Intraoperative MR Imaging during Glioma Resection

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One of the major issues in the surgical treatment of gliomas is the concern about maximizing the extent of resection while minimizing neurological impairment. Thus, surgical planning by carefully observing the relationship between the glioma infiltration area and eloquent area of the connecting fibers is crucial. Neurosurgeons usually detect an eloquent area by functional MRI and identify a connecting fiber by diffusion tensor imaging. However, during surgery, the accuracy of neuronavigation can be decreased due to brain shift, but the positional information may be updated by intraoperative MRI and the next steps can be planned accordingly. In addition, various intraoperative modalities may be used to guide surgery, including neurophysiological monitoring that provides real-time information (e.g., awake surgery, motor-evoked potentials, and sensory evoked potential); photodynamic diagnosis, which can identify high-grade glioma cells; and other imaging techniques that provide anatomical information during the surgery. In this review, we present the historical and current context of the intraoperative MRI and some related approaches for an audience active in the technical, clinical, and research areas of radiology, as well as mention important aspects regarding safety and types of devices.

Keywords: fluorescence guidance surgery, intraoperative magnetic resonance imaging, neurophysiological monitoring, surgical safety, ultrasound guidance surgery

Introduction

Glioma has an infiltrative nature, and neurosurgeons need to correctly identify the tumor margin to ensure maximum resection without affecting the surrounding areas of the eloquent cortex, such as Broca’s area, Wernicke’s area, the primary motor cortex, arcuate fasciculus, or the internal capsule. In general, the outcome of glioma surgery is strongly related to how much tissue is removed,1,2 and careful surgical planning is required. The UK National Institute for Health and Care Excellence guideline (NG99) for brain tumors (primary) and metastasis in adults (published July 11, 2018, last Update January 2021) includes the following information. With respect to the surgical expertise in the multidisciplinary team, one must include access to awake craniotomy with language and appropriate functional monitoring, intraoperative neurophysiological monitoring, and intraoperative imaging guidance. For technical considerations, if a suspected high-grade glioma with an enhanced lesion is possible, fluorescence-guided resection is offered as an adjunct to maximize resection. One can consider intraoperative MR (ioMR) imaging and intraoperative ultrasound (ioUS) imaging to facilitate achieving surgical resection of both low-grade and high-grade gliomas while preserving neurological function unless MRI is contraindicated. In addition, diffusion tensor imaging overlays with neuronavigation, which can contribute to minimizing the damage to functionally important fiber tracts during resection.

Neurosurgeons usually detect an eloquent area by functional MR imaging and identify connecting fibers by diffusion tensor imaging. Tumor grade is determined preoperatively by methionine positron emission tomography or MR spectroscopy. Neuronavigation information obtained from preoperative images processed through a computed reconstruction system4 guides the surgeon to the appropriate corridors into the surgical field.

During the neurosurgical procedure, the patient’s skull is fixed to the operating table to maintain the positional relationship between the neuronavigation information and the skull. However, once the dura mater is opened, cerebrospinal fluid leaks from the surgical field and, coupled with the removal of the glioma, can cause the brain to deform in all directions, leading to brain shift and misregistration of neuronavigation.5
The information can be updated by ioUS imaging, computed tomographic imaging, and ioMR throughout the surgical strategy of the next surgical steps. The neurophysiological status can also be monitored via awake craniotomy, motor-evoked potentials (MEPs), and somatosensory evoked potential (SEPs). Fluorescence-guidance surgery can identify the high-grade tumor cells in the excision margin under the surgical microscope. Scanners for ioMR have been adopted globally for aiding the surgical treatment of brain tumors, including glioma.

This review aims to deepen the understanding of ioMR imaging for those who are active in technical, clinical, and research areas of radiology. We present background information on the origin of ioMR imaging, describe the different types of theater layout that may be used to accommodate ioMR scanners and medical safety in magnetic fields, and, finally, we discuss how to use ioMR images for formulating surgical strategies.

History of Image-guided Surgery Using ioMR Imaging

When talking about the history of ioMR imaging, Ferenc Andras Jolesz (May 21, 1946–December 31, 2014) must be mentioned. After graduating in 1971 from the Hungarian School of Medicine, Dr. Jolesz completed a biomedical engineering and computer science research fellowship, as well as a Neurosurgery residency in his native Hungary before departing to Boston, MA, USA. There, he worked as a research fellow in the Department of Neurology at the Massachusetts General Hospital, as a resident in Diagnostic Radiology, and as a research fellow in Neuroradiology at Brigham and Women’s Hospital. He became the Director of the Division of Magnetic Resonance Imaging in 1988. Dr. Jolesz was appointed as the first incumbent B Leonard Holman Chair in Radiology at the Harvard Medical School in 1998. At the same time, Peter McLaren Black was a Professor of Neurosurgery at the Brigham and Women’s Hospital, and, in 1993, Drs. Jolesz and Black jointly introduced the first ioMR scanner within which they could work to remove a brain tumor (Fig. 1). This scanner, commercialized as GE Signa SP by GE Medical Systems (Milwaukee, WI, USA), provides rapid image processing and allows frameless stereotactic brain biopsy and real-time image-based intraoperative guidance. It consists of two coils arranged vertically (it is nicknamed the double donut because of its unique morphology), and the coils create a magnetic field of 0.5 Tesla (T). There is a space of 56 cm between the two coils, within which two surgeons may operate face to face, using MR conditional surgical instruments and a microscope to check the images projected on the monitor inside the coil.

Other approaches to ioMR have been considered, and some have been developed commercially. For instance, in 1998, Steinmeier et al. described their experience with a 0.2 T MR scanner with the magnets placed horizontally, one above the other in a hamburger shape and a wide side opening to enable access for patient and physicians (Magnetom Open; Siemens, Erlangen, Germany). Hitachi produced a similar hamburger-shaped MR scanner. Sutherland et al. suspended a 1.5 T mobile high-field MR scanner with a 70-cm bore from the ceiling and moved it to the operating table using a ceiling-mounted rail system. Usually, the patients from operating room are taken to the heavy-weighted MR scanner; hence, the idea of moving the MR scanner itself is unique and distinctive. Martin et al. proposed a system in which the operating table and MR scanner were placed in a straight line. Patients are moved on to an MR conditional surgical tabletop plate.
that is slid into the MR scanner bore. The PoleStar ioMR imaging system (Odin Technologies, Yokneam, Israel, and Medtronic Surgical Navigation Technologies, Louisville, KY, USA) was developed by Hadani et al.28 This system is a low-field (0.15 T) compact system on a gantry that can be stored under the operating table and moved into place when needed during the surgery.

**Why Do Neurosurgeons Need ioMR Images?**

When intracranial pressure is elevated, brain bulging occurs immediately after craniotomy (Fig. 2). In addition, the brain shifts in various directions due to the progress of glioma resection, aspiration of the cerebrospinal fluid, expansion of the compressed brain, and increasing brain edema. This brain shift increases as the surgery progresses, and, consequently, the accuracy of neuronavigation based on preoperative MR images decreases. 8,29–31 Therefore, neurosurgeons need to update and reregister images for neuronavigation throughout surgery, which is achieved with ioMR imaging.9,10 Moreover, ioMR images may be used to evaluate the percentage of the lesion that has been removed and might reveal unexpected remnants to surgeons (Fig. 3).6,32 Yet, identification of tumor remnants in the MR images is an important prognostic factor and guides decisions regarding the selection of adjuvant therapy.33 In addition, imaging can clarify the relationship between the remnant lesion and eloquent regions, connecting fibers, ventricular wall, major vessels, and so on,34,35 and can reveal unexpected vascular complications.36 However, it should be noted that there is a report that the hyperacute ischemic change could not be detected even by 3 T ioMR imaging.37 Therefore, one cannot exclusively rely on ioMR to determine possible complications.

### ioMR Imaging Theater Layout and Cost Performance

Initially, ioMR imaging systems used low-magnetic-field MR scanners,23–25,38–41 As the need for high-resolution and high-quality MR images increases, higher-field MR scanners have become mainstream.26,27,29,34,42–63 The use of ioMR imaging, however, has high initial costs and prolongs the operation time.64–69

Multi-theater layouts are generally used for high-magnetic-field MR scanners: in a single-theater type, the scanner is installed within the operating room to minimize the transfer distance to and fro the operating table;28,42,44,70,71 in a multi-theater type, the MR scanner is housed in separate room or an area that may be closed off when the scanner is not in use (Fig. 4).46–50,55,62,72 The latter multi-theater type may extend the transfer distance or require that the scanner is moved into the operating room.26

The multi-theater type was pioneered by a German group. They used a 0.2 T MR scanner and the patient was moved to and fro the operating table by trolley.24,73 The approach was introduced so that the scanner could be used as a diagnostic device when not needed during surgery to ameliorate the high cost.49 In addition, since the separate MR scanner room is completely shielded, it prevents interference with magnetic fields, noise, radio waves, etc., in the operating theater. Therefore, as the throughput of imaging equipment increases and the multi-theater type has high-cost performance, the layout has been adopted in many hospitals,48,49,55,62,63,72,74,75 as sharing imaging equipment has a positive economic impact for hospitals. An increasing number of facilities are introducing imaging devices of different modalities, between which the patient is moved on a tabletop. The idea of using different modalities in this way began with the opening of a facility designated for endovascular treatment at the University of California in San Francisco, CA, USA, in 2001.76 When not
in combined use, each device can be separated and used individually for routine diagnostic imaging to maximize cost performance by high throughput. The same idea was introduced to neurosurgical facilities in 2006 when Tokai University Hospital, Kanagawa, Japan, began to use a suite where MR and CT imaging and angiography could be performed. Shielded doors meant that the devices could be separated to use independently or in different combinations. In 2011, the Brigham and Women’s Hospital in Boston, MA, USA, launched its Advanced Multimodality Image-Guided Operating Suite (AMIGO) suite, which combines one operating area and three imaging areas for a 3 T MR, angiography, and positron emission tomography-CT. The suite has also facilitated

Fig. 3 Illustrative case of tumor remnant in FLAIR image. a: A 47-year-old woman with high signal intensity in the right-temporal lobe on preoperative FLAIR MRI. b: The first intraoperative FLAIR image shows deep-seated tumor remnant, and the distance between remnant lesion and internal capsule was well identified. After identifying this relationship, the surgeon has chased the lesion more deeply. c: The arrow shows unexpected focal high signal intensity on the margin, which is suspected to be residual tumor requiring further resection when the patient is brought back to the operating room. This small amount of lesion is diagnosed as glioma by frozen-section pathological diagnosis. d: The postoperative images reached nearly total removal of the tumor. FLAIR, fluid-attenuated inversion recovery.

Fig. 4 Two types of theater layouts of MR with operating system. a: A one theater type in which an ioMR scanner installed in the operating room, the surgical patient’s transfer distance is short, and ioMR imaging is completed in the operating room. However, an MR scanner installed in an operating room is mostly used to assist with surgery. The depreciation of the MR scanner depends on the turnover rate of surgery. b: A multi-theater type in which the operating room and imaging room are separated, and thus the surgical patient’s transfer distance is long. However, imaging equipment can be used for routine diagnostic imaging when performing surgery in the operating room. ioMR, intraoperative magnetic resonance.
innovative treatments using new technologies, such as laser thermoablation therapy, focused ultrasound therapy, MRI-assisted endoscopic surgery, and robotic surgery. Today, multimodality image-guided therapy has expanded not only to the neurosurgical field but also toward brachytherapy for gynecologic malignancies, skull base surgery for otorhinolaryngology, and image-guided-breast-conserving therapy.

Safety in a Magnetic Field

Specifications that comply with the International Electrotechnical Commission 60601-2-33 standard are required for operating rooms in which ioMR imaging is performed and for MR gantry use. MR magnets produce a strong magnetic field. The attractive force on magnetic material largely depends on its mass and the strength and spatial gradient of the static magnetic field, and, therefore, great care must be taken when surgical instruments are present. As one of the measures for the safety zoning regarding the static magnetic field, some facilities employ floor markings that indicate strong magnetic fields to 5 Gauss (0.0005 T) (Fig. 5a). Furthermore, when devices, such as anesthesia machines, monitoring equipment, and infusion pumps, are in the vicinity of the MR scanner, it is necessary to pay close attention not only to displacement force to the equipment induced by the magnetic field gradient of the equipment by the magnetic field but also to possible malfunction of the medical equipment due to radiofrequency interference (Fig. 5b).

The American Society for Testing and Materials classifies articles related to MR in three categories. MR safe refers to products that are not conductors, metals, or magnetic (e.g., plastics), which are scientifically and physically safe in principle (i.e., not based on testing). MR conditional replaces the previous term MR compatible, which is deemed ambiguous, and refers to products that are judged to be nonhazardous based on testing under specific conditions, such as displacement, torque, spatial field gradient, time-varying magnetic field, heat generation due to the RF, and absorption rate. Further studies are required to assess risks of burns, current/voltage generation, noise, types of magnets, device arrangement (e.g., nerve stimulator leads), and interference between multiple devices (e.g., cardiac pacemaker and electrode). MR unsafe corresponds to materials that are dangerous in MR environments, such as surgical scissors and forceps.

Preventing eddy current-induced complications in the patient

Consideration must be given to eddy currents, which are generated in nearby conductors, including the largest eddy current generated in an MR scanner, which is a shield panel placed inside the gradient coil, which is part of the MR scanner, and when there is ferrous, eddy current is not the only cause of heat generation but also there is so-called antenna effect and current inflow. The loop formed by the MR conductor is especially dangerous. It is also important to check the monitoring cables as care must be taken in order for it to not come into contact with each other or make loops, thus avoiding creation of eddy current. As the human body is a conductor, the patient’s body temperature increases due to the radiofrequency electromagnetic field, and in some cases, the induced eddy current can lead to burns. When placing the patient in position on the surgical table, skin-to-skin contact should be avoided, for instance by sandwiching a cushion between the knees, heels, and the arms and trunk. Finally, direct contact must be avoided between the skin and
the MR gantry and monitoring cables (Fig. 5c). These may be new safety issues for operating room staff.

**Training**

With respect to safety management in operating rooms, the World Health Organization (WHO) has published a checklist that is widely used\(^{110}\) and has contributed to improving surgical safety.\(^{111,112}\) It is verbally administered and summarizes the minimum checks necessary to ensure the safety of patients when entering and leaving the operating room.\(^{113}\) Unfortunately, avoidable mistakes, such as craniotomy performed on the opposite side from the lesion, can still occur.\(^{114}\) The arguably first verbal checklist has been used for airline pilots since the 1930s, stipulating the simple operation checks to be performed aloud before or after performing one routine task, such as takeoff or landing.\(^{115}\)

**Multidisciplinary training**

Medical personnel with various backgrounds are involved in ioMR-imaging-assisted surgery. To ensure the safety of patients and staff during the procedure, MR staff must be given physical and electrical safety education.\(^{103,104,116}\) All operating room staff, including surgeons, must also receive pathophysiological and physiological safety education.\(^{117}\) Finally, a key concept for ioMR imaging is a good communication between all staff. For instance, before making the first skin incisions, the WHO checklist suggests that everyone participating in the surgery verbally introduce themselves with their names and their roles.\(^{110}\) This has been shown to enhance communication during surgery.\(^{116}\) The final item on the WHO surgical safety checklist refers to obtaining confirmation of nonroutine steps, such as key concerns for the recovery and management of the patient from surgeons, nurses, and anesthetists. Some facilities are also trying to improve safety team building further by introducing briefing for procedure plans, manuals, and modified verbal checklists specific to ioMR-imaging-assisted surgery (Fig. 6a).\(^{74,75,92,119,120}\)

In surgeries involving ioMR imaging, the usual workflow is interrupted, while the patient is moved (Fig. 6b).\(^{121}\) Therefore, to enable unfamiliar workflows to be performed smoothly, it is necessary for all involved staff, including neurosurgeons, circulating nurses, scrub nurses, neuroradiology technicians, anesthesiologists, neurologists, radiology technicians, and residents, to participate in discussions and simulations to standardize the processes and create a procedure manual.\(^{122,123}\)

**The role of a safety manager**

A safety manager should be appointed to oversee safety during transfer of the patient between the MR scanner and operating table because, once surgery begins, neurosurgeons are devoted to surgical planning and procedure, anesthesiologists to anesthesia management, and radiologists to imaging quality.\(^{74,75,111,119,124}\) Some facilities appoint nurses who belong to sections other than the operating room and imaging staff to work as on-duty safety managers in order to objectively perform a series of operations from the standpoint of a third party (Fig. 6c).\(^{119,121}\)

**Key Issues for Interpretation of ioMR Images**

**FLAIR images**

Low-grade gliomas generally appear as gadolinium-unenhanced lesions that are visible as high intensity lesions on T2-weighted images. Fluid attenuated inversion recovery
Preoperative high intensity at the tumor edges on FLAIR MR imaging is generally due to peritumoral edema, although glioma cells within this region were detected, too.\textsuperscript{126,127} The \textit{liner} FLAIR high-signal alterations on the margin of cavity (Fig. 7) visible on postsurgical MRI are rather due to surgical artifacts and should not be interpreted as a tumor remnant.\textsuperscript{128} Either way, for a better differential diagnosis (artifact vs tumor remnant), a comparison of FLAIR images before and after excision is recommended.

\subsection*{Enhanced $T_1$-weighted image}
Several studies have reported thin \textit{liner} new enhancements around the surgical margin seen during or immediately after surgery on $T_1$-weighted images.\textsuperscript{129--131} These anomalous enhancements are caused by disruption of the blood–brain barrier or bleeding caused by surgical intervention or contrast leaking into the tumor cavity, and should not be confused with residual tumor.\textsuperscript{132} The preoperative enhanced lesion and the intraoperatively and immediately postoperative occurring enhanced region must be carefully compared. These transient surgically induced enhanced lesions diminish soon after surgery.\textsuperscript{53,131,133}

\subsection*{Preventing susceptibility artifacts on ioMR images}
Good image quality is obtained from high-field MR machines when used intraoperatively, but susceptibility to artifacts can negatively influence the quality of the images (Fig. 8a). Diffusion-weighted imaging can be used to detect neural fibers and ischemia, but it is very sensitive to artifacts, especially air bubbles at the surgical site.\textsuperscript{134} Filling of the tumor cavity with irrigation fluid may help to prevent such artifacts (Fig. 8b) and enable adequate positioning of the patient’s head with respect to the MR isocenter.\textsuperscript{135}

\section*{Additional Intraoperative Modalities}

\subsection*{Neurophysiological monitoring}
As ioMR images cannot be updated frequently, neurosurgeons need to use other forms of intraoperative monitoring, such as MEP and SEP (Fig. 9), in order to avoid damage to the surrounding brain. Evoked potentials can identify both location and function of cortical and subcortical connections.\textsuperscript{13} MEP uses transcranial and transcortical stimulation of the primary motor cortex to elicit evoked electromyograms of muscles in the extremities.

Direct subcortical stimulation (during the dissection) of the tumor cavity wall can then be used to infer the distance to the corticospinal tract by means of the degree of response to the stimulation intensity,\textsuperscript{14,29} along with the neuronavigation data.

While doing this, careful attention must be paid to white-matter-fiber tract shift, following craniotomy and durotomy and during lesion resection.\textsuperscript{136} During surgery, intermittent stimulation of the motor cortex is performed when the MEP signal decreases, and subcortical stimulation is performed there to expand the resection range and approach the corticospinal tract.\textsuperscript{14,31,40} A correlation has been reported between subcortical

Fig. 7 Illustrative case of a right frontal glioma. a: A 47-year-old woman with high signal intensity the right frontal lobe on pre-operative FLAIR image. b: Usually ioMR FLAIR images show a linear (like a border of the margin) high signal around the cavity; this should not be misdiagnosed as tumor remnant. FLAIR, fluid-attenuated inversion recovery; ioMR, intraoperative magnetic resonance.
Neuronavigation, motor-evoked potentials, and somatosensory evoked potentials provide real-time anatomical and neurophysiological information to the surgeons.

**Fig. 8** Illustrative case of a right frontal glioma. 

- **a:** A 47-year-old woman with the right frontal lobe glioma. Diffusion-weighted ioMR imaging shows a minimal susceptibility artifact around the cavity. Note also that some artifacts related to the head pin were identified in both occipital lobes (arrows).
- **b:** After removing the tumor, the surgeon decides to take intraoperative MR images. Before moving the patient into the intraoperative MR scanner, large enough surgical gauze (with X-ray-enhanced fiber containing polypropylene, barium sulphate, and polyester, which does not affect MR images) is placed into the tumor-removed cavity. It is filled with fluid so that it will not collapse the cavity, and this step prevents the cavity wall falling inward. The cavity is filled with irrigation fluid preventing air bubbles, which can induce susceptibility artifacts on ioMR images. ioMR, intraoperative magnetic resonance.

**Fig. 9** Neuronavigation, motor-evoked potentials, and somatosensory evoked potentials provide real-time anatomical and neurophysiological information to the surgeons. 

- **a:** The surgeon is handling a pointer device and touches the surgical field; the navigation monitor shows the exact position on the upper monitor. The lower monitor shows the motor-evoked potential. 
- **b:** The evoked potential electrode is screwed into the scalp for transcranial motor-evoked potential monitoring. 
- **c:** The monitoring electrode is slipped underneath the dura mater for testing of somatosensory and motor-evoked potentials through the cortical surface.
stimulation and the distance to the corticospinal tract, where 10 mA corresponds to roughly 10 mm and 5 mA to 5 mm. When there is no response after stimulation at 10 mA, the area is safe for deeper removal. If there is a weak response at 5 mA, the removal plan is close to the corticospinal tract. According to Kamada et al., 1.8 mA could be considered as the electrical threshold of the corticospinal tract. SEP is a reliable method for identifying the central sulcus in phase reversal and is used to identify the primary motor cortex in the first step of surgery.

**Awake craniotomy**

The language-dominant hemisphere has important language networks, and, therefore, simple neurofunctional monitoring is insufficient. Awake craniotomy and language mapping with electrical stimulation are being applied with increasing frequency to avoid postoperative language dysfunction when tumors are located close to the eloquent area associated with language. Surgical accuracy may be improved by combining awake craniotomy and ioMR imaging. When awake craniotomy is performed, special anesthetic management is required and must be performed by an expert anesthesiologist. In addition, language tasks might be performed by speech therapists and psychologists before and after awake craniotomy. The patient should be fully informed about the benefits and risks of the procedure because their cooperation is needed, and they should not be significantly distressed by the awake craniotomy.

Awake surgery is a useful method when the tumor is located in the language-dominant hemisphere. Full anesthesia is initially induced before craniotomy. After the craniotomy, the dura mater is blocked with local anesthesia, the dura is opened, and the patient is gradually awakened. Electrical stimulation and awake testing are performed to detect the language functioning area. When surgeons decide to conduct ioMR imaging, general anesthesia is reapplied according to the regular operating room technique. This procedure is called the asleep-awake-anesthetic technique.

**Intraoperative fluorescence guidance under excitation light**

Radical resection of glioma can be obtained only in a low percentage of cases due to glioma infiltration into both eloquent cortex and subcortical regions. There is also difficulty in intraoperatively distinguishing the respectable glioma tissue at the margin of the resection even in noneloquent areas. Photodynamic detection, which is the use of photosensitive materials that enhance tumor visualization by fluorescence, has been proposed during the removal of glioma. Fluorescence-guided surgery using 5-aminolevulinic acid (5-ALA) is highly specific for the detection of high-grade glioma on the surgical field. Using fluorescence real time guided surgery by 5-ALA is a tool for neurosurgeons in identifying high-grade glioma that can be visually recognized simultaneously under the surgical microscope. Therefore, fluorescence-guided surgery by 5-ALA provides navigation in the right resection area during the surgery. 5-ALA is a building block in the heme synthesis pathway that is naturally converted to protoporphyrin IX, a fluorescent molecule that accumulates in glioma tissue due to local disruption of the blood–brain barrier and increased synthesis by tumor cells. 5-ALA mostly accumulates in high-grade tumors (WHO Grades III or IV) and emits fluorescence in real time. When the tumor is irradiated with excitation light, protoporphyrin IX fluorescence can be intraoperatively visualized with special filter for the operating microscope, resulting in red at the tumor core and pink at the margins where concentrations are lower and may be used to guide the excision area. In addition, the alternative option of fluorescence-guided surgery is sodium fluorescein. Sodium fluorescein is a dye that accumulates in high-grade glioma due to their disruption of the blood–brain barrier. It is administered by intravenous injection during surgery and, with the use of a special filter in the operating microscope, results in yellow appearance of the tumor compared to pink appearance of the normal brain tissue. A limitation of the above method is the lack of fluorescence in the majority of low-grade glioma. Moreover, deeper seated glioma tissues might fail to be detected. However, fluorescence-guided surgery is not limited by brain shift or navigation inaccuracy; hence, it is a suitable tool to achieve gross total resection of high-grade glioma.

Several randomized controlled trials have shown that 5-ALA photodynamic diagnosis is beneficial with respect to indicating resection margins, which improves progression-free survival when compared with standard surgery, although the overall survival is not improved. Sodium fluorescence is limited to small cohort studies without uniform results.

**Intraoperative ultrasound**

ioUS, including microbubble contrast-enhanced and 3D ioUS, provides simultaneous visualization of tumor with the information of surrounding structures. Gliomata appear hypoechoic on ioUS, and this characteristic can be reliably used to navigate toward glioma during surgical procedure. The use of ioUS is gaining popularity due to accuracy in localizing glioma, evaluating the extent of resection and cost-effectiveness. In particular, ioUS may be used to provide information on brain shift. The application of ultrasound–MR image fusion can improve the total resection rate of glioma, thus playing an important role in clinical practice. Its use is expected to further increase as software development progresses. Limitations of ioUS are the necessary training of the personnel in order to create good quality images, as well as problems with artifacts.
due to bone, blood, and hemostatic materials. However, ioUS can still serve as a cheaper alternative to ioMR and is easy to handle. A meta-analysis showed that ioUS is effective for assessing resection of diffuse glioma, but that accuracy is greater for low-grade glioma than high-grade lesions. Accuracy might be affected in patients who have undergone previous treatment, particularly radiation therapy, or by surgical artifacts (e.g., blood clots or hemostatic agents) or small tumor remnants (generally < 5 mL).

Since ioMR images cannot be frequently updated, both fluorescence and ioUS without time lag guide the neurosurgeon to the right corridors into the glioma resection area during the surgery. Therefore, ioUS and fluorescence guide surgery complete MRI in this procedure.

Changing the Surgical Strategy for Shifting to Adjuvant Therapy without Chasing the Lesion

Neurosurgeons use several modalities, such as MEP, neuronavigation, fluorescence, and ioUS, to obtain simultaneous information in order to perform maximum tumor resection while preserving nerve function, to evaluate their surgical procedures, and to make decisions to move forward to the next surgical step. This contributes to improving their skills and, of course, patient outcomes.

Occasionally, the surgeon changes the surgical strategy based on the progress of the surgery and the ioMR images. Carefully reviewing the surgical steps and neuronavigation monitoring, neurosurgeons may decide to not chase the lesion deeper, and then treatment of the remaining lesion may include postoperative radiation 2 Gy per day, 5 days a week for a total 60 Gy, and, at the same time as radiation, temozolomide (chemotherapeutic agent) administered orally, 75 mg/m² of body surface area per day, 7 days a week for high-grade glioma. Following 6 weeks of radiation and oral temozolomide, followed by six cycles of adjuvant temozolomide (150–200 mg per square meter for 5 days during each 28-day cycle) bevacizumab is administered intravenously at a dose of 10 mg/kg once every 2 weeks for high-grade glioma. The newly developed U.S. Food and Drug Administration-approved Optune transducer array (Novocure, Haifa, Israel) is a noninvasive regional therapeutic agent that aims to inhibit the growth of glioblastoma multiforme cells via the use of alternating electric fields.

Photodynamic therapy

Several studies have revealed that 80%–90% of local recurrence within 2 cm of the original margin has appeared in high-grade glioma patients. Therefore, local control after surgery by adjuvant therapy delivered intraoperatively could potentially improve patient’s overall survival. Intraoperative photodynamic therapy using 5-ALA has potentially permitted targeting of residual glioma cells at infiltrative margin after fluorescein-guided surgery and is used worldwide. Photodynamic therapy actually relies on a photochemical reaction occurring after the laser light activation of the photosensitive 5-ALA metabolite, protoporphyrin IX, which results in the release of free radicals, including singlet oxygen species. The intracellular accumulation of protoporphyrin IX and free radicals can lead to a very local tumor cytotoxic effect sparing normal cells. On the other hand, the alternative option of photodynamic therapy for glioma by means of talaporfin sodium is mainly used in Japan.

Interstitial chemotherapy

If excision is stopped because maximum safe resection has been reached, but ioMR images confirm remnant lesion that has infiltrated into eloquent regions, surgeons have the option of implanting carmustine-impregnated wafers in the tumor cavity. The indication for implantation is a diagnosis of malignant glioma by frozen-section pathological diagnosis during surgery. Biodegradable carmustine-impregnated wafers are the only approved interstitial chemotherapy for newly diagnosed malignant glioma and recurrent glioblastoma (Fig. 10). The drug is able to penetrate the blood–brain barrier at the site of delivery. The wafers are placed on the surface of the tumor cavity and slowly release carmustine over 5 days, during which the drug infiltrates into brain parenchyma to around 6 mm. Of note, carmustine induces localized brain edema that may be seen on postoperative images and should not be confused with tumor remnant. Carmustine-impregnated wafers improve survival compared with placebo without increased incidence of adverse events.

Interstitial chemotherapy and photodynamic therapy are useful as a bridge between surgery and standard postoperative radiation and chemotherapy for high-grade glioma.

The Impact of Intraoperative Imaging on Brain Tumor Surgery

Kubben et al. in a 2014 randomized trial of ultra-low-field ioMR in glioblastoma resection, found no advantage with respect to the extent of resection, clinical performance, or survival when compared with conventional neuronavigation-guided glioblastoma resection. Moreover, they found that ultra-low-field ioMR imaging was not cost effective compared with conventional neuronavigation. In contrast, Fountain et al. published a meta-analysis (including several RCTs, such as those reported by Senft et al. and Willems et al.), which revealed that ioMR imaging might help to maximize the extent of resection in patients with high-grade glioma, although this conclusion was based on low-certainty evidence. This supported the findings of a previous review by Jenkinson et al. In a recent meta-
analysis report by Lo et al., the usage of ioMR imaging led to improved gross total resection of gliomas, but no benefits were seen for progression-free or overall survival.

Golub et al. performed a network meta-analysis, which showed that ioMR imaging is superior to conventional neuro-navigation for achieving gross total resection of high-grade gliomas. Wu et al. performed a randomized, triple-blind, parallel, controlled trial using 3.0 T ioMR imaging and reported clinical utility for safe maximum resection in glioma surgery. Shah et al. reported in a retrospective multicenter registry comparative study of patients with newly diagnosed glioblastoma that ioMR imaging increased the gross total resection, which in turn was associated with improved overall survival after adjustment for other prognostic factors. However, ioMR imaging was not an independent predictor of overall survival in multivariate analysis.

Another significant aspect of the ioMR imaging procedure concerns a possible increase in surgical site infection because craniotomy patients need to be moved into unsterilized diagnostic MR scanner. We were able to identify only two reports dealing with this issue, where it was noted that the rate of surgical site infection and the frequency of new neurologic deficits after ioMR image-guided surgery were within the normal range of pediatric neuro-oncologic surgery, as well as wide age ranged (1–84 years old) at the multi-theater type system.

Overall, ioMR imaging seems to have improved the safety and increased the amount of tumor resected in patients with glioma, but the certainty of the evidence is low. There is no consensus on outcomes, such as survival. Therefore, the long-term outcomes remain unclear and additional studies are necessary. Network analyses have not been possible due to the identified adverse events, and even the existing information was incomplete and suggestive of significant reporting bias (very low-certainty evidence). Overall, the proportion of reported events was low in most trials, and even the survival outcomes were not adequately reported. The existing data regarding the quality of life are also insufficient and biased in order to extract valuable knowledge from it.

**Conclusion**

In the treatment of glioma, which infiltrates into the brain parenchyma, it is important to remove as much as
possible the tumor while preserving neurological function. The diagnosis of glioma is based on MR images, and, therefore, the use of intraoperative MRI can help neurosurgeons understand how much of the tumor has been removed, how far the excision site is from eloquent regions, and how to correct brain shift in the neuronavigation system. The use of multiple intraoperative imaging devices, various neurophysiological monitors, and photodynamic diagnosis, increases the likelihood of achieving maximum extent of resection while preserving neurological function. The layout of the MR equipment and operating room is important in order to achieve the best results and, taking into consideration the cost of MR and other imaging machines, can contribute to improving the cost-effectiveness. Important aspects to consider are the safety of patients and staff during intraoperative MRI. The usual operation procedure is interrupted, the patient must be moved, and multidisciplinary training is required to minimize the associated risks. It is imperative to design a manual and assign a safety manager.

When intraoperative MRI indicates that excision should not continue because of neurofunctional risks, the availability of indwelling chemotherapeutic agents and effective postoperative radiation therapy means that some therapeutic effect can still be expected even with tumor remnants. However, the field is evolving, and neurosurgeons continue trying to maximize tumor resection while preserving neurological function. Since the correction of brain shift by combined use of intraoperative ultrasound can be performed in real time during surgery, and it is also useful for the confirmation of tumor remnant or eloquent area of the connecting fibers, we are confident that the combined use of intraoperative neuronavigation, neumonitoring, and multimodality imaging-assisted surgery has the potential to contribute to significant developments in glioma surgery in the future.

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The development and implementation of intraoperative MRI in our hospital involves not only neurosurgeons and anesthesiologists but also multidisciplinary paramedics. Hereafter, we would like to introduce and acknowledge them for their contributions.

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Informed Consent

All figures were taken with the consent of the patients, with the explanation and consent form obtained from the Internal Review Board of our hospital (19R-299).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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