

Intraoperative Low-Field Magnetic Resonance Imaging-Guided Tumor Resection in Glioma Surgery: Pros and Cons

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Background: Intraoperative magnetic resonance imaging (MRI) is useful for identifying residual tumors during surgery. It can improve the resection rate; however, complications related to prolonged operating time may be increased. We assessed the advantages and disadvantages of using low-field intraoperative MRI and compared them with non-use of iMRI during glioma surgery.

Methods: The study included 22 consecutive patients who underwent total tumor resection at Shinshu University Hospital between September 2017 and October 2020. Patients were divided into two groups (before and after introducing 0.4-T low-field open intraoperative MRI at the hospital). Patient demographics, gross total resection (GTR) rate, postoperative neurological deficits, need for reoperation, and operating time were compared between the groups.

Results: No significant differences were observed in patient demographics. While GTR of the tumor was achieved in 8/11 cases (73%) with intraoperative MRI, 2/11 cases (18%) of the control group achieved GTR ($p=0.033$). Seven patients had transient neurological deficits: 3 in the intraoperative MRI group and 4 in the control group, without significant differences between groups. There was no unintended reoperation in the intraoperative MRI group, except for one case in the control group. Mean operating time (465.8 vs. 483.6 minutes for the intraoperative MRI and control groups, respectively) did not differ.

Conclusions: Low-field intraoperative MRI improves the GTR rate and reduces unintentional reoperation incidence compared to the conventional technique. Our findings showed no operating time prolongation in the MRI group despite intraoperative imaging, which considered that intraoperative MRI helped reduce decision-making time and procedural hesitation during surgery.

(J Nippon Med Sch 2022; 89: 269–276)

Key words: glioma, gross total resection, intraoperative MRI, residual tumors

Introduction

The use of intraoperative magnetic resonance imaging (MRI) in brain tumor surgery is reported to have various benefits, such as an increased tumor resection rate and avoidance of unexpected complications. Particularly, it is implemented for the resection of glioma, pituitary tumors, and pediatric brain tumors¹. In glioma surgery, the boundary between the tumor and the normal tissue is

unclear in microscopic surgery. There are often unexpected residual tumors even when surgeons think that the tumor is satisfactorily removed. The use of intraoperative MRI for visualizing residual tumors during surgery is expected to improve resection rates. Improvement in the resection rate for glioma prolongs the period until reoperation for tumor recurrence and leads to improved prognosis²⁻⁴. However, problems associated with using in-

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https://doi.org/10.1272/jnms.JNMS.2022_89-301

Journal Website (<https://www.nms.ac.jp/sh/jnms/>)

traoperative MRI have also been reported, including the prolongation of operating time due to MRI, increased complications in moving the patient to the gantry of MRI, and the running cost of maintaining MRI⁵. Glioma surgery performed at Shinshu University Hospital has routinely used intraoperative MRI since its introduction in July 2018. Hence, this study aimed to evaluate the usefulness of intraoperative MRI in improving glioma surgery outcomes at our hospital compared to conventional glioma surgery before introducing intraoperative MRI.

Materials and Methods

Patient Population

Of the 20 patients who underwent glioma surgery using intraoperative magnetic resonance imaging (iMRI) between July 2018 and October 2020, we examined 11 patients that had aimed to undergo total tumor resection. Surgical outcomes for this group and those for the control group consisting of 11 consecutive cases of glioma who underwent surgery for total tumor resection between September 2017 and July 2018, before the introduction of intraoperative MRI, were retrospectively compared. The following covariates were also compared between patients in the two groups: sex, age, left- or right-sided tumors, tumor location, pathological malignancy, and maximum tumor size. Gross total resection (GTR) was defined as the disappearance of the tumor in post-operative MRI in the FLAIR high-signal area for low-grade glioma and the contrast-enhanced area for high-grade glioma.

This study was approved by the Shinshu University Ethics Committee (Approval No. 4067). All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all individual participants included in the study.

Intraoperative MRI

Intraoperative MRI at this hospital was conducted through a 0.4T low-field open MRI (APERTO Lucent; Hitachi, Ibaraki, Japan) installed in the operation room^{6,7}. The rotary operating table (Mizuho Co., Tokyo, Japan) was installed outside the 5-gauss line, and surgeries were performed on this table. While iMRI was taken, the bed was rotated around the foot and head into the gantry. The patient's head is fixed with an MRI-compatible head frame, and the receiving coil can be attached to and detached from the frame. The 5-gauss line, inside which the effect of the magnetic field was strong, could be as nar-

row as 1.7 m due to the low magnetic field (0.4T), and it was possible to use ordinary equipment that was not MRI-compatible during surgical procedures along with the MRI equipment. Intraoperative MRI was taken after judgment to achieve satisfactory tumor resection by operators. Sequences of intraoperative MRI were T1-weighted image, T2-weighted image, FLAIR, and a contrast-enhanced T1-weighted image. Intraoperative MRI was taken once in a glioma surgery, and the imaging time was approximately 30 minutes. If there is any residual tumor in intraoperative MRI imaging, then the image is updated using the Curve Dual Display™ (Brainlab AG, Munich, Germany) navigation system for additional tumor resection.

Operation Procedures

The aim of surgery is GTR of the tumor in all cases included in this study. The surgery was performed by senior neurosurgeons (authors T.O. and T.G.) with the navigation system under general anesthesia or awake craniotomy. For the intraoperative MRI group, an MRI-compatible frame and a navigation reference unit were implemented. In both groups, tumor boundaries were identified using the fence post method^{8,9}, ecosonography, and 5-aminolevulinic acid (5-ALA)¹⁰, and the tumor was removed for maximal tumor resection. Neurophysiological monitoring such as motor-evoked potential and somatosensory-evoked potential was also implemented for tumors close to the eloquent area. Tissues of tumor boundaries were evaluated using an intraoperative frozen section and by intraoperative flow cytometry^{11,12}. In the control group, tumor resection was finished when the surgeon judged that GTR was completed. In the intraoperative MRI group, intraoperative MRI was performed when the surgeon judged that the tumor was removed totally or when any further excision would confer the patient with a risk of neurological deficits. When the residual tumor was detected in intraoperative MRI, additional tumor resection was performed using an update navigation system. iMRI scans were taken once for each patient in the intraoperative MRI group. A 1,3-bis [2-chloroethyl]-1-nitrosourea wafer was implanted in the excision cavity of patients with a rapid intraoperative diagnosis of a high-grade glioma.

Statistical Analysis

Statistical analysis was performed using free EZR software (<http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html>). Fisher's exact test was used to compare background factors between the two groups, and the Mann-Whitney U test was used to compare the operating

Table 1 Patient characteristics

	All (N = 22)	Intraoperative MRI (N = 11)	Control (N = 11)	<i>p</i> value
Sex				0.087
Male	12 (55%)	4 (36%)	8 (73%)	
Female	10 (45%)	7 (64%)	3 (27%)	
Mean age (years)	47.2±15.1	46.7±9.1	47.7±19.9	0.511
Side of tumor				0.193
Right	9 (41%)	6 (55%)	3 (27%)	
Left	13 (59%)	5 (45%)	8 (73%)	
Tumor location				0.392
Frontal lobe	12 (55%)	7 (64%)	5 (45%)	
Temporal lobe	5 (23%)	1 (9%)	4 (36%)	
Parietal lobe	4 (18%)	3 (27%)	1 (9%)	
Insular	1 (5%)	0 (0%)	1 (9%)	
Pathology				1
High grade	12 (55%)	6 (55%)	6 (55%)	
Low grade	10 (45%)	5 (45%)	5 (45%)	
Mean maximal diameter (mm)	44.5±18.3	45.4±14.7	43.7±22.0	0.533
With intraoperative neurophysiological monitoring	15 (68%)	7 (64%)	8 (73%)	1
Awake craniotomy	3 (14%)	0 (0%)	3 (27%)	0.214

Abbreviations: MRI: magnetic resonance imaging

time. A statistically significant difference between groups was defined by a two-sided $p < 0.05$.

Results

Patient Presentation and Clinical Data

Patient characteristics are described in **Table 1**. A total of 22 cases of glioma patients were analyzed. Intraoperative MRI had been used for 11 of these patients. There were 4 (36%) and 8 (73%) male patients in the intraoperative MRI and control groups, respectively. Patient ages varied between 18 and 78 years old (mean age: 47.2 years overall, 46.7 years in the intraoperative MRI group, and 47.7 years in the control group). Six patients (55%) in the intraoperative MRI group and 3 patients (27%) in the control group were presented on the right side. In terms of tumor location, 12 patients (55%) were in the frontal lobe, 5 patients (23%) were in the temporal lobe, 4 patients (18%) were in the parietal lobe, and an insular gyrus tumor was found in one patient (5%). The pathological malignancy was high grade for 12 patients (55%) and low grade for 10 patients (45%). The mean maximum tumor size was 45.4 mm in the intraoperative MRI group and 43.7 mm in the control group. None of the background factors differed significantly between the two groups. Intraoperative neurophysiological monitorings including motor-evoked potential and somatosensory-evoked potential were applied in 7 cases (64%) in the intraoperative MRI group, and 8 cases (73%) in the control

group, respectively. All patients underwent tumor resection under general anesthesia in the intraoperative MRI group, while 3 patients (27%) in the control group underwent surgery with awake craniotomy. Intraoperative neurophysiological monitoring and especially awake craniotomy might affect operating time, however, the situation of using these operative techniques was not statistically differed between two groups.

Comparison of Surgical Outcomes

Table 2 shows a comparison of perioperative data between the groups. GTR was achieved in 8/11 cases (73%) in the intraoperative MRI group (**Fig. 1**) and 2/11 cases (18%) in the control group. The GTR rate was significantly higher with the use of iMRI ($p = 0.033$). The tumors which were located adjacent to eloquent area were subtotally resected in 3/11 cases (27%) in the intraoperative MRI group. In terms of postoperative neurological deficits, a total of 7 cases (32%) presented with transient disorders: 3 patients (27%) in the intraoperative MRI group and 4 patients (36%) in the control group, with no statistically significant differences between the groups. Postoperative hemorrhage occurred in one case in the control group. Among patients who could not achieve GTR, there was also one case of unintended reoperation for a removable residual tumor tissue in the control group (**Fig. 2**). The other patients were also offered reoperation, but the patient consent was not obtained.

As previously reported, operating time could be ex-

Table 2 Comparison of surgical outcomes between the intraoperative MRI group and the control group

	All (N = 22)	Intraoperative MRI (N = 11)	Control (N = 11)	<i>p</i> value
Extent of resection (%)				0.033*
Gross total resection	11 (50%)	8 (73%)	2 (18%)	
Subtotal resection	11 (50%)	3 (27%)	9 (82%)	
Neurological deterioration				0.572
None	15 (68%)	8 (73%)	7 (64%)	
Permanent	0 (0%)	0 (0%)	0 (0%)	
Transient	7 (32%)	3 (27%)	4 (36%)	
Postoperative bleeding	1 (5%)	0	1 (9%)	0.306
Unintended second surgery	1 (5%)	0	1 (9%)	0.306
Operation time (min)	474.2±162.3	465.8±132.0	483.6±194.3	0.974
Additional resection	7 (32%)	7 (64%)	N/A	N/A

Abbreviations: N/A = not available; MRI: magnetic resonance imaging

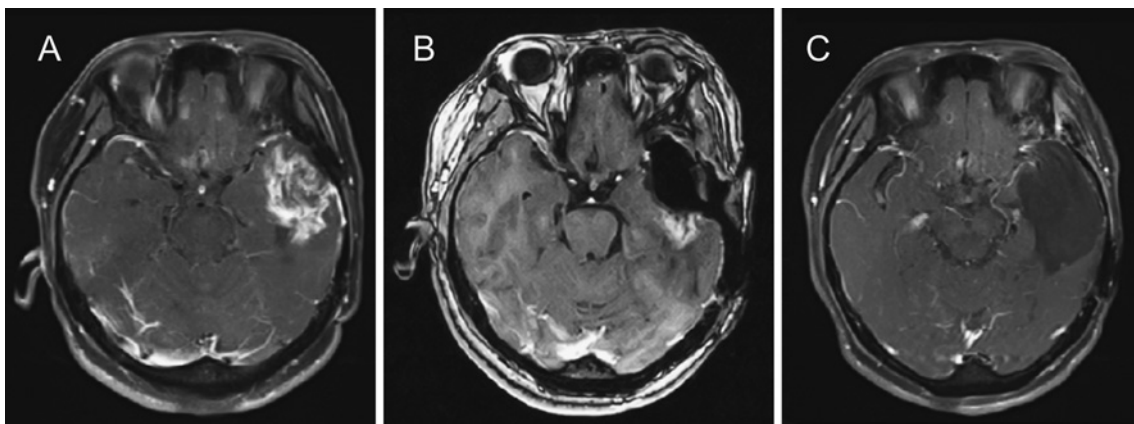


Fig. 1 A 47-year-old female patient in the intraoperative MRI group with recurrent glioblastoma. A tumor with a non-uniform contrast effect was found in the left temporal lobe (A). The tumor was excised to the extent possible before intraoperative MRI imaging. Additional excision was performed after confirmation of a contrast effect behind the excision cavity (B). Postoperative MRI scans showed no residual contrast effect and that total excision had been achieved (C). MRI: magnetic resonance imaging

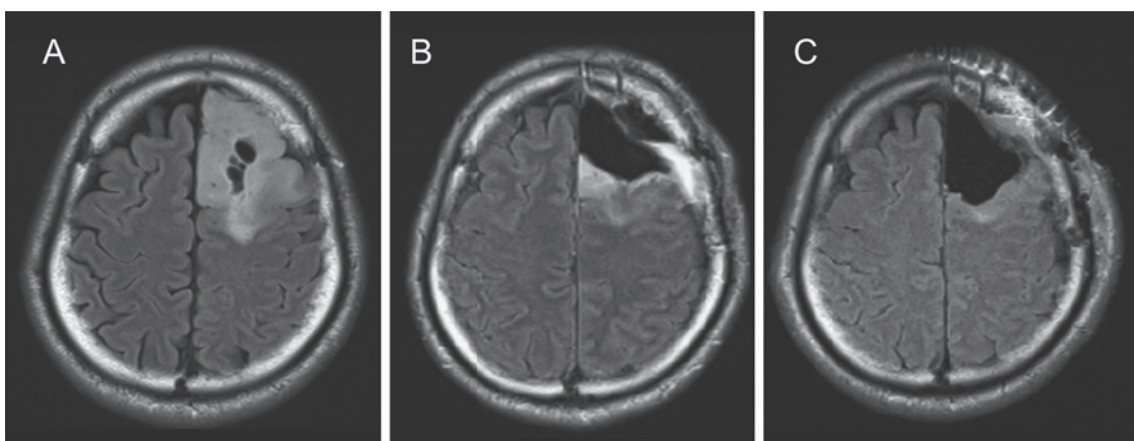


Fig. 2 A 35-year-old male patient in the control group with primary-onset anaplastic astrocytoma. A FLAIR high-signal mass with a low signal was found in the upper left frontal gyrus (A). When the tumor was excised to the extent possible, and MRI scans were taken after surgery, a FLAIR high-signal residual mass was observed on the inner side behind the excision cavity (B). The patient was reoperated, and total excision was achieved (C). MRI: magnetic resonance imaging

tended by the time taken for intraoperative MRI imaging; however, the mean operating time was 465.8 minutes in the intraoperative MRI group and 483.6 minutes in the control group, with no statistically significant differences between the groups in our study. Seven cases (64%) underwent additional tumor resection following intraoperative MRI imaging. Neither group had patients presenting with adverse events associated with the usage of intraoperative MRI, including infection, lung embolism, CSF leakage, trouble related to a magnetic field, and patient transfer to the gantry of MRI.

Discussion

The merits of intraoperative MRI include improved tumor resection rate (i.e., increasing GTR rate) because intraoperative MRI can identify residual tumors, which operator cannot confirm a hidden tumor during surgery. Our results demonstrated a statistically significant improvement in the GTR rate using intraoperative MRI and previous reports^{13,14}. Furthermore, navigation can also be updated based on intraoperative MRI for anatomical correction, contributing to this surgical outcome. The accuracy of the navigation systems based on preoperative imaging decreases with surgical manipulation due to a phenomenon called “brain shift,” caused by various factors including gravity effect on the brain, escape of the cerebrospinal fluid, brain swelling, and surgical maneuvers¹⁵. Previous reports have found that a brain shift of up to 24 mm occurs on the brain surface and a brain shift of approximately 3 mm occurs even in the deep parts of the brain¹⁶. However, updating navigation using intraoperative MRI scans can allow for tumor resection under accurate navigation guidance even after brain shift¹⁷. It has been reported that 47% of glioma surgery cases in which the surgeon felt that GTR had been achieved had a residual tumor detected by intraoperative MRI that required additional resection¹⁸. In our study, while there was one case that required reoperation due to an unintended residual lesion (detected by postoperative MRI) in the superior frontal gyrus, additional tumor resection was performed in 64% of the patients after intraoperative MRI using update navigation. Thus, additional tumor resection using intraoperative MRI and update navigation leads to an improvement in the resection rate and avoids unintended reoperation.

In addition to intraoperative MRI, it is known that the use of 5-ALA (i.e., visualizing lesions through fluorescence in high-grade glioma) also contributes to the improvement of the resection rate. While reports indicate

that 5-ALA and intraoperative MRI can improve resection rates in glioma surgery, a recent systematic review presents evidence that the combined use of these procedures can be greatly beneficial¹⁰. It is also known that a higher resection rate significantly improves patients' prognosis following glioma surgery regardless of its malignancy^{3,4,16,19-22}. This study routinely used 5-ALA for the resection of a malignant glioma.

Another merit of intraoperative MRI is the ability to avoid neurological deficits. For tumors close to the eloquent area, it is necessary to aim for maximum tumor resection with neurological function preservation. It may be necessary to combine awake surgery and intraoperative physiological monitoring to ensure functional preservation²³. With these modalities, no permanent neurological deficit was observed in this study, and transient neurological deficits were less in the intraoperative MRI group than in the control group but not significantly different.

However, the following points are demerits associated with the use of intraoperative MRI in glioma surgery. First, The process of introducing and maintaining intraoperative MRI is very costly. The cost incurred is due to the intraoperative MRI device itself and the cost of renovating the operating room for noise reduction and shielding purposes and purchasing MRI-compatible instruments. It is also necessary to hire specialist staff to maintain the system and operate intraoperative MRI imaging. High-field MRI costs 3-7 million US dollars due to superconductivity¹, although low-field MRI is often a permanent magnet; hence, it is cheaper than high-field MRI. According to a report published by the University of Minnesota, intraoperative MRI imaging for brain tumor surgery can shorten the inpatient period by 54.9% and reduce hospitalization costs by 14.4%²⁴. In addition, because low-field MRI has a narrow 5-gauss line that does not affect general electrical equipment, and ordinary medical equipment can be used outside the 5-gauss line, it would be possible to reduce the cost of purchasing MRI-compatible equipment, although even relatively cheaper low-field MRI can be difficult to introduce in all facilities. However, because glioma is a rare disease, developing a framework where glioma surgery is focused in core institutions (such as university hospitals) would provide a solution to limitations related to cost. Thus, glioma patients requiring intraoperative MRI can be referred to core institutions that already have an intraoperative MRI.

Another major issue is the prolongation of operating

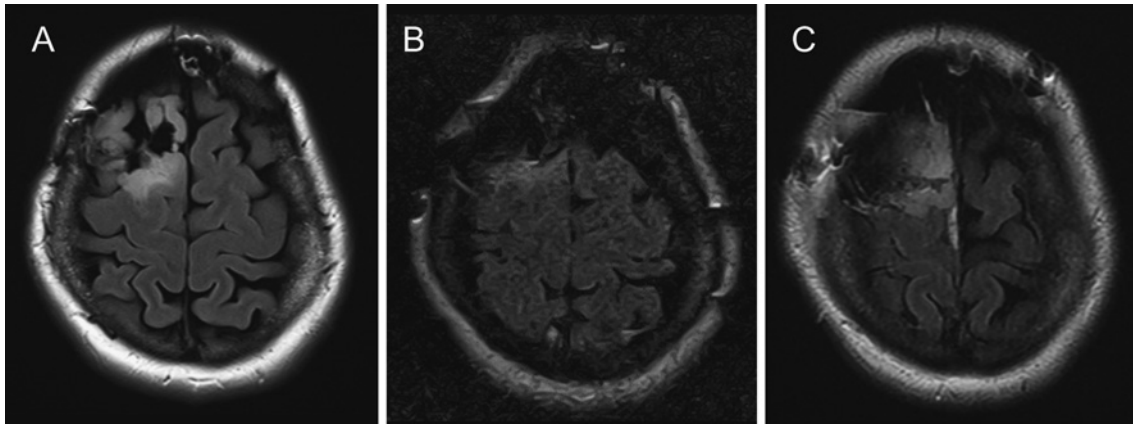


Fig. 3 A 39-year-old female patient in the intraoperative MRI group with recurrent anaplastic oligodendroglioma. A recurrent lesion with a FLAIR high signal was observed around the previous excision cavity in the upper right frontal gyrus (A). After removing as much of the tumor as possible, intraoperative MRI scans were taken. These scans suggested the achievement of total excision (B). However, postoperative MRI scans revealed a slight residual tumor tissue behind the excision cavity (C). Retrospective examination showed slight signal changes even in intraoperative MRI images. MRI: magnetic resonance imaging

time. Although there is no increase in serious adverse events such as infections with this procedure, some authors have reported that intraoperative MRI-guided surgery can prolong operating time because of the time taken for MRI imaging¹⁵. However, our study did not indicate any prolongation of operating time with the introduction of intraoperative MRI. In conventional surgical techniques, manipulating tumor boundaries and near-eloquent areas tend to be a meticulous process and can be time-consuming, instead of intraoperative MRI imaging that involves anatomical information during resection procedures using updated navigation to remove the tumor without hesitation. Moreover, the time spent on intraoperative decision-making could also be reduced by intraoperative MRI. Hence, the time taken for MRI image acquisition might be compensated by shortening the time taken for tumor resection. Update for navigation system also takes about 10 minutes, however, there was no extension of operation time due to update navigation, because it was carried out during returning the patient to set up in continuous surgery from intraoperative MRI position. In addition, non-prolongation of surgical time related to the usage of iMRI during surgery may contribute to improving the quality of life for neurosurgeons, anesthesiologists, and all staff in the operating room in the life-work balance. To the best of our knowledge, there has not been any report that intraoperative MRI contributed to shortening the tumor resection time.

The risk associated with patient movement is another disadvantage of this procedure. With ultra-low-magnetic field MRI, surgery can be performed in the same room,

and there is no need to move the patient. However, the working space is small and MRI-compatible equipment is required. On the contrary, in high-field MRI, the magnetic field is strong, and the stray magnetic field (that is, the 5-gauss line) is wide. Therefore, it is impossible to perform an operation in the MRI room; a 2-room system is required.

For this reason, the movement distance becomes longer, and it is necessary to move the anesthesia machine, which in turn increases the risk of erroneous removal of tubing and the infusion line. In our hospital, a low-field open-type MRI was installed in the operating room. The operation was performed in the space opposite the MRI device; thus, the bed is rotated around the foot side, and the head is slid into the gantry during imaging, making the movement distance short. This allows for relatively safe imaging and hence lessening this concern.

Finally, there is a possibility of false-negative results (Fig. 3). This study investigated a right frontal glioma patient deemed to have been totally excised based on intraoperative MRI. However, this was a false-negative case with a residual tumor confirmed by postoperative MRI. Because the intraoperative MRI setup of our hospital has a low magnetic field, the resolution is lower than that of 1.5-T or 3-T high-magnetic field MRI images and artifacts are likely to occur. Furthermore, operators must read the intraoperative MRI, and the results would need to be interpreted immediately so that a surgical strategy may be formulated in real time. For this reason, there is a possibility of false-negative results when residual tumors

are overlooked in the intraoperative low-field MRI. Therefore, iMRI acquisition prior to tumor resection for an accurate decision of residual tumor should be considered to prevent this false-negative phenomenon.

Limitations

This was a single-center, retrospective, observational study with a limited number of consecutive patients with glioma. Although this study is valuable due to the inclusion of consecutive patients, there is a mix of histological malignancy levels among patients undergoing glioma surgery. Further studies conducted in larger cohorts are needed to distinguish differences in prognosis according to varying clinical characteristics. There is another limitation, which improved the surgeon's skill in performing tumor resection in glioma surgery might have affected the surgical results, especially in operating time, in this study. However, the main surgeons (authors T.O. and T. G.) are experienced glioma surgeons, and the status of their surgical technique is on a flat or gentle learning curve. Therefore, we think that there is not much difference in skill between the early phase (control group) and late phase (iMRI group).

Conclusions

Implementation of intraoperative low-field MRI led to the improvement of the total excision rate in glioma surgery relative to conventional surgical techniques. In addition, despite intraoperative MRI imaging, there was no prolongation of operating time in the intraoperative MRI group. This might result from reduced decision-making and procedural hesitation during surgery due to intraoperative MRI imaging.

Disclosure of Funding: None.

Conflict of Interest: None.

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(Received, April 30, 2021)

(Accepted, August 4, 2021)

(J-STAGE Advance Publication, September 14, 2021)

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