Current Surgical Management of Insular Gliomas

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KEYWORDS

• Insula • Gliomas • Maximal resection
• Neurologic morbidity • Intraoperative functional mapping

In 1809, Johann Christian Reil (1759–1813), the German anatomist, physiologist, and psychiatrist, first described the island (or insula) of Reil.[1,2] This anatomically and functionally complex structure is located in the depth of the sylvian fissure, overlies the basal ganglia block, and is hidden by the opercula of the frontal, parietal, and temporal lobes. It is thought to play roles in autonomic sensation, gustatory function, olfaction, memory, drive, auditory–vestibular function, and the motor integration and motor planning of speech in the dominant hemisphere.[3–5] The insula is also associated with cardiooregulatory and vasomotor functions, pain per ception, and bio-behavioral dysfunction characteristics of schizophrenia.[6] Moreover, the insula is adjacent to essential peri-sylvian language areas (ie, Broca areas and Wernicke areas and their association fibers, the primary auditory area, and both the primary motor and sensory areas).

Therefore, intrinsic tumors located in the insular and peri-insular areas present with a variety of ill-defined symptoms and neurologic signs dominated by a single entity, such as motor dysphasia with or without lower facial paresis.[1,7,8] The anatomic complexity of the insula and its functionally critical nature have caused radical insula operations to be taboo among neurosurgeons for a long time, and they have often recommended a conservative strategy for the treatment of intrinsic insular tumors.[9] However, since the seminal 1992 study by Yasargil and colleagues,[2] which demonstrated that it was possible to extirpate intrinsic insular tumors with less risk than initially thought, some experienced neurosurgeons have reported favorable outcomes of insular tumor surgery based on a detailed understanding of the pertinent anatomy and the application of modern microneurosurgical techniques.[5,10–15]

Nonetheless, achieving both maximal resection and a favorable functional outcome in intrinsic insular tumor surgery has been challenging for most neurosurgeons. This article reviews the anatomic and surgical characteristics of insular gliomas (which are the most frequent intrinsic tumor in the insula) and evaluates the reported oncological and functional outcomes after insular glioma surgery.

ANATOMY OF INSULAR GLIOMA AND SURGICAL APPROACHES

A detailed understanding of the complex anatomy of the insula and its surrounding structures is required for the removal of insular gliomas with minimal morbidity. The insula, a well-defined cerebral cortical surface, is a pyramidal structure whose 3 sides meet at a peak called the insular apex, the most lateral projection of the insula. The central sulcus separates the larger anterior portion from the smaller posterior portion. The anterior portion is composed of 3 short gyri (ie, the anterior, middle, and posterior short insular gyri) as well as the transverse gyrus and the accessory gyrus. The posterior portion is composed of the anterior and posterior long insular gyri. The limen insulae, a white matter

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structure in the anterobasal portion of the insula, parallels the course of the lateral olfactory stria, extending from the anterior perforated substance medially to the insular pole along what is known as the sylvian stem.[4,16]

In the central portion of the insula, the extreme capsule, claustrum, external capsule, putamen, and globus pallidus lie in a lateral-to-medial direction. The perimeter of the insula is provided by the anterior, superior, and inferior peri-insular sulci, which separate the insula from the fronto–orbital, fronto–parietal, and temporal opercula, respectively. These are critical internal landmarks that define the internal extent of the insula for the neurosurgeon.[1,4,11] Superior to the central portion of the insula, at the level of the superior peri-insular sulcus, is the corticospinal tract in the corona radiata; the uncinate fasciculus is located anteroinferiorly, and the arcuate fasciculus is located posteriorly along the same sulcus. The anterior and posterior limits of the insula are defined as the meeting point of the anterior with the superior peri-insular sulcus and that of the superior with the inferior peri-insular sulcus, respectively.

The course and supply of the middle cerebral artery (MCA) and its perforating vessels are most important for insular glioma surgery. The blood supply of insular gliomas is largely derived from the M2 segment of the MCA through its short- and medium-sized perforating vessels. Devascularization of an insular glioma can be achieved by advertent coagulation and cutting each of the M2 perforators after subpial dissection. Long perforating vessels of the M2 overlying the posterior portion of the insula supply the corona radiate, particularly the corticospinal and thalamocortical fibers, and they therefore must be preserved during surgery.[11,17,18] The M1 segment of the MCA lies at the anteroinferior portion of the insula, extending laterally from the carotid bifurcation under the anterior perforated substance, and it supplies the basal ganglia and internal capsule via lateral lenticulostriate perforating vessels. The mean distance from the insular apex to the most lateral lenticulostriate artery is less than 1.5 cm, and the neurosurgeon must preserve the first lenticulostriate artery encountered, which is usually located in the medial side of the tumor, without creating a dense hemiplegia.[11,18,19]

Yasargil and colleagues[2] reported an extensive surgical series of limbic and paralimbic intrinsic tumors (including insular gliomas), and they demonstrated for the first time that microsurgery is possible for tumors occupying that region without critical neurologic deterioration. They proposed a classification scheme for tumors in paralimbic regions. In this scheme, type 3a tumors (purely insular tumors), type 3b tumors (those infiltrating the peri-sylvian opercula), and type 5 tumors (those extending to other paralimbic areas) were included in the broad category of insular gliomas.

Tables 1 and **2** present the summarized data of the patients with insular gliomas in the previously reported surgical series. The traditional approach for insular gliomas had been the trans-sylvian approach because of the seminal work of Yasargil and colleagues.[2] The advantages of the trans-sylvian approach include a direct corridor to the insular region, the possibility of a wide surgical view by widely opening the sylvian fissure, and the great familiarity of this approach to neurosurgeons. However, the risk of vascular damage, in particular to the perforating vessels, by means of the trans-sylvian approach to the insular region, is never negligible. Therefore, in recently reported papers,[5,13,14] a transcortical approach (ie, a transopercular approach) has been used as an alternative or adjunctive method to the traditional trans-sylvian approach. A transcortical approach by means of subpial dissection prevents injuries to and iatrogenic spasms of the MCA and its branches. In addition, intraoperative monitoring, such as of somatosensory-evoked potentials and motor-evoked potentials, is necessary to preserve the integrity of the peri-insular regions. Likewise, awake craniotomy enables the neurosurgeon to monitor the language function of the patient, which is especially important for tumors in the dominant hemisphere.[20]

CLINICAL CHARACTERISTICS AND DIAGNOSIS OF INSULAR GLIOMAS

Insular gliomas are the most frequent intrinsic tumor in the insular region, and they accounted for up to 25% of all low-grade gliomas (LGGs) and 10% of all high-grade gliomas (HGGs) in a recent epidemiologic study.[21] Sanai and colleagues[5] reported characteristics that distinguish insular gliomas from other gliomas beyond the critical neurologic nature and anatomic complexity of the insula. There is a clear tendency toward low-grade histology that is unique to the insula and distinct from other regions, and this propensity may be caused by a particular microenvironment within the insula or by the nature of the originating glioma cells that propagate these tumors. Additionally, patients with insular gliomas generally show a prolonged and slowly progressing clinical course. However, an unpredictable natural course is characteristic of insular gliomas of both low- and high-grade histology. The representative surgical series reported that LGGs accounted for 36% to 74% of insular tumors, and the median age of the patients ranged from 36 to 41 years (see **Table 1**).

Table 1
Demographical and clinical data of the patients with insular gliomas in previous representative reports

Author, Year	Total Number	Age (Range)	Sex	Description of Seizure	Presenting Symptoms and Signs	Histology	F/U Duration (Range)
Yasargil et al,[2] 1992	80	Peak age 41–50 y	NA	SPS (5%) CPS (28%) 2nd GTCS (13%) GTCS (10%) Absence (15%) Others (4%)	Seizure (78%) Sensorimotor hemideficit (26%) Speech impairment (26%) Neuropsychological defect (35%) Visual acuity decrease (10%) Visual field defect (10%)	LGG (44%) HGG (56%)	NA
Vanaclocha et al,[15] 1997	23	Median 40 y (12–64 y)	Male (65%) Female (35%)	NA	NA	LGG (70%) HGG (30%)	Median 2.5 y (1–6.5 y)
Lang et al,[18] 2001	22	Median 36 y (2–78 y)	Male (32%) Female (68%)	Total (64%)	Seizure (64%) Weakness/hemiparesis (32%) Dysphasia/dysnomia (18%)	LGG (50%) HGG (50%)	Median 1.2 y (0.2–4 y)
Moshel et al,[12] 2008	38	Mean 38 y (15–59 y)	Male (61%) Female (39%)	SPS (8%) CPS (34%) GTCS (29%)	Seizure (71%) Hemiparesis (8%) Hemianesthesia (8%) Dysphasia (16%) Headache (29%) Memory deficits (8%) Visual problems (3%)	LGG (74%) HGG (26%)	NA
Duffau,[13] 2009	51	Mean 36 y (19–57 y)	Male (59%) Female (41%)	SPS (69%) GTCS (29%) Intractable (35%)	Seizure (98%) Intracerebral hemorrhage (2%) Hemiparesis (2%)	LGG (100%) HGG (0%)	Median 4 y (0.3–10.1 y)
Simon et al,[14] 2010	94	Median 41 y (9–77)	Male (61%) Female (39%)	Total (82%) Intractable (13%)	Seizure (82%) Hemiparesis or dysphasia (24%)	LGG (36%) HGG (64%)	Median 3.1 y (0–17.1 y)
Sanai et al,[5] 2010	104	Median 40 y (18–75)	Male (40%) Female (60%)	Total (72%)	Seizure (72%) Sensory impairments (13%) Headache (7%) Languade deficits (5%) Incidental (4%)	LGG (60%) HGG (40%)	Median 4.2 y (1.4–10.2 y)

Abbreviations: CPS, complex partial seizure; F/U, follow-up; GTCS, generalized tonic–clonic seizure; HGG, high-grade glioma; LGG, low-grade glioma; NA, not available; SPS, simple partial seizure.

Table 2
Surgical and functional outcome of the patients with insular gliomas in previous representative reports

Author, Year	Total Number	Approach	Extent of Resection	Immediate N/D	Permanent N/D	Survival Data	F/U Duration (Range)
Yasargil et al,[2] 1992	80	Trans-sylvian	NA	NA	Total (11%)	NA	NA
Vanaclocha, et al,[15] 1997	23	Trans-sylvian	GTR (87%) STR (13%)	Total (26%) Hemiparesis (22%) Dysphasia (4%)	Total (0%)	Alive at last F/U (87%)	Median 2.5 y (1–6.5 y)
Lang et al,[18] 2001	22	Trans-sylvian (36%) + ATL (36%) + transopercular (28%)	>90% (45%) 75%–90% (27%) <75% (28%)	Total (36%) Weakness (18%) Speech impairment (27%)	Total (9%) Weakness (9%)	Alive at last F/U (68%)	Median 1.2 y (0.2–4 y)
Moshel et al,[12] 2008	38	Trans-sylvian	GTR (55%) NTR (18%) STR (26%)	Total (16%) Hemiparesis (16%) Dysphasia (3%)	Total (13%) Hemiparesis (13%) Dysphasia (5%)	NA	NA
Duffau,[13] 2009	51	Transopercular (94%) Transsylvian (6%)	GTR (16%) STR (61%) PR (24%)	Total (59%) Hemiparesis (37%) Dysphasia (20%) Athymhormic syndrome (14%) FCMS (8%)	Total (4%) Hemiparesis (4%)	Alive at last F/U (82%)	Median 4 y (0.3–10.1 y)
Simon et al,[14] 2010	94	Trans-sylvian (25%) Transopercular (50%) Combined (25%)	>90% (42%) 70%–90% (51%) <70% (7%)	NA	Total (20%) Hemiparesis (13%) Dysphasia (5%)	[a]	Median 3.1 y (0–17.1 y)
Sanai et al,[5] 2010	104	Transcortical	>90% (23%) 80%–90% (39%) 60%–80% (28%) <60% (11%)	Total (14%) Motor deficits (9%) Speech deficits (5%)	Total (6%) Motor deficits (5%) Speech deficits (1%)	Alive at last F/U (91%)	Median 4.2 y (1.4–10.2 y)

Abbreviations: ATL, anterior temporal lobectomy; FCMS, Foix-Chavany-Marie syndrome; F/U, follow-up; GTR, gross total removal; NA, not available; N/D, neurologic deficits; NTR, near total removal; PR, partial removal; STR, subtotal removal.

[a] The 5-year overall survival (OS) and progression-free survival (PFS) rates in WHO grade 2 gliomas were 68% and 58%, respectively. The median OS and PFS in anaplastic astrocytomas were 61 months and 51 months, respectively. The 5-year OS and PFS rates in anaplastic oligodendrogliomas were 83% and 80%, respectively.

Medically intractable epilepsy is the most common presenting symptom of patients with insular gliomas, especially those with LGGs. According to previous reports,[2,5,12–14,18] 64% to 98% of patients with insular tumors suffer from intractable epilepsy, among whom simple and complex partial seizures accounted for 33% to 69% of cases and generalized seizures 23% to 29% of cases (see **Table 1**). The semiology of insular epilepsy reflects the diverse characteristics of the region's functional anatomy.[22] It may present as temporal lobe epilepsy[8,22–24] or frontal lobe epilepsy,[22,25] manifesting as a simple partial seizure with respiratory, viscero-sensitive, or oroalimentary features.[7,26] Spreading to the suprasylvian opercular cortex in the frontal or parietal lobe may induce facial sensory disturbances or tonic–clonic laryngeal constriction, gustatory illusions and hypersalivation with postictal facial paresis.[8,27] Spreading to the infra-sylvian operculum in the temporal lobe may produce auditory hallucinations or sensory dysphasia.[1,28]

Regarding HGGs in the insular region, the presenting symptoms (such as headache, sensorimotor impairment, or language disturbance) are associated with mass effects and peri-tumoral vasogenic edema. Cognitive dysfunction is often induced by regional edema, electrophysiological abnormalities, and adverse effects of antiepileptic drugs.[29,30] Various clinical symptoms and neurologic signs, including memory impairment, attention deficits, and visual disturbances may manifest due to the functional complexity of the insula (see **Table 1**).

Magnetic resonance imaging (MRI) is the gold standard diagnostic tool for insular gliomas. The exact location and boundary of the tumor and the relationship between the tumor and adjacent vessels must be preoperatively defined by MRI scans with cerebral angiography. Their proximity to functionally critical cerebral cortex, white matter tracts, and basal ganglia make the recently developed functional evaluation methods crucial to insular glioma surgery. Functional MRI,[31] magnetoencephalography,[32] and positron emission topography[33] provide useful information regarding functional–anatomic correlations, and diffusion tensor imaging with tractography reveals specific white matter tracts.[34]

SURGICAL RESULTS AND ONCOLOGICAL OUTCOME

In microsurgery for insular gliomas, both maximal resection for oncological control and a functional outcome without a catastrophic neurologic impairment are essential aspects. Since the seminal work of Yasargil and colleagues,[2] several groups have achieved favorable resection outcomes (see **Table 2**). Gross total resection (>90%) rates range from 16% to 87%, and subtotal resection rates (>70%) range from 62% to 100%. A sophisticated understanding of the surgical anatomy of the insular region and its relationship to the adjacent MCA and its perforating vessels has enabled neurosurgeons to achieve maximal resection without catastrophically impacting neurologic status.

It is well known that maximal resection of gliomas (including LGGs and HGGs) guarantees longer overall survival (OS) and progression-free survival (PFS), and this surgical strategy can be applied intuitively to insular gliomas. However, studies demonstrating a concrete association between the extent of resection and survival have been very rare, and most previous surgical series have focused on functional outcome rather than survival and progression.

Only 2 studies (Simon and colleagues[14] and Sanai and colleagues[5]) have conducted detailed survival analysis and prognostic factor assessment including extent of resection in the surgical management of insular gliomas. Simon and colleagues[14] enrolled 94 patients with LGGs (36%) and HGGs (64%). In their series, the 5-year OS and PFS rates for World Health Organization (WHO) grade 2 gliomas were 68% and 58%, respectively. Notably, the rates for anaplatic oligodendrogliomas were 83 and 80%, respectively. The median OS and PFS of patients with anaplastic astrocytomas were 61 and 51 months, respectively. These survival results are markedly better than those of historical controls.[35–38] Moreover, they demonstrated that patient age, tumor histopathology, Yasargil type 5 with frontal lobe involvement, and degree of resection were all significant prognostic factors for OS and PFS by multivariate analysis.

The recent work of Sanai and colleagues[5] was the largest such study. They enrolled 104 patients, including 60% with LGGs and 40% with HGGs. Of note, they analyzed both tumor location and extent of resection in detail, and they proposed a classification in which the location of the tumor was divided into 4 zones: zone 1, anterior–superior; zone 2, posterior–superior; zone 3, posterior–inferior; and zone 4, anterior–inferior. They demonstrated that zone 1 is associated with the highest median extent of resection, and the insular quadrant anatomy was found to be predictive of the extent of resection. In their work, patients with LGGs resected over 90% had a 5-year OS rate of 100%, whereas those with lesions resected less than 90% had a 5-year OS rate of 84%. In the same context, patients with HGGs resected over 90% had a 2-year OS rate of 91%, whereas

those with lesions resected less than 90% had a 2-year OS rate of 75%. Finally, they concluded that the extent of resection was a significant predictor of OS and PFS after surgery for insular LGGs and HGGs.

NEUROLOGIC DEFICITS AND FUNCTIONAL OUTCOME

Although the evidence that maximal resection guarantees longer OS and PFS is convincing, neurosurgeons face several obstacles to removing insular tumors radically, because radical resection can induce prominent neurologic complications after surgery. Thus, even in the pioneering surgical series (see **Table 2**), immediate and permanent neurologic complication rates reached 14% to 59% and 0% to 20%, respectively. These complications consisted of hemiparesis, facial palsy, dysphasia, and dysarthria. Postoperative neurologic complications are caused by the direct injury of functional peri-insular neural tissue and vascular compromise, especially that of perforating vessels of the MCA.

Splitting and retraction injuries of the frontal operculum in the dominant hemisphere cause Broca dysphasia with dysnomia, and damage to the horizontal fibers of the arcuate fasciculus near the superior peri-insular sulcus or to the uncinate fasciculus near the inferior peri-insular sulcus causes conduction aphasia, impaired perception, and short-term memory deficits.[39] The external capsule is a vulnerable structure during the medial dissection of insular gliomas, and injury to this region results in semantic paraphasias.[39,40] The corona radiata, with its motor and sensory fibers, is also vulnerable when on the superior edge of the tumor. Inadvertent dissection deep into the superior peri-insular sulcus can directly disrupt these fibers, and damage to the lateral fibers results in sensorimotor impairment of the upper limbs and face. Damage to the medial fibers results in sensori-motor impairment of the lower limbs.[11,18]

Perforating vessels likely to be involved in prominent neurologic deficits after insular region surgery include the lateral lenticulostriate arteries and the long perforators of M2. The lateral lenticulostriate arteries originating from the M1 trunk supply the internal capsule and course along the medial side of insular tumors. Because injury to these vessels results in a dense hemiplegia, defining the first lateral lenticulostriate artery is an essential step during inferomedial dissection of the tumor. Moreover, Duffau[13] indicates that gross total removal of a tumor is impossible if the tumor involves the region medial to these vessels and encases them. The long perforating vessels arise from the M2 segment in the upper portion of the insula and supply the corona radiate. Injury to these vessels by means of dissection of the superior portion of the tumor results in the previously mentioned hemiparesis.

Previous authors suggested several sophisticated techniques for avoiding such neurovascular injuries. Lang and colleagues[18] used specific methods (including wide sylvian dissection) to identify the base of the peri-insular sulcus and the superior and inferior dissection planes of the tumor. They performed subpial dissection of the tumor with preservation of all the large perforating arteries from the posterior M2 segment and awake craniotomy with brain stimulation. In contrast, Sanai and colleagues[5] used the transcortical approach to avoid any injury to or iatrogenic spasming of the MCA and its perforating vessels. Duffau[13] recommended a multiple stage surgical approach in the case of tumor removal involving the medial portion over the lateral lenticulostriate arteries or the posterior part of the insula. He noted that an initially incomplete surgery could generate a functional remapping of the residual parts, and a second surgery could be safer in terms of neurologic outcome.

The intraoperative functional monitoring is also important for achieving favorable functional outcome with these sophisticated surgical techniques. Berger and his colleagues were the leading neurosurgeons of the intraoperative functional monitoring and described the intraoperative language and sensorimotor mapping using cortico–subcortical electrical stimulation for glioma resection.[5,41] They applied a bipolar electrode with an interelectrode distance of 5 mm, delivering biphasic current to the cerebral cortex as well as the subcortical area. This monitoring was performed under general anesthesia with a nondominant-side tumor and under awake anesthesia with a dominant-side tumor for monitoring sensorimotor and language functions. Once functional areas had been identified, transcortical incisions above and below the sylvian fissure were created through nonfunctional cortex, taking care to maintain at least a 1 cm margin from any functional site.[5]

NONSURGICAL MANAGEMENT ALTERNATIVES

Due to the risk of neurologic complications associated with radical surgery for insular gliomas, some authors have reported alternative treatment methods for these tumors.[42,43] Mehrkens and colleagues[42] evaluated the long-term outcome of interstitial radiosurgery with I-125 for WHO grade 2 astrocytomas. In that study, 55 consecutive

patients underwent interstitial radiosurgery with I-125 by permanent or temporary implant after a stereotactic biopsy. The 5-year OS and PFS rates of the patients were 55% and 41%, respectively, and the 10-year OS and PFS rates were 28% and 20%, respectively. Although the patients had no postoperative neurologic morbidities, 26% of them experienced transient and progressive radiogenic complications, and the 1-year overall complication rate was 18%. Radiogenic complications were significantly associated with a tumor diameter over 3.5 cm.

SUMMARY

The primary goals of the management of insular gliomas are oncological control of the tumor by maximal resection and functional preservation by avoiding neurologic complications. A sophisticated understanding of the anatomic and functional characteristics of the neurovascular structures adjacent to the insular region and of the insula itself and an intraoperative functional mapping using cortico–subcortical electrical stimulation can help neurosurgeons achieve these goals in the treatment of insular gliomas.

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