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TOPIC REVIEW

Cytoreductive surgery in the management of newly diagnosed glioblastoma in adults: a systematic review and evidence-based clinical practice guideline update

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Abstract

Target population These recommendations apply to adults with newly diagnosed or suspected glioblastoma.

Question What is the effect of extent of surgical resection on patient outcome in the initial management of adult patients with suspected newly diagnosed glioblastoma?

Recommendation Level II: Maximal cytoreductive surgery is recommended in adult patients with suspected newly diagnosed supratentorial glioblastoma with gross total resection defined as removal of contrast enhancing tumor.

Level III: Biopsy, subtotal resection, or gross total resection is suggested depending on medical comorbidities, functional status, and location of tumor if maximal resection may cause significant neurologic deficit.

Question What is the role of cytoreductive surgery in adults with newly diagnosed bi-frontal "butterfly" glioblastoma?

Recommendation Level III: Resection of newly diagnosed bi-frontal "butterfly" glioblastoma is suggested to improve overall survival over biopsy alone.

Question What is the goal of cytoreductive surgery in elderly adult patients with newly diagnosed glioblastoma?

Recommendation Level III: Elderly patients (> 65 years) show survival benefit with gross total resection and it is suggested they undergo cytoreductive surgery.

Question What is the role of advanced intraoperative guidance techniques in cytoreductive surgery in adults with newly diagnosed glioblastoma?

Recommendation Level III: The use of intraoperative guidance adjuncts such as intraoperative MRI (iMRI) or 5-aminolevulinic acid (5-ALA) are suggested to maximize extent of resection in newly diagnosed glioblastoma. There is insufficient evidence to make a suggestion on the use of fluorescein, indocyanine green, or intraoperative ultrasound.

Keywords Glioblastoma · Surgery · Cytoreduction · Guideline

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Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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Rationale

Glioblastoma (GBM) continues to be a challenging disease to treat, often with rapid progression and limited overall survival. Surgical resection is central to treatment paradigms in combination with radiation therapy and chemotherapy for treatment of newly diagnosed glioblastoma. Cytoreductive surgery for maximal safe surgical resection with preservation of preoperative neurologic function remains the standard surgical goal.

Many publications report reproducible improvement in median survival times with increasing extent of resection, supporting maximal safe resection. A natural next step in thought focuses on the infiltrative zone of peritumoral FLAIR signal beyond the border of contrast enhancement, with the concept of supramaximal or supratotal resection being explored. To aid in safely maximizing resection, the use of intraoperative adjuncts such as intraoperative magnetic resonance imaging (iMRI) and 5-aminolevulinic acid (5-ALA) has been evaluated in an increasing number of studies. The aggressiveness of a treatment plan is tailored to each patient and there have been many studies which patient- and tumor-specific factors are examined to determine which patients benefit the most from cytoreductive surgery.

Our goal with this update is to assess the literature since the last set of clinical guidelines for cytoreductive surgery by Ryken et al. was published in 2008 [1]. We seek to further elucidate the evidence in newly available literature since that analysis and update the recommendations in regard to cytoreductive surgery.

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 an update of the guidelines for management of newly diagnosed glioblastoma. A series of writers were identified and screened for conflict of interest. This group in turn agreed on a set of questions addressing the topic at hand and conducted a systematic review of the literature relevant to the role of surgery in the management of newly diagnosed glioblastoma.

Literature review and eligibility criteria

The MEDLINE and EMBASE databases were searched for the publications between January 1, 2005 and October 31, 2018 using relevant MesH and non-MeSH terms, including "glioblastoma," "astrocytoma," "high-grade glioma," "surgery," "surgical resection," and "cytoreductive" specifying those citations addressing human subjects. We also searched the bibliographies of recent systematic reviews and other review articles for potentially relevant citations.

Citations were manually reviewed by the team with specific inclusion and exclusion criteria as outlined below. Three independent reviewers reviewed and abstracted full text data for each article. Inconsistencies were reviewed and disagreements were resolved by consensus. Citations that addressed adult patients focusing on the surgical management of newly diagnosed glioblastoma were considered. To be included in our guideline, a publication had to meet the following criteria:

Inclusion criteria

- Published between January 1, 2005 and October 31, 2018
- Published in English.
- Adult patients (age ≥ 18) with newly diagnosed glioblastoma were included in the study and the data on their outcomes could be separated from other histologic tumor types.
- Fully published (i.e., not in abstract form) peer-reviewed primary studies.
- Number of study participants with newly diagnosed glioblastoma ≥ 5.
- For studies with mixed histologic populations, baseline pretreatment and outcome information on study participants is provided for patients with newly diagnosed glioblastoma separate from other histopathologic types.
- For studies with consideration of more than one treatment regimen, baseline pretreatment and outcome information on study participants is provided in a manner that can be separated by treatment.

Exclusion criteria

- In vitro only
- Animal only

We did not specifically include systematic reviews, guidelines or meta-analyses conducted by others. These documents were developed using different inclusion

criteria than those specified in the evidence base for this guideline, but they are included in discussion and references as relevant.

Data collection process

Those abstracts that met with the selection criteria mentioned above were retrieved in full text form. A total of 7684 citations were screened and assessed for eligibility based on the criteria noted above. Of these, 212 were chosen as relevant for full text review and assessment. A total of 51 publications met the criteria for inclusion.

To determine how the data could be classified the information in the full text manuscripts were then evaluated to determine whether they were providing results of therapy or were more centered on diagnostic or prognostic information. Consensus was reached on these assessments and on the salient points regarding the type of study design, objectives, conclusions, and class of evidence. This information was then organized into the evidentiary tables.

Classification of evidence and recommendation levels

Standardized nomenclature used by the American Medical Association (AMA) and many specialty societies, including the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS) was utilized. In the paradigm for therapeutic maneuvers, evidence is classified into that which is derived from the strongest clinical studies (e.g., well-designed, randomized controlled trials), or Class I evidence. Class I evidence is used to support recommendations of the strongest type, defined as Level I recommendations, indicating a high degree of clinical certainty. Non-randomized cohort studies, randomized controlled trials with design flaws, and case–control studies (comparative studies with less strength) are designated as Class II evidence. These are used to support recommendations defined as Level II reflecting a moderate degree of clinical certainty. Other sources of information, including observational studies such as case series and expert opinion, as well as randomized controlled trials with flaws so serious that the conclusions of the study are truly in doubt are considered Class III evidence and support Level III recommendations, reflecting unclear clinical certainty. Additional information on the method of data classification and translation to recommendation level can be found at: https://www.cns.org/guidelines/guideline-development-methodology.

Assessment for risk of bias

Our search generated a list of abstracts, which were screened, and those articles that addressed our identified questions underwent full 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, etc., size of study population, baseline characteristics between study groups which could account for survivorship bias, selection bias, and appropriate statistical analyses of reported data.

Summary of prior recommendations

In the previously published guidelines on the surgical management of newly diagnosed GBM [1], for supratentorial glioblastoma in adults that the maximally safe resection be undertaken (i.e. the maximal cytoreductive procedure provided that post-operative neurological deficit can be minimized) by Level II recommendation based on available prospective data and a general consensus of retrospective data. Biopsy, partial resection or gross total resection may all be considered in the initial management of glioblastoma depending on the condition of the patient, the size and the location of the tumor as a Level III recommendation.

Results of individual studies

Question: What is the effect of extent of surgical resection on patient outcome in the initial management of adult patients with suspected newly diagnosed glioblastoma?

Extent of resection and overall survival

Many studies have continued to assess the effect of extent of resection (EOR) on overall survival (OS) as well as progression free survival (PFS) since the initial guideline publication in 2008 [1]. These studies sought to isolate the impact of EOR and separate it from other patient level or tumor related factors. Kreth et al. [2] prospectively enrolled 345 patients in a multicenter study of surgical outcomes. The cohort was divided into GTR (n = 125), STR (n = 148), or biopsy (n = 72) assessing the prognostic influence of EOR when compared with biopsy. Only GTR made a difference in survival over biopsy alone. Stummer et al. [3] performed a prospective cohort study investigating 143 patients with primary GBM. Age at diagnosis and EOR were independently associated with OS. Allahdini et al. [4] prospectively analyzed 35 patients with primary GBM and found EOR was an independent variable associated with longer survival times. Scoccianti et al. [5] performed a multicenter retrospective review of primary GBM in 1059 patients. Resection was undertaken in 911 patients, with GTR achieved in 485 and STR in 434. Age, postoperative KPS, EOR, use of

radiotherapy or chemotherapy all were prognostic factors predicting improved OS.

Padwal et al. [6] retrospectively analyzed SEER data in 21,962 patients with primary GBM with EOR categorized into gross total resection (GTR), subtotal resection (STR), biopsy, or no resection. EOR was associated with OS, with greater resection improving survival. Noorbakhsh et al. [7] retrospectively analyzed SEER data on 20,705 patients with newly diagnosed GBM, dividing patients into no surgery, STR and GTR and found that, regardless of age, GTR gave a 2–3 month improvement in OS compared to STR. McGirt et al. [8] retrospectively reviewed 1215 patients undergoing for high-grade glioma with 700 of those patients having GBM. For primary GBM resection, median survival for GTR was 13 months, near-total resection was 11 months, and STR was 8 months, all of which were significant differences in adjusted analysis. Awad et al. [9] retrospectively reviewed 330 patients undergoing initial resection of GBM. EOR correlated with survival. However, tumors with deep-seated locations, in poorly accessible areas or with multifocal enhancement had worse OS independent of EOR. Orringer et al. [10] retrospectively analyzed 46 patients who underwent primary GBM surgery and investigated factors associated with EOR. EOR greater than 90% was associated with a greater survival.

Two studies in particular performed a sub-analysis within the larger 5-ALA glioma study [11]. Pichimeier et al. [12] performed a re-stratification of glioblastoma patients from a prospective 5-ALA study, and they assessed OS based on RTOG-RPA class and EOR, concluding that RPA class predicts survival of GBM patients, with RPA Class IV and V having improved survival with GTR. However, RPA class III was not associated with longer survival based on EOR. Stummer et al. [13] reanalyzed data from a prospective 5-ALA study based on 243 patients with GBM and found that younger age and non-eloquent tumor location favored complete resection. However, when controlled for, EOR remained an independent predictor of OS (GTR vs other) along with improved PFS.

Other studies have focused on residual volume (RV) as a continuous variable allowing for more variation than strict categorization of GTR versus STR/biopsy. Chaichana et al. [14] retrospectively reviewed 259 patients that underwent resection of primary GBM. 3D volumetric MRI measurements were used to determine EOR and residual volume (RV). EOR correlated with improved survival and recurrence if greater than 70%. RV also correlated to survival and recurrence if less than 5 cm^3. Chaichana et al. [15], retrospectively analyzed another 292 patients focusing on patients (n = 84) where surgeons preoperatively felt GTR could successfully be performed (blinded and determined independently by three neurosurgeons). EOR and RV were evaluated, and both were found to be significantly associated with recurrence and survival. Fukui et al. [16] retrospectively reviewed 168 initial GBM patients. EOR and residual tumor volume were significantly associated with survival and recurrence comparing GTR to STR. Grabowski et al. [17] performed a retrospective analysis of 128 patients that underwent resection of primary GBM. Volumetric analysis for EOR, residual enhancing (CE-RTV) and T2/FLAIR hyperintense tumor volume (T2/F-RV) was performed. All were significant predictors of survival when controlling for age and KPS. The benefit in survival occurred with a CE-RTV less than 2 cm^3 or EOR greater than 98%. Marko et al. [18] retrospectively performed prediction modeling in 721 newly diagnosed patients with GBM to model factors affecting survival after surgical excision, and then validated this model with 109 patients from a separate institution. They found a continuous, nonlinear relationship between median OS and EOR providing evidence supporting maximum safe resection approach to GBM surgery, rather than a rigid EOR threshold approach.

Supramaximal/supratotal resection

A newer area in the realm of extent of resection focuses on extending the area of surgical resection beyond the border of contrast enhancement with the goal of resecting the infiltrative zone. It was of enough interest the authors searched the topic based on a question generally formatted as: What is the effect of supramaximal or supratotal (beyond area of contrast enhancement) resection on survival in adults with newly diagnosed glioblastoma? Glenn et al. [19] performed a retrospective review of 32 patients with temporal lobe glioblastoma undergoing initial resection. EOR was defined as STR, GTR or supramaximal resection (resection of all enhancing tissue plus 1 cm of brain tissue surrounding enhancement). OS was significantly improved for SMR (24 months) and improved for GTR (11 months) in comparison to STR (9 months). Mampre et al. [20] performed a retrospective review of 245 patients undergoing initial resection of glioblastoma. EOR was assessed by enhancing volume (GTR) or enhancing volume plus T2 hyperintense region (SMR). Survival was associated with residual postoperative contrast enhancing volume, but not with residual T2 hyperintense region (FLAIR residual volume). Pessina et al. [21] performed a retrospective analysis of 282 initial glioblastoma patients undergoing resection. EOR was assessed by resection of all contrast enhancing volume (GTR), 10–89% of enhancing volume resected (STR), less than 10% of enhancing volume resected (biopsy) or 100% of contrast enhancing volume plus all FLAIR hyperintense region resected (SMR). EOR correlated with survival, with SMR having the highest PFS and OS in comparison to GTR, STR or biopsy.

Table 1 Extent of resection evidentiary table

Author (year)	Description of study	Data class	Conclusions
Glenn et al. (2018)	Retrospective review of 32 patients with temporal lobe GBM who underwent resection. Progression-free survival and overall survival were analyzed based on resection categories of sub-total resection (STR), gross total resection (GTR), and supramaximal resection (SMR). SMR defined as resection of all enhancing tumor plus at least 1 cm of brain tissue surrounding the enhancement	III	Median PFS was 15 months for SMR, 7 months for GTR, and 6 months for STR. Median OS was 24 months for SMR, 11 months for GTR, and 9 months for STR. Adjusted HR for SMR in comparison to other groups was 0.093 for PFS and 0.169 for OS. No difference in complication rates. SMR improved survival in temporal lobe GBM compared to GTR or STR Limitations include retrospective nature and small sample size
Mampre et al. (2018)	Retrospective review of 245 patients who underwent resection of newly diagnosed GBM. EOR assessed for the contrast enhancing (CE) volume of tumor and the FLAIR volume, then correlated with survival and recurrence	III	Postoperative median CE volume 1.9 [0–7.1] cm^3 and FLAIR volume 59.7 [29.7–94.2] cm^3. In multivariate analysis FLAIR volume was not significantly associated with recurrence or median survival. This held in the subset of patients who underwent GTR or SMR. Postoperative CE volume was significantly associated with recurrence and overall survival. CE residual volume but not FLAIR residual volume was important for overall survival Limitations include retrospective nature
Awad et al. (2017)	Retrospective review of 330 patients with primary GBM undergoing surgical resection. Outcomes of OS based on EOR was followed	III	Median EOR was 96.0% (67.4–94.7%). 1-, 2-, and 5- year survival rates were 59.3, 27.2 and 4.1%. Extent of resection and improvement in KPS postoperatively both correlated to improved survival. Tumors with deep-seated, poorly accessible, or multifocal locations had worse OS independent of EOR Limitations include retrospective nature
Fukui et al. (2017)	Retrospective review of 168 initial GBM patients undergoing resection with intraoperative MRI. Median PFS and median OS were analyzed along with EOR and residual tumor volume (RV)	III	Median OS for GTR vs STR was 23.0 vs 12.8 months ($p=.003$). Median PFS for GTR vs STR was 11.4 vs 5.9 months ($p<.001$). EOR and RV were significantly associated with survival (HR 1.56; $p=.018$) and recurrence (HR 1.53; $p=.013$). A threshold RV of 3 cm^3 was the maximum RV associated with survival Limitations include retrospective nature
Pessina et al. (2017)	Retrospective review of 282 patients with newly diagnosed GBM undergoing surgical resection. Patients were divided into SMR, GTR, STR, or biopsy only. SMR defined as 100% of enhancing and FLAIR hyperintense areas resected. GTR defined as 90–100% of contrast enhancement resected. Patients were followed for PFS and OS	III	Median PFS was 24.5 months with SMR, 11.9 months for GTR, 10.3 months for STR and 7.2 months for biopsy. Median OS was 28.6 months with SMR, 16.2 months for GTR, 13.8 months for STR and 7.2 months for biopsy ($p<.001$). A FLAIR resection threshold of 45% was associated with improved survival benefit when dichotomized to achieve maximal PFS/OS difference between SMR and GTR Limitations include retrospective nature and EOR definition for GTR
Padwal et al. (2016)	Retrospective analysis utilizing Surveillance, Epidemiology, and End Results (SEER) database. 2,755 patients with anaplastic astrocytoma (AA) compared to 21,962 patients with GBM from 1999 to 2010. Extent of surgical resection categorized into: GTR, STR, biopsy, or no surgery	III	Median OS in GBM patients with GTR was 13 months versus 9 months with STR. Multivariate cox proportional hazards model showed 24% decrease hazard of death in GBM patients with GTR compared to STR ($p<.0001$) Limitations include retrospective nature and reporting bias of database
Chaichana et al. (2014a)	Retrospective study of 259 patients that underwent surgery for newly diagnosed GBM between 2007 and 2011. 3D volumetric MRI measurements used to determine EOR and RV. Multivariate proportional hazards regression analysis used to identify association between EOR and RV with survival and recurrence. EOR and RV thresholds established by multivariate analysis in increments of 5% and 1 cm^3 respectively	III	203/259 patients (78%) died, and 156 (60%) had tumor recurrence at time of study. Median OS 13.4 months; median PFS 8.9 months. Minimum EOR for survival ($p=.008$) and recurrence ($p=.005$) benefit was 70%. Maximum RV threshold for survival ($p=.01$) and recurrence ($p=.01$) was 5 cm^3 Limitations include retrospective nature

Table 1 (continued)

Author (year)	Description of study	Data class	Conclusions
Chaichana et al. (2014b)	Retrospective review of 292 patients at a single institution who underwent surgery for newly diagnosed GBM between 2007 and 2011. Included only those tumors appearing amenable to GTR on preoperative imaging as determined by 3 independent, blinded neurosurgeons. Examined association between RV and EOR on survival and recurrence. Of 292 patients reviewed, 84 (29%) were deemed amenable to GTR by all 3 neurosurgeons pre-operatively and were included in the analysis. RV and EOR evaluated in increments of 1 cm^3 and 1% respectively in multivariate analysis	III	Median pre-operative tumor volume was 29 cm^3 and the median post-operative tumor volume was 0.9 cm^3 with a mean extent of resection of 91.7%. RV ($p = .006$) and EOR ($p = .003$) were independently associated with OS and PFS in multivariate analysis. RV < 2 cm^3 and EOR > 95% resulted in greatest reduction of risk of death. RV ($p = .001$) and EOR ($p = .04$) significantly associated with recurrence respectively. Authors conclude that RV and EOR are independently associated with survival and recurrence in tumors amenable to GTR Limitations include retrospective nature
Grabowski et al. (2014)	A retrospective review of 128 patients who underwent primary resection of supratentorial GBM followed by standard radiation/chemotherapy was undertaken utilizing quantitative, volumetric analysis of pre- and postoperative MR images. The purpose of this study was to evaluate the effect of contrast-enhancing residual tumor volume (CE-RV) and T2/FLAIR residual volume (T2/F-RV) on overall survival	III	Median OS was 13.8 months. The median contrast-enhancing preoperative tumor volume (CE-PV) was 29.0 cm^3, and CE-RV was 1.2 cm^3, with median EOR of 95.8%. Median T2/F-RV was 36.8 cm^3. CE-PV, CE-RV, T2/F-RV, and EOR were all statistically significant predictors of survival in multivariate analysis. A statistically significant benefit in survival was seen with a CE-RV less than 2 cm^3 or EOR > 98%. Authors conclude the volume of residual contrast-enhancing tumor may be a more accurate and meaningful predictor Limitations include retrospective nature
Marko et al. (2014)	The authors used accelerated failure time (AFT) modeling using data from 721 newly diagnosed patients with GBM to model the factors affecting individualized survival after surgical resection. Variables included age, KPS, EOR, and use of adjuvant chemotherapy. The model was then validated using independent data from 109 patients from a second institution	III	Nonlinear, multivariable AFT modeling outperforms current methods for estimating individual survival after GBM resection. EOR has a nonlinear, continuous relationship to OS with increasing EOR providing increasing survival benefit. The authors conclude that the continuous, nonlinear relationship identified between expected median OS and EOR argues against a surgical management strategy based on rigid EOR thresholds and instead support a maximum safe resection Limitations include retrospective nature
Noorbakhsh et al. (2014)	Retrospective analysis of 20,705 adult GBM patients collected in the SEER database. Analyzed according to EOR	III	EOR decreased stepwise across increasing age groups with GTR achieved in 36% of patients age 18–44 years, decreasing to 24% for patients age ≥ 75 ($p < .001$). Multivariate analysis showed that regardless of age, GBM patients with GTR had 2–3 months improvement in OS ($p < .001$) compared to STR or biopsy Limitations include retrospective nature
Kreth et al. (2013)	Prospective multicenter study assessed the prognostic influence of the EOR when compared with biopsy only in a patient population with newly diagnosed GBM. Histology, O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, and clinical data were analyzed. Survival analysis and proportional hazard models were utilized to analyze prognostic factors	II	Of 345 patients, 273 underwent open tumor resection and 72 biopsies; 125 patients had GTR and 148 STR. Median OS ranged from 33.2 months for patients with MGMT-methylated tumors after GTR and radiation therapy (RT) plus chemotherapy (CT) to 3 months for biopsied patients receiving supportive care only. Favorable prognostic factors in multivariate analyses for OS were age ≤ 60 years, preoperative KPS ≥ 80, GTR, MGMT promoter methylation, and RT plus CT Limitations include lack of control group

Table 1 (continued)

Author (year)	Description of study	Data class	Conclusions
Orringer et al. (2012)	Retrospective review of 46 patients who underwent surgery for GBM between 2006 and 2009. Investigated factors associated with EOR and survival. Also examined surgeon perceived EOR	III	EOR > 90% associated with greater 1-year survival (76.5%) than EOR < 90% (p = .005). EOR decreased for tumors in eloquent areas (p = .014), abutting the ventricles (p = .031), and left parietal location (p = .042). When GTR was perceived by the surgeon, MRI-verified residual tumor was seen in 69.6% of cases Limitations include retrospective nature and small sample size
Stummer et al. (2012)	Prospective cohort study of patients who underwent surgery for newly diagnosed GBM with little or no residual postoperatively. Aim was to examine whether extensive cytoreductive surgery is beneficial under current standard of care: surgical resection followed by concomitant temozolomide and radiation. 143 patients included in study	II	107/143 patients with residual tumor diameter ≤ 1.5 cm; median follow up 24 months. Median OS for 32 patients with residual tumor diameter 0–1.5 cm was 16.9 months compared to median OS of 13.9 months for 36 patients with residual tumor diameter ≥ 1.5 cm (p < .001). Age at diagnosis, EOR independently associated with OS. The authors conclude that completeness of resection acts synergistically with adjuvant therapies to confer the best prognosis Limitations include lack of generalizability due to selection bias
Allahdini et al. (2010)	Prospective analysis of a cohort of 35 consecutive patients with histologically proven GBM who underwent tumor resection in surgically amenable areas for the first time at Sina Hospital, Tehran, between 2003 and 2005. This study sought to delineate effect of EOR on survival in developing countries with limited resources. Cox proportional hazards modeling utilized	III	Multivariate analysis identified the following independent positive predictors of survival: KPS ≥ 80 (p = .01), EOR (p = .01), frontal tumor location (p = .002), postoperative RT (p = .004), and postoperative chemotherapy (p = .001). Authors conclude maximal resection is associated with longer survival times in patients with GBM in developing countries similar to prior results Limitations include small sample size, single institution, selection bias
Scoccianti et al. (2010)	Multicenter retrospective review of 1059 patients with GBM from the Central Nervous System Study Group of Airo (Italian Association of Radiation Oncology). 936 patients (86%) underwent surgical resection	III	GTR in 485 (45.8%) patients, STR in 434 (41%) patients. 88% and 72.9% of patients underwent radiotherapy and chemotherapy respectively. Median OS for whole series was 9.5 months; Multivariate analysis showed age (p = .002), pre-RT/post-op KPS (p = .01), EOR (p < .001), use of RT (p < .001), and chemotherapy (p < .001) as significant predictors of survival Limitations include retrospective nature, reporting bias
McGirt et al. (2009a)	Retrospective review of 1215 patients (949 in analysis) who underwent surgery for high-grade glioma at a single institution. EOR evaluated on postoperative MRI a subdivided as GTR, near-total resection (NTR) defined as thin rim enhancement of resection cavity only, STR. Includes both WHO grade III (n = 249) and grade IV lesions (n = 700) in total cohort	III	For primary GBM resection, median survival for GTR was 13 months, NTR was 11 months, and STR was 8 months; all significant differences in adjusted analysis Limitations include retrospective nature
Pichimeier et al. (2008)	Re-stratification of patients with WHO grade IV lesions from the prospective 5-ALA study. EOR and survival based on Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) was analyzed. Patients assigned to RTOG-RPA classes III-V based on age, KPS, neurological condition	III	Median OS for RPA classes III, IV, and V was 17.8, 14.7, and 10.7 months respectively. Stratified for EOR, complete resection resulted in longer survival in RPA class IV (17.7 months vs 12.9 months, p = .002) and class V (13.7 months vs 10.4 months, p = .04). EOR not associated with longer survival in RPA class III patients. Authors conclude that RPA classes can predict differences in survival of GBM patients depending on EOR Limitations include post hoc analysis of prospectively obtained data

Table 1 (continued)

Author (year)	Description of study	Data class	Conclusions
Stummer et al. (2008)	Retrospective analysis of prospectively gathered data regarding 243 patients with GBM from the 5-ALA study. Re-stratification of database patients based on prognostic factors (tumor size, KPS, age, location) to account for distribution bias. Comparison of patients who underwent GTR versus all others	III	243 patients with GBM. GTR in 122 (50.2%). Median OS GTR 16.7 months versus STR 11.8 months. Multivariate analysis showed independent prognostic impact on survival for GTR (HR 1.752; p = .004), KPS score (HR 0.624; p = .017), and age (HR 1.536; p = .009) Limitations include post hoc analysis of prospectively obtained data

Synthesis The articles discussed above are summarized in evidentiary Table 1. Evidence for complete resection of enhancing tumor recommendation continues to build since the last guideline publication. Previous recommendations were based on 30 studies, 6 of which provided Class II evidence and the remaining 24 gave Class III data. In this update, there were an additional 4 studies with Class II evidence and 15 studies providing Class III data regarding EOR and OS. A survival advantage to cytoreductive surgery in the initial management of GBM has been repeatedly demonstrated. This was typically measured as EOR, although a number of studies also looked at residual tumor burden, with a preponderance of studies also demonstrating this was predictive of overall survival. The recommendation for maximal cytoreductive surgery remains a Level II recommendation based on the support of Class II and III data. Maximizing EOR must be considered in the context of specific tumor characteristics which increase likelihood of complication such as postoperative neurologic deficit. Sub-analyses in several studies illustrate this point and contextualize the individual qualities of a tumor which deserve thought when considering surgery [9, 10, 12]. This is supported by a majority Class III data leading to a Level III recommendation to consider complete resection, subtotal resection, or biopsy on an individual case basis.

With the success of maximizing EOR of the contrast enhancing tumor, it is a natural progression to investigate supramaximal of supratotal resection as a more aggressive strategy to resection a portion of the infiltrative zone. Three Class III studies investigated resection beyond the contrast enhancing region. All 3 studies demonstrated improved survival with complete resection of enhancing tumor. Only 2 of the 3 demonstrated improved survival with resection of greater than the contrast enhancing portion of tumor, with the other showing no difference. Although supramaximal resection was initially identified as a topic worthy of a question and recommendation, only a few small studies provided Class III evidence, and no clear recommendation can be made regarding resection of more than the contrast enhancing region of glioblastoma, although there is some early evidence it may improve survival.

Question: What is the role of cytoreductive surgery in adult patients with newly diagnosed bifrontal "butterfly" glioblastoma?

Butterfly GBM (bGBM)

Butterfly glioblastomas (bGBMs), which invade and cross the corpus callosum or interhemispheric commissure to involve the contralateral hemisphere, are thought to have extremely poor outcomes. Currently, the therapeutic approach for bGBM is variable, with a lack of objective data

available to providers. Opoku-Darko et al. [22] report on 5 bGBM who underwent resection compared to 24 bGBM who underwent biopsy alone and show improved survival in the former: 7.8 months versus 2.8 months, respectively. Chaichana et al. [23] report on 29 bGBM who underwent resection compared to 19 bGBM who underwent biopsy alone and show improved survival in the former: 7 months versus 3.5 months, respectively. Dayani et al. [24] report on 29 bGBM with improved survival for those who underwent resection versus biopsy alone, 14 months versus 2.5, respectively. In all 3 studies the preoperative KPS appears to significantly affect the overall survival and should be taken into consideration in the treatment decision-making process.

Controversial specific tumor location sub-types

Eloquent areas Eloquent brain areas include those supporting a primary function such as motor, sensory activities and speech. Three retrospective reviews reported on resections of GBM from motor/sensory/language areas [25–27]. Only one reports on OS after resection observing a 0% 2-year survival for patients who acquired a speech deficit. Noell et al. [26] report on 17 patients with GBM in primary motor and 12 with GBM in primary sensory areas. They show that GTR (defined as > 95% EOR) was achieved in 50% of patients. At 3 months, 16% demonstrated worsening for motor function, 4% of sensory function, 28% decreased KPS. They conclude that surgical resection of these tumor is feasible when using intra-operative guidance. They do no report on OS. Ohue et al. [27] using fence-posting resection technique in 45 GBM patients near the pyramidal tract achieved GTR in 21/45 (47%). One patient had worsening of motor function. They conclude that this technique in conjunction with DTI and intra-op monitoring is useful in preserving motor function. McGirt et al. [25] report on 19 pts who reported post-operative motor deficits and 15 who developed speech deficits. Median OS was compared to a cohort of 272 GBM patients who did not report surgical deficits. The 2-year survival was 23% for patients without acquired deficits, 8% with those with motor deficit, 0% with those with language deficit.

Insular GBM The insula of Reil is located deep to the Sylvian fissure and the frontal, temporal, parietal, opercula. It has been shown to play an important role in the processing of various sensory stimuli and in the control of various autonomic and emotional functions, but also cognitive, motor, and language-planning functions [28]. Simon et al. [29] reported on 94 patients with an insular glioma, 21 of which were GBM. These accounted for the highest proportion of Yasargil Type 3 (growth restricted to insula/insulo-opercular region) and Type 5 (insular tumor with mesial temporal and with or without frontal involvement). More permanent deficits were observed in patients with > 90% resection compared to > 70%. GBM had statistically worse outcome (measured as KPS at 3 months after surgery) when compared with the other tumor grades and worse OS. GBM patients only rarely presented with a history of seizures. Interestingly Yasargil Type 5 (larger) tumors had a significantly better outcome compared to the other types. Due to the large frontal component, these tumors were approached through a frontal route.

Cerebellar GBM Cerebellar glioblastoma multiforme (GBM) occurs rarely in adults, accounting for 0.4–1% of all GBM. Weber et al. [30] report 45 adult patients with cerebellar GBM, 9 who underwent GTR, 29 STR, 5 biopsy alone and 2 supportive care. The 2-year OS and PFS rates were 17.9% and 12.6% in the resection (STR/GTR) group vs. 0% and 0% in the biopsy group.

Multicentric GBM Multicentric glioblastoma, defined as multiple concurrent lesions which appear to be totally independent of each other in contrast to multifocal glioblastoma consisting of multiple lesions linked by a clear path of spread (hyperintense in T2-FLAIR weighted sequences) [31]. While 12% to 35% of glioblastomas are multifocal, multicentric glioblastomas are much rarer and only account for 2% to 6% of cases. There were no data relevant to the resection of multicentric GBM most likely due to their overall poor prognosis [32].

Synthesis The articles discussed above are summarized in evidentiary Table 2. Three Class III studies support resection over biopsy alone in newly diagnosed bGBM as this improves OS. Preoperative KPS should be taken into consideration in the treatment decision-making process as it appears to significantly affect the overall survival. Data to provide recommendation regarding OS after surgical resection in patients with newly diagnosed GBM located in eloquent brain areas, insula, cerebellum and/or multi-center data are scarcer, precluding a meaningful recommendation. The evidence for this guideline was primarily drawn from studies with Class III evidence. Currently, no Class I or II evidence exists to guide recommendations for this topic. For GBM in eloquent areas and insula it is important to note that a new deficit, particular speech is associated with poor outcome, therefore, a more conservative extent of resection should be discussed with these patients until additional data are available.

Question: What is the goal of cytoreductive surgery in elderly adult patients with newly diagnosed glioblastoma?

Elderly patients (age ≥ 65 years)

The working definition of an elderly patient varied throughout the studies with most using age > 65 years

Table 2 Eloquent brain areas, bi-frontal "butterfly", insula, cerebellum, or multi-centric GBM evidentiary table

Author (year)	Description of study	Data class	Conclusions
Dayani et al. (2018)	Retrospective review of 39 patients diagnosed with a butterfly GBM (bGBM). 14 underwent resection and 25 underwent biopsy alone	III	Median OS was 3.2 months. Multivariate analysis found resection was associated with a survival benefit (HR 0.37, p = .009), but required a minimum of 86% EOR to achieve benefit over biopsy alone. Persistent neurologic deficit postoperatively occurred in 7.14% The authors conclude there is survival benefit for resection in bGBM if minimum 86% resection can be achieved Limitations include retrospective nature, small sample size
Opoku-Darko et al. (2018)	Retrospective review of 29 patients with a bGBM. 9 underwent resection and 20 underwent biopsy alone. EOR and survival were assessed	III	5 patients underwent GTR. Median OS higher in resection group versus biopsy alone, 7.8 vs 2.8 months (p = .002). Increased age (p = .02) was independently associated with risk of death. Adjuvant therapy (p = .01) was independently associated with increased length of survival Limitations include retrospective nature, small sample size
Noell et al. (2015)	Retrospective series of 29 patients with primary malignant brain tumors in the Rolandic area: 17 patients with tumor in the precentral gyrus, 12 patients with tumor in the post central gyrus. 21/29 patients (72%) had newly diagnosed primary GBM. Resection was performed using a combination of neuronavigation, ultrasonography, 5-ALA fluorescence, and intraoperative electrophysiological monitoring. Pre- and post-operative motor function, sensory function, and KPS score were analyzed	III	At 3-month follow up, 56% of all patients had improvement in motor function, 8% improved sensory function, and 27% had improved KPS. Worsened motor function in 16% of patients, worsened sensory function in 4%, and decreased KPS in 28% at 3 months. GTR in 50% of patients. The authors conclude that total to subtotal resection of malignant glioma in the Rolandic region is feasible Limitations include retrospective nature, small sample size, lack of survival data
Ohue et al. (2015)	Retrospective study of 49 patients with GBM near the pyramidal tracts who underwent resection using diffusion tensor imaging (DTI) tractography, cortical and subcortical motor evoked potentials (MEP), and fence-post catheter techniques	III	Fence-post catheter techniques used in 45/49 patients; GTR in 21 patients, STR in 21 patients, and partial resection in 7 patients. 1 patient had worse motor function after resection. The authors conclude that DTI tractography, MEP, and fence-post catheter techniques may preserve motor function associated with resection of GBM near pyramidal tracts Limitations include retrospective nature, small sample size
Chaichana et al. (2014c)	Retrospective review at a single institution of 336 patients who underwent surgery for newly diagnosed GBM between 2007 and 2012; 29 patients presented with bGBM and underwent surgical resection while 19 patients had bGBM and underwent surgical biopsy	III	Median survival for bGBM surgical resection patients 7.0 months versus 3.5 months for biopsy (p = .03). Multivariate analysis showed bGBM was independently associated with poorer survival (HR 1.848; p = .003); increasing percent resection (p = .01), RT (p = .009), and temozolamide chemotherapy (p = .007) were each independently associated with increased survival. The authors conclude patients with bGBM may have survival benefit from aggressive treatment Limitations include retrospective nature, small sample size of bGBM
McGirt et al. (2009c)	Retrospective review of 306 consecutive patients who underwent primary GBM resection at a single institution relating surgically acquired motor or language deficit to survival. 19 (6%) developed motor deficits and 15 (5%) developed language deficits	III	Median OS was significantly decreased to 9.6 months in those with surgically acquired motor deficit (p < .05), 9.0 months in those with surgically acquired language deficits (p < .05) as compared to 12.8 months for those without postoperative neurologic deficit. 2-year survival 8% for surgically acquired motor deficits, 0% for surgically acquired language deficit, compared to 23% for those without new-onset neurologic deficit. The authors conclude there is decreased survival in patients with new post-operative neurologic deficit despite similar extent of resection and adjuvant therapy Limitations include retrospective nature, single institution

Table 2 (continued)

Author (year)	Description of study	Data class	Conclusions
Simon et al. (2009)	Retrospective review of 94 patients undergoing insular glioma resection between 1995 and 2005 at a single institution. The histopathology of these tumors varied with 21 diagnosed with GBM	III	High proportion of GBM were Yasargil Type 3 and Type 5. More permanent deficits were observed in patients with > 90% resection compared to > 70%. GBM had statistically worse outcome (measured as KPS at 3 months after surgery) when compared with the other tumor grades and worse OS as would be expected. The authors conclude that a cautious approach should be taken in patients with suspected insular GBM Limitations include retrospective nature, large heterogeneity, lack of comparison group
Weber et al. (2006)	Retrospective multicenter study (Rare Cancer Network) of 45 adult patients with cerebellar GBM	III	EOR: GTR 9, STR 29, biopsy only 5. The 2-year OS and PFS rates were 17.9% and 12.6% respectively in the GTR + STR group as compared to 0% and 0% in the biopsy only group. The authors conclude there may be survival benefit to those who undergo any surgical resection Limitations include retrospective nature, small sample size

and several focusing on older patients using age cutoffs of > 70 years, > 75 years, or > 80 years. Some surgeons may have apprehension about recommending cytoreductive surgery to older patients as the benefit of surgery is less certain in this patient group. Several retrospective studies have attempted to demonstrate surgical benefit in this population. Heiland et al. [33] retrospectively reviewed 342 patients aged > 65 years at time of diagnosis of whom 216 underwent surgical resection. Median OS was 10.8 months longer in the GTR group as compared to STR or biopsy, with higher preoperative KPS predicting increased length of OS. Hofferman et al. [34] retrospectively reviewed 124 patients aged > 65 years at time of diagnosis and found that the survival advantage of GTR (15 months) over STR (11 months) or biopsy (4 months) was preserved in this group. Tanaka et al. [35] retrospectively reviewed 105 patients aged > 65 years at time of diagnosis who underwent biopsy (n = 52) versus resection (n = 53). Median PFS and OS were 3.5 and 5.5 months respectively, but with combined therapy of resection, radiation therapy, and chemotherapy the median PFS and OS were 8 and 12.5 months respectively. Chaichana et al. [36] retrospectively reviewed 129 patients aged > 65 years at time of diagnosis who underwent resection focusing on preoperative factors associated with decreased survival. Preoperative factors identified were KPS < 80 ($p = .001$), COPD ($p = .01$), motor deficit ($p = .01$), language deficit ($p = .005$), cognitive deficit ($p = .02$), tumor size > 4 cm ($p = .02$). Median OS was 9.2 months for patients with 0–1 factors, 5.5 months for 2–3 factors, and 4.4 months for 4–6 factors. Ewelt et al. [37] retrospectively reviewed 103 patients aged > 65 years at time of diagnosis and found that median OS was 13.9 months for GTR as compared to 7.0 and 2.2 months for STR and biopsy respectively. Uzuka et al. [38] retrospectively reviewed 71 patients aged > 70 years and/or KPS < 70 at time of diagnosis then divided them by EOR for analysis. Median OS was 15.8, 12.8, and 12.1 months in subtotal resection, partial resection, and biopsy groups respectively. There were not enough patients in which GTR was achieved for meaningful analysis. Karsy et al. [39] retrospectively reviewed 82 patients aged > 75 years at time of diagnosis of whom 74 underwent surgical resection. The patients were dichotomized into long-term (> 12 months) and short-term survivors with similar preoperative KPS, but lower KPS in short-term survivors. They concluded that improved survival from resection was only observed for patients without significantly lower postoperative KPS. Abdullah et al. [40] retrospectively reviewed 58 patients aged > 80 years at time of diagnosis who underwent surgical resection with a goal of maximal resection. Median OS was 4.2 months, though those patients with higher preoperative KPS ($p < .05$) and those receiving postoperative adjuvant therapy ($p < .05$) had longer OS.

Low preoperative functional performance

Few studies evaluate the specific effect of low preoperative functional status. Most often this is measured with KPS, but the definition of low varies widely with some defining as < 70 or < 80 versus more stringent cutoffs of < 50. As may be expected many studies report an association of worsened survival with decreasing KPS. Marina et al. [41] retrospectively reviewed 74 patients who were referred for radiation therapy with a KPS ≤ 50 at time of diagnosis of whom 38 underwent biopsy and 36 underwent resection. Median OS was 2.3 months for all patients. On multivariate analysis only Radiation Therapy Oncology Group recursive partitioning analysis (RTOG RPA) class (p = .01), any resection (p = .001), and radiation therapy (p = .02) were significant predictors of decreased mortality rate.

Synthesis The articles discussed above are summarized in evidentiary Table 3. Eight Class III studies evaluated the potential benefit of surgical resection in elderly patients with newly diagnosed GBM. Based on these studies patients of advanced age (> 65 years) at time of diagnosis show preserved evidence of significant survival benefit of maximal surgical resection and it is suggested that these patients undergo surgical resection. In multiple studies low preoperative functional performance status as measured by KPS is associated with worsened OS, however, there is insufficient evidence for a recommendation in this group based on KPS alone. The evidence for this guideline was primarily drawn from studies with Class III evidence. Currently, no Class I or II evidence exists to guide recommendations for elderly or low preoperative functional performance status patients.

Question: What is the role of advanced intraoperative guidance techniques in cytoreductive surgery in adults with newly diagnosed glioblastoma?

Intraoperative MRI

Intraoperative MRI has been increasingly evaluated in the literature for a variety of indications including glioblastoma. Marongiu et al. [42] retrospectively reviewed 114 patients with newly diagnosed glioblastoma in which 78 utilized iMRI. GTR was achieved in 88.5% with iMRI as compared to 44% without iMRI (p < .001). The 6-month PFS was similarly improved showing 73% with iMRI versus 44% with non-iMRI (p < .001). Familiari et al. [43] retrospectively reviewed 129 patients who underwent resection of newly diagnosed glioblastoma with 64 using iMRI. EOR was 94.01% with iMRI and 86.32% without the use of iMRI (p = .005). PFS was 7.89 months with iMRI compared to 5.38 months without (p = .001) and OS was 16.43 months with iMRI compared to 13.38 months without iMRI (p = .001). Kuhnt et al. [44] retrospectively reviewed 135 patients who underwent resection with iMRI. Residual tumor was identified intraoperatively in 88 patients (65%) with resection continued in 19 of those patients. Further resection resulted in GTR for 9 additional patients. As a result of continued resection based on iMRI, GTR increased from 47 (34.8%) to 56 (41.5%) patients. Median OS was 14 months for EOR ≥ 98% and 9 months for EOR < 98% (p < .001). Median OS was 9 months for patients ≥ 65 years and 12 months for patients < 65 years (p < .05).

5-aminolevulinic acid

With the recent FDA approval of 5-ALA there has been increasing interest in the use of this modality as well as other advanced guidance techniques with the overall goal of maximizing EOR. Stummer et al. [11] provide the only level I evidence with a prospective, randomized controlled multicenter trial enrolling 322 patients with high-grade glioma to either undergo resection with 5-ALA guidance or conventional white-light microsurgery. The study cohort included in the final analysis included a total of 270 patients with both WHO grade IV (n = 260) and WHO grade III (n = 9) lesions. GTR was achieved in 90/139 (65%) of the 5-ALA group versus 47/131 (36%) in the conventional microsurgery group (p < .001), however, all analyses included both WHO grade III and IV lesions thereby excluding it for our evidentiary tables. Yan et al. [45] retrospectively reviewed 31 patient who underwent resection with 5-ALA for newly diagnosed glioblastoma. GTR of contrast enhancement was achieved in 24/31 (77%). Additional analysis of DTI sequences divided into isotropic (p) and anisotropic (q) components as well as FLAIR was assessed pre- and post-operatively. Mean EOR of abnormal p, q, and FLAIR regions was 57%, 83%, and 59% respectively. Increased resection of abnormal p and q areas was associated with increased PFS (p = .009) and OS (p = .006). Eljamel et al. [46] reported a meta-analysis of 5-ALA studies in 2015 which included 20 studies meeting criteria with 565 total patients treated. Mean GTR was 75.4% with mean OS advantage over control groups of 6.2 months (p < .001). The sensitivity of histopathologic samples was reported as 82.6% (p < .001) and specificity of 88.9% (p < .001) among the analyzed studies. These technologies have also been applied to tumor resections in difficult locations with high risk of neurologic injury such as involvement of speech or motor cortex. Schucht et al. [47] retrospectively reviewed 103 patients who underwent resection with 5-ALA and intraoperative cortical mapping. Complete resection of enhancing tumor (CRET) was attempted in only 53 of those patients, with CRET achieved in 89%. Four patients experienced new or worsened neurologic deficit post-operatively.

Table 3 Elderly, low preoperative functional performance status evidentiary table

Author (year)	Description of study	Data Class	Conclusions
Heiland et al. (2018)	342 patients aged ≥ 65 years were retrospectively reviewed. EOR, adjuvant treatment, OS, KPS, and neuro-oncology-score were collected. Median age at diagnosis 73.4 years. Resection performed in 216 patients	III	Median OS 10.8 months in GTR as compared to 8.1 months STR or 3.0 months with biopsy ($p < .001$). In multivariate analysis age was not associated with OS ($p = .58$). Higher preoperative KPS ($p = .001$) was associated with increased OS Limitations include retrospective nature
Karsy et al. (2018)	82 patients aged ≥ 75 years were retrospectively reviewed for EOR, post-operative treatments, and complications. Surgical resection undertaken in 74 patients	III	EOR: GTR 23.2%, STR 40.2%, biopsy 22.0%, and no surgery in 9.8%. Median OS was 6.3 months. 34 complications were observed in 23 patients. Preoperative KPS was similar between long-term survivors (> 12 months) and short-term survivors, but postoperative KPS differed significantly ($p = .02$) between groups. The authors conclude improved survival from resection only observed for patients without postoperative complication Limitations include retrospective nature
Abdullah et al. (2015)	Retrospective review of patients over the age of 80 with a new diagnosis of GBM and who underwent surgical resection with intent for maximal resection. Patients who had only stereotactic biopsies were excluded. 58 patients were included in analysis with mean age of 83 years. Stepwise logistic regression and Kaplan–Meier survival curves were plotted to determine correlations to OS	III	Median OS was 4.2 months. EOR: GTR in 12 (21%), STR in 40 (69%). There was no significant difference in OS based on EOR. There was a statistically significant correlation between pre-operative KPS and OS ($p < .05$). OS advantage was conferred to those with higher preoperative KPS, postoperative adjuvant therapy, and lack of protein expression of EGFR and p53, but not EOR Limitations include retrospective nature, small sample size, single institution
Hoffermann et al. (2015)	Retrospective review of 124 consecutive patients over 65 years of age with supratentorial GBM	III	Median OS was 6.0 months. Advanced age did not have any impact on survival ($p = .59$). GTR (15.0 months) and STR (11.0 months) led to significantly improved overall survival ($p < .02$) compared to partial resection or biopsy (4.0 months). EOR ($p = .031$) and form of adjuvant treatment ($p < .001$) were the only factors of independent prognostic value in multivariate analysis. The authors conclude that GTR should be offered whenever safely possible; otherwise, biopsy may be preferred Limitations include retrospective nature, single institution
Tanaka et al. (2013)	Retrospective review of 105 consecutive patients (age ≥ 65) undergoing biopsy (n = 52) versus resection (n = 53) of newly diagnosed GBM. Median age 74 years; median KPS 80	III	Median PFS 3.5 months and OS 5.5 months. Combined therapy with surgical resection, RT, and chemotherapy resulted in median PFS 8 months and OS 12.5 months. In multivariate analysis younger age (RR 0.34; $p = .03$), single lesion (RR 0.51; $p = .02$), resection (RR 0.54; $p = .04$), and adjuvant treatment (RR 0.24; $p < .001$) were associated with increased OS. Only adjuvant treatment was significantly associated with improved PFS (RR 0.27; $p < .001$). The authors conclude that advanced age should not preclude elderly patients with GBM from maximal safe resection and adjuvant therapy
Uzuka et al. (2012)	Retrospective review of 107 consecutive patients with newly diagnosed GBM treated at a single institution. High risk group defined as patients age > 70 years and/or KPS < 70%, totaling 71 patients. Based on EOR, patients also divided into biopsy only, partial resection, and more than subtotal resection groups	III	Median OS 13.2 months in high-risk group; Median OS 15.8 months STR, 12.8 months partial, and 12.1 months biopsy. Multivariate analysis within the subtotal/partial section group showed age ≤ 65 yr ($p = .047$), MGMT negative ($p = .027$), and more than subtotal resection ($p = .003$) were positive prognostic factors on survival. The authors recommend maximal safe resection for GBM even in older patients or those with low KPS scores Limitations include retrospective nature, single institution, lack of consistent EOR definitions

Table 3 (continued)

Author (year)	Description of study	Data Class	Conclusions
Chaichana et al. (2011)	Retrospective review of 129 patients older than 65 years who underwent GBM resection from 1997 to 2007. Sought to identify preoperative factors associated with decreased survival in elderly patients undergoing surgery for primary GBM. Mean age 73 years	III	Median survival 7.9 months. Preoperative factors independently associated with decreased survival: KPS < 80 (p = .001), COPD (p = .01), motor deficit (p = .01), language deficit (p = .005), cognitive deficit (p = .02), and tumor size > 4 cm (p = .002). Median survival was significantly longer at 9.2 months for patients with 0–1 pre-operative factors, as compared to 5.5 months for 2–3 factors (p = .004), and 4.4 months for 4–6 factors (p < .001). The authors conclude that survival benefit may be decreased in older patients undergoing surgery as these preoperative factors increase Limitations include retrospective nature, single institution
Ewelt et al. (2011)	Retrospective, single-center review of 103 patients with newly diagnosed, primary supratentorial GBM > 65 years (median 70.8 years). These patients were retrospectively divided into treatment with surgery alone, surgery + radiation, or surgery + RT + chemotherapy. PFS and OS were determined in each group and correlated to age, KPS, and EOR	III	For all patients PFS was 3.2 months and OS was 5.1 months. Age < 75 (p = .01), KPS ≥ 70 (p < .001) was correlated with improved OS. Increased EOR correlated with improved PFS (p < .001) and OS (p < .001). The authors conclude that elderly GBM patients can benefit from maximum treatment procedures with cytoreductive microsurgery, radiation therapy, and chemotherapy Limitations include retrospective nature, single institution
Marina et al. (2011)	Retrospective review of patients who underwent primary treatment for pathologically confirmed GBM and with a KPS score ≤ 50 on initial evaluation for radiation therapy at a tertiary care institution between 1977 and 2006. 74 patients with a median age of 69 years and a median KPS score of 50 were reviewed. Patients underwent biopsy (n = 38) or resection (n = 36). 47 patients received radiation. 19 patients also received chemotherapy (53% temozolomide), initiated concurrently (47%) or after radiotherapy	III	Median OS was 2.3 months (range 0.2–48 months). On multivariate analysis, only RPA class (p = .01), resection (HR 0.37, p = .001), and radiation therapy (HR 0.39, p = .02) were significant predictors of a decreased mortality rate. The authors conclude patients with a KPS score ≤ 50 appear to have increased survival and functional status following tumor resection and radiation Limitations include retrospective nature, small sample size, selection bias, limited assessment of surgical variables such as EOR

Intraoperative MRI and 5-ALA in combination

Many studies assess multiple techniques at the same time such as concomitant use of iMRI and 5-ALA. This represents the reality of the current practice landscape as multiple techniques are often employed in the same setting. Schatlo et al. [48] retrospectively reviewed 200 patients who underwent resection with 5-ALA + iMRI as compared to a control group without iMRI. 166 of those patients had WHO grade IV histopathology. Multivariate analysis of the glioblastoma patients only found no significant effect of iMRI (p = .56) or 5-ALA (p = .65) use on OS. Coburger et al. [49] prospectively reviewed 33 patients undergoing resection with 5-ALA and iMRI as compared to a matched retrospective control cohort of patients who underwent iMRI assisted resection. GTR was achieved in 100% of cases utilizing both 5-ALA and iMRI as compared to 82% with iMRI alone (p < .01). Median OS was similar between groups with 18 months for 5-ALA + iMRI versus 17 months for iMRI alone (p = .71). Eyupoglu et al. [50] prospectively evaluated 30 patients undergoing resection with iMRI and 5-ALA with a goal of supratotal resection beyond contrast enhancement compared to a retrospective group of 75 patients who underwent GTR with iMRI. Median OS was 18.5 months with iMRI + 5-ALA resection versus 14 months with iMRI resection (p < .001).

Two studies prospectively compared the detection ability for residual tumor with biopsy protocols. Hauser et al. [51] prospectively evaluated 12 patients undergoing resection with iMRI and 5-ALA in which fluorescent tissue was completely resected followed by iMRI. Any area suspicious for tumor on iMRI was biopsied, then resected. In 11 of 12 cases iMRI showed residual contrast enhancement after complete resection of 5-ALA fluorescent tissue. The 28 biopsies of areas suspicious for tumor on iMRI showed tumor in 39.3%, infiltration zone in 25%, reactive central nervous system tissue in 32.1%, and normal brain in 3.6%. Ninety-three fluorescent and 24 non-fluorescent tissue samples collected before iMRI contained tumor in 95.7% and 87.5%, respectively. The authors conclude that iMRI might detect areas suspicious for tumor even after complete resection of all fluorescent tissue; however, with limited accuracy of iMRI in predicting tumor remnant (64.3%) based on histopathology. Conversely Coburger et al. [52] prospectively enrolled 45 patients (34 with glioblastoma) who then underwent resection with both 5-ALA and iMRI utilizing a protocol where traditional white light resection was performed followed by marking fluorescent areas, performing iMRI then taking additional biopsies. The primary goal was to determine comparative sensitivity and specificity of 5-ALA and iMRI for residual tumor. In GBM patients, sensitivity for tumor detection with 5-ALA was 85% compared to 41% with iMRI (p < .001); specificity with 5-ALA was 43% compared to 70% with iMRI (p < .001). For detection of pathological tissue (at infiltrative border zone), 5-ALA significantly exceeded iMRI in sensitivity (91% vs 66%) and specificity (80% vs 60%) (p < .001).

Few studies attempt to directly compare iMRI and 5-ALA guidance. In one such study Roder et al. [53] retrospectively reviewed 117 patients who underwent resection with either 5-ALA or iMRI assistance. Mean tumor residual volume was significantly reduced with iMRI (0.5 cm^3) compared to 5-ALA (1.9 cm^3; p = .022) and conventional white-light resection (4.7 cm^3; p = .007). GTR achieved at a higher rate with iMRI (74%) compared to 5-ALA (46%; p = .05) and conventional white-light resection (13%; p = .03).

Fluorescein, indocyanine green

Several other fluorescent agents have been utilized to aid in resection. Data concerning the effectiveness of these fluorescent modalities remains sparse and consists of mostly case-series or small retrospective cohorts. Acerbi et al. [54] performed a phase II trial of fluorescein-guided resection (FLUOGLIO) with 44 glioblastoma patients. GTR was achieved in 81.8% of patients with a median volumetric EOR of 99.1%. Survival data included WHO grade III/IV lesions and is therefore not included. Okuda et al. [55] presented a case series of 10 patients with newly diagnosed glioblastoma in whom fluorescein was used intraoperatively. Adequate fluorescence of pathologic tissue was observed in all cases with GTR achieved in 5, STR in 2, and biopsy alone in 3 patients. Shinoda et al. [56] retrospectively reviewed 105 patients who underwent craniotomy for resection of newly diagnosed glioblastoma with fluorescein guidance utilized in 32 patients. GTR was achieved in 84.4% using fluorescein guidance versus 46.7% without (p < .001). Yano et al. [57] present a case series of 8 patients with glioblastoma in which a double-staining technique was used with both fluorescein and 5-ALA utilized. The bulk of the tumor was removed under white-light and the margins were then inspected with filters for both 5-ALA and fluorescein. The authors noted 5-ALA to be more sensitive at the border zone than fluorescein due to its sole reliance on blood–brain barrier breakdown with hypervascularity.

Indocyanine green (ICG) is readily available and has had a resurgence in interest with exploration of the concept of second-window ICG and the use of near-infrared (NIR) imaging, a theory that high-dose ICG can be administered and will sequester intratumorally [58]. Zeh et al. [59], present preliminary human data from 10 patients undergoing resection of glioblastoma (8 primary, 2 recurrence). The protocol gave patients an infusion of 5.0 mg/kg ICG approximately 24 h prior to surgery. At the time of surgery, resection was performed per usual and biopsies were taken of suspicious areas seen by white-light and with NIR. Under

Table 4 Intraoperative guidance evidentiary table

Author (year)	Description of study	Data class	Conclusions
Acerbi et al. (2018)	Prospective multicenter phase II trial (FLUOGLIO) of fluorescein-guided HGG resection. Patients deemed to have tumor amenable to surgical resection were eligible. 46 patients completed the trial and were included in the analysis. 44 diagnosed with GBM, 1 gliosarcoma, 1 anaplastic astrocytoma	III	GTR was achieved in 36 of 44 (81.8%) patients with GBM for a median volumetric EOR of 99.1% OS and PFS data were analyzed with all patients including non-GBM histopathology Limitations include small sample size, degree of heterogeneity with inability to separate GBM from other histopathologic types in the primary analysis, lack of comparison group
Familiari et al. (2018)	Retrospective review of 129 patients who underwent resection for newly diagnosed GBM. For 64 patients intraoperative MRI (iMRI) was utilized. Single surgeon series. EOR was assessed with volumetric analysis	III	EOR was 94.01% with iMRI and 86.32% without the use of iMRI ($p=.005$). PFS was 7.89 months with iMRI compared to 5.38 months without ($p=.001$). OS was 16.43 months with iMRI compared to 13.38 months without iMRI ($p=.001$). The authors conclude that iMRI confers additional survival benefit mediated by increased EOR Limitations include retrospective nature, single institution/surgeon, selection bias
Yan et al. (2017)	Retrospective review of 31 patients who underwent 5-ALA guided surgical resection for newly diagnosed GBM. Pre- and post-operative MRI obtained with contrasted, FLAIR, and DTI sequences. DTI sequence divided into isotropic (p) and anisotropic (q) components. EOR assessed by abnormal area on p, q, FLAIR, and post contrast sequences	III	GTR based on post-contrast MRI was obtained in 24/31 (77%) patients. Mean EOR of abnormal p, q, and FLAIR regions was 57%, 83%, and 59% respectively. Increased resection of abnormal p and q areas was associated with increased PFS ($p=.009$) and OS ($p=.006$). The authors conclude that PFS and OS were improved in GBM patients after resection of abnormal p and q areas, highlighting potential role for resection based on DTI maps in surgical treatment of GBM Limitations include retrospective nature, lack of control group
Eyüpoglu et al. (2016)	Prospective evaluation of 30 patients with newly diagnosed GBM undergoing surgical resection with the combination of i-MRI with neuronavigation and 5-ALA with "supratotal resection" defined as greater than contrast enhancing region resected according to both modalities of treatment, referred to as dual intraoperative visualization approach (DiVA). Analyzed in comparison to a retrospective control group of 75 patients previously treated to gross total resection based on iMRI alone	III	Median OS was 18.5 months in the DiVA supratotal resection group vs 14 months in the iMRI GTR cohort ($p<.001$). There was no significant difference in pre- vs post-operative neurologic deficits observed between the resection groups Limitations include small sample size, single institution
Hauser et al. (2016)	Prospectively enrolled 14 patients with suspected GBM suitable for complete resection of contrast-enhancing portions. Surgery was carried out using 5-ALA fluorescence and frameless neuronavigation. Areas suspicious for tumor underwent biopsy. After complete resection of fluorescent tissue, low-field iMRI was performed. Areas suspicious for tumor remnant underwent biopsy under navigation guidance and were resected. The histological analysis was blinded	II	In 11 of 12 operations, residual contrast enhancement on iMRI was found after complete resection of 5-ALA fluorescent tissue. The 28 biopsies of areas suspicious for tumor on iMRI in the remaining 10 cases showed tumor in 39.3%, infiltration zone in 25%, reactive central nervous system tissue in 32.1%, and normal brain in 3.6%. Ninety-three fluorescent and 24 non-fluorescent tissue samples collected before iMRI contained tumor in 95.7% and 87.5%, respectively. The authors conclude that iMRI might detect areas suspicious for tumor even after complete resection of all fluorescent tissue; however, due to the limited accuracy of iMRI in predicting tumor remnant (64.3%), resection of this tissue has to be considered with caution in eloquent regions Limitations include small sample size, lack of control group

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Marongiu et al. (2016)	Retrospective review of 114 patients with newly diagnosed GBM. 78 were operated with the assistance of intraoperative MRI and 36 without. EOR was assessed by imaging within 72 h of surgery	III	iMRI group with GTR in 88.5% of patients compared to GTR in 44% without iMRI ($p < .001$). 6-month PFS was 73% with iMRI vs 44% without ($p < .001$). The authors conclude iMRI provides greater EOR and improved 6-month PFS Limitations include retrospective nature, unbalanced control group with selection bias
Prada et al. (2016)	Prospective, small study examining EOR in GBM patients undergoing resection with contrast enhanced ultrasound (CEUS)	III	In all 10 cases, residual tumor was seen as hyperechoic areas on B-mode, seen as CEUS positive, and confirmed as tumor by histological analysis. CEUS failed to partially show a portion of residual tumor in one case due to the tissue being de-vascularized. The authors conclude that CEUS can play a role in maximizing extent of resection for GBM Limitations include small sample size, lack of control group
Coburger et al. (2015)	Prospective study of 33 patients with GBM undergoing intended GTR surgery with 5-ALA and iMRI. Matched retrospective control cohort of 144 GBM patients who underwent iMRI surgery. Median follow up 31 months	III	GTR achieved in 100% of patients using 5-ALA and iMRI versus 82% for iMRI alone ($p < .01$). No difference in new permanent neurological deficits between groups ($p = .52$). Median PFS was 6 months in both groups ($p = .31$) and median OS was 17 months for iMRI group vs 18 months for 5-ALA and iMRI group ($p = .71$) Limitations include small sample size in treatment group
Eljamel (2015)	Meta-analysis of 5-ALA assisted surgical resection. Review of the literature produced 503 potential publications; 20 of these fulfilled the inclusion criteria of this analysis, including a total of 565 patients treated with 5-ALA reporting on its outcomes and 800 histological samples reporting 5-ALA sensitivity and specificity	II	Mean gross total resection (GTR) rate was 75.4%. Mean PFS was 8.1 months. The mean OS gain reported compared to control was 6.2 months ($p < .001$). Specificity was 88.9% ($p < .001$) and the sensitivity was 82.6% ($p < .001$). The authors conclude 5-ALA is highly sensitive and specific with significantly higher rates of GTR and longer PFS Limitations include retrospective nature of some included studies, significant amount of heterogeneity, differing control groups
Neidert et al. (2015)	Retrospective review of 76 GBM patients who underwent resection with either iMRI ($n = 22$), intraoperative ultrasound (iUS) ($n = 48$) or neither ($n = 11$) who all had GTR (five patients had iMRI and iUS, and some had 5-ALA). Patients included in study only if GTR achieved	III	OS was 21.9 months in iUS group vs 18.8 months in non-iUS group ($p = .18$). Median PFS in the iUS group was 7.1 months vs 3.4 months in non-iUS group ($p = .07$) Limitations include retrospective nature, significant heterogeneity, poor generalizability
Schatlo et al. (2015)	Retrospective review of 200 patients with high-grade glioma undergoing resection with 5-ALA and iMRI versus control group without iMRI. Includes WHO grade III ($n = 34$) and IV ($n = 166$) tumors	III	Multivariate Cox proportional hazards modeling of the WHO grade IV patients found no significant effect of iMRI use ($p = .56$) or 5-ALA use ($p = .65$) on OS Limitations include retrospective nature, confounding variables

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Coburger et al. (2014)	Prospective study of 45 patients harboring contrast-enhancing lesions, in whom gross-total resection was intended. All patients underwent surgical resection with the assistance of iMRI and 5-ALA. Protocol: A standard white-light tumor resection was performed. Then, spatial location of residual fluorescence was marked. After that, an iMRI was performed and residual uptake of contrast was marked. Navigated biopsy samples were taken from all marked areas and from additional sites according to the surgeon's judgment. Goal to assess for additional benefit of 5-ALA beyond iMRI in tumor detection. 34 patients with GBM and 11 with metastases were enrolled	II	In GBM patients, sensitivity for tumor detection with 5-ALA was 85% compared to 41% with iMRI ($p < .001$); specificity with 5-ALA was 43% compared to 70% with iMRI ($p < .001$). For detection of pathological tissue (at infiltrative border zone), 5-ALA significantly exceeded iMRI in sensitivity (91% vs 66%) and specificity (80% vs 60%) ($p < .001$). The authors conclude the use of 5-ALA in addition to iMRI might be beneficial to maximize extent of resection specifically in the infiltrative zone Limitations include small sample size
Roder et al. (2014)	Retrospective study of 117 patients comparing results of GBM surgery with iMRI vs conventional white-light resection with and without 5-ALA. Tumor residual volume and 6-month PFS rates examined	III	Mean tumor residual volume was significantly reduced with iMRI (0.5 cm^3) compared to 5-ALA (1.9 cm^3; $p = .022$) and conventional white-light resection (4.7 cm^3; $p = .007$). GTR achieved at a higher rate with iMRI (74%) compared to 5-ALA (46%; $p = .05$) and conventional white-light resection (13%; $p = .03$). The authors conclude that iMRI may be superior to 5-ALA or conventional white-light resection for achieving GTR Limitations include retrospective nature
Schucht et al. (2012)	Retrospective review of 103 consecutive patients who underwent resection of GBM using 5-ALA and intraoperative mapping/monitoring. Analysis performed on patients who were deemed to be candidates for GTR and complete resection of enhancing tumor (CRET) by preoperative imaging. 53 patients eligible for GTR (43 newly diagnosed, 10 recurrent)	III	GTR achieved in 51 (96%) and CRET achieved in 47 (89%) patients. 4 patients experienced new or worsened neurologic deficits post-operatively. The authors conclude the combination of 5-ALA and intraoperative mapping leads to a high rate of complete resection without a high rate of neurological deficits Limitations include retrospective nature, lack of comparison group
Kuhnt et al. (2011)	Retrospective review of 135 patients who underwent resection of GBM with iMRI assistance at a single institution. Tumor volume was quantified by manual segmentation. 108 patients with newly diagnosed GBM, 27 recurrent GBM	III	iMRI detected residual tumor volume in 88 patients (65%). In 19 patients, resection was continued; further resection resulted in GTR for 9 additional patients. As a result of continued resection based on iMRI, GTR increased from 47 (34.8%) to 56 (41.5%) patients. Median OS was 14 months for EOR ≥ 98% and 9 months for EOR < 98% ($p < .001$). Median OS was 9 months for patients ≥ 65 years and 12 months for patients < 65 years ($p < .05$). The authors conclude that iMRI can improve survival by increasing GTR rates Limitations include retrospective nature, lack of comparison group, single institution
Koc et al. (2008)	Prospectively collected data of 80 patients undergoing resection of GBM. No randomization. 47 patients received fluorescein during resection, 33 underwent conventional microsurgery without fluorescein	III	GTR achieved in 83% with fluorescein compared to 54.5% without ($p = .012$). There was no significant difference in median OS with 43.9 weeks in the fluorescein resection group compared to 41.8 weeks in the non-fluorescein group Limitations include lack of randomization, single institution

white-light tumor sensitivity was 76.5% and specificity 100%, while under NIR tumor sensitivity was 85.7% and specificity 25%.

Intraoperative ultrasound

While the use of iMRI and 5-ALA guidance dominate much of the surgical guidance technology, there are other technologies described such as intraoperative ultrasound (iUS) with and without contrast enhancement. Prada et al. [60] prospectively analyzed 10 patients undergoing resection of newly diagnosed glioblastoma with the assistance of contrast enhanced ultrasound (CEUS). At completion of initial resection in all 10 cases additional tumor was identified as hyperechoic areas on B-mode and confirmed by histopathology. Neidert et al. [61] retrospectively reviewed 76 patients undergoing resection of glioblastoma with iMRI, iUS, or neither technique who all achieved GTR. Median OS was 21.9 months with iUS versus 18.8 months without iUS (p = .18). Median PFS was 7.1 months in the iUS group versus 3.4 months in the non-iUS group (p = .07).

Synthesis The articles discussed above are summarized in evidentiary Table 4. There is a growing body of literature supporting the use of advanced intraoperative guidance techniques with the most common being iMRI and 5-ALA. The primary goal of these techniques is to maximize EOR which is the presumed mechanism for improving patient outcomes. These techniques are often used in combination making to exact contribution of each difficult to fully assess, however, both iMRI and 5-ALA have an association with increased EOR and increased number of patients in whom GTR was achieved. The evidence for this guideline was drawn from 5 Class II and 11 Class III studies. There is a single Class I RCT supporting the use of 5-ALA guided resection, but the analysis includes WHO grade III tumors without the ability to separate out WHO grade IV tumors and therefore was not included. Use of 5-ALA guidance and iMRI can assist in surgical management to maximize EOR. There is limited and insufficient evidence to make any recommendation regarding other modalities such as ultrasound, fluorescein, or ICG.

Conclusion

Currently available literature continues to support maximal extent of resection while avoiding persistent neurologic deficit. Investigation continues into the utility of extending resection into the infiltrative zone, however, there is insufficient evidence to recommend supramaximal resection as routine practice. Cytoreductive resection affords a survival advantage in elderly patients and those with butterfly GBM, which were groups previously thought not to derive significant benefit from resection. These data should be utilized when counseling patients regarding overall survival and the potential utility of cytoreductive surgery. As intraoperative guidance technologies continue to improve, their use to assist in achieving maximal extent of resection is recommended.

Key issues for future investigation

Future investigation should continue to focus on correlating surgical techniques with overall survival and maximizing extent of resection. Further elucidating the magnitude of survival advantage in supratentorial GBM as well as more specific circumstances such as bGBM and multicentric GBM. Surgical technique adjuncts may provide important advantages towards maximal safe resection. Further studies should be conducted to better elucidate the value of fluorescein, indocyanine green, and intraoperative ultrasound. When feasible, the concept of supramaximal resection beyond the contrast enhancement into areas of FLAIR hyperintensity deserves further attention.

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Data availability Evidentiary tables contain all articles included in the systematic review.

Compliance with ethical standards

Conflict of interest The Update on Newly Diagnosed Glioblastoma Task Force members were required to report all possible COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Committee (JGRC), 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.

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