Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines Update for the Role of Emerging Therapies in the Management of Patients With Metastatic Brain Tumors

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Sponsored by: Congress of Neurological Surgeons (CNS) and the Section on Tumors.

Endorsed by: Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS).

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Received, October 30, 2024; **Accepted,** November 21, 2024; **Published Online,** March 17, 2025.

Neurosurgery 00:1–6, 2025 https://doi.org/10.1227/neu.0000000000003383

BACKGROUND: Patients with metastatic brain tumors (MBTs) require a multidisciplinary team-based approach to select the best diagnostic, surgical, and radiation interventions.

OBJECTIVE: The aim of this guideline was to provide an update of the evidence-based recommendations of the guideline produced in 2019 regarding the use of emerging therapies for adult patients with MBTs.

METHODS: PubMed and Embase were searched from January 1, 2016, through May 3, 2022, using search strategies pertinent to the therapeutic topics: targeted agents, immune-modulating agents, interstitial modalities, radiosensitizers, laser interstitial thermal therapy, and magnetic resonance imaging–guided focused ultrasound. The search results were screened using pre-established exclusion/inclusion criteria. Evidence tables were constructed using these data, and the recommendations from the 2019 version were left unchanged, updated or, where appropriate, new recommendations were formulated.

RESULTS: Of 6403 qualifying abstracts, 162 met the inclusion criteria and were included in the evidence tables. They provided 8 class I recommendations, 3 class II recommendations, and 17 class III recommendations. In three instances, there was insufficient evidence to support a recommendation. The proliferation of qualifying literature since the end of 2015 was greatest regarding the topics related to targeted therapy and immunotherapy of MBTs. Fewer were available for laser interstitial thermal therapy and radiosensitizers, but enough information was available to formulate recommendations on these two topics. For interstitial modalities and magnetic resonance imaging–guided focused ultrasound, insufficient qualifying data were identified to create recommendations.

CONCLUSION: This systematic review provides evidence-based recommendations for adult patients with MBTs regarding the use of therapies beyond standard surgical, radiation, and cytotoxic chemotherapy.

KEY WORDS: Brain metastases, Targeted therapy, Immunotherapy, Leptomeningeal, Laser interstitial thermal therapy, Radiation sensitizer

ABBREVIATIONS: ALK, anaplastic lymphoma kinase; **CNS,** central nervous system; **EGFR,** epidermal growth factor receptor; **HIFU,** high-intensity focused ultrasound; **ICI,** immune checkpoint inhibitor; **IT,** intrathecal; **LITT,** laser interstitial thermal therapy; **MBT,** metastatic brain tumors; **NSCLC,** non–small-cell lung carcinoma; **OS,** overall survival; **SRS,** stereotactic radiosurgery; **TKI,** tyrosine kinase inhibitor; **WBRT,** whole-brain radiation therapy.

PICO QUESTIONS AND RECOMMENDATIONS

Target Population: Adults with metastatic brain tumors (MBTs).

Question 1

In patients with parenchymal brain metastases, does the use of molecular targeted agents provide benefit regarding local control, overall survival (OS), progression-free survival (PFS), performance status, or reduction in central nervous system (CNS) side effects compared with standard management with chemotherapy, immune modulators, stereotactic radiosurgery (SRS), whole-brain radiation therapy (WBRT), and surgical resection?

RECOMMENDATIONS

Unchanged Recommendation

Level I: The use of afatinib is not recommended in patients with brain metastasis due to breast cancer.

New Recommendations

Targeted Therapy for the Treatment of EGFR–Mutant NSCLC Parenchymal Brain Metastases

Level I: In patients with ≥3 untreated brain metastases from epidermal growth factor receptor (EGFR)-mutant non–small-cell lung carcinoma (NSCLC), the use of icotinib and WBRT is recommended to improve intracranial PFS.

Level III: In patients with brain metastases from EGFR-mutant NSCLC, the addition of EGFR tyrosine kinase inhibitors (TKIs) to radiation therapy in the form of WBRT or SRS is suggested to improve OS, PFS, and intracranial PFS.

Targeted Therapy for the Treatment of ALK Mutation–Positive NSCLC Parenchymal Brain Metastases

Level I: In patients with anaplastic lymphoma kinase (ALK) mutation–positive NSCLC with untreated brain metastases, the use of alectinib is recommended to delay the time to intracranial tumor progression.

Level II: In patients with untreated brain metastases from ALK mutation–positive NSCLC, lorlatinib is recommended to prolong intracranial tumor control and improve overall PFS.

Targeted Therapy for the Treatment of NSCLC Parenchymal Brain Metastases Not Assessed for EGFR and ALK Mutation Status

Level I: It is recommended that for patients with newly diagnosed brain metastases secondary to NSCLC not assessed for EGFR and ALK mutation status and for whom WBRT is indicated, gefitinib be added to the treatment regimen to improve local tumor control and OS.

Level III: For patients with brain metastases secondary to NSCLC not assessed for EGFR and ALK mutation status and for whom targeted therapy in the form of gefitinib or the combination of pemetrexed and platinum compounds are otherwise indicated, it is suggested that bevacizumab, when not contraindicated by other underlying medical conditions, be added to the treatment regimen to improve CNS control and to a lesser extent PFS and OS.

Targeted Therapy for the Treatment of EGFR-Negative, ALK-Negative NSCLC Parenchymal Brain Metastases

Level III: For patients with brain metastases secondary to NSCLC that are EGFR and ALK mutation negative and for whom targeted therapy in the form of TKIs are indicated, it is suggested that TKIs, when not contraindicated by other underlying medical conditions, be added to the treatment regimen, including radiation therapy, to improve CNS control and to a lesser extent PFS and OS.

Targeted Therapy for the Treatment of Melanoma Parenchymal Brain Metastases

Level I: It is recommended that for patients with newly diagnosed brain metastases secondary to melanoma that is BRAFV600E positive, dabrafenib plus trametinib be added to the treatment regimen to obtain improved local tumor control.

Level III: For patients with brain metastases secondary to BRAF-altered melanoma for whom targeted therapy in the form of BRAF inhibitors are indicated, it is suggested that immunotherapy, when not contraindicated by other underlying medical conditions, be added to the treatment regimen to improve CNS control and to a lesser extent PFS and OS.

Targeted Therapy for the Treatment of Breast Adenocarcinoma Parenchymal Brain Metastases

Level III: In adult patients with brain metastases from breast adenocarcinoma that are HER2 positive for whom radiation therapy is indicated, it is suggested that trastuzumab be added to the treatment regimen to improve PFS, median survival, and OS.

Level III: In adult patients with brain metastases from breast adenocarcinoma for whom SRS is indicated, it is suggested that lapatinib be added to that treatment to improve intracranial response rate and median survival.

Question 2

In patients with leptomeningeal brain metastases, does the use of molecular targeted agents provide benefit regarding local control, OS, PFS, performance status, or reduction in CNS side effects compared with standard management with chemotherapy, immune modulators, SRS, WBRT, and surgical resection?

New Recommendations

Level III: In patients with leptomeningeal disease from NSCLC with EGFR mutations, it is suggested that EGFR TKIs be used to increase median survival, specifically the third-generation TKI osimertinib for patients with EGFR-mutant NSCLC and the second-generation ALK-TKI alectinib for the treatment of leptomeningeal metastases in ALK-positive NSCLC.

Level III: In patients with leptomeningeal metastases from Her2-positive breast cancer, it is suggested that intrathecal (IT) trastuzumab be used to increase median survival.

Question 3

In patients with parenchymal brain metastases, does the use of immune modulators provide benefit in terms of local control, OS, PFS, performance status, or reduction in CNS side effects compared with standard management with chemotherapy, molecular targeted agents, SRS, WBRT, and surgical resection?

New Recommendations

Level I: In patients with active, untreated, asymptomatic parenchymal melanoma brain metastases, ipilimumab plus nivolumab is recommended to increase the median OS and be used without radiation to improve the median OS.

Level III: In patients with parenchymal brain metastases from NSCLC, it is suggested that immune checkpoint inhibitors (ICIs) be used with radiation therapy to increase median survival, decrease incidence of local failure, increase intracranial PFS, and decrease distant intracranial failure.

Level III: In patients with parenchymal brain metastases from NSCLC that are clinically stable for at least 4 weeks and with programmed death-ligand 1 tumor proportion score >50%, it is suggested that ICIs be used without radiation to improve median OS.

Level III: In patients with parenchymal brain metastases from breast cancer or colon carcinoma, it is suggested that therapy with ICIs be considered alone or with radiation therapy to increase the median survival and decrease the incidence of local failure.

Question 4

In patients with leptomeningeal brain metastases, does the use of immune modulators provide benefit regarding local control, OS, PFS, performance status, or reduction in CNS side effects compared with standard management with chemotherapy, molecular targeted agents, SRS, WBRT, and surgical resection?

New Recommendation

There is insufficient evidence to make a recommendation regarding the use of immune modulators for the therapy of leptomeningeal brain metastases.

Question 5

In patients with parenchymal brain metastases, does the use of interstitial modalities, in the form of interstitial chemotherapy or radiation (brachytherapy, intraoperative radiation therapy), provide benefit regarding local control, OS, PFS, performance status, or reduction in CNS side effects compared with standard management with chemotherapy, immune modulators and molecular targeted agents, SRS, WBRT, and surgical resection?

Unchanged Recommendation

There is insufficient evidence to make a recommendation regarding the use of interstitial modalities in the form of interstitial chemotherapy or radiation.

Question 6

In patients with parenchymal brain metastases, does the use of radiosensitizers provide benefit in terms of local control, OS, PFS, performance status, or reduction in CNS side effects compared with standard management with chemotherapy, immune modulators and molecular targeted agents, SRS, WBRT, and surgical resection?

Unchanged Recommendations

Level I: The use of temozolomide as a radiation sensitizer is not recommended in the setting of whole-brain radiation therapy (WBRT) for patients with breast cancer brain metastases.

Level I: The use of chloroquine as radiation sensitizer is not recommended in the setting of WBRT for patients with brain metastases.

New Recommendations

Level II: When WBRT is used for brain metastases from NSCLC, it is recommended that temozolomide be added to provide a smaller incidence of local failure, longer intracranial PFS, and longer OS.

Level III: For brain metastases from NSCLC with EGFR mutation–positive status where WBRT or SRS is indicated, it is suggested that EGFR TKIs be added to that therapy to improve intracranial response rate and survival.

Question 7

In patients with parenchymal or leptomeningeal brain metastases, does the use of laser interstitial thermal therapy (LITT) provide benefit regarding local control, OS, PFS, performance status, or reduction in CNS side effects compared with standard management with chemotherapy, immune modulators and molecular targeted agents, SRS, WBRT, and surgical resection?

New Recommendations

Level III: For adults who have undergone SRS for brain metastases with subsequent imaging progression due to tumor progression, it is suggested that LITT be considered as equivalent to craniotomy in terms of PFS and OS and the choice of management should be individualized based on the unique characteristics of the tumor location and the patient's clinical status.

Level III: For adults who have undergone SRS for brain metastases with subsequent imaging progression due to radiation necrosis, it is suggested that LITT be considered as equivalent to medical management for radiation necrosis and the choice of management should

be individualized based on the unique characteristics of the tumor location and the patient's clinical status.

Question 8

In patients with parenchymal or leptomeningeal brain metastases, does the use of high-intensity focused ultrasound (HIFU) provide benefit regarding local control, OS, PFS, performance status, or reduction in CNS side effects compared with standard management with chemotherapy, immune modulators and molecular targeted agents, SRS, WBRT, and surgical resection?

Unchanged Recommendation

There is insufficient evidence to make a recommendation regarding the use of HIFU for parenchymal and leptomeningeal brain metastases.

INTRODUCTION

Goals and Rationale

Advancements in the understanding of the biology of MBTs, the ability to create more sophisticated systemic treatments through improved pharmacologic chemistry, radiation therapy software and hardware advancements, and surgical equipment have yielded new information worthy of dissemination. As suggested by the Institute of Medicine, now the National Academy of Medicine, it is suggested that guidelines be updated in the range of every 5 years.[1] Thus, interval updates of the guideline on emerging therapies for MBTs published by the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) in 2018 were planned to update the information in that publication.[2]

Objectives

This document seeks to update the recommendations for molecular and targeted agents, immune-modulating agents, interstitial modalities, radiosensitizers, intraoperative radiation therapy, LITT, and HIFU published in the 2018 guideline on emerging therapies for MBTs.[2] To accomplish this, the Joint Tumor Section of the AANS/CNS recruited representatives from the section to review and update the questions from the previous guideline to Patient, Intervention, Comparison, Outcome (PICO) format, search the literature published regarding the items in each question since the search of the 2018 publication, and determine if that new information confirmed previous recommendations, required an update of previous recommendations, or new recommendations.

METHODOLOGY

Literature Search

To accomplish this update, new literature in PubMed and Embase from January 1, 2016, through May 3, 2022, was searched using the questions with their new PICO format, and data from the qualifying manuscripts for each topic were used to either confirm previous recommendations, update them, or create new ones. The search strategy used combinations of subheadings and key words and is documented in previous methodology articles. Search strategies for the root brain metastasis search and the 6 categories of emerging therapy (molecular and targeted agents, immune-modulating agents, interstitial modalities, radiosensitizers, LITT, and HIFU) are found in Appendix I of the full-text document found at the CNS Guidelines Website. Manuscripts selected for review on screening of abstracts met the criteria described below. All citations were reviewed by 2 authors and acceptance or rejection recorded along with the reasons. When there was disagreement, the 2 reviewers met in live session to resolve the disagreement. The Guidelines Task Force used DistillerSR (which uses artificial intelligence) to cull, narrow, and aid its review of the relevant literature. All abstracts were reviewed, and relevant full-text articles were retrieved and graded [by individuals on the Guidelines Task Force].

Inclusion/Exclusion Criteria

- Published in English
- Involves human patients with brain metastases
- Fully published primary study published between September 2008 and December 2015
- Article evaluates ≥1 of the therapies in question:
  - Molecular and targeted agents for parenchymal brain metastases
  - Molecular and targeted agents for leptomeningeal brain metastases
  - Immune modulating agents for parenchymal brain metastases
  - Immune modulating agents for leptomeningeal brain metastases
  - Interstitial modalities
  - Radiosensitizers
  - LITT
  - HIFU
- Number of patients with brain metastases in the study ≥5 per study arm for ≥2 of the study arms for comparative studies and ≥5 total patients if a noncomparative study

Data Collection Process

Manuscripts selected for review underwent full review by 2 authors to confirm that it met eligibility criteria; if not, the manuscript was rejected. As with the abstracts, when there was disagreement, the 2 reviewers met in live session to resolve the disagreement. Data gleaned from the manuscript included type of study (eg, phase 2 clinical trial, retrospective chart review, etc.), therapeutic agent evaluated, and the outcome measures and results yielded by the study.

Assessment for Risk of Bias

Each manuscript was evaluated by the writing group for bias, and the summation of different forms of bias are reflected in the data classification system. Inherent to emerging therapy agents, initial reports were noted to be in the form of small case series, anecdotal reports, and early phase clinical trials. As such, there is inevitable selection bias imposed by retrospective reviews and prospective studies with small numbers of patients. For example, patients selected for study, especially early phase trials, may have better medical status relative to patients not selected for

study. In addition, small series of patients may have bias because of random variability. Our expectation is that the more promising techniques and agents mentioned in this guideline will be studied further as part of larger clinical trials, which will eliminate some of the inherent bias of smaller, retrospective studies.

Rating Quality of Evidence and Recommendation Formulation

Each manuscript that met eligibility criteria and was found to have data relevant to the question was rated as providing class I, II, or III evidence based on the definitions provided in the AANS/CNS criteria. The pertinent classification levels and data for each article were entered into an evidence table for each emerging therapy subtopic. The evidence tables were then validated among the writing group before the formulation of recommendations. The summation of the information from qualifying manuscripts was then synthesized and used to create level I, II, or III recommendations based on the classification of evidence on therapeutic effectiveness (Appendix II of the full text document found at the CNS Guidelines Website). An expanded description of the data classification system and translation to recommendation level designation is provided at Guideline Development Methodology - cns.org.

Revision Plans

In accordance with the National Academy of Medicine's standards for developing clinical practice guidelines, the writers of the emerging therapies for MBTs task force will monitor related publications after the release of this document and will revise the entire document and/or specific sections "if new evidence shows that a recommended intervention causes previously unknown substantial harm, that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective, or that a recommendation can be applied to new populations."[3] In addition, within 5 years from the date of publication, the task force plans to assess the content of this guideline to that it still reflects the clinical practice and treatment of patients with MBTs. In those cases where it does not, the recommendations will either be updated or new recommendations will be created.

SUMMARY OF PREVIOUS GUIDELINE

The prior version of this guideline topic included a single key question: What evidence is available regarding emerging and investigational treatment options for MBTs?[2] This was then applied over a range of topics in order of consideration at that time, including HIFU, LITT, radiosensitizers, interstitial modalities, immune modulators, and molecular targeted agents.

RESULTS

The literature results in 6403 abstracts. Task force members performed a comprehensive, double-blind review and selected 263 articles for full-text review and data extraction (Appendix I).

A total of 101 were rejected for not meeting inclusion criteria or for being off topic. One hundred sixty-two articles were included in this systematic review (Appendix III).

The recommendations for the different tumor types are provided after the synthesis for each circumstance to ease understanding of where the recommendations apply.

DISCUSSION

Overall, and as is reflected in the comparative information in Table 1 of the full-text document found at the CNS Guidelines Website, a greater body of information on the emerging therapies for brain metastases has developed as the 2019 version of this guideline. This has allowed for concrete recommendations to be made on various levels to assist medical and surgical practitioners to manage this population of patients.

Key Issues for Future Investigation

Ideally, future studies of all the modalities noted in this document would be directed toward cases with brain metastases as the group of primary interest, facilitating class II or even class I data and providing the ability to make stronger recommendations. Application of targeted therapy and immunotherapy is often applied in an adjuvant setting after surgery. Now, more often than in the past, these options are being explored as the initial therapy and such steps, even if investigational, are encouraged. Success on this front may preclude the need for surgery or radiation or at least delay need for those interventions or provide smaller and safer surgical or radiation targets. Truly prospective and comparative studies of LITT, beyond simple registries, looking at its value in relation with localized forms of radiation, and medical/targeted therapies will clarify its value in the management of brain metastases. Until that is accomplished, increasing volumes of class III data are unlikely to increase acceptance and use of the technology. Similarly, HIFU is an exciting technology whose value is yet to be determined. As with LITT, it will require prospective, comparative studies to truly delineate its place on the menu of options for management of brain metastases.

CONCLUSION

Advancement of nonsurgical and surgical therapies for MBTs is occurring at a rapid rate as confirmed in this document. The most coherent approaches will be developed with cooperative study development across the specialties of radiation oncology, medical oncology, and neurosurgery. Enrollment of patients in trials of these interventions, be they sponsored by industry, academic institutions, or cooperative groups, is encouraged as this will assist in crystalizing our understanding of their role in MBTs.

Conflicts of Interest

All Guideline Task Force members were required to disclose all potential conflicts of interest (COIs) prior to beginning work on

the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs. See Appendix V of the full text document found at the CNS Guidelines Website for a complete list of disclosures.

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a physician volunteer task force as an educational tool that reflects the current state of knowledge at the time of completion. Each chapter is designed to provide an accurate review of the subject matter covered. This guideline is 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.

Funding

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

Disclosures

Jeffrey J. Olson received payment from Verastem, Inc. and American Cancer Society. The remaining authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

The guidelines task force would like to acknowledge the CNS Guidelines Committee for their contributions throughout the development of the guideline, the AANS/CNS Joint Guidelines Review Committee, as well as the contributions Trish Rehring, MPH, Director for Evidence-Based Practice Initiatives for the CNS, and Janet Waters, MLS, BSN, RN, for assistance with the literature searches. The guidelines task force would also like to acknowledge the following CNS Guidelines Fellows: Miracle C. Anokwute, MD, Indiana University School of Medicine, Silky Chotai, MD, Cleveland Clinic Foundation, Michael Brendan Cloney, MD, MPH, University of Michigan, Andrew Mark Erwood, MD, Neurosurgical Associates P.C., George W. Koutsouras, D.O., M.P.H., Upstate University Hospital, Syracuse, NY, Brandon Laing, MD, Medical College of Wisconsin, Shawn Singh Rai, MD, HCA Florida Ocala Hospital. 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: Ketan Bulsara, MD, Marshall Holland, MD, Emanuella Binello, MD.