CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE-BASED PRACTICE GUIDELINE ON THE ROLE OF SURGERY IN THE MANAGEMENT OF ADULTS WITH METASTATIC BRAIN TUMORS

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Brian V. Nahed, MD, MSc, Christopher Alvarez-Breckenridge, MD, PhD, Priscilla K. Brastianos, MD, Helen Shih, MD, MS, MPH, Andrew Sloan, MD, Mario Ammirati MD, MBA, John S. Kuo, MD, PhD, Timothy C. Ryken, MD, Steven N. Kalkanis, MD, and Jeffrey J. Olson, MD

1. Department of Neurosurgery, Massachusetts General Hospital, Boston, Massachusetts, USA
2. Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA
3. Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts, USA
4. Department of Neurosurgery, Case Western Reserve University, Cleveland, Ohio, USA
5. Department of Neurosurgery, St. Rita Medical Center, Lima, Ohio, USA
6. Department of Neurosurgery and Mulva Clinic for the Neurosciences, Dell Medical School, University of Texas at Austin, Austin, Texas
7. Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA
8. Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan, USA
9. Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia, USA

Correspondence:
Brian V. Nahed, MD, MSc
Massachusetts General Hospital
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Abbreviations
ECOG: Eastern Cooperative Oncology Group
GTR: Gross total resection
KPS: Karnofsky performance status
LMD: Leptomeningeal disease
MTR: Microscopic total resection
RPA: Recursive partitioning analysis
SRS: Stereotactic radiosurgery
STR: Subtotal resection
WBRT: Whole brain radiation therapy

No part of this manuscript has been published or submitted for publication elsewhere.
**Target population:** These recommendations apply to adult patients with newly diagnosed metastatic brain tumors, excluding radiosensitive tumor histologies.

**Surgery for metastatic brain tumors at new diagnosis**

**Question:** Should patients with newly diagnosed metastatic brain tumors undergo surgery, stereotactic radiosurgery (SRS), or whole brain radiation therapy (WBRT)?

**Recommendations:**

**Level 1:** Surgery + WBRT is recommended as first-line treatment in patients with single brain metastases with favorable performance status and limited extracranial disease to extend overall survival, median survival, and local control.

**Level 3:** Surgery + SRS is recommended to provide survival benefit in patients with metastatic brain tumors.

**Level 3:** Multimodal treatments including either surgery + WBRT + SRS boost or surgery + WBRT are recommended as alternatives to WBRT + SRS in terms of providing overall survival and local control benefits.

**Surgery and radiation for metastatic brain tumors**

**Question:** Should patients with newly diagnosed metastatic brain tumors undergo surgical resection followed by WBRT, SRS, or another combination of these modalities?

**Recommendations:**

**Level 1:** Surgery + WBRT is recommended as superior treatment to WBRT alone in patients with single brain metastases.

**Level 3:** Surgery + SRS is recommended as an alternative to treatment with SRS alone to benefit overall survival.

**Level 3:** It is recommended that SRS alone be considered equivalent to surgery + WBRT.

**Target population:** These recommendations apply to adult patients diagnosed with recurrent, non-radiosensitive metastatic brain tumors.

**Surgery for recurrent metastatic brain tumors**

**Question:** Should patients with recurrent metastatic brain tumors undergo surgical resection?

**Recommendation:**

**Level 3:** Craniotomy is recommended as a treatment for intracranial recurrence after initial surgery or SRS.
Surgical technique and recurrence

**Question A:** Does the surgical technique (en bloc resection or piecemeal resection) affect recurrence?

**Recommendation:**

*Level 3:* En bloc tumor resection, as opposed to piecemeal resection, is recommended to decrease the risk of postoperative leptomeningeal disease when resecting single brain metastases.

**Question B:** Does the extent of surgical resection (gross total resection or subtotal resection) affect recurrence?

**Recommendation:**

*Level 3:* Gross total resection is recommended over subtotal resection in recursive partitioning analysis Class I patients to improve overall survival and prolong time to recurrence.
INTRODUCTION

Rationale
Surgery is recommended for brain metastases that are large, have significant perilesional edema, result in neurological deficits, and present with uncertain pathology. In addition, surgery provides tissue diagnosis, when needed. Smaller targeted craniotomies and an emphasis on minimizing postoperative deficits have led to faster operations and discharge a few days after a craniotomy. Given the limitations of radiation therapy and other targeted therapies, surgery plays a critical role for patients, the timing of which is discussed in this guideline.

METHODS

Writing Group and Question Establishment
The writers represent a multi-disciplinary panel of clinical experts encompassing neurosurgery, neuro-oncology, and radiation oncology. Together, they were recruited to develop these evidence-based practice guidelines for surgery for metastatic brain tumors. Questions were developed following salient clinical questions from the collective clinical panel. Questions were framed to build upon prior surgical guidelines for brain metastases and incorporate new developments in the field.

Literature Review

Article Inclusion and Exclusion Criteria
Eligibility Criteria
1. Peer-reviewed publications.
2. Patients with newly diagnosed and recurrent brain metastases who have had surgery.
3. Each study had ≥5 or more subjects.
4. Patients <18 years of age. Studies with mixed adult and child populations were included if the adult cohorts could be isolated and analyzed separately.
5. Publications in English.
Study selection and quality assessment

The search criteria were developed and abstract review was performed by two independent reviewers. Citations were independently reviewed and included if they met the a priori criteria for relevance. No discrepancies in study eligibility were noted. Corresponding full-text PDFs were obtained for all citations meeting the criteria, and were reviewed. Data were extracted by the first reviewer and verified by another, all of which were compiled into evidence tables. The tables and data were reviewed by all of the authors. Articles that did not meet the selection criteria were removed.

Evidence Classification and Recommendation Levels

Each reviewer independently determined the strength of the evidence, classified it according to the criteria described above, and a consensus level of recommendation was achieved. Additional information on the method of data classification and translation to recommendation level can be found at https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

Guideline Development Process

Assessment for Risk of Bias

The literature search generated a list of abstracts, which were screened, and those articles that addressed the identified questions underwent full manuscript independent review by the authors. Reviewers were critical in their assessment of trial design, including whether the study was retrospective, a single surgeon cohort, 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. Given the diversity in primary sites of metastatic brain tumors, articles were screened for their conclusions as they related to a single type of brain metastasis (eg, melanoma) or brain metastases in general (eg, lung, breast, and melanoma combined into one group). Studies were rated on the quality of the published evidence and the factors mentioned above. Level I was reserved for well-designed randomized controlled studies with clear mechanisms to limit bias. Level II recommendations described studies that were randomized control studies with design flaws leading to bias that limits the paper’s conclusions, non-randomized cohort studies, and case-control studies. Level III recommendations were reserved for single surgeon, single institutional case series, comparative
studies with historical control, and randomized studies with significant flaws related to under-
powered studies and statistical analysis. Additional information on study classification and
recommendation development can be found at https://www.cns.org/guidelines/guideline-
procedures-policies/guideline-development-methodology.

RESULTS

Study Selection and Characteristics

The search criteria yielded 1060 publications, which were reviewed by two authors
independently. Of these, 121 studies met the eligibility criteria and were screened for inclusion.
Of these, 32 studies met the criteria and specifically focused on surgery for metastatic brain
tumors either at initial diagnosis or at recurrence. Figure 1 depicts the number of studies in each
part of the selection and review process.

Summary of Prior Recommendations

In the previously published guidelines on surgery for the management of newly diagnosed brain
metastases, two questions were answered by Level 1 recommendations. First, the question of
surgical resection plus WBRT versus surgical resection alone, Kalkanis et al.\(^1\) concluded that
surgery followed by WBRT represented a superior treatment modality in terms of improving
tumor control at the original site of metastasis and in the brain when compared to surgical
resection alone. Second, for the question of surgical resection plus WBRT versus WBRT alone,
Kalkanis et al.\(^1\) concluded surgery plus WBRT is superior in patients with good performance
status and limited extracranial disease.

Should patients with newly diagnosed metastatic brain tumors undergo surgery, stereotactic
radiosurgery, or whole brain radiation therapy?

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

Multiple Class III retrospective studies investigated the question of surgery versus radiation
therapy as a first-line treatment for newly diagnosed brain metastases. Among these studies
across various metastatic histologies, surgery resulted in significant\(^2-10\) or nearly significant\(^11,12\)
improvement in overall survival compared to either whole brain radiation therapy (WBRT) or
stereotactic radiosurgery (SRS). These results were distributed among studies investigating
single \(^3,4,9\) and multiple brain metastases.\(^5-8,10-12\) In these studies, patients were treated with
either surgery alone\(^8,9,12\) or surgery plus radiation therapy. Combinations of surgery and
radiation therapy included WBRT,\(^3,4,6,11\) SRS,\(^7,12\) or a combination of approaches.\(^2,5,10,13\)
Lindvall et al\textsuperscript{4} compared surgery plus WBRT to hypofractionated stereotactic irradiation. Surgery plus WBRT for small tumors (volumes <10 cc) may provide a survival advantage, particularly in areas of non-eloquent brain. Several retrospective Class III studies have identified factors to consider prior to proceeding with surgery. Low Karnofsky Performance Status (KPS) was associated with poor surgical outcome in multiple studies.\textsuperscript{3, 14-16} Two Class III studies demonstrated that surgery as part of a multimodal treatment was non-inferior to WBRT plus SRS. Rades et al\textsuperscript{13} performed a matched pair analysis of 92 patients across various histologic subtypes to demonstrate equivalent 1-year local control, 1-year intracerebral control, and 1-year survival between surgery plus WBRT plus radiation boost and WBRT plus SRS. Additionally, the retrospective analysis by d’Agostino et al\textsuperscript{17} evaluated surgery plus WBRT compared to WBRT plus SRS and yielded similar rates of local control or overall survival at 1 or 5 years, suggesting equivalence of both approaches. However, the authors failed to account for tumor size or control of extracranial disease between groups, making the interpretation of these results challenging. Examples of additional limitations from these studies include treatment group imbalances,\textsuperscript{2, 6, 12} retrospective analyses,\textsuperscript{2-5, 7} non-randomization into surgical versus radiation treatment groups, variations in adjuvant therapies,\textsuperscript{9} small study size,\textsuperscript{2, 7, 8} combination of multiple tumor histologies into a single brain metastases group,\textsuperscript{3, 4} lack of control for tumor location,\textsuperscript{2, 3} lack of consideration of tumor size in enrollment criteria,\textsuperscript{3} and incomplete statistical analyses.\textsuperscript{5}

\textbf{Synthesis of Results}

Consistent with previously published guidelines by Kalkanis et al.,\textsuperscript{1} surgery plus WBRT has been re-demonstrated as a superior treatment modality to WBRT alone.\textsuperscript{2, 3, 6} Surgery plus SRS was superior to SRS alone in multiple studies.\textsuperscript{7, 10} The data for surgery versus SRS alone were conflicting\textsuperscript{8, 9, 12} and was explained in part by treatment selection bias inherent in retrospective analyses. Similar uncertainty was seen in the comparison between surgery plus WBRT and SRS alone.\textsuperscript{11} Additionally, Baykara et al\textsuperscript{6} demonstrated improved overall survival in the surgery plus WBRT group compared with WBRT plus SRS, although additional studies are warranted to validate the superiority of either treatment approach. Also the strength of the conclusions about the value of combinations of these modalities is limited by the lack of randomized controlled trials addressing these questions.

\textit{Should patients with newly diagnosed metastatic brain tumors undergo surgical resection}
followed by WBRT, SRS, or other combination of these modalities?

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

Two Class III studies indicate that surgery followed by WBRT results in improvement in median survival\(^6,18\) and local failure relapse-free survival\(^6\) for surgery combined with WBRT compared to WBRT alone. However, both studies were limited in their imbalance between treatment groups \(^6\) or lack of baseline characteristics between treatment groups.\(^18\) There are 2 Class II and 5 Class III studies to support a benefit for surgery followed by WBRT,\(^6,11,17-19\) SRS,\(^20,21\) or WBRT plus SRS.\(^20,21\) In contrast, the data for surgery followed by WBRT compared to SRS alone are less clear. The studies of Muacevic et al\(^19\) and Marko et al\(^11\) failed to demonstrate a difference between these 2 groups in terms of overall survival. However, the study by Marko et al\(^11\) demonstrated a trend towards improved mean survival in patients treated with surgery plus WBRT compared with SRS alone (20.1 months vs 12.3 months, \(p = .07\)). Surgery combined with WBRT compared with WBRT plus SRS was equivalent between groups.\(^17\) The retrospective study by d’Agostino et al\(^17\) failed to demonstrate a difference in local control or overall survival at 1 or 5 years but also failed to demonstrate an association between traditional prognostic factors and overall survival.

In a matched pair analysis for patients with 1 to 2 brain metastases, patients undergoing surgery with WBRT and an SRS boost had similar median survival, 1-year survival, and 1-year local control compared to patients undergoing WBRT and SRS.\(^21\) Similarly, Wang et al\(^20\) demonstrated in a retrospective analysis of 528 patients that surgery combined with SRS and WBRT resulted in improved overall survival compared to SRS alone on multivariate analysis but was equivalent to SRS plus WBRT or surgery plus SRS.

**Synthesis of Results**

Consistent with previously published guidelines by Kalkanis et al.,\(^1\) surgery plus WBRT has been re-demonstrated as a superior treatment modality to WBRT alone.\(^2,3,6\) Although Class III published reports suggest the benefit of surgery plus WBRT compared with WBRT alone,\(^6,18\) findings of surgery plus WBRT compared to multimodal radiation approaches was conflicting and underpowered in class II and III studies.\(^6,13,17,19\) Similarly, surgery plus SRS was shown to be superior to SRS alone\(^7,10,20\) but superiority among surgery plus SRS, SRS plus WBRT, or surgery plus SRS plus WBRT was not demonstrated. These findings suggest a lack of overarching evidence to support surgery plus SRS or surgery plus WBRT compared to multi-
modal radiation approaches and requires interpretation of clinical features such as performance status, number of brain metastases, intracranial tumor location, and control of extracranial disease.

Should patients with recurrent metastatic brain tumors undergo surgical resection?

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

Two Class III studies found a benefit for the role of reoperation for recurrence after an initial craniotomy for metastatic disease.22, 23 Three Class III studies have suggested a role for surgery following failed stereotactic radiotherapy.24-26 Although a time interval between SRS and resection of ≥3 months was associated with improved overall survival,24 these findings raise the concern that these patients with delayed recurrence are biased to have improved overall survival compared to short-term SRS failure. Additionally, patients with viable tumor on resection had a decreased mean survival in contrast to those patients with radiation necrosis,25 suggesting that surgery can be useful in distinguishing tumor recurrence from pseudo-progression and its associated impact on overall survival, but did not provide a comparison between surgery for recurrence compared to other treatment modalities.

Synthesis of Results

Although craniotomy for recurrence was associated with improved survival, attention should be given to preoperative functional status, age, extracranial disease, and the interval between SRS and resection.22, 24 In particular, the role of surgery for recurrence in patients >65 years of age or with an interval between SRS and surgery of <3 months is uncertain. Additionally, Obermueller et al26 suggest that surgery for recurrence after radiation in either eloquent or non-eloquent cortex leads to a higher risk of postoperative deficits. These results suggest that additional studies are warranted to investigate how resection following radiation therapy affects patients in terms of quality of life and distinguishes radiation necrosis from tumor recurrence by providing diagnostic information to guide future therapy. Moreover, these findings demonstrate the need to systemically investigate novel treatments, such as laser interstitial thermal therapy for recurrent disease that is refractory to SRS and that is located in surgically inaccessible areas.

Does surgical technique (en bloc resection or piecemeal resection) affect recurrence? Does the extent of surgical resection (gross total resection or subtotal resection) affect recurrence?

Results of Individual Studies, Discussion of Study Limitations, and Risk of Bias
En bloc resection or piecemeal resection

Three Class III studies demonstrate en bloc resection to be superior to piecemeal resection and a decreased risk of leptomeningeal disease (LMD) in single melanoma brain metastases located in the lateral ventricle, improved overall survival, a lower complication rate, and local recurrence, particularly in tumors < 9.71 cm³. However, Patel et al demonstrated that the median volume of tumors resected by a piecemeal approach was 15.87 cm³ compared with 7.59 cm³ for en bloc resection, suggesting that these non-standardized treatment groups and associated technical limitations may have biased these results. Additional limitations from Patel et al were reflected in the retrospective design. For instance, there were significant differences between treatment groups requiring statistical correction, and the authors were unable to assess 30-day postoperative KPS due to incomplete clinical documentation, and there were limitations in accounting for surgical limitations that could prevent en bloc resection in eloquent cortex.

Gross total resection or subtotal resection

Consistent with the advantages of en bloc resection, gross total resection (GTR) was shown to be generally superior to subtotal resection (STR) in terms of median survival and time to local recurrence. Of note, the improved overall survival demonstrated by Lee et al was found in recursive partitioning analysis (RPA) Class I patients with KPS ≥ 70 and age < 65 years with controlled primary and no extracranial metastases. There was a significant improvement in median survival for GTR plus SRS (14.1 months) compared with either STR plus SRS (7.1 months) or SRS alone (6.9 months) (p = .032). LMD was not associated with en bloc nor subtotal resection on univariate analysis. A potential limitation of studies looking at GTR and en bloc resection is the role of infiltrating tumor cells beyond the border of a brain metastasis. To address this, a Class III study found that microscopic total resection (MTR) was associated with improved local control and decreased local recurrence, but was not associated with improved overall survival compared to GTR.

Synthesis of Results

Several studies have directly examined the role of en bloc resection and GTR in terms of improved overall survival, fewer postoperative complications, reduction of LMD, and time to local recurrence. The literature supports resection of brain metastases with the goal of GTR ideally through an en bloc approach. Future studies are warranted to investigate the role of surgical approach and LMD. In particular, identification of surgical patients who are at highest
risk of developing LMD is needed. This may include tumor location, histology, and tumor
features (solid, cystic, or encapsulated) and the development of techniques to reduce the risk of
LMD in high-risk groups. Clinical judgment is critical to application of these considerations
when the tumor resides in eloquent cortex. Additionally, prospective studies are needed to
evaluate the benefit of GTR through en bloc resection for multiple brain metastases, to
differentiate across multiple RPA classes, and to investigate MTR to target infiltrating tumor
cells.

**SUMMARY AND DISCUSSION**

Multiple retrospective studies demonstrated the benefit of initial surgery compared with radiation
therapy alone, particularly in patients with KPS > 70,2 younger age,7 favorable RPA class,5 and
lower Eastern Cooperative Oncology Group (ECOG) score,7 control of primary tumor,8 brain
metastases diameter < 4 cm,9 and complete surgical resection.7 However, conclusions regarding
these findings were limited due to the lack of high-quality randomized controlled trials.

The findings of Rades13 (Class II) and D’Agostino17 (Class III) raise further questions about the
role of surgery followed by adjuvant SRS and WBRT compared to WBRT plus SRS. Although
a multimodal surgical approach was non-inferior to WBRT plus SRS, further studies are
warranted to understand the appropriate use of surgery in terms of the number of brain
metastases, tumor location, and optimal timing between surgery and adjuvant radiotherapies.
Lastly, Lindvall et al raised a point regarding optimal tumor size for radiation therapy versus
surgery. Although smaller tumors are typically targeted with radiotherapy rather than surgery,
these authors demonstrated that surgery plus WBRT was superior to hypofractionated
stereotactic irradiation for tumors <10 cc. These findings suggest that surgery plus WBRT
should be considered for smaller lesions in non-eloquent cortex. The validity of these findings in
a randomized controlled study is warranted, particularly given the risk of neurotoxicities
associated with WBRT and the increasing use of SRS among neuro-oncologists and radiation
oncologists. In particular, attention should be given towards surgery alone compared with
surgery plus adjuvant SRS or surgery plus multimodal SRS + WBRT radiotherapy, as well as a
determination of a lower tumor volume threshold for surgical resection.

The role of surgery for recurrence warrants further investigation with delineation between
surgery and SRS as the initial treatment modality. In particular, there is a propensity towards treating patients with SRS in the setting of tumor in eloquent cortex, smaller tumor size, and an increased number of brain metastases. A current NRG study is attempting to control for these factors in a randomized fashion in order to determine if the role of surgery is most beneficial after initial surgical resection\textsuperscript{22, 23} rather than initial SRS.\textsuperscript{26} As future developments in radiographic imaging help clarify pseudo-progression following SRS, it will guide in surgical decision making with respect to concern for tumor recurrence.

Surgical technique, particularly piecemeal versus en bloc resection and GTR versus STR, was addressed in several studies. Collectively, these analyses found that en bloc resection and GTR were superior surgical approaches and that piecemeal resection was associated with an increased risk of LMD. A limitation of these studies, however, was the difference in initial tumor size between piecemeal and en bloc resection. Given limitations based on tumor size and location, an en bloc resection may not be feasible and may predispose a patient to an increased risk of postoperative complications. In addition to controlling for these factors, future studies are needed to study the role of adjuvant radiation therapy (SRS, WBRT, or both) in the setting of en bloc and piecemeal resection.

**CONCLUSIONS AND KEY ISSUES FOR FUTURE INVESTIGATION**

Looking towards the future, the authors found that there were several topics that were not adequately addressed in the literature. In particular, studies typically included patients with 1 to 4 brain metastases who had surgery for the largest or symptomatic lesion. Although initial publications are encouraging, additional studies are necessary to establish the settings in which there is value in the routine use of surgical resection of two or more metastases. Several studies investigated the role of surgery for recurrence after SRS or initial surgery. However, there is a lack of studies examining the role of synchronous surgical resection for multiple intracranial metastases, as well as a lack of studies examining the appropriate adjuvant radiation regimen for patients undergoing resection of these lesions.

An additional area of interest is the role of surgery in patients undergoing immunotherapy for brain metastases. Lonser et al. presented an initial retrospective analysis of patients with metastatic melanoma treated with surgery and immunotherapy (interleukin-2 [IL-2], IL-12,
immunotoxin, vaccine, adoptive cell therapy, and monoclonal antibody). Among the cohort, adjuvant WBRT in 36% of the patients was not associated with improved survival, local, or distant brain recurrence rates. However, these findings warrant further attention as novel immunotherapeutic approaches are being applied to brain metastases. Additionally, the role of SRS, WBRT, and the combination of both adjuvant agents have not been investigated in the setting CTLA-4 and PD-1 blockade.

Advances in the management of metastatic brain tumors have led to better outcomes and longer survival. Surgery plays a large role at initial diagnosis and recurrence. Future investigation into the timing of when and how often to perform surgery while taking into account newer chemotherapeutic/immunological regimens, and radiation therapy, especially at recurrence, is critical to clearly define the role of surgery with respect to progression-free and overall survival. Lastly, emerging surgical techniques including laser interstitial therapy and minimally invasive tubular approaches are emerging surgical techniques that warrant investigation for single versus multiple brain metastases, time to adjuvant therapy, need for post-operative immunosuppressants, optimal tumor locations, and quality of life metrics as compared with conventional craniotomy.

Conflict of Interest (COI)
The Update Brain Metastases Guidelines Task Force members were required to report all possible COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines 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.

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.

Disclosures

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Figure 1: PRISMA flowchart

Records Identified through database searching
(n=1060)

Records screened
(n=1060)

Records excluded at title and abstract
(n=942)

Full-text articles assessed for eligibility
(n=118)

Studies included in qualitative synthesis
(n=32)

Full-text articles excluded
(n=86)
Less than 5 surgical patients: 1
Non-consistent inclusion criteria: 4
Non-extractable data: 24
Non-comparative study: 16
Comparison of radiosurgical approaches: 12
Statistical concerns: 8
Reviews: 21
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<tr>
<th>Author, Year</th>
<th>Study Description</th>
<th>Data Class</th>
<th>Conclusion</th>
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<td>Bougie et al, 2015</td>
<td>Retrospective single institution study of 115 patients with a single brain metastasis from non–small cell lung cancer who were treated initially with either surgery (43 patients) or SRS (72 patients)</td>
<td>III</td>
<td>The SRS cohort on average had smaller tumors (4.4 mL) compared with the surgery cohort (25.3 mL). Local control was the same between groups. Median survival for surgical group was 13.3 months compared with 7.8 months for SRS ($p = .047$). In multivariate analysis of the surgical group, brain metastasis diameter &lt;4 cm and thoracic management of primary lung cancer with curative intent were both associated with prolonged survival ($p = .001$). Within the SRS group, patients with metachronous metastasis showed improved survival ($p &lt; .001$). Brain metastasis diameter &lt;4 cm was associated with improved local control in the surgical group ($p = .005$). Among the SRS group, radiation dose &gt;20 Gy to the margin was associated with improved local control ($p = .007$). Of note, patients in both groups received variable adjuvant therapies for local and distant recurrences.</td>
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Patel et al, 2015

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<tr>
<th>Authors</th>
<th>Study Description</th>
<th>Results</th>
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<tr>
<td>Patel et al, 2015</td>
<td>Single institution retrospective analysis of 1033 patients undergoing resection of a previously untreated single brain metastasis. Patients underwent either en bloc resection (62%) or piecemeal resection (38%)</td>
<td>There were significant differences between the two groups, including preoperative tumor volume, KPS, tumor functional grade, preoperative tumor volume, hemorrhagic tumor, cystic tumor, and symptoms. The 1-month mortality between groups was similar between groups. The complication rate for en bloc resection was 13%, compared to 19% for piecemeal resection ($p = .007$), and for major complication rates were 7% vs 10% between the two groups ($p = .04$). These differences were significant on multivariate analysis. The 30-day neurologic complication rate for piecemeal resection was 13% compared to 8% for en bloc resection ($p = .03$); however, the incidence of major neurologic complications was similar between groups. The incidence of overall complications, neurologic complications, and select neurologic complications was significantly higher for piecemeal resection in eloquent brain compared to en bloc resection; however, there was not a difference in 1-year mortality or major neurologic complications.</td>
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<td>Quigley et al, 2015</td>
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<td>Retrospective analysis of 162 consecutive patients with oligometastatic disease who underwent surgery + SRS boost (49 patients) or SRS alone (113 patients). Patients who received prior WBRT were excluded.</td>
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<td>RPA class was statistically different between groups. The surgery + SRS group had larger maximal tumor dimension, larger treatment volume, lower average radiation dose to tumor margin, and initial tumor volume. Median survival for complete resection + SRS vs incomplete resection + SRS vs SRS alone was 14.1 months, 7.1 months, and 6.9 months respectively (p = .032). Overall survival was associated with complete surgical resection (HR = 0.55, p = .01), age (HR = 1.21/decade, p = .37), and ECOG score (HR = 1.9, p = .01). Time to local recurrence was associated with radiation-sensitive pathology (HR = 0.34, p = .001), treatment volume (HR = 1.078/mL, p = .002), and complete tumor resection (HR = 0.37, p = .015). Incomplete tumor resection and SRS alone had equivalent time to local recurrence and median survival. Using propensity score matching ad Cox regression demonstrated that complete resection was a significant factor in survival (HR = 0.52, p = .03)</td>
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<td>Wang et al, 2015</td>
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CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; GTR, gross total resection; HCSRT, hypofractionated stereotactic irradiation; HR, hazard ratio; KPS, Karnofsky Performance Status; LMD, leptomeningeal disease; MTR, microscopic total resection; RCC, renal cell carcinoma; RPA, recursive partitioning analysis; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.
Appendix A: Primary Search Strategies

**OVID MEDLINE, searched on Aug 9, 2016:**

1. brain neoplasms/
2. brain neoplasms/su
3. (brain neoplasm$ or brain tumor$ or brain tumour$ or brain cancer or brain lesion$).ti,ab.
4. (surgery or surgical or operative or resect$).ti,ab.
5. Neoplasm Metastasis/
6. (Metastasis or Metastases or metastatic or metastasize$ or metastasise$).ti,ab.
7. 1 and 4 and (5 or 6)
8. 2 and (5 or 6)
9. 3 and 4 and (5 or 6)
10. 7 or 8 or 9
11. age-18-and-under/
12. (pediatr$ or paediatr$ or child$ or infan$ or adolesc$).ti,ab,hw,jn,jw,de.
13. 11 or 12
14. 10 not 13
15. (brain or surgery or surgical or operative or resect$ or metas$).ti.
16. 14 and 15
17. ("more than 1" or "1 or more" or multiple).ti,ab.
18. (case report$ or comment or editorial or letter or news or patient education handout or portraits).pt,ti.
19. 16 not 18
20. limit 19 to (english language and yr="2008 - 2015")
21. 17 and 20
22. 22. 20 or 21

**PUBMED (NLM), searched on August 17, 2016:**

((Metastasis[Title] OR Metastases[Title] OR metastatic[Title] OR metastasize*[Title] OR metastasise*[Title])) AND (surgery[Title] OR surgical[Title] OR operative[Title] OR resect*[Title])) AND brain[Title]

OR

((Metastasis[Title] OR Metastases[Title] OR metastatic[Title] OR metastasize*[Title] OR metastasise*[Title])) AND (surgery[Title] OR surgical[Title] OR operative[Title] OR resect*[Title])) AND Brain Neoplasms [Majr]

(multiple[Title/Abstract] OR "more than 1"[Title/Abstract])
Filters: Publication date from 2008/01/01 to 2015/12/31; Humans; English; Adult: 19+ years
Total: 1060 results
REFERENCES


