Congress of neurological surgeons systematic review and evidence-based guidelines update on the role of cytoreductive surgery in the management of progressive glioblastoma in adults

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Abstract

Question: In patients with previously diagnosed glioblastoma who are suspected of experiencing progression, does repeat cytoreductive surgery improve progression free survival or overall survival compared to alternative interventions?

Target population: These recommendations apply to adults with previously diagnosed glioblastoma who are suspected of experiencing progression of the neoplastic process and are amenable to surgical resection.

Recommendation:

Level II: Repeat cytoreductive surgery is recommended in progressive glioblastoma patients to improve overall survival.

Introduction

Rationale

Primary malignant brain tumors carry with them a dismal prognosis, and the most aggressive subtype of malignant gliomas, glioblastoma multiforme (GBM), is also the most common [1]. Despite advances in diagnostic techniques, surgical interventions and medical treatments, long-term survival remains poor. Because of the poor survival outcomes associated with malignant glioblastoma, initial treatment strategies include an aggressive multimodal approach combining surgical resection, chemotherapy and radiation. However, due to the malignant nature of these tumors, recurrence and progression of disease is extremely common. In order to prolong survival in these patients, treatment strategies at the time of recurrence have also become more aggressive, with an increasing number of patients undergoing repeat operations in addition to salvage chemotherapy and adjuvant radiotherapy [2]. The role of repeat operation has been widely debated due to the relatively low amount of high-level data. Previously, recommendations have supported the use of repeat operations in carefully selected patients.

Since the previous clinical practice guidelines were published in 2014, there have been several studies published that address the topic of repeat cytoreductive surgery and provide additional guidance in treatment strategies for patients with recurrent GBM. To evaluate the role of repeat surgery in these patients, this review examines the up-to-date literature using an evidence-based technique.

Objectives

The overall objectives of this paper are:

1. To systematically review the up-to-date evidence available for the role of repeat open surgical resection in patients with previously diagnosed malignant glioblastoma, suspected of undergoing recurrence or progression following initial treatment.

2. To make recommendations based on the up-to-date evidence for the role of surgery in the management of these patients.

Methods

Writing Group and Question Establishment

The evidence-based clinical practice guideline taskforce members and the joint Tumor Section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) have prioritized updating the guidelines for cytoreductive surgery in the management of recurrent glioblastoma. The authors for the development of these guidelines were recruited and screened for conflicts of interest. The methodology and findings of the previous guidelines were reviewed, and the authors agreed upon an updated version of the question to be addressed in order to incorporate recent literature addressing the management of patients with recurrent GBM.

Literature Search

For the initial search strategy, Pubmed (National Library of Medicine), Cochrane, Embase and Medline databases were used. The search was limited to peer-reviewed articles that were published in the English language within the dates of July 1, 2012 and March 31, 2019. The search included relevant MeSH and non-MeSH terms that replicated the previous guideline search published in 2014, using “ALL FIELDS” and entering “RECURRENT GLIOBLASTOMA” and “SURGERY.” The updated search yielded 223 peer-reviewed articles.

Study Selection and Eligibility Criteria

To be included for review in this guideline, publications had to meet the following criteria.

Inclusion Criteria:

- Published between July 1, 2012 and March 31, 2019
- Peer-reviewed publications
- Clinical studies including patients with progressive glioblastoma where their data can be separated from that of other histologies, if mixed histologies are reported upon.
- Each study reporting on at least five or more subjects with progressive glioblastoma
- Adult patients (≥ 18 years of age)
- Publications written in English
- Addressed the PICO question

The inclusion criteria were developed by two independent reviewers. Abstracts from each citation were reviewed and included if they met the a priori criteria. Corresponding full-text articles were reviewed for

potentially relevant papers. The data were reviewed by all the authors, and discrepancies were resolved by consensus.

Data Collection Process

The updated database search yielded a total of 223 publications, which were reviewed by two independent authors. Among these, 53 citations met the eligibility criteria and were reviewed in full text form. The two independent reviewers excluded citations that were not relevant to the PICO question, did not present novel data, or did not improve upon the class of evidence or level of previous recommendations. The reviewers sought to include citations that investigated populations or outcome measures that had not been reviewed in previous guidelines. Ultimately, 4 articles were found to meet all inclusion criteria and present novel data relevant to the PICO question. Data were extracted and compiled into evidence tables, which were reviewed by all of the authors.

Assessment of Risk of Bias

Our search generated a list of abstracts, which were screened, and those articles that addressed our identified questions underwent independent review by the authors. Reviewers were critical in their assessment, specifically in regard to trial design, such as randomization of treatment, blinding, prospective character, size of study population, adequacy of control group, and baseline characteristics between study groups which could account for survivorship bias, and selection bias, and whether appropriate statistical analyses were utilized for the reported data.

Description of the Data Classification System and Recommendation Formulation

Each reviewer independently determined the quality of the evidence and strength of recommendations generated by the evidence, according to a three-tiered system as approved by the AANS/ CNS Joint Guideline Review Committee. Discrepancy in level of recommendations were discussed amongst the reviewers until a consensus was reached. For each article, a level of classification was achieved. Class I evidence was reserved for well-designed, prospective, randomized and controlled studies with clear mechanisms to limit bias. Class I evidence used to support recommendations of the strongest type, defined as Level I recommendations, indicating a high degree of clinical certainty. Class II evidence described studies that were randomized and controlled studies, but with design flaws leading to potential bias and limiting the paper's conclusions, non-randomized cohort studies, and case-control studies. Level II recommendations are derived from Class II evidence and indicate a moderate degree of clinical certainty. Class III evidence was reserved for single surgeon, single institutional case series, comparative studies with historical control, and randomized studies with significant flaws related to studies with limited power and compromised statistical analysis. Level III recommendations indicate unclear clinical certainty. Additional information on study classification and recommendation development can be found at https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

Results

Prior Guideline Question and Recommendation

In the previously published guideline a single question was asked: “Should patients with previously diagnosed malignant glioma who are suspected of experiencing progression of the neoplasm process undergo repeat open surgical resection?” A level II recommendation was formulated stating: “Repeat cytoreductive surgery is recommended in symptomatic patients with locally recurrent or progressive malignant glioma. The median survival in these patients diagnosed with glioblastoma is expected to range from 6 to 17 months following a second procedure. It is recommended that the following preoperative factors be considered when evaluating a patient for repeat operation: location of recurrence in eloquent/critical brain regions, Karnofsky Performance Status and tumor volume.” This was based on based on 32 studies, 1 of which provided Class II data, 30 of which provided Class III data, and a systemic review provided both Class II and Class III data [3]. The information below was used to refine this recommendation.

Cytoreductive surgery scientific foundation

This literature review resulted in four fully published studies that are summarized in Table 1. These studies were published after July 2012 and therefore were not included in the previous systematic review and evidence-based clinical practice guidelines published in 2014 [3].

Table 1
Repeat cytoreductive surgery evidence table

Author (year):	Description of study:	Data class:	Conclusions:
Hager et al (2018)	Study Description: Single center, retrospective study of 59 elderly patients who either underwent stereotactic biopsy (STX), first resection or second resection of GBM Patient Population: GBM patients (n = 59) Age range: 65–81 years old Median age for group was 71 years Treatments: Stereotactic biopsy – 17/59 (29%) Single resection – 15/59 (25%) Reresection – 27/59 (46%)	III	Results: Median overall survival STX group: 221 days vs. Surgery group (single resection and reresection): 622.5 days (p = 0.041) Single resection: 422 days vs. Reresection group: 634 days (p = 0.1) Progression free survival STX group: 167 days Single resection group: 169 days Reresection group: 305 days (p = 0.1) Author's Conclusions: Neither overall median survival nor progression free survival differed significantly between patients over and under 71 years. Elderly patients should be judged by their individual conditions such as KPS (> 70), frailty and co-morbidities before considering reoperation. Comments and Conclusions: Classified as Class III because study is retrospective nonrandomized review. Study showed significant survival benefit in surgery over STX in elderly patients, but not in one resection over two resections. This study is limited by a low sample size.

Abbreviations: CRET, complete resection of enhancing tumor; GBM, glioblastoma multiforme; KPS, Karnofsky Performance Status; MRI, magnetic resonance imagin; STX, stereotactic biopsy; TMZ, temozolomide.

Author (year):	Description of study:	Data class:	Conclusions:
Suchorska et al (2016)	Study Description: Multicenter, prospective randomized trial of 105 patients with recurrent GBM treated with 2 dose-intensified temozolomide regimens, evaluating extent of resection of post-operative MR imaging. Patient Population: Recurrent GBM patients (n = 105) Reresection: 71/105 (68%) No surgery after recurrence: 34/105 (32%) The 71 patients that received surgery were balanced with the 34 patients that did not receive surgery. Treatments: Complete resection of enhancing tumor (CRET) rate: 40/105 (38%) Incomplete resection rate: 19/105 (18%)	II	Results: Post-recurrence survival Complete resection group: 12.9 months vs. Incomplete resection group: 6.5 months (p = 0.001) Quality of life regarding cognitive and neurological function was superior in the complete resection cohort. Compared with the non-resected cohort, incomplete resection did not result in better outcome regarding either survival or QoL. Author's Conclusions: Reoperation at first recurrence of GBM improves outcomes if complete resection of contrast-enhancing tumor is achieved. "Although the data were collected prospectively, it is still a retrospective, exploratory analysis that was not prespecified." Comments and Conclusions: Classified as Class II because, while it is a prospective randomized multicenter trial, this study was not powered or designed to assess surgery. The DIRECTOR trial was designed to assess tolerability and efficacy of two dose-intensified TMZ regimens. However, since outcomes in the two TMZ arms were identical, retrospective analysis of surgery and extent of re-resection showed significant effect on survival.

Abbreviations: CRET, complete resection of enhancing tumor; GBM, glioblastoma multiforme; KPS, Karnofsky Performance Status; MRI, magnetic resonance imagin; STX, stereotactic biopsy; TMZ, temozolomide.

Author (year):	Description of study:	Data class:	Conclusions:
D'Amico et al (2015)	Study Description: Single center, retrospective cohort study of 319 elderly patients aged 65 years or older with GBM undergoing biopsy, single resection, or re-resections. Patient Population: GBM patients 65 years or older Treatments: Biopsy only: 59/319 (18.5%) Single resection: 215/319 (67.4%) Two resections: 28/319 (8.7%) Three resections: 3/319 (0.9%)	III	Results: Overall survival Biopsy only group: 3.4 months vs. Single resection group: 8.9 months ($p < 0.05$) Single resection group: 8.9 months vs. Re-resection groups: 18.4 months ($p < 0.05$) Cardiovascular risk was found to be negatively associated with receiving reoperation for recurrent disease ($P < 0.05$), and KPS was found to be positively associated with selection for reoperation ($P < 0.05$). There was not a significant difference in overall complication rates between single-resection and reoperation groups (21.9% vs. 25.8%; $P > 0.10$), although a selection bias was detected based on cardiovascular risk and KPS. Author's Conclusions: Surgical resection in carefully selected elderly patients is likely a safe therapeutic option for primary and recurrent disease and should be considered as part of an aggressive treatment approach. Comments and Conclusions: Classified as Class III because study is a retrospective review. This study showed a survival benefit in re-resection of recurrent GBM in elderly patients. However, there is significant selection bias in patients with low cardiovascular risk and high KPS who were able to tolerate re-resection without morbidity.

Abbreviations: CRET, complete resection of enhancing tumor; GBM, glioblastoma multiforme; KPS, Karnofsky Performance Status; MRI, magnetic resonance imagin; STX, stereotactic biopsy; TMZ, temozolomide.

Author (year):	Description of study:	Data class:	Conclusions:
Yong et al (2014)	Study Description: Single center, prospective cohort study with 97 patients who underwent reoperation of recurrent GBM, evaluating post-operative volume of contrast-enhancing tumor on MR imaging Patient Population: Recurrent GBM patients (n = 97) Age range: 23–74 years old Median age for group was 49 years Treatment: All patients underwent resection of recurrent GBM and underwent repeat contrast-enhanced MR imaging within 24 hours following reoperation.	III	Results: Median overall survival Residual tumor size: > 3 cm^3: 5.1 months vs. 0–3 cm^3: 10.6 months ($p < 0.001$) > 3 cm^3: 5.1 months vs. Radiologically absent: 19.9 months ($p < 0.001$) Eloquent tumor location ($p < 0.001$) and larger preoperative tumor volume ($p < 0.001$) were significantly associated with larger postoperative residual tumor volume. Author's Conclusions: Decreasing postoperative residual tumor volumes during reoperations of recurrent GBM improves overall survival. Comments and Conclusions: Classified as Class III because it is a single center prospective study without a control group. This study and its conclusions have significant limitations because it was a single arm study. While there was a survival benefit with decreasing residual tumor volumes in recurrent GBM, there were also significant confounding variables influencing whether complete resection could be achieved.

Abbreviations: CRET, complete resection of enhancing tumor; GBM, glioblastoma multiforme; KPS, Karnofsky Performance Status; MRI, magnetic resonance imagin; STX, stereotactic biopsy; TMZ, temozolomide.

Prospective Studies

Two prospective studies are summarized in Table 1. Yong et al published a single center, prospective cohort study with 97 patients with recurrent glioblastoma who underwent reoperation for GBM resection [4]. Each patient had post-operative contrast-enhanced MR imaging performed within 24 hours of

reoperation, and residual tumor size was measured for all patients. Residual tumor sizes were classified into three categories: radiologically absent, small (0–3 cm^3) and large (> 3 cm^3). The primary outcome for the study was median overall survival, which was measured from the date of reoperation to the date of death. Yong et al reported that patients with large residual tumors following reoperation had significantly decreased survival when compared to patients with small residual tumors (5.1 vs. 10.6 months; $p < 0.001$) and radiologically absent residual tumors (5.1 vs. 19.9 months; $p < 0.001$). Subsequent serial follow-up imaging for 87 patients demonstrated that large residual tumors had faster regrowth rates, and faster regrowth rates were significantly associated with decreased post-operative survival (HR = 4.01; $p < 0.001$). In order to determine potential causes of incomplete resection, preoperative factors were reviewed for patients with large residual tumor volumes. Of all the factors evaluated in multiple regression analysis, both eloquent tumor location and large preoperative tumor volume were significantly associated with larger residual tumor volume. The authors concluded that reoperation of recurrent GBM improved overall survival if resection could be safely achieved with small or radiologically absent residual tumors. As a single-center, prospective study, it was classified as Class III because it was a single arm study without a comparative group described.

Suchorska et al. published a multicenter, prospective randomized trial comparing 2 dose-intensified temozolomide regimens in 105 patients with recurrent GBM in the DIRECTOR trial [5]. In this study, 71 of the 105 total patients underwent reoperation for resection of recurrent GBM, and 59 patients had post-operative MR imaging available for analysis. Patients were not randomized for reoperation, but post hoc analysis of the data showed that complete resection of enhancing tumor on MR imaging had a significant benefit for post-recurrence survival when compared to incomplete resection (12.9 vs. 6.5 months; $p = 0.001$), as well as an improvement in quality of life. In this study, complete resection was defined as the absence of any contrast-enhancing tumor volume in post-operative imaging. Patients who had incomplete resections at reoperation had a trend towards worse overall survival when compared to the group of 34 patients who did not undergo reoperation (6.5 vs. 9.8 months; $p = 0.052$), without improving quality of life. The authors concluded that reoperation improved post-recurrence survival and quality of life outcomes if complete resection of contrast-enhancing tumor could be safely achieved. Although the DIRECTOR trial was a multi-center, prospective randomized trial, this study is derived from a retrospective, exploratory analysis of the data. While patients were randomized for 2 dose-intensified temozolomide regimens instead of reoperation versus no reoperation, the reoperation group was well balanced with the non-operative group by KPS score, initial first-line treatment, progression-free survival from first diagnosis, steroid intake, and MGMT promoter methylation. Therefore, this data is classified as Class II data.

Retrospective Studies

Two retrospective studies are summarized in Table 1, both studying elderly patients 65 years or older. D'Amico et al published a single center, retrospective cohort study of 319 elderly patients aged 65 years or older with GBM undergoing biopsy, single resection, or multiple resections [6]. The study found that overall survival was significantly improved in the reoperation group when compared to the single

resection group (18.4 vs 8.9 months; $p < 0.05$) and the single resection group when compared to the biopsy only group (8.9 vs. 3.4 months; $p < 0.05$). There was not a significant difference in overall complication rates between the single resection group and the multiple resection groups (21.9% vs. 25.8%; $p > 0.10$), but older age and lower KPS scores were associated with more systemic complications from reoperation. The authors found that both higher cardiovascular risk and lower KPS scores significantly decreased the likelihood of elderly patients undergoing multiple resections. The authors concluded that age itself should not exclude patients from being considered for reoperation in recurrent GBM. Reoperation in carefully selected elderly patients is a safe therapeutic option, as long as patients are healthy enough to undergo surgical resection. Due to the significant selection bias in patients having lower cardiovascular risk and high pre-operative KPS scores undergoing multiple resections, this retrospective cohort study was classified as a Class III study.

Hager et al published a single center, retrospective cohort study of 59 elderly patients who underwent either stereotactic biopsy, first resection or second resection of GBM [7]. Patient age ranged from 65–81 years, with a median age of 71 years. A relatively large proportion of the study sample underwent reoperation (27/59). The study found that patients that underwent surgical resection (single or multiple resections) had a significantly improved median overall survival (622.5 vs. 221 days; $p = 0.041$). There is a trend towards survival benefit in reoperation for recurrent GBM when compared to single resection for overall survival (634 vs. 422 days; $p = 0.1$) and progression free survival (305 vs. 169 days; $p = 0.1$); however, these differences are not significant. Neither overall survival nor progression free survival differed significantly between patients older than the median age of 71 year and those younger than 71 years. Ultimately, the authors concluded that elderly patients should be considered for maximal treatment of GBM, including single or multiple surgical resections as it may provide a survival benefit. This data was classified as Class III because it was a retrospective nonrandomized review that was limited by a low sample size and selection bias for reoperation.

Synthesis of Results

Evidence on the role of cytoreductive surgery for progressive glioblastoma continues to build since the last guidelines publication. As mentioned above, previous recommendations were based on 32 studies, 1 of which provided Class II data, 30 of which provided Class III data, and a systemic review provided both Class II and Class III data. In this update, there were an additional 4 studies where one study presented Class II data and 3 studies presented Class III data. A survival advantage to cytoreductive surgery in a select group of patients with progressive glioblastoma has consistently been reported. The additional studies identified in the current update clarifies both the benefit of maximal cytoreductive surgery in this patient populations as well as the benefit of cytoreductive surgery in the elderly for improving overall survival. With regard to the former, one Class II study displayed improved patient outcome with complete resection of the contrast-enhancing tumor while one class III study displayed improved survival as the degree of resection increased among patients within the cohort. Maximal EOR, however, can only be considered in the context of minimizing post-operative neurological deficits. With regard to the latter, two class III studies supported re-resection in a select group of elderly patients when taking into account such

factors as KPS, frailty, and medical co-morbidities. These additional studies collectively indicate the importance of taking into account age, Karnofsky Performance Status, cardiovascular risk, tumor size, eloquent brain involvement, histological characteristics, and quality of life when considering patients for surgery.

Discussion

The amount of high level, prospective data on the role of cytoreductive surgery for progressive GBM has not changed significantly since the most recent clinical practice guidelines were published in 2014 [3]. The majority of data available remains Class II or III with retrospective reviews or non-randomized prospective trials. However, current data continues to support the recommendation for reoperation in progressive GBM in carefully selected patients, with the goal of maximal safe resection.

Two of the studies discussed above (Yong et al, Surchorska et al) were included in this review because they investigated the significance of extent of resection in recurrent GBM. The conclusion in both studies – that complete resection is associated with a significant survival benefit – follows the trend of several recent studies that demonstrate the survival advantages of maximizing extent of resection, balanced with limiting the risks of neurological morbidities in aggressive cytoreductive strategies. Oppenlander et al published a retrospective review of 170 patients concluding that the threshold for extent of resection associated with a significant survival advantage was only 80% [8]. They reported that once extent of resection exceeded 80%, there was a significant increase in neurological morbidity, emphasizing the balance of maximizing resection while still avoiding surgical complications and eloquent brain tissue. Though in a different population, this conclusion mirrors a study published by Sanai et al in 2011 reviewing 500 patients who underwent resection of newly diagnosed GBM in between 1997 and 2009 [9]. In this study, subtotal resection as low as 78% still showed a survival benefit. However, a recent study published by Bloch et al showed that for 107 patients with recurrent GBM, gross total resection at their second resection was a more significant predictor of overall survival than extent of resection at their first resection. Patients with subtotal resections at their initial operation still had a significant survival benefit if they had gross total resections at their reoperation [10].

Recent developments in intraoperative adjuncts, such as fluorescence-guided surgery, intraoperative MRI, motor mapping and 3D image guidance, provide technical advantages to modern surgeons for maximal safe resection in order to improve overall survival while minimizing risk of neurological morbidity. The use of intraoperative fluorescence with 5-ALA was shown in 2006 to provide a significant increase in complete resections of malignant gliomas, as well as improvement in 6-month progression free survival [11]. A supplemental analysis published in 2011 reported that although 5-ALA improved extent of resection, patients were more likely to experience deterioration on the NIH stroke scale 48 hours after surgery. However, when stratified by extent of resection, patients with subtotal resections were more likely to have long-term neurologic deteriorations compared to patients with complete resections [12]. In patients undergoing reoperation of their recurrent GBM, Nabavi et al demonstrated that 5-ALA remains a useful tool in detecting recurrent gliomas, even after previous treatments with radiation, chemotherapy, or

prior resections [13]. Recently, fluorescein sodium has been shown to be a viable alternative to 5-ALA in fluorescence-guided resection of malignant gliomas for both primary [14] and recurrent gliomas [15]. Intraoperative MRI, in conjunction with fluorescence-guided resection, has also been shown to be a useful surgical tool as well [16]. These surgical modalities support the recommendation for reoperation for recurrent GBM because they help make complete resection more achievable. As described above, degree of resection must still be quelled by the risk of post-operative morbidity.

Two of the studies featured above (Hager et al, D'Amico et al) focus on the elderly population with recurrent GBM. These studies were included in this review because they support the recommendation that carefully selected patients gain a survival benefit from reoperation, and that patients should not be excluded from surgical consideration solely based on their age. Careful patient selection is an important means of minimizing both neurological and non-neurological morbidity and mortality. Ringel et al published a multicenter, retrospective review of 503 patients undergoing resection of recurrent GBM with specific focus on both survival and complication rates. The authors concluded that while the complication rates are slightly higher for reoperation than for initial resection, the complication rates are acceptable due to the survival benefit that complete resection at reoperation provides. Age, preoperative KPS score, tumor location and chemotherapy after first resection were all evaluated and found to be prognostic factors for reoperation [17].

The consideration to treat recurrent GBM with reoperation should include several important and well-studied factors. Park et al initially published a validated outcome score in 2010 that stratified post-operative survival in recurrent GBM based on tumor volume (>50 cm^3), KPS score (<80), and involvement in eloquent brain regions [18]. That prognostic outcome score was later simplified in 2013 to stratify patients based on only KPS score (<70) and ependymal involvement. The authors concluded that patients with both poor functional status and contrast enhancement in the ventricular wall had the poorest prognosis [19]. Alternatively, Pala et al demonstrated the importance of MGMT promoter methylation in the consideration of reoperation. They reported that patients with either methylated or unmethylated MGMT promoter had a significant survival benefit by undergoing reoperation. However, subgroup analysis revealed that gross total resection in patients with unmethylated MGMT promoter had significantly better outcomes than subtotal resection, indicating that aggressive surgical treatment should be considered in more malignant tumors [20]. This emphasizes the importance of biological analysis of tumor specimens from the initial resection to guide future treatments for chemotherapy and radiation, as well as the possibility of reoperation at the time of recurrence.

Conclusion And Key Issues For Future Investigation

The goals of reoperation for recurrent GBM is not only to prolong survival, but also to alleviate neurological symptoms and preserve good quality of life. Therefore, selecting patients that would benefit from reoperation without significant morbidity or mortality is crucial. The decision to pursue reoperation for recurrent GBM should be individualized to the patient. This recommendation has not changed since the previous guidelines, but our understanding for selecting candidates for reoperation and how to

maximize survival in those patients continues to improve. The studies included in this review add to the existing pool of data by addressing the survival impact of extent of resection for recurrent GBM and the inclusion of the elderly population for consideration of reoperation.

However, the amount of high-level data addressing the question of reoperation in recurrent GBM is still limited. Many of the studies are downgraded to Class III data because of small sample sizes and retrospective designs lacking control groups. In order improved the level of data obtained in the future, study design will need to be fashioned in a manner that minimizes bias. For instance, study designs need to minimize selection bias for patients undergoing reoperation. Younger patients with better functional status based on KPS scores are more likely to undergo reoperation, such that some authors have argued that the survival benefit seen in reoperation is blurred by selection bias. These patients with more favorable prognostic factors are better surgical candidates, but also have better survival outcomes independent of reoperation [21].

An additional source of bias to investigate further is the timing of reoperation. A recent meta-analysis demonstrated that timing of recurrence and reoperation has an impact on survival. The authors concluded that the survival benefit of reoperation may be overestimated in studies measuring overall survival as the primary outcome. Patients with prolonged pre-progression survival before recurrence have an inherent bias towards an improved overall survival from time of initial diagnosis to death [22]. Patients who experience earlier recurrence of their GBM typically have more malignant tumors that exhibit aggressive histological and molecular risk factors, such as lack of MGMT methylation [23]. This introduces a length-time bias where the heterogeneity of GBM characteristics between patients can lead to an overestimation of survival benefit in some patients. Tumor banking and histological analysis should be included in study designs for future investigation into the survival benefit of reoperation in recurrent GBM.

The literature identified for this guideline continues to support the recommendation that reoperation is an important treatment strategy for recurrent GBM and can provide a survival benefit in carefully selected patients. The decision for reoperation should be individualized to the patient, taking into account factors such as age, KPS scores, eloquent brain involvement, cardiovascular risk, tumor size, histological characteristics, and quality of life. Prospective data collection and improved study designs are crucial for future investigation if we are to improve our understanding of repeat cytoreductive surgery as a treatment strategy.

Abbreviations

CRET, complete resection of enhancing tumor; EOR, extent of resection; GBM, glioblastoma multiforme; KPS, Karnofsky Performance Status; MRI, magnetic resonance imaging; PFS, progression free survival; STX, stereotactic biopsy; TMZ, temozolomide; OS, overall survival

Declarations

Potential Conflicts of Interest (COI)

All Guideline Task Force members were required to disclose all potential 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. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this series of articles.

Disclosures

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Compliance with Ethical Standards

All authors involved in this review have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this series of articles. The authors declare that they have no conflict of interest. This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was not necessary for obtaining data for this review.

Data availability

The studies used to compile the dataset for the current manuscript are available through PubMed. All authors have ensured all data and materials as well as software applications or custom code supports their published claims and comply with field standards.

Author statement

All authors listed on this publication agree with the content included and give explicit consent to the submission of this publication. The authors obtained consent from the responsible authorities at the institute/organization where the work has been carried out, before the work was submitted.

All authors whose names appear on the submission:

1) made substantial contributions to the conception or design of the work; or the acquisition,

analysis, or interpretation of data; or the creation of new software used in the work;

2) drafted the work or revised it critically for important intellectual content;

3) approved the version to be published; and

4) agree to be accountable for all aspects of the work in ensuring that questions related to the

accuracy or integrity of any part of the work are appropriately investigated and resolved.

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. The presentations are 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 its 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 physician should be sought. The proposals contained in this guideline may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in this guideline 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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