Surgical Paradigms in Diffuse Low-grade Glioma: Insular Glioma Case Illustration

Nardin Samuel, Aristotelis Kalyvas*, Mark Bernstein§, Paul Kongkham*

Keywords: Insular glioma, Awake craniotomy, fMRI, Diffuse low grade glioma

doi:10.1017/cjn.2021.10 Can J Neurol Sci. 2021; 48: 874–878

Introduction

Low-grade gliomas (LGGs) comprise a group of neuroepithelial tumors derived from supporting glial cells. These lesions include diffuse low-grade tumors (grade II) as classified by the World Health Organization (WHO). The mean age at diagnosis is 41 years with an average overall survival (OS) of 7 years following diagnosis.[1] Nearly all adult LGGs inevitably progress to high-grade tumors (WHO grade IV, glioblastoma) and are subsequently fatal.[1] The management of LGG has been a source of controversy in the field of neuro-oncology, and current adjunct treatment regimens vary based on tumor characteristics and extent of resection (EOR) and include ongoing surveillance, chemotherapy, and radiation therapy.[2,3] While prospective, randomized data are lacking, EOR has been shown in some studies to be the most important predictor of outcome including OS, symptom management, and time to malignant transformation.[4] Despite the importance of EOR in LGG, one must strive not to aim for greater EOR at the expense of incurring neurologic deficits with negative impact on quality of life.[5]

While at present there is a lack of clear consensus regarding the treatment of LGG, emerging literature continues to favor early and aggressive surgical resection for these tumors, when possible.[6] An individualized approach to treatment is paramount to successful management, and the decision to operate must take into consideration anatomic constraints, anticipated meaningful EOR, surgical risk, and patient preferences.[7]

Accordingly, we present herein the case of a young patient with an insular LGG. Insular LGGs remain among the most technically challenging tumors to manage surgically, and we utilize the clinical case conference format to discuss the surgical management of LGG, providing a framework for management of these patients. This case highlights that with careful consideration and surgical planning, even the most formidable of LGGs may benefit from a strategy of upfront surgical resection.

Case Presentation

History and Work-up

We present the case of a 28-year-old right-handed female with an insular LGG in the left (dominant) hemisphere. She first presented to medical attention at an outside hospital following an episode of right upper and lower extremity sensory-type seizures, described as paresthesias, numbness, and vibrations accompanied by dysgeusia and occasional expressive aphasia without any loss of consciousness. She was started on oral levetiracetam with a reported reduction in seizure frequency. She was subsequently referred to our service for surgical consideration. The patient did not endorse any neurologic symptoms, including speech or motor deficits, no visual disturbances, did not have any obvious cognitive changes, and her mood was euthymic. On examination, the patient was neurologically intact with no deficits, including absence of receptive or expressive speech deficits. Orientation, cranial nerve, motor, and sensory examination were unremarkable.

Magnetic resonance imaging (MRI) demonstrated a large (7 cm × 6 cm × 4.4 cm), non-enhancing T2 hyper-intense lesion in the left insula with mild expansion of the Sylvian fissure (Figure 1). Mass effect secondary to the lesion caused a rightward subfalcine shift and herniation. Computed tomography angiogram demonstrated branches of the left middle cerebral artery (MCA) coursing around the tumor, while the lenticulostriate arteries were displaced medially (Figure 2). Functional MRI using our standard language paradigm including sentence completion, naming, and phonemic fluency tasks demonstrated activations in canonical left frontal and middle/inferior temporal regions, together with ipsilateral supplementary motor area and premotor areas, confirming language dominance (Figure 3).

The patient underwent further testing in the epilepsy monitoring unit (EMU). Numerous push button events (patient-initiated event marking epileptiform activity on EMU recording) were noted. Some events featured attenuation of the left hemispheric alpha rhythm followed by emergence of left hemispheric semirhythmic delta/theta activity. Overall, these features were compatible with an electrographic onset in the left hemisphere, likely arising from the insula. A regimen of three antiepileptic drugs was initiated.

Management

In the present case, the most likely diagnosis was LGG. There were extensive discussions made with the patient and family at multiple junctures. With respect to the oncologic management, it

From the Division of Neurosurgery, Toronto Western Hospital/University Health Network, University of Toronto, Toronto ON, Canada (NS, AK, MB, PK)

Received July 4, 2020. Final Revisions Submitted January 12, 2021. Date of Acceptance January 12, 2021.

Correspondence to: Paul Kongkham, Assistant Professor, Division of Neurosurgery, University of Toronto, Toronto Western Hospital, 399 Bathurst St, West Wing, Room 4-450, Toronto ON, Canada. Email: paul.kongkham@uhn.ca

*Dr. Samuel and Dr. Kalyvas contributed equally to this study.

§Dr. Mark Bernstein is the expert discussant for this Clinical Case Conference.

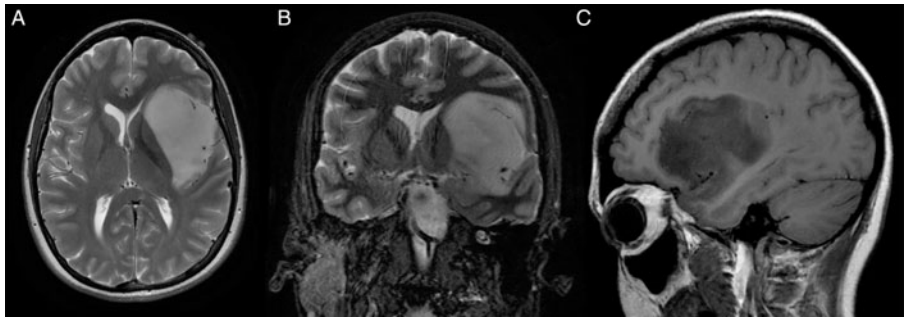

Figure 1: *Axial (A) and sagittal (B) T2-weighted magnetic resonance imaging (MRI), as well as sagittal T1-weighted imaging (C) demonstrating a large (7 × 6 × 4.4 cm), T2-hyperintense lesion (hypointense on T1) in the left insula with mild expansion of the Sylvian fissure.*

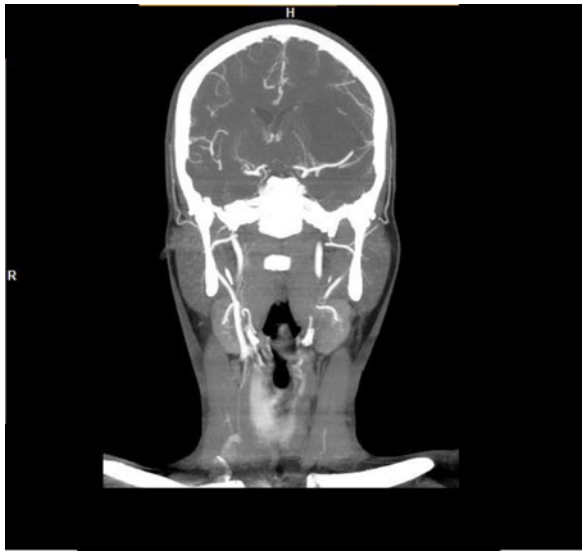

Figure 2: *Computed tomography angiogram (CTA) demonstrating branches of the left middle cerebral artery (MCA) coursing around the tumor, while the lenticulostriate arteries are displaced medially.*

was discussed that the treatment options include a "watch and wait" approach, or upfront maximal safe resection. However, the field is experiencing a paradigmatic shift in philosophy whereby upfront surgical resection may be the preferred option in select cases as it is associated with delay to malignant progression and extended OS. Importantly, a discussion pertaining to the anatomical location of this patient's tumor, both from a functional and vascular perspective, was had and that tumors in this location were traditionally regarded as challenging from an operative perspective. The decision was made by the patient to proceed with surgical resection with the goal of maximal safe resection in order to decrease the risk of malignant transformation and improve the odds for favorable OS.

Discussant Commentary: Part 1

Regarding the "watch and wait" approach, this is felt to be a safe and reasonable approach for tumors that do not meet the "MEAN" criteria (M is for massive or mass effect, E is for enhancement, A is for advanced age (perhaps over 40), and N is for neurological deficit more than just seizures). As there is currently an absence of Class I evidence to provide guidance, surgeons making recommendations to adult patients with presumed LGG must also be aware of the inherent biases in decision-making in order to avoid them as much as possible.[8,9] There have been European and North American studies indicating what the "local" practice is vis-à-vis newly discovered LGG which demonstrate the variability in approaches.[2]

Intraoperative Surgical Strategy

Surgical strategies that may be pursued when resecting an insular glioma include a trans-sylvian versus trans-cortical approach. A trans-sylvian approach takes advantage of natural corridors to approach the tumor and may be necessary when functional opercular cortex surrounds the lesion. However, a dominant draining vein traversing the sylvian fissure requiring sacrifice is reported in up to 87% of cases.[10] This approach also requires the surgeon to be comfortable with microsurgical techniques to widely dissect the fissure. It should also be noted that a common cause of morbidity following trans-sylvian dissection is excessive retraction on the opercular regions which can result in injury to Broca's area, the fibers of the arcuate fasciculus or those of the uncinated fasciculus.[11] As such, fixed retraction in this region should be avoided. Alternatively, a trans-cortical approach involves resection of portions of the operculum to provide a subpial route to the lesion that avoids the need to widely dissect the sylvian fissure vasculature. The insular component of the tumor can be resected through these cortical working windows. In cases of tumor invading the insular opercula, many consider this approach preferable to the trans-sylvian corridor when the involved opercula are safely resectable.

Our patient underwent an awake craniotomy with direct cortical electrical stimulation to map critical language hubs and identify possible silent cortical windows for access to the tumor. Since the tumor did not invade the opercular cortical surface, we anticipated a hybrid approach incorporating a trans-sylvian approach would be required. A sylvian fissure dissection provided an additional window providing a wider corridor to access the core of the tumor. Once the trans-Sylvian exposure was maximized, the patient was roused from conscious sedation in order to facilitate awake speech and motor mapping, thereby identifying transcortical windows for further exposure (Figure 4). With the patient awake, naming and counting tasks were performed and areas of speech arrest were identified, representing motor face areas. In addition, delay in the initiation of speech as well as phonemic paraphasia in the region of the pars triangularis was identified. The pars orbitalis and pars opercularis appeared to be silent. Subsequently, trans-cortical windows were made in the

https://doi.org/10.1017/cjn.2021.10 Published online by Cambridge University Press

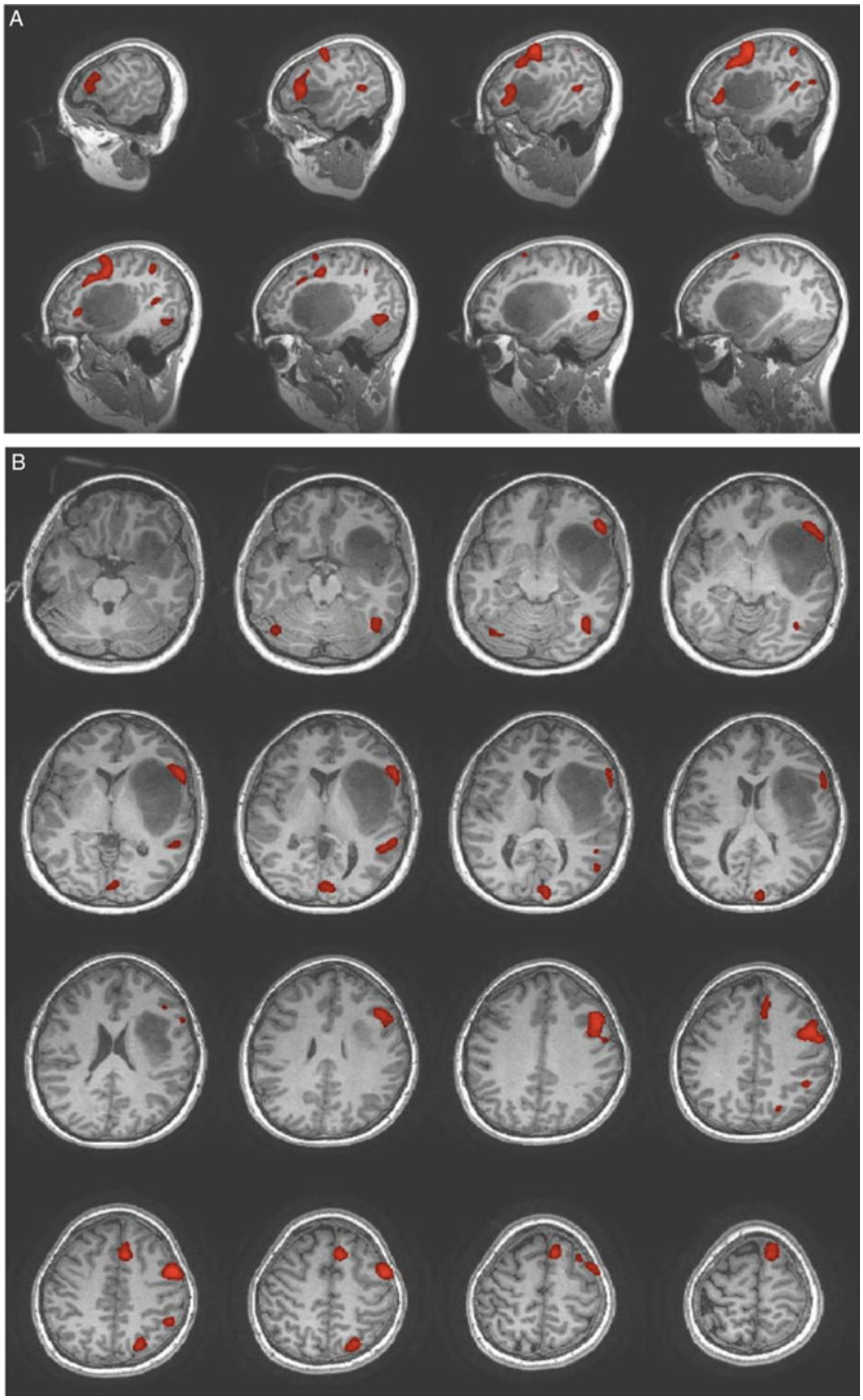

Figure 3: *A (sagittal) and B (axial) images obtained by functional MRI (fMRI) demonstrating activations in canonical left frontal and middle/inferior temporal regions, together with ipsilateral supplementary motor area (SMA) and premotor areas, confirming language dominance.*

pars opercularis and pars orbitalis. Functionally, it should be noted that the perisylvian subcortical network is implicated in the processing of speech and language. The SLF/arcuate fasciculus complex traveling at the level of inferior frontal gyrus is heavily involved in the dorsal stream of language processing according to the dual stream model of language by Hickok and Poeppel.[12,13] While the uncinate and the inferior fronto-occipital fasciculus (IFOF) both extending through the subcortical limen insula region subserve the ventral stream of language processing. In the present case, cortical and subcortical mapping was employed to interrogate for function in the region of the frontal opercula using naming and counting tasks, mapping at the level of the IFOF at later stages of our case proved to be less reliable due to patient fatigue, but was useful in demarcating the medial EOR in

https://doi.org/10.1017/cjn.2021.10 Published online by Cambridge University Press

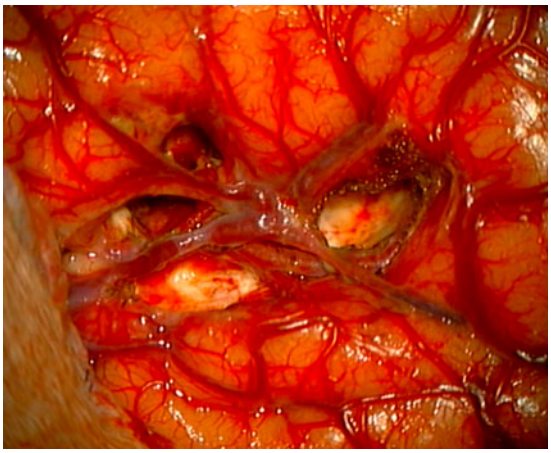

Figure 4: *Intra-operative image demonstrating cortical windows through the frontal and temporal opercula mapped intra-operatively to maximize access to the lesion.*

this region to avoid medial transgression and injury to lenticulostriate perforators.

The transcortical windows provided sub-pial access to the superior aspect of the tumor at the level of the superior limiting sulcus and the anterior aspect of the tumor at the level of the anterior limiting sulcus, respectively. An additional window was created at the level of the anterior temporal operculum, where a portion of the operculum was infiltrated by tumor. With the patient awake and while moving her right upper and lower extremities, systematic debulking was pursued via the sylvian fissure window until the two M2 branches of the MCA were identified and flanked the most central portion of the tumor. Notably, insular perforating arteries arising off of M2 branches were also identified, and care was taken to avoid injuring long perforators.

The resection continued through the pars orbitalis, anterior sylvian fissure, and anterior temporal operculum to address the anterosuperior, anterior, and anteroinferior part of the tumor, respectively. The pars opercularis and posterior sylvian fissure windows were used to gain access and resect the posterosuperior and posterior part of the tumor, respectively. Iterations between resection followed by use of intra-operative adjuncts such as ultrasound and neuronavigation were performed until the lateral lenticulostriate arteries were identified. At this point, we felt maximal safe resection was reached.

Post-operative Course

MRI 3 months post-operatively demonstrated a satisfactory subtotal resection of 85% (pre-operative volume of 97 ml versus post-operative volume of 15 ml). Residual tumor was identified medial and superior to the pars triangularis and in the posterosuperior part of the tumor (Figure 5). Immediately post-op, the patient suffered mild transient phonemic and semantic paraphasia in the immediate postoperative period for which she underwent a course of outpatient speech therapy and on the 8-week follow-up, had returned back to normal. Regarding seizure control, the patient reported some scattered brief episodes of vibrations on the right upper and lower extremity. She remained well controlled on three anti-epileptic agents and has ongoing follow-up with her neurologist.

Neuropathology and Adjuvant Treatment

The final pathology was signed out as a WHO grade 2 astrocytoma as anticipated. The tumor was 1p/19q co-deletion negative, *IDH1 R132H* mutation positive, and *BRAF V600E* negative. *ATRX* and *p53* status were equivocal. The MIB1 proliferation index was 1–2%. Since her surgery, the patient was assessed by the neuro-oncology team at her home hospital. LGG may be classified into low- versus high-risk categories. Criteria to stratify LGG patients as 'high risk' versus 'low-risk' were developed on the basis of prognostic scores developed by the European Organization for Research and Treatment of Cancer and the Radiation Therapy Oncology Group. The common variables among both scoring systems include age (>40 years) and a subtotal tumor resection as being high-risk.[14] While the aim of these scoring systems was to aid in clinical decision-making for adjuvant therapy, there is a lack of consensus among the two scoring systems and additional work is needed to better refine molecular characteristics as adjuncts to these clinical criteria to aid in risk stratification of this patient population. In the present case, post-operative strategies including observation with serial imaging versus active adjuvant care were discussed and the patient was initiated on adjuvant radiotherapy and chemotherapy. Factors that weighed into the decision to pursue upfront adjuvant care included the astrocytic nature of her LGG, eloquent adjacent cortex at risk with tumor progression, extent of residual tumor, and the patient's preference.

Discussant Commentary: Part 2

Traditionally, if the tumor is truly grade 2 and gross total resection has been achieved, most centers would likely monitor this patient with regular MRI with no adjuvant treatment. If a subtotal or partial resection is achieved as in the present case, the options are to proceed with adjuvant treatment or monitor with regular MRI. In the case of observation, at first signs of tumor recurrence, treatment would be initiated consisting of conformal radiation and/or chemotherapy (depending on histology and molecular markers) with or without reoperation.

Discussion

The present case highlights two important considerations. First, the emerging role of upfront surgical resection in the management of diffuse LGGs and second, the fact that with careful patient selection, surgical planning and application of operative adjuncts LGGs in traditionally challenging locations such as the insula may benefit from consideration for surgery. The use of pre- and intra-operative adjuncts in the present case was paramount to achieving a maximal safe resection of this insular tumor. This is driven by literature demonstrating that the thought and practice surrounding insular gliomas, previously thought to be inoperable tumors, have substantially evolved.[4] The management of LGG by many has been a "watch and wait" approach either with or without a biopsy. This was supported by evidence that upfront conservative management may facilitate maintenance of a good quality of life through surgical risk avoidance.[15] However, these studies were limited in that molecular sub-classifications of gliomas were not utilized.

Conversely, more recent studies demonstrating survival benefit with upfront surgery have challenged the watch-and-wait paradigm. A recent large population-based natural history study

https://doi.org/10.1017/cjn.2021.10 Published online by Cambridge University Press

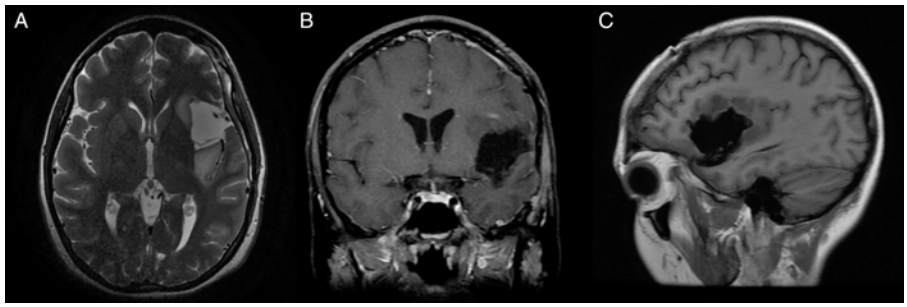

Figure 5: *Axial T2-weighted (A), as well as coronal (B) and sagittal (C) T1-weighted magnetic resonance imaging (MRI) obtained 3 months post-operatively, demonstrating a satisfactory subtotal resection of approximately 85% (Pre-operative volume of 97 ml versus Post-operative volume of 15 ml). Residual tumor was disclosed medial to the pars triangularis and to the posteriormost part of the insula.*

of patients with LGG showed that upfront maximal safe resection at the time of diagnosis conferred a significant survival benefit whereby the 5-year survival was 60% for biopsy patients and 74% for patients receiving early surgery.[2] Importantly, this long-term follow-up stratified patients based on key molecular markers (*IDH1* mutation status and 1p19q codeletion status), finding a survival benefit of upfront resection after adjustment for molecular-risk group. In fact, there was a non-significant trend for a more favorable molecular profile in the biopsy-alone cohort.

Similarly, a recent meta-analysis highlighted the significant decrease in mortality and likelihood of disease progression in patients who undergo gross total resection.[16] In general, the most important factor in determining the safety and resectability of a LGG is its location relative to functional areas, such as the motor cortex, somatosensory areas, and language areas. Intraoperative cortical and subcortical mapping using direct electrical stimulation represent the gold standard for direct functional interrogation.[17]

Taken together, LGGs generally follow a more indolent course compared with similar lesions elsewhere in the brain, and aggressive resection of all grades improves survival and can be achieved with an acceptable morbidity profile.[3] The present case illustrates that we can endeavor to achieve maximal safe resection even in challenging anatomical locations to impact outcomes for patients with LGGs.

Disclosures

The authors have no conflicts of interest to declare.

Statement of Authorship

All authors contributed to the design, writing, and editing of the manuscript. Expert recommendations were provided by MB.

References

1. Claus EB, Walsh KM, Wiencke JK, et al Survival and low-grade glioma: the emergence of genetic information. Neurosurg Focus. 2015;38:E6.
2. Jakola AS, Myrmel KS, Kloster R, et al. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. JAMA. 2012;308:1881–8.
3. Sanai N, Chang S, Berger MS. Low-grade gliomas in adults. J Neurosurg. 2011;115:948–65.
4. Hervey-Jumper SL, Berger MS. Maximizing safe resection of low- and high-grade glioma. J Neurooncol. 2016;130:269–82.
5. Whittle IR. The dilemma of low-grade glioma. J Neurol Neurosurg Psychiatry. 2004;75:ii31–6.
6. Khan OH, Mason W, Kongkham PN, Bernstein M, Zadeh G. Neurosurgical management of adult diffuse low grade gliomas in Canada: a multi-center survey. J Neurooncol. 2016;126:137–49.
7. Duffau H, Taillandier L. New concepts in the management of diffuse low-grade glioma: proposal of a multistage and individualized therapeutic approach. Neuro Oncol. 2015;17:332–42.
8. Deekonda P, Bernstein M. Decision making, bias, and low grade glioma. Can J Neurol Sci. 2011;38:193–4.
9. Hayhurst C, Mendelsohn D, Bernstein M. Low grade glioma: a qualitative study of the wait and see approach. Can J Neurol Sci. 2011;38:256–61.
10. Berger MS, Rostomily RC. Low grade gliomas: functional mapping resection strategies, extent of resection and outcome. J Neurooncol. 1997;24(1):85–101.
11. Rey-Dios R, Cohen-Gadol AA. Technical nuances for surgery of insular gliomas: lessons learned. Neurosurg Focus. 2013;34(2):E6.
12. Chang EF, Raygor KP, Berger MS. Contemporary model of language organization: on overview for neurosurgeons. J Neurosurg. 2015;122(2):250–61.
13. Hickok G, Poeppel D. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. Cognition. 2004;92:67–99.
14. Lanese A, Franceschi E, Brandes AA. The risk assessment in low-grade gliomas: an analysis of the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) criteria. Oncol Ther. 2018;6(2):105–8.
15. Reijneveld JC, Sitskoorn MM, Klein M, Nuyen J, Taphoorn MJ. Cognitive status and quality of life in patients with suspected versus proven low-grade gliomas. Neurology. 2001;56:618–23.
16. Brown TJ, Bota DA, van Den Bent MJ, et al. Management of low-grade glioma: a systematic review and meta-analysis. Neurooncol Pract. 2019;6(4):249–58.
17. Ghinda CD, Duffau H. Network Plasticity and Intraoperative Mapping for Personalized Multimodal Management of Diffuse Low-Grade Gliomas. Front Surg. 2017;4:3.

https://doi.org/10.1017/cjn.2021.10 Published online by Cambridge University Press