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Treatment for Brain Metastases

Published in:
Journal of Clinical Oncology

Publication status and date:
Published: 10/02/2022

DOI (link to publisher):
10.1200/jco.21.02314

Document Version
Publisher's PDF, also known as Version of record

Document License/Available under:
Unspecified

Citation for the published version (APA):
Vogelbaum, M. A., Brown, P. D., Messersmith, H., Brastianos, P. K., Burri, S., Cahill, D., Dunn, I. F., Gaspar, L. E., Gatson, N. T. N., Gondi, V., Jordan, J. T., Lassman, A. B., Maues, J., Mohile, N., Redjal, N., Stevens, G., Sulman, E., van den Bent, M., Wallace, H. J., ... Schiff, D. (2022). Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. *Journal of Clinical Oncology*, *40*(5), 492-516. https://doi.org/10.1200/jco.21.02314

Link to publication on the EUR Research Information Portal

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Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

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abstract

PURPOSE To provide guidance to clinicians regarding therapy for patients with brain metastases from solid tumors.

METHODS ASCO convened an Expert Panel and conducted a systematic review of the literature.

RESULTS Thirty-two randomized trials published in 2008 or later met eligibility criteria and form the primary evidentiary base.

RECOMMENDATIONS Surgery is a reasonable option for patients with brain metastases. Patients with large tumors with mass effect are more likely to benefit than those with multiple brain metastases and/or uncontrolled systemic disease. Patients with symptomatic brain metastases should receive local therapy regardless of the systemic therapy used. For patients with asymptomatic brain metastases, local therapy should not be deferred unless deferral is specifically recommended in this guideline. The decision to defer local therapy should be based on a multidisciplinary discussion of the potential benefits and harms that the patient may experience. Several regimens were recommended for non–small-cell lung cancer, breast cancer, and melanoma. For patients with asymptomatic brain metastases and no systemic therapy options, stereotactic radiosurgery (SRS) alone should be offered to patients with one to four unresected brain metastases, excluding small-cell lung carcinoma. SRS alone to the surgical cavity should be offered to patients with one to two resected brain metastases. SRS, whole brain radiation therapy, or their combination are reasonable options for other patients. Memantine and hippocampal avoidance should be offered to patients who receive whole brain radiation therapy and have no hippocampal lesions and 4 months or more expected survival. Patients with asymptomatic brain metastases with either Karnofsky Performance Status $\leq$ 50 or Karnofsky Performance Status $<$ 70 with no systemic therapy options do not derive benefit from radiation therapy.

Additional information is available at www.asco.org/neurooncology-guidelines.

J Clin Oncol 40:492-516. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on October 27, 2021 and published at ascopubs.org/journal/jco on December 21, 2021: DOI https://doi.org/10.1200/JCO.21.02314

Clinical Practice Guidelines Committee approval: August 12, 2021

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INTRODUCTION

In the United States, it is estimated that between 8% and 10% of patients with cancer will develop brain metastases representing approximately 200,000 new patients with brain metastases every year.[1] The point prevalence of brain metastases on initial diagnosis varies widely between different cancer histologies. For example, the incidence proportion of patients with metastatic cancer who have brain metastases on diagnosis is estimated to be over 25% in metastatic melanoma and metastatic lung adenocarcinoma, 10% in metastatic renal cell cancer, 7% in metastatic breast cancer, 5% in metastatic head and neck cancer or esophageal cancer, and 2% in nonesophageal metastatic gastrointestinal cancers.[2] In addition, many patients will develop brain metastases after initial diagnosis. Depending on disease histology, the proportion of patients who develop brain metastases within 1 year may be as high as 20% in patients with lung cancer and 5%-7% in patients with breast cancer, renal cell cancer, and melanoma.[3]

The approach to the treatment of patients who develop metastatic spread to the brain has evolved over the past few decades. Early attempts (circa 1970s) at developing guidelines were largely empiric in nature and emphasized the use of palliative measures—steroids and whole brain radiation therapy (WBRT)—with the acknowledgment that there were no controlled,

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THE BOTTOM LINE

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Guideline Questions

Surgery.

- What are the benefits and harms of surgery in adult patients with brain metastases?
- What are the benefits and harms of laser interstitial thermal therapy?

Systemic therapy.

- What systemic therapy (chemotherapy, immunotherapy, and targeted agents) options, alone or in combination, have demonstrated clinical benefits in adults with brain metastases?

Radiation therapy.

- What are the benefits and harms of whole brain radiation therapy (WBRT) in adults with brain metastases?
- What approaches have been found to mitigate the harms of WBRT (eg, radioprotectants, memantine, and hippocampal avoidance)?
- What are the benefits and harms of stereotactic radiosurgery (SRS) or radiation therapy in adults with brain metastases?
- What are the relative benefits and harms of SRS or radiation therapy compared to WBRT?
- What are the benefits and harms of using radiation sensitizers?

Timing and interaction of therapy.

- How does the relative timing of surgery, radiation therapy, and systemic therapy affect the benefits and/or harms of those therapies?

Target Population

Patients with brain metastases from cancer from nonhematologic solid tumors. Secondary CNS lymphoma is outside the scope of the guideline.

Target Audience

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

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

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 (Type: informal consensus; Evidence quality: mixed, see the Clinical Interpretation section; Strength of recommendation: moderate).

Recommendation 1.2. Where surgery is considered, no recommendation regarding the method of resection (piecemeal *v* en bloc) can be made (Type: informal consensus; Evidence quality: low; Strength of recommendation: none).

Recommendation 1.3. No recommendation can be made for or against laser interstitial thermal therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: none).

Recommendation 2.1. Patients with symptomatic brain metastases should be offered local therapy (radiosurgery and/or radiation therapy and/or surgery) as recommended in this guideline regardless of the systemic therapy used for the systemic disease (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

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 multidisciplinary discussion (neuro- or medical oncology, neurosurgery, and radiation oncology) of the potential benefits and harms the patient may experience (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

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THE BOTTOM LINE (CONTINUED)

Recommendation 2.3. Osimertinib or icotinib may be offered to patients with asymptomatic brain metastases from *EGFR*-mutant non–small-cell lung cancer (NSCLC). If these agents are used, local therapy may be delayed until there is evidence of intracranial progression (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Qualifying Statement: The expert panel recognizes that as of this publication, icotinib is not approved by the US Food and Drug Administration or the European Medicines Agency.

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 (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 2.5. Pembrolizumab may be offered to patients with asymptomatic brain metastases from immunotherapy-naïve, programmed death-ligand 1–NSCLC who are also receiving pemetrexed and a platinum agent (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak). *NOTE: See Recommendation 2.2 regarding local therapy.*

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 (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 2.7. The combination of tucatinib, trastuzumab, and capecitabine may be offered to patients with human epidermal growth factor receptor 2–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 (Type: evidence-based; Evidence quality: low; Strength of recommendation: weak).

Recommendation 3.1. Radiation therapy should not be offered to patients with asymptomatic brain metastases who have:

- Performance status Karnofsky Performance Status (KPS) $\leq$ 50 or less, *or*
- Performance status KPS $<$ 70 and no systemic therapy options (Type: evidence-based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.2. SRS alone (as opposed to WBRT or combination of WBRT and SRS) should be offered to patients with one to four 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 in diameter and did not include radioprotectant strategies of memantine or hippocampal avoidance (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.3. SRS alone should be offered to patients with one to two 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) (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.4. SRS, WBRT, and the combination of SRS plus WBRT are all reasonable options for patients with more than four unresected or more than two resected brain metastases and better performance status (eg, KPS $\geq$ 70). SRS may be preferred for patients with better prognosis or where systemic therapy that is known to be active in the CNS is available (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

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 (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.6. Radiation-sensitizing agents should not be offered to patients (Type: Evidence-based; Evidence quality: low; Strength of recommendation: strong).

Recommendation 4.1. For patients who will receive both radiation therapy and surgery, no recommendation regarding the specific sequence of therapy can be made (Type: informal consensus; Evidence quality: low; Strength of recommendation: none).

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THE BOTTOM LINE (CONTINUED)

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/neurooncology-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net. American Society for Radiation Oncology guidelines are available at https://www.astro.org/Patient-Care-and-Research/Clinical-Practice-Statements/Clinical-Practice-Guidelines. Society for Neuro-Oncology guidelines are available at https://www.soc-neuro-onc.org/WEB/Resources_Content/Guidelines_Endorsement.aspx.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

randomized studies to guide the use of surgery and chemotherapy.[4] Additional guidelines largely reflected the expert opinions of their authors.[5] The earliest development of guidelines supported by a more objective, structured process failed to provide meaningful guidance because of the lack of evidence of sufficient quality to make definitive recommendations.[6] Subsequent evidence-based guidelines have generally treated therapeutic modalities (eg, surgery, radiation therapy, and systemic therapy) separately or did not include recently published studies that have evaluated therapeutic combinations and targeted systemically delivered therapies.[7-12] In 2019, ASCO, the Society for Neuro-Oncology (SNO), and the American Society for Radiation Oncology (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, neurooncology, medical oncology, and radiation oncology) was convened and engaged in a highly structured guideline development process.

GUIDELINE 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

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 (eg, number of metastases and status of extracranial disease) of patients who do not benefit from surgery?

What are the benefits and harms of laser interstitial thermal therapy (LITT)?

Systemic Therapy

What systemic therapy (chemotherapy, immunotherapy, and targeted agents) options, alone or in combination, have demonstrated clinical benefits in adults with brain metastases?

- Are there subpopulations of patients (ie, clinical features, biomarker status, specific form of cancer, status of extracranial status, and receiving steroids) who benefit more or less from those options?
- Is there an interaction between the benefit of systemic therapy and the use or form of radiation (eg, stereotactic radiation therapy and WBRT)?
- Is there an interaction between the benefit of systemic therapy and the number of metastases?
- Do these benefits and/or harms differ for patients with newly diagnosed disease versus recurrent disease?
- Do these benefits and/or harms differ for patients with resected versus unresected metastases?
- When can systemic therapy be used without any surgery or radiation therapy?

Radiation Therapy

What are the benefits and harms of WBRT in adults with brain metastases?

- Are there subpopulations of patients (ie, clinical features, biomarker status, specific form of cancer, and resected or unresected) who benefit more or less from those options?
- Is there an interaction between the benefit of WBRT and the number of metastases?
- Do these benefits differ for patients with newly diagnosed disease versus recurrent disease?

What approaches have been found to mitigate the harms of WBRT (eg, radioprotectants, memantine, and hippocampal avoidance)?

What are the benefits and harms of stereotactic radiosurgery (SRS) or radiation therapy in adults with brain metastases?

- Are there subpopulations of patients (ie, clinical features, biomarker status, specific form of cancer, and resected or unresected) who benefit more or less from those options?
- Is there an interaction between the benefit of SRS and the number of metastases?

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- Do these benefits differ for patients with newly diagnosed disease versus recurrent disease?
- Do these benefits and risks differ between SRS and stereotactic radiation therapy, and when is either more appropriate?

What are the relative benefits and harms of SRS or radiation therapy compared to WBRT?

- Do the relative benefits and harms differ in subpopulations of patients (ie, clinical features, biomarker status, specific form of cancer, and resected or unresected)?
- Do these benefits differ for patients with newly diagnosed disease versus recurrent disease?
- Is there benefit from combining WBRT and SRS compared to either WBRT or SRS alone?

What are the benefits and harms of using radiation sensitizers?

Timing and Interaction of Therapy

How does the relative timing of surgery, radiation therapy, and systemic therapy affect the benefits and/or harms harms of those therapies?

- Are there other important interactions between these forms of therapy?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel met via webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. This guideline was reviewed and approved by the Expert Panel, the ASCO Clinical Practice Guidelines Committee on August 12, 2021, the SNO Guidelines Committee on August 4, 2021, and the ASTRO Board of Directors on September 24, 2021, prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of randomized trials and other nonrandomized evidence published from January 2008 to April 2020, selected nonsystematically reviewed randomized trials of great importance published prior to 2008, as well as clinical experience. The systematic review literature search consisted of three phases. First, prior to 2015 the review made use of the reference lists of the series of guidelines published by the Congress of Neurological Surgeons.[13] The search strategy and screening process used by the authors of those guidelines were evaluated and considered to be comprehensive between 2008 and 2015, such that it was unlikely they had not included any important studies. Second, a new systematic review of PubMed was conducted for articles published from January 2015 to August 17, 2020. Third, as the guideline was being developed, concerns were raised that the Congress of Neurological Surgeons systematic review might have missed relevant randomized controlled trials (RCTs) and nonrandomized phase II clinical trials. Therefore, a separate search of PubMed was conducted for such trials back to 2008. Additional nonsystematically identified studies prior to 2008 were incorporated based on the expert opinion of the Panel.

Articles were selected for inclusion in the systematic review of the evidence based on the following criteria (applied equally to both phases of the literature search):

- Population: Patients with brain metastases.
- Study design:
  - Randomized trials. This included randomized trials of patients with metastatic disease not specific to brain metastases, so long as a subgroup analysis of patients with brain metastases was identifiable in the title and/or abstract. As a post hoc alteration to the criteria, only randomized trials that randomly assigned at least 50 total patients received quality assessment and data extraction in detail, and only subgroup analyses with at least 50 patients were reported.
  - Comparative studies (eg, case-control, cohort studies, and historical control) with $\geq$ 50 patients in each comparison group.
  - Noncomparative studies (eg, institutional series) with $\geq$ 300 patients.
  - Meta-analyses of relevant studies if published in 2018 or later.
  - As a post hoc alteration to the criteria, noncomparative prospective protocol-based clinical trials (eg, phase II trials) of systemic therapy were included if they had $\geq$ 50 patients.
- Interventions and comparisons:
  - Systemic therapy: Any form of chemotherapy; any form of immunotherapy; any form of targeted agent therapy.
  - Radiation therapy: WBRT; SRS or radiation therapy; radiation sensitizers; and memantine, hippocampal avoidance, and similar radioprotectant strategies.
  - Surgery.
  - LITT.
  - Best supportive care and/or observation and/or surveillance.

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Articles were excluded from the systematic review if they were: (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support methodology and accompanying BRIDGE-Wiz software.[14] In addition, a guideline implementability review is conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Summary of Key Trials Published Prior to 2008

Several key trials published prior to 2008 provide important context. These trials were identified nonsystematically based on the consensus of the Expert Panel. They are summarized in Table 14 of the Data Supplement (online only) and are noted where they are relevant in the Literature Review sections associated with each research question.

TABLE 1. Included Evidence From the Systematic Review, 2008 and Later

Type of Evidence	Surgery	Radiation Therapy	Systemic Therapy	Multiple Modalities
Meta-analyses	Two papers[15,16]	Five papers[17-21]	Six papers[22-27]	None
RCTs	None	17 trials[28-43]	15 trials[44-58]	One trial[59]
Prospective nonrandomized (eg, phase II)	None	None	10 trials[60-69]	None
Other nonrandomized	Six studies[70-75]	51 studies[76-86,87-99,100-126]	18 studies[127-144]	Three studies[145-147]

Abbreviation: RCTs, randomized controlled trials.

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Evidence Identified in the Systematic Review

A total of 13 meta-analyses, 32 randomized trials, and 88 nonrandomized studies published in 2008 or later met eligibility criteria and form the primary evidentiary base for the guideline recommendations. This evidence is described in detail in the Data Supplement and is reported in the Literature Review sections for each research question as relevant. Table 1 summarizes the included evidence. One meta-analysis, Fuentes et al,[15] was a Cochrane review of surgery versus SRS for patients with one brain metastasis. It only identified two small RCTs with 85 total patients, and as the evidence was so limited in size and quality that no conclusions could be reached, this meta-analysis will not be discussed further.

Risk of bias of randomized trials. The risk of bias assessed with the Cochrane Risk of Bias 2 tool[148] of the included randomized trials was mixed and is detailed in Table 2 of the Data Supplement. Seven trials were considered at high risk of bias; common issues leading to that assessment included incomplete reporting of the outcomes of interest on all patients and poor or no reporting of masking procedures. Of the trials not considered at high risk of bias, reporting was often incomplete as to whether the allocation sequence was masked and there were several trials that stopped early because of futility in at least one arm outside of the protocol or because of low recruitment.

Quality of nonrandomized studies. The quality of the nonrandomized studies was not formally assessed, but the most common study design was a retrospective cohort study (comparative or noncomparative) of patients treated at one or a small number of institutions. The next most common study design was retrospective database review (eg, national or regional cancer registries). All nonrandomized studies were considered at high risk of bias because of their design.

RECOMMENDATIONS

What are The Benefits and Harms of Surgery in Adult Patients With Brain Metastases?

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 (Type: informal consensus; Evidence quality: mixed, see Clinical Interpretation; Strength of recommendation: moderate).

Literature review and analysis. Three small trials of surgery for single brain metastases published prior to 2008 continue to be relevant as the only randomized trials of surgery and radiation therapy versus radiation therapy alone: Patchell et al,[149] Vecht et al,[150] and Mintz et al.[151] Of these, both Patchell et al[149] and Vecht et al[150] reported clinically meaningful and statistically significant improvements in overall survival (OS), while Mintz et al[151] did not.

Several nonrandomized studies have been published on surgery after 2008, as summarized in Table 12 of the Data Supplement. These nonrandomized studies investigated the benefit of surgery versus no surgery in the context of eitherSRS, WBRT, or both, and the results were mixed with no clear interpretation to account for the differences in outcome.

Clinical interpretation. The value of surgery is likely greatest in the context of patients who have minimal intracranial and overall disease burden, and this interpretation may also extend to those patients undergoing active treatment with therapies likely to provide a survival benefit with respect to systemic (non-CNS) disease. There is very little evidence to support survival benefit from surgery in patients with uncontrolled systemic disease or with multiple brain metastases and to address the question of the value of surgery versus other local treatment options (eg, SRS).

It is unlikely that further high-quality data will be available in the future; therefore, the Panel agreed that surgery may be offered to patients with limited brain metastases. However, the Panel recognized that the decision for surgery must be made on a case-by-case basis between the patient and the surgeon or multidisciplinary team based on the factors listed in the recommendation. In patients with larger tumors with mass effect surgery is likely more reasonable, while it may be less reasonable in patients with smaller metastases who may be effectively treated via noninvasive options (eg, SRS). In patients for whom the primary cancer is unknown or the genetic context is unclear, the added benefit of establishing a histologic diagnosis via resection of a brain metastasis makes resection reasonable. The Panel considers this a moderate strength recommendation as there was strong consensus that surgery was valuable for some patients, but defining these patients is challenging and subject to clinical discretion.

Recommendation 1.2. Where surgery is considered, no recommendation regarding the method of resection (piecemeal *v* en bloc) can be made (Type: informal consensus; Evidence quality: low; Strength of recommendation: none).

Literature review and analysis. One retrospective comparative cohort study was identified in the systematic review, Patel et al[71] (detailed in Table 12 of the Data Supplement). Among 1,033 patients with a single brain metastasis treated at one US institution, the complication rate was 13% with en bloc resection compared to 19% with piecemeal, $P = .07$; however, preoperative tumor volume was significantly greater in patients who received piecemeal resection.

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Clinical interpretation. The consensus of the Expert Panel was that the existing data do not support a recommendation with respect to the method of resection.

What Are the Benefits and Harms of LITT?

Recommendation 1.3. No recommendation can be made for or against LITT (Type: informal consensus.; Evidence quality: low; Strength of recommendation: none).

Literature review and analysis. No studies were identified to inform recommendations on this issue.

Clinical interpretation. LITT is a recently emerging treatment technology, developed for two potential purposes: local control and management of radiation necrosis. The value of LITT in patients with radiation necrosis was not a topic considered in this guideline, but its development for that purpose may be more widely supported than for its use as a local control therapy.[152-154] However, in the absence of prospective trials of sufficient size, its role in treatment of brain metastasis is unclear. This is an area of active research and, with the results of randomized studies, in the future more definitive recommendations may be made.

Systemic Therapy

What systemic therapy (chemotherapy, immunotherapy, and targeted agents) options, alone or in combination, have demonstrated clinical benefits in adults with brain metastases?

Recommendation 2.1. Patients with symptomatic brain metastases should be offered local therapy (radiosurgery or radiation therapy and/or surgery) as recommended in this guideline regardless of the systemic therapy used for the systemic disease (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

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 multidisciplinary discussion (neuro- or medical oncology, neurosurgery, and radiation oncology) of the potential benefits and harms the patient may experience (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Literature review and analysis. Evidence of benefit of systemic therapy in patients with brain metastases is limited. To some degree, this paucity of evidence is due to the fact that the presence of brain metastases is very frequently an exclusion criterion for randomized trials of systemic therapy, so that even when an agent has been demonstrated to be highly effective for metastatic disease there is a lack of evidence specific to brain metastases. The studies identified by the systematic review for this guideline and documented in the Data Supplement have few patients and only cover a subset of patients with brain metastases.

Two small, randomized trials were identified that studied WBRT with temozolomide versus without temozolomide in patient populations not specific to a single cancer type: Liu et al[46] (78 patients) and Gamboa-Vignolle et al[50] (55 patients). In both trials, progression-free survival (PFS) significantly improved with temozolomide. In Gamboa-Vignolle et al,[50] OS was also significantly improved. A trial reported by Verger et al[155] (82 patients) in 2005 found improved PFS at 90 days ($P = .03$).

Clinical interpretation. Radiation therapy and surgery have been established as appropriate local therapy for patients with brain metastases as recommended elsewhere in this guideline. One possible goal of systemic therapy, beyond treating other systemic disease, is the ability to defer local therapy until disease progression, potentially avoiding adverse effects of local therapy without meaningful reductions in OS. However, the consensus of the Expert Panel was that this goal should only be pursued if evidence of benefit for the specific context (patient, disease, drug, etc) is available and compelling. In the absence of such evidence, deferral should only be considered in a clinical trial. The Expert Panel recognizes that the evidence is constantly changing and that these recommendations may evolve as CNS activity is demonstrated for other agents.

In considering which systemic therapy regimens may warrant potential deferral of local therapy, the Panel only recommended regimens in Recommendations 2.3 through 2.7 where there was prospective evidence of local control that would warrant such deferral. It was the consensus of the Panel that although this evidence is from smaller and often nonrandomized (eg, phase II) studies, all of these regimens have demonstrated benefits for systemic disease, and therefore a lower threshold of evidence for use in patients with brain metastases was reasonable. However, given the weakness of this evidence, any decision for referral should be made after multidisciplinary discussion that includes neuro- or medical oncology, neurosurgery, and radiation oncology representation. Also, if local therapy is deferred, close monitoring for progression is crucial to ensure that local therapy can be offered when it will be most valuable.

The consensus of the Expert Panel was that no formal definition of *symptomatic* could be made. Therefore, the interpretation of the recommendations necessarily involves clinical judgment. In patients with asymptomatic brain metastases for whom deferral might be considered, the nature and intracerebral location (eg, eloquent versus noneloquent) of those metastases must be taken into account. Some patients with asymptomatic metastases may still benefit from local therapy as recommended elsewhere in this guideline in terms of decreased likelihood of harms to motor or other neurologic capabilities. Conversely, some patients with mild symptoms controlled with supportive therapy (eg, steroids) may reasonably defer local therapy while receiving a CNS-active systemic therapy recommended in this guideline.

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Although the two randomized trials of the addition of temozolomide to WBRT did report significant benefits, given their small size and the difficulty of integrating temozolomide into the therapy of patients who may be receiving other regimens for their systemic disease, the consensus of the Expert Panel was that temozolomide could not be recommended.

Non–Small-Cell Lung Cancer

Recommendation 2.3. Osimertinib or icotinib may be offered to patients with asymptomatic brain metastases from *EGFR*-mutant non–small-cell lung cancer (NSCLC). If these agents are used, local therapy may be delayed until there is evidence of intracranial progression (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

> Qualifying Statement: The Expert Panel recognizes that as of this publication, icotinib is not approved by the US Food and Drug Administration or the European Medicines Agency.

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 (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 2.5. Pembrolizumab may be offered to patients with asymptomatic brain metastases from immunotherapy-naïve, programmed death-ligand 1 (PD-L1)–expressing NSCLC who are also receiving pemetrexed and a platinum agent (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak). *NOTE: See Recommendation 2.2. regarding local therapy.*

Literature review and analysis.

Randomized trials of patients with brain metastases from NSCLC. Multiple randomized trials have been reported that were conducted in patients with NSCLC and brain metastases. Most were small (< 100 patients). In nearly all trials, patients also received WBRT. Of these trials, the majority are irrelevant to recommendations in this guideline:

- Chua et al[45] (temozolomide *v* no temozolomide), Quantin et al[48] (cisplatin plus vinorelbine plus ifosfamide *v* high-dose ifosfamide), Neuhaus et al[49] (topotecan *v* no topotecan), and Chabot et al[52] (veliparib at two different doses *v* placebo) addressed regimens that are not considered the current standard of care for NSCLC. None found any significant differences in important outcomes.
- Lee et al[54] (erlotinib *v* placebo), RTOG 0320[56] (erlotinib *v* temozolomide *v* no other therapy), Lee et al[59] (gemcitabine plus vinorelbine followed by WBRT *v* WBRT followed by gemcitabine plus vinorelbine), and SAKK 70/03[55] (gefitinib *v* temozolomide) included regimens in at least one arm that are considered current standard-of-care options in NSCLC in at least some circumstances, but also found no significant differences in important outcomes. The trials of erlotinib and gefitinib were not limited to patients with *EGFR*-mutated cancer.

The BRAIN trial reported by Yang et al[57] warrants further discussion. This trial compared icotinib up front with WBRT on progression to the combination of WBRT and chemotherapy (platinum-based doublet in first-line, single-agent docetaxel, or pemetrexed in second-line) in 176 patients with *EGFR*-mutant NSCLC. Twenty-two percent of the patients receiving up-front icotinib and 27% of the patients receiving chemotherapy and WBRT had multiple organ metastases. Patients receiving icotinib with WBRT at progression experienced better intracranial PFS (hazard ratio [HR], 0.56; 95% CI, 0.36 to 0.90) and PFS (HR, 0.44; 95% CI, 0.31 to 0.63), but no difference was found in OS (HR, 0.93; 95% CI, 0.60 to 1.44).

Meta-analyses. Zhang et al[25] reported in 2019 on a meta-analysis of overall response rate (ORR) conducted on 20 studies (2,715 patients) of *ALK* inhibitors in patients with brain metastases from NSCLC. They estimated that the intracranial ORR for *ALK* inhibitors varied widely from 79% for alectinib to 18% for crizotinib. The estimated ORR also varied widely by study type. Erickson et al[156] reported in 2020 on a separate meta-analysis focusing on osimertinib in patients with brain metastases from *ALK*-rearranged NSCLC. They estimated the CNS ORR for osimertinib to be 64% and the CNS disease control rate to be 90%.

Dai et al[157] reported in 2020 on a network meta-analysis of the brain metastases subgroups in six trials conducted in patients with *EGFR*-mutant NSCLC. They found no significant differences between the study combinations, although the network was sparse and had low power to detect any differences. Their analysis reported that the combination of gefitinib and pemetrexed and carboplatin had the highest probability of the best OS (47%), with osimertinib the next highest (29%).

Known subgroup analyses of patients with brain metastases from randomized trials of metastatic NSCLC. The FLAURA trial compared osimertinib to gefitinib or erlotinib.[158] In the subgroup of patients with CNS lesions at baseline (61 *v* 67 patients, respectively), the median CNS PFS (counting only CNS progression or death as events) was not reached for osimertinib and was 13.9 months for earlier generation *EGFR*–tyrosine kinase inhibitor (HR, 0.48; 95% CI, 0.26 to 0.860; $P = .14$). The ORR was 66% with osimertinib versus 43% with gefitinib or erlotinib (odds ratio, 2.5; 95% CI, 1.2 to 5.2; $P = .011$).

Gadgeel et al[63] reported on the combined analysis of the CNS metastases subgroups of two phase II studies of alectinib in patients with *ALK*-rearranged metastatic NSCLC, with no previous crizotinib therapy. The ORR was 42.6%, the median PFS was 8.3 months, and the 6-month

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PFS rate was 58.0%. A subgroup analysis of 67 patients with baseline CNS metastases in the ALESIA trial,[159] which compared alectinib to crizotinib as first-line therapy for *ALK*-rearranged NSCLC, found that alectinib was associated with significantly longer PFS (HR, 0.11; 95% CI, 0.05 to 0.28). A subgroup analysis[160] of 122 patients with CNS metastases in the ALEX trial, which compared alectinib to crizotinib in patients with *ALK*-mutated NSCLC, found that alectinib was associated with significantly longer PFS (HR, 0.40; 95% CI, 0.25 to 0.64).

The ALTA trial[161] compared brigatinib at two doses (90 mg and 180 mg once daily) in patients with crizotinib-refractory *ALK*-rearranged metastatic NSCLC. Camidge et al[162] reported on the subgroup of patients with brain metastases in detail. The intracranial ORR was 46% and 67%, and the intracranial disease control rate was 85% and 83% in patients receiving the lower and higher doses of brigatinib, respectively.

The LUX-Lung 7 trial[163,164] compared afatinib to gefitinib in patients with previously untreated *EGFR*-mutated advanced NSCLC. In the subgroup of 51 patients with baseline CNS metastases, no significant difference in OS (HR, 1.16; 95% CI, 0.61 to 2.21) or PFS (HR, 0.76; 95% CI, 0.41 to 1.44) was reported.

In 2010, Edelman et al[165] reported on a subgroup analysis of 194 patients with brain metastases from advanced NSCLC treated with either gemcitabine and carboplatin, gemcitabine and paclitaxel, or paclitaxel and carboplatin. No significant differences in ORR or survival were reported.

The updated results of the Keynote-189 trial[166] were published after the search window but, in the opinion of the Expert Panel, required considerations. Keynote-189 was a trial of pembrolizumab versus placebo in patients with PD-L1 expressing, previously untreated, metastatic NSCLC who were receiving pemetrexed plus either cisplatin or carboplatin. In the subgroup of patients with brain metastases, median OS was significantly improved with pembrolizumab (HR, 0.41; 95% CI, 0.24 to 0.62; median 19.2 months *v* 7.5 months). Median PFS was also improved (HR, 0.42; 95% CI, 0.27 to 0.67; median 6.9 months to 4.7 months).

Other studies. Several studies were not identified by the systematic review as they did not report their brain metastases subgroup analysis in the title or abstract, but the Panel believed that they warranted comment. The ASCEND trial[167] was a phase I trial of ceritinib in patients with metastatic *ALK*-rearranged NSCLC. The intracranial disease control rate was 79% (95% CI, 54 to 94) in the 19 *ALK* inhibitor–naive patients and 65% (95% CI, 54 to 76) in the 75 *ALK* inhibitor–pretreated patients with baseline brain metastases. The ASCEND-2 trial[168] was a phase II trial of ceritinib in patients with crizotinib-refractory *ALK*-rearranged metastatic NSCLC. The ORR in the subgroup of patients with baseline brain metastases was 33.0% (95% CI, 23.9 to 43.1), the disease control rate was 74.0% (95% CI, 64.3 to 82.3), and the median PFS was 5.4 months.

A combined analysis of the subgroup of patients with asymptomatic brain metastases enrolled in the PROFILE 1005 and PROFILE 1007 trials was reported in 2015 by Costa et al.[169] In these studies, all patients had *ALK*-rearranged advanced NSCLC and all analyzed patients received crizotinib. The intracranial ORR was 18% and 33%, the intracranial disease control rate was 56% and 62%, and the median PFS was 5.9 months and 6.0 months for the 109 patients with previously untreated brain metastases and the 166 patients with previously treated brain metastases, respectively.

Multiple phase II single-arm studies and non—phase II nonrandomized studies were identified and are described in the Data Supplement, but none of these studies were considered of sufficient quality and size to inform recommendations unless mentioned previously.

Clinical interpretation. For most patients with NSCLC, radiation therapy or radiosurgery and surgery remain the backbone of brain metastasis management. Targeted agents should not be used in the treatment of brain metastases for patients whose tumors do not have a driver alteration. However, in patients with an *EGFR* or *ALK* driver alteration, accruing evidence supports the utility of targeted therapy. Reasonable ORR, disease control rates, and other outcomes have been reported for multiple agents: icotinib[57] and osimertinib[158] in patients with *EGFR* mutation; alectinib,[63,159] brigatinib,[162] and ceritinib[167,168] in patients with *ALK* mutation; and pembrolizumab[166] in patients with PD-L1 expression. While only the icotinib BRAIN trial[57] randomly assigned patients to either systemic therapy or radiation therapy, it is the consensus of the Expert Panel that in patients with these specific driver mutations, the evidence is sufficient to recommend these specific agents. Although data from the Profile 1005 and Profile 1007 trials of crizotinib are similar to those for alectinib or brigatinib or ceritinib, the overall data from the ALESIA trial[159] and the ALEX trial[160] suggest that the three recommended agents may be more beneficial than crizotinib; therefore, the Panel did not include crizotinib in Recommendation 2.4. While the Panel achieved a consensus that local therapy could be delayed in Recommendations 2.3 and 2.4, the Panel did not reach consensus regarding delay of local therapy when pembrolizumab plus pemetrexed and a platinum agent are used. Some on the Panel believed that the PFS and OS benefits reported in the Keynote 189 trial[166] were sufficient to make that recommendation, and others believed that in the absence of a full reporting of intracranial control rates, a recommendation to defer local therapy was premature. In the absence of consensus, no recommendation regarding deferring local therapy was made. The potential advantages over the traditional local therapies in patients with asymptomatic brain metastases include the ability to treat concomitant systemic disease and the possibility of deferring the risk of focal therapies in the brain.

In patients without these driver alterations, there is insufficient evidence to recommend any systemic therapy (immunotherapy,

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chemotherapy, and other targeted agents) specifically for treatment of brain metastases.

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 (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Literature review and analysis.

Randomized trials of patients with brain metastases from melanoma. There was only one randomized trial identified that met inclusion criteria specifically conducted in patients with brain metastases from melanoma. The trial reported in 2018 by Long et al[58] compared nivolumab plus ipilimumab versus nivolumab alone in 60 patients. This trial found an intracranial response of 46% in the combination arm versus 20% with nivolumab alone. At the time of the report, the median intracranial PFS and OS had not yet been reached on the combination arm and were 2.5 and 18.5 months, respectively, with nivolumab alone.

Relevant nonrandomized phase II trials. Five relevant nonrandomized phase II trials were identified and considered relevant. In 2012, Margolin et al[66] investigated ipilimumab in 51 patients with asymptomatic brain metastases. They reported an ORR of 10% (no complete responses), a CNS disease control rate of 24%, a median PFS of 1.4 months, and a median OS of 7.0 months. The CheckMate 204 trial[61] investigated the combination of ipilimumab and nivolumab in 94 patients. It reported an ORR of 51%, a 6-month PFS rate of 64.2%, and a 12-month OS rate of 81.5%. The BREAK-MB trial[62] investigated dabrafenib in 172 patients in two cohorts, 74 patients with no previous local therapy, and 65 patients with previous local therapy. All patients had Val600Glu *BRAF*–mutated melanoma. The ORR was 37.8% and 30.8%, the intracranial disease control rate was 81.1% and 89.2%, the median PFS was 16.1 weeks and 16.6 weeks, and the median OS was 33.1 weeks and 31.4 weeks for the no previous local therapy and previous local therapy cohorts, respectively. In 2017, McArthur et al[67] investigated vemurafenib in patients with *BRAF*-positive melanoma in two cohorts: 90 patients previously untreated for brain metastases, and 56 patients previously treated. The intracranial ORR was 18% and 18%, the median brain-only PFS was 3.7 months and 4.0 months, and the median OS was 8.9 months and 9.6 months for the previously untreated and previously treated cohorts, respectively. The COMBI-MB trial[170] had four cohorts of patients enrolled; of these, one cohort had 76 patients and met the criteria for inclusion. This cohort was of patients with asymptomatic brain metastases from *BRAF*-v600E melanoma and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. Patients received the combination of dabrafenib and trametinib. The ORR was 58%, and the intracranial ORR and extracranial ORR were 58% and 55%, respectively. The median PFS was 5.6 months, the median OS was 10.8 months, and the 6-month PFS and 12-month OS rates were 44% and 46%, respectively.

Other studies. Multiple non–phase II nonrandomized studies were identified and are described in the Data Supplement, but none of these studies were considered of sufficient quality and size to inform recommendations unless mentioned previously.

Clinical interpretation. The current standard of care of metastatic melanoma—as described in the recent ASCO guideline[171]—is in summary ipilimumab plus nivolumab, nivolumab alone, or pembrolizumab alone in all patients, or a combination of a *BRAF* inhibitor and a *MEK* inhibitor in patients with *BRAF* mutation. However, many of the randomized trials that underpin those recommendations excluded patients with brain metastases.[172]

Only one randomized trial, Long et al,[58] investigated regimens currently recommended for metastatic melanoma in patients with brain metastases. That trial reports clinical benefits for the combination of ipilimumab and nivolumab over nivolumab alone in patients with brain metastases, especially regarding similar results from CheckMate 204.[61] The evidence from the COMBI-MB trial[170] also reports important clinical benefits for patients receiving dabrafenib and trametinib; this is supported by the evidence of the BREAK-MB trial.[62]

Despite the lack of randomized evidence specific to patients with brain metastases, the consensus of the Panel was that patients receiving ipilimumab and nivolumab or dabrafenib and trametinib therapy as described in the recent ASCO guideline[171] for metastatic melanoma who have asymptomatic brain metastases may reasonably defer local therapy until there is evidence of progression.

Breast Cancer

Recommendation 2.7. The combination of tucatinib, trastuzumab, and capecitabine may be offered to patients with human epidermal growth factor receptor 2 (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 (Type: evidence-based; Evidence quality: low; Strength of recommendation: weak).

Literature review and analysis.

Known subgroup analyses of patients with brain metastases from randomized trials of metastatic breast cancer. The HER2CLIMB trial[173] compared tucatinib to placebo when combined with trastuzumab and capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and trastuzumab

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emtansine. In the subgroup of patients with baseline brain metastases (291 patients), significant improvements in both OS (HR, 0.58; 95% CI, 0.40 to 0.85) and PFS (HR, 0.48; 95% CI, 0.34 to 0.69) were reported with tucatinib.

The BEACON trial[174] compared etirinotecan pegol to physician's choice of chemotherapy in patients with locally recurrent or metastatic breast cancer. In a predefined subgroup analysis of 67 patients with controlled brain metastases, a significant improvement in OS was reported for etirinotecan pegol (median 10 months *v* 4.8 months, $P < .01$), but there was no reported difference in PFS.

The EMILIA trial[175] compared trastuzumab emtansine to lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane. In the subgroup of patients with baseline CNS metastases (95 patients), a significant improvement in OS (HR, 0.38; $P = .008$) but not PFS (HR, 1.00) was reported.

Randomized trials in patients with brain metastases from breast cancer. Two randomized trials[44,51] were identified that met inclusion criteria specifically conducted in patients with brain metastases from breast cancer. The trial reported in 2014 by Cao et al[44] was a phase II randomized trial of 100 patients with at least one brain metastasis from breast cancer who had received WBRT comparing temozolomide to no temozolomide. No significant differences in ORR, OS, or PFS were reported. The LUX-Breast-3 trial[51] was a phase II randomized trial of 121 patients with at least one CNS metastasis from breast cancer that had progressed on trastuzumab and/or lapatinib. It had three arms: imatinib, afatinib plus vinorelbine, or investigator's choice of therapy. No significant differences in ORR, OS, or PFS were reported.

Relevant nonrandomized phase II trials. One nonrandomized phase II trial was identified. The trial reported in 2009 by Lin et al[65] studied the use of lapatinib for patients with HER2-positive breast cancer who had completed WBRT or SRS and had prior therapy with trastuzumab. The reported ORR was 6%, the median PFS was 2.40 months, and the median OS was 6.37 months.

Other studies. Multiple nonrandomized studies were identified and are described in the Data Supplement, but none of these studies were considered of sufficient quality and size to inform recommendations unless mentioned previously.

Clinical interpretation. There is a wide array of accepted systemic therapy options for metastatic breast cancer depending on HER2 status and hormone receptor status. However, few of these options have been studied in patients with brain metastases, and there is only limited evidence for those that have. The only systemic therapy regimen for which the Expert Panel was able to find direct trial evidence that may support its use was the combination of tucatinib, trastuzumab, and capecitabine,[173] compared to trastuzumab and capecitabine alone in patients with HER2-positive cancer who have progressed after receiving trastuzumab, pertuzumab, and/or trastuzumab emtansine.

The consensus of the Expert Panel was that at this time, a formal recommendation in favor of the use of tucatinib, trastuzumab, and capecitabine based on the subgroup analysis from the HER2CLIMB trial,[173] but no other formal recommendation for or against any other specific regimen, could be made.

Other Disease Sites

Literature review and analysis. No randomized trial evidence or nonrandomized phase II prospective evidence meeting the inclusion criteria was identified regarding systemic therapy for patients with brain metastases from other cancers.

Clinical interpretation. The Expert Panel acknowledges that increasingly, oncologists are advising deferral of radiation therapy and/or surgery of brain metastases while patients are receiving systemic therapy that is believed to be potentially active in the brain. There is a great need for further research on this strategy, especially in the case of targeted agents known to be effective against the wider systemic disease with the relevant alteration and in histologies where brain metastases are frequent, such as small-cell lung cancer. However, at this time the evidence supporting this choice is very weak, and the consensus of the Expert Panel was that this strategy could not be recommended except in the limited fashion described in the recommendations for NSCLC, melanoma, and breast cancer. Patients with brain metastases should be managed by a multidisciplinary team and considered for clinical trials if initial management with systemic agents is contemplated, as even the best data for these patients are limited.

RADIATION THERAPY

What are the benefits and harms of WBRT in adults with brain metastases?

What approaches have been found to mitigate the harms of WBRT (eg, radioprotectants, memantine, and hippocampal avoidance)?

What are the benefits and harms of SRS or radiation therapy in adults with brain metastases?

What are the relative benefits and harms of SRS or radiation therapy compared to WBRT?

What are the benefits and harms of using radiation sensitizers?

NOTE: ASTRO is currently developing a guideline on radiation therapy for brain metastases, intended for publication in late 2021 or early 2022.

Recommendation 3.1

Radiation therapy should not be offered to patients with asymptomatic brain metastases and who have either:

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- Performance status Karnofsky Performance Status (KPS) ≤ 50, *or*
- Performance status KPS < 70 and no systemic therapy options (Type: evidence-based; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. The only randomized trial of radiation therapy identified by the systematic review that included patients with lower performance status was the QUARTZ trial (Mulvenna et al[33]), which compared WBRT to no WBRT in patients with NSCLC brain metastases receiving dexamethasone and best supportive care. It included patients with KPS as low as 30, and 203 of the total 538 patients had KPS < 70. That trial reported no significant difference in either OS or quality-adjusted life years between WBRT and no WBRT, although analyses found improved survival associated with WBRT for subgroups with better prognosis such as those < 60 years old.

While several identified nonrandomized studies included patients with low performance status, and many of those studies reported a multivariate analysis, no nonrandomized study was identified that reported separately on the benefit of radiation therapy versus no radiation therapy in patients with lower performance status.

Clinical interpretation. The vast majority of RCTs and most nonrandomized studies have lower performance status (KPS < 70, ECOG/WHO PS > 2) as an exclusion criterion. Therefore, the population of patients with brain metastases and lower performance status is not well studied. It is the consensus of the Expert Panel that patients with KPS ≤ 50 and patients with KPS < 70 with no systemic therapy options will not benefit from radiation therapy within a meaningful time frame.

Recommendation 3.2

SRS alone (as opposed to WBRT or combination of WBRT and SRS) should be offered to patients with one to four 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 (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. Multiple randomized trials have investigated SRS, WBRT, and SRS combined with WBRT versus observation in patients with small numbers of brain metastases (no more than three or four) and higher performance status (ECOG PS 0-2, KPS ≥ 70). These trials are detailed in the Data Supplement and briefly summarized in Table 2. Of these trials, the N0574,[30] Aoyama,[176] RTOG 9508,[177] and Chang[31] trials were in patients who did not receive surgery, whereas in the EORTC 22952-26001[32] and ANZMTG 01.07[38] trials, patients received either surgery or SRS before WBRT. One trial, El Gantery et al 2014,[43] did not report on surgery before radiation therapy.

Multiple nonrandomized studies have been published that report on the effect of radiation therapy in patients with one to four metastases, as detailed in Data Supplement Table 9. However, none of these studies were of sufficient size and/or quality to inform recommendations.

Clinical interpretation. While the relevant randomized trials have slightly different inclusion criteria in terms of number of metastases and sizes of tumor, when considered together, the Panel has interpreted the evidence as follows:

- Radiation therapy is associated with improved disease control and potentially with improved survival in patients with few unresected brain metastases of smaller size, compared to the expected outcomes that would be experienced with no radiation therapy.
- Compared SRS to conventional WBRT (without radioprotectant strategies of memantine or hippocampal avoidance), SRS is associated with less cognitive deterioration, while WBRT is associated with greater intracranial control. In one to four brain metastases, neither has been determined to be superior in terms of OS.
- In one to four brain metastases, the combination of SRS plus conventional WBRT (without radioprotectant strategies of memantine or hippocampal avoidance) is associated with potentially more cognitive deterioration and has not been found to be associated with an improvement in survival, should one exist.

Based on the premise that patients value cognitive function over intracranial control, noting that survival appears comparable between the different comparisons, the consensus of the Panel is that SRS, as opposed to WBRT or the combination of SRS and WBRT, is suitable therapy for patients with one to four smaller (< 4 cm) brain metastases. While the Panel believed that recommending specific radiation doses and schedules was beyond the scope of the guideline, radiation delivered in a manner similar to that in the underlying trials is appropriate.

The results of the NRG CC001 trial,[37] fully discussed under Recommendation 3.5, suggest that hippocampal avoidance with WBRT while the patient is receiving memantine might have risks to cognition that are more comparable to SRS. However, in the absence of a randomized trial directly comparing WBRT with hippocampal avoidance and memantine to SRS, the consensus of the Panel was that SRS remained the first choice for patients with small numbers of resected metastases.

Small-cell lung cancer has been excluded, as patients with that histology were excluded from the key randomized trials. The ongoing NRG BN009 trial, NCT04588246,

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TABLE 2. RCTs of SRS, WBRT, and Combination in Patients With Small Numbers of Brain Metastases and Higher Performance Status

Study ID, Authors, Year, Size, Design	Treatment Setting and Interventions Studied	Key Outcomes
ANZMTG 01.07: Hong et al,[38] 215 patients, phase III RCT	Patients with one to three brain metastases from melanoma, ECOG PS 0-2. All patients received surgery or SRS. Any form of systemic therapy permitted (Surgery or SRS) + WBRT *v* (surgery or SRS)	**Distant intracranial failure rate at 12 months:** 42.0% *v* 50.5%, OR 0.72 (95% CI, 0.41 to 1.23, $P = .22$) Local failure rate at 12 months: 20.0% *v* 33.6%, OR 0.49 (95% CI, 0.26 to 0.93, $P = .03$) Median OS: 16.5 months *v* 13 months, $P = .86$ OS rate at 12 months: 58.4% *v* 54.0%
Aoyama et al,[176] 132 patients, RCT[a]	Patients with one to four brain metastases < 3 cm WBRT + SRS *v* SRS alone	Median OS: 7.5 months *v* 8 months ($P = .42$) 12-month survival: 38.5% *v* 28.4% 12-month recurrence rate: 46.8% *v* 76.4% ($P < .001$)
Chang et al,[31] 58 patients, institution-based RCT	Patients with one to three newly diagnosed brain metastases eligible for SRS, KPS ≥ 70 SRS *v* SRS + WBRT	**Cognitive deterioration:** 24% (of 20 evaluated) *v* 52% (of 11 evaluated) of patients experienced HVLT-R total recall reduction of 5 points or more from baseline at 4 months OS: 67% *v* 89% died during follow-up. HR 2.47 (95% CI, 1.34 to 4.54, $P = .0036$), showing decreased survival for SRS + WBRT 12-month local control rate: 67% *v* 100%, $P = .012$ 12-month distant brain control rate: 45% *v* 73%, $P = .02$
El Gantery et al,[43] 60 patients, institution-based RCT	Patients with one to three brain metastases, KPS ≥ 70 SRS *v* WBRT *v* SRS + WBRT	Local control rate: 22.2% *v* 19% *v* 42.9%, $P = .04$ Median OS: no significant difference
EORTC 22952-26001: Kocher et al,[32] 359 patients, phase III RCT	Patients with one to three brain metastases, WHO PS 0-2. All patients had either surgery or SRS. (SRS or surgery) + WBRT *v* (SRS or surgery)	**Median survival with functional independence** (WHO PS > 2): 9.5 months *v* 10 months; HR, 0.96 (95% CI, 0.76 to 1.20; $P = .71$) Median PFS: 4.6 months *v* 3.4 months, $P = .20$ Median survival: 10.7 months *v* 10.9 months; HR, 0.98 (95% CI, 0.78 to 1.24; $P = .89$)
JCOG0504: Kayama et al,[29] 271 patients, phase III noninferiority RCT	Patients with ≤ 4 resected brain metastases, ECOG PS 0-2 Observation with salvage SRS *v* WBRT	**Median OS:** 15.6 months *v* 15.6 months; HR, 1.05 (95% CI, 0.83 to 1.33; $P = .03$ for noninferiority of SRS for margin of HR 1.385) Median intracranial PFS: 4.0 months *v* 10.4 months; HR, 1.91 (95% CI, 1.46 to 2.51)
Mahajan et al,[36] 132 patients, phase III institution-based RCT	Patients with one to three resected brain metastases, KPS ≥ 70 SRS *v* no SRS	**Median time to local recurrence:** not reached *v* 7.6 months; HR, 0.46 (95% CI, 0.24 to 0.88; $P = .015$) 12-month freedom from local recurrence: 72% *v* 43% Median OS: 17 months *v* 18 months; HR, 1.29 (95% CI, 0.84 to 1.98; $P = .24$)
N0574: Brown et al,[30] 213 patients, phase III RCT	Patients with one to three brain metastases < 3 cm, ECOG PS 0-2 SRS *v* SRS + WBRT	**Cognitive deterioration:** 63.5% *v* 91.7% experienced deterioration at 3 months, difference –28.2% (90% CI, –41.9% to –14.4%; $P < .001$). Time to intercranial failure: HR, 3.6 (95% CI, 2.2 to 5.9; $P < .001$) 3-month intercranial tumor control rate: 75.3% *v* 93.7%, difference 18.4% (95% CI, 7.8% to 29.0%; $P < .001$) 6-/12-month local control rate: 81.6%/72.8% *v* 92.6%/90.1% ($P = .034$/$P = .003$) 6-/12-month distant brain control rate: 76.7%/69.9% *v* 94.7%/92.3% ($P < .001$/$P < .001$) Median OS: 10.4 months *v* 7.4 months; HR, 1.02 (95% CI, 0.75 to 1.38; $P = .92$)
NCCTG N107C/CEC3: Brown et al,[28] 194 patients, phase III RCT	Patients with one resected brain metastasis and resection cavity < 5 cm, ECOG PS 0-2 SRS *v* WBRT	**Median CDFS:** 3.7 months *v* 3.0 months; HR, 0.47 (95% CI, 0.35 to 0.63; $P < .0001$) Median OS: 12.2 months *v* 11.6 months; HR, 1.07 (95% CI, 0.76- to 0.50; $P = .70$) Time to intracranial tumor progression: 6.5 months *v* 27.5 months; HR, 2.45 (95% CI, 1.62 to 3.72; $P < .0001$) 6-month surgical bed control rate: 80.4% *v* 87.1% ($P = .00068$)

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TABLE 2. RCTs of SRS, WBRT, and Combination in Patients With Small Numbers of Brain Metastases and Higher Performance Status (continued)

Study ID, Authors, Year, Size, Design	Treatment Setting and Interventions Studied	Key Outcomes
Patchell et al,[178] 95 patients, RCT[a]	Patients with one resected brain metastasis WBRT *v* no WBRT	**Brain recurrence rate:** 18% *v* 70%, $P < .001$ Median survival: 43 weeks *v* 48 weeks; $P = .39$; RR for death 0.91 (95% CI, 0.59 to 1.40)
RTOG 9508: Andrews et al,[177] 331 patients, RCT[a]	Patients with one to three newly diagnosed brain metastases SRS + WBRT *v* WBRT	**Median OS:** 5.7 months *v* 6.5 months; $P = .1356$ Time to intracranial progression, no difference, $P = .1278$ 12-month local control rate: 82% *v* 71%; $P = .01$

NOTE. Bold indicates primary outcomes.

Abbreviations: CDFS, cognitive deterioration–free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; KPS, Karnofsky performance status; OR, odds ratio; OS, overall survival; PFS, progression-free survival; PS, performance status; RCT, randomized controlled trial; RR, risk ratio; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

[a]Trial was published in the 2008 cutoff of the systematic review and was identified nonsystematically by the Panel.

randomly assigns patients to salvage SRS alone or salvage SRS plus hippocampal-avoiding WBRT and memantine. However, this study is not estimated to be completed until 2025.

Recommendation 3.3

SRS alone should be offered to patients with one to two 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) (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. Several randomized trials have investigated the value of radiation therapy in patients with limited (generally < 5) numbers of resected brain metastases: NCCTG N107C/CEC3,[28] JCOG0504,[29] Patchell et al,[178] and Mahajan et al.[36] In addition, in the EORTC 22952-26001[32] and ANZMTG 01.07[38] trials, patients received either surgery or SRS prior to WBRT. These trials are fully described in the Data Supplement and briefly summarized in Table 2. Few studies included patients with more than two metastases, and even when included, these patients were small in number.

Multiple nonrandomized studies have been published that report on the effect of radiation therapy in patients with one to two metastases, as detailed in Table 9 of the Data Supplement. However, none of these studies were considered by the Panel to be of sufficient size and/or quality to inform recommendations.

Clinical interpretation. The evidence for radiation therapy in patients with small numbers of resected brain metastases is similar to that in patients with unresected brain metastases. The overall interpretation of the Panel is similar as well: radiation therapy is beneficial in many patients; SRS can provide better cognitive outcomes, while WBRT can provide better intracranial control; the combination of SRS plus WBRT has not been extensively studied in the postoperative setting. The randomized trials evaluating SRS in the postoperative setting used single-fraction SRS. However, there is interest in fractionated radiosurgery (ie, three to five fractions) to potentially improve surgical bed control and decrease the risk of radiation necrosis. The ongoing A071801 trial, NCT04114981, randomly assigns patients after complete resection of a brain metastasis to single-fraction SRS or fractionated SRS. However, this study is not estimated to be completed until 2023. While the Panel believed that recommending specific radiation doses and schedules was beyond the scope of the guideline, radiation delivered in a manner similar to that in the underlying trials is appropriate.

As with patients with unresected metastases, the results of the NRG CC001 trial[37] suggest that cognitive outcomes with hippocampal avoidance with WBRT and memantine may be more similar to SRS, but with no direct comparison this intervention cannot be recommended at this time.

Recommendation 3.4

SRS, WBRT, and the combination of SRS plus WBRT are all reasonable options for patients with more than four unresected or more than two resected brain metastases and better performance status (eg, KPS ≥ 70). SRS may be preferred for patients with better prognosis or where systemic therapy that is known to be active in the CNS is available (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Literature review and analysis. No randomized trials that focused on patients with more than four brain metastases were identified. In the systematic review, QUARTZ[33] (WBRT *v* no WBRT in NSCLC) and NRG CC001[37] (hippocampal avoidance *v* no hippocampal avoidance with WBRT) are the only trials that included these patients but they also included patients with fewer than five metastases.

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The results of the QUARTZ trial suggest that, at least in NSCLC, WBRT with supportive care may not be better than supportive care alone in the poor prognosis patient population enrolled in that trial, but neither trial can directly inform therapy in all patients in this population. Among the nonrandomized studies that were identified by the systematic review, only the JLGK901[179] prospective cohort study reported on patients with more than four brain metastases. In patients with five to ten newly diagnosed brain metastases treated with SRS, the median OS was 10.8 months, the 1-year local tumor progression rate was 8.7%, and the cumulative rate of Mini Mental State Examination maintenance at 12 months was 92% in patients treated with SRS.

Clinical interpretation. The consensus of the Panel, in the absence of any directly relevant randomized evidence, was that radiation therapy likely provides more benefit than harm in many patients whose life expectancy is such that they will experience those benefits, and that radiation therapy should be recommended in patients with good performance status and more than four brain metastases. However, the lack of evidence means that the Panel is unable to provide clear guidance to clinicians on the form of radiation therapy. Factors such as metastases volume, number of metastases, or brain metastasis velocity may be relevant, but at this time the evidence is such that the Panel could not recommend specific thresholds for these factors. It seems reasonable that better prognosis and the availability of good systemic therapy options would be a reason to favor SRS over WBRT, although it is possible that hippocampal avoidance and memantine may make WBRT an equivalent, or potentially superior, option. The ongoing NRG BN009 trial, NCT04588246, randomly assigns patients to salvage SRS alone or salvage SRS plus hippocampal avoidance WBRT and memantine. However, this study is not estimated to be completed until 2025.

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 (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Literature review and analysis. The RTOG 0614 trial[42] compared memantine to placebo in 554 patients with brain metastases receiving WBRT; it is fully described in the Data Supplement. While it did not find a significant difference in its primary outcome—preservation of cognitive function at 24 weeks on the HLVT-R DR instrument—it did find clinically meaningful and statistically significant benefits in other cognitive outcomes, including cumulative incidence of cognitive failure and cognitive function measured by the Mini Mental State Examination instrument. Memantine was not associated with any clinically meaningful toxicity or adverse events compared to placebo. The NRG CC001 trial[37] compared hippocampal avoidance to no hippocampal avoidance in patients receiving WBRT and memantine and who did not have lesions within 5 mm of the hippocampus; it is fully described in the Data Supplement. That trial reported that among 518 patients, time to cognitive failure was significantly longer with hippocampal avoidance than without hippocampal avoidance (HR, 0.745; 95% CI, 0.582 to 0.954; $P = .0200$) with no significant difference in survival or PFS.

Clinical interpretation. The results of the RTOG 0614[42] and NRG CC001[37] trials, taken together, convincingly demonstrate that when WBRT is offered, memantine should be offered as well and the hippocampus should be avoided if possible.

Recommendation 3.6

Radiation-sensitizing agents should not be offered to patients (Type: evidence-based; Evidence quality: low; Strength of recommendation: strong).

Literature review and analysis. Three randomized trials of radiation sensitizers were identified in the systematic review and met inclusion criteria: El-Hamamsy et al[39] (simvastatin); the PCYC-0211 trial[40] (motexafin gadolinium); and Rojas-Puentes et al[41] (chloroquine). These trials are detailed in the Data Supplement, but none found any statistically significant and clinically meaningful difference in important outcomes between sensitizer use and not using the sensitizer.

Clinical interpretation. As no sensitizing agent has been demonstrated to provide meaningful benefits, they are not recommended.

TIMING AND INTERACTION OF THERAPY

How does the relative timing of surgery, radiation therapy, and systemic therapy affect the benefits and/or harms of those therapies?

Recommendation 4.1

For patients who will receive both radiation therapy and surgery, no recommendation regarding the specific sequence of therapy can be made (Type: informal consensus; Evidence quality: low; Strength of recommendation: none).

Literature review and analysis. There were no studies (randomized or nonrandomized) identified that specifically investigated the timing of surgery and SRS. In the randomized trials described under Recommendation 3.2, surgical resection (ie, postoperative) was an inclusion criterion in the trial.

Clinical interpretation. When taken together, Recommendations 1.1, 3.1, 3.2, and 3.3 indicate that many patients with brain metastases should be offered both surgery and radiation therapy. In patients with symptomatic brain metastases there may be benefits to surgery to reduce symptoms, particularly mass effect, but durable local

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control requires that some form of radiation therapy (WBRT or SRS) be provided shortly after surgery. Alternatively, there are grounds[180-182] to believe that SRS provided shortly before surgery may provide similar local control benefit and also lower the risks of growth in the vicinity of the resection cavity, risk of leptomeningeal disease, and radiation injury. In the absence of direct evidence—ideally a randomized trial—practical considerations (eg, timing of access to surgical or radiation services) may reasonably drive the decision on relative timing of these interventions.

DISCUSSION

To the Panel's knowledge, this guideline represents the only current guideline on the management of brain metastases across tumor types that addresses all possible interventions (systemic therapy, surgery, and radiation therapy) in a comprehensive fashion in one document.

PATIENT AND CLINICIAN COMMUNICATION

With all cancers, clinician expertise when informing patients about their disease, their diagnosis, and their treatments, and when offering and recruiting patients regarding clinical trials, is vital. Information given to the patient should allow the patient to feel enabled. Patients who find agency with the information they receive are likely more motivated, more proactive, more adherent, and better able to cope with their diagnoses.

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 (eg, frailty, number of metastases). 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 whether the patient is receiving care in a community versus an academic center setting.[183-185] Clinicians should work to inform themselves of relevant clinical trials. Clinicians may also encourage patients to seek out local, regional, and national patient support organizations. ASCO's Cancer.Net online resource provides information on such organizations in the United States. Patients are not experimental subjects, they are individuals; providers should avoid making patients feel as though they are a part of an academic laboratory study. For recommendations and strategies to optimize patient-clinician communication, see "Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline."[186]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and/or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[187,188] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients in order to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlight the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

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COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[189] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[190,191]

Discussion of cost can be an important part of shared decision making.[192] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[192]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[192]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data and agents that are not currently available in either the United States or Canada or are industry-sponsored.

As only a few specific recommendations were made for systemic therapy, and as the cost of radiation therapy and surgery may vary considerably depending on context and region, no specific cost information was sought for this guideline. The inter-relationship of the recommendations for surgery, radiation, and systemic therapy makes any simple presentation of costs more likely to be misleading than informative. Recent cost-effectiveness studies[193,194] identified nonsystematically suggest that SRS alone may be cost-effective compared to SRS plus WBRT and that hippocampal avoidance may be cost-effective compared to no avoidance, but these studies do not comprehensively address the different treatment strategies presented in the recommendations. Further cost-effectiveness research is needed.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from March 5 through March 22, 2021. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation. Forty-seven responses were received. In general, respondents agreed or agreed with suggested modifications (at least 93% agreement) with nearly all of the recommendations. There were no consistent themes to the proposed modifications. The Expert Panel cochairs reviewed these comments and decided that no changes to the recommendations were needed except for minor editorial revisions.

However, 15% of respondents disagreed with Recommendation 4.1; all but one of these respondents indicated that they believed the data on preoperative SRS were premature and therefore a recommendation against preoperative SRS should be made. Other respondents indicated that recommendation 4.1 as worded was confusing, as it could be interpreted as suggesting WBRT before surgery was potentially reasonable. The Expert Panel cochairs reviewed these comments, but continued to believe that the evidence was sufficiently mixed that no recommendation regarding the appropriate timing of radiation therapy and surgery could be made and that the clinical interpretation section appropriately described the evidence and clinical situation.

The draft was submitted to two external reviewers with content expertise. It was rated as high quality, and it was agreed that it would be useful in practice. Review comments were minimal; minor revisions were made by the staff methodologist and approved by the cochairs.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the Panel. The additional roles of this PGIN representative on the guideline Panel are to assess the suitability of the recommendations to implementation in the community setting and to identify any other barrier to implementation that a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners, survivors of cancer, and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/neurooncology-guidelines. Patient information is available at www.cancer.net.

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RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Practice[195] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[186] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- ASCO has published multiple guidelines on the treatment of metastatic cancer, such as the ones listed below. Clinicians should refer to the appropriate guidelines on:
  - Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer[196] (https://ascopubs.org/doi/full/10.1200/JCO.2018.79.2697)
  - Therapy for Stage IV Non–Small-Cell Lung Cancer with Driver Alterations[197] (https://ascopubs.org/doi/full/10.1200/JCO.20.03570)
- ASTRO intends to publish a guideline on radiation therapy for brain metastases in late 2021 or in 2022. It will be available at https://www.astro.org/Patient-Care-and-Research/Clinical-Practice-Statements/Clinical-Practice-Guidelines

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/neurooncology-guidelines.

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EQUAL CONTRIBUTION

M.A.V. was the ASCO lead, D.S. was the Society for Neuro-Oncology lead, and P.D.B. was the American Society for Radiation Oncology lead. All contributed equally to leadership of the project.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02314.

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ACKNOWLEDGMENT

The Expert Panel would like to thank Glenn Bauman and Nancy Lin for external review; Pavan Reddy and Dr Michele Halyard for ASCO CPGC review; Alvin Cabrera, Madeera Kathpal, Aruna Turaka, and Jason Ye for ASTRO review; and the ASCO CPGC, SNO Guideline Committee, and ASTRO Guideline Committee and Board for their thoughtful reviews and insightful comments on this guideline.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

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This author is a member of the *Journal of Clinical Oncology* Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.
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No other potential conflicts of interest were reported.

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APPENDIX

TABLE A1. Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
David Schiff, MD, cochair	University of Virginia Medical Center, Charlottesville, VA	Neurooncology
Michael Vogelbaum, MD, PhD, cochair	Moffit Cancer Center, Tampa, FL	Neurosurgical Oncology
Paul Brown, MD, radiation lead	Mayo Clinic Cancer Center, Rochester, MN	Radiation Oncology
Priscilla K. Brastianos, MD	Massachusetts General Hospital, Boston, MA	CNS/AANS Representative Neurooncology
Stuart Burri, MD	Levine Cancer Institute at Atrium Health, Charlotte, NC	Radiation Oncology
Dan Cahill, MD, PhD	Massachusetts General Hospital, Boston, MA	Neurosurgical Oncology
Ian F. Dunn, MD	Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK	Neurosurgical Oncology
Laurie E. Gaspar, MD, MBA	University of Colorado School of Medicine, Aurora, CO, and University of Texas MD Anderson Cancer Center Northern Colorado, Greeley, CO	Radiation Oncology
Na Tosha N. Gatson, MD, PhD	Banner MD Anderson Cancer Center, Phoenix, AZ, and Geisinger Neuroscience Institute, Danville, PA	Neurooncology
Vinai Gondi, MD	Northwestern Medicine Cancer Center Warrenville and Proton Center, Warrenville, IL	Radiation Oncology
Justin T. Jordan, MD	Massachusetts General Hospital, Boston, MA	Neurooncology
Andrew B. Lassman, MD	Columbia University Irving Medical Center, New York, NY	Neurooncology
Julia Maues, MA	Georgetown Breast Cancer Advocates, Washington, DC	Patient Representative
Nimish Mohile, MD	University of Rochester Medical Center, Rochester, NY	Neurooncology
Navid Redjal, MD	Capital Health Medical Center – Hopewell Campus, Princeton, NJ	CNS/AANS Representative Neurosurgical Oncology
Glen Stevens, DO, PhD	Cleveland Clinic, Cleveland, OH	Neurooncology
Erik Sulman, MD, PhD	NYU Langone Health, New York, NY	Radiation Oncology
Martin van den Bent, MD	Brain Tumor Center at Erasmus MC Cancer Institute, Rotterdam, Netherlands	Neurology
H. James Wallace, MD	University of Vermont, Burlington, VT	PGIN Representative, Radiation Oncology
Jeffrey S. Weinberg, MD	University of Texas MD Anderson Cancer Center, Houston, TX	Neurosurgical Oncology
Gelareh Zadeh, MD, PhD	University of Toronto, Toronto, ON, Canada	Neurosurgical Oncology
Hans Messersmith, MPH	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

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TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of Evidence	
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (eg, balance of benefits versus harms), and further research is very unlikely to change either the magnitude or direction of this net effect
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available
Strength of Recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: 1. strong evidence for a true net effect (eg, benefits exceed harms); 2. consistent results, with no or minor exceptions; 3. minor or no concerns about study quality; and/or 4. the extent of panelists' agreement Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: 1. good evidence for a true net effect (eg, benefits exceed harms); 2. consistent results with minor and/or few exceptions; 3. minor and/or few concerns about study quality; and/or 4. the extent of panelists' agreement Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: 1. limited evidence for a true net effect (eg, benefits exceed harms); 2. consistent results, but with important exceptions; 3. concerns about study quality; and/or 4. the extent of panelists' agreement Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation

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