Late CNS Toxicity

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Disclosure

I have no conflicts of interest to disclose.

Outline

• Describe RT Associated Late CNS Toxicity
• Current Practice: Discuss RT parameters to reduce late radiation CNS toxicity
• The future: Imaging biomarkers for early detection of late radiation CNS toxicity

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Introduction

• Radiation is an effective treatment for many brain tumors

• Late neurocognitive dysfunction secondary to RT can be a devastating clinical problem in long-term survivors

Radiation Induced Brain Injury

Acute Radiation-Induced Edema

Mike Robbins

Brown, Seminars in Oncology 04
Late Delayed Effects (> 1 yr)
- Neuropsychological effects
- Leukoencephalopathy
- Diffuse white matter injury
- Focal radiation necrosis

Focal Radiation Necrosis
Spreading wave-front refers to ill-defined feathery margins of enhancement

Swiss cheese and spreading wave front pattern of enhancement (arrow).

Late Neuro-Cognitive Effects Following RT
- Cognitive decline, attention, information processing speed, working memory, learning and executive function
- Impaired cognition is most pronounced in children less than 7 yrs and greater than 60 yrs
- Decrease in IQ noted in children after whole brain irradiation
Neuro-Cognitive Decline 8 mths post Chemo-RT in Malignant Gliomas

Contributing Factors

- RT Factors: Total dose, fraction size, treatment volume
- Patient Factors: Age, pre-existing brain injury (tumor/surgery), vascular disease
- Others: Chemotherapy, drugs (anti-epileptic)

Neuro-Cognitive Deficits in Meningioma pts following Sx
MD Anderson Randomized Trial Schema

- RPA class I vs. II
- 1 or 2 vs. 3 Brain Mets
- Melanoma / Renal cell carcinoma vs. Other

SRS + WBRT

SRS alone

Randomize

Mean Probability of NCF Decline

<table>
<thead>
<tr>
<th></th>
<th>Intracranial Failure Rate at 1 year</th>
</tr>
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<tbody>
<tr>
<td>SRS</td>
<td>73%</td>
</tr>
<tr>
<td>SRS + WBRT</td>
<td>27%</td>
</tr>
</tbody>
</table>

Neuro-cognitive Decline 4 months post RT
HVLT Immediate Recall

HVLT Immediate Recall 96%

Intracranial Failure at 1 year

Intracranial Failure Rate is Higher with SRS Alone

Chang E, Lancet Oncology 10(11):1037-1044, 2009

Mean Probability of NCF Decline

SRS 23%

SRS + WBRT 49%

Conf
Late CNS toxicity following RT

- Clinical, radiological, behavioral and biological signs of late CNS injury are complex
- Early vascular toxicity (e.g., blood-brain-barrier disruption and vessel dilation)
- Subacute focal and diffuse demyelination (depletion of glial precursors)
- Late structural degeneration (e.g., necrosis)

RT parameters associated with late CNS toxicity following:

- Single fraction stereotactic radiosurgery (SRS)
- Fractionated stereotactic radiotherapy (FSRT) given in 3-5 fractions
- Whole Brain (WB RT) Radiation

Neuro-cognitive decline correlates with tumor progression

Imaging Changes Following Stereotactic Radiosurgery for AVM

17 mths post SRS MR T2

When does RT Necrosis occur following SRS?

% AVM Patients with Post-Radiosurgery T2 Changes


RT Dose Associated Timing of Post-RT Imaging Changes

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Risk of RN Following SRS is Dependent on Volume Receiving > 12 Gy

Minniti et al, Radiat Oncol 15;6:48, 2011

RN Risk is Associated with AVM Location


Lesion Diameter Correlates with 12 Gy Volume

### Stereotactic Radiosurgery (SRS)

- For AVM, risk of late RN necrosis is due to eloquent location, and to lesser extent by volume, V12
- For brain metastases, similar findings regarding location and V10 (10.5 cm³) and V12 (8 cm³) have been analyzed as potential predictors of RN.


### Fractionated Stereotactic Radiotherapy

- Frameless technique using Cyberknife and/or image guided RT (IGRT) given typically in 3 to 5 fractions for brain metastases
- Fractionation and more precise treatment may further reduce risk of RN
- Large tumor lesions in critical locations

### Potential Dosimetric Parameters

- Fractionated stereotactic radiosurgery (FSRT) for brain metastases not amenable to single fraction SRS used 5 fractions × 7 Gy in a prospective clinical trial
- RN was higher in those where the normal brain volume receiving > 4 Gy per fraction exceeded 20 cc

Ernst-Stiecken, Radiother Oncol 81(1):18-24, 2006
Whole Brain and Partial Brain RT

- Whole Brain TDS/5 45 Gy risk of radiation necrosis
  - 30 Gy in 10 fractions or 37.5 Gy in 15 fractions
- Partial Brain TD 5/5 60 Gy

RT Dose Effects of Hippocampus

Axial

Coronal

Sagittal

Patient Data Suggests Chemotherapy and RT Ablates Hippocampal Neurogenesis

Hippocampal Sparing Whole Brain IMRT

Gondi V. Int J Radiat Biol Phys 2010

RTOG 0933

Table 6. Study schema for RTOG 0933, a multi-institution Phase II trial of hippocampal sparing during WBRT for brain metastases.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Within 2 weeks before treatment</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>E</td>
<td>1. Repeat MRI with fused CT simulation</td>
<td>WBRT with hippocampal avoidance</td>
</tr>
<tr>
<td>I</td>
<td>2. NCP testing</td>
<td>Using IMRT G05 in 10 fractions</td>
</tr>
<tr>
<td>J</td>
<td>3. Quality of life assessment</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>4. Central review of hippocampal contours</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>and HA-WBRT treatment plan</td>
<td></td>
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<td>icic</td>
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</table>

Hippocampal Formation

thebrain/roegil.ca
Clinical Feasibility in 33 patients

Neural Progenitor Cell Sparing VMAT

Conventional VMAT  Neural Progenitor Cell Sparing VMAT

Spare progenitor cells but no change in PTV coverage!


Neural Progenitor Sparing in Mouse Brain

Ipsilateral subventricular zone

Ipsilateral dentate gyrus

24 hrs After RT, Neural Progenitor Sparing in Mouse Brain

Green: Proliferation with Ki-67. Blue: Nuclear stain DAPI

Conventional  Sparing

Treatment Plan  10x  Inset, 60x

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Conclusion

- Potential strategies being developed to reduce the late neuro-cognitive deficits associated with WB or partial brain RT include hippocampal or neural stem cell sparing techniques
- No clinical data to support using these techniques at the current time

Re-Irradiation Data in Recurrent GBM

- Re-irradiation is a valuable treatment with for recurrent GBM with modern RT techniques
- 147 high grade gliomas using FSRT 35 Gy in 10 fx was safe, well-tolerated and OS for GBM was 11 mths in limited tumor volumes (Fogh et al., JCO 2010)

Re-Irradiation of High Grade Gliomas Using Conventional RT

<table>
<thead>
<tr>
<th>Author</th>
<th>No</th>
<th>Dose</th>
<th>Median Survival (Months)</th>
<th>Toxicity (pts.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antczak 1999</td>
<td>31</td>
<td>20-RT 34.5/1.5 Gy</td>
<td>13.7</td>
<td>-</td>
</tr>
<tr>
<td>Barlow 2005</td>
<td>22</td>
<td>14 Pat. 45-54 Gy 8 Pat. 35 Gy</td>
<td>7.5</td>
<td>0</td>
</tr>
<tr>
<td>Combs 2005</td>
<td>172</td>
<td>30-2.5 Gy</td>
<td>WHO IV 10, WHO III 16, LGG 22</td>
<td>1 recurred</td>
</tr>
<tr>
<td>Chu 1999</td>
<td>25</td>
<td>37.5/1.5 frac.</td>
<td>11.8</td>
<td>3 HN OR</td>
</tr>
<tr>
<td>Veitch 2001</td>
<td>42</td>
<td>40/2.5 Gy</td>
<td></td>
<td>3 recurred 1 metast</td>
</tr>
<tr>
<td>Combs 2005</td>
<td>54 WHO IV 28WHO II</td>
<td>Stereotact. RT 36 Gy/2.0 Gy</td>
<td>11.8</td>
<td>0</td>
</tr>
</tbody>
</table>

Stephanie E Combs, ESTRO 2008
Re-Irradiation and Reducing Risk of RN

- Time between RT Course
- RT Dose/ Fraction + Treatment Volume
- Cumulative NTD < 100 Gy

Bevacizumab in Recurrent GBM

- Phase II studies using the monoclonal VEGFR inhibitor, bevacizumab with high response rates in recurrent gliomas
- 6 mth PFS 42% leading to recent FDA approval but overall survival remains poor at 8 months (Friedman et al, JCO 2009)

Mechanism of Action of Bevacizumab
Hypofractionated SRS + Bevacizumab in Recurrent High Grade Glioma (HGG)

- Bevacizumab 10mg/kg IV q 2 wks of a 28-day cycle
- Hypofractionated SRS 30 Gy in 5 fractions over 2 wks
- Brain MRI was performed every two cycles after cycle 2

Bevacizumab Decreases Vascular Permeability

Randomized Double Blind Placebo Controlled Study of Bevacizumab for CNS Radiation Necrosis

Toxicities Associated with Bevacizumab

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 wk after 2nd cycle developed ischemic changes with worsening of visual field; removed from study but no SAE.</td>
</tr>
<tr>
<td>5</td>
<td>3 wk after 2nd cycle had possible ischemic changes and worsening of hemiplegia but no SAE</td>
</tr>
<tr>
<td>6</td>
<td>Week 24 visit revealed ischemic changes but no SAE</td>
</tr>
<tr>
<td>9</td>
<td>Admitted for pneumonia and aspiration pneumonia; SAE filed</td>
</tr>
<tr>
<td>11</td>
<td>3 wk after 2nd cycle had dramatic improvement in radiation necrosis but developed superior sagittal sinus thrombosis; SAE filed</td>
</tr>
<tr>
<td>13</td>
<td>Developed DVT and PE within 1 wk of BVZ; SAE filed but continued with Lovenox</td>
</tr>
</tbody>
</table>

Schema
Bevacizumab Naïve Patients

Randomized 1:1

Arm 1 IMRT 35 Gy in 10 fx
Concurrent Bev 10 mg/kg IV q2 wks

Arm 2 Bev 10 mg/kg IV q 2 wks

Phase II study for toxicity/efficacy; estimated sample size 178 patients

Conclusions

• Bevacizumab (5 mg/kg given 4 cycles) is a potential effective therapy for radiation necrosis

• Moderate side effects and therefore must be used cautiously
Functional MR Imaging as a Biomarker

- Functional MR imaging may provide early assessment of late normal tissue toxicity
- to identify patients at risk for developing radiation induced late effects
- early intervention to reduce risk of late CNS toxicity

Anisotropic Water Diffusion in WM

Anisotropic diffusion imaging can be used to study the microstructure of brain tissue. Myelin sheaths restrict water diffusion perpendicular to the long axis of the axon ($\lambda_\perp$), resulting in $\lambda_\perp < \lambda\parallel$. Demyelination causes an increase in $\lambda_\perp$ or a decrease in fraction anisotropy (FA).

Hypothesis

- Radiation may lead to demyelination and structural degradation of NAWM
- Extent of demyelination and axonal injury may be dose-dependent
- May occur prior to development of neurocognitive deficits or MR imaging changes
**MR Diffusion Tensor Imaging**

- Able to assess response of individual fibers to therapy such as RT

- DTI indices are potential surrogate markers capable of assessing severity of pathology in normal appearing white matter

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**Decrease in White Matter FA as a Potential Biomarker of Late Neuro-cognitive dysfunction**

![Graph showing decrease in white matter FA](image)

**Prospective DTI Studies**

**Diffusion Tensor Imaging (Structural Integrity)**

- Pre RT
- During RT: Week 3 and 6
- Post RT: Week 10 and 18

**Neuro-cognitive Tests**

- Trail Making A and B (executive function)
- Hopkins Verbal Learning (memory)
- Controlled Word Association (verbal fluency)
- Pre-RT
- Post-RT: Week 10, 32, 78
Temporal Changes in Fractional Anisotropy of Normal Tissue

<table>
<thead>
<tr>
<th>Region</th>
<th>Pre RT (week 0)</th>
<th>During RT (week 3)</th>
<th>Post RT (week 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Contralateral</td>
<td>&lt;1%</td>
<td>-33%</td>
<td>-26%</td>
</tr>
</tbody>
</table>

Hypothesis

- Degradation occurring in specific neural structures of the functional pathways post irradiation may cause neuro-cognitive dysfunction

Prospective MR DTI Study to Assess Changes in WM following WBRT
Hippocampal White Matter

T1WI
WM bright

$\lambda_3$: diffusivity perpendicular to long axis
WM (dark blue)

Para Hippocampal
Pre RT
1 month after WBRT

$\lambda_3$ increases

Longitudinal DTI changes in Parahippocampal WM after WB RT

<table>
<thead>
<tr>
<th>Pre RT</th>
<th>End RT</th>
<th>Post RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_3$</td>
<td>$\lambda_3$</td>
<td>$\lambda_3$</td>
</tr>
</tbody>
</table>

Perpendicular ($\lambda_3$)

Parallel ($\lambda_3$)

p<0.02

Early DTI Changes in Hippocampus associated with neuro-cognitive decline

% Change in HVLT Immediate Recall 6 months post RT

% Change in $\lambda_3$ 1 month post RT

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Summary

• DTI indices able to detect early changes in micro-structural integrity

• Early changes in structural properties of normal tissue may relate to delayed neuro-cognitive decline

Vascular Changes Following RT

Dynamic Contrast Enhanced MRI

• Prospective DCE MRI: Baseline, Wk 3 & Wk 6 RT, and post RT (1, 6 and 18 months)

• HVLT: Baseline and Post RT

• Early changes in Vascular volume (Vp) were correlated with HVLT
Dose Dependent Change in Vp of Frontal and Temporal Lobe

Early Changes in Vp Correlated to Changes in Learning Scores 6 months post RT

Summary

• Significant changes occur in both frontal and temporal lobe and the hippocampus after partial brain radiation

• These changes suggest that sparing the hippocampus alone may not be sufficient to reduce memory function decline after WBRT
Conclusions

- Late RT toxicity is a devastating problem
- Current clinical and RT parameters may help to reduce risk of late RT necrosis
- Future advances in both imaging biomarkers and therapeutic agents may help to prevent late RT toxicity

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