REVIEW

State-of-the-art imaging for glioma surgery

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Abstract

Diffuse gliomas are infiltrative primary brain tumors with a poor prognosis despite multimodal treatment. Maximum safe resection is recommended whenever feasible. The extent of resection (EOR) is positively correlated with survival. Identification of glioma tissue during surgery is difficult due to its diffuse nature. Therefore, glioma resection is imaging-guided, making the choice for imaging technique an important aspect of glioma surgery. The current standard for resection guidance in non-enhancing gliomas is T2 weighted or T2w-fluid attenuation inversion recovery magnetic resonance imaging (MRI), and in enhancing gliomas T1-weighted MRI with a gadolinium-based contrast agent. Other MRI sequences, like magnetic resonance spectroscopy, imaging modalities, such as positron emission tomography, as well as intraoperative imaging techniques, including the use of fluorescence, are also available for the guidance of glioma resection. The neurosurgeon's goal is to find the balance between maximizing the EOR and preserving brain functions since surgery-induced neurological deficits result in lower quality of life and shortened survival. This requires localization of important brain functions and white matter tracts to aid the pre-operative planning and surgical decision-making. Visualization of brain functions and white matter tracts is possible with functional MRI, diffusion tensor imaging, magnetoencephalography, and navigated transcranial magnetic stimulation. In this review, we discuss the current available imaging techniques for the guidance of glioma resection and the localization of brain functions and white matter tracts.

Keywords Glioma · Extent of resection · Imaging · Brain functionality · Neurosurgery

Introduction

Surgical resection is the first treatment in the majority of patients with a diffuse glioma. Surgery aims at providing adequate tissue for diagnosis, relieving mass effect and achieving cytoreduction. To achieve maximal cytoreduction, pursued to improve patient's survival [8, 86], the neurosurgeon needs to identify glioma infiltration during surgery. This is difficult due to the diffuse dissemination of glioma cells in the normal brain. The most widely used aid for the detection of glioma infiltration during surgery is imaging. Standard magnetic

resonance imaging (MRI), T1-weighted gadolinium-enhanced (T1G) for enhancing gliomas (Fig. 1A), and T2 (T2w) or fluid attenuation inversion recovery (FLAIR) weighted for non-enhancing gliomas (Fig. 1B) are recommended [18].
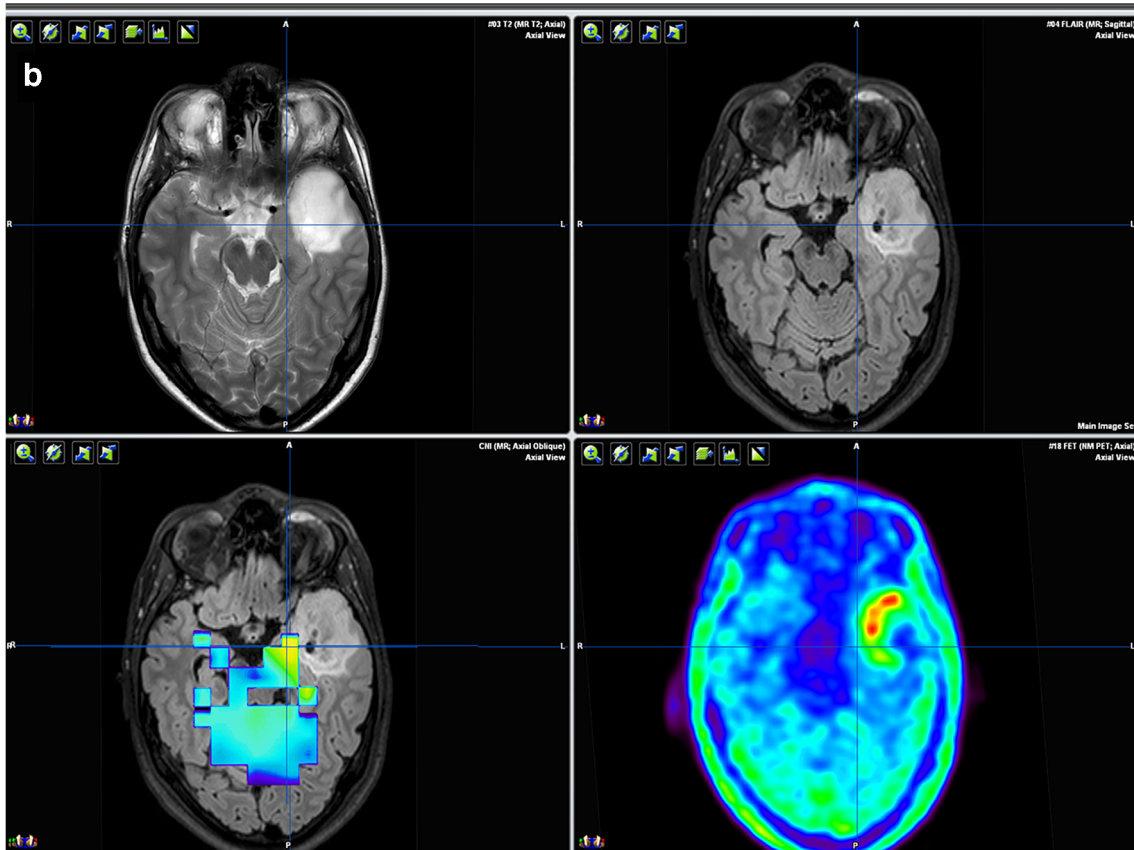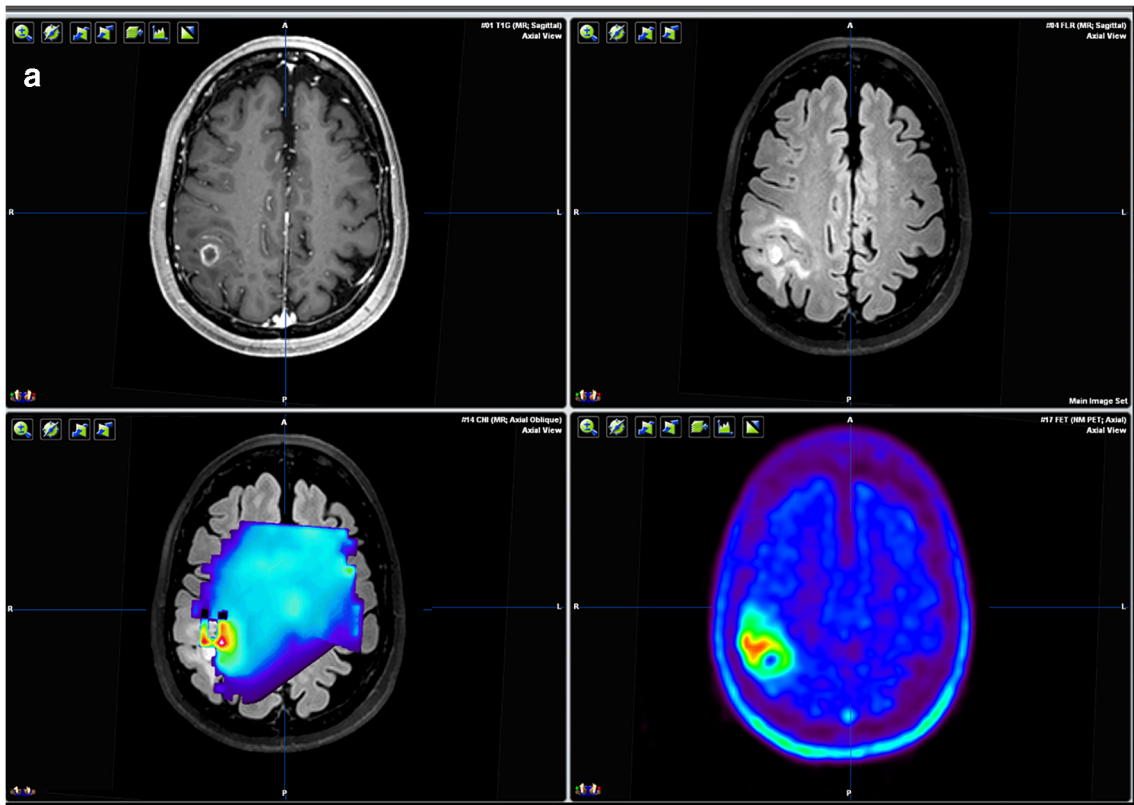
These standard MRI sequences, however, are less accurate for the detection of glioma infiltration than advanced MRI sequences and imaging modalities [93]. Therefore, advanced imaging, as well as the use of intraoperative fluorescence, holds the potential to expand the resection beyond the standard MRI abnormalities, which may improve patient's outcome [37, 52, 68, 71, 72, 89].

When expanding the resection, one must be aware of the potential loss of brain function due to the infiltration of tumor cells in normal functioning brain. Important brain functions, such as motor function, language, and neurocognitive functioning, need to be preserved since severe morbidity is not only associated with a decline in quality of life but also with survival [19]. The current standard to identify brain functions and white matter tracts is intraoperative direct cortical stimulation (DCS), a technique that provides an electrical stimulation to accomplish local excitation or inhibition in the cortex

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◀ **Fig. 1** Exemplary standard and advanced imaging. **A** Patient with a right parietal enhancing glioblastoma, IDH-wild type. Upper left: T1-weighted MRI with a gadolinium-based contrast agent, Upper right: FLAIR MRI, lower left: multivoxel MRSI CNI projected on the FLAIR MRI. Lower right: amino acid ([^{18}F]FET) PET. **B** Patient with a left temporal non-enhancing diffuse astrocytoma, IDH-mutant. The crosshair is projected to indicate the region with MRSI CNI and PET abnormalities just outside the FLAIR MRI abnormalities. Upper left: T2-weighted MRI, Upper right: FLAIR MRI, Lower left: multivoxel MRSI CNI projected on the FLAIR MRI, Lower right: amino acid ([^{18}F]FET) PET

or white matter tracts that will result in a functional response [15]. Multiple techniques are available for the localization of brain functions or white matter tracts.

The neurosurgeon's goal is to find the balance between the optimal oncological outcome by maximizing the resection and preventing severe morbidity by loss of brain functionality. Here, we discuss the state-of-the-art imaging techniques to guide glioma resection and imaging techniques to localize functions and white matter tracts, in order to achieve a maximal safe resection.

Imaging techniques for the guidance of glioma resection

Pre-operative imaging

Standard MRI The current standard MRI sequences for the guidance of glioma resection have historically grown into use since their widespread availability. Clinical trials supporting the use of standard MRI for the guidance of glioma resection are lacking. Therefore, we discuss the indirect evidence for these sequences. This evidence comes from studies that investigated the effect of the extent of image-guided glioma resection on survival.

In enhancing glioma, the strongest evidence for the use of T1G MRI comes from a post hoc analysis of 243 patients from a randomized controlled trial (RCT), comparing fluorescence-guided surgery with standard neuronavigation [69, 89]. In this study—after correction for tumor size, edema, midline shift, location, age, Karnofsky Performance Scale and National Institutes of Health Stroke Scale—complete resection of contrast enhancement on post-operative T1G MRI, compared to incomplete resection, resulted in longer OS (16.7 versus 11.8 months, $p < 0.01$) [69].

In non-enhancing glioma, the choice for T2w or FLAIR MRI aided surgery depends on the surgeon's preference, since direct comparison is lacking, which is reflected in the used imaging sequences in a recent review [2], where T2w, FLAIR, and T2w or FLAIR MRI were respectively used in 36%, 46%, and 18% of the studies. A possible benefit of FLAIR MRI is the suppression of the water signal intensity,

which allows for better contrast of tumor in periventricular areas. Both T2w and FLAIR MRI aided resections are supported by retrospective studies [33, 86]. These studies prove the goal of complete resection of the standard MRI abnormalities in both enhancing and non-enhancing gliomas. The lack of studies directly comparing standard MRI- versus other imaging-guided resection, however, makes it impossible to judge if standard MRI is the best option for the guidance of glioma resection. Considering the evidence of diagnostic accuracy studies [93], more is to be expected from other MRI sequences or imaging modalities.

FLAIR MRI in enhancing glioma In the majority of enhancing glioma, FLAIR abnormalities expand beyond the regions with contrast enhancement (Fig. 1A) [30]. These surrounding FLAIR abnormalities are sometimes addressed as peritumoral edema; however, many studies have proven the presence of glioma cells within these regions [24, 27, 38, 39, 76]. Extending the resection beyond contrast-enhanced regions using FLAIR has shown great potential. A large ($n = 643$) retrospective study found an improved OS for a more extensive ($\geq 53\%$) resection of the surrounding FLAIR abnormalities after complete resection of contrast-enhanced regions, compared to less extensive resections (median OS 20.7 and 15.5 months, respectively; $p < 0.01$). Remarkably, a more extensive resection resulted in a lower complication rate (18% versus 26%, $p = 0.04$), which reflects, according to the authors, the increased use of DCS and imaging to visualize brain functions and white matter tracts. These promising results are a bit tempered by the fact that an extensive resection was only achieved in 25% of the patients [52]. Both FLAIR resection threshold, number of patients receiving extensive resection, and the lower complication rate with more extensive resection were confirmed in another study with 282 patients [68]. These are the largest studies comparing, although not randomized and prospective, different MRI sequences to aid glioma resection, therefore providing the strongest evidence for the use of other sequences than the current standard.

Magnetic resonance spectroscopy imaging Magnetic resonance spectroscopy imaging (MRSI) measures biochemical components of a region of interest, which can be used to calculate, among others, the choline-*N*-acetyl aspartate index (CNI) to detect glioma (Fig. 1 A and B). The only study describing MRS-aided surgery reported an extended resection beyond contrast enhancement in 86% of seven enhancing gliomas and beyond FLAIR MRI abnormalities in 88% of eight non-enhancing gliomas. The target volume for resection was based on the lowest CNI threshold that allowed a safe resection, defined by functional imaging and anatomy. The survival benefit in this study is not clear due to the limited follow-up of 1 year, in which one enhancing glioma and none of the non-enhancing gliomas recurred [101]. A limitation of MRSI is the

technical difficulty of obtaining a good-quality 3D MRS image due to the artifacts of non-brain tissue [51]. The concept of different threshold-based target volumes, as well as the possibility to aid resections beyond FLAIR abnormalities, makes MRSI an interesting technique that deserves further research.

Positron emission tomography Positron emission tomography (PET) is a nuclear imaging technique that uses radioactive tracers to visualize perfusion, proliferation, metabolism, and neurotransmitters (Fig. 1 A and B). Multiple tracers are available for glioma imaging of which only the amino acid L-[methyl-11C]methionine (MET) is used to aid glioma resection. The only group reporting MET PET aided resection selected gliomas with ill-defined borders or enhancing gliomas with T2w or FLAIR abnormalities beyond the contrast enhancement. Two strategies were used for these gliomas: (1) to extend the resection beyond standard MRI abnormalities or (2) a focused resection of the most metabolic active parts of the tumor if a complete resection of MRI abnormalities was not possible. In enhancing gliomas, each strategy was achieved in one-third of patients, while PET was not contributive in the remaining one-third of patients. In non-enhancing gliomas, the first strategy was achieved in 74%; the second strategy in 14% and 12% of patients did not have a contributive MET PET. OS in enhancing gliomas was predicted by complete resection of MET uptake, achieved in 56% of patients, while complete resection of contrast enhancement, achieved in 35% of patients, did not [71]. Unfortunately, survival data was not collected. Limitations of PET imaging are the costs, an estimated 1600–2100 dollars for one scan [40], although a cost-effectiveness analysis showed that the use of MRI and PET is cost-effective [29]. Other limitations are the necessity of an on-site cyclotron for tracers with a short half time, and one-third of the non-enhancing gliomas are amino acid PET negative [49]. Although these retrospective results are biased by the specific inclusion criteria and the low percentage of complete resection of contrast enhancement, they show the potential of PET-aided glioma surgery.

Limitations pre-operative imaging Three limitations of all pre-operative imaging are interobserver variation for tumor delineation, image fusion and registration setup inaccuracy, and inability to compensate for intraoperative surgery-induced changes. Interobserver variation for the delineation of gliomas is the difference in tumor volumes, as assessed on imaging, between different interpreters. In enhancing gliomas, this in only a minor issue since observer agreements are good (range 0.97–0.99) [47, 95]. In non-enhancing gliomas, however, agreements are considerably lower (range 0.48–0.77) for both T2w and FLAIR MRI [4, 95]. Possible causes for this lower agreement are the interpretation of the hyperintense T2w and FLAIR signal as edema or glioma infiltration and the less well-defined borders of the T2w and FLAIR abnormalities

[95]. MRSI and PET are less limited by interobserver variability due to their quantitative analysis and the use of a threshold. Image fusion and registration setup inaccuracy occurs due to the translation of pre-operative images to the intraoperative situation. Since the intraoperative navigation is based on the 3D model of one MRI sequence, mostly 3D T1G or 3D FLAIR MRI, all other images that are used for the delineation need to be fused with this 3D sequence. This fusion is mostly performed with a linear method and inaccuracies of 1.0 to 3.0 mm have been reported [31]. Registration inaccuracy occurs due to the translation of the 3D MRI model to the actual patient. Depending on setup, inaccuracy varies between 1.59 and 3.86 mm [88]. The last but foremost limitation is the inability of pre-operative imaging to adjust to the new situation after surgical induces changes such as brain shift, tissue deformation, and tissue removal. Shifts between 7 mm inward and 8 mm outward were found after dura opening, and 9.7 mm inward and 15 mm outward (mean 2.7–5.4 mm) after tumor resection [62, 80]. The influence of these effects on the resection can be limited by circumscribing the tumor, instead of piecemeal removal, thereby limiting the brain shift.

Intraoperative imaging

Intraoperative MRI Intraoperative MRI (iMRI) has the advantage over pre-operative MRI that it can overcome its above-mentioned limitations. Since the images are acquired in the same position as the surgery, registration inaccuracy is lower for iMRI than pre-operative MRI [91]. Even more important, iMRI can visualize the altered anatomy due to intraoperative changes, which reduces their influence on navigation inaccuracy (Fig. 2A) [57].

Besides these advantages in navigation accuracy, iMRI allows for the detection of residual tumor after a first attempt for a maximal resection. In enhancing glioma, a RCT with 49 patients found a higher percentage of complete resections of contrast enhancement in the iMRI group (96% versus 68%, $p < 0.01$) [85], although the effect on survival is still awaited for. In non-enhancing glioma, multiple retrospective studies report improved complete resection rates (14 to 19%) of T2w or FLAIR abnormalities using iMRI [58, 63, 67]. Two major drawbacks of iMRI are the high initial costs, 3.8 million dollars for the ultra low-field model in 2011, and the prolonged duration of the surgery, up to 2 h, due to scan time [48, 55]. Although iMRI has proven its value for the purpose of complete resection of standard MRI abnormalities, studies using iMRI to extend the resection beyond these standard imaging abnormalities are lacking. Even if this is possible, alternatives could be considered due to the high cost and prolonged surgical time of iMRI.

Ultrasound The visualization of returning sound waves can be used to detect glioma by direct application of the ultrasound
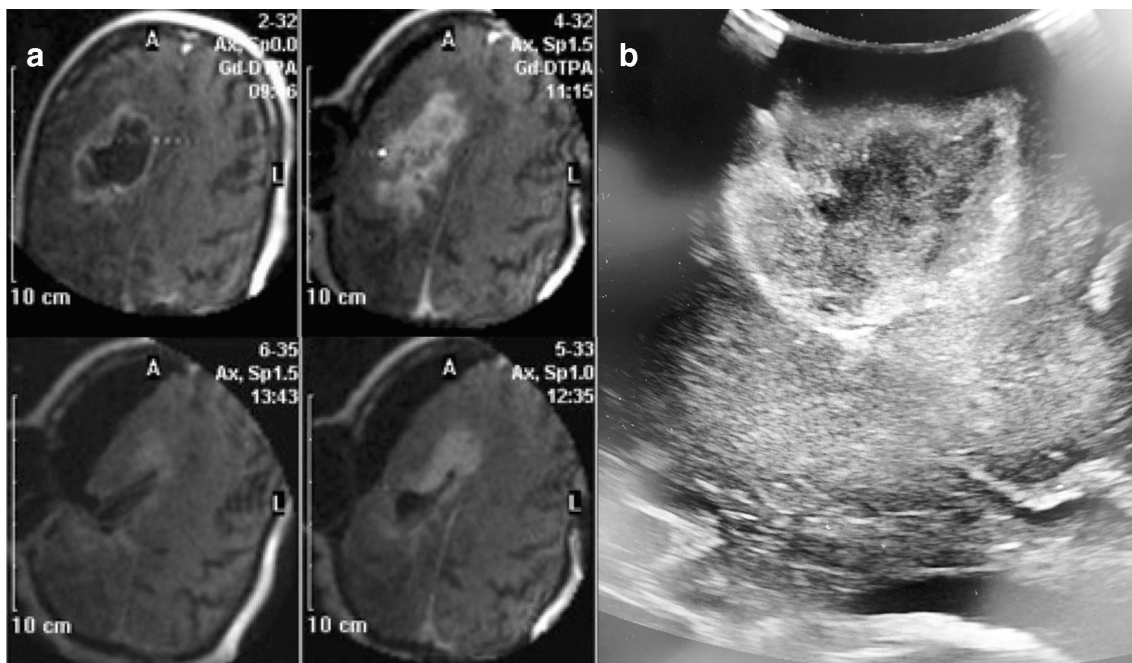
Fig. 2 Examples of intraoperative imaging. **A** Intraoperative MRI of an enhancing right frontal glioblastoma with clockwise images of the progression of the resection with clear brain shift. Image courtesy of Dr. P Kubben [46]. **B** Intraoperative ultrasound of a left parietal glioblastoma

(US) probe on the tissue (Fig. 2B). Like with iMRI, this results in real-time imaging that is not influenced by navigation inaccuracy or intraoperative changes. US-guided resection achieved a complete resection of US abnormalities in 67% of the 61 enhancing and 61% of the 51 non-enhancing glioma patients. This resulted in an improved 2-year OS compared to a random selected control group (32.8% versus 13.3% and 88.2% versus 53.3%, both $p < 0.05$, respectively enhancing and non-enhancing glioma) [97]. New US techniques like high-frequency linear probes and ultrasonic contrast are introduced and hold potential to maximize resections compared to standard US [10, 75]. Direct comparison of high frequency US with iMRI, using biopsies from residual tumor and normal control sites after resection, resulted in a significantly higher sensitivity for US (sensitivity 76% versus 55%, $p = 0.021$) and not significant difference in specificity (specificity 74% versus 58%) [11]. Besides detection of glioma tissue, US can be used to update the pre-operative MRI-based neuronavigation [74]. Limitations of US are the training necessary to create a good-quality image; problems with artifacts due to blood, hemostatic material, bone and other structure material; and the 2D aspect of US. This makes the acquisition and interpretation of US for glioma delineation challenging [83]. Still, US can serve as a good and cheaper alternative for iMRI.

Fluorescence Although not a standard imaging technique per se, the use of fluorescence during glioma resection aids the surgeon in the visualization of the tumor. Multiple agents are available for intraoperative fluorescence of which 5-aminolevulinic acid (5-ALA) and sodium fluorescein (SF) are most common in daily practice. 5-ALA is a non-fluorescent prodrug that leads to intracellular accumulation of fluorescent porphyrins in malignant gliomas. These porphyrins can be visualized intraoperatively with a special filter for the operating microscope resulting in a pink appearance of the tumor, while the normal tissue appears blue (Fig. 3). A large RCT ($n = 322$) reported higher GTR rates of contrast enhancement (65% versus 36%, $p < 0.0001$) and prolonged
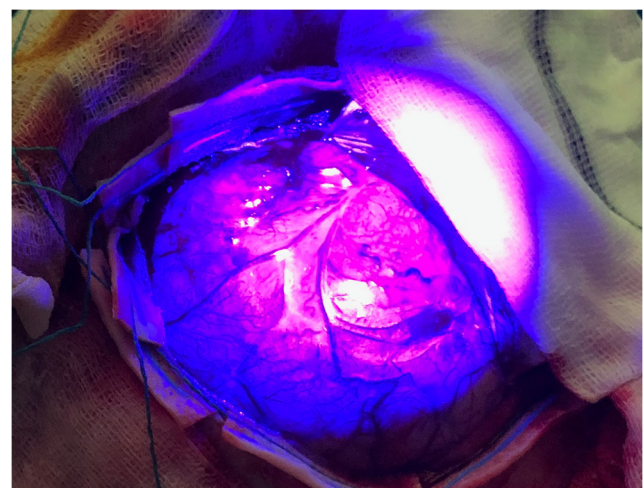

Fig. 3 Example of intraoperative fluorescence. Intraoperative image of 5-ALA-guided resection of superficial glioblastoma with clear pink fluorescence of the tumor with the surrounding normal tissue appearing blue

6-month PFS (41% versus 21%, $p = 0.0003$) in patients with a high-grade glioma assigned 5-ALA compared to those assigned standard operative care [89]. This study showed the usefulness of fluorescence-guided surgery for the purpose of GTR of contrast enhancement. Still, the choice of primary (GTR rate) and secondary (6-months PFS) endpoint did not permit a definitive conclusion regarding the influence of 5-ALA-guided resection on OS. Also, the standard surgical care did not include the use of neuronavigation, which is reflected by the low GTR rate in that arm. SF is a dye that accumulates in malignant glioma due to their disruption of the BBB. It is administrated by intravenous injection during surgery and, with use of a special filter in the operating microscope, results in a yellow appearance of the tumor compared to a pink appearance of the normal brain tissue. The best evidence comes from a prospective multicenter phase II trial in which 46 patients underwent SF-guided resection of a high-grade glioma that led to a GTR of contrast enhancement in 38 patients (82%). Biopsies were collected from areas with and without fluorescence in 13 of the patients and assessed for tumor presence, resulting in an 80% sensitivity and specificity [1]. The higher GTR rate in this study compared to the 5-ALA trial should be interpreted with caution since the SF study was smaller and non-randomized. Direct comparison of 5-ALA and SF is limited to small cohort studies without uniform results [16, 99]. A meta-analysis found no significant difference in the GTR rate between the agents, although it reported a much higher cost per quality added life years for 5-ALA (US$16,218) compared to SF (US$3181) [36].

Multiple studies compared 5-ALA with amino acid PET and iMRI for the detection of tumor tissue. All but one of the PET studies found a higher sensitivity for PET [20, 65] or residual post-operative tracer uptake after complete resection of 5-ALA [42, 59]. It has to be mentioned that these were all retrospective studies with different thresholds or qualitative interpretation of tracer uptake. The one study reporting 5-ALA to be more sensitive only marked deliberate residual 5-ALA fluorescence during surgery to compare with post-operative FET PET [79]. Therefore, it is unclear if there were also 5-ALA negative FET PET–positive areas. A recent meta-analysis of iMRI and 5-ALA found higher GTR rates for both techniques compared to standard operative care, yet no difference between the two techniques. They therefore concluded that a combination of 5-ALA and iMRI could have its advantages, yet future studies need to confirm this [26].

Limitation of both fluorescence agents is the lack of fluorescence in the majority of low-grade gliomas. Also, tumor tissue has been found outside the area of fluorescence of both 5-ALA and SF [28, 78, 99]. However, fluorescence-guided surgery is not limited by brain shift or navigation inaccuracy, making it therefore a suitable technique to achieve GTR of contrast enhancement in high-grade gliomas.

Imaging for localization of brain functions and white matter tracts

Pre-operative imaging

Functional MRI BOLD-Functional MRI (fMRI) measures the blood oxygenation level changes caused by perfusion, which is a surrogate for neuronal activity. This allows for visualization of specific tasks-related activity such as motor function or language (Fig. 4A) [50]. Applying fMRI to localize language areas resulted in a 59–100% sensitivity and 0–97% specificity in a systematic review, with the wide ranges attributed to the heterogeneity in language tasks and imaging protocols. The authors conclude that fMRI is not an alternative for DCS language mapping [25]. Accuracy for motor function localization, compared to DCS, varies between studies, with smaller studies reporting higher accuracies (up to 100%) than the larger studies (66–72%) [3, 34, 45, 82]. In the largest study, 210 cortical sites were tested in 29 patients, resulting in an 83% sensitivity and 82% specificity. In patients with glioblastoma, however, sensitivity was only 65%, which is, according to the authors, a possible effect of the neurovascular uncoupling [7]. The limitations of fMRI have been recently described extensively and include statistical power, flexibility in data-analysis, multiple comparisons, software errors, insufficient study reporting, and lack of independent replications [56, 73]. Taken together, fMRI is not accurate enough to aid in the surgical planning, let alone replace DCS.

Diffusion tensor imaging Diffusion tensor imaging (DTI) is a technique that relies on Brownian movement of water molecules in tissue. The direction of these movements is restrained in white matter fibers, which can be used to visualize the anatomical location of white matter tracts, so-called DTI tractography (Fig. 4B) [64]. This technique solemnly visualizes anatomy and does localize brain functionality. Studies comparing DTI tractography with the gold standard DCS reported mean distances between DTI tractography and positive stimulations of 5.2 to 8.7 mm [5, 27, 102]. Therefore, a minimum safe distance of 10 mm from a tract has been recommended. In an RCT comparing resection with and without pre-operative DTI in 214 patients with diffuse glioma involving the pyramidal tract, the use of DTI in patients with enhancing glioma resulted in a higher complete resection rate (74.4% versus 33.3%, $p < 0.001$), 6-month good clinical condition (70.0% versus 36.8%, $p = 0.001$), and improved median OS (21.2 versus 14.0 months, $p = 0.048$). In non-enhancing glioma patients, complete resection rate did not significantly differ, yet 6-month good clinical condition was higher in the DTI group (93.4% versus 79.1%, $p = 0.013$) [98]. Although this study clearly shows the benefit of DTI tractography in glioma resection, one must take into account that 63% of patients in the control group had poor clinical condition
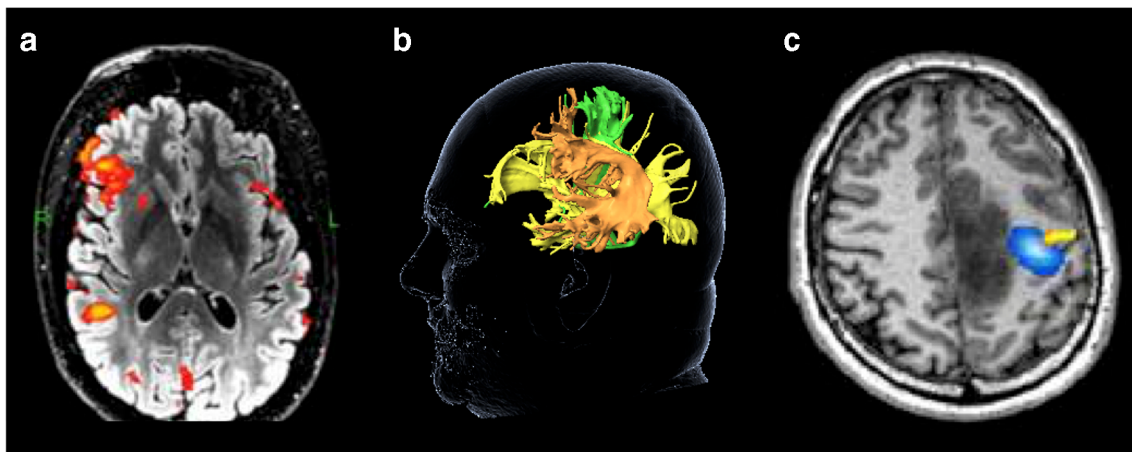
Fig. 4 Examples of imaging for localization of brain functions and white matter tracts. **A** Functional MRI of a patient with a language located in the right hemisphere, which was confirmed with a WADA test. **B** Visualization of the left corticospinal tract (green), fasciculate arcuatus (orange) and inferior fronto-occipital fasciculus (yellow) using DTI in a patient with a left temporal diffuse astrocytoma, IDH-mutant. **C** Localization of the left motor cortex using MEG in a patient with a diffuse astrocytoma, IDH-mutant

6 months after surgery, which is remarkably high and would exclude these patients from adjuvant therapy in most neuro-oncology centers. High angular resolution diffusion-weighted imaging (HARDI) with q-ball algorithms is a new tractography technique with improved fiber tracking resolution at voxels with crossing fiber populations [6, 92]. One study reported that an intact left arcuate fasciculus and temporal part of the superior longitudinal fasciculus on post-operative HARDI tractography was associated with intact language, whereas an alteration or damaging of these structures resulted in, respectively, temporary or long-term language deficits [9]. Limitations of DTI are the variability of tracking algorithm settings and region-of-interest (ROI) placement. Tracking algorithm settings can lead to under- but mostly overestimation of white matter tracts. Still, 90% of the ground truth fibers are present in most of the algorithms [54]. ROI placement is subject to moderate to substantial interobserver variability but can be improved with protocols for ROI positioning [96]. Also, for HARDI DTI, considerable technical expertise is required, making it not yet available for standard practice. The high sensitivity and proven clinical value make DTI an indispensable technique for glioma surgery.

Magnetoencephalography Magnetoencephalography (MEG) detects magnetic fields as result of the electric currents from neuronal activity [90]. Although this is not an imaging technique, registration of the MEG with a 3D MRI sequence allows for visualization (Fig. 4C). Like fMRI, MEG can be used for the assessment of task-based activity in the pre-operative phase. Two small studies found MEG predicted motor function areas at 4 to 17 mm from DCS sites [41, 60]. A direct comparison of MEG and fMRI for the localization of the motor cortex showed an overlap with DCS in, respectively, 100% and 73% of the patients [43], demonstrating the higher accuracy of MEG. Indirect evidence shows that if the MEG

predicted functional areas within or at the margin the tumor, the EOR waspartial in 88% and complete in 12% compared to an equal division of partial and complete resections in patients with all MEG predicted functional areasoutside the tumor. Complete resection led to neurological deterioration in 2 of the 11 patients without and 2 of the 2 patients with MEG-predicted functional areas within or at the margin of the tumor, respectively [84]. On the other hand, using sensorimotor, visual, and speech MEG as a risk assessment for operation feasibility resulted in 46% of patients not to be considered for surgery due to glioma invasion of functional cortex, with only 6% of the patients who were operated suffering from neurological deterioration [22]. A major limitation of MEG is the availability, mostly in dedicated academic centers, and technical expertise needed to interpret the results. Therefore, although accuracy is considerable and the clinical application proven, MEG is not likely to become a standard modality in glioma treatment.

Transcranial magnetic stimulation Transcranial magnetic stimulation (TMS), like MEG, is not an imaging technique. Due to the integration with neuronavigation (nTMS), however, it can be used to locate and visualize brain functions in the pre-operative phase. By stimulating or inhibiting cortical activity with directed magnetic fields, specific functional tasks can be localized [12]. The accuracy of nTMS, compared with DCS, for localization of the motor cortex is between 3.4–6.2 mm [44, 70]. Another function of nTMS is the combination with DTI tractography, where nTMS regions, instead of user-selected regions of interest (ROI), are used to guide the tractography. In a study comparing ROI-based with nTMS-based tractography for language pathways, respectively, 40% and 76% of the tracts were detected with DSC [61]. Using nTMS for pre-operative planning, multiple studies found a minimum distance (range 8–12 mm) from nTMS motor

function or nTMS-fiber tracking that prevented any neurological deterioration [61, 81, 87]. Clinical implementation of nTMS in a large ($n = 250$) cohort of patients with brain tumors in motor eloquent locations, in comparison with a historical case-matched non-nTMS cohort, resulted in a significantly increased complete resection rate (59% versus 42%, $p = 0.05$; respectively) and increased PFS for patients with non-enhancing glioma (15.4 months versus 22.4 months, p = 0.05; respectively). Planned biopsies or non-surgical strategies were changed into resections in 68.5%, and overall post-operative deficit rate did not significantly differ between the groups (6.1% versus 8.5%; respectively) [21]. One must realize that DCS was still used in 66% of the patients and that the authors conclude that nTMS is crucial for pre-operative planning.

Only one small ($n = 4$) study used nTMS and nTMS tractography instead of DCS in patients not suitable for awake surgery with left-sided perisylvian lesions. This resulted in a GTR in all patients without any new neurological deficit with only one patient needing a second nTMS-based resection within days to achieve the GTR [32]. Overall, nTMS is a promising new technique that, combined with DTI, can overcome the ROI selection limitation of DTI and has proven its usefulness for surgical planning.

Intraoperative imaging

Intraoperative MRI Both fMRI and DTI can be acquired intraoperatively using iMRI. Intraoperative fMRI (ifMRI) can successfully localize the motor cortex during awake procedures using the task-based fMRI technique [53]. More interesting is the use of ifMRI resting state that allows for the localization of the motor cortex in patients under general anesthesia [23, 77]. Comparison of this technique with DCS in 14 patients resulted in a 62% sensitivity and 94% specificity [77]. Intraoperative DTI (iDTI) tractography has a high accuracy (100% sensitivity and 72% specificity) for the localization of the corticospinal tract, as demonstrated in a study with twenty glioma patients [35]. Another study replaced DCS with iDTI tractography for the localization of white matter tracts involved in language, resulting in a GTR in 78% and PR in 22% of the patients without any post-operative neurological deterioration [13]. The limitations of iMRI have been described above. Although ifMRI is not likely to replace DCS, iDTI has the potential to increase the safety of non-awake surgery.

Discussion

How can imaging aid glioma surgery? We know gliomas are widespread in the brain by the time of diagnosis, so a curative resection is not possible [14]. Still, there is accumulating evidence that removing more of the tumor improves PFS and OS

[8, 86]. Since glioma is an infiltrative disease, macroscopic recognition of the tumor within the normal brain can be very difficult. Imaging has the possibility to visualize the tumor and thus overcoming the macroscopic problems. Ideally, an imaging modality would not miss any tumor, 100% sensitivity, and only show tumor, 100% specificity. Unfortunately, current available imaging is not that accurate [93]. Still, using the current standard MRI to guide glioma resection has a positive impact on the treatment. Intraoperative MRI, fluorescence, and ultrasound can aid in achieving a complete resection of these standard MRI abnormalities. Since we know that gliomas extend beyond the current standard imaging abnormalities [38, 66], the next logical step is to extend the resection beyond these abnormalities. Evidence is starting to accumulate that other modalities like PET and MRSI, or FLAIR MRI in case of enhancing tumors, could guide these extended resections.

A different approach is the use of functional boundaries instead of imaging to guide a resection, whereas intraoperative mapping during awake surgery defines the limits of resection. This strategy postpones malignant transformation in LGG [17, 100]. The pitfall of functional boundaries is the choice of functions to test; removing more of the brain will lead to more deficits depending on how thoroughly the functions are tested. Translating this strategy into accuracy gives a high sensitivity and little residual tumor, but low specificity; not all resected tissue is tumor. A combination of image-guided extended resection and intraoperative stimulation mapping could improve the specificity by removing less normal brain, while keeping a high sensitivity.

Future directions

Randomized clinical trials are needed to compare the influence of image-guided glioma resection, possibly with addition of intraoperative fluorescence, based on standard MRI versus the most optimal imaging. In order to determine the most optimal imaging for the detection of glioma infiltration, studies directly comparing different imaging modalities, MRI sequences, and combinations of imaging, such as the FRONTIER study [94], have to be conducted. Besides pre-operative imaging, intraoperative ultrasound has demonstrated great potential and the results of the randomized US-GLIOMA trial (NCT03531333) are awaited for. Extending the resection implies that more frequently, functional areas will be encountered. DCS remains the gold standard for the localization of important brain functions and white matter tracts. Imaging, however, is indispensable for surgical planning, including the choice of awake versus non-awake surgery. DTI has proven its clinical value in an RCT, and studies exploring the increased accuracy of HARDI DTI, possibly in combination with nTMS, are needed.

Compliance with ethical standards

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