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Surgical Strategies for Nonenhancing Slow-Growing Gliomas With Special Reference to Functional Reorganization: Review With Own Experience

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Abstract

Nonenhancing intrinsic brain tumors have been empirically treated with a strategy that has been adopted for World Health Organization (WHO) grade II gliomas (low-grade gliomas: LGGs), even though small parts of the tumors might have been diagnosed as WHO grade III gliomas after surgery. However, the best surgical strategy for nonenhancing gliomas, including LGGs, is still debatable. LGGs have the following features: slow growth, high possibility of histologically malignant transformation, and no clear border between the tumor and adjacent normal brain. We retrospectively examined 26 consecutive patients with nonenhancing gliomas who were surgically treated at Kanazawa University Hospital between January 2006 and May 2012, with special reference to functional reorganization, extent of resection (EOR), and functional mapping during awake surgery. These categories are closely related with the features of LGG, i.e. functional reorganization due to slow-growing nature, EOR with related malignant transformation, and functional mapping for delineating the unclear tumor border. Finally, we discuss surgical strategies for slow-growing gliomas that are represented by LGGs and nonenhancing gliomas. In conclusion, slow-growing gliomas tend to undergo functional reorganization, and the functional reorganization affects the presurgical evaluation for resectability based on tumor location related to eloquence. In the clinical setting, to definitely identify the reorganized functional regions, awake surgery is recommended. Therefore, awake surgery could increase the extent of the resection of the tumor without deficits, resulting in the delay of malignant transformation and increase in overall survival.

Key words: functional reorganization, nonenhancing glioma, low-grade glioma

Introduction

A surgical strategy for brain tumors is generally developed based on the presurgical magnetic resonance (MR) imaging findings. Although the possibility that some cases of high-grade gliomas are less enhanced with contrast medium cannot be ruled out,[2,58] low-grade gliomas (LGGs), mainly diffuse astrocytoma, oligodendroglioma, and oligoastrocytoma, are predominantly nonenhancing tumors, and are best visualized on fluid-attenuation inversion recovery (FLAIR) and T_2-weighted images. Given that histological information can be obtained only after surgical resection, and that LGG is a post hoc diagnosis, it is reasonable to develop a surgical strategy to treat nonenhancing tumors as slow-growing gliomas that are represented by LGGs.

Based on the growing evidence for the need for greater extent of resection (EOR) in reducing the malignant transformation rate and the importance of eloquence in determining tumor resectability, surgical management paradigms for LGGs have been shifting over the last 10–20 years.[9,18,19,34,41,44,48,53,60,61,70,73] Greater EOR, which is the maximum resection that can be achieved without postoperative

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functional deficits, should be the primary goal of the initial surgical intervention for LGG. One of the major limiting factors that limit the EOR is the functional eloquence of tumor location, which should be influenced by functional organization and reorganization.

This review with our institutional experience and previous reports discusses cortical and subcortical functional reorganization due to brain plasticity that is caused by slow-growing gliomas (nonenhancing gliomas in our series), and the use of awake surgery with direct functional mapping. These categories are closely related to the eloquence of tumor location, the EOR in surgery, and subsequent malignant transformation.

Methods

Our study included 26 consecutive patients (19 men, 7 women) who underwent surgical resections, except for 1 case of biopsy, at the Department of Neurosurgery, Kanazawa University Hospital, between January 2006 and May 2012. All patients were diagnosed presurgically with slow-growing gliomas, probable LGGs, based on FLAIR/T_2-weighted MR imaging findings of hyperintense tumors with almost no enhancement. Although volumetric analysis of growth kinetics for slow-growing nature was not performed, the hyperintense lesions showed little change in size over at least several months of presurgical period in all cases. The mean age of the patients was 42 years (range 26–63 years). The demographic characteristics of the patients are summarized in Table 1. The study was approved by the In-

Table 1 Summary of the 26 patients with nonenhancing slow-growing gliomas

Case No.	Age (yrs)	Sex	Symptom	Site	Awake surgery	EOR (%)	MT	Diagnosis	fMR imaging (reorganization)
1	43	M	seizure	rt SMA + motor	no	30	yes	DA → AA	N/A
2	50	M	seizure	lt SMA	no	15	yes	DA → AA	N/A
3	36	M	seizure	rt SMA + motor	no	4	yes	O → AO	N/A
4	58	F	incidental	lt parietal	no	0 (biopsy)	yes	DA → AA	N/A
5	57	F	seizure	lt insular	yes	74	no	O	N/A
6	48	M	seizure	lt insular	no	11	yes	DA → AA	N/A
7	48	M	incidental	rt frontal	no	100	no	DA	N/A
8	27	M	seizure	rt insular	no	73	no	AA	N/A
9	42	M	seizure	rt temporal	no	100	no	AO	N/A
10	24	F	headache	lt temporal	yes	78	no	AA	reorganization suspected
11	29	M	headache	rt frontal	no	82	no	DA	N/A
12	36	M	headache	bi-frontal	no	75	no	AA	N/A
13	22	M	seizure	lt frontal	no	100	no	AO	N/A
14*	63	M	seizure	rt insular	no	23	no	O	reorganization suspected
15	26	F	seizure	lt frontal	no	73	no	AA	reorganization suspected
16	38	F	seizure	lt insular	yes	57	no	AA	reorganization suspected
17	55	M	headache	lt frontal	no	100	no	DA	N/A
18	58	M	seizure	rt frontal	no	100	no	O	N/A
19	39	M	seizure	rt SMA	no	100	no	O	N/A
20	46	F	incidental	rt parietal	no	100	no	DA	N/A
21	51	M	incidental	rt straight gyrus	no	100	no	DA	N/A
22	34	M	seizure	lt insular	yes	60	no	O	reorganization suspected
23	48	M	sensory disturbance	rt parietal	no	53	no	AO	N/A
24	36	M	seizure	rt motor	yes	20	no	AO	reorganization suspected
25	39	M	seizure	lt SMA	yes	93	no	AO	reorganization suspected
26	28	F	seizure	lt temporoparietal	yes	79	no	AA	reorganization not suspected

*Right hemisphere is dominant hemisphere. AA: anaplastic astrocytoma, AO: anaplastic oligodendroglioma, DA: diffuse astrocytoma, EOR: extent of resection, F: female, fMR: functional magnetic resonance, M: male, MT: malignant transformation, N/A: not applicable, O: oligodendroglioma, SMA: supplementary motor area.

stitutional Review Board of Kanazawa University Hospital.

Whole-brain functional MR (fMR) imaging was acquired with a T_2*-weighted echo-planar sequence that was sensitive to the blood oxygen-level dependent (BOLD) signal (repetition time 3000 msec, echo time 35 msec, matrix 64 × 64 mm, field of view 200 mm, imaging 44 contiguous slices of 3-mm thickness) with a 3-tesla MR imaging scanner (Signa Excite HDx; GE Healthcare, Little Chalfont, Buckinghamshire, UK). Each fMR imaging session consisted of 3 dummy image volumes, 3 activation periods, and 3 baseline (rest) periods. Language and motor tasks were performed by 8 of the 26 patients in whom the lesions were located in proximity to eloquent regions (language and motor) in the dominant hemisphere. As a language task, each patient was asked to generate a verb related to visually or acoustically presented nouns during the active condition, and to remain silent with no stimulation during the rest condition. After acquiring the data, functional activation maps were calculated with analysis software (Brain Wave PA version 14; GE Healthcare). For display purposes, BOLD activations were superimposed onto three-dimensional normalized T_1-weighted spoiled gradient recalled acquisition in steady state images of each subject's head.

Tumor volume was measured as an ellipsoid based on the hyperintense lesion on FLAIR imaging. Tumor volume was calculated with the $4\pi/3 \times a/2 \times b/2 \times c/2$ technique (a: maximum length on axial image, b: maximum vertical length for a, c: maximum length on coronal image).[72] EOR was calculated as follows: (preoperative volume − postoperative volume)/preoperative volume. Postoperative MR imaging was performed within 48 hours after surgery. Cases with EOR over 100% and no postoperative hyperintense lesion on FLAIR imaging were defined as total resection (EOR = 100%) in our series. Malignant transformation within 3 years after the first surgery was evaluated as the appearance of new intense enhanced lesions and histological upgrading that was confirmed by a second surgery. In 15 of the 26 cases, which were followed over 3 years, EOR was evaluated in relation to malignant transformation, and, in 9 of the 26 cases, in whom the tumor was located in/around the eloquent region in the dominant hemisphere, EOR was evaluated in relation to awake surgery.

Results

Seven of the 8 patients who were examined with fMR imaging preoperatively exhibited BOLD activity in an atypical anatomical region. A representative case with a left insular glioma that slowly grew during a 7-year period is shown in Fig. 1, and representative fMR images of each patient with suspected functional reorganization are shown in Fig. 2.

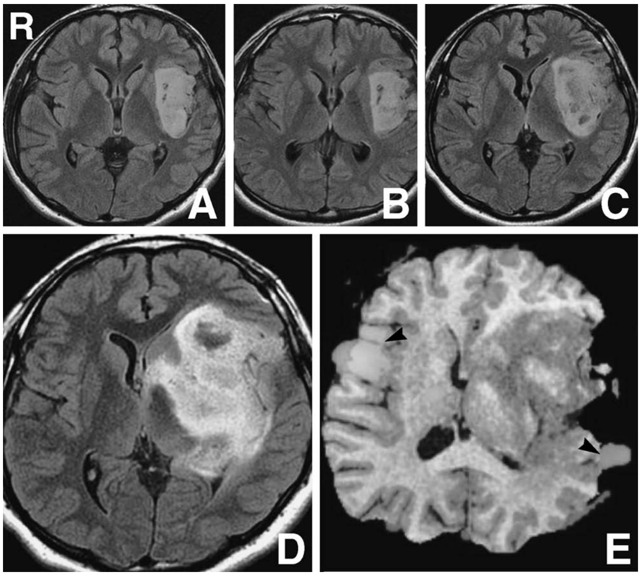

Fig. 1 Preoperative magnetic resonance (MR) images and functional MR (fMR) images of the illustrative case (Case 22, 34-year-old right-handed man). A–D: Axial fluid-attenuated inversion recovery MR images showing a chronologically slow-growing insular tumor during a 7-year period. E: Preoperative fMR image with language tasks showing blood oxygen level-dependent activities (*arrowheads*) at the right inferior frontal gyrus (mirror region to Broca's speech center in the left hemisphere) and left posterior superior temporal gyrus (suspected Wernicke's speech center).

Fifteen of the 26 patients (Cases 1 to 15) could be evaluated for the occurrence of malignant transformation within 3 years. The EOR tended to be lower in patients with malignant transformation within 3 years from the first treatment (data not shown). Nine of the 26 patients (Cases 5, 10, 16, 22, 25, and 26 with awake surgery, and Cases 2, 6, and 14 with general anesthesia) in whom the tumor was located in/around the eloquent region in the dominant hemisphere could be evaluated for EOR relative to awake surgery. EOR was significantly higher in patients with awake surgery than in patients with general anesthesia (Fig. 3).

Discussion

I. Possible functional reorganization

Recently, the possibility of functional reorganization, including motor, language, and visual function,

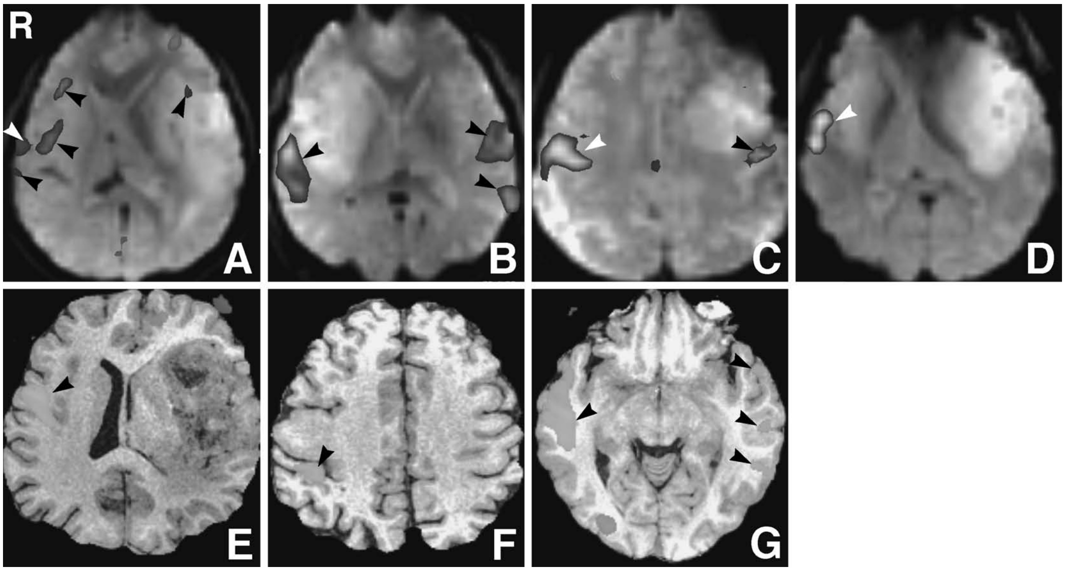

Fig. 2 Preoperative functional magnetic resonance images of each case with suspected functional reorganization. With the language task, interhemispheric language reorganizations were suspected in all patients except Case 24, as blood oxygen level-dependent (BOLD) activities (*arrowheads*) presented in nondominant mirror regions to classical anatomical speech centers in dominant hemispheres. In Case 24 with the finger tapping task, the BOLD activity presented in the post-central gyrus, or sensory cortex in normal anatomy (suspected motor function reorganization). Right hemisphere is dominant in Case 14. A: Case 10, B: Case 14, C: Case 15, D: Case 16, E: Case 22, F: Case 24, G: Case 25.

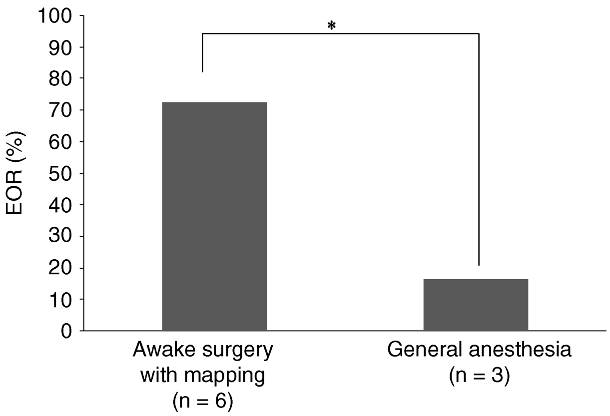

Fig. 3 Extent of resection (EOR) in nine patients with lesions located in/around eloquent areas in the dominant hemisphere. Significantly greater EOR was achieved in patients who underwent surgeries involving awake craniotomies and direct electrical stimulation mapping (*p = 0.025, Mann-Whitney U test).

has been reported in various pathological or artificial conditions.[4,7,24–27,30,37–40,50,62,68,71] From the perspective of surgical intervention, three mechanisms of reorganization that occur pre-, intra-, and postoperatively due to brain plasticity are possible: preoperatively slow-growing or long-standing lesions could affect functional networks and induce rewiring and new connections,[15,32,49,56,63,65,66] intraoperative manipulations may directly induce cortical hyperexcitability and redistribution through the unmasking of functional networks that are active before surgery,[17,47] and postoperative intensive rehabilitation programs could facilitate network sprouting that compensates for surgically disturbed functions.[8,35,36]

Our study with preoperative fMR imaging indicated that, with a very high frequency (approximately 90%), BOLD activity was depicted in a region that could be evaluated as atypical, namely, the region was located apart from the usually expected regions based on normal functional topography. This finding can be explained by the common occurrence of functional reorganization in patients with nonenhancing gliomas that are represented by slow-growing LGGs. Several limitations of fMR imaging of brain tumors should be taken into consideration.[6,16,31,57,67] For example, BOLD activity does not measure neuronal activity directly but rather the changes in the hemodynamic properties of the region of interest and the measurement is highly dependent on the specific tasks that are chosen and collaboration on the patient side. In glioma patients, the absence of BOLD activity in a particular region does not necessarily indicate that neuronal activity within the area is nonexistent or vice versa.

Nonetheless, even if the above limitations are taken into account, the concept and possible evidence of functional reorganization in LGGs might be quite useful for initial surgical strategies in treating tumors that are located in eloquent areas because lesions that invade topographically eloquent areas, including Broca's and Wernicke's speech centers and the primary motor cortex, could be resected due to possible brain reorganization.[4,24,28,39,40,46,48,71] Of note, although possible functional reorganization can be detected by preoperative fMR imaging, if the region of the possible functional reorganization is located in the surgical field, direct electrical stimulation (DES) should be performed intraoperatively to evaluate and confirm the findings of fMR imaging. In terms of the methods that can be used to observe brain functions, to overcome the limitations of presurgical neuroimaging, including fMR imaging, the current gold standard is DES that is based on reversibly inhibiting neuronal functions in certain areas.[20–22]

Functional reorganization in LGGs has been suspected in many cases, and the concept has been accepted widely. However, the question arises whether the anatomically atypical functional localization that is observed is really compensatory in nature and whether it can be interpreted as reorganization due to brain plasticity. In most clinical cases, including our cases in which compensative functional reorganization was suspected, it is impossible to present direct evidence for a compensatory transfer of functions because the anatomical functional localization before LGG onset is unknown, except in a few cases.[49] In such cases, even if the slow-growing kinetics of LGGs could be confirmed with chronological neuroimaging from the very early stages of the onset of the tumor, the state of the functional localization was unfortunately not examined in the very early stage. In the future, if possible, we recommend that the chronological changes in functional localization are examined and followed during the LGG growth period.

II. EOR, eloquent regions, and awake surgery

In recent years, several non-volumetric and volumetric studies with a large number of cases have indicated positive effects of greater EOR in patients with LGGs.[1,3,5,10,13,43,45,52,55,59,60] First, greater EOR prolongs overall survival and progression-free survival. Second, greater EOR reduces the chance of histological upgrading, which is the malignant transformation of LGGs. Third, greater EOR improves the accompanying symptoms, including seizure.[23] Although we examined only a few cases, our study revealed that, for nonenhancing gliomas, a greater EOR reduced the rate of malignant transformation within 3 years after the primary surgery.

In line with the benefits of greater EOR, total or supratotal resections of LGGs or nonenhancing gliomas may become expected goal of a surgical intervention. In addition to the depth of the tumor location and its relationship with major vessels in proximity to the tumor, the main limiting factor against total or supratotal resections should be the eloquence of the tumor location, both in cortical and subcortical regions. To confirm the presence of an eloquent region and minimize functional deficits, several intraoperative modalities, including intraoperative neuro-navigational systems and the monitoring of motor-evoked and sensory-evoked potentials, have been introduced for use in patients under general anesthesia. However, as monitoring for language functions, visuospatial functions, executive functions, and other cognitive functions is impossible in patients under general anesthesia, intraoperative functional monitoring of cortical and subcortical regions with DES during awake craniotomy is the best tool and the gold standard at the present. In fact, several studies have indicated that awake surgery could support the intraoperative identification of functional regions and greater EOR could be obtained during awake craniotomy than with general anesthesia.[11,14,33,51,54] In our series, although the possibility could not be excluded that less aggressive surgeries were adopted under general anesthesia based on the risk of permanent functional deficits devastating the patient's quality of life (QOL), significantly greater EORs could be performed with DES during awake craniotomies in cases with tumors that were located in/around the eloquent regions.

While planning a surgical strategy, the commonly accepted eloquent regions are as follows: dominant hemisphere perisylvian language cortex (superior temporal, inferior frontal, and inferior parietal areas), sensory and motor cortices, calcarine visual cortex and the optic tract, pyramidal tract/internal capsule, basal ganglia, and thalamus. From the point of view of executive functions and emotion, the prefrontal region, which is regarded as a non-eloquent region in typical surgical interventions, should be considered an eloquent area, and the right parietal-frontal network should be considered important for visuospatial awareness. To maintain or improve the QOL of patients with brain tumors who elect to undergo surgical intervention, regions that are related to complex cognitive functions, including executive functions, emotion, and visuospatial awareness, should be considered possibly indispensable functional regions that need to be preserved. In our experience with 1 of these 26 cases, a neuroradiologically adequate EOR of gross total resection of a tumor that was located in the left supplementary motor area was achieved at the price of working memory disturbance. Although the patient's scores on standard cognitive examinations gradually improved and returned to the normal range, the patient could not return to the previous profession for a long time. In addition, another patient with a right high-parietal nonenhancing glioma suffered visuospatial awareness disturbance after supratotal tumor resection, and the patient could not return to the previous profession as a care-worker. In both cases, these functions could not be evaluated intraoperatively. Although awake surgery was performed in the former case, an appropriate task to evaluate working memory was not applied, and, in the latter case, the surgery was performed under general anesthesia.

III. Future research

Tasks to evaluate simple language or motor functions are generally performed during awake surgery, whereas appropriate tasks to examine more complex cognitive functions, including executive functions, emotion, and visuospatial awareness, have not generally been established. Several limitations, including the patient's position on the operating table, for performing tasks to evaluate complex cognitive functions are present during awake surgery, and tasks that are commonly performed in a neuropsychological examination room may be difficult to complete.[12,29,42,64,69] However, in order to not affect QOL, including the ability to continue a profession, appropriate tasks that can be performed intraoperatively and that examine a targeted function correctly should be introduced to critically evaluate whether the region of interest is resectable or not.

Last but not least, although nonenhancing gliomas were treated with a surgical strategy for slow-growing LGGs in the present series, in 12 of the 26 cases, part of the resected specimen, usually a small part, was diagnosed as World Health Organization (WHO) grade III glioma based on the relatively high tumor cellularity and MIB-1 labeling index, and the final diagnoses of such cases were WHO grade III gliomas or anaplastic high-grade gliomas. The initial surgical strategy is generally impossible to establish based on post hoc histological diagnoses, but determining the strategy based on the assumption that the tumor is a LGG is not unreasonable. Nonetheless, the question arises whether a nonenhancing glioma with a very small part that is probable grade III glioma should be treated as anaplastic glioma after the initial surgery, even if the probable grade III part was resected supratotally. Because no definitive histological diagnostic criteria that distinguishes grade III gliomas from grade II have been established, and common postoperative irradiation potentially disturbs cognitive functions following impaired QOL, such tumors could be treated generally as LGG without postoperative irradiation or with de-escalated radiation. To answer the question, a prospective study with a large number of such tumors is necessary from the perspective of not only oncological prognosis, but also the patient's QOL.

Conflicts of Interest Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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