Role of protons, heavy ions and BNCT in brain tumors

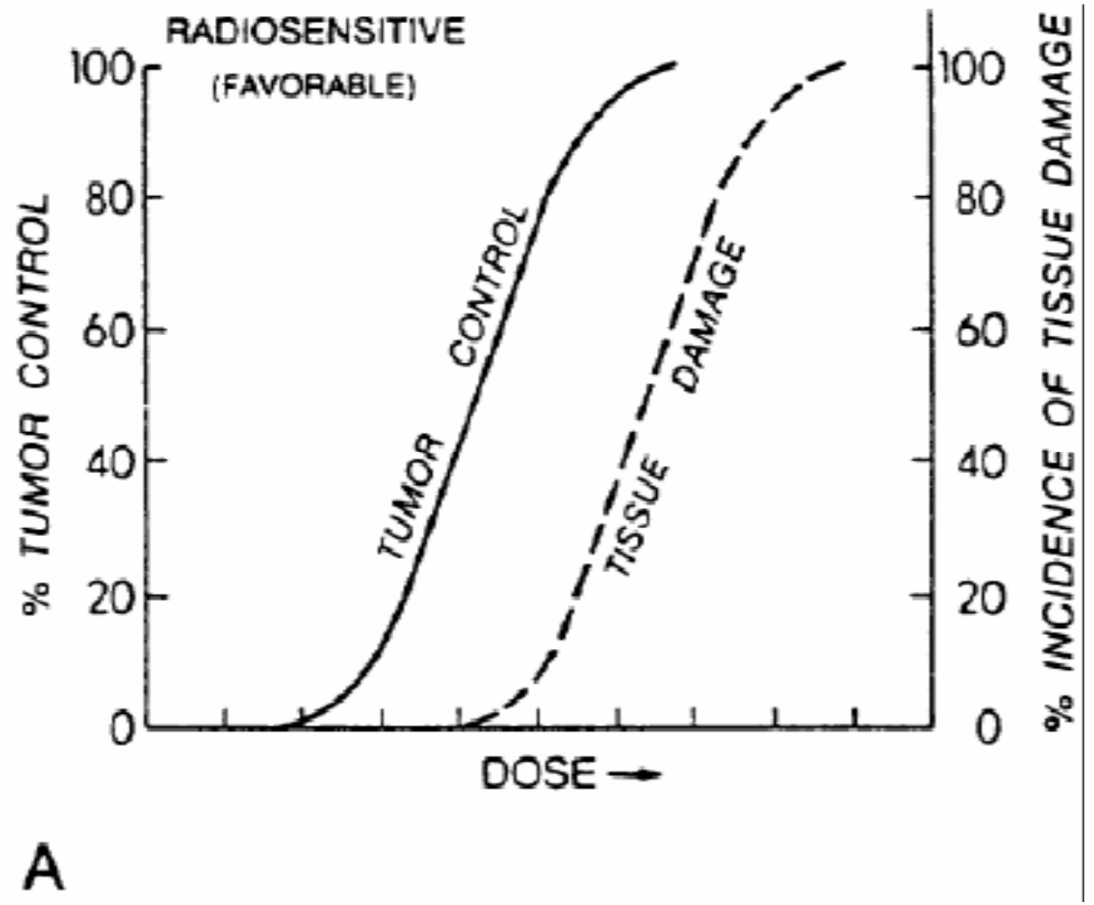
Prof G K Rath
Head, NCI (AIIMS-2)
Chief, Dr. BRA IRCH, Professor Radiation Oncology
All India Institute of Medical Sciences, New Delhi

Overview of presentation

- Physics of Protons, Heavy ions
- Radiobiology of Protons, Heavy ions
- Rationale and Indications of protons
- Dosimetric and clinical results of protons
- Principles of boron neutron capture therapy (BNCT)
- Clinical results and challenges of BNCT
- Conclusion

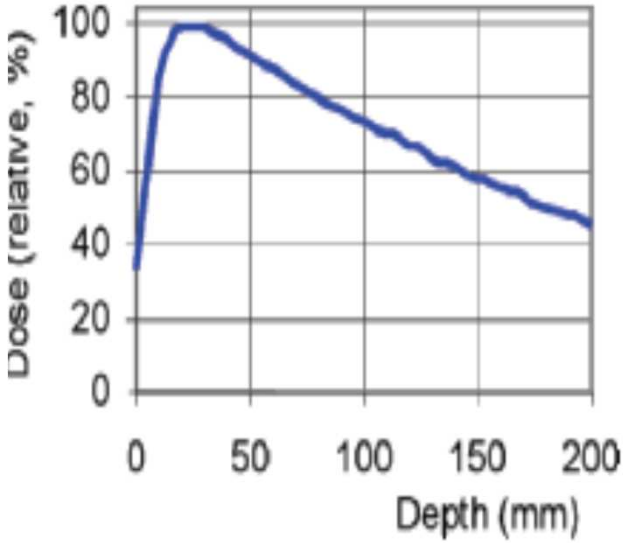
Aim of Radiation therapy in clinical practice

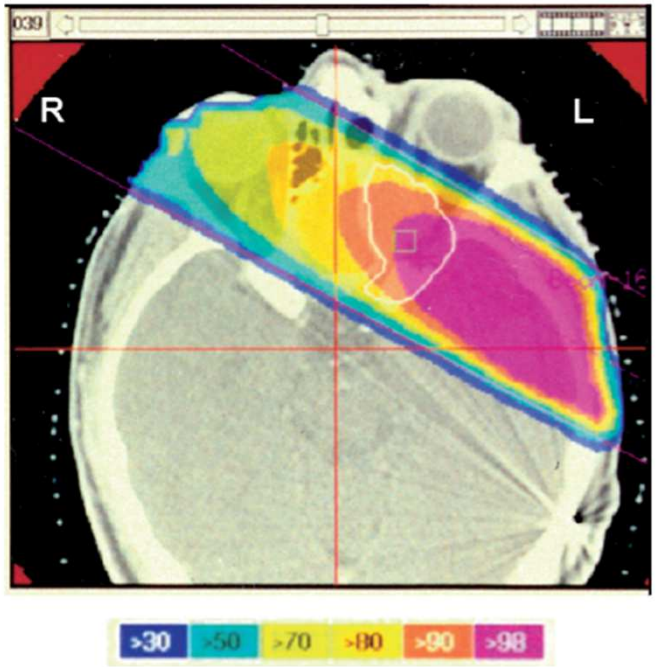
Complete eradication of tumor & Minimal normal tissue toxicity



Radiation with Tissue: Physics

- Number of photon gets attenuated as depth increases .
- The dose that they deposit decreases also (proportionately).
- Entry dose and exit dose



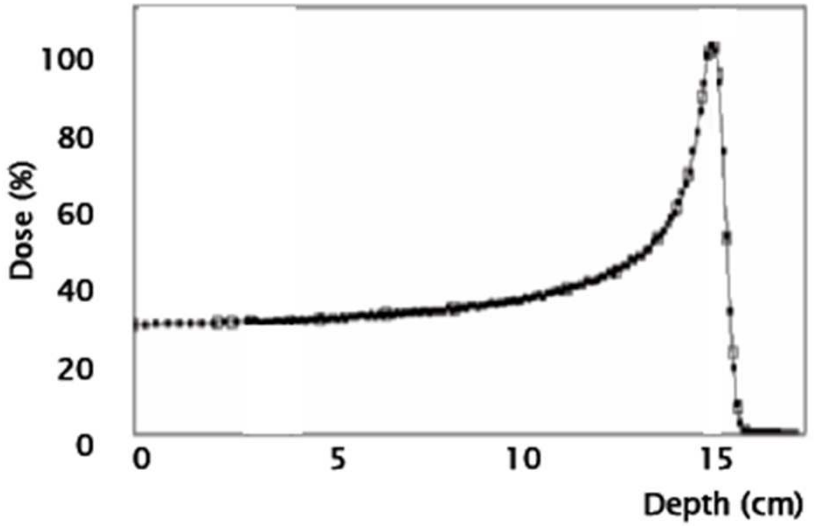


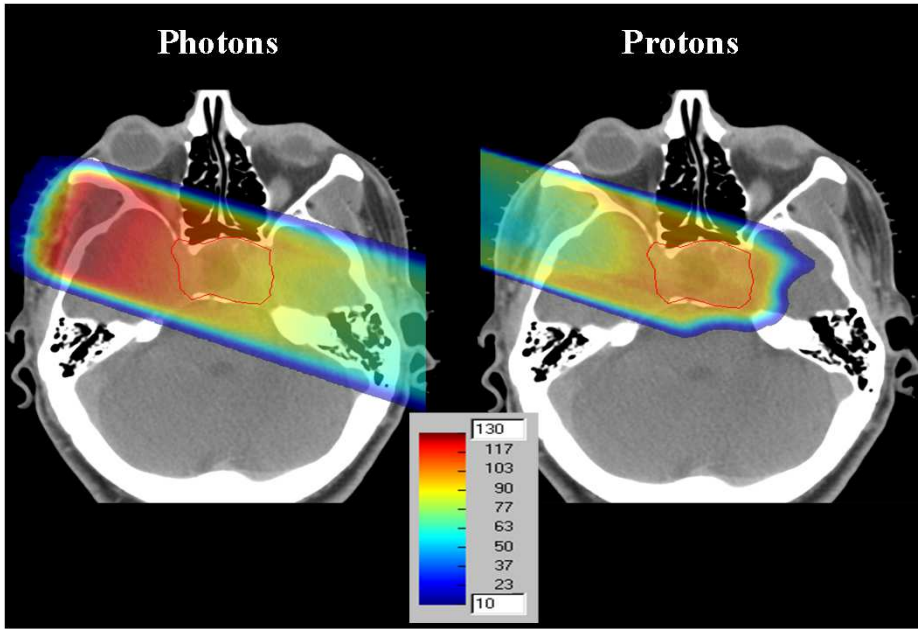
Limitations of Conventional Photon based treatments

- Significant exit dose
- Dependent biological effect on oxygen (indirect effect; 70-80%)
- Dose escalation not possible beyond a limit
- Second malignancies

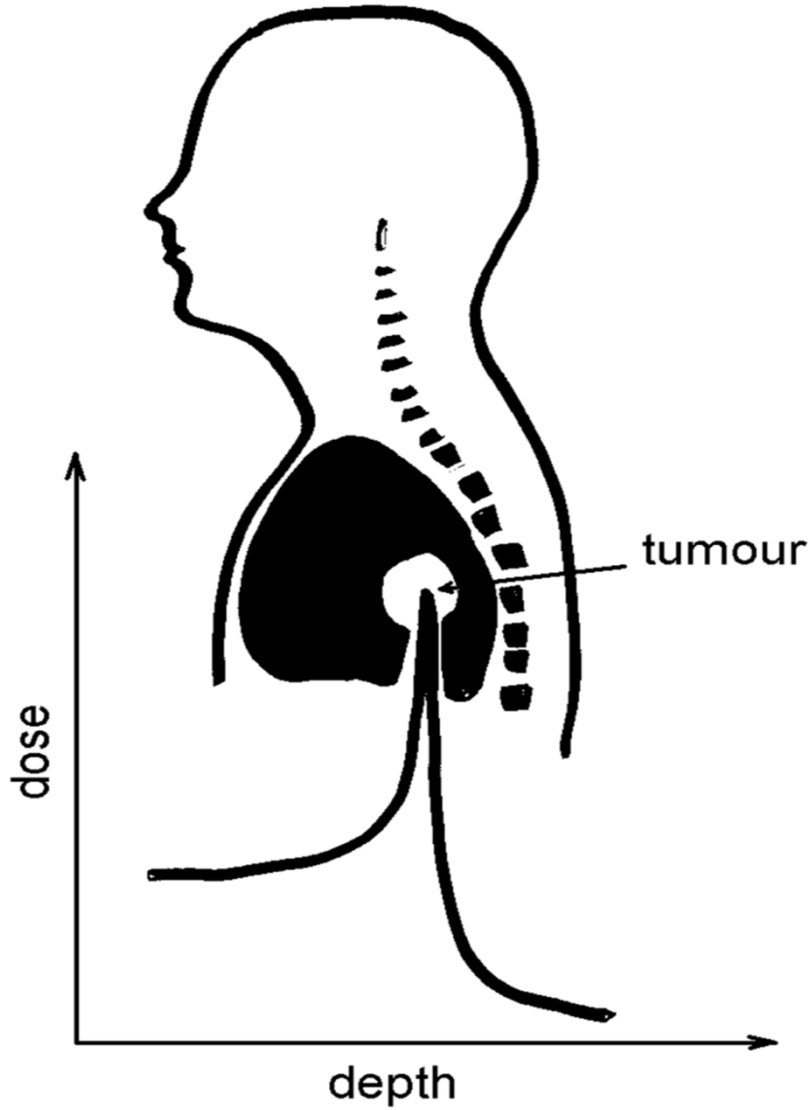
Proton dose distribution

- Low entrance dose (plateau)
- Maximum dose at depth (Bragg peak)
- Rapid distal dose fall-off



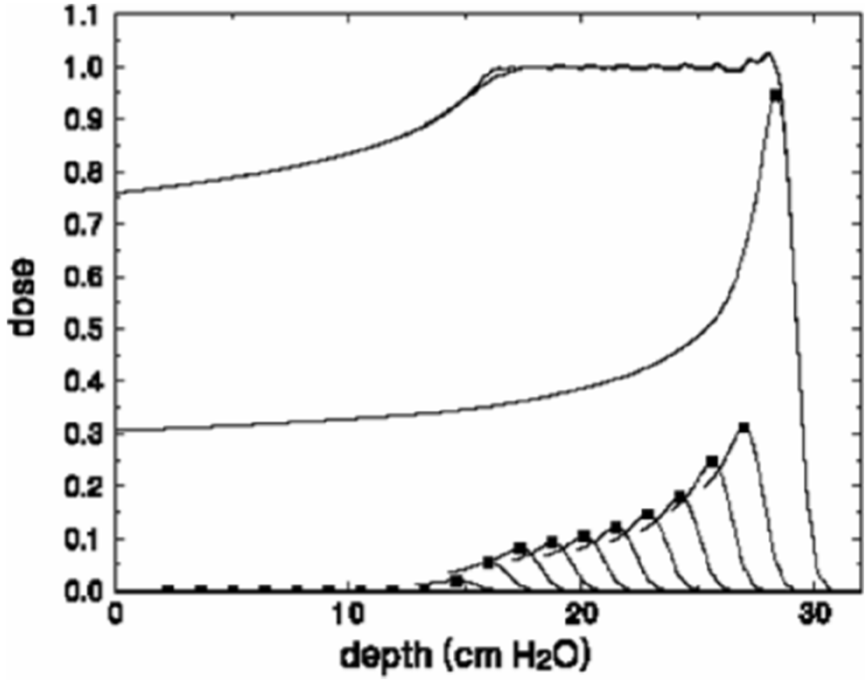


Problem with the “Bragg Peak”



Spread out Bragg Peak

- The spread-out Bragg peak (SOBP):
  - Extending the dose in depth
  - Many Bragg peaks with different energies



Superposition of Bragg-peaks by energy variation

Relative Biological Effectiveness of proton

- Relative biologic efficiency is a ratio of doses from two beams to produce the same effect
- RBE = dose (standard beam)/dose (test beam).
- Protons has exactly the same biologic effects as X-rays: RBE is 1.1

Similar biological effect with improved physical properties!!

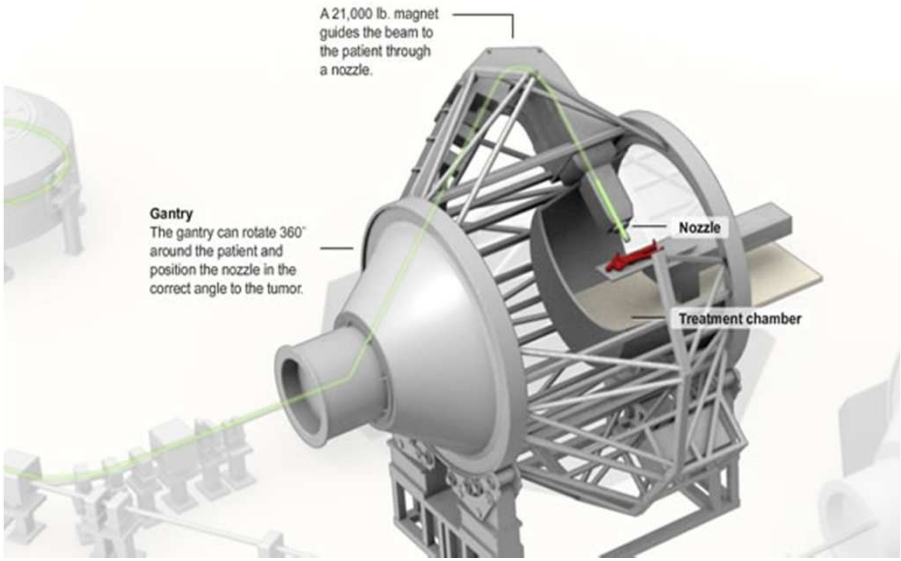
End of History and Beginning of a New future!!

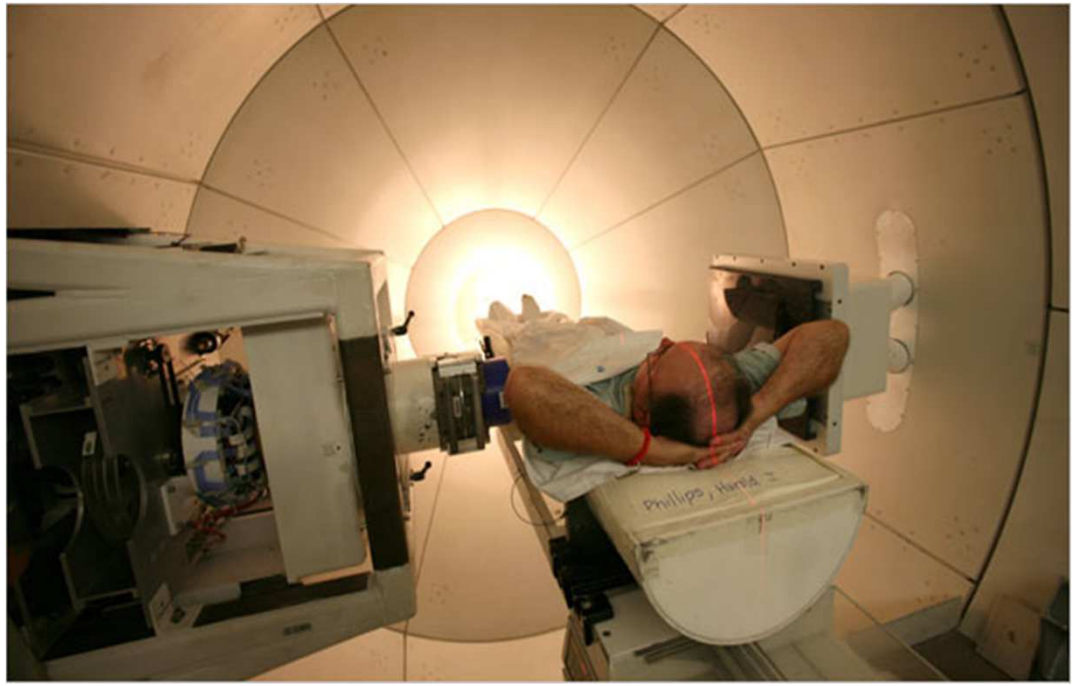
- 1954: First treatment of pituitary tumors
- 1958 : First use of protons as a neurosurgical tool
- 1990: First hospital based proton therapy facility was opened at the Loma Linda University Medical Center (LLUMC) in California.

LOMA LINDA UNIVERSITY
MEDICAL CENTER

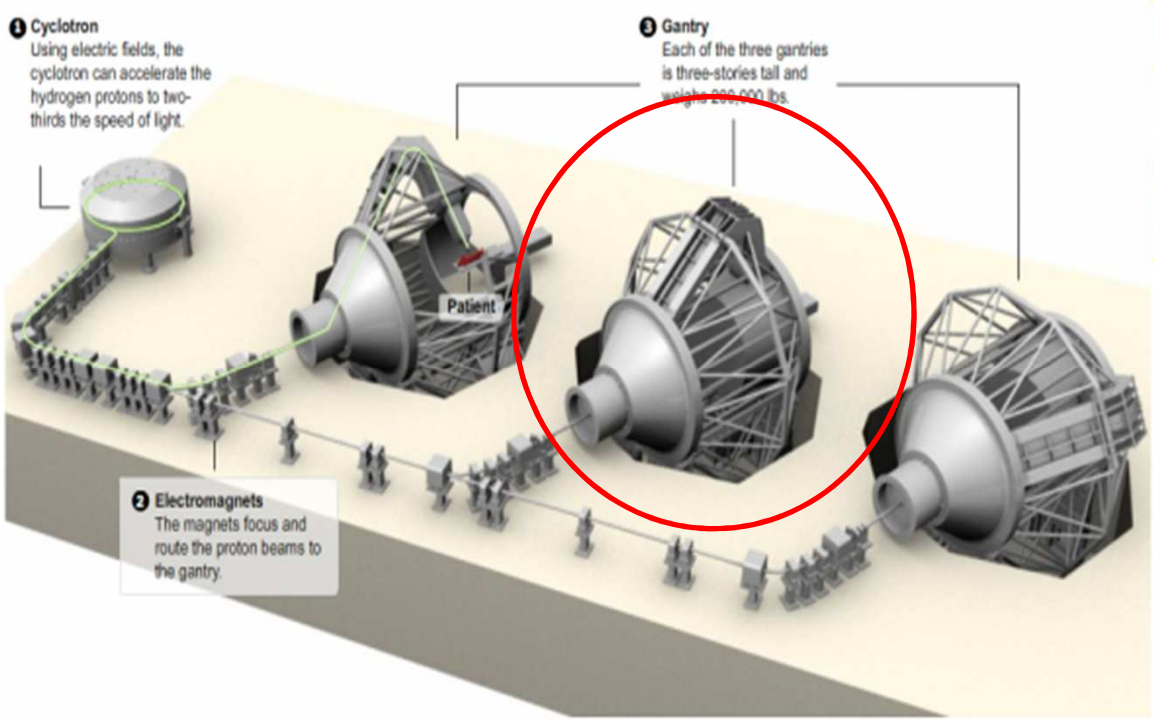
Components of proton beam therapy

- Proton accelerator
- Beam transport system
- Treatment Rooms
- Gantry
- Standard table





Cyclotron and Beam Line



Potential use of protons in CNS

- Reduction of toxicities & second neoplasms: pediatric tumors
- Dose escalation: Increase control & survival
  - Skull base tumors
  - HGG
  - Benign tumors: Acoustic neuroma, AVMs
- In adults: decrease neurocognitive deficits- LGG

Particle therapy for CNS tumors: So far

- Several dosimetric studies:
  - Protons versus photons
  - Majority suggest better or equivalent than IMRT or stereotactic techniques for tissue sparing
  - IMPT: Improves homogeneity & conformality
- Very few prospective trials
- Limited number of patients treated
- Follow up of patients short in these trails

Indications of protons & heavy ions

- Re-irradiation
- Benign brain tumors:
  - Vestibular Schwannomas/Acoustic Neuromas
  - Meningioma
  - Pituitary adenoma
  - Arteriovenous malformation
- Skull base tumors: Chordoma/Chondrosarcomas
- **Pediatric brain tumors**: Medulloblastoma, Ependymoma, Pilocytic astrocytoma, Germ cell tumors
- Low grade & High grade glioma
- Others

TCP/NTCP rationale

Chordoma
Chondrosarcoma
Other sarcomas

High dose RT
Sensitive structures

G2/3 meningioma

Higher dose RT
Large volume

GBM

Mixed Data

G1 meningioma, pit adenoma, LGG, mets

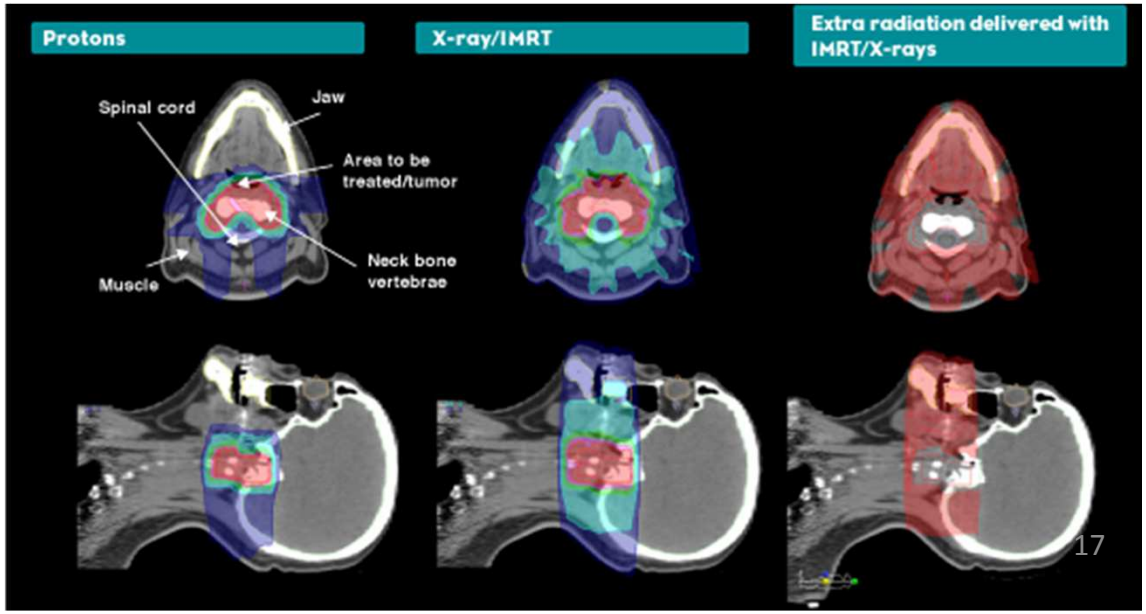
Good tumor control
?Benefit of PRT

Chordomas/ Chondrosarcoma /Meningioma

- **Local control of chordomas* > 80%, better than conventional photon therapy**

- **5 year local control rates >95% and OS >90% for skull base Chondrosarcoma*****

- **Meningioma** : 3 years local control of 92–100% with grade 3 or greater toxicity of 0–12.5%**



***Habrand JL et al IJROBP 2008;71:672–5**
****Weber DC et al. Radiother Oncol 2004;71:251–8**
*****Ares C et al. IJROBP 2009;75:1111-18**

Rationale for use of protons for pediatric CNS tumors

- **Most results are for Medulloblastoma & Ependymoma**
- **Better sparing of OARs**:
  - Cochlea and heart [St Clair et al. Int J Radiat Oncol Biol Phys 2004;58:727–34]
  - Hippocampus & Sub ventricular zone [Blomstrand et al. Neuro Oncol 2012;14:882–9]
- **Cost-effective**
  - Reduced oto-toxicity, endocrine deficiency, cardiac disease, secondary malignancy [Cancer 2013;119:4299–307]

NEURO-ONCOLOGY

Proton radiotherapy for pediatric central nervous system ependymoma: clinical outcomes for 70 patients

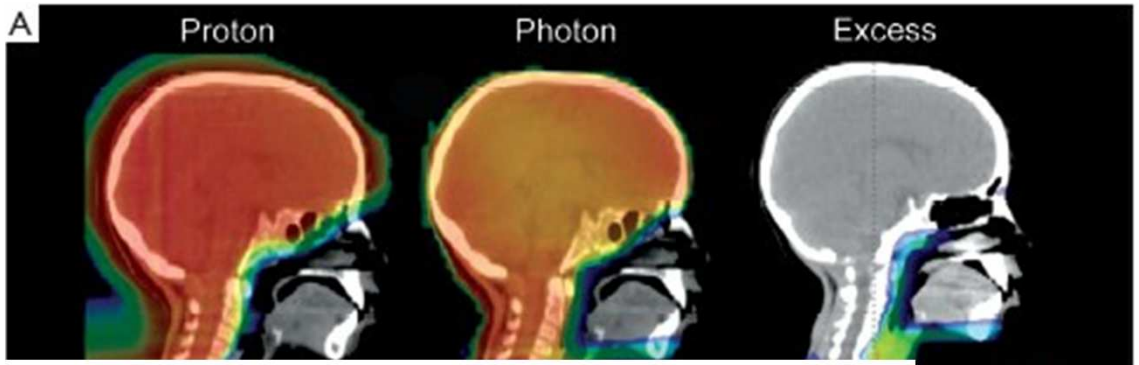
Neuro-Oncology 15(11):1552–1559, 2013.

Shannon M. MacDonald, Roshan Sethi, Beverly Lavally, Beow Y. Yeap, Karen J. Marcus,

- 70 patients (2000-2011; t/t at MGH)
- 27% Supratentorial and 73% Infratentorial.
- 66% GTR and 34% STR
- Median follow up: 46 months
- 3 year local control, PFS, OS: 83%; 76%; 95% respectively compare favorably with photons
- *Merchant et al reported 5 year PFS: 74% & 5 Year OS: 85% treated with* ***photon beam therapy***

Medulloblastoma : A case scenario for ideal PBT

Dosimetric Advantage: lesser radiation dose to OARs



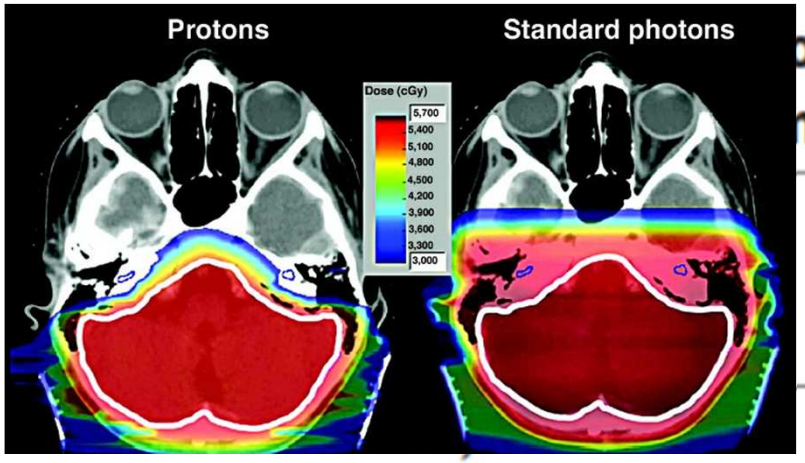
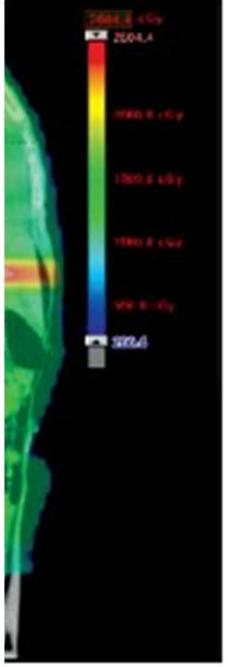


Table 2 Dose to cochlea and heart by radiation delivery
ospinal irradiation for
na

	Dose to 90% of the cochlea, %	Dose to 50% of the heart volume, %
Intensity modulated x-ray beam	101.2	72.2
Proton beam	33.4	29.5
	2.4	0.5



Medulloblastoma: Late Toxicity

Table 1 Estimated risk of radiation-induced cancer by radiation delivery technique following spinal irradiation for childhood medulloblastoma

Radiation delivery technique	Risk of radiation-Induced cancer, %
Intensity modulated x-ray beam	30
Electron beam	21
Conventional x-ray beam	20
Intensity modulated electron beam	15
Intensity modulated proton beam	4

Medulloblastoma: Clinical outcome

- Limited and mixed literature
- Early clinical outcomes favorable and encouraging
- **MGH Experience***: 15 patients treated to a median CSI dose of 21.6 Gray and boost dose of 54.0 Gy. Median follow up 39 months , local control >90%
- **Adult patients**: 2 year PFS of 94% for protons versus 85% for photons treated with same protocol

*Jimenez RB et al. IJROBP, 2013;87(1):120-26

** Brown et al. IJROBP 2013;86:277-284

Patterns of Failure After Proton Therapy in Medulloblastoma: Linear Energy Transfer Distributions and Relative Biological Effectiveness Associations for Relapses

Roshan V. Sethi, BS,* Drosoula Giantsoudi, PhD,† Michael Raiford, MD,†

Volume 88, Issue 3, 1 March 2014, Pages 655–663

- 109 patients of Medulloblastoma [2002-2011; treated at MGH]
- Median follow up: 38.8 months (1.4-119.2 months)
- 16 relapses/109 patients: patterns of failure similar to photon beam therapy
- No failure in 70 patients with involved field tumor bed boost
- ***Promising results!!***

Cost-Effectiveness of Proton Radiation in the Treatment of Childhood Medulloblastoma

Cancer 2005;103:793–801.

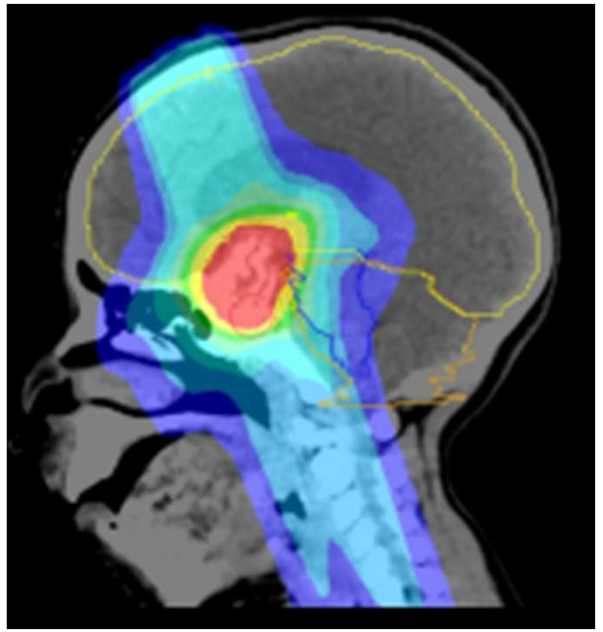
TABLE 1
Cost and Clinical Outcome per Patient for the Base-Case Assumptions

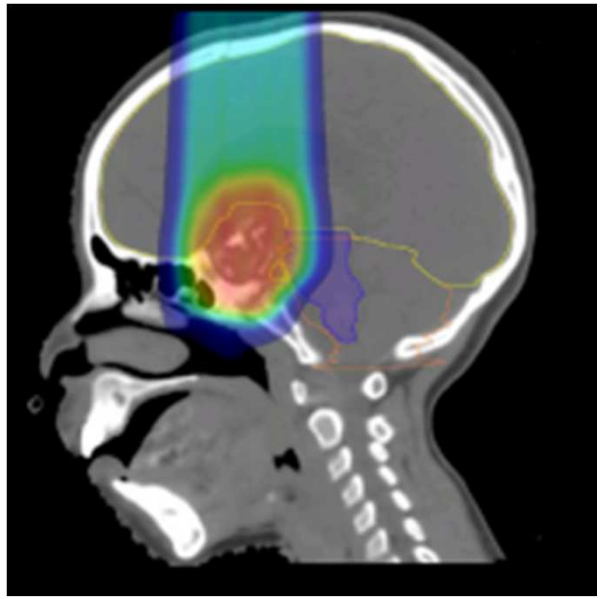
Variable	Proton radiation	Conventional radiation	Difference
Radiation cost (€)	10217.9	4239.1	5978.8
Cost from adverse events (€)	4231.8	33857.1	−29625.3
Total cost (€)	14449.7	38096.2	−23646.5
LYG	13.866	13.600	0.266
QALY	12.778	12.095	0.683

Craniopharyngioma

- **MGH Experience***
  - 15 patients (5 child &10 adults; 1981-1988) treated at MGH with combined photon+proton
  - 10 year survival rate:72%; 5 year & 10 year local control rates: 93% & 85%
- **Loma Linda Experience**
  - 15 patients
  - 14/15 local control
  - Only 1 patient had pan-hypo-pituitarism

* Fitzek M. IJROBP 2006; 64 (5):1348-1354





Pituitary tumors

- 2 studies of proton-SRS for functioning pituitary tumors- MGH - Petit et al
  - Acromegaly (22 pt) - 59% off meds at 6.3 y
  - ACTH (38 pt) – CR 100% with Nelsons, 52% with Cushings

- 1 study with fractionated proton (Ronson et al)
  - Loma Linda – 47 pt 54 GyRBE, LC 100%, Hormone control in 19/21 secreting tumors
  - 1 temp tip necrosis at 19 mo, 7 new visual changes, 11 pt with new hormonal deficiencies

AVMs/Acoustic Neuromas

- **Single fraction stereotactic proton RT for AVM***: Median time to obliteration 31 months; 5 & 10 year cumulative obliteration rates: 70% & 90% respectively [Equivalent to photon therapy]
- **Acoustic Neuromas****:
  - 95-100% local control rates
  - ~90% preservation of facial and trigeminal nerves
  - Hearing preservation rates: 50-60%

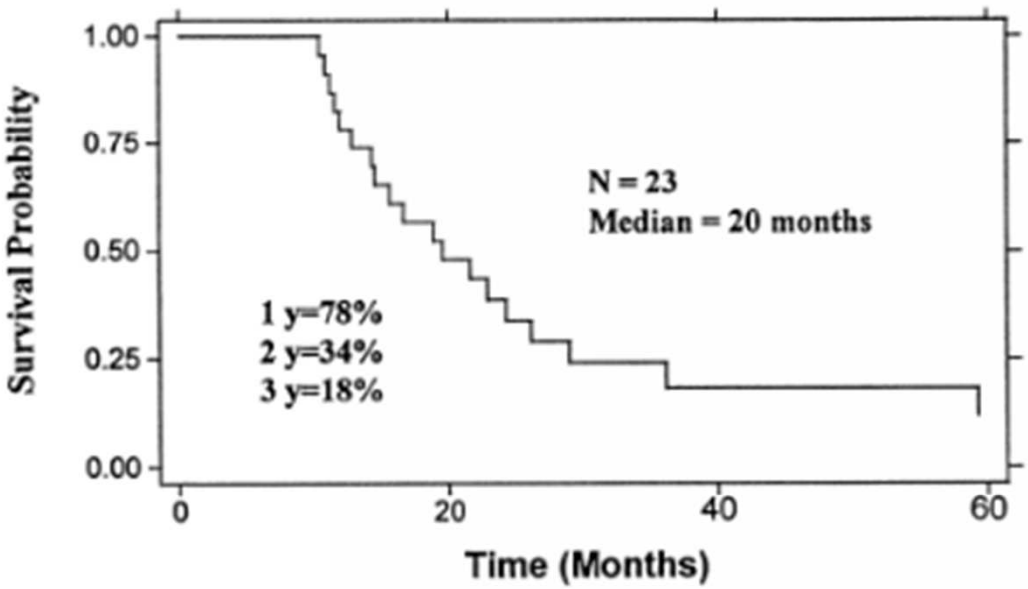
*Hattangadi-Gluth JA et al. IJROBP 2014;89(2):338-46

**Weber DC et al. Neurosurgery. 2003 Sep;53(3):577-86

MGH Glioblastoma trial

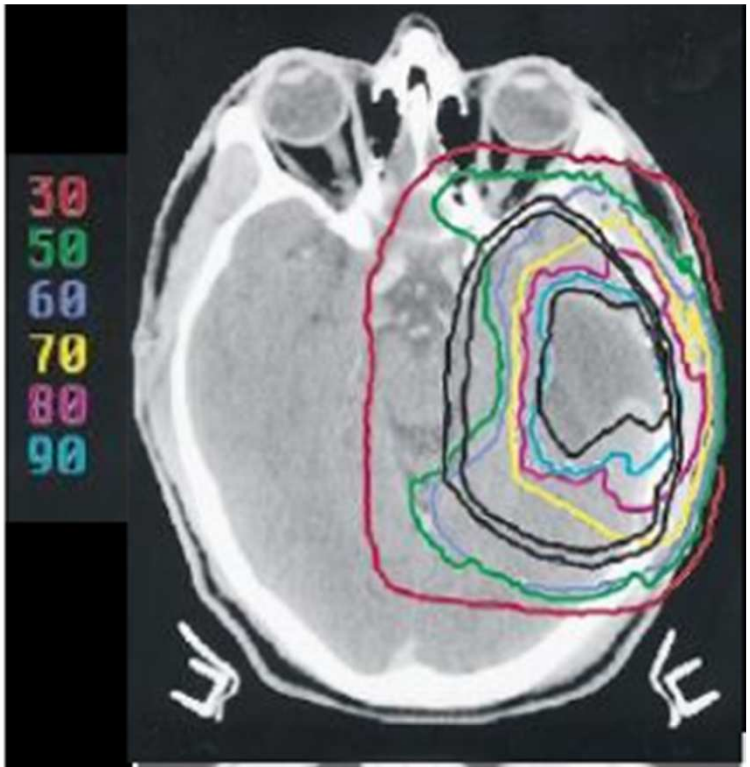
- 23 patients 1992-1996
- 3D planning:
  - V1= surgical cavity+residual 90.0 CGE
  - V2=V1 + 2cm 64.8 CGE
  - V3=T2 + 2cm 50.4 CGE
- BID regimen with P+X, P>33% of dose
- Med OS 20 mo from dx, 2y OS 34%, 3y OS 18%
- High incidence of steroid use, 57% had surgery after RT

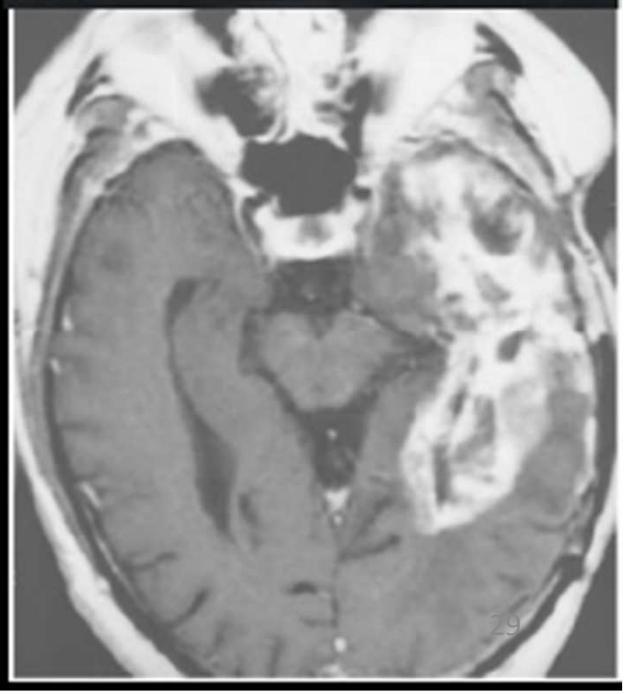
Treatment effect 90CGE



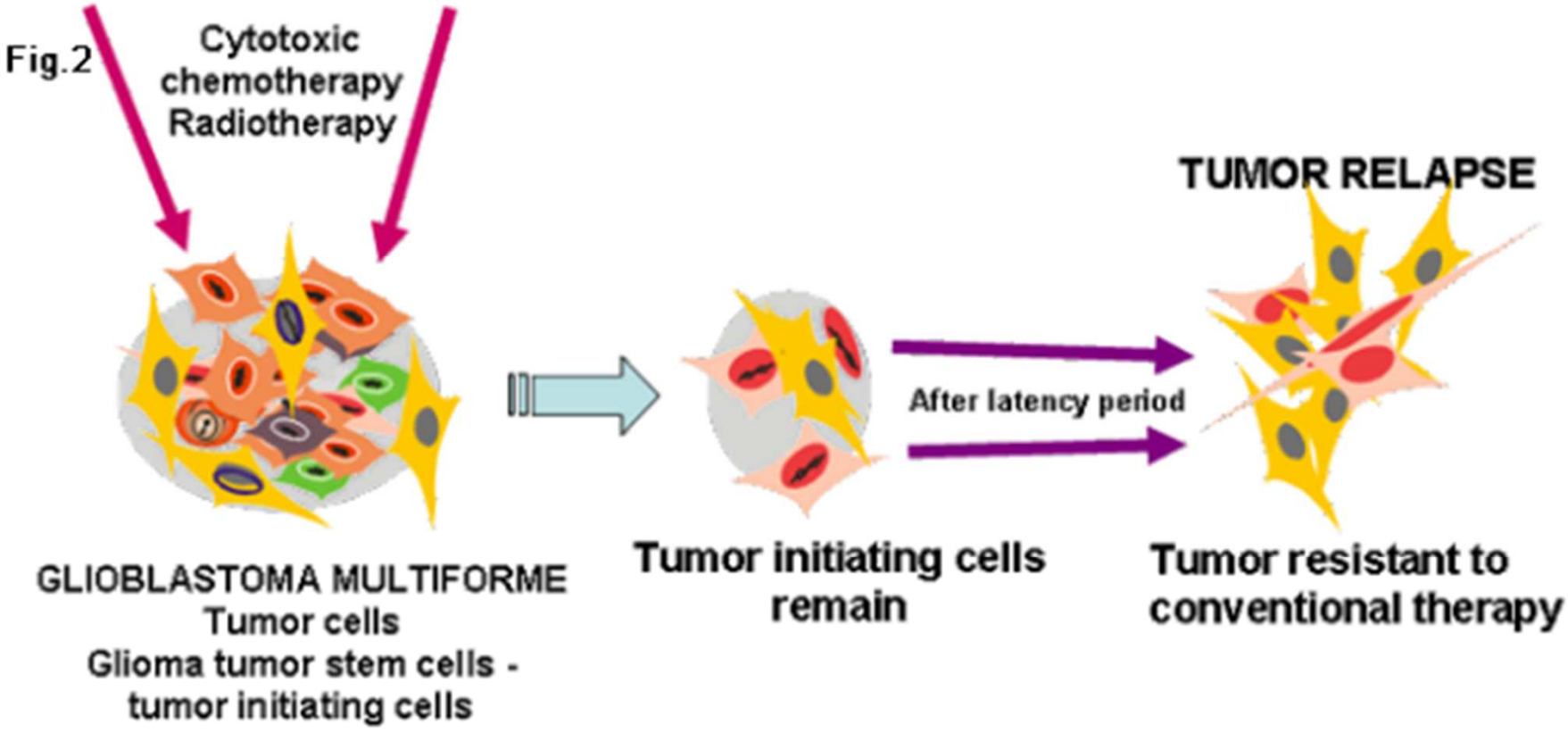
*Reoperation following development of clinical and imaging changes after radiotherapy**

Op No. & Type	No. of Patients	Necrosis Only	Necrosis W/ Tumor
2nd			
biopsy	8	6	2
resection	5	4	1
3rd			
biopsy	1		1
resection	6	4	2
4th			
biopsy	1	1	
resection	1	1	

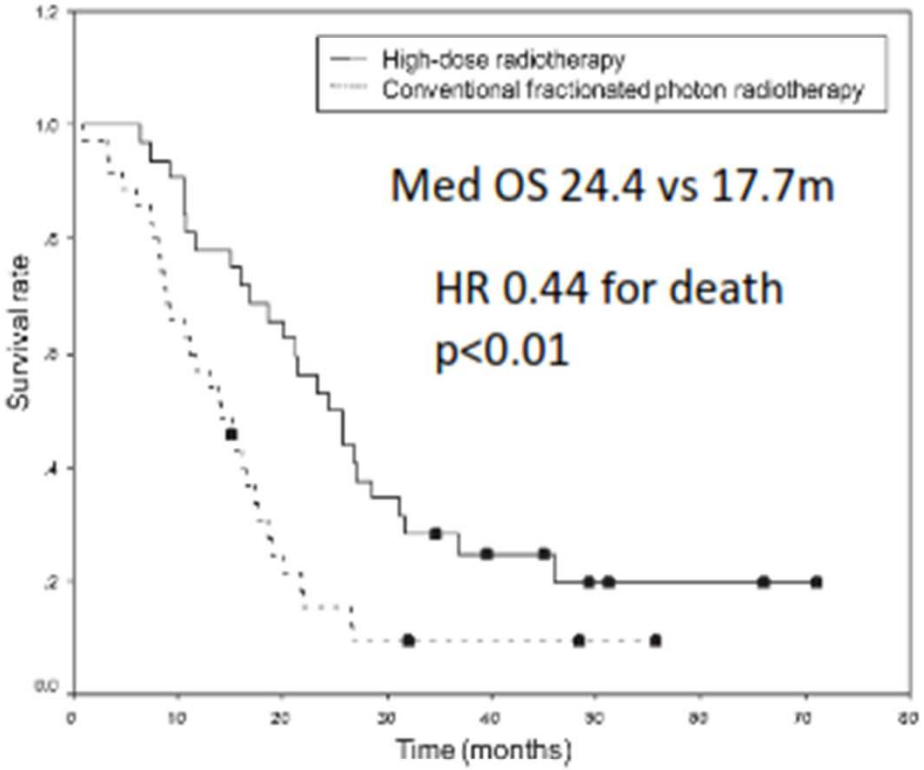




Dose Escalation for Malignant Glioma- Overcome Resistance to Therapy



Conventional vs high dose Retrospective



- Conventional
  - Photons 60-61.2 Gy / 30-34
- High Dose (with particles)
  - BNCT: 30GyE/1 + 30Gy/15
  - Proton: 50.4Gy/28 photons +/- 23.1GyE/14 boost to GTV
- Multivariate analysis
  - WHO PS
  - RPA class
  - High vs Low dose RT

Matsuda et al BJR, 84, S54-60, 2011

Re-irradiation for Gliomas

- N=18, proton re-irradiation for recurrent glioma
- Median dose: 50.4 CGyE
- Median OS:
  - 12.4 mo bev-naïve pt
  - 7.4 mo bev-refractory pt
- Radiation necrosis: 1 grade 3 (brainstem glioma reRT), 1 grade 2
- Large-volume re RT with proton for recurrent glioma appears to be safe with promising OS outcomes

*Desai BM et al. IJROBP 2014; 90: S286

Second Malignancies: PBT

- MGH-Harvard Cyclotron Laboratory
- Matched 503 HCL proton patients with 1591 SEER patients
- Median f/u: 7.7 years (protons) and 6.1 years (photon)
- Second malignancy rates
  - **6.4% of proton patients (32 patients)**
  - **12.8% of photon patients (203 patients)**
- **Photons are associated with a higher second malignancy risk**: **Hazard Ratio 2.73, 95% CI 1.87 to 3.98, p< 0.0001**

Chung et al. ASTRO 2008

Ongoing randomized trials

- **GBM: Proton versus Photons (IMPT vs. IMRT):**
  - https://clinicaltrials.gov/show/NCT01854554
  - Currently recruiting: MDACC,Texas
  - Prospective phase II randomized trail
  - Primary outcome: Time to neurocognitive failure
- **GBM: Dose escalated Proton versus Photons**
  - Prospective phase II study [OS primary aim]
  - Multicentric study; PI: Minesh Mehta
  - Conventional RT (60 Gray) vs. Dose escalated (50 Gray in 30# with SIB of 75 Gray/30#)
- **GBM CLEOPATRA Trail [Germany]**
  - Phase II randomized study comparing proton boost with carbon ions (10 GyE in 5# versus 18 GyE in 6#)

Carbon Ion trail for HGG

- 1994 – 2002: 48 patients
  - 16 AA, 32 GBM
  - 50Gy Photons+ escalating C ion (16.8 - 24.8 GyE in 8 fractions over 2 wk)
  - Median survival AA 35 mo, GBM 17 mo
  - No grade 3 acute reaction
  - 8 grade 2 late reactions

* Mizoe et al IJROBP, 69, 390-396, 2007

Challenges in Proton Therapy

- Technical challenges: Beam and Range Uncertainties
- Motion management: Not incorporated in to routine practice
- Imaging: Onboard for treatment verification not available
- Limited phase III RCTs
- Cost effectiveness

Technology Development

- Multi-leaf Collimators
- Cone Beam CT scan
- On-Board PET Imaging
- Intensity Modulated Proton therapy (IMPT)
- Single room proton therapy delivery systems

Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No

Herman Suit[a,*], Hanne Kooy[a], Alexei Trofimov[a], Jonathan Farr[b], John Munzenrider[a]
Thomas DeLaney[a], Jay Loeffler[a], Benjamin Clasie[a], Sairos Safai[a], Harald Paganetti[a]

[a]Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, [b]Midwest Proton Radiotherapy Institute, Bloomington, IN, USA

Radiotherapy and Oncology 86 (2008) 148–153

- Clinical and dosimetric superiority obvious
- Talent, effort and funds for Phase III trials huge!!
- Sample size required is large for certain clinical endpoints
- Alternative is to pool data in Registry

Time to adopt and see the results (Safety and efficacy already documented)

Economics of Proton therapy

Photons:

- Initial set up cost less
- Operating cost less
- Machines depreciation: 7-10 years
- Longer treatment course
- Higher costs: Treatment toxicity and disease recurrences

Protons

- Initial set up cost 10 folds more
- Operating cost 1-3 fold higher
- Machine depreciation: 20-40 years
- Shorter treatment course
- Cost effective: Less toxicity and effective

High Tech Photon therapy vs. Proton therapy

Photons:

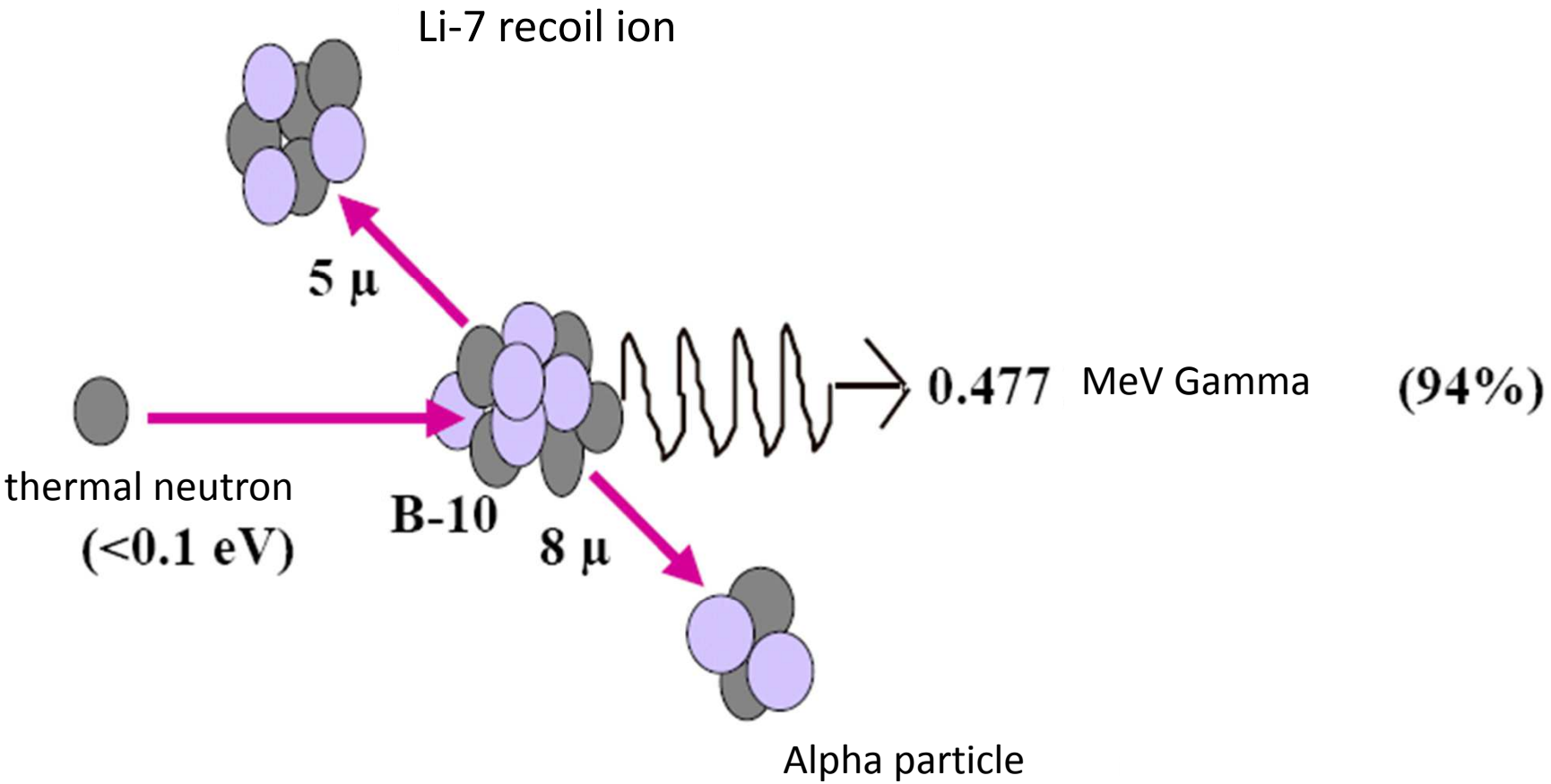
- Vast experience, time tested
- Level 1 evidence
- Multiple motion management options
- Onboard Imaging
- Dose prescription/plan evaluation/organ constraints standardized

Protons

- Limited experience
- Level 1 evidence for 1-2 cancers
- Motion management NA
- No onboard imaging
- Standardized guidelines lacking

The BNCT Reaction

2.33 MeV of kinetic energy is released per neutron capture:
initial LET 200-300 ke V/µm



Rationale behind use of BNCT

- **Highly localized t/t:**
  - Thermal neutrons interact with boron containing tumor cells
  - The charged particles produced are limited to the tumor area working as “magic bullets”
- **Radiobiological Advantages:**
  - High LET radiation: steeper cell survival curve and lower OER
  - Higher RBE compared to X-rays

Clinical results with BNCT

- Sweet et al [MIT, 1950s]: 18 patients of GBM, massive brain necrosis. Later also sued for the trails.
- At present, BNCT facilities have ceased in USA. This is active in few areas like Japan & China
- **Impressive results reported from Japan by Kawabata et al***
  - 21 patients [10 with BNCT alone; 11 with BNCT & EBRT 20-30 Gray]
  - Mean OS OF 20.7 months; Median 15.6 months
  - Showed survival benefit for all RPA classes
- Future trails evaluating: BNCT & Temozolomide; BNCT & EBRT

* Appl Radiat Isot. 2009 Jul;67(7-8 Suppl):S15-8

Challenges with BNCT

- Inadequate tumor specificity of boron compounds
- Considerable contamination of thermal neutrons with gamma rays & fast neutrons
- Interaction of normal tissues with thermal neutrons: causing damage to non-boron containing tissues
- **Future efforts:**
  - Tumor selective agents like L-4 dihydroxyborylphenylanine (BPA); BPA-Fructose
  - Modification of nuclear reactors with selective neutron production
  - Use of alternative neutron sources like californium.
  - Development & evaluation of dosimetric techniques

Conclusions

- Proton therapy and heavy ions have potential for enhanced TCP and decreased NTCP
- Dosimetric superiority as compared to photon based treatments
- Clinical evidence limited to few tumors sites
- Promising role in pediatric CNS tumors, chordomas, Chondrosarcoma
- Randomized trails underway for GBM: Results awaited
- Role of BNCT controversial and needs research