GREY MATTERS, GRAY MATTERS, TOO

Current Role and Future Development of Radiation Therapy in Treating Brain Tumors

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Grey Versus Gray
- Radiation therapy for brain tumors

Grey matter in brain: neurons

Gray matters:
Radiation dose is important in treating various brain tumors.

Gray (Gy): unit of radiation energy deposited in the tissue (Joule/kg)
Focus of Today’s Talk

- Most aggressive/lethal primary brain cancer:
  - Glioblastoma (GBM)
  - 12,390 new cases predicted in 2017.

- Most common brain cancer:
  - brain metastasis from cancers such as lung, breast, skin, kidney cancers, etc.
  - Annual US incidence > 170,000
Different Types of Brain Radiation

- Cranio-spinal Irradiation (CSI)
- Whole brain Radiation Therapy (WBRT)
- Partial brain
- Intensity-modulated RT (IMRT)
- Stereotactic radiosurgery (SRS)
Standard Care for GBM Patients < 70yo
EORTC-NCIC Phase III (Stupp) Trial
RT plus Concomitant and Adjuvant Temozolomide (TMZ)

Median OS (M): 12.1 14.6 p<0.001
2-yr survival: 10% 26% p<0.001
PFS (M): 5.0 7.2 P<0.001
# Less Radiation for GBM - Treatment in the ‘Elderly’

<table>
<thead>
<tr>
<th>Citation</th>
<th>Patient enrolled</th>
<th>Treatment</th>
<th>Median OS (months)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keime-Guibert, NEJM 356, 2007</td>
<td>Age≥70yo, good PS</td>
<td>No RT</td>
<td>4.3</td>
<td>RT better than supportive care</td>
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<tr>
<td></td>
<td></td>
<td>50.4Gy</td>
<td>7.3</td>
<td></td>
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<tr>
<td>Roa JCO 22, 2004</td>
<td>Age≥60yo</td>
<td>60Gy in 6 weeks</td>
<td>5.1</td>
<td>Short course no different from long course</td>
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<tr>
<td></td>
<td></td>
<td>40Gy in 3 weeks</td>
<td>5.6</td>
<td></td>
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<tr>
<td>Wick NOA-08, Lancet 2012</td>
<td>Age≥65yo **</td>
<td>60Gy in 6 weeks</td>
<td>9.6</td>
<td>TMZ is non-inferior to 60Gy RT</td>
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<tr>
<td></td>
<td></td>
<td>TMZ only</td>
<td>8.6</td>
<td>EFS for MGMT Me’d: TMZ better (8.4 vs 4.6)</td>
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<tr>
<td></td>
<td></td>
<td>60Gy in 6 weeks</td>
<td>9.6</td>
<td>EFS for MGMT not Me’d: RT better (4.6 vs. 3.3)</td>
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<tr>
<td>Malmstrom Lancet 2012</td>
<td>Age≥60yo *</td>
<td>60Gy in 6 weeks</td>
<td>6.0</td>
<td>60Gy in 6 wks worse than 34 Gy; 34Gy in 2 weeks not different from TMZ</td>
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<tr>
<td></td>
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<td>34Gy in 2 weeks</td>
<td>7.5</td>
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<tr>
<td></td>
<td></td>
<td>TMZ only</td>
<td>8.3</td>
<td></td>
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<tr>
<td>Roa IAEA JCO 33, 2015</td>
<td>Age≥65yo or frail</td>
<td>40Gy in 3 weeks</td>
<td>6.4</td>
<td>25Gy in 1 week not worse than 40Gy in 3 weeks for poor KPS</td>
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<tr>
<td></td>
<td></td>
<td>25Gy in 1 week</td>
<td>7.9</td>
<td></td>
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<tr>
<td>Perry NEJM 2017</td>
<td>Age &gt;65yo, no fit for combined tx</td>
<td>40Gy in 3 weeks RT only</td>
<td>9.3</td>
<td>+ TMZ better than RT alone. MGMT Me’d pts with RT+TMZ: 13.5M</td>
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<tr>
<td></td>
<td></td>
<td>40Gy in 3 weeks RT + TMZ</td>
<td>7.6</td>
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More Radiation for GBM

- NRG-BN001, currently ongoing phase III randomized clinical trial

Newly diagnosed GBM, age 18-70, KPS≥ 70

Standard treatment: 60Gy RT with concurrent and adjuvant temozolomide

Dose-intensified RT: 75Gy RT with concurrent and adjuvant temozolomide

(Photon or Proton treatment allowed)
Brain Metastasis

- Most common brain cancer
- Annual US incidence > 170, 000
- Brain metastases occur in up to 30% of patients with systemic cancer
- Latency to brain metastases diagnosis:
  (median time from initial cancer diagnosis)
  - Lung (6-9 mo)
  - Renal cell (1 yr)
  - Breast, Melanoma, Colon (2 yr)
- Brain metastases histologies:
  - 40-50% from lung cancer
  - 15% from breast cancer
  - 9% from Melanoma
  - 5% from colon cancer
  - 11% from unknown primary
  - Other 13%
Standard Care for Brain Metastasis
- Whole Brain Radiation Therapy (WBRT)

- Corticosteroids (poor prognostic patients)
- Whole Brain Radiation Therapy (WBRT) (30Gy in 10fx or 37.5Gy in 15fx) [standard]
- Surgery + WBRT [standard] (Patchell NEJM 1990)
- WBRT + Stereotactic Radiosurgery (SRS) [standard] (RTOG 9508, Lancet 2004)

WBRT to the entire brain
SRS to only the three brain metastases
Questions about Whole Brain RT

• Why do we still need to do brain RT after brain surgery which completely resected the tumor?
  • 1 year local recurrence: surgery only: ~66%; surgery + WBRT: ~20%
  • 1 year distant failure: surgery only ~50%; surgery +WBRT: ~18%
  • Neurologic death: surgery only: 44%; surgery + WBRT: 14%
  • WBRT added after surgery did not improve survival. (Patchell JAMA 1998)

• Toxicities?
  • + WBRT increases risk of memory decline at 4m.
  • SRS: 24% sig decline vs.
  • +WBRT: 52%
# Questions about SRS

- Pros and Cons of SRS?

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<tr>
<th>Pros</th>
<th>Cons</th>
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<tr>
<td>• much less neurocognitive toxicities,</td>
<td>• higher rate of distant intracranial recurrence, needs for</td>
</tr>
<tr>
<td>• higher local control for RT-resistant tumors (brain mets from</td>
<td>close imaging followup,</td>
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<tr>
<td>melanoma, lung cancer, kidney cancer, etc),</td>
<td>• higher rate of radiation necrosis,</td>
</tr>
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<td></td>
<td>• higher cost.</td>
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</tbody>
</table>

- What is the maximal number of brain lesions that can be treated with SRS?
  - Current most accepted number is 4.

- What is the maximal size of the brain mets that can be treated with SRS?
  - Most accepted maximal size is 3cm.
Questions about SRS

• Should the volume or number of brain metastases be the limitation of SRS?

Volume is More Important than Number for Survival!!
SRS for Up to 10 Brain Metastases

- 1-10 metastases treated with SRS alone
- Survival non-inferior for 5-10 vs. 2-4 metastases
- WBRT 9%

Yamamoto Lancet Onc 15, 2014
Future Treatment Strategies: Brain Metastases

- Corticosteroids (poor prognostic patients)
- Whole Brain Radiation Therapy (WBRT) (30Gy in 10fx or 37.5Gy in 15fx) [standard]
- Surgery + WBRT [standard]
- WBRT + Stereotactic Radiosurgery (SRS) [standard]

- Hippocampal-sparing WBRT (investigational)
- SRS alone [cutting edge]
- Surgery +/- localized radiation [cutting edge]
- Chemotherapy
- Targeted therapy (TKIs)

- WBRT + radiation sensitizers (investigational)
- WBRT + chemotherapy (no hi quality evidence to support)
- WBRT+immunotherapy
Can Large-sized Brain Metastasis Be treated with SRS?

What to do about this? Too large for single Fraction SRS (>4 cm)

Hypofractionated SRS

9Gy x 3, 6Gy x 4, 5-6Gy x 5
Machines

CT-on-Rail
GammaKnife
TrueBeam (Arc Therapy)
DR
Carbon ion therapy
Thank you!
EORTC 22952-26001

- SRS
- SRS + WBRT (30Gy)
- Surgery
- Surgery + WBRT (30Gy)

SRS:  GTV + 1-2mm to 20Gy
      3.5cm max or 2.5cm if multiple

Surgery: GTR required (surgeon defined or MRI)

Primary Outcome:
  Duration of Functional Independence (Time to WHO PS>2)

Kocher JCO 29, 2011
24 Month failure:  

- Surgery  
  Local: 59  
  Distant: 42  

- Surgery+WBRT  
  Local: 27  
  Distant: 23  

- SRS  
  Local: 31  
  Distant: 48  

- SRS + WBRT  
  Local: 19  
  Distant: 33

Kocher JCO 29, 2011
**Stereotactic Radiosurgery**

- Corticosteroids (poor prognostic patients)
- Whole Brain Radiation Therapy (WBRT) (30Gy in 10fx or 37.5Gy in 15fx) [standard]
- Surgery + WBRT [standard]
- WBRT + Stereotactic Radiosurgery (SRS) [standard]
- What about SRS alone

### Median OS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
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<tbody>
<tr>
<td>Supportive Care</td>
<td>1 mo</td>
</tr>
<tr>
<td>Steroids</td>
<td>2 mo</td>
</tr>
<tr>
<td>WBRT</td>
<td>4 - 7 mo</td>
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<tr>
<td>Sx + WBRT</td>
<td>6 - 20 mo</td>
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