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Safe surgery for glioblastoma: Recent advances and modern challenges

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Abstract

One of the major challenges during glioblastoma surgery is balancing between maximizing extent of resection and preventing neurological deficits. Several surgical techniques and adjuncts have been developed to help identify eloquent areas both preoperatively (fMRI, nTMS, MEG, DTI) and intraoperatively (imaging (ultrasound, iMRI), electrostimulation (mapping), cerebral perfusion measurements (fUS)), and visualization (5-ALA, fluoresceine)). In this review, we give an update of the state-of-the-art management of both primary and recurrent glioblastomas. We will review the latest surgical advances, challenges, and approaches that define the onco-neurosurgical practice in a contemporary setting and give an overview of the current prospective scientific efforts.

Keywords:
glioblastoma | intraoperative mapping | imaging | preoperative mapping | review

Glioblastoma (grade IV astrocytoma) is the most common form of primary brain malignancy in adults. Patients face a dim prognosis of approximately 16 months, which has not significantly improved over the last 15 years.[1] Standard therapy includes resection followed by adjuvant chemoradiation, which can be administered in various ways dependent on the patient's age and performance (Stupp protocol, Perry protocol).[2,3]

One of the most important factors in determining the patient's prognosis is surgery (the extent of resection).[4–6] First, glioblastoma patients who have undergone tumor resection experience on average a longer overall survival than those who have undergone tissue biopsy.[6] Second, the extent of resection (EOR) in surgery plays a major role, since higher EOR percentages correlate with better survival outcomes.[4,5]

Due to their invasive nature, glioblastomas infiltrate the surrounding parenchyma and despite a gross-total resection, recurrence is inevitable. Still, neurosurgeons aim to safely resect as much tumor tissue as possible, often striving for complete resection of the contrast-enhancing (CE) part of the tumor on MR-imaging, adhering to the fact that complete resection of the contrast-enhancing tumor has shown to convey a survival benefit.[7] Recent evidence suggests that it might be beneficial to expand the resection to the noncontrast-enhancing (NCE) part as well in two distinct subgroups of patients: (1) patients with *IDH* wildtype tumors, regardless of MGMT methylation status and (2) in younger patients, regardless of *IDH* status.[8]

Since >50% of glioblastomas are located in or near eloquent areas, aggressive resection has the potential to lead to postoperative neurological deficits, thereby severely harming the patient's quality of life (QoL) and functioning.[4–6] In order to preserve the patient's quality of life (and protect neurological functioning), while maximizing the extent of resection, several preoperative and intraoperative methods have been developed to help the surgeon balance between these two—sometimes conflicting—goals. The postoperative functioning is of utmost importance, since suboptimal postoperative QoL or KPS negatively impact survival chances of glioblastoma patients.[9]

In this review, we will briefly elaborate on the standard of care for both primary and recurrent glioblastoma. We will describe the recent advances in the surgical management of glioblastoma patients and the current challenges neurosurgeons are facing. We will discuss both grade 4 astrocytoma and glioblastoma, according to the 2021 WHO classification (formerly known as *IDH*mt and *IDH*wt glioblastoma in the 2016 WHO classification). Various surgical techniques will be discussed as well as the use of intraoperative imaging and surgical adjuncts. At last, we will provide an overview of the studies that have recently been completed, are currently active, or are prospectively planned. Nonsurgical adjuncts for glioma resections such as LITT (laser interstitial thermal therapy), OCT (optical coherence tomography), mass spectrometry, and tumor treating fields (TTF) are outside the scope of this paper.

Contemporary Management of Glioblastoma

Glioblastomas can be divided in primary, secondary, and recurrent glioblastomas. Standard of care for primary glioblastoma consists of maximal safe resection followed by adjuvant chemoradiotherapy.[2,3] Extent of resection (EOR), expressed as the percentage of tumor resected or postoperative residual tumor volume, has shown to be a prognostic factor.[4–6] Generally, a distinction can be made between subtotal (STR) versus near-total (NTR) versus gross-total resections (GTR), but there is no consensus of standard, validated cutoff values for STR, NTR, and GTR for neither extent of resection or residual tumor volume. Other well-known prognostics include age, preoperative patient functioning (Karnofsky Performance Scale, KPS), and molecular status (MGMT and IDH).[2,10–13]

With very rare exceptions, these tumors regrow and no explicit standard-of-care exists at recurrence. Viable treatment options include, but are not restricted to: re-resection, re-irradiation, re-challenge TMZ, second-line chemotherapy (Lomustine), or experimental study treatments, dependent on the patient's clinical performance.[14]

Previous randomized controlled trials with second-line drug regimens including i.a. anti-VEGF (Bevacizumab, Cediranib),[15–17] anti-TGFβ-receptor-I (Galunisertib),[18] TKI-inhibitor (Axitinib),[19] anti-receptor tyrosine kinase (RTK) (Regorafenib),[20] anti-protein kinase C (PKC) (Enzastaurin)[21] and anti-EGFR (Depatux-M)[22] failed to show significant outcome improvements.

Brain Mapping

A substantial portion of glioblastomas is located in or near eloquent areas, which can affect the patient's neurological functioning. Eloquent brain areas include the bilateral frontal motor areas (cortical structures such as the primary motor cortex, premotor cortex, and the supplementary motor cortex, and subcortical structures such as the corticospinal tract, arcuate fasciculus, inferior fronto-occipital fasciculus, and internal capsule), the bilateral parietal somatosensory areas (postcentral gyrus), the bilateral primary visual cortex in the occipital lobes, and the speech areas of Broca and Wernicke in respectively the left frontal and temporal lobes.[23]

Resection of tumors in these areas proves to be challenging, since the exact location of eloquent areas differs between patients. Furthermore, delineaton of glioblastoma is often difficult due to their invasiveness. An accurate and reliable method to differentiate eloquent brain areas from both noneloquent areas and tumor tissue is therefore necessary. Since extent of resection is important for the patient's survival, maximizing the percentage of tumor resected (minimizing the residual tumor volume) is one of the most important goals of glioblastoma surgery. For this purpose, brain mapping is one of the most commonly used methods. Brain mapping can be performed both preoperatively (nTMS, MEG, DTI, fMRI) and intraoperatively (awake mapping or asleep mapping). Motor and somatosensory mapping can be performed both awake and asleep, while speech function (Broca's area and Wernicke's area) can only be tested while the patient is awake.

Preoperative Brain Mapping

Four modalities are mainly used for the preoperative brain mapping in glioma and glioblastoma resections: nTMS (navigated transcranial magnetic stimulation), MEG (magnetoencephalography), fMRI (functional MRI), and DTI (diffusion tract imaging).

nTMS stimulates the brain with transcranial magnetic pulses, thereby creating a cortical electrical field that leads to neuronal stimulation or inhibition. The obtained results are then paired with the neuronavigation system, in order to combine the information regarding functional areas with the raw MRI images for intraoperative assessment. Neuronal stimulation can be achieved by a single magnetic pulse, while a repetitive pulse causes inhibition of the cortical area. nTMS is most frequently used for motor mapping,[24] but retrospective evidence regarding its use for language mapping is reported as well.[25,26] To reduce TMS-noise in TMS-based language mapping, automated speech algorithms have been built for which proof of concept has been established.[27] A major factor of concern is the correlation between functional areas identified preoperatively by nTMS and the respective identification of these areas by direct electrostimulation intraoperatively. A recent meta-analysis by Jeltema *et al.* demonstrates that the average correlation between these two modalities is between 2 and 16 mm,[28] but most articles found <10 mm achievable. Moreover, they found that the validity of nTMS

for language mapping varied greatly when compared with DES: sensitivity differed between 10 and 100%, specificity from 13.3–98%, negative predictive value from 57 and 100%, and positive predictive value between 17 and 75%.[28]

The group in Munich has done extensive work on the use of nTMS in glioma surgery.[26,29–31] In a retrospective 2015 paper, they found that, in comparison with the non-nTMS group, nTMS was associated with a smaller size of the craniotomy, less residual tumor tissue, shorter length-of-stay, increased proportion of patients receiving adjuvant therapy and improved survival at 3, 6, and 9 months in glioblastoma patients. No significant difference was found for surgery-induced neurological deficits.[26] In contrast, Frey *et al* found in a prospective cohort of 250 glioma patients significant less postoperative deficits in the nTMS group than in the control group (8.5% vs. 6.1%) as well as a higher proportion of gross-total resections (59% vs. 42%).[32] In 2013, Picht *et al* prospectively compared nTMS with DES during awake craniotomy in 20 patients with language-eloquent gliomas in a collaborative study of the Berlin and the Munich groups.[33] They reported a sensitivity and negative predictive value of 100% for Broca's area for nTMS, even though its reliability and specificity in Wernicke's area proved to be rather limited. Moreover, they found that on a total of 10 glioblastoma patients, 6 patients maintained their preoperative speech functionality, 3 patients had an improvement and the aphasia of 1 patient was permanently worsened at 3 months postoperatively. For motor-eloquent gliomas, the Leuven group retrospectively developed a realistic electric field-based model of nTMS outperforming the point-cloud models in term of prediction of motor responses intraoperatively.[34]

Thus, nTMS can be used for mapping of primary motor areas during motor-eloquent glioblastoma resections. Though, due to uncertainties of nTMS and possible intraoperative confounding factors (such as brain shift), real-time intraoperative monitoring control is warranted for maximal safety. In language-eloquent gliomas, nTMS is mainly used for the preoperative surgical planning and should be mainly used as an adjunct next to conventional DES to map and resect these tumors adequately.

We searched the United States National Library of Medicine and National Institute of Health Trial Register (clinicaltrials.gov), the EU Clinical Trials Register, the Netherlands Trial Register (NTR), and the ISRCTN register for recently completed trials (between 1 January 2018 and 1 November 2020), currently active trials and planned trials evaluating the surgical management for primary or recurrent glioma. We found that the use of nTMS in motor-eloquent gliomas is currently evaluated by the Munich group in a quadruple-blinded RCT including 330 patients, comparing nTMS-guided resections with conventional resections with postoperative neurological deficits at 3 months as primary outcome (still accruing without current results, Table 1).

MEG (magnetoencephalography) is a comparatively new mapping tool, which detects magnetic fields that are elicited by neuronal electrical currents in order to delineate functional from nonfunctional brain areas. MEG identifies functional areas before the operation based on task-based activity, similar to fMRI. Zimmerman *et al* retrospectively compared MEG with fMRI for localization of functional perirolandic areas in 13 patients with gliomas, AVMs, and hemangiomas.[35] They found a solid congruency between both modalities with an average spatial distance of 10 mm. In a 2012 paper, Tarapore *et al* retrospectively compared MEG and nTMS with intraoperative DES in 24 glioma patients.[36] They reported that the average distance between the nTMS and DES motor-eloquent sites was 2.1 mm and between nTMS and MEG 4.7 mm. nTMS was deemed reliable for negative mapping: no motor sites that were identified as negative by nTMS were found positive for motor function during intraoperative DES. Of the 7 glioblastoma patients included, only 1 patient experienced a minor postoperative deficit of the right arm (MRC grade 4 paresis).

More recently, Traut *et al* reported on the use of MEG for evaluating neuroplasticity and language organization after glioma surgery.[37] They concluded that functional reorganization is present in most glioma patients postoperatively, more so in patients who had undergone resection of tumors in the language-dominant hemisphere.

One of the major drawbacks of MEG is the cost of the necessary equipment and the need for a dedicated setting with adequate expertise. Consequently, this modality is still scarcely used despite its potential in clinical practice.

DTI (diffusion tract imaging) is used for white-matter fiber tracking based on diffusion-weighted imaging (DWI) MRI sequences. Four tracts are commonly visualized by DTI: the corticospinal tract (CST), arcuate fasciculus (AF), optic radiation (OR), and inferior fronto-occipital fasciculus (IFOF). DTI is based on the anisotropy (diffusion varies with direction) of water molecules, thereby deriving the precise direction of the axons within every voxel. The white matter tracts can be derived from the magnetic gradients of all voxels combined, indicating the orientation of single fibers. FA (fractional anisotropy) is the most frequently used method to measure these gradients. When these measurements are combined with anatomical ROIs (regions-of-interest), a 3D map of the four tracts mentioned above can be incorporated in weighted MR-images to visualize the specific, individual trajectory in which the color represents the orientation of the most dominant eigenvector of that particular voxel. It, therefore, supplies information regarding displacement, disruption and infiltration of the white matter with the concurrent presence or absence of edema. Therefore, DTI is often used in glioblastoma patients as a tool for preoperative surgical planning,[38] outcome prediction,[39,40] and intraoperative decision making.[41,42]

Sensitivity and specificity of DTI in comparison with DES are >90% but it suffers from important limitations.[43] Since there is no standard protocol for DTI (e.g., selecting ROIs and fiber tracking), external generalizability, precision, and accuracy can be adversely affected. Furthermore, it is susceptible to challenges that are common to preoperatively conducted imaging such as unreliable spatial congruency due to brain shift. Last, an important inherent limitation of DTI is commonly described as the "crossing fiber problem", for which DTI has a very limited visualization accuracy. Advanced DTI techniques such as HARDI q-ball imaging have been tested. Although they are effective in identifying language tracts preoperatively and in predicting functional outcome postoperatively, they generally suffer from the same limitations as standard DTI.[44] New techniques such as CSD (constrained spherical

Table 1. Current Prospective Surgical Studies in Glioma Patients

Study	Register	Design	Population	Intervention	Control	Primary outcome	Initiating center	Status	Timespan
General									
RESURGE: Randomized Controlled Comparative Phase II Trial on Surgery for Glioblastoma Recurrence	NCT02394626	Randomized controlled trial, open label, parallel, 120 patients	Recurrent GBM	Resection followed by adjuvant second-line therapy	Adjuvant second-line therapy	Overall survival	Inselspital Bern (SUI)	Active, recruiting	1 May 2015–1 Oct 2021
Supramarginal Resection in Patients With Glioblastoma: A Randomized Controlled Trial	NCT04243005	Randomized controlled trial, double-blinded, parallel, 90 patients	GBM	Supramarginal resection with >10mm margin on T2 MRI	Conventional resection	Overall survival	St. Olav's University Hospital Trondheim (NOR)	Active, recruiting	1 Jul 2020–1 Mar 2027
Assessing Impact of Surgically-induced Deficits on Patient Functioning and Quality of Life (SIND Study)	NCT04007185	Prospective cohort study, 150 patients	High-grade glioma	Maximum safe resection	Biopsy	Impact of new deficit on quality of life (EORTC QLQ-30 and BN20)	Cambridge University Hospitals NHS Foundation Trust (UK)	Not yet recruiting	1 Feb 2020–1 Dec 2024 (Estimated)
Intraoperative mapping									
The SAFE-trial: Safe Surgery for Glioblastoma Multiforme: Awake Craniotomy versus Surgery Under General Anesthesia. A Multicenter Prospective Randomized Study	NCT03861299	Randomized controlled trial, open label, parallel, 246 patients	Primary, eloquent GBM	Awake craniotomy	Resection under general anesthesia	Proportion of gross-total resections, postoperative neurological morbidity	Erasmus MC Rotterdam (NL)	Active, recruiting	1 Apr 2019–1 Apr 2024
Awake vs. Asleep Craniotomy for Noneloquent Gliomas	NCT03621748	Randomized controlled trial, single-blinded, parallel, 50 patients	Primary, noneloquent glioma	Awake craniotomy	Resection under general anesthesia	Extent of resection	Mayo Clinic Jacksonville (FL, USA)	Active, recruiting	1 Jun 2020–1 Dec 2022
The PROGRAM-study: Awake mapping versus asleep mapping versus no mapping for glioblastoma resections	NCT04708171	Prospective cohort study, open label, parallel, 453 patients	High-grade glioma	Awake or asleep mapping	Conventional resection	Extent of resection, postoperartive neurological morbidity	Erasmus MC Rotterdam (NL)	Active, recruiting	1 April 2022-1 April 2027 (Estimated)
Preoperative mapping									
The Application of ZOOMit-fMRI to Identify Motor Functional Cortex	NCT03091270	Prospective case-crossover study, 60 patients	Motor-eloquent gliomas	ZOOMit-fMRI-guided resection	BOLD-fMRI-guided resection	Accuracy of motor cortex localization	Beijing Neurosurgical Institute (CHN)	Active, recruiting	1 Feb 2016–1 Jan 2025
nTMS for Motor Mapping of Rolandic Lesions	NCT02879682	Randomized controlled trial, quadruple-blinded, parallel, 330 patients	Motor-eloquent gliomas	nTMS-guided resection	Conventional resection	Postoperative neurological deficits at 3 months	Technical University Munich (GER)	Active, recruiting	1 Aug 2016–1 Feb 2022

Table 1. Continued

Study	Register	Design	Population	Intervention	Control	Primary outcome	Initiating center	Status	Timespan
Safety and Feasibility of Preoperative and Intraoperative Image-Guided Resection of Gliomas	NCT03542409	Nonrandomized clinical trial, open label, parallel, 40 patients	Primary glioma	Preoperative and intraoperative 2HG spectroscopy	Preoperative and intraoperative MR perfusion	Intraoperative imaging completion, postoperative complications	University of Utah (UT, USA)	Active, recruiting	6 Feb 2017–6 Feb 2023
Predicting Sites of Tumour Progression in the Invasive Margin of Glioblastomas (PRaM-GBM Study)	NCT03294434	Prospective cohort study, 120 patients	High-grade glioma	Resection with DTI	NA	Site of GBM true progression correctly predicted by DTI	Cambridge University Hospitals NHS Foundation Trust (UK)	Active, recruiting	2 Mar 2017–30 Sep 2021
Resting-State Functional MRI in Glioma Patients Before and After Surgery	NCT03964909	Single-arm clinical trial, open label, 30 patients	Speech-eloquent primary glioma	fMRI, CVR MRI or rs-fMRI	NA	Detectability of language networks	M.D. Anderson Cancer Center (TX, USA)	Active, recruiting	24 Apr 2017–12 May 2022
Intraoperative fluorescence and imaging									
5-Aminolevulinic Acid (5-ALA) to Enhance Visualization of Malignant Tumor	NCT02632370	Prospective cohort study, 69 patients	Primary or recurrent glioma	5-ALA guided resection	NA	Incidence of diagnostic tissue presence	Mount Sinai (NY, USA)	Completed	1 May 2016–31 Dec 2018
Intraoperative Ultrasound guided Glioma Surgery: a Randomized, Controlled Trial (US-GLIOMA)	NCT03531333	Randomized controlled trial, single-blinded, parallel, 50 patients	Primary high-grade glioma	Resection with intraoperative ultrasound	Resection without intraoperative ultrasound	Proportion of patients with gross-total resection	Erasmus MC Rotterdam (NL)	Completed	1 Nov 2016–1 Aug-2020
Interest of Fluorescein in Fluorescence-guided Resection of Gliomas (FLEGME study).	NCT03291977	Randomized controlled trial, open label, parallel, 62 patients	GBM	Resection with fluorescein	Conventional resection	Proportion of gross-total resections	Rennes University Hospital (FRA)	Active, recruiting	5 Oct 2017–1 Oct 2021
Quantification of ALA-induced PpIX Fluorescence During Brain Tumors Resection	NCT02191488	Single-arm nonrandomized clinical trial, open label, 540 patients	Primary or recurrent glioma	5-ALA guided resection	NA	Intraoperative PpIX measurements vs coregistered histopathology	Dartmouth-Hitchcock Medical Center (NH, USA)	Active, not recruiting	1 Jul 2014–1 Jul 2021 (Estimated)
Diagnostic Performance of Fluorescein as an Intraoperative Brain Tumor Biomarker	NCT02691923	Randomized controlled trial, open label, parallel, 30 patients	Primary glioma	Fluorescein+5-ALA guided resection	Fluorescein-guided resection	Fluorescein performance	Dartmouth-Hitchcock Medical Center (NH, USA)	Active, not recruiting	1 Mar 2016–1 Dec 2021 (Estimated)
Improving Fluorescence-guided Brain Tumour Surgery With Ultra-high Sensitivity Imaging	NCT04556929	Single-arm clinical trial, open label, 20 patients	Primary glioma	5-ALA guided resection, biopsies from resection cavity	NA	Level of tumor fluorescence in images of resection cavity captured during surgery	Oxford University Hospitals NHS Foundation Trust (UK)	Not yet recruiting	1 Oct 2020–1 Aug 2022 (Estimated)

Table 1. Continued

Study	Register	Design	Population	Intervention	Control	Primary outcome	Initiating center	Status	Timespan
Stereotactical Photodynamic Therapy With 5-aminolevulinic Acid (Gliolan) in Recurrent Glioblastoma	NCT04469699	Randomized controlled trial, open label, parallel, 106 patients	Recurrent GBM	Biopsy followed by photodynamic therapy (PDT) with 5-ALA	Biopsy	Progression-free survival	University Hospital Münster (GER)	Not yet recruiting	1 Nov 2020–1 Nov 2025 (Estimated)
Impact of iMRI on the Extent of Resection in Patients with Newly Diagnosed Glioblastomas	NCT02379572	Nonrandomized clinical trial, single-blinded, parallel, 315 patients	Primary GBM	Resection with iMRI guidance	Resection with 5-ALA guidance	Proportion of gross-total resections	University Hospital Tübingen (GER)	Active, recruiting	1 Jun 2015–1 Jun 2021
FUTURE-GB study: Functional and ultrasound-guided resection of glioblastoma	ISRCTN38834571	Randomized controlled trial, open label, parallel, 357 patients	Primary GBM	5-ALA, DTI, and US guided resection	5-ALA guided resection	Quality of life, overall survival, progression-free survival	Oxford University Hospitals NHS Foundation Trust (UK)	Active, recruiting	1 Apr 2020–30 Nov 2025
3.0T High-field Intraoperative MRI Guided Extent of Resection in Cerebral Glioma Surgery: a Single Center Prospective Randomized Triple-blind Controlled Clinical Trial	NCT01479686	Randomized controlled trial, triple-blinded, parallel, 321 patients	Primary glioma	3.0T iMRI-guided resection	Conventional neuronavigation-guided resection	Extent of resection	Fudan University Shanghai (CHN)	Active, not recruiting	1 Sept 2011–1 July 2021 (Estimated)

deconvolution), DKI (diffusional kurtosis imaging), and DSI (diffusion spectrum imaging) show promising results and are potentially more adept at improving reproducibility and intraoperative accuracy.[45–47]

Two British studies are currently investigating the use of DTI in glioma patients in the PRaM-GBM study (Cambridge) and the FUTURE-GBM study (Oxford) (Table 1).

fMRI (functional MRI) identifies eloquent areas based on task paradigms and consequently increased levels of blood oxygen in the respective functional areas as a surrogate for increased neuronal activity. BOLD (blood oxygen level-dependent) MRI sequences are used as contrast images. The correlation between fMRI-identified eloquent areas is high with Wada testing but not always with direct electrostimulation, with considerable variances being found in different retrospective and review studies.[48,49] Moreover, fMRI has been shown to suffer from suboptimal specificity caused by neurovascular uncoupling. This can occur due to disruption of regular white matter perfusion as caused by intraparenchymal tumors.[50–52] fMRI-based detection of eloquent areas can therefore only be used as a surgical adjunct and remains heavily reliable on confirmation by intraoperative methods. As of now, the Beijing Neurosurgical Institute and the M.D. Anderson Cancer Center are prospectively evaluating the use of fMRI in glioma patients (Table 1).

Intraoperative Brain Mapping: Awake and Asleep

Motor mapping can be performed when the patient is awake (awake craniotomy under local anesthesia) or asleep (general anesthesia). Cortical stimulation of the motor areas can be performed with two methods: direct electrostimulation (DES) with a handheld probe or the usage of a subdural grid with strip (grid) electrodes (adjacent to the central sulcus).[53,54] DES in its turn can be performed with the low-frequency technique, in which a stimulator with a 50-Hz (Europe) or 60-Hz (USA, Canada) frequency is used for functional localization, or with the high-frequency technique (train-of-five stimulation).[53,55] Both the low-frequency technique and the high-frequency technique can be carried out safely with a monopolar or bipolar stimulation device. The stimulation intensity of the device ranges between 1 and 20 mA with increasing steps of 0.5–1.0 mA. Subcortical motor mapping can be achieved by DES with a handheld probe with similar or slightly adjusted stimulation settings. Gogos *et al* recently reported on their prospective study evaluating "triple motor mapping" (transcranial, bipolar, and monopolar), in which they found that monopolar high-frequency stimulation was more effective at identification of subcortical motor pathways (86.4% of cases) than bipolar stimulation (10.2% of cases).[56]

The identification of motor-eloquent areas under awake circumstances differs from mapping when the patient is asleep. During awake mapping, motor function is assessed by the involuntary movement (positive response) or impaired motor function (negative response) of muscles in the face, arm, or leg. In contrast, during asleep mapping, MEPs (motor-evoked potentials) are used to assess the integrity of cortical motor structures and its descending subcortical tracts.[57] Evoked potentials are recorded with the use of EMG needle electrodes in the contralateral extremity. Generally, reduction of the amplitude of the evoked potentials of more than 50% or the necessity to increase the stimulation current significantly represent clinically significant changes. Amplitude reductions can be reversible, which generally are a sign of temporary motor deficits, and irreversible, rather suggesting new motor deficits.[58,59]

Speech mapping can be performed only when the patient is awake. Cortical stimulation near speech areas is performed most commonly with the use of a bipolar stimulator with the electrodes 0.5 cm apart. The surgeon usually starts with a low stimulus between 1.0 and 2.0 mA and maps the cortex for 2 seconds every 0.5–1.0 cm. Positive or negative stimulation sites are noted and eloquent areas are avoided. Frequently used tests for language function include the Boston naming test, Token test, semantic associations, counting, verb generation, and word fluency.[59] The surgeon maps the surface various times with increasing currents. Subcortical stimulation of language-associated fibers can be performed similarly (Figure 1).[53,59]

One of the most promising new awake mapping techniques includes functional ultrasound (fUS). fUS uses Doppler ultrasound images to detect changes in brain tissue perfusion while the patient carries out certain motor or linguistic tasks, allowing the surgeon to identify eloquent areas based on a vascular, rather than a mechanical basis. Advantages of fUS include its high spatiotemporal resolution, wide field of view, high depth penetration, and its low-cost of implementation. Imbault *et al* described this technique in 2017 as a proof-of-principle, using fUS to successfully identify eloquent areas in all 28 low-grade glioma patients.[60] In 2020, the Rotterdam group published their experience with using fUS during awake surgery in 10 low-grade and high-grade glioma patients. They demonstrated with this prospective study that fUS can be used to map both motor and language function accurately.[61]

New developments in asleep mapping techniques led to the progression towards continuous monitoring of the motor structures' integrity with a technique called continuous dynamic mapping (CDM). This technique utilizes a monopolar probe at the tip of the suction device and has been pioneered by the team from Bern. Thanks to the known current-distance relationship of monopolar stimulation, the surgeon can resect tumor tissue close to motor pathways with stepwise decreasing stimulation intensity while continuously being guided by the different sounds of the device (indicating the distance to the motor fibers).[62] Subcortical mapping is performed using a monopolar with the train-of-five technique with a 0.5 ms pulse duration, an interval of 4 ms, and an intensity ranging from 1 to 20 mA. Recently, they published their update on the CDM technique in 182 patients with intra-axial tumors within 1 cm of the CST.[63] Six of those patients (3%) had a permanent motor decrease of 0.5 points or more on the MRC scale: half of them were due to ischemic injury, half of them were due to mechanic injury (1.7%).[63] CDM can therefore be deemed as a very safe, feasible, and intuitive alternative for conventional asleep mapping methods in order to prevent neurological deficits after motor-eloquent glioma surgery.

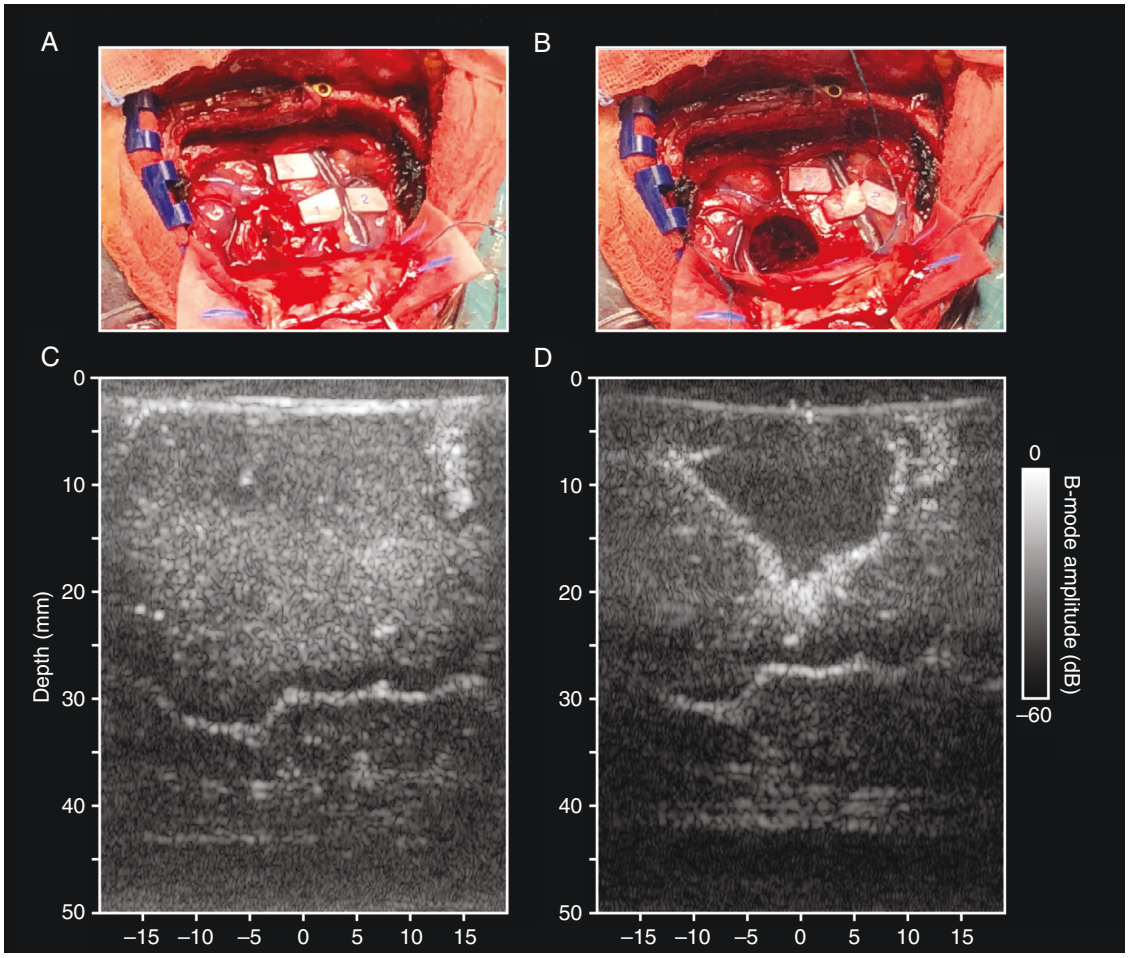

Figure 1. Intraoperative ultrasound. A: Intraoperative image of a glioma in the right parietal lobe. B: Intraoperative image of the cavity after tumor resection. C: Pre-resection B-mode image of the tumor and surrounding tissue. D: Post-resection B-mode ultrasound image of the resection cavity.

The benefit of brain mapping in glioma surgery has been demonstrated by various groups. Sanai *et al* published in 2008 a large well-known study investigating 245 patients undergoing awake craniotomy (AC) for speech-eloquent gliomas.[53] They found that the use of AC permits the surgeon to maximize extent of resection while minimizing language deficits: the incidence of permanent language deficits after 6 months was 1.6% with a mean extent of resection of 69.0% among glioblastoma patients. In 2011, Sacko *et al* prospectively compared awake craniotomy with surgery under general anesthesia for resections of supratentorial lesions in a prospective setting.[64] They included 575 patients with gliomas, metastases, cavernous malformations, and meningiomas, and found that patients who had undergone awake craniotomy had better postoperative neurological outcomes and increased extent of resection rates. They observed permanent postoperative neurological deficits in 4.6% of patients operated with awake craniotomy and in 16% of patients operated under general anesthesia. De Witt Hamer *et al* published their landmark paper in 2012, evaluating the impact of intraoperative stimulation mapping (ISM) in a meta-analysis including 90 papers covering a total of 8,091 patients.[65] They found that resections with mapping led to fewer late severe neurologic deficits (3.4% vs. 8.2%) and were simultaneously more extensive (GTR in 75% vs 58%). These results were in line with the meta-analysis of Gerritsen *et al* published in 2018 which evaluated the impact of mapping techniques in high-grade glioma specifically.[66] They found that ISM-led resections were associated with improved overall survival (16.9 months in the ISM group vs. 12.0 months in the GA group), less postoperative complications (13% vs. 21%), and a higher incidence of GTR (79% vs 48%).

Awake mapping has several limitations. First, reliable mapping information often can be obtained only when patients have near-intact or intact function of language or motor-based tasks. Function impairments can hamper the reliability of the procedure which can harm the accuracy and precision of the mapping. Second, awake craniotomies are known to have the potential to cause after-discharges (ADs—stimulation-induced epileptic discharges) and stimulation-evoked seizures.[67] ADs can be recorded with EEG or ECoG

and are electro-encephalographic alterations after electrostimulation that are similar to seizures or can progress into them.[68] Intraoperative seizures can be managed by applying ice-cold saline to the exposed brain surface, administration of anti-epileptic drugs (AEDs), benzodiazepines, propofol, or even by terminating the mapping procedure and continuing the resection under general anesthesia.[69,70] However, intraoperative stimulation-evoked seizures tend to not occur if the current is low (i.e., 2–2.5 mA). Third, extreme obesity could interfere with a safe airway surveillance and is, therefore, an important anesthesiological contraindication for awake craniotomies. Last, false positive findings during intraoperative stimulation can occur due to mental fatigue of patients during long procedures which may challenge the interpretation of the patient's performance and the identification of eloquent areas, consequently.

There is no general consensus regarding mapping techniques and procedures. A 2014 survey evaluating stimulation mapping techniques in epilepsy surgery found a wide range of local paradigms.[71] Though, the inconsistencies between centers and countries in glioma mapping are virtually unknown at this moment. For example, the choice between awake mapping and asleep mapping is largely based on the surgeon's expertise, as is the preference for DES versus subdural grid electrodes, bipolar versus monopolar probe, the current's range and increasing steps, the assessment of motor and speech function during awake craniotomy (neurophysiologist/neuro-linguist vs. trained assessor vs. patient himself/herself), the use of ECoG or intraoperative EEG to detect epileptic activity intraoperatively, the use of additional surgical adjuncts during mapping procedures such as 5-ALA, DTI, ioMRI, and ultrasound; and the anesthesia technique during awake craniotomy (awake-awake-awake versus asleep-awake-asleep or asleep-awake-awake) for example. Moreover, one of the most challenging parts of mapping techniques during glioma surgery is the decision-making process, i.e., on which information the decision to alter the surgical strategy or to end the resection is based. For many surgeons, this decision frequently is based on the combination of multiple concurrent information sources: the patient's task performance (during awake craniotomy), the evoked potentials' amplitude (during asleep mapping), the imaging (neuronavigation with or without DTI), and the macroscopy (expertise and fluorescence). To gain understanding in the local techniques and procedures that are used for glioma resections in different centers and countries, the ENCRAM Consortium has carried out two international surveys evaluating this inter-center variability in mapping procedures and decision making.[72,73] Together with large, well-designed prospective studies, the results from this survey may be the first step towards reaching a general consensus regarding the use of these techniques in glioblastoma patients.

Currently, three prospective clinical studies are currently evaluating the use of intraoperative mapping techniques in glioma patients: two randomized controlled trials (RCT): a large one in the Netherlands and Belgium (SAFE trial, 246 patients) and a smaller one at the Mayo clinic (50 patients); and one prospective cohort study from the transatlantic ENCRAM Consortium (PROGRAM study) (Table 1).[74]

Intraoperative Fluorescence and Imaging

Three main tools are used during surgery to increase the extent of resection and minimize residual tumor volume: fluorescence (including 5- aminolevulinic acid (5-ALA) and fluorescein), ultrasound, and intraoperative MRI (ioMRI).

The use of 5-ALA (Gliolan®), a precursor of hemoglobin, results in the accumulation of fluorescent porphyrin IX in cells lacking ferrochelatase (e.g. glioblastoma cells) and is therefore used to visualize tumor cells *in vivo* with the use of an adjusted neurosurgical microscope. Another fluorescence agent, (sodium) fluoresceine, designed to be an intravascular fluorophore, passes the (dysfunctional) blood-brain barrier in glioma patients, as opposed to the intratumoral synthesis of 5-ALA.

Fluorescence is mainly used to increase extent of resection in glioma surgery. However, the ultimate goal is maximizing EOR while minimizing postoperative deficits. Stummer *et al,* found that GTR was confirmed in 65% of the patients in the 5-ALA group which was a significantly higher proportion than in the white light group (36%).[75] Moreover, the 5-ALA group had a higher progression-free survival at 6 months postoperatively (41% vs. 21%). Although their study was not powered for overall survival, they found that the 5-ALA group had a nonsignificant shorter OS than the white-light group (13.5 months vs. 15.2 months, $P = .1$). Notably, in 2011 a supplemental analysis was published which showed that patients in the 5-ALA group had more early postoperative neurological deficits.[76] Forty-eight hours after surgery, the proportion of patients with NIHSS (National Institute of Health Stroke Scale) deterioration of 1 point of more in the 5-ALA group was 26.2% versus 14.5% of patients in the white light group. After 6 weeks, this was decreased to 17.1% in the 5-ALA group and 11.3% in the white light group ($P = .29$) and 3 months postoperatively, the difference was negligible between groups (19.6% in the 5-ALA group and 18.6% in the white light group, $P = .77$). KPS deterioration did not differ significantly between groups during follow-up. They concluded that a postoperative transient deficit weighs up against the long-term benefits of using 5-ALA (longer PFS, higher chance of GTR).[75,76] Since then, various studies have demonstrated the benefit of 5-ALA among different subgroups of brain tumor patients.[77–79] However, the differentiation between tumorous and healthy tissue in the marginal area of the tumor remains a common challenge during 5-ALA guided resections.[80] Since the levels of fluorescence are much lower in this area, the delineation between different tissues is obscured which makes 5-ALA guided resections somewhat subjective to the surgeon's expertise. Objective quantification remains therefore moderately limited. Another major limitation of 5-ALA is the lack of guidance in the resection of the noncontrast-enhancing part of the tumor, which has recently been shown to be of utmost importance in glioma surgery. Molinaro *et al* from the UCSF group demonstrated in a large retrospective cohort of 761 patients that maximum resection of the noncontrast-enhancing part of the tumor leads to increased overall survival, regardless of their IDH status.[8]

A recent study by Hansen *et al* retrospectively compared the use of 5-ALA with fluorescein during high-grade glioma resections,[81] which showed no difference regarding mean extent of resection (96.9% in the 5-ALA group, 97.4% in the fluorescein group), the proportion of patients with GTR (defined as residual tumor volume of <0.175m^3; 29.5% in the 5-ALA group and 36.2% in the fluorescein group), median overall survival (14.8 months in the 5-ALA group and 19.7 months in the fluorescein group) or median progression-free survival (8.7 months in the 5-ALA group and 9.2 months in the fluorescein group).

Two prospective studies have investigated the use of yellow fluorescein in high-grade glioma patients. Falco *et al* reported on their preliminary results of the FLUOCERTUM study, in which they found a 74.2% rate of GTR in their high-grade glioma subgroup of 128 patients.[82] Acerbi *et al* found in their FLUOGLIO study that GTR was achieved in 82.6% of their HGG patients (n = 57).[83] Moreover, 6-month PFS was 56.6%, 12 month PFS was 15.2% and median overall survival was 12 months.

Recently, Schipmann *et al* reported on the combined use of 5-ALA and photodynamic therapy (PDT) in a prospective cohort study in recurrent high-grade glioma patients.[84] The accumulated porphyrins caused by 5-ALA are both fluorescence agents and photosensitizers, which in combination with PDT leads to cellular damage by reactive oxygen species (ROS). They included 20 patients in their series in which they achieved GTR in 45% of patients, median PFS of 6 months (95% CI 4.8–7.2), and no adverse events, deeming this novel application of 5-ALA a safe and promising tool for recurrent glioma surgery. Therefore, the team from Münster (Germany) has planned a randomized controlled trial including 106 patients in which biopsy will be compared with biopsy + PDT with 5-ALA for recurrent glioblastoma patients with PFS as primary outcome (Table 1).

Intraoperative ultrasound (ioUS) is the use of sonography to locate tumor tissue during surgery and to delineate it from healthy brain tissue (Figure 2). Similar to 5-ALA, ioUS is one of the tools to potentially increase the extent of resection. However, ioUS is able to identify both low-grade and high-grade glioma (as opposed to 5-ALA, which can only identify high-grade glioma). Theoretically, 5-ALA and ioUS can be considered complementary techniques since the former visualizes tumor tissue macroscopically and the latter is able to detect nodular remnants that might get hidden behind collapsing cavity walls after large tumor resections. One of the main advantages of ioUS over preoperative imaging modalities is the possibility to visualize the tumor in real-time (with taking into account brain shift), which is especially useful for subcortical lesions. Moreover, its corresponding costs (and duration to acquire images) are much lower than other intraoperative imaging methods, such as intraoperative MRI (ioMRI; the cost of which is a well-known limitation), with a significantly lower spatial resolution than ioMRI as a consequence.

There is an increasing amount of research interest in using ioUS in glioma surgery, in particular retrospective evidence in low-grade glioma patients. In 2015, Petridis *et al* evaluated the use of ioUS in low-grade glioma surgery.[85] They found that it was well-suited for identification of tumor tissue and major blood vessels. Gerganov *et al* compared ioUS with ioMRI for resections of low-grade gliomas and concluded that both modalities are well-suited to locate the tumor and its borders before resection starts.[86] However, based on their results the quality of ioMRI proves to be superior to ioUS during the resection, and is better suited to detect residual tumor, particularly because the difference in spatial resolution and the subsequent interpretation of the images. ioUS proved to be prone to problems in differentiating artifacts such as blood clots and fluids from true residual tumor tissue, which has been reported before.[87] Though, other studies found ioUS to be accurate in identifying tumor tissue after glioma resection and assessing extent of resection.[88,89] Coburger *et al* suggested a comparable sensitivity and specificity of ioMRI to ioUS, deeming ioUS ideal for centers lacking a ioMRI.[90] Trevisi *et al* recently published a large meta-analysis regarding the use of ioUS in glioma patients including 13 studies.[91] They demonstrated that the pooled sensitivity of ioUS in detecting residual tumor tissue was 72.2% and the specificity was 93.5%. Detection was complicated by artifacts, small volume of residual tumor (<5 ml), and previous radiotherapy.[89]

Scientific evidence for the use of ioUS in high-grade glioma is rarer. Incekara *et al* published the results of their single-center randomized controlled trial in 2021.[92] They included 50 glioblastoma patients and randomized them with a 1:1 ratio between resection with or without the use of ioUS. They found that gross-total resection was achieved more often in the ioUS group (8 of 23 vs. 2 of 24, P = .036) without increased rates of postoperative neurological deficits. Furthermore, there is evidence that ioUS can be used to detect residual tumor and therefore could increase extent of resection in high-grade glioma, equal to ioMRI.[93] This is supported by the study of Solheim *et al,* in which they used ioUS in a series of 156 high-grade glioma patients. They found that medium or good ultrasound image quality was independently associated with a higher incidence of gross-total resection.[94]

Wang *et al* prospectively compared 137 patients undergoing glioma resection with the help of ioUS with a control group of 60 patients.[95] They found that the 1-year and 2-year survival in for both low-grade and high-grade glioma patients was longer in the ioUS group than in the control group. Recently, Liang *et al* and Prada *et al* have reported on their use of contrast-enhanced ultrasound (CEUS) in high-grade glioma patients with improved differentiation between artifacts and residual tumor tissue.[96–98] Colleagues from Norway are working on improving the spatial resolution of ioUS by developing a new fluid (as compared to the conventional Ringer's lactate) to decrease image noise.[99] Another development is the integration of ioUS with neuronavigation (navigated intraoperative ultrasound; nUS) with subsequent 3D image acquisition (n3DUS).[100] nUS has been shown to be able to detect residual tumor volume more reliably than conventional ultrasound.[101]

The use of ioUS in glioma surgery is promising but is currently subject to contradictory results, since studies are mostly retrospective, small and heterogenous in study population. Currently, two prospective studies are evaluating its use for this patient group: the US-GLIOMA trial (results are expected soon) and the FUTURE-GBM study (recently started) (Table 1).

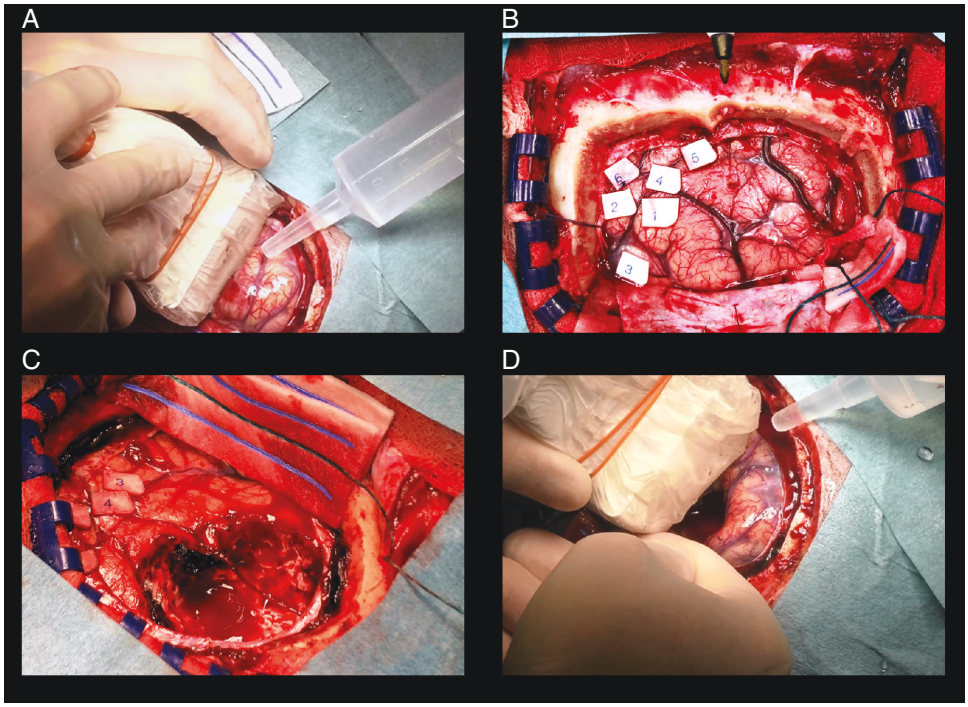

Figure 2. Electrocortical stimulation with intraoperative ultrasound. A: Intraoperative ultrasound before starting tumor removal. B: Electrocortical stimulation mapping using awake craniotomy to determine eloquent brain areas. C: Tumor resection based on mapping procedure, aided by the neuro-linguist. D: Intraoperative ultrasound after tumor resection to identify potential residual tumor.

ioMRI is used to assess tumor extent of resection intraoperatively with the highest spatial resolution currently possible. Senft *et al* published their RCT evaluating the use of ioMRI in glioma surgery in 2011, including 58 patients.[102] They found that tumor resections in the ioMRI arm proved more often GTR than in the control group (96% versus 68%) with no difference in postoperative neurological complications. Furthermore, no patients in the ioMRI with GTR experienced postoperative neurological deterioration. Whiting *et al* reported on their retrospective series regarding the combined use of minimal access craniotomy with ioMRI and awake mapping in grade I–IV gliomas.[103] They found a median EOR of 98.5%, with GTR being achieved in 60.7% of LGG cases and in 30.3% of HGG cases. More than twenty-seven percent of the total group achieved an increase in EOR of more than 15% due to the use of ioMRI. A recent paper by Pichierri *et al* retrospectively compared the combined use of ioMRI and awake mapping with ioMRI in asleep patients and a (third) control group.[104] They found that the addition of ioMRI led to increased GTR rates among resections of all glioma grades, but there were no significant differences in EOR, tumor recurrences, or overall survival between the awake ioMRI and asleep ioMRI group, although the three groups were biased for patient selection.

Recent evidence suggests that ioMRI might play a major role in enabling supratotal resection (i.e. resection of the tumor beyond the contrast-enhancing (CE) part into the surrounding noncontrast-enhancing (NCE) part, but with radiological abnormalities on T2/FLAIR images). Two retrospective studies evaluated the association between ioMRI and supratotal resection. Li *et al* demonstrated that resection 53% of the NCE part led to additional survival benefit,[105] whereas Pessina *et al* found that 45% would already lead to a significant improvement in survival outcomes.[106] Furthermore, Eyüpoglu *et al* showed in a prospective cohort series that the addition of ioMRI to resections with 5-ALA increased the NCE extent of resection, which was directly correlated to overall survival.[107]

Major limitations of ioMRI are its high costs of installation and maintenance and the increased duration of the operation. Moreover, the use of ioMRI during eloquent gliomas is ideally combined with intraoperative mapping such as awake craniotomy or asleep mapping to test for tissue functionality and preserve speech and motor tracts.

Prospective evidence is needed to provide Level I evidence for the use of ioMRI. Currently, two prospective studies are conducted at the University Hospital Tübingen (Germany) and University Hospital Fudan (China) (Still accruing without current results, Table 1).

Intraoperative Tissue Sampling

Currently there are a few emerging techniques for intraoperative tissue sampling as an alternative to fluorescence. Vibrational spectroscopy is one of the most notable new techniques, with Raman spectroscopy (RS,

based on inelastic scattering of photons) and Fourier-Transform Infrared spectroscopy (FTIS, based on the interaction of infrared radiation with tissue) as the two main modalities. RS and FTIS provide in a noninvasive manner real-time information about the molecular buildup of specific tissues. Consequently, they can potentially be used intraoperatively to assist the surgeon in distinguishing healthy brain parenchyma from tumor tissue. Recent evidence indeed suggests that spectroscopy can be used (1) to delineate the tumor margin, (2) to discern between specific histological tumor areas (e.g. tumor core, necrosis, infiltrative zone), (3) to evaluate the molecular tumor buildup (e.g. *IDH* status), and (4) to identify molecular tumor heterogeneity on both fresh tissue, frozen tissue, and formalin-fixed paraffin-embedded (FFPE) brain tissue samples.[108–111] However, the use of these techniques is still in its experimental phase: studies focusing on *in vivo* validation, the interplay with intraoperative fluorescence and imaging, and the added benefit when employed simultaneously with intraoperative mapping techniques are awaited.

Supratotal Resection

Recently there has been growing interest in evaluating the benefit of "supratotal resection" (also called "supramarginal" or "supramaximal" resection, abbreviated: SpTR). The term "supratotal" applies to the extent of resection of the tumor outside the borders of the contrast-enhancing part of the tumor (as evaluated on T1 + Gd images), i.e., the noncontrast-enhancing part (as evaluated on T2/FLAIR images). It can therefore be defined as GTR plus resection of some noncontrast-enhancement, as concluded by a recent crowdsourced consensus.[112] 2019, colleagues De Leeuw and Vogelbaum evaluated the use of supratotal resection in glioma in a systematic review.[113] They concluded that the available evidence was insufficient for "carte blanche" application and stressed the importance of validation in prospective cohort studies. In 2020, Molinaro *et al* published their well-known multicenter, retrospective cohort study, including 716 patients from UCSF, the Mayo Clinic, and the Cleveland Clinic.[8] They found a significant association between supratotal resection and longer overall survival in younger patients, regardless of *IDH* status, as well as in patients with *IDH*wt tumors regardless of MGMT status. Therefore, they proposed that in younger patients (<65 years old), maximal resection of the contrast-enhancing part should be pursued; and when safely feasible, the noncontrast-enhancing part as well (regardless of molecular status). Based on their dataset, maximal resection of the noncontrast-enhancing part was not recommended for patients aged >65 years. A smaller retrospective study by Hirono *et al,* which included 30 glioblastoma patients, also found that supratotal resection led to improved survival outcomes and was not associated with increased postoperative neurological deficits.[114] The results of these retrospective studies will be validated in the ENCRAM Consortium's prospective PROGRAM study.[74]

Conclusions and Future Directions

Glioma surgery means balancing between maximizing extent of resection and preventing postoperative neurological complications. Various surgical techniques and adjuncts can be used, either to detect (residual) tumor tissue and to increase EOR (decrease residual volume), or to identify eloquent brain areas to preserve functionality. In recent years, a sizable amount of progress has been made for both goals by numerous scientific efforts. Neurosurgeons can choose from a wide array of possibilities their preoperative and intraoperative modality of choice. Different modalities can be used for the same goal, often with comparable outcomes or without strong, prospective evidence for one modality in particular. For some of these modalities and patient subgroups, the clinical impact is not always based on high-level evidence. Therefore, sizable prospective studies such as RCTs or multicenter cohort studies are needed to compare various modalities in a multimodal setting to determine which modality is best suited for which patient (grade, location, etc.). We gave an overview of current evidence for different surgical modalities and adjuncts for glioma surgery. Furthermore, we elaborated on the current prospective scientific efforts which will define the neurosurgical practice and decision making in the near future.

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