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Low-grade glioma surgery in eloquent areas: volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients

Clinical article

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Object. A growing number of published studies have recently demonstrated the role of resection in overall survival (OS) for patients with gliomas. In this retrospective study, the authors objectively investigated the role of the extent of resection (EOR) in OS in patients with low-grade gliomas (LGGs).

Methods. Between 1998 and 2011, 190 patients underwent surgery for LGGs. All surgical procedures were conducted under corticosubcortical stimulation. The EOR was established by analyzing the pre- and postoperative volumes of the gliomas on T2-weighted MRI studies. The difference between the preoperative tumor volumes was also investigated by measuring the volumetric difference between the T2- and T1-weighted MRI images (ΔVT2T1) to evaluate how the diffusive tumor-growing pattern affected the EOR achieved.

Results. The median preoperative tumor volume was 55 cm^3, and in almost half of the patients the EOR was greater than 90%. In this study, patients with an EOR of 90% or greater had an estimated 5-year OS rate of 93%, those with EOR between 70% and 89% had a 5-year OS rate of 84%, and those with EOR less than 70% had a 5-year OS rate of 41% ($p < 0.001$). New postoperative deficits were noted in 43.7% of cases, while permanent deficits occurred in 3.16% of cases. There were 41 deaths (21.6%), and the median follow-up was 4.7 years.

A further volumetric analysis was also conducted to compare 2 different intraoperative protocols (Series 1 [intraoperative electrical stimulation alone] vs Series 2 [intraoperative stimulation plus overlap of functional MRI/fiber tracking diffusion tensor imaging data on a neuronavigation system]). Patients in Series 1 had a median EOR of 77%, while those in Series 2 had a median EOR of 90% ($p = 0.0001$). Multivariate analysis showed that OS is influenced not only by EOR ($p = 0.001$) but also by age ($p = 0.003$), histological subtype ($p = 0.005$), and the ΔVT2T1 value ($p < 0.0001$). Progression-free survival is similarly influenced by histological subtype (fibrillary astrocytoma, $p = 0.003$), EOR ($p < 0.0001$), and ΔVT2T1 value ($p < 0.0001$), as is malignant progression–free survival ($p = 0.003$, $p < 0.0001$, and $p < 0.0001$, respectively). Finally, the study shows that the higher the ΔVT2T1 value, the less extensive the currently possible resection, highlighting an apparent correlation between the ΔVT2T1 value itself and EOR ($p < 0.0001$).

Conclusions. The EOR and the ΔVT2T1 values are the strongest independent predictors in improving OS as well as in delaying tumor progression and malignant transformation. Furthermore, the ΔVT2T1 value may be useful as a predictive index for EOR. Finally, due to intraoperative corticosubcortical mapping and the overlap of functional data on the neuronavigation system, major resection is possible with an acceptable risk and a significant increase in expected OS.
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Key Words • **low-grade glioma** • **brain mapping** • **extent of tumor resection** • **direct electrical stimulation** • **tumor volume** • **survival** • **oncology**

Diffuse infiltrative LGGs of the cerebral hemispheres in adults represent up to 30% of gliomas.[20] Despite an initial indolent subclinical growth rate, the normal pattern is for continuous growth and systematic progression to malignant transformation, in turn leading to neurological disability and ultimately to death.[19,55]

The most critical factor in achieving a radical resection in LGGs is their involvement of eloquent cortical areas and subcortical functional pathways.[20,34] Consequently, for many years, the role of surgery in LGG management has been a matter of debate.[7,23,54]

Recently, a large number of surgical studies based on the objective evaluation of EOR have been published, suggesting that EOR has a significant effect not only on the rate of tumor progression and OS but also on the decrease

Abbreviations used in this paper: ΔVT2T1 = volumetric difference between preoperative tumor volumes on T2- and T1-weighted MRI studies; DTI = diffusion tensor imaging; EBRT = external-beam radiation therapy; EOR = extent of resection; fMRI = functional MRI; HR = hazard ratio; ICC = intraclass correlation coefficient; IES = intraoperative electrical stimulation; KPS = Karnofsky Performance Scale; LGG = low-grade glioma; LOH = loss of heterozygosity; MPFS = malignant progression–free survival; OS = overall survival; PFS = progression-free survival.

in risk of anaplastic transformation.[28,35,36,46–49,54] Moreover, it is generally thought that an extensive resection, performed at the time of initial diagnosis, is the greatest factor for improving patient OS.[35,36,49,52]

However, no randomized trials have specifically addressed the effect of EOR on OS, PFS, and MPFS among patients with LGGs. Most studies since 1990 have provided a subjective analysis, based on the surgeon's intraoperative impression, rather than a statistical analysis to examine the efficacy of EOR in improving patient survival and delaying tumor progression.[1,2,15,16,27,32,35,36,38,39,42,43,49,52,54,58,60,61] Only 5 studies have included a volumetric analysis of EOR, multivariate, and univariate analyses, to determine the statistical significance of EOR.[16,49,52,54,58] Of these, the largest analysis with volumetric quantification of EOR demonstrated a major effect of EOR on OS for hemispheric LGGs. Indeed, for patients who undergo gross-total resection, the 10-year survival rate approaches 100%, while the survival rate progressively decreases as the EOR approaches 40%.[48] Consequently, despite the lack of Class I evidence,[28,46,47,54] surgical treatment has recently been identified as the first option in the management of LGGs.[55]

A prospective study evaluating patients with LGGs is highly unlikely to be conducted; therefore, as a more practical way to address the lack of Class I evidence, a randomized study with prospective observations was conducted to better define the role of EOR of LGGs and to confirm the value of the few volumetric studies published to date.

Although EOR has been statistically proven to be the most significant independent factor for OS, preservation of patients' simple and complex functions is clearly mandatory.[3,7,10,16,18,45,54] For these reasons, at our institution the first option in the treatment of LGGs is resection performed using intraoperative brain mapping techniques. This allows maximization of tumor resection while minimizing postoperative morbidity.[4,7,8,11,18,21,22,54] In this study, we present our paradigm for the surgical treatment of LGGs, focusing on the effect of EOR on OS, PFS, and MPFS.

Finally, the ΔVT2T1 value, a preoperative estimation of the difference between tumor volumes on T2-weighted MRI studies and on contrast-enhanced T1-weighted MRI studies, has been proposed as a predictive analytical index of EOR to discriminate between the proliferative growth mechanism and the diffusive spreading mechanism along the white matter in LGG development.[52] Therefore, on the basis of pre- and postoperative MRI volumetric tumor analyses, we also investigated the correlation between this neuroradiological preoperative index and the degree of resection achieved.

Methods

Study Population

We analyzed 190 patients who underwent resection for supratentorial LGGs between June 1998 and May 2011. All surgical procedures were performed by the senior author (M.S.). Clinical, radiological, and operative data and hospital course records were reviewed retrospectively.

Preoperatively, all patients underwent neuropsychological evaluation and fMRI for motor and language functions. In addition, language handedness dominance was evaluated using the Edinburgh Inventory Questionnaire.[41] One hundred twenty-six patients had a lesion involving the dominant hemisphere. No patient had enhancement on contrast-administered T1-weighted MRI sequences. Histological type was determined according to the WHO brain tumor classification.[33] To create a more uniform study population, patients with gemistocytic histology were excluded, as were patients with foci of anaplastic transformation present in the histological analysis.

Follow-up evaluation was uniform in all patients; that is, neurological examination and control MRI studies were obtained at regular intervals. This study was approved by the local institutional ethics committee on human research.

Surgical Technique and Brain Mapping

All 190 patients had a tumor involving eloquent areas. The surgical procedures were conducted under cortical and subcortical white matter IES, according to the intraoperative technique previously described by Berger and based on the methodology of Ojemann and Berger.[5,6,40] A neuronavigation system (StealthStation, Medtronic) was used in all cases.

Awake surgery was performed in 66.3% of patients. The 126 patients with lesions located in the somatosensory area and in the dominant temporal lobe, premotor lobe, insula, and inferior parietal lobe underwent surgery after administration of local anesthesia while intraoperative sensorimotor and language mapping were performed. Conversely, the 64 patients harboring lesions involving nondominant supplementary and primary motor areas and nondominant insular lobes underwent surgery after induction of general anesthesia, in which cortical and subcortical IES enabled the detection of corticospinal pathways.

A standard anesthesiology protocol was used for the surgical procedure, with all patients remaining awake from the beginning of the procedure with light sedation during skull opening and closing. Electroencephalography and electrocorticography recordings were obtained throughout the procedure to monitor the occurrence of afterdischarge phenomena and intraoperative seizures, both electrical and clinical. Motor evoked potential and somatosensory evoked potential recordings were also made throughout the duration of surgery with the aid of an Eclipse Neurological Workstation (Axon Systems, Inc.) and Brain Quick Plus (Micromed, Inc.).

In performing the cortical and subcortical brain mapping, a maximum of 4 mA of current intensity was generally sufficient for the cortex, and 6 or 8 mA was sufficient for subcortical simulation. As the surgery proceeded, resection of thin tumor layers was alternated with subcortical IES to detect the functional subcortical motor and language pathways, in accordance with previous technical surgical glioma studies.[17,22] Standard language tests such as counting, picture naming, and reading tasks

were systematically performed to determine the essential cortical language sites. More recently, in addition to the IES and standard language tasks, enriched and continuous testing was introduced throughout the procedure, providing complementary information to that provided by the IES.

In the present study, we analyzed a population of patients who underwent surgery for LGG in eloquent areas between June 1998 and May 2011, during which the intraoperative technical protocol was changed. Therefore, 2 consecutive periods were identified to evaluate the impact of each protocol on EOR. In Series 1 (June 1998–December 2004), 73 patients underwent surgery with the aid of corticosubcortical IES, neurophysiological monitoring, and intraoperative use of the neuronavigation system. In Series 2 (January 2005–May 2011), 117 patients underwent surgery using the same intraoperative protocol used in Series 1 but with the addition of overlapping fMRI/DTI data on the T1-weighted/T2-weighted 3D MRI studies to plan the surgery more precisely.

Patient Outcome Measurements

Postoperative functional outcome was assessed using the same protocol as before surgery, during the immediate postoperative stage, and at 3 and 6 months after surgery. In addition to neurological morbidity, OS, PFS, and MPFS were assessed. Overall survival was defined as the time between initial surgery and death. Progression-free survival was defined as the time between the initial surgery and demonstration of unequivocal increase in tumor size as shown on follow-up images, malignant progression, or death. Malignant PFS was defined as the time between initial surgery and demonstration of Gd enhancement on follow-up imaging and/or higher-grade tumor identification from a subsequent biopsy, or death.[54] Patients with no clinical improvement at the 6-month follow-up examination were considered to have a permanent deficit.

Volumetric Analysis

Magnetic resonance images in DICOM format were used to assess both pre- and postoperative tumor volume by using axial T2-weighted MRI studies. All pre- and postoperative tumor segmentations were performed manually across all MRI slices using the OsiriX software tool.[24,44,52] After segmentation, the volumes were calculated in cubic centimeters. The postoperative volume was measured using images acquired 4 months after surgery.

To avoid subjective bias in manual segmentation for tumor volumes, the preoperative volumetric analysis (computed on T2- and T1-weighted MRI studies) and postoperative volumetric analysis (computed on T2-weighted MRI studies) were performed in a double-blinded manner by 2 authors (T.I. and M.S.). No discrepancies regarding the tumor volume computed on T2- and T1-weighted MRI studies were found. The interobserver agreement for preoperative tumor volume on T1- and T2-weighted images and postoperative tumor volume on T2-weighted images was expressed as the ICC.

The EOR was calculated as follows: (preoperative tumor volume − postoperative tumor volume)/preoperative tumor volume, as previously described by Smith et al.[54] Finally, with the aim of evaluating the role of the diffusive tumor growth pattern on OS, PFS, and MPFS, and using the methodological procedure described by Skrap et al.,[52] we also assessed the volumetric preoperative tumoral difference on T2- and T1-weighted MRI studies for each case as follows: ΔVT2T1 value = preoperative volumetric tumor volume segmented on T2-weighted images − preoperative volumetric tumor volume segmented on T1-weighted images.

Statistical Analysis

General standard statistical measures were calculated as follows. Characteristics of the study population are described using the median and range for continuous variables and percentages for categorical variables. Data were tested for normal distribution using the Kolmogorov-Smirnov test. The t-test or Mann-Whitney test, as appropriate, was used to compare continuous variables. For categorical variables, cross-tabulations were generated, and a chi-square or Fisher exact test was used to compare distributions. Interobserver reproducibility of tumor volumes was assessed using the ICC and 95% CI.

For OS, PFS, and MPFS, the Kaplan-Meier approach was used. Patients with no known progression, malignant or otherwise, were censored as of their last scan date. Analysis of survival was done using Cox proportional hazard models, after the proportional hazards assumption had been verified.

In univariate analysis, variables considered as possible prognostic factors were age, sex, KPS score, preoperative tumor volume, tumor histological subtype, tumor location, tumor side, intraoperative protocol used, EOR, residual tumor volume, ΔVT2T1 value, chemotherapy, and EBRT performed at tumor recurrence or malignant transformation.

The EOR was modeled both as a continuous and an ordinal variable (< 70%, 70%–89%, and ≥ 90%) in univariate analysis to ensure consistency with previous studies that focused on the impact of glioma resection in terms of volumes.[49,52,54]

The ΔVT2T1 value and residual tumor volumes were similarly treated as both continuous and ordinal variables. The ΔVT2T1 interval was either smaller than 30 cm^3 or was 30 cm^3 or more, and the residual tumor volume was subdivided into the following 4 groups: smaller than 10 cm^3, 10–19 cm^3, 20–29 cm^3, and 30 cm^3 or larger.

Preoperative tumor volume was treated as a continuous variable, and a log transformation (base 10) was performed to help prevent inappropriate weighting of the results by tumors with large volumes. Multivariate stepwise backward analyses included all variables significant at $p \leq 0.15$ in univariate analysis. Retention in the stepwise model required the variable to be significant at $p < 0.05$ in a multivariate analysis.[57]

Results are presented as HRs and 95% CIs. Parametric or nonparametric correlation analysis, as appropriate, was used to explore a possible association between differences in preoperative tumor volumes computed on T2-weighted MRI studies, ΔVT2T1 value, and EOR

achieved. All analyses were conducted using Stata/SE (version 12.0 Stata Corp.) for Microsoft Windows. All 2-tailed statistical significance levels were set at $p < 0.05$.

Results

Study Population

Patient demographic, preoperative clinical, and radiological data are listed in Table 1. All lesions were near or within the so-called eloquent areas. Motor and speech mapping were performed in 136 (71.6%) and 126 (66.3%) patients, respectively. Symptoms included seizures in 171 patients, headaches in 6 patients, and neurological deficit of recent onset in 8 patients. In 5 patients the tumor diagnosis was incidental to other investigations. None of the patients in this series underwent preoperative chemotherapy or radiotherapy. In all cases, preoperative MRI studies showed a lesion that was hypointense on a T1-weighted MRI sequence without Gd contrast enhancement and hyperintense on a T2-weighted MRI sequence. The median preoperative tumor volume, measured on T2-weighted images, was 55 cm^3 (range 4–260 cm^3).

TABLE 1: Summary of preoperative clinical and radiological features in 190 patients with LGGs in eloquent areas

Parameter	Value*
sex	
male	111 (58.4)
female	79 (41.6)
age at diagnosis in yrs	
<40	119 (62.6)
40–60	58 (30.5)
>60	13 (6.8)
median age at diagnosis in yrs	37 (18–75)
symptoms at presentation	
seizures of recent onset	171 (90)
generalized	107 (56.3)
partial	64 (33.7)
incidental	5 (2.6)
headache	6 (3.2)
neurological deficits	8 (4.2)
preop KPS score	
80	5 (2.6)
90	52 (27.4)
100	133 (70)
median preop KPS score	96.7 (80–100)
tumor location	
precentral area	83 (43.7)
insula	56 (29.5)
temporal lobe	30 (15.8)
postcentral area	21 (11.1)
side of tumor	
lt	106 (55.8)
rt	84 (44.2)
preop tumol vol on T2-weighted MRI in cm^3	
<25	41 (21.6)
25–50	51 (26.8)
51–100	47 (24.7)
100–250	51 (26.8)
median tumor vol on T2-weighted MRI in cm^3	55 (4–260)
ΔVT2T1 in cm^3	
<30	116 (61)
≥30	74 (39)

* Median values are presented as the median (range). All other values represent the number of patients (%).

Postoperative Course

The clinical, histological, radiological, and follow-up data are summarized in Table 2. In summary, new postoperative deficits were noted in 83 patients (43.7%). At the 6-month follow-up examination, all but 6 patients (3.16%) improved and returned to their initial level or better. Moreover, the 8 patients with preoperative neurological deficits completely recovered 3 months after surgery. Results of the neuropathological examination revealed a WHO Grade II glioma in all cases. Tumor diagnosis was as follows: 98 fibrillary astrocytomas, 58 oligodendrogliomas, and 34 mixed oligoastrocytomas.

Radiotherapy alone (in 43 patients) or together with chemotherapy (in 27 patients) was administered when tumor resection was less than 70% or at malignant tumor transformation. Chemotherapy alone was administered when tumor progression was noted on imaging (20 patients). A detailed description of these data is beyond the scope of this study.

Volumetric Analysis

The interobserver agreement for preoperative tumor volume on T1- and T2-weighted images, as well as the measurement of postoperative tumor volume on T2-weighted images, was expressed as the ICC.

The intraobserver agreement was high for all volumetric analyses performed. In detail, the ICC was 0.999 (95% CI 0.999–0.999), 0.999 (95% CI 0.999–0.999), and 0.996 (95% CI 0.994–0.997) for preoperative tumor volume segmented on T1- and T2-weighted MRI studies and postoperative tumor volume computed on T2-weighted MRI studies, respectively.

Data on tumor resections are shown in Table 2. The median residual tumor volume, computed on postoperative T2-weighted MRI studies, was 7 cm^3 (range 0–125 cm^3). Notably, in almost half of the patients, the EOR was greater than 90%. In particular, the median EOR was 87.5% (range 28%–100%). The impact of each intraoperative protocol used on EOR achieved was also evaluated by separating the study population based on the intraoperative protocol adopted (Series 1 vs Series 2). Patients in Series 1 had a mean EOR of 77% (range 28%–100%), while patients in Series 2 had a mean EOR of 90% (range 49%–100%) (Mann-Whitney test, $z -4.99$; $p < 0.0001$) (Fig. 1). Finally, the effect of the preoperative ΔVT2T1 value on EOR achieved was investigated.

TABLE 2: Summary of postoperative clinical findings, histological results, and volumetric analysis of EOR*

Parameter	Value
immediate postop clinical findings	
no deficits	107 (56.3)
neurological deficits	83 (43.7)
motor deficits	48 (25.3)
SMA syndrome	10 (5.3)
facial droop	7 (3.7)
UL/LL paresis	14 (7.4)
UL/LL weakness	18 (9.5)
speech disorders	29 (15.3)
expressive aphasia	21 (11.1)
dysarthria	8 (4.2)
partial Gerstmann syndrome	1 (0.5)
sensory UL &/or LL deficit	4 (2.1)
postop EDH†	1 (0.5)
clinical outcome at 6 mos	
no deficits	184 (96.8)
neurological deficits	6 (3.16)
motor deficits	2 (1.05)
SMA syndrome	0 (0.0)
facial droop	0 (0.0)
UL/LL paresis	2 (1.05)
UL/LL weakness	0 (0.0)
speech disorders	2 (1.05)
expressive aphasia	2 (1.05)
dysarthria	0 (0.0)
partial Gerstmann syndrome	0 (0.0)
UL &/or LL sensory deficit	2 (1.05)
diagnosis (WHO Grade II)	
fibrillary astrocytoma	98 (51.6)
oligoastrocytoma	34 (17.9)
oligodendroglioma	58 (30.5)
% EOR‡	
≥90	91 (47.9)
70–89	69 (36.3)
<70	30 (15.8)
median % EOR	87.5 (28–100)
Series 1 (IES)	
no. of patients	73 (38.4)
median % EOR	77.4 (28–100)
Series 2 (IES +fMRI/DTI overlap)	
no. of patients	117 (61.6)
median % EOR	90 (49–100)
Subgroup A (ΔVT2T1 <30 cm^3)	
no. of patients	116 (61.1)
median % EOR	91 (49–100)

(continued)

TABLE 2: Summary of postoperative clinical findings, histological results, and volumetric analysis of EOR* ***(continued)***

Parameter	Value
Subgroup B (ΔVT2T1 ≥30 cm^3)	
no. of patients	74 (38.9)
median % EOR	79 (28–100)
postop tumor vol in cm^3	
<10	111 (58.4)
11–20	41 (21.6)
21–30	16 (8.4)
≥30	22 (11.6)
median postop tumor vol in cm^3	7 (0.00–125)
clinical follow-up§	
median follow-up in mos	57 (4–155)
no. of patient deaths	41 (21.6)
no. w/ disease progression	79 (41.6)
median time to progression	3.5 yrs (4–155 mos)
no. w/ malignant disease progression	62 (32.6)
median time to malignant disease progression	3.96 yrs (4–148 mos)

* EDH = epidural hematoma; LL = lower limb; SMA = supplementary motor area; UL = upper limb.
† The patient developed a new mild hemiparesis that completely resolved after evacuation.
‡ Determined on the basis of pre- and postoperative T2-weighted MRI studies, following the methodological procedure described by Smith et al.[38]
§ Since the first operation.

For this purpose, the study population was divided into the following 2 subgroups: Subgroup A, patients with ΔVT2T1 values smaller than 30 cm^3 (116 patients); and Subgroup B, patients with a ΔVT2T1 value of 30 cm^3 or larger (74 patients).

Our results showed that Subgroup A had a median EOR of 91%, while Subgroup B had a median EOR of 79%, ($z = 4.75$, Mann-Whitney test; $p < 0.0001$) (Table 2). Even considering EOR as an ordinal variable (< 70%, 70%–89%, and ≥ 90%), the association with the ΔVT2T1 value subgroups remains significant (Table 3). In particular, the association between postoperative tumor volume on T2-weighted MRI images and ΔVT2T1 value ($r_s = 0.77$, $p < 0.0001$) is illustrated in Fig. 2, taking into consideration the percentage of the EOR volume also.

Consequently, our data show that the greater the preoperative ΔVT2T1 value, the less extensive the resection currently possible; this finding points to a possible predictive correlation between ΔVT2T1 value and EOR achievable.

Overall Survival

Overall, 41 patients died (21.6%), and the median follow-up in the surviving patients was 4.7 years (range 4–155 months). The estimated 5- and 8-year OS rates were 80% and 66%, respectively. The prognostic factors, associated ($p \leq 0.15$) with OS in the univariate proportional hazard model, were as follows: age, log preopera-

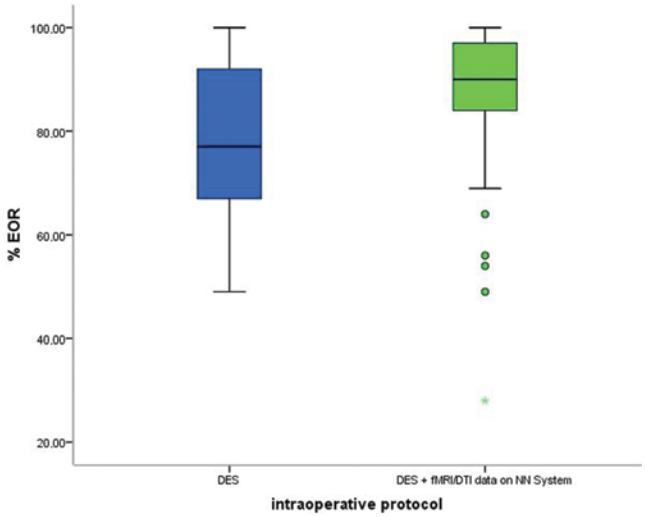

Fig. 1. Box plot showing the difference achieved in tumor resection between Series 1 *(blue box)* and Series 2 *(green box)*. Series 1 had a mean EOR of 77%, while Series 2 had a mean EOR of 90%. The intraoperative use of a guided navigation system (NN) enriched with fMRI/DTI data, in addition to IES used in the second series, significantly increased the EOR achieved. The *asterisk* represents the outlier, and the *circles* indicate the suspected outliers. DES = direct electrical stimulation.

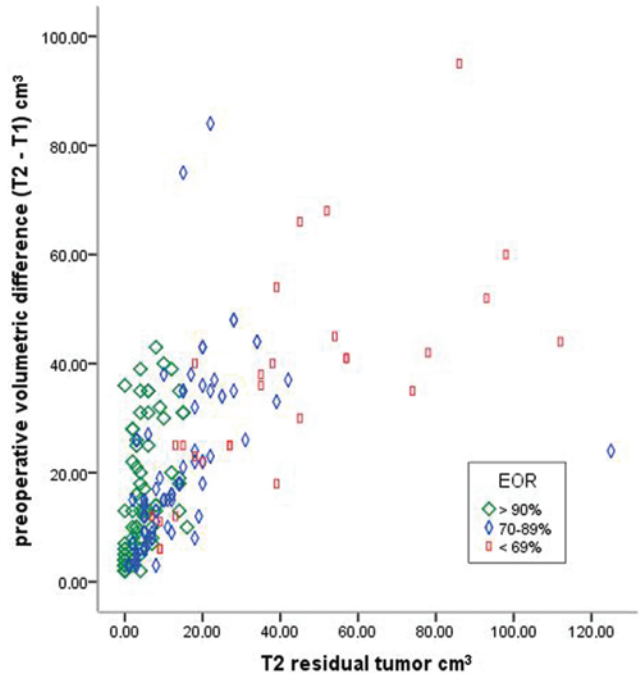

Fig. 2. Graph showing the association between postoperative tumor volumes computed on T2-weighted MRI studies and preoperative ΔVT2T1 values (r_s = 0.77, p < 0.0001). Although there is a tendency toward higher EOR (≥ 90%) and smaller tumors, the data highlight a correlation tendency between a higher ΔVT2T1 value and a lesser EOR achieved. A major volumetric difference between T2- and contrast-enhanced T1-weighted MRI sequences suggests a greater propensity of the tumor to have a diffuse growing pattern and consequently to be less resectable.

tive tumor volume, intraoperative protocol used, histological tumor subtype, EOR, ΔVT2T1 value, and postoperative residual tumor.

Univariate analysis results are summarized in Table 4. An increase in age and in log preoperative tumor volume were associated with a significantly worse OS, while the introduction of fMRI/DTI data on the neuronavigation system (Series 2 vs Series 1) improved the EOR and consequently the OS.

The OS was also significantly improved (HR 4.262 [95% CI 1.748–10.388], p = 0.001) for patients with histological diagnosis of oligodendrogliomas compared to those with fibrillary astrocytomas. The estimated 5- and 8-year OSs were 88% and 85% for patients with WHO Grade II oligodendrogliomas and 73% and 44% for patients with astrocytomas, respectively.

No significant differences were found between patients with a histological diagnosis of oligoastrocytoma compared with those with oligodendroglioma (p = 0.636) (Fig. 3A). Furthermore, the EOR, treated as a continuous variable, was associated with a significant improvement in OS (HR 0.93 [95% CI 0.92–0.95], p < 0.0001).

With EOR divided into 3 categories, the estimated 5- and 8-year OS rates were 93% and 89% for patients with an EOR of 90% or more; 84% and 59% for patients with an EOR of 70%–89%; and 41% and 17% for patients with an EOR less than 70%, respectively (Fig. 3B).

Overall, our results show that patients with an EOR less than 70% had a risk of death 19.7 (95% CI 7.08–54.8) times higher than patients with an EOR of 90% or more.

The impact of residual tumor volume on OS was also analyzed. Patients with a smaller postoperative tumor volume had a significantly better OS. Considering the 4 subgroups defined according to the residual tumor volume value (< 10 cm^3, 10–19 cm^3, 20–29 cm^3, and ≤ 30 cm^3), the estimated 5-year OS rates were 93%, 85%, 57%, and 37%, respectively, and the estimated 8-year OS rates were 87%, 56%, 57%, and 14%, respectively (Fig. 3C). Moreover, the univariate Cox proportional hazard analysis showed that the ΔVT2T1 value, treated as a continuous variable, was associated with a worse OS (HR 1.04 [95% CI 1.03–1.06], p < 0.0001).

For graphic visualization purposes, the ΔVT2T1 value was divided into 2 categories as follows: ΔVT2T1 value less than 30 cm^3 and ΔVT2T1 value 30 cm^3 or higher. The estimated 5- and 8-year OS rates were 91% and 78% for a ΔVT2T1 value less than 30 cm^3 and 56% and 38% for a ΔVT2T1 value of 30 cm^3 or higher, respectively (Fig. 3D).

In particular, this analysis shows that patients with a ΔVT2T1 value of 30 cm^3 or higher were at a risk of death

TABLE 3: Linear association between ΔVT2T1 and EOR*

	No. of Patients (%)		
% EOR	ΔVT2T1 <30 cm^3	ΔVT2T1 ≥30 cm^3	Total
≥90	68 (58.62)	22 (29.73)	90 (47.4)
70–89	42 (36.21)	28 (37.84)	70 (36.8)
<70	6 (5.17)	24 (32.43)	30 (15.8)
total	116	74	190

* Pearson χ^2 = 29.256, df 2, p < 0.001.

TABLE 4: Univariate analysis of clinical data, tumor parameters, and volumetric tumor data with OS, PFS, and MPFS in 190 patients with LGGs*

	OS			PFS			MPFS		
Factor	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
age†	1.030	1.007–1.055	**0.011**	1.006	0.988–1.025	0.513	1.015	0.995–1.036	0.137
sex									
male	1			1			1		
female	0.709	0.366–1.372	0.308	1.324	0.848–2.066	0.220	0.780	0.460–1.323	0.352
KPS score at diagnosis†	0.963	0.916–1.013	0.163	0.980	0.848–2.066	0.220	0.965	0.925–1.006	0.091
log preop tumor vol in cm^3†	8.201	2.691–24.988	**<0.0001**	3.256	1.595–6.643	**0.001**	4.406	1.880–10.327	**0.001**
tumor location									
precentral area	1			1			1		
insular lobe	1.642	0.189–3.291	0.162	1.691	1.022–2.797	1.141	1.358	0.786–2.345	0.272
temporal lobe	1.164	0.450–3.011	0.753	1.044	0.584–2.145	0.906	0.868	0.392–1.921	0.729
postcentral area	1.269	0.363–4.433	0.708	2.107	0.948–4.682	0.067	0.533	0.125–2.257	0.393
tumor site									
lt	1			1			1		
rt	1.533	0.828–2.840	0.175	1.231	0.782–1.937	0.372	1.550	0.959–2.638	0.08
tumor subtype									
oligodendroglioma	1			1			1		
oligoastrocytoma	1.332	0.405–4.373	0.636	1.078	0.533–2.181	0.833	1.078	0.533–2.181	0.833
fibrillary astrocytoma	4.262	1.748–10.388	**0.001**	2.273	1.326–3.895	**0.003**	2.273	1.326–3.895	**0.003**
intraop protocol									
Series 1	1			1		1			
Series 2	0.388	0.179–0.839	**0.016**	0.969	0.604–1.553	0.056	0.600	0.336–1.072	0.085
% EOR†	0.933	0.915–0.952	**<0.0001**	0.930	0.915–0.946	**<0.0001**	0.944	0.928–0.960	**<0.0001**
% EOR									
≥90	1			1			1		
70–90	4.845	1.792–13.098	**0.002**	3.402	1.869–6.191	**<0.0001**	2.552	1.345–4.844	**0.004**
<70	19.702	7.077–54.843	**<0.0001**	13.60	7.18–25.79	**<0.0001**	9.77	4.85–19.65	**<0.0001**
ΔVT2T1†	1.040	1.026–1.055	**<0.0001**	1.034	1.023–1.045	**<0.0001**	1.034	1.021–1.046	**<0.0001**
ΔVT2T1									
<30 cm^3	1			1			1		
≥30 cm^3	3.699	1.992–6.867	**<0.0001**	3.427	2.201–5.334	**<0.0001**	2.992	1.815–4.930	**<0.0001**
postop tumor vol on T2-weighted images†	1.022	1.014–1.031	**<0.0001**	1.023	1.016–1.029	**<0.0001**	1.021	1.013–1.029	**<0.0001**
postop tumor vol on T2-weighted images									
<10 cm^3	1			1			1		
10–20 cm^3	3.281	1.340–8.035	**0.009**	1.746	0.946–3.222	0.074	1.536	0.795–2.967	0.200
21–30 cm^3	6.500	2.434–17.353	**<0.0001**	5.842	3.049–11.191	**<0.0001**	2.982	1.368–6.501	**0.006**
>31 cm^3	13.980	5.677–34.423	**<0.0001**	13.061	6.961–24.506	**<0.0001**	8.739	4.407–17.329	**<0.0001**
postop chemotherapy									
no	1			1			1		
yes	1.395	0.584–3.330	0.436	1.005	0.572–1.767	0.986	1.178	0.595–2.332	0.639
postop EBRT									
no	1			1			1		
yes	0.598	0.323–1.106	0.101	0.600	0.385–0.935	**0.024**	0.578	0.351–0.954	**0.032**

* Values in boldface are statistically significant from 2-sided tests (Cox regression) and were statistically significant when $p < 0.05$.
† Modeled as a continuous variable.

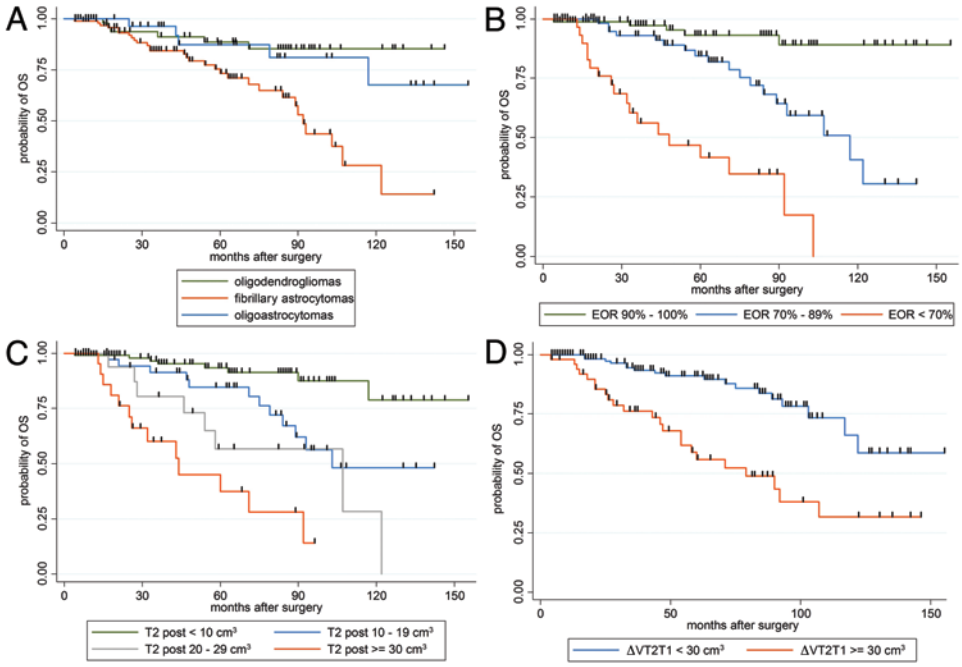

Fig. 3. Kaplan-Meier curves revealing the OS in patients with LGGs, stratified by histological subtype **(A)**, EOR **(B)**, postoperative residual tumor volume computed on T2-weighted images (T2 post) **(C)**, and preoperative ΔVT2T1 value **(D)**. Patients with a diagnosis of oligodendroglioma, EOR of at least 90%, residual tumor smaller than 10 cm^3, and ΔVT2T1 value less than 30 cm^3 have significantly longer OS.

4 times greater than patients with a preoperative difference of less than 30 cm^3 (HR 3.70 [95% CI 1.99–6.87], $p < 0.0001$) due to the greater difficulty of complete resection of the glioma without excessive postoperative morbidity.

Finally, multivariate Cox analysis showed that OS was significantly worse in older patients, as well as in patients with a histological diagnosis of fibrillary astrocytoma, as compared to those with oligodendroglioma and to patients with higher ΔVT2T1 values (Table 5).

Tumor Progression and Malignant Transformation

Tumor progression was identified in 79 patients (41.6%) and malignant progression was noted in 62 patients (32.6%), as indicated by new contrast enhancement on follow-up imaging (Table 2). Forty-eight of the 62 patients with malignant progression underwent a second surgery, and a higher-grade tumor was identified. Among the remaining 14 patients with MPFS in whom a second surgery was not performed, 9 received EBRT before malignant progression.

The median PFS and MPFS were 3.5 years (range 4–155 months) and 3.96 years (range 4–148 months), respectively. The estimated 5- and 8-year survival rates were 59% and 35% for PFS and 74% and 47% for MPFS, respectively.

Univariate analysis showed that the following prognostic factors were associated with PFS and MPSF ($p < 0.05$): log preoperative tumor volume, tumor subtype, EOR, ΔVT2T1 value, residual tumor, and EBRT. These results are summarized in Table 4. In particular, a higher log preoperative tumor volume was significantly associated with a worsening of both PFS and MPFS. As far as histological subtype data are concerned, PFS was significantly improved for patients with histological diagnosis of oligodendroglioma compared with those with fibrillary

TABLE 5: Variables independently associated with OS, PFS, and MPFS after resection of LGGs in a multivariate proportional hazard analysis (Cox model)*

	OS			PFS			MPFS		
Factor	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
age†	1.035	1.011–1.060	0.003		NS			NS	
histological subtype‡	2.974	1.401–6.315	0.005		NS		3.202	1.489–6.886	0.003
% EOR†	0.958	0.936–0.981	0.001	0.940	0.924–0.956	<0.0001	0.963	0.944–0.982	<0.0001
ΔVT2T1†	1.035	1.017–1.054	<0.0001	1.021	1.008–1.034	0.001	1.029	1.014–1.045	<0.0001

* NS = not significant in multivariate Cox analysis.
† Modeled as a continuous variable.
‡ Fibrillary astrocytoma versus oligodendroglioma and oligoastrocytoma.

astrocytoma, while both oligoastrocytoma and fibrillary astrocytoma were associated with a worse MPFS than oligodendroglioma.

The EOR, treated as both a continuous and an ordinal variable, was associated with significant improvement of both PFS and MPFS values. The Kaplan-Meier curves demonstrating the PFS and MPFS in patients with LGGs, stratified by EOR subgroups, are shown in Figs. 4A and 5A, respectively. In quantitative terms, our analysis shows that patients with an EOR of less than 70% have a much higher risk of disease progression and malignant transformation than do patients with an EOR of 90% or more (13.6 [95% CI 7.18–25.79] times higher risk for disease progression and 9.77 [95% CI 4.85–19.65] times higher for malignant progression).

Similarly, patients with a smaller postoperative tumor volume showed significantly longer periods of PFS and MPFS. The PFS and MPFS estimates for 4 residual tumor volume subgroups are shown in Figs. 4B and 5B, respectively.

An increase in ΔVT2T1 value, modeled as both continuous and dichotomous variables, was associated with an earlier tumor progression as well as malignant transformation. The Kaplan-Meier PFS and MPFS plots, estimated for ΔVT2T1 as a dichotomous variable, are shown in Figs. 4C and 5C, respectively.

Finally, multivariate Cox analysis shows that PFS was significantly worse in patients with higher ΔVT2T1 values and histological diagnosis of fibrillary astrocytoma versus oligodendroglioma. Conversely, higher EOR values and lower ΔVT2T1 values were associated with a longer PFS.

In the final model, MPFS was shown to be significantly worse in patients with higher ΔVT2T1 values, histological diagnosis of oligoastrocytoma, and fibrillary astrocytomas versus oligodendrogliomas, whereas higher EOR values and lower ΔVT2T1 values were associated with a better MPFS (Table 5).

Discussion

Low-grade gliomas are infiltrative cerebral tumors, characterized by a systematic progression to malignant transformation.[19,50,55,59] In the literature, 5-year survival ranges from 42% to 98%.[16,31,32,35,38,42,43,58,61] To date, there is still no general consensus regarding the effect of EOR on OS among patients with LGGs, due to the lack of Class I evidence. However, since 1990, many different studies have been published evaluating the benefit of the maximum EOR of glioma in improving OS and delaying tumor progression.[1,15,27,32,35,38,39,42,43,49,52,54,58,60,61] The most critical point in achieving a radical resection in LGGs is represented by their tendency to infiltrate eloquent cortical areas and subcortical pathways.[20,34]

Extent of Resection and Surgical Technique

Recent advances in microsurgical and brain mapping techniques with neurophysiological monitoring have led to an increase in the use of surgery for LGGs. The neuroradiological techniques, such as fMRI and 3D reconstruction of white matter tracts, represent useful tools to preoperatively analyze the tridimensional relationships between the tumor and the neighboring cortical functional areas and subcortical pathways, respectively.[2,9,29,52,56]

The fMRI/DTI data loaded into the neuronavigation system, which are available intraoperatively, may provide useful intraoperative guidance.[3,8,52] It was demonstrated that the location and course of the tract were dependent on the characteristics of the tumor, such as histology, edema, location,[3,10] and on some technical factors, such as the fractional anisotropy threshold used for start and stop tracking.[4,30,37] Consequently, all functional areas and subcortical pathways must be continuously verified with IES. In addition to IES, we have recently introduced enlarged, continuous, and variant neuropsychological testing, which is helpful during subcortical stimulation on the dominant side. Our results demonstrate that the intraoperative use of a guided navigation system enriched with functional and DTI data used in Series 2 significantly increase the EOR possible. Patients in Series 1 had a mean EOR of 77%, while those in Series 2 had a mean EOR of 90% ($p = 0.0001$).

Specifically, the combination of DTI fiber tracking and IES allowed the accurate identification of eloquent fiber tracts and increased surgical performance, maintaining a high rate of functional preservation. In addition, the routine use of intraoperative transcranial motor evoked potential monitoring is helpful in preventing direct injury to the pyramidal tract.[51,52] In our experience, motor evoked potentials are useful in warning us about direct

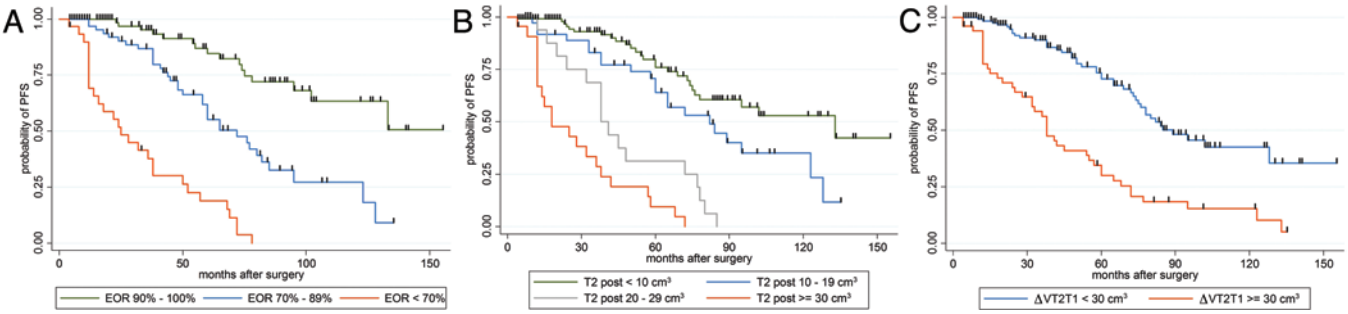

Fig. 4. Kaplan-Meier curves revealing the PFS in patients with LGGs, stratified by EOR **(A)**, postoperative residual tumor volume (T2 post) **(B)**, and ΔVT2T1 value **(C)**. Patients with EOR of at least 90%, preoperative ΔVT2T1 smaller than 30 cm^3, and postoperative residual tumor volume computed on T2-weighted images smaller than 10 cm^3 have a significant delay in tumor progression.

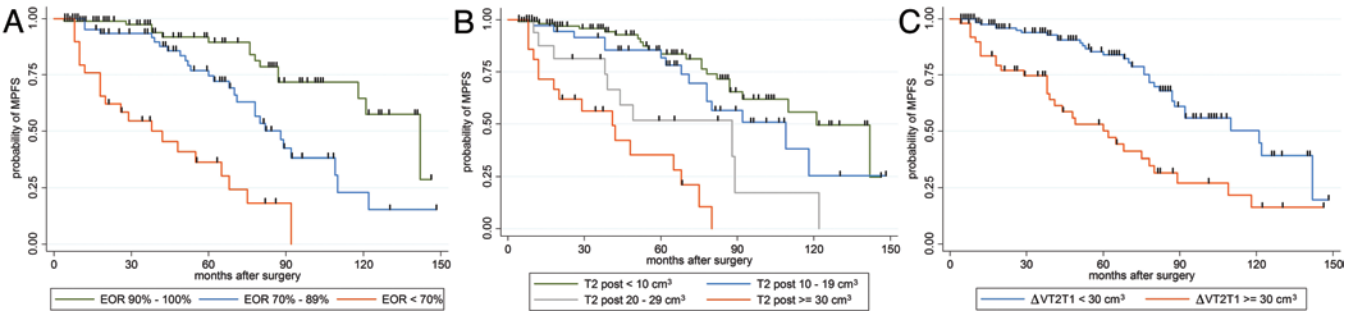

Fig. 5. Kaplan-Meier curves revealing the MPFS in patients with LGGs, stratified by EOR **(A)**, postoperative residual tumor volume computed on T2-weighted images (T2 post) **(B)**, and preoperative ΔVT2T1 **(C)**. Patients with EOR equal to or greater than 90%, with ΔVT2T1 less than 30 cm^3, and with postoperative residual tumor volume computed on T2-weighted images less than 10 cm^3 demonstrate an improvement in MPFS.

mechanical trauma to the fibers, but they do not guarantee the prevention of vascular damage.

Finally, we always use intraoperative electrocorticography, which is, in our opinion, essential to record afterdischarge phenomena and electrical and clinical seizures. In particular, short-duration focal seizures, which can interfere with the patient's collaboration during mapping, may be highlighted.

Volumetric and Survival Analysis

Until recently, EOR has often been estimated solely on the basis of the intraoperative interpretation of the surgeon, resulting in erroneous conclusions about the actual role of surgery.[19] No studies have randomized the patients with respect to EOR, and in only 5 recent studies was the volumetric analysis of EOR applied.[16,49,54,55,58]

Among the nonvolumetric studies, 8 demonstrated evidence supporting EOR as a statistically significant predictor of 5-year survival by comparing gross-total resection, near-total resection, and subtotal resection,[1,15,32,35,38,39,42,61] while all volumetric studies showed evidence supporting EOR as a statistically significant predictor of OS by a combination of multivariate and univariate analyses (Table 6).

All volumetric investigations demonstrated that a more aggressive resection predicts a significant improvement in OS,[16,49,52,52,58] although the cutoff threshold of EOR is different in each publication and varied from 75% to 100%. Van Veelen et al.[58] and Claus et al.[16] were the first to assess the volumetric evaluation of EOR in LGG surgery, reporting 5-year Kaplan-Meier estimations of survival of 62% and 92%, respectively, for tumor resection greater than 75%.

Most recently, Smith et al.[54] performed a retrospective volumetric analysis of EOR in 216 patients with LGGs and found that patients with at least 90% resection had 5- and 8-year OSs of 97% and 91%, respectively, whereas patients with less than 90% resection had 5- and 8-year OS rates of 76% and 60%, respectively. In line with these papers, our volumetric analysis provides further evidence that a more aggressive resection correlates with a significant improvement in OS ($p = 0.001$), as well as in PFS ($p < 0.0001$) and MPFS ($p < 0.0001$), compared with a simple debulking procedure.

Overall, the present volumetric analysis shows 5-year OS rates, 5-year PFS, and 5-year MPFS rates of 93%, 88%, and 91% respectively, when EOR was at least 90%. In addition, the multivariate analysis in our study population shows that EOR is an independent prognostic factor for OS, as well as for PFS and MPFS.

Since oligodendrogliomas, particularly those with 1p19q LOH, have more benign courses,[25,26] we separated these histological subtypes as a covariate in a multivariate analysis. Our analysis, as previously reported by McGirt et al.,[35] showed that patients with oligodendroglioma and oligoastrocytoma have a better prognosis with respect to those with fibrillary astrocytoma (5-year OS rates of 88% vs 5-year OS rates of 87% and 73%, respectively), confirming a different natural history between low-grade oligodendroglioma-oligoastrocytoma and low-grade astrocytomas.[50] In our series, 1p19q status was assessed in the minority of specimens; therefore, survival comparison between LOH-negative and LOH-positive LGGs was not possible because only 14 cases of oligodendrogliomas were proven to have 1p19q LOH.

Finally, in our investigation of the impact of residual tumor volume on OS, PFS, and MPFS, we found a significant advantage for all outcome measures when the residual volume was smaller than 10 cm^3. Indeed, the decrease in the number of remaining cells theoretically decreases the risk of malignant cellular degeneration and hence potentially prolongs OS.[25,54]

As far as the methodological procedure is concerned, the present study was designed to follow the methodology proposed by Smith et al.[54] for the assessment of EOR along with with careful consideration of the limitations of many previous studies.

We recruited only adult patients and excluded cases of pilocytic astrocytoma (WHO Grade I), gemistocytic astrocytoma, and patients treated with upfront radiation therapy or chemotherapy to create a more uniform study population. Nonetheless, our study also has limitations. First, it is a retrospective study, and this analytical approach does not allow for a standardized patient follow-up. Moreover, patients who underwent a biopsy procedure were excluded; therefore, our data cannot offer a direct comparison between patients undergoing biopsy only and patients undergoing maximum resection. Furthermore, the end points of PFS and MPFS have several potential limitations. New contrast enhancement can appear after

TABLE 6: Statistical relationship of EOR to OS and PFS in patients with LGGs in a review of the literature*

				5-Yr OS		5-Yr PFS	
Authors & Year	No. of Cases	EOR Evaluation	% EOR (no. of cases)	% OS	Multivariate p Value	% PFS	Multivariate p Value
van Veelen et al., 1998	90	volumetric	stereotactic biopsy (18) PR (59)† GTR (13)‡	NA 18 62	NA 0.04	NA NA	NA NA
Claus et al., 2005	156	volumetric	100 (56) <100 (100)	98.2 92.0	<0.05	NA	NA
Smith et al., 2008	216	volumetric	100 (75) 90–99 (26) 79–89 (55) 41–69 (39) 0–40 (21)	98.0 97.0 NA NA NA	0.005	78.0 75.5 NA NA NA	<0.001
Sanai et al., 2010§	104 (70 LGGs)	volumetric	91–100 (14), 81–90 (25), 71–80 (17), <70 (14)	100 for EOR >90%, 84 for EOR <90%	<0.05	90 69	<0.05
Skrap et al., 2012¶	66 (53 LGGs)	volumetric	>90 (22) 90–70 (30) <70 (14)	92 82 57	0.002	NA	NA
Philippon et al., 1993	179	nonvolumetric	GTR (45) STR (95) biopsy (39)	80 50 45	0.002	NA	NA
Rajan et al., 1994	82	nonvolumetric	GTR (11), STR (30), PR (22), biopsy (19)	52 for total LGG cohort	NA	NA	NA
Leighton et al., 1997	167	nonvolumetric	GTR (85), STR (23), biopsy (59)	median 72	0.006	median 50	NA
Nakamura et al., 2000	88	nonvolumetric	GTR (43), STR (45)	median 78	<0.001	median 45	NA
Yeh et al., 2005	93	nonvolumetric	GTR (13) STR (80)	92 52	0.016	84 41	0.002
McGirt et al., 2008	170	nonvolumetric	GTR (65) NTR (39) STR (66)	95 80 70	0.017	NA	NA
Ahmadi et al., 2009	130	nonvolumetric	GTR (91), STR (39)	NA	0.005	NA	NA
Shaw et al., 2002	203	nonvolumetric	GTR (29) STR (71) biopsy (103)	88 56 71	0.0349	NA	NS

* Since 1990, many different nonvolumetric and volumetric studies have used statistical analysis to examine the role of EOR in improving survival and delaying tumor progression in patients with LGGs, demonstrating a survival benefit for greater EOR. The overall trend favors the value of greater EOR in improving patient outcome. Abbreviations: GTR = gross-total resection; NA = not assessed; NS = not significant; NTR = near-total resection; PR = partial resection; STR = subtotal resection.

† Estimated tumor removal < 75%.

‡ Estimated tumor removal > 75%.

§ Paper focused on insular glioma surgery.

¶ Paper focused on insular nonenhancing glioma surgery.

radiotherapy;[53] in the present series, in 14 of 62 patients with MPFS (9 of whom received EBRT before malignant progression), the diagnosis of malignant transformation was made on the basis of imaging alone without histological confirmation. We recognize that it could be difficult to distinguish radiation effects from progression; however, these 9 patients diagnosed with malignant progression on the basis of imaging alone were far enough out from EBRT to expect that any effect of treatment on imaging results had been resolved. A further limitation is that at the time of tumor progression or malignant transformation, patients were treated with nonstandardized chemo- and radiotherapeutic protocols. Lastly, the molecular markers, which are increasingly used for the assessment and management of LGGs, were not included in the multivariate analysis due to their recent discovery and introduction in clinical practice.[12,13,55]

Clinical Role of ΔVT2T1 Value and Future Perspectives

The major limitation in achieving a complete resec-

tion is the infiltrative growing pattern of these lesions, especially at the subcortical level. Consequently, the definition of the best management of a residual tumor represents the main open question in clinical practice.[12,55] To this end, neoadjuvant chemotherapy was recently advocated for LGG management, with the aim of inducing tumor shrinkage before operation or reoperation.[12,19,55] As it is usually believed that postoperative tumor volume influences the prognosis for patients with this disease,[5,17,28,61] it may be more advantageous to start active treatment with radiotherapy or even chemotherapy.[12–14] It is therefore of the utmost importance to develop a standard tool that enables an objective preoperative estimation of the postoperative tumor volume. Lang et al.[30] first asserted that lesions with diffuse margins on T2-weighted MRI are less amenable to radical resection than those with sharp margins. Recently, Skrap et al.[52] introduced a preoperative method to discriminate the proliferative growing mechanism from the diffusive spreading mechanism along the white matter and to assess preoperatively the degree of resection. Data reported showed that when proliferation is the major diffusivity phenomenon, it does not affect the tumor shape (resulting in a regular shape, comparable on both preoperative contrast-enhanced T1- and T2-weighted MRI studies), which is grossly bulky. By contrast, when the diffusive pattern is predominant, the tumor will result in a complex shape with digitations along the white matter, which is more visible on T2-weighted images.[34,52]

In the present study, our findings confirmed the data reported by Skrap et al.[52] on the role of the ΔVT2T1 value in OS and in representing a prognostic preoperative index of EOR itself. Our findings also confirmed the role of this preoperative value in tumor progression and malignant transformation. Patients with a ΔVT2T1 value of less than 30 cm^3 have a better prognosis than those with a ΔVT2T1 value more than 30 cm^3 in terms of OS ($p < 0.0001$), PFS ($p < 0.0001$), and MPFS ($p < 0.0001$). Even after having applied a multivariate analysis, the ΔVT2T1 value was found to be a significant preoperative prognostic factor for OS ($p < 0.0001$), PFS ($p = 0.001$), and MPFS ($p < 0.0001$). Moreover, our results show that in cases with a ΔVT2T1 value less than 30 cm^3 (Subgroup A) the median EOR was 91%, whereas when this difference was more than 30 cm^3 (Subgroup B) the mean EOR was 79% ($p < 0.0001$). Thus, the present investigation confirms the possibility of identifying in the ΔVT2T1 value a prognostic preoperative index of EOR itself. The significant correlation between the preoperative ΔVT2T1 value and the EOR indicates that this index is a promising tool to use in the decision-making process over whether to operate on a LGG or start preoperative neoadjuvant chemotherapy to reduce the infiltrative growing pattern of the tumor and, consequently, to increase the possibility of a total resection. Finally, for patients who undergo chemotherapy as an initial treatment or at recurrence after a previous partial resection due to the invasion of functional subcortical pathways, the ΔVT2T1 value may represent a useful tool to assess the efficacy of the treatment itself and its effectiveness in decreasing the infiltrative tumor component.

Conclusions

In line with recent volumetric studies on the objective evaluation of EOR, our data confirm the role of surgery as the first-line treatment for LGGs. The EOR is a strong independent factor associated with improved OS, as well as with delay of progression and malignant transformation. Due to intraoperative corticosubcortical mapping, neurophysiological monitoring, and overlap of fMRI/DTI data on the neuronavigation system, a major resection is possible with an acceptable risk and a significant improvement in long-term patient outcomes. However, the major limitation in achieving a complete resection is due to the infiltrative growing pattern of these lesions, particularly at the subcortical level. Consequently, the preoperative assessment of the prevailing pattern of growth (infiltrative vs proliferative), by computing the ΔVT2T1 value, may constitute a predictive index of EOR itself. This index could also represent a new tool to help with surgical decision making and therefore standardize the therapeutic strategy in LGG management. In addition, how to best manage the residual tumor represents the main open question in clinical practice, and the impact of the residual tumor on OS, PFS, and MPFS should also be investigated in the context of molecular prognostic factors to define better postoperative standardized adjuvant protocols. Finally, to develop a dynamic strategy for the management of LGGs, further prospective studies focusing on detailed molecular and genetic differentiation among LGGs should be undertaken.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Ius, Skrap. Acquisition of data: Ius. Analysis and interpretation of data: Ius, Isola, Skrap. Drafting the article: Ius, Isola, Skrap. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ius. Statistical analysis: Ius, Isola. Administrative/technical/material support: Ius. Study supervision: Ius, Skrap.

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