Public Comment Draft

Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline

Task Force Members' Disclosure Statements

All task force members' disclosure statements were reviewed before being invited and were shared with other task force members throughout the guideline's development. Those disclosures are published within this guideline. Where potential conflicts were detected, remedial measures to address them were taken.

Table of Contents

Preamble

As the leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy — ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Appendix 1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members — ASTRO strives to avoid bias by selecting a multidisciplinary group of experts with variation in geographic region, gender, ethnicity, race, practice setting, and areas of expertise. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology — ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Appendix 2 for a list of abbreviations used in the guideline.

Consensus Development — Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree". A prespecified threshold of ≥75% (≥90% for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates — Guidelines are evaluated annually beginning 2 years after publication for new potentially practice-changing studies that could result in a guideline update. In addition, the Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE, individual study quality, and panel consensus, all of which inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

*A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

1. Introduction

Brain metastases develop in up to 20% to 40% of cancer patients and can have a significant impact on patient survivorship because of the detrimental effects on neurocognitive function, neurologic symptoms, and survival.[3,4] This evidence review and guideline updates previous ASTRO guidance[3] to reflect recent developments in the management of patients with brain metastases, including advanced radiation therapy (RT) techniques such as stereotactic radiosurgery (SRS) and hippocampal avoidance whole brain radiation therapy (HA-WBRT) to reduce side effects of RT; emerging central nervous system (CNS)-active systemic therapies such as targeted therapies and immunotherapy as alternatives or adjuncts to RT; and, more detailed tools to estimate patient survival such as the graded prognostic assessment.[4-7] Accounting for multiple tumor- and patient-related factors requires a patient-centered decision-making process by a multidisciplinary team.

In 2019, the American Society of Clinical Oncology (ASCO), Society for Neuro-Oncology (SNO), and ASTRO initiated a systematic review to develop a brain metastases guideline to better inform clinical practice.(*ref when published*) In conjunction with this collaborative effort, ASTRO commissioned a task force to formulate and review clinical key questions (KQs) specific to radiation oncology practice.

2. Methods

2.1. Task Force Composition

The task force consisted of a multidisciplinary team of radiation, medical, and neurosurgical oncologists; a radiation oncology resident; a medical physicist; and a patient representative. This guideline was developed in collaboration with the American Association of Neurological Surgeons/Congress of Neurological Surgeons, ASCO, and SNO, who provided representatives and peer reviewers.

2.2. Document Review and Approval

The guideline was reviewed by 20 official peer reviewers (Appendix 1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment in September 2021. The final guideline was approved by the ASTRO Board of Directors and endorsed by the TBD.

2.3. Evidence Review

In June 2019, ASTRO submitted a proposal for the Agency for Healthcare Research and Quality (AHRQ) to develop a comparative effectiveness evidence review on RT for brain metastases, which was accepted and funded by the Patient-Centered Outcomes Research Institute (PCORI).[8,9] This review aimed to support a replacement of the prior ASTRO brain metastases guideline.[3] AHRQ performed a systematic search of the databases Ovid MEDLINE, EMBASE, Web of Science, Scopus, CINAHL, clinicaltrials.gov, and published guidelines, through July 2020. The inclusion criteria incorporated randomized controlled trials (RCTs) and large observational studies (for safety assessments), evaluating WBRT and SRS alone or in combination, as initial or postoperative treatment, with or without systemic therapy for adults with brain metastases due to lung cancer. For KQ1, small cell lung cancer, for which prophylactic cranial irradiation historically was the treatment paradigm, was excluded from the RCTs evaluated.[10] For KQ4 addressing the risks of symptomatic radionecrosis, the eligible study design was expanded to also include nonrandomized studies to consider rare adverse events that are difficult to detect in smaller and short-term trials. In total, 97 studies were included for data abstraction. For details on the AHRQ methodology and systematic review explanation, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the number of articles screened, excluded, and included in the evidence review, see Appendix A of the AHRQ systematic review report.[8]

AHRQ methodology required specific criteria to include studies and perform a comparative effectiveness evidence review. As a result, the AHRQ methodology generated conclusions deemed to be incongruent with clinical practice. As an example, the lack of uniform testing, analysis, and reporting of neurocognitive and patient-reported outcomes in prospective clinical trials precluded a comparative effectiveness review of this important endpoint in brain metastasis management. Therefore, in the generation of this guideline, the task force evaluated outcomes (eg, neurocognitive function, quality of life (QoL)) of studies that were part of the systematic review but were excluded by AHRQ's methodology. In addition, the task force extended the literature end date to September 2020 to allow for the inclusion of the HyTEC report on dose-volume tolerances of the brain, given its relevance to KQ4.[11] Lastly, because the AHRQ systematic review lacked evidence related to radionecrosis, an additional literature search was performed for KQ4 from 1998 through September 2020 using the search terms: *radiation necrosis, radionecrosis, SRS, stereotactic radiosurgery, fSRS, FSRT*, and *brain metastases*. This resulted in the inclusion of 6 additional studies for review with 3 of them ultimately included in the evidence table.

The data used by the task force to formulate recommendations are summarized in evidence tables available in the supplementary materials. References selected and published in this document are

representative and not all-inclusive. Additional ancillary references are included in the text but were not used to support the recommendations. The outcomes of interest are listed in Table 2.

2.4. Scope of the Guideline

This guideline covers only the subjects specified in the KQs (Table 2). The scope is limited to the radiotherapeutic management of intact (ie, unresected) and resected brain metastases. It provides guidance on the reasonable use of modern RT strategies, including single-fraction and fractionated SRS and HA-WBRT, and discusses clinical considerations in selecting the optimal RT strategy or in deferring RT in favor of best supportive care or close neuro-oncologic surveillance. Outside the scope of this guideline are many other important questions that may be subjects of other guidelines, including the appropriate role for CNS-active systemic therapies and/or surgical intervention. These topics are discussed extensively in the ASCO/SNO/ASTRO Brain Metastases Guidelines (ref-when published).

Table 2 KQs in Population, Intervention, Comparator, Outcome (PICO) format

KQ	Population	Intervention	Comparator	Outcomes
1	**What are the indications for SRS alone for patients with intact brain metastases?**			
	Patients with intact brain metastases	• Observation • WBRT	SRS	• Intracranial control • Progression-free survival • Overall survival • Neurocognitive function • Patient-reported outcomes
2	**What are the indications for observation, preoperative SRS, or postoperative SRS or WBRT in patients with resected brain metastases?**			
	Patients with resected brain metastases	• Observation • WBRT	SRS	• Intracranial control • Progression-free survival • Overall survival • Neurocognitive function • Patient-reported outcomes
3	**What are the indications for WBRT for patients with intact brain metastases?**			
	Patients with intact brain metastases	• Observation • SRS	• Conventional WBRT • HA-WBRT • HA-WBRT plus memantine	• Intracranial control • Progression-free survival • Overall survival • Neurocognitive function • Patient-reported outcomes
4	**What are the risks of symptomatic radionecrosis with WBRT and/or SRS for patients with brain metastases?**			
	Patients with brain metastases	WBRT	SRS	• Symptomatic radionecrosis • Other adverse effects

Abbreviations: HA-WBRT = hippocampal avoidance whole brain radiation therapy KQ = key questions; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

3. Key Questions and Recommendations

3.1. KQ1: Indications for SRS alone for patients with intact brain metastases (Table 3)

See evidence tables in Supplementary Materials for the data supporting the recommendations for KQ1.

What are the indications for SRS alone for patients with intact brain metastases?

Table 3 Indications for SRS alone for intact brain metastases

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with an ECOG performance status of 0 to 2 (KPS 70 to 100) and up to 4 intact brain metastases, SRS is recommended.	Strong	High [12-17]
2. For patients with an ECOG performance status of 0 to 2 (KPS 70 to 100) and 5 to 10 intact brain metastases, SRS is conditionally recommended.	Conditional	Low [18-20]
3. For patients with intact brain metastases measuring <2 cm in diameter, single-fraction SRS with a dose of 2000 to 2400 cGy is recommended. Implementation remarks: • Multifraction regimens may be an acceptable option using 2700 cGy in 3 fractions or 3000 cGy in 5 fractions (see KQ4). • A lower dose prescription should be considered for adjacent critical structures (eg, brain stem, optic apparatus).	Strong	Moderate [12,15,18,21,22]
4. For patients with intact brain metastases measuring ≥2 cm to <3 cm in diameter, single-fraction SRS using 1800 cGy or multifraction SRS is conditionally recommended. Implementation remarks: • Multifraction regimens may be an acceptable option using 2700 cGy in 3 fractions or 3000 cGy in 5 fractions (see KQ4). • A lower dose prescription should be considered for adjacent critical structures (eg, brain stem, optic apparatus).	Conditional	Low [22-24]
5. For patients with intact brain metastases measuring ≥3 cm to 4 cm in diameter, multifraction SRS is conditionally recommended. Implementation remarks:	Conditional	Low [23,24]

• Multifraction regimens may be an acceptable option using 2700 cGy in 3 fractions or 3000 cGy in 5 fractions. • 1500 cGy single-fraction SRS may also be used (see KQ4). • Surgery should be considered for tumors exerting mass effect. • A lower dose prescription should be considered for adjacent critical structures (eg, brain stem, optic apparatus).		
6. For patients with intact brain metastases measuring >4 cm in diameter, multifraction radiation therapy is recommended. Implementation remarks: • Given limited evidence, SRS for tumor size >6 cm is discouraged. • Surgery should be considered for tumors >4 cm and/or exerting mass effect.	Strong	Low [18,22-24]
7. For patients with *symptomatic* brain metastases who are candidates for local therapy and CNS-active systemic therapy, upfront local therapy is recommended.	Strong	Low [25,26]
8. For patients with *asymptomatic* brain metastases eligible for CNS-active systemic therapy, multidisciplinary and patient-centered decision making is conditionally recommended to determine whether local therapy may be safely deferred. Implementation remark: The decision to defer local therapy should consider factors such as brain metastasis size, parenchymal brain location, number of metastases, likelihood of response to specific systemic therapy, access to close neuro-oncologic surveillance, and availability of salvage therapies.	Conditional	Expert Opinion

Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky performance status; KQ = key question; SRS = stereotactic radiosurgery.
Note: Local therapy is defined as brain metastasis-directed radiation therapy and/or surgery.

Progression of intracranial metastases can lead to neurologic morbidity and death. WBRT remained the standard of care for decades, but the development of SRS allowed treatment of limited brain metastases alone, often in a single fraction, while largely sparing surrounding brain. Initially, neither the risks of omitting treatment of grossly uninvolved brain nor the exact benefits of sparing normal brain were known. Three RCTs

compared SRS alone to SRS plus WBRT,[17,21,27] and 2 RCTs compared local therapy alone (SRS or surgery) to local therapy plus WBRT.[12,28] All 5 trials included only patients with 1 to 3 brain metastases (1 trial allowed up to 4) and a performance status of Karnofsky performance status (KPS) ≥70 or ECOG 0-2. In aggregate, they demonstrated that while adding WBRT to SRS or surgery improves intracranial control, neither improved survival. Two RCTs found worse performance on the recall portion of the Hopkins Verbal Learning Test Revised at 4 months in their respective WBRT arms,[17,28] while N0574, the study with the most robust assessment of neurocognition and QoL, found worse neurocognitive deterioration and QoL following SRS plus WBRT compared to SRS alone.[21] One additional RCT randomized patients with 1 to 3 brain metastases to SRS versus WBRT versus SRS plus WBRT.[13] This study, although limited by its size (n=60), also found better local control and worse neurocognitive deterioration with SRS plus WBRT compared to SRS alone, and no difference in overall survival. As WBRT offers no survival benefit over SRS and worse neurocognitive outcomes, SRS for patients with up to 4 intact brain metastases and reasonable performance status is recommended.

Despite the strong evidence supporting the use of SRS for patients with 1 to 4 intact brain metastases, optimal treatment for patients with 5 or more metastases remains controversial because of the lack of published prospectively randomized data in this patient population. A prospective observational study in patients with 1 to 10 brain metastases and cumulative brain metastasis volume of 15 cc or less treated with SRS (JLGK0901) demonstrated noninferiority in the post-SRS survival time in patients with 5 to 10 brain metastases when compared to those with 2 to 4 metastases.[18] Additionally, there was no difference in the incidence of neurologic death, deterioration of neurologic function, local recurrence, new lesion appearance, salvage treatment (repeat SRS and WBRT), Mini-Mental State Examination (MMSE) scores, and adverse events observed between these 2 cohorts.[18] Subsequent long-term or subgroup analyses of the trial confirmed long-term validity of these results in terms of the local control,[29] MMSE and treatment-related complications,[30] as well as validation in elderly patients,[31] and patients with non-small cell lung cancer (NSCLC),[32] including those who received EGFR inhibitors.[33] Based on this prospective comparative registry trial, the task force conditionally recommends SRS to patients with 5 to 10 intact brain metastases who have a performance status of ECOG 2 or better. Additional evidence to support this recommendation came from a large retrospective study analyzing over 2000 patients from 8 institutions that demonstrated similar overall survival in patients with 2 to 4 versus 5 to 15 brain metastases.[19] Of note, despite the inclusion of patients with 11 to 15 brain metastases in this retrospective study, extending the conditional recommendation of SRS to patients with 11 to 15 brain metastases is not recommended because only 10 patients in this study had 11 to 15 brain metastases (versus 190 patients with 5-10 brain metastases and 882 patients with 2-4). Furthermore, another large Japanese retrospective study comparing patients with 5 to 15 versus 2 to 4 brain metastases showed a shorter post-SRS survival time in the subgroup with 5 to 15 brain metastases with increased need for salvage

WBRT, raising the possibility that the worse survival in these patients could be driven by the subgroup of patients with 11 to 15 brain metastases.[20] A phase III RCT comparing SRS versus WBRT in patients with 5 to 15 intact brain metastases *(NCT01592968)* has completed, and the final report had not yet been published when this guideline was developed. In addition, the ongoing trial CCTG CE.7 *(NCT03550391)* compares the neurocognitive effects of SRS to HA-WBRT plus memantine, which impacts neurocognition less than traditional WBRT and was not comparatively tested to SRS in these prior trials (see KQ3).

While the recommendation of SRS for patients with intact brain metastases is driven largely by the number of brain metastases, it is critical that other tumor- or patient-related factors, such as tumor size/volume, location, total tumor volume, brain metastasis velocity,[34-36] access to magnetic resonance imaging (MRI) surveillance and subsequent SRS, histology, age, extracranial disease status, molecular profile, systemic treatment options, performance status, prognosis, and baseline neurocognitive function, should be taken into consideration in the patient-centered decision-making process by the multidisciplinary team. In addition, for SRS to be utilized in the treatment of brain metastases which are often small targets, the SRS system must have high-resolution imaging for planning, appropriate immobilization, accurate dosimetry, precise image guidance and localization, and robust quality assurance. Given the higher risk of intracranial relapse because of the emergence of distant brain metastases, for SRS to be utilized in the absence of WBRT requires close radiographic surveillance (eg, Brain MRI every 2-3 months for 1-2 years, then every 4-6 months indefinitely).

There are no published prospective randomized trials or prospective controlled comparative studies evaluating clinical outcomes according to SRS dose and fractionation. The Radiation Therapy Oncology Group (RTOG) phase 1 dose escalation study RTOG 90-05 set the standard for single-fraction SRS for intact brain metastases ≤4 cm in maximum diameter, with the maximum tolerated dose found to be 2400 cGy, 1800 cGy, and 1500 cGy for metastasis of maximum diameter ≤2 cm, 2.1 to 3 cm, and 3.1 to 4 cm, respectively (all patients treated with prior focal or WBRT).[37] Subsequently, prospective trials including single-fraction SRS have used doses of 2000 to 2400 cGy for metastases ≤2 cm in diameter or <4 cc volume.[5,12,18,27] Large retrospective cohort studies have demonstrated excellent local control for tumors ≤2 cm treated with 2400 cGy single-fraction SRS alone.[22] However, metastases ≥2 cm treated with single-fraction SRS doses of 1500 to 1800 cGy have been associated with poor local control.[22] For metastases of this size, one study compared 1500 to 1800 cGy single-fraction SRS (median size 8.8 cc) with 2700 cGy in 3 fractions SRS (median size 12.5 cc) and demonstrated that multifraction SRS was associated with significantly higher local tumor control and lower rates of radionecrosis.[23] The benefit of multifraction SRS was most pronounced for tumor sizes >3 cm, which demonstrated the highest rates of local failure and radionecrosis when treated with single-fraction SRS. Multiple small retrospective cohort series using a variety of dose-fractionation regimens have likewise demonstrated similar or improved rates of local tumor control and reduced incidence of radionecrosis with

multifraction SRS as compared with single-fraction SRS for metastases >2 cm.[23,38] Based on these data, single-fraction SRS with a dose of 2000 to 2400 cGy is recommended for metastases <2 cm, either single-fraction or multifraction SRS are conditionally recommended for metastases 2.0 to 2.9 cm, and multifraction SRS for metastases ≥3 cm to 4 cm in diameter are conditionally recommended. Examples of acceptable multifraction regimens may include 2700 cGy in 3 fractions or 3000 cGy in 5 fractions for intact metastases. Fractionation regimens of 3500 cGy in 5 fractions have been prospectively evaluated as well.[39] When different fractionation regimens are considered, a BED_{10} ≥5000 cGy has been associated with improved local tumor control by a multi-institutional retrospective analysis using a variety of multifraction SRS regimens.[24] Metastases with maximum diameter ≥4 cm have been excluded from prospective studies testing single-fraction SRS, therefore multifraction SRS is recommended for treatment of these large intact lesions that are otherwise not amenable to surgical resection. An upper size limit for metastases eligible for multifraction SRS has not been defined in the literature. Due to limited evidence, SRS for tumor size >6 cm is discouraged.[40]

Systemic Therapy

There is no randomized evidence to guide the decision for upfront versus delayed RT for patients with brain metastases who are candidates for immunotherapy or CNS-active targeted therapies. Multidisciplinary assessment and patient-centered decision making are essential to optimally select patients in whom local therapy (ie, brain metastasis-directed RT and/or surgery) for brain metastases may be safely and appropriately delayed. In the absence of randomized data, the long-term CNS disease control, neurologic morbidity, neurologic mortality, neurocognitive and QoL outcomes following primary systemic therapy (with deferral of local therapy until progression) are unknown. While genomic advancements continue to redefine the patient- and disease-subsets for whom CNS-active systemic therapies may be considered in the management of CNS metastases, these guidelines apply to a subset of patients with melanoma, NSCLC, and breast cancer brain metastases, in whom immunotherapy (ie, anti-PD-1 and anti-CTLA4 checkpoint inhibitors) and CNS-active therapies targeting BRAF, EGFR, HER2, ALK and ROS1 have been prospectively assessed. (Refer to the ASCO/SNO/ASTRO Brain Metastases Guidelines for additional information (ref-when publishes)). Decision-making for future, yet undefined genomic patient subsets with CNS-active systemic treatment options may similarly employ the principles outlined in these guidelines.[25,26,41-46]

The majority of studies assessing the benefit of primary immunotherapy or CNS-active targeted therapies for brain metastases excluded patients with neurologic symptoms or steroid requirement. For patients with symptomatic brain metastases who are candidates for immunotherapy or CNS-active targeted therapy, based on eligibility and clinical context upfront local therapy (radiation and/or surgery) is recommended because studies of immunotherapy and CNS-active targeted therapy have demonstrated limited response rates and/or limited durability of radiographic stability.[25,26]

Selection of asymptomatic patients for primary immunotherapy or CNS-active targeted therapy and delay of local therapy should incorporate factors including brain metastasis size, location, and number; expected response rates and durability with systemic therapy; access to close neuro-oncologic surveillance; relative pace and burden of extracranial systemic disease; and facilities capable of delivering appropriate local salvage therapies (RT and/or surgery). Among phase II-III studies of systemic therapy with deferred RT with available data, the majority of patients had ≤4 brain metastases, and most commonly ≤2 lesions of limited size <2 cm.[25,41,42,44]Additionally , because up to 40% of patients will demonstrate early progression without any response, the eloquence of the involved brain regions (eg, precentral gyrus) and thereby potential for symptomatic progression should be carefully considered when deferring local therapy.[25,41] To facilitate determination of eloquence of involved brain regions, multidisciplinary review of neuro-imaging with neuro-radiology is encouraged. Single-arm, phase II and randomized phase III trials demonstrate response rates to primary immunotherapy and CNS-active targeted therapies ranging from approximately 30% to 75%, superior to systemic agents with suboptimal CNS activity, but not directly compared to SRS in any randomized trials.[25,26,41-46] The wide range of CNS response rates with various agents also underscores the lack of criteria for what constitutes a "CNS-active" agent and the absence of accepted thresholds for deferring local therapy in a given setting.[47] Because a predominant reported failure pattern is local progression in pre-existing brain metastases,[25,41] many patients who receive upfront systemic therapy will require local therapy,[48] and retrospective studies have suggested benefits to incorporating local therapy with both targeted and immunotherapy agents.[49] Future prospective studies are needed to assess the optimal combination of local therapy with the evolving landscape of systemic therapies to maximize CNS-tumor control and patient survival.

3.2. KQ2: Indications for observation, preoperative SRS, or postoperative SRS WBRT in patients with resected brain metastases (Table 4)

See evidence tables in Supplementary Materials for the data supporting the recommendations for KQ2.

What are the indications for observation, preoperative SRS, or postoperative SRS or WBRT in patients with resected brain metastases?

Table 4 Indications for observation, postoperative SRS, WBRT, or preoperative SRS

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with resected brain metastases, radiation therapy (SRS or WBRT) is recommended to improve intracranial disease control.	Strong	High 12,50,51

2. For patients with resected brain metastases and limited additional brain metastases, SRS is recommended over WBRT to preserve neurocognitive function and patient-reported QoL.	Strong	Moderate [52]
3. For patients whose brain metastasis is planned for resection, preoperative SRS is conditionally recommended as a potential alternative to postoperative SRS.	Conditional	Low [53,54]

Abbreviations: KQ = key question; SRS = stereotactic radiosurgery; QoL = quality of life; WBRT = whole brain radiation therapy.

RT is indicated for all patients following resection of brain metastases. Modern prospective series report local recurrence in the resection cavity with surgery alone of at least 50%.[12,50] Historically, WBRT was routinely used following resection; multiple RCTs demonstrated a reduction in risk of local failure, distant intracranial failure, and neurologic death compared to surgery alone.[12,51,55] Although WBRT is effective in promoting CNS disease control, the management of brain metastases has evolved to favor the delivery of focal therapies, where possible, to reduce the risk of neurocognitive toxicities associated with WBRT. As compared to WBRT, focal therapies (such as postoperative SRS or salvage SRS for recurrences in the surgical bed) have been associated with longer neurocognitive deterioration-free survival[52] and lower overall risk of neurocognitive dysfunction.[56] This has led to the expansion in the use of postoperative SRS.

Two prospective trials evaluated the role of single-fraction postoperative SRS to the surgical cavity in patients with limited metastatic disease in the brain. The first evaluated postoperative SRS versus observation and showed a significant improvement in surgical bed control in the SRS group (72% versus 43% at 12 months).[50] The other study randomized patients with resected brain metastases to postoperative SRS versus WBRT.[52] This trial showed inferior surgical bed control for SRS versus WBRT, but similar overall survival and significantly less neurocognitive decline with SRS. Thus, with equivalent survival and reduced neurocognitive toxicity, postoperative SRS has become the preferred treatment modality for appropriately selected patients with surgically-resected brain metastases and limited metastatic disease in the brain.

The shift from postoperative WBRT to tumor cavity focal therapy has led to the observation of a unique form of local recurrence – nodular meningeal disease. Surgical perturbation of the tumor can lead to the risk of tumor spillage via the cerebrospinal fluid and the development of nodular tumor recurrence outside the resection cavity. This nodular meningeal disease has been reported as high as a 1-year Kaplan-Meier estimated risk of 28% in patients treated with postoperative cavity SRS,[50] and those who develop nodular meningeal recurrence may experience poor survival outcomes with up to three-quarters having a neurologic death.[57,58] Preoperative SRS is under investigation as a potential strategy to mitigate the risk of surgical perturbation failure and resultant nodular meningeal disease. A retrospective comparative analysis of preoperative versus postoperative SRS reported a reduction in nodular meningeal disease from 16.6% (postoperative) to 3.2% (preoperative), in addition to lower rates of radionecrosis.[59]

Multifraction postoperative SRS is also being investigated *(NCT04114981)* in hopes of improving local control and reducing rates of radionecrosis in comparison to postoperative single-fraction SRS. Data supporting preoperative SRS and multifraction postoperative SRS are currently limited to nonrandomized studies.[59-63] Ongoing and developing trials are evaluating the timing and dose-fractionation regimens for SRS in patients who require surgical resection of brain metastases. Current single-fraction SRS dosing guidance is from a randomized trial of single-fraction postoperative SRS versus WBRT (N107C/CEC.3) and supported by existing literature (Table 5).[52]

Table 5. Recommended postoperative cavity single-fraction SRS dosing guidance[52]

Cavity volume (cc)*	Single-fraction SRS dose (cGy)
<4.2 cc	2000 cGy
≥4.2 to <8.0 cc	1800 cGy
≥8.0 to <14.4 cc	1700 cGy
≥14.4 to <20 cc	1500 cGy
≥20 to <30 cc	1400 cGy
≥30 cc to <5 cm max	1200 cGy

Abbreviation: SRS = stereotactic radiosurgery
*Given the irregular shape of surgical cavities, the total prescribed dose should be based on the surgical cavity volume with a maximum cross-sectional diameter of <5.0 cm.

3.3. KQ3: Indications for WBRT in patients with intact brain metastases (Table 6)

See evidence tables in Supplementary Materials for the data supporting the recommendations for KQ3 and Figure 1 and Figure 2.

What are the indications for WBRT in patients with intact brain metastases?

Table 6 Indications for WBRT for intact brain metastases

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with favorable prognosis and brain metastases ineligible for surgery and/or SRS, WBRT is recommended as primary treatment. Implementation remarks: • Prognosis should be estimated using a validated brain metastases prognostic index. • Recommended dose for WBRT is 3000 cGy in 10 fractions. • Multidisciplinary and patient-centered decision making should be used to determine whether WBRT may be safely deferred	Strong	High 64-67

for asymptomatic brain metastases eligible for CNS-active systemic therapy.		
2. For patients with brain metastases and favorable prognosis receiving WBRT, hippocampal avoidance is recommended. Implementation remarks: • Hippocampal avoidance is not appropriate in cases of brain metastases in close proximity to the hippocampi or in cases of leptomeningeal disease. • Simultaneous in-field boost of metastases or sequential SRS combined with hippocampal avoidance may be considered.	Strong	High 4,68-70
3. For patients with brain metastases and favorable prognosis receiving WBRT or hippocampal avoidance WBRT, addition of memantine is recommended.	Strong	Low 71
4. For patients with favorable prognosis and limited brain metastases, routine adjuvant WBRT added to SRS is **not** recommended. Implementation remarks • To maximize intra-cranial control and/or when close imaging surveillance with additional salvage therapy is not feasible, adjuvant WBRT may be offered in addition to SRS. • If offered, the recommended dose for adjuvant WBRT is 3000 cGy in 10 fractions. See recommendations 2 and 3 in KQ3 for neuroprotective strategies of hippocampal avoidance and memantine.	Strong	High 15,16,72
5. For patients with brain metastases and poor prognosis, early introduction of palliative care for symptom management and caregiver support are recommended. Implementation remarks: • Supportive care only (with omission of WBRT) should be considered. • If WBRT is utilized, brief schedules (eg, 5 fractions) are preferred.	Strong	Moderate 73,74

Abbreviations: KQ = key question; SRS = stereotactic radiosurgery (refers to both single- and multi-fraction stereotactic radiation treatments); WBRT = whole brain radiation therapy; CNS = central nervous system

Based upon numerous phase III and other trials evaluating various dose-fractionation regimens, WBRT is recommended as primary treatment for patients ineligible for surgery and/or SRS.[64,65,75-77] Since patients with brain metastases can have variable prognoses, a validated brain metastases prognostic index should be used to estimate the benefit of WBRT.[7,78] Based on a Cochrane analysis and analysis of NCCTG N107C [Alliance]/CEC.3, the recommended dose for WBRT is 3000 cGy in 10 fractions noting increased toxicity without conferred benefit for higher biological WBRT dose-fractionation regimens (eg, 3750 cGy in 15

fractions).[66,67] The identification of molecular drivers of various cancers such as NSCLC, breast cancer and melanoma and the development of immune checkpoint inhibitors have changed the therapeutic landscape of metastatic cancers. As a result, CNS-active targeted agents and immunotherapy are emerging as an alternative to WBRT.[79]

Neurocognitive and physical decline are well-described side effects of WBRT.[80,81] Many strategies have been tried in an effort to provide neuroprotection or enhancement during and/or after WBRT, including donepezil,[82] armodafinil,[83] methylphenidate,[84] melatonin,[85] and memantine.[71] Donepezil administered daily for >6 months after partial or whole brain irradiation demonstrated improved recognition memory, motor speed and dexterity, but did not improve the study's overall composite score, and results were not reported separated by primary versus metastatic tumors.[82] RTOG 0614 randomized patients with brain metastases to receive placebo or memantine (starting with WBRT 5-mg morning dose week 1, 5 mg twice a day week 2, morning dose 10 mg and evening dose 5 mg week 3, and 10 mg twice a day weeks 4-24).[71] Among memantine-treated patients there was a nonsignificant trend towards less decline in delayed recall (the primary endpoint) and significantly longer time to neurocognitive decline as well as superior executive functioning; processing speed and delayed recall. Because memantine is very well tolerated and appears to delay neurocognitive decline in specific domains, use of memantine for patients with good prognosis receiving WBRT or HA-WBRT is recommended, but with a "low" level of evidence given the primary endpoint was not met.[71]

Since the hippocampus contains neural stem cells responsible for memory function, a reduction of the radiation dose to the hippocampus using HA-WBRT was tested in RTOG 0933, a phase II study as a neuroprotective strategy.[86] This study demonstrated a reduction in the mean relative decline in performance on the Hopkins Verbal Learning Test Revised delayed recall test of 7% at 4 months with HA-WBRT compared with the historical control of 30% with standard WBRT. The use of HA-WBRT was tested in the phase III NRG-CC001 trial to compare the efficacy and safety of standard WBRT with that of HA-WBRT, with both arms receiving memantine.[4] The group receiving HA-WBRT had significantly lower neurocognitive failure (26% relative risk reduction) compared with standard WBRT. For patients with brain metastases in close proximity to the hippocampi or with leptomeningeal disease, hippocampal avoidance may not be appropriate as these were exclusion criteria for RTOG 0933 and NRG-CC001.[4,86] Simultaneous integrated boost of metastases combined with WBRT with hippocampal avoidance is an emerging strategy designed to maximize intra-cranial control while preserving neurocognitive function.[68]

Patients with limited brain metastases often have surgery and/or SRS for local control of disease. Because local therapies do not prevent distant intracranial recurrences, combining these approaches with WBRT has been explored as a method to improve outcomes. Randomized studies have demonstrated that WBRT added to local therapies (surgery and SRS) increases intracranial control rates, but does not improve overall survival, although the addition of WBRT to surgery reduces risk of neurologic death.[15,16,51,72,87] The

addition of WBRT may contribute to neurocognitive decline and decreased QoL, but this question has not been tested with modern neuroprotective strategies of HA-WBRT and memantine.[16] The panel recognizes that not all patients have access to the close follow-up imaging (eg, MRI scans every 2-3 months during the first year), SRS, or neurosurgery that is required when using local treatment in lieu of WBRT. Additionally, some patients and/or health care providers may prioritize intracranial control, for instance in the setting of multiple recurrent brain metastases and/or high brain metastasis velocity.[34-36] In these cases, adjuvant WBRT added to SRS may be considered with a recommended dose of 3000 cGy in 10 fractions, but this intervention may incur additional toxicities and its use should be contingent upon the values and preferences of the patient.[5,67]

For patients with anticipated poor prognosis, WBRT may not improve outcomes compared to supportive care alone. The QUARTZ non-inferiority trial studied patients with poor prognosis and NSCLC with brain metastases not suitable for resection or SRS. Patients were randomized to WBRT with supportive care versus supportive care alone (oral dexamethasone).[73] There was no evidence of a difference in overall survival, QoL, or dexamethasone usage between the 2 groups. Estimates of patient prognosis can be derived from the RTOG recursive partitioning analysis classification[78] or the diagnosis-specific graded prognostic assessment,[7] which is an alternate validated prognostic score based on histologic cancer subtype and includes components of performance status, age, extra-cranial disease, and number of brain metastases. Reasonable options for patients with poor prognosis and brain metastases include palliative care or hospice, or short-course WBRT (eg, 2000 cGy in 5 fractions) for patients with symptomatic brain metastases.[73,74,]

3.4. KQ4: Risks of symptomatic radionecrosis with WBRT and/or SRS for patients with brain metastases (Table 7)

See evidence tables in Supplementary Materials for the data supporting the recommendations for KQ4.

What are the risks of symptomatic radionecrosis with WBRT and/or SRS for patients with brain metastases?

Table 7 Risks of symptomatic radionecrosis with WBRT and/or SRS

KQ4 Recommendation	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with brain metastases, limiting the single-fraction V_{12Gy} to brain tissue (normal brain *plus* target volumes) to ≤10 cm^3 is conditionally recommended. Implementation remark: Any brain metastasis with an associated tissue V_{12Gy} >10 cm^3 may be considered for fractionated SRS to reduce risk of radionecrosis (see KQ1).	Conditional	Low 11,88

Abbreviations: KQ = key question; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

Rates of radionecrosis with radiation alone for patients with brain metastases are relatively low, though higher with SRS approaches. Among studies of SRS or fractionated SRS only, reported rates of radionecrosis range from 0 to 20% and 1% to 8%, respectively.[5,12,13,17,23,56,89-92] For WBRT only, studies suggest a radionecrosis rate of 0 to 1.6%.[13,56,91] For combinations of SRS and WBRT, radionecrosis rates range from 0 to 5.6%.[5,12,13,17,93] Since higher rates of radionecrosis are observed with larger brain metastases (>8 cm^3 tumor volume), fractionated SRS is conditionally recommended to reduce the rates of radionecrosis in these cases.[11]

While SRS appears to convey a higher risk of radionecrosis than WBRT, careful planning with attention to dosimetric predictors and dose-volume cut offs to normal brain tissue allow mitigation of this risk. For patients with resected brain metastases, when treating the resection cavity with linear accelerator-based SRS, hot spots in the expansion margin to <110% of the prescription dose may increase the risk of radionecrosis.[94]Additionally , when single-fraction normal tissue constraints for critical structures (eg, optic nerves, optic chiasm, brainstem) cannot be met, WBRT or fractionated SRS may be considered as an alternative to single-fraction SRS.

The HyTEC report on brain metastases treated with SRS gives specific dose and volume cut-off recommendations.[11] Their analysis suggests that for total irradiated volumes (normal brain plus target volumes) of 5 cm^3, 10 cm^3, and 20 cm^3receiving a single-fraction equivalent dose of 1400 cGy (V_{14Gy}), the risks of grade 3 radionecrosis are approximately 0.4%, 0.8%, and 3.4%, respectively.[11] The report found that for single-fraction SRS for brain metastases, total irradiated volumes (normal brain plus target volumes) of 5 cm^3, 10 cm^3, or >15 cm^3 receiving 1200 cGy (V_{12Gy}) were associated with risks of symptomatic radionecrosis of approximately 10%, 15%, and 20%, respectively. Thus, the report concludes that the QUANTEC recommendation to limit single-fraction V_{12Gy} to 5 to 10 cm^3 remains prudent.[88]

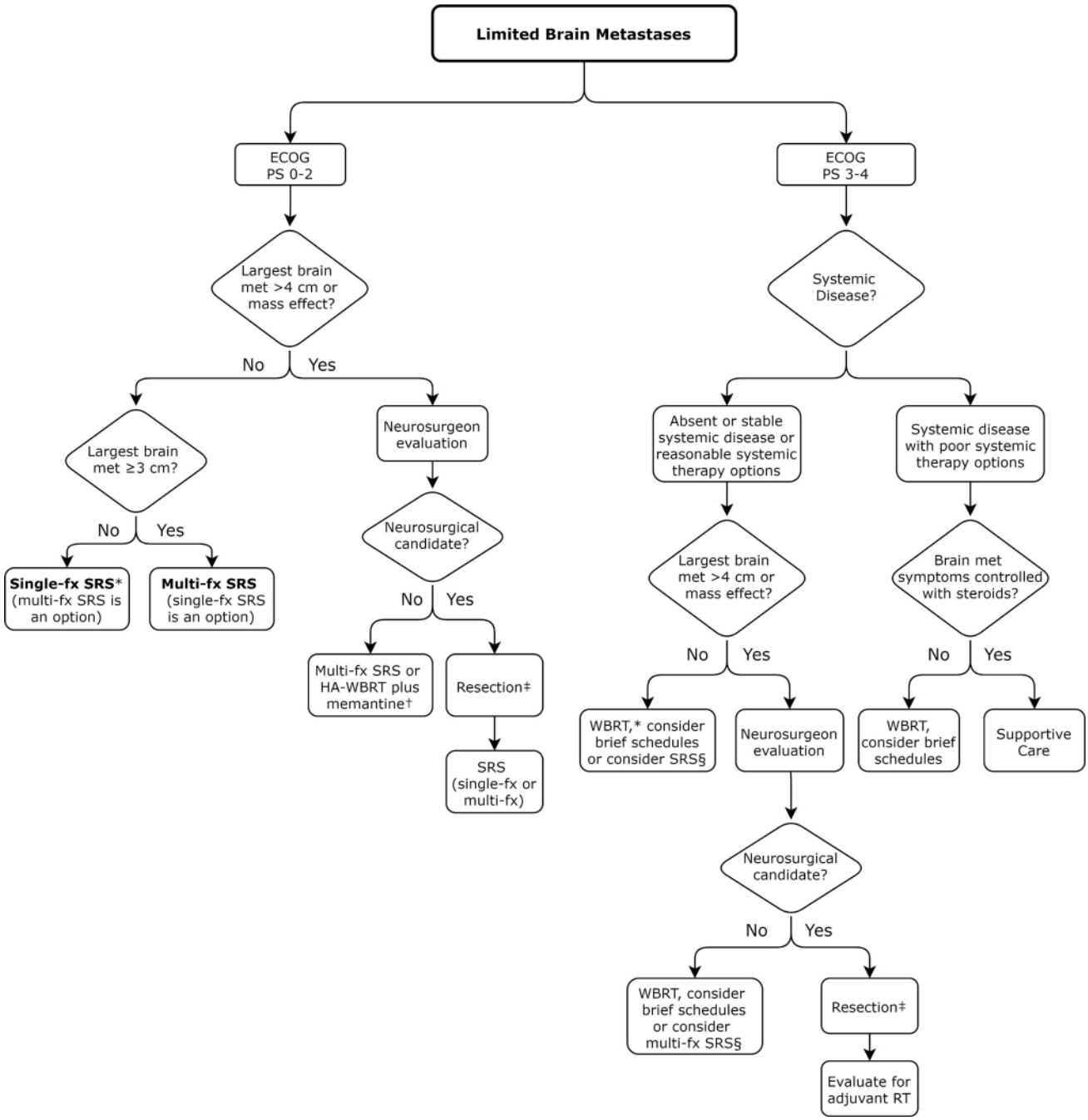
For brain metastases treated with fractionated SRS, the HyTEC analysis found that if the total irradiated volumes (normal brain plus target volumes) receiving 2000 cGy (V_{20Gy}) in 3 fractions or 2400 cGy (V_{24Gy}) in 5 fractions is kept to <20 cm^3, then the associated risk of any necrosis or edema is <10%, and risk of radionecrosis requiring resection is <4%.[11]

For single-fraction SRS, one study[95] suggested limiting the V_{12Gy} of normal brain (volume of brain, *excluding* the target volume, receiving ≥1200 cGy) to <8 cm^3 and another study[96] advised to keep the V_{12Gy} total volume (includes brain and target) to <8 cm^3 implying that treatment with a V_{12Gy} >8 cm^3 may be considered for fractionated SRS. For patients treated with 5-fraction fractionated SRS these studies suggest keeping the V_{30Gy} of normal brain (total brain *minus* target volume) to <10.5 cm^3.[97,98]

While reports are limited and quality of evidence is mixed, there may be combinations of certain systemic therapy agents (TKIs, T-DM1) and SRS which are associated with a higher risk of radionecrosis (30%-40%) than those reported with SRS alone.[92,99] With respect to combinations of immune checkpoint inhibition with SRS, reports are also mixed, some showing a higher incidence of radionecrosis with combination therapy.[100-102] However, there are also several reports showing that the incidence of radionecrosis is low with combination of immune checkpoint inhibition and SRS[103-105] and similar to rates reported for SRS alone.[106] This continues to be an area of active investigation, and caution is advised in combining SRS with systemic therapy and immunotherapy, with close attention to radiation planning parameters previously discussed.

Figure 1 and Figure 2 are treatment algorithms based on the recommendations from all KQs.

Figure 1. Limited Brain Metastases



Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; fx = fraction; HA-WBRT = hippocampal avoidance whole brain radiation therapy; LMD = leptomeningeal disease; met = metastases; SIB = simultaneous in-field boost; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

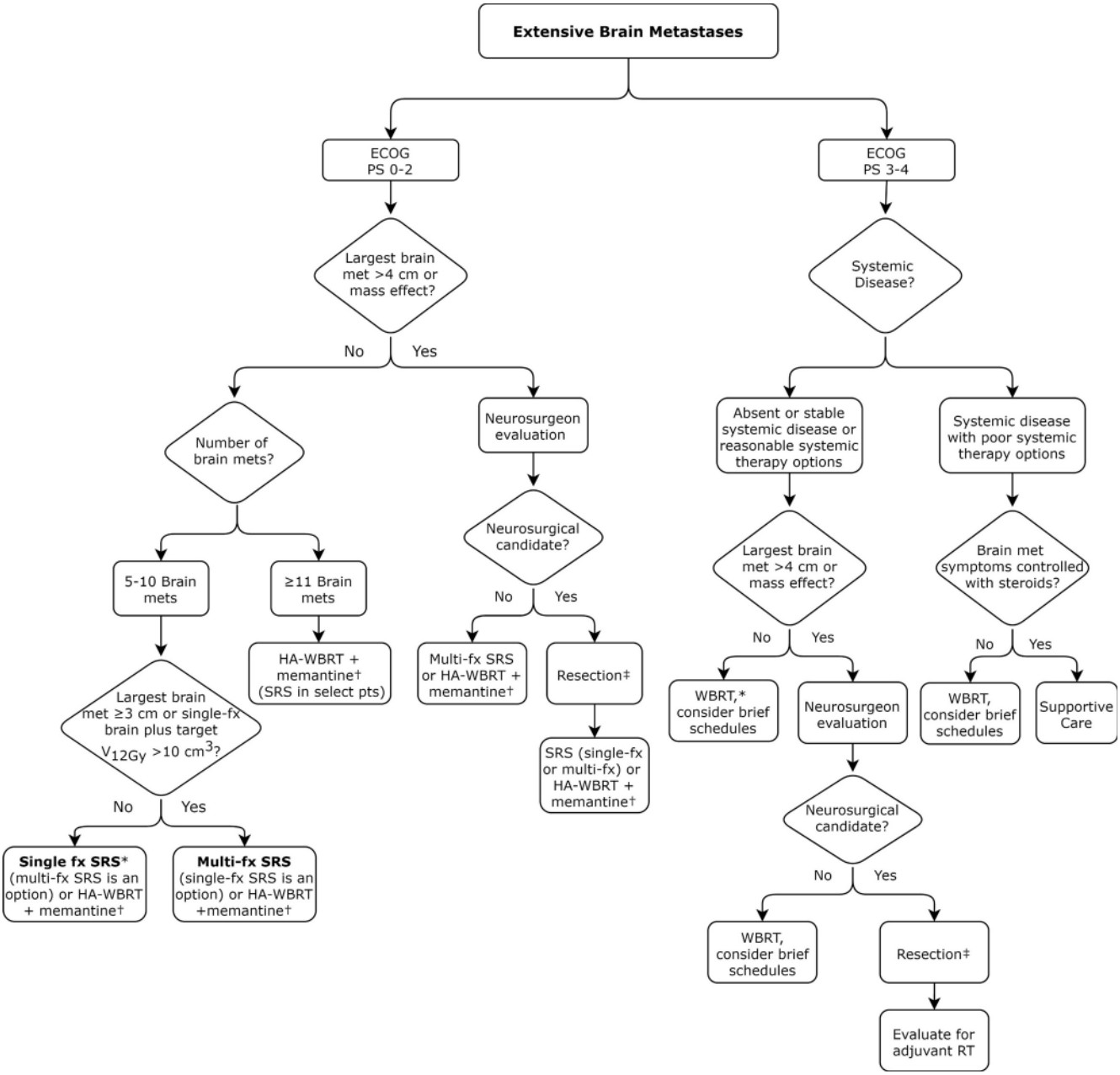
* For patients with *asymptomatic* brain metastases eligible for CNS-active systemic therapy, multidisciplinary and patient-centered decision making is conditionally recommended to determine whether local therapy may be safely deferred.

† Hippocampal avoidance is not recommended if brain metastases are in close proximity to hippocampi or if LMD. In certain situations, SIB or sequential SRS combined with HA-WBRT plus memantine may be considered.

‡ Preoperative SRS is conditionally recommended as an alternative to postoperative SRS.

§While outside the scope of the guideline's evidence review, SRS is a reasonable option based on the expert opinion of the task force.

Figure 2. Extensive Brain Metastases



Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; fx = fraction; HA-WBRT = hippocampal avoidance whole brain radiation therapy; LMD = leptomeningeal disease; met = metastases; SIB = simultaneous in-field boost; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

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‡ Preoperative SRS is conditionally recommended as an alternative to postoperative SRS.

4. Conclusions/Future Directions

In the decade since the previous ASTRO brain metastases guideline,[3] there has been a tremendous evolution in the management of this patient population. Novel RT techniques such as HA-WBRT have been developed which improve the therapeutic ratio, SRS has a more predominate role, and newer systemic agents have demonstrated unprecedented CNS activity. Treatment and management decisions (Figure 1 and Figure 2) depend on multiple factors (eg, number of brain metastases, brain metastasis size, and performance status). Many treatment decisions require multidisciplinary input, especially decisions to defer focal therapy (eg, SRS, surgery) for salvage, noting the numerous clinical trials that have established the safety and effectiveness of focal therapy for brain metastases. As these significant advances in brain metastasis management have been driven by clinical trials, there is an ongoing need for development of inclusive clinical trials with broader eligibility criteria when appropriate, that assess different modalities (eg, RT, imaging, systemic therapy, surgical intervention, and their interactions), and incorporate clinically meaningful trial endpoints such as survival, cognitive outcomes, and QoL. Finally, clinicians are encouraged to offer clinical trial participation where appropriate and available.

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The task force thanks the peer reviewers for their comments and time spent reviewing the guideline. See Appendix 1 for their names and disclosures.

Appendix 1. Peer Reviewers and Disclosures (Comprehensive)

Added prior to publication

Appendix 2. Abbreviations

AHRQ = Agency for Healthcare Research and Quality
BED = biological effective dose
cGy = centigray
CNS = central nervous system
ECOG = Eastern Cooperative Oncology Group
HA-WBRT = hippocampal avoidance whole brain radiation therapy
KPS = Karnofsky performance status
KQ = key question
MMSE = Mini-Mental State Examination
MRI = magnetic resonance imaging
NSCLC = non-small cell lung cancer
PCORI = Patient-Centered Outcomes Research Institute
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework
QoL = quality of life
RCT = randomized controlled trial
RT = radiation therapy
RTOG = Radiation Therapy Oncology Group
SRS = stereotactic radiosurgery
WBRT = whole brain radiation therapy

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