Perioperative outcomes following reoperation for recurrent insular gliomas

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OBJECTIVE Greater extent of resection (EOR) improves overall survival and progression-free survival for patients with low- and high-grade glioma. While resection for newly diagnosed insular gliomas can be performed with minimal morbidity, perioperative morbidity is not clearly defined for patients undergoing a repeat resection for recurrent insular gliomas. In this study the authors report on tumor characteristics, tumor EOR, and functional outcomes in patients undergoing reoperation for recurrent insular glioma.

METHODS Adult patients with insular gliomas (WHO grades II–IV) who underwent index resection followed by reoperation were identified through the University of California San Francisco Brain Tumor Center. Treatment history and functional outcomes were collected retrospectively from the electronic medical record. Pre- and postoperative tumor volumes were quantified using software with region-of-interest analysis based on FLAIR and T1-weighted postgadolinium sequences from pre- and postoperative MRI.

RESULTS Forty-four patients (63.6% male, 36.4% female) undergoing 49 reoperations for recurrent insular tumors were identified with a median follow-up of 741 days. Left- and right-sided tumors comprised 52.3% and 47.7% of the cohort, respectively. WHO grade II, III, and IV gliomas comprised 46.9%, 28.6%, and 24.5% of the cohort, respectively. Ninety-five percent (95.9%) of cases involved language and/or motor mapping. Median EOR of the insular component of grade II, III, and IV tumors were 82.1%, 75.0%, and 94.6%, respectively. EOR during reoperation was not impacted by Berger-Sanai insular zone or tumor side. At the time of reoperation, 44.9% of tumors demonstrated malignant transformation to a higher WHO grade. Ninety-day postoperative assessment confirmed that 91.5% of patients had no new postoperative deficit attributable to surgery. Of those with new deficits, 3 (6.4%) had a visual field cut and 1 (2.1%) had hemiparesis (strength grade 1–2/5). The presence of a new postoperative deficit did not vary with EOR.

CONCLUSIONS Recurrent insular gliomas, regardless of insular zone and pathology, may be reoperated on with an overall acceptable degree of resection and safety despite their anatomical and functional complexities. The use of intraoperative mapping utilizing asleep or awake methods may reduce morbidity to acceptable rates despite prior surgery.

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KEYWORDS insula; glioma; reoperation; oncology

INSULAR gliomas remain challenging lesions to address surgically. Anatomically, nearby medial and lateral lenticulostriate and insular arteries supply surrounding functional language and motor pathways and are at risk of injury if not identified and preserved. Yet, with the use of functional mapping and microsurgical techniques, these insular gliomas are accessible and surgically resectable with low rates of morbidity.[3,5,8,10,13,19] It is well established that greater extent of resection (EOR) improves overall

and progression-free survival as well as seizure control for patients with newly diagnosed low- and high-grade insular glioma.[5,7,11,13] Similarly, repeat resection of gliomas has also been shown to significantly improve these same outcomes for patients with recurrent low- and high-grade gliomas.[2,12,16–18]

Although outcomes after resection for newly diagnosed insular gliomas have been previously reported, perioperative morbidity for patients undergoing a repeat resection

for a recurrent insular glioma is understudied and not separately reported. In this paper we report on the EOR, morbidity rates, and technical challenges that arose in a cohort of patients undergoing reoperation for recurrent insular gliomas.

Methods

Patient Selection and Characteristics

After obtaining approval from the IRB of the University of California, San Francisco (UCSF), a search query was performed through the UCSF tumor registry to include patients with a pathologic diagnosis of a glioma (WHO grades II–IV) located within the insular region who underwent an index resection followed by reoperation. Patients were excluded if their glioma involved any part of the insula but resection of the insular component of the tumor was not undertaken during reoperation. Forty-four patients with operations between 2004 and 2017 met criteria for inclusion. The majority of patients had their index surgery performed at UCSF (42 of the 44 patients). Patient and tumor characteristics in addition to perioperative outcomes were collected retrospectively from operative, radiology, pathology, and scanned documents available through the UCSF electronic medical record. Consistent with prior reports, the Berger-Sanai insular glioma classification system was used to identify the location of each tumor based on preoperative FLAIR or T1-weighted postgadolinium scans depending on the tumor grade.[1,5,13] In brief, the insula was divided into 4 zones, and tumor location was assigned to one or more of these zones. For tumors occupying more than one zone, this condition was denoted as such (e.g., zone I + II). In cases in which the tumor occupied all 4 zones, these insular gliomas were defined as "giant."[5,13]

Patient Outcome Measurements

Patients underwent sequential neurological examinations performed by 4 clinicians during the perioperative period (the senior attending neurosurgeon, a neurosurgical resident, a speech and language neurophysiologist, and an attending neurooncologist). Clinical examinations were performed every day during the postoperative period, and at each follow-up appointment by at least 1 of the above-mentioned clinicians. Short-term neurological morbidity was defined as new-onset language or sensorimotor deficits by the time of discharge (within 3–5 days of surgery). Long-term neurological morbidity was defined as persistent dysfunction 90 days after surgical intervention. If differences existed between findings of the 4 examiners, the results showing the greatest impairment at a given time point was used. MRI results were reviewed to confirm that the patient's symptoms were not a function of tumor progression at each time point. Patients were excluded from analysis when examining 90-day postoperative neurological deficits if they were lost to follow-up or had new neurological symptoms after discharge related to rapid tumor progression and not attributable to surgery.

Surgical Approach

After patient positioning, patients were registered for navigation based on preoperative imaging obtained within 24 hours prior to surgery using Brainlab software. During the surgical approach the prior bone flap was used for exposure unless the size or location of recurrent tumor called for enlargement of the surgical field by enlarging the craniotomy. Microsurgical technique was used for tumor removal and intraoperative mapping was used in the majority of cases with patients either asleep or awake based on the clinical need.

Volumetric Analysis and EOR Quantification

Preoperative and postoperative tumor volumes within the insular component only were quantified using Brainlab SmartBrush software. Manual segmentation was performed with region-of-interest analysis based on FLAIR and T1-weighted postgadolinium sequences from pre- and postoperative MRI scans to quantify insular-specific tumor volume. EOR was calculated as: (preoperative tumor volume − postoperative tumor volume)/preoperative tumor volume × 100%. Manual segmentations were performed by 1 operator (R.A.M.) with tumor volumetrics verified for accuracy after an initial training period (S.L.H.J.). Knowledge of clinical outcomes was withheld from all study participants involved in tumor volumetrics and perioperative outcome data collection. Preoperative MR images were obtained within 24 hours prior to resection, and postoperative images were all obtained within 48 hours after resection. To ensure that postoperative FLAIR signal was not surgically induced edema or ischemia, FLAIR pre- and postoperative MR images were carefully compared alongside diffusion-weighted imaging (DWI) sequences prior to including each region in the volume segmentation.

Statistical Analysis

Descriptive statistics were used to define the patient cohort, tumor locations and characteristics, treatment details, EOR, and neurological outcomes. One-way ANOVA and chi-square tests were performed for univariate analysis. The level of significance was 0.05 for all analyses. Statistical analysis was performed using the JMP Pro statistical program (version 13, SAS Institute).

Results

Patient and Tumor Characteristics

Forty-four patients (63.6% male, 36.4% female) undergoing 49 reoperations for recurrent insular gliomas were identified and had a median follow-up of 2 years (Table 1). Left- and right-sided tumors comprised 52.3% and 47.7% of the cohort, respectively. WHO grade II, III, and IV gliomas comprised 46.9%, 28.6%, and 24.5% of the cohort, respectively. Additionally, 81.6% had undergone some form of adjuvant therapy (chemotherapy, radiation therapy [RT], or a combination of both) preoperatively. When examining the Berger-Sanai insular zone, 22 tumors were localized to 1 insular zone, 22 were localized to 2 zones, and 5 tumors were classified as involving all 4 zones (i.e., giant) at the time of reoperation. Compared to tumor zone at index surgery, 17 (34.7%) of recurrent insular gliomas occurred at least in some part within a new insular zone.

TABLE 1. Patient and tumor characteristics

Characteristic	Value
No. of patients	44
No. of surgeries	49
Mean age ± SD, yrs	41.8 ± 9.4
Sex, n (%)	
Male	28 (63.6)
Female	16 (36.4)
Laterality, n (%)	
Rt	21 (47.7)
Lt	23 (52.3)
WHO grade, n (%)	
II	23 (46.9)
III	14 (28.6)
IV	12 (24.5)
Median time to reop ± SD,* yrs	4.5 ± 3.0
Malignant transformation, n (%)	22 (44.9)
Berger-Sanai zone, n (%)	
I	2 (4.1)
II	3 (6.1)
III	4 (8.2)
IV	13 (26.5)
I + IV	10 (20.4)
II + III	8 (16.3)
III + IV	4 (8.2)
Giant	5 (10.2)
Recurrence w/in new insular zone, n (%)	17 (34.7)
Mean preop tumor volume ± SD, cm³	
Grade II	20.7 ± 19.3
Grade III	17.0 ± 14.4
Grade IV	14.5 ± 12.4
Primary symptom at recurrence, n (%)	
Asymptomatic	35 (71.4)
Worsening frequency of seizures	10 (20.4)
Worsening hemiparesis	2 (4.1)
Headaches	1 (2.0)
Facial numbness	1 (2.0)
Prior adjuvant treatment, n (%)	
None	9 (18.4)
Chemotherapy	23 (46.9)
RT	3 (6.1)
Chemotherapy + RT	14 (28.6)
Median follow-up after reop (range), yrs	2.03 (2 days–9.19 yrs)

* From index surgery.

At the time of reoperation, 44.9% of previously grade II or III tumors demonstrated malignant transformation to a higher WHO grade.

Surgical Approach and Treatment Details

During reoperation, 95.9% of cases utilized language and/or motor mapping (Table 2). Median EORs of grade II,

TABLE 2. Treatment details

Treatment Characteristic	Value (%)
Language mapping	23 (46.9)
Motor mapping	40 (81.6)
Awake surgery	26 (53.1)
Adjuvant therapy (prior to progression)	
None	9
Alone RT	2
Alone chemotherapy	22
RT + chemotherapy	13
Convection enhanced delivery/chemotherapy	1
Unknown	2

III, and IV tumors were 82.1%, 75.0%, and 94.6%, respectively (Table 3), when analyzing the insular component only. Two cases are depicted demonstrating the degree of resection (Figs. 1 and 2). Postoperatively, the majority of patients underwent chemotherapy and/or radiation therapy (86.4%). EOR was not significantly impacted by a number of tumor and patient factors including sex, tumor laterality, insular zone, and awake mapping (Table 4). Furthermore, age, time to reoperation, preoperative insular or total tumor volume, and percentage of tumor within the insula were not significantly associated with EOR (data not shown).

Perioperative Morbidity

No immediate postoperative complications were observed in 79.6% (n = 39) of cases (Table 5). Apart from postoperative neurological deficits, the 5 other complications observed included 1 wound infection that required washout, 1 case of hyponatremia that required intervention, 1 postoperative seizure, 1 case of a deep vein thrombosis (DVT), and 1 stroke within the ipsilateral lentiform nucleus. At the time of hospital discharge, 83.7% of cases had no new or worsened neurological deficit after resection. In terms of postoperative deficits attributable to the insular region, there were 2 cases (4.1%) of an isolated mild facial droop, 1 case (2.0%) of hemiplegia (Medical Research Council [MRC] grade 0/5), and 1 case (2.0%) of a hemineglect syndrome. As these tumors often extended into neighboring frontal or temporal cortex along with adjacent subcortical language tracts, deficits related to these structures were also observed. This included 3 patients (6.1%) who developed mild word-finding difficulty and 3 (6.1%) who developed a new or worsened visual field cut postoperatively.

Ninety-day postoperative assessment (n = 47) demon-

TABLE 3. Extent of resection according to WHO grade

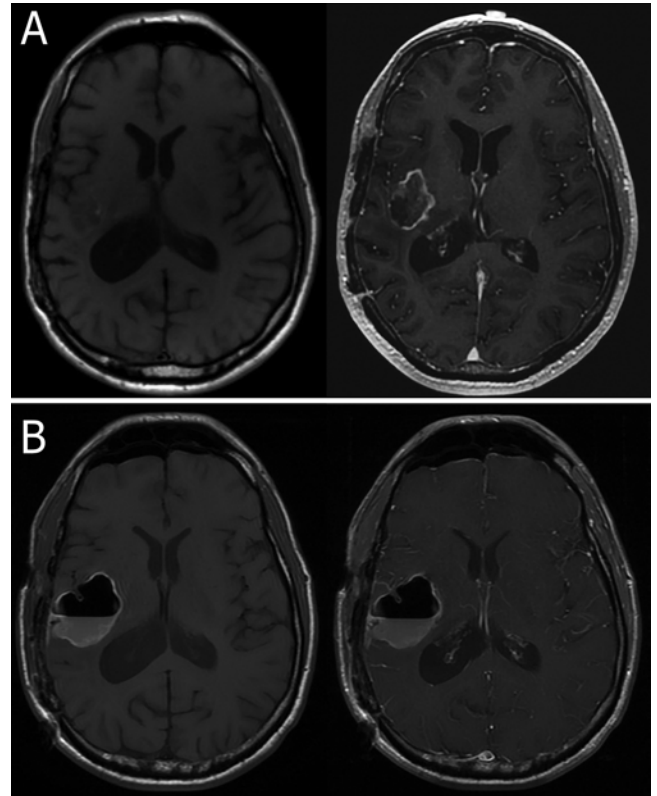| Grade	Median EOR ± SD, %
II	82.1 ± 16.5
III	75.0 ± 18.6
IV	94.6 ± 20.3
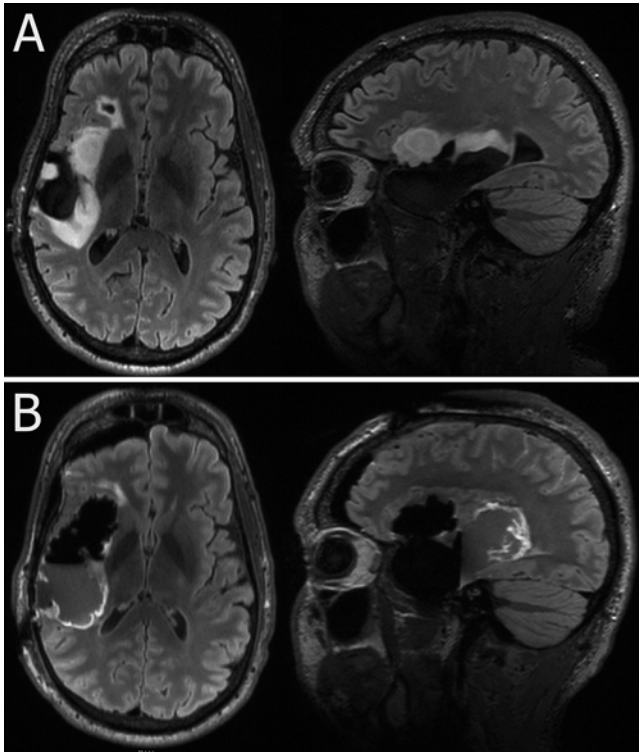
FIG. 1. Preoperative (**A**) and postoperative (**B**) axial and sagittal MR FLAIR images from the case of a 42-year-old man who had previously undergone two resections of a grade II oligoastrocytoma and subsequently underwent repeat resection after presenting with gradual tumor progression on imaging. Pathology demonstrated a grade II diffuse glioma with 95% of the insular component resected during the operation.

FIG. 2. Preoperative (**A**) and postoperative (**B**) axial T1-weighted MR images without and with contrast from the case of a 47-year-old man who had previously undergone two resections of a grade II oligoastrocytoma and subsequently underwent repeat resection after presenting a new contrast-enhancing portion on imaging. Pathology demonstrated a grade III anaplastic oligodendroglioma with 100% of the contrast-enhancing insular component resected during the operation.

strated that 91.5% of patients had no postoperative deficit. Of the patients with a deficit at 90 days, 3 (6.4%) had a visual field cut, and 1 (2.1%) had hemiparesis (MRC grade 1/5) attributable to a pericavity infarct as seen on DWI noted initially postoperatively. Of note, the patient with persistent hemiparesis had a glioblastoma that progressed rapidly within 6 weeks of surgery, which prevented further recovery of the dense hemiparesis observed initially after surgery. All visual field cuts observed were persistent on follow-up, but all patients with word-finding difficulty had symptomatic resolution by the end of follow-up.

The presence of a new or worsened postoperative deficit at discharge or 90 days was not significantly impacted by age, insular zone, tumor side, awake mapping, time to reoperation, or preoperative insular or total tumor volume (Table 6). However, gadolinium-enhancing masses, larger preoperative total volume but not preoperative insular volume was predictive of a persistent postoperative deficit (p = 0.0242). Additionally, patients with a persistent postoperative deficit and an enhancing tumor were found to have a lower EOR (p = 0.0158) suggesting that more difficult, higher-grade lesions that could not be removed completely were also associated with a greater risk of postoperative deficit.

Discussion

Insular gliomas remain challenging lesions to resect, especially upon reoperation. Anatomically, these lesions are in close proximity to important vascular structures including middle cerebral artery (MCA) branches and lenticulostriate vessels. Furthermore, primary motor and sensory areas and the perisylvian language network are adjacent to these tumors and at risk of mechanical or ischemic injury intraoperatively. Some authors believe that the risk of vascular injury is much lower upon reoperation due to the prior dissection of the MCA and its branches at the time of primary surgery.[6] However, others believe that adhesions, gliosis, and recurrent tumor tissue may obscure previously exposed vessels and disrupt anatomical landmarks. Gliosis and adhesions may also pose a risk to underlying functional tissue. Upon opening dura, for example, excess tension via adhesions underlying the dura may disrupt nearby cortex. Prior reports also state that tumor recurrence in this region often manifests as tumor expansion into an empty resection cavity, implying that tumors often do not recur outside their initial insular zone.[6] While this may be the case in some patients, we have observed numerous instances of new invasion into neighboring insular zones with 34.7% of tumors recurring within a new insular zone. Reoperation can, however, be facilitated by the prior resection cavity that often provides a clear operative corridor to approach recurrent gliomas.

TABLE 4. Tumor and patient factors versus EOR

Factor	Mean % EOR ± SD	p Value
Sex		0.45
Male	78.1 ± 3.2	
Female	82.2 ± 4.3	
Laterality		0.56
Lt	78.0 ± 3.7	
Rt	81.0 ± 3.6	
Mapping		0.57
Awake	78.2 ± 3.5	
Asleep	81.1 ± 3.7	
Berger-Sanai zone		0.27
I	93.3 ± 12.4	
II	94.0 ± 10.1	
III	84.1 ± 8.8	
IV	82.7 ± 4.9	
2 quadrants	73.4 ± 3.7	
Giant	80.4 ± 7.8	

TABLE 5. Outcomes

Outcome	Value (%)
No complications	39 (79.6)
Postop complications*	
New neurological deficit	8 (16.3)
Wound infection	1 (2.04)
Hyponatremia	1 (2.04)
Postop seizures	1 (2.04)
DVT	1 (2.04)
Infarct	1 (2.04)
Neurological deficits at discharge	
None	41 (83.7)
Mild word-finding difficulty (names >50%)	3 (6.1)
Mild facial droop	2 (4.1)
Hemiplegia	1 (2)
Hemineglect	1 (2)
Visual field cut	3 (6.1)
Neurological deficits at 90 days†	
None	43 (91.5)
Visual field cut	3 (6.4)
Hemiparesis (strength grade 1–2/5)	1 (2.1)

* Patients may have ≥ 1 complication.
† Two patients were lost to follow-up and 1 patient had rapid tumor progression with associated new neurological deficits (hemiparesis) within 3 months of the operation.

As prior studies, focusing primarily on newly diagnosed insular gliomas, demonstrate that median EOR of 80%–82% is associated with low perioperative and long-term morbidity and a survival benefit regardless of location, it is important to provide evidence of similar findings for recurrent gliomas in this region.[3,4,13,14] However, outcomes after reoperation for recurrent gliomas within the insula have been underreported. With this in mind, our goal was to determine the morbidity and the EOR achievable in addition to technical considerations during reoperation.

Historically, some surgeons speculated that infiltration into functional tissue combined with nearby vascular structures made the risk of a permanent deficit due to stroke or violation of functional tissue too great to attempt repeat operation for insular gliomas.[6,9] Evidence from this study, in addition to prior studies, does not support this contention. Ius and colleagues[6] reported outcomes for 23 patients with previously diagnosed insular low-grade gliomas who underwent repeat operations. Focusing on low-grade glioma, all cases involved subcortical mapping, and median EOR for tumor recurrence was reported to be 82%, similar to our study. In terms of morbidity, the group reported new neurological deficits in 34.78% of patients (17.39% motor, 13.04% speech, and 4.35% visual field deficit). At 6 months, however, neurological deficits were noted in only 1 patient (4.35%).[6] Martino and colleagues examined outcomes in 19 patients undergoing repeat resection of tumors in eloquent cortex, with 3 of these patients harboring tumors within the insula. With the use of cortical mapping techniques, all 3 cases were associated with partial or subtotal resection.[9] Our results, which include both low- and high-grade gliomas, demonstrate that 91.5% of patients undergoing reoperation had no new or worsened postoperative deficit at 90-day follow-up. Additionally, although a rare complication in our study occurring only once, the most marked morbidity was sec-

ondary to an infarct, which emphasizes the importance of identifying vascular structures during resection, especially when adhesions are present. Yet, even if vascular structures are carefully protected, the occurrence of ischemic injury may be difficult to prevent. Indeed, we typically apply small pieces of papaverine-soaked Gelfoam to exposed arteries to prevent vasospasm-related ischemia, which did not appear to prevent stroke in this particular patient. While our total rate of postoperative deficits on follow-up was slightly higher than previously reported, this included visual field deficits that were likely due to resection of components of the tumor extending into visual pathways of the temporal lobe and not within the confines of the insular region.

In terms of morbidity, reoperation on insular tumors has similar rates of postoperative deficits in both the short- and long-term when compared to newly diagnosed gliomas. Our prior reports demonstrate a rate of long-term (90-day) motor or language deficits in 3.2%–5.8% of patients.[5,13] Skrap and colleagues reported a median EOR of 80% in nonenhancing newly resected insular gliomas and found that about one-third of patients had an immediate postoperative speech or motor deficit, with 95% of patients returning to their neurological baseline at 6 months.[14] Median EOR rates for insular tumor reoperation also closely match those seen for newly treated tumors, which have been reported to be 80%–85%.[5,13,14]

Patient selection for reoperation is critical, and predictors for benefit from reoperation in prior studies have included Karnofsky Performance Scale score > 70, age < 50

TABLE 6. Tumor and patient factors versus deficits at discharge and by 90 days' follow-up

Factor	Deficits at Discharge			Deficits at 90 Days*		
	Yes	No	p Value	Yes	No	p Value
Mean age ± SD, yrs	43.7 ± 3.3	43.7 ± 3.3	0.53	42.0 ± 4.8	41.8 ± 1.5	0.98
Lt laterality, n (%)	3 (6.1)	21 (42.9)	0.48	1 (2.1)	22 (46.8)	0.31
Awake mapping, n (%)	5 (10.2)	21 (42.9)	0.56	2 (4.3)	23 (48.9)	0.89
Mean time to reop, yrs	4.4	4.5	0.88	3.0 ± 1.5	4.6 ± 0.5	0.31
Mean preop insular FLAIR volume ± SD, cm³	18.4 ± 2.4	23.2 ± 3.5	0.58	22.7 ± 11.5	22.5 ± 3.5	0.99
Mean preop total FLAIR volume ± SD, cm³	66.0 ± 18.4	55.3 ± 8.1	0.60	80.4 ± 26.4	55.1 ± 8.1	0.37
Mean % EOR ± SD	78.5 ± 6.4	79.7 ± 2.8	0.86	78.2 ± 8.7	80.0 ± 2.7	0.84
Berger-Sanai zone, n (%)			0.74			0.67
I	0 (0)	2 (4.1)		0 (0)	2 (4.3)	
II	1 (2.0)	2 (4.1)		0 (0)	3 (6.4)	
III	0 (0)	4 (8.2)		0 (0)	4 (8.5)	
IV	2 (4.1)	11 (22.5)		2 (4.3)	11 (23.4)	
2 quadrants	4 (8.2)	18 (36.7)		2 (4.3)	18 (38.3)	
Giant	1 (2.0)	4 (8.2)		0 (0)	5 (10.6)	

* Data not available for 2 patients.

years, greater initial EOR, and longer interval between operations.[4] These data suggest that insular location can and should be considered for reoperation at recurrence. Even if tumor recurrence is observed in areas of previously noted functional tissue (i.e., at the time of prior mapping of these regions during index surgery), this is not necessarily a contraindication to reoperation as reorganization of functional networks may make these areas accessible. Prior reports examining glioma reoperations found reorganization of motor and language areas at the time of second surgery at a rate of 30%.[15] Such reorganization often allows for further resection of tumor tissue upon reoperation.[9,15]

These results add to our understanding of the operative management of insular gliomas in several ways. First, we report on specific outcomes in the largest cohort of recurrent low- and high-grade insular glioma patients undergoing reoperation to date. Unlike with newly diagnosed insular gliomas, we did not find a significant effect of insular zone classification on EOR or frequency of postoperative deficits. One reason for this may be that operative corridors created by the first operation allow easier access to the site of recurrence, making approaches to the various zones similar in technical difficulty. Of note, EOR did not significantly vary based on insular tumor size, suggesting that even larger recurrences may be amenable to extensive resection. There are limitations associated with this study due to its retrospective nature. In addition, although this is the largest reported cohort of patients with insular glioma, we did not report the impact of EOR on survival because this was not the goal of conducting the study. Furthermore, although we report a low morbidity rate, the results of this single-center study may not be generalizable to other clinical settings.

Conclusions

This study demonstrates that recurrent insular gliomas of all degrees of insular involvement and tumor grade can be safely and extensively resected. Therefore, reoperation should be considered and offered to patients when recurrence is identified as part of the management plan.

Acknowledgments

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Disclosures

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