Importance and Evidence of Extent of Resection in Glioblastoma

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Abstract

Maximal safe resection is an essential part of the multidisciplinary care of patients with glioblastoma. A growing body of data shows that gross total resection is an independent prognostic factor associated with improved clinical outcome. The relationship between extent of glioblastoma (GB) resection and clinical benefit depends critically on the balance between cytoreduction and avoiding neurologic morbidity. The definition of the extent of tumor resection, how this is best measured pre- and postoperatively, and its relation to volume of residual tumor is still discussed. We review the literature supporting extent of resection in GB, highlighting the importance of a standardized definition and measurement of extent of resection to allow greater collaboration in research projects and trials. Recent developments in neurosurgical techniques and technologies focused on maximizing extent of resection and safety are discussed.

Keywords
- glioblastoma
- extent of resection
- survival
- gross total resection
- supramaximal resection

Glioblastoma: Incidence and Demographics

Gliomas are the most common primary tumor of the central nervous system (CNS) with an estimated annual incidence of 6.6 per 100,000 individuals in the United States,[1] which is predicted to rise to 22 per 100,000 by 2035.[2] The revised 2016 World Health Organization (WHO) classification of tumors of the CNS divides gliomas into low-grade glioma (LGG; WHO I–II) and high-grade glioma (HGG; WHO III–IV) based on integrated classic histologic features and molecular biomarkers.[3] Approximately half of all newly diagnosed gliomas are classified as glioblastoma (GB; WHO IV), the most malignant type of brain cancer. The WHO classification further divides GB into isocitrate dehydrogenase wild type (IDHwt; 90%) that corresponds to the primary or de novo GB and predominates in patients aged >55 years and IDH mutant (IDHmut) corresponding to secondary GBs that develop from lower grade or diffuse astrocytomas and occur in younger patients.

The annual incidence of GB is currently 3.2 per 100,000 population. However, tumors occur more frequently with advancing age, ranging from 0.4 per 100,000 population aged 20 to 34 years, to >15 per 100,000 population aged 75 to 84 years.[1] It is widely recognized that elderly populations are rapidly increasing globally that will have a significant impact on the burden of GB disease. Despite this trend, most studies still focus on patients <65 years.

The current gold standard treatment for newly diagnosed GB is gross total resection (GTR), followed by radiotherapy with concomitant and adjuvant temozolomide. The aim of

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treatment is to delay tumor progression and extend overall survival (OS).[4] Despite decades of refinement, this approach results in a median survival time of 12 to 14 months. The exception is a subgroup of patients with methylguanine methyltransferase promotor methylation who receive temozolomide and have a 46% OS at 2 years.[5] Overall, these malignant CNS tumors hold the poorest prognosis, are responsible for the highest estimated number of years of potential life lost (mean: 20 years) among all cancers,[6] and survival trends have remained mainly static in comparison with other cancers.[7]

Extent of Resection: Definition and Measurement

GB is an intrinsic primary brain tumor that has no distinct brain–tumor interface microscopically. Autopsy and imaging studies demonstrate that gliomas infiltrate diffusely along vessels and the white matter tracts of the brain into regions that appear to be normal on magnetic resonance imaging (MRI).[8,9] Historically, hemispherectomies for GB were attempted, but these failed to provide disease cure because the tumor recurred on the contralateral side.[10] Currently, the relationship between the extent of resection (EOR) of GB and clinical outcomes in terms of OS, progression-free survival (PFS), and symptom control remain incompletely understood. No validated metric is available to quantify EOR, and randomized clinical trials are impractical, hindering achievement of level 1 evidence for EOR.

A challenge in determining the EOR has been assessing the tumor burden through modern imaging technology. In a 2016 systematic review and meta-analysis of the association of the EOR with GB survival,[11] the EOR was defined by the authors of the individual studies as the percentage volume of total tumor resected including reports of GTR, subtotal resection (STR), partial resection (PR) or biopsy. EOR was measured in various ways including absence of contrast-enhanced tumor on postoperative contrast computed tomography (CT) performed within the first week postoperatively,[12] absence of residual contrast enhancement on postoperative MRI performed within 48 hours of surgery,[13] and manual segmentation of tumor volume and volumetric analysis of pre- and postresection intraoperative contrast-enhanced MRI scans.[14] A further caveat regarding reporting EOR is that it does not adequately depict the residual volume (RV) and hence disease burden that must be targeted with adjuvant therapies. For example, a 90% resection of a large tumor may result in a greater volume of residual tumor than a lesser resection of a smaller tumor. Thus the benefits of cytoreduction may not be highlighted.[15]

In response to a need for better standardization of image acquisition, and to aid comparison in GB clinical trials, the following recommendations were made including the Response Assessment in Neuro-Oncology criteria (two-dimensional tumor measurement)[16] and an international brain tumor imaging protocol with recommended sequences and parameters.[17,18] The key aspect of these protocols are parameter-matched pre- and postcontrast volumetric images to allow bidimensional and volumetric measurement of residual enhancing tumor. However, both these techniques have limitations. Bidimensional measurement has high measurement variability,[19,20] particularly with lesions that are irregularly shaped, poorly defined, or have satellite regions,[21] and is sensitive to imaging quality.[22] Volume measurement requires an operator to outline the lesion manually and differentiate between the different tissue compartments of the tumor and the peritumoral region. This work requires considerable expertise and training, and thus is highly operator dependent. Consequently, manual tumor volumetry is time consuming, prone to subjectivity, and associated with large interobserver variability.[23–25] One proposed solution is an automated segmentation approach to assist with lesion delineation and grading, and fully or semiautomated segmentation techniques have been published.[26–28]

Currently there is an increasing trend toward neural network based *deep learning* approaches.[29] Although promising, these techniques still fail to outperform expert clinician manual segmentation,[29] and none are established in routine clinical practice. These approaches depend highly on the number of labeled training samples available, and very large annotated data sets are typically required to achieve high accuracies while avoiding problems with overfitting.[30] As publicly available labeled data sets continue to increase in size and availability, these automated methods may well provide quick, accurate, and clinically viable tools that can be used reliably and reproducibly across a wide spectrum of tumor types but also to acquire data across different centers, MRI scanners, and field strengths.

Even with optimized segmentation methods, the problem remains that tumor infiltration can spread diffusely far beyond visible lesion boundaries and cannot be detected using standard MRI techniques. Microstructural changes associated with infiltration provide opportunities for more advanced imaging methods. For example, MRI techniques optimized for vascular imaging, such as brain perfusion imaging using modified arterial spin labeling[31] or susceptibility weighted imaging,[32] can be used to measure the associated disruption of the blood-brain barrier and neoangiogenesis. Diffusion-weighted imaging (DWI) allows differences in water diffusion in, or surrounding, white matter tracts to be quantified. A number of noninfiltrative processes may also modify brain diffusion properties including peritumor edema. Previously, single-shell DWI acquisitions failed to correlate with tumor cell density.[33] DWI acquisitions involving three or more b-values were used to model the non-Gaussian diffusion properties of brain tissue, and they have identified abnormalities in normal-appearing white matter that are proposed to be biomarkers of tumor infiltration.[34] Tissue validation, however, is still pending. Magnetic resonance spectroscopy (MRS) is a noninvasive way of measuring the metabolic changes associated with increased cellular proliferation and has biopsy-proven validation linking some of the spectra changes to tumor infiltration.[35] Currently ultra-high field 7-T MRI coupled with MRS is under development and may offer high-resolution multimetabolite mapping for glioma.[36] It represents an excellent opportunity for translational research.

Extent of Resection in Newly Diagnosed Glioblastoma

The pursuit of maximal EOR in glioma surgery requires great caution and must be balanced against functional outcome. Failure to identify and preserve eloquent brain regions can significantly compromise the patient's quality of life and performance status. It can also potentially render the patient ineligible for further adjunctive treatment options with consequent serious prognostic implications.[37–39] In the last decade, major advances have been made in brain tumor imaging, intraoperative technologies, and neurosurgical techniques. A growing body of clinical data supports the prognostic importance of GTR in GB (►**Table 1**, adapted from Ma et al[40]). This is being incorporated into European guidelines for the management of patients with GB.[41,42]

One of the first studies on EOR in GB using pre- and postoperative volumetric MRI was performed by Lacroix et al.[43] It suggested a resection $\geq$ 98% was necessary to have an impact on OS. This led to the concept that only maximal surgical resection was relevant in glioma management.[43] Studies by Orringer et al[44] and Grabowski et al[15] also supported the need for high percentages of EOR to improve OS ($>$ 90% and $>$ 98%, respectively). Publications in more homogeneous patient populations rejected the idea that complete or near-complete resections offered the only survival benefit.[13,14,45,46] Chaichana and colleagues reported a minimal EOR threshold of 70% to have an impact on survival and recurrence, and they introduced a new concept of evaluating the relationship between survival and RV. An RV $\leq$ 5 cm^3 was identified as the threshold to achieve an impact in survival.[47] Subsequently a lower threshold for a significant benefit to OS both for EOR ($>$ 60%) and RV ($<$ 8 cm^3) was reported.[48] Awad et al disputed the step-like influence of EOR because their study did not find that a specific threshold for EOR or postoperative RV was essential for improving OS. Rather there is a graded response in that the greater the EOR, the better the OS statistically.[49]

A meta-analysis of 37 studies (41,117 patients with newly diagnosed GB) concluded GTR substantially improved OS and PFS in comparison with STR, PR, or biopsy; however, the quality of the supporting evidence was moderate to low.[11] Data extrapolated from two randomized trials support the benefit of EOR in GB. In a phase 3 study, 176 patients with malignant gliomas underwent fluorescence-guided microsurgery using 5-aminolevulinic acid (5-ALA), and 173 patients underwent conventional white-light microsurgery.[50,51] More patients in the 5-ALA group had complete resection (absence

Table 1 Summary of literature of extent of resection and survival advantage in newly diagnosed glioblastoma

Study	No. of patients	Maximal survival advantage	Volumetric imaging study	Minimum resection required
Lacroix et al [43]	416	4.2 mo	Yes	89%
Stummer et al[115]	243	4.9 mo	No	GTR
McGirt et al[13]	451	2 mo (GTR vs. NTR) 5 mo (GTR vs. STR)	No	Improvement in OS with GTR
Kuhnt et al[14]	88	5 mo	Yes	98%
Sanai et al[45]	500	3.8 mo	Yes	78%
Orringer et al[44]	46	44% 1-y survival	Yes	90%
Stummer et al[53]	143	$>$ 7.1 mo	No	RTV $<$ 1.5 cm^3
Grabowski et al[15]	128	4.5 mo	Yes	98% or $<$ 2 cm^3 RTV
Chaichana et al[47]	259	3.9 mo	Yes	70% or $<$ 5 cm^3 RTV
Chaichana et al[46]	292	4.7 mo GTR, 4.2 mo RTV	Yes	95% or $<$ 2 cm^3
Brown et al[11]	20,769 20,699	16.1% 1-y survival 10.3% 2-y survival	No	$>$ 89%
Li et al[58]	1229	5.4 mo + 5.2 mo extra for addition of $>$ 50% FLAIR resection	Yes	100% $\pm$ $>$ 50% FLAIR resection
Pessina et al[59]	178	3.2 mo (GTR vs. STR)	Yes	GTR
Yan[61]	31	3.4 mo (EOR $>$ 89% vs. $<$ 89%)	Yes	$>$ 89%
Awad et al[49]	330	9 mo (EOR $>$ 90% vs. 70–80%)	Yes	Incremental survival benefit with EOR
Coburger et al[48]	67	$>$ 60% resection median OS 11 mo; $<$ 8 cm^3 RT median OS 13 mo	Yes	EOR $>$ 60% $<$ 8 cm^3 RTV
Roh et al[63]	40	25.4 mo (noneloquent GTR + lobectomy vs. GTR)	Yes	GTR

Abbreviations: EOR, extent of resection; FLAIR, fluid-attenuated inversion recovery; GTR, gross total resection; NTR, near-total resection; OS, overall survival; RT, residual tumor; RTV, residual tumor volume; STR, subtotal resection.
Source: Adapted from Ma et al.[40]

of contrast-enhancing tumor on MRI; 65% vs 36%; $p < 0.0001$), and EOR was positively associated with PFS and OS.[50,52]

When stratified by completeness of resection, patients with incomplete resections had more rapid neurologic deterioration than those with complete resections.[51] Furthermore, a prospective cohort study of patients with GB receiving radiotherapy and concomitant and adjuvant temozolomide chemotherapy revealed that patients with no or minimal residual enhancing tumor after surgery had an advantage in terms of PFS and OS.[53] A prospective trial evaluating intraoperative MRI (iMRI) to enhance EOR in patients with glioma demonstrated that complete tumor resection corresponded to an extended PFS on univariate and multivariate analysis, and EOR was a stronger prognostic factor than age.[54] Optimal EOR for GB according to site, extension, and size was investigated in GB patients who underwent GTR, STR, or open biopsy between 2005 and 2014 using the Surveillance, Epidemiology, and End Results database.[55] Although GTR remains the gold standard treatment for GB, STR/open biopsy was performed more frequently in clinical practice. GTR had a significant beneficial effect on OS in cases where the tumor was confined to one cerebral hemisphere with a size < 6 cm and when tumor crossed the midline with a size of 4 to 8 cm. For small-size tumors that crossed the midline, GTR failed to increase OS compared with other surgery types.

Gliomas have a strong propensity to infiltrate through white matter tracts, and it has been proposed that fluid-attenuated inversion recovery (FLAIR) altered areas may represent nonenhancing normal brain with pathologic invasion of GB that eventually represent sites of recurrence. An emerging concept in neuro-oncology is supramaximal resection: where "functionally safe," the resection is extended beyond the MRI abnormalities seen on T1-enhanced and T2-FLAIR imaging. Duffau pioneered this approach with promising results in patients with LGGs[56] and in GB.[57] Li et al reported the largest single-center series of 1,229 patients undergoing complete resection of GB.[58] Resection of all T1 contrast-enhancing tumor volume was achieved in 70% of patients, with a median survival of 15.2 months, significantly longer than patients with less than complete resection of 78 to 99% (9.8 months; $p = 0.001$). This survival advantage was independent of age, preoperative tumor volume, Karnofsky Performance Score (KPS), and prior treatment status. Importantly, complete resection was not associated with increased neurologic deficit postoperatively. Additional resection $\geq 53\%$ of the surrounding FLAIR abnormality beyond the complete contrast-enhancing resection was associated with significant survival advantage in comparison with less extensive resections (20.7 vs. 15.5 months; $p < 0.001$).

The concept that surgical resection beyond the contrast-enhancing boundaries improves PFS and OS was supported by further studies[59,60] including by extending the resection to include abnormality documented by diffusion tensor imaging (DTI).[61] Recently a comparison of an intralesional versus perilesional surgical resection and effect on EOR and outcome suggested that a circumferential perilesional resection of GB is associated with significantly higher rates of GTR and lower rates of neurologic complications than intralesional resection. This was also the case for tumors arising in eloquent locations.[62] A retrospective review of the survival benefit of additional lobectomy after GTR versus GTR alone in IDHwt GB located in either the nondominant frontal or temporal lobe was recently performed.[63] Of 40 patients evenly divided into each arm, the median PFS for GTR was 11.5 months and 30.7 months for lobectomy ($p = 0.007$) and the OS for GTR was 18.7 months versus 44.1 months for lobectomy 44.1 ($p = 0.04$). The patient's functionality as assessed by the KPS was not impaired. Because the EOR is the only modifiable prognostic factor demonstrated for GB to date, the application of this surgical method could improve the OS of GB patients. However, further review, particularly with more detailed analysis of cognitive function and quality of life, needs to be performed.

Interpreting the results reported in the literature reviewing the advantages of EOR in GB is fraught with limitations due to the heterogeneity of the available data. However, collectively they emphasize the importance of minimal residual tumor volume (RTV) and demonstrate the advantages of STR, GTR, and even supramaximal EOR in terms of PFS and OS when permanent neurologic deficits are avoided. Prospective multicenter trials with standardized imaging and data capture with a focus on quality-of-life outcomes will provide further information and help us counsel patients with newly diagnosed GB. A review throughout the United Kingdom of residual enhancing disease after surgery for GB identified a subset of patients for whom GTR was thought possible preoperatively but not achieved at surgery (16.3%).[40] There are minimal data on whether immediate revision surgery to resect residual enhancing disease would be of benefit.[64] Furthermore, multiple factors need to be considered including extended hospital stay with the inherent increased surgical and anesthetic risks of infection, venous thromboembolic events, the social and psychological factors, and also additional financial pressures including longer hospital stay and scheduling additional operating room time on emergency/elective operating lists.

Extent of Resection in Recurrent Glioblastoma

The main aims of repeat surgery for recurrent GB are to increase PFS and OS, reduce symptoms and steroid dose, and obtain an up-to-date pathologic diagnosis to enroll patients in further adjuvant treatment or clinical trials. In keeping with newly diagnosed GB, when GTR re-resection was achieved, OS was improved in comparison with STR.[65–69] A survival benefit was reported when the EOR exceeds 80%[70] or with an RTV < 3 cm^3.[71] At best these studies represent level 2 and level 3 evidence. A study of 578 patients reported that recurrent GB can have improved survival with multiple repeated resections.[66] The median survival for patients who underwent one, two, three, and four resections was 6.8, 15.5, 22.4, and 26.6 months ($p < 0.05$), respectively.

A more recent study of 503 patients undergoing resection for recurrent GB suggested the patient's median survival after initial diagnosis was 25 months and 11.9 months after first re-resection.[68] Pre- and postoperative KPS, EOR and chemotherapy after first re-resection were identified as parameters that influenced survival significantly. Pessina et al reported that

repeat GTR resection in 64 recurrent GB patients provided a median OS of 10.3 months with 1- and 2-year OS rates of 31.3%.[69] The oncologic benefits of re-resection need to be carefully balanced against the complication rates of repeat surgery. However, the risk of infection and iatrogenic deficit did not increase with repeated resections ($p > 0.05$[65]) and was similar to the rate of permanent new deficits after initial resection (9%) and first re-resection (8%).[68]

Extent of Resection and Molecular Analysis

As the molecular characteristics of glioma are better understood, attempts to classify patients into more homogeneous groups based on similar genetic etiology and clinical outcomes have been made. Eckel-Passow et al grouped gliomas based on codeletion of chromosome arms 1p and 19q (1p19q codeletion), mutations in IDH, and the telomerase reverse transcriptase gene promoter (TERTp) mutations.[72] Kaplan-Meier estimates of OS demonstrated that gliomas (WHO grade II and III) with TERTp mutation only (i.e., IDHwt, non-1p19q codeleted) had poor survival with a similar prognosis to GB with TERTp and IDHmut. Furthermore, genetic aberrations identified in primary GB are also reported in IDHwt-diffuse LGG and have a similarly poor prognosis. These molecular characteristics include a combination of trisomy of chromosome 7, loss of chromosomal arm 10q, and the TERTp mutation.[73–76] As we begin to better understand the molecular biology of glioma, timely translational genomic approaches are essential for improving point-of-care diagnosis and will be critical in defining the relationship between specific molecular characteristics in glioma and EOR. Novel technologies such as intraoperative molecular genotyping[77] and Raman scattering microscopy[78] can assist with intraoperative brain tumor diagnosis and will be essential to delivering precision medicine in the operating room.

Extent of Resection in the Older Population

The incidence of GB increases with age to peak in the 9th decade.[2] Because the global population of older people is rising, the disease burden of GB will increase. The current gold standard treatment of GB is the Stupp regime.[4] However, patients aged > 70 years were excluded from the study. Subgroup analysis in patients aged 60 to 65 years only had a trend toward a survival advantage, and patients aged 65 to 70 years had no survival advantage.[79] A randomized trial of newly diagnosed GB in patients aged ≥ 65 years examined the addition of temozolomide to radiotherapy (40 Gy in 15 fractions) over radiotherapy alone. An advantage in both a PFS and OS was seen in the combined treatment and is now becoming the standard of care in this age bracket.[80] Underrepresentation of this population in many GB trials and concerns regarding treatment challenges (including comorbidities and frailty) are thought to impact why older patients are more often treated conservatively. They are more likely to undergo biopsy alone and are less likely to receive radiotherapy and/or chemotherapy after surgery.[81,82]

Recently Pessina et al reviewed the effect of EOR on prognosis of 178 patients aged ≥ 65 years with newly diagnosed GB.[83] Patients who underwent complete resection, GTR, or STR had better outcomes in comparison with patients receiving STR or biopsy, suggesting a resection of at least 80% is required to obtain a survival benefit.[83] Furthermore, worsening or development of new postoperative neurologic deficits was found to strongly and negatively influence survival at 1 year. Similarly, a study by Babu and colleagues reviewed the effect of EOR on the prognosis of 120 patients aged ≥ 65 years with newly diagnosed GB. More than 60% underwent a GTR that conferred an OS median of 14.1 months versus 9.6 months ($p = 0.038$) in those who underwent STR.[84] A KPS score < 80 was inversely correlated with survival outcomes; however, advanced age did not have an impact on survival.[85] This study also observed that elderly patients with resection survived longer than those who underwent biopsy alone; however, the complication rates were higher in the resection group. These recent studies agree with the previous literature suggesting that elderly patients with newly diagnosed GB who undergo maximal resection rather than biopsy alone have an improved PFS and OS and that EOR correlates with an incremental survival benefit as reported in younger patients.[86–89] Jordan et al[90] provide a review.

Limited studies exist on the surgical management of recurrent GM following maximal first-line therapy in the elderly. A multicenter retrospective analysis of 777 adult patients with recurrent GB following maximal first-line treatment was performed in which 117 GB patients were > 70 years of age.[91] Elderly patients were less likely to be offered further repeat resective surgery (< 15% versus 33% if < 70 years) or further oncologic care. Age > 70 years did not significantly or independently impact OS from recurrence. When treated for recurrence, elderly patients with KPS > 70 experienced a similar OS as younger patients.[91] Treatment of GB in the elderly patient remains an individual decision with priority on quality of life. Future studies incorporating molecular advances need to be performed.

Surgical Adjuncts to Optimize Extent of Resection in Glioblastoma

Despite the limitations of the trials and studies reviewed, collectively the data for patients with GB support the fundamental concept of neurosurgical oncology that maximal safe surgical resection is positively correlated with clinical outcome. Over the last decade, numerous intraoperative tools have been developed to enhance the neurosurgeon's ability to identify tumor boundaries and augment resection while simultaneously preserving eloquent brain function.

Fluorescent-Guided Resection Technique

The best studied intraoperative fluorescence imaging technology is 5-aminolevulinic acid (5-ALA). It allows real-time intraoperative identification of residual tumor, thereby maximizing EOR in HGG.[91,92] Oral administration of the prodrug 5-ALA (20 mg/kg body weight) ~ 2 to 4 hours before surgery

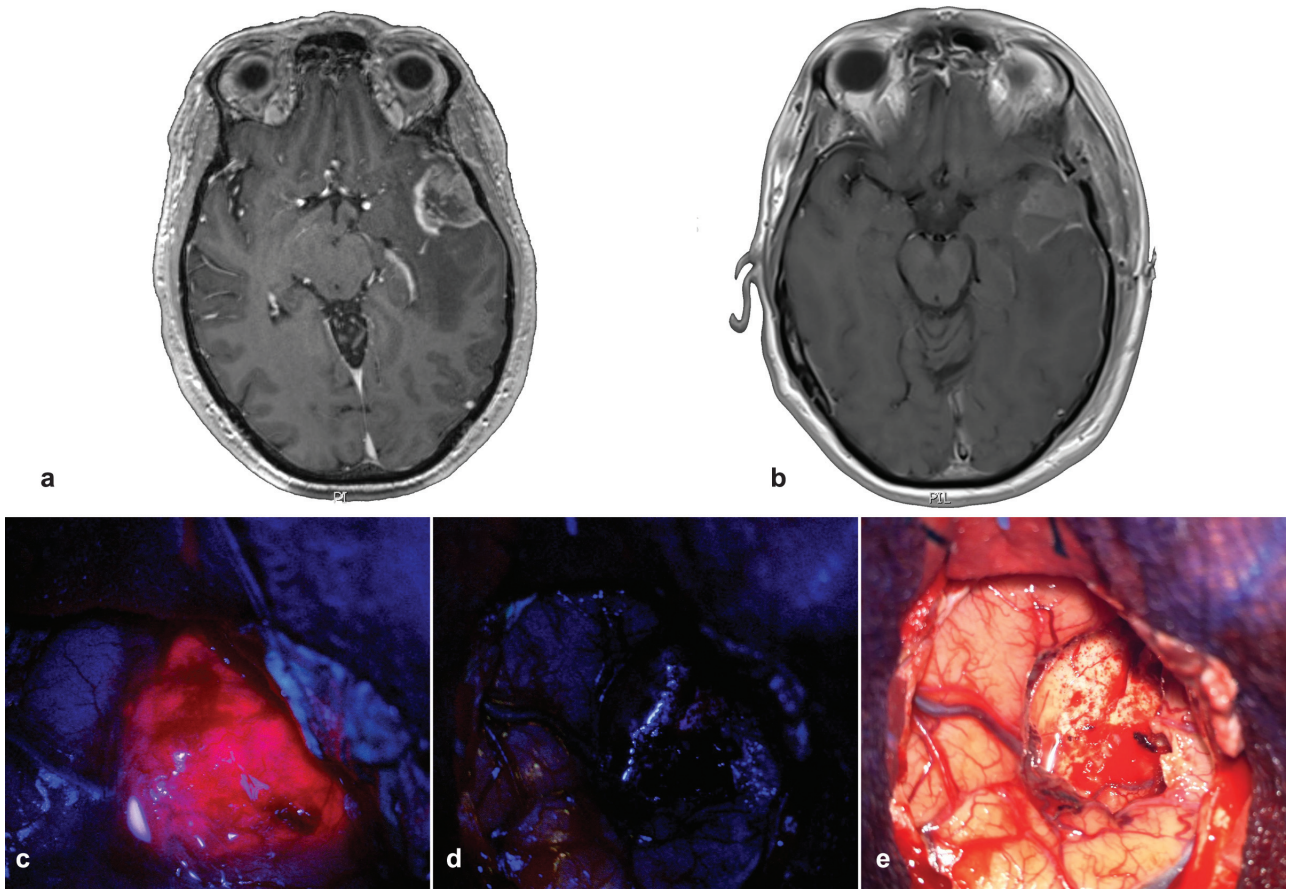

Fig. 1 A 5-aminolevulinic acid (5-ALA)–guided resection of glioblastoma. (**a**) Preoperative and (**b**) 24-hour postoperative axial contrast-enhanced magnetic resonance imaging demonstrating complete resection of left temporal contrast-enhancing, pathology-confirmed glioblastoma. (**c**) Microscope view under blue light at a wavelength of 400 nM on opening dura to visualize coral pink following 5-ALA administration in patient with glioblastoma. Microscope view (**d**) under blue light and (**e**) under white light showing complete tumor resection.

results in preferential accumulation of fluorescent protoporphyrin IX (PpIX) in proliferating tumor cells as a result of incorporation into the heme-biosynthesis pathway. Under a microscope with violet blue excitation light to visualize fluorescence, PpIX is seen as bright pink and can guide resection of HGG (►**Fig. 1**). In a phase 3 multicenter randomized controlled trial, resection guided by 5-ALA resulted in a 29% reduction in the proportion of patients with HGG RV on early postoperative MRI and correlated with an increase in PFS at 6 months[50] and increased OS in Radiation Therapy Oncology Group-Recursive Partitioning Analysis class IV and V patients.[52]

A systemic literature review of 5-ALA–guided surgery and intraoperative MRI in GB demonstrated no superiority of one technique over the other in outcome parameters, and it suggested a combined use of 5-ALA and iMRI may be promising to achieve a resection beyond gadolinium enhancement.[93] A recent review suggests that 5-ALA is also useful adjunct in the resection of recurrent HGG.[94] The authors report that 5-ALA has a high positive predictive value, that is, intraoperatively a strong fluorescent signal is correlated with the presence of cellular tumor even in recurrent HGG. Coupled with a favorable safety profile, they recommend 5-ALA be used routinely as a standard of care in recurrent HGG resection.[94] Commercially available fluorescence imaging systems rely solely on visual assessment of fluorescence patterns by the surgeon, making the resection more subjective than necessary. New technologies are being developed to optimize accurate estimation of PpIX and allow more quantitative analysis.[95]

Intraoperative Cortical and Subcortical Stimulation Mapping

Resection of GB involving eloquent areas requires preservation of both cortical and subcortical structures to optimize postoperative functional status. A review of the various techniques and approaches used for intraoperative cortical and subcortical electrostimulation mapping either during awake craniotomy or under general anesthesia are described in detail elsewhere.[96,97]

Briefly, the aim of electrical stimulation mapping is to identify and localize the cortical areas reliably and reproducibly and the subcortical pathways involved in language, motor, sensory, and cognitive function. Cortical functional organization varies considerably between patients, tumor mass effect may distort anatomical relationships, and cortical plasticity may result in reorganization of neural networks. Functional MRI and DTI are useful in planning resections (►**Fig. 2**); however, they do not always directly correlate with functional

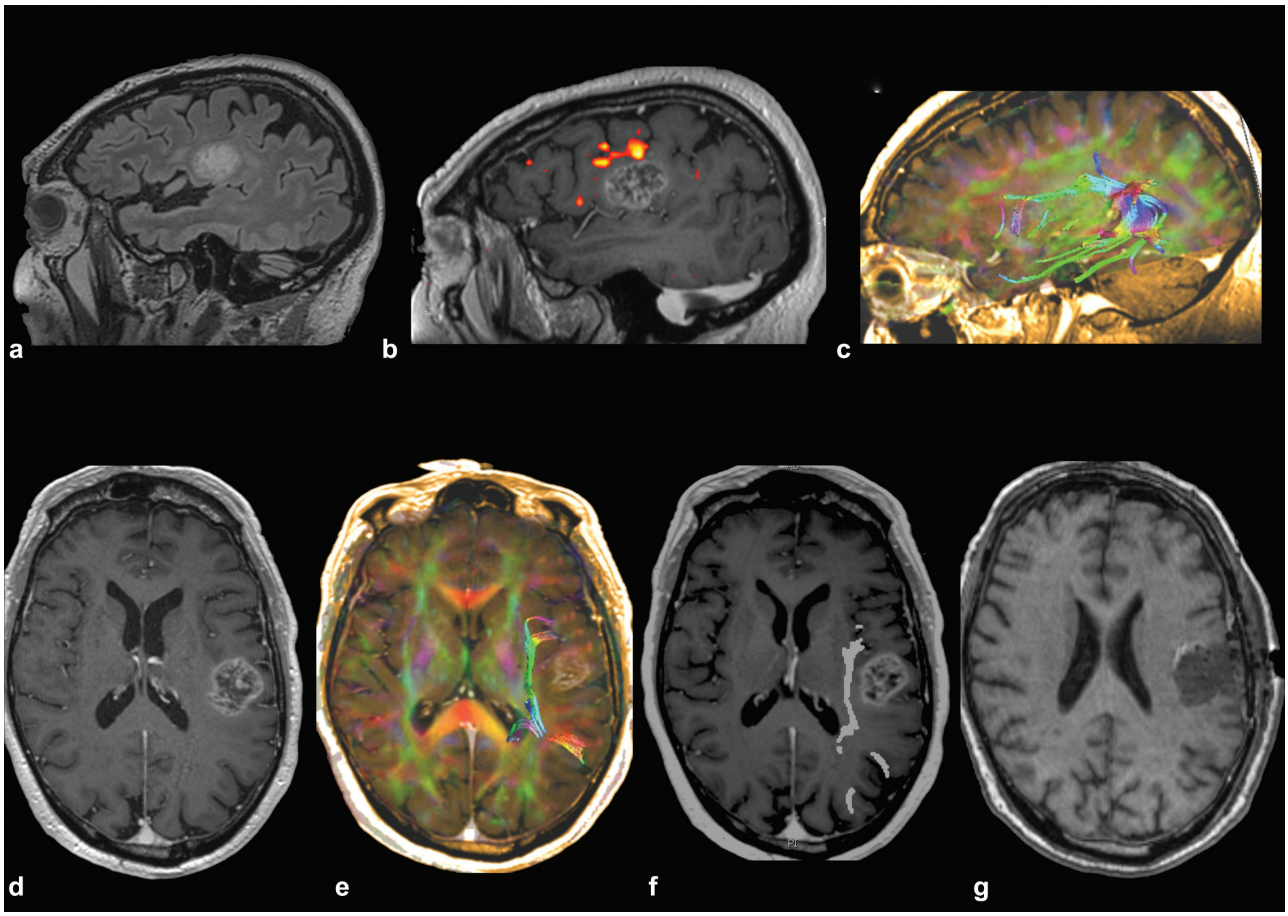

Fig. 2 Preoperative diffusion tensor imaging (DTI) tractography of the arcuate fasciculus (AF) to inform planning of awake craniotomy with speech and motor mapping and monitoring in a 72-year-old right-handed man diagnosed with glioblastoma. (**a, d**) Preoperative sagittal and axial contrast-enhanced magnetic resonance imaging (MRI) demonstrating enhancing lesion in the dominant subcentral gyrus extending into the posterior insular. (**b**) Silent word generation language functional MRI shows left-side language dominance. The activated anterior language areas are seen in the inferior and middle frontal gyri, in close proximity to the anterior and superior border of the lesion. (**c, e**) Left AF three-dimensional reconstruction to demonstrate relation of the tract to the lesion. (**f**) Intraoperative neuronavigation MRI with DTI tractography of the AF. (**g**) Postoperative contrast-enhanced MRI demonstrates > 95% extent of resection. Postoperatively there was a transient subtle deterioration in expressive dysphasia that improved to the patient's baseline by postoperative day 10.

anatomy and cannot be used as a substitute for intraoperative awake mapping and monitoring or neurophysiologic evaluation to guide surgery.[98] "The DTI challenge" recently demonstrated a lack of standardization in reconstruction of different tractography algorithms, producing different results that could significantly impact clinical outcomes.[99]

Monitoring of eloquent function during resective surgery can be performed by testing the function intraoperatively during awake craniotomy. Language testing by the speech and language team using preoperative and perioperative paradigm testing[100] or perioperative motor function testing can be augmented with neurophysiologic techniques. Using a strip electrode, a short train of electrical stimulation can be delivered to elicit muscle responses. These motor-evoked potentials can be recorded either by needle electrodes or surface electrodes and provide a way of monitoring the integrity of motor pathways. A suction monopolar system was designed that can be used for dynamic "real-time" continuous cortical and subcortical stimulation for mapping of the distance from the subcortical corticospinal tract.[101]

Meta-analysis demonstrated that intraoperative stimulation mapping reduces late severe neurologic deficits without compromising EOR and suggests that stimulation mapping should be integrated into standard of care for glioma surgery when tumors arise in eloquent brain regions.[102] Schucht and colleagues demonstrated that for GB surgery, 5-ALA guidance combined with intraoperative neurophysiologic mapping and monitoring resulted in increased GTR and reduced mortality.[103] Furthermore, in cases where GB is adjacent to the motor eloquent areas, a synergistic benefit of using both suction monopolar for intraoperative continuous dynamic subcortical mapping to identify the corticospinal tract and surgery guided by 5-ALA was demonstrated to achieve high rates of complete resection of contrast-enhancing tumor.[104] When combined with neuronavigation, tractography offers an intraoperative approximation of major tract positions, decreasing the number of subcortical stimulations needed and making surgery quicker and easier.[105] Reduced direct electrical stimulation decreases the risk of stimulation-induced seizures.

Intraoperative Imaging Technologies

Recent advances in intraoperative neurosurgical imaging including intraoperative neuronavigation, intraoperative MRI (iMRI, and intraoperative ultrasound (iUS) have significantly enhanced the potential to achieve complete radiologic resection of contrast-enhancing tumor, associated FLAIR anomaly, and supramaximal resection. Real-time information regarding location, size, and adjacent structures including vascular structures can be obtained. Intraoperative MRI offers the advantage of intraoperative real-time interval updates in the three-dimensional neuronavigation imaging that can compensate for brain shift resulting from cerebrospinal fluid loss after opening the dura and for tissue edema. EOR in HGG was significantly greater in patients operated using iMRI compared with conventional surgery.[106,107] A randomized controlled trial demonstrated that iMRI is a helpful tool to increase the EOR, and the use of iMRI did not result in any neurologic deterioration.[54] Intraoperative MRI for glioma in 100 consecutive patients suggested iMRI-neuronavigated surgery provided maximal EOR whatever the type of glioma and location. It was even more useful for nonenhancing or minimally enhancing tumors.[108]

Intraoperative US is convenient, immediate, simpler to use, and more readily available, particularly in a resource-constrained setting, and it may provide a more pragmatic cost-effective adjunct in comparison with iMRI. Intraoperative US is accurate in distinguishing tumor from normal parenchyma. Two studies that reviewed iUS use in the resection of predominantly HGG highlighted its efficacy.[109,110] However, a recent Cochrane review of intraoperative imaging technology to maximize EOR for glioma concluded that although there was evidence of benefit from iMRI and 5-ALA, the quality of evidence was low, and impact on OS, PFS, and quality of life was unclear.[111]

Integrated multimodal neuronavigation refers to novel techniques to coregister multiple imaging modalities including functional and structural information allowing real-time integrated intraoperative information to assist safe and complete resection of intracranial lesions, particularly within eloquent brain areas. Functional MRI, MRI-based DTI tractography (►**Fig. 3**), and navigated transcranial magnetic stimulation (nTMS) enable the neurosurgeon to incorporate functional data into preoperative planning and intraoperative navigation. Both functional MRI and DTI were demonstrated to influence clinical decision making, surgical approach, and EOR in glioma including GB.[112]

Navigated TMS is an emerging technology for preoperative cortical mapping and planning before glioma resection located within or in proximity to the motor and language areas. It is used before surgery to plan a tailored strategy of maximal safe resection and during surgery, with integrated nTMS-based tractography, as a further guide to intraoperative neurophysiologic mapping. The role of nTMS on the surgical outcome in GB was reviewed in a controlled observational study by Picht et al.[113] Supplementing standard intraoperative cortical mapping with preoperative nTMS motor mapping and nTMS-based fiber tracking results in improved surgical outcomes without compromising functional outcome in patients with GB. It is further suggested that nTMS mapping can expand the population of patients who can be safely offered surgical treatment.[113] Meta-analysis suggests nTMS is associated with a reduced occurrence of postoperative permanent motor deficits, an increased GTR rate, and a better tailored surgical approach compared with standard surgery without using preoperative nTMS mapping.[114] However, further research is required to provide high-level evidence of this emerging technology.

Conclusion

The available data from patients with GB overwhelmingly support the fundamental principle of neurosurgical oncology that safe maximal tumor resection improves PFS, OS,

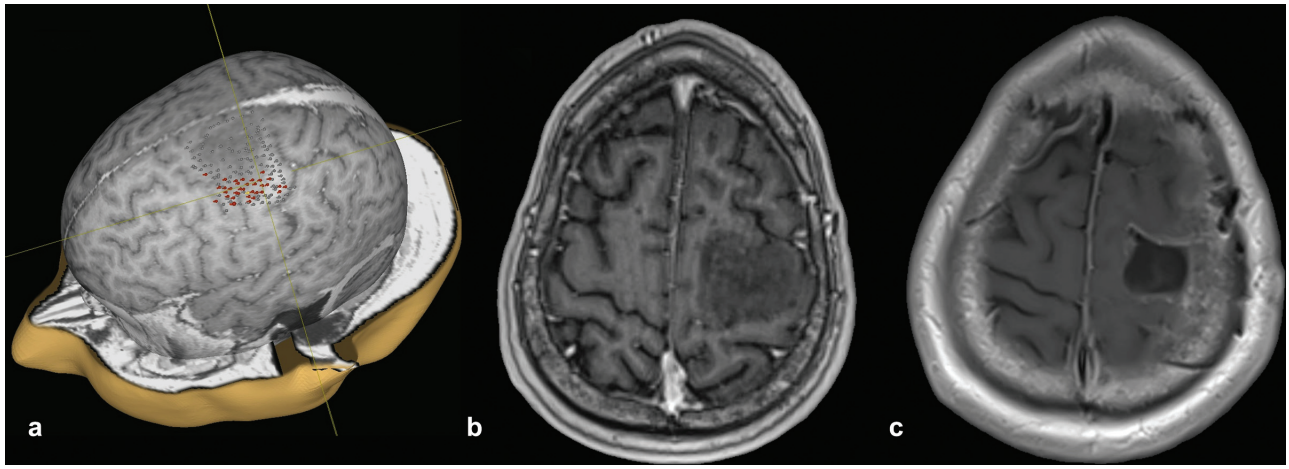

Fig. 3 Use of navigated transcranial magnetic stimulation on a patient with left frontal high-grade glioma to maximize safe extent of resection. (**a**) Three-dimensional magnetic resonance imaging (MRI) coregistered with preoperative navigated transcranial magnetic stimulation (nTMS). Red arrows represent points with positive motor response of the right hand and arm recorded in preoperative nTMS mapping. (**b**) Preoperative contrast-enhanced head MRI demonstrating lesion anterior to the motor strip. (**c**) Postoperative contrast-enhanced head MRI demonstrating complete resection of the tumor with no neurologic deficit. Histopathologic analysis confirmed oligodendroglioma World Health Organization class III, isocitrate dehydrogenase mutant, 1p19q codeleted.

symptom control, and quality of life. Standardizing definitions of EOR and imaging techniques, and harmonizing clinical data collection in terms of outcomes including quality of life will allow us to perform large-scale prospective studies to better understand the importance of EOR in GB. It will also help us quantify the value of surgical adjuncts in achieving this goal. In recent years, new intraoperative techniques have been introduced into the neurosurgical armamentarium to improve EOR, minimize RV, and improve the safety of surgery. They have different merits and range from tools that assist in the planning of surgery and resection of the tumor to techniques that improve patient safety. Continued surgical research will be essential if we are to optimize how different techniques can be used in combination in molecularly stratified patient cohorts and to quantify their clinical and cost-benefit value.

Conflict of Interest
None declared.

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