CONTOURING AND DOSIMETRY FOR IMPROVED PEDIATRIC NEUROCOGNITIVE OUTCOMES

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The Brain...It’s Complicated
Things We Do Know....

1) Younger brains are much more sensitive to RT damage

Merchant, JCO 2009:78 LGG pts who received 54 Gy RT

Things We Do Know....

2) Larger RT volumes = larger losses

St. Jude Lifetime cohort study: 224 adult survivors of pediatric CNS tumors (Brinkman et al., JCO 2016)
3) There are ways we as radiation oncologists and planners can reduce RT damage while still curing our patients!!!
COG ACNS0331: Pediatric Medulloblastoma

Children ages 3-7
Randomize

Reduced-dose CSI
(18 Gy)

Randomize
Boost to tumor bed

Standard-dose CSI
(23.4 Gy)

Randomize
Boost to Posterior fossa

Maintenance Chemotherapy
9 Cycles
Low-dose (18 Gy) vs. Standard-dose (23.4 Gy) CSI: IQ

Patients receiving reduced-dose CSI exhibited less decline in IQ over time (p=.04)

Time GLM model included gender and age (both non-significant).
Low-dose CSI group model estimate = 6.58, p=.04

Reduced boost vs. PF boost: IQ

Patients receiving reduced boost had higher IQ scores 3-4 years after diagnosis (p = .01)

GLM model included gender and age.
CSI group model estimate for reduced-boost group at T2 = 6.25, p=.01;
Age at evaluation estimate at T2 = 1.10, p < .01
Conclusions

- Reduced CSI dose is associated with less decline in IQ over the first 3-4 years post-diagnosis
- Reduced boost volumes associated with better IQ over time for all patients
- Reduction of dose to which structures leads to improved outcomes???

Hippocampus

- The hippocampus is involved in learning, consolidation and retrieval of information, and creation of new memories
- Neural stem cells in the HC are extremely sensitive to radiation and even a dose of 2 Gy delivered to human NSCs leads to decreased numbers of cells undergoing neuronal differentiation (Parihar Proc Natl Acad Sci 2013)
- Mouse models suggest that damage to neural stem cells in the subgranular zone of the dentate gyrus leads to subsequent neurocognitive loss, most notably in memory-related domains (Yoneoka Br J Radiol 1999)
Hippocampus: Clinical Evidence

Gondi IJROBP 2011:
• 18 adult pts with low grade brain tumors and 6 matched controls
• FSRT to 50-54 Gy or 20 Gy in 5 fx
• NCF tested at baseline and 18 months

Results:
1. Impairment in Delayed Recall and D40% > 7.3 Gy to the bilateral hippocampi (P=0.025)
2. Impairment in Delayed Recall and D100% > 0.0 Gy of the bilateral hippocampi (p=0.047)

Hippocampus: Clinical Evidence

Mahajan IJROBP 2014 (ASTRO):
• 24 pediatric pts treated with protons and with serial NCF evaluations
• Glioma (11), Cranio (5), EP (3), MB (2), GCT (1), Meningioma (1)
• Mediat RT dose 50.4 GyRBE (45 Gy-60 GyRBE)
• Median R/L hippo dose was 17 GyRBE (0.2-55)/ 16 GyRBE (0-46)

Results:
• DMax > 50 GyRBE to Rt. Hippo associated with IQ loss of 6.4 points/yr (p=0.01)
• D10% ≥ 30 GyRBE to Rt. Hippo associated with IQ loss of 4 points/yr (p<0.01)
• Lt. Hippocampal dose not associated with IQ loss

Images courtesy of Dr. Andrew Zureick
Hippocampal Contouring

Contouring the hippocampus can be challenging

- T1+C MRI with 1-3mm slices is necessary
  - Typically cannot be seen on CT
- The grey-matter of hippocampus will be hypointense on T1 MRI compared to white matter surrounding it

Hippocampal Contouring

Start contouring in the middle section!
  - Easiest location to see it
- The HC the ovoid gray matter tucked in the medial aspect of the temporal horn of the lateral ventricle.
  - The **temporal horn** of the lateral ventricle is the **anterior and lateral border** at this level
  - The **amygdala** is the gray matter on the other side of the temporal horn and **anterior** to the HC
  - The **medial border** is the **ambient cistern** adjacent to the brainstem.
  - The **posterior border** is defined by white matter tract called the **subiculum**.
Hippocampal Contouring

Then contour inferiorly to the bottom of the hippocampus
- Follow the lateral ventricles inferiorly to inferior temporal horn of ventricle
- The inferior border should be at the level of the pituitary and pons
- Hippocampus is a smaller ovoid at this level

Hippocampal Contouring

- On each successive superior slice the hippocampus is the most medial gray matter area in the temporal lobe, just lateral to the quadrigeminal cistern and brainstem (midbrain).
- The HC moves posteriorly as the scan moves superiorly.
- The most cranial extent of the hippocampus is below the splenium of the corpus callosum, before the emergence of the crus of the fornix at the level of the tectal plate (top of midbrain)
- The HC neural connections extend more superiorly but the relevant neural stems cells for neuroprotection end at the level of the top of the midbrain/tectal plate
Hippocampal Contouring

Hippocampus: RT Avoidance?

Gondi JCO 2014: RTOG 0933
- 113 pts accrued, 42 pts analyzable
- HA-WBRT 30 Gy in 10 Fx (Hippo D100 < 9 Gy, Dmax < 16 Gy)
- HVLT-R DR tested at baseline and 4 months after RT

Results:
- Mean decline in HVLT-R DR from baseline was 7%, less than the 30% decline seen in historical controls.
Hippocampal Avoidance in Pediatric WBRT?

**Adult Indications for Hippo Avoidance**
- WBRT for metastatic disease excluding:
  - Hematopoietic malignancies
  - GCT
  - SCLC (+/-)

**Pediatric Indications**
- ???

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**Hippocampal Avoidance in Pediatric WBRT?**

**Adult Indications for Hippo Avoidance**
- WBRT for metastatic disease excluding:
  - Hematopoietic malignancies
  - GCT
  - SCLC (+/-)

**Pediatric Indications**
- ???

Han PLoS one, 2014
Temporal Lobes

- TLs are involved in processing sensory input into derived meanings for retention of visual memory, language comprehension, and emotion association
- Medial TL communicates with the hippocampus to form long-term memory, modulated by the amygdala
- Damage to dominant hemisphere results in impaired verbal memory and learning (LTL in right handed individuals)
- Bilateral injury results in more severely impaired learning and memory

Study Population Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Findings</th>
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</table>
| Jalali (IJROBP 2009) | -28 PBT pts -Focal RT -Prospective NCF (2 yr) | • 1/3rd of patients had >10% decrease in FSIQ at 2 yrs  
• Dose >43.2 Gy to >13% of LTL linked to drop in FSIQ (p = 0.048)  
• Dose to ST brain, RTL, and frontal lobes did not show correlation |
| Armstrong (NeuroOnc 2010) | -818 CCSS pts -Focal and CSI | • Increased dose to temporal lobes associated with memory decline  
• LTL and RTL not analyzed separately  
• No association found for other brain regions |
| Greenberger (IJROBP 2014) | -32 pts with LGG -Focal protons | • D20 > 15 GyRBE to LTL/hippo trended toward poorer NCF |
| Redmond (NeuroOnc 2010) | -19 PBT pts, 55 controls -Focal RT & CSI -Prospective study -27 mo F/U NCF | • Motor speed and dexterity with dose to TLs (p <0.03)  
• Visual perception with dose to LTL (p <0.04) |
| Zureick (IJROBP 2017) | -128 PBT pts -Focal and CSI Protons -Prospective NCF (3 yr) | • LTL dose was correlated with decline in FSIQ and PRI scores  
• WB dose was correlated with decline in PS scores  
• Model: FSIQ drops 1 point per additional 6 Gy to LTL |
Contouring The Temporal Lobes

Inferior Border: Middle Cranial Fossa
- Butterfly-shaped depression of the skull base

Contouring The Temporal Lobes

Posterior Border (Lower): Pre-occipital notch
Contouring The Temporal Lobes

Anterior Border: Sylvian fissure
- Frontal lobe if fissure cannot be visualized (younger brains)
- Anterior Middle Cranial Fossa (lower)

Posterior Border (Upper):
Parieto-occipital line
- Imaginary line separating the TL and OL
- Runs between the middle temporal and middle occipital gyri

14 = middle temporal gyrus
15 = middle occipital gyrus
Contouring The Temporal Lobes

**Medial Border:** Sylvian fissure
- Brainstem, cerebellum basal ganglia
- Contours include the hippocampus until it turns into fornix bundle superiorly (at the level of the tectal plate/top of midbrain)

Contouring The Temporal Lobes

**Superior Border:** Sylvian Fissure
- Separates the frontal & parietal lobes superiorly from the TLs inferiorly
- Heschl's gyrus, also known as transverse temporal gyrus is another landmark
Contouring The Temporal Lobes

[Images of brain scans with contours]

Contouring The Temporal Lobes

[Images of brain scans with contours]
Temporal Lobe Sparing (VMAT)

Posterior Arc  Table Kick

Temporal Lobe Sparing (Protons)

AAMD 43rd Annual Meeting
June 17 -21, 2018
The Hypothalamus

- The hypothalamus serves as the link between the endocrine system and nervous system.
- It is responsible for signaling the pituitary gland to release hormones important for growth and development.
- Radiation to the hypothalamus can cause hormone deficiencies in growth hormone, thyroid hormone, ACTH, and those involved in puberty and metabolism.
- Risk of loss at RT Dose:
  - ~16 Gy = Growth Hormone
  - ~30 Gy = Thyroid Hormone
  - ~50-60 Gy = Complete Loss

Contouring The Hypothalamus

Anatomic Boundaries

- **Superior**: the level of the anterior commissure
  - White matter tract that connects TLs
- **Anterior**:
  - Inferior = anterior border is the optic chiasm
  - Superiorly it is the anterior commissure
- **Medial**: the 3rd ventricle
- **Posterior**: the mammillary bodies inferiorly and the thalamus and fornix more superiorly
- **Inferior (floor)**: the infundibulum stalk
Contouring The Hypothalamus

- Contouring begins at the level of the optic chiasm, as the infundibulum terminates into the hypothalamus
  - Find pituitary and scroll superiorly along infundibulum until it widens and splays
- As you move superiorly, the hypothalamus is bordered by the optic tracts anteriorly and laterally
- The posterior border is formed by the mammillary bodies
  - Bi-lobed structures with role in memory
  - Some consider them part of hypothalamus and can be included in hypothal volume

Contouring The Hypothalamus

- As you move superiorly, the hypothalamus tracks the lateral walls of the 3rd ventricle
- Superiorly it is bounded anteriorly by the anterior commissure and posteriorly by the thalamus and fornix and laterally by the internal capsule
- The hypothalamic contour stops superiorly at the level of the lateral crossing of the anterior commissure
Contouring The Hypothalamus

Tectal Glioma 50.4 CGE
White Matter Tracts

- Myelination allows for faster conduction of electrical impulses
- Unlike the unmyelinated gray matter that develops rapidly by 4 years of age, the process of myelination in the WM continues into the second decade of life.
- WM has shown significant vulnerability to injury from cranial radiation and chemotherapy, especially during periods of rapid myelination.
- After RT, both older and younger patients lost WM volume at a similar rate. However, because younger children begin treatment with a lower volume of mature WM, they experience greater deviation from expected developmental norms.

Diffusion tensor imaging (DTI) allows for evaluation of the myelination of white matter (WM)
- WM integrity is measured as fractional anisotropy (FA).
- As a child ages, FA increases, corresponding to increasing axon myelination.
- Radiation leads to reduced FA and correlates with poorer neurocognitive status.

Processing Speed: Red voxels demonstrate areas of reduced FA significantly different between 40 MB patients vs controls in their association with processing speed

-Palmer NeuroOnc 2012
White Tracts Matter

- Multiple studies show WM loss after RT leads to neurocognitive decline

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aukema (2009)</td>
<td>6 MB (RT)</td>
<td>• FA decreased in MB pts (RT) &gt; ALL pts (MTX) vs controls</td>
</tr>
<tr>
<td></td>
<td>11 ALL (MTX)</td>
<td>• FA in the splenium &amp; body of CC associated w/ neurocog decline</td>
</tr>
<tr>
<td></td>
<td>17 matched controls</td>
<td>• FA in inf and fronto-occipital fasciculus associated w/ motor processing</td>
</tr>
<tr>
<td>Brinkman (2012)</td>
<td>20 MB pts (RT)</td>
<td>• FA in the parietal lobe was positively associated with working memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA loss in multiple brain regions associated with declining executive fxn</td>
</tr>
<tr>
<td>Rueckriegel (2015)</td>
<td>13 PA (no RT)</td>
<td>• ratio of WM to GM associated with FSIQ loss</td>
</tr>
<tr>
<td></td>
<td>18 MB (RT)</td>
<td>• FA associated w/cognitive function, FSIQ, &amp; processing speed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA decreased in MB compared to PA in fronto-cerebellar tracts</td>
</tr>
<tr>
<td>King (2015)</td>
<td>27 adult BT pts (14 RT) 27 healthy controls</td>
<td>• FA in WM of anterior CC, temporal lobes, &amp; frontal regions in RT pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA associated with poorer intellectual performance</td>
</tr>
<tr>
<td>Uh (2015)</td>
<td>51 Cranio pts receiving Surg + RT</td>
<td>• FA in CC was greater in areas that saw Surg +RT (9%) vs RT alone (1.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA recovery was greater in non-surgical tract areas</td>
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Corpus Callosum

Roles:
- Genu = Motor Speed, Visuomotor Integration, Visual/Auditory/Verbal Working Memory
- Body = Visual attention, Visual/Auditory/Verbal Working Memory
- Splenium = Visual attention, Visual matching
- Splenium = Visual attention, Visual matching

In healthy children, overall corpus callosum volume continues to increase throughout adolescence, largely driven by growth in the mid-regions and the splenium due to myelination
**Corpus Callosum**

- Palmer et al (2002): Quantitative MR imaging of 35 patients showed total corpus callosum area decreased with time from CSI (-18.0 mm/yr; P < .0001) over 4 yr f/u
- Palmer et al (2014): Fractional anisotropy in 3 areas of the corpus callosum was examined in relation to processing outcome in 40 MB pts and 40 controls:
  - Genu FA was significantly related to visual matching (P < .03) and overall PS (P < .05).
  - Body FA significantly related to visual matching (p < .017), decision speed (p < .044), and overall PS (p < .016).
  - Splenium FA showed a significant relation to decision speed (p < .19, overall PS (P < .018).

**Contouring the Corpus Callosum**

- Using the sagittal MRI at midline, contour the white matter tract of the CC from superior to inferior.
The Brainstem

- Potentially higher rates of brainstem necrosis are occurring with proton treatments in the PF
  - 5-10% in protons vs 3-4% in photons
- Proton RBE is 1.1 on average but RBE at distal Bragg peak may be 1.2 or 1.3
- Great care should be taken when contouring brainstem in these cases to ensure safe DVHs

313 pediatric patients treated at UFPTI from 2007-2013

- Dose for all patients was > 50.4 CGE (Median 54 CGE)
- Median age = 6 years
- Median f/u of 2 yrs

RESULTS

- Brainstem Toxicity = 3.8% (11 pts)
  - Grade 3+ = 2.1%
  - Grade 5 (Death = 1)
- 9/10 Living pts stabilized or resolved after presentation

Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy

<table>
<thead>
<tr>
<th>Histologies</th>
<th>73 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma</td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>46 pts</td>
</tr>
<tr>
<td>Low-grade glioma</td>
<td>46 pts</td>
</tr>
<tr>
<td>Medulloblastoma/primitive</td>
<td>38 pts</td>
</tr>
<tr>
<td>Neuroectodermal tumor</td>
<td></td>
</tr>
<tr>
<td>Parameningeal rhabdomyosarcoma</td>
<td>13 pts</td>
</tr>
<tr>
<td>Other</td>
<td>55 pts</td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Supratentorial</td>
<td>164 pts</td>
</tr>
<tr>
<td>Posterior fossa</td>
<td>114 pts</td>
</tr>
<tr>
<td>Skull base</td>
<td>35 pts</td>
</tr>
</tbody>
</table>

Pre-RT treatment details

Operations prior to RT

1. 213 pts
2. 76 pts
> 2. 18 pts

Treatment based on radiographic characteristics alone, without biopsy

Gross total or near total resection

| History of hydrocephalus           | 109 pts |
| Extended or permanent shunting to manage hydrocephalus | 73 pts |
| Disease-specific chemotherapy      | 155 pts |
| Intrathecal or high-dose intravenous methotrexate | 48 pts |
The Brainstem

Predictors of Proton Brainstem Toxicity
- PF Location (10.7%)
- Histology (Ependymoma 8/11 pts)
- Age < 5 years (12.5%)
- V55 > 18%
- V60 > 0

Recommendations
- Max dose shouldn’t exceed 56.6 CGE
- Mean brainstem dose (50%) < 52.2 CGE

MGH Guidelines
- 59.4 CGE is never used unless gross residual
- Spinal cord max 48.6 CGE
- 50.4 CGE for LGG
- 52.2 CGE max dose for Cranio
- Hot spots for Medullo < 55 CGE

The Brainstem

Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy  
*Ann Oncology, 2006; 17: 1298-1304*

Contouring The Brainstem

- Sensitivity to RT damage decreases as you move up the brainstem 
  - Medulla > Pons > Midbrain
The Benefit of Protons

**CASE:**
- 14 y/o boy with PF Ependymoma
- GTR after surgery
- Focal Proton RT to 54 Gy
The Benefit of Protons

- Volumes have almost identical fall off at 80-100% rx dose
  - VMAT has sharper fall off in high dose regions
  - Main benefit to protons is in the 10-50% dose range

Ependymoma to 54 Gy

Case:
- VMAT gives TLs 40% of Rx dose and Hypothalamus 40% of Rx dose
- Protons give TLs 7% of Rx dose and Hypothalamus 3% of Rx dose
AAMD 43rd Annual Meeting
June 17 - 21, 2018

Sidney Kimmel Cancer Center at Sibley Memorial Hospital in Washington DC

Thank You!

John’s Hopkins Proton Center At Sibley Memorial Hospital

Thank You!