TOPIC REVIEW

Technical principles in glioma surgery and preoperative considerations

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Abstract The goal of glioma surgery is maximal safe resection. These intrinsic brain neoplasms, however, lack a clear margin and frequently infiltrate eloquent areas of the brain thus making their surgical resection challenging. This review first focuses on discussion of preoperative investigations that aid in anatomical and functional tumor characterization that help define tumor extent and determine the feasibility of complete resection. The second part of this review outlines intraoperative adjuncts that help identify tumor infiltrated tissues during surgery to maximize the extent of resection. In addition, we discuss the principles of intraoperative functional cortical and subcortical mapping and monitoring that enable maximal tumor resection while minimizing the risk of postoperative neurological deficit. Combined use of different modalities before and during surgery is encouraged to meet surgical goals and to ensure best patient outcome.

Keywords Glioma surgery · Eloquent · Cortical mapping · Monitoring · Direct electrical stimulation · Awake craniotomy

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Introduction

Gliomas constitute a group of intrinsic brain neoplasms for which no curative therapies currently exist. Cytoreductive surgery remains the cornerstone of glioma treatment, and while surgical resection alone is not sufficient to halt tumor progression, the importance of maximizing the extent of resection (EOR) has been increasingly recognized for lowgrade, as well as high-grade gliomas $[1-5]$ $[1-5]$. Preservation of neurological function postoperatively, however, is equally as important, as it influences patient survival [[6](#page-7-2)]. Many tools are available at neurosurgeons disposal today that help maximize the EOR. Addition of only one modality such as diffusion tensor imaging (DTI) of corticospinal tracts preoperatively, or intraoperative direct cortical stimulation (DCS) and mapping can improve the rates of complete resection by 30–40% while preserving neurological function [\[7](#page-7-3), [8](#page-7-4)]. This review focuses on outlining commonly used techniques in neurosurgery to help identify eloquent cortical areas and subcortical pathways to achieve maximal safe tumor resection.

Preoprerative investigations

A great deal of information on tumor location and its relationship to the functional cortical and subcortical areas can be gained before patient's surgery. This information can be used to determine the most optimal surgical strategy, predict feasibility of complete resection, and identify additional tools required intraoperatively to maximize tumor resection (Tables [1](#page-1-0), [2\)](#page-1-1).

Advanced brain imaging

Contrast-enhanced magnetic resonance imaging (MRI) is the gold standard initial study for brain tumor anatomic

fMRI Cortical areas involved in motor

MEG Cortical areas involved in motor

nTMS Stimulation based non-invasive

DTI Delineation of subcortical white

DAT **Atlas-based functional maps**

and language function

and language function

cortical mapping

matter

Table 1 Summary of preoperative investigations and the information they provide for preoperative planning

MRI magnetic resonance imaging, *PET* positron emission tomography, *fMRI* functional MRI, *MEG* magnetoencephalography, *nTMS* navigated transcranial magnetic stimulation, *DTI* diffusion tensor imaging, *DAT* deformable anatomic templates

^a Advanced MRI techniques can further contribute to characterization of tumor composition and extent

characterization. It provides great soft tissue detail, while contrast enhancement highlights areas of blood-brain barrier breakdown typical in high-grade neoplasms. Low-grade gliomas, on the other hand, have intact blood-brain barrier and do not enhance with contrast administration, thus making delineation of tumor margins more challenging. The high T2 or FLAIR signal is commonly used to define the extent of the tumor [\[9](#page-7-9)]. In high-grade gliomas, on the other hand, the surrounding FLAIR hyperintensity is considered to represent tumor edema. Nevertheless, a recent study by Li et al. demonstrated, that resection of more than 53.21% of the surrounding T2 hyperintensisty results in improved patient survival [\[1](#page-7-0)]. In addition to traditional MRI sequences, advanced brain imaging techniques can be used to further characterize the anatomic, metabolic, and microvascular ultrastructure of the lesion to help with surgical planning and to determine more aggressive areas of tumor for biopsy or resection. These techniques include MR spectroscopy (MRS), dynamic contrast enhanced (DCE) MRI, dynamic susceptibility contrast (DSC) MRI, perfusion weighted sequences (PWS), and diffusion weighted imaging (DWI).

Positron emission tomography (PET)

In situations where MRI imaging is inconclusive, positron emission tomography (PET) using amino acid tracers can be used to highlight neoplastic areas, characterize the extent of

Table 2 Summary of intraoperative techniques and their specific intraoperative uses

US ultrasound, *5-ALA* 5-aminolevulinic acid, *SSEPs* somatosensory evoked potentials, *cMEPs* continuous motor evoked potentials, *eCOG* electrocorticography

tumor, identify anaplastic foci as biopsy targets, and to differentiate between tumor recurrence versus treatment effect [\[10](#page-7-5)[–13](#page-7-6)]. It detects the accumulation of radioactively labeled biologically active molecules that are actively transported into the tumor tissue. Commonly used tracers in neurooncology include 11C-methyl-l-methionine (MET), *O*-(2-[18F] fluoroethyl)-l-tyrosine (FET), and 3,4-dihydroxy-6-[18F] fluoro-l-phenylalanine (FDOPA). Incorporating metabolic information from PET into resection planning improves patient survival [[11\]](#page-7-7). Whereas dynamic PET studies may help predict tumor histology [[12\]](#page-7-8). The limitations of PET imaging are related to its poor spatial resolution, and combining PET with MRI imaging would allow more accurate characterization of tumor extent. The limited availability of certain tracers with a short half-life, such as MET, limits application of this technology only to centers that have a cyclotron.

While MRI and PET studies provide anatomical characterization of tumor location, they lack functional information on location of eloquent cortical areas that is required to prevent new postoperative deficits. The following preoperative studies help define functional areas and aid greatly in surgical planning.

Functional MRI

Functional MRI (fMRI) is a commonly used preoperative imaging and functional modality to help identify areas of cortical activation by detecting a higher amount of blood flow to these areas as a result of neurovascular coupling [\[14](#page-7-16)]. This relative difference in blood flow allows mapping of cortical areas involved in motor and speech function. While the results of the motor mapping correlate well with functional areas identified by DCS, fMRI is not sensitive or specific enough for mapping speech areas beyond the determination of language dominance [[15–](#page-7-17)[17\]](#page-7-18). The sensitivity and specificity for identification of language areas ranges between 37–91 and 64–83% respectively, in contrast to 95–100% for motor areas $[17, 18]$ $[17, 18]$ $[17, 18]$ $[17, 18]$. Furthermore, abnormal vascularization pattern near the tumor may result in neurovascular uncoupling phenomenon and subsequent false–negative results, while perilesional edema and brain plasticity may contribute to false-positive activations [[19,](#page-7-20) [20](#page-7-21)]. In summary, even though fMRI cannot determine whether a particular cortical area is required for a particular function, it alerts the surgeon of the proximity of the lesion to the eloquent cortical areas, and allows better planning of ancillary studies prior to surgery.

Magnetoencephalography

Another modality that is capable of visualizing functional cortical areas is magnetoencephalography (MEG). It detects magnetic fields established as a result of cortical activation during a task. When co-registered with the patient's MRI scan, MEG can accurately map areas of motor, visual, and auditory cortex, as well as help with language lateralization, as confirmed by intraoperative DCS [[21](#page-7-22), [22\]](#page-7-10). Magnetic fields that are set up as a result of cortical activation have very low values, however. Therefore, specialized equipment including magnetically shielded rooms and superconductors are required resulting in high equipment costs and subsequent limited availability of this technology for pre-operative planning.

Navigated transcranial magnetic stimulation (nTMS)

In contrast to fMRI and MEG that identify cortical areas activated during task execution, navigated transcranial magnetic stimulation (nTMS) enables the surgeon to determine eloquent areas that are required for a given function. Upon co-registration of the patient's MRI scan with pre-determined landmarks, cortical electrical current is induced by applying transcranial magnetic field to a specific area of cortex under real-time navigation. This allows to either directly activate the cortex below the area of stimulation resulting in a corresponding motor response, or to produce a temporary

Fig. 1 Navigated transcranial magnetic stimulation (nTMS) mapping of motor and language cortical areas in left hemisphere. The tumor (high-signal area) is located in the left hemisphere deep to the motor cortex. The results of nTMS are overlapped onto patient's MRI brain. Motor area controlling hand movement is localized above the tumor. Speech areas are identified during language testing as either hesitation or dysarthria (*yellow pegs*) during naming tasks, paraphasic errors (*red pegs*), or speech arrest (*white pegs*)

lesion by applying the stimulation repeatedly over the same area (Fig. [1](#page-2-0)). The latter method is used for mapping of eloquent language areas.

Comparison of functional areas identified from nTMS mapping to the results of the intraoperative DCS demonstrated good accuracy of nTMS in delineating primary motor cortex with reported correlation within 2–6 mm [\[22](#page-7-10), [23\]](#page-7-11). In addition, the use of nTMS preoperatively has been correlated with improved patient outcomes resulting in 16–17% greater rate of gross total resection and longer progression-free-survival of low-grade glioma patients of 22.4 versus 15.4 months in control group [\[24](#page-7-12)[–26](#page-7-13)]. Furthermore, even though the details of the protocol for language mapping using nTMS are still evolving, the high negative predictive value of 83–100% and good overall correlation with awake DCS results make it a promising adjunct for pre-operative speech mapping [\[27](#page-7-14), [28](#page-7-15)]. Of note, however, is that the specificity of language testing remains poor in the range of 13–60% thus the use of awake DCS language mapping techniques is recommended for lesions involving speech areas [\[27](#page-7-14), [28\]](#page-7-15). Finally, low cost and relative ease of use contribute to the increasing use of this modality in preoperative planning.

Diffusion tensor imaging (DTI)

Recently the importance of preserving subcortical white matter tracts has been recognized. Preoperative

visualization of corticospinal tract (CST) and arcuate fasciculus can influence the decision on completeness of surgical resection and help plan for intraoperative adjuncts (Fig. [2\)](#page-3-0). DTI is a T2-based MRI technique that is used most widely for subcortical fiber mapping. It relies on detection of the preferential movement of water molecules along the axis of the axon. The reliability of CST mapping by DTI was compared to the results obtained with direct electrical stimulation, and demonstrated the specificity and sensitivity of >90% [\[29](#page-7-23)]. Moreover, preoperative use of DTI fiber tracking has been associated with improved outcomes with a decrease in postoperative deficits from 32.8 to 15.3% and a longer median survival in high-grade glioma patients of 21.2 months compared to 14.0 months in the control group [\[8](#page-7-4)]. The main limitation of DTI fiber tracking relates to the fact that it is a computational process, and depending on the protocol used, the rendering of white matter tracts will be different. This variability is independent of the presence of neoplastic tissue or tumor-associated edema [\[30](#page-8-6)]. Standardization of DTI processing protocols across different centers may help improve reliability of white matter tract maps and reduce the rate of false–positive and false–negative results. Furthermore, the accuracy of DTI is limited and subject to artifact at the point of crossing fibers resulting in false connections or premature terminations. Advanced white matter imaging techniques such as diffusion spectrum imaging (DSI) [\[31](#page-8-7)] and high angular resolution diffusion imaging

Fig. 2 A composite rendering of eloquent cortical areas and subcortical pathways as they relate to the tumor location. The motor area for the hand (*light yellow object*) and speech areas (*magenta objects*) were determined from pre-operative functional MRI testing and overlaid onto the patient's anatomic 3D-MRI brain image highlighting the tumor (*dark yellow object*). The fiber tracking protocol using diffusion tensor imaging sequences was applied to outline the location of the descending corticospinal tracts (*blue*) and arcuate fasciculus (*green*)

(HARDI) [[32\]](#page-8-0) can overcome some of these limitations and provide improved resolution of subcortical fiber anatomy.

Deformable anatomic templates

In addition to fiber tracking, the use of deformable anatomic templates (DAT) to identify eloquent areas and subcortical white matter tracts has recently been investigated for both preoperative planning, as well as intraoperative navigation [\[33](#page-8-1), [34](#page-8-2)]. The patient's MRI images are subjected to threedimensional deformation to allow close matching to the digital atlas images. While helpful in cortical and subcortical function determination in the vicinity of the tumor, the application of this modality is still limited to tumors with minimal or no mass effect, and requires additional training and equipment [\[34](#page-8-2)].

Intraoperative adjuncts

Frameless stereotaxy

Preoperative imaging and functional studies provide excellent information on tumor location and its relation to the eloquent cortical and subcortical areas. Neuronavigation allows the surgeon to use this information obtained from preoperative imaging studies in real time during surgery. This is achieved by first registering the position of the patient's head relative to a rigidly attached frame by using pre-defined landmarks. Once registration is completed, a free-hand probe can be used to navigate in real time and the location of the tip of the probe is cross-referenced on the initial MRI or CT data set. The exact coordinates of the frame and the probe are detected using an infrared transmitter/detector system. This system is now routinely used in many centers worldwide, and while it was not shown to affect the EOR, it helps optimize surgical approach and minimize the size of incision and craniotomy opening [\[35](#page-8-3)]. Recently, incorporation of results of functional information obtained from DTI, fMRI and MEG to the navigated scan was shown to decrease the incidence of new postoperative motor deficits, and in some cases improve motor function [\[8](#page-7-4), [36](#page-8-4)].

Intraoperative MRI

The main limitation of frameless stereotaxy is its inaccuracy near the end of the resection secondary to the intraoperative brain shift as a result of CSF drainage and tumor resection. Acquiring a new scan intraoperatively allows to correct for the brain shift, and to effectively identify the residual tumor, resulting in greater EOR of high- and low-grade gliomas with reported gross-total resection rates of 75.6–96% [[37,](#page-8-5)

[38](#page-8-13)]. Clinically, this was correlated with improved outcomes with longer progression-free-survival of 226 days in patients with complete resection versus 119 days in patients with incomplete resection, and no increase in the rate of new neurological deficits [[38](#page-8-13)]. The drawbacks of this technique, however, include the high upfront cost of the scanner, as well as increase in the length of the procedure.

Ultrasound navigation

In contrast to the intraoperative MRI, the use of intraoperative ultrasound does not require a special operating suite, nor does it add significantly to the length of the procedure. It allows for accurate tumor localization and can be used repeatedly throughout the procedure to follow the progress of resection. Eighty to one hundred percent of low-grade gliomas and nearly all high-grade gliomas are readily identified by ultrasound and allow for discrimination between normal and pathologic tissues [[39–](#page-8-14)[41\]](#page-8-15). The major challenge of intraoperative ultrasound relates to the difficultly of image interpretation, low signal-to-noise ratio, and presence of artifact from blood and air [\[42](#page-8-16)]. To overcome these limitations, integration with MRI-based neuronavigation, the use of different ultrasound probes, as well as the addition of contrast enhancement can be used to minimize artifact and facilitate image interpretation [\[43](#page-8-17), [44](#page-8-18)].

5-ALA

Recently, the use of fluorescent agents to facilitate surgical resection of brain tumor was introduced. Several agents are available, among which 5-aminolevulinic acid (5-ALA) has been most studied. 5-ALA is a product of hemoglobin metabolism. When administered exogenously, it penetrates blood brain barrier and accumulates within the tumor. It is further metabolized within tumors cells to protoporphyrin IX, a fluorescent compound that can be detected intraoperatively as red-pink fluorescence under blue light. The presence of fluorescence has a sensitivity and specificity for lesional tissue of about 90% [\[45](#page-8-19)]. The implementation of 5-ALA as an adjunct to resection has been shown to at least double the rate of complete tumor resection, and if fluorescence is visualized after tumor resection in white light, the positive predictive value is reported 92–97% of having tumor present within the highlighted region [\[46,](#page-8-20) [47\]](#page-8-21).

The major advantage of 5-ALA use is real time visualization of tumor tissue that is independent of neuronavigation or brain shift. The limitations of this technique is that its application is limited to glioblastoma, as fluorescence of low grade lesions is too low to be readily detected intraoperatively. Furthermore, the surgeon has to be mindful of the fact that tissue overhangs or blood could obscure fluorescent region leading to incomplete resection. Overall, however,

the ease of use of this technique has a great potential to help maximize the extent of tumor resection in patients with high-grade gliomas.

Raman spectroscopy

While fluorescence is useful for lesion delineation, the uptake of the fluorescent molecules is quite variable. Raman spectroscopy analyzes physical properties of tissues within the resection cavity and is able to identify tissues containing tumor cells in real time during resection. It takes advantage of the fact that due to increased cellularity tumor infiltrated tissues produce a signal that is different from normal brain or white matter. Reports in animal models and frozen tissue demonstrated the ability of Raman spectroscopy to differentiate between normal brain and tissues containing tumor [\[48](#page-8-8), [49\]](#page-8-9). In addition, with the development of the handheld probe integrated with neuronavigation, this system has the potential to provide accurate diagnosis of tumor infiltrated tissues intraoperatively during resection [\[50](#page-8-10)]. While this system is still under investigation of its validity, first reports of intraoperative use have indicated >90% rate of specificity and sensitivity in detecting affected brain [\[51](#page-8-11)].

Direct cortical stimulation

Intraoperative imaging adjuncts allow the surgeon to visualize important anatomical structures and to help identify residual tumor. They do not provide functional information, however. Direct electrical stimulation of brain surface and subcortical white matter has been used for many decades to help define eloquent brain areas to be avoided during tumor resection. The use of DCS allows for a better EOR with 75% of tumor resected completely (versus 58% without DCS) and is associated with a lower risk of late postoperative neurological deficits (3.4% versus 8.2%) [[7\]](#page-7-3).

The typical set up uses a constant current generator to produce an electrical pulse of a square monophasic wave of 0.2–0.5 msec in duration. Two paradigms of electrical stimulation are presently used. The low-frequency protocol delivers trains of pulses continuously at a frequency of 50 or 60 Hz, and is commonly used in an awake patient. In 1993 Taniguchi et al. developed high-frequency stimulation protocol that delivers a train of five pulses at a frequency of 350–500 Hz that enabled motor cortical stimulation in anesthetized patients [\[52\]](#page-8-12).

To deliver the current for DCS there are two types of probes available: bipolar and monopolar (Fig. [3](#page-5-0)). The monopolar probe delivers the current in a radial pattern, which allows greater area of coverage and stimulation of targets that are farther away from the probe. The bipolar probe, on the other hand, consists of two electrodes, an anode and a cathode, separated by 5–10 mm. The current is focused

between the tips of the electrodes, which allows for high precision stimulation but has a higher risk of triggering seizures.

The two major functional areas that are frequently mapped and monitored intraoperatively include motor function and language. Furthermore, it is equally as important to identify subcortical pathways in addition to determining eloquent cortical areas to avoid new neurological deficits. The following sections highlight particulars to mapping each of these two domains of functioning.

Motor mapping and monitoring

Somatosensory evoked potentials

Mapping of the primary motor cortex can be conducted in a patient that is awake or asleep. Several anatomic landmarks are used for identification of the primary motor cortex, including the superior frontal gyrus to identify the precentral sulcus, the characteristic omega-shaped cortical area corresponding to the hand motor area, to a name a few [\[53](#page-8-24)]. The tumor, however, frequently distorts these landmarks making the identification of the primary motor area challenging. Somatosensory evoked potentials (SSEPs) can be used intraoperatively to identify the central sulcus. Stimulation of the contralateral median nerve produces SSEPs that are recorded using a 4×2 , or 8×1 platinum grid electrode. The direction of depolarization changes as it traverses the central sulcus producing a mirror image of the SSEP recording, a phenomenon called "phase reversal". This provides a simple and noninvasive way of accurately identifying primary motor cortex in more than 90% of patients, and can be conducted under general anesthesia [[54\]](#page-8-22). Furthermore, the same electrode strip can be used at a later point in surgery for continuous motor evoked potentials (cMEPs) recording or electrocorticography (eCoG).

Direct cortical stimulation

In addition to SSEPs, DCS can be used to identify eloquent motor areas. Low-frequency stimulation using a bipolar probe is frequently used in an awake patient. However, the use of the train-of-five technique with the monopolar probe is equally effective and requires smaller amount of current to be delivered thus minimizing the risk of seizures [\[55](#page-8-23)]. Stimulation over the primary motor area produces clonic movement, whereas stimulation over the supplementary motor cortex requires longer stimulus administration to produce movement, and results in tonic contraction, thus allowing to functionally differentiate eloquent cortical areas. In some cases, however, stimulation over the supplemental motor area may inhibit the movement, and this has to be distinguished from patient's fatigue.

Motor evoked potentials

Once the primary motor area is identified, motor function can be monitored continuously using MEPs. A small strip of 4–8 electrodes is placed over the motor cortex and the trainof-five monopolar stimulation through one of the contacts is conducted at regular intervals during tumor resection.

Fig. 3 The tools used for intraoperative direct cortical electrical stimulation and subcortical mapping. **a** Ojemann stimulator is a bipolar probe with two electrodes separated by 5 mm used for high precision cortical and subcortical mapping. **b** A grid containing four electrodes embedded into silicone matrix is used for SSEP recording and for identification of the central sulcus location via phase-reversal technique.

In addition, it can be used throughout the case for continuous MEP recording for intraoperative monitoring of motor function, or for elecrocorticography to detect seizure activity. **c** Monopolar Prass probe is used for cortical or subcortical mapping, and can be co-registered with the intraoperative navigation system. (*SSEP* somatosensory evoked potentials, *MEP* motor evoked potentials)

Monitoring the amplitude and the amount of energy required to elicit the motor response allows the surgeon to monitor the integrity of the motor pathways. The decrease in amplitude more than 50%, or the need to go up on the current more than 4 mA to maintain the same amplitude indicates potential compromise to the descending CST fibers [[56](#page-8-25)[–58](#page-8-26)]. Reversible cMEP decline is associated with a reversible neurological deficit post operatively. If the cMEP signals are lost or permanently decreased, the patient will experience a new neurological deficit postop [[57](#page-8-27)]. Therefore, the cMEP monitoring has a high predictive value with respect to the neurological outcome, but has a limited monitoring value as only 60% of cMEP declines are reversible [[58\]](#page-8-26).

Despite unaltered cMEP recordings during the surgery, about 4.5% of patients will wake up with a new neurological deficit [[57](#page-8-27)]. In these cases, the neurological deficit was determined to be due to an ischemic insult, postoperative hematoma formation, or lack of monitoring in that particular limb. Therefore, the false-negative rate of cMEP monitoring is considered to be essentially zero thus emphasizing the importance of this technique in assisting the resection of tumors near motor pathways [\[57\]](#page-8-27).

Subcortical stimulation

The importance of mapping of subcortical fibers has recently been recognized. Preoperative imaging, in particular DTI, can help predict the relationship between the tumor and the descending CST tract. Intraoperatively, however, as the tumor is excised, the fibers shift in an unpredictable direction, making any intraoperative navigation inaccurate [\[59](#page-8-28)]. Direct electrical stimulation on the other hand has proved to be accurate at identifying the location of the CST intraoperatively. For subcortical stimulation, high-frequency protocol using trainof-five technique with a monopolar probe has been shown to identify the descending motor tracts most effectively [[55](#page-8-23)]. The range of current settings used is 1–20 mA. Moreover, the amount of current that is required to generate MEPs has been correlated with the physical distance of the tracts. A linear relation has been shown with 1 mA of stimulation corresponding to 1 mm of distance $[60-62]$ $[60-62]$. The distance of greater than 5 mA was shown to be safe to prevent new postoperative permanent neurological deficits [[62](#page-8-30)]. Some centers however encourage resection up to 1 mA value of stimulation reporting only 3% rate of postoperative neurological deficit beyond 3 months [[63\]](#page-8-31). Overall, direct electrical stimulation of subcortical fibers remains the gold standard to accurately map the location of CST to avoid its injury.

Language assessment

Awake craniotomy for the purpose of localization of eloquent language cortex is commonly employed in many

centers as it has been shown to result in fewer postoperative permanent language deficits and improve the extent of tumor resection [[7\]](#page-7-3). This procedure is well tolerated with reported failure rates between 0.5 and 6.4% [[64,](#page-9-0) [65\]](#page-9-1).

A craniotomy is planned to expose 2–4 cm margin of brain around the tumor for the purposes of cortical mapping. Stimulation is done according to the low-frequency protocol (50–60 Hz) using a bipolar probe starting at 1 mA and increasing the current to a maximum of 6 mA in 0.5 mA increments. The cortex is stimulated at 5–10 mm intervals, and stimulation duration should not exceed 3 s per site due to high risk of triggering of an intraoperative seizure. The patient is asked to either count, name objects, or asked to perform semantic tasks during the stimulation (Video 1). The areas of speech arrest are marked by placing a sterile label.

It is routine practice to perform electrocorticography during cortical stimulation to detect after-discharge potentials or non-convulsive seizure activity (Video 1). The incidence of intraoperative seizures is about 3% [\[65](#page-9-1)]. Seizures are extinguished by applying ice-cold Ringer's saline to cortical surface or by administering a bolus of propofol in resistant cases.

Traditionally, language mapping was only limited to cortical areas. Recently, a better appreciation of importance of subcortical pathways involved in language functions has evolved [[66\]](#page-9-2). Subcortical mapping of language pathways is conducted in a manner similar to cortical stimulation. Application of high-frequency train-of-five protocol has also been shown to be effective at identifying subcortical tracts.

Surgical resection technique: enbloc (sulcal to sulcal) versus piecemeal

Enbloc resection is preferred when feasible as it maintains margins throughout the resection with no interference from the vascularity of tumor. Naturally present cortical sulci are used to initiate the dissection and are followed to their depth until the white matter is encountered. The white matter interface between the tumor and adjacent brain is identified and preserved during the entire resection. This technique also allows early identification of subcortical functional areas compared to a piecemeal resection. Piecemeal resections are preferred for tumors directly infiltrating eloquent areas and in patients with a significant preoperative functional deficit.

Conclusion

Maximizing the EOR while minimizing the risk of postoperative neurological deficits is the goal of glioma surgery. The key to achieving these goals is to be able to take advantage of a spectrum of preoperative imaging and functional studies as well as intraoperative techniques to characterize tumor location and its relation to the eloquent cortical areas and subcortical tracts. Many of these techniques are described in this review, and the combined use of several modalities is encouraged to help achieve maximal tumor resection and ensure best patient outcome.

References

- 1. Li YM, Suki D, Hess K, Sawaya R (2016) The influence of maximum safe resection of glioblastoma on survival in 1229 patients: can we do better than gross-total resection? J Neurosurg 124:977–988
- 2. Lacroix M, Abi-Said D, Fourney DR et al (2001) A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 95:190–198
- 3. Sanai N, Polley M-Y, McDermott MW, Parsa AT, Berger MS (2011) An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 115:3–8
- 4. Jakola AS, Myrmel KS, Kloster R, Torp SH, Lindal S, Unsgård G, Solheim O (2012) Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in lowgrade gliomas. JAMA 308:1881–1888
- 5. Coburger J, Merkel A, Scherer M et al (2016) Low-grade glioma surgery in intraoperative magnetic resonance imaging: results of a multicenter retrospective assessment of the German Study Group for intraoperative magnetic resonance imaging. Neurosurgery 78:775–786
- 6. McGirt MJ, Mukherjee D, Chaichana KL, Than KD, Weingart JD, Quinones-Hinojosa A (2009) Association of surgically acquired motor and language deficits on overall survival after resection of glioblastoma multiforme. Neurosurgery 65:463–469
- 7. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS (2012) Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol 30:2559–2565
- 8. Wu J-S, Zhou L-F, Tang W-J, Mao Y, Hu J, Song Y-Y, Hong X-N, Du G-H (2007) Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation: a prospective, controlled study in patients with gliomas involving pyramidal tracts. Neurosurgery 61:935–948
- 9. Fouke SJ, Benzinger T, Gibson D, Ryken TC, Kalkanis SN, Olson JJ (2015) The role of imaging in the management of adults with diffuse low grade glioma. J Neurooncol 125:457–479
- 10. Terakawa Y, Tsuyuguchi N, Iwai Y, Yamanaka K, Higashiyama S, Takami T, Ohata K (2008) Diagnostic accuracy of 11C-methionine PET for differentiation of recurrent brain tumors from radiation necrosis after radiotherapy. J Nucl Med 49:694–699
- 11. Pirotte BJM, Levivier M, Goldman S, Massager N, Wikler D, Dewitte O, Bruneau M, Rorive S, David P, Brotchi J (2009) Positron emission tomography-guided volumetric resection of supratentorial high-grade gliomas: a survival analysis in 66 consecutive patients. Neurosurgery 64:471–481
- 12. Jansen NL, Suchorska B, Wenter V et al (2014) Dynamic 18F-FET PET in newly diagnosed astrocytic low-grade glioma identifies high-risk patients. J Nucl Med 55:198–203
- 13. Kunz M, Thon N, Eigenbrod S et al (2011) Hot spots in dynamic (18)FET-PET delineate malignant tumor parts within suspected WHO grade II gliomas. Neuro-Oncology 13:307–316
- 14. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K (1992) Intrinsic signal changes accompanying

sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci USA 89:5951–5955

- 15. Krings T, Schreckenberger M, Rohde V et al (2002) Functional MRI and 18F FDG-positron emission tomography for presurgical planning: comparison with electrical cortical stimulation. Acta Neurochir (Wien) 144:889–899
- 16. Roux FE, Boulanouar K, Ranjeva JP, Tremoulet M, Henry P, Manelfe C, Sabatier J, Berry I (1999) Usefulness of motor functional MRI correlated to cortical mapping in rolandic low-grade astrocytomas. Acta Neurochir (Wien) 141:71–79
- 17. Trinh VT, Fahim DK, Maldaun MVC et al (2014) Impact of preoperative functional magnetic resonance imaging during awake craniotomy procedures for intraoperative guidance and complication avoidance. Stereotact Funct Neurosurg 92:315–322
- 18. Kuchcinski G, Mellerio C, Pallud J et al (2015) Three-tesla functional MR language mapping: comparison with direct cortical stimulation in gliomas. Neurology 84:560–568
- 19. Schreiber A, Hubbe U, Ziyeh S, Hennig J (2000) The influence of gliomas and nonglial space-occupying lesions on blood-oxygenlevel-dependent contrast enhancement. AJNR Am J Neuroradiol 21:1055–1063
- 20. Ulmer JL, Hacein-Bey L, Mathews VP, Mueller WM, DeYoe EA, Prost RW, Meyer GA, Krouwer HG, Schmainda KM (2004) Lesion-induced pseudo-dominance at functional magnetic resonance imaging: implications for preoperative assessments. Neurosurgery 55:569–579
- 21. Korvenoja A, Kirveskari E, Aronen HJ et al (2006) Sensorimotor cortex localization: comparison of magnetoencephalography, functional MR imaging, and intraoperative cortical mapping. Radiology 241:213–222
- 22. Tarapore PE, Tate MC, Findlay AM, Honma SM, Mizuiri D, Berger MS, Nagarajan SS (2012) Preoperative multimodal motor mapping: a comparison of magnetoencephalography imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation. J Neurosurg 117:354–362
- 23. Krieg SM, Shiban E, Buchmann N, Gempt J, Foerschler A, Meyer B, Ringel F (2012) Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas. J Neurosurg 116:994–1001
- 24. Krieg SM, Sabih J, Bulubasova L, Obermueller T, Negwer C, Janssen I, Shiban E, Meyer B, Ringel F (2014) Preoperative motor mapping by navigated transcranial magnetic brain stimulation improves outcome for motor eloquent lesions. Neuro-Oncology 16:1274–1282
- 25. Frey D, Schilt S, Strack V, Zdunczyk A, Rösler J, Niraula B, Vajkoczy P, Picht T (2014) Navigated transcranial magnetic stimulation improves the treatment outcome in patients with brain tumors in motor eloquent locations. Neuro-Oncology 16:1365–1372
- 26. Picht T, Frey D, Thieme S, Kliesch S, Vajkoczy P (2016) Presurgical navigated TMS motor cortex mapping improves outcome in glioblastoma surgery: a controlled observational study. J Neurooncol 126:535–543
- 27. Picht T, Krieg SM, Sollmann N et al (2013) A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. Neurosurgery 72:808–819
- 28. Krieg SM, Tarapore PE, Picht T et al (2014) Optimal timing of pulse onset for language mapping with navigated repetitive transcranial magnetic stimulation. Neuroimage 100:219–236
- 29. Zhu F-P, Wu J-S, Song Y-Y, Yao C-J, Zhuang D-X, Xu G, Tang W-J, Qin Z-Y, Mao Y, Zhou L-F (2012) Clinical application of motor pathway mapping using diffusion tensor imaging tractography and intraoperative direct subcortical stimulation in cerebral glioma surgery: a prospective cohort study. Neurosurgery 71:1170–1183
- 30. Pujol S, Wells W, Pierpaoli C et al (2015) The DTI challenge: toward standardized evaluation of diffusion tensor imaging tractography for neurosurgery. J Neuroimaging 25:875–882
- 31. Wedeen VJ, Hagmann P, Tseng W-YI, Reese TG, Weisskoff RM (2005) Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. Magn Reson Med 54:1377–1386
- 32. Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ (2002) High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. Magn Reson Med 48:577–582
- 33. Kumar VA, Hamilton J, Hayman LA, Kumar AJ, Rao G, Weinberg JS, Sawaya R, Prabhu SS (2013) Deformable anatomic templates improve analysis of gliomas with minimal mass effect in eloquent areas. Neurosurgery 73:534–542
- 34. Vabulas M, Kumar VA, Hamilton JD, Martinez JJ, Rao G, Sawaya R, Prabhu SS (2014) Real-time atlas-based stereotactic neuronavigation. Neurosurgery 74:128–134
- 35. Willems PWA, Taphoorn MJB, Burger H, van der Berkelbach Sprenkel JW, Tulleken CAF (2006) Effectiveness of neuronavigation in resecting solitary intracerebral contrast-enhancing tumors: a randomized controlled trial. J Neurosurg 104:360–368
- 36. Mert A, Kiesel B, Wöhrer A, Martínez-Moreno M, Minchev G, Furtner J, Knosp E, Wolfsberger S, Widhalm G (2015) Introduction of a standardized multimodality image protocol for navigation-guided surgery of suspected low-grade gliomas. Neurosurg Focus 38:E4
- 37. Knauth M, Wirtz CR, Tronnier VM, Aras N, Kunze S, Sartor K (1999) Intraoperative MR imaging increases the extent of tumor resection in patients with high-grade gliomas. AJNR Am J Neuroradiol 20:1642–1646
- 38. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V (2011) Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol 12:997–1003
- 39. Serra C, Stauffer A, Actor B, Burkhardt J-K, Ulrich NH-B, Bernays R-L, Bozinov O (2012) Intraoperative high frequency ultrasound in intracerebral high-grade tumors. Ultraschall Med 33:E306–E312
- 40. Gerganov VM, Samii A, Giordano M, Samii M, Fahlbusch R (2011) Two-dimensional high-end ultrasound imaging compared to intraoperative MRI during resection of low-grade gliomas. J Clin Neurosci 18:669–673
- 41. Le Roux PD, Berger MS, Wang K, Mack LA, Ojemann GA (1992) Low grade gliomas: comparison of intraoperative ultrasound characteristics with preoperative imaging studies. J Neurooncol 13:189–198
- 42. Selbekk T, Jakola AS, Solheim O, Johansen TF, Lindseth F, Reinertsen I, Unsgård G (2013) Ultrasound imaging in neurosurgery: approaches to minimize surgically induced image artefacts for improved resection control. Acta Neurochir (Wien) 155:973–980
- 43. Rivaz H, Chen SJ-S, Collins DL (2015) Automatic deformable MR-ultrasound registration for image-guided neurosurgery. IEEE Trans Med Imaging 34:366–380
- 44. Prada F, Mattei L, Del Bene M et al (2014) Intraoperative cerebral glioma characterization with contrast enhanced ultrasound. Biomed Res Int 2014:1–9
- 45. Panciani PP, Fontanella M, Schatlo B, Garbossa D, Agnoletti A, Ducati A, Lanotte M (2012) Fluorescence and image guided resection in high grade glioma. Clin Neurol Neurosurg 114:37–41
- 46. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen H-J, ALA-Glioma Study Group (2006) Fluorescenceguided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 7:392–401
- 47. Nabavi A, Thurm H, Zountsas B, Pietsch T, Lanfermann H, Pichlmeier U, Mehdorn M, 5-ALA Recurrent glioma study group

(2009) Five-aminolevulinic acid for fluorescence-guided resection of recurrent malignant gliomas: a phase ii study. Neurosurgery 65:1070–1076

- 48. Ji M, Orringer DA, Freudiger CW et al (2013) Rapid, labelfree detection of brain tumors with stimulated Raman scattering microscopy. Sci Transl Med 5:201ra119
- 49. Kalkanis SN, Kast RE, Rosenblum ML, Mikkelsen T, Yurgelevic SM, Nelson KM, Raghunathan A, Poisson LM, Auner GW (2014) Raman spectroscopy to distinguish grey matter, necrosis, and glioblastoma multiforme in frozen tissue sections. J Neurooncol 116:477–485
- 50. Jermyn M, Mok K, Mercier J, Desroches J, Pichette J, Saint-Arnaud K, Bernstein L, Guiot M-C, Petrecca K, Leblond F (2015) Intraoperative brain cancer detection with Raman spectroscopy in humans. Sci Transl Med 7:274ra19
- 51. Desroches J, Jermyn M, Mok K et al (2015) Characterization of a Raman spectroscopy probe system for intraoperative brain tissue classification. Biomed Opt Express 6:2380–2397
- 52. Taniguchi M, Cedzich C, Schramm J (1993) Modification of cortical stimulation for motor evoked potentials under general anesthesia: technical description. Neurosurgery 32:219–226
- 53. Shah KB, Hayman LA, Chavali LS, Hamilton JD, Prabhu SS, Wangaryattawanich P, Kumar VA, Kumar AJ (2015) Glial tumors in brodmann area 6: spread pattern and relationships to motor areas. Radiographics 35:793–803
- 54. Cedzich C, Taniguchi M, Schäfer S, Schramm J (1996) Somatosensory evoked potential phase reversal and direct motor cortex stimulation during surgery in and around the central region. Neurosurgery 38:962–970
- 55. Szelényi A, Senft C, Jardan M, Forster MT, Franz K, Seifert V, Vatter H (2011) Intra-operative subcortical electrical stimulation: a comparison of two methods. Clin Neurophysiol 122:1470–1475
- 56. Kombos T, Suess O, Ciklatekerlio O, Brock M (2001) Monitoring of intraoperative motor evoked potentials to increase the safety of surgery in and around the motor cortex. J Neurosurg 95:608–614
- 57. Krieg SM, Shiban E, Droese D, Gempt J, Buchmann N, Pape H, Ryang Y-M, Meyer B, Ringel F (2012) Predictive value and safety of intraoperative neurophysiological monitoring with motor evoked potentials in glioma surgery. Neurosurgery 70:1060–1071
- 58. Seidel K, Beck J, Stieglitz L, Schucht P, Raabe A (2013) The warning-sign hierarchy between quantitative subcortical motor mapping and continuous motor evoked potential monitoring during resection of supratentorial brain tumors. J Neurosurg 118:287–296
- 59. Nimsky C, Ganslandt O, Hastreiter P, Wang R, Benner T, Sorensen AG, Fahlbusch R (2007) Preoperative and intraoperative diffusion tensor imaging-based fiber tracking in glioma surgery. Neurosurgery 61:178–185
- 60. Nossek E, Korn A, Shahar T et al (2011) Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological assessment and 3-dimensional ultrasonography-based navigation. Clinical article. J Neurosurg 114:738–746
- 61. Ohue S, Kohno S, Inoue A, Yamashita D, Harada H, Kumon Y, Kikuchi K, Miki H, Ohnishi T (2012) Accuracy of diffusion tensor magnetic resonance imaging-based tractography for surgery of gliomas near the pyramidal tract: a significant correlation between subcortical electrical stimulation and postoperative tractography. Neurosurgery 70:283–293
- 62. Prabhu SS, Gasco J, Tummala S, Weinberg JS, Rao G (2011) Intraoperative magnetic resonance imaging-guided tractography with integrated monopolar subcortical functional mapping for resection of brain tumors. J Neurosurg 114:719–726
- 63. Raabe A, Beck J, Schucht P, Seidel K (2014) Continuous dynamic mapping of the corticospinal tract during surgery of motor eloquent brain tumors: evaluation of a new method. J Neurosurg 120:1015–1024
- 64. Nossek E, Matot I, Shahar T, Barzilai O, Rapoport Y, Gonen T, Sela G, Korn A, Hayat D, Ram Z (2013) Failed awake craniotomy: a retrospective analysis in 424 patients undergoing craniotomy for brain tumor. J Neurosurg 118:243–249
- 65. Hervey-Jumper SL, Li J, Lau D, Molinaro AM, Perry DW, Meng L, Berger MS (2015) Awake craniotomy to maximize glioma

resection: methods and technical nuances over a 27-year period. J Neurosurg 123:325–339

66. Chang EF, Raygor KP, Berger MS (2015) Contemporary model of language organization: an overview for neurosurgeons. J Neurosurg 122:250–261