Particle Therapy for CNS Tumors
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PTCOG, Shanghai
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The Potential for Protons in the CNS

- Increase TCP
  - increased dose to tumor
- Decrease NTCP
  - Reduce dose to normal tissue
- Expand the therapeutic window
TCP/NTCP rationale

Good Evidence
- Chordoma
- Chondrosarcoma
- Other sarcomas

High dose RT
- Sensitive structures

Higher dose RT
- Large volume

Mixed Data
- G2/3 meningioma

Good tumor control
- GBM
- G1 meningioma, pit adenoma, LGG, mets

?Benefit of PRT
- Not Much Data
- mets
Decreasing NTCP

- Neuro-endocrine toxicity reduction
- Visual function, auditory function
- Second neoplasms

=> Easier to establish in children

- In adults: Cognitive brain function by decreasing cortical dose
RT Ablates Hippocampal Neurogenesis

Blue: Granule Cell Layer
Green: Subgranular Zone

Cranial RT: 97% reduction in newborn neurons 2 mo

NeuN: nuclear antigen for mature neurons; Tuj-1: immature neurons; GFAP: astrocytes; NG2: immature oligodendrocytes; RECA: endothelial cells; IB4: microglial lineage; ED1: activated microglia

Courtesy of V. Gondi
Monje, M et al. Nat Med 2002
Hippocampal Stem Cell Transplantation

NSCs differentiate into neurons and functionally integrate into the hippocampus

CON: Control; IRR: Irradiated; hNSC: human neural stem cells

Courtesy of V. Gondi
Acharya, M et al. Cancer Res 2011
Dose Response Relationship

Prospective trial of benign/LG adult brain tumors s/p RT
Serial neurocognitive testing x 18 mo

2-Gy fractions to 40% of the BL hippocampi & impairment in list-learning delayed recall at 18 mo

7.3 Gy: impairment seen ($p=0.043$)

12.8 Gy: 50% risk (95% CI: 11.5-14.1 Gy)

Gondi V, Mehta MP et al. IJROBP 2012.
Dosimetric Predictors of Cognition Outside the Hippocampus

Other radiosensitive cognition-specific structures outside the hippocampus

<table>
<thead>
<tr>
<th>STRUCTURE</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>Verbal Recall Nonverbal Memory</td>
</tr>
<tr>
<td>Corpus Callosum</td>
<td>Processing Speed</td>
</tr>
<tr>
<td>Precentral Gyrus</td>
<td>Attention Executive Function</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Attention Executive Function Visuomotor Skills</td>
</tr>
</tbody>
</table>

Peiffer AM et al., Neurology 2013

Courtesy of V. Gondi
Proton Therapy for Craniopharyngioma

Photon Therapy for Craniopharyngioma

Courtesy of D. Grosshans
Normal Tissue Delineation

Functional MRI for eloquent areas
Memory, speech, motor...
Particle Therapy for CNS Tumors – So FAR

- Limited number of patients treated
- Very few prospective trials
- Endpoints for relevant clinical diagnosis achieved only after many years
General Dosimetric Studies

• Many studies evaluating proton versus other modalities.
• All studies suggest better or equivalent to IMRT, stereotactic techniques for normal tissue sparing
• IMPT appears to improve homogeneity and conformality
A Typical Dosimetry Study

Baumert et al, IJROBP 2004
Conditions That Have Been Treated

• Chordoma
• Meningioma
• Craniopharyngioma
• Acoustic Neuroma
• Pituitary adenoma
• Arteriovenous malformation
• Gliomas
Craniopharyngioma

- MGH (Fitzek et al) 15 pt, 10y LC 85%, OS 72%
- LLMUC (Luu et al) 15 pt, 14/15 LC, late toxicity included panhypopit, 1 out of field meningioma
- Mixed experience of adults and pediatric
Acoustic Neuroma – MGH
Stereotactic proton radiosurgery

• 68 pt 1992-98
• Mean vol 2.49 cc, 12 CGE to 70%
• Median f/u 34 mo: 2 y LC 94%, 5 y LC 84%
• Clinical outcome
  – 3 shunt placement
  – 4/6 hearing worse
  – 13/21 tinnitus unchanged, 2/21 tinnitus worse
  – 3 severe CN VII
  – 9 mild CN V

Harsh et al, IJROBP, 54, 35-44 2002
Acoustic Neuroma – S Africa

- 51 patients
- 19.8-33 GyRBE / 3 fractions
- 72 mo follow up
- 5y LC 98%
- Hearing preservation 42%

Vernimmen et al, Radiother & Oncol, 90, 208-12, 2009
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 these 2 pt died (ACTH tumors)
  - 1 temp tip necrosis at 19 mo, 7 new visual changes, 11 pt with new hormonal deficiencies
Fractionated proton for pituitary tumors

Tumor Resolution

Hormone Normalization

Hypopituitarism

Fig. 2. Actuarial incidence of complete tumor regression. Dot symbols indicate censored events.

Fig. 3. Actuarial incidence of hormonal normalization. Dot symbols indicate censored events.

Fig. 4. Actuarial incidence of new hypopituitarism. Dot symbols indicate censored events.
40 Adult Medulloblastoma

- 21 x-CSI & 19 p-CSI
- 2003-2011
- Age 16.6-60.4y
- 2y OS & PFS
  - 94% p-CSI
  - 90 & 85% x-CSI
- Blood count drop correlated with mean vert body dose

Brown et al IJROBP, 86, 277-284, 2013
Intrinsic Spinal Cord Tumors

No studies, but could avoid esophagus, lung, thyroid etc.
Emerging Indications

• Dose-escalation for malignant glioma
  – Improve therapeutic efficacy

• Low-grade/benign brain tumors
  – Preserve neurocognition

• Re-Irradiation for recurrent glioma
  – Reduce volume of high-dose re-irradiation
Dose Escalation for GBM
Patterns of Recurrence for GBM with Tem

<table>
<thead>
<tr>
<th>Location of Rec</th>
<th>N=54 (%)</th>
<th>Med Time to Rec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Rec (17 mo med f/u)</td>
<td>39 (72%)</td>
<td></td>
</tr>
<tr>
<td>In-Field</td>
<td>31 (80%)</td>
<td>7 mo</td>
</tr>
<tr>
<td>Marginal</td>
<td>6 (15%)</td>
<td>18 mo</td>
</tr>
<tr>
<td>Distant</td>
<td>8 (20%)</td>
<td>20 mo</td>
</tr>
</tbody>
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Majority of relapses **still** occur in the RT field

Milano, MT et al.  IJROBP 2010
Glioma Stem Cells - Cause for Resistance?

Figure 5. The role of hypoxia in the cancer stem cell hypothesis. (A) The hierarchical model of tumor heterogeneity includes plasticity of cellular differentiation based on the effects of the tumor microenvironment. (B) Cancer stem cells reside in two niches: (1) the perivascular niche and (2) areas of hypoxia.

Heddleston et al, Cell Cycle 8 (20) 2009
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

Altaner, atlasgeneticsoncology.org 2012
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

Survival Probability

Time (Months)

N = 23
Median = 20 months

1 y = 78%
2 y = 34%
3 y = 18%

Reoperation following development of clinical and imaging changes after radiotherapy

<table>
<thead>
<tr>
<th>Op No. Type</th>
<th>No. of Patients</th>
<th>Necrosis Only</th>
<th>Necrosis W/ Tumor</th>
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<tbody>
<tr>
<td>2nd biopsy</td>
<td>8</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>resection</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>3rd biopsy</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
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<td>6</td>
<td>4</td>
<td>2</td>
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<td>4th biopsy</td>
<td>1</td>
<td>1</td>
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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
Carbon Ion Trial for HGG

• 1994 – 2002: 48 patients
  – 16 AA, 32 GBM
  – 50Gy X + escalating C ion (16.8 - 24.8 GyE in 8 fractions over 2 wk)
  – ACNU given wk 1,4 or 5 of Xray
  – 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
Phase I/II C ion HGG Trial: PFS & OS

High Dose Group: MST 26 mo
Mid Dose Group: MST 19 mo
Low Dose Group: MST 7 mo

Mizoe et al IJROBP, 69, 390-396, 2007
IMPT Reduces the Irradiated Volume

IMPT: improved tumor tissue coverage & OAR sparing
Randomized Trials – Ongoing & Planned

• CLEOPATRA TRIAL - Germany
  – 50Gy photons + Carbon (18GyE/6) or Proton boost (10Gy/5)

• IMPT vs IMXT – MDA
  – Neurocognitive outcomes

• Soon to be open (NRG)
  – Photons vs Protons with dose escalation
MDACC Phase IIR: IMPT vs. IMRT for Newly Diagnosed GBM

Hypothesis: IMPT will result in better cognitive outcomes

- Primary endpoint: Cognitive failure at 4 mo
- Sample size: n=80 (40/arm)
  - 80% power to detect reduction in cognitive failure: 45% IMRT vs. 30% IMPT
- Accrued 40 of 80 patients to date

Eligible Patients
Screened for Inclusion/Exclusion Criteria

Informed Consent

Stratify:
- RPA Class III or IV vs. V
- MMSE: 21-26 vs. 27-30
- Age: Less than 65 vs. 65 and older

Neurocognitive testing (post-surgery, pre-radiotherapy)

Arm 1
IMRT

Arm 2
IMPT

PI’s: S. McAvoy, P. Brown MD
NRG BN001

Group II: Proton Centers

STEP 1 REGISTRATION
Central Pathology Review for confirmation of histology and adequacy of tissue for MGMT analysis
NOTE: Tumor tissue must be received and central review confirmation completed before STEP 2 registration can occur.

STEP 2 REGISTRATION

STRATIFY
RPA Class: III, IV, or V
MGMT Status: Methylated, Unmethylated, or Indeterminate

RANDOMIZE*

Arm A2: Reference Arm
Photon irradiation using 3DCRT or IMRT:
46 Gy in 23 fractions followed by a sequential boost for an additional 7 fractions to 60 Gy
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide × 12 cycles

Arm C: Experimental Arm
Proton dose-intensified irradiation using passive scattered, uniform scanning beam, PBS or IMPT:
50 Gy in 30 fractions with a simultaneous integrated boost to 75 Gy in 30 fractions.
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide × 12 cycles

Primary Endpoint: Overall Survival
Built-in comparison of photon IMRT to proton therapy

Co-Principal Investigators: M.P. Mehta and V. Gondi
Proton Co-Chairs: A. Mahajan and H. Shih
Low-Grade/Benign Brain Tumors:

Preserve Neurocognition
Concern for LGG

• Patients are younger, live longer; protons would be attractive
• The tumor cells are infiltrative
• Tumor delineation very important due to sharp RT dose gradient
Re-irradiation for Recurrent Glioma:

Reduce Volume of High Dose Re-Irradiation
Re-Irradiation for Recurrent Gliomas

Dose $\geq 40$ Gy & large TV’s predict for RT toxicity

Shepherd, SF et al. IJROBP 1997
What should the tumor volume be for Re-RT

T1C component

T2/FLAIR Abnormality

Courtesy of V. Gondi
Re-Irradiation for Recurrent Gliomas

- PRT can minimize irradiated volume
- Could PRT reduce RT toxicity?
Chicago Re RT -- Proton Series

• N=18, proton re-irradiation for recurrent glioma

• PTV = T1C+ FLAIR
  – Median PTV = 232 cc; 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 B et al. ASTRO 2014 Submitted
Summary

• Very little prospective data on the benefit of particle therapy for adult CNS diseases
• All dosimetric studies suggest a reduction in normal tissue doses
• More information is needed to determine the benefit in mature nervous tissue
• Better functional imaging and testing should be incorporated in planning and follow up
Conclusions

- PRT has potential in CNS tumors to:
  - enhance TCP
  - decrease NTCP
- More work needed:
  - Tumor/OAR delineation
  - Optimal dosing
  - Functional benefits
  - RBE / LET effect

Chordoma
Chondrosarcoma
Other sarcomas
G2/3 meningioma
GBM
G1 meningioma, pit adenoma, LGG, mets
QUESTIONS?