

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Michael A. Vogelbaum, MD, PhD¹; Paul D. Brown, MD²; Hans Messersmith, MPH³; Priscilla K. Brastianos, MD⁴; Stuart Burri, MD⁵; Dan Cahill, MD, PhD⁴; Ian F. Dunn, MD⁶; Laurie E. Gaspar, MD, MBA^{7,8}; Na Tosha N. Gatsen, MD, PhD^{9,10}; Vinai Gondi, MD¹¹; Justin T. Jordan, MD⁴; Andrew B. Lassman, MD¹²; Julia Maues, MA¹³; Nimish Mohile, MD¹⁴; Navid Redjal, MD¹⁵; Glen Stevens, DO, PhD¹⁶; Erik Sulman, MD, PhD¹⁷; Martin van den Bent, MD¹⁸; H. James Wallace, MD¹⁹; Jeffrey S. Weinberg, MD²⁰; Gelareh Zadeh, MD, PhD²¹; and David Schiff, MD²²

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 ≤ 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
Reprint Requests: 2318 Mill Road, Suite 800, Alexandria, VA 22314; guidelines@asco.org.

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,

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).

(continued on following page)

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) ≤ 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 ≥ 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).

(continued on following page)

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?

- 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 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 non-systematically 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 ≥ 50 patients in each comparison group.
 - Noncomparative studies (eg, institutional series) with ≥ 300 patients.
 - Meta-analyses of relevant studies if published in 2018 or later.
 - As a post hoc alteration to the criteria, non-comparative prospective protocol-based clinical trials (eg, phase II trials) of systemic therapy were included if they had ≥ 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.

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 coauthors 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.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates

that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an “as is” basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

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.

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 tool¹⁴⁸ 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 al¹⁴⁹ and Vecht et al¹⁵⁰ reported clinically meaningful and statistically significant improvements in overall survival (OS), while Mintz et al¹⁵¹ 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 either SRS, 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 al⁷¹ (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.

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 al⁴⁶ (78 patients) and Gamboa-Vignolle et al⁵⁰ (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 al¹⁵⁵ (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.

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 al⁴⁵ (temozolomide v no temozolomide), Quantin et al⁴⁸ (cisplatin plus vinorelbine plus ifosfamide v high-dose ifosfamide), Neuhaus et al⁴⁹ (topotecan v no topotecan), and Chabot et al⁵² (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 al⁵⁴ (erlotinib v placebo), RTOG 0320⁵⁶ (erlotinib v temozolomide v no other therapy), Lee et al⁵⁹ (gemcitabine plus vinorelbine followed by WBRT v WBRT followed by gemcitabine plus vinorelbine), and SAKK 70/03⁵⁵ (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 al⁵⁷ 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 al²⁵ 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 al¹⁵⁶ 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 al¹⁵⁷ 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 al⁶³ 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

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 analysis¹⁶⁰ 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 trial¹⁶¹ compared brigatinib at two doses (90 mg and 180 mg once daily) in patients with crizotinib-refractory *ALK*-rearranged metastatic NSCLC. Camidge et al¹⁶² 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 al¹⁶⁵ 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 trial¹⁶⁶ 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 trial¹⁶⁷ 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-naïve patients and 65% (95% CI, 54 to 76) in the 75 *ALK* inhibitor-pretreated patients with baseline brain metastases. The ASCEND-2 trial¹⁶⁸ 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: icotinib⁵⁷ and osimertinib¹⁵⁸ in patients with *EGFR* mutation; alectinib,^{63,159} brigatinib,¹⁶² and ceritinib^{167,168} in patients with *ALK* mutation; and pembrolizumab¹⁶⁶ in patients with PD-L1 expression. While only the icotinib BRAIN trial⁵⁷ 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 trial¹⁵⁹ and the ALEX trial¹⁶⁰ 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 trial¹⁶⁶ 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,

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 al⁵⁸ 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 al⁶⁶ 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 trial⁶¹ 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 trial⁶² 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 al⁶⁷ 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 trial¹⁷⁰ 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 guideline¹⁷¹—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 trial¹⁷⁰ 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 guideline¹⁷¹ 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 trial¹⁷³ 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

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 trial¹⁷⁴ 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 trial¹⁷⁵ 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 al⁴⁴ 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 trial⁵¹ 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 al⁶⁵ 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:

- 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 al³³), 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 Chang³¹ trials were in patients who did

not receive surgery, whereas in the EORTC 22952-26001³² and ANZMTG 01.07³⁸ 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](#),

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 HVL-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% ($P = .00068$)

(continued on following page)

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.

^aTrial 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 22952-26001³² and ANZMTG 01.07³⁸ 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 trial³⁷ 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 $\geq$ 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).

Literature review and analysis. No randomized trials that focused on patients with more than four brain metastases were identified. In the systematic review, QUARTZ³³ (WBRT v no WBRT in NSCLC) and NRG CC001³⁷ (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.

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 JLGK901¹⁷⁹ 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 trial⁴² 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 HLT-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 trial³⁷ 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 0614⁴² and NRG CC001³⁷ 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 al³⁹ (simvastatin); the PCYC-0211 trial⁴⁰ (motexafin gadolinium); and Rojas-Puentes et al⁴¹ (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

control requires that some form of radiation therapy (WBRT or SRS) be provided shortly after surgery. Alternatively, there are grounds¹⁸⁰⁻¹⁸² 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.

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 coauthors 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 coauthors 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 coauthors.

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.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Practice¹⁹⁵ (<http://ascopubs.org/doi/10.1200/JCO.2016.70.1474>)
- Patient-Clinician Communication¹⁸⁶ (<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 Cancer¹⁹⁶ (<https://ascopubs.org/doi/full/10.1200/JCO.2018.79.2697>)
 - Therapy for Stage IV Non–Small-Cell Lung Cancer with Driver Alterations¹⁹⁷ (<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>

AFFILIATIONS

- ¹Moffitt Cancer Center, Tampa, FL
- ²Mayo Clinic Cancer Center, Rochester, MN
- ³American Society of Clinical Oncology ASCO, Alexandria, VA
- ⁴Massachusetts General Hospital, Boston, MA
- ⁵Levine Cancer Institute at Atrium Health, Charlotte, NC
- ⁶Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK
- ⁷University of Colorado School of Medicine, Aurora, CO
- ⁸University of Texas MD Anderson Cancer Center Northern Colorado, Greeley, CO
- ⁹Banner MD Anderson Cancer Center, Phoenix, AZ
- ¹⁰Geisinger Neuroscience Institute, Danville, PA
- ¹¹Northwestern Medicine Cancer Center Warrenville and Proton Center, Warrenville, IL
- ¹²Columbia University Irving Medical Center – New York Presbyterian Hospital, New York, NY
- ¹³Georgetown Breast Cancer Advocates, Washington, DC
- ¹⁴University of Rochester Medical Center, Rochester, NY
- ¹⁵Capital Health Medical Center – Hopewell Campus, Princeton, NJ
- ¹⁶Cleveland Clinic, Cleveland, OH
- ¹⁷YU Langone Health, New York City, NY
- ¹⁸Brain Tumor Center at Erasmus MC Cancer Institute, Rotterdam, the Netherlands

REFERENCES

- Eichler AF, Chung E, Kodack DP, et al: The biology of brain metastases-translation to new therapies. *Nat Rev Clin Oncol* 8:344-356, 2011
- Cagney DN, Martin AM, Catalano PJ, et al: Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: A population-based study. *Neuro Oncol* 19:1511-1521, 2017

¹⁹University of Vermont, Burlington, VT

²⁰University of Texas MD Anderson Cancer Center, Houston, TX

²¹University of Toronto, Toronto, Ontario, Canada

²²University of Virginia Medical Center, Charlottesville, VA

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

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.

© 2021 by American Society of Clinical Oncology. This guideline was developed jointly by the Society for Neuro-Oncology, the American Society for Radiation Oncology, and the American Society of Clinical Oncology. All rights reserved.

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>.

AUTHOR CONTRIBUTIONS

Conception and design: Michael A. Vogelbaum, Paul D. Brown, Hans Messersmith, Stuart Burri, Vinai Gondy, Julia Maues, Navid Redjal, Erik Sulman, Martin van den Bent, Jeffrey S. Weinberg, Gelareh Zadeh, David Schiff

Collection and assembly of data: Michael A. Vogelbaum, Paul D. Brown, Hans Messersmith, Laurie E. Gaspar, Vinai Gondy, Martin van den Bent, Gelareh Zadeh, David Schiff

Data analysis and interpretation: Michael A. Vogelbaum, Paul D. Brown, Hans Messersmith, Priscilla K. Brastianos, Stuart Burri, Dan Cahill, Ian F. Dunn, Laurie E. Gaspar, Na Tosha N. Gatson, Vinai Gondy, Justin T. Jordan, Andrew B. Lassman, Julia Maues, Nimish Mohile, Navid Redjal, Glen Stevens, Martin van den Bent, H. James Wallace, Jeffrey S. Weinberg, David Schiff

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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.

3. Davis FG, Dolecek TA, McCarthy BJ, et al: Toward determining the lifetime occurrence of metastatic brain tumors estimated from 2007 United States cancer incidence data. *Neuro Oncol* 14:1171-1177, 2012
4. Black P: Brain metastasis: Current status and recommended guidelines for management. *Neurosurgery* 5:617-631, 1979
5. Bindal RK, Sawaya R, Leavens ME, et al: Surgical treatment of multiple brain metastases. *J Neurosurg* 79:210-216, 1993
6. Rock JP, Haines S, Recht L, et al: Practice parameters for the management of single brain metastasis. *Neurosurg Focus* 9:ecp2, 2000
7. Tsao MN, Lloyd NS, Wong RK: Clinical practice guideline on the optimal radiotherapeutic management of brain metastases. *BMC Cancer* 5:34, 2005
8. Soffietti R, Cornu P, Delattre JY, et al: EFNS guidelines on diagnosis and treatment of brain metastases: Report of an EFNS Task Force. *Eur J Neurol* 13: 674-681, 2006
9. Kalkanis SN, Kondziolka D, Gaspar LE, et al: The role of surgical resection in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline. *J Neurooncol* 96:33-43, 2010
10. Gaspar LE, Mehta MP, Patchell RA, et al: The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline. *J Neurooncol* 96:17-32, 2010
11. Elder JB, Nahed BV, Linskey ME, et al: Congress of Neurological Surgeons systematic review and evidence-based guidelines on the role of emerging and investigational therapies for the treatment of adults with metastatic brain tumors. *Neurosurgery* 84:E201-E203, 2019
12. Graber JJ, Cobbs CS, Olson JJ: Congress of Neurological Surgeons systematic review and evidence-based guidelines on the use of stereotactic radiosurgery in the treatment of adults with metastatic brain tumors. *Neurosurgery* 84:E168-E170, 2019
13. Olson JJ, Kalkanis SN, Ryken TC: Congress of Neurological Surgeons systematic review and evidence-based guidelines for the treatment of adults with metastatic brain tumors: Executive summary. *Neurosurgery* 84:550-552, 2019
14. Shiffman RN, Michel G, Rosenfeld RM, et al: Building better guidelines with BRIDGE-Wiz: Development and evaluation of a software assistant to promote clarity, transparency, and implementability. *J Am Med Inform Assoc* 19:94-101, 2012
15. Fuentes R, Osorio D, Exposito Hernandez J, et al: Surgery versus stereotactic radiotherapy for people with single or solitary brain metastasis. *Cochrane Database Syst Rev* 8:CD012086, 2018
16. Xin Y, Guo W, Yang CS, et al: Meta-analysis of whole-brain radiotherapy plus temozolomide compared with whole-brain radiotherapy for the treatment of brain metastases from non-small-cell lung cancer. *Cancer Med* 7:981-990, 2018
17. Akanda ZZ, Hong W, Nahavandi S, et al: Post-operative stereotactic radiosurgery following excision of brain metastases: A systematic review and meta-analysis. *Radiother Oncol* 142:27-35, 2020
18. Lehrer EJ, Peterson J, Brown PD, et al: Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data. *Radiother Oncol* 130:104-112, 2019
19. Lehrer EJ, Peterson JL, Zaorsky NG, et al: Single versus multifraction stereotactic radiosurgery for large brain metastases: An international meta-analysis of 24 trials. *Int J Radiat Oncol Biol Phys* 103:618-630, 2019
20. Dong K, Liang W, Zhao S, et al: EGFR-TKI plus brain radiotherapy versus EGFR-TKI alone in the management of EGFR-mutated NSCLC patients with brain metastases. *Transl Lung Cancer Res* 8:268-279, 2019
21. Zaorsky NG, Lehrer EJ, Kothari G, et al: Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): A meta-analysis of 28 studies. *Eur Urol Oncol* 2:515-523, 2019
22. Khan M, Lin J, Liao G, et al: SRS in combination with ipilimumab: A promising new dimension for treating melanoma brain metastases. *Technol Cancer Res Treat* 17:1533033818798792, 2018
23. Lu VM, Goyal A, Rovin RA, et al: Concurrent versus non-concurrent immune checkpoint inhibition with stereotactic radiosurgery for metastatic brain disease: A systematic review and meta-analysis. *J Neurooncol* 141:1-12, 2019
24. Petrelli F, De Stefani A, Trevisan F, et al: Combination of radiotherapy and immunotherapy for brain metastases: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 144:102830, 2019
25. Zhang Z, Guo H, Lu Y, et al: Anaplastic lymphoma kinase inhibitors in non-small cell lung cancer patients with brain metastases: A meta-analysis. *J Thorac Dis* 11:1397-1409, 2019
26. van Opijnen MP, Dirven L, Coremans IEM, et al: The impact of current treatment modalities on the outcomes of patients with melanoma brain metastases: A systematic review. *Int J Cancer* 146:1479-1489, 2020
27. Rulli E, Legramandi L, Salvati L, et al: The impact of targeted therapies and immunotherapy in melanoma brain metastases: A systematic review and meta-analysis. *Cancer* 125:3776-3789, 2019
28. Brown PD, Ballman KV, Cerhan JH, et al: Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCTG N107C/CEC.3): A multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 18:1049-1060, 2017
29. Kayama T, Sato S, Sakurada K, et al: Effects of surgery with salvage stereotactic radiosurgery versus surgery with whole-brain radiation therapy in patients with one to four brain metastases (JCOG0504): A phase III, noninferiority, randomized controlled trial. *J Clin Oncol* 36:3282-3289, 2018
30. Brown PD, Jaeckle K, Ballman KV, et al: Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: A randomized clinical trial. *JAMA* 316:401-409, 2016
31. Chang EL, Wefel JS, Hess KR, et al: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. *Lancet Oncol* 10:1037-1044, 2009
32. Kocher M, Soffietti R, Abacioglu U, et al: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 study. *J Clin Oncol* 29:134-141, 2011
33. Mulvenna P, Nankivell M, Barton R, et al: Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): Results from a phase 3, non-inferiority, randomised trial. *Lancet* 388:2004-2014, 2016
34. Kepka L, Tyc-Szczepaniak D, Bujko K, et al: Stereotactic radiotherapy of the tumor bed compared to whole brain radiotherapy after surgery of single brain metastasis: Results from a randomized trial. *Radiother Oncol* 121:217-224, 2016
35. Lim SH, Lee JY, Lee MY, et al: A randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small-cell lung cancer. *Ann Oncol* 26:762-768, 2015
36. Mahajan A, Ahmed S, McAleer MF, et al: Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: A single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol* 18:1040-1048, 2017
37. Brown PD, Gondi V, Pugh S, et al: Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: Phase III trial NRG Oncology CC001. *J Clin Oncol* 38:1019-1029, 2020

38. Hong AM, Fogarty GB, Dolven-Jacobsen K, et al: Adjuvant whole-brain radiation therapy compared with observation after local treatment of melanoma brain metastases: A multicenter, randomized phase III trial. *J Clin Oncol* 37:3132-3141, 2019
39. El-Hamamsy M, Elwakil H, Saad AS, et al: A randomized controlled open-label pilot study of simvastatin addition to whole-brain radiation therapy in patients with brain metastases. *Oncol Res* 24:521-528, 2016
40. Mehta MP, Shapiro WR, Phan SC, et al: Motexafin gadolinium combined with prompt whole brain radiotherapy prolongs time to neurologic progression in non-small-cell lung cancer patients with brain metastases: Results of a phase III trial. *Int J Radiat Oncol Biol Phys* 73:1069-1076, 2009
41. Rojas-Puentes LL, Gonzalez-Pinedo M, Crismatt A, et al: Phase II randomized, double-blind, placebo-controlled study of whole-brain irradiation with concomitant chloroquine for brain metastases. *Radiat Oncol* 8:209, 2013
42. Brown PD, Pugh S, Laack NN, et al: Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: A randomized, double-blind, placebo-controlled trial. *Neuro Oncol* 15:1429-1437, 2013
43. El Gantery MM, Abd El Baky HM, El Hossieny HA, et al: Management of brain metastases with stereotactic radiosurgery alone versus whole brain irradiation alone versus both. *Radiat Oncol* 9:116, 2014
44. Cao KI, Lebas N, Gerber S, et al: Phase II randomized study of whole-brain radiation therapy with or without concurrent temozolomide for brain metastases from breast cancer. *Ann Oncol* 26:89-94, 2015
45. Chua D, Krzakowski M, Chouaid C, et al: Whole-brain radiation therapy plus concomitant temozolomide for the treatment of brain metastases from non-small-cell lung cancer: A randomized, open-label phase II study. *Clin Lung Cancer* 11:176-181, 2010
46. Liu HP, Zheng KB, Wang JW: Efficacy and safety of temozolomide plus whole-brain radiotherapy in the treatment of intracranial metastases. *J Cancer Res Ther* 13:785-789, 2017
47. Lin NU, Eierman W, Greil R, et al: Randomized phase II study of lapatinib plus capecitabine or lapatinib plus topotecan for patients with HER2-positive breast cancer brain metastases. *J Neurooncol* 105:613-620, 2011
48. Quantin X, Bozonnet MC, Pujol JL: Recursive partitioning analysis groups II-III brain metastases of non-small cell lung cancer: A phase II randomized study comparing two concurrent chemoradiotherapy regimens. *J Thorac Oncol* 5:846-851, 2010
49. Neuhaus T, Ko Y, Muller RP, et al: A phase III trial of topotecan and whole brain radiation therapy for patients with CNS-metastases due to lung cancer. *Br J Cancer* 100:291-297, 2009
50. Gamboa-Vignolle C, Ferrari-Carballo T, Arrieta Ó, et al: Whole-brain irradiation with concomitant daily fixed-dose temozolomide for brain metastases treatment: A randomised phase II trial. *Radiother Oncol* 102:187-191, 2012
51. Cortes J, Dieras V, Ro J, et al: Afatinib alone or afatinib plus vinorelbine versus investigator's choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): A randomised, open-label, multicentre, phase 2 trial. *Lancet Oncol* 16:1700-1710, 2015
52. Chabot P, Hsia TC, Ryu JS, et al: Veliparib in combination with whole-brain radiation therapy for patients with brain metastases from non-small cell lung cancer: Results of a randomized, global, placebo-controlled study. *J Neurooncol* 131:105-115, 2017
53. Gupta A, Roberts C, Tysoe F, et al: RADVAN: A randomised phase 2 trial of WBRT plus vandetanib for melanoma brain metastases - results and lessons learnt. *Br J Cancer* 115:1193-1200, 2016
54. Lee SM, Lewanski CR, Counsell N, et al: Randomized trial of erlotinib plus whole-brain radiotherapy for NSCLC patients with multiple brain metastases. *J Natl Cancer Inst* 106:dju151, 2014
55. Pesce GA, Klingbiel D, Ribí K, et al: Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03). *Eur J Cancer* 48:377-384, 2012
56. Sperduto PW, Wang M, Robins HI, et al: A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys* 85:1312-1318, 2013
57. Yang JJ, Zhou C, Huang Y, et al: Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): A multicentre, phase 3, open-label, parallel, randomised controlled trial. *Lancet Respir Med* 5:707-716, 2017
58. Long GV, Atkinson V, Lo S, et al: Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: A multicentre randomised phase 2 study. *Lancet Oncol* 19:672-681, 2018
59. Lee DH, Han JY, Kim HT, et al: Primary chemotherapy for newly diagnosed nonsmall cell lung cancer patients with synchronous brain metastases compared with whole-brain radiotherapy administered first : Result of a randomized pilot study. *Cancer* 113:143-149, 2008
60. Besse B, Le Moulec S, Mazières J, et al: Bevacizumab in patients with nonsquamous non-small cell lung cancer and asymptomatic, untreated brain metastases (BRAIN): A nonrandomized, phase II study. *Clin Cancer Res* 21:1896-1903, 2015
61. Tawbi HA, Forsyth PA, Algazi A, et al: Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med* 379:722-730, 2018
62. Long GV, Trefzer U, Davies MA, et al: Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): A multicentre, open-label, phase 2 trial. *Lancet Oncol* 13:1087-1095, 2012
63. Gadgeel SM, Shaw AT, Govindan R, et al: Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non-small-cell lung cancer. *J Clin Oncol* 34:4079-4085, 2016
64. Goss G, Tsai CM, Shepherd FA, et al: CNS response to osimertinib in patients with T790M-positive advanced NSCLC: Pooled data from two phase II trials. *Ann Oncol* 29:687-693, 2018
65. Lin NU, Diéras V, Paul D, et al: Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res* 15:1452-1459, 2009
66. Margolin K, Ernstoff MS, Hamid O, et al: Ipilimumab in patients with melanoma and brain metastases: An open-label, phase 2 trial. *Lancet Oncol* 13:459-465, 2012
67. McArthur GA, Maio M, Arance A, et al: Vemurafenib in metastatic melanoma patients with brain metastases: An open-label, single-arm, phase 2, multicentre study. *Ann Oncol* 28:634-641, 2017
68. Yang JC, Ahn MJ, Kim DW, et al: Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. *J Clin Oncol* 35:1288-1296, 2017
69. Brem S, Meyers CA, Palmer G, et al: Preservation of neurocognitive function and local control of 1 to 3 brain metastases treated with surgery and carmustine wafers. *Cancer* 119:3830-3838, 2013
70. Minniti G, Paolini S, D'Andrea G, et al: Outcomes of postoperative stereotactic radiosurgery to the resection cavity versus stereotactic radiosurgery alone for melanoma brain metastases. *J Neurooncol* 132:455-462, 2017

71. Patel AJ, Suki D, Hatiboglu MA, et al: Impact of surgical methodology on the complication rate and functional outcome of patients with a single brain metastasis. *J Neurosurg* 122:1132-1143, 2015
72. Prabhu RS, Press RH, Patel KR, et al: Single-fraction stereotactic radiosurgery (SRS) alone versus surgical resection and SRS for large brain metastases: A multi-institutional analysis. *Int J Radiat Oncol Biol Phys* 99:459-467, 2017
73. Rades D, Kieckebusch S, Haatanen T, et al: Surgical resection followed by whole brain radiotherapy versus whole brain radiotherapy alone for single brain metastasis. *Int J Radiat Oncol Biol Phys* 70:1319-1324, 2008
74. Minniti G, Scaringi C, Lanzetta G, et al: Comparative effectiveness of multi-fraction stereotactic radiosurgery for surgically resected or intact large brain metastases from non-small-cell lung cancer (NSCLC). *Lung Cancer* 132:119-125, 2019
75. Frati A, Pesce A, Palmieri M, et al: Surgical treatment of the septuagenarian patients suffering from brain metastases: A large retrospective observational analytic cohort-comparison study. *World Neurosurg* 114:e565-e572, 2018
76. Byeon S, Ham JS, Sun JM, et al: Analysis of the benefit of sequential cranial radiotherapy in patients with EGFR mutant non-small cell lung cancer and brain metastasis. *Med Oncol* 33:97, 2016
77. Chen Y, Yang J, Li X, et al: First-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor alone or with whole-brain radiotherapy for brain metastases in patients with EGFR-mutated lung adenocarcinoma. *Cancer Sci* 107:1800-1805, 2016
78. Churilla TM, Chowdhury IH, Handorf E, et al: Comparison of local control of brain metastases with stereotactic radiosurgery vs surgical resection: A secondary analysis of a randomized clinical trial. *JAMA Oncol* 5:243-247, 2018
79. Choi CY, Chang SD, Gibbs IC, et al: Stereotactic radiosurgery of the postoperative resection cavity for brain metastases: Prospective evaluation of target margin on tumor control. *Int J Radiat Oncol Biol Phys* 84:336-342, 2012
80. Dobi A, Fodor E, Maraz A, et al: Boost irradiation integrated to whole brain radiotherapy in the management of brain metastases. *Pathol Oncol Res* 26:149-157, 2020
81. Halasz LM, Uno H, Hughes M, et al: Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. *Cancer* 122:2091-2100, 2016
82. Haque W, Verma V, Butler EB, et al: Utilization of stereotactic radiosurgery for renal cell carcinoma brain metastases. *Clin Genitourin Cancer* 16:e935-e943, 2018
83. Jiang T, Su C, Li X, et al: EGFR TKIs plus WBRT demonstrated No survival benefit other than that of TKIs alone in patients with NSCLC and EGFR mutation and brain metastases. *J Thorac Oncol* 11:1718-1728, 2016
84. Jiang W, Haque W, Verma V, et al: Stereotactic radiosurgery for brain metastases from newly diagnosed small cell lung cancer: Practice patterns and outcomes. *Acta Oncol* 58:491-498, 2019
85. Ke SB, Qiu H, Chen JM, et al: Therapeutic effect of first-line epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) combined with whole brain radiotherapy on patients with EGFR mutation-positive lung adenocarcinoma and brain metastases. *Curr Med Sci* 38:1062-1068, 2018
86. Mainwaring W, Bowers J, Pham N, et al: Stereotactic radiosurgery versus whole brain radiation therapy: A propensity score analysis and predictors of care for patients with brain metastases from breast cancer. *Clin Breast Cancer* 19:e343-e351, 2019
87. Minniti G, Scaringi C, Paolini S, et al: Single-fraction versus multifraction (3 × 9 Gy) stereotactic radiosurgery for large (>2 cm) brain metastases: A comparative analysis of local control and risk of radiation-induced brain necrosis. *Int J Radiat Oncol Biol Phys* 95:1142-1148, 2016
88. Rades D, Janssen S, Bajrovic A, et al: A matched-pair analysis comparing whole-brain radiotherapy with and without a stereotactic boost for intracerebral control and overall survival in patients with one to three cerebral metastases. *Radiat Oncol* 12:69, 2017
89. Rades D, Janssen S, Dziggel L, et al: A matched-pair study comparing whole-brain irradiation alone to radiosurgery or fractionated stereotactic radiotherapy alone in patients irradiated for up to three brain metastases. *BMC Cancer* 17:30, 2017
90. Robin TP, Jones BL, Amini A, et al: Radiosurgery alone is associated with favorable outcomes for brain metastases from small-cell lung cancer. *Lung Cancer* 120:88-90, 2018
91. Rydzewski NR, Khan AJ, Strauss JB, et al: Mortality after stereotactic radiosurgery for brain metastases and implications for optimal utilization: A national cancer database study. *Am J Clin Oncol* 41:1142-1147, 2018
92. Viani GA, Godoi da Silva LB, Viana BS, et al: Whole brain radiotherapy and stereotactic radiosurgery for patients with recursive partitioning analysis I and lesions <5 cm(3): A matched pair analysis. *J Cancer Res Ther* 12:770-774, 2016
93. Wegner RE, Hasan S, Williamson RW, et al: Management of brain metastases from large cell neuroendocrine carcinoma of the lung: Improved outcomes with radiosurgery. *Acta Oncol* 58:499-504, 2019
94. Zhu Q, Sun Y, Cui Y, et al: Clinical outcome of tyrosine kinase inhibitors alone or combined with radiotherapy for brain metastases from epidermal growth factor receptor (EGFR) mutant non small cell lung cancer (NSCLC). *Oncotarget* 8:13304-13311, 2017
95. Elaimy AL, Mackay AR, Lamoreaux WT, et al: Multimodality treatment of brain metastases: An institutional survival analysis of 275 patients. *World J Surg Oncol* 9:69, 2011
96. Renz P, Hasan S, Wegner RE: Survival outcomes after whole brain radiotherapy for brain metastases in older adults with newly diagnosed metastatic small cell carcinoma: A national cancer database (NCDB) analysis. *J Geriatr Oncol* 10:560-566, 2019
97. Jia F, Cheng X, Zeng H, et al: Clinical research on stereotactic radiosurgery combined with epidermal growth factor tyrosine kinase inhibitors in the treatment of brain metastasis of non-small cell lung cancer. *J Buon* 24:578-584, 2019
98. Lee JH, Chen HY, Hsu FM, et al: Cranial irradiation for patients with epidermal growth factor receptor (EGFR) mutant lung cancer who have brain metastases in the era of a new generation of EGFR inhibitors. *Oncologist* 24:e1417-e1425, 2019
99. Moraes FY, Winter J, Atenafu EG, et al: Outcomes following stereotactic radiosurgery for small to medium-sized brain metastases are exceptionally dependent upon tumor size and prescribed dose. *Neuro Oncol* 21:242-251, 2019
100. Ten Berge D, Aarts MJ, Hanssens PEJ, et al: Referral patterns and outcome of patients with synchronous brain metastases from non-small cell lung cancer treated with gamma knife radiosurgery in a third-line treatment centre in the Netherlands—A retrospective analysis. *Clin Oncol (R Coll Radiol)* 32:52-59, 2020
101. Li Z, Shen D, Zhang J, et al: Relationship between WBRT total dose, intracranial tumor control, and overall survival in NSCLC patients with brain metastases—A single-center retrospective analysis. *BMC Cancer* 19:1104, 2019
102. Lu F, Hou Y, Xia Y, et al: Survival and intracranial control outcomes of whole-brain radiotherapy (WBRT) alone versus WBRT plus a radiotherapy boost in non-small-cell lung cancer with brain metastases: A single-institution retrospective analysis. *Cancer Manag Res* 11:4255-4272, 2019
103. Susko MS, Garcia MA, Ma L, et al: Stereotactic radiosurgery to more than 10 brain metastases: Evidence to support the role of radiosurgery for ideal hippocampal sparing in the treatment of multiple brain metastases. *World Neurosurg* 135:e174-e180, 2020
104. Aiyama H, Yamamoto M, Kawabe T, et al: Complications after stereotactic radiosurgery for brain metastases: Incidences, correlating factors, treatments and outcomes. *Radiother Oncol* 129:364-369, 2018

105. Ali MA, Hirshman BR, Wilson B, et al: Survival patterns of 5750 stereotactic radiosurgery-treated patients with brain metastasis as a function of the number of lesions. *World Neurosurg* 107:944-951.e1, 2017
106. Atkins KM, Pashtan IM, Bussiere MR, et al: Proton stereotactic radiosurgery for brain metastases: A single-institution analysis of 370 patients. *Int J Radiat Oncol Biol Phys* 101:820-829, 2018
107. Brigell RH, Cagney DN, Martin AM, et al: Local control after brain-directed radiation in patients with cystic versus solid brain metastases. *J Neurooncol* 142:355-363, 2019
108. Buecker R, Hong ZY, Liu XM, et al: Risk factors to identify patients who may not benefit from whole brain irradiation for brain metastases—A single institution analysis. *Radiat Oncol* 14:41, 2019
109. Chan S, Rowbottom L, McDonald R, et al: Could time of whole brain radiotherapy delivery impact overall survival in patients with multiple brain metastases? *Ann Palliat Med* 5:267-279, 2016
110. Chang WS, Kim HY, Chang JW, et al: Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: Is stereotactic radiosurgery effective for multiple brain metastases? *J Neurosurg* 113:73-78, 2010 (suppl)
111. Cho KR, Lee MH, Kong DS, et al: Outcome of gamma knife radiosurgery for metastatic brain tumors derived from non-small cell lung cancer. *J Neurooncol* 125:331-338, 2015
112. Golanov AV, Banov SM, Il'yakov SR, et al: Overall survival and intracranial relapse in patients with brain metastases after gamma knife radiosurgery alone [in Russian]. *Zh Vopr Neurokhir Im N N Burdenko* 80:35-46, 2016
113. Hansen HC, Janssen S, Thieme C, et al: Whole-brain radiotherapy (WBRT) for brain metastases: Does the interval between imaging and treatment matter? *Anticancer Res* 38:6835-6840, 2018
114. Jeene PM, de Vries KC, van Nes JGH, et al: Survival after whole brain radiotherapy for brain metastases from lung cancer and breast cancer is poor in 6325 Dutch patients treated between 2000 and 2014. *Acta Oncol* 57:637-643, 2018
115. Koiso T, Yamamoto M, Kawabe T, et al: Follow-up results of brain metastasis patients undergoing repeat Gamma Knife radiosurgery. *J Neurosurg* 125:2-10, 2016
116. McTyre E, Ayala-Peacock D, Contessa J, et al: Multi-institutional competing risks analysis of distant brain failure and salvage patterns after upfront radiosurgery without whole brain radiotherapy for brain metastasis. *Ann Oncol* 29:497-503, 2018
117. McTyre ER, Johnson AG, Ruiz J, et al: Predictors of neurologic and nonneurologic death in patients with brain metastasis initially treated with upfront stereotactic radiosurgery without whole-brain radiation therapy. *Neuro Oncol* 19:558-566, 2017
118. Miller JA, Bennett EE, Xiao R, et al: Association between radiation necrosis and tumor biology after stereotactic radiosurgery for brain metastasis. *Int J Radiat Oncol Biol Phys* 96:1060-1069, 2016
119. Mohammadi AM, Schroeder JL, Angelov L, et al: Impact of the radiosurgery prescription dose on the local control of small (2 cm or smaller) brain metastases. *J Neurosurg* 126:735-743, 2017
120. Moraes FY, Winter J, Atenafu EG, et al: Outcomes following SRS for small- to medium-sized brain metastases are exceptionally dependent upon tumor size and prescribed dose. *Neuro Oncol* 21:242-251, 2018
121. Randolph DM, McTyre E, Klepin H, et al: Impact of radiosurgical management of geriatric patients with brain metastases: Clinical and quality of life outcomes. *J Radiosurg SBRT* 5:35-42, 2017
122. Shuto T, Akabane A, Yamamoto M, et al: Multiinstitutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases from non-small cell lung cancer (JLGK0901 study-NSCLC). *J Neurosurg* 129:86-94, 2018
123. Trifiletti DM, Lee CC, Kano H, et al: Stereotactic radiosurgery for brainstem metastases: An international cooperative study to define response and toxicity. *Int J Radiat Oncol Biol Phys* 96:280-288, 2016
124. Trifiletti DM, Hill C, Cohen-Inbar O, et al: Stereotactic radiosurgery for small brain metastases and implications regarding management with systemic therapy alone. *J Neurooncol* 134:289-296, 2017
125. Shi S, Sandhu N, Jin MC, et al: Stereotactic radiosurgery for resected brain metastases: Single-institutional experience of over 500 cavities. *Int J Radiat Oncol Biol Phys* 106:764-771, 2020
126. Hughes RT, Masters AH, McTyre ER, et al: Initial SRS for patients with 5 to 15 brain metastases: Results of a multi-institutional experience. *Int J Radiat Oncol Biol Phys* 104:1091-1098, 2019
127. Chen L, Douglass J, Kleinberg L, et al: Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 100:916-925, 2018
128. Deng X, Zheng Z, Lin B, et al: The efficacy and roles of combining temozolomide with whole brain radiotherapy in protection neurocognitive function and improvement quality of life of non-small-cell lung cancer patients with brain metastases. *BMC Cancer* 17:42, 2017
129. Iorgulescu JB, Harary M, Zogg CK, et al: Improved risk-adjusted survival for melanoma brain metastases in the era of checkpoint blockade immunotherapies: Results from a national cohort. *Cancer Immunol Res* 6:1039-1045, 2018
130. Moro-Sibilot D, Smit E, de Castro Carpeno J, et al: Non-small cell lung cancer patients with brain metastases treated with first-line platinum-doublet chemotherapy: Analysis from the European FRAME study. *Lung Cancer* 90:427-432, 2015
131. Yang RF, Yu B, Zhang RQ, et al: Bevacizumab and gefitinib enhanced whole-brain radiation therapy for brain metastases due to non-small-cell lung cancer. *Braz J Med Biol Res* 51:e6073, 2017
132. Gabani P, Fischer-Valuck BW, Johanns TM, et al: Stereotactic radiosurgery and immunotherapy in melanoma brain metastases: Patterns of care and treatment outcomes. *Radiother Oncol* 128:266-273, 2018
133. Juloori A, Miller JA, Parsai S, et al: Overall survival and response to radiation and targeted therapies among patients with renal cell carcinoma brain metastases. *J Neurosurg* 132:150-158, 2020
134. Sperduto PW, Deegan BJ, Li J, et al: Effect of targeted therapies on prognostic factors, patterns of care, and survival in patients with renal cell carcinoma and brain metastases. *Int J Radiat Oncol Biol Phys* 101:845-853, 2018
135. Zhang G, Zeng R, Wang K, et al: Clinical efficacy and safety evaluation of pemetrexed combined with radiotherapy in treatment of patients with lung adenocarcinoma brain metastasis. *Oncol Lett* 17:2874-2880, 2019
136. Kim JM, Miller JA, Kotecha R, et al: The risk of radiation necrosis following stereotactic radiosurgery with concurrent systemic therapies. *J Neurooncol* 133:357-368, 2017
137. Li B, Dai ZX, Chen YD, et al: Systemic therapy after radiotherapy significantly reduces the risk of mortality of patients with 1-3 brain metastases: A retrospective study of 250 patients. *Chin Med J (Engl)* 130:2916-2921, 2017
138. Shen CJ, Kummerlowe MN, Redmond KJ, et al: Stereotactic radiosurgery: Treatment of brain metastasis without interruption of systemic therapy. *Int J Radiat Oncol Biol Phys* 95:735-742, 2016

139. Taggar A, MacKenzie J, Li H, et al: Survival was significantly better with surgical/medical/radiation Co-interventions in a single-institution practice audit of frameless stereotactic radiosurgery. *Cureus* 8:e612, 2016
140. Jiang Y, Zhang J, Huang J, et al: Erlotinib versus gefitinib for brain metastases in asian patients with exon 19 EGFR-mutant lung adenocarcinoma: A retrospective, multicenter study. *BMC Pulm Med* 18:171, 2018
141. Jiang T, Zhang Y, Li X, et al: EGFR-TKIs plus bevacizumab demonstrated survival benefit than EGFR-TKIs alone in patients with EGFR-mutant NSCLC and multiple brain metastases. *Eur J Cancer* 121:98-108, 2019
142. Lanier CM, Hughes R, Ahmed T, et al: Immunotherapy is associated with improved survival and decreased neurologic death after SRS for brain metastases from lung and melanoma primaries. *Neurooncol Pract* 6:402-409, 2019
143. Yomo S, Serizawa T, Yamamoto M, et al: The impact of EGFR-TKI use on clinical outcomes of lung adenocarcinoma patients with brain metastases after gamma knife radiosurgery: A propensity score-matched analysis based on extended JLGK0901 dataset (JLGK0901-EGFR-TKI). *J Neurooncol* 145:151-157, 2019
144. Crinò L, Bronte G, Bidoli P, et al: Nivolumab and brain metastases in patients with advanced non-squamous non-small cell lung cancer. *Lung Cancer* 129: 35-40, 2019
145. Magnuson WJ, Lester-Coll NH, Wu AJ, et al: Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: A retrospective multi-institutional analysis. *J Clin Oncol* 35:1070-1077, 2017
146. Miyawaki E, Kenmotsu H, Mori K, et al: Optimal sequence of local and EGFR-TKI therapy for EGFR-mutant NSCLC with brain metastases stratified by number of brain metastases. *Int J Radiat Oncol Biol Phys* 104:604-613, 2019
147. Wang TJ, Saad S, Qureshi YH, et al: Outcomes of gamma knife radiosurgery, bi-modality & tri-modality treatment regimens for patients with one or multiple brain metastases: The Columbia University Medical Center experience. *J Neurooncol* 122:399-408, 2015
148. Sterne JAC, Savović J, Page MJ, et al: RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 366:l4898, 2019
149. Patchell RA, Tibbs PA, Walsh JW, et al: A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 322:494-500, 1990
150. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al: Treatment of single brain metastasis: Radiotherapy alone or combined with neurosurgery? *Ann Neurol* 33: 583-590, 1993
151. Mintz AH, Kestle J, Rathbone MP, et al: A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 78:1470-1476, 1996
152. Rahmathulla G, Recinos PF, Valerio JE, et al: Laser interstitial thermal therapy for focal cerebral radiation necrosis: A case report and literature review. *Stereotact Funct Neurosurg* 90:192-200, 2012
153. Sharma M, Balasubramanian S, Silva D, et al: Laser interstitial thermal therapy in the management of brain metastasis and radiation necrosis after radiotherapy: An overview. *Expert Rev Neurother* 16:223-232, 2016
154. Bastos DCA, Rao G, Oliva ICG, et al: Predictors of local control of brain metastasis treated with laser interstitial thermal therapy. *Neurosurgery* 87:112-122, 2020
155. Verger E, Gil M, Yaya R, et al: Temozolomide and concomitant whole brain radiotherapy in patients with brain metastases: A phase II randomized trial. *Int J Radiat Oncol Biol Phys* 61:185-191, 2005
156. Erickson AW, Brastianos PK, Das S: Assessment of effectiveness and safety of osimertinib for patients with intracranial metastatic disease: A systematic review and meta-analysis. *JAMA Netw Open* 3:e201617, 2020
157. Dai L, Luo CY, Hu GX, et al: Comparative analysis of first-line treatment regimens for advanced EGFR-mutant non-small cell lung cancer patients with stable brain metastases. *Ann Palliat Med* 9:2062-2071, 2020
158. Reungwetwattana T, Nakagawa K, Cho BC, et al: CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol* 36:3290-3297, 2018
159. Zhou C, Kim SW, Reungwetwattana T, et al: Alectinib versus crizotinib in untreated asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): A randomised phase 3 study. *Lancet Respir Med* 7:437-446, 2019
160. Gadgeel S, Peters S, Mok T, et al: Alectinib versus crizotinib in treatment-naïve anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann Oncol* 29:2214-2222, 2018
161. Kim DW, Tiseo M, Ahn MJ, et al: Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: A randomized, multicenter phase II trial. *J Clin Oncol* 35:2490-2498, 2017
162. Camidge DR, Kim DW, Tiseo M, et al: Exploratory analysis of brigatinib activity in patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer and brain metastases in two clinical trials. *J Clin Oncol* 36:2693-2701, 2018
163. Park K, Tan EH, O'Byrne K, et al: Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial. *Lancet Oncol* 17:577-589, 2016
164. Paz-Ares L, Tan EH, O'Byrne K, et al: Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: Overall survival data from the phase IIb LUX-Lung 7 trial. *Ann Oncol* 28:270-277, 2017
165. Edelman MJ, Belani CP, Socinski MA, et al: Outcomes associated with brain metastases in a three-arm phase III trial of gemcitabine-containing regimens versus paclitaxel plus carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol* 5:110-116, 2010
166. Gadgeel S, Rodríguez-Abreu D, Speranza G, et al: Updated analysis from KEYNOTE-189: Pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. *J Clin Oncol* 38:1505-1517, 2020
167. Kim DW, Mehra R, Tan DSW, et al: Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): Updated results from the multicentre, open-label, phase 1 trial. *Lancet Oncol* 17:452-463, 2016
168. Crino L, Ahn MJ, De Marinis F, et al: Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: Results from ASCEND-2. *J Clin Oncol* 34:2866-2873, 2016
169. Costa DB, Shaw AT, Ou SH, et al: Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. *J Clin Oncol* 33:1881-1888, 2015
170. Davies MA, Saiag P, Robert C, et al: Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): A multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol* 18:863-873, 2017
171. Seth R, Messersmith H, Kaur V, et al: Systemic therapy for melanoma: ASCO guideline. *J Clin Oncol* 38:3947-3970, 2020
172. Pasquali S, Hadjinicolaou AV, Chiarion Sileni V, et al: Systemic treatments for metastatic cutaneous melanoma. *Cochrane Database Syst Rev* 2:CD011123, 2018
173. Murthy RK, Loi S, Okines A, et al: Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med* 382:597-609, 2020

174. Cortes J, Rugo HS, Awada A, et al: Prolonged survival in patients with breast cancer and a history of brain metastases: Results of a preplanned subgroup analysis from the randomized phase III BEACON trial. *Breast Cancer Res Treat* 165:329-341, 2017
175. Krop IE, Lin NU, Blackwell K, et al: Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: A retrospective, exploratory analysis in EMILIA. *Ann Oncol* 26:113-119, 2015
176. Aoyama H, Shirato H, Tago M, et al: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. *JAMA* 295:2483-2491, 2006
177. Patchell RA, Tibbs PA, Regine WF, et al: Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial. *JAMA* 280:1485-1489, 1998
178. Andrews DW, Scott CB, Sperduto PW, et al: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. *Lancet* 363:1665-1672, 2004
179. Serizawa T, Yamamoto M, Higuchi Y, et al: Local tumor progression treated with gamma knife radiosurgery: Differences between patients with 2-4 versus 5-10 brain metastases based on an update of a multi-institutional prospective observational study (JLKG0901). *J Neurosurg* 132:1480-1489, 2019
180. Prabhu RS, Dhakal R, Vaslow ZK, et al: Preoperative radiosurgery for resected brain metastases: The PROPS-BM multicenter cohort study. *Int J Radiat Oncol Biol Phys* 111:764-772, 2021
181. Prabhu RS, Miller KR, Asher AL, et al: Preoperative stereotactic radiosurgery before planned resection of brain metastases: Updated analysis of efficacy and toxicity of a novel treatment paradigm. *J Neurosurg* 131:1658-1667, 2018
182. Patel KR, Burri SH, Asher AL, et al: Comparing preoperative with postoperative stereotactic radiosurgery for resectable brain metastases: A multi-institutional analysis. *Neurosurgery* 79:279-285, 2016
183. Fouad MN, Lee JY, Catalano PJ, et al: Enrollment of patients with lung and colorectal cancers onto clinical trials. *JCO Oncol Pract* 9:e40-e47, 2013
184. Go RS, Frisby KA, Lee JA, et al: Clinical trial accrual among new cancer patients at a community-based cancer center. *Cancer* 106:426-433, 2006
185. Rogers JL, Acquaye A, Vera E, et al: Provider-reported challenges and barriers to referring patients to neuro-oncology clinical trials: A report from the Society for Neuro-Oncology member survey. *Neurooncol Pract* 7:38-51, 2020
186. Gilligan T, Coyle N, Frankel RM, et al: Patient-clinician communication: American Society of Clinical Oncology consensus guideline. *J Clin Oncol* 35:3618-3632, 2017
187. American Cancer Society: Cancer Facts & Figures 2019. Atlanta, GA, American Cancer Society, 2019
188. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2016. Bethesda, MD, National Cancer Institute, 2019
189. Schnipper LE, Davidson NE, Wollins DS, et al: American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. *J Clin Oncol* 33:2563-2577, 2015
190. Streeter SB, Schwartzberg L, Husain N, et al: Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *JCO Oncol Pract* 7:46s-51s, 2011
191. Dusetzina SB, Winn AN, Abel GA, et al: Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *J Clin Oncol* 32:306-311, 2014
192. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: The cost of cancer care. *J Clin Oncol* 27:3868-3874, 2009
193. Lester-Coll NH, Dosoretz AP, Magnuson WJ, et al: Cost-effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for up to 10 brain metastases. *J Neurosurg* 125:18-25, 2016
194. Tran AD, Fogarty G, Nowak AK, et al: Cost-effectiveness of subsequent whole-brain radiotherapy or hippocampal-avoidant whole-brain radiotherapy versus stereotactic radiosurgery or surgery alone for treatment of melanoma brain metastases. *Appl Health Econ Health Policy* 18:679-687, 2020
195. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 35:96-112, 2017
196. Giordano SH, Temin S, Chandarlapaty S, et al: Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO clinical practice guideline update. *J Clin Oncol* 36:2736-2740, 2018
197. Hanna NH, Robinson AG, Temin S, et al: Therapy for stage IV non-small-cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. *J Clin Oncol* 39:1040-1091, 2021



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

Michael A. Vogelbaum

Stock and Other Ownership Interests: Infusion Therapeutics

Honoraria: Tocagen, Celgene, Cellinta, Plus Therapeutics

Research Funding: Celgene (Inst), OncoSynergy (Inst), Denovo Biopharma (Inst), Olympus (Inst)

Patents, Royalties, Other Intellectual Property: Patents for drug delivery devices for the brain

Paul D. Brown

Honoraria: UpToDate

Priscilla K. Brastianos

Honoraria: Pfizer

Consulting or Advisory Role: ElevateBio, Dantari Pharmaceuticals, SK Life Sciences, Pfizer, Voyager Therapeutics, Sintetica

Research Funding: Merck (Inst), Bristol Myers Squibb (Inst), Lilly (Inst), Mirati Therapeutics (Inst)

Stuart Burri

Employment: Southeast Radiation Oncology Group

Stock and Other Ownership Interests: Southeast Radiation Oncology Group, Radiation Oncology Centers of the Carolinas

Travel, Accommodations, Expenses: Novocure

Other Relationship: Novocure

Dan Cahill

Stock and Other Ownership Interests: Pyramid Biosciences

Consulting or Advisory Role: Lilly, Boston Pharmaceuticals, GlaxoSmithKline

Laurie E. Gaspar

Employment: Banner MD Anderson Colorado

Speakers' Bureau: Cancer Experts Now

Other Relationship: NCI

Open Payments Link: <https://openpaymentsdata.cms.gov/physician/275039/summary>

Na Tosha N. Gatson

Honoraria: Novocure

Consulting or Advisory Role: Novocure

Travel, Accommodations, Expenses: Novocure

Vinai Gondi

Honoraria: UpToDate

Justin T. Jordan

Stock and Other Ownership Interests: Navio Theragnostics

Consulting or Advisory Role: Guidepoint Global, ClearView Healthcare Partners, Recursion Pharmaceuticals, GLG, CereXis, Navio Theragnostics, Health2047, EMP Advisory,

Patents, Royalties, Other Intellectual Property: Textbook royalties

Expert Testimony: Medical Mutual Insurance of Maine

Other Relationship: Shepherd Therapeutics, Shepherd Foundation, Neurofibromatosis Network, American Academy of Neurology (AAN)

Andrew B. Lassman

Honoraria: Abbott Molecular

Consulting or Advisory Role: Karyopharm Therapeutics, Sapience Therapeutics, QED Therapeutics, FORMA Therapeutics, Bayer, Orbus Therapeutics, BioClinica, Novocure, Elsevier, Vivacitas Oncology

Research Funding: AbbVie (Inst), Novartis (Inst), Genentech/Roche (Inst), Aeterna Zentaris (Inst), Celldex (Inst), Kadmon (Inst), BeiGene (Inst), VBI Vaccines (Inst), Pfizer (Inst), Millennium (Inst), Oncoceutics (Inst), Karyopharm Therapeutics (Inst), Bayer (Inst), QED Therapeutics (Inst), Agios (Inst), Orbus Therapeutics (Inst), BMS (Inst), RTOG Foundation (Inst)

Patents, Royalties, Other Intellectual Property: Elsevier

Travel, Accommodations, Expenses: AbbVie, BioClinica, Abbott Molecular, FORMA Therapeutics, Karyopharm Therapeutics, QED Therapeutics, Bayer, Novartis, Pfizer, VBI Vaccines

Julia Maues

Honoraria: Pfizer, AstraZeneca

Consulting or Advisory Role: AstraZeneca

Nimish Mohile

Consulting or Advisory Role: Sapience Therapeutics

Research Funding: Vascular Biogenics, Boston Biomedical, Quell, Tocagen

Erik Sulman

Honoraria: Merck Sharp & Dohme, Novocure, Zai Lab

Consulting or Advisory Role: Merck Sharp & Dohme, Novocure

Research Funding: Novocure (Inst)

Travel, Accommodations, Expenses: Merck Sharp & Dohme, Novocure, Brainlab, PER, Zai Lab

Martin van den Bent

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.

Employment: AstraZeneca (I)

Consulting or Advisory Role: AbbVie, Bristol Myers Squibb, Celgene, Agios, Boehringer Ingelheim, Bayer, Carthera, Genenta Science, Nerviano Medical Sciences, Boston Pharmaceuticals

Research Funding: AbbVie (Inst)

Jeffrey S. Weinberg

Consulting or Advisory Role: OsteoMed

David Schiff

Consulting or Advisory Role: Orbus Therapeutics, GlaxoSmithKline, PRA, AstraZeneca

Research Funding: Bayer (Inst)

No other potential conflicts of interest were reported.

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)

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