Hypothalamic-Pituitary Axis and Hippocampus Sparing with Cranio-Spinal Intensity Modulated Proton Therapy

Presented by: Shadonna Maes

Agenda

I. SCCA Proton Therapy Center
II. Anatomy Review
III. Why should we spare these structures
IV. How we create our treatment plan
V. Dosimetric comparison to VMAT and TOMO
VI. Conclusion
SCCA Proton Therapy Center

A few facts

• Opened March 2013
• Pencil Beam Scanning and Uniform Scanning
• IBA proton beam equipment
• Currently treating about 60-70 patients a day
• Sites: Head and Neck, Liver, Breast, Lung, Esophagus, Prostate, CNS, pediatrics, and Ocular

The Center

4 treatments rooms
1 fixed beam (PBS)
2 incline beam rooms (US)
1 gantry room (PBS)
The Physics of Protons

X-rays deliver a greater dose outside the target for the same dose within the target volume as protons.

Depth dose curves for protons and photons.

10 MeV photons

Proton "Spread Out Bragg Peak"

Additional Dose outside the target delivered with Photons

Why Functional CSI?
What is Functional CSI?

- CSI with sparing of the hippocampus and hypothalamic-pituitary axis (HPA) or "functional CSI" can potentially reduce toxicity.

- It is a Novel treatment planning technique that spares the hypothalamic-pituitary axis and both hippocampus to improve neuroendocrine and neurocognitive sequelae in the pediatric and young adult population.

Standard CSI Late Effects

Cranio-spinal irradiation (CSI) improves clinical outcomes for several CNS malignancies, yet at the cost of long-term adverse events.

**Potential Late CSI Adverse Events**
- Neuro-endocrine dysfunction
- Neurocognitive delay
- Neurocognitive dysfunction
- Abnormal bone growth
- Impaired muscle development
- Organ atrophy
- Immune system dysfunction
- Thyroid dysfunction
- Early or delayed puberty
- Adreno-corticotropin insufficiency
- Hypogonadism
Hypothalamic Pituitary Axis

- Neuroendocrine system that is responsible for the stress response and regulates many body processes including digestion, emotions, sexuality, energy and the immune system.

Hormones Released by the Pituitary Gland
- Growth Hormone (Growth)
- Prolactin (Milk production)
- Thyroid-Stimulating Hormone (Metabolism)
- Adrenocorticotropic Hormone (Stress)
- Follicle-Stimulating Hormone (Reproduction)
- Luteinizing Hormone (Reproduction)
- Melanocyte Stimulating Hormone (Sleep)
- Antidiuretic Hormone (Water absorption)
- Oxytocin (Childbirth)
Hypothalamic Pituitary Axis

Median Hypothalamic & Pituitary Dose
Matters in pediatric & young adult population

189 evaluable patients <26y with brain tumors.
Treated with proton RT on 3 prospective studies (2003-2016)
68.8% of patients treated with CSI, the rest with involved field only.
Median follow up of 4.4 years.
The 4-year actuarial rate of hormone deficiencies were 48.8% (any hormone), 37.4% (growth hormone), 20.5% (thyroid hormone), 6.9% (adrenocorticotropic hormone) and 4.1% (gonadotropins).
Highly correlated factors with deficiency:
1- Combined hypothalamus and pituitary median dose.
2- Age at start of RT
3- Time interval since treatment
Median dose equally important to age

Large curve separation by mean dose

Endocrine outcome in children with medulloblastoma treated with 18 Gy of craniospinal radiation therapy

Table 2

<table>
<thead>
<tr>
<th>CD n.</th>
<th>18 Gy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Neurocognitive delay</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CD, conventional dose; NS, not significant.
Hippocampus

- Component of the limbic system, located in each of the medial temporal lobes. The hippocampus plays an important role in cognitive memory function, spatial memory, and regulating emotions.

Hippocampus

Hippos = Horse (Greek)  Kampos = Sea monster (Greek)
Hippocampus Sparing Preserves Memory and neuro-cognitive function

Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial

- 42 analyzable patients at 4 months
- Evaluated cognitive function with the Hopkins Verbal Learning Test-Revised Delayed Recall tool
- Score deterioration was 19% for WBRT with hippocampus sparing
- In comparison to MD Anderson study (PIII)*
- Score deterioration was 24% with SRS alone and 52% with SRS plus WBRT

Concerns for Hippocampus Recurrence?
- 371 patients with a total of 1133 brain mets evaluated
- 8.6% of patients and 3% of mets occurred within 5mm of the hippocampus; 0% occurred in the Hippocampus
- HA-WBRT deemed safe for clinical trial RTOG 0933

Recent Publication with photon sparing in WBRT

**Purpose**

Simultaneously avoiding the hippocampus and hypothalamic-pituitary axis during whole brain radiotherapy: A planning study

Xing-Wen Fan, MD,1,5,11 Juan-Qi Wang, MS,5,11 Jun-Lan Wu, MD,4,11 Hong-Bing Wang, MD,3,11 and Kai-Liang Wu, MD, PhD,1,11

1Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai 200032, China; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China; and Department of Oncology, Shanghai Armed Police Corps Hospital, Shanghai 200333, China

**Trending approach worldwide?**
Study Purpose

- Our previous study evaluated functional CSI with IMRT modalities such as Helical Tomotherapy (HT) & Volumetric Modulated Arc Therapy (VMAT).

- This study aims to describe the technical feasibility and dosimetric outcome with intensity modulated proton therapy (IMPT) then compare it with the previously generated IMRT plans (Tomo & VMAT).

Methods
Methods

- 10 patients with medulloblastoma (6 Supine & 4 prone)
  - Ages 3-18

- Targets delineated per ACNS0331 guideline
- HPA and hippocampus contours were verified by an experienced neuroradiologist

- Initial course to 23.4 Gy (RBE) with boost to 54Gy (RBE)
  - Primary objective: CTV D95 >99% with robustness
  - Secondary objective: HPA and hippocampus composite Dmean ≤18 Gy (RBE)
  - Third objective: Brain stem V54<5cc (protons only)

- IMPT plans generated with Raystation v6 at the SCCA proton facility
- VMAT and TOMO plans generated at the University of Ottawa

### Contouring & Dose Constraints

<table>
<thead>
<tr>
<th>Target</th>
<th>Prescription</th>
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</thead>
<tbody>
<tr>
<td>CTV1, CTV2</td>
<td>D95 &gt;99%</td>
</tr>
<tr>
<td>HPA</td>
<td>Dmean ≤18Gy (RBE)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>V54&lt;5cc (protons only)</td>
</tr>
<tr>
<td>Other Contours (for planning considerations)</td>
<td></td>
</tr>
<tr>
<td>HPA</td>
<td>Dmean ≤18Gy</td>
</tr>
<tr>
<td>CTV2</td>
<td>V54&lt;5cc (protons only)</td>
</tr>
</tbody>
</table>
Proton Treatment Technique

- Target is split up into a brain and two spine optimization targets
- Junction gradient area of 6cm
- Be sure to keep the brain optimization structure 2cm above the shoulders

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Proton Treatment Technique

• Cropped the PRVs out of the CTV Brain
• 5mm PRV for hippocampus and HPA for optimization

Beam Arrangement:
• 3 beams for the Brain-PA, LPO, RPO
• 1 beam for the Upper Spine-PA
• 1 beam for the Lower Spine-PA
Proton Treatment Technique

- Used 3% range uncertainty for robustness
- 6mm sup/inf robustness to create dose gradient
- Independent beams
### Proton Treatment Technique

<table>
<thead>
<tr>
<th>Function</th>
<th>Constraint</th>
<th>Beam</th>
<th>Beam Weighting</th>
<th>Description</th>
<th>Value</th>
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<tr>
<td>Min Dose</td>
<td>Beam Set</td>
<td>CTRPT _ BRAIN</td>
<td>Min Dose &amp; EOL</td>
<td>Beam &quot;3&quot;</td>
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<td>Min Dose</td>
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<td>Min Dose &amp; EOL</td>
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<td>Beam &quot;5&quot;</td>
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<tr>
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<td>EOL</td>
<td>Min Dose &amp; EOL</td>
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<tr>
<td>Dose Cut-Off</td>
<td>Beam Set</td>
<td>EOL</td>
<td>Dose Cut-Off</td>
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<td>Min Dose &amp; EOL</td>
<td>Beam &quot;1&quot;</td>
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</tr>
<tr>
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<td>Min Dose &amp; EOL</td>
<td>Beam &quot;2&quot;</td>
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<tr>
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<td>CTRPT _ BRAIN</td>
<td>Min Dose &amp; EOL</td>
<td>Beam &quot;3&quot;</td>
<td>0.0000</td>
</tr>
<tr>
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<td>Min Dose &amp; EOL</td>
<td>Beam &quot;4&quot;</td>
<td>0.0000</td>
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<td>Beam &quot;6&quot;</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

**Finished Product!**

![Image of proton therapy setup and finished product]
VMAT and TOMO Technique

VMAT and TOMO plans were created by experienced dosimetrist at Ottawa General Hospital

**VMAT**
- 2-3 isocenters used
- Brain treated with 360 degree arc and a non-coplanar vertex arc
- Upper spine treated using bowtie arcs (ant and post)
- Lower spine treated with 360 arc
- Max dose constraint on HPA and Hippo
- 3mm PRV

**TOMO**
- 5cm jaw width with 0.225 pitch
- Brain and spinal portion separated for optimization only to achieve dose uniformity
- 3mm PRV subtracted from target

Results & Dosimetric Comparison
Dosimetric Comparison

Protons  TOMO  VMAT

Medullo3

35

Dosimetric Comparison

Protons  TOMO  VMAT

Medullo3

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Dosimetric Comparison

Protons  TOMO  VMAT

Medullo3

Dosimetric Comparison

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Protons = Solid
Tomo = Dotted
VMAT = Dashed

PTV_5400_3mm  Hippo_IR
PTV_CRT_1340_3mm  Hippo_L
HIFU
Proton Results

- The CSI CTV mean D95 (cGy RBE) was 97.3% (2276, SD 54.4), and the boost CTV mean D95 was 95.8% (2938, SD 114.4). The hot spot (mean D2) was 103% (5568, SD 35).

- The boost CTV volume overlapped with the brainstem in 6 cases (as per ACNS0331 protocol). This required intentional reduction of coverage to limit the brain stem V54 to <5cc.

- HPA CSI Dmean was 1412 (SD, 119.53), the boost Dmean was 383 (SD, 277.5), total Dmean was 1786 cGy RBE.

- Hippocampus (both) CSI Dmean was 1467 (SD, 114.9), the boost Dmean was 636 (SD, 446.3), total Dmean was 2100 cGy RBE.

Statistical Analysis of all 10 cases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VMAT</th>
<th>TOMO</th>
<th>IMPT</th>
<th>One-way ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite HPA (Dmean)</td>
<td>21.8</td>
<td>21.2</td>
<td>17.8</td>
<td>P= 0.053</td>
</tr>
<tr>
<td>Composite Hippo – Both</td>
<td>27.5</td>
<td>27.2</td>
<td>21</td>
<td>P=0.023</td>
</tr>
<tr>
<td>CTV 23.4 (D95)</td>
<td>23.2</td>
<td>22.8</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>CTV 54 (D95)</td>
<td>54.6</td>
<td>54.6</td>
<td>53*</td>
<td></td>
</tr>
<tr>
<td>CTV 54 (D2)</td>
<td>56.6</td>
<td>55.6</td>
<td>55.7</td>
<td></td>
</tr>
<tr>
<td>Brain Stem (V54)</td>
<td>13.2 cc</td>
<td>12.6 cc</td>
<td>2.7 cc*</td>
<td></td>
</tr>
<tr>
<td>Heart (Dmean)</td>
<td>7.2</td>
<td>5.3</td>
<td>0.1</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Lungs – Both (Dmean)</td>
<td>8</td>
<td>6.3</td>
<td>2.9</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Thyroid (Dmean)</td>
<td>16.6</td>
<td>15.8</td>
<td>5.8</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Esophagus (Dmean)</td>
<td>15.3</td>
<td>15.4</td>
<td>5</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Bowel Bag (Dmean)</td>
<td>9</td>
<td>8.1</td>
<td>0.4</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Kidneys – Both (Dmean)</td>
<td>6.6</td>
<td>4.5</td>
<td>1.4</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Liver (Dmean)</td>
<td>6.2</td>
<td>5.6</td>
<td>0.2</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

*IMPT CTV coverage was decreased intentionally around brainstem to limit the V54 <5cc
Endocrine Deficiency As a Function of Radiation Dose to the Hypothalamus and Pituitary in Pediatric and Young Adult Patients With Brain Tumors

Ralph S. Nager, Andrea Ranzato, Mathew M. Minn, Elizabeth A. Hayman, Claire P. Goebel, David H. Schiff, Robin M. Jones, Mary A. Huang, Anelia Marchaj, David R. Givens, Arnold C. Putnam, Takura Nanba, Shannon M. MacDonald, Nancy J. Baribell, and Brian J. Yock

<table>
<thead>
<tr>
<th>Parameter (Mean Dose in Gy, n=59)</th>
<th>VMAT</th>
<th>TOMO</th>
<th>IMPT</th>
<th>One-way ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite HPA (D&lt;30 Gy)</td>
<td>21.8</td>
<td>21.2</td>
<td>17.8</td>
<td>P&lt;0.053</td>
</tr>
<tr>
<td>Composite Hippo – Both (D&lt;30 Gy)</td>
<td>27.5</td>
<td>27.2</td>
<td>23</td>
<td>P=0.023</td>
</tr>
<tr>
<td>CVY 23±4 (D&lt;30 Gy)</td>
<td>29.4</td>
<td>24.4</td>
<td>22.4</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Summary table of actual rates of hormone deficiency at 5 years stratified by mean hypothalamic and pituitary mean dose.

<table>
<thead>
<tr>
<th>Hormone Deficiency</th>
<th>&lt; 20 Gy&lt;sub&gt;nmax&lt;/sub&gt;</th>
<th>20-40 Gy&lt;sub&gt;nmax&lt;/sub&gt;</th>
<th>&gt; 40 Gy&lt;sub&gt;nmax&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>9.0</td>
<td>39.5</td>
<td>78.8</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>4.2</td>
<td>24.5</td>
<td>42.0</td>
</tr>
<tr>
<td>ACTH</td>
<td>4.2</td>
<td>4.2</td>
<td>18.2</td>
</tr>
<tr>
<td>Gonadotropin</td>
<td>0</td>
<td>2.9</td>
<td>14.0</td>
</tr>
</tbody>
</table>

NOTE: Data presented as %. Abbreviations: ACTH, adrenocorticotropic hormone; GH, growth hormone; RBE, relative biological effectiveness.

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Functional CSI vs. Standard CSI

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Functional CSI vs. Standard CSI

- There could be a potential increased risk of local recurrence due to the sparing of these vital intracranial structures as they are in close proximity to intracranial CSF space.

- However, the combined sparing volume has been consistently small <2% of the total CTV volume (combined HPA & hippo mean volume was 19.8cc vs whole brain CTV 1476cc)

- Prospective studies (that mainly include low risk CNS tumors) will be required to determine the safety and efficacy of this approach.
Conclusion

- Functional CSI is technically feasible with IMPT, VMAT and TOMO
- Functional CSI can greatly reduce the dose to the HPA and hippocampus while maintaining coverage
- IMPT plans provide superior HPA & Hippo sparing compared to VMAT and TOMO at the cost of slight decrease in coverage near the brainstem
- Location of the boost target greatly affected our ability to spare the HPA and Hippocampus
- A prospective clinical trial is required to establish safety, efficiency and toxicity of this novel CSI approach
References

7. ACNS0331 : A Study Evaluating Limited Target Volume Boost Irradiation and Reduced Dose Craniospinal Radiotherapy (18.00 Gy) and Chemotherapy in Children with Newly Diagnosed Standard RiskMedulloblastoma: A Phase III Double Randomized Trial An Intergroup Study for Participation by COG and the Dutch Childhood Oncology Group – SION (Stichting KinderOncologie Nederland)
8. Long-term neuro-endocrine sequelae After Treatment for Childhood Medulloblastoma J. Hekkers, I E M C. Muthu, D. Behrendt, E. Endert, P. J M. Bakker and E. Fiers

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Thank You

Questions?