

Insular gliomas: the case for surgical management

Clinical article

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Object. Treatment for insular (paralimbic) gliomas is controversial. In this report the authors summarize their experience with microsurgical resection of insular tumors.

Methods. The authors analyzed complications, functional outcomes, and survival in a series of 101 operations performed in 94 patients between 1995 and 2005.

Results. A > 90% resection was achieved in 42%, and 70–90% tumor removal was accomplished in 51% of cases. Functional outcomes varied considerably between patient subgroups. For example, in neurologically intact patients ≤ 40 years of age with WHO Grade I–III tumors, good outcomes (Karnofsky Performance Scale Score 80–100) were seen in 91% of cases. Predictors of an unfavorable functional outcome included histological features of glioblastoma, advanced age, and a low preoperative Karnofsky Performance Scale score. One year after surgery, 76% of patients who had presented with epilepsy were seizure free or experienced only isolated, nondebilitating seizures. Surprisingly good survival rates were seen after surgery for anaplastic gliomas. The median survival for patients with anaplastic astrocytomas (WHO Grade III) was 5 years, and the 5-year survival rate for those with anaplastic oligodendroglial tumors was 80%. Independent predictors of survival included younger age, favorable histological features (WHO Grade I and oligodendroglial tumors), Yaşargil Type 5A/B tumors with frontal extensions, and more extensive resections.

Conclusions. Insular tumor surgery carries substantial complication rates. However, surprisingly similar figures have been reported in large unselected craniotomy series and also after alternative treatment regimens. In view of the oncological benefits of resective surgery, our data would therefore argue for microsurgery as the primary treatment for most patients with a presumed WHO Grade I–III tumor. Patients with glioblastomas and/or age > 60 years require a more cautious approach. (DOI: 10.3171/2008.7.JNS17639)

KEY WORDS • functional outcome • insular glioma • microsurgery • prognostic factor • survival

THE insula of Reil overlies the basal ganglia block and is located deep to the sylvian fissure and the frontal, parietal, and temporal opercula. Prominent subcortical fiber bundles, including the uncinate and the arcuate fascicle, connect the insula to the frontoorbital and temporopolar and temporomesial regions. The insular mesocortex probably serves as a relay between neocortical areas and the phylogenetically older allocortical parts of the limbic system. Hence, the insula, the frontoorbital and the temporopolar cortices, and their white matter connections have also been referred to as the paralimbic system.^{32,33} The paralimbic system and more specifically the insula have been shown to play an important role in the processing of various sensory stimuli and in the con-

trol of various autonomic and emotional functions, but also some cognitive, motor, and particularly language-planning, functions.^{6,25}

Intrinsic tumors of the insula are not infrequently encountered in neurosurgical practice. The insula appears to be a preferential site for the growth of low-grade gliomas.⁷ Insular gliomas typically grow into the overlying opercula and along the frontotemporal fiber tracts into the temporal and/or frontal lobe ('paralimbic tumors'). Temporal tumor growth will eventually involve the temporomesial structures, that is, the limbic system (Yaşargil Type 5B tumors). Insular tumors tend to respect the basal ganglia until late in their course.³³

Optimal treatment for insular tumors remains controversial. Pioneering work by Yaşargil and colleagues^{32,33} was followed by several reports from different groups that showed that resecting insular gliomas is possible with substantial but acceptable complication rates.^{8–12,18,30,34} Tumors can usually be safely removed up to the level of the first lenticulostriate artery. If surgery is taken more medially,

Abbreviations used in this paper: KPS = Karnofsky Performance Scale; MEP = motor evoked potential; OS = overall survival; PFS = progression-free survival.

this may result in damage to perforating vessels and in subcortical ischemias.^{8,18,32,33} The superior and the inferior M₂ trunks of the middle cerebral artery course over the insular surface in the sylvian cistern and can be engulfed by tumors growing in this region, putting them at risk during insular tumor surgery. Small branches originating from the M₂ segment provide the blood supply of the insula and insular tumors. The majority of the insular arteries will penetrate no deeper than the claustrum and can therefore be sacrificed during surgery. However, there are a few vessels, usually originating from the more posterior M₂ branches, that also supply parts of the internal capsule.^{18,27} Damage to these long perforating vessels is a prominent cause of postoperative (hemimotor) deficits.^{18,21}

Surgery for intrinsic brain tumors will quickly relieve neurological signs and symptoms related to the lesion's mass effect. The oncological benefits of resective surgery for gliomas are less well delineated. A recent prospective randomized study of the use of intraoperative fluorescence as an adjunct to surgery for glioblastomas provided strong evidence that complete versus incomplete removal of the contrast-enhancing tumor will substantially improve survival.²⁶ A large body of retrospective data and also some prospective analyses support resections of low-grade gliomas.^{5,13}

The potential benefits of a tumor resection need to be balanced against the risk of incurring a new postoperative deficit. A significant new deficit will have an adverse impact on the patient's quality of life, which may well outweigh any prolongation of survival. In addition, the postoperative performance status is a powerful prognostic factor itself; iatrogenic worsening of the functional status may not only diminish the patient's quality of life, but also his or her survival. This latter issue is of particular importance with respect to surgery for tumors located in or close to eloquent brain structures. Consequently, a conservative approach to the treatment of insular tumors, that is, obtaining a tissue diagnosis followed by radiation treatment or chemotherapy, as indicated by the tumor's histological features, has been recommended by some authors.^{16,20,24}

Few follow-up data after surgery for insular tumors have been published to date. What is the overall prognosis for a particular patient? What is the functional prognosis? Of note, such information is essential if one attempts to arrive at individualized treatment recommendations. Following an analysis of our initial experience with insular gliomas,³⁴ surgery has been systematically recommended at our institution for insular gliomas, with the exception of most glioblastomas. For the present paper, we reviewed our experience with a series of 101 operations in 94 patients performed between 1995 and 2005, that is, after the period covered in the paper by Zentner et al.³⁴ We contrast the surgical risks and complications with the functional outcomes and survival. We also provide a detailed analysis of prognostic factors. Our data confirm that surgery for insular tumors carries considerable risks. However, complication rates do not compare unfavorably to large unselected craniotomy series,^{1,4} and in particular to the results of alternative treatment strategies. The overall prognosis is often surprisingly good. Together, these results suggest microsurgery as a good therapeutic option,

if not the primary treatment, for many if not most patients with insular tumors.

Methods

Patient Identification and Demographic Data

Patient charts and operating notes from all patients undergoing surgery in the Department of Neurosurgery at the University of Bonn from 1995 to 2005 were searched to identify cases treated for intrinsic brain tumors growing in the insular region, that is, after the recruitment period of our initial study.³⁴ We excluded all patients undergoing a biopsy only (12 patients) or a subtotal resection in which the insular part of the tumor was deliberately left behind (38 patients).

This left 101 operations in 94 patients. Overall, 12 surgeries were performed for recurrent insular tumor (including 1 surgery for a second tumor recurrence and 4 surgeries in patients who underwent operation for the first time before 1995). Eight patients underwent surgery for an insular recurrence after removal of a primarily frontal or temporal glioma ('secondary insular gliomas'). Overall, there were 57 male (61%) and 37 female (39%) patients. The median age at surgery was 41.3 years (range 9–77 years), and the mean follow-up (calculated after the patient's first surgery) was 4.1 years (median 3.1 years, range 0–17.1 years). Patient age was treated as a quantitative variable or categorized (≤ 20 , 21–40, 41–60, and > 60 years) as indicated.

Clinical and Radiological Data

Relevant data were collected through a chart review and telephone interviews, if necessary, and entered in a computerized data bank. The KPS scores were categorized as 100, 90–80, 70–60, and so on. Patients who were able to continue their preoperative activities without external help (corresponding to a KPS score of 80–100) were considered to have a favorable outcome. The PFS was defined by the initiation of surgery, radiotherapy, or chemotherapy for recurrent tumor. Eighty-three cases (82%) presented with epilepsy (including 12 patients with refractory epilepsy who were specifically referred to our department for surgical treatment of their symptomatic seizure disorder following a formal epileptological evaluation, and 12 patients who underwent operation following their first seizure). Preoperative focal neurological deficits (mostly aphasia or a hemiparesis) were present in 24 patients (24%).

Operating notes, preoperative MR imaging studies, and/or radiology reports were reviewed to classify the tumors according to a proposal outlined by Yaşargil and colleagues.^{32,33} Our series comprises 10 Type 3A (10%; growth restricted to the insula), 20 Type 3B (20%; insuloopercular tumors), 37 Type 5A (37%; tumor growth in the insula with prominent extension into either the frontobasal region or the temporal lobe), and 34 Type 5B tumors (34%; insular tumors with temporomesial/hippocampal involvement with or without extension into the frontal lobe). Therefore, we operated on 30 (30%) small (growth more or less confined within the anatomical boundaries of the insula; Types 3A and B) and 71 (70%) large tumors (Types 5A and

Insular gliomas: surgical management

B; tumors with prominent temporal or frontal lobe involvement). Substantial involvement of both the frontal and the temporal lobes ('frontoinsulotemporal' tumors) was seen in 49 cases (49%), and 40 (40%) of the tumors were located in the dominant hemisphere (Figs. 1–4).

The degree of resection was assessed using postoperative MR imaging within the 1st week in 85 cases; after 1 week in 2 patients; using CT scans in 8 cases; and was based on the surgeon's impression in 6 cases. Tumor resections were categorized as > 90% (no or only minimal residual tumor); 90–70%; and partial (see Fig. 4). Assessments were based on bidimensional measurements. No routine quantitative volumetric analysis was performed. Diffusion-weighted imaging was used to distinguish between ischemic and direct injury as the cause of postoperative (motor) deficits.^{21,22}

Surgical Management

During the study period, we routinely recommended a tumor resection for suspected insular gliomas if a meaningful (defined as > 70%) cytoreduction seemed feasible, if a glioblastoma was deemed unlikely, and if the patients presented with a preoperative KPS score of ≥ 60 . If the imaging findings were consistent with glioblastoma histological features, patients with Yaşargil Type 3 tumors were generally advised to have a biopsy procedure only. Patients with Type 5 tumors were scheduled for partial resections, that is, a frontal and/or temporal lobar resection. These patients were not included in the present study. Selected patients were accepted for insular surgery (for example if they were young, in a good clinical condition, and/or an intermediate-grade tumor was suspected).

Three principal surgical approaches were used.^{21,22,34} Tumors restricted to the insula were usually exposed and resected via a transsylvian approach (25%) (Figs. 1 and 4). Opercular extensions were removed through a separate transopercular route, if necessary. For large Type 5 tumors, we generally preferred to start with the removal of the temporal and/or frontal tumor component (75%). Tumor removal was sometimes facilitated by additionally opening the sylvian fissure (26%). Frontal tumor extensions were excised through a frontolateral vertical craniotomy. For tumors of the dominant hemisphere, the frontal lobe was incised well in front of the Broca area (Figs. 2 and 4). Temporal tumor was removed via a standard lobectomy including the uncus, and the hippocampal and parahippocampal gyri as necessary (Fig. 3). We paid careful attention to removing tumor-infiltrated hippocampus, but we also worked to spare healthy hippocampal tissue to maximize the epileptological benefits of the operation and to avoid a postoperative memory deficit. Electrophysiological monitoring, including the placement of a subdural strip electrode in the region of the central sulcus for continuous MEP monitoring, was attempted in the majority of cases. We have recently described our experience with this technique in a subset of the patients included in this series (84 operations, successful monitoring in 87%).^{21,22} We did not perform awake craniotomies and we did not use intraoperative brain mapping. Intraoperative orientation was sometimes facilitated by the use of a neuronavigational system.

Tumor Histological Features

All histopathological diagnoses were made at the Department of Neuropathology/German Brain Tumor Reference Center at the University of Bonn based on the WHO criteria.¹⁴ Histological diagnoses were as follows: 1 dysembryoplastic neuroepithelial tumor (WHO Grade I); 1 pilocytic astrocytoma (WHO Grade I); 4 gangliogliomas (WHO Grade I); 20 astrocytomas (WHO Grade II); 9 oligoastrocytomas (WHO Grade II); 1 oligodendroglioma (WHO Grade II); 23 anaplastic astrocytomas (WHO Grade III); 1 anaplastic pleomorphic xanthochromic astrocytoma (WHO Grade III); 2 anaplastic pilocytic astrocytomas (WHO Grade III [2 operations in the same patient]); 14 anaplastic oligoastrocytomas (WHO Grade III); 4 anaplastic oligodendrogliomas (WHO Grade III); and 21 glioblastomas multiforme (WHO Grade IV). Glioblastomas accounted for a higher proportion of Yaşargil Type 3 (11 [37%] of 30) than Type 5 tumors (10 [14%] of 71; $p = 0.011$). All but 1 of the WHO Grade I lesions were Type 3 tumors ($p = 0.003$).

Statistical Analysis

Commercially available software was used for statistical analysis (version 14.0, SPSS, Inc.). Univariate as well as multivariate (logistic regression) analyses were performed to study the influence of different variables on the patients' functional outcomes. Kaplan-Meier estimates were used to calculate survival rates. Secondary and recurrent insular gliomas were excluded from the survival analysis. Differences were analyzed for statistical significance by using the log-rank test (univariate analysis). For multivariate analysis, prognostic factors were analyzed using a Cox proportional hazards method.

Results

Extent of Resection

Removal of > 90% of the tumor mass was achieved in 42% of cases (Fig. 4 *lower*), and > 70% resections were accomplished in a further 51% of cases. Partial resections (< 70% of the tumor mass) were performed in 7% of cases (Fig. 4 *upper*). More extensive resections were more often performed in younger patients ($p = 0.023$), in patients with a higher preoperative KPS score ($p = 0.010$), and for Yaşargil Type 3 versus Type 5 (that is, for small vs large) tumors ($p = 0.023$). No correlations were found with the surgical approach, tumor histological features, surgery for dominant versus nondominant hemisphere, or recurrent or secondary insular tumors. We observed a trend toward more extensive resections in recent years (percentage of cases with > 90% resections, 28 [50%] of 56 in 2000–2005 vs 14 [32%] of 44 in 1995–1999). Even though more permanent motor deficits were seen in patients with a > 90% resection (6 [15%] of 41) compared with patients with a 70–90% tumor removal (5 [10%] of 48), this trend did not reach statistical significance.

Surgical Complications

Complication rates are presented in detail in Table

1.²⁹ A new or worsened permanent hemiparesis was seen after 12 (13%) of 96 operations (including 3 surgeries in patients with a preexisting motor deficit), but remained significant (that is, interfered significantly with the daily activities of living as evidenced by a KPS Score < 80) in only 9 (9%) of 96. The present series differs from the cohort reported in a recent publication from our group.²¹ For the present analysis, we excluded 5 cases treated surgically before 1995 and included 22 patients who underwent surgery without electrophysiological monitoring. Permanent motor deficits occurring after these latter operations account for the higher hemiparesis rate in the present cohort when compared with the data detailed by Neuloh et al.²¹ New (motor) deficits were usually due to ischemia caused by small-vessel compromise rather than direct injury of white matter tracts, as evidenced by postoperative diffusion-weighted imaging investigations.²¹

A new or worsened dysphasia was observed after 5 (13%) of 39 surgeries for tumors of the dominant hemisphere. The overall number of patients with postoperative deficits did not differ significantly between the groups with surgery for tumors of the dominant versus nondominant hemisphere.

There was a trend toward fewer permanent new and worsened neurological deficits in more recent years (2000–2005: 9 [16%] of 55 vs 1995–1999: 11 [27%] of 41). Specifically, from 2000 to 2005 we observed new or worsened hemipareses in only 5 (9%) of 55 cases.

The following variables were found to correlate with the occurrence of a new or worsened neurological deficit (univariate analysis): lower preoperative KPS score ($p = 0.004$), increasing age ($p = 0.036$), and preoperative neurological deficit ($p = 0.032$). No correlations were seen with the choice of the surgical approach. Complication rates after surgery for secondary insular or recurrent insular tumor were generally somewhat higher; however, the overall small number of cases available for analysis (8 secondary insular gliomas and 12 recurrent insular gliomas) precluded statistical significance of these findings.

Multivariate logistic regression (variables: age, sex, preoperative KPS score, clinical presentation, histological findings, Yaşargil classification, frontal and/or temporal lobe involvement, surgery for recurrent insular tumor, surgery for tumors of the dominant vs nondominant hemisphere, degree of resection, surgery before vs during or after 2000) revealed only a low preoperative KPS score as an independent predictor of a new postoperative deficit.

Functional Outcomes

The KPS scores at discharge and at 3 months after surgery were used as measures of the functional postoperative outcome. Given the large variations in OS for different patient subsets, an assessment 3 months after surgery was deemed meaningful for all patient groups, including both patients with glioblastomas and with benign WHO Grade I growths.

At discharge, improved KPS scores were seen after 9% of operations, stable scores after 49%, and deteriorated KPS scores after 41%. At the 3-month follow-up,

TABLE 1: Perioperative complications in 101 operations for insular gliomas

Deficits & Complications	Patients/Assessable Ops (%)
new/worsened hemiparesis	
permanent	12 of 96 (13)
permanent (2000–2005)	5 of 55 (9)
permanent & significant	9 of 96 (9)
new/worsened dysphasia*	
permanent	5 of 39 (13)
permanent (2000–2005)	3 of 23 (9)
permanent & significant	4 of 39 (10)
other neurological deficits†	6 of 97 (6)
any neurological deficit	
all	19 of 97 (20)
WHO Grade I/II	3 of 36 (8)
tumors of the dominant hemisphere	7 of 39 (18)
complications	
local	
all	23 of 101 (23)
requiring surgery‡	5 of 101 (5)
systemic§	5 of 101 (5)
any neurological, local, or systemic complication	35 of 101 (35)
death at 30 days	3 of 101 (3)

* Including 1 case with global aphasia; 1 with severe and 1 with mild mixed motor and sensory aphasia; and 1 with mild and 1 with minimal anomia. Numbers refer to tumors of the dominant hemisphere only.

† Including 2 cases with homonymous hemianopia.

‡ Including 1 cerebellar hemorrhage and 3 ischemic infarcts (posterior cerebral artery, cortical middle cerebral artery branch, and brainstem); 2 epidural hemorrhages; 2 ventriculoperitoneal shunts; and 1 revision surgery for a cerebrospinal fluid fistula.

§ Requiring hospitalization.

|| One patient died of a pulmonary embolus 11 days after surgery, and another died of brainstem dysfunction 8 days after resection of a recurrent insular glioma with brainstem involvement. A third patient died after uneventful surgery, possibly related to the use of a closed suction drainage, as described by Van Roost et al.

the mean KPS score was 79 ± 8 (median 90, range 0–100; compared with mean preoperative KPS score of 85 ± 14 , median 90, range 40–100). Sixty-eight percent of patients had a KPS score of 80–100 (preoperative KPS Score 80–100 in 82%), and the KPS score was 60–70 in 25% of patients (preoperative KPS Score 60–70 in 13%). Excluding surgically related deaths, there were 10 cases with a postoperative KPS score of < 60. At 3 months, 7 patients had improved to a KPS score of 60–100. Table 2 summarizes the 3-month outcomes for various patient groups.

The following variables correlated significantly with high KPS scores 3 months after surgery (univariate analysis): high preoperative and postoperative KPS scores, younger age ($p < 0.001$), seizure(s) ($p < 0.001$), and no neurological deficit at presentation ($p < 0.001$). There was

TABLE 2: Functional outcomes 3 months after surgery for insular gliomas in specific patient subsets*

Subset	No. of Cases	No. w/ KPS Score (%)		
		80–100	60–70	<60
all	100	68 (68)	25 (25)	7 (7)
seizure(s)	83	60 (72)	18 (22)	5 (6)
neurological deficit at presentation	23	7 (30)	14 (61)	2 (9)
recurrent insular tumors	12	5 (42)	5 (42)	2 (17)
patient age in yrs				
≤40	54	46 (85)	6 (11)	2 (4)
41–60	33	18 (55)	12 (36)	3 (9)
>60	13	4 (31)	7 (54)	2 (15)
tumor grade				
WHO I	6	6 (100)	0	0
WHO II	30	26 (87)	2 (7)	2 (7)
WHO III	44	29 (66)	12 (27)	3 (7)
WHO IV (glioblastomas multiforme)	20	7 (35)	11 (55)	2 (10)
preop KPS score				
100	28	28 (100)	0	0
80–90	51	33 (65)	13 (25)	5 (10)
60–70	12	4 (33)	7 (58)	1 (8)
no preop deficit, WHO Grade I–III tumor, patient age ≤40 yrs	46	42 (91)	2 (4)	2 (4)†

* Outcomes at 3 months could not be assessed for all 101 surgeries.

† Including 1 death due to a pulmonary embolus.

a trend for better outcomes after more extensive resection ($p = 0.07$). Tumor growth pattern and the choice of the surgical approach did not correlate with the 3-month KPS scores. Glioblastomas had a statistically worse outcome when compared with all other histological types ($p < 0.001$). Predictors of an unfavorable 3-month outcome included the occurrence of a new neurological deficit ($p < 0.001$). Outcomes after surgery for recurrent or secondary insular tumors were somewhat but not statistically significantly worse.

Multivariate logistic regression (variables: age, sex, preoperative KPS score, clinical presentation, histological findings, new postoperative permanent deficit, Yaşargil classification, frontal and/or temporal lobe involvement, surgery for recurrent insular tumor, surgery for tumors of the dominant vs nondominant hemisphere, degree of resection, surgery before vs during or after 2000) revealed only the incurring of a new permanent neurological deficit as an independent predictor of an unfavorable outcome (KPS Score ≤ 70 at 3 months; $p = 0.001$).

Epileptological Aspects

Eighty-three operations were performed in patients with seizures. Patients with glioblastomas only rarely presented with a history of seizures ($p < 0.001$). Temporo-insular ($p = 0.02$) and frontoinsula-temporal ($p = 0.004$) tumors were most likely to present with epilepsy. Epilep-

tological 1-year outcomes were available in 55 cases with more than one preoperative seizure: 42 (76%) of 55 patients were free of disabling seizures (Engel Class I; that is, seizure free or with auras or simple partial seizures only; with medication [22 patients], without medication [9 patients]; medication status unknown in 11 patients). Eight patients had rare disabling seizures (Engel Class II). In 12 cases, patients presented with drug-resistant epilepsy. Epileptological outcomes were as follows: Engel Class I in 9; Class II in 2; and Class III (worthwhile improvement) in 1.

Survival Analysis

The OS varied considerably between patient subsets. Kaplan-Meier estimates of OS are shown for selected patient groups in Fig. 5. For comparison, the median survival for patients with paralimbic tumors undergoing a subtotal resection within the study period was 11 months and for patients undergoing biopsy procedures it was 7 months only. Glioblastomas were diagnosed in 65% of these patients, the median age was 62 years (range 29–79 years), and the mean preoperative KPS score was 77 ± 19 (median 85).

The preoperative, postoperative, and 3-month KPS score; tumor histological findings; age class (≤ 20 , 21–40, 41–60, > 60 years); and presentation (first seizure, several seizures, neurological deficit, other) correlated signifi-

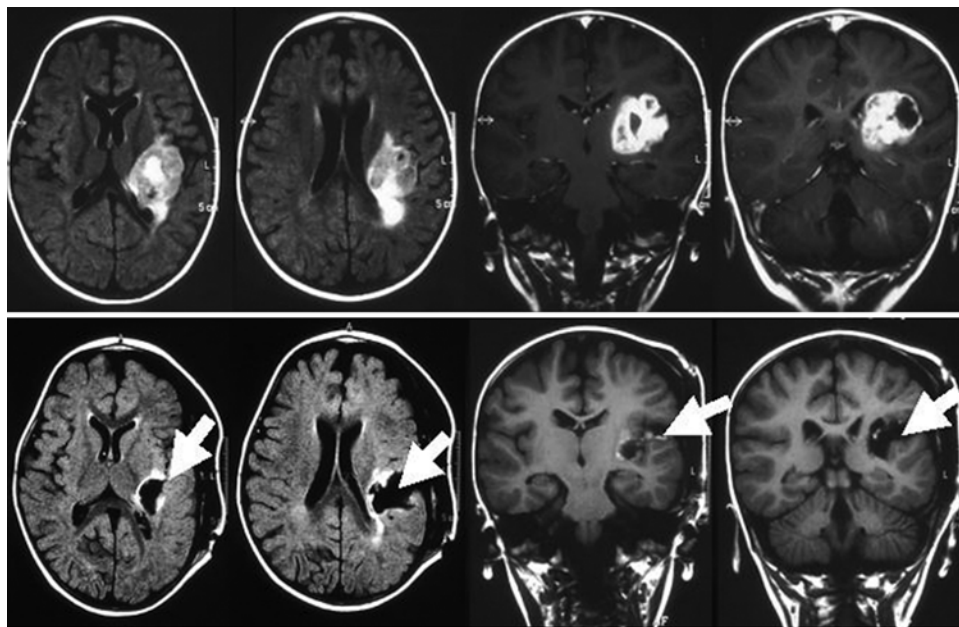


FIG. 1. Tumors restricted to the insula (Yaşargil Types 3A and B) are usually exposed and resected after opening of the sylvian fissure (arrows). Upper: Preoperative axial FLAIR (left panels) and coronal T1-weighted (right panels) contrast-enhanced MR images of a ganglioglioma, WHO Grade I, of the dorsal left insula. The growth of gangliogliomas and other epilepsy-associated WHO Grade I tumors is often confined to the insula. Note the proximity of the tumor to the posterior limb of the internal capsule. The patient, a 26-year-old man, presented with an 8-year history of refractory epilepsy. Lower: Corresponding early postoperative (noncontrast-enhanced) images showing a > 90% resection. There was no postoperative deficit, and the patient became seizure free. There was no recurrence after a follow-up period of 142 months.

cantly with OS and PFS (Table 3). Of note, much of the impact of the postoperative KPS score on OS and PFS was due to the difference between patients with a KPS score of 70 and worse compared with a score of 80–100. Prognosis also correlated with the degree of resection, with more extensive surgeries resulting in the relatively best OS ($p = 0.006$) and PFS ($p = 0.023$).

Because recommendations for postoperative radiation treatment and chemotherapy were prominently based on histological findings and tumor grade, adjuvant treatment was not included as a variable in the survival analysis. The intensity of adjuvant therapy (none, radiation or chemotherapy, radiotherapy and chemotherapy) did not correlate with the degree of resection; that is, the impact of the degree of resection on survival seemed independent of the effects of adjuvant radiation and chemotherapy.

Interestingly, the prognosis varied significantly with the tumor size and growth pattern. The prognosis was best for large Yaşargil Type 5A frontoinsular and Type 5A/B frontoinsulotemporal tumors (vs all others: OS, $p < 0.001$; PFS, $p = 0.003$) (Table 3). As a corollary, tumors approached through a frontal route (that is, with a sizable frontal lobe component) had a significantly better overall prognosis ($p = 0.006$).

Multivariate Cox regression analysis (variables: age, time of surgery < 2000 vs ≥ 2000 , clinical presentation, histological findings, growth pattern, degree of resection, postoperative KPS score) revealed age, histological features of glioblastoma, favorable growth pattern/location, and the degree of resection as independent predictors of OS and PFS (Table 4).

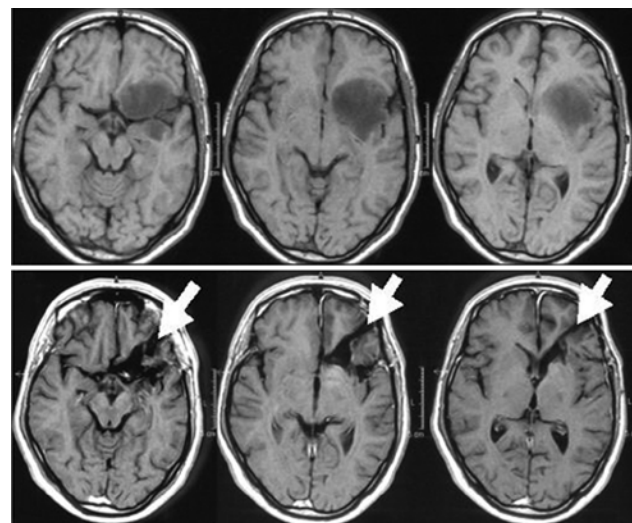


FIG. 2. Prominent frontal tumor extensions in Yaşargil Type 5 tumors can be removed through a vertical frontal corticotomy. Type 5A tumors can often be surgically treated exclusively via a frontal approach. The incision is placed well in front of the Broca area for tumors of the dominant hemisphere (arrows). Upper: Preoperative axial T1-weighted MR images of a left-sided frontoinsular (Yaşargil Type 5A) oligoastrocytoma, WHO Grade II, diagnosed in a 36-year-old man presenting with a 6-month history of partial seizures. A combined transfrontal and transsylvian approach was performed. Lower: Early postoperative T1-weighted contrast-enhanced images showing a > 90% tumor resection. The patient experienced a transient postoperative dysphasia, but was neurologically intact at the 3-month follow-up. At the 1-year follow-up, he reported no seizures. Surgery for recurrent insular tumor was performed 45 months later (histological finding: glioblastoma multiforme) followed by radiotherapy and temozolomide chemotherapy. The patient was alive at the time of the last follow-up, 59 months after the initial operation.

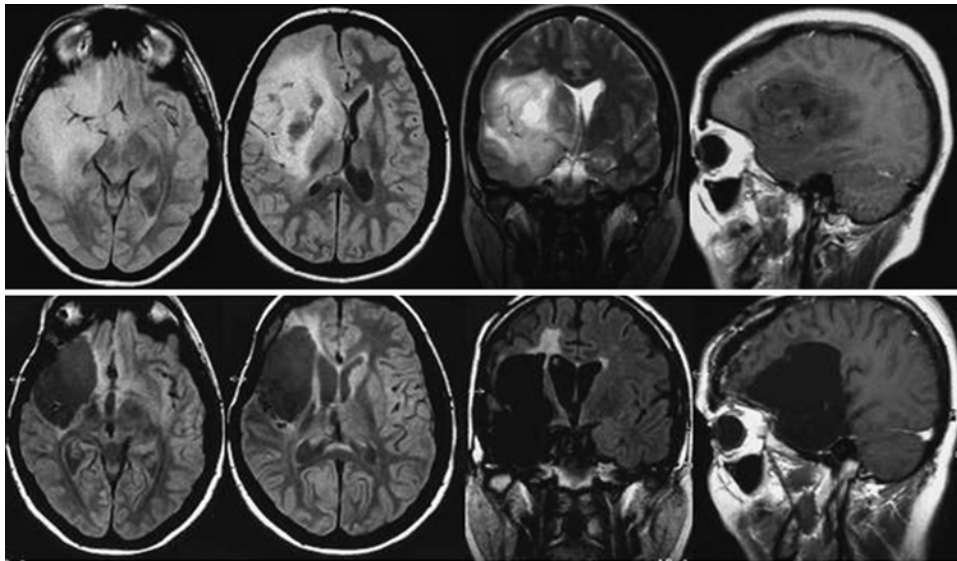


Fig. 3. Surgery for tumors infiltrating the temporal lobe may be facilitated by a temporal lobectomy. *Upper:* Preoperative axial FLAIR images, coronal T2-weighted, and sagittal T1-weighted contrast-enhanced MR images of a right-sided Yaşargil Type 5B anaplastic astrocytoma, WHO Grade III, with sizable frontal as well as temporal tumor components. The tumor was diagnosed in a 40-year-old woman presenting with symptomatic epilepsy of approximately 12 months in duration. *Lower:* Postoperative FLAIR (axial and coronal) and T1-weighted contrast-enhanced MR imaging studies demonstrating a > 90% resection. The insular tumor was removed after a temporal lobectomy and resection of the frontal tumor extension through a separate frontal corticotomy (see Fig. 2). Postoperatively, there was a mild permanent hemiparesis; however, the 3-month KPS score was 90, and the patient became seizure free. Adjuvant treatment included fractionated radiotherapy and PCV (procarbazine, CCNU, and vincristine) chemotherapy. The patient died of multifocal tumor progression 113 months after the initial surgery.

Discussion

Treatment of insular tumors is controversial. To a considerable degree, this controversy reflects the general debate surrounding resections of gliomas in eloquent regions. What is an acceptable complication rate in view of the fact that the oncological benefits of glioma resections are not as well delineated as one would wish? Scarce follow-up data after insular tumor surgery have been published.^{8–12,18,30,32–34} In the present paper we therefore attempted to contrast survival after insular tumor surgery with the surgical risks in a large patient series.

Neurological Deficits and Functional Outcomes

Our data confirm that surgical treatment for insular gliomas carries a substantial neurological morbidity.^{8–12,18,30,32–34} However, surprisingly similar figures, that is, rates of new neurological deficits in the range of 13–26%, have been reported in various publications detailing the general risks and complications of craniotomies for unselected brain tumors in population-based series and also in tertiary centers.^{1,4} It would seem that the risks of insular surgery, if performed by experienced groups, are at least not much higher than the widely accepted complication rates in brain tumor surgery in general.

Of note, patient selection is an important factor determining functional outcomes. Relatively low complication rates and generally favorable outcomes were seen in certain patient subgroups. For example, 91% of patients ≤ 40 years of age who presented without a neurological deficit and with a WHO Grade I–III glioma had a 3-months KPS score of 80–100. Only 1 (4%) of 28 patients with a preoperative KPS score of 100 suffered a permanent postop-

erative neurological deficit. Permanent new or worsened postoperative deficits were seen in 15% of patients with WHO Grade I–III tumors and in 14% of patients who were neurologically intact preoperatively, but in 37% of patients with glioblastoma, and in 39% of patients who already presented with a neurological deficit.

A proper assessment of the functional outcomes after insular tumor surgery also requires some attention to the results of alternative treatment strategies. Mehrkens et al.²⁰ and Schätz and coworkers²³ have provided some outcome data after interstitial radiosurgery for low-grade astrocytomas of the insula. They report 24% transient radiogenic complications and an 18% complication rate at 1 year; 7% of their patients required surgery for progressive radiation necrosis. The number of patients eventually suffering a permanent deficit was not provided. The median KPS score at the time of the last follow-up was 90. Combining surgery for the temporal and frontal tumor extensions with interstitial radiosurgery for the insular tumor may result in lower complication rates in relatively large tumors (F. Kreth, personal communication, 2003). Comparing our data to the figures reported in Mehrkens et al. and Schätz and coworkers is difficult because these authors do not detail explicit deficit rates. Also, their series includes only tumors up to a maximum diameter of 5 cm and no tumors with involvement of the temporomesial structures. We observed new or worsened permanent neurological deficits in 3 (8%) of 36 patients with WHO Grade I/II gliomas. The median KPS score at 3 months was also 90, with 89% of patients having a KPS score of 80–100.

Our experience with surgery even for selected glio-

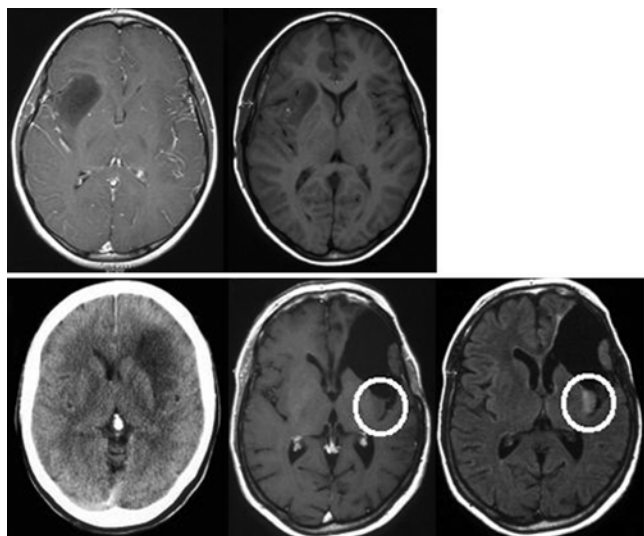


FIG. 4. Problems encountered with gross-total resections of insular tumors. *Upper:* Preoperative contrast-enhanced and early postoperative axial T1-weighted MR imaging studies of a right-sided Yaşargil Type 3B astrocytoma, WHO Grade II, diagnosed in a 9-year-old boy. The patient presented with a 1- to 2-month history of partial seizures. A tumor resection was attempted via a transsylvian route with the help of MEP monitoring. The operation was stopped when repeated reversible MEP deteriorations were encountered, which could not be attributed with reasonable certainty to a technical problem. There was no postoperative deficit, and there were no postoperative seizures. Successful repeat surgery (> 90% tumor resection, unchanged histological findings) and radiotherapy were performed for tumor progression 19 months later. The overall follow-up duration is now 33 months. *Lower:* Preoperative CT scan (*leftmost panel*), and postoperative axial T1-weighted and FLAIR MR images of a Yaşargil Type 5A astrocytoma, WHO Grade II. The tumor was resected via a combined transfrontal and transsylvian approach. The patient, a 39-year-old man, suffered from symptomatic epilepsy for 7 months. There was no postoperative deficit, and the patient became seizure-free. Note the residual tumor in the dorsal aspect of the insula (*open circle*). This portion of the tumor is located deep in the surgical field and potentially close to the long M₂ branches supplying parts of the internal capsule pyramidal tract (and the pyramidal tract itself). It is encountered last during the operation. Surgically induced changes of the tissue texture and color, and the ongoing brain shift, render its identification (even with the use of a neuro-navigating device) difficult.

blastomas has been quite disappointing, but what about the possible alternatives? Kreth et al.¹⁵ have detailed their results of stereotactic biopsy versus resective surgery followed by radiation therapy for (lobar) glioblastomas. In the patient subgroup with a midline shift (that is, with significant mass effect) who had no cytoreductive surgery, 13 (43%) of 30 patients deteriorated during radiotherapy. All of our patients with insular glioblastoma showed a midline shift on MR imaging, and 40% of our cases, that is, a very similar number, showed a drop in the KPS scores at the 3-month follow-up. This would suggest that the alternative to surgical debulking, that is, a biopsy, will not necessarily result in better functional outcomes even in this subgroup of patients with a relatively unfavorable functional prognosis.

TABLE 3: Prognostic factors and OS and PFS: univariate analysis*

Factor	p Value	
	PFS	OS
age class (≤ 20 , 21–40, 41–60, >60 yrs)	<0.001	<0.001
sex	0.138 (NS)	0.596 (NS)
time of op (≥ 2000 vs <2000)	0.289 (NS)	0.234 (NS)
presentation (several seizures vs 1st seizure vs neurological deficit vs other)	<0.001	<0.001
histological findings†	<0.001	<0.001
dominant vs nondominant hemisphere	0.371 (NS)	0.643 (NS)
Yaşargil Type 5A/B w/ frontal tumor component	0.003	<0.001
degree of resection (>90% vs 70–90% vs <70%)	0.023	0.006
KPS score		
preop (100, 80–100, 60–70, etc.)	0.021	<0.001
postop (100, 80–100, 60–70, etc.)	<0.001	<0.001
at 3 mos (100, 80–100, 60–70, etc.)	<0.001	<0.001

* NS = not significant.

† Glioblastoma versus anaplastic astrocytoma (WHO Grade III) versus anaplastic oligodendroglioma/mixed glioma (WHO Grade III) versus astrocytoma (WHO Grade II) versus oligodendroglioma/mixed glioma (WHO Grade II) versus tumors in WHO Grade I.

Nevertheless, the complication and deficit rates reported in this study as well as in others^{8–12,18,30,34} warrant improvement. Surgical experience may play a role. In the second half of the study period (2000–2005), the hemiparesis and overall neurological deficit rates dropped to 9 and 16%, respectively. This may also be due in part to the routine use of intraoperative electrophysiological MEP monitoring. As detailed above and in Neuloh et al.,²¹ motor deficit rates may be considerably higher if insular surgery is attempted without monitoring. In our experience, many motor deficits are related to ischemic rather than direct injury.^{21,22} Others have used intraoperative cortical and subcortical stimulation and local anesthesia to avoid neurological deficits.^{8–11,18,30}

Survival After Insular Tumor Surgery

Surgical complications and reduced KPS scores can be seen as the price that patients may have to pay to realize improved survival resulting from cytoreductive surgery. The OS and PFS after glioma surgery depends on many variables, including histological features, age, and KPS scores. The present study confirms that these findings can also be applied to insular gliomas. In addition, our results suggest a prognostic role for certain other factors as well.

Of note, the degree of resection proved an independent predictor of both OS and PFS in the Cox proportional hazards model. We observed a better survival for patients in whom a > 90% versus 70–90% resection was

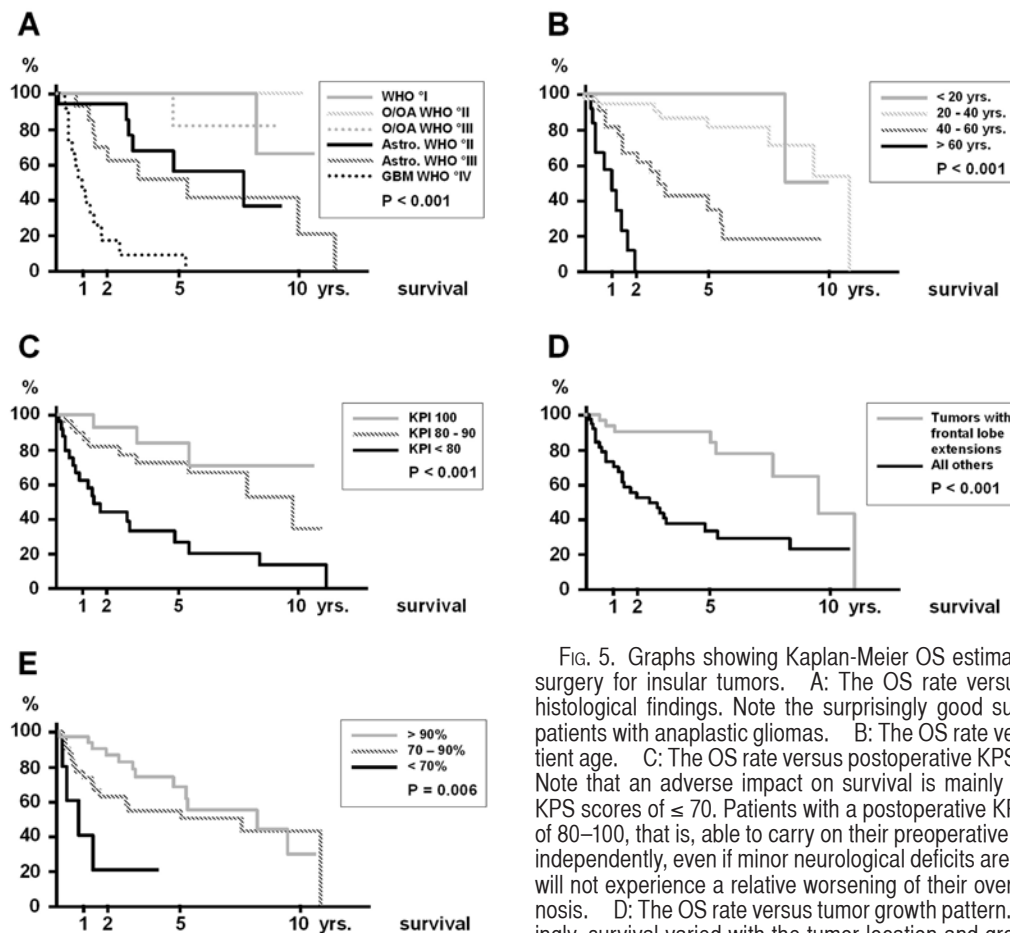


FIG. 5. Graphs showing Kaplan-Meier OS estimates after surgery for insular tumors. A: The OS rate versus tumor histological findings. Note the surprisingly good survival of patients with anaplastic gliomas. B: The OS rate versus patient age. C: The OS rate versus postoperative KPS scores. Note that an adverse impact on survival is mainly seen for KPS scores of ≤ 70 . Patients with a postoperative KPS score of 80–100, that is, able to carry on their preoperative life style independently, even if minor neurological deficits are present, will not experience a relative worsening of their overall prognosis. D: The OS rate versus tumor growth pattern. Surprisingly, survival varied with the tumor location and growth pat-

tern. This finding casts some doubt on the concept of insular/paralimbic gliomas as a single entity. The relatively best prognosis was seen in patients harboring Yaşargil Type 5A and B tumors with substantial frontal lobe extensions. E: The OS rate versus degree of resection. More extensive resections may provide a survival advantage. The degree of resection is the only truly therapeutic variable and proved to be an independent predictor of patient survival in the multivariate Cox regression analysis.

achieved, but much of the statistical effect was due to the relatively unfavorable prognosis of patients with a $< 70\%$ tumor resection (Fig. 5E). We are aware of the possible selection bias involved. Nevertheless, the degree of resection is the only variable (besides the incurrance of a neurological deficit) affecting postoperative survival that can be influenced by the neurosurgeon.

The analysis of prognostic factors also produced some unexpected results. Conventional neurooncology does not pay much attention to the location and extension of diffuse supratentorial gliomas as important determinants of the patient's prognosis. However, patients in the present series with frontoinsular or frontotemporo-insular tumors (Yaşargil Type 5 tumors with growth into the frontal lobe) had a significantly better prognosis than other patients with insular glioma (Fig. 5D). These effects proved to be independent of other prognostic parameters such as histological features. This may point to the presence of significant biological differences between tumors growing in different parts of the insular region, and it

casts some doubt on the concept of insular gliomas as a single entity defined by growth in a specific functional and anatomical system.

The OS and PFS rates in our series were generally quite good. The 5-year OS and PFS for WHO Grade II gliomas were 68 and 58%, respectively. For comparison, Mehrkens and coworkers²⁰ reported only a 54.6% 5-year OS and a 40.7% PFS rate after interstitial radiosurgery for WHO Grade II astrocytomas and mixed gliomas. The median OS and PFS of patients with anaplastic astrocytomas (mean age 41 ± 13 years, median age 39 years) in the present series were 61 and 51 months, respectively. The 83 and 80% 5-year OS and PFS rates for anaplastic oligodendroglial tumors (mean age 41 ± 11 years, median age 41 years) are also surprising and even higher than the figures for low-grade astrocytomas (WHO Grade II; 5-year OS 57%, PFS 53%). For comparison, 5-year survival in the Surveillance, Epidemiology, and End Results 1973–2002 cohort (www.cbtrus.org [accessed September 2007]) for patients with anaplastic astrocytomas was 48% (20–44

TABLE 4: Prognostic factors and OS and PFS: multivariate analysis (Cox proportional hazards model)*

Factor	PFS		OS	
	HR (95% CI)	p Value	HR (95% CI)	p Value
age (yrs)	0.945 (0.912–0.979)	0.002	0.931 (0.898–0.965)	<0.001
time of op (≥ 2000 vs < 2000)	1.405 (0.548–3.603)	0.479 (NS)	1.807 (0.696–4.694)	0.225 (NS)
presentation: seizure(s) vs other	1.333 (0.478–3.717)	0.583 (NS)	1.241 (0.456–3.374)	0.673 (NS)
histological findings (glioblastoma vs other)	0.200 (0.053–0.749)	0.017	0.173 (0.052–0.578)	0.004
Yaşargil Type 5A/B w/ frontal tumor component	3.270 (1.250–8.554)	0.016	4.345 (1.596–11.825)	0.004
degree of resection ($> 70\%$ vs other)	8.901 (1.893–41.856)	0.006	14.631 (3.396–63.031)	<0.001
postop KPS score (80–100 vs other)	1.420 (0.577–3.497)	0.445 (NS)	1.436 (0.594–3.473)	0.422 (NS)

* HR = hazards ratio.

years old at the time of diagnosis) and 26% (45–54 years old at diagnosis), and for anaplastic oligodendrogliomas it was 56% (20–44 years old at diagnosis) and 46% (45–54 years old at diagnosis). The median survival and PFS of patients with anaplastic astrocytomas were only 28 and 27 months, respectively, in a recent radiochemotherapy series from our own institution.¹⁷ In 2 recently published major randomized studies of anaplastic oligodendroglial gliomas,^{2,28} investigators reported a median survival of < 5 years in the first study and 3 years in the second one, and they reported a PFS of < 2.6 in the first and 2 years in the second study, as well as a 5-year OS rate of $< 50\%$ and a PFS rate of $< 40\%$.

Treatment Recommendations

The prognosis for patients with glioblastomas is poor. This seriously questions aggressive surgical treatment in this patient group. Hence, insular surgery should be reserved for young patients in good clinical condition (with a better than average survival prognosis) and possibly tumors with a large frontal component. Anecdotal evidence suggests lesser motor deficits after anterior when compared with posterior insular surgery, possibly reflecting the anatomical course of the pyramidal tract and its vascular supply. Because adjuvant therapy alone for glioblastomas with mass effect will not produce acceptable functional outcomes,¹⁵ we currently recommend debulking surgery restricted to the temporal or frontal tumor extensions in most other cases.

Patients with insular gangliogliomas, dysembryoplastic neuroepithelial tumors, and pilocytic astrocytomas are good surgical candidates despite the eloquent location of the tumors. Surgery may be curative.¹⁹ In the present series, functional outcomes were good. This is an important subgroup, even though such patients are relatively rare, accounting for only 6% of cases in this series. All patients maintained a KPS score of 80–100 after surgery. Refractory epilepsy was common and responded well to a tumor resection (even a subtotal one). A careful MR imaging study, together with certain clinical characteristics (age < 30 –40 years, epilepsy), will usually suggest the histological diagnosis preoperatively.

Most often, surgical treatment will be considered

for a presumed WHO Grade II or III insular glioma in a young or middle-aged adult presenting with a first seizure or epilepsy. At the time of this writing, the surgical risks at our institution include a $< 10\%$ rate of hemiparesis and $< 15\%$ overall neurological deficit rate in patients with WHO Grade II and III gliomas. The chance for epilepsy control is $\sim 80\%$. Survival will exceed 5 and possibly even 10 years, especially in patients with oligodendroglial tumors and Yaşargil Type 5 tumors with large frontal lobe components. The extent of resection seems to correlate with patient survival. Surgery allows for a comprehensive histological diagnosis and the institution of histologically guided adjuvant radiation and chemotherapy. Stereotactic biopsies may underestimate the histological grade of the tumors or miss an oligodendroglial component.^{3,31} We therefore believe that microsurgery is at least a good treatment option, if not the treatment of choice for these patients. However, there are factors that may warrant a more cautious approach. Age at presentation > 60 years, a preoperative neurological deficit, or a KPS score of ≤ 70 (most likely resulting in a similar if not worse postoperative KPS score) all correlate with relatively increased complication rates, adverse outcomes, and reduced OS.

Conclusions

Appropriate patient counseling and the decision to operate on an insular tumor involve a comprehensive assessment of the individual patient's postoperative function as well as prognosis *quoad vitam*. In the present paper we detail complications, functional outcomes, and survival in a large series of surgically treated insular tumors. We believe that our results support resection as the primary treatment for many patients with gliomas of the insula.

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