Contouring in the brain: barriers to tumor spread, avoidance structures, and future directions

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Learning objectives

• Gain a better understanding of white matter tracts in the brain & how they impact radiation planning
• Understand barriers to spread of brain tumors and how these can relate to common errors in contour delineation
• Review normal structures in the brain including the hippocampus
Outline

• Glioblastoma
  – Current state of target delineation and RT planning
    • Neurocognition
    • Tumor recurrence patterns
  – Development of guidance document
    • Anatomic considerations
• Brain metastases
  – Impact of whole brain RT on neurocognition
  – Hippocampal avoidance
• Future directions

Scope of the problem

• 226,000 new CNS cancers worldwide per year
  – 1.7% of all new cancers
• 142,000 deaths from CNS tumors annually
  – 2.1% of all deaths
• Brain tumors are the 2\textsuperscript{nd} leading cause of all cancer-related deaths in people <20 years old
• Brain tumors are the 2\textsuperscript{nd} and 5\textsuperscript{th} leading cause of cancer deaths in males and females 20-40 years old respectively

Glioblastoma Multiforme

- 18,500 primary CNS malignancies/year in US
  - Malignant gliomas account for 50%
  - GBM accounts for 60% of malignant gliomas
- Aggressive local tumors, frequently crosses midline
- Diffusely infiltrative with malignant cells present in peritumoral edema
- Rarely metastasize, rarely multifocal

Current state of target delineation in GBM (NRG BN001)

- **CTV_4600** - Either the T2 or FLAIR abnormalities on the post-operative MRI scan, inclusive of all contrast-enhancing T1 abnormality on the postoperative MRI and the surgical cavity, plus a margin of 2 cm, which may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc.

- **CTV_6000** - Contrast-enhancing T1 abnormality and the surgical cavity on the post-operative MRI scan plus a margin of 2 cm. The CTV_6000 margin may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc.
International Guideline

Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, LACA, DAHANCA, EORTC, GEC-ESTRO, GORTEC, HNSPCSG, HNCTG, JAG-KITIT, LPRHIT, NCIC CTG, NCRI, NRG Oncology, PINS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines
CLINICAL INVESTIGATION Prostate

RTOG GU Radiation Oncology Specialists Reach Consensus on Pelvic Lymph Node Volumes for High-Risk Prostate Cancer

Lawton C et al. IJROBP 2009
Michalski et al. IJROBP 2009

CLINICAL INVESTIGATION Cervix

Consortium Guidelines for Delineation of Clinical Target Volume for Intensity-Modulated Pelvic Radiotherapy for the Definitive Treatment of Cervix Cancer

<table>
<thead>
<tr>
<th>Table 2. CTV components</th>
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<td>OTV</td>
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<tr>
<td>Cervix</td>
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<tr>
<td>Uterus</td>
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<td>Parametrium</td>
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<td>Vagina</td>
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<thead>
<tr>
<th>Table 3. Anatomical boundaries of parametrium</th>
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<tr>
<td>Location</td>
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<tr>
<td>Anteriorly</td>
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<td>Posteriorly</td>
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<td>Laterally</td>
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<tr>
<td>Superiorly</td>
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<td>Inferiorly</td>
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Current state of target delineation in GBM  
(NRG BN001)

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Image Fusion

Planning CT and T2-FLAIR MR
Overlay of 3D MP-RAGE over planning CT scan and T2-FLAIR over planning CT scan

GBM treatment dose planning
Radiotherapy field design—extent of tumor

- T1 enhancing region is usually the extent of resection to preserve optimal function
  - Primarily neoplastic and necrotic tissue
- Autopsy, biopsy, MRSI studies show tumor infiltration beyond contrast enhanced region
- Tumor cells intermixed with normal neural tissue
Radiotherapy field design—patterns of recurrence

- Studies correlating autopsies to serial CT scans have demonstrated that greater than 80% of recurrences occur within 2- to 3-cm of the surgical cavity.
- Autopsy study\(^1\) demonstrated that tumor cells are not demonstrable > 3 cm from the main tumor in untreated lesion.
- Biopsy studies\(^2\) show
  - contrast enhancement consistently reflects tumor without any significant brain parenchyma
  - isolated tumor cells infiltrated to at least the border of T2 hyperintensity, and beyond.

\(^1\)Burger PC et al J Neurosurg 1983
\(^2\)Earnest FT et al Radiology 1988

Field design for GBM—an area of debate

<table>
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<tr>
<th>Image set</th>
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<th>EORTC</th>
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<tr>
<td>T2/FLAIR</td>
<td>Expand by 2 cm, cover to 46 Gy</td>
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<td>T1c residual + cavity</td>
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Niyazi et al Radiotherapy & Oncology 2016
Field design for GBM—an area of debate

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<tr>
<td>T2/FLAIR</td>
<td>Expand by 2 cm, cover to 46 Gy</td>
<td>Only consider inclusion for secondary GBM (IDH1 mutant)</td>
</tr>
<tr>
<td>T1c residual + cavity</td>
<td>“Cone down” to cavity plus 2 cm to 60 Gy</td>
<td>Single phase treatment of cavity + 2 cm to 60 Gy</td>
</tr>
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Niyazi et al Radiotherapy & Oncology 2016

- 833 patients randomized to 60 Gy RT + standard temozolomide or dose-dense temozolomide
- Two radiation protocols allowed
  - 82% treated per RTOG protocol including 2 cm coverage beyond T2/FLAIR
  - 18% treated per EORTC to T1c cavity/residual plus 2 cm alone
- No difference in outcomes observed between radiation design strategies
Patterns of relapse after GBM radiation

- The median total brain volume was 1326 cc
- Median PTV$_{2cm}$ volume was 266 cc
- Median PTV$_{1cm}$ volumes was 158 cc

<table>
<thead>
<tr>
<th>Technique</th>
<th>In-field relapse</th>
<th>Marginal relapse</th>
<th>Distant relapse</th>
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<tbody>
<tr>
<td>3DRT</td>
<td>54 (91%)</td>
<td>7 (17%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>IMRT</td>
<td>25 (96%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TMS</td>
<td>6 (100%)</td>
<td>0</td>
<td>0</td>
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Table 1: Patterns of recurrence correlation unadjusted models

- Median total brain volume was 1326 cc
- Median PTV$_{2cm}$ volume was 266 cc
- Median PTV$_{1cm}$ volumes was 158 cc

Necessity for accurate target delineation: neurocognition

- 33 patients adults 6-25 years s/p brain RT
- All patients had white matter changes
- Severe white matter changes correlated with worse clinical status and quality of life
- Neuroendocrine abnormalities were noted in 16/25 patients

Table 2: Percentages of patients with neuroendocrine abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White matter changes</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Grade 1: Low</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Grade 2: High</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Lateral and/or spinal</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Central</td>
<td>10 (30)</td>
</tr>
<tr>
<td>Cerebellar and/or trigeminal</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Tolaniaglotta</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>


Johannsen TB et al. Radiother Oncol 2013
Neurocognitive dysfunction after fractionated RT

- 18 patients received brain RT on prospective protocol
  - Schwannoma
  - Meningioma
  - Low-grade glioma
- Impairment at 18 months on:
  - Trail-making test (25%)
  - Verbal memory test (29%)
  - IQ testing (21%)
- Correlated impairment in delayed recall of a list of words to the hippocampal dosimetry

Gondi V et al. IJROBP 2013

Brain deterioration after focal radiation

- Examined MRI changes in 15 patients with high-grade glioma after RT
- Measured the cortical thickness (gray matter) pre-RT and 1 year post-RT

Karunamuni R et al. IJROBP 2016
Brain deterioration after focal radiation

- Cortical thickness decreased by 0.0033 mm (P<.001) for every 1-Gy increase in RT dose
- Dose-dependent thinning of the cerebral cortex, with varying neuroanatomical regional sensitivity, 1 year after fractionated partial brain RT.

Temporal and limbic cortex exhibited the largest changes in cortical thickness per Gy.
- The magnitude of thinning parallels 1-year atrophy rates seen in neurodegenerative diseases and may contribute to cognitive decline following high-dose RT.
The Effect on the Brain

Frontal lobe
- Changes in personality and intellect. Uncoordinated walking or weakness of one side of the body. Loss of smell, occasional speech difficulties.

Temporal lobe
- Fits, fear, intense familiarity, strange smells or blackouts. Speech difficulties and memory problems.

Brain stem
- Unsteadiness and an uncoordinated walk. Facial weakness, a one-sided smile or drooping eyelid. Double vision, difficulty in speaking and swallowing.

Parietal lobe
- Speech and understanding, writing, reading, calculations, numbness or weakness on one side of the body.

Occipital lobe
- Loss of vision on one side.

Cerebellum
- Lack of coordination (walking and speech), unsteadiness, flickering involuntary movement of the eyes. Vomiting and neck stiffness.

Brain deterioration after focal radiation

Patient Perspective

“Everything I do is slow. I walk, talk, and think slowly. . . I still have no short-term memory. . . Much of the time I can’t even remember the names of relatives and close friends. . . I am always confused. . . Because I look normal and often sound normal, people assume I am normal. But I’m not. . . I get depressed a lot knowing that I will never have my competence back”

Susan Sontag
16 year survivor after brain RT
Awards Ceremony speech
Society for Neuro-Oncology Meeting 2004
NRG Consensus Contouring Guidelines

- NRG protocols for GBM allow for (CTV) reductions at natural barriers to tumor growth
  - no guidelines have been delineated to review the relevant white matter pathways and the aforementioned barriers
- Four postoperative GBM cases in the brain were selected.
  - 10 academic rad oncs specializing in brain tumor treatment
- Focus was depicting anatomic trimming and common mistakes made in GBM contouring
  - Demonstrated this trimming reduces brain exposure to radiation by ~15-20% per case

Kruser TJ et al ASTRO 2018

Right temporal GBM volumes
Left temporal GBM volumes
Left temporal GBM volumes

Left frontal GBM volumes
Right parietal GBM volumes

Mistakes made during GBM CTV delineation

- Poor attention to MRI-CT fusion quality near the target region prior to target delineation.
- Failure to utilize coronal and sagittal reconstructions to craft and review CTVs.
Mistakes made during GBM CTV delineation

- Failure to trim the infratentorial component of post-expansion CTV for supratentorial (temporal, occipital) tumors.

- Failure to trim the contralateral hemisphere out of the post-expansion CTV, giving respect to the barrier that the interhemispheric falx represents to tumor spread.

Mistakes made during GBM CTV delineation

- Over-aggressive trimming of the post-expansion CTV at the midline at the level of the corpus callosum

- Over-aggressive trimming of the post-expansion CTV from the brainstem
  - tumors that involve the thalamus have the potential for inferior spread down the cerebral peduncle into the mid-brain.
**Diffusion-Tensor MRI (DTI)** is a special kind of diffusion imaging that uses computer software to map white matter tracts in the brain.

Descending tracts from thalamus into brainstem

Crossing tracts at midline in the corpus callosum

Crossing tracts aka the anterior and posterior commissures

**Brain Metastases Epidemiology**

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>Relative Prevalence of Brain Metastases</th>
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<tbody>
<tr>
<td>Colon: 5%</td>
<td>Annual incidence: 170,000-300,000</td>
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<tr>
<td>Melanoma: 9%</td>
<td>Autopsy incidence: 10% - 30%</td>
</tr>
<tr>
<td>Unknown primary: 12%</td>
<td>Mean age: 55 - 65 years</td>
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<tr>
<td>Other known primary:13%</td>
<td>Median survival: ~6 months</td>
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<tr>
<td>Breast: 15%</td>
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<tr>
<td>Lung: 48%</td>
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</tbody>
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Wen PY. In: DeVita. Cancer: Principles & Practice of Oncology. 2001:
Subacute effects of WBRT

- Patients may develop transient worsening of neurologic symptoms after WBRT\(^1\)
- Those who receive WBRT may be more likely to suffer from a significant decline in learning and memory function\(^2,3\)

\(^1\) Sun A et al. (2011) J Clin Oncol.
\(^2\) Chang EL et al. (2009) Lancet Oncol.
\(^3\) Gondi V et al. (2010) Radiother Oncol.

SRS +/- WBRT—What is the neurologic impact?

- Primary endpoint—cognitive deterioration of > 1 standard deviation from baseline at 3 mo
- Less cognitive deterioration with SRS alone at 3 mo (63%) versus SRS plus WBRT (92%)
- Quality of life was higher at 3 mo SRS alone
- Conclusion: For patients with 1-3 brain metastases, SRS alone may be the preferred approach

Brown PD et al JAMA 2016
Neurotoxicity with WBRT

- Pooled analysis of lung CA pts receiving either PCI (410 pts) or observation (173 pts)
- Excluded pts with brain relapse to minimize confounder
- HVLT decline associated with WBRT (Odds ratio 2-4 range)

Why do we see these neurocognitive changes?
Preclinical studies

Radiation

- Oligodendroglia cell depopulation
- Microglial cell activation
- Endothelial cell depopulation

White Matter Necrosis

Early effects?

Neuro-inflammation

Late effects?

Neurocognitive Deficits

Complex interactions of many cell types

Stunted white matter connectivity

Neural Stem Cells

- Neurogenesis persists through adulthood in primarily two neurogenic centers: subventricular zone, subgranular zone\(^1\)
- Responsible for self-renew, differentiation, intrinsic brain plasticity and repair

\(^1\) Barani et al. 2007 Int J Radiat Oncol Biol Phys.
Radiation-induced changes to the Hippocampus

- After RT:
  - increase in hippocampal apoptosis
  - decrease in hippocampal proliferation
  - decrease in neurogenesis correlated with a progressive decline in neurocognitive function
- Inflammation-mediated changes in the microenvironment contributed to destruction of neurogenic centers and adversely affected normal proliferation and differentiation of surviving NSCs
- The extent of inflammation correlated with radiation and was directly proportional to decreased neurogenesis

1 Peissner W et al. 1999 Brain Res Mol Brain Res
2 Chiang CS et al. 1997 Int J Radiat Biol
3 Monje ML et al. 2003 Science

Hippocampal avoiding whole brain RT

- New memory associated with neural stem cells in the subgranular zone of the hippocampus
- Standard WBRT associated with 4- and 6-mo decline in verbal recall measure (HVLT-R) and decreased patient quality of life

Gondi V et al. IROBP 2010
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


- 113 accrued patients
- Mean relative decline in Hopkins verbal learning test was 7%
  - Significantly lower than historical control (30% from previous WBRT trial)
- No significant quality of life score decline was noted
- Median survival was 6.8 months

Gondi V et al. JCO 2014

Ongoing HA-WBRT Trials (with memantine)

NRG ONCOLOGY
NRG-CC001
(ClinicalTrials.gov NCT #: 02360215) (6/10/15)
A RANDOMIZED PHASE III TRIAL OF MEMANTINE AND WHOLE-BRAIN RADIOThERAPY WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE IN PATIENTS WITH BRAIN METASTASES

NRG ONCOLOGY
NRG-CC003
(ClinicalTrials.gov NCT #TBD)
RANDOMIZED PHASE II/III TRIAL OF PROPHYLACTIC CRANIAL IRRADIATION WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE FOR SMALL CELL LUNG CANCER
Concerns with HA-WBRT

- Is the potential for preserved QOL and memory cost-effective when there is limited survival in these patients?
  - 6.8 mo vs 4.9 months
- Perihippocampal metastases
  - Most limbic metastases occur in patients with non-oligometastatic disease
  - 3% of metastases within hippocampal region¹
- Concerns with reproducibility, implementation

Begin contouring at the most caudal (inferior) extent of the crescentic-shaped floor of the temporal horn of the lateral ventricle and contour the hypointense grey matter located medial to the CSF hypointensity, not the white, bright white matter.

Continue contouring in a cephalad (superior) direction, medial to the temporal horn of the lateral ventricle and contour the hypointense grey matter, not the white, bright white matter. Note that the contours are progressively moving in a supero-posterior direction, keeping in line with the curved banana shaped structure of the hippocampus. Avoid the fimbriae and also avoid the grey matter (amygdala and uncus) located anterior to the tip of the temporal horn of the ventricles.
Continue contouring in a cephalad (superior) direction, medial to the temporal horn of the lateral ventricle and contour only the hypointense grey matter, not the white, bright white matter. Continue to avoid the fimbriae and avoid the grey matter (amygdala and uncus) located anterior to the tip of the temporal horn of the ventricles.

Continue contouring in a cephalad (superior) direction; note that at this level, the temporal horn of the lateral ventricle may no longer be visible on every slice, but the quadrigeminal cistern serves as a medial reference landmark. Contour only the hypointense grey matter, not the bright white matter.
The hippocampus remains medial to the temporal horn of the lateral ventricle throughout its extent, and so on slices where you can visualize it, use it as a consistent reference. The quadrigeminal cistern remains a good medial landmark.

The hippocampal tail remains posterior to the thalamus as it curves medially toward the splenium of the corpus callosum. Note that it is still medially located relative to the lateral ventricle. Also note that the thalamus, basal ganglia and internal capsule now become visible.
Even in its cephalad (superior) extent, the hippocampal tail remains lateral to the lateral edge of the quadrageminal cistern.

Terminate hippocampal contours at the point where the T1-hypointense structure no longer borders the atrium of the lateral ventricle. At this point, the crux of the fornix emerges anteriorly and the splenium of the corpus callosum can be visualized posteriorly.
**Dosimetry of HA-WBRT**

<table>
<thead>
<tr>
<th>Name of Structure</th>
<th>Dosimetric Parameter</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>V (&lt; 0.3 cc)</td>
<td>0.3 cc</td>
<td>0.3 cc</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V (%)</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Hippocampus Max</td>
<td></td>
<td>16 Gy</td>
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<td></td>
</tr>
<tr>
<td>Hippocampus Neve_L</td>
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<td>3.0 Gy</td>
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**Hippocampal avoidance—ready for prime time?**

- 60 patients receiving PCI +/- HA
- Primary endpoint was NCF at 3 mo
- HA-WBRT limited dose to hippocampus
  - Received ~8 Gy on average
- Decline in delayed free recall
  - 27% vs 3%; p = 0.01 at 3 months
  - 48% vs 5%; p = 0.001 at 6 months
- Total free recall
  - 33% vs 5%; p = 0.01 at 6 months

Gondi V et al. UROBP 2010
“Higher functions require input from spatially disparate brain regions, producing a complex interaction between the radiation dose distribution and neurologic outcomes.”

“The designation and avoidance of ‘key’ areas of the brain is needed.”

Clinical Studies

- 49 patients with primary HGG all receiving surgery followed by RT +/- chemo underwent DTI pre- and post-treatment

Regions of interest were discrete white matter regions based on a population-averaged “white matter parcellation map”

The corpus callosum, cingulum bundle, and fornix show the most prominent dose-dependent changes following RT
Modern Neuroscience: It’s all about CONNECTIONS

Diffusion-weighted MRI uses the diffusion of water to generate contrast in MR images.

- Diffusion patterns can reveal microscopic and macroscopic details about tissue architecture.

Diffusion-Tensor MRI (DTI) is a special kind of diffusion imaging that uses computer software to map white matter tractography in the brain.
Modern Neuroscience: It’s all about CONNECTIONS

Functional MRI (fMRI) measures brain activity by detecting changes in blood flow when regions of the brain are activated.

- During a study, the awake person performs a task, fMRI records all the areas of the brain that are simultaneously activated.

Connectome (like genome) = An accounting for all structural and functional connections that constitute the whole spectrum of cognition and behavior.
Novel approaches in defining residual GBM post-surgery?

- FET-PET to craft “Biologic tumor volumes” in 17 pts
  - Biologic tumor volumes were larger than MRI
    • “significant” differences in target volumes in 11/17 cases
- 41 patients
  - Congruence of MRI and FET signals for target volumes is poor, mean uniformity indices of 0.39
  - MRI-based target volumes miss FET-defined tumor in 17% of cases
- Hypothesis-generating—no gold standard

Learning objectives—conclusions

- Gain a better understanding of white matter tracts in the brain & how they impact radiation planning
  - Corpus callosum, cerebral peduncle important to consider
- Understand barriers to spread of brain tumors and how these can relate to common errors in contour delineation
  - Respect to ventricles, cerebral falx, cerebellar tentorium has potential to reduce neurotoxicity
- Review normal structures in the brain including the hippocampus
  - comfort with this technique will be increasingly necessary

Niyazi et al. Radiotherapy & Oncology 2011
Rieken et al. Radiotherapy & Oncology 2013