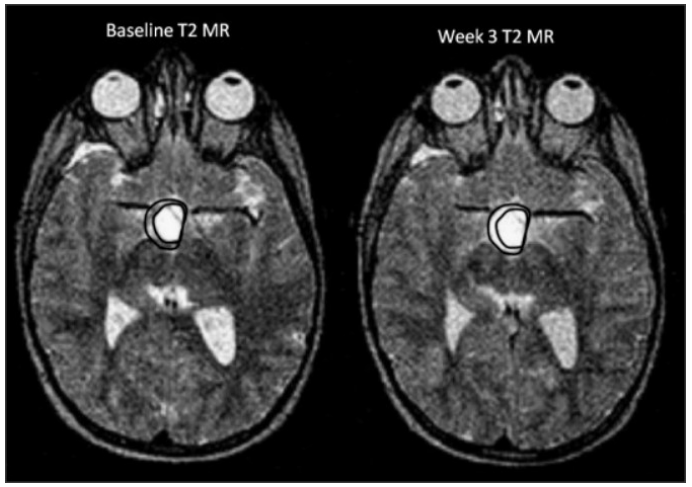


Figure 10: CT images of the MoldCare cushion system 0, 6 and 24 hours (left to right) after activation. Note that changes in shape are not a result of the curing process, but rather from imaging different positions in the cushion.

Wroe et al, Technol Cancer Res Treat, 2014:13:217-226

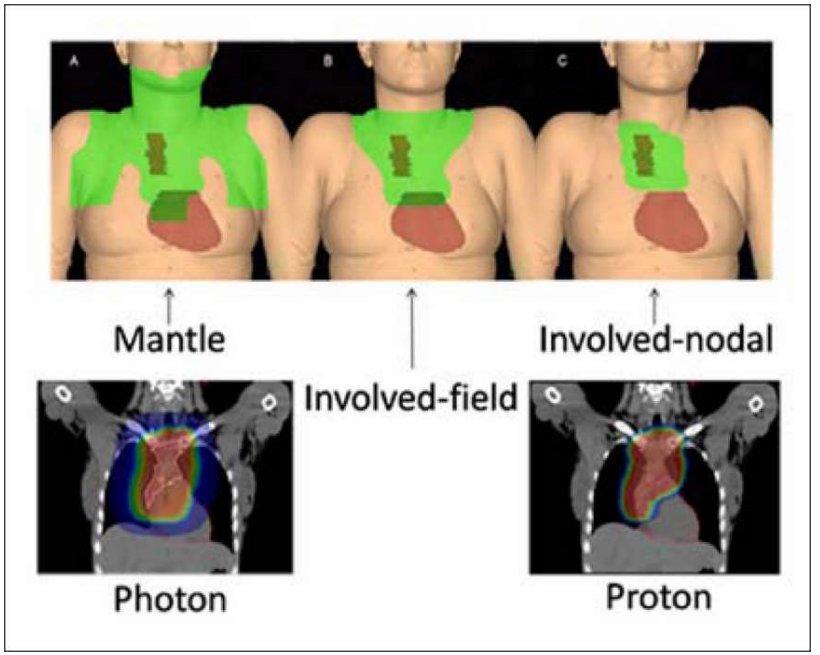


Beltran et al, Int J Radiat Oncol Biol Phys, 2012:82:e281-e287

Therapeutic Trends for Pediatric Hodgkin Lymphoma

- Late toxicities of pediatric Hodgkin treatment continue to emerge as patients survive longer (heart disease, second cancers). (review paper by Hodgson 2011 Hematology)
- 2 most recent thrusts within the RT community (Hoppe 2014 IJROBP).
  - treat a minimal target volume, the "**involved node**" or "**involved site**" as defined by volumetric and PET imaging
  - modify **radiation doses** based on chemotherapy response (response-adapted)
- Proton therapy is expected to further reduce the integral dose and late effects.

Conventional to contemporary targeting



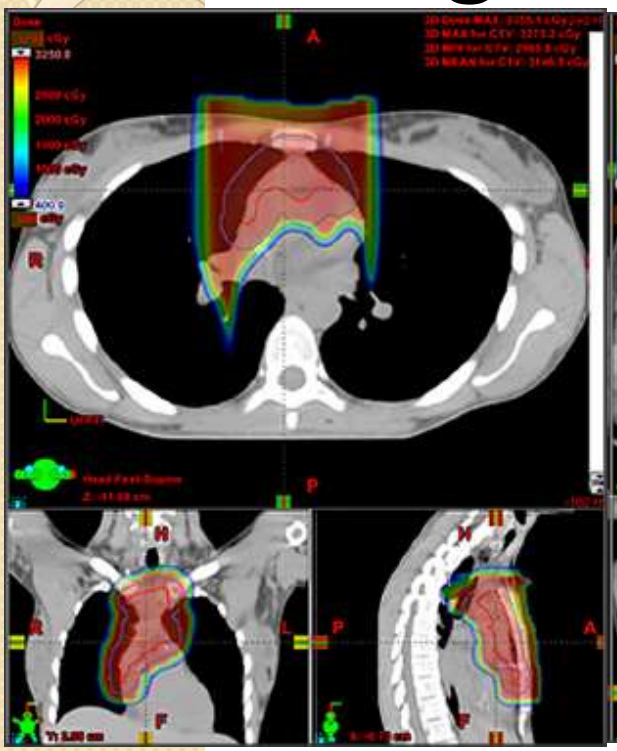
Merchant, Semin Radiat Oncol, 2013:23:97-108

15 patients

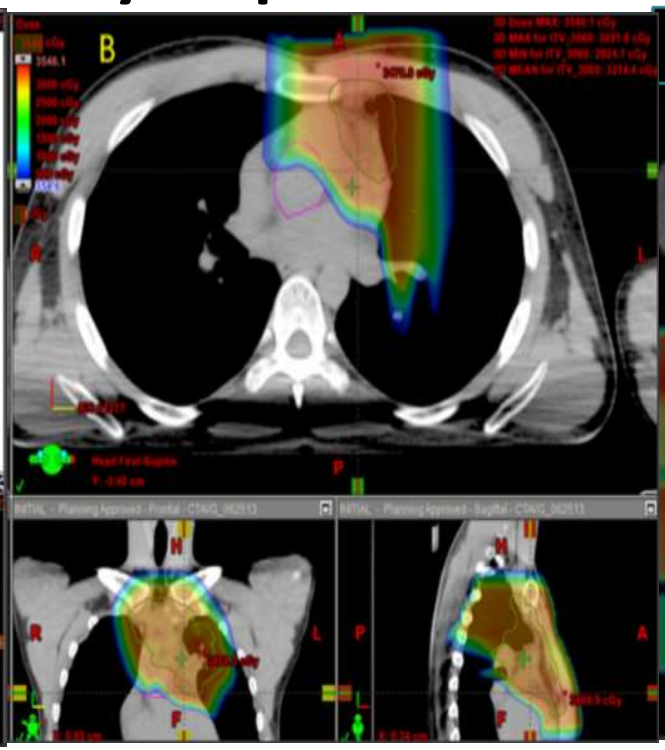
Structure	3DCRT Mean	3DCRT ±SD	IMRT Mean	IMRT ±SD	PT Mean	PT ±SD
Integral dose (joules)	122.9	62.3	103.8	48.6	53.6	32.0
Heart (Gy)	16.5	7.6	12.3	6.2	8.9	5.1
Lung (Gy)	11.6	3.7	9.8	2.8	7.1	2.5
Breast (Gy)	6.3	3.5	6.0	3.4	4.3	3.0
Thyroid (Gy)	19.3	10.1	17.7	9.3	15.8	9.7
Esophagus (Gy)	20.3	4.8	16.4	3.9	13.4	5.6

Hoppe et al, Int J Radiat Oncol Biol Phys, 2014;89;1053-1059

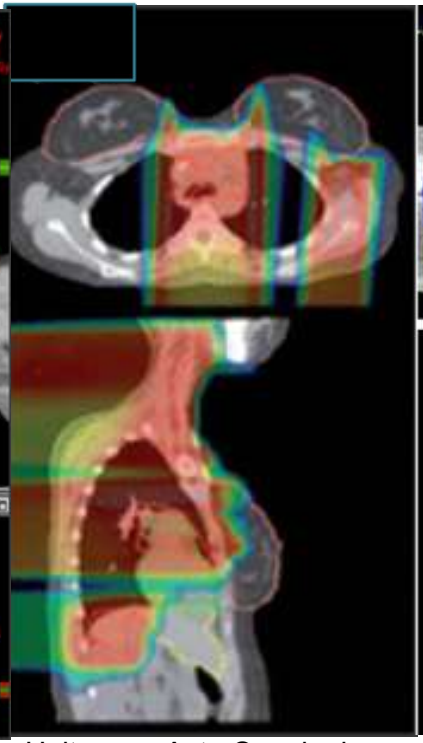
Proton Techniques for Pediatric Hodgkin Lymphoma



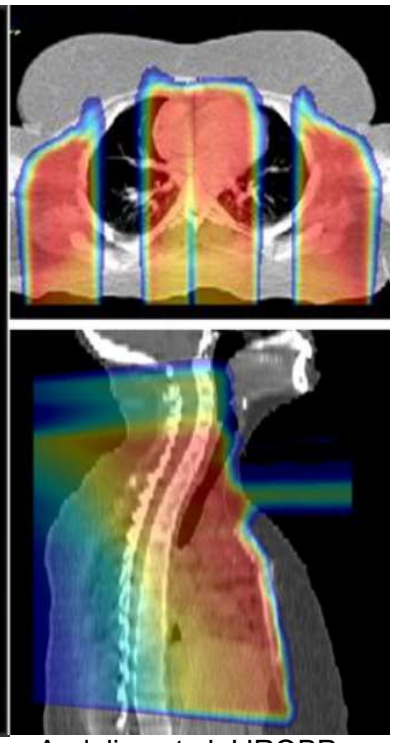
Hoppe et al, IJROBP, 2014:89:1053-1059



Plastaras et al, Semin Oncol, 2014:41:807-819



Holtzman, Acta Oncologica, 2013:52:592-594



Andolino et al, IJROBP, 2014:81:e667-e671

- Unless pre-chemo FDG PET can be performed in RT position, usually have to position RT patients to match pre-chemo imaging position for better image registration.
- 4DCT is typically performed to assess motion. Breath hold may be used to reduce heart and lung doses.
- UFPTI OAR priorities (after mean lung dose<18Gy):

  Heart > Lungs > Breasts (woman only) > esophagus (Hoppe 2014 IJROBP)
- Cardiac radiation exposure of ≥15Gy increased the relative hazard of congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities by 2-6 fold compared to non-irradiated survivors (Mulrooney 2009 BMJ).

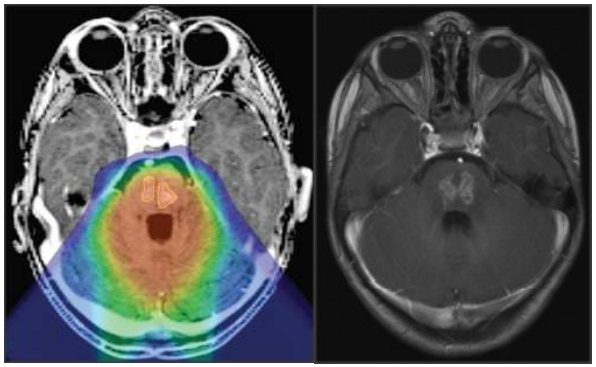
Pediatric Hodgkin Lymphoma: Proceed With Caution

- Appropriate margins to account for range uncertainty and going through heterogeneous tissues?
- Distal edges in critical organs. Uncertain increased RBE effect?
- Robustness evaluation or robust optimization for range and setup uncertainties
- Accuracy of proton dose calculation in thorax?
- CT image artifacts in thorax and shoulder regions
- Interplay effect significant from respiratory motion and pencil beam scanning?
- Volumetric image guidance is not available in many proton centers
- Patient selection for proton therapy depends on disease location and extent?

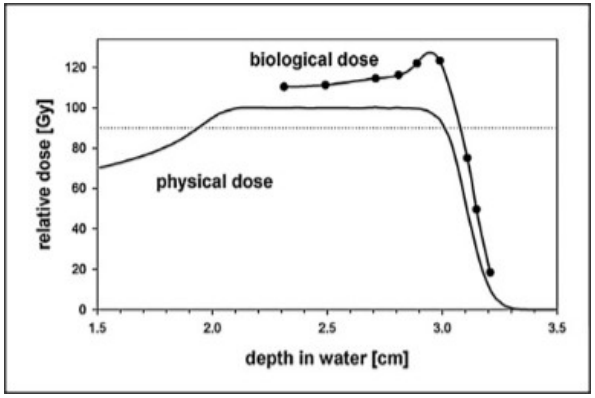
For more discussions, see the following publications
Lohr et al, Strahlenther Onkol, 2014:190:864-871
Hodgson & Dong, Leuk & Lymphoma, 2014:51:1397-1398

Controversy on Brainstem Necrosis from Proton Therapy

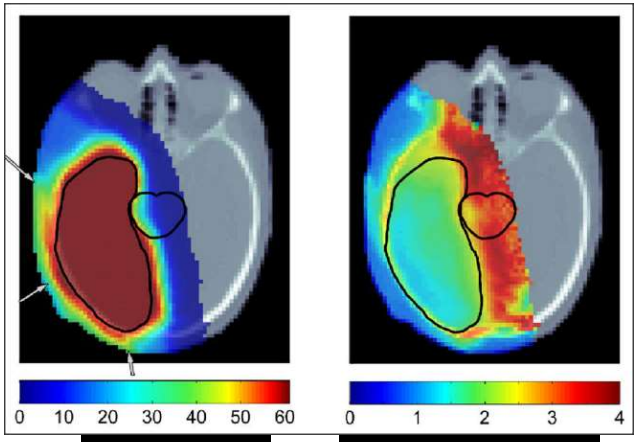
- Unanticipated complication of brainstem necrosis developed in pediatric patients receiving proton therapy.
  - 43% post-PT MRI changes in brain/brainstem of ependymoma patients (MDACC, Gunther 2015 IJROBP)
  - 3.8% incidence for >50.4 CGE to brainstem, but 10.7% for patients with posterior fossa tumors and 12.5% for <5 y.o. (UFPTI, Indelicato 2014 Acta Oncologica)
- Researchers suspected increased RBE at the end of range explains brainstem necrosis and proposed biological proton planning considering RBE variation.
- Evidence of strong association between LET distribution and brainstem toxicity or recurrence to be demonstrated
  - Elevated RBE values due to increased LET at the distal end of treatment fields do not clearly correlate with radiation induced brainstem injury (Giantsoudi 2015 PTCOG meeting, Giantsoudi 2014 IJROBP).
  - No correlation between recurrence and Monte-Carlo calculated LET distribution in medulloblastoma patients receiving proton therapy (Sethi 2014 IJROBP).



Sabin et al, Am J Neuroradiol, 2013:34:446-450



Paganetti, Phys Med Biol, 2012:57:R99-R117



Wedenberg et al, Med Phys, 2014:41:091706

Controversy on Brainstem Necrosis from Proton Therapy

- Approaches to mitigate effects of ↑RBE at distal edge
  - Multiple fields with large angular separation
  - Proper angles to avoid distal ends of SOBP inside critical structures
  - Smear the distal fall off: split the dose for a field in half; deliver half of the dose as planned and then other half with range modified by 3mm (Buchsbaum 2014 RO)

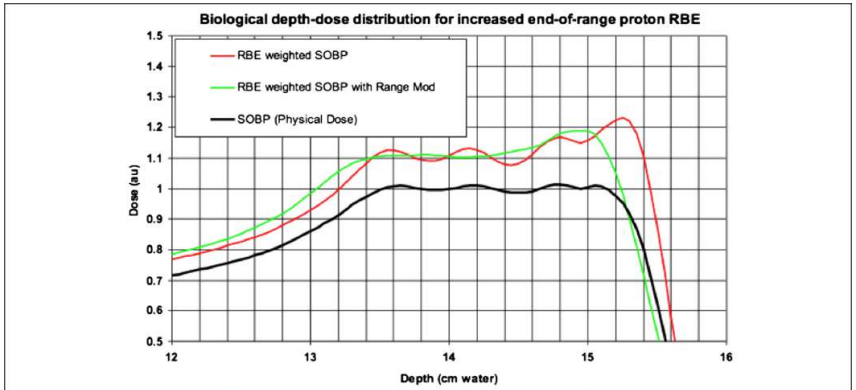


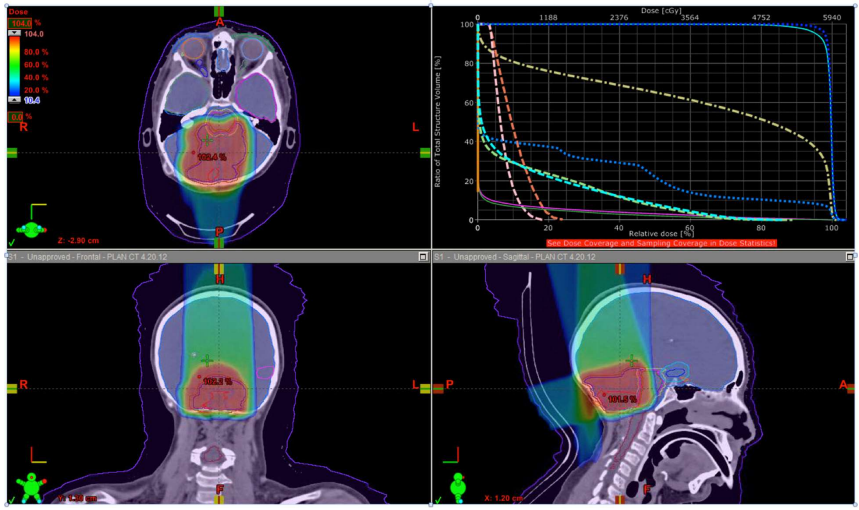
Figure 1 The physical dose for a SOBP composed of four pristine Bragg peaks each separate by 6 mm water equivalent. Applying our illustrative model of increased distal RBE to the individual pristine peaks produces the RBE weighted SOBP. The "range mod" technique mitigates the changes in SOBP plateau flatness, range, and effective dose at the distal edge. Here the modulation is achieved by splitting the SOBP into two parts and shifting one by 3 mm to both smooth out the SOBP and decrease the RBE at the end of the beam.

Buchsbaum et al, Radiat Oncol, 2014:9:2

- No consensus on brainstem tolerance for proton therapy. Currently err on the side of caution with brainstem.

  UFPTI guidelines: **D_{max} to brainstem ≤ 56.6 Gy**
  $D_{50\%}$ to brainstem ≤ 52.4 Gy

  For young patients with posterior fossa tumors who undergo aggressive surgery, more conservative dosimetric guidelines should be considered. (Indelicato Acta 2014 Oncologica)



Buchsbaum et al, Radiat Oncol, 2014:9:2

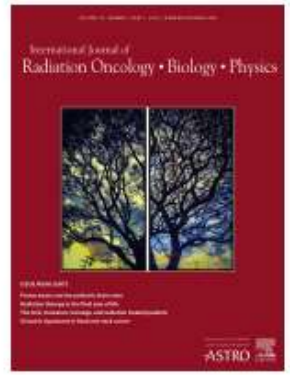
Controversy on Brainstem Necrosis from Proton Therapy

FULL TEXT ARTICLE

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

Daphne Haas-Kogan MD, Daniel Indelicato MD, Harald Paganetti PhD, Natia Esiashvili MD, Anita Mahajan MD, Torunn Yock MD, Stella Flampouri PhD, Shannon MacDonald MD, Maryam Fouladi MD, Kry Stephen PhD, John Kalapurakal MD, Stephanie Terezakis MD, Hanne Kooy PhD, David Grosshans MD, PhD, Mike Makrigiorgos PhD, Kavita Mishra MD, MPH, Tina Young Poussaint MD, Kenneth Cohen MD, Thomas Fitzgerald MD, Vinai Gondi MD, Arthur Liu MD, PhD, Jeff Michalski MD, Dragan Mirkovic PhD, Radhe Mohan PhD, Stephanie Perkins MD, Kenneth Wong MD, Bhadrasain Vikram MD, Jeff Buchsbaum MD and Larry Kun MD

International Journal of Radiation Oncology, Biology, Physics, 2018-05-01, Volume 101, Issue 1, Pages 152-168, Copyright © 2018 Elsevier Inc.



International Journal of Radiation Oncology, Biology, Physics
Volume 101, Issue 1

The average rate of symptomatic brainstem toxicity from the 3 largest US pediatric proton centers was 2.38%. The actuarial rate of grade ≥2 brainstem toxicity was successfully reduced from 12.7% to 0% at 1 center after adopting modified radiation guidelines. Guidelines for treatment planning and current consensus brainstem constraints for proton therapy are presented.

More recent papers on Brain Necrosis from Proton Therapy

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Decoding Patient Heterogeneity Influencing Radiation-Induced Brain Necrosis

Ibrahim Chamseddine[1], Keyur Shah[1], Hoyeon Lee[1], Felix Ehret[1,2,3], Jan Schuemann[1], Alejandro Bertolet[1], Helen A. Shih[1], and Harald Paganetti[1]

The analysis highlighted tumor location and proximity to critical structures such as white matter and ventricles as major determinants of necrosis risk.

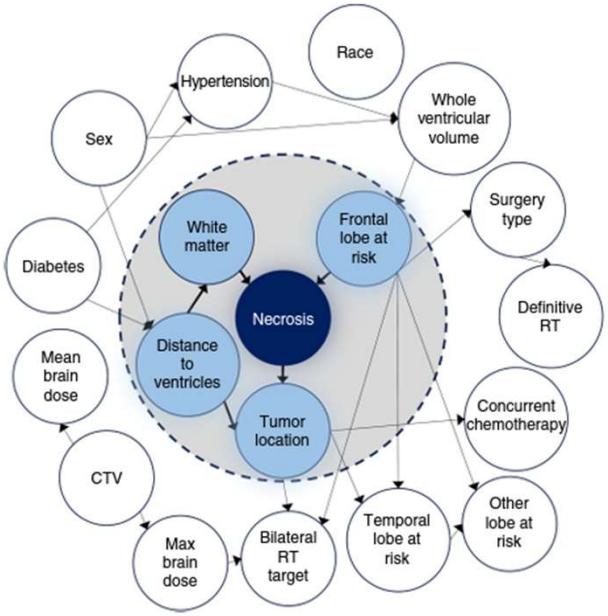


Figure 2.
Bayesian network centered on radiation necrosis. This graphical representation positions radiation necrosis at the heart of the network, with its MB distinctly shaded in gray. The diagram underscores the intricate interplay of variables in close proximity to our focal node, capturing both direct influences and reciprocations, essential for understanding radiation treatment outcomes.

ELSEVIER
Radiotherapy and Oncology
Volume 163, October 2021, Pages 143-149

Original Article

Study of relationship between dose, LET and the risk of brain necrosis after proton therapy for skull base tumors

Magdalena Garbacz [a], Francesco Giuseppe Cordoni [b,c], Marco Durante [d,e], Jan Gajewski [a], Kamil Kisielewicz [f], Nils Krah [g,l], Renata Kopeć [a], Paweł Olko [a], Vincenzo Patera [h,i], Ilaria Rinaldi [j], Marzena Rydygier [a], Angelo Schiavi [i], Emanuele Scifoni [c], Tomasz Skóra [f], Francesco Tommasino [c,k], Antoni Rucinski [a]

This study **does not** confirm the influence of the high DRBE/LETd on necrosis occurrence. The large inter-patient variability hinders the identification of a clear effect.

ELSEVIER
International Journal of Radiation Oncology*Biology*Physics
Volume 109, Issue 1, 1 January 2021, Pages 109-119

Physics Contribution

Brain Necrosis in Adult Patients After Proton Therapy: Is There Evidence for Dependency on Linear Energy Transfer?

Andrzej Niemierko PhD [*], Jan Schuemann PhD [*], Maximilian Niyazi MD, MSc [*,†,‡,§], Drosoula Giantsoudi PhD [*], Genevieve Maquilan MD [*], Helen A. Shih MD [*], Harald Paganetti PhD [*]

LET adjusted for dose was **not found** to be associated with the risk of brain necrosis. The effect might be obscured by inter-patient variability of radiosensitivity.

Affecting Proton Range: Bowel Gas, Metal Artifact, and Beam Hardening

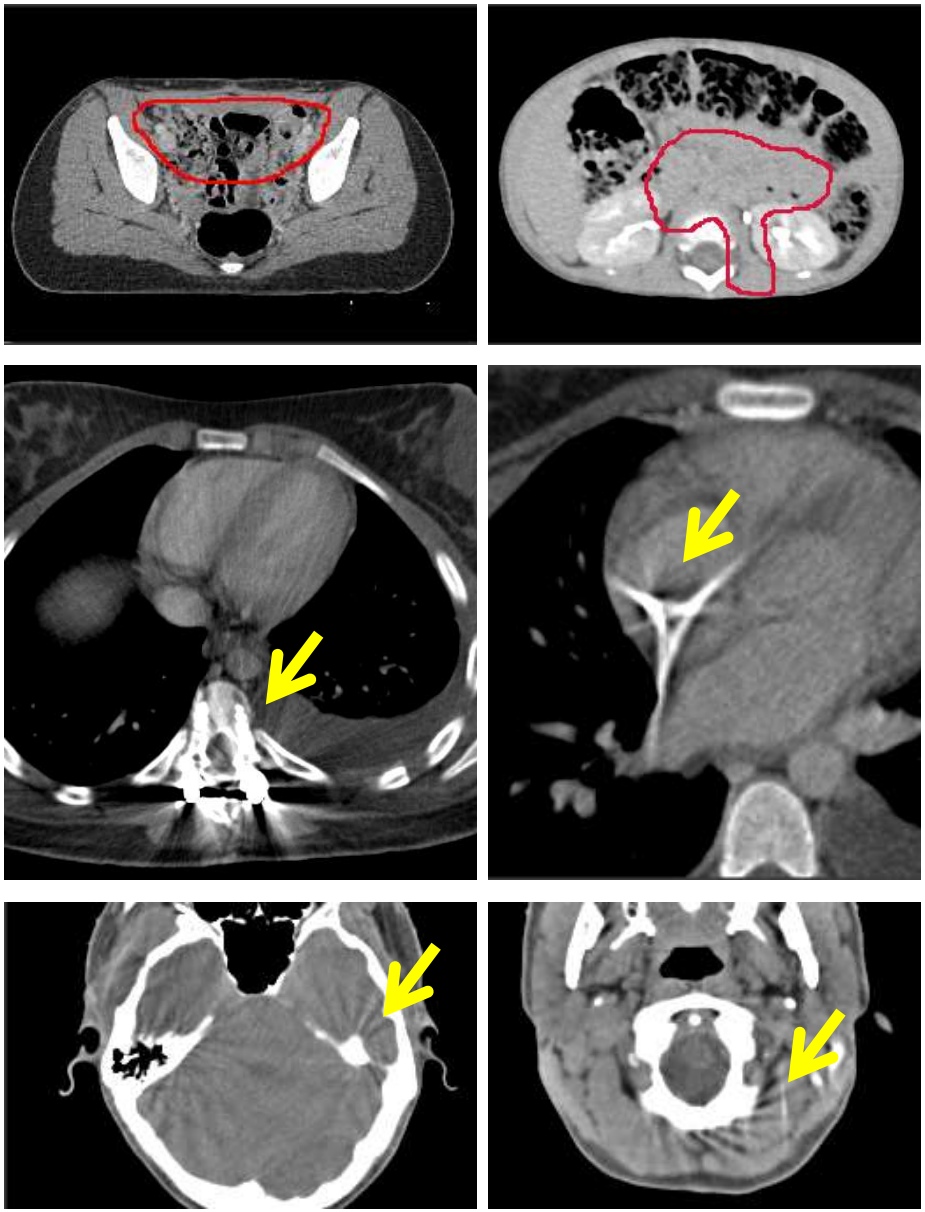
Bowel gas

- Often near neuroblastoma, Wilm's tumor, rhabdomyosarcoma, and bone sarcoma in abdomen and pelvis
- Vary in size and location every day
- Avoid shooting through bowel gas
- Override density within beam path on planning CT? Expect to average out?
- Pose a problem for whole abdominal RT

Metal artifact

- Spinal implant, dental braces, surgical clips
- Apply metal artifact reduction on CT? Need to overwrite CT numbers
- Need to know hardware material to assign proper proton stopping power

Beam hardening artifact without metal



Summary for Pediatric Proton Therapy

- Proton therapy is compelling for children and adolescents because of the promise in reducing **late effects and second cancer risk**.
- Most children used to be treated with passively scattered beams a decade ago but **IMPT with scanning beams** of smaller spot sizes is now dominating.
- Data on OAR tolerance and RBE effects in children are extremely limited. Planners and physicists should be careful in translating photon experience into proton (CT scan, margin design, OAR constraints, beam angle selection, setup and immobilization devices, etc). PENTEC dose-volume recommendations were mostly developed based on photon therapy outcomes.
- Opportunities await and abound for physicists –
  - safe and efficient delivery to this vulnerable patient population
  - disease-specific treatment techniques including reirradiation and motion management
  - uncertainty analysis and margin design
  - sharing planning and delivery experience with the community
  - Proton dose-volume effect modeling

Please contact authors for questions and requests to use materials in this slide set for publication or presentation.

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