Current Concepts in the Management of Brain Metastases from Breast Cancer

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Atlanta, GA
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Disclosures

None
Learning Objectives

1. To understand the epidemiology of brain metastases.
2. To understand the recently published ASTRO/AANS guidelines on the management of patients with brain metastases and the key randomized trials supporting the guidelines.
3. To understand the how to estimate prognosis.
4. To review current concepts and clinical trials.
Epidemiology of Brain Metastases

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>Relative Prevalence of Brain Metastases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon: 5%</td>
<td>Annual U.S. incidence: &gt; 170K</td>
</tr>
<tr>
<td>Melanoma: 9%</td>
<td>Ratio Mets/Primary: 10:1</td>
</tr>
<tr>
<td>Unknown primary: 11%</td>
<td>All Cancer Patients: 15 - 30%</td>
</tr>
<tr>
<td>Other known primary: 13%</td>
<td>Autopsy incidence: 10 - 30%</td>
</tr>
<tr>
<td>Breast: 15%</td>
<td>Mean age: 60 years</td>
</tr>
<tr>
<td>Lung: 48%</td>
<td>Median survival: 4-6 months</td>
</tr>
</tbody>
</table>

*Incidence increasing with better systemic Rx and improved survival

Risk of Brain Metastasis (Breast Cancer) by Stage at Diagnosis

- Localized: 2.5%
- Regional: 7.6%
- Distant (Stage IV): 13.5%

Breast cancer is the 2nd most common solid tumor associated with CNS metastases

Barnholtz-Sloan et al, JCO 2004
Factors Increasing Risk for Brain Metastases in Breast Cancer

Younger age
Presence of visceral metastases
Hormone receptor negativity
HER-2/neu overexpression

## CNS Metastases in Women with HER2+ MBC

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendell et al</td>
<td>34%</td>
<td>Cancer 2003</td>
</tr>
<tr>
<td>Weitzen et al</td>
<td>29%</td>
<td>ASCO 2002</td>
</tr>
<tr>
<td>Heinrich et al</td>
<td>43%</td>
<td>ASCO 2003</td>
</tr>
<tr>
<td>Clayton et al</td>
<td>39%</td>
<td>Br J Cancer 2004</td>
</tr>
<tr>
<td>Altaha et al</td>
<td>33%</td>
<td>ASCO 2004</td>
</tr>
<tr>
<td>Stemmler et al</td>
<td>31%</td>
<td>SABCS 2004</td>
</tr>
</tbody>
</table>
## CNS Metastases in Women with Triple Neg MBC

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al</td>
<td>Cancer 2008</td>
</tr>
<tr>
<td>Kennecke et al</td>
<td>J Clin Oncol 2010</td>
</tr>
</tbody>
</table>
### Survival after CNS diagnosis by subtype

<table>
<thead>
<tr>
<th>Study</th>
<th>HER2+*</th>
<th>TN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendell et al, 2003</td>
<td>13 mo</td>
<td></td>
</tr>
<tr>
<td>Gori et al, 2007</td>
<td>23 mo</td>
<td></td>
</tr>
<tr>
<td>Eichler et al, 2008</td>
<td>17.1 mo</td>
<td>4.0 mo</td>
</tr>
<tr>
<td>Nam et al, 2008</td>
<td></td>
<td>3.4 mo</td>
</tr>
<tr>
<td>Park et al, 2009</td>
<td>14.9 mo</td>
<td></td>
</tr>
<tr>
<td>Dawood et al, 2008</td>
<td>11.6 mo</td>
<td></td>
</tr>
<tr>
<td>Lin et al, 2008</td>
<td></td>
<td>4.9 mo</td>
</tr>
<tr>
<td>Melisko et al, 2008</td>
<td>23.1 mo</td>
<td></td>
</tr>
<tr>
<td>Hines et al, 2008</td>
<td></td>
<td>7 mo</td>
</tr>
<tr>
<td>Niwinska et al, ASCO 2009</td>
<td>10-13 mo</td>
<td>3-4 mo</td>
</tr>
</tbody>
</table>

*trastuzumab-treated pts
Trends

Overall, the incidence of brain mets from breast cancer is probably stable

HER-2 + disease more commonly metastasizes to the brain

Trastuzumab prolongs survival and potentially changes the natural history of the disease

Trastuzumab does not readily penetrate the blood-brain barrier

Incidence of brain metastases is probably increasing in HER-2 + breast cancer patients
Purpose: To elucidate best practices for these patients.

Methods: Computerized search of the literature revealed over 2000 articles on this topic. Systematic review of Level I evidence yielded 36 randomized controlled trials met criteria were reviewed by a panel of experts from radiation oncology and neurosurgery in order to answer 9 key clinical questions.
ASTRO/AANS Guidelines on Brain Metastases

Nine Key Clinical Questions

1. What is the prognosis?
2. What is the role of surgery?
3. Surgery vs Stereotactic Radiosurgery (SRS)?
4. WBRT vs WBRT + SRS?
5. SRS vs SRS + WBRT?
6. What to do for the pt with poor prognosis?
7. Optimal WBRT dose/fractionation scheme
8. What is the role of radiosensitizers?
9. What is the role of chemotherapy?
Key Question #1: Prognosis

Several prognostic indices have been published:

- RTOG-RPA
- SIR
- BSBM
- Graded Prognostic Assessment (GPA)
- Diagnosis- Specific GPA
RTOG Recursive Partitioning Analysis

Class I
- KPS \( \geq 70 \)
- Primary: Controlled
- Age: <65
- Extracranial metastases: No

MST 7.1 m
20%

Class II
- KPS \( \geq 70 \)
- Primary: Uncontrolled
- Age: \( \geq 65 \)
- Extracranial metastases: Yes

MST 4.2 m
65%

Class III
- KPS <70

MST 2.3 m
15%

Graded Prognostic Assessment (GPA)

A prognostic index used to estimate survival for patients with brain metastases. The index is normalized such that a GPA of 4.0 correlates with the best prognosis and 0.0 correlates with the worst prognosis.

This is preferable to the RTOG-RPA because less subjective, more objective, less dependent on the type and timing of staging/restaging tests and better identifies the pts w best px.
1. Sperduto et al. IJROBP 70:510-514;2008
   1960 pts from 4 randomized RTOG trials showed Age, KPS, #BM, ECM;

2. Sperduto et al. IJROBP 77:655-661;2010
   4259 pts from a retrospective database from 11 institutions underwent univariate and multivariate analyses of prognostic factors (PF) for survival by primary site and treatment. PF found to be significant were used to define the diagnosis-specific GPA prognostic indices.

3. Sperduto et al. IJROBP 82:2111-2117;2012
   Refinement of Breast GPA to include tumor subtype based on 400 breast cancer patients with brain metastases.

4. Sperduto et al. JCO 30:419-425;2012
   Summary report of the updated diagnosis-specific GPA indices with a user-friendly worksheet.
Graded Prognostic Assessment

9 Independent Validation Studies

8. Nieder C, Mehta M. Radiat Oncol 4:10; 2009
## Survival by Diagnosis & GPA

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>GPA</th>
<th>0-1.0</th>
<th>1.5-2.0</th>
<th>2.5-3.0</th>
<th>3.5-4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC/SCLC</td>
<td>3.0</td>
<td>5.5</td>
<td>9.4</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>3.4</td>
<td>4.7</td>
<td>8.8</td>
<td>13.2</td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>3.4</td>
<td>7.7</td>
<td>15.1</td>
<td>25.3</td>
<td></td>
</tr>
<tr>
<td>Renal Cell CA</td>
<td>3.3</td>
<td>7.3</td>
<td>11.3</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal CA</td>
<td>3.1</td>
<td>4.4</td>
<td>6.9</td>
<td>13.5</td>
<td></td>
</tr>
</tbody>
</table>
# Lung GPA

## GPA SCORING CRITERIA FOR NSCLC & SCLC

<table>
<thead>
<tr>
<th>PF</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>Pt. Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;60</td>
<td>50-60</td>
<td>&lt;50</td>
<td>________</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt;70</td>
<td>70-80</td>
<td>90-100</td>
<td>________</td>
</tr>
<tr>
<td>ECM</td>
<td>Present</td>
<td>n/a</td>
<td>Absent</td>
<td>________</td>
</tr>
<tr>
<td>#BM</td>
<td>&gt;3</td>
<td>2-3</td>
<td>1</td>
<td>________</td>
</tr>
</tbody>
</table>

**Sum Total = ________**

**ECM:** Extracranial Metastases  
**#BM:** Number of Brain Metastases

**MST (mo):**

<table>
<thead>
<tr>
<th>GPA</th>
<th>MST (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>5.5</td>
</tr>
<tr>
<td>2.5-3.0</td>
<td>9.4</td>
</tr>
<tr>
<td>3.5-4.0</td>
<td>14.8</td>
</tr>
</tbody>
</table>
# Breast GPA

## GPA SCORING CRITERIA FOR BREAST CANCER

<table>
<thead>
<tr>
<th>PF</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>Pt. Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>&lt;50</td>
<td>60</td>
<td>70-80</td>
<td>90-100</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>≥ 60</td>
<td>&lt; 60</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Subtype</td>
<td>basal</td>
<td>n/a</td>
<td>LumA HER2</td>
<td>LumB</td>
<td></td>
<td>Sum Total</td>
</tr>
</tbody>
</table>

- **basal**: triple negative
- **Luminal A**: ER/PR-positive, HER2-negative
- **Luminal B**: triple positive
- **HER2**: HER2-positive, ER/PR-negative

**MST (mo):**

- GPA 0-1.0: 3.4
- GPA 1.5-2.0: 7.7
- GPA 2.5-3.0: 15.1
- GPA 3.5-4.0: 25.3
Among the best prognosis pts, which system best predicts survival?

<table>
<thead>
<tr>
<th>% of pts</th>
<th>Median Survival Time (mo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBRT</td>
<td>WBRT + SRS</td>
</tr>
<tr>
<td>RPA Class I</td>
<td>27%</td>
<td>9.6</td>
</tr>
<tr>
<td>GPA 3.5-4.0</td>
<td>19%</td>
<td>10.3</td>
</tr>
</tbody>
</table>
### Melanoma GPA

<table>
<thead>
<tr>
<th>GPA Scoring Criteria for Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PF</strong></td>
</tr>
<tr>
<td><strong>KPS</strong></td>
</tr>
<tr>
<td><strong>#BM</strong></td>
</tr>
<tr>
<td><strong>Sum Total</strong></td>
</tr>
</tbody>
</table>

**MST (mo):**  
- GPA 0-1.0: 3.4  
- GPA 1.5-2.0: 4.7  
- GPA 2.5-3.0: 8.8  
- GPA 3.5-4.0: 13.2
# Renal GPA

## GPA SCORING CRITERIA FOR RENAL CELL CANCER

<table>
<thead>
<tr>
<th>PF</th>
<th>0</th>
<th>1.0</th>
<th>2.0</th>
<th>Pt. Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>&lt; 70</td>
<td>70-80</td>
<td>90-100</td>
<td></td>
</tr>
<tr>
<td>#BM</td>
<td>&gt; 3</td>
<td>2-3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Sum Total: __________

**MST (mo):**

- GPA 0-1.0: 3.3
- GPA 1.5-2.0: 7.3
- GPA 2.5-3.0: 11.3
- GPA 3.5-4.0: 14.8
# Gastrointestinal GPA

## GPA SCORING CRITERIA FOR GASTROINTESTINAL CA

<table>
<thead>
<tr>
<th>PF</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Pt. Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>&lt;70</td>
<td>70</td>
<td>80</td>
<td>90</td>
<td>100</td>
<td>_________</td>
</tr>
</tbody>
</table>

Sum Total _________

## MST (mo):

<table>
<thead>
<tr>
<th>GPA</th>
<th>MST (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1.0</td>
<td>3.1</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>4.4</td>
</tr>
<tr>
<td>2.5-3.0</td>
<td>6.9</td>
</tr>
<tr>
<td>3.5-4.0</td>
<td>13.5</td>
</tr>
</tbody>
</table>
“Launch” of the GPA Smart Phone App

1. To simplify use of the GPA, a free mobile web app was created which works on any smart phone or computer with internet access.

2. Go to:  www.brainmetgpa.com

3. Or if you have a phone with a QR code reader, take a photograph of the QR-code, press it and it should take you directly to the site.

4. Follow the instructions on the site. It will walk you through the dx-specific pxtic factors and provide the survival (median & 25-75%iles).
ASTRO/AANS Guidelines on Brain Metastases

Nine Key Clinical Questions

1. What is the prognosis?
2. What is the role of surgery?
3. Surgery vs Stereotactic Radiosurgery (SRS)?
4. WBRT vs WBRT + SRS?
5. SRS vs SRS + WBRT?
6. What to do for the pt with poor prognosis?
7. Optimal WBRT dose/fractionation scheme
8. What is the role of radiosensitizers?
9. What is the role of chemotherapy?
Key Question #2: What is the role of surgery?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Yr</th>
<th>Rx</th>
<th>N</th>
<th>MS</th>
<th>FI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchell</td>
<td>90</td>
<td>S</td>
<td>25</td>
<td>40</td>
<td>38</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>23</td>
<td>15</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Noordijk</td>
<td>94</td>
<td>S</td>
<td>32</td>
<td>43</td>
<td>34</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>31</td>
<td>26</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Mintz</td>
<td>96</td>
<td>S</td>
<td>41</td>
<td>24</td>
<td></td>
<td>ns</td>
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<tr>
<td></td>
<td></td>
<td>RT</td>
<td>43</td>
<td>27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For pts w good prognosis, good performance status (KPS > 70), limited extracranial dz, and a single BM in resectable location, surgery can improve survival. Especially useful when relief of mass effect and/or tissue confirmation of diagnosis is needed.
ASTRO/AANS Guidelines on Brain Metastases

Nine Key Clinical Questions

1. What is the prognosis?
2. What is the role of surgery?
3. Surgery vs Stereotactic Radiosurgery (SRS)?
4. WBRT vs WBRT + SRS?
5. SRS vs SRS + WBRT?
6. What to do for the pt with poor prognosis?
7. Optimal WBRT dose/fractionation scheme
8. What is the role of radiosensitizers?
9. What is the role of chemotherapy?
Key Question #3: Surgery vs SRS in patients with a single brain met?

There are no randomized trials comparing these two treatments. Either is reasonable. Local control is similar, approximately 80% at one year.
ASTRO/AANS Guidelines on Brain Metastases

Nine Key Clinical Questions

1. What is the prognosis?
2. What is the role of surgery?
3. Surgery vs Stereotactic Radiosurgery (SRS)?
4. WBRT vs WBRT + SRS?
5. SRS vs SRS + WBRT?
6. What to do for the pt with poor prognosis?
7. Optimal WBRT dose/fractionation scheme
8. What is the role of radiosensitizers?
9. What is the role of chemotherapy?
Key Question #4: WBRT +/- SRS

RTOG 9508:

Arm 1: WBRT (37.5 Gy) + SRS: n=164
Arm 2: WBRT (37.5 Gy) alone: n=167

Stratification
1. Number of brain metastases (1 vs 2 - 3)
2. Extracranial mets (none vs present)

15% & 24% of 1 & 2-3 brain met pts randomized to SRS did not receive it

### Key Question #4: WBRT +/- SRS

<table>
<thead>
<tr>
<th></th>
<th>WBRT &amp; SRS (mo)</th>
<th>WBRT (mo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RTOG 9508 Survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>6.5</td>
<td>5.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Single brain met</td>
<td>6.5</td>
<td>4.9</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Unplanned Subset Analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 mets and age &lt;50</td>
<td>9.9</td>
<td>8.3</td>
<td>0.04</td>
</tr>
<tr>
<td>1-3 mets &amp; NSCLC</td>
<td>5.0</td>
<td>3.9</td>
<td>0.05</td>
</tr>
<tr>
<td>1-3 mets &amp; RPA Class 1</td>
<td>11.6</td>
<td>9.6</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Key Question #4: WBRT +/- SRS

RTOG 9508 Conclusions

1. WBRT+SRS did not improve survival overall but did improve survival for patients with a solitary metastasis

2. Local control, quality of life, and steroid dependence were all improved in the WBRT+SRS group

3. Post-hoc, unplanned subset analysis (which cannot be regarded as Level 1 evidence) suggested survival benefit for patients with:
   - 1 to 3 mets, age <50
   - 1 to 3 mets with NSCLC (led to RTOG 0320)
   - 1 to 3 mets with RPA Class 1

ASTRO/AANS Guidelines on Brain Metastases

Nine Key Clinical Questions

1. What is the prognosis?
2. What is the role of surgery?
3. Surgery vs Stereotactic Radiosurgery (SRS)?
4. WBRT vs WBRT + SRS?
5. SRS vs SRS + WBRT?
6. What to do for the pt with poor prognosis?
7. Optimal WBRT dose/fractionation scheme
8. What is the role of radiosensitizers?
9. What is the role of chemotherapy?
Key Question #5: SRS vs SRS + WBRT


<table>
<thead>
<tr>
<th></th>
<th>SRS</th>
<th>SRS + WBRT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MST (mo)</td>
<td>8</td>
<td>7.5</td>
<td>nsd 0.42</td>
</tr>
<tr>
<td>1 Yr Brain Recurrence</td>
<td>76.4%</td>
<td>48.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to fall in MMSE (mo)</td>
<td>7.6</td>
<td>16.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Conclusions:
1. No difference in survival.
2. Greater brain recurrence rates in the SRS alone group.
3. Fall in MMSE attributed to distant brain recurrence in the SRS alone group but MMSE is a poor measure of neurocognition.
4. Options remain broad: SRS alone, WBRT alone or WBRT + SRS.
JROSG 99-1: SRS +/- WBRT

Also, longer time to neurocognitive deterioration with WBRT (16.5 mo v 7.6 mo), using 3-point drop in MMSE as the metric

No difference in overall survival

Aoyama et al. JAMA 2006
Aoyama et al. IJROBP 2007
What is the role of SRS alone in Breast Cancer?

Gamma Knife Radiosurgery for Brain Metastases from Breast Cancer

- 176 breast cancer pts underwent SRS for brain metastases between 1991-2005

- Median survival time:
  - 16.0 months for 95 newly diagnosed patients
  - 11.7 months for 81 patients with recurrent brain metastases

- In the newly diagnosed pts, omission of upfront WBRT did not significantly affect survival, freedom from progression in brain or from new brain metastases

- Longer survival associated with:
  - Age <50 years
  - KPS >/=70
  - Primary tumor control
  - Estrogen receptor positivity
  - Her2/neu overexpression

- No association between number of treated brain metastases and survival

ASTRO/AANS Guidelines on Brain Metastases

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5. SRS vs SRS + WBRT?
6. What to do for the pt with poor prognosis?
7. Optimal WBRT dose/fractionation scheme
8. What is the role of radiosensitizers?
9. What is the role of chemotherapy?
In patients with an estimated survival of ≤ 3 months (GPA 0-1.0), choices for rx include:

1. Short course WBRT (20 Gy in 5 fx in 1 wk) which may relieve symptoms, or
2. Comfort care / Hospice
ASTRO/AANS Guidelines on Brain Metastases

Nine Key Clinical Questions

1. What is the prognosis?
2. What is the role of surgery?
3. Surgery vs Stereotactic Radiosurgery (SRS)?
4. WBRT vs WBRT + SRS?
5. SRS vs SRS + WBRT?
6. What to do for the pt with poor prognosis?
7. Optimal WBRT dose/fractionation scheme?
8. What is the role of radiosensitizers?
9. What is the role of chemotherapy?
Key Question #7: Optimal Dose/Fractionation for WBRT

Multiple RTOG studies in the 1970s and 1980s studied a variety of different dose/fractionation schemes. No difference in survival was found. Standard fractionation schemes are:

- 300 cGy x 10 = 3000 cGy in two weeks
- 250 cGy x 15 = 3750 cGy in three weeks
- 200 cGy x 20 = 4000 cGy in four weeks
Nine Key Clinical Questions

1. What is the prognosis?
2. What is the role of surgery?
3. Surgery vs Stereotactic Radiosurgery (SRS)?
4. WBRT vs WBRT + SRS?
5. SRS vs SRS + WBRT?
6. What to do for the pt with poor prognosis?
7. Optimal WBRT dose/fractionation scheme?
8. What is the role of radiosensitizers?
9. What is the role of chemotherapy?
Key Question #8: Radiosensitizers?

There have been 6 prospective randomized trials of WBRT +/- lonalidamine, metronidazole, misonidazole, bromodeoxyuridine, motexafin gadolinium, efaproxyn (RSR-13). None have shown a survival advantage. There is no role for radiosensitizers in pts w brain mets.
ASTRO/AANS Guidelines on Brain Metastases

Nine Key Clinical Questions

1. What is the prognosis?
2. What is the role of surgery?
3. Surgery vs Stereotactic Radiosurgery (SRS)?
4. WBRT vs WBRT + SRS?
5. SRS vs SRS + WBRT?
6. What to do for the pt with poor prognosis?
7. Optimal WBRT dose/fractionation scheme?
8. What is the role of radiosensitizers?
9. What is the role of chemotherapy?
Key Question #9: Role of Chemotherapy?

8 randomized trials have investigated the role of chemotherapy in pts with brain metastases. Some trials have shown reported improved brain response rates when chemo is combined with WBRT but at the cost of increased toxicity. None have shown a survival benefit.

There is no role for chemotherapy in pts with brain metastases outside of a clinical trial.
Chemotherapy Trials in Brain Mets: fully published randomized controlled trials.

2. Ushio. JCO 2002;20:3644-3650. Temozolamide
   Thalidomide (RTOG 0118)

None of these trials showed a survival benefit.
Chemotherapy for Brain Metastases: Concerns & Controversies

Blood-brain barrier
Pathogenesis of brain metastases
Lack of effective chemotherapy agents
Extensive prior treatment
Concurrent systemic disease
Measurement of response/efficacy
Neurocognitive Effects of Chemotherapy

Tannock et al. JCO 2004;22:2233-2239

Review of 11 trials (10 in breast cancer) showed chemotherapy can cause “cognitive deficits that are often subtle, although are observed in a proportion (16-75%) of patients, may be durable and can be disabling.”

Any clinical trial (chemo and/or RT) in patients with brain metastases should have a neurocognitive endpoint.
Current Clinical Trials

1. RTOG 1119: WBRT +/- Lapatinib in HER2-Pos
2. WBRT +/- Veliparib in HER2-Neg
3. Lapatinib + capecitabine
4. Chemoprevention Trials
RTOG 1119: Phase II Randomized Study of Whole Brain Radiotherapy in Combination with Concurrent Lapatinib in Patients with Brain Metastasis from Her2-Positive Breast Cancer: A Collaborative Study of RTOG and KROG

PI: In Ah Kim, co-chair: David Peereboom, Paul Sperduto, Jennifer DL Santos

**Schema**

<table>
<thead>
<tr>
<th>STRATIFY</th>
<th>RANDOMIZE</th>
</tr>
</thead>
</table>
| **Graded Prognostic Assessment:** 1.5-2 vs. 2.5-3 vs. 3.5-4 | **Arm A**
| **Concurrent Use of Non-CNS–Penetrating HER2 Blockade at Study Entry:** Yes vs. No: trastuzumab ± pertuzumab | **WBRT:** 37.5 Gy in 15 fx for 3 weeks vs. **Arm B**
| **Previous Stereotactic Radiosurgery or Surgical Resection:** Yes vs. No | **WBRT:** 37.5 Gy in 15 fx for 3 wks Plus **Lapatinib**: 1000mg once daily starting up to 1 day before the first day of WBRT and continuing until 21 days after the final day of WBRT |
Eligibility Criteria

- Histologically or cytologically confirmed invasive breast cancer with HER2 overexpression (IHC 3+ or FISH/SISH ≥ 2.2 amplification)
- At least 1 measurable, unirradiated parenchymal brain lesion
  (≥ 10 mm on T1-weighted gadolinium enhanced MRI)
- Progressive parenchymal brain metastases following SRS or surgical resection for 1-3 brain metastases as long as at least 1 brain metastasis is measurable
- ECOG performance status 0-2 or KPS ≥60
- Adequate hematologic, renal and hepatic function
- Normal LV ejection fraction ≥ 50 by echocardiogram or MUGA scan
What’s New in Targeted Therapy

- HER2-Directed:
  - Lapatinib
  - Neratinib
  - BIBW2992

- Angiogenesis Inhibitors:
  - Bevacizumab
  - AZD2171
  - Sunitinib
  - Pazopanib

- Parp Inhibitors:
  - BSI-201 (Parp inhibitor)
  - Olaparib
  - ABT888
  - Others
EGFR inhibitors

- Gefitinib, Erlotinib
  - RR 10-38%

- EGFR activating mutation
  - 10-25% NSCLC (up to 55% in Asian women who never smoked)
  - RR in brain metastases 70-100%

Soffietti R, CurrOpin Oncol. 2012;24(6):679-86
RTOG 0320: Schema

Phase III three-arm trial in patients with NSCLC and 1-3 brain metastases comparing whole brain radiation and stereotactic radiosurgery alone versus with temozolomide or with erlotinib.

RPA Class
1. Class I: < 65 yrs old & no extra-cranial metastases
2. Class II: ≥ 65 yrs old or extra-cranial metastases

Number of Metastases
1. One
2. Two or Three

Extent of Extracranial Disease
1. None
2. Present

Randomize
Arm 1
WBRT + SRS

Arm 2
WBRT + SRS + Temozolomide

Arm 3
WBRT + SRS + Erlotinib
## RTOG 0320 Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>MST</th>
<th>Grade 3-5 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT + SRS</td>
<td>44</td>
<td>13.4</td>
<td>11%</td>
</tr>
<tr>
<td>WBRT + SRS + Temozolamide</td>
<td>40</td>
<td>6.3</td>
<td>41%</td>
</tr>
<tr>
<td>WBRT + SRS + Erlotinib</td>
<td>41</td>
<td>6.1</td>
<td>49%</td>
</tr>
</tbody>
</table>

Study closed early due to poor accrual. Results suggest but do not prove that toxicity in the drug arms was the cause of early mortality.

Randomized phase 2: WBRT + veliparib in HER2 neg breast cancer brain metastases

> 1 new parenchymal brain met
Prior surgical resection and/or SRS allowed
No prior WBRT or veliparib

Stratify
GPA 0-2.0 v 2.5-3.0
Prior SRS and/or resection (no vs yes)
Lapatinib/capecitabine
HER2+ Breast cancer brain metastases

<table>
<thead>
<tr>
<th>Lapatinib/capecitabine</th>
<th>N</th>
<th>Response rate$^3$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression after WBRT$^1$</td>
<td>240</td>
<td>20</td>
</tr>
<tr>
<td>Before WBRT$^2$</td>
<td>45</td>
<td>67</td>
</tr>
</tbody>
</table>

$^1$Lin, Clin Cancer Res, 2009
$^2$Batchelot, ASCO 2011
$^3$≥50% volumetric reduction of CNS lesions
Evidence for prevention

- Bevacizumab – breast, RCC, NSCLC
- Breast - ↓ rate of CNS relapse with
  - Lap/capecitabine vs capecitabine alone
- NSCLC (EGFR-mutated) – CNS relapse at 1 and 2 yrs of erlotinib/gefitinib 6-13% (~40% historical controls)
- RCC – sorafenib (3 vs 12% in TARGET trial)

Reck M. JCO 2009; Ann Oncol 2010
Heon S. Clin Cancer Res 2010; 16:5873–5882
Chemoprevention Strategies
Brain Metastases

• Primary
  – no prior detectable brain metastases
  – e.g., PCI for small cell lung cancer
  – HER2+ or triple negative breast ca

• Secondary
  – prior treated metastases
  – e.g., 1-3 mets after SRS

PCI = prophylactic cranial irradiation
SRS = stereotactic radiosurgery
# Primary Prevention Trials

<table>
<thead>
<tr>
<th>Title</th>
<th>Sponsor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nab-Paclitaxel and temozolomide + oblimersen in advanced melanoma</td>
<td>Genta Incorporated</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>Trastuzumab-radiotherapy: impact on the cerebral prevention</td>
<td>Centre Oscar Lambret</td>
<td>Stopped due to poor accrual</td>
</tr>
<tr>
<td>Lapatinib/capecitabine vs trastuzumab/capecitabine (Her2+ breast)</td>
<td>GlaxoSmithKline</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>Temozolomide as prevention against brain mets in patients w/ metastatic breast cancer</td>
<td>Schering-Plough Italy</td>
<td>Stopped due to poor accrual</td>
</tr>
<tr>
<td>Maintenance temozolomide versus observation in stable or responding stage III/IV non-small cell lung cancer patients</td>
<td>Schering-Plough Italy</td>
<td>Completed</td>
</tr>
</tbody>
</table>
### Secondary Prevention Trials

<table>
<thead>
<tr>
<th>Title</th>
<th>Sponsor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotactic radiosurgery with sunitinib for brain metastases</td>
<td>University Health Network, Toronto</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Sunitinib after stereotactic radiosurgery for patients with 1-3 newly diagnosed brain metastases</td>
<td>Cleveland Clinic</td>
<td>Stopped due to poor accrual</td>
</tr>
<tr>
<td>SRS $\rightarrow$ temozolomide (1-3 mets)</td>
<td>Univ Florida</td>
<td>Stopped due to poor accrual</td>
</tr>
</tbody>
</table>

*SRS = stereotactic radiosurgery*
## Pre-irradiation Chemotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temozolomide 7 on/7 off</td>
<td>19</td>
</tr>
<tr>
<td>Cisplatin/etoposide</td>
<td>39</td>
</tr>
<tr>
<td>Carboplatin + pemetrexed</td>
<td>40</td>
</tr>
<tr>
<td>Cisplatin + pemetrexed</td>
<td>42</td>
</tr>
<tr>
<td>Cisplatin + ifosfamide + CPT-11</td>
<td>47</td>
</tr>
<tr>
<td>Cyclophosph, 5-FU, prednisone, mtx, vinc</td>
<td>50</td>
</tr>
<tr>
<td>Erlotinib/gefitinib</td>
<td>70</td>
</tr>
</tbody>
</table>

Chemotherapy as active in brain as in systemic compartment

Franciosi V. *Cancer* 1999;85:1599  
Rosner D. *Cancer* 1986;58:832  
Fujita A. *Oncology*. 2000;59:291  
Kim JE. *Lung Cancer*. 2009;65:351  
Barlesi. *Ann Oncol* 2011 [epub]  
Bailon O, *Neuro Oncol* 2012
# Current Clinical Trials

## Pre-irradiation

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib/capecitabine (HER2+ breast)</td>
<td>Lyon, France</td>
</tr>
<tr>
<td>Bevacizumab (lung, non-squam)</td>
<td>France</td>
</tr>
<tr>
<td>Sunitinib (RCC)</td>
<td>France</td>
</tr>
<tr>
<td>Bevacizumab/temozolomide (melanoma)</td>
<td>Mt Sinai, Miami FL</td>
</tr>
<tr>
<td>Ipilimumab/fotemustine (melanoma)</td>
<td>Italy</td>
</tr>
</tbody>
</table>
Can we do anything to mitigate the cognitive dysfunction associated with whole brain radiation?
Memantine for the Prevention of Cognitive Dysfunction in Patients Receiving WBRT: First Report of RTOG 0614, a Placebo-controlled, Double-blind, Randomized Trial

- Phase III trial evaluated the potential protective effects of memantine on cognitive function
- 508 patients with brain tumors who received WBRT between 3/08-7/10
- The study analyzed the length of time before experiencing cognitive decline, overall survival (OS) and progression-free survival (PFS)
- Pts received WBRT of 37.5 Gy in 15 fractions and were randomized to receive placebo or a 20mg dose of memantine per day within three days of initiating radiotherapy for 24 weeks
- Patients underwent standardized tests of cognitive function, which were performed at baseline, eight, 16, 24 and 52 weeks.

Laack et al, American Society for Radiation Oncology 54th Annual Meeting Oct 2012
1. Patients in the memantine group experienced a 17 percent relative reduction in cognitive decline at 24 weeks compared to those in the placebo group.

2. Trends of all three cognitive tests for the 149 eligible patients who survived 24 weeks indicate that the memantine group yielded better results than the placebo at all points.

3. Only 32 percent of patients completed the drug therapy and assessments mainly due to poorer than estimated survival and progressive disease, which led to poor compliance with the treatment protocol.

4. Patients in both groups reported similar levels of Grade 3 and 4 toxicities, including hair loss, fatigue, headache and nausea.

5. There was no difference in patients' OS or PFS between the treatment arms.
RTOG 0933: Phase II Trial of Hippocampal Avoidance WBRT

Plenary Presentation at ASTRO, 9-22-13, N = 113

Endpoints: Hopkins Verbal Learning Test (HVLT) & QOL

Results: Both HVLT & QOL better at at 4 and 6 months compared to historical controls.

Related RTOG Trials:

1. A phase III RTOG trial (WBRT vs HA-WBRT) with neurocognitive endpoints, open
2. WBRT + Memantine vs HA-WBRT + Memantine in development
Conclusions

1. Incidence of BM in BC pts at dx is 13.5%, but lifetime risk is ~20%, and higher (30-40%) in HER2+ and TN pts.

2. See ASTRO Guidelines for best practices (PRO 2012).

3. Use the Breast-GPA to estimate survival.

4. Surgery for resectable BM with mass effect or if dx uncertain.

5. SRS alone for < 5 BM.

6. WBRT reduces distant brain failure and protects from cognitive decline associated with progressive tumor.

7. Memantine and Hippocampal-Avoidance WBRT reduce cognitive decline associated with WBRT.

8. Chemotherapy and radiosensitizers for BM should only be used on a clinical trial.