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

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Jerome J. Graber, MD, MPH,[1] Charles S. Cobbs, MD,[2] Jeffrey J. Olson, MD[3]

1. Ben and Catherine Ivy Center for Advanced Brain Tumor Treatment, Department of Neurology, Swedish Neuroscience Institute; University of Washington Department of Neurology, Alvord Brain Tumor Center, Seattle, Washington, USA

2. Ben and Catherine Ivy Center for Advanced Brain Tumor Treatment, Swedish Neuroscience Institute, Department of Neurosurgery, Seattle, Washington, USA

3. Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia, USA

Correspondence:

Jerome J. Graber, MD, MPH

Ben and Catherine Ivy Center for Advanced Brain Tumor Treatment

Swedish Neuroscience Institute

Department of Neurology

550 17th Avenue

Suite 540

Seattle, Washington 98122

Email: jgraber@uw.edu

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Abbreviations

SRS: Stereotactic radiosurgery

WBRT: Whole brain radiation therapy

GPA: Graded Prognostic Assessment

CNS: Central Nervous System

KPS: Karnofsky Performance Scale

MMSE: Mini Mental Status Examination

EGFR: Epidermal Growth Factor Receptor

ALK: Anaplastic Lymphoma Kinase

HER2: Human Epidermal Growth Factor Receptor-2

NSCLC: Non-Small Cell Lung Cancer

No part of this article has been published or submitted for publication elsewhere.

ABSTRACT

Target Population: These recommendations apply to adult patients with new or recurrent solitary or multiple brain metastases from solid tumors as detailed in each section.

Question 1: Should patients with newly diagnosed metastatic brain tumors undergo stereotactic radiosurgery (SRS) compared with other treatment modalities?

Recommendations:

Level 3: SRS is recommended as an alternative to surgical resection in solitary metastases when surgical resection is likely to induce new neurological deficits and tumor volume and location are not likely to be associated with radiation-induced injury to surrounding structures.

Level 3: Stereotactic radiosurgery should be considered as a valid adjunctive therapy to supportive palliative care for some patients with brain metastases when it might be reasonably expected to relieve focal symptoms and improve functional quality of life in the short term if this is consistent with the overall goals of the patient.

Question 2: What is the role of SRS after open surgical resection of brain metastasis?

Recommendation:

Level 3: After open surgical resection of a solitary brain metastasis, SRS should be used to decrease local recurrence rates.

Question 3: What is the role of SRS alone in the management of patients with 1 to 4 brain metastases?

Recommendations:

Level 3: For patients with solitary brain metastasis, SRS should be given to decrease the risk of local progression.

Level 3: For patients with 2 to 4 brain metastases, SRS is recommended for local tumor control, instead of whole brain radiation therapy, when their cumulative volume is < 7 ml.

Question 4: What is the role of SRS alone in the management of patients with more than 4 brain metastases?

Recommendation:

Level 3: The use of stereotactic radiosurgery alone is recommended to improve median overall survival for patients with more than 4 metastases having a cumulative volume < 7 ml.

INTRODUCTION

Brain metastases from systemic cancers are by far the most common cause of malignant central nervous system (CNS) tumors in adults, and the majority of these derive from systemic breast or lung cancers. Historically, these patients lived on average 2 to 7 months from the time of their diagnosis; however, the last 2 decades have seen significant advances in the diagnosis, prognosis, and treatment of patients with brain metastases.[1] There has remained considerable debate regarding the relative benefits in terms of survival, cancer control, and preservation of function and quality of life using stereotactic radiosurgery (SRS) or whole brain radiation (WBRT) in this population. No Class I evidence was available in this review to establish whether SRS is recommended over other treatment options, alone or in combination, for adults with brain metastases. Prior major trials addressing this question usually include mixed populations of adult patients with different histologies that were stratified based on the previously described Recursive Partitioning Analysis prognostic factors of age, number of metastases, and functional status.[2] Most of these trials only address WBRT or SRS as solitary interventions at a single time point, under the assumption that prior benefits of surgical interventions were independent and that subsequent treatments had no influence on these outcomes.[3, 4]

Newer information and possibly more effective modalities force re-interpretation of the prior data on this topic, especially based on the diagnosis-specific Graded Prognostic Assessment. Total tumor volume has emerged as an important prognostic factor for outcomes and complications of SRS.[5] It is also now apparent that patients with different histologies and molecular subtypes of the same histologies (HER2Neu-positive breast cancer, epidermal growth

factor receptor [EGFR] mutant lung cancer) have very different prognoses, and some common subsets of adult patients have significant CNS responses to systemic therapies alone or in combination with radiation therapy.[6, 7] The American Society of Clinical Oncology published a Clinical Practice Guideline specifically for brain metastases from HER2-positive breast cancer, recognizing the different behavior of these tumors and the need for an approach that recognizes this.[8]

There is also no gold standard for leptomeningeal disease, which can mimic solitary or multiple brain metastases, especially in the posterior fossa, so misdiagnosis of leptomeningeal disease at the initial diagnosis or recurrence may also be a common factor confounding study populations. It should also be noted that no gold standard exists to differentiate necrotic pseudoprogression from recurrent tumor growth, so that studies reporting intracranial recurrence may also be hampered by misdiagnosis, especially because this phenomenon is dose-dependent and more common with sequential or additive radiation treatments. Few of these studies have used truly rigorous measures of cognitive outcomes or patient reported outcomes on quality of life. Mini-Mental Status Exam (MMSE) is relatively insensitive to the predominantly subcortical deficits commonly seen after WBRT, so assessments of cognitive outcomes from studies only using MMSEs are likely to under report cognitive decline. Many of the available studies did not control or track subsequent treatments, and because single or multiple rounds of SRS are commonly given at recurrence, the main question is which sequential treatments may be best for patients at both initial diagnosis and with changing circumstances at recurrence. It is also recognized that in terms of cognitive outcomes, systemic therapies, including both chemotherapy and hormonal therapy, can affect cognition independent of radiation. The relative safety and feasibility of various surgical and focal radiation interventions depend on the precise size and location of the target tumor also cannot be reduced into a general guideline or adequately described in the context of a large clinical trial. Other anatomic factors may also play an important role in treatment decisions and are rarely captured in the context of large studies. Large cystic and necrotic lesions may present their own particular challenges, due to their higher local recurrence rate, especially when they co-exist with other solid metastases.[5] Studies of SRS versus fractionated radiotherapy for arteriovenous malformations showed that SRS has a higher toxicity rate when applied to deep gray matter and brainstem, as well as cranial nerves II and VIII.[9] Patient treatment must be more individualized and requires multi-disciplinary decision-

making with the input of neurosurgeons, radiation oncologists, neurologists and neuro-oncologists, medical oncologists, neuroradiologists, and neuropathologists.

For the above reasons, the levels of evidence of the recommendations in this updated guideline were substantially downgraded from the previous guideline.[10] Despite the study type (randomized control trials), there are serious design flaws that limit their application to individual patients. New prognostic factors and effective treatment modalities must now be accounted for in these treatment decisions. For example, even for the largest, most commonly included patient group, non-small cell lung cancer (NSCLC), it is now recognized that EGFR and anaplastic lymphoma kinase status can significantly affect CNS prognosis, as well as response to both radiation and systemic treatments and may have led to unrecognized imbalance and bias between randomized groups.[6, 11-14]

Rationale

The main focus of this guideline is on intracranial metastases from solid malignances in adults > 18 years of age. There continues to be no clear consensus on which patients are most appropriate for SRS, WBRT, surgical resection, chemotherapy, or palliative care, and when these modalities should be combined. Since the last guideline was published in 2010, there is greater recognition of distinct subtypes of patients with different prognoses and responses to therapy that suggest significant possible bias, which force a reinterpretation of the previously available data. Therefore, the majority of prior evidence available on these topics has been downgraded to Class III evidence because these are now considered to have major flaws in design that introduce significant possible bias and limit the interpretation and confident application of the available evidence to patients, as well as new prognostic factors and changing effectiveness of other treatment modalities that must be considered.

Objectives

To critically re-evaluate the previously available evidence on the use of SRS in adults with metastatic brain tumors in light of the emerging and evolving data on individualized diagnosis-specific prognosis for patients with brain metastases and other changes in therapeutic options since the previous guideline published in 2010.

METHODS

Writing Group and Question Establishment

The authors represent a multi-disciplinary panel of clinical experts, including neurosurgeons, radiation oncologists, and neuro-oncologists. Multiple disciplines interact in decision-making for these patients and individual practitioners, as well as expertise from neuroradiologists, neuropathologists, medical oncologists, and hospice and palliative care teams for overall assessments of prognosis and quality of life. Questions were developed by the collective clinical guidelines task force.

Search Method

The following electronic databases were searched for the period of January 1, 1990, through December 31, 2015: PubMed, Embase, and Cochrane Central. The searches extended prior to the end date of the previously published guideline to account for the significant change in the questions related to SRS in this new guideline. An additional bibliography search of these candidate papers revealed an additional study. The search strategies for each question can be found in Appendix A.

Study Selection and Eligibility Criteria

Eligibility Criteria

1. Peer-reviewed publications
2. Patients with any number of brain metastases. A small number of older studies that mixed primary and secondary brain tumors in the same patient population were excluded. Studies that mixed hematologic (e.g., lymphoma), small cell lung cancer brain metastases and leptomeningeal tumor were excluded unless these patient populations could be analyzed separately. Studies that included spinal metastases were also excluded unless the brain population could be analyzed separately.
3. More than 10 patients included
4. Adult patients, usually defined as 18 years of age
5. Study full results available in English language. Studies with only abstracts in English were not included.

Data Collection Process

Citations were independently reviewed and included if they met the *a priori* criteria for relevance. Corresponding full-text PDFs were obtained for all citations meeting the criteria and were reviewed. Articles that did not meet the selection criteria were removed. Full-text

manuscripts were more carefully reviewed to make sure there were no discrepancies in study eligibility. Data were extracted and compiled into evidence tables. The evidence tables and data were reviewed by all authors.

Evidence Classification and Recommendation Levels

The search generated a list of abstracts that were screened. Articles that addressed the identified questions underwent full-text independent review by the authors. Reviewers were critical in their assessment of trial design, including whether the study was retrospective, study size, randomization of treatment, baseline characteristics between study groups that could account for survivorship bias, blindness, selection bias, and appropriate statistical analyses of reported data. Studies were also evaluated as single surgeon experiences, single institution, or multi-institution studies. Studies were rated on the quality of the published evidence and the factors mentioned above.

Only therapeutic studies were included to establish levels of evidence, which were evaluated based on the CNS Guideline Methodology, which have been updated since the previous guideline on this topic (https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.) "While no uniform methodology exists for evaluating and classifying [meta-analysis and systematic reviews], in general, the Class of Evidence provided by these reports can be no better than the preponderance of the class of evidence in the individual papers that have been used" to generate them. Therefore, high-quality relevant meta-analysis were included.

Level 1 recommendations are based on well-designed randomized controlled trials ascertained to have limited bias. Level 2 recommendations are based on randomized controlled trials with design flaws leading to potential bias limiting interpretation and broad application, non-randomized cohort studies and case-control studies. Level 3 recommendations were based on randomized studies with significant design flaws hampering interpretation and application to all patients, single institution case series, and comparative studies based on historical controls. The methodological quality of randomized controlled trials and the risk of bias were assessed using the following 6 criteria: treatment group allocation and concealment, blinding, complete reporting of outcome data without selective reporting and other potential threats to validity. The majority of trials conducted did not have blinding or concealment and did have other potential threats to validity (heterogeneous composition of patient groups). For these reasons, the majority

of recommendations are classified as Level 2 or Level 3. Additional information on the method of data classification and translation can be found at https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

Assessment for Risk of Bias

The authors critically evaluated the studies based on randomization procedures, stratification procedures possibly affecting study outcomes, retrospective or prospective nature, study size, potential bias and single or multi-site study. It is important to note that geographic locations of studies and predominant ethnic background of patient populations must be taken into account, as various molecular subtypes of breast and lung cancers that influence outcomes and make up the majority of study populations can be substantially different (eg, higher incidence of EGFR mutant lung cancers and HER2neu-postivie breast cancers in various countries).

RESULTS

Study Selection and Characteristics

The search yielded 1,780 unique articles. After reviewing the titles and abstracts, the authors excluded 997 articles based on the criteria above (pediatric patients, <10 patients, etc.), as well as articles that did not directly address clinical outcomes of stereotactic radiosurgery for brain metastases or relevant prognostic information for patients with brain metastases that impacted the interpretation of prior studies, which left us with 783 articles. Of these, 31 studies met the defined criteria for inclusion (Figure 1). The authors considered therapeutic studies and did not include reviews, meta-analyses, or small case studies.

Summary of Prior Recommendations

One of the major differences in the current guideline compared with the previous version of this guideline is a downgrading of the level of several recommendations. The prior version of this guideline[10] concluded that SRS along with WBRT leads to: significantly longer survival compared to WBRT alone for solitary brain metastases in patients with KPS score ≥70 (Level 1 recommendation) and 2 to 3 brain metastases (Level 3 recommendation); and superior local control and maintaining function for patients with 1 to 4 brain metastases and KPS score ≥70 (Level 2 recommendation). Later studies found that WBRT added after SRS worsened quality of life and cognitive outcomes, compared with SRS alone without improving overall survival.[15] The prior version of this guideline also concluded that SRS alone was superior to WBRT for survival

of patients with 1 to 3 brain metastases (Level 3 recommendation), but that both modalities were effective.

Question 1: Should patients with newly diagnosed metastatic brain tumors undergo stereotactic radiosurgery compared with other treatment modalities?

Results of Individual Studies, Discussion of Study Limitations and Risk of Bias

No available Class I evidence exists to establish whether SRS should be preferred over surgical resection, alone or in combination. A single Class III study examined the addition of WBRT versus observation after either non-randomized surgical resection or SRS for 1 to 3 brain metastases and found no impact on functional independence based on the initial SRS versus resection.[16] Most outcomes of this study compared the secondary randomization to WBRT versus observation. Several Class III retrospective single center uncontrolled studies compared surgical resection versus SRS prior to WBRT in patients with single brain metastasis of mixed histologies (primarily lung), and were mostly conducted before the modern chemotherapeutic era.[17-21] Only 1 study suggested improved survival in the surgical resection group, suggesting that, in general, the 2 modalities have similar efficacy in terms of overall survival for most patients.[20]

However, there is an overt bias in uncontrolled studies of this nature, such that when physicians could freely choose to perform either surgery or SRS, they likely did so in an educated manner. Numerous complex factors determine whether a particular patient may be better served by SRS or surgical resection. Whether patients with newly diagnosed metastatic brain tumors should undergo SRS versus attempted surgical resection depends on whether surgical tissue is needed for diagnostic and therapeutic purposes, the overall surgical risk for the patient, surgical accessibility, radiation risk to adjacent structures, total tumor volume (and the degree it might be improved by resection), and whether surgical resection may provide more immediate relief of severe or life-threatening neurologic symptoms due to tumor (eg, herniation, obstructive hydrocephalus). It should be noted that in patients with known systemic disease that is unlikely to produce CNS metastases, or with a remote history of systemic disease without recent active systemic tumor, it is often prudent to obtain new diagnostic tissue to verify the histologic diagnosis and tumor marker expression, which can change with time and in different organ sites, and may have important impacts on therapeutic and prognostic decisions (especially

for breast and lung primaries wherein different molecular subtypes have different prognoses and therapeutic options, including in the CNS).

In a patient with multiple metastases who may be an appropriate candidate for SRS, it should be considered whether debulking of a particular metastasis, even if it cannot achieve gross total resection, might make SRS more feasible by creating space from radiosensitive structures or reducing the total tumor volume needing treatment, which is a better predictor of outcome than the overall number of metastases. Patients with overt leptomeningeal disease may be less appropriate candidates for resection, except when resection is needed for urgent symptomatic or obstructive relief. Recovery time from surgery should be considered in patients with actively symptomatic systemic disease who have a highly beneficial systemic therapy option, especially if it may also be effective for CNS disease.

SRS or WBRT alone should be favored over WBRT + SRS for most patients, suggesting a detrimental effect of the combination on cognitive function and quality of life (Hasan et al[15]). Prior Class III evidence had suggested a possible improvement in median overall survival (mOS) for SRS + WBRT and other studies had reported improvements in intracranial recurrence, which is a less relevant clinical outcome than measures like mOS, functional independence, quality of life and rigorously tested cognitive function.[22-24]

There is no available Class I evidence on whether patients with newly diagnosed metastatic brain tumors should undergo SRS versus WBRT. Factors that favor SRS or WBRT based on available Class III studies depend on total tumor volume and location, diagnosis-specific GPA and patient-specific molecular histology and radiosensitivity, status of systemic disease and systemic therapeutic options, patient performance status and overall prognosis, and consideration of the possibility of occult or impending diffuse leptomeningeal involvement. Kocher et al. studied the addition of WBRT after either surgical resection or SRS for 1 to 3 brain metastases and found no impact on mOS.[16]

No higher-class evidence yet exists on whether patients with newly diagnosed metastatic brain tumors should undergo SRS versus or in addition to systemic or intrathecal chemotherapy. This decision should primarily depend on whether systemic therapy is also necessary and likely to be effective for systemic and CNS disease. Class III data suggests that patients with EGFR mutant NSCLC and HER2-positive breast cancer may have a significant and durable response to

systemic tyrosine kinase inhibitors with CNS penetrance, so these tumors in particular may be more amenable to systemic therapy than other cancers and their use as adjunctive therapy after SRS should be considered, but there are not yet available studies directly comparing these therapies to SRS.[7, 25] In NSCLC unselected by molecular subtype, the addition of temozolomide or erlotinib to WBRT in combination with SRS appeared to worsen survival, so these should only be considered when the actionable mutation is present.[26] Studies of combination systemic and radiation treatment for brain metastases are ongoing. Patients with overt leptomeningeal disease with an effective chemotherapeutic option should be considered for SRS mainly when there is a relatively small total volume of symptomatic lesions that are not amenable to surgical resection.[7, 26]

No higher-level evidence exists on which patients should receive SRS versus supportive palliative care only. Because SRS can rapidly reduce focal neurology symptoms in a significant portion of patients and is generally safe and well-tolerated, SRS should be considered as a possible palliative intervention in these patients, based on the nature of their focal symptoms and overall function and quality of life, and how much SRS may be expected to improve and maintain these, depending on tumor histology, volume and location in relation to focal symptoms.[27] Symptomatic response to and tolerance of corticosteroids, which are the mainstay of symptomatic management in patients with brain metastases, should also be considered and radiation may variably increase or decrease corticosteroid needs.[27]

Synthesis of Results

SRS is a valid option compared to surgical resection in solitary metastases when surgical risks are high, and tumor volume and location are acceptable for employment of SRS.

SRS alone is preferred to WBRT + SRS for most patients due to increased cognitive consequences with WBRT + SRS, without an improvement in other patient-relevant outcomes.

SRS should be compared to WBRT on an individual patient basis using total tumor volume, disease-specific GPA and tumor histology and molecular status, as well as other factors, in deciding between the two.

SRS is a valid adjunctive therapy option to supportive palliative care and can improve patient symptoms and quality of life.

Question 2: What is the role of stereotactic radiosurgery after open surgical resection of brain metastasis?

Based on Class III evidence, after open surgical resection of a solitary brain metastasis, SRS should be considered to decrease local recurrence rates depending on the presence of residual tumor, radiation risk of adjacent structures, and sensitivity to radiation versus systemic therapeutic options in the CNS based on molecular histology.[28, 29] No higher class studies have compared whether SRS should be used instead of WBRT after resection, but Class III evidence from retrospective studies suggests a higher intracranial recurrence rate after SRS versus WBRT without a notable difference in OS.[30] Some studies have observed a high rate of leptomeningeal recurrence (especially in breast cancer patients) and postulated that surgical resection may increase the risk of this phenomenon.[31] It should be noted that association does not imply causation, and that some histologies and locations have a high risk of leptomeningeal spread before any surgery has occurred, or after multifocal SRS or even WBRT, and that leptomeningeal disease can radiographically mimic a solitary parenchymal metastasis, especially in the cerebellar folia. Hopefully, ongoing studies comparing WBRT to SRS will help verify risk factors for leptomeningeal relapse and establish whether WBRT can prevent or delay this occurrence in high risk patients. A single observational study using neoadjuvant SRS prior to planned resection of 1 to 3 metastases found no cases of postoperative leptomeningeal recurrence, so this may be another strategy to address at risk patient populations once they are better defined.[32] Cystic and necrotic metastases are at higher risk of rapid recurrence and may be a particular population to evaluate, although there are no high-quality data on this particular topic.

Synthesis of Results

SRS is a valid option after open resection of solitary brain metastases to decrease the risk of local recurrence. SRS should be compared to WBRT after resection of 1 or multiple brain metastases in patients with multiple brain metastases depending on residual total tumor volume, diagnosis-specific GPA and tumor histology.

Question 3: What is the role of stereotactic radiosurgery alone in the management of patients with 1 to 4 brain metastases?

Class III evidence supports the statement that patients with solitary brain metastasis can mostly be treated with SRS with equivalent or possibly improved outcomes and side effects compared to WBRT.[27, 33-37] It should be again noted that tumor size, total volume and location may not always make SRS feasible.

Class III evidence suggests that SRS should be compared to WBRT for patients with 2 to 4 brain metastases (and possibly more), depending on total tumor volume, diagnosis-specific GPA and patient-specific molecular histology and radiosensitivity, status of systemic disease and systemic therapeutic options, and consideration of the possibility of occult or impending diffuse leptomeningeal involvement.[7, 26, 38, 39] Total tumor volume appears to be more important than tumor number.[32-35, 37, 40, 41] A prospective study of SRS for 1 to 10 brain metastases found no difference in mOS for patients with 2 to 4 versus 5 to 10 brain metastases.[40]

Synthesis of Results

SRS alone is an appropriate treatment option when total tumor volume is "low" (generally < 7 cc, but up to 13 cc). However, other patient-specific factors must be considered on an individual patient basis using total tumor volume, disease-specific GPA and tumor histology and molecular status, as well as other factors in deciding between SRS and WBRT.

SRS alone is preferred to WBRT + SRS for most patients, due to increased cognitive consequences with WBRT + SRS without an improvement in measured outcomes.[33-37]

Question 4: What is the role of stereotactic radiosurgery alone in the management of patients with more than 4 brain metastases?

Several Class III studies have addressed the use of SRS alone in patients with >4 brain metastases and confirmed that overall survival is not different for patients with >4 brain metastases compared with 1 or 2 to 4 metastases when total tumor volume was <13 cc, and no single metastasis was > 3 cc in volume.[40, 42, 43] Patients with total tumor volumes >7 cc or >15 metastases had higher intracranial recurrence rates, but appear to have similar overall survival.[42, 44, 45]

Synthesis of Results

SRS alone is an appropriate treatment option when total tumor volume is "low" (generally < 7 cc but $\leq$13 cc), however other patient-specific factors must be considered.

DISCUSSION

The ongoing intergroup trial (RTOG 1270 NCCTG N107C) randomizes patients with 1 to 4 brain metastases to WBRT or SRS in a non-blinded fashion.[46] Primary outcome measures are both overall survival at 6 months and neurocognitive outcome at 6 months, measured by the Hopkins Verbal Learning Test, with delayed recall and recognition, Controlled Oral Word Association Test and Trail Making. Secondary measures include outcomes up to 5 years, quality of life measurements, intracranial failure rates and biomarkers that attempt to identify patients at greater risk of neurocognitive decline after radiation. Patients are stratified based on age, histology (lung, radioresistant sarcoma, melanoma or renal, or "other"), and number of metastases (1 or 2 to 4). Hopefully, a parallel study of 5 or greater metastases stratified by tumor volume and different histologies will eventually provide higher quality evidence to guide individual patient care decisions. A meta-analysis of 3 randomized controlled trials of SRS versus WBRT, not included as evidence for recommendations in this guideline, suggested a survival advantage of SRS (10 vs 8 months) for patients younger than 50 with < 5 brain metastases.[47]

Post-hoc analysis of data from the randomized phase 3 trials with retroactive application of the diagnosis-specific GPA may provide some insight to aid decisions. Two such analyses support the conclusion that WBRT + SRS provided improved OS versus SRS or WBRT alone in non-breast brain metastases (mostly non-small cell lung cancer) with 1 to 3 or 4 brain metastases and a "good" diagnosis-specific GPA score (2.5 or 3.5 to 4.0).[24, 37] However, adding WBRT to SRS increases cognitive side effects, so treatment should be individualized for each patient, using known prognostic information, such as total tumor volume and histology-specific prognosis to weigh competing risks of cognitive consequences versus short-term risk of mortality and morbidity from systemic and intracranial disease. One major study on this topic was published after the cut-off date for the literature search for this systematic review, but is included in this discussion, due to its high quality and relevance to the guidelines.[48] This study randomized 213 patients with 1 to 3 brain metastases (two-thirds from lung cancer) to SRS alone versus SRS plus WBRT and found more cognitive deterioration and lower quality of life at 3 months with SRS plus WBRT without any significant differences in functional independence or overall survival, although time to intracranial failure was shorter with SRS alone. Notably, cognitive deterioration was still less at 12 months in the SRS alone group. This study suffered

from the common biases affecting others in this field (mainly heterogeneous and uncontrolled histologies among the groups, lack of blinding except for cognitive testing), which could have affected survival but theoretically should not affect cognitive and functional deterioration due to radiation. However, tumor progression could vary by these factors and also commonly affects cognitive and functional outcomes. This study would therefore meet Class II criteria that SRS should not be combined with WBRT as upfront therapy in patients with 1 to 3 brain metastases, though there may be some reasonable exceptions depending on individual patient factors. This study confirmed the findings of the Hasan et al meta-analysis published in 2014.

If the recently initiated phase 3 trial of memantine and hippocampal avoidance with WBRT[49] shows a significant decrease in long-term neurocognitive consequences, as suggested by phase 2 studies, the cognitive consequences of WBRT may decrease for a substantial number of patients, thereby influencing treatment choices in favor of WBRT in some cases. If the benefits are substantial and sustained, it may even re-open the question of whether some patients might be best served by upfront SRS together with WBRT, because the cognitive consequences and impairment of functional independence (seen in Brown et al[48]) are the main reason to avoid this currently.

Another complicating factor is the expanding landscape of treatment options that confound imaging interpretation. Immunotherapies can provoke inflammatory responses around CNS metastases that mimic progressive disease, and anti-angiogenic agents can mimic response, so that interpretation of imaging regarding disease "progression" and "response" are more complicated than in the past, and may even be disparate in different lesions from the same patient. The Radiologic Assessment in Neuro-Oncology group has proposed a set of guidelines on interpreting imaging for brain metastases.[50]

CONCLUSION AND KEY ISSUES FOR FUTURE INVESTIGATIONS

While high-quality evidence is lacking, participation in well-designed clinical trials that will provide answers to these important and common dilemmas is encouraged. In the meantime, a rational application of the available data to each particular patient is the best approach. This field will rapidly evolve if improvements in the reduction of neurocognitive consequences of WBRT are confirmed, and more effective systemic treatments improve both systemic and intracranial prognosis for patients with brain metastases, depending on their molecular histology.

Future investigations should stratify patients by new prognostic criteria, especially tumor histology and molecular type, and account for difficulties in interpretation of imaging. In addition, more rigorous assessment of cognitive outcomes and patient-reported quality of life are needed to weigh the various therapeutic options. As alternate effective therapies emerge, future investigations should follow sequential therapies to determine the best order of employment of the various therapeutic options.

Potential Conflicts of Interest

The Brain Metastases Guideline Update Task Force members were required to report all possible conflicts of interest (COIs) prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair are given latitude to approve nominations of task force members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs. The conflict of interest findings are provided in detail in the companion introduction and methods manuscript.

Disclosures

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Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a multidisciplinary physician volunteer task force and serves as an educational tool designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation

contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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468 **Figure 1.** PRISMA diagram showing flow of study evaluation for inclusion

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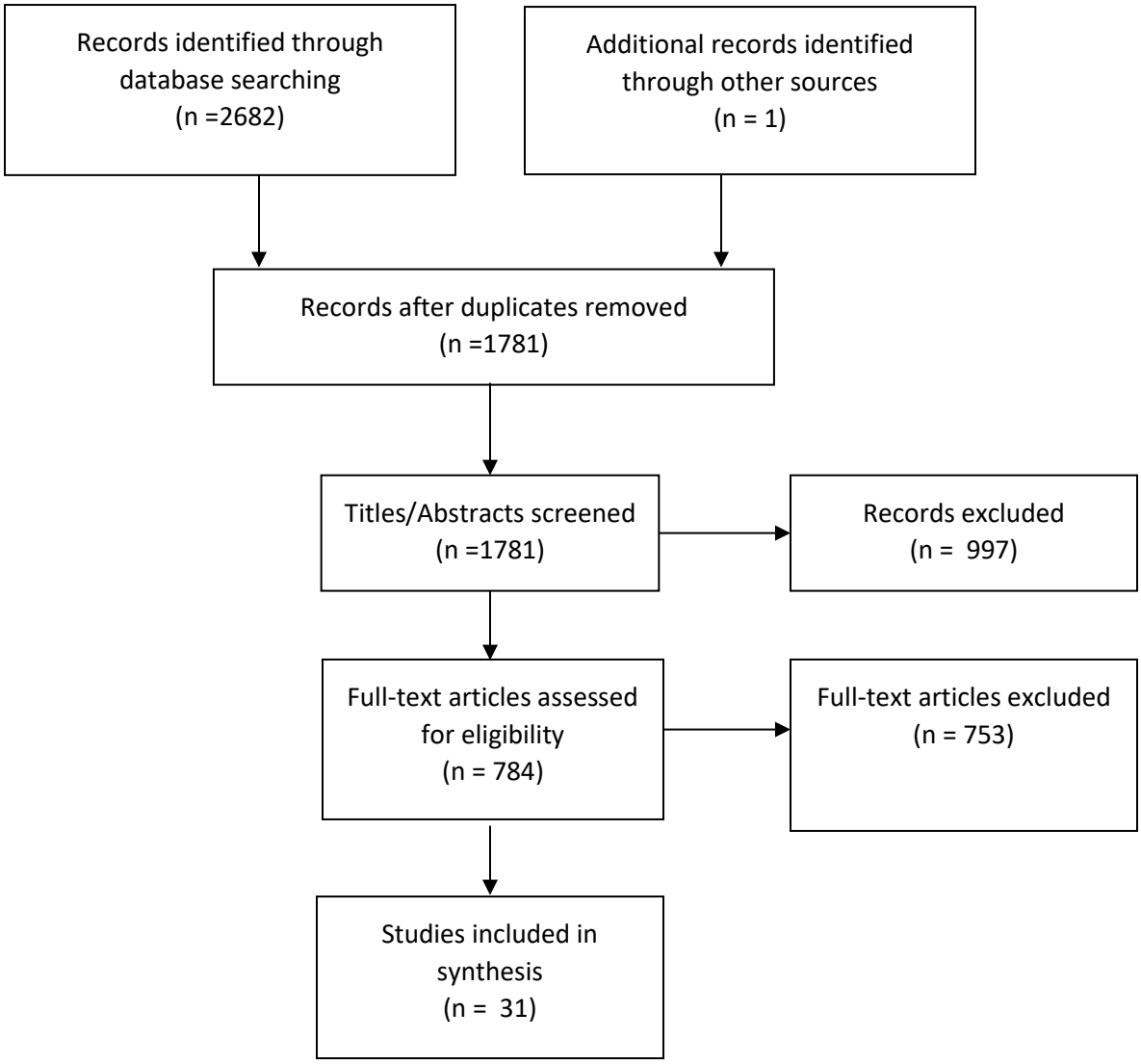

Table 1. Should patients with newly diagnosed metastatic brain tumors undergo stereotactic radiosurgery compared with other treatment modalities?

Author and Year	Description of Study	Data Class	Conclusions
Kocher et al[16] (2011)	RCT Multiple institutions 1-3 BMs SRS ± WBRT (n = 199 then WBRT n = 99) vs surgery ± WBRT (n = 160 then WBRT n = 81) 53% lung 12% breast (brainstem excluded)	II	Most outcomes reported compared WBRT vs observation after either SRS or surgery, not initial randomization to SRS vs surgery
Kim et al[25] (2009)	Retrospective review Single Institution Newly diagnosed asymptomatic brain metastases from lung adenocarcinomas in nonsmokers given erlotinib or gefitinib (n = 23)	III	CNS response rate of 73.9%, median time to WBRT was 19.3 months
Kano et al[27] (2009)	Retrospective review Single institution various BMs invading cavernous sinus (n = 37), 29 of 37 had failed fractionated RT, chemotherapy, or both	III	35.3% of patients showed improvement in neurologic symptoms after SRS

Andrews et al[23] (2004); secondary analysis by Sperduto et al[24] (2014)	RCT Multiple institutions WBRT (n = 167) vs WBRT + SRS (n = 163) for 1 (56%) or 2 to 3 BM (44%) 63% lung, 10% breast Secondary analysis, n = 252 (84% lung)	III	WBRT + SRS > WBRT alone for patients with 1 BM (6.5 vs 4.9 months, $p = .039$) WBRT + SRS also favored for subgroups with RPA class 1, largest tumor >2 cm, and lung primary. No difference in OS for 2-3 BM or total pooled patient population. KPS and steroid use were also more likely to be stable or improved in the WBRT + SRS group for the 50% of patients surviving at 6 months. Secondary analysis found WBRT + SRS vs SRS mOS 21 vs 10 months) in patients with DS-GPA 3.5-4.0 "Mixed histologies included with highly varying prognoses were well balanced but no molecular subtypes known, limits application of results to individual patients."
O'Neill et al[21] (2003)	Observational Single Center Retrospective n = 97 solitary BMs treated with SRS (n = 23) vs resection (n = 74) ± WBRT	III	SRS = surgery for mOS ($p = .15$) and 1-year survival rate (56% vs 62%). SRS > surgery for local failure (0% vs 58%)
Sanghavi et al[22] (2001)	Retrospective cohort vs historical controls Multiple institutions WBRT (n = 1200) vs WBRT + SRS (n = 502) ~60% lung, 13% breast, 22% melanoma in WBRT + SRS vs 0% melanoma in WBRT historical cohort	III	WBRT + SRS superior OS across RPA classes [RPA I 16 vs 7 months; RPA II 10 vs 4 months; RPA III 9 vs 2 months ($p < .05$)] Mixed histologies, especially disparity in melanoma cases

Schoggl et al[19] (2000)	Case-control Single Center Retrospective n = 133 patients treated with SRS (n = 67) vs "microsurgery" (n = 66) ± WBRT	III	SRS = "microsurgery" for mOS (12 months vs 9 months $p = .19$) SRS > microsurgery for local control ($p < .05$), especially for "radioresistant" metastases ($p < .005$) Critique: SRS group had smaller tumor volume compared with microsurgery group.
Garell et al[17] (1999)	Observational Single Center Retrospective n = 45 patients with solitary BMs treated with surgery + WBRT (n = 37) vs SRS + WBRT (n = 8)	III	mOS = 8 months (surgery + WBRT) vs 12.5 months (SRS + WBRT) not significantly different. Critique: Small SRS group size, mixed histologies
Auchter et al[18] (1996)	Observational Multicenter Retrospective n = 122 (48% NSCLC) SRS + WBRT for newly diagnosed resectable solitary BMs	III	Survival comparable to historical controls treated with surgical resection followed by WBRT KPS ($p < .0001$) and non-CNS metastasis ($p = .02$) were significant prognostic factors for survival
Bindal et al[20] (1996)	Observational Single Center Retrospective n = 75 BMs treated with SRS (n = 31) vs resection (n = 62) ± WBRT ± chemotherapy	III	Surgery > SRS for mOS ($p = .0009$) Critique: Significant difference in chemotherapy between groups, small SRS group, mixed histologies

BM, brain metastasis; CNS, central nervous system; DS-GPA, diagnosis-specific Graded Prognostic Assessment; KPS, Karnofsky Performance Scale; mOS, median overall survival; NSCLC, non–small cell lung cancer; RPA, recursive partitioning analysis; RT, radiation therapy; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

Table 2. What is the role of stereotactic radiosurgery after open surgical resection of brain metastasis?

Author and Year	Description of Study	Data Class	Conclusions
Brennan et al[28] (2014)	Observational Single Center SRS after resection (n = 49)	III	Local and regional failure highest for superficial dural/pial tumors, infratentorial, >3 cm
Patel et al[30] (2014)	Observational Retrospective Single Center Surgery followed by WBRT (n = 36) or SRS (n = 96)	III	1-year survival 56% vs 55% (p = .64) leptomeningeal relapse at 18 months after WBRT 13% vs SRS 31% (p = .045) Uncontrolled, mixed histologies
Asher et al[32] (2014)	Observational Single Center n = 23 retrospective and n = 24 prospective Neoadjuvant preoperative SRS prior to resection of 1-3 BMs; 37.25% NSCLC, 23.5% breast, and 20% melanoma	III	0/47 cases had leptomeningeal failure Tumor volume >10 cc had lower OS (p = .0021)
Atalar et al[31] (2013)	Observational Retrospective Single Center SRS after resection of BMs n = 175 resection cavities in 165 patients 43% NSCLC, 15% breast, and 14% melanoma	III	Risk of leptomeningeal relapse was higher in breast cancer compared with other histologies (24% at 1 year vs 9%, p = .004)
Choi et al[29] (2012)	Observational Retrospective Single Center Surgery followed by SRS without (n = 54) or with (n = 58) a 2-mm margin 43% NSCLC, 16% breast, and 16% melanoma	III	Local failure at 12 months was lower with a 2-mm margin (3% vs 16%, p = .042) Melanoma histology or >1 metastasis had higher distant failure (p = .038 and .0097)

BM, brain metastasis; OS, median overall survival; NSCLC, non–small cell lung cancer; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

Table 3. What is the role of stereotactic radiosurgery alone in the management of patients with 1 to 4 brain metastases?

Author and Year	Description of Study	Data Class	Conclusions
Asher et al[32] (2014)	Observational single center (n = 23) retrospective and (n = 24) prospective Neoadjuvant preoperative SRS prior to resection of 1-3 BMs 37.25% NSCLC, 23.5% breast, and 20% melanoma	III	0/47 cases had leptomeningeal failure Tumor volume >10 cc had lower OS (p = .0021)
Yamamoto et al[40] (2014)	Prospective single arm study Multicenter 1-10 brain BMs (total volume <15 mL) treated with SRS alone n = 1194, 76% lung and 10% breast	III	No difference in mOS for patients with 2-4 vs 5-10 BM (p = .0001) Total cumulative tumor volume had to be <15 mL for patients to be included
Sperduto et al[26] (2013)	Prospective randomized controlled trial Multicenter 1-3 BMs from NSCLC Arm 1: WBRT + SRS, (n = 44) Arm 2: WBRT + SRS + temozolomide, (n = 40) Arm 3: WBRT + SRS + erlotinib, (n = 41)	II	mOS Arm 1 = 13.4 months, Arm 2 = 6.3 months, Arm 3 = 6.1 months (p = .93) Performance status decline at 6 months Arm 1 = 52.5%, Arm 2 = 85.7%, Arm 3 = 85.7% (p = .002) Systemic chemotherapy with temozolomide or erlotinib should NOT be added to WBRT + SRS in an unselected patient population
Bachelot et al[7] (2013)	Prospective single arm study Multicenter ≥1 unresectable BMs >1.0 cm from her2neu+ breast cancer without prior SRS or WBRT treated with upfront lapatinib and capecitabine (n = 45)	III	5% complete response and 52% partial response by RECIST 82% received some form of radiation at a median of 8.3 months mOS = 17.0 months shows efficacy of systemic therapy alone prior to any form of radiation in BMs

Banfill et al[41] (2012)	Single institution retrospective review of various brain metastases (≥1) patients treated with SRS alone, before or after failure of WBRT (n = 58)	III	Total tumor volume is a strong predictor of prognosis (<5 cc vs >10 cc) or largest single tumor <5 cc Mixed population of histologies and mix of SRS alone, before or after failure of WBRT
Kano et al[27] (2009)	Single institution retrospective review various BMs invading cavernous sinus, (n = 37), 29 of 37 had failed fractionated RT, chemotherapy, or both	III	35.3% of patients showed improvement in neurologic symptoms after SRS
Muacevic et al[36] (2008)	RCT Multiple Center SRS (n = 31) vs resection + WBRT (n = 33) for single BM <3 cm	III	mOS 10.3 mos with SRS and 9.5 mos with WBRT Trial was stopped early for poor accrual, mixed histologies Because this study was stopped for poor accrual, and the accrual that did occur had diverse histologies impairing the data analysis further, the data yielded are evidence class III
Aoyama et al[34] (2006) and Aoyama et al[37] (2015)	RCT Multiple SRS (n = 67) vs SRS + WBRT (n = 65) for patients with 1-4 BMs <3 cc each 67% lung included in 2015 secondary analysis based on new DS-GPA	III	Adding WBRT to SRS decreased brain recurrence rate, but did not improve overall survival, functional preservation, or MMSE at 12 months. Secondary analysis found better mOS in NSCLC patients with DS-GPA of 2.5 to 4.0 with SRS + WBRT vs SRS alone (17 vs 11 months). Mixed population of histologies, single-institution, nonblinded
Rades et al[35] (2007)	Retrospective Single Center WBRT (n = 91) or SRS (n = 95) for 1-3 BMs in RPA class 1 or 2 patients (37% lung, 17% breast, and 46% other; 53% solitary metastases)	III	mOS not significantly different local control and brain control possibly improved with SRS vs WBRT mixed histologies without molecular subtypes or tumor volumes accounted for

Li (2000)	Prospective RCT Single Center 1 BM <4.5 cm SRS (n = 23) vs WBRT (n = 19) vs WBRT+ SRS SCLC and NSCLC	III	SRS vs WBRT mOS 9 vs 6 months. Inclusion of SCLC with high rate of leptomeningeal spread

BM, brain metastasis; DS-GPA, diagnosis-specific Graded Prognostic Assessment; MMSE, Mini-Mental State Examination; mOS, median overall survival; NSCLC, non–small cell lung cancer; RCT, randomized controlled trial; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

Table 4. What is the role of stereotactic radiosurgery alone in the management of patients with more than 4 brain metastases?

Author and Year	Description of Study	Data Class	Conclusions
Yamamoto et al[40] (2014)	Prospective single arm study Multicenter 1-10 BMs (total volume <15 mL) treated with SRS alone (n = 1194), 76% lung and 10% breast	III	No difference in mOS for patients with 2-4 vs 5-10 brain metastases (p = .0001) Total cumulative tumor volume had to be <15 mL for patients to be included
Chang et al[42] (2010)	Single institution retrospective review of various BMs (≥4) patients treated with SRS alone, together with WBRT or after failure of WBRT (n = 323)	III	>15 metastases had higher intracranial recurrence than <15, but similar survival "Mixed population of histologies and mix of SRS alone, SRS + WBRT, and SRS given at recurrence after WBRT
Bhatnagar et al[44] (2006) and Bhatnagar et al[45] (2007)	Single institution retrospective review of various BMs (≥4) patients treated with SRS alone, together with WBRT, or after failure of WBRT (n = 205)	III	Total tumor volume is a strong predictor of prognosis, <7 cc and 4-6 total metastases "Mixed population of histologies and mix of SRS alone, SRS + WBRT, and SRS given at recurrence after WBRT

BM, brain metastasis; mOS, median overall survival; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

Table 5. Factors influencing prognosis and treatment options for patients with brain metastases

Factor	Favors SRS	Favors WBRT
Total tumor volume	Low (< 7-13 cc)*	High (> 7-13 cc)*
DSGPA/RPA Prognosis	"Good"@	"Poor"@
Tumor radiosensitivity	Radioresistant$	Radiosensitive
Tumor number	1-2	≥5*
Chemotherapy efficacy in CNS	Effective#	Ineffective#
Leptomeningeal Risk	"Low"^	"High"^

*Most studies support total tumor volume as more predictive than total tumor number, but varying cut off volumes and dose levels were found in different studies, generally between 5-10 cc

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$Relatively radioresistant tumors would include melanoma, thyroid, renal, most sarcoma and squamous histologies

#Low quality data to support, but EGFR mutant lung cancer and Her2Neu positive breast cancer, possibly BRAF mutant melanoma. SCLC and lymphoma can be very responsive to systemic chemotherapy, but also have a high likelihood of widespread dissemination with leptomeningeal involvement and are radiosensitive. Early studies suggest some targeted agents may be given together with radiation and potentially improve its efficacy (erlotinib, lapatinib, tyrosine kinase inhibitors for renal clear cell). Durable responses to immunotherapies in the CNS have been reported in a subset of patients. Some have postulated that radiation-induced apoptosis might theoretically increase immunogenic stimulation prior to immunotherapies.

^Breast, especially triple negative and small cell lung cancer. Infratentorial tumor location and superficial dural/pial involvement may also confer higher risk.

Table 6. SRS after WBRT

In patients with recurrent brain metastases after receiving WBRT, studies support possible benefit of SRS, which also varies based on factors including recurrent tumor total volume (more than number), tumor histology, KPS, and systemic control (Caballero et al IJROBP 2012).[51]

Factor	Favors SRS	Favors Resection
Other accessible diagnostic source	Yes#	No#
Surgical risk	High	Low
Radiation risk of adjacent structures	Low	High
Total tumor volume	Low (<10 cc)	High (>10 cc)
Tumor radiosensitivity	Radiosensitive$	Radioresistant$
Tumor number	1-2	≥5

#Several studies have documented that molecular markers relevant for treatment may differ systemically and intracranially, and in comparison to markers obtained systemically prior to cranial involvement (e.g. her2neu status of breast adenocarcinoma). In addition, patients with prior histories of treated and controlled systemic cancers may present with second primaries of different histology.

$ relatively radioresistant tumors would include melanoma, thyroid, renal, most sarcoma and squamous histologies

Appendix A Search Strategies

PUBMED SEARCH

1. Brain Neoplasms [Mesh]
2. (brain OR brainstem OR intracranial) AND (cancer OR tumor* OR tumour* OR neoplasm*) [TIAB]
3. #1 OR #2
4. Neoplasm Metastasis [Mesh]
5. (brain OR brainstem OR intracranial) AND (Metastas*) [TIAB]
6. #4 OR #5
7. #3 AND #6
8. Brain neoplasms/secondary [Mesh]
9. #7 OR #8
10. Radiosurgery [Mesh]
11. Radiosurg* [TIAB] OR radio-surg* [TIAB] OR radio surg* [TIAB] OR SRS [TIAB] OR "gamma knife" [TIAB]
12. #10 OR #11
13. #9 AND #12
14. #13 AND English [Lang]
15. (animals [MeSH] NOT humans [MeSH]) OR case reports [PT] OR review [PT] OR comment [PT] OR letter [PT] OR editorial [PT] OR addresses [PT] OR news [PT] OR "newspaper article" [PT]
16. #14 NOT #15
17. #16 AND ("1990/01/01"[PDAT] : "2015/12/31"[PDAT])

EMBASE SEARCH

1. 'Brain tumor'/exp
2. ((brain OR brainstem OR intracranial) NEAR/3 (cancer OR tumor* OR tumour* OR neoplasm*)):ab,ti
3. #1 OR #2
4. 'brain metastasis'/exp
5. ((brain OR brainstem OR intracranial) NEXT/3 metastas*):ab,ti
6. #4 OR #5
7. #3 AND #6
8. 'Radiosurgery'/exp
9. 'Stereotaxic surgery'/exp
10. 'gamma knife'/exp
11. radiosurg*:ab,ti OR 'radio surg*':ab,ti OR 'radio-surg*':ab,ti OR srs:ab,ti OR 'gamma knife':ab,ti

12. #8 OR #9 OR #10 OR #11
13. #7 AND #12
14. #13 AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim) AND [embase]/lim AND [humans]/lim AND [english]/lim AND [1990-2015]/py
15. #14 NOT 'case report'/de

COCHRANE CENTRAL SEARCH

1. MeSH descriptor: [Brain Neoplasms] explode all trees
2. ((brain OR brainstem OR intracranial) NEAR/3 (cancer OR tumor* OR tumour* OR neoplasm*)):ti,ab,kw
3. #1 or #2
4. MeSH descriptor: [Neoplasm Metastasis] explode all trees
5. ((brain OR brainstem OR intracranial) NEAR/3 Metastas*):ti,ab,kw
6. #4 OR #5
7. #3 AND #6
8. MeSH descriptor: [Brain neoplasms/secondary]
9. #7 OR #8
10. MeSH descriptor: [Radiosurgery] explode all trees
11. (Radiosurg* OR radio-surg* OR radio surg* OR SRS OR "gamma knife"):ti,ab,kw
12. #10 OR #11
13. #9 AND #12

Publication year from 1990 to 2015, in Trials

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