Clinical Practice Guidelines for the Treatment of Brain Metastases

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Cancer Data
American Cancer Society Registry, 1998-2006

- 1,228,600 cancer patients diagnosed per year in the US alone
- 20-40% of these patients, or 245,720 – 491,440 new patients, will develop brain metastases every year
- Lung/Bronchus, GI, Prostate, Breast most common sites for cancer; lung and breast most common brain metastases

What do we know about brain metastases?

- Survival is related to how well extracranial (primary) disease responds to treatment, and how aggressively intracranial disease is treated especially since nearly 25% of patients succumb to CNS progression of their disease
- Aggressive control of intracranial disease also improves quality of life and reduces the rate of death from neurologic causes
- Prolonged survivals are possible
Milestones from the Literature

- Smalley (Mayo, 1983): Surgically resect single brain mets only with controlled extracranial disease

- Patchell (Kentucky, 1990): Landmark *NEJM* randomized control study reports that resection plus WBRT better than WBRT alone

- Patchell (Kentucky, 1998): Widely-cited *JAMA* RCT concluding that resection plus WBRT better than resection alone, in terms of recurrence (surgery doesn’t eliminate microscopic tumor islands beyond the resection cavity) and death from neurologic causes, but overall survival unchanged

- Kondziolka (Pittsburgh, 1999): Combined WBRT plus radiosurgery boost for 2-4 (multiple) brain mets significantly improves control of brain disease compared to WBRT alone

Milestones from the Literature

- Sneed (UCSF, 1999): Is WBRT necessary? The omission of WBRT in the initial management of patients treated with radiosurgery alone for up to 4 brain metastases does not compromise survival or intracranial control, allowing for future salvage therapy with WBRT as indicated

- Andrews (RTOG RCT, 2004): *Lancet* study reports that WBRT plus radiosurgery boost for a single unresectable brain metastasis significantly improves survival (6.5 mos vs. 4.9) and quality of life (KPS) compared to WBRT alone
Treatment Decisions

Single or less than 3 metastatic brain tumors

Uncontrolled systemic disease
KPS<70
WBRT

Limited, controlled systemic disease
KPS>70

Surgically accessible
Surgery
WBRT

Surgically inaccessible
Radiosurgery
WBRT

Brain Mets: Why Guidelines are Important

- Remarkably prevalent, most common brain cancer
- More high quality data that can be used to guide therapies than for most other areas of neuro-oncology
- BUT… NO national consensus regarding the best management paradigms; extreme variability in patient care (various interpretations of existing data, economic factors, training, variability in multidisciplinary cooperation, etc)
- Unfortunately very minimal data on critical outcomes measures, especially Quality of Life and Neurocognition
Comprehensive Brain Mets Treatment Guidelines

- Introduction and Methodology plus 8 clinical chapters
- Role of Whole Brain Radiation Therapy (WBRT)
- Role of Surgical Resection
- Role of Stereotactic Radiosurgery (SRS)
- Role of Chemotherapy
- Treatment options for Recurrent/Progressive Metastases
- Role of Anticonvulsants
- Role of Steroids
- Role of New, Emerging Novel Therapies

Identify areas where more research is needed, while enumerating ongoing relevant clinical trials for each category.

Brain Mets Guidelines

How was our process different?

I. Timeline

- Produced in ~12 months
- Most similar projects take on average >3 years to complete
- Given an average “shelf-life” of 5-7 years, our expedited timeline leads to maximum impact and relevance for the longest duration

II. Panel Composition

- Many guidelines projects are special-interest endeavors sponsored by one clinical specialty
- A diverse, representative panel of authors ensures ownership and ultimate general acceptance of the recommendations
- Ours is the most multidisciplinary guidelines effort to date, with 20 authors including neurosurgeons, radiation oncologists, neuro-oncologists and medical oncologists
Brain Mets Guidelines

How was our process different?

III. Absolute High Fidelity of Evidence-Based Methodology

- Two-step process: first, a systematic review/ranking the quality of each study; second, creating recommendations linked to evidence

<table>
<thead>
<tr>
<th>AANS / CNS Management of Brain Metastases Guidelines: AANS / CNS Scales for rating quality of the evidence and strength of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of the evidence rated on a three-tiered scale:</td>
</tr>
<tr>
<td>Class 1</td>
</tr>
<tr>
<td>Class 2</td>
</tr>
<tr>
<td>Class 3</td>
</tr>
<tr>
<td>Strength of recommendations rated on a three-tiered scale:</td>
</tr>
<tr>
<td>Level 1 recommendations</td>
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</tr>
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</table>

Brain Metastases Guidelines

Exhaustive Literature Review

- Completed screening process for over 27,500 titles and abstracts for all 8 chapters
- After a meticulous validation analysis, nearly 600 articles progressed to the full-text stage, and, of those, we identified 310 which address directly one of several specific head-to-head clinical comparison scenarios posed throughout our 8 chapters

“You only find gold when you wash a lot of sand.”
### Evidence Table

#### Example: Surgical Resection

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Study Design</th>
<th>Population</th>
<th>Medication</th>
<th>Follow-up</th>
<th>Medium-time to recurrence / progression</th>
</tr>
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<tbody>
<tr>
<td>Example</td>
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<table>
<thead>
<tr>
<th>Summary Table</th>
<th>Example: Surgical Resection</th>
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**Evidence**

**Table**

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**Summary Table**

**Example: Surgical Resection**

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</table>
Brain Metastases Guidelines

The Final Product

- Publication in the *Journal of Neuro-oncology* 2010; 96:1-142
  (January 2010) plus websites of various member organizations (CNS, AANS, Tumor Section, SNO, ASTRO)
  - Commentary – Pg 1-5
  - Introduction – Pg 7-10
  - Methodology – Pg 11-16
  - (1) WBRT – Pg 17-32
  - (2) Surgical resection – Pg 33-43
  - (3) Stereotactic Radiosurgery – Pg 45-68
  - (4) Chemotherapy – Pg 71-83
  - (5) Re-treatment – Pg 85-96
  - (6) Anticonvulsants – Pg 97-102
  - (7) Steroids – Pg 103-114
  - (8) Investigational Therapies – Pg 115-142
- Ongoing review of open clinical trials
- Plan for update in 5 years

What do we know about brain metastases?

- Whole Brain Radiation Therapy (WBRT, systemic) historically the treatment of choice for brain mets and is still used today, especially in patients with multiple brain lesions or with poor KPS scores or active primary disease; an important adjunct to surgical resection

- Radiosurgery (focal) now offered as a standard treatment option across the country, including for those lesions in locations with very high surgical risk
Should patients with brain metastases receive chemotherapy in addition to whole brain radiotherapy (WBRT)?

**Level 1**: No. Routine use of chemotherapy following WBRT has not been shown to increase survival and is not recommended. Four class I studies examined the role of carboplatin, chloroethylnitrosoureas, tegafur and temozolomide, and all resulted in no survival benefit. Two caveats for the treating physician to individualize decision-making: First, most data limited to non small cell lung (NSCLC) and breast cancer; therefore, in other tumor histologies, the possibility of clinical benefit cannot be ruled out. Second, the addition of chemotherapy to WBRT improved response rates in some, but not all trials; response rate was not the primary endpoint in most of these trials. Enrollment in chemotherapy-related clinical trials is encouraged.

Do prophylactic anticonvulsants decrease the risk of seizure in patients with metastatic brain tumors compared with no treatment?

**Level 3**: No. For adults with brain mets without prior seizure, routine prophylactic use of anticonvulsants is not recommended. Only a single underpowered randomized controlled trial (RCT), which did not detect a difference in seizure occurrence, provides evidence for decision-making purposes.
### Brain Metastases Guidelines Conclusions

**Recommendations – Steroids**

<table>
<thead>
<tr>
<th>Asymptomatic brain metastases patients without mass effect</th>
<th>Insufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain metastases patients with mild symptoms related to mass effect</td>
<td></td>
</tr>
<tr>
<td><strong>Level 3</strong>: Corticosteroids provide temporary relief of symptoms related to increased ICP, peritumoral edema. Starting dose: consider 4 to 8 mg/day of dexamethasone</td>
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</table>

| Brain metastases patients with moderate to severe symptoms related to mass effect |
| **Level 3**: If patients exhibit severe symptoms of increased intracranial pressure, it is recommended that higher doses such as 16 mg/day or more be considered. |

**Choice of steroid**

| **Level 3**: If corticosteroids given → dexamethasone |

**Duration of Corticosteroid Administration**

| **Level 3**: Taper slowly over two weeks (longer in symptomatic patients) with full understanding of the long-term sequelae of corticosteroid therapy |

### Brain Metastases Guidelines Conclusions

**Recommendations – Recurrent/Progressive Mets**

What evidence is available regarding the use of WBRT, SRS, surgical resection or chemotherapy for the treatment of recurrent/progressive brain metastases?

| **Level 3**: Insufficient data → individualize based on functional status, extent of disease, volume/number of metastases, recurrence or progression at original versus non-original site, previous treatment and type of primary cancer, and enrollment in clinical trials is encouraged. Depending on patient’s specific condition: no further treatment (supportive care), re-irradiation (either WBRT and/or SRS), surgical excision or, to a lesser extent, chemotherapy. |

If WBRT is used in the setting of recurrent/progressive brain metastases, what impact does tumor histopathology have on treatment outcomes?

| No studies were identified that met the eligibility criteria for this question. |
WBRT

**What is the evidence for WBRT?**
- Does it improve survival for patients with metastatic brain tumors?
- Does the dose fractionation scheme matter?
- Which patients benefit most from WBRT?

**Going beyond WBRT: Who benefits from local control?**
- Surgery plus WBRT
- Stereotactic Radiosurgery (SRS) plus WBRT

Multiple RTOG studies in the 1970’s demonstrated that WBRT could double, or even triple median survival from 1-2 months to 4-6 months. Just as importantly, cerebral death was reduced from 90-95%, down to ~50%; quality of life benefit as well.


- 30 Gy in 10, 3-Gy fractions established as standard (2 weeks)
Brain Metastases Guidelines Conclusions

**Recommendations – WBRT**

Should whole brain radiation therapy (WBRT) be used as the sole therapy in patients with newly-diagnosed, surgically accessible, single brain metastases, compared with WBRT plus surgical resection?

**Level 1**: No. Surgical resection plus post-op WBRT superior to WBRT alone, in patients with good performance status (functionally independent) and limited extracranial disease; insufficient data for poor KPS, advanced systemic disease, or multiple brain metastases.

If WBRT is used, is there an optimal dosing/fractionation schedule?

**Level 1**: No significant differences in median survival, local control or neurocognitive outcomes when compared with “standard” WBRT dose / fractionation. (i.e., 30 Gy in 10 fractions or a biologically effective dose (BED) of 39 Gy10).

If WBRT is used, what impact does tumor histopathology have on treatment outcomes?

Insufficient evidence to choose any particular dose/fractionation based on histopathology.

**WBRT +/- Surgical Resection**

- 7 studies met inclusion criteria
  - 6 unique studies, 1 companion paper
  - 3 Class 1 evidence
    - 3 RCT’s
  - 3 Class 2 evidence
    - 1 RCT and 2 Retrospective cohort studies
  - **Level 1 recommendation** – Class 1 evidence supports the use of surgical resection +WBRT for patients with good functional performance status & limited extracranial disease
Brain Metastases Guidelines Conclusions

**Recommendations – Surgical Resection**

**Surgical resection plus WBRT vs. surgical resection alone**

*Level 1:* Surgical resection followed by WBRT superior to resection alone, in terms of improving both local and distant tumor control.

**Surgical resection plus WBRT vs. SRS ± WBRT**

*Level 2:* Surgical resection plus WBRT, versus SRS plus WBRT, both are effective treatments with relatively equal survival; limited SRS data for larger lesions (>3cm) or for those causing significant mass effect (>1cm midline shift).

*Level 3:* Underpowered, conflicting evidence suggests that SRS alone may provide equivalent functional and survival outcomes compared with resection + WBRT for single brain mets, so long as ready detection of distant site failure and salvage SRS are possible.

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**WBRT +/- Stereotactic Radiosurgery**

  - 5 unique studies
    - Class 1 evidence – 2 RCT’s
    - Class 2 evidence – 1 prospective cohort, 1 retrospective cohort
    - Class 3 evidence – 1 prospective cohort c historical controls
## Brain Metastases Guidelines Conclusions

### Recommendations – SRS

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
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</thead>
<tbody>
<tr>
<td><strong>SRS plus WBRT vs. WBRT alone</strong></td>
<td>SRS + WBRT → longer survival, for single mets and KPS ≥70.</td>
<td>SRS + WBRT → significantly longer survival than WBRT alone, for 2-3 mets.</td>
<td>SRS + WBRT → longer survival, for single or multiple mets and KPS &lt;70.</td>
</tr>
<tr>
<td><strong>SRS + WBRT</strong></td>
<td>SRS + WBRT → superior local control &amp; functional status, for 1-4 mets &amp; KPS ≥70</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WBRT alone</strong></td>
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</table>

**SRS alone vs. WBRT alone**

- Both yield equivalent survival. Regular careful surveillance with SRS alone to provide early detection of local and distant recurrences → initiate early salvage therapy.

**SRS plus WBRT vs. SRS alone**

- Both effective; SRS alone appears to be superior to WBRT alone for patients with up to three metastatic brain tumors in terms of patient survival advantage.

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### What if a WBRT Patient Lives >6 Months?

- **WBRT-induced dementia of 1.9-5.1% with 25-39 Gy delivered with 3-6 Gy/fractions**

- **Encephalopathic effects of 3 Gy fractions**
  - latency of onset 6 months –3 yrs (usually 1-2 yrs)
WBRT Conclusions

- WBRT is an effective treatment for brain mets patients
  - Increased survival
  - Improved quality of life vs no treatment
- If overall life expectancy is ≤ 6 months, there is no survival, local control or neurocognitive advantage to any regimen other than 30 Gy in 10 fractions
- Candidates for a more aggressive local control approach include patients
  - with four or less tumors
  - those with high KPS
  - those with controlled systemic disease
- If an aggressive local control approach is taken, consider modifying WBRT to < 3 Gy fractions (e.g. 40 Gy in 20 fractions) to lower neurocognitive risk

Role of WBRT vs. focused therapies

Where is the balance?
Tumor Growth Occurs Rapidly Without WBRT

Observations regarding WBRT

- Relapse at local site is lowered
- Failure anywhere in the brain is diminished
- Time to brain failure is lengthened
- Neurologic death rate is lowered
- Overall survival probably unchanged
- Formal NCF testing not done

So, WBRT reduces intracranial relapse
SRS +/- WBRT

- Guidelines process identified 1 prospective randomized, 1 prospective non-randomized cohort, and 9 retrospective cohort studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>MS</th>
<th>% LF</th>
<th>% BF</th>
<th>MTR WB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aayoma</td>
<td>SRS =67</td>
<td>8 mo</td>
<td>28</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SRS/WBRT = 65</td>
<td>7.5 mo</td>
<td>11</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Li</td>
<td>SRS = 23</td>
<td>9.3 mo</td>
<td>~</td>
<td>N/A</td>
<td>6.7 mo</td>
</tr>
<tr>
<td></td>
<td>SRS/WBRT = 18</td>
<td>10.6 mo</td>
<td>~</td>
<td>N/A</td>
<td>8.6 mo</td>
</tr>
<tr>
<td>Tufts</td>
<td>SRS =</td>
<td></td>
<td>13</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Unpublished</td>
<td>SRS/WBRT</td>
<td></td>
<td>9</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Chang</td>
<td>SRS = 30</td>
<td>15.2 mo</td>
<td>35</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SRS/WBRT = 28</td>
<td>5.7 mo</td>
<td>0</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

Observations regarding SRS/WBRT

- Relapse at local site is lowered
- Failure anywhere in the brain is diminished
- Time to brain failure is lengthened
- Overall survival probably unchanged
- NCF testing done in 2 trials
  - MMSE in Japanese trial, MDACC trial

So, WBRT reduces intracranial relapse
But at what cost?
Neurocognition Balance

- **WBRT reduces intracranial relapse and prolongs time to relapse**
  - This should preserve NCF or slow down its decline, as tumor progression is associated with NCF decline

- **WBRT damages the brain**
  - This should cause an early decline in brain function

So, where is the balance

Tumor Growth Correlates with Neurocognitive Decline

Median Change in Neurocognitive Test Performance (Z-score) at 4 Months in Patients with MRI Data

Meyers JCO 2004
Regression of brain mets after WBRT correlates with survival and improved neurocognitive function.

Motexafin Gadolinium (MGd or Xcytrin) is a novel radiation sensitizer and anti-cancer agent which functions by targeting oxidative stress-related proteins. Because MGd contains the ferromagnetic compound gadolinium and it tends to accumulate in malignant cells, it can be used as a contrast agent during MRI scans.


**WBRT + MGd Response Analysis**

- Volume reduction ≥ 45%
  - Good responders
  - 135 pts at 2 mo
- Volume reduction < 45%
  - Poor responders

**Median tumor volume reduction at 2 mo:** 45%

**Median tumor volume reduction at 2 mo:** 45%
Impact of WBRT on MMSE

- 82 pts on JROSG 99-1 had MMSE ≥ 27

- Median time to 3 point drop:
  - 16.5 vs. 7.6 months, in favor of WBRT+SRS (p = .05)
  - 12 and 24 month freedom from ≥3 point drop:
    - 76 and 69% for WBRT+SRS vs. 59 and 52% for SRS alone

- *Progressive disease is worse than WBRT*

Mean Probability of NCF Decline at 4 months

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>SRS</td>
<td>23%</td>
</tr>
<tr>
<td>SRS+WBRT</td>
<td>49%</td>
</tr>
</tbody>
</table>

Conclusions

- WBRT reduces intracranial relapse
- WBRT prolongs time to intracranial relapse
- Tumor progression results in NCF decline
- WBRT can induce measurable HVLT changes reflecting early decline in recall memory
- Future research should focus on integrating the benefits of WBRT with attempts to ameliorate memory decline
  - Drug approaches
  - Technology approaches
Brain Metastases Guidelines Conclusions

Recommendations – New Investigational Therapies

New radiation sensitizers

- **Level 2:** Early use of motexafin-gadolinium (MGd) delays time to neurological progression in subgroup analysis, but not borne out in overall study population.

Interstitial modalities

- No evidence to support routine use of interstitial modalities.

New chemotherapeutic agents

- **Level 2:** Treatment of melanoma brain mets with WBRT + temozolomide is reasonable based on one class II study.
- **Level 3:** Depending on individual circumstances there may be patients who benefit from the use of temozolomide or fotemustine in the therapy of their brain metastases.

Molecular targeted agents

- **Level 3:** Epidermal growth factor receptor inhibitors may be useful in non-small-cell lung carcinoma brain metastases.

How would YOU treat this patient?
# Brain Metastases Guidelines

*Clinical practice parameters for multiple treatment scenarios*

<table>
<thead>
<tr>
<th>Brain Mets</th>
<th>Historical Paradigm</th>
<th>New Paradigm</th>
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<tbody>
<tr>
<td>Incidence</td>
<td>100,000</td>
<td>400,000</td>
</tr>
<tr>
<td>Treatment</td>
<td>WBRT</td>
<td>WBRT/Local/SRS</td>
</tr>
<tr>
<td>Cause of Death</td>
<td>Brain disease</td>
<td>Systemic disease</td>
</tr>
<tr>
<td>Surgeon’s Role</td>
<td>Limited</td>
<td>Expanded</td>
</tr>
<tr>
<td>Multidisciplinary Tumor Board</td>
<td>Rare, Academic Centers</td>
<td>Critically important Standard of Care</td>
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A special thank you to Dr. Beverly Walters, and the entire Brain Mets Guidelines Team:

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  Dept. of Neurosurgery, Henry Ford Health System, Detroit, MI
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