Cancer Pathogenesis and Therapy 2 (2024) 256–267

Contents lists available at ScienceDirect

Cancer Pathogenesis and Therapy

journal homepage: www.journals.elsevier.com/cancer-pathogenesis-and-therapy

Review article

Intraoperative glioblastoma surgery-current challenges and clinical trials: An update

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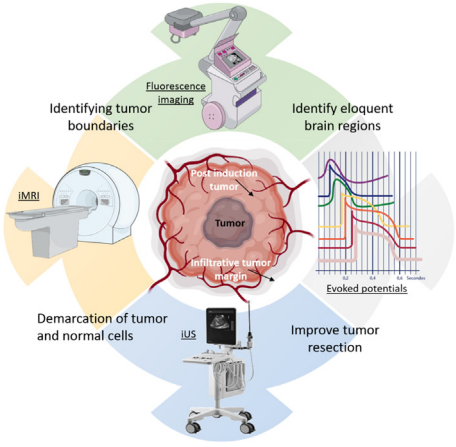
HIGHLIGHTS

- The balance between maximal safe resection and minimal neurological deficits is a challenge in glioblastoma surgery.
- Intraoperative imaging can help surgeons to accurately distinguish tumor tissue from normal brain tissue.
- Intraoperative mapping techniques can be combined with intraoperative imaging for greater efficiency.

GRAPHICAL ABSTRACT



Intraoperative mapping techniques for visualization and resection of glioblastoma. iMRI: Intraoperative magnetic resonance imaging; iUS: Intraoperative ultrasound.

ARTICLE INFO

Managing Editor: Peng Lyu
Edited by: Lili Wang and Peng Lyu

Keywords:
Glioblastoma
Infiltrative tumor
Awake craniotomy
Evoked potentials
Neuroimaging
Navigation

ABSTRACT

Surgical excision is an important part of the multimodal therapy strategy for patients with glioblastoma, a very aggressive and invasive brain tumor. While major advances in surgical methods and technology have been accomplished, numerous hurdles remain in the field of glioblastoma surgery. The purpose of this literature review is to offer a thorough overview of the current challenges in glioblastoma surgery. We reviewed the difficulties associated with tumor identification and visualization, resection extent, neurological function preservation, tumor margin evaluation, and inclusion of sophisticated imaging and navigation technology. Understanding and resolving these challenges is critical in order to improve surgical results and, ultimately, patient survival.

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https://doi.org/10.1016/j.cpt.2023.11.006
Received 17 August 2023; Received in revised form 23 November 2023; Accepted 30 November 2023

Introduction

Glioblastoma, the most prevalent and aggressive primary brain tumor in adults, exhibits an infiltrative growth pattern and a high recurrence rate despite aggressive treatment modalities. It is often treated with a combination of chemotherapy, radiation therapy, and surgery. Surgery holds a pivotal role in managing glioblastoma as it strives to achieve the safest resection of the tumor.[1,2] However, the infiltrative nature of glioblastoma presents a considerable challenge during surgical intervention. Tumor cells infiltrate the adjacent healthy brain tissue, creating difficulties in defining distinct boundaries between the tumor and normal brain tissue.[3] This infiltration extends beyond the observable tumor margins on imaging studies and results in the persistence of microscopic residual disease even after an apparently complete resection.[4,5]

The presence of residual tumor cells contributes to tumor recurrence and adversely affects patient outcomes. Glioblastoma surgery focuses on identifying and visualizing the tumor in order to guide resection and minimize residual disease. This requires overcoming the challenge of differentiating the tumor from healthy brain tissue intraoperatively.[6,7] Visual identification of the tumor is essential to ensure safe resection while minimizing damage to critical brain structures. To aid in tumor identification and visualization, various intraoperative imaging techniques have been developed. Intraoperative magnetic resonance imaging (iMRI) allows real-time imaging during surgery, thus providing updated information on tumor location and extent. It enables surgeons to assess the extent of resection and detect any residual tumor that might have been missed during the initial resection.[8,9] Intraoperative ultrasound (iUS) is another valuable tool that provides real-time imaging and helps surgeons to identify tumor boundaries and detect residual disease.[9–11] Additionally, fluorescence-guided surgery using 5-aminolevulinic acid (5-ALA) has gained popularity. 5-ALA is a photosensitizing agent that, when administered prior to surgery, selectively accumulates in glioblastoma cells, causing them to fluoresce at specific wavelengths of light. This fluorescence helps surgeons visualize the tumor and distinguish it from the surrounding healthy brain tissue. Additionally, other intraoperative techniques, such as awake mapping and advanced imaging modalities, help to preserve critical brain functions and minimize postoperative neurological deficits.[8,12] It is crucial to address the challenges in tumor identification and visualization as they directly impact the extent of resection and the likelihood of achieving complete tumor removal. Overcoming these challenges improves the chances of reducing residual disease, delaying tumor recurrence, and ultimately improving patient outcomes. In this review, the authors attempt to describe the difficulties that arise during tumor resection, the importance of current intraoperative imaging procedures in the determination of tumor boundaries, the preservation of neurocognitive deficits by electrical stimulations, and the advancement in neuro-navigation techniques.

Tumor identification and visualization challenges

Difficulties in differentiating tumors from healthy brain tissue

Differentiating tumor tissue from healthy brain tissue presents significant difficulties in the context of glioblastoma surgery. Glioblastoma cells infiltrate the surrounding brain tissue, making it challenging to visually distinguish between tumor and healthy tissue during surgery.[13] This is particularly true for infiltrative tumor margins that extend beyond the tumor boundaries seen on radiological images. The poor demarcation between tumor and healthy brain tissue increases the risk of leaving behind tumor cells during resection, which can lead to tumor recurrence.[14,15] To overcome this challenge, surgeons rely on advanced imaging techniques such as iMRI and iUS to provide real-time visualization and guidance during surgery, as described in Figure 1. These imaging modalities highlight subtle differences in tissue characteristics and aid in distinguishing tumor from healthy brain tissue, thus improving the accuracy of tumor resection and reducing the risk of residual disease.[16–18] Additionally, molecular and genetic profiling of tumor tissue can provide valuable information to aid in the differentiation of tumor cells from normal brain cells, further assisting surgeons in achieving maximal safe resection.

Role of intraoperative imaging techniques

Intraoperative MRI

iMRI has emerged as a valuable tool in glioblastoma surgery, providing real-time imaging capabilities that enhance the accuracy and safety of tumor resection. By integrating an MRI scanner into the operating room, surgeons can obtain real-time images during surgery[19,20] iMRI allows for

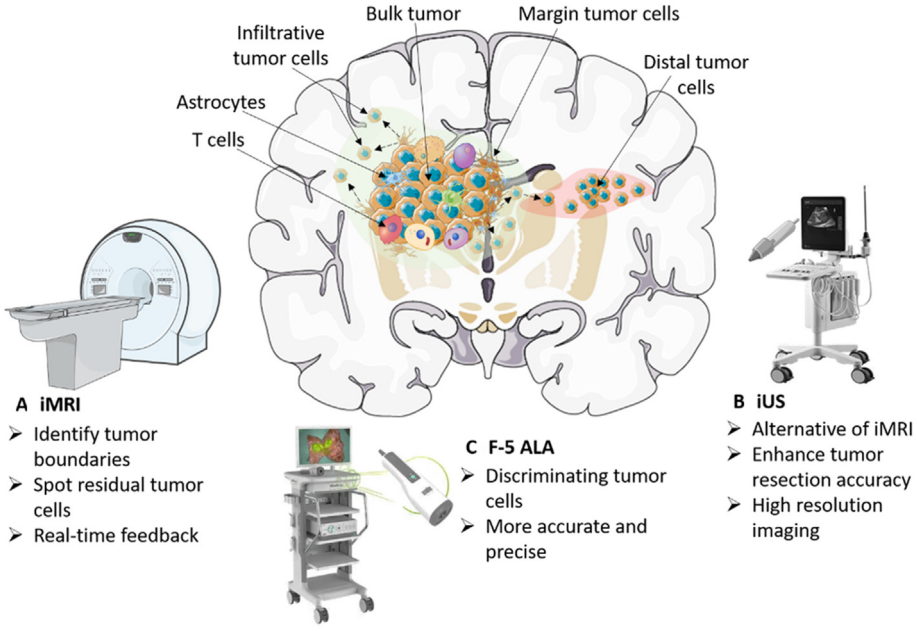

Figure 1. Demarcation of the infiltrative tumor using various intraoperative imaging techniques. (A) iMRI; (B) iUS; (C) F-5 ALA. F-5 ALA: Fluorescence-guided surgery with 5-aminolevulinic acid; iMRI: Intraoperative magnetic resonance imaging; iUS: Intraoperative ultrasound.

precise visualization of tumor boundaries, including infiltrative areas that may be difficult to distinguish from normal brain tissue. This real-time feedback enables surgeons to optimize the extent of tumor resection and reduce the risk of leaving behind residual tumor cells. Furthermore, iMRI facilitates the identification and preservation of critical brain structures and functional areas, thus minimizing postoperative neurological deficits.[21]

Intraoperative ultrasound

iUS is another valuable imaging utilized in glioblastoma surgery to aid real-time visualization and guidance intraoperatively. It involves the use of high-frequency sound waves that are emitted and detected by a handheld probe, providing immediate imaging feedback.[22] One of the key advantages of iUS is its ability to provide detailed and high-resolution images of the brain and tumor in real-time. This allows surgeons to accurately identify tumor boundaries, assess the extent of resection, and detect any residual tumor that may have been missed.[10] iUS is particularly useful as an alternative means of intraoperative imaging in situations where iMRI is not available or feasible. By incorporating iUS into glioblastoma surgery, surgeons can improve the accuracy and precision of tumor resection, and thus achieve better patient outcomes.[23]

Fluorescence-guided surgery with 5-aminolevulinic acid

Fluorescence-guided surgery using 5-ALA is a valuable technique that enhances the visualization and resection of tumor tissue in glioblastoma surgery. 5-ALA is a fluorescent compound that selectively accumulates in glioblastoma cells, causing them to emit a distinct red fluorescence at specific wavelengths of light.[24,25] By administering 5-ALA to patients prior to surgery, surgeons can use specialized imaging systems to visualize the fluorescent tumor tissue intraoperatively. This allows for real-time differentiation between tumor and normal brain tissue, aiding precise identification and removal of tumor cells.[26] This technique has been shown to increase the rate of complete resection and improve patient outcomes, including progression-free survival and overall survival.[27,28]

Raman spectroscopy

Raman spectroscopy (RS) can be used during glioblastoma surgery to rapidly examine the chemical composition of brain tissue. The surgeon can obtain spectra that describe the tissue's molecular structure by shining a laser onto the tissue and analyzing the Raman-scattered light. Since glioblastoma tissue differs from healthy brain tissue in terms of its DNA, proteins, lipids, and other macromolecules, it often displays distinctive molecular profiles. The surgeon uses this information to marginate the infiltrative tumor.[29,30] A previous study discovered that RS could distinguish between low-grade and high-grade gliomas based on their genetic characteristics by analyzing RS acquired from biopsy samples.[31] Thus, surgeons may evaluate the efficacy of therapy and even modify the therapy regimen by monitoring changes in the molecular composition of glioma tissue.[32] Further, surgeons can get a better understanding of the tumor and surrounding tissue by combining molecular data from RS with anatomical information from MRI. This multifaceted strategy improves the precision of tumor margin definition. Surface-enhanced Raman scattering (SERS) is a spectroscopic method that has the potential to simultaneously detect up to 10 substances and is based on plasmon-assisted scattering of molecules absorbed on a noble metal surface.[33] An intelligent SERS navigation system to direct the removal of brain tumors was reported by Jin et al.[34] They discovered metabolic acidosis (pH 6.2–6.9) in tumor tissues as a result of the switchover in glucose metabolism from oxidative phosphorylation to aerobic glycolysis. The efficiency of this system has been studied in both human and animal models. By avoiding external imaging probes, this method expedites the clinical use of acidic margin-guided surgery.[34]

Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) is an innovative technology that enables the histological visualization of living tissue in real-time. In a group of 12 patients, Höhne J et al assessed the advantages of CLE in surgical practice. They noted that CLE had the potential to facilitate brain tumor surgery by providing superior visualization of small structures and revealing hidden anatomical details.[35] Hong et al created a CLE with a "Lissajous scanning pattern." They established its viability for indocyanine green (ICG) fluorescence-guided brain tumor diagnosis with *in vitro* and *ex vivo* tests. This modality can demonstrate the tumor–brain interface and identify tumor cell invasion in the nearby healthy brain through direct tumor cell visualization.[36]

Intraoperative radiotherapy

Intraoperative radiotherapy (IORT) has been used as part of the initial therapy for controlling local recurrence of anaplastic astrocytoma and glioblastoma multiforme, using microtron. A recent study showed that treatment outcomes of malignant glioma are still poor, and precise diagnosis and radiation necrosis are impossible from the clinical course and neurological findings.[37] Clinicopathological result shows that IORT dose per session is limited to no more than 30 Gy. Follow-up examination using computed tomography (CT) in another study showed that IORT is the most favorable treatment modality if a malignant glioma is located near the brain surface.[38] While IORT is not typically considered an intraoperative mapping technique like those involving imaging or spectroscopy, it is sometimes used in combination with mapping technologies to optimize treatment. The integration of mapping techniques and imaging modalities such as functional MRI (fMRI), iMRI, and iUS ensures that IORT is delivered accurately to the residual tumor, thus maximizing the chances of effective treatment and reducing the risk of recurrence.[39] Recently a prospective, single-arm phase I/II study was conducted to determine the safety and efficacy of IORT with low-energy X-rays added to standard-of-care adjuvant therapy (radiochemotherapy and maintenance chemotherapy). It was shown that the addition of IORT was not only tolerable but also yielded a median local progression-free survival of roughly 18 months despite the high portion of patients with postoperative residual disease (13 of 15) and unmethylated O^6-methylguanine DNA methyltransferase (MGMT) promoters (10 of 15) in the trial.[40,41]

Challenges of achieving maximal safe resection

Proximity to eloquent brain regions

Achieving maximal safe resection in glioblastoma surgery is challenging due to the proximity of the tumor to eloquent brain regions. Eloquent areas of the brain are responsible for critical functions such as language, motor control, sensory perception, and cognition.[42] Preserving the functionality of these regions is crucial in order to minimize postoperative neurological deficits and maintain the patient's quality of life.[43] The location of glioblastoma varies among patients, and it can occur near or within eloquent brain regions. Surgical resection in these areas requires careful consideration and planning to balance the extent of resection with the preservation of neurological function.[44] To address the challenge of preserving neurological function during surgery, intraoperative mapping techniques are employed as shown in Figure 2.

Role of intraoperative mapping techniques

Awake craniotomy

Awake craniotomy with intraoperative mapping is an advanced surgical approach to glioblastoma management that helps to protect vital brain functions while obtaining maximum tumor excision. This method includes keeping the patient awake during part of the procedure,

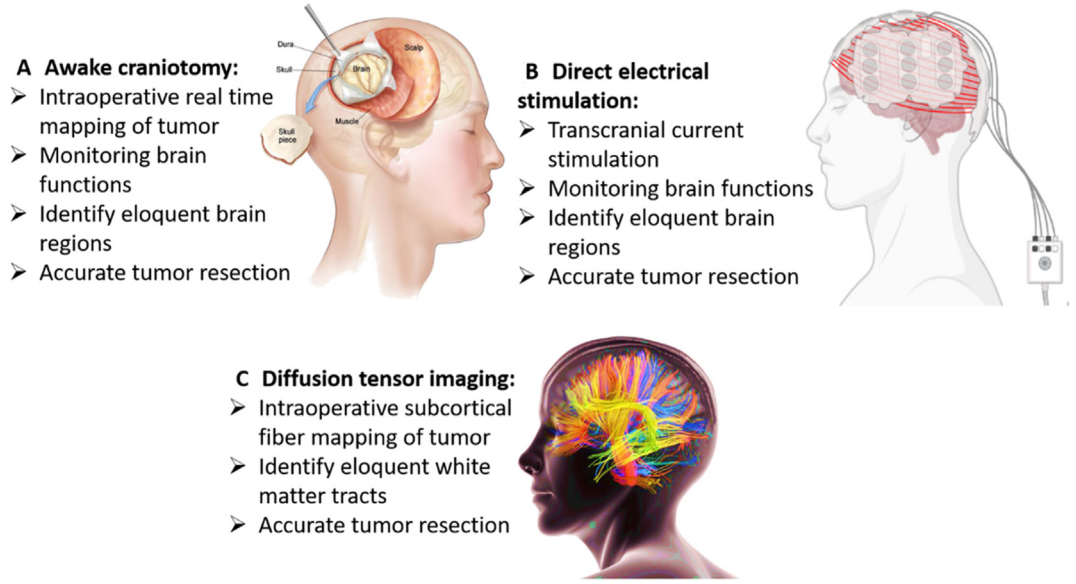

Figure 2. Intraoperative mapping of eloquent brain regions using different methods. (A) Awake craniotomy; (B) Direct electrical stimulation; (C) Diffusion tensor imaging.

allowing for real-time mapping and monitoring of brain functions.[45,46] Surgeons can identify eloquent brain regions by stimulating particular brain areas and measuring the patient's reaction. Awake craniotomy combined with intraoperative mapping allows surgeons to maneuver around these functional regions while reducing the risk of postoperative neurological deficits.[47,48] This approach also enables surgeons to differentiate between healthy brain tissue and tumor-invaded regions, thus allowing for more precise tumor resection.[49]

Direct electrical stimulation

Direct electrical stimulation (DES) is a powerful intraoperative mapping technique used in glioblastoma surgery to identify eloquent brain regions and preserve critical brain functions. This technique involves the application of small electrical currents directly to the brain tissue, allowing surgeons to assess functional areas and neural pathways.[50,51] By stimulating specific regions, surgeons can observe the patient's response and identify eloquent brain areas involved in motor control, language, sensory perception, and cognition. This information guides surgical decision-making, enabling surgeons to avoid or minimize damage to these essential functional areas during tumor resection.[52,53] DES provides real-time feedback and enhances the accuracy of tumor resection, ensuring that vital brain functions are preserved.[54] This technique has revolutionized intraoperative mapping, allowing surgeons to tailor their approach based on individual patients' functional anatomy, and ultimately leading to improved surgical outcomes and quality of life.[55]

Utilization of advanced imaging modalities

Functional magnetic resonance imaging

fMRI is a non-invasive intraoperative mapping approach that detects brain activity in real-time by monitoring changes in blood flow and oxygenation, thus allowing surgeons to map functional regions of the brain.[26,56] While undergoing fMRI scanning, patients are prompted to execute certain activities or respond to stimuli. This approach generates precise maps of brain areas associated with language, motor control, sensory perception, and cognition.[57] Surgeons can precisely identify and navigate around crucial functional regions during tumor excision by combining fMRI data with surgical navigation systems, thus reducing the likelihood of postoperative deficits.[54] fMRI-based intraoperative mapping improves surgical precision, allows for maximum tumor removal, and reduces the risk of harm to critical brain regions, ultimately improving patient outcomes.[58]

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a valuable intraoperative subcortical fiber mapping technique used in glioblastoma surgery to visualize and preserve critical white matter tracts. It measures the direction and integrity of water diffusion within brain tissue, providing information about the structural connectivity of neural pathways.[59] By reconstructing white matter tracts, surgeons can identify and preserve fiber bundles that serve essential functions. During the surgical procedure, DTI data is integrated into navigation systems, allowing surgeons to navigate around eloquent white matter tracts.[60,61] This technique aids in the avoidance of damage to motor pathways, language pathways, and other critical neural networks. By incorporating DTI into intraoperative mapping, surgeons can optimize the balance between tumor resection and functional preservation, leading to improved patient outcomes and minimal postoperative neurological deficits.[62]

Challenges of preservation of neurological function

One of the most difficult aspects of glioblastoma surgery is achieving minimal compromise between tumor removal and neurocognitive function preservation.[63] While aggressive tumor excision improves patient outcomes, it must be weighed against the possibility of postoperative neurological impairments. To avoid injuring vital brain circuits, surgeons must maneuver around eloquent zones. Advanced mapping methods, such as fMRI, DES, and awake craniotomy, aid in the identification and preservation of these crucial regions during surgery.[8] The challenge, however, is to achieve maximum safe resection while minimizing the risk of functional damage. Surgeons must make intelligent choices based on preoperative imaging, intraoperative mapping, and patient-specific criteria to maximize the balance between tumor removal and functional preservation.[64] Individualized surgical approaches, multidisciplinary collaboration, and ongoing advancements in intraoperative neuromonitoring techniques all contribute to addressing this challenge and improving the delicate balance between resection extent and neurological function preservation in glioblastoma surgery. Figure 3 depicts the electrical stimulation approaches used to identify neurocognitive abnormalities intraoperatively.

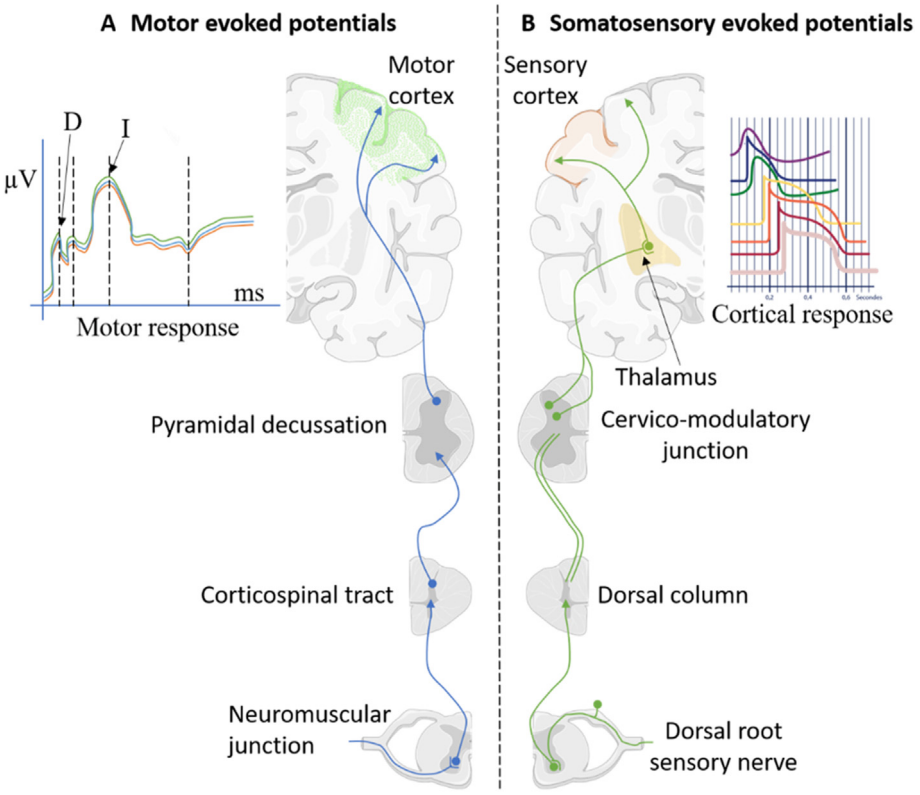

Figure 3. Detection of neurocognitive dysfunctions during glioma surgery using two ways: (A) Motor-evoked potentials; (B) Somatosensory-evoked potentials. D: Direct wave; I: Indirect wave.

Motor-evoked potentials

Intraoperative monitoring of motor-evoked potentials (MEPs), which enables real-time monitoring of the functional integrity of motor networks, is a helpful adjunct during neurosurgical procedures.[65] Direct cortical stimulation (DCS) employs strip electrodes to stimulate directly over the exposed motor cortex and can be utilized for intraoperative MEP stimulation. To record the responses [Direct wave (D)], muscle MEPs or, less commonly, epidural electrodes are used.[66,67] In brief, in order to record muscle MEPs intraoperatively, the aesthetic suppression of lower motor neuron excitability generated by the spatial and temporal accumulation of excitatory postsynaptic aptitudes must be overcome.[68] The 10/20 worldwide strategy serves as a foundation for stimulating scalp montages. Scale stimulating arrays are placed at quantifiable places across the motor cortex to provide hemispheric stimulation (C3/Cz-1 and C4/Cz-1) or interhemispheric stimulation (C3/C4, C4/C3, C1/C2, and C2/C1).[69] When classical stimulus intensity is just above the motor threshold, many muscles can respond at once. Direct cortical and subcortical stimulation can be directed at the primary motor cortex or corticospinal tract (CST), eliciting MEP in a small number of muscles within a particular anatomical area.[70,71] Acute interruption of nerve action potential conduction along the corticospinal axons (as a consequence of compression, thrust, ischemia, or mechanical injury) may result in intraoperative MEP signal alterations.[72] Non-surgical factors, however, may complicate MEP alterations. MEPs are affected by trial-to-trial variability, neuromuscular blockade, volatile anesthetics, systemic variables (including hypothermia and hypotension), and local factors such as nerve conduction failure caused by malpositioning.[73] MEP irregularities should alert the surgical team to act or stop while the possible neurological injury is still manageable, assuming that non-surgical causes have been ruled out.

Somatosensory-evoked potentials

Since the turn of the century, local ischemia has been recognized as a prevalent kind of brain damage that may be anticipated by somatosensory-evoked potentials (SSEPs) following spinal cord surgery.[74] The phase reversal of SSEP is one of the current reliable indicators for central sulcus localization following tumor resections. Here is a brief overview of how SSEP functions. Following the opening of the dura mater, the recording electrode is introduced into the central sulcus. Stimulating electrodes are implanted on the opposite side of the tumor, adjacent to the median or posterior tibial nerve. This results in a stable SSEP. The electrodes N20 and P22 are then set to represent the postcentral and precentral gyrus positions, respectively, in order to establish the anatomical position rendering to the waveform direction. If the waveform were reversed, the center groove would be positioned midway between the two points.[75–77] SSEP phase reversal technology has certain unresolved issues in the excision of glioblastoma with structures and features while being a regularly used technique with excellent accuracy to detect the core trench.[78,79]

Incorporation of advanced imaging and navigation technologies

Positron emission tomography imaging with radiolabeled tracers

Current positron emission tomography (PET) indicators highlight cancer-related traits that are shared by all tumor types. The majority of these are indicators of long-term proliferation, which suggest an increase in DNA replication, protein synthesis, and glucose consumption. Neurotheranostics aims to improve therapeutic and diagnostic results by transforming neurological illness staging. Conventional imaging has difficulty distinguishing between primary brain tumors and metastases, whereas

18F-fluorodeoxyglucose (^{18}F-FDG) PET may be able to show implicated abrasions or identify the primary cancer site.[80] Particularly in glioblastoma multiforme with necrosis, heterogeneous primary brain tumors may exhibit low or high uptake. For instance, despite their low grade, astrocytoma and gangliogliomas exhibit a comparatively high FDG uptake.[81] Due to extended radiotracer retention in the tumor, relative to the gray matter and radio-necrosis, delayed ^{18}F-FDG imaging can occasionally improve discrimination between tumor and normal tissue, thus overcoming the biggest clinical obstacle in brain tumor imaging.[82] As a first-line choice in brain tumor imaging, radiolabeled amino acid tracers are used because they have strong tumor-to-brain contrast in malignant tissues and low absorption in normal brain tissue. These tracers include carbon-11-methyl-L-methionine (^{11}C-MET), O-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET), 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine (FDOPA) (^{18}F-FDOPA), ^{18}F-fluciclovine (^{18}F-FACBC), and α-[^{11}C]methyl--L-tryptophan (^{11}C-AMT). For defining the tumor extent in moderated gliomas, amino acid-based imaging modalities using ^{11}C-MET and ^{18}F-FET have a high degree of accuracy.[83] FDOPA is a dopamine analog that can be used to treat neuroendocrine tumors. It is metabolized by monoamine oxidases or catechol-O-methyltransferase. For assessing recurrence in low-grade tumors, FDOPA is superior to ^{18}F-FDG PET; however, it has no effect on high-grade gliomas.[84,85] The kynurenine pathway, which oversees the generation of nicotinamide adenine dinucleotide from the breakdown of tryptophan, is where high quantities of ^{11}C-AMT accumulate in gliomas.[86] It is also possible to employ ^{18}F-FACBC PET for primary staging of gliomas. In a pilot research including six patients, Tsuyuguchi et al discovered that ^{18}F-FACBC may offer a superior response to ^{11}C-MET for the identification of new as well as recurrent high-grade gliomas.[87] When compared to ^{11}C-MET PET/MRI, ^{18}F-FACBC PET/MRI produced much better outcomes (82% *vs.* 10%). According to the study, ^{18}F-FACBC has a greater exposure rate for progressive and recurrent gliomas than ^{11}C-MET, and its images have superior contrast since the background in healthy brain cortex is lower.[88]

Stereotactic navigation

Identification of viable diagnostic tissue and vascular avoidance, which can be done *ex vivo* or *in vivo*, are the two key areas of current study for enhancing the efficiency and safety of stereotactic brain biopsy.[89] Advances in surgical equipment that enable fast vessel recognition are critical since vessel avoidance is a critical element in the safety of any stereotactic needle-based technique, including needle brain biopsy, interstitial laser thermal therapy, and deep brain stimulation (DBS).[90] Some of the vessel detection methods that have been incorporated into biopsy needles are interstitial sub-diffuse tomography, laser Doppler flowmetry, optical coherence, remission spectrometry, and detection of fluorescent intravascular contrast.[91,92]

Augmented reality platforms

A situated visualization or virtual representation of the surgeon's mental projections, such as tumor borders or nearby risk structure, can be produced through the integration of augmented reality (AR) with surgically relevant information. AR visualization integrates the overlay in the proper location, scale, and orientation. A decrease in intraoperative cognitive burden, reduction of surgical risk, and enhanced accessibility of thorough visual representations for the entire surgical team are all potential advantages.[93–95] Commercial software development has concentrated on integrating AR functions into the surgical microscope, thus making the guided microscope the most common and widely accessible sub-modality of AR in neurosurgery today, even though many applications are still restricted to research-only use.[96,97] Recent research has established the clinical feasibility and broad use of AR in the design of skin incisions, craniotomies, subsurface lesion targeting, and risk management in all neurosurgery subspecialties.[98,99] Although the benefits of employing AR intraoperatively are becoming more widely recognized, it is yet unknown how AR-guided treatments will impact surgical decision-making, intraoperative workflow, and patient outcomes. Aside from registration accuracy issues, which are a known limitation of current software production, the quality of the visualizations has also proved to be a barrier to broader clinical use.[100,101]

Clinical trials related to glioblastoma surgery

Table 1 summarizes some clinical trials that have been conducted with respect to glioblastoma surgery.

This article has several limitations. Glioblastomas vary greatly in molecular and cellular properties, and the limits of current imaging

Table 1
Clinical trials related to perioperative glioblastoma neurosurgeries.

No.	Clinical trial no.	Title	Treatment regimen/device	Population size (*n*)	Phase	Status	Sponsor
1	NCT01394692	Comparative study of intraoperative MRI-guided *vs.* conventional glioma surgery[102]	PoleStar-N20 intraoperative MRI	58	–	Completed	Goethe University, Germany
2	NCT03542409	Assessment of safety and feasibility of preoperative and intraoperative image-guided resection of gliomas and tumor region-specific biomarker correlation[103]	Group A (MR perfusion scan) and group B (2HG spectroscopy scan)	60	–	Recruiting	Huntsman Cancer Institute, US
3	NCT05470374	Intraoperative sonographically guided resection of non-enhancing gliomas (SONOGLIO)[104]	Intraoperative sonography	96	–	Recruiting	Sklifosovsky Institute of Emergency Care, Russia
4	NCT05484245	Sonography-guided resection of brain mass lesions (SOMALI)[105]	Intraoperative sonography	100	–	Recruiting	Sklifosovsky Institute of Emergency Care, Russia
5	NCT05475522	Intraoperative sonographically versus fluorescence-guided resection of contrast-enhancing gliomas and brain metastases (SONOFLUO)[106]	Ultrasound-guided brain tumor resection *vs.* 5-ALA-guided brain tumor resection (MRI)	134	–	Recruiting	Sklifosovsky Institute of Emergency Care, Russia
6	NCT03762343	Ultrasound-guided greater occipital nerve block in children undergoing posterior fossa craniotomy[107]	Ultrasound-guided greater occipital nerve block with bupivacaine 0.5%	40	III	Completed	Kasr El Aini Hospital, Cairo University, Egypt
7	NCT00870779	Fluorescence-guided resection of brain tumors[108]	5-ALA	105	I	Completed	Dartmouth-Hitchcock Medical Center, US
8	NCT04055688	Novel exoscope system for 5-ALA fluorescence-guided surgery for gliomas[109]	5-ALA, Orbeye surgical video microscope	20	I	Completed	H. Lee Moffitt Cancer Center and Research Institute, US
9	NCT00241670	Fluorescence-guided resection of malignant gliomas with 5-aminolevulinic acid[110]	5-ALA	415	III	Completed	medac GmbH, Germany

(*continued on next page*)

Table 1 (*continued*)

No.	Clinical trial no.	Title	Treatment regimen/device	Population size (*n*)	Phase	Status	Sponsor
10	NCT04738162	Clinical safety study on 5-aminolevulinic acid in children and adolescents with supratentorial brain tumors[111]	Oral 5-ALA	80	II	Recruiting	Westfälische Wilhelms-Universität Münster, Germany
11	NCT02685605	Intraoperative radiotherapy in newly diagnosed glioblastoma multiforme (INTRAGO-II)[112]	IORT	314	III	Recruiting	University Hospital Mannheim, Germany
12	NCT03226483	Intraoperative radiotherapy after the resection of brain metastases (INTRAMET)[113]	IORT	50	–	Recruiting	University Hospital Mannheim, Germany
13	NCT04690348	Intracavitary carrier-embedded Cs131 brachytherapy for recurrent brain metastases: a randomized phase II study[114]	Cesium-131 brachytherapy	76	II	Recruiting	Memorial Sloan Kettering Cancer Center, US
14	NCT03861299	The SAFE-trial: awake craniotomy versus surgery under general anesthesia for glioblastoma patients[115]	Intraoperative brain mapping with (sub)cortical electrostimulation	246	–	Recruiting	Erasmus Medical Center, Netherlands
15	NCT03010943	Brain awake surgery using virtual reality headset (CERVO1)[116]	Virtual reality headset	45	–	Completed	University Hospital, Angers, France
16	NCT04742231	Handheld dynamometer during awake craniotomy pilot[117]	Hand-held dynamometer	25	–	Recruiting	Mayo Clinic, US
17	NCT05202899	Effect of sugammadex for reversal of rocuronium-induced neuromuscular block on perioperative management of awake craniotomy[118]	Sugammadex	40	IV	Recruiting	Guangzhou General Hospital of Guangzhou Military Command
18	NCT01545297	Comparison of dexmedetomidine and propofol-remifentanil conscious sedation for awake craniotomy for tumor surgery[119]	Dexmedetomidine, propofol, remifentanil	50	–	Completed	University Health Network, Toronto, Canada
19	NCT05023434	A study to measure the effect of brain stimulation on hand strength and function in patients with brain tumors[120]	DES mapping, CyberGlove III	60	–	Recruiting	Medical College of Wisconsin
20	NCT02359565	Pembrolizumab in treating younger patients with recurrent, progressive, or refractory high-grade gliomas, diffuse intrinsic pontine gliomas, hypermutated brain tumors, ependymoma or medulloblastoma[121]	Dynamic contrast-enhanced MR perfusion, DTI-MRI, DWI-MRI, DSCP-WI, pembrolizumab	110	I	Recruiting	National Cancer Institute, US
21	NCT02277561	Voxel based diffusion tensor imaging in predicting response in patients with brain metastases undergoing whole Brain radiation therapy or stereotactic radiosurgery[122]	VB-DTI, whole-brain radiation therapy, stereotactic radiosurgery	0	–	Withdrawn	Albert Einstein College of Medicine, US
22	NCT02810626	DTI & tractography in pediatric tumor surgery[123]	BrightMatter™	24	–	–	London Health Sciences Centre
23	NCT02006407	A pilot study to evaluate neurocognitive injury and longitudinal changes in white matter during radiation therapy in children with primary brain tumors[124]	Cranial radiotherapy, DTI-MRI, CogState	5	–	Terminated	University of Michigan Rogel Cancer Center, US
24	NCT03591315	Clinical study of structural and functional evaluation of the visual pathway[125]	DTI-fMRI	60	–	–	Xiangya Hospital of Central South University, China
25	NCT05261724	Diffusion-tensor imaging in brain tumors evaluation[126]	MRI	100	–	Recruiting	George Emil Palade University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, Romania
26	NCT03208387	Understanding the late effects of surviving a pediatric brain tumor[127]	DTI, rs-fcMRI, WISC-V, CVLT-C	42	–	Active	Memorial Sloan Kettering Cancer Center, US
27	NCT01988675	MRI study of radiation-induced damage to white matter and blood-brain-barrier[128]	DTI-MRI	91	–	Completed	University of Michigan Rogel Cancer Center, US
28	NCT00285324	Diffusion tensor MRI to distinguish brain tumor recurrence from radiation necrosis[129]	DTI-MRI	29	–	Completed	National Institute of Neurological Disorders and Stroke, US
29	NCT01018329	Magnetic resonance imaging in evaluating response to radiation therapy in patients with high-grade glioma[130]	MRI	10	–	Completed	Abramson Cancer Center at Penn Medicine, US
30	NCT00437060	Brain function in young patients receiving methotrexate for acute lymphoblastic leukemia[131]	MRI, DTI	233	–	Completed	Children's Oncology Group, US
31	NCT05658731	Cognitive outcomes after Brain Substructure-informed Radiation planning in pediatric patients[132]	DTI, rs-fcMRI, WISC-V, CVLT-C	338	–	Recruiting	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, US
32	NCT01699269	Histopathologic evaluation of high-grade brain tumors by high-order diffusion tensor imaging (tedi-C2)[133]	DTI-MRI, peritumoral glial cell infiltration	10		Completed	University Hospital, Clermont-Ferrand, France
33	NCT01351337	Functional monitoring for motor pathway in brain tumor surgery within eloquent area[134]	DTT	58	–	Completed	Huashan Hospital, China
34	NCT04463979	Perioperative evaluation of cerebellar tumors[135]	DTT-MRI	66	–	Recruiting	Duke University, US
35	NCT02402075		TES, DCS	40	–	–	

(*continued on next page*)

Table 1 (*continued*)

No.	Clinical trial no.	Title	Treatment regimen/device	Population size (*n*)	Phase	Status	Sponsor
		Spinal motor evoked potentials in brain surgery[136]					Heinrich-Heine University, Duesseldorf, Germany
36	NCT04768400	MEP and neuromuscular blocker[137]	Neuromuscular blocking agent	100	–	Completed	Gangnam Severance Hospital, Korea
37	NCT01512147	Dexmedetomidine on intraoperative somatosensory and motor evoked potential monitoring during neurosurgery in pediatric patients[138]	Isoflurane, propofol, dexmedetomidine	20	–	Completed	Oregon Health and Science University, US
38	NCT01690364	Comparison of the effects of vecuronium and cisatracurium on electrophysiologic monitoring during neurosurgery[139]	Vecuronium, cisatracurium	74	–	Completed	Samsung Medical Center, Korea
39	NCT04136860	Long-term outcomes after different management strategies for high-level cerebral arteriovenous malformation (OHAVM)[140]	^{18}F-FDG	1000	–	Recruiting	Beijing Tiantan Hospital, China
40	NCT01806675	^{18}F-FPPRGD2 PET/CT or PET/MRI in predicting early response in patients with cancer receiving anti-angiogenesis therapy[141]	^{18}F-FDG,^{18}F-FPPRGD2	25	I/II	Completed	Stanford University, US
41	NCT02902757	FDG PET/CT in monitoring very early therapy response in patients with glioblastoma[142]	^{18}F-FDG	50	–	Recruiting	Jonsson Comprehensive Cancer Center, US
42	NCT03732352	^{18}F-FDG PET and osimertinib in evaluating glucose utilization in patients with EGFR-activated recurrent glioblastoma[143]	^{18}F-FDG, osimertinib	12	–	Active	Jonsson Comprehensive Cancer Center, US
43	NCT04315584	FDG and FDOPA PET demonstration of functional brain abnormalities[144]	^{18}F-FDG,^{18}F-FDOPA	5	I	Recruiting	University of Virginia, US
44	NCT00110032	Positron emission tomography using fluorine F 18 EF5 to find oxygen in tumor cells of patients who are undergoing surgery or biopsy for newly diagnosed brain tumors[145]	^{18}F-EF5	46	I	Terminated	National Cancer Institute, US
45	NCT04566185	Evaluation of the predictive value of ^{18}F-fluorodeoxyglucose positron emission tomography and brain perfusion computed tomography for the efficacy of anti-angiogenic therapy (bevacizumab) in recurrent glioblastoma (EVA DOPA)[146]	Bevacizumab,^{18}F-FDG	30	–	Recruiting	Centre Hospitalier Universitaire de Nîmes, France
46	NCT02885272	FDG PET imaging in diagnosing patients with glioblastoma[147]	^{18}F-FDG	21	I	Completed	M.D. Anderson Cancer Center, US
47	NCT00662506	Cediranib, temozolomide, and radiation therapy in treating patients with newly diagnosed glioblastoma[148]	^{18}F-FDG, cediranib maleate, temozolomide, DCE-MRI	46	I/II	Completed	National Cancer Institute, US
48	NCT01165632	Fluorine F 18 fluorodopa-labeled PET scan in planning surgery and radiation therapy in treating patients with newly diagnosed high- or low-grade malignant glioma[149]	^{18}F-FDOPA	24	I	Active	Mayo Clinic, US
49	NCT05386043	Registering genomics and imaging of tumors (ReGIT)[150]	^{18}F-FET,^{15}O water	20	–	Recruiting	Indiana University, US
50	NCT03926507	F18 fluciclovine PET/CT in assessing tumor volume and radiation therapy response in patients with glioblastoma undergoing surgery[151]	^{18}F-FACBC	12	–	Completed	M.D. Anderson Cancer Center, US
51	NCT03990285	[^{18}F]Fluciclovine in post-treatment glioblastoma (Axumin)[152]	^{18}F-FACBC	30	I	Completed	Abramson Cancer Center at Penn Medicine, US
52	NCT03409549	Multi-parametric MRI/fluorine-18 fluciclovine PET-CT in glioblastoma[153]	^{18}F-FACBC	12	–	–	The Leeds Teaching Hospitals NHS Trust, US
53	NCT05608395	^{11}C-methionine in diagnostics and management of glioblastoma multiforme patients (GlioMET)[154]	^{11}C-MET	72	II	Recruiting	Masaryk Memorial Cancer Institute, Czech Republic
54	NCT03739333	Early diagnosis of pseudoprogression using^{11}C-methionine PET-MRI after concomitant radiochemotherapy treatment for glioblastoma[155]	^{11}C-MET	40	–	Recruiting	Hospices Civils de Lyon, France
55	NCT01873469	Impact of [^{11}C]-methionine PET/MRI for individual tailoring postoperative radiochemotherapy for glioblastoma multiforme[156]	^{11}C-MET	102	–	Completed	Technische Universität Dresden, Germany

2HG: 2-Hydroxyglutarate; 5-ALA: 5-Aminolevulinic acid; C-MET: Carbon-11-methyl-L-methionine; CT: Computed tomography; CVLT-C: California Verbal Learning Test, Children's Version; DCE: Dynamic contrast-enhanced; DCS: Direct cortical stimulation; DES: Direct electrical stimulation; DSCP-WI: Dynamic Susceptibility Contrast-Weighted Imaging; DTI: Diffusion tensor imaging; DTT: Diffusion tensor tractography; DWI: Diffusion weighted imaging; EGFR: Estimated glomerular filtration rate; ^{18}F-FACBC: ^{18}F-fluciclovine; ^{18}F-FDG: ^{18}F-fluorodeoxyglucose; ^{18}F-FDOPA: 3,4-Dihydroxy-6-^{18}F-fluoro-L-phenylalanine; ^{18}F-EF5: F-pentafluorinated etanidazole (2-(2-Nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)-acetamide); ^{18}F-FET: O-(2-^{18}F-fluoroethyl)-L-tyrosine; ^{18}F-FPPRGD2: Fluorine-18 (phenylalanine-proline-proline-arginine-glycine–aspartic acid); fMRI: Functional magnetic resonance imaging; IORT: Intraoperative radiotherapy; MR: Magnetic resonance; MRI: Magnetic resonance imaging; PET: Positron emission tomography; rs-fcMRI: Resting state functional connectivity magnetic resonance imaging; TES: Transcranial electrical stimulation; VB-DTI: Voxel Based Diffusion Tensor Imaging; WISC-V: Wechsler Intelligence Scale for Children® Fifth Edition.

methods may result in an insufficient knowledge of this variety, affecting treatment planning. Current imaging technologies frequently lack real-time input during surgery, which is critical for surgeons to dynamically alter and optimize resection tactics. Furthermore, these methods' failure to predict treatment response reliably impedes the tailoring of post-operative therapy based on an individual patient's reaction. Resection procedures pose the inherent danger of creating neurological abnormalities by mistakenly injuring healthy brain tissue, particularly in crucial locations, with the goal of optimal tumor removal.

Conclusion

Glioblastoma surgery is a complicated and difficult subject that needs multidisciplinary and modern imaging approaches in order to overcome the numerous associated hurdles. In this review, we have discussed the difficulties, challenges, and current issues related to glioblastoma surgery. The infiltrative nature of glioblastoma, the difficulty in distinguishing tumors from healthy brain tissue, and the need for intraoperative mapping methods have all been extensively discussed. Furthermore, we highlighted the role of intraoperative tumor-differentiating techniques like MRI, ultrasound, RS, CLE, fluorescence-guided surgery, and various mapping techniques (such as awake craniotomy, DES, and fMRI) in improving surgical outcomes. Despite these challenges, advancements in technology, ongoing research, and collaborative efforts among healthcare professionals continue to improve the safety and efficacy of glioblastoma surgery.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors contribution

Vimal Patel: conceptualization, data curation, and mining, writing—original draft preparation. Vishal Chavda: conceptualization, data curation and mining, writing—original draft preparation, writing—review and editing. All authors reviewed and approved the submission of the final version of the manuscript.

Ethics statement

None.

Data availability statement

The script and database search protocol used in this review are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

References

1. Chavda V, Patel V, Yadav D, Shah J, Patel S, Jin JO. Therapeutics and research related to glioblastoma: advancements and future targets. *Curr Drug Metabol*. 2020; 21:186–198. https://doi.org/10.2174/1389200221666200408083950.
2. De La Garza-Ramos R, Kerezoudis P, Tamargo RJ, Brem H, Huang J, Bydon M. Surgical complications following malignant brain tumor surgery: an analysis of 2002-2011 data. *Clin Neurol Neurosurg*. 2016;140:6–10. https://doi.org/10.1016/j.clineuro.2015.11.005.
3. Jakola A, Sagberg L, Gulati S, Solheim O. Advancements in predicting outcomes in patients with glioma: a surgical perspective. *Expert Rev Anticancer Ther*. 2020;20: 167–177. https://doi.org/10.1080/14737140.2020.1735367.
4. John JK, Robin AM, Pabaney AH, et al. Complications of ventricular entry during craniotomy for brain tumor resection. *J Neurosurg*. 2017;127:426–432. https://doi.org/10.3171/2016.7.JNS16340.
5. Jackson C, Westphal M, Quiñones-Hinojosa A. Complications of glioma surgery. *Handb Clin Neurol*. 2016;134:201–218. https://doi.org/10.1016/B978-0-12-802997-8.00012-8.
6. Chaichana KL, Cabrera-Aldana EE, Jusue-Torres I, et al. When gross total resection of a glioblastoma is possible, how much resection should Be achieved? *World Neurosurg*. 2014;82:e257–e265. https://doi.org/10.1016/J.WNEU.2014.01.019.
7. Saleh T, Tyutyunyk-Massey L, Gewirtz DA. Tumor cell escape from therapy-induced senescence as a model of disease recurrence after dormancy. *Cancer Res*. 2019;79: 1044–1046. https://doi.org/10.1158/0008-5472.CAN-18-3437.
8. Parney IF, Goerss SJ, McGee K, Huston J, Perkins WJ, Meyer FB. Awake craniotomy, electrophysiologic mapping, and tumor resection with high-field intraoperative MRI. *World Neurosurg*. 2010;73:547–551. https://doi.org/10.1016/J.WNEU.2010.02.003.
9. Haddad AF, Aghi MK, Butowski N. Novel intraoperative strategies for enhancing tumor control: future directions. *Neuro Oncol*. 2022;24:S25–S32. https://doi.org/10.1093/neuonc/noac090.
10. Dixon L, Lim A, Grech-Sollars M, Nandi D. Camp S. Intraoperative ultrasound in brain tumor surgery: a review and implementation guide. *Neurosurg Rev*. 2022;45: 2503–2515. https://doi.org/10.1007/s10143-022-01778-4.
11. Sales AHA, Beck J, Schnell O, Fung C, Meyer B, Gempt J. Surgical treatment of glioblastoma: state-of-the-art and future trends. *J Clin Med*. 2022;11:5354. https://doi.org/10.3390/jcm11185354.
12. Corns R, Mukherjee S, Johansen A, Sivakumar G. 5-aminolevulinic acid guidance during awake craniotomy to maximise extent of safe resection of glioblastoma multiforme. *BMJ Case Rep*. 2015;2015:bcr2014208575. https://doi.org/10.1136/bcr-2014-208575.
13. Motekallemi A, Jeltema HR, Metzemaekers JDM, van Dam GM, Crane LMA, Groen RJM. The current status of 5-ALA fluorescence-guided resection of intracranial meningiomas—a critical review. *Neurosurg Rev*. 2015;38:619–628. https://doi.org/10.1007/S10143-015-0615-5/FIGURES/2.
14. Suarez-Meade P, Marenco-Hillembrand L, Prevatt C, et al. Awake vs. asleep motor mapping for glioma resection: a systematic review and meta-analysis. *Acta Neurochir (Wien)*. 2020;162:1709–1720. https://doi.org/10.1007/s00701-020-04357-y.
15. Cote DJ, Balak N, Brennum J, et al. Ethical difficulties in the innovative surgical treatment of patients with recurrent glioblastoma multiforme. *J Neurosurg*. 2017; 126:2045–2050. https://doi.org/10.3171/2016.11.JNS162488.
16. Akbari H, Macyszyn L, Da X, et al. Imaging surrogates of infiltration obtained via multiparametric imaging pattern analysis predict subsequent location of recurrence of glioblastoma. *Neurosurgery*. 2016;78:572–580. https://doi.org/10.1227/NEU.0000000000001202.
17. Varuna Shree N, Kumar TNR. Identification and classification of brain tumor MRI images with feature extraction using DWT and probabilistic neural network. *Brain Inf*. 2018;5:23–30. https://doi.org/10.1007/s40708-017-0075-5.
18. Coburger J, Scheuerle A, Kapapa T, et al. Sensitivity and specificity of linear array intraoperative ultrasound in glioblastoma surgery: a comparative study with high field intraoperative MRI and conventional sector array ultrasound. *Neurosurg Rev*. 2015;38:499–509. https://doi.org/10.1007/s10143-015-0627-1.
19. Rogers CM, Jones PS, Weinberg JS. Intraoperative MRI for brain tumors. *J Neuro Oncol*. 2021;151:479–490. https://doi.org/10.1007/S11060-020-03667-6/METRICS.
20. Choudhri AF, Siddiqui A, Klimo P, Boop FA. Intraoperative MRI in pediatric brain tumors. *Pediatr Radiol*. 2015;45:397–405. https://doi.org/10.1007/s00247-015-3322-z.
21. Bisdas S, Roder C, Ernemann U, Tatagiba MS. Intraoperative MR imaging in neurosurgery. *Clin Neuroradiol*. 2015;25:237–244. https://doi.org/10.1007/s00062-015-0443-6.
22. Moiyadi AV. Intraoperative ultrasound technology in neuro-oncology practice—current role and future applications. *World Neurosurg*. 2016;93:81–93. https://doi.org/10.1016/J.WNEU.2016.05.083.
23. Bastos DCDA, Juvekar P, Tie Y, et al. Challenges and opportunities of intraoperative 3D ultrasound with neuronavigation in relation to intraoperative MRI. *Front Oncol*. 2021;11:656519. https://doi.org/10.3389/fonc.2021.656519.
24. Mahmoudi K, Garvey KL, Bouras A, et al. 5-aminolevulinic acid photodynamic therapy for the treatment of high-grade gliomas. *J Neuro Oncol*. 2019;141:595–607. https://doi.org/10.1007/s11060-019-03103-4.
25. Ferraro N, Barbarite E, Albert TR, et al. The role of 5-aminolevulinic acid in brain tumor surgery: a systematic review. *Neurosurg Rev*. 2016;39:545–555. https://doi.org/10.1007/s10143-015-0695-2.
26. Gerritsen JKW, Broekman MLD, De Vleeschouwer S, et al. Safe surgery for glioblastoma: recent advances and modern challenges. *Neurooncol Pract*. 2022;9: 364–379. https://doi.org/10.1093/nop/npac019.
27. Gandhi S, Meybodi AT, Belykh E, et al. Survival outcomes among patients with high-grade glioma treated with 5-aminolevulinic acid–guided surgery: a systematic review and meta-analysis. *Front Oncol*. 2019;9:466230. https://doi.org/10.3389/fonc.2019.00620.
28. Mirza AB, Christodoulides I, Lavrador JP, et al. 5-Aminolevulinic acid-guided resection improves the overall survival of patients with glioblastoma - a

comparative cohort study of 343 patients. *Neurooncol Adv*. 2021;3:1–11. https://doi.org/10.1093/noajnl/vdab047.
29. Pekmezci M, Morshed RA, Chunduru P, et al. Detection of glioma infiltration at the tumor margin using quantitative stimulated Raman scattering histology. *Sci Rep*. 2021;11:1–11. https://doi.org/10.1038/s41598-021-91648-8.
30. Herta J, Cho A, Roetzer-Pejrimovsky T, et al. Optimizing maximum resection of glioblastoma: Raman spectroscopy versus 5-aminolevulinic acid. *J Neurosurg*. 2023;39:334–343. https://doi.org/10.3171/2022.11.JNS22693.
31. Romanishkin I, Savelieva T, Kosyrkova A, et al. Differentiation of glioblastoma tissues using spontaneous Raman scattering with dimensionality reduction and data classification. *Front Oncol*. 2022;12:944210. https://doi.org/10.3389/fonc.2022.944210.
32. Kouri MA, Spyratou E, Karnachoriti M, et al. Raman spectroscopy: a personalized decision-making tool on clinicians' hands for in situ cancer diagnosis and surgery guidance. *Cancers (Basel)*. 2022;14:1144. https://doi.org/10.3390/cancers14051144.
33. Spedalieri C, Kneipp J. Surface enhanced Raman scattering for probing cellular biochemistry. *Nanoscale*. 2022;14:5314–5328. https://doi.org/10.1039/d2nr00449f.
34. Jin Z, Yue Q, Duan W, et al. Intelligent SERS navigation system guiding brain tumor surgery by intraoperatively delineating the metabolic acidosis. *Adv Sci (Weinh)*. 2022;9:e2104935. https://doi.org/10.1002/ADVS.202104935.
35. Höhne J, Schebesch KM, Zoubaa S, Proescholdt M, Riemenschneider MJ, Schmidt NO. Intraoperative imaging of brain tumors with fluorescein: confocal laser endomicroscopy in neurosurgery. Clinical and user experience. *Neurosurg Focus*. 2021;50:1–6. https://doi.org/10.3171/2020.11.FOCUS20783.
36. Hong DH, Kim JH, Won JK, et al. Clinical feasibility of miniaturized Lissajous scanning confocal laser endomicroscopy for indocyanine green-enhanced brain tumor diagnosis. *Front Oncol*. 2023;12:1–15. https://doi.org/10.3389/fonc.2022.994054.
37. Sarria GR, Sperk E, Han X, et al. Intraoperative radiotherapy for glioblastoma: an international pooled analysis. *Radiother Oncol*. 2020;142:162–167. https://doi.org/10.1016/j.radonc.2019.09.023.
38. Diehl CD, Giordano FA, Grosu AL, et al. Opportunities and alternatives of modern radiation oncology and surgery for the management of resectable brain metastases. *Cancers (Basel)*. 2023;15:3670. https://doi.org/10.3390/cancers15143670.
39. Ylanan AMD, Pascual JSG, Cruz-Lim EMD, Ignacio KHD, Cañal JPA, Khu KJO. Intraoperative radiotherapy for glioblastoma: a systematic review of techniques and outcomes. *J Clin Neurosci*. 2021;93:36–41. https://doi.org/10.1016/j.jocn.2021.08.022.
40. Giordano FA, Brehmer S, Abo-Madyan Y, et al. INTRAGO: intraoperative radiotherapy in glioblastoma multiforme - a Phase I/II dose escalation study. *BMC Cancer*. 2014;14:992. https://doi.org/10.1186/1471-2407-14-992.
41. Ayala Alvarez DS, Watson PGF, Popovic M, et al. Evaluation of dosimetry formalisms in intraoperative radiation therapy of glioblastoma. *Int J Radiat Oncol Biol Phys*. 2023;117:763–773. https://doi.org/10.1016/j.ijrobp.2023.04.031.
42. Gómez Vecchio T, Neimantaite A, Corell A, et al. Lower-Grade gliomas: an epidemiological voxel-based analysis of location and proximity to eloquent regions. *Front Oncol*. 2021;11:748229. https://doi.org/10.3389/fonc.2021.748229.
43. Schucht P, Seidel K, Jilch A, Beck J, Raabe A. A review of monopolar motor mapping and a comprehensive guide to continuous dynamic motor mapping for resection of motor eloquent brain tumors. *Neurochirurgie*. 2017;63:175–180. https://doi.org/10.1016/j.neuchi.2017.01.007.
44. Klein E. Eloquent brain, ethical challenges: functional brain mapping in neurosurgery. *Semin Ultrasound CT MRI*. 2015;36:291–295. https://doi.org/10.1053/j.sult.2015.05.009.
45. Dziedzic T, Bernstein M. Awake craniotomy for brain tumor: indications, technique and benefits. *Expert Rev Neurother*. 2014;14:1405–1415. https://doi.org/10.1586/14737175.2014.979793.
46. Gogos AJ, Young JS, Morshed RA, Hervey-Jumper SL, Berger MS. Awake glioma surgery: technical evolution and nuances. *J Neuro Oncol*. 2020;147:515–524. https://doi.org/10.1007/S11060-020-03482-Z/METRICS.
47. Foster CH, Morone PJ, Cohen-Gadol A. Awake craniotomy in glioma surgery: is it necessary? *J Neurosurg Sci*. 2019;63:162–178. https://doi.org/10.23736/S0390-5616.18.04590-3.
48. Chua TH, See AAQ, Ang BT, King NKK. Awake craniotomy for resection of brain metastases: a systematic review. *World Neurosurg*. 2018;120:e1128–e1135. https://doi.org/10.1016/j.wneu.2018.08.243.
49. Incekara F, Olubiyi O, Ozdemir A, Lee T, Rigolo L, Golby A. The value of pre- and intraoperative adjuncts on the extent of resection of hemispheric low-grade gliomas: a retrospective analysis. *J Neurol Surg A Cent Eur Neurosurg*. 2015;77:79–87. https://doi.org/10.1055/s-0035-1551830.
50. Jenkins EPW, Finch A, Gerigk M, Triantis IF, Watts C, Malliaras GG. Electrotherapies for glioblastoma. *Adv Sci*. 2021;8:2100978. https://doi.org/10.1002/advs.202100978.
51. Duffau H. Stimulation mapping of white matter tracts to study brain functional connectivity. *Nat Rev Neurol*. 2015;11:255–265. https://doi.org/10.1038/nrneurol.2015.51.
52. Lang S, Gan LS, McLennan C, Kirton A, Monchi O, Kelly JJP. Preoperative transcranial direct current stimulation in glioma patients: a proof of concept pilot study. *Front Neurol*. 2020;11:593950. https://doi.org/10.3389/fneur.2020.593950.
53. Pallud J, Rigaux-Viode O, Corns R, et al. Direct electrical bipolar electrostimulation for functional cortical and subcortical cerebral mapping in awake craniotomy. Practical considerations. *Neurochirurgie*. 2017;63:164–174. https://doi.org/10.1016/j.neuchi.2016.08.009.
54. Jech R, Mueller K. Investigating network effects of DBS with fMRI. In: *Connectomic deep brain stimulation*. Academic Press; 2021:275–301. https://doi.org/10.1016/B978-0-12-821861-7.00026-9.
55. You H, Qiao H. Intraoperative neuromonitoring during resection of gliomas involving eloquent areas. *Front Neurol*. 2021;12:658680. https://doi.org/10.3389/FNEUR.2021.658680/BIBTEX.
56. Conti Nibali M, Rossi M, Sciortino T, et al. Preoperative surgical planning of glioma: limitations and reliability of fMRI and DTI tractography. *J Neurosurg Sci*. 2019;63:127–134. https://doi.org/10.23736/S0390-5616.18.04597-6.
57. Emch M, von Bastian CC, Koch K. Neural correlates of verbal working memory: an fMRI meta-analysis. *Front Hum Neurosci*. 2019;13:447322. https://doi.org/10.3389/fnhum.2019.00180.
58. Liu Y, Fu H, Wang T. Neuroinflammation in perioperative neurocognitive disorders: from bench to the bedside. *CNS Neurosci Ther*. 2022;28:484–496. https://doi.org/10.1111/cns.13794.
59. Jones TL, Byrnes TJ, Yang G, Howe FA, Bell BA, Barrick TR. Brain tumor classification using the diffusion tensor image segmentation (D-SEG) technique. *Neuro Oncol*. 2015;17:466–476. https://doi.org/10.1093/neuonc/nou159.
60. Papageorgiou TS, Chourmouzi D, Drevelengas A, Kouskouras K, Siountas A. Diffusion Tensor Imaging in brain tumors: a study on gliomas and metastases. *Phys Med*. 2015;31:767–773. https://doi.org/10.1016/j.ejmp.2015.03.010.
61. Bernardo A. Virtual reality and simulation in neurosurgical training. *World Neurosurg*. 2017;106:1015–1029. https://doi.org/10.1016/j.wneu.2017.06.140.
62. Khan KA, Jain SK, Sinha VD, Sinha J. Preoperative diffusion tensor imaging: a landmark modality for predicting the outcome and characterization of supratentorial intra-axial brain tumors. *World Neurosurg*. 2019;124:e540–e551. https://doi.org/10.1016/j.wneu.2018.12.146.
63. Dadario NB, Brahimaj B, Yeung J, Sughrue ME. Reducing the cognitive footprint of brain tumor surgery. *Front Neurol*. 2021;12:711646. https://doi.org/10.3389/fneur.2021.711646.
64. Wu C, Ferreira F, Fox M, et al. Clinical applications of magnetic resonance imaging based functional and structural connectivity. *Neuroimage*. 2021;244:118649. https://doi.org/10.1016/j.neuroimage.2021.118649.
65. Sollmann N, Bulubas L, Tanigawa N, Zimmer C, Meyer B, Krieg SM. The variability of motor evoked potential latencies in neurosurgical motor mapping by preoperative navigated transcranial magnetic stimulation. *BMC Neurosci*. 2017;18:1–15. https://doi.org/10.1186/s12868-016-0321-4.
66. Sasaki R, Tamura K, Yamazaki S, et al. Effects of intraoperative motor evoked potential amplification following tetanic stimulation of the pudendal nerve in pediatric craniotomy. *J Neurosurg Pediatr*. 2023;31:1–8. https://doi.org/10.3171/2023.1.peds22505.
67. Abalkhail TM, MacDonald DB, AlThubaiti I, et al. Intraoperative direct cortical stimulation motor evoked potentials: stimulus parameter recommendations based on rheobase and chronaxie. *Clin Neurophysiol*. 2017;128:2300–2308. https://doi.org/10.1016/j.clinph.2017.09.005.
68. Nace T, Fulop B, Pfeiffer C, et al. *Exploring the evidence on music-based interventions for executive functioning and emotional wellbeing in stroke rehabilitation: a scoping review (Version 2)*. Temple University Health Sciences Libraries; May 5 2023. Systematic Review Service. [Accessed July 7, 2023].
69. Asimakidou E, Abut PA, Raabe A, Seidel K. Motor evoked potential warning criteria in supratentorial surgery: a scoping review. *Cancers (Basel)*. 2021;13:2803. https://doi.org/10.3390/cancers13112803.
70. Siebner HR, Funke K, Aberra AS, et al. Transcranial magnetic stimulation of the brain: what is stimulated? – a consensus and critical position paper. *Clin Neurophysiol*. 2022;140:59–97. https://doi.org/10.1016/J.CLINPH.2022.04.022.
71. Ortiz KJ, Hawayek MI, Middlebrooks EH, et al. Intraoperative direct stimulation identification and preservation of critical white matter tracts during brain surgery. *World Neurosurg*. 2021;146:64–74. https://doi.org/10.1016/J.WNEU.2020.10.100.
72. Sanders B, Catania S, Luoma AM. An updated review on the principles of intraoperative neurophysiological monitoring and the anaesthetic considerations. *Anaesth Intensive Care Med*. 2022;23:788–796. https://doi.org/10.1016/J.MPAIC.2022.10.009.
73. Guo D, Fan X, You H, et al. Prediction of postoperative motor deficits using intraoperative motor-evoked potentials in middle cerebral artery aneurysm. *Neurosurg Rev*. 2021;44:495–501. https://doi.org/10.1007/s10143-020-01235-0.
74. Strahm C, Min K, Boos N, Ruetsch Y, Curt A. Reliability of perioperative SSEP recordings in spine surgery. *Spinal Cord*. 2003;41:483–489. https://doi.org/10.1038/sj.sc.3101493.
75. Xie T, Wu Z, Schalk G, et al. Automated intraoperative central sulcus localization and somatotopic mapping using median nerve stimulation. *J Neural Eng*. 2022;19:46020. https://doi.org/10.1088/1741-2552/ac7dfd.
76. Scerrati A, Mongardi L, Cavallo MA, et al. Awake surgery for skills preservation during a sensory area tumor resection in a clarinet player. *Acta Neurol Belg*. 2021;121:1235–1239. https://doi.org/10.1007/s13760-020-01368-5.
77. Paldor I, Doron O, Peso D, Jubran M, Sviri GE. Intraoperative neuromonitoring during resection of cranial meningiomas and its effect on the surgical workflow. *Neurosurg Rev*. 2022;45:1481–1490. https://doi.org/10.1007/s10143-021-01667-2.
78. Al-Adli NN, Young JS, Sibih YE, Berger MS. Technical aspects of motor and language mapping in glioma patients. *Cancers (Basel)*. 2023;15:2173. https://doi.org/10.3390/cancers15072173.
79. Pan SY, Chen JP, Cheng WY, Lee HT, Shen CC. The role of tailored intraoperative neurophysiological monitoring in glioma surgery: a single institute experience. *J Neuro Oncol*. 2020;146:459–467. https://doi.org/10.1007/s11060-019-03347-0.

80. Treglia G, Muoio B, Trevisi G, et al. Diagnostic performance and prognostic value of PET/CT with different tracers for brain tumors: a systematic review of published meta-analyses. *Int J Mol Sci*. 2019;20:4669. https://doi.org/10.3390/ijms20194669.
81. Barkley A, Hauptman JS. Pediatric brainstem tumors. In: Alexiou G, Prodromou N, eds. *Pediatric neurosurgery for clinicians*. Springer International Publishing; 2022: 327–344. https://doi.org/10.1007/978-3-030-80522-7_22.
82. Lee ST, Burvenich I, Scott AM. Novel target selection for nuclear medicine studies. *Semin Nucl Med*. 2019;49:357–368. https://doi.org/10.1053/j.semnuclmed.2019.06.004.
83. Cui M, Zorrilla-Veloz RI, Hu J, Guan B, Ma X. Diagnostic accuracy of pet for differentiating true glioma progression from post treatment-related changes: a systematic review and meta-analysis. *Front Neurol*. 2021;12:671867. https://doi.org/10.3389/FNEUR.2021.671867/BIBTEX.
84. Somme F, Bender L, Namer IJ, Noël G, Bund C. Usefulness of 18F-FDOPA PET for the management of primary brain tumors: a systematic review of the literature. *Cancer Imag*. 2020;20:70. https://doi.org/10.1186/s40644-020-00348-5.
85. Jain S, Dhingra VK. An overview of radiolabeled amino acid tracers in oncologic imaging. *Front Oncol*. 2023;13:983023. https://doi.org/10.3389/fonc.2023.983023.
86. Au - Yue X, Au - Nikam RM, Au - Kecskemethy HH, et al. Radiosynthesis of 1-(2-[18F]Fluoroethyl)-L-Tryptophan using a one-pot, two-step protocol. *JoVE*. 2021;21: e63025. https://doi.org/10.3791/63025.
87. Tsuyuguchi N, Terakawa Y, Uda T, Nakajo K, Kanemura Y. Diagnosis of brain tumors using amino acid transport pet imaging with (18)F-fluciclovine: a comparative study with L-methyl-(11)C-methionine pet imaging. *Asia Ocean J Nucl Med Biol*. 2017;5:85–94. https://doi.org/10.22038/aojnmb.2017.8843.
88. Kondo A, Ishii H, Aoki S, et al. Phase IIa clinical study of [18F]fluciclovine: efficacy and safety of a new PET tracer for brain tumors. *Ann Nucl Med*. 2016;30:608–618. https://doi.org/10.1007/s12149-016-1102-y.
89. Akshulakov SK, Kerimbayev TT, Biryuchkov MY, Urunbayev YA, Farhadi DS, Byvaltsev VA. Current trends for improving safety of stereotactic brain biopsies: advanced optical methods for vessel avoidance and tumor detection. *Front Oncol*. 2019;9:947. https://doi.org/10.3389/fonc.2019.00947.
90. Manjila S, Rosa B, Price K, Manjila R, Mencattelli M, Dupont PE. Robotic instruments inside the MRI bore: key concepts and evolving paradigms in imaging-enhanced cranial neurosurgery. *World Neurosurg*. 2023;176:127–139. https://doi.org/10.1016/j.wneu.2023.01.025.
91. Wårdell K, Klint E, Milos P, Richter J. One-insertion stereotactic brain biopsy using in vivo optical guidance—a case study. *Oper Neurosurg*. 2023. Published online 9900. https://journals.lww.com/onsonline/Fulltext/9900/One_Insertion_Stereotactic_Brain_Biopsy_Using_In.696.aspx.
92. Bex A, Mathon B. Advances, technological innovations, and future prospects in stereotactic brain biopsies. *Neurosurg Rev*. 2022;46:5. https://doi.org/10.1007/s10143-022-01918-w.
93. Shan Q, Doyle TE, Samavi R, Al-Rei M. Augmented reality based brain tumor 3D visualization. *Procedia Comput Sci*. 2017;113:400–407. https://doi.org/10.1016/j.procs.2017.08.356.
94. Guerroudji MA, Amara K, Benbelkacem S, et al. Automatic brain tumor segmentation, and 3D reconstruction and visualization using augmented reality. In: *2021 proceedings of the international conference on artificial intelligence for cyber security systems and privacy, AI-CSP 2021*. Institute of Electrical and Electronics Engineers Inc.; 2021. https://doi.org/10.1109/AI-CSP52968.2021.9671223.
95. Maruyama K, Watanabe E, Kin T, et al. Smart glasses for neurosurgical navigation by augmented reality. *Oper Neurosurg*. 2018;15:551–556. https://doi.org/10.1093/ons/opx279.
96. Alsaif H, Guesmi R, Alshammari BM, et al. A novel data augmentation-based brain tumor detection using convolutional neural network. *Appl Sci*. 2022;12:3773. https://doi.org/10.3390/app12083773.
97. Alfonso-Garcia A, Bec J, Sridharan Weaver S, et al. Real-time augmented reality for delineation of surgical margins during neurosurgery using autofluorescence lifetime contrast. *J Biophotonics*. 2020;13:e201900108. https://doi.org/10.1002/jbio.201900108.
98. Cutolo F, Meola A, Carbone M, et al. A new head-mounted display-based augmented reality system in neurosurgical oncology: a study on phantom. *Comput Assist Surg*. 2017;22:39–53. https://doi.org/10.1080/24699322.2017.1358400.
99. Roethe AL, Rösler J, Misch M, Vajkoczy P, Picht T. Augmented reality visualization in brain lesions: a prospective randomized controlled evaluation of its potential and current limitations in navigated microneurosurgery. *Acta Neurochir (Wien)*. 2022;164:3–14. https://doi.org/10.1007/s00701-021-05045-1.
100. Dho YS, Park SJ, Choi H, et al. Development of an inside-out augmented reality technique for neurosurgical navigation. *Neurosurg Focus*. 2021;51:E21. https://doi.org/10.3171/2021.5.FOCUS21184.
101. Satoh M, Nakajima T, Yamaguchi T, Watanabe E, Kawai K. Evaluation of augmented-reality based navigation for brain tumor surgery. *J Clin Neurosci*. 2021;94:305–314. https://doi.org/10.1016/j.jocn.2021.10.033.
102. *Comparative study of intraoperative MRI-guided vs. Conventional glioma surgery | ClinicalTrials.gov*. ClinicalTrials.gov; 2012. https://clinicaltrials.gov/study/NCT01394692?intr=NCT01394692&rank=1. [Accessed November 20, 2023].
103. *Safety and feasibility of preoperative and intraoperative image-guided resection of gliomas*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT03542409?cond=Glioblastoma&rank=1&limit=50&term=NCT03542409. [Accessed October 2, 2023].
104. *Intraoperative sonographically guided resection of non-enhancing gliomas*. ClinicalTrials.gov; 2022. https://clinicaltrials.gov/study/NCT05470374. [Accessed October 2, 2023].
105. *Sonography-guided resection of brain mass lesions*. ClinicalTrials.gov; 2022. https://clinicaltrials.gov/study/NCT05484245?term=NCT05484245&rank=1. [Accessed October 2, 2023].
106. *Intraoperative sonographically versus fluorescence-guided resection of contrast-enhancing gliomas and brain metastases*. ClinicalTrials.gov; 2022. https://clinicaltrials.gov/study/NCT05475522?term=NCT05475522&rank=1. [Accessed October 2, 2023].
107. *Ultrasound-guided greater occipital nerve block in children undergoing posterior fossa craniotomy*. *ClinicalTrials.gov*; 2022. https://clinicaltrials.gov/study/NCT03762343?term=NCT03762343&rank=1. [Accessed October 2, 2023].
108. *Fluorescence guided resection of brain tumors*. ClinicalTrials.gov; 2019. https://clinicaltrials.gov/study/NCT00870779?term=NCT00870779&rank=1. [Accessed October 2, 2023].
109. *Novel exoscope system for 5-ALA fluorescence-guided surgery for gliomas*. *ClinicalTrials.gov*; 2022. https://clinicaltrials.gov/study/NCT04055688?term=NCT04055688&rank=1. [Accessed October 2, 2023].
110. Fluorescence-guided resection of malignant gliomas with 5-aminolevulinic acid. https://clinicaltrials.gov/study/NCT00241670?term=NCT00241670&rank=1. [Accessed October 2, 2023].
111. Schwake M, Schipmann S, Müther M, Köchling M, Brentrup A, Stummer W. 5-ALA fluorescence–guided surgery in pediatric brain tumors—a systematic review. *Acta Neurochir (Wien)*. 2019;161:1099–1108. https://doi.org/10.1007/S00701-019-03898-1.
112. *Intraoperative radiotherapy in newly diagnosed glioblastoma multiforme*. ClinicalTrials.gov; 2016. https://clinicaltrials.gov/study/NCT02685605?cond=Brain Tumor&intr=NCT02685605&rank=1. [Accessed October 4, 2023].
113. Brehmer S. Intraoperative radiotherapy of brain metastases. *Onkologe*. 2022;28: 381–388. https://doi.org/10.1007/s00761-021-01080-w.
114. *Intracavitary carrier-embedded Cs131 brachytherapy for recurrent brain metastases: a randomized phase II study*. ClinicalTrials.gov; 2020. https://clinicaltrials.gov/study/NCT04690348?term=NCT04690348&rank=1. [Accessed October 4, 2023].
115. The SAFE-Trial. *Awake craniotomy versus surgery under general anesthesia for glioblastoma patients*. ClinicalTrials.gov; 2022. https://clinicaltrials.gov/study/NCT03861299?term=NCT03861299&rank=1. [Accessed October 2, 2023].
116. *Brain awake surgery using virtual reality headset*. ClinicalTrials.gov; 2020. https://clinicaltrials.gov/study/NCT03010943?term=NCT03010943&rank=1. [Accessed October 2, 2023].
117. *Handheld dynamometer during awake craniotomy pilot*. ClinicalTrials.gov; 2022. https://clinicaltrials.gov/study/NCT04742231?term=NCT04742231&rank=1. [Accessed October 2, 2023].
118. *Effect of sugammadex for reversal of rocuronium-induced neuromuscular block on perioperative management of awake craniotomy*. ClinicalTrials.gov; 2022. https://clinicaltrials.gov/study/NCT05202899?term=NCT05202899&rank=1. [Accessed October 2, 2023].
119. *Comparison of dexmedetomidine and propofol-remifentanil conscious sedation for awake craniotomy for tumor surgery*. ClinicalTrials.gov; 2016. https://clinicaltrials.gov/study/NCT01545297?term=NCT01545297&rank=1&limit=10. [Accessed October 2, 2023].
120. *A study to measure the effect of brain stimulation on hand strength and function in patients with brain tumors*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT05023434?term=NCT05023434&rank=1&limit=10. [Accessed October 2, 2023].
121. *Pembrolizumab in treating younger patients with recurrent, progressive, or refractory high-grade gliomas, diffuse intrinsic pontine gliomas, hypermutated brain tumors, ependymoma or medulloblastoma*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT02359565?term=NCT02359565&rank=1&limit=10. [Accessed October 2, 2023].
122. *Voxel based diffusion tensor imaging in predicting response in patients with brain metastases undergoing whole brain radiation therapy or stereotactic radiosurgery*. ClinicalTrials.gov; 2020. https://clinicaltrials.gov/study/NCT02277561?term=NCT02277561&rank=1&limit=10. [Accessed October 2, 2023].
123. *DTI & tractography in pediatric tumor surgery*. ClinicalTrials.gov; 2016. https://clinicaltrials.gov/study/NCT02810626?term=NCT02810626&rank=1&limit=10. [Accessed October 2, 2023].
124. *A pilot study to evaluate neurocognitive injury and longitudinal changes in white matter during radiation therapy in children with primary brain tumors*. ClinicalTrials.gov; 2016. https://clinicaltrials.gov/study/NCT02006407?term=NCT02006407&rank=1&limit=10. [Accessed October 2, 2023].
125. *Clinical study of structural and functional evaluation of the visual pathway*. ClinicalTrials.gov; 2018. https://clinicaltrials.gov/study/NCT03591315?term=NCT03591315&rank=1&limit=10. [Accessed October 2, 2023].
126. *Diffusion-tensor imaging in brain tumors evaluation*. ClinicalTrials.gov; 2022. https://clinicaltrials.gov/study/NCT05261724?term=NCT05261724&rank=1&limit=10. [Accessed October 2, 2023].
127. *Understanding the late effects of surviving a pediatric brain tumor*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT03208387?term=NCT03208387&rank=1&limit=10. [Accessed October 2, 2023].
128. *MRI study of radiation-induced damage to white matter and blood-brain-barrier*. ClinicalTrials.gov; 2018. https://clinicaltrials.gov/study/NCT01988675?term=NCT01988675&rank=1&limit=10. [Accessed October 2, 2023].
129. *Diffusion tensor MRI to distinguish brain tumor recurrence from radiation necrosis*. ClinicalTrials.gov; 2017. https://clinicaltrials.gov/study/NCT00285324?term=NCT00285324&rank=1&limit=10. [Accessed October 2, 2023].
130. *Magnetic resonance imaging in evaluating response to RadiationTherapy in patients with high grade glioma*. ClinicalTrials.gov; 2012. https://clinicaltrials.gov/study/NCT01018329?term=NCT01018329&rank=1&limit=10. [Accessed October 2, 2023].

131. *Brain function in young patients receiving methotrexate for acute lymphoblastic leukemia*. ClinicalTrials.gov; 2017. https://clinicaltrials.gov/study/NCT00437060?term=NCT00437060&rank=1&limit=10. [Accessed October 2, 2023].
132. *Cognitive outcomes after brain substructure-informed radiation planning in pediatric patients*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT05658731?term=NCT05658731&rank=1&limit=10. [Accessed October 2, 2023].
133. *Histopathologic evaluation of high grade brain tumors by high order diffusion tensor imaging*. ClinicalTrials.gov; 2014. https://clinicaltrials.gov/study/NCT01699269?term=NCT01699269&rank=1&limit=10. [Accessed October 2, 2023].
134. *Functional monitoring for motor pathway in brain tumor surgery within eloquent area*. ClinicalTrials.gov; 2015. https://clinicaltrials.gov/study/NCT01351337?term=NCT01351337&rank=1&limit=10. [Accessed October 2, 2023].
135. *Perioperative evaluation of cerebellar tumors*. ClinicalTrials.gov; 2022. https://clinicaltrials.gov/study/NCT04463979?term=NCT04463979&rank=1&limit=10. [Accessed October 2, 2023].
136. *Spinal motor evoked potentials in brain surgery*. ClinicalTrials.gov; 2015. https://clinicaltrials.gov/study/NCT02402075?term=NCT02402075&rank=1&limit=10. [Accessed October 2, 2023].
137. *MEP and neuromuscular blocker*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT04768400?term=NCT04768400&rank=1&limit=10. [Accessed October 2, 2023].
138. *Dexmedetomidine on intraoperative somatosensory and motor evoked potential monitoring during neurosurgery in pediatric patients*. ClinicalTrials.gov; 2018. https://clinicaltrials.gov/study/NCT01512147?term=NCT01512147&rank=1&limit=10. [Accessed October 2, 2023].
139. *Comparison of the effects of vecuronium and cisatracurium on electrophysiologic monitoring during neurosurgery*. ClinicalTrials.gov; 2013. https://clinicaltrials.gov/study/NCT01690364?term=NCT01690364&rank=1&limit=10. [Accessed October 2, 2023].
140. *Long-term outcomes after different management strategies for high-level cerebral arteriovenous malformation*. ClinicalTrials.gov; 2020. https://clinicaltrials.gov/study/NCT04136860?term=NCT04136860&rank=1&limit=10&page=1. [Accessed October 2, 2023].
141. *18F-FPPRGD2 PET/CT or PET/MRI in predicting early response in patients with cancer receiving anti-angiogenesis therapy*. ClinicalTrials.gov; 2019. https://clinicaltrials.gov/study/NCT01806675?term=NCT01806675&rank=1&limit=10. [Accessed October 2, 2023].
142. *FDG PET/CT in monitoring very early therapy response in patients with glioblastoma*. ClinicalTrials.gov; 2022. https://clinicaltrials.gov/study/NCT02902757?term=NCT02902757&rank=1&limit=10. [Accessed October 2, 2023].
143. *18F-FDG PET and osimertinib in evaluating glucose utilization in patients with EGFR activated recurrent glioblastoma*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT03732352?term=NCT03732352&rank=1&limit=10. [Accessed October 2, 2023].
144. *FDG and FDOPA PET demonstration of functional brain abnormalities*. ClinicalTrials.gov; 2020. https://clinicaltrials.gov/study/NCT04315584?term=NCT04315584&rank=1&limit=10. [Accessed October 2, 2023].
145. *Positron emission tomography using fluorine F 18 EF5 to find oxygen in tumor cells of patients who are undergoing surgery or biopsy for newly diagnosed brain tumors*. ClinicalTrials.gov; 2013. https://clinicaltrials.gov/study/NCT00110032?term=NCT00110032&rank=1&limit=10. [Accessed October 2, 2023].
146. *Evaluation of the predictive value of 18F-fluorodeoxyglucose positron emission tomography and brain perfusion computed tomography for the efficacy of anti-angiogenic therapy (bevacizumab) in recurrent glioblastoma*. ClinicalTrials.gov; 2021. https://clinicaltrials.gov/study/NCT04566185?term=NCT04566185&rank=1&limit=10. [Accessed October 2, 2023].
147. *FDG PET imaging in diagnosing patients with glioblastoma*. ClinicalTrials.gov; 2022. https://clinicaltrials.gov/study/NCT02885272?term=NCT02885272&rank=1&limit=10. [Accessed October 2, 2023].
148. *Cediranib, temozolomide, and radiation therapy in treating patients with newly diagnosed glioblastoma*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT00662506?term=NCT00662506&rank=1&limit=10. [Accessed October 2, 2023].
149. *Fluorine F 18 fluorodopa-labeled PET scan in planning surgery and radiation therapy in treating patients with newly diagnosed high- or low-grade malignant glioma*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT01165632?term=NCT01165632&rank=1&limit=10. [Accessed October 2, 2023].
150. *Registering genomics and imaging of tumors (ReGIT)*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT05386043?term=NCT05386043&rank=1&limit=10. [Accessed October 2, 2023].
151. *F18 fluciclovine PET/CT in assessing tumor volume and radiation therapy response in patients with glioblastoma undergoing surgery*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT03926507?term=NCT03926507&rank=1&limit=10. [Accessed October 2, 2023].
152. *[18F]Fluciclovine in post-treatment glioblastoma (axumin)*. ClinicalTrials.gov; 2021. https://clinicaltrials.gov/study/NCT03990285?term=NCT03990285&rank=1&limit=10. [Accessed October 2, 2023].
153. *Multi-parametric MRI/Fluorine-18 fluciclovine PET-CT in glioblastoma*. ClinicalTrials.gov; 2019. https://clinicaltrials.gov/study/NCT03409549?term=NCT03409549&rank=1&limit=10. [Accessed October 2, 2023].
154. *11C-methionine in diagnostics and management of glioblastoma multiforme patients (GlioMET)*. ClinicalTrials.gov; 2023. https://clinicaltrials.gov/study/NCT05608395?term=NCT05608395&rank=1&limit=10&page=1. [Accessed October 2, 2023].
155. *Early diagnosis of pseudoprogression using 11C-methionine PET-MRI after concomitant radiochemotherapy treatment for glioblastoma*. ClinicalTrials.gov; 2020. https://clinicaltrials.gov/study/NCT03739333?term=NCT03739333&rank=1&limit=10. [Accessed October 2, 2023].
156. *Impact of [11C]-Methionine PET/MRI for individual tailoring postoperative radiochemotherapy for glioblastoma multiforme*. ClinicalTrials.gov; 2017. https://clinicaltrials.gov/study/NCT01873469?cond=Glioblastoma&intr=11C-Methionine PET-MRI&rank=3&limit=50&page=1. [Accessed October 1, 2023].