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Clinical application of 3.0 T intraoperative magnetic resonance combined with multimodal neuronavigation in resection of cerebral eloquent area glioma

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Abstract

Glioma is the most common tumor among central nervous system tumors; surgical intervention presents difficulties. This is especially the case for gliomas in so-called "eloquent areas," as surgical resection threatens vital structures adjacent to the tumor. Intraoperative magnetic resonance imaging (iMRI) combined with multimodal neuronavigation may prove beneficial during surgery. This study explored the applicability of 3.0 T high field iMRI combined with multimodal neuronavigation in the resection of gliomas in eloquent brain areas.

We reviewed 40 patients with a glioma located in the eloquent brains areas who underwent treatment in the Neurosurgery Department of Peking University International Hospital between December 2015 and August 2017. The experimental group included 20 patients treated using iMRI assistance technology (iMRI group). The remaining 20 patients underwent treatment by conventional neuronavigation (non-iMRI group). Tumor resection degree, preoperative and postoperative ability of daily living scale (Barthel index), infection rate, and operative time were compared between the 2 groups.

No difference in infection rate was observed between the 2 groups. However, compared with the non-iMRI group, the iMRI group had a higher resection rate ($96.55 \pm 4.03\%$ vs $87.70 \pm 10.98\%$, P = .002), postoperative Barthel index (90.75 ± 12.90 vs 9.25 ± 16.41 , P = .018), as well as a longer operation time (355.85 ± 61.40 vs 302.45 ± 64.09 , P = .011).

The use of iMRI technology can achieve a relatively higher resection rate among cases of gliomas in eloquent brain areas, with less incidence of postoperative neurological deficits. Although the operative time using iMRI was longer than that taken to perform conventional navigation surgery, the surgical infection rate in these 2 procedures showed no significant difference.

Abbreviations: DCS = direct cortical stimulation, DTI = diffusion tensor imaging, iMRI = intraoperative magnetic resonance imaging, MRI = magnetic resonance imaging, nTMS = navigated transcranial magnetic stimulation.

Keywords: cerebral eloquent area glioma, intraoperative magnetic resonance image, multimodal neuronavigation, navigated transcranial magnetic stimulation (nTMS)

1. Introduction

Glioma is one of the most common intracranial tumors, the treatment for which is surgical resection. Cerebral gliomas in eloquent brain areas are closely associated with important structures, such as the language center, motor center, visual center, pyramidal tract, internal capsule, and basal ganglia. The deep location of such gliomas renders complete resection

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Received: 29 January 2018 / Accepted: 4 July 2018 http://dx.doi.org/10.1097/MD.000000000011702 difficult^[1]; overlaying structures can be injured, causing hemiplegia, aphasia, coma, and other severe complications. The degree of resection directly influences the prognosis of patients.^[2–4] With the development of electrophysiological monitoring, imaging, and microsurgery, favorable outcomes can now be achieved with glioma resection surgery.^[5–7] The application of neuronavigation by Roberts et al^[8] enables the accurate localization of lesions during surgery, significantly improving microneurosurgery. The accuracy of navigation, however, has typically been compromised by several factors, including operation error, shifting of registration system, and intraoperative brain tissue deformation (brain shift).^[9] Without intraoperative imaging compensation, image shift during surgery is difficult to correct. The development of intraoperative imaging technology has contributed an additional advancement to microneurosurgery, as it allows an objective evaluation of the intraoperative situation and ensures quality control during surgery.^[10-12] In 1996, Black et al^[13] applied intraoperative magnetic resonance imaging (iMRI) to intracranial tumor surgery for the first time. Compared with conventional neuronavigation, which is based only on preoperative imaging, iMRI can detect and correct navigation errors caused by intraoperative brain shift in real time. In recent years, the development and application of multimodal neuronavigation, including modalities such as BOLD-fMRI, diffusion tensor imaging (DTI), motor evoked potential, and navigated transcranial

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magnetic stimulation (nTMS), has achieved further progress in the treatment of glioma. TMS is a relatively new and promising method for both the investigation and therapeutic treatment of psychiatric and neurologic disorders^[14]; it correlates well with intraoperative direct cortical stimulation (DCS) and is highly valuable for surgical planning.^[15,16] Since February 2017, we have employed 3.0 T high field strength iMRI combined with multimodal neuronavigation in the microsurgical treatment of gliomas in eloquent areas.

2. Methods

2.1. Data collection

The study was approved by our institutional review board. We recruited an experimental group of 20 individuals with gliomas in eloquent brain areas. All patients were treated using iMRI assistance technology (iMRI group) at Peking University International Hospital from February 2017 to August 2017.

The inclusion criteria consisted of the following: The lesion was situated either in the language, visual, or motor functional areas of the cerebrum, or adjacent to important white matter fiber bundles, such as pyramidal tracts and arcuate fibers. Patients did not exhibit any significant neurological dysfunction, such as hemiplegia, aphasia, or blindness, before surgery. The glioma under consideration was the only lesion. The patient consented to the intraoperative MRI examination. The exclusion criteria were as follows: Multiple lesions were present. The lesion was located in nonfunctional areas, the cerebellum, or the brain stem. The patient exhibited preoperative hemiplegia or aphasia. The patient refused intraoperative MRI examination. This study has been open for enrollment since the clinical implementation of iMRI at our institutions. All patients meeting the inclusion criteria were enrolled, yielding a total of 20 patients in the experimental group. None of the patients died during the operation or perioperative period. To compile a control group, we randomly selected 20 patients with gliomas in eloquent areas who underwent treatment by conventional neuronavigation at our institutions before February 2017. Each of these individuals was paired with a corresponding patient in the experimental group based on gender, age, preoperative Barthel index, and other basic conditions. The number of participants thus totaled 40 patients (18 men, 22 women; average age, 45 years; age range, 18-69), of whom 37 underwent a single operation; tumors recurred in the remaining 3 patients, requiring a second operation. Table 1 shows a comparison of the tumor distribution between the 2 groups.

2.2. Preoperative preparations

The treatment plans represent a consensus reached by all the doctors of the neurosurgery department and conducted with the consent of patients and their families. Experienced deputy chief and

Comparison of p	atient tumor locations in t	he 2 groups.
	IMRI group	Control group

lumor location	Left	Right	Lett	Right
Frontal lobe	7	4	5	3
Temporal lobe	3	1	2	4
Occipital lobe	1	1	1	1
Parietal lobe	2	1	2	2

iMRI = intraoperative magnetic resonance imaging.

senior doctors performed the operations. Before each surgery, patients underwent an MRI examination to inform the operative procedure. An intelligent mobile 3.0 T super high-field strength, very large aperture (70 cm) scanner (MAGNETOM Verio, Siemens, Germany) was used for preoperative, intraoperative, and postoperative scanning of the patients in the iMRI group. A 3.0 T Siemens magnetic resonance scanner (MAGNETOM Skyra, Siemens, Germany) was used in the preoperative and postoperative scanning of the control group. Imaging assessments were performed 1 day before surgical opening of the cranium to obtain the navigation image. In the iMRI group, individual structure images, reconstructed corticospinal tracts, motion activation diagrams, and nTMS images were imported into Medtronic neuronavigation (TRIA i7, Medtronic Inc). The individual structure images were merged to create functional images. In the control group, only the individual structure images were imported. To visualize the lesion, cortical spinal tract, and motor functional cortex in 3 dimensions, T1-MPRAGE or T2-FLAIR images were used to enhance or delineate the border of the lesion, layer by layer. T1-MPRAGE plain scan images were used to build a 3dimensional brain structure. Finally, several images were simultaneously superimposed on the reference image (T1-MPRAGE plain image) to determine the location of the lesion and its anatomical relationship with surrounding structures. This method helped to develop individual operation plans, including the identification of the corticospinal tract and eloquent areas close to the resection border; the assessment of resection range; potential operative risk; and postoperative neurological deficits.

2.3. Surgical treatment

All patients in both groups received general anesthesia during the surgery. In the experimental group, preoperative MRIs were acquired using a 3.0 T MAGNETOM Verio MRI scanner (Siemens, Germany) with the following acquisition parameters: T1W1 3D MPRAGE: TE, 2.98 ms; TR, 2530 ms; matrix size, 256×256 ; FOV, 256×256 mm²; slice thickness, 1 mm. DTI: TE, 77 ms; TR, 14,200 ms; matrix size, 112×112 ; FOV, 224×224 mm²; slice thickness, 2 mm; bandwidth, 1718 Hz /px; b value, 0 and 1000 s/mm^2 ; Voxel, $2.0 \text{ mm} \times 2.0 \text{ mm} \times 2.0 \text{ mm}$; 70 slices. BOLD-f MRI: TE, 30 ms; TR, 2000 ms; FOV, 224×224 mm²; slice thickness, 3.5 mm. Fiber tracking used the "stealth viz 1.3" software. Following anesthesia, the patient's head was fixed using a head frame, and the reference frame (tracer) was positioned to the side of the head frame. The facial profile registration method was then used to register. After the 3-dimensional position of the lesion and the surrounding structures were displayed and verified, the surgical trajectory and incision were designed accordingly. During the surgery, the navigation probe was used in real time to explore the tumor and its surroundings to determine the range of lesion resection. The surgical system (IMRIS, Canada) was used in conjunction with an intelligent mobile 3.0 T super high field strength, very large aperture (70 cm) scanner (MAGNETOM Verio) for intraoperative scanning; its parameters were identical to those used in the preoperative scans. The intraoperative MRI scan acquisition took approximately 20 minutes, while image reconstruction required about 10 minutes. The former was performed by an MRI technician after confirmation from the surgeon, nurse, and anesthesiologist. The image reconstruction was performed by the neurosurgeon at the workstation. The operation was suspended when the surgeon judged that the degree of tumor resection reached the extent established in the preoperative plan. This decision was based both on what the surgeon observed through the microscope and the navigation information. The iMRI was then employed to assess the actual degree of tumor resection. If a residual tumor remained, the navigation reference image was updated based on the intraoperative real-time image. Resection then continued until the iMRI demonstrated the achievement of total tumor resection according to preoperative expectations. For the control group, preoperative DTI and BOLD scans were not acquired. Only the preoperative T1 MPRAGE scan was obtained for treatment planning using a 3.0 T MAGNETOM Skyra MRI scanner (Siemens, Germany) with the same parameters as the T1 scan of the experimental group. In addition, no intraoperative MRI was acquired. The treatment planning and surgical navigation were otherwise the same as those in the experimental group. Figure 1A provides a



Figure 1. A, Workflow comparison between the iMRI group and the control group. B, A schematic drawing of the iMRI operating suite. iMRI = intraoperative magnetic resonance imaging.

workflow diagram for the 2 groups and Fig. 1B shows a schematic of the iMRI operating suite.

2.4. Effect evaluation

We calculated the degree of tumor resection according to the following formula: (preoperative tumor volume – postoperative tumor volume)/preoperative tumor volume. In cases that included DICOM image data, the tumor volume was calculated using 3DSlicer. When images were provided as film or JPG files, the tumor volume was calculated using Coniglobus formula: surgical resection degree = [(preoperative tumor volume – postoperative residual tumor volume)/preoperative tumor volume] × 100%. Neurological function was evaluated using preoperative ability of daily living (Barthel index); evaluations were conducted 1 day before (Bpre) and 3 weeks after (Bpost3w) the operation. The operation time was sourced from the infection record, and the infection rate was obtained from the infection control section's record.

2.5. Statistical analysis

Statistical tests were performed using SPSS 19.0 (SPSS Inc, Chicago), and the test level was set to $\alpha = 0.05$. Age, operation time, preoperative, and postoperative Barthel index, and tumor resection degree of the 2 groups were expressed as mean \pm standard deviation ($\overline{\mathbf{x}} \pm \mathbf{s}$). The results were compared using an independent *t* test. The gender, pathological grade, and the infection rate of patients in the 2 groups were expressed as a frequency (percentage). The results were compared using either the χ^2 test or definite probability method.

3. Results

3.1. Comparison of patient characteristics

There was no statistical significance between the 2 groups in sex, pathologic grades, age, or preoperative neurological status (P > .05), indicating that the 2 groups of patients were comparable (Table 2).

3.2. Analysis of operative effects in the 2 groups

3.2.1. Resection rates. The iMRI group featured a higher resection rate than that of the non-iMRI group (P=.002; Table 3); this result was consistent among patients in the iMRI group with low-grade glioma (P=.014; Table 4) and those in the iMRI group with high-grade glioma (P=.016; Table 4).

3.2.2. Postoperative neurological function. The Bpost of the iMRI group was significantly higher than the Bpost of the non-iMRI group (P=.018; Table 3).

Table 2

Comparison between the characteristics of the 2 groups of patients.

Grouping	Sex (male/female)	Pathologic grades (low/high)	Age $(\overline{x} \pm s)$	Preoperative scales $(\overline{x} \pm s)$
iMRI group	9/11	8/12	44.90±14.79	85.75±19.35
Control group	9/11	4/16	45.45±15.21	86.50 ± 14.52
Chi ² /t	0.000	1.905	-0.116	-0.139
Р	1.000	.168	.908	.890

iMRI = intraoperative magnetic resonance imaging

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Comparison	between	clinical	data	and	outcomes	of	the 2	group
patients.								

	Resection	Operative time	Postoperative scale	Infection rate
Grouping	$(\overline{x} \pm s (\%))$	$(\overline{x} \pm s)$	$(\overline{x} \pm s)$	(n (%))
iMRI group Control group	96.55±4.03 87.70±10.98	355.85 ± 61.40 302.45 ± 64.09	90.75±12.90 79.25±16.41	1 (5.0) 2 (10.0)
Chi ² /t	3.384	2.691	2.464	_
Р	.002	.011	.018	.500

iMRI = intraoperative magnetic resonance imaging.

3.2.3. Operative time. The operative time of the iMRI group was 355.85 minutes, while that of the non-iMRI group was 302.45 minutes. The difference was statistically significant (*P*=.011; Table 3).

3.2.4. Infection rate. The infection rate of the iMRI group was 5.0%, while that of the non-iMRI group was 10.0%. The difference was not statistically significant (P=.50, Table 3).

3.3. A typical case

A 51-year-old woman was diagnosed with left frontal lobe glioma. Major clinical manifestations included intermittent headache and seizure for a month. Physical examination showed normal muscle strength and limb tension, and no sensory disorder of the limbs. Preoperative MRI showed a low grade of glioma. Intraoperative DTI, BOLD, and nTMS were performed and the functional areas were located; a large residual tumor from the deep-seated tumor was detected during the first scan. Resection continued after the navigation was updated. As part of the lesion was located in the hand motor area, the tumor was not entirely resected to avoid postoperative neurological deficits. A second iMRI scan confirmed that the tumor was satisfactorily resected. After the operation, the patient demonstrated no new neurological deficits (Fig. 2).

4. Discussion

"Maximally resect tumors, minimally impair neurological function" is the driving principle of an effective glioma surgery. Various advanced assistance technologies, such as intraoperative stimulation, functional neuronavigation, and iMRI, have been employed to achieve this goal. Evidence-based medicine has shown that for patients with an intracranial tumor, maximally resecting the tumor results in fewer neurological deficits and an extension of the patients' lifespan.^[17,18] However, for gliomas in eloquent brain regions, a blind resection would cause neurological deficits. The compromise between lesion resection and

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Comparison of the resection rate based on glioma grade.

	Resection	esection rate ($\overline{x} \pm s$)		
Grouping	Low grade	High grade		
iMRI group	96.25 ± 4.06	96.75±4.18		
Control group	89.75 ± 2.06	87.19±12.26		
χ^2 / t	2.964	2.580		
Р	.014	.016		

iMRI = intraoperative magnetic resonance imaging.



Figure 2. A, A T2 FLAIR image displaying that the tumor is in the high signal area. B, A functional magnetic resonance image showing the hand motor area (red area). C, nTMS was used to locate the language area. D, nTMS was used to locate the motor functional area. E, Preoperative navigation planning. F, Preoperative navigation planning. G, First intraoperative scan showing tumor residue. H, Intraoperation rectification of navigation. I, Second intraoperative scan showing that tumor resection has achieved a favorable effect.

preservation of neurological function presents a continuous challenge to neurosurgeons. Real-time quantitative monitoring of lesion resection range by iMRI compensates for the limitation of solely relying on the surgeon's experience. According to Gerganov et al^[19] the frequency of tumor residue attributable to misjudgment during the operation was 45.71%. In a report by Nimsky et al,^[20] 47 patients with glioma underwent 1.5T iMRI during the operation; among these, 7 cases of total resection benefited from intraoperative scanning. In a large sample study reviewing 137 cases of glioma, intraoperative scanning allowed for the identification of residual tumors in 41% of the cases; the residual tumors were subsequently removed, with 32% of the cases achieving total resection.^[21] The benefits of iMRI include its display of real-time progress of lesion resection and provision of crucial reference information that enables the surgeon to create an effective operation plan. The latter advantage is critical when a lesion is adjacent to important structures, such as the pyramidal

tract. The method can also rebuild images of important nerve structures, such as white matter fibers, and update the operation plan continually throughout the procedure, thus helping surgeons adjust to intracranial tissue shifts during operation and allowing for the modification of white matter fiber bundle reconstruction before the procedure.^[22–24] However, the application of the iMRI system does have disadvantages. It can prolong operative time by an average of approximately 30 minutes and increase surgical cost accordingly. Despite these consequences, the benefits that the technology offers patients justifies the increases in the cost and duration of the procedure.^[25]

Compared with the commonly used clinical 1.5 T iMRI, the 3.0 T iMRI features a higher signal-to-noise ratio, faster scanning speed, improved ability to find small lesions, and better DTI and BOLD (deoxyhemoglobin imaging) effects. The application of fMRI in the resection of gliomas in eloquent brain areas allows for a more accurate localization of the target area and plays an

important role in creating the surgical plan. The DTI test provides a basis for tracing the fiber bundle. Our center also applied nTMS before the operation to locate the motor area. Aiming to reduce the incidence of dysfunctions in postoperative limbs and language, and to improve the success rate of surgery, we combined the use of iMRI with multimodal neuronavigation. This study found that the employment iMRI resulted in more favorable outcomes than did the use of conventional navigation (control, non-iMRI) as evinced by improvements in lesion resection rate and postoperative functional status. However, the operation was of a longer duration in the iMRI group. Infection rates in the 2 groups did not differ.

The advantages of iMRI combined with multimodal neuronavigation in the treatment of gliomas in eloquent brain regions are as follows: One of the crucial elements of a successful resection of gliomas in eloquent brain areas is to objectively determine the spatial relationship among the lesion, eloquent area, and pyramidal tract in stereoscopic space, and choose the optimal operative trajectory accordingly.^[26] The intraoperative navigation plan can be used to rebuild images of important structures, such as the tumor, eloquent area, and pyramidal tract. The plan may further inform surgeons of relevant factors when selecting a rational operative trajectory, as well as when deciding to follow or modify the plan during surgery. When resection is adjacent to an eloquent area or pyramidal tract, the operation should be suspended and intraoperative scanning should be performed to determine the tumor resection status; if tumor residue exists within a safe range, the navigation will be updated to correct the brain shift and the surgery can then be resumed according to the navigation information. The combination of iMRI with multimodal neuronavigation thus improves the safety of an operation. The method permits the timely detection of tumor residue, or even of a new hematoma, which can then be treated to avoid postoperative rebleeding and neurological deficits caused by a subsequent surgery.

The limitations of this study include the lack of randomness and the small sample size. In addition, apart from evaluations concerning tumor recurrence, survival, and other post-operative complications, long-term follow-up data concerning the treated patients is not currently available. Further studies addressing these limitations are currently being conducted.

5. Conclusion

The present study combined iMRI with multimodal neuronavigation to achieve real-time intraoperative imaging navigation for glioma resection surgery. The technique increased the resection rate of gliomas in eloquent brain regions and protected patients' neurological functions. Although the use of iMRI prolongs operative time, it did not cause any increase in infection rate. As the most advanced intraoperative imaging technology, iMRI combined with a multimodal neuronavigation system could prove to be a valuable assisting technology in microneurosurgery and has the potential for broad clinical applications.

Author contributions

Conceptualization: Yuanli Zhao. Data curation: Xiao-Lei Chen. Formal analysis: Chang-Yu Lu, Xiao-Lei Chen. Funding acquisition: Yuanli Zhao. Investigation: Xiao-Lin Chen. Methodology: Xiao-Lin Chen, Xiao-Lei Chen, Xiaojing Fang. Validation: Xiaojing Fang.

Writing - original draft: Chang-Yu Lu, Xiaojing Fang.

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