Update on Proton Therapy for Brain Tumors

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Penn Brain Tumor Academy: Innovation Meets Best Practice
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Disclosures

None relevant to topic

Genentech, advisory board
Outline

• What is proton therapy?
• Potential clinical benefits of proton therapy
• Potential clinical benefits of proton therapy in brain tumor patients
• Clinical experiences of proton therapy in CNS patients
Proton: Hydrogen atom nucleus
Proton beam

Dose (%)

Depth (cm)
Protons vs Photons

Proton beam vs Photon beam

Single energy proton beam vs 6MV X-Rays

Radiation dose vs Depth into tissue

Graphs showing the comparison between proton beams and photon beams in terms of radiation dose distribution.
Passive Scattering: Proton Spread Out Bragg Peak

[Graph showing dose vs. depth in water with a peak labeled SOBP]

Jones DTL: [www.canberra.edu.au/.../vol15no34/mempap.html]
Proton Delivery Systems

Passive Scattering/Double Scattering (DS)

Pencil Bean Scanning (PBS)
Pencil beam scanning CSI
MGH Proton Radiosurgery Experience

1961-1991
Kjellberg (HCL)
2929 cases

1991-2002
STAR (HCL)
754 cases

2002-present
FHBPTC Gantry (MGH)

2004-present
FHBPTC STAR (MGH)
Proton stereotactic radiosurgery
Potential benefit of proton radiation

• Reduction of normal tissue radiation exposure
  ▪ Result of less upstream dose, no exit dose, and sharp lateral fall off
  ▪ May reduce radiation-related side effects

• Ability to dose escalate
  ▪ Result of Bragg peak
  ▪ May improve local control with same or lower radiation toxicity

• Achieving a more uniform dose delivery to the target
  ▪ Physical property of protons with either SOBP or PBS
  ▪ May reduce toxicity to underlying normal tissues
Greatest Gains with Protons

Greatest gain for protons is where the largest reduction in integral dose can be achieved

- Large target volume, e.g. craniospinal irradiation
- Large target relative to the affected organ; e.g. eye
- High doses, e.g. chordoma
Rationale of proton therapy in the CNS

Patients & disease:

• Benign tumors

• Curable/controllable tumors, with expectant at least moderately long-term survival

Anatomy & dosimetry:

• Proximity to critical radiation sensitive structures
  ▪ e.g., optic chiasm, pituitary

• Large volume targets
  ▪ e.g., craniospinal

• High doses
  ▪ e.g., AVM

• Patients with increased radiation sensitivity
  ▪ e.g., pediatrics

AND
Gliomas
MGH Pilot LGG Study

• To demonstrate the feasibility of proton therapy in the management of LGG patients, toxicity, & outcomes
• 20 patients
• Eligibility
  ▪ WHO grade 2 low-grade glioma
  ▪ Standard indication for radiation therapy (new diagnosis, progression)
• Treatment
  ▪ 54 Gy(RBE), 30 fractions
  ▪ Target: T2/FLAIR, enhancement, cavity, 1 cm CTV
• Patients removed from study at time of disease progression
Dosimetric superiority of Protons

Protons

Photons

Shih HA et al. Cancer 2015
Assessments

• Neurocognitive function
  ▪ Intellect
  ▪ Language
  ▪ Visuospatial & motor function
  ▪ Attention and executive function
  ▪ Memory

• Neuroendocrine evaluation
  ▪ Growth hormone axis
  ▪ Hypothalamic pituitary adrenal (HPA) axis
  ▪ Hypothalamic pituitary thyroid axis (HPT)
  ▪ Hypothalamic pituitary gonadal axis (HPG)
  ▪ Prolactin

• Quality of life/ emotional functioning

• Toxicity
  ▪ Graded by CTCAE v3

• Progression free survival

• Overall survival
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
</tr>
<tr>
<td><strong>Median Age</strong></td>
<td>37.5</td>
</tr>
<tr>
<td></td>
<td>(range 22-56)</td>
</tr>
<tr>
<td><strong>Disease Status</strong></td>
<td></td>
</tr>
<tr>
<td>Newly Diagnosed</td>
<td>8</td>
</tr>
<tr>
<td>Recurrent Tumor</td>
<td>12</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>7</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>4</td>
</tr>
<tr>
<td>Mixed Oligoastrocytoma</td>
<td>9</td>
</tr>
<tr>
<td><strong>MIB-1 Index (n=13)</strong></td>
<td>3.3%</td>
</tr>
<tr>
<td></td>
<td>(range 0-12%)</td>
</tr>
</tbody>
</table>

Shih HA et al. Cancer 2015
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>9</td>
</tr>
<tr>
<td>Temporal</td>
<td>5</td>
</tr>
<tr>
<td>Frontotemporal</td>
<td>3</td>
</tr>
<tr>
<td>Parietal</td>
<td>2</td>
</tr>
<tr>
<td>Occipital</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presenting Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>10</td>
</tr>
<tr>
<td>Weakness</td>
<td>5</td>
</tr>
<tr>
<td>Numbness</td>
<td>3</td>
</tr>
<tr>
<td>Memory Loss</td>
<td>3</td>
</tr>
<tr>
<td>Imbalance</td>
<td>2</td>
</tr>
<tr>
<td>Confusion</td>
<td>0</td>
</tr>
</tbody>
</table>
MGH Pilot LGG Proton Study

Results:
- Proton therapy well tolerated
- No decline in any neurocognitive endpoints at 4 years
- No decrement in emotional function or QOL
- All but 1 patient with new endocrine deficit had RT to HPA
- No atypical or severe toxicities experienced

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>3 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>100%</td>
<td>95%</td>
<td>81%</td>
</tr>
<tr>
<td>Progression free survival</td>
<td>100%</td>
<td>85%</td>
<td>45%</td>
</tr>
<tr>
<td>New endocrine deficit</td>
<td>15%</td>
<td>25%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Shih HA et al. Cancer 2015
Neurocognitive & QOL outcomes:
No drop in function or status

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests</th>
<th>Baseline Score: Mean ± SD (Range)</th>
<th>Average Score Change per Year: Average ± SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual</td>
<td>WAIS-III Full Scale IQ</td>
<td>0.47 ± 0.56 (-0.47, -1.40)</td>
<td>0.07 ± 0.04</td>
<td>.1400</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>WAIS-III Perceptual Organization Index</td>
<td>0.54 ± 0.69 (-0.60, -2.33)</td>
<td>0.13 ± 0.05</td>
<td>.0187</td>
</tr>
<tr>
<td>Language</td>
<td>WAIS-III Verbal Comprehension Index, Boston Naming Test, Auditory Naming Test</td>
<td>-0.50 ± 2.19 (-5.72, -1.00)</td>
<td>0.07 ± 0.09</td>
<td>.4462</td>
</tr>
<tr>
<td>Attention and working memory</td>
<td>WAIS-III Working Memory Index and Spatial Span; Continuous Performance Test: Inattention Score and Vigilance Score</td>
<td>0.24 ± 0.49 (-0.37, -1.58)</td>
<td>0.04 ± 0.04</td>
<td>.3292</td>
</tr>
<tr>
<td>Processing speed</td>
<td>WAIS-III Processing Speed Index; Trail Making Test A</td>
<td>0.06 ± 0.83 (-1.86, -1.33)</td>
<td>0.10 ± 0.07</td>
<td>.1679</td>
</tr>
<tr>
<td>Executive function</td>
<td>Trail Making Test B; Controlled Oral Word Association Test F-A-S; Wisconsin Card Sorting Test; Continuous Performance Test Impulsivity Score</td>
<td>-0.18 ± 0.62 (-1.18, -0.77)</td>
<td>0.12 ± 0.06</td>
<td>.0501</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>HVLT-R: Total Recall, Delayed Recall, and Retention</td>
<td>-0.72 ± 1.19 (-2.67, -0.93)</td>
<td>0.04 ± 0.07</td>
<td>.5316</td>
</tr>
<tr>
<td>Visual memory</td>
<td>BVMT-R: Total Recall and Delayed Recall</td>
<td>-0.81 ± 1.41 (-3.00, -1.05)</td>
<td>-0.003 ± 0.06</td>
<td>.9644</td>
</tr>
<tr>
<td>Clinical trials battery</td>
<td>HVLT-R Total Recall; WMS-III Trails A and Trails B; Controlled Oral Word Association Test F-A-S</td>
<td>-0.35 ± 0.78 (-1.57, -1.13)</td>
<td>0.11 ± 0.06</td>
<td>.0742</td>
</tr>
<tr>
<td>Emotional</td>
<td>Beck Anxiety Inventory</td>
<td>8.9 ± 8.0 (0-25)</td>
<td>-0.50 ± 0.36</td>
<td>.1870</td>
</tr>
<tr>
<td></td>
<td>Beck Depression Inventory</td>
<td>12.71 ± 9.85 (0-31)</td>
<td>-0.05 ± 0.54</td>
<td>.9212</td>
</tr>
<tr>
<td>Quality of life</td>
<td>FACT-G Total Score</td>
<td>77.0 ± 18.4 (39-102)</td>
<td>0.41 ± 0.58</td>
<td>.4919</td>
</tr>
<tr>
<td></td>
<td>FACT-Fatigue Score</td>
<td>32.7 ± 14.8 (8-52)</td>
<td>1.05 ± 0.44</td>
<td>.0265</td>
</tr>
<tr>
<td></td>
<td>FACT-Br Total Score</td>
<td>131.0 ± 28.5 (84-174)</td>
<td>1.47 ± 0.89</td>
<td>.1154</td>
</tr>
</tbody>
</table>


*a Three patients were not assessed by Beck Inventories at baseline.
Neuroendocrine outcomes

<table>
<thead>
<tr>
<th>Axis</th>
<th>Baseline Deficits</th>
<th>New Deficits&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total Deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone</td>
<td>4/20 (20)</td>
<td>0/16 (0)</td>
<td>4/20 (20)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2/20 (10)</td>
<td>3/18 (17)</td>
<td>5/20 (25)</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>0/20 (0)</td>
<td>4/20 (20)</td>
<td>4/20 (20)</td>
</tr>
<tr>
<td>Gonadal, men</td>
<td>0/13 (0)</td>
<td>2/13 (15)</td>
<td>2/13 (15)</td>
</tr>
<tr>
<td>Gonadal, women</td>
<td>0/7 (0)</td>
<td>0/7 (0)</td>
<td>0/7 (0)</td>
</tr>
<tr>
<td>Prolactin, women</td>
<td>0/7 (0)</td>
<td>0/7 (0)</td>
<td>0/7 (0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Crude rates are shown.

Patients receiving > 30 Gy(RBE) to the pituitary:
- 33% (2/6) patients developed new deficits affecting 7 axes

Patients receiving < 30 Gy(RBE) to the pituitary:
- 14% (2/14) patients developed new deficits affecting 2 axes
Open MGH glioma proton study

Phase II study:
• Endpoint: PFS, OS, treatment toxicities
• Eligibility:
  • All Grade 1-2 gliomas
  • “Favorable” grade 3 gliomas: IDH mutant, 1p/19q codeleted
• Using reduced margins in tumor definition
  • CTV 7-15 mm
• Revised (shortened) neurocognitive, neuroendocrine, QOL assessments
• Follow up for 7 years
RT Dose escalation for GBM

NRG BN-001:

- 60 vs 75 Gy
- Options:
  - 60 Gy: standard photons (3D or IMRT)
  - 75 Gy: IMRT or protons, 30 fx
- Concurrent TMZ
- Max 5 cm enhancing lesion postop
NRG-BN001: Phase II R Trial HypoFx Dose-Esc IMRT or proton therapy vs. conventional photon RT with TMZ in newly diagnosed glioblastoma

Basic Eligibility: Newly dxed GBM; Residual tumor/postop cavity ≤5cm; KPS ≥70

- Stratify
- Randomize

- RPA
- MGMT

- IMRT or PBT Dose-Painting 75 Gy/50 Gy in 30 fx + TMZ
- Standard Photon RT 60 Gy/30 + TMZ

Sample Size: 576 patients
Primary endpoint: Overall survival

Basic Statistical Design:
Median survival 16 months with standard photon RT vs. 22.2 months with dose-esc IMRT or PBT
Arteriovenous Malformations
Proton SRS for AVM

74 patients, 1965-1978
Single fx proton SRS
F/u range 2-16 yrs
Beam diameter 7-50 mm

Angiography:
20% complete obliteration
56% partial obliteration (>50%)

2 fatal hemorrhages in <12 mo, none beyond

Kjellberg RN et al. NEJM 1983
Dose versus Volume: Impact on AVM Complications

1250 patients, 1965-1993

Large lesions:
  median volume 33.7 cc
  range volume 0.02-93 cc

Dose range 4-65 Gy(RBE)

Significant underprediction of actual risk:
  4.1% (vs 1%) significant neurological complication

Barker FG et al. J Neurosurg 2003
Proton SRS for AVMs

254 AVMs, 1991-2010
median  3.5 cc
cmedian  15 Gy(RBE)

Obliteration rate:
  5-yr  70%
  10-yr  91%

5-yr actuarial risk:
Hemorrhage  7%
Fatal hemorrhage  1.2%

Hattangadi J et al. IJROBP 2014
What is the Efficacy of Protons for Large AVMs?
Proton SRS for Large AVMs

Obliteration in 9/11 pts, all \( \geq 3 \) cm
Mean dose 25.3 Gy x 1 protons

Ito Y et al. Neurol Med Chir(Tokyo) 2011
2 Fraction Proton SRS for large AVM

Hattangadi JA et al. IJROBP 2012
2 Fraction Proton SRS in High Risk AVMs: Modest Efficacy, Modest Toxicity

59 patients, 1991-2009
Proton SRS: 16 Gy(RBE) in 2 fx
Median volume 23 cc (1.4-58.1)
  70% ≥ 14 cc
  34% critical location (deep, brainstem)
Median f/u 56.1 months

Obliteration:
  15% complete
  34% partial
Associated with higher dose

AVM hemorrhage 22%

Toxicity:
  14% headache
  12% seizure

Hattangadi JA et al. IJROBP 2012
Obliteration by fractionation

64 patients
median vol 16 cc (1.7-110.6)
10-22 Gy(RBE) protons in 1-3 fx
Some transient symptoms
No permanent toxicity

Vernimmen et al. IJROBP 2005
# Staged Dose: Proton Hypofractionation

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose &amp; fractions</th>
<th>Patients</th>
<th>Median volume</th>
<th>Median follow up</th>
<th>Obliteration</th>
<th>Symptoms/Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silander 2004</td>
<td>20-25 Gy, 2-4 fx</td>
<td>26</td>
<td>13 cc</td>
<td>~40 mo</td>
<td>&lt;25 cc, 70%</td>
<td>• 19% transient&lt;br&gt;• 8% persistent&lt;br&gt;• No new/worsening neuro symptoms&lt;br&gt;• 4% hemorrhage</td>
</tr>
<tr>
<td>Uppsala, Sweden</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥25 cc, 30%</td>
<td></td>
</tr>
<tr>
<td>Vernimmen 2005</td>
<td>30 Gy, 6 fx</td>
<td>64</td>
<td>16 cc</td>
<td>62 mo</td>
<td>&lt;14 cc, 67%</td>
<td>• 16% transient acute&lt;br&gt;• 23% transient late&lt;br&gt;• No permanent&lt;br&gt;• 11% hemorrhage</td>
</tr>
<tr>
<td>iThemba LABS, S Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥14 cc, 43%</td>
<td></td>
</tr>
<tr>
<td>Hattangadi 2011</td>
<td>16 Gy, 2 fx (range 12-28)</td>
<td>59</td>
<td>23 cc</td>
<td>56.1 mo</td>
<td>15%</td>
<td>• 32% transient acute&lt;br&gt;• 20% late, 7% persistent&lt;br&gt;• 25% hemorrhage</td>
</tr>
<tr>
<td>MGH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pituitary Adenomas
Dosimetric benefit of protons for pituitary adenoma

Temporal lobes sparing

Hypothalamus & brain sparing

Brain sparing
Proton vs Photon

Isovalues (cGy)
- 5400
- 5040
- 4500
- 3500
- 2500
- 1500
- 1000
- 500

Protons

Photons
MGH proton experience

165 Patients (152 SRS, 13 SRT)
Median f/u 4.3 years

Local control 98%

Complete response at 5 yrs:
Cushing’s (74)  67%
Nelson’s (8)    75%
Acromegaly (50) 49%
Prolactinoma (9) 38%
Thyroid (3)     50%

Wattson DA et al. IJROBP 2014
MGH experience: Biochemical control by adenoma subtype

Number at risk

<table>
<thead>
<tr>
<th>Type</th>
<th>Initial</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>74</td>
<td>54</td>
<td>37</td>
<td>26</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>NS</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>GH</td>
<td>50</td>
<td>46</td>
<td>39</td>
<td>28</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>PRL</td>
<td>9</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative incidence of CR

Time to CR (months)
MGH experience: Hypopituitarism

Hypopituitarism
3 year, actuarial 45%
5 year, actuarial 62%
Median time to new hypopit 40 mo

Wattson et al. IJROBP 2014
Meningiomas
# Protons: Benign Meningiomas

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>5</td>
<td>16</td>
<td>51</td>
<td>46</td>
</tr>
<tr>
<td>Dose, Gy(RBE) (range)</td>
<td>54-62</td>
<td>56 (52.2-64)</td>
<td>60.6 (55-61) mix ph/pr</td>
<td>59 (53.1-74.1) mix ph/pr</td>
</tr>
<tr>
<td>Med follow up</td>
<td>40 mo</td>
<td>34.1 mo</td>
<td>25.4 mo (mean)</td>
<td>53 mo</td>
</tr>
<tr>
<td>Local control</td>
<td>100%</td>
<td>LC 3y 92%</td>
<td>98%</td>
<td>LC5 100% LC10 88%</td>
</tr>
<tr>
<td>Toxicity</td>
<td>1 memory deficit</td>
<td>1 retinopathy, 1 optic nerve, 1 paralysis</td>
<td>1 hearing loss, 1 hypopit</td>
<td>1 brainstem necrosis (gr5), 2 hearing, 4 vision, 4 neuro</td>
</tr>
</tbody>
</table>
Second tumor risk after radiation therapy for meningioma

Arvold N et al. IJROBP 2011
Protons for meningiomas
Meningiomas: Proton Radiosurgery

MGH Experience
52 meningiomas
Median dose 13 Gy(RBE)

Local control at 3 yr 89%

Halasz L et al. IJROBP 2012
High grade meningioma

[Diagram of high grade meningioma with Protons and Photons]
High-grade meningiomas: Survival improved with higher RT dose

15 grade 2

16 grade 3

Figure 3. Actuarial local control of 15 patients with atypical meningioma following RT to either <60 Gy/CGE or ≥ 60 Gy/CGE target dose.

Figure 4. Actuarial local control of 13 patients with malignant meningioma following RT to either <60 Gy/CGE or ≥ 60 Gy/CGE target dose.

Hug et al. IJROBP 2009
31 pts, 15 grade 2, 16 grade 3
Mean f/u 59 months
New Meningioma Study

**Primary Objective**

To assess if increased radiation dose delivery to high-grade meningiomas by use of IMPT can achieve:

1. improved tumor local control and
2. acceptable radiation associated normal tissue toxicity
# Dose schema

<table>
<thead>
<tr>
<th>Histology &amp; Resection</th>
<th>CTV dose [Gy(RBE)] (microscopic disease)</th>
<th>GTV dose [Gy(RBE)] (gross disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total dose</td>
<td>Dose/fx</td>
</tr>
<tr>
<td>Grade 2</td>
<td>STR</td>
<td>59.4</td>
</tr>
<tr>
<td></td>
<td>GTR</td>
<td>63.0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>STR</td>
<td>63.0</td>
</tr>
</tbody>
</table>

GTR: gross total resection, Simpson grade 1-3; STR: subtotal resection
Dose schedules: 33-35 fractions, simultaneous integrated boost for gross disease
# Dose schema with reduced doses

<table>
<thead>
<tr>
<th>Histology &amp; Resection</th>
<th>CTV dose [Gy(RBE)] (microscopic disease)</th>
<th>GTV dose [Gy(RBE)] (gross disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total dose</td>
<td>Dose/fx</td>
</tr>
<tr>
<td>Grade 2</td>
<td>STR</td>
<td>59.4</td>
</tr>
<tr>
<td>Grade 3</td>
<td>GTR</td>
<td>63.0 → 59.4</td>
</tr>
<tr>
<td></td>
<td>STR</td>
<td>63.0 → 59.4</td>
</tr>
</tbody>
</table>

GTR: gross total resection, Simpson grade 1-3; STR: subtotal resection

Dose schedules: 33-35 fractions, simultaneous integrated boost for gross disease
Vestibular Schwannoma
# Protons for Acoustic Neuromas

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts</th>
<th>RT, Gy(RBE)</th>
<th>LC5</th>
<th>CN Preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tygerberg, S Africa (Vernimmen 2009)</td>
<td>51</td>
<td>mean 26, 3fx</td>
<td>98%</td>
<td>Hearing: 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CN7: 90.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CN5: 93%</td>
</tr>
<tr>
<td>MGH (Weber 2003)</td>
<td>88</td>
<td>12, 1fx</td>
<td>94%</td>
<td>20% (5y)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89%</td>
</tr>
<tr>
<td>Loma Linda (Bush 2002)</td>
<td>13</td>
<td>54, 30 fx</td>
<td>100%</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

**Notes:**
- MGH: Mass General Hospital
- Loma Linda: Loma Linda University Medical Center
Open MGH Protocol for Vestibular Schwannoma

Purpose:
- Hearing preservation with fractionated protons

Rationale:
- fractionated
- more modest dose, 50.4 Gy(RBE)
- more conformal
- more uniform target dose
Others
Ependymoma

MacDonald et al. 2008
Myxopapillary ependymoma
Multiple brain metastases
Summary

The rationale for proton therapy is based upon its physical characteristic of favorable dose distribution.

Clinical benefits of proton radiation in the CNS

- Reduction of acute & late toxicities from normal tissue irradiation
- Reduction of risk of secondary malignancies
- Enabling more aggressive therapy (e.g., improved target coverage, dose escalation)
Summary

LGG patients tolerate proton therapy well
- No decline in neurocognitive function or QOL
- No atypical toxicity
- Expectant neuroendocrine deficits

Efficacy & safety from retrospective data support use for AVM, pituitary adenoma, acoustic neuroma, and meningiomas

Carefully designed prospective studies are needed and underway to quantify the clinical benefit of protons