Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Management of Progressive Glioblastoma in Adults: Update of the 2014 Guidelines

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BACKGROUND: The Institute of Medicine best practice recommendation to review guidelines every 5 years is followed by the Congress of Neurological Surgeons Guidelines Committee. The aim of this work was to provide an updated literature review and evidence-based recommendations on the topic of diagnosis and treatment of patients with progressive glioblastoma (pGBM).

OBJECTIVE: To review the literature published since the last guidelines on pGBM dated 2014, with literature search ending in June 2012.

METHODS: PubMed, Embase, and Cochrane were searched for the period July 1, 2012, to March 31, 2019, using search terms and search strategies to identify pertinent abstracts. These were then screened using published exclusion/inclusion criteria to identify full-text review articles. Evidence tables were constructed using data derived from full-text reviews and recommendations made from the evidence derived.

RESULTS: From the total 8786 abstracts identified by the search, 237 full-text articles met inclusion/exclusion criteria and were included in this update. Two new level II recommendations derived from this work. For the diagnosis of patients with GBM, the use of diffusion-weighted images is recommended to be included in the magnetic resonance images with and without contrast used for surveillance to detect pGBM. For the treatment of patients with pGBM, repeat cytoreductive surgery is recommended to improve overall survival. An additional 21 level III recommendations were provided.

CONCLUSION: Recent published literature provides new recommendations for the diagnosis and treatment of pGBM. The Central Nervous System Guidelines Committee will continue to pursue timely updates to further improve the care of patients with diagnosis. https://www.cns.org/guidelines/browse-guidelines-detail/guidelines-management-of-progressive-glioblastoma

KEY WORDS: Chemotherapy, Cytoreductive surgery, Immunotherapy, Molecular testing, MR imaging, Progressive glioblastoma, Radiation therapy

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BRIEF COMMUNICATION

Potential benefits of medical guidelines include improving the quality and consistency of care received by our patients. To ensure the data used in making management decisions remain current with scientific developments, the Institute of Medicine (now the Academy of Medicine) recommends issuing updates every 5 years.[1] Accordingly, the Joint Tumor Section of the American Association of Neurological Surgeons/Congress of Neurological Surgeons (CNS) proceeded with a planned 5-year update of the guidelines on progressive glioblastoma (pGBM) published in 2014.[2] The term progressive as opposed to recurrent was then chosen to highlight the fact that GBM are almost never eradicated at

ABBREVIATIONS: pGBM, progressive glioblastoma; **TMZ,** temozolomide; **TTF,** tumor treatment field.

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initial therapy. Therefore, the evidence of new disease after initial therapy represents a progression rather than a recurrence.

The 2014 guidelines on this topic were based on the literature ending on June 30, 2012. In the current update, PubMed, Embase, and Cochrane were searched for the period July 1, 2012, to March 31, 2019, using search terms and search strategies to identify pertinent abstracts. In addition, for cytotoxic therapies other than chemotherapy previously not included, the review spanned from January 1, 2000, through March 31, 2019. A summary of the methodology used for the development of this evidence-based update, including techniques for classification of data and its linkage to recommendations can be found at https://www.cns.org/guidelines/guideline-development-methodology.

A total of 8786 abstracts were identified by the new search. Full-text articles meeting inclusion/exclusion criteria and included in this update totaled 237. All recommendations provided were based on the evidence from these qualifying manuscripts and are pertinent to adult patients with pGBM. This resulted in 6 sets of recommendations divided by each of the standard topics involved in managing those with pGBM.

The first part of the updated guidelines focuses on the *imaging* best suited to making the diagnosis of pGBM. The previous guidelines provided a level II recommendation for the use of gadolinium contrast-enhanced magnetic resonance imaging for the diagnosis of pGBM.[3] After review of the 92 full-text articles pertinent to imaging, this update confirms the previous recommendation and yields the new level II recommendation that diffusion-weighted imaging should be considered as part of the standard MRI sequences used for the diagnosis of pGBM.[4,5] The current literature search also focused on the numerous recent imaging techniques including new MRI sequences, such as perfusion-weighted imaging and nuclear medicine techniques, such as improved single-photon emission computed tomography and positron emission tomography with conventional (18F-fluorodeoxyglucose) and new radiotracers. These mainly include ^{11}C-methyl-methionine, O-(2-[^{18}F]-fluoroethyl)-L-tyrosine, and 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine. A level III recommendation is provided indicating that ^{18}FDG is not recommended for routine diagnosis of pGBM. For the other techniques, level III recommendations are provided indicating that their use could assist in the diagnosis of pGBM.

The second part examines the role of *cytoreductive surgery* for patients with pGBM. The previous guidelines provided level II recommendation that cytoreductive surgery should be used for patients with symptomatic pGBM.[6] Review of the 4 pertinent full-text articles on this topic allowed a further refinement of the level II recommendation that cytoreductive surgery is also recommended to improve overall survival in patients with pGBM.[7-10]

The third part of the updated guidelines review the new literature pertinent to *pathology* testing that best facilitated the diagnosis of pGBM. Since the publication of the 2014 guidelines,[11] the importance of the tumor's molecular signatures on progression-free and overall survival for patients with brain tumors has been recognized and included in the fourth edition of the World Health Organization Classification of Tumors of the Central Nervous System.[12] Review of the 53 pertinent full-text articles provides a level III recommendation that repeat assessment of 06-methylguanine-DNA methyltransferase methylation and isocitrate dehydrogenase status is not indicated, and PDL1/mismatch repair enzyme enzyme activity is not a useful component of standard testing for the diagnosis of pGBM.[13-17] A level III recommendation is also provided that states if a measurement of epidermal growth factor receptor amplification was not previously obtained, it's assessment at progression may be of value in the diagnosis of pGBM.[18] A level III recommendation is also provided to indicate that large panel sequencing may be considered in patients who are eligible or interested in molecularly guided therapy or clinical trials.[19-21]

The fourth part of the updated guidelines evaluates the use of *cytotoxic agents* for treatment of pGBM. The 2014 guidelines[22] provided a level II recommendation for temozolomide (TMZ) as being superior compared with procarbazine in patients with their first progression of GBM. Since 2014, cytotoxic agents other than chemotherapy have become broadly available. These include tumor treatment fields (TTFs)[23-28] and virotherapy.[29-36] Therefore, these 2 new subfields were included in a new search encompassing a broader time period. Review of the 89 pertinent full-text articles resulted in 7 level III recommendations. Three level III recommendations addressed benefits derived from treating patients with pGBM with one of the following: (1) TMZ (especially those who progress after more than 5 months off of TMZ), (2) TTF with other chemotherapy, and (3) fotemustine in elderly patients. Level III recommendations suggest not using the following: (1) a combination of TMZ with other cytotoxic agents, chemotherapy including platinum compounds, and topoisomerase inhibitors; (2) other cytotoxic therapies such as perillyl acohol and ketogenic diet and; (3) oncolytic virotherapy. Regarding oncolytic virotherapy, the results of the randomized phase II/III clinical trial using the oncolytic retroviral replicating vector Toca 511 (vocimagene amiretrorepvec) published after the time period assigned for review for these guidelines showed no benefit on overall survival in the experimental arm compared with control.[37] Based on one study,[38] 1,3-bis (2-chloroethyl)-1-nitroso-urea (BCNU)-impregnated biodegradable polymers were recommended as level II in the guidelines published in 2014. Since then, Stupp protocol consisting of radiation with concomitant TMZ has increasingly become the standard of care for newly diagnosed GBM.[35,39] In this updated guideline, there is insufficient evidence to make a suggestion about the use of in situ nitrosourea in patients with pGBM who underwent the Stupp regimen. Level III data were available to state TTF with chemotherapy may be considered in the setting of pGBM. Insufficient data were available to provide recommendations about which alternative TMZ dosing regimen might provide the best overall survival benefit or to recommend TTF to increase overall survival.

The fifth part of the updated guidelines assesses the role of *radiation therapy* for patients with pGBM. The previous level III recommendation included that reirradiation should be considered because it provides improved local tumor control to maintain or improves a patient's neurological status and quality of life.[40] Review of the 9 full-text articles pertinent to this topic corroborated previous recommendations and confirmed that reirradiation can be safely used in the elderly patients.[41-49]

The sixth part of this update explores the value of *targeted and immunotherapy* for the treatment of patients with pGBM. The previous guidelines provided level III evidence that bevacizumab should be used to provide improved progression-free survival at 6 months.[50] Review of the 86 new qualifying full-text articles provided 2 level III recommendations: (1) bevacizumab does not provide increased overall survival when used for treatment of patients with pGBM and (2) the ability to identify the benefit or harm of its use in combination with other agents was not possible because of insufficient or conflicting data.[51-54] In addition, there were insufficient data to provide recommendations regarding the benefit of the following therapies in patients with pGBM when compared with salvage cytotoxic chemotherapy: the use of bevacizumab as a combination therapy with targeted agents, use of targeted agents as monotherapy, use of targeted agents in combination with cytotoxic therapies, use of immunotherapy as monotherapy, use of immunotherapy in combination with targeted agents, and use of immunotherapy in combination with bevacizumab.

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Conflict of Interest (COI)

All Guideline Task Force members were required to disclose all potential COIs before beginning work on the guideline, using the COI disclosure form of the American Association of Neurological Surgeons/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. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this series of articles.

Disclaimer of Liability

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

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