



**CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND  
EVIDENCE-BASED GUIDELINES FOR THE TREATMENT OF ADULTS WITH  
METASTATIC BRAIN TUMORS: INTRODUCTION AND METHODS**

*Sponsored by*

The Congress of Neurological Surgeons and the Section on Tumors

*Affirmation of Educational Benefit by*

The Congress of Neurological Surgeons and the American Association of Neurological Surgeons

Jeffrey J. Olson, MD,<sup>1</sup> Steven N. Kalkanis, MD,<sup>2</sup> and Timothy C. Ryken, MD, MS<sup>3</sup>

1. Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia

2. Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan

3. Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

*Correspondence:*

Jeffrey J. Olson, MD

Department of Neurosurgery

Emory University School of Medicine

1365B Clifton Road, NE,

Atlanta, GA 30322

E-mail: [jolson@emory.edu](mailto:jolson@emory.edu)

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

**ABSTRACT**

**Background:** The Congress of Neurological Surgeons systematic review and evidence-based clinical practice parameter guidelines for the treatment of adults with metastatic brain tumors

was first published in 2010. Based upon the time elapsed since that publication, an update of this set of guidelines based upon literature published since is now indicated.

**Objectives:** The objective of these guidelines was to establish the best evidence-based management of metastatic brain tumors over all commonly used diagnostic and treatment modalities in regularly encountered clinical situations.

**Methods:** Literature searches regarding the management of metastatic brain tumors with whole brain radiation therapy, surgery, stereotactic radiosurgery, chemotherapy, prophylactic anticonvulsants, steroids, instances of multiple brain metastases, and emerging and investigational therapies were carried out to answer questions designed by consensus of a multidisciplinary writing group.

**Results:** Recommendations were created and their strength linked to the quality of the literature data available thus creating an evidence-based guideline. Importantly, shortcomings and biases to the literature data are addressed to provide guidance for future investigation and improvements in the management of metastatic brain tumors.

**Conclusions:** This series of guidelines was constructed to assess the most current and clinically relevant evidence for management of metastatic brain tumors. They set a benchmark regarding the current evidence base for this management while also highlighting important key areas for future basic and clinical research, particularly on those topics for which no recommendations could be formulated.

## **INTRODUCTION**

### **Background and Rationale**

Guidelines on the management of metastatic brain tumors were published in 2010 and endorsed by the American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS).<sup>1-8</sup> A component of that set of guidelines was recognition that updates would eventually be necessary so as to allow the recommendations to be modified to stay abreast of advances in the care and management of metastatic brain tumors. This updated set of guidelines has been created in response to that recognition.<sup>9-16</sup>

Although there are data to show that it is declining in incidence, cancer remains an important health problem as it is estimated there were more than 1.6 million new cancer cases in the United States in 2015.<sup>17</sup> Although there a number of ways of measuring it, the estimated

prevalence of new brain metastases in the United States is between 7 and 14 persons per 100,000 based on population studies. On the basis of an official census of nearly 310 million people in the United States, the expected incidence of newly diagnosed patients with brain metastases is estimated to be between 21,651 and 43,301 annually.<sup>18, 19</sup> Metastases from lung, breast, and melanoma primary tumors make up the bulk of the lesions identified.<sup>20</sup> The reasons for this increase in incidence cannot be discerned exactly but is probably due to a combination of improved imaging, an increase in the prevalence of cancers prone to metastasize to the brain, and improved survival of patients with cancer.<sup>21</sup> Between 1983 and 2009, Nieder et al. reported a decline in the incidence of lung cancer brain metastases, and an increase in the incidence of melanoma, colorectal, and kidney brain metastases, as well as the relative stability in the incidence of breast cancer brain metastases cases.<sup>22</sup>

These guidelines include sections similar to those previously published, including topics such as surgery, radiation and chemotherapy. Additionally, the task force concluded that there would be value in adding sections on the management of multiple metastases and radiation necrosis.

The methods and style used here are adapted from and similar to other guidelines projects endorsed by the AANS and CNS. This coherence and repetitive nature is intentionally used for the purposes of reproducibility and streamlining the administration of their creation. Each section was developed with recognition of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist items.<sup>23</sup> The manner in which these points are addressed varies by section depending on the nature of the information available.

By way of definition, this systematic review and subsequent set of guidelines defines brain metastases as solid metastases to the brain from systemic cancer. The definition excludes leptomeningeal metastatic disease.

## **Objectives and Guideline Panel Development**

Recognizing the important health impact of metastatic brain tumors along with the lack of consensus among various treatment options, the Joint Tumor Section recommended that evidence-based guidelines be developed as a top priority, for the diagnosis, management, and treatment of patients with metastatic brain tumors. The objectives of these guidelines are to

establish the best evidence-based management of metastatic brain tumors in terms of whole brain radiation therapy, surgery, stereotactic radiosurgery, chemotherapy, prophylactic anticonvulsants, steroids, and instances of multiple brain metastases. Because the management of these tumors remains imperfect, it was also recommended that information on promising emerging therapies be assessed in the same manner to determine the possible application of these findings.

Having identified the topical objectives, the Guidelines Committee of the Joint Tumor Section then recruited experts in the field from each of the parent organizations as lead authors of each section (Table 1). These authors, in turn, recruited experts in non-neurosurgical specialties relevant to the field of management and therapy chosen. The authors were provided with training on the method of guideline development as used in this guideline set, using stepwise written instructions and then providing direct guidance as needed for each writer. The senior authors and CNS Guidelines Manager then worked with them on a step-by-step basis to confirm that the methods were followed as the literature was collected and assessed, and the documents were developed. When the authors were approached and preliminarily agreed to participate, they were asked to complete a formal conflict of interest (COI) questionnaire confirming the appropriateness of their participation. The authors also agreed to report any new conflicts of interest that might develop during the writing process. In this manner, a multidisciplinary panel of authors referred to as the Metastatic Brain Tumor Guidelines Task Force was assembled (with significant administrative, logistical, and analytical support from the CNS Guidelines Committee). The method of this evidence-based clinical practice parameter guideline has been written in a manner to be as transparent as possible using published assessment criteria.

## **METHODS**

### **Topic Range of this Systematic Review and Evidence-Based Clinical Practice Guideline**

Having identified authors for each topic, the members assessed the questions from the previously published guidelines.<sup>2-8</sup> They either kept them as they were or in some cases modified and updated them, and also added additional questions to allow for assessment of the literature in a manner that would provide guidance for the management of metastatic brain tumors. These questions are presented at the beginning of each of the eight guideline chapters spanning the topics of whole brain radiation therapy, surgical resection, stereotactic radiosurgery, chemotherapy, prophylactic anticonvulsants, steroid use, management of multiple brain

metastases, and emerging and investigational therapies. The questions developed for each section are summarized in Table 2.

### **Literature Examination Approach**

A wide-ranging literature search strategy was undertaken to identify all citations relevant to the management of metastatic brain tumors. The MEDLINE (utilizing the PubMed or Ovid interface) and Embase® electronic databases were searched with additional data being gleaned from the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials. The date range was from October 2008 through December 2015 for questions that were unchanged from the guidelines published in 2010. For new questions or questions modified significantly from the 2010 publication, the date range for the searches was chosen as January 1990 through December 2015. Additionally, important articles from before this interval were reviewed and included if deemed to be critical evidence by the task force. The search strategies used a combination of controlled vocabulary terms and text words. The specifics of the searches for a given topic are outlined in each respective guideline section. Reference lists of the publications chosen for full-text review were also screened for potentially relevant studies.

### **Study Selection, Quality Assessment and Statistical Methods**

The search of the bibliographic databases identified possibly relevant citations for a given topic and often these were large in number. The eligibility (inclusion/exclusion) criteria to screen the citations for each of the questions were determined ahead of time for each section by the respective writing group. These are documented in the individual clinical practice guideline sections in this series to assist the reader in understanding the development process. At least two authors evaluated the titles and abstracts using the inclusion and exclusion criteria with broad interpretation of the criteria being used initially so as to maximize the likelihood of capturing pertinent information. Cases of disagreement about pertinence were resolved by a third author when needed. The full-text articles of the selected abstracts were then collected and the same process of applying the eligibility criteria was carried out again with the more detailed information available in the manuscripts. Articles that met the eligibility criteria were grouped according to the questions they addressed and used to create the evidence tables and results sections. Reasons for exclusion for papers were also documented to be able to discuss pertinent problem citations in the results sections as needed.

Studies that met the eligibility criteria were subject to more detailed scrutiny. Their data were extracted by one reviewer and the extracted information was checked by one or more other reviewers. Evidence tables, reporting the extracted study information and evidence classification, were generated for all of the included studies. Evidence tables were created with the most recent data first and subsequent listings in retrograde chronological order. The table headings consisted of first author name and year, followed by a brief study description, chosen data class, and conclusion. The authors were directed to craft the data in the tables in a succinct and fact-filled manner to allow for rapid understanding of the literature entry by the readership. The literature in the evidence tables was expanded upon in the results section of each section to emphasize important points supporting its classification and contribution to recommendations. Additional information about the methods used in this systematic review can be found at <https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology>.

Internal drafts of the tables and manuscripts were developed by sharing them between authors electronically, by telephone, and in person meetings. Summary and conclusion statements were included for each section, with comments on key issues for future investigation being added where pertinent. When adequate data were presented in the manuscripts, the authors made an effort to measure the agreement between observations or observers beyond chance using the kappa statistic.

### **AANS/CNS Evidence Classes and Levels of Recommendations**

The evidence classifications were then used to create recommendations, the strength of which were graded according to the Joint Guidelines Review Committee (JGRC) Guideline Development Methodology (Tables 3-6). The class of evidence assigned to each study was based on study design (ie, Class I, II, or III). The strength of the recommendations made (ie, Level 1, 2, or 3) was directly linked to the evidence classification and took into account aspects of study quality and whether or not the plan was accomplished, not just study design. To restate, Class I evidence could be extrapolated to Level 1 recommendations or lower, Class II evidence could be extrapolated to Level 2 evidence or lower, and Class III evidence could only yield Level 3 recommendations. Specifically, the level of a recommendation made could be decreased, based on consensus input by the writing group, if there were methodological concerns regarding the studies that provided evidence for that particular recommendation. Additional information about

the methods used in this systematic review can be found at

<https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology>.

### **Guideline Panel Consensus and Approval Process**

As previously mentioned, a multidisciplinary task force was created for each section based on author expertise to address each of the disciplines and particular areas of therapy selected for these clinical guidelines. Each group was involved with literature selection, creation and editing of the evidence tables and results for their specific section and discipline. Using this information, the task force then drafted the recommendations in response to the questions formulated at the beginning of the process, culminating in the clinical practice guideline for their respective discipline. The draft guidelines were then circulated to the entire task force to allow for multidisciplinary feedback, discussion, and ultimately approval.

Two topics originally identified for consideration in this set of guidelines documents were eventually removed from consideration and further development. In the previous set of guidelines published in 2010, there was a section on retreatment,<sup>6</sup> that included 2 questions. This resulted in 1 Class III recommendation for the first question, which stated that treatment should be individualized using whatever modality is deemed appropriate by the treating clinician. No recommendation could be formulated for the second question. A literature search to address 3 updated questions for retreatment of metastatic brain tumors was mounted for this update. A total of 1739 citations were generated, of which 44 were deemed worthy of full-text review. It was concluded that no meaningful new guidance could be provided for retreatment of metastatic brain tumors. Because the previous publication on retreatment provided the lowest level or no recommendations on that topic, the task force chose to not include a section on this topic in this iteration of the metastatic brain tumor management guidelines. In the other sections of this set of guidelines, some data were found to support comments on treatment of recurrent metastatic brain tumors. The readers are referred to them for elaboration.

Additionally, there was a planned section on management of radiation necrosis. A literature search to address 5 questions was mounted. This resulted in 1253 unique citations. Review of these resulted in the realization that there is not a broadly accepted definition of radiation necrosis in this disease setting, and there was no properly designed clinical research

available beyond simple case series to make concrete and declarative recommendations. Based on these findings, this section was abandoned.

The completed evidence-based clinical practice guidelines for the management of metastatic brain tumors were presented to the JGRC of the AANS/CNS for peer review. The reviewers for the JGRC were vetted by *Neurosurgery* for suitability and expertise to serve as reviewers for the purposes of publication in that journal. The final product was then approved and endorsed by the executive committees of both the AANS and CNS prior to publication in *Neurosurgery*.

Figure 1 provides an outline of the key steps in the process of developing these clinical practice guidelines.

## **DISCUSSION**

This series of guidelines was constructed to assess the most current and clinically relevant evidence for the management of metastatic brain tumors in order to set a benchmark for standard of care while also highlighting important key areas for future research. Only by designing future investigations in a high-quality manner that recognizes and overcomes prior weaknesses noted in these guidelines will advancement toward a remedy of this disease be achieved. Secondarily, the suggestions provided are set forth for conscientious use by the practicing physician who must take into account all of the unique individual conditions in the therapy of a given person during his or her illness. The application of published guidelines information is an activity that results in strong and often polarizing opinions. The guidelines presented in this current project are not meant to resolve these issues, and it is unlikely that any could accomplish such a goal. Fortunately, new research is constantly underway, and these guidelines are meant to be improved as this new evidence matures and is published. One will note that the PRISMA checklist serves as a forerunner to the 2011 Institute of Medicine Clinical Practice Guideline Development Process. An important part of that document, called Standard 8, suggests timely updating the data and recommendations.<sup>24</sup> To that point, the data analyzed for this set of guidelines has been collected through 2015. It is estimated that the updated iteration of this guideline overall will be written in approximately 5 years with modification of this timeline dependent on emergence of important scientific and therapeutic advances.

### **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 Table 7.

### **Disclosures**

These evidence-based clinical practice guidelines were funded exclusively by the Congress of Neurological Surgeons and the Tumor Section of the Congress of Neurological Surgeons and the American Association of Neurological Surgeons, which received no funding from outside commercial sources to support the development of this document.

### **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.

### **Acknowledgments**

The authors acknowledge the CNS Guidelines Committee for its contributions throughout the development of the guideline and the AANS/CNS Joint Guidelines Review Committee for its review, comments, and suggestions throughout peer review, as well as Trish Rehring, MPH, CHES, CNS Guidelines Senior Manager, and Mary Bodach, MLIS, Senior Guidelines Specialist, for their assistance. Throughout the review process, the reviewers and authors were blinded from

one another. At this time, the guidelines task force would like to acknowledge the following individual peer reviewers for their contributions: Manish Aghi, MD, PhD, Manmeet Ahuwalia, MD, Sepideh Amin-Hanjani, MD, Edward Avila, MD, Maya Babu, MD, MBA, Kimon Bekelis, MD, Priscilla Brastianos, MD, Paul Brown, MD, Andrew Carlson, MD, MS, Justin Jordan, MD, Terrence Julien, MD, Cathy Mazzola, MD, Adair Prall, MD, Shayna Rich, MD, PhD, Arjun Sahgal, MD, Erik Sulman, MD, May Tsao, MD, Michael Voglebaum, MD, Stephanie Weiss, MD, and Mateo Ziu, MD.

**Table 1. Metastatic Brain Tumor Guidelines Authors**

<b>Guideline Author</b>	<b>Affiliations</b>
Christopher Alvarez-Breckenridge, MD, PhD	Department of Neurosurgery, Massachusetts General Hospital, Boston, Massachusetts
Mario Ammirati, MD, MBA	Department of Neurosurgery, St. Rita Medical Center, Lima, Ohio
David W. Andrews, MD	Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, Pennsylvania
Priscilla K. Brastianos, MD	Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts
Clark C. Chen, MD, PhD	Department of Neurosurgery, University of Minnesota Medical School, Minneapolis, Minnesota
Charles S. Cobbs, MD	Department of Neurosurgery, Ben and Catherine Ivy Center for Advanced Brain Tumor Treatment, Swedish Neuroscience Institute, Seattle, Washington
J. Bradley Elder, MD	Department of Neurological Surgery, The Ohio State University Wexner Medical Center, Columbus, Ohio
Laurie E. Gaspar, MD, MBA	Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, Colorado
Jerome J. Graber, MD, MPH	Department of Neurology, Ben and Catherine Ivy Center for Advanced Brain Tumor Treatment, Swedish Neuroscience Institute, Seattle, Washington
Alia Hdeib, MD	Department of Neurosurgery, Case Western Reserve University
Steven N. Kalkanis, MD	Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan
John S. Kuo, MD, PhD	Department of Neurosurgery and Mulva Clinic for the Neurosciences, Dell Medical School, University of Texas at Austin, Austin Texas
George F. Lasker, MD, PhD	Department of Neurological Surgery, University of California, San Francisco, San Francisco, California
Mark E. Linskey, MD	Department of Surgery, University of California, Irvine, Orange, California
Yiping Li, MD	Department of Neurosurgery, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
Simon S. Lo	Department of Radiation Oncology, University of Washington School of Medicine, Seattle, Washington
D. Jay McCracken, MD	Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia
Michael W. McDermott, MD	Department of Neurological Surgery, University of California, San Francisco, San Francisco, California

<b>Guideline Author</b>	<b>Affiliations</b>
Brian Nahed, MD, MSc	Department of Neurosurgery, Massachusetts General Hospital, Boston, Massachusetts
Jeffrey J. Olson, MD	Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia
Roshan S. Prabhu, MD, MS	Southeast Radiation Oncology Group, Levine Cancer Institute, Carolinas Healthcare System, Charlotte, North Carolina
Robert C. Rennert, MD	Department of Neurosurgery, University of California, San Diego, San Diego, California
Timothy C. Ryken, MD, MS	Department of Neurosurgery, University of Kansas Medical Center, Kansas City, Kansas
Jonathan H. Sherman, MD	Department of Neurosurgery, The George Washington University, School of Medicine and Health Sciences, Washington, DC
Helen Shih, MD, MS, MPH	Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts
Andrew E. Sloan, MD	Department of Neurological Surgery, University Hospital Cleveland Medical Center, Cleveland, Ohio

**Table 2. Questions Addressed in this Guideline**

<b>Guideline Topic</b>	<b>Questions</b>
Whole Brain Radiation Therapy	
	If WBRT is used, is there an optimal dose/fractionation schedule?
	What impact does tumor histopathology or molecular status have on the decision to use WBRT, the dose fractionation scheme to be utilized, and its outcomes?
	Separate from survival outcomes, what are the neurocognitive consequences of WBRT, and what steps can be taken to minimize them?
	Does the addition of WBRT after surgical resection or radiosurgery improve progression-free or overall survival outcomes when compared to surgical resection or radiosurgery alone?
Surgical Resection	

Guideline Topic	Questions
	Should patients with newly diagnosed metastatic brain tumors undergo surgery, SRS, or WBRT?
	Should patients with newly diagnosed metastatic brain tumors undergo surgical resection followed by WBRT, SRS, or another combination of these modalities?
	Should patients with recurrent metastatic brain tumors undergo surgical resection?
	Does the surgical technique (en bloc resection or piecemeal resection) affect recurrence?
	Does the extent of surgical resection (gross total resection or subtotal resection) affect recurrence?
Stereotactic Radiosurgery	
	Should patients with newly diagnosed metastatic brain tumors undergo SRS compared with other treatment modalities?
	What is the role of SRS after open surgical resection of brain metastasis?
	What is the role of SRS alone in the management of patients with 1 to 4 brain metastases?
	What is the role of SRS alone in the management of patients with more than 4 brain metastases?
Chemotherapy	
	Should patients with brain metastases receive chemotherapy in addition to WBRT for the treatment of their brain metastases?

Guideline Topic	Questions
	Should patients with brain metastases receive chemotherapy in addition to SRS for the treatment of their brain metastases?
	Should patients with brain metastases receive chemotherapy alone?
Prophylactic Anticonvulsants	
	Do prophylactic AEDs decrease the risk of seizures in non-surgical patients with brain metastases who are otherwise seizure free?
	Do prophylactic AEDs decrease the risk of seizures in patients with brain metastases and no prior history of seizures in the postoperative setting?
Steroids	
	Do steroids improve neurologic symptoms and/or quality of life in patients with metastatic brain tumors compared to supportive care only or other treatment options?
	If steroids are given, what dose should be used?
Emerging Therapy	
	What evidence is available regarding emerging and investigational treatment options for metastatic brain tumors?
	High Intensity Focused Ultrasound
	Laser Interstitial Thermal Therapy
	Radiation sensitizers
	Interstitial modalities
	Immune modulators

Guideline Topic	Questions
	Molecular targeted agents
Multiple Metastases	
	In what circumstances should WBRT be recommended to improve tumor control and survival in patients with multiple brain metastases?
	In what circumstances should SRS be recommended to improve tumor control and survival in patients with multiple brain metastases?
	In what circumstances should surgery be recommended to improve tumor control and survival in patients with multiple brain metastases?

AED, Antiepileptic drug; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

**Table 3. AANS/CNS Classification of Evidence on Therapeutic Effectiveness and Levels of Recommendation**

Evidence Classification	
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials
Class II	Evidence provided by well-designed observational studies with concurrent controls (eg case-control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls
Levels of Recommendation	
Level 1	Generally accepted principles for patient management, which reflect a high degree of clinical certainty (usually this requires Class I evidence which directly addresses the clinical questions or overwhelming Class II evidence when circumstances preclude randomized clinical trials)
Level 2	Recommendations for patient management which reflect clinical certainty (usually this requires Class II evidence or a strong consensus of class III evidence)
Level 3	Other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion)

**Table 4. AANS/CNS Classification of Evidence on Diagnosis and Levels of Recommendation**

Class I Evidence Level 1 Recommendation	Evidence provided by one or more well-designed clinical studies of a <i>diverse</i> population using a “gold standard” reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios.
Class II Evidence Level 2 Recommendation	Evidence provided by one or more well-designed clinical studies of a <i>restricted</i> population using a “gold standard” reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios.
Class III Evidence Level 3 Recommendation	Evidence provided by expert opinion or studies that do not meet the criteria for the delineation of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios.

**Table 5. AANS/CNS Classification of Evidence on Clinical Assessment and Levels of Recommendation**

Class I Evidence Level 1 Recommendation	Evidence provided by one or more well-designed clinical studies in which interobserver and/or intraobserver reliability is represented by a <b>Kappa statistic <math>\geq 0.60</math>.</b>
Class II Evidence Level 2 Recommendation	Evidence provided by one or more well-designed clinical studies in which interobserver and/or intraobserver reliability is represented by a <b>Kappa statistic <math>\geq 0.40</math>.</b>
Class III Evidence Level 3 Recommendation	Evidence provided by one or more well-designed clinical studies in which interobserver and/or intraobserver reliability is represented by a <b>Kappa statistic <math>&lt; 0.40</math>.</b>

**Table 6. AANS/CNS Classification of Evidence on Prognosis and Levels of Recommendation**

In order to evaluate papers addressing *prognosis*, five technical criteria are applied:

- Was a well-defined representative sample of patients assembled at a common (usually early) point in the course of their disease?
- Was patient follow-up sufficiently long and complete?
- Were objective outcome criteria applied in a “blinded” fashion?



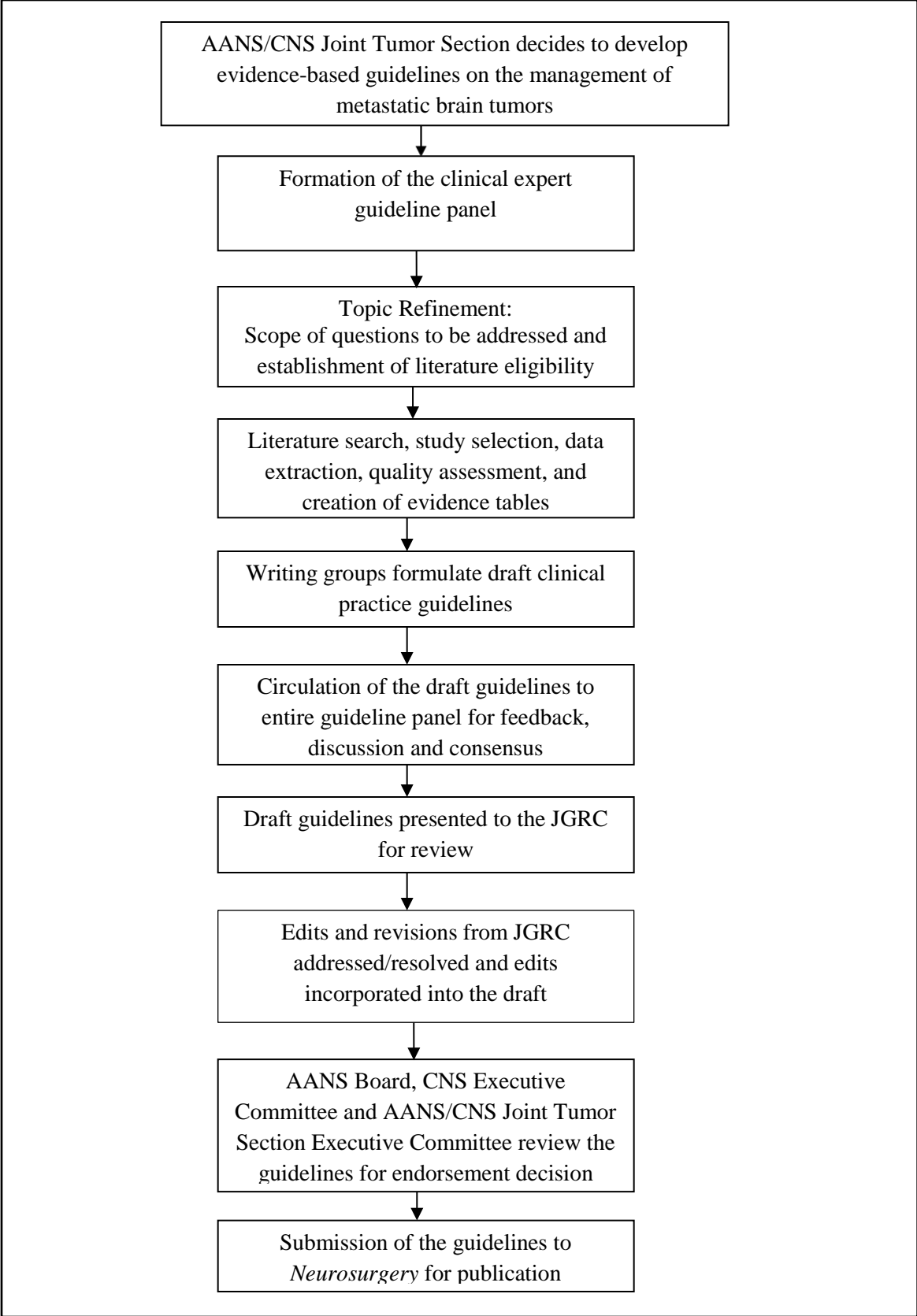
- If subgroups with different prognoses were identified, was there adjustment for important prognostic factors?
- If specific prognostic factors were identified, was there validation in an independent “test set” group of patients?

Class I Evidence Level 1 Recommendation	All 5 technical criteria above are satisfied.
Class II Evidence Level 2 Recommendation	Four of 5 technical criteria are satisfied.
Class III Evidence Level 3 Recommendation	Everything else.

**Table 7 COI Disclosures**

<b>Guideline Authors</b>	<b>Potential COI</b>
<b>David W. Andrews, MD</b>	<ol style="list-style-type: none"> <li>1. Brainlab: Consultant fee</li> <li>2. IMVAX: Stock shareholder</li> <li>3. IMVAX: Board/Trustee/Officer position (CEO)</li> </ol>
<b>Priscilla K. Brastianos, MD</b>	<ol style="list-style-type: none"> <li>1. Genentech: Consultant fee</li> <li>2. Roche: Consultant fee</li> <li>3. Angiochem: Consultant fee</li> <li>4. Merck: Honorarium</li> </ol>
<b>Clark C. Chen, MD, PhD</b>	<ol style="list-style-type: none"> <li>1. Medtronic: Grants/research support</li> <li>2. Tocagen : Consultant fee</li> <li>3. MRI Interventions: Consultant fee</li> <li>4. Monteris: Consultant Fee</li> <li>5. Varian: Honorarium</li> </ol>
<b>Jerome Graber, MD, MPH</b>	<ol style="list-style-type: none"> <li>1. Scientific Advisory Board, Novocure, Inc.: Consultant fee</li> <li>2. Data Safety Monitoring Board, Stemedica, Inc.: Other</li> </ol>
<b>Simon S. Lo, MD</b>	<ol style="list-style-type: none"> <li>1. Elekta AB: Grants/research support</li> <li>2. Accuray: Honorarium</li> <li>3. Accuray: Gifts over value of \$100</li> </ol>
<b>Brian V. Nahed, MD, MSc</b>	<ol style="list-style-type: none"> <li>1. Medtronic: Honorarium</li> </ol>
<b>Jeffrey J. Olson, MD</b>	<ol style="list-style-type: none"> <li>1. American Cancer Society: Consultant fee</li> <li>2. Takeda: Research grant</li> <li>3. Arbor Pharmaceuticals: Research grant</li> </ol>
<b>Timothy C. Ryken, MD, MS</b>	<ol style="list-style-type: none"> <li>1. Medtronic, Inc.: Consultant fee</li> <li>2. EBM Care, Inc.: Consultant fee</li> <li>3. Arbor Pharmaceuticals, LLC: Consultant fee</li> </ol>

<b>Guideline Authors</b>	<b>Potential COI</b>
	4. K2M Spine, Inc.: Consultant fee



**Figure 1. An outline of the key steps in the process of developing these clinical practice guidelines**

AANS: American Association of Neurological Surgeons; CNS: Congress of Neurological Surgeons; JGRC: Joint Guidelines Review Committee

## REFERENCES

1. Robinson PD, Kalkanis SN, Linskey ME, Santaguida PL. Methodology used to develop the AANS/CNS management of brain metastases evidence-based clinical practice parameter guidelines. *J. Neurooncol.* Jan 2010;96(1):11-16.
2. Gaspar LE, Mehta MP, Patchell RA, et al. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J. Neurooncol.* Jan 2010;96(1):17-32.
3. Kalkanis SN, Kondziolka D, Gaspar LE, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J. Neurooncol.* Jan 2010;96(1):33-43.
4. Ryken TC, McDermott M, Robinson PD, et al. The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. *J. Neurooncol.* Jan 2010;96(1):103-114.
5. Mehta MP, Paleologos NA, Mikkelsen T, et al. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J. Neurooncol.* Jan 2010;96(1):71-83.
6. Ammirati M, Cobbs CS, Linskey ME, et al. The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. *J. Neurooncol.* Jan 2010;96(1):85-96.
7. Mikkelsen T, Paleologos NA, Robinson PD, et al. The role of prophylactic anticonvulsants in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. *J. Neurooncol.* Jan 2010;96(1):97-102.
8. Olson JJ, Paleologos NA, Gaspar LE, et al. The role of emerging and investigational therapies for metastatic brain tumors: a systematic review and evidence-based clinical practice guideline of selected topics. *J. Neurooncol.* Jan 2010;96(1):115-142.
9. Nahed BV, Alvarez-Breckenridge C, Brastianos PK, et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Surgery in the Management of Adults With Metastatic Brain Tumors. *Neurosurgery.* Mar 1 2019;84(3):E152-e155.
10. Gaspar LE, Prabhu RS, Hdeib A, et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Whole Brain Radiation Therapy in Adults With Newly Diagnosed Metastatic Brain Tumors. *Neurosurgery.* Mar 1 2019;84(3):E159-e162.
11. Graber JJ, Cobbs CS, Olson JJ. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Use of Stereotactic Radiosurgery in the Treatment of Adults With Metastatic Brain Tumors. *Neurosurgery.* Mar 1 2019;84(3):E168-e170.
12. Sherman JH, Lo SS, Harrod T, et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Chemotherapy in the Management of Adults With Newly Diagnosed Metastatic Brain Tumors. *Neurosurgery.* Mar 1 2019;84(3):E175-e177.
13. Ammirati M, Nahed BV, Andrews D, Chen CC, Olson JJ. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on Treatment Options for Adults With Multiple Metastatic Brain Tumors. *Neurosurgery.* Mar 1 2019;84(3):E180-e182.
14. Ryken TC, Kuo JS, Prabhu RS, Sherman JH, Kalkanis SN, Olson JJ. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role

- of Steroids in the Treatment of Adults With Metastatic Brain Tumors. *Neurosurgery*. Mar 1 2019;84(3):E189-e191.
15. Chen CC, Rennert RC, Olson JJ. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Prophylactic Anticonvulsants in the Treatment of Adults with Metastatic Brain Tumors. *Neurosurgery*. Mar 1 2019;84(3):E195-e197.
  16. Elder JB, Nahed BV, Linskey ME, Olson JJ. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Emerging and Investigational Therapies for the Treatment of Adults With Metastatic Brain Tumors. *Neurosurgery*. Mar 1 2019;84(3):E201-e203.
  17. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J. Clin.* Jan-Feb 2015;65(1):5-29.
  18. U.S. Census Bureau. Population Distribution and Change: 2000 to 2010. 2011; <http://www.census.gov/prod/cen2010/briefs/c2010br-01.pdf>. Accessed May 19, 2017.
  19. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G. Epidemiology of metastatic brain tumors. *Neurosurg. Clin. N. Am.* Jan 2011;22(1):1-6, v.
  20. Taillibert S, Le Rhun E. Epidemiology of brain metastases. *Cancer Radiother.* Feb 2015;19(1):3-9.
  21. Owonikoko TK, Arbiser J, Zelnak A, et al. Current approaches to the treatment of metastatic brain tumours. *Nat. Rev. Clin. Oncol.* Apr 2014;11(4):203-222.
  22. Nieder C, Spanne O, Mehta MP, Grosu AL, Geinitz H. Presentation, patterns of care, and survival in patients with brain metastases: what has changed in the last 20 years? *Cancer.* Jun 01 2011;117(11):2505-2512.
  23. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J. Clin. Epidemiol.* Oct 2009;62(10):1006-1012.
  24. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In: Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, eds. *Clinical Practice Guidelines We Can Trust*. Washington (DC): National Academies Press (US); 2011.