Pediatrics: The Greatest Margin of Benefit for Protons

MassGeneral Hospital for Children

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Goals for the talk

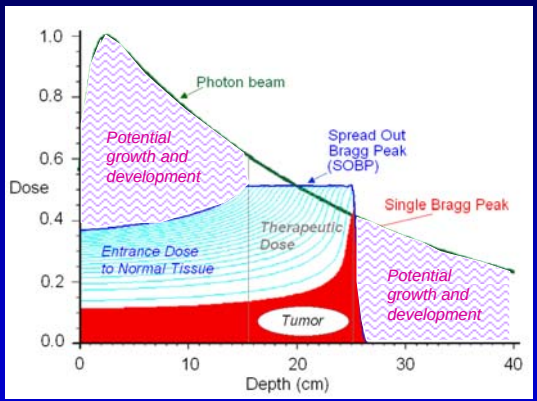
- The clinical cost of radiotherapy in children
- Second malignancy risks and the neutron debate
- Pediatric case selection
- MGH Pediatric Experience--including late effect data
  - Toxicities (Orbit, PM RMS population)
  - Neurocognitive outcomes in brain tumor patients
  - QOL outcomes
- Economics of protons for peds

Radiation Effects in Children

- ***Over 70% of pediatric cancer patients are cured***.
- Late effects of radiotherapy in children can be severe.
- ***Radiation inhibits growth and development of whatever tissue we irradiate*** in a dose dependent manner, (and age dependent manner).
- Brain radiotherapy affects neurocognitive and neuroendocrine function.
- Outside the brain, RT functional and cosmetic effects
- Second malignancy

How can we minimize morbidity in the children requiring radiotherapy?

- ***Minimize dose to normal tissues***
  - *Delay radiation* with chemo to allow development
  - *Use surgery* to try to avoid or dose reduce radiotherapy (ie medulloblastoma)
- High dose conformality is excellent with both IMRT and protons, but protons are much better for minimizing intermediate and low dose to normal tissues, which ARE significant in the kids.
- Growth and development deficits occur with as low doses as 10 Gray

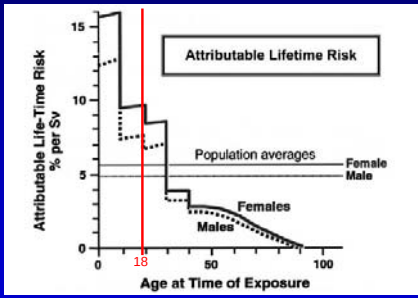


Protons *REDUCE* the 2nd cancer risk

- Mirabell et al mathematically modeled (based on ICRP estimates) the reduction of second malignancy risk in a Parameningeal RMS and a Medulloblastoma patient.
- They found reductions in risk by factor of 2 for the PMRMS and 8-15 for the medulloblastoma case.

Miralbell et al, IJROBP 54:284, 2002;

Attributable lifetime risk of ***RT induced malignancy*** by age and sex



Hall, IJROBP 65:1, 2006

The Neutron Debate: 2nd cancers

- Hall postulated that due to whole body neutron scatter the RT induced malignancy rate could be *increased* compared with photons
- Overstated: 3 major reasons
  1. Experimental data, not clinical data used. Overestimates neutron production
  2. Only total body dose considered; the different integral dose from photons and protons ignored.
  3. No clinically relevant data on carcinogenesis RBE of the energy neutrons generated by clinical proton facilities.
- The clinical data confirms the neutron second malignancy risks are overstated.

Hall et al, IJROBP 2006;65:1-7

2nd Malignancy Proton Study

(Chung et al, ASTRO, 2008)

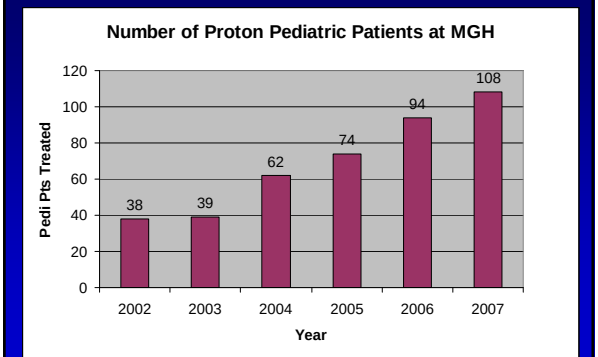
- Comparison of proton patients with SEER photon patients matched by age, histology, year, and site.
- N=1006 patients, proton f/u 6.8 yrs, photons 5.2 yrs
- Crude rates:
  - 6.4% of proton patients developed second malignancies
  - 13.1% of patients treated with photon radiation developed second malignancies
- The incidence rate of second malignancies was 8.2 cancers per 1000 person years for the proton patients and 21.6 per 1000 person years for the photon patients

Which kids get protons?

- Patients with a defined tumor or bed to treat:
  - Curable pediatric brain tumors
    - Ex. Medulloblastoma, LGGs, craniopharyngiomas, ependymoma, etc
  - Curable solid tumors outside of the brain
    - Ex: Rhabdos, Ewings, some neuroblastomas, retinoblastomas, etc.
  - Not as good for poor prognosis patients, as late effects aren't the issue for them.
  - However, we get "palliative" referrals because of decreased acute toxicity as well. (We don't have beam time to accept them)
- We too often have to turn away appropriate patients.
- Allotted times fill up, and as you have seen, protons are a major advance for adults as well as children.

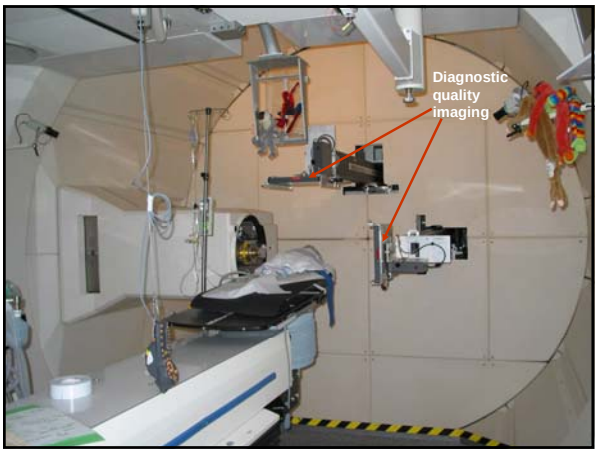
MGH Pediatric Proton Experience

- Currently treating ~60-65 patients per day
- Pediatric 20% of patient numbers
  - Gantry time required
    - 20 minutes (no anesthesia)
    - 30 minutes (anesthesia)
    - 1 hour (CSI) to treat a patient
- As of April 24, 2009:
  - 902 Pediatric patients
  - 367 at HCL (Harvard Cyclotron, 1974-2002)
    - 1st patient, 1974, 4 yo with RMS
  - 535 at BPTC (since 2002)



Pediatric Protocols: Morbidity Reduction

- ***Medulloblastoma:*** hearing, neurocognitive and endocrine endpoints
- ***RMS protocol:*** late effect endpoints (organ function, growth, cosmesis)
- ***Other sarcoma protocol:*** same as RMS
- ***Retinoblastoma:*** morphometric endpoints
- ***QOL protocol:*** PedsQL based assessment, during and after treatment
- Coming soon:
  - ***Misc Brain Tumor Protocol:*** neurocognitive/ neuroendocrine/neurologic endpoints
  - ***Germ Cell Tumor protocol:*** same as above

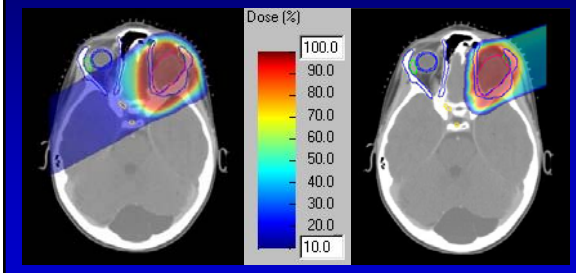


Protons for Orbital RMS: Clinical Late Effects and a Dosimetric Comparison

- 1st 7 patients treated with protons for Orbital RMS reviewed and late effects reported
- Comparison photon plans generated
- Median f/u 6.3 yrs
- 7/7 NED at last f/u, 1 LF salvaged with enucleation and SRS. (age <1, progressed through chemotherapy)

Yock et al, *IJROBP* 63:1161,2005

X-Rays **Protons**



Orbital RMS, pre, during, post

Clinical Late Effects with Protons for Orbital RMS

- Protons appear to decrease the risk of most side effects compared to published accounts
  - All intact treated orbits have excellent vision (impaired in 50%+ with XRT).
  - No cataracts thus far (compare to 50%+ with XRT)
  - No keratitis/conjunctivitis thus far (30% with XRT)
  - No neuroendocrine issues (60%+ with XRT)
  - No painful dry eye (10% with XRT)
  - Only mild orbital asymmetry in our population

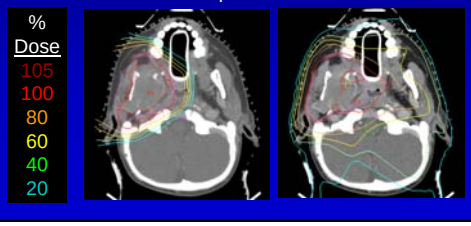
Yock et al, *IJROBP* 63:1161,2005 Oberlin et al. *JCO* 19:197-204, 2001

Parameningeal RMS: Dose Comparison (IMRT v Protons)

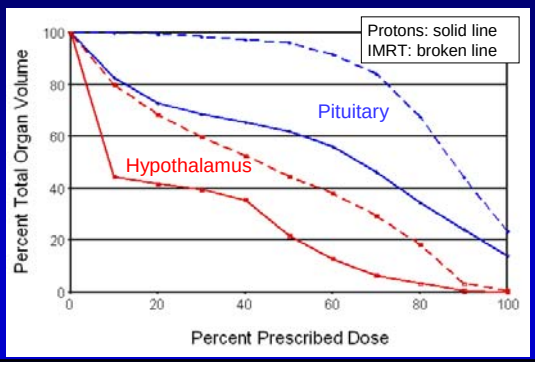
(Kozak, Yock, *in press IJROBP*)

Results:

- Improved dose conformality of protons spared most normal tissues examined except for a few ipsilateral structures such as the parotid and cochlea.



PM RMS collective DVH difference for Protons and IMRT



Clinical Outcome including late effects of PM RMS

(Krejcarek, Yock, PTCOG, 2006, manuscript in preparation)

Patient population:

- 17 patients treated at HCL/BPTC
- 1996-2005
- Data from medical records AND referring physician survey of survivors.

Clinical Outcome for Protons in PM RMS (Krejcarek, Yock, PTCOG, 2006)

Results: Disease control

- ***Median age: 3.4 years [range, 1.5-17.6 years].***
- 59% had intracranial extension (ICE).
- Median dose: 50.4 (CyE) [range, 50.4-55.8 CyGE]
- ***Median f/u of survivors: 4.3 years***
- ***Median time to RT 8 weeks (high for ICE pts)***
- ***3 yr FFS was 58%, 3-year OS 61%***
- 7 patients failed

Late Effect Comparison: PM RMS

(Krejcarek, Yock, PTCOG, 2006)

Late Effect	Protons (MGH) N=10	IRSII-III N=213 *	IMRT: MSKCC N=22**	Iowa N=17 ***
Decreased height	20%	48%	NR	60%
Facial hypoplasia	60%	97%	5%	73%
Visual complications	0%	21%	9%	82%
Hearing loss	0%	17%	NR	75%
Dentition	30%	NR	NR	100%
Cognitive deficits	10%	49%	5%	20%
2nd malignancy	0%	2%	9%	6%

*Raney, 1999; ** Wolden, 2005, (median f/u 2 years); ***Paulino, 2000

Pedi CNS tumors

Radiation to the Brain Causes Neurocognitive Deficits that Manifest with Time

- Primary impairments in:
  - Overall IQ
  - Learning
  - Attention (sustained; working memory)
  - Information processing speed/cognitive flexibility
  - Memory (visual more impaired than verbal)
- Effects could be complicated by chemotherapy—white matter injury is associated with methotrexate and other such medications (many ALL patients exhibit some neurocognitive decline without CSI).

RT Effects on Neurocognition

(Merchant et al. IJROBP 2006; Merchant et al. IJROBP 2005)

- IQ Modeling study performed on Medulloblastoma/ PNET patients and ependymoma patients.
- **Methods:** Correlated dose to brain with IQ over time.
- **Results:**
  - Age is important.
  - Dose to all brain was important. Less dose denoted less effect. "Each Gy of exposure had a similar effect on IQ regardless of dose level."
  - Supratentorial brain was more sensitive than infratentorial brain to effects on IQ.

Improved IQ profile in kids with Medullo, Optic Glioma, and craniopharyngiomas

(Merchant et al. Ped Blood Cancer 51:110, 2008)

- 10 patients each treated with IMRT and planned with protons for medullos, cranios, and optic gliomas. (ependymomas too)
- Applied math models based on IQ decline and dosimetry showed decreased dose to normal brain predicted improved IQ outcome.

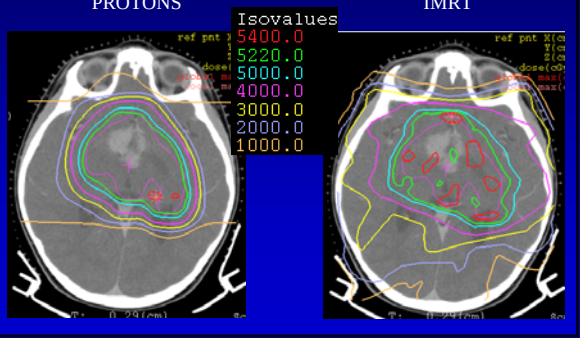
Pediatric Low Grade Gliomas—MGH Experience: (Yock, 2008, ISPNO Chicago)

Patient population:

- 36 pts with Who grade I/II gliomas age ≤21 treated 1995-2006
- median age 10.5 (2-21)
- 58% supratentorial, 31% infratentorial, 11% spinal gliomas.
- Median dose: 52.2 (49.8 to 54 GyE).

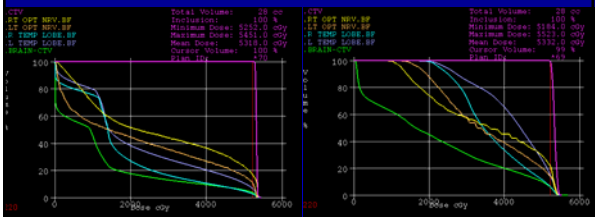
IMRT vs 3D Proton comparison

PROTONS IMRT



3D Proton vs IMRT comparison

PROTONS IMRT

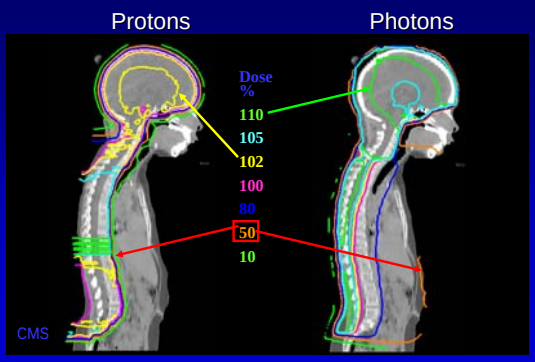


Pediatric Low Grade Gliomas—MGH Experience: (Yock, 2008, ISPNO Chicago, manuscript in progress)

Results:

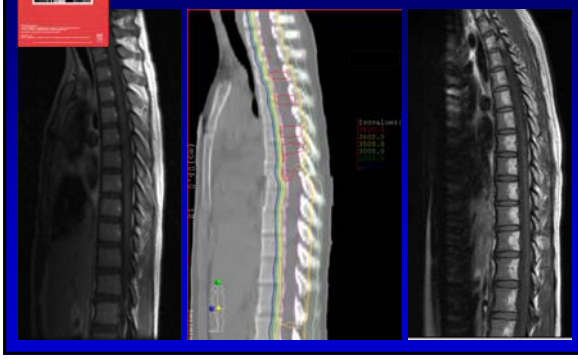
- Median f/u: **39 months** (1.5-12 yrs)
- At median f/u: PFS and OS was 100%
- Two pts failed at 4.1 and 4.4 yrs
- Crude rate DFS: 94%, OS 100%
- 28 neuropsyche assessments, 8 patients have baseline (BL) and f/u evaluations.
  - Average BL and FU spanned 2.3 years.
  - ***No significant loss of IQ (and 5 other measures) detected yet.***
- 38% had neuroendocrine deficits at baseline, and 47% patients developed a new deficit after radiotherapy.

Medulloblastoma: CSI

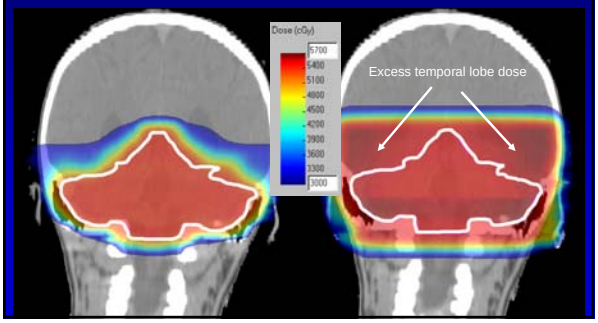


Proton CSI: Thecal Sac Only

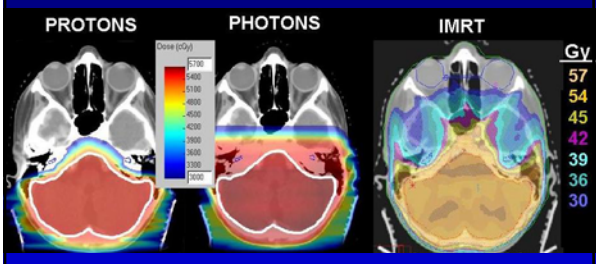
Krejcarek,Yock IJROBP 68:646-649, 2007



Medulloblastoma
Whole Brain + Posterior Fossa Boost



Medulloblastoma: Comparison of RT Technique for PF Boost



Proton Neuropsychologic Data

- Hypothesis: Protons should improve the neurocognitive outcomes in pediatric brain tumor patients receiving RT.
- Prospective neurocognitive assessments in pediatric proton patients with brain tumors lesion since September 2002.
- Cohort
  - 153 assessed at baseline
  - 37 baseline & follow-up (at MGH, f/u at outside institutions not included)

Areas of Functioning Assessed

- Intelligence
- Language
- Visual-Spatial/Motor
- Attention/Executive Functioning
- Memory
- Processing Speed
- Academic Achievement
- Behavior (and Emotional)
- Adaptive Abilities

DATA TO BE PRESENTED

- Still preliminary and unpublished so it is not distributed with the syllabus

Conclusions from Neuropsychological Data

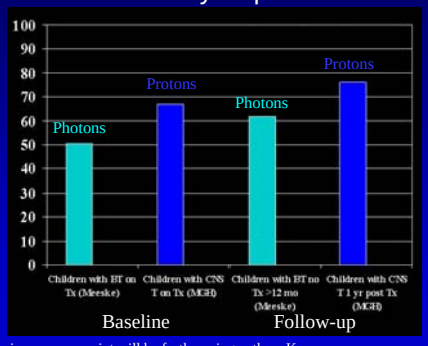
- At nearly 2 year follow-up after proton radiation, no significant change in overall neurocognitive functioning.
  - Including IQ, language, attention/working memory, cognitive flexibility, academic skills, behavior and adaptive skills.
  - Results ***compare favorably*** to reports from photon radiation treatment. (Supports Merchants math models).
- Declines seen in aspects of executive functioning: visuospatial organization and processing speed suggestive of white matter injury (also seen with photon irradiation).
- Baseline difficulties in visual organization/memory (Rey) persisted at follow-up.

Note: Preliminary, manuscript will be forthcoming authors M Pulsifer and T Yock

MGH Pediatric CNS Tumor Assessments

- Assessments twice during radiation and annually thereafter
- Assessing with:
  - PedsQL generic
  - PedsQL brain tumor module (formerly cancer and pain modules)
  - For above using both the child and parent proxy tools
- Neurocognitive assessments
- Our cohort is 154 children assessed at treatment of whom 123 have CNS tumors, 77 with at least one year follow-up

PedsQL Scores Compared to Published Data Parent Proxy Report



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K Meeske et al. Cancer, 2004

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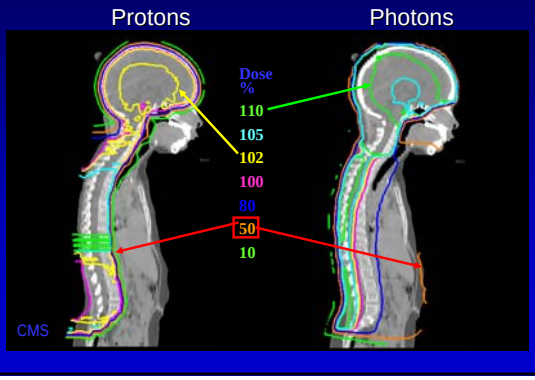

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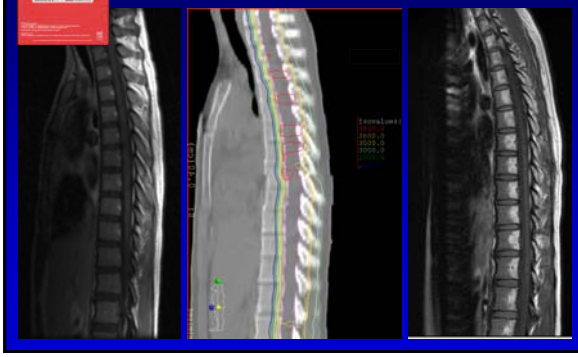
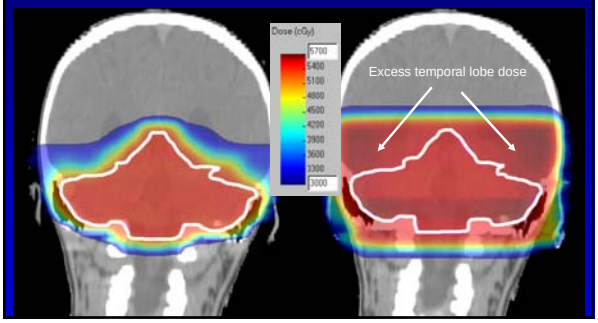


Medulloblastoma
Whole Brain + Posterior Fossa Boost

Protons **Standard Photons**



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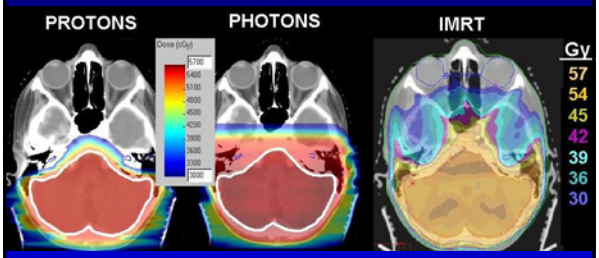

Case Mix Economics: Charges
Prostate vs CSI

- Gantry treated patients fall in to 3 treatment categories: simple, intermediate and complex.
- Charge per treatment (technical only)
  - Simple: 1 unit
  - Intermediate: 1.4 units
  - Complex: 2 units
- Example: prostate cancer is considered “simple”, treated in 12 minutes. CSI is considered complex, treated in 60 minutes. 5 Prostate cancer treatments can be achieved in 60 minutes with 2.5x the benefit in compensation.

Ethics vs. Economics - Pediatrics

- Pediatric patients arguably stand to benefit more than other patients from proton therapy
- Reimbursement per machine time-unit is typically less (a lot less)

Prostate versus CSI: Medicare Reimbursements

- Medicare reimbursement for treatment course
  - ~ $40,460 prostate treatment course (40 tx, 12 minutes)
  - ~ $43,431 CSI/boost (30 tx, 20 CSI, 60 minutes, 10 boost, 20 minutes)
- Medicare reimbursement per hour
  - ~ $5,000/hr in the room for prostate
  - ~ $1,900/hr in the room for CSI pt

Marc Bussiere and S MacDonald

Does NOT include

- Planning time for physics staff
  - 20 hours for CSI plan
  - 3 hrs for prostate plan
- Additional time for physicians (radiation oncologists and others)
- Anesthesia (time in room increases)
- Nursing (more intensive nursing needed for CSI and pedi patients)

Economics versus Ethics

- Currently, there is an economic disincentive to treat pediatrics (protons), but the benefits are clear and data is coming available to show that.
- When debating the utility of protons PLEASE PLEASE PLEASE consider the worthwhile populations outside of the prostate proton debate.

Overall Conclusions:

- The majority of pediatric solid tumor patients are cured--making late effects of therapy problematic due to impacts on growth, development and second malignancy risks.
- ***Proton radiation is the most conformal*** external beam radiotherapy available in the US, and dramatically reduces dose to normal tissues.
- The data presented here show that protons reduce the late effects including:
  - Toxicity
  - Second malignancy risks
  - Neurocognitive effects
  - AND improve QOL
- ***It should become the standard of care in children over the next 5-10 years***

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Thank you!

MassGeneral Hospital for Children

Thank you!

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