Role of protons, heavy ions and BNCT in brain tumors

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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
• 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.
Components of proton beam therapy

- Proton accelerator
- Beam transport system
- Treatment Rooms
- Gantry
- Standard table
Cyclotron and Beam Line

1. Cyclotron: Using electric fields, the cyclotron can accelerate the hydrogen protons to two-thirds the speed of light.

2. Gantry: Each of the three gantries is three-stories tall and weighs up to 100 lbs.

3. Electromagnets: The magnets focus and route the proton beams to the gantry.
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 trials
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

- **Good Evidence**
  - Chordoma
  - Chondrosarcoma
  - Other sarcomas
  - G2/3 meningioma
  - GBM

- **Not Much Data**
  - G1 meningioma, pit adenoma, LGG, mets

- **High dose RT Sensitive structures**
  - Mixed Data
  - Higher dose RT Large volume
  - 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
***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:
- Cost-effective
  - Reduced oto-toxicity, endocrine deficiency, cardiac disease, secondary malignancy [Cancer 2013;119:4299–307]
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: Spinal irradiation for medulloblastoma

<table>
<thead>
<tr>
<th>Dose to 90% of the cochlea, %</th>
<th>Dose to 50% of the heart volume, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protons</td>
<td>Standard photons</td>
</tr>
<tr>
<td>101.2</td>
<td>72.2</td>
</tr>
<tr>
<td>33.4</td>
<td>29.5</td>
</tr>
<tr>
<td>2.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Intensity modulated x-ray beam
Proton beam
# Medulloblastoma: Late Toxicity

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

<table>
<thead>
<tr>
<th>Radiation delivery technique</th>
<th>Risk of radiation-Induced cancer, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity modulated x-ray beam</td>
<td>30</td>
</tr>
<tr>
<td>Electron beam</td>
<td>21</td>
</tr>
<tr>
<td>Conventional x-ray beam</td>
<td>20</td>
</tr>
<tr>
<td>Intensity modulated electron beam</td>
<td>15</td>
</tr>
<tr>
<td>Intensity modulated proton beam</td>
<td>4</td>
</tr>
</tbody>
</table>
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
• 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


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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Proton radiation</th>
<th>Conventional radiation</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation cost (€)</td>
<td>10217.9</td>
<td>4239.1</td>
<td>5978.8</td>
</tr>
<tr>
<td>Cost from adverse events (€)</td>
<td>4231.8</td>
<td>33857.1</td>
<td>-29625.3</td>
</tr>
<tr>
<td>Total cost (€)</td>
<td>14449.7</td>
<td>38096.2</td>
<td>-23646.5</td>
</tr>
<tr>
<td>LYG</td>
<td>13.866</td>
<td>13.600</td>
<td>0.266</td>
</tr>
<tr>
<td>QALY</td>
<td>12.778</td>
<td>12.095</td>
<td>0.683</td>
</tr>
</tbody>
</table>
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  
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

![Kaplan-Meier survival curve](image)

- **N = 23**
- **Median = 20 months**

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

<table>
<thead>
<tr>
<th>Op No. &amp; Type</th>
<th>No. of Patients</th>
<th>Necrosis Only</th>
<th>Necrosis W/ Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd biopsy</td>
<td>8</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>2nd resection</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>3rd biopsy</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>3rd resection</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>4th biopsy</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4th resection</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* indicates additional details about reoperation.
Dose Escalation for Malignant Glioma - Overcome Resistance to Therapy

Fig. 2

Cytotoxic chemotherapy
Radiotherapy

GLIOBLASTOMA MULTIFORME
Tumor cells
Glioma tumor stem cells - tumor initiating cells

Tumor initiating cells remain

After latency period

Tumor resistant to conventional therapy

TUMOR RELAPSE
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](https://clinicaltrials.gov/show/NCT01854554)
  - Currently recruiting: MDACC, Texas
  - Prospective phase II randomized trial
  - 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 into 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

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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

\textit{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 keV/µm

Li-7 recoil ion

thermal neutron
(<0.1 eV)

B-10
8 µ

0.477 MeV Gamma

(94%)

Alpha particle
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