Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Vogelbaum et al.
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Background & Methodology
Introduction

• In the US, it is estimated that between 8% and 10% of patients with cancer will develop brain metastases representing ~200,000 new patients with brain metastases every year.¹
• The approach to the treatment of patients who develop metastatic spread to the brain has evolved over the past few decades.
• Previous attempts to develop guidelines were based on expert opinion, or subsequent evidence-based guidelines have generally treated therapeutic modalities separately or did not include recently published studies that have evaluated therapeutic combinations and targeted systemically delivered therapies.²-⁷
• In 2019, ASCO, SNO, and ASTRO agreed on the need for a guideline that addressed the treatment of brain metastases from non-hematologic solid tumors comprehensively in one document. A panel of experts from multiple disciplines (neurosurgery, neurology, neuro-oncology, medical oncology, radiation oncology) was convened and engaged in a highly structured guideline development process.
Guideline Development Methodology

• The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  ▪ a systematic literature review by ASCO guidelines staff
  ▪ an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  ▪ final guideline approval by ASCO EBMC

• Additionally, this guideline was reviewed and approved by the SNO Guidelines Committee and the ASTRO Board of Directors.

• The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology
Clinical Questions

This clinical practice guideline addresses the role of surgery, radiation therapy, and systemic therapy in the treatment of patients with brain metastases. For each form of therapy, a set of clinical questions was considered:

**Surgery**

1. What are the benefits and harms of surgery in adult patients with brain metastases?
   - Do these benefits differ for patients with newly diagnosed disease versus recurrent disease?
   - Are there subpopulations (e.g. number of metastases, status of extra-cranial disease) of patients who do not benefit from surgery?

2. What are the benefits and harms of laser interstitial thermal therapy (LITT)?
Clinical Questions

Systemic Therapy

3. What systemic therapy (chemotherapy, immunotherapy, targeted agents) options, alone or in combination, have demonstrated clinical benefits in adults with brain metastases?
   a. Are there subpopulations of patients (i.e. clinical features, biomarker status, specific form of cancer, status of extra-cranial status, receiving steroids) who benefit more or less from those options?
   b. Is there an interaction between the benefit of systemic therapy and the use/form of radiation (e.g. stereotactic radiation therapy, whole brain radiation)?
   c. Is there an interaction between the benefit of systemic therapy and the number of metastases?
   d. Do these benefits/harms differ for patients with newly diagnosed disease versus recurrent disease?
   e. Do these benefits/harms differ for patients with resected versus unresected metastases?
   f. When can systemic therapy be used without any surgery or radiation therapy?
Clinical Questions

Radiation Therapy

4. What are the benefits and harms of whole brain radiation therapy in adults with brain metastases?
   a. Are there subpopulations of patients (i.e. clinical features, biomarker status, specific form of cancer, resected/unresected) who benefit more or less from those options?
   b. Is there an interaction between the benefit of whole brain radiation therapy and the number of metastases?
   c. Do these benefits differ for patients with newly diagnosed disease versus recurrent disease?

5. What approaches have been found to mitigate the harms of whole brain radiation therapy (e.g. radio-protectants, memantine, hippocampal avoidance)?
Clinical Questions

Radiation Therapy (cont.)

6. What are the benefits and harms of stereotactic radiosurgery/radiation therapy in adults with brain metastases?
   a. Are there subpopulations of patients (i.e. clinical features, biomarker status, specific form of cancer, resected/unresected) who benefit more or less from those options?
   b. Is there an interaction between the benefit of stereotactic radiosurgery and the number of metastases?
   c. Do these benefits differ for patients with newly diagnosed disease versus recurrent disease?
   d. Do these benefits and risks differ between stereotactic radiosurgery and stereotactic radiation therapy and when is either more appropriate?

7. What are the relative benefits and harms of stereotactic radiosurgery/radiation therapy compared to whole brain radiation therapy?
   a. Do the relative benefits and harms differ in subpopulations of patients (i.e. clinical features, biomarker status, specific form of cancer, resected/unresected)?
   b. Do these benefits differ for patients with newly diagnosed disease versus recurrent disease?
   c. Is there benefit from combining whole brain radiation therapy and stereotactic radiosurgery compared to either whole brain radiation therapy or stereotactic radiosurgery alone?
Clinical Questions

Radiation Therapy (cont.)

8. What are the benefits and harms of using radiation sensitizers?

Timing and Interaction of Therapy

9. How does the relative timing of surgery, radiation therapy, and systemic therapy affect the benefits/harms of those therapies?
   a. Are there are other important interactions between these forms of therapy?
Target Population and Audience

**Target Population**

• Patients with brain metastases from cancer from non-hematologic solid tumors. Secondary central nervous system lymphoma is outside the scope of the guideline.

**Target Audience**

• Surgeons, oncologists, neurologists, and other clinicians involved in the care of the target population.
Summary of Recommendations
Summary of Recommendations

Surgery

Recommendation 1.1

- Surgery may be offered for patients with brain metastases, considering the following factors:
  - Patients with suspected brain metastases without a primary cancer diagnosis may benefit from surgery to attain a diagnosis and undergo tumor removal.
  - Patients with large tumors with mass effect likely benefit from surgery.
  - Patients with multiple brain metastases and/or uncontrolled systemic disease are less likely to benefit from surgery unless the remaining disease is controllable via other measures.

Informal consensus

Evidence Quality

Mixed

Strength of Recommendation

Moderate
Summary of Recommendations

Recommendation 1.2

- Where surgery is considered, no recommendation regarding the method of resection (piecemeal vs. en-bloc) can be made.

Recommendation 1.3

- No recommendation can be made for or against LITT.
Summary of Recommendations

Systemic Therapy

Recommendation 2.1

• Patients with symptomatic brain metastases should be offered local therapy (radiosurgery/radiation therapy and/or surgery) as recommended in this guideline regardless of the systemic therapy used for the systemic disease.

Evidence-based

Evidence Quality: High

Strength of Recommendation: Strong
Summary of Recommendations

Recommendation 2.2

• For patients with asymptomatic brain metastases, local therapy should not be deferred unless deferral is specifically recommended in Recommendations 2.3 through 2.7 of this guideline. The decision to defer local therapy should be based on a multi-disciplinary discussion (neuro or medical oncology, neuro-surgery, and radiation oncology) of the potential benefits and harms the patient may experience.
Summary of Recommendations

Non-Small Cell Lung Cancer

Recommendation 2.2

- Osimertinib or icotinib may be offered to patients with asymptomatic brain metastases from EGFR-mutant NSCLC. If these agents are used, local therapy may be delayed until there is evidence of intracranial progression.

Qualifying Statement

- The expert panel recognizes that as of this publication, icotinib is not approved by the US Food & Drug Administration (FDA) or the European Medicines Agency.
Summary of Recommendations

Recommendation 2.4

- Alectinib, brigatinib, or ceritinib may be offered to patients with asymptomatic brain metastases from ALK-rearranged NSCLC. If these agents are used, local therapy may be delayed until there is evidence of intracranial progression.

Recommendation 2.5

- Pembrolizumab may be offered to patients with asymptomatic brain metastases from immunotherapy-naive PD-L1 expressing NSCLC who are also receiving pemetrexed and a platinum agent.

Note. See Recommendation 2.2. regarding local therapy.
Summary of Recommendations

Melanoma

Recommendation 2.6

- Ipilimumab plus nivolumab (for all patients regardless of \(BRAF\) status) or dabrafenib plus trametinib (for patients with \(BRAF\)-\(V600E\) mutation) may be offered to patients with asymptomatic brain metastases from melanoma. If these agents are used, local therapy may be delayed until there is evidence of intracranial progression.
Breast Cancer

Recommendation 2.7

• The combination of tucatinib, trastuzumab, and capecitabine may be offered to patients with HER2-positive metastatic breast cancer who have asymptomatic brain metastases and have progressed on previous trastuzumab, pertuzumab, and/or trastuzumab emtansine-based therapy. If these agents are used, local therapy may be delayed until there is evidence of intracranial progression.
Summary of Recommendations

Radiation Therapy

Recommendation 3.1

• Radiation therapy should not be offered to patients with asymptomatic brain metastases and who have either:
  ▪ Performance status KPS ≤ 50, OR
  ▪ Performance status KPS <70 and no systemic therapy options.

Evidence-based

Evidence Quality
Low

Strength of Recommendation
Moderate
Summary of Recommendations

Recommendation 3.2

- SRS alone (as opposed to WBRT or combination of WBRT and SRS) should be offered to patients with 1 to 4 unresected brain metastases, excluding small cell carcinoma.

Qualifying Statement

- The inclusion criteria of the randomized trials that underly this recommendation were generally tumors of less than 3 or 4 cm diameter and did not include radioprotectant strategies of memantine or hippocampal avoidance.
Summary of Recommendations

Recommendation 3.3

• SRS alone should be offered to patients with 1 to 2 resected brain metastases if the surgical cavity can be safely treated and considering the extent of remaining intracranial disease.

Qualifying Statement

• The randomized trials upon which this recommendation is based were of single-fraction SRS and conventional WBRT (without radioprotectant strategies of memantine or hippocampal avoidance).
Summary of Recommendations

**Recommendation 3.4**

- SRS, WBRT, and the combination of SRS plus WBRT are all reasonable options for patients with more than 4 unresected or more than 2 resected brain metastases and better performance status (e.g. KPS ≥ 70). SRS may be preferred for patients with better prognosis or where systemic therapy that is known to be active in the central nervous system is available.

**Recommendation 3.5**

- Memantine and hippocampal avoidance should be offered to patients who will receive WBRT and have no hippocampal lesions and 4 months or more expected survival.
Summary of Recommendations

Recommendation 3.6

- Radiation sensitizing agents should not be offered to patients.

Evidence-based

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Timing and Interaction of Therapy

Recommendation 4.1

- For patients who will receive both radiation therapy and surgery, no recommendation regarding the specific sequence of therapy can be made.

Informal consensus

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Discussion
Patient and Clinician Communication

• Clinician expertise when informing patients about their disease, their diagnosis, and their treatments and when offering and recruiting patients regarding clinical trials, is vital.

• Brain metastases are a complex condition, with multiple factors that contribute to diagnosis and prognosis.

• Patients with brain metastases need resources and time with their clinicians to understand the details of their condition and what it may mean for them.

• The recommendations in this guideline allow for customization of treatment based on the specific context of the patient. Providers should ensure that patients are fully informed about the benefits and harms they may experience with each potential strategy.

• Patients’ access to information on and opportunities to enroll in clinical trials may vary substantially depending on where the patient is receiving care.8-10

• For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.
Additional Resources

• More information, including a supplement and clinical tools and resources, is available at [www.asco.org/neurooncology-guidelines](http://www.asco.org/neurooncology-guidelines)

• Patient information is available at [www.cancer.net](http://www.cancer.net)
# Guideline Panel Members

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Abbreviations

- ALK, anaplastic lymphoma kinase
- ASCO, American Society of Clinical Oncology
- ASTRO, American Society for Radiation Oncology
- EBMC, Evidence Based Medicine Committee
- EGFR, epidermal growth factor receptor
- FDA, US Food & Drug Administration
- HER2, human epidermal growth factor receptor 2
- KPS, Karnofsky performance status
- LITT, laser interstitial therapy therapy
- NSCLC, non-small cell lung cancer
- PD-L1, programmed death ligand 1
- SNO, Society for Neuro-Oncology
- SRS; stereotactic radiosurgery
- US, United States
- WBRT, whole brain radiotherapy
References

2. Tsao MN, Lloyd NS, Wong RK: Clinical practice guideline on the optimal radiotherapeutic management of brain metastases. BMC Cancer 5:34, 2005
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