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# The benefit of early surgery on overall survival in incidental low-grade glioma patients: A multicenter study

**Tamara Ius, Sam Ng, Jacob S. Young, Barbara Tomasino, Maurizio Polano, David Ben-Israel, John J. P. Kelly, Miran Skrap, Hugues Duffau,[†] and Mitchel S. Berger[†]**

*Neurosurgery Unit, Department of Neurosciences, Santa Maria della Misericordia University Hospital, Udine, Italy (T.I., M.S.); Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Center, Montpellier, France (S.N., H.D.); INSERM U1191, Team "Plasticity of Central Nervous System, Human Stem Cells and Glial Tumors", Institute of Functional Genomics, Montpellier, France (S.N., H.D.); Department of Neurological Surgery, Brain Tumor Research Center, University of California, San Francisco, CA, USA (J.S.Y., M.S.B.); Scientific Institute IRCCS "Eugenio Medea", Polo FVG, San Vito al Tagliamento, Italy (B.T.); Experimental and Clinical Pharmacology Unit, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy (M.P.); Division of Neurosurgery, University of Calgary, Calgary, Alberta, Canada (D.B.-I., J.J.P.K.); Arne Charbonneau Cancer Institute, University of Calgary, Calgary, Alberta, Canada (D.B.-I., J.J.P.K.).*

[†]M.S.B. and H.D. share senior authorship.

**Corresponding Author:** Tamara Ius, MD, PhD, Neurosurgery Unit, Department of Neurosciences, Santa Maria della Misericordia University Hospital, Piazzale Santa Maria della Misericordia 15,33100, Udine, Italy (tamara.ius@gmail.com).

## Abstract

**Background.** The role of surgery for incidentally discovered diffuse incidental low-grade gliomas (iLGGs) is debatable and poorly documented in current literature.

**Objective.** The aim was to identify factors that influence survival for patients that underwent surgical resection of iLGGs in a large multicenter population.

**Methods.** Clinical, radiological, and surgical data were retrospectively analyzed in 267 patients operated for iLGG from 4 neurosurgical Centers. Univariate and multivariate analyses were performed to identify predictors of overall survival (OS) and tumor recurrence (TR).

**Results.** The OS rate was 92.41%. The 5- and 10-year estimated OS rates were 98.09% and 93.2%, respectively. OS was significantly longer for patients with a lower preoperative tumor volume ($P = .001$) and higher extent of resection (EOR) ($P = .037$), regardless the WHO-defined molecular class ($P = .2$). In the final model, OS was influenced only by the preoperative tumor volume ($P = .006$), while TR by early surgery ($P = .028$). A negative association was found between preoperative tumor volumes and EOR ($rs = –0.44$, $P < .001$). The median preoperative tumor volume was 15 $cm^3$. The median EOR was 95%. Total or supratotal resection of T2-FLAIR abnormality was achieved in 61.62% of cases. Second surgery was performed in 26.22%. The median time between surgeries was 5.5 years. Histological evolution to high-grade glioma was detected in 22.85% of cases (16/70). Permanent mild deficits were observed in 3.08% of cases.

**Conclusions.** This multicenter study confirms the results of previous studies investigating surgical management of iLGGs and thereby strengthens the evidence in favor of early surgery for these lesions.

## Key Points

- Lower preoperative tumor volume and higher extent of resection in iLGGs are strongly associated with survival benefits.
- Tumor recurrence occurred in 38.73% of patients. iLGGs are not indolent, however, they are progressive lesions that can benefit from early surgery.

## Importance of the Study

In current literature, the optimum management for incidental low-grade gliomas (iLGGs) is debated and poorly documented, mainly due to the rarity of iLGGs and the difficulty in long-term follow-up. A multicenter study approach was adopted to overcome this limitation. In this clinical setting important questions arise: Are iLGGs indolent lesions? Which is the best treatment, the "wait and see" approach or early surgery? In this investigation, based on the largest cohort of surgical iLGGs, 10-year estimated overall survival (OS) was 93.2%, a result significantly higher than OS for sLGGs. Preoperative tumor volume was the sole independent predictor of OS and was negatively associated with extent of resection (EOR). The tumor recurrence (TR) delay was mainly influenced by early surgery. TR was detected in 38.73% of patients during follow-up, highlighting that iLGGs cannot be considered indolent lesions, but rather slowly developing tumors and thus greatly supporting the importance of early surgery.

Diffuse low-grade gliomas (LGGs) are a heterogeneous population of intrinsic brain tumors in which the natural history of the pathology is characterized by a slow and continuous growth along the white-matter pathway with a consequent intrinsic high tendency for recurrence and malignant transformation.[1,2] Incidental low-grade gliomas (iLGGs) represent the clinically silent phase of glioma evolution. At this biological point, the gliomas become visible at magnetic resonance imaging (MRI), while the patient remains asymptomatic. These tumors represent an extremely rare clinical subgroup of LGGs, in which the incidence ranges between 0.04% and 0.2% in the general population.[3]

Interestingly, iLGG size and growth patterns could explain why white-matter status does not markedly differ with respect to healthy controls.[4] In addition, from a neuropsychological perspective, iLGG patient performance is still within the normal range, although some neuropsychological scores are borderline, suggesting possible pathological development upon tumor growth.[5] Importantly, iLGGs invariably show continuous growth along white-matter pathways, ultimately becoming symptomatic tumors over a median interval of 48 months.[2,6–8] In sum, the natural history of iLGGs is characterized by slow and continuous growth along white-matter pathways with intrinsic tendency for progression with malignant transformation.[1,2]

Although early and maximal resection is widely recognized as the first-line treatment for symptomatic LGGs (sLGGs), the dilemma of clinical management of iLGGs has become a topic of increasing interest and debate.[6,7,9–22] Over the past decade, the approach to management of iLGGs has begun to shift. Traditionally the approach to iLGGs has been a "wait and see" approach, where surgery is deferred until the patient becomes symptomatic or develops MRI features suggestive of transformation to high-grade gliomas (HGGs). A number of groups have pushed the surgical boundaries for iLGGs with early intervention while the patient remains asymptomatic,[6,7,21–23] this strategy has been termed early surgery. The early surgery approach is supported by an increasing number of studies that have demonstrated greater extent of resection (EOR) and longer survival for iLGGs in comparison with sLGGs.[7–9,14,22] Due to the rarity of iLGGs and difficulty in long-term follow-up, prospective and retrospective studies clarifying questions regarding optimal management for these tumors are lacking.[1,9,13,24] Thus, we set out to identify the factors that influence outcome and survival for patients that underwent early surgery for iLGGs in a large multicenter study population based on data collected from 4 specialized neurooncological centers.

## Materials and Methods

### Data Collection

We analyzed a shared co-operative retrospective database of 267 adult patients surgically treated for iLGG from 4 specialized surgical oncological centers.

In our consecutive cohort, the time period was from December 1998 to June 2019.

The selected cases were defined as iLGG when a glioma was found on MRI imaging studies obtained for reasons unrelated to the underlying tumor such as trauma, headache without associated mass effect, other neurological or neurosurgical workup or research studies.

Three different approaches were adopted as indications for selecting surgery:

1. Detection of tumor volume evolution at 2 serial MRI follow-up (Montpellier, San Francisco).
2. Detection of preoperative hydrogen-magnetic resonance spectroscopy (H-MRS) suggestive for LCG with a reduction of N-acetyl aspartate (NAA) peak and a slight or moderate increase of the choline peak (Udine).
3. MRI images that were highly suggestive of LGG and patient preference for rapid intervention (Calgary, San Francisco).

The collected data included age, sex, neurological symptoms, neuroimaging findings (EOR), patient clinical postoperative outcomes, and molecular profiles.

The inclusion criteria were:

- Age ≥18 years;
- No previous surgery;
- Supratentorial hemispheric location;
- No preoperative chemo- or radiotherapy;
- No clinical symptoms related to the tumor (eg, seizure) occurred from the initial diagnosis to the surgical procedure;

- Histopathological diagnosis of World Health Organization (WHO) grade II gliomas;
- Objective evaluation of preoperative tumor volume and EOR on MRI images in DICOM format based on 3D T2-FLAIR weighted MRI sequences;
- Availability of data about post-surgery neurological and clinical status.

Needle biopsies were excluded from the study.

Considering that the study was retrospective, written consent to participate in the study was not applicable. Written informed consent was obtained for surgery and each Center conducted the study in accordance with the local Hospital Ethics Committee and/or IRB (protocol IN.0036567/P/GEN/EGAS, ID study 2540 Comitato Etico Unico Regionale del Friuli Venezia Giulia, Italy; IRB# 15-17500 University of California, San Francisco, USA; No. IRB_MTP_2020_07_202000563 of the University Hospital of Montpellier, France; REB 16-1467 Health Research Ethics Board of Alberta Cancer Committee at the University of Calgary, Canada).

### Patient Outcome Measurements

Neurological examinations were performed before surgery, after surgery at discharge, and 6 months after surgery. Neurological morbidity was defined by tracking new-onset deficits related to motor, sensory, visual, and language function.

Postoperative neurological deficits were graded as mild (minimal, unnoticeable deficit), moderate (deficit interfering with functions but potentially reversible), or severe (deficit that significantly disables functions). Transient deficits were defined as those that appeared after surgery and resolved within the 6-month follow-up period. Patients without clinical improvement at the 6-month follow-up examination were considered to have a permanent deficit.

In case of tumor recurrence (TR), all patients were discussed at a multidisciplinary local tumor board, and the treatment strategy was agreed upon by neurosurgeons, neuro-oncologists, and radiation oncologists.

### Tumor Volume Analysis

The volumes were all calculated on 3D T2-FLAIR weighted MRI sequences, but they were performed locally and the sites had some differences in their practice.

At UCSF, tumor volumes and EOR were calculated from the pre- and immediate postoperative 3D volumetric T2-FLAIR sequences by using the Brainlab Elements SmartBrush tool (version 2.6) by 3 reviewers with a blinded validation of a subset of volumes by an independent investigator. For the analysis validated Custom in-house software written in C and Matlab was used.[7]

For the other sites, EOR and postoperative tumor residuals were determined on the 3-month postoperative MRI. Tumor volumes were computed onto 3D volumetric T2-FLAIR MRI sequences with manual segmentation by using validated dedicated software (Myrian, Intrasense, Montpellier, France, Osirix/Horos Calgary, and Udine).[6,21,22] In these 3 last centers, the volumetric analysis was performed by 2 blinded investigators. Intraoperative MRI was used only in Calgary Center.

EOR was evaluated by using 3D T2-FLAIR weighted MRI axial images as follows: (preoperative tumor volume – postoperative tumor volume)/preoperative tumor volume), as previously described.[25]

Tumor resection was considered gross total resection (GTR) when EOR was ≥90%.[26] The resection was also classified in accordance with the postoperative residual tumor volume (RTV) as follows[26]:

1. Supratotal: for tumor resection beyond T2-FLAIR MRI borders;
2. Complete: for RTV = 0 $cm^3$;
3. Near total: for RTV < =5 $cm^3$;
4. Subtotal: for RTV <= 25 $cm^3$;
5. Partial: for RTV > 25 $cm^3$.

### Intraoperative Surgical Protocol

Surgical procedures were conducted under cortical and subcortical white-matter brain mapping, according to the intraoperative techniques previously described.[6,7,21,22] The main goal of surgery was to resect the maximum volume of T2-FLAIR MRI abnormality as safely possible.

## Histological and Molecular Analysis

Histological and molecular data were retrospectively analyzed according to the 2016 WHO classification.[27]

Immunohistochemistry (IHC) for Ki67 and IDH1 R132H, fluorescence in situ hybridization (FISH) to evaluate 1p/19q codeletion and isocitrate dehydrogenase (IDH1/2) genes were performed. All patients underwent IDH1/2 mutation research by immunochemistry.

Immunochemistry-negative patients underwent molecular biologic evaluation (currently next-generation sequencing [NGS]) of both IDH1 and IDH2 genes in order to detect less common mutations.

NGS was available in the different neurosurgical Centers at varying time points from 2010.

### Statistical Analysis

Characteristics of the study population were described using the median and range for continuous variables and percentages for categorical variables.

Data were tested for normal distribution using the Shapiro-Wilk test. Student *t* test or Mann-Whitney *U* test were used to compare continuous variables between groups, as appropriate. Comparisons of categorical variables were performed by chi-square analysis or Fisher's exact test, as appropriate.

The overall survival (OS) was defined as the time between the dates of surgery to death. Tumor recurrence (TR) was defined as time between first and second surgical procedure and/or tumor relapse at last MRI follow-up analysis.

ANOVA analyses between cases were performed to compare clinical, volumetric, and molecular distribution amongst patients with and without postoperative deficits.

Survival analysis was done using Cox proportional hazard models, after the proportional hazards assumption had been verified using the survival package (v3.2.3). In univariate analysis, variables considered as possible prognostic factors were age, sex, KPS score, preoperative tumor volume, tumor location, tumor side, EOR, postoperative RTV, IDH1/2 mutation, and 1p/19q codeletion on 258 patients from the complete cohort of 267. The optimal EOR cutoff value to stratify high- and low-risk OS groups was estimated using the log-rank test. Results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

All analyses were conducted using Stata/SE (version 14.0 Stata Corp.) for Mac and RStudio (R version 3.6). All 2-tailed statistical significance levels were set at $P < .05$.

## Results

iLGGs were defined as gliomas found on imaging studies obtained for a reason unrelated to the underlying tumor.

ILLs were detected after MRI examination requested for headaches (33.33%), other medical reasons included unrelated neurological deficits (25.84%) or head trauma (13.10%).

Regarding patients with headache, none of them in this cohort, had MRI evidence of mass effect and/or signs of raised intracranial pressure.

Additionally, their neurological examination and history were unremarkable for clinical signs of intracranial hypertension and were absent at preoperative examination (no vomiting, no nausea, no changing of pain with body position, no papilledema, no other neurological symptoms).

When information on the headache quality and character were available, the description was consistent with a migraine. In this subgroup, the median preoperative tumor volume was 20 $cm^3$.

The baseline demographic, clinical, histological, and radiological characteristics of the study population are summarized in Table 1.

Postoperative volumetric data and molecular class data were accessible in 258 and 232 cases, respectively.

### Volumetric Analysis

The median preoperative tumoral volume, measured on 3D T2-FLAIR MRI images, was 15 $cm^3$. The median EOR achieved was 95%. The median postoperative RTV was 0 $cm^3$ (range 0-87).

Distribution of molecular class among the EOR class did not demonstrate statistical differences ($P = .19$).

We found a negative association between preoperative tumor volume and the EOR achieved ($rs = –0.44$, $P < .001$) (Figure 1A).

The larger the preoperative tumor volume, the smaller the EOR achieved. In addition, a positive association between preoperative tumor volume and postoperative RTV ($rs = 0.54$, $P < .001$) was detected. No association was identified between type of surgery (awake versus general anesthesia) and EOR achieved ($r = –0.06$, $P = .927$).

### Postoperative Course

Data regarding the postoperative transient and long-term follow-up deficits were available in 263/267 and 259/267 cases, respectively. Transient and permanent deficits were recorded in 73/263 (27.76%) and 8/259 (3.08%) patients (Table 2).

Seizure outcome data were recorded in 238 cases. Early postoperative seizure was observed in 5.88% of cases (14/238), among them, only 3 patients developed postoperative seizures (1.26%).

Results indicated that there was a significant relationship between the lesion side and transient postoperative deficit (chi-square with 1 degree of freedom = 6.242, $P = .009$), meaning that these deficits were more frequent following surgery in the left hemisphere. Specifically, there were 34.02% transient deficits in left iLGGs and 20.16% in right iLGGs.

There was no significant relationship between the lesion side and permanent postoperative deficit (chi-square with 1 degree of freedom = 0.216, $P = .73$).

With respect to lesion site, a significant relationship was not demonstrated between lesion site and either transient postoperative deficit (chi-square with 1 degree of freedom = 4.362, $P = .115$, n.s.) or permanent postoperative deficit (chi-square with 1 degree of freedom = 7.435, $P = .115$).

The relationship between lesion volume and transient postoperative deficit, with point-biserial correlation coefficient rpb of –.125, was significant ($P = .047$), while for the permanent postoperative deficit, there was only a trend towards significance (rpb, is –.122, $P = .053$).

### Molecular Class

Clinical and radiological variables of the iLGG study population were stratified according to molecular class. Patients belonging to the IDH wild-type (IDH-wt) subgroup were characterized by a median preoperative tumor volume of 17.3 $cm^3$, mean age of 41.76 years, and median EOR of 95.1%.

For patients with IDH1/2 mutation (IDH-mt) the results were 29.5 $cm^3$, 35.68 years, and 95.9%, respectively. For the IDH-mt subgroup also with 1p19q codeletion, the results were as follows: preoperative tumor volume of 29.0 $cm^3$, mean age of 41.61 years, and a median EOR of 94.1%.

### Postoperative Treatments

Data were available in 250 cases. Postoperative adjuvant treatments were delayed in the majority of ILGGs (90%).

Immediate postoperative adjuvant treatments were administered in low-grade high-risk patients with less than GTR and over 40 years in UCSF, Udine, and Calgary.

Overall, 15 patients (5.62%) received adjuvant chemotherapy following initial surgical resection and 10 patients

**Table 1** Baseline Characteristics of the Study Population: Characteristics of the Study Population Are Described Using Means ± SD or Median and Range for Continuous Variables, Number of Cases With Relative Percentages Reported in Parentheses for Categorical Variables

| Variables | Value (No. and %, mean ± SD or median and range) |
|---|---|
| No. of patients | 267 |
| Sex | |
| Female | 155 (58.05%) |
| Male | 112 (41.95%) |
| Age | 39.19 yr (18-71) |
| Tumor side | |
| Left | 119 (44.57%) |
| Right | 148 (55.43%) |
| Tumor site | |
| Frontal | 140 (52.44%) |
| Insular | 50 (18.73%) |
| Temporal | 41 (15.35%) |
| Parietal | 29 (10.86%) |
| Cingulate gyrus | 2 (0.75%) |
| Occipital | 3 (1.12%) |
| Other (thalamus and parietal-occipital) | 2 (0.75%) |
| Type of surgery | |
| Awake | 174 (65.17%) |
| General anesthesia | 93 (34.83%) |
| Preoperative tumoral volume computed on 3DT2-FLAIR MRI images, $cm^3$ (data available in 258 cases) | 15 (1-189) |
| Preoperative tumor volume Subgroups | |
| <=15 $cm^3$ | 136 (86.07%) |
| 15-30 $cm^3$ | 56 (35.44%) |
| >=30 $cm^3$ | 66 (41.77%) |
| Preoperative KPS | 97.7 (50-100) |
| Postoperative RTV computed on 3DT2-FLAIR MRI images, $cm^3$ (data available in 258 cases) | 0 (0-87) |
| Postoperative RTV =0 $cm^3$ | 159 (61.62%) |
| Postoperative RTV <=5 $cm^3$ | 66 (25.58%) |
| Postoperative RTV >6 $cm^3$ | 33 (12.80%) |
| EOR % (EOR data are available in 258 cases) | 61.87 % (50-supratotal) |
| EOR >100% (supratotal) | 24 (9.3%) |
| EOR = 100% | 135 (52.32%) |
| EOR < 100% | 99(38.38%) |
| Molecular class (data available in 232 cases) | |
| Diffuse astrocytoma IDH1/2 mutated | 83 (35.78%) |
| Diffuse astrocytoma IDH1/2 wild-type | 34 (14.65%) |
| Oligodendroglioma | 115 (49.57%) |
| Time between diagnosis and surgery (mo) | 22 (1-170) |
| Hospitalization length (days) | 4 (1-12) |
| Median follow-up after surgery (mo) | 88 (6-258) |
| Reason to perform MRI | |
| Headache | 89 (33.33%) |
| Head trauma | 35 (13.10%) |
| Other medical reasons included unrelated neurological deficits | 69 (25.84%) |
| Otolaryngology disorders | 49 (18.35%) |
| MRI follow-up for other neurosurgical pathologies | 13 (4.87%) |
| MRI research studies | 9 (3.37%) |
| NA | 3 (1.12%) |
| Time between first and second surgery (yr) | 5.5 |

**Abbreviations:** EOR, extent of resection; IDH, isocitrate dehydrogenase; MRI, magnetic resonance imaging; NA, not applicable; No., number of patients; RTV, residual tumor volume.

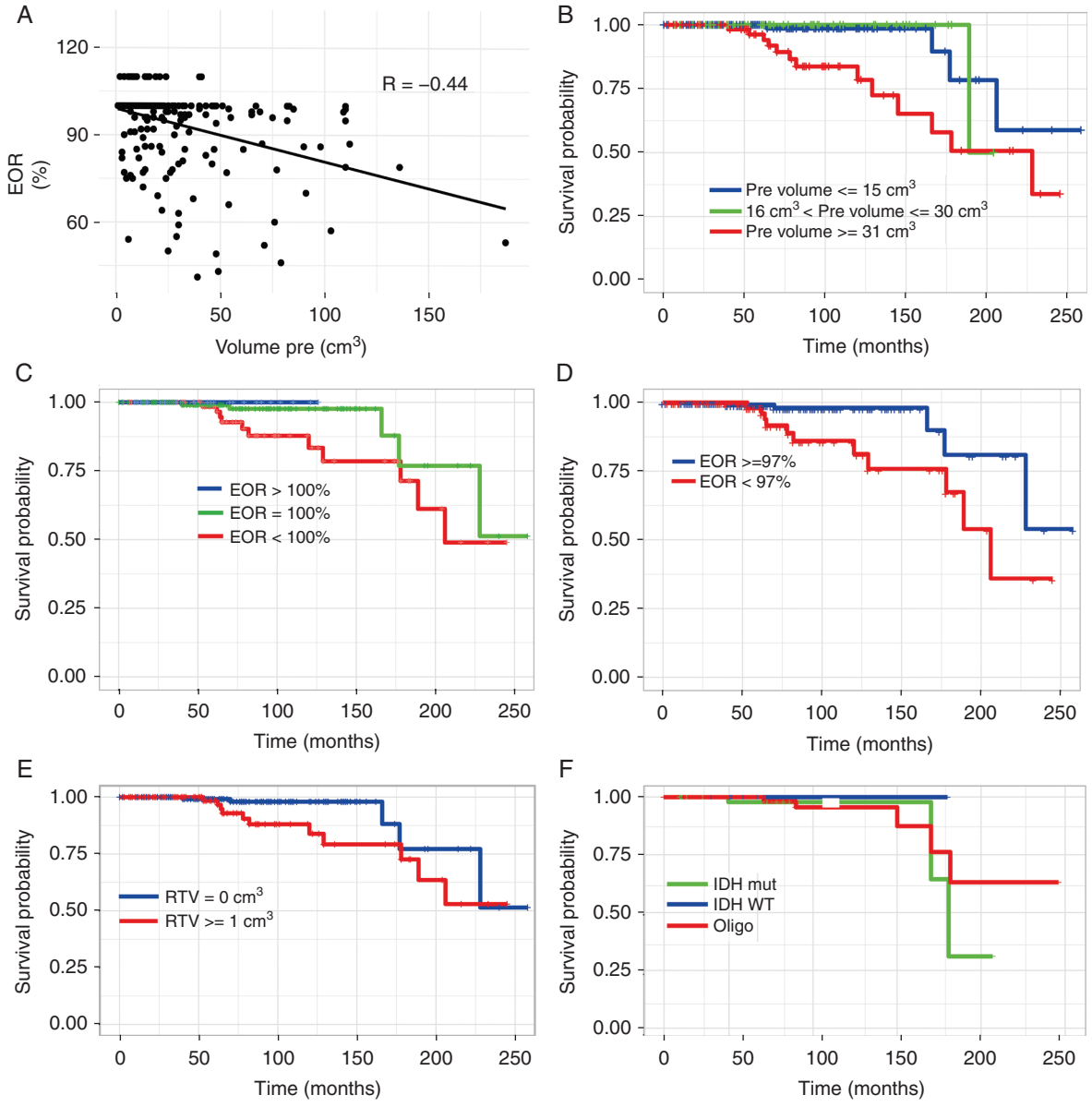


**Fig. 1** (A) Graph showing the negative association between preoperative tumor volumes and EOR achieved ($rs = –0.44$, $P < .001$). Higher preoperative tumor volume value suggests a greater propensity of the tumor to have a diffuse growing pattern and consequently to be less resectable. (B) OS in iLGGs stratified according to preoperative tumor volume (HR = 1.02; 95% CI = 1.01-1.03; $P = .001$). (C) OS in iLGGs stratified according to the EOR (HR = 0.97; 95% CI = 0.94-1.0; $P = .037$). No death event occurred in patients with supratotal resection. (D) OS in iLGGs in accordance with the EOR cutoff value able to stratify high- and low-risk OS groups (HR = 4.09; 95% CI = 1.41-11.9; $P = .01$). (E) OS stratified according to postoperative RTV (HR = 2.93 [95% CI 1.00-8.60]; $P = .05$). (F) OS stratified according to WHO-defined categories. No deaths occurred among patients belonging to IDH-wt subgroup. No survival benefit was observed between IDH-mt iLGGs and IDH-mt/1p19q codel iLGGs ($P = .2$; HR = 2; 95% CI = 0.74-5.43). Abbreviations: CI, confidence interval; EOR, extent of resection; HR, hazard ratio; IDH, isocitrate dehydrogenase; iLGGs, incidental low-grade gliomas; OS, overall survival; RTV, residual tumor volume.

(3.74%) received adjuvant radiotherapy following initial surgical resection.

In Montpellier subgroup, none of the patients received early postoperative adjuvant treatments. In detail, patients with incomplete resection had a residual tumor less than 10 $cm^3$ and were younger than 40 years in all cases except one.

Therefore, these patients were followed closely postoperatively with imaging occurring between 3- and 6-month interval. An adapted second stage of treatment was planned in case of volumetric expansion.

## Survival Analysis

For the entire study population, the OS rate was 92.41%. The estimated 5- and 10-year OS rates were 98.09% and 93.2%, respectively.

Data regarding univariate analysis are summarized in Table 3.

**Table 2** Patients' Postsurgical Status, Relative to Transient and Permanent Changes, and Information About Tumor Recurrence and Post-Surgery Treatments. Each Patient Can Have One, or a Combination of These Factors

| Parameters | No. of Cases (% value) |
|---|---|
| Transient deficits | |
| Total cases | 77/263 (32.63%) |
| Mild language deficits | 42 (15.73%) |
| SMA syndrome | 13 (4.94%) |
| Motor deficits | 7 (2.66%) (2 severe motor deficit 0/5, 5 mild motor deficits 4/5) |
| Visual field deficits | 4 (1.52%) (2 homonymous hemianopsia, 2 superior quadrantopsy) |
| Facial drop | 4 (1.52%) |
| Spatial neglect syndrome | 3 (1.14%) |
| Upper limb coordination deficits | 2 (0.76%) |
| Decrease in psycho-motor speed | 1 (0.38%) |
| Gerstman's syndrome | 1 (0.38%) |
| Permanent deficits | |
| Total cases | 8/259 (3.08%) |
| Mild dysarthria | 2 (0.78%) |
| Facial weakness | 1 (0.39%) |
| Hemiparesis (3/5) | 2 (0.78%) |
| Mild hyposthenia | 1 (0.39%) |
| Upper quadrantanopsy | 2 (0.78%) |
| Treatment at tumor recurrence | |
| Second surgery | 70/267 (26.22%) |
| Chemotherapy | 32/267 (11.98%) |
| Chemo and radio | 6/267 (2.2%) |
| Histological diagnosis at second surgery | |
| WHO grade II | 47/70 (67.15%) |
| WHO grade III | 9/70 (12.85%) |
| WHO grade IV | 7/70 (10%) |
| NA | 7/70 (10%) |
| Treatment after second surgery | |
| None | 26 (37.14%) |
| CT | 11 (15.71%) |
| RT | 2 (2.86%) |
| CT + RT | 27 (38.57%) |
| NA | 4 (5.72%) |
| Time between first and second surgery<br>Months | 66.71 (9-215)<br>5.5 yr |

**Abbreviations:** CT, chemotherapy; NA, not applicable; RT, radiotherapy; SMA, supplementary motor area.

A better prognosis was detected in patients with lower preoperative tumor volume ($P$ = .001) (Figure 1B) and higher EOR ($P$ = .037) (Figure 1C).

The optimal EOR cutoff value to stratify high- and low-risk OS groups was 97%.

Patients belonging to subgroup with an EOR lower than 97% had a higher risk of poor prognosis (HR = 4.09; 95% CI = 1.41-11.9; $P$ = .01) (Figure 1D).

Moreover, patients with lower postoperative tumoral volume demonstrated a tendency for improved OS ($P$ = .083). This could be due to the higher percentage of cases with supratotal or complete resection. The impact of RTV on OS was thus analyzed as dichotomous variable: patients with supratotal and complete resection versus those with RTV >= 1 $cm^3$ ($P$ = .050, Figure 1E).

All iLGG patients with supratotal resection remain alive at last follow-up. Overall, molecular class did not affect the survival in the study population. No deaths occurred among patients belonging to IDH-wt subgroup. No survival benefit was observed between IDH-mt iLGGs and IDH-mt/1p19q codel iLGGs ($P$ = .2; HR = 2; 95% CI = 0.74-5.43) (Figure 1F).

Interestingly, all patients belonging to the IDH-wt molecular class were also alive at last follow-up. The type of treatments selected after first surgery (none, versus radiotherapy [RT] or chemotherapy [CT]) did not affect OS in the whole population ($P$ = .129).

The multivariate Cox analysis only identified preoperative tumor volume as an independent predictor of OS ($P$ = .006) (Table 3).

## Tumor Recurrence

The estimated TR rate at 5 and 10 years was 36.9% and 57.7%, respectively. TR was detected in 40.44% of cases (108 patients).

Among them, 70 patients (26.21%) received reoperation first at recurrence, 32 patients (11.98%) received chemotherapy first at recurrence and 6 patients (2.2%) received radiotherapy first at recurrence. No association was found between TR and molecular class type ($r$ = –0.037; $P$ = .558) or EOR achieved ($r$ = –0.166; $P$ = .348).

Among patients with TR, second surgery was performed in 70 cases (71.4%).

Overall 16 on 255 patients evolved in HGG during the disease history (6.27%)

Data regarding treatment at TR are reported in Table 2.

Comparison of demographic and radiological data between iLGGs with and without TR during the oncological history was performed. The preoperative tumor volume was 22.58 $cm^3$ and 31.21 $cm^3$ in patients without TR and with TR, respectively ($P$ = .006).

With regard to patients without TR, average age and median EOR were 39.86 years and 94.86%, while patients with TR showed an average age of 38.39 years and median EOR of 93.81% ($P$ = .284, $P$ = .910). TR was significantly more frequent in patients with higher preoperative tumor volume ($P$ = .023) and right-sided lesions ($P$ = .003).

The impact of time between diagnosis and surgery and risk of TR development was also explored by Cox analysis. When considering the differences between patients who underwent surgery within 6 months (true early surgery) and patients surgically treated after 6 months, our results highlighted that patients that underwent earlier surgery had less risk of TR compared to those that had surgery later ($P$ = .035; HR = 1.62; 95% CI = 1.03-2.53).

**Table 3** Predictors of OS at Univariate and Multivariate Analyses

| Variable | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | Odds Ratio | 95% CI | *P*-value | Odds Ratio | 95% CI | *P*-value |
| Age (yr) | 1.017 | 0.977-1.058 | .42 | | | |
| Sex | | | | | | |
| Male | 1 | | | 1 | | |
| Female | 0.40 | 0.16-0.98 | **.045** | 0.22 | 0.14-0.88 | .42 |
| Tumor side | | | | | | |
| Left | 1 | | | | | |
| Right | 1.15 | 0.46-2.85 | .80 | | | |
| Tumor site | | | | | | |
| Frontal | 1 | | | | | |
| Parietal | 1.74 | 0.48-6.38 | .40 | | | |
| Temporal | 1.50 | 0.41-5.51 | .50 | | | |
| Insula | 0.58 | 0.07-4.62 | .60 | | | |
| Preoperative KPS | 0.98 | 0.89-1.08 | .70 | | | |
| Preoperative tumoral volume, $cm^3$ Continuous variable | 1..02 | 1.01-1.03 | **.001** | 1.03 | 1.01-1.05 | **.006** |
| Preoperative tumoral volume, $cm^3$ | | | | | | |
| 0-15 | 1 | | | | | |
| 15-30 | 0.58 | 0.06-5.18 | **.60** | | | |
| >30 | 4.47 | 1.44-13.8 | **.009** | | | |
| % EOR Continuous variable | 0.97 | 0.94-1.0 | **.037** | 0.95 | 0.90-1.01 | .12 |
| Postoperative RTV $cm^3$ Continuous variable | 1.03 | 1.00-1.06 | .083 | | | |
| Postoperative RTV $cm^3$ | | | | | | |
| Supratotal and complete resection | 1 | | | 1 | | |
| RTV ≥1 $cm^3$ | 2.93 | 1.00-8.60 | **.050** | 1.09 | 0.27-4.36 | .95 |
| Molecular class | | | | | | |
| Oligodendroglioma | 1 | | | | | |
| Diffuse astrocitoma IDH1/2 mutated | 2 | 0.74-5.43 | .20 | | | |
| Early adjuvant treatment after surgery | | | | | | |
| Yes vs No | 0.99 | 0.67-5.43 | .19 | | | |

**Abbreviations:** CI, confidence interval; EOR, extent of resection; MRI, magnetic resonance imaging; *P*-value, level of marginal significance; RTV, residual tumor volume.
Table showing the influence of different factors on the OS rates as per univariate survival analysis and multivariate analysis ($P < .05$ at log-rank test). Bold values represent statistical significant results ($P < .05$). Tumor volume analysis was performed on 3D T2-FLAIR MRI. Patients belonging to IDH1/2 wild-type molecular class were not included in survival analysis because no deaths occurred in this subgroup.

At multivariate Cox analysis, the time between diagnosis and surgery was confirmed as independent predictor for TR (Table 4).

## Discussion

Diffuse LGGs are a heterogeneous population of intrinsic brain tumors in which the natural history is characterized by initially indolent growth with significant tendency for recurrence and malignant transformation.[1,2,8,23,28–33] There is a paucity of data regarding management of iLGGs mainly due to the rarity of these tumors and difficulty in their long-term follow-up.[1,9,13] While early and maximal, safe resection is currently the first-line treatment for sLGGs,[23,28–33] the optimal management for iLGGs has only begun to be addressed.[6,7,9–22] We set out to develop and strengthen an evidence-based approach for management of iLGGs and improve our understanding of the role for early surgery in their treatment. Given the rarity of these tumors, a multicenter study approach was employed in order to generate the largest and most robust dataset of iLGGs to date. Based on this investigation of 267 adult patients that underwent surgery for supratentorial iLGGs, we were able to identify and analyze the factors that influence

**Table 4** Predictors of Tumor Recurrence at Univariate and Multivariate Analyses

| Variable | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | Odds Ratio | 95% CI | *P*-value | Odds Ratio | 95% CI | *P*-value |
| Age (yr) | 1.00 | 0.98-1.03 | .50 | | | |
| Sex | | | | | | |
| Male | 1 | | | | | |
| Female | 0.94 | 0.64-1.38 | .70 | | | |
| Tumor side | | | | | | |
| Left | 1 | | | | | |
| Right | 0.71 | 0.48-1.04 | .075 | | | |
| Tumor site | | | | | | |
| Frontal | 1 | | | | | |
| Parietal | 1.16 | 0.56-2.43 | .70 | | | |
| Temporal | 1.52 | 0.77-3.0 | .20 | | | |
| Insula | 1.73 | 0.85-3.50 | .13 | | | |
| Preoperative KPS | 1.04 | 0.98-1.10 | .20 | | | |
| Preoperative tumoral volume, $cm^3$ Continuous variable | 1.02 | 1.00-1.02 | **.006** | 1.0 | 0.99-1.01 | .5 |
| Preoperative tumoral volume, $cm^3$ | | | | | | |
| 0-15 | | | | | | |
| 15-30 | 1.62 | 0.99-2.64 | .053 | | | |
| >30 | 1.31 | 0.72-2.42 | .10 | | | |
| % EOR Continuous variable | 1.00 | 0.98-1.02 | .90 | | | |
| Postoperative RTV $cm^3$ Continuous variable | | | | | | |
| Postoperative RTV $cm^3$ | 1.02 | 1.0-1.05 | .074 | | | |
| Supratotal and complete resection | 1 | | | | | |
| RTV ≥1 $cm^3$ | 0.95 | 0.63-1.43 | .8 | | | |
| Molecular class | | | | | | |
| Oligodendroglioma | 1 | | | | | |
| Diffuse astrocytoma IDH1/2 mutated | 1.39 | 0.85-2.28 | .20 | | | |
| Time of surgery | | | | | | |
| </= 6 months | 1 | | | 1 | | |
| >6 months | 1.62 | 1.03-2.53 | **.036** | 1.67 | 1.03-2.63 | **.028** |

**Abbreviations:** CI, confidence interval; EOR, extent of resection; MRI, magnetic resonance imaging; *P*-value, level of marginal significance; RTV, residual tumor volume.
Table showing the influence of different factors on the OS rates as per univariate survival analysis and multivariate analysis ($P < .05$ at log-rank test). Bold values represent statistical significant results ($P < .05$). Tumor volume analysis was performed on 3D T2-FLAIR MRI.

postoperative outcome and survival in this patient population. Our results are comparable with those published in this field (Table 5).

Overall, our study population was characterized by patients of relatively young age (median 35.5 years), with small preoperative tumor volumes 15 $cm^3$) and low postoperative RTV. Small tumor volume at diagnosis was not surprising and is almost certainly correlated with the absence of symptoms when tumors were discovered. Small tumor size notwithstanding, excellent extents of resection, including supratotal and total resection, were achieved in 61.62% of cases. It is important to note that iLGGs have been demonstrated to be more amenable to complete resection when compared to sLGGs, which is in accordance with the conclusions of other authors who support the role of early surgery as the first option in iLGG management.[1,6,7,11–14,21,22]

Specifically, the median preoperative iLGG volume was significantly smaller in comparison with the preoperative sLGG volume, as previously demonstrated in comparative series (12 $cm^3$ versus 46 $cm^3$).[7,9,22] A smaller preoperative tumor volume normally seen in iLGGs implies a more likely possibility of obtaining a complete resection when compared to the larger sLGGs and this study provides more evidence for this.

**Table 5** Literature Review of Principal iLGG Surgical Studies

| Authors | No. of Cases | Comparison With Symptomatic Group | Histological Diagnosis | Preoperative Tumoral Volume ($cm^3$) | EOR | PFS | Dead Patients | MPFS | Postoperative Deficits | Second Surgery | Median FU (yr) | Risk Factors From Comparative Analysis With Symptomatic Group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pallud et al 2010[8] | 47 | Yes<br>47 incidental on 1249 (3.76% of cases) | Astrocytoma 7<br>Oligodendroglioma 31<br>Oligoastrocytoma 9 | 17.2 | GTR = 14<br>STR = 12<br>PR = 1<br>Biopsy = 16 | 68 mo (8-152) | 4 | NA | NA | NA | 6.6 | iLGGs have a female predominance ($P = .05$), smaller initial tumor volumes ($P < .001$), lower incidence of contrast enhancement ($P = .009$), and are more likely to undergo gross total surgical removal ($P < .001$) |
| Potts et al 2012[9] | 35 | Yes<br>35 incidental on 197 (17.76% of cases) | Astrocytoma 16<br>Oligodendroglioma 12<br>Oligoastrocytoma 6<br>Ganglioglioma 1 | 20.2 | GTR = 21<br>STR = 14 | 29 (5-70) | 1 | n/a | 3 recorded operative morbidities among patients with incidental lesions (8.6%) | 6 | 5.1 | iLGGs have a significantly lower preoperative tumor volumes than sLGGs(20.2 vs 53.9 $cm^3$, $P = .001$), less likely to have tumors in eloquent locations (14.3% vs 61.9%, $P = .001$), and a higher prevalence of females (57.1% vs 36%, $P = .02$). In addition, patients with iLGGs were also more likely to undergo gross total resection (60% vs 31.5%, $P = .001$) and had improved overall survival on Kaplan-Meier analysis ($P = .039$) |
| Duffau et al 2012[11] | 11 | No | Glioma WHO grade II | 32.6 | sTR = 3<br>GTR = 4<br>STR = 14 | 64<br>28-73 | 0 | NA | Transient = 7<br>Permanent = 0 | NA | 1.7 | NA |
| Zhang et al 2014[14] | 23 | Yes<br>23 incidental on 196 (11.73% of cases) | Astrocytoma 6<br>Oligodendroglioma 6<br>Oligoastrocytoma 11 | 23.8 | GTR = 21<br>STR = 0<br>PR = 2 | 85<br>34-108 | 5 | 22<br>95.6% | NA | 6/23 | 9.3 | iLGGs had higher preoperative KPS ($P < .001$), smaller tumor volume ($P = .014$), lower frequency of eloquent areas involvement ($P < .001$) and higher rate of complete resection ($P = .037$) comparing to those with sLGGs |
| Lima et al 2016[18] | 19 | No | Glioma WHO grade II | 51.4 | sTR = 5<br>GTR = 4<br>STR = 7<br>PR = 2 | 28<br>3-79 | 0 | NA | Transient = 7<br>Permanent = 0 | NA | 5.1 | NA |
| Opoku-Darko et al 2018[20] | 34 | No | Astrocytoma IDH1/2 mutated 12<br>Oligodendroglioma 16<br>Astrocytoma IDH wild-type 3<br>Others 3 | 36.8 | EOR 100%= 8<br>EOR75-99%= 11<br>EOR <75% = 15 | | | | Transient = 1<br>Permanent = 1 | | 5.1 | NA |
| Ius et al 2020[22] | 34 | Yes<br>34/223<br>10.2% | Astrocytoma IDH1/2 mutated 28<br>Oligodendroglioma 14<br>Astrocytoma IDH wild-type 4 | 16 $cm^3$ | EOR 100% = 34 | 4/34<br>78-mo<br>38-98 | 0 | NA | Transient = 3<br>Permanent = 0 | 4 | 5.8 | iLGGs had higher preoperative Karnofsky performance scale (KPS) ($P = .003$), smaller tumor volume ($P = .0001$), lower frequency of eloquent areas involvement ($P = .0001$), and higher rate of complete resection ($P = .0001$) compared to those with sLGGs |

**Table 5** Continued

| Authors | No. of Cases | Comparison With Symptomatic Group | Histological Diagnosis | Preoperative Tumoral Volume ($cm^3$) | EOR | PFS | Dead Patients | MPFS | Postoperative Deficits | Second Surgery | Median FU (yr) | Risk Factors From Comparative Analysis With Symptomatic Group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gogos et al 2020[7] | 113 | Yes 113/657 17.2% | Astrocytoma IDH1/2 mutated 26 Oligodendroglioma 48 Astrocytoma IDH wild-type 11 | 22.5% | EOR 100% = 113 | | NA | 11 | Transient = 25 Permanent = 5 | | 6.6 | Complete resection of the FLAIR abnormality was achieved in 57% of patients with incidental lesions but only 23.8% of symptomatic lesions ($P < .001$), and the residual volumes were smaller for iLGGs (2.9 vs 13.5 $cm^3$, $P < .0001$). Overall survival was significantly longer for patients with incidental tumors (median survival not reached for patients with iLGGs vs 14.6 yr for those with sLGGs, $P < .0001$) |
| Boetto et al 2020[6] | 101 | No | Astrocytoma IDH1/2 mutated 28 Oligodendroglioma 36 IDH wild-type 13 Others 5 | 16 | Supratotal resection in all cases | NA | NA | | NA | NA | 3.2 | NA |
| Present study 2021 | 267 | No | Molecular data in 232 cases Astrocytoma IDH1/2 mutated 83 Oligodendroglioma 115 IDH wild-type 34 | 26 | EOR 100% = 135 Supratotal resection = 24 EOR <100% = 99 | NA | 47/70 (67.15%) | | Permanent deficits were detected in 3.01% of cases 6 mo after surgery | 16/70 (22.85%) | 7.3 | NA |

**Abbreviations:** EOR, extent of resection; FU, follow-up; GTR, gross total resection; iLGGs, incidental low-grade gliomas; MPFS, malignant progression-free survival; NA, not applicable; PFS, progression-free survival; PR, partial resection; sLGGs, symptomatic low-grade gliomas; STR, subtotal resection; sTR, supratotal resection.

EOR has been demonstrated to be an independent prognostic factor for OS and TR in iLGGs.[23,25,28–33] Based on these data, the management of iLGGs is moving towards an approach that includes early surgery and individualized oncological treatment.[6,7,21,22] Our study uncovered 3 interesting findings related to EOR. Firstly, a confirmation of survival benefit associated with low preoperative tumor volume and higher EOR. Secondly, a higher percentage of cases with supratotal or total resection (61.62%), lastly no deaths occurred in the small, supratotal resection subgroup.

Recent studies have reported that absolute RTV might be more relevant than the proportion of removed tumor in terms of prognosis, being the latter the expression of tumor burden.[26]

In this investigation, when assessing the correlation of survival rate-based resection as a percentage (EOR), the relationship appears slightly stronger compared to the RTV, which represents the absolute RTV in $cm^3$ (0.037 versus 0.050). This result reflects the lower preoperative tumor volume and RTV displaced by iLGGs in comparison to sLGGs. Indeed the postoperative RTV was <= 5 $cm^3$ in the majority of cases (61.62% of cases with RTV = 0 $cm^3$ and 25.58% of cases with RTV <= 5 $cm^3$). It is known that the postoperative RTV represents the tumor burden, however, considered alone, it may not be sufficient to define the biological behavior without an appropriate molecular stratification. Future prospective long-term studies based on integration of biological extensive information within each category of resection subgroup, in the context of both iLGGs and sLGGs, are thus needed to better understand this issue.

Supratotal resection is increasingly being advocated in LGGs in accordance with the principle of cytoreduction of residual infiltrating tumor cells at cavity margins with a presumed consequent reduction of their propensity for malignant transformation. Recently, Rossi et al published a large retrospective study based on a volumetric and molecular analysis of 460 presumptive LGGs. The authors demonstrated a prolonged progression-free survival (PFS) and longer OS in the supratotal resection subgroup, regardless of molecular subtype and tumor grade.[34] Although the practice for pursuing total versus supratotal resections varied amongst institutions, in this investigation, the fact that iLGG are smaller than sLGGs makes either total or supratotal resection safer and/or more feasible, which is likely advantageous given the improved outcomes shown with gross total or better resections.

The most intriguing finding based on our molecular data was that molecular class did not affect the prognosis in the study population. Surprisingly, in this investigation patients belonging to the IDH-wt molecular class had a good prognosis without a single death occurring during the follow-up period. IDH-wt grade II gliomas are a rare and heterogeneous entity with conflicting prognostic results.[35–38]

A recent retrospective study by Aibaidula et al reported that patients with IDH-wt LGGs display a survival similar to those patients with IDH1/2 wild-type glioblastoma.[35]

Conversely, other investigations have identified a smaller subgroup of IDH-wt LGGs with a more indolent course and long-term survival, especially those with isolated TERT promoter mutation.[36,38] The prognostic stratification of IDH-wt grade II gliomas is still under investigation, and the integration with other molecular factors is fundamental for an appropriate tumor evolution analysis.[38]

The degree of EOR affects the outcome of IDH-wt tumors, confirming the independent role of surgical resection, beyond the 3 molecular profiles considered (IDH1/2 mutation, IDH-wt, IDH1/2 mutation plus 1p19q codeletion). With regard to patients with IDH1/2 mutation, the presence of 1p19q codeletion did not affect the OS.

These results could of course be due to the small sample size, the limited observation time, and the lack of cIMPACT-NOW analysis.[36,39]

In addition, in this clinical context, it would be interesting to explore the mitogen-activated protein kinase (MAPK) pathway activation and CDKN2A mutation that has been proven to be a predictor of favorable patient outcome in pediatric glioma.[40,41]

Regarding the preoperative tumor volume, small values are likely associated with an earlier stage of tumor development with lower mutational burden and less progress along the pathway of transformation. Thus, each of our findings support the oncological benefit expected from removal of radiologically normal but microscopically infiltrated peritumoral tissue,[2,21,22] thereby providing more support for the early surgery approach aiming to achieve supratotal resection.

These results support the fact that maximal surgical resection is an important therapeutic factor per se to optimize prognosis, independently of the WHO 2016 molecular classification.[27]

The "wait and see" approach to management of iLGGs has been justified by the slow-growing nature of iLGGs, the absence of preoperative symptoms, and the potential risks of postoperative neurological deficits and/or seizure onset.[7,19] In our cohort, we observed a very low rate of permanent postoperative deficit in 3.08% of cases. Fortunately, most permanent postoperative deficits were not of major functional significance. Therefore, the theoretical risk of initiating epilepsy or causing permanent deficits does not represent an argument against early surgery in patients with iLGGs.

Not surprisingly, transient neurological deficits were more frequently encountered for lesions in the dominant hemisphere and for lesions in higher risk areas such as the insula and left temporal lobe. The postoperative deficits observed in this study reinforce previous results demonstrating such deficits tend to be related to potential tumor infiltration of subcortical language pathways, highlighting the importance of personalized preoperative surgical planning in the management of these patients.

These results further reinforce the proposal of early surgery for iLGGs in a more systematic manner.

The average time between imaging diagnosis and surgery in our cohort was 22 months, thus the term "early surgery" may not be appropriate in some patients.

Unfortunately, randomized trials evaluating the impact of early surgery versus a "wait and see" approach in patients with iLGGs are highly unlikely due to the rarity of this condition and a lack of equipoise, especially when MRI spectroscopy or MRI tumor growth analysis suggest a diagnosis of LGG. This limited class I evidence is a challenge for the field of neurosurgery. However, observational

studies have shown worse outcomes with the "wait and see" approach compared to early surgical intervention for patients with LCGs (incidental or symptomatic).[12]

Surgery was performed on the basis of patient preference, locoregional practice patterns, serial MRI scans demonstrating changes in tumor characteristics, tumor growth, and/or MRI spectroscopy suggestive of LGG, especially in patients with lesions less than 15 $cm^3$. The cohort can be considered homogeneous because surgery was performed in patients harboring iLGGs that were all and remained asymptomatic, even if time elapsed from imaging identification with a later surgery date. Investigating the growth rates of iLGGs that were observed, the UCSF group found that these tumors grow at a rate of 3.9 $cm^3$/year, although certainly some tumors grow much faster and given the low rate of complications. In this cohort, the risks of waiting for tumor growth seem to outweigh any perceived benefit.[7]

To investigate the relationship between time from diagnosis to surgery and TR, we explored our patients who underwent surgery within 6 months (true early surgery) to the patients who underwent surgical resection more than 6 months after the lesion was identified by Cox analysis. Our data highlighted that patients who underwent earlier surgery had less risk of recurrence compared to those that had surgery later.

This result is in line with previous comparative study in which Jakola et al demonstrated that early surgical resection was associated with better OS than biopsy and "wait and see" approach.[12] It may suggest that delaying surgery while awaiting tumor growth could permit further microscopic tumor infiltration and the transformation of more aggressive tumor subclones.[7,22] Our finding that early surgery is beneficial even amongst asymptomatic patients paves the way for prospective studies in the future.

In addition, it was demonstrated that when not treated, iLGGs became symptomatic at a median interval of 48 months after radiological discovery.[8]

Therefore, the data detailed here support a better functional outcome after early surgery. Importantly, immediate postoperative adjuvant treatments were delayed in the majority of iLGGs (90%), as this cohort had a higher percentage of GTR. Adjuvant treatment after surgery was selected in accordance with 2 criteria.

Adjuvant treatment was withheld for patients not considered to be "low grade, high risk" (ie, any patient over 40 with less than a GTR) in UCSF, Calgary, and Udine Center.[42]

In Montpellier subgroup, none of the patients received postoperative adjuvant treatments considering young age and a residual tumor less than 10 $cm^3$.

Knowing that most patients with iLGGs still benefit from a non-interventional "wait and see" approach without any treatment in some centers, and because patients belonging to this subset are asymptomatic (ie, still enjoy normal professional and social lives without or with only limited cognitive deficits),[5,43,44] functional outcomes was considered as a higher priority in this subpopulation.

Despite the variability in postoperative treatment selection, the type of treatments selected after first surgery did not affect OS, again suggesting a different biological behavior of iLGGs in comparison with sLGGs.[45] At imaging follow-up, in case of volumetric expansion a personalized therapeutic approach was defined. In other words, an "online" therapeutic multidisciplinary management over years was tailored, depending on the clinical evolution, the radiological changes, and the histo-molecular profile.[23,46]

At recurrence, reoperation was considered as a first option if supratotal, total, or subtotal resection was felt to be safely achievable by an expert surgeon of the field. In a limited number of cases, chemotherapy was used as a neoadjuvant treatment before proposing reoperation.[47]

This study, which represents the largest and only multi-institutional analysis investigating the role of surgical management for iLGG, demonstrates that iLGGs cannot be considered indolent lesions. In this series, second operations for TR were performed in 26.22% of cases, and evolution in HGGs was detected in 6.27% of the whole cohort.

In detail, second surgery for TR was performed in 29.16%, 20%, 29.41%, and 32.14% of cases with supratotal-total, subtotal, and partial resection, respectively.

In symptomatic recurrent glioma, the evolution in HGG at second surgery occurs approximately in 50% of cases with TR.[48,49]

This may indicate that iLGGs have different biological behavior when compared to sLGGs, representing an earlier phase of glioma evolution.

The resection at first surgery amongst these patients was supratotal in 7 cases and total (EOR = 100%) in 35 patients.

Despite the infiltrative nature of these lesions, resection of visibly normal tissue beyond the T2-FLAIR MRI margins decreases thus the number and density of remaining tumor cells, with consequent reduction in their propensity to progress toward a malignant phenotype.[34]

Interestingly, these patients demonstrated TR, independent of both their molecular features and EOR achieved at first surgery, highlighting the importance to integrate volumetric and NGS analysis to better stratify glioma patient prognosis.

As far as time to second surgery is concerned, the results are in line with previous investigations on sLGGs.[2,29,32,34] Despite this similarity, the percentage of reoperation has a different distribution when considering EOR and lower tendency to evolve in HGGs in comparison to the symptomatic counterpart.

Even if time to second surgery is comparable to sLGGs, the 10-year estimated OS is greater in iLGGs. It may be that total resection is more feasible when the second surgery is performed for iLGGs because the recurrences could be more focal. Finding the tumor when it is less diffuse initially could allow for recurrences that are more surgically resectable compared to the sLGGs. Another explanation could be due to a difference in the molecular and/or genetic make-up between iLGGs and sLGGs that remain unknown and will require a comparative NGS study between these groups.[22,34,50]

## Limitations and Future Perspectives

Despite the authors' efforts to generate the largest series exploring surgical intervention for iLGGs to date, this study is limited due to the retrospective nature. Further

prospective multicenter studies with reasonably long survivals are needed to confirm the presented results.[6,7,21,22]

Our data highlight the central role of early surgery in iLGGs management and demonstrate that iLGGs are amenable to EOR in comparison with sLGGs, likely due to lower preoperative tumor volume and lower infiltration of subcortical pathways.

In this investigation, the 10-year estimated OS was 98% for iLGGs, while in sLGGs it is about 50% when total resection is achieved,[22] and with additional follow-up differences between molecular subgroups of tumors may become more apparent. Delayed surgery in the symptomatic phase may promote greater infiltration of functional white matter, thereby limiting resection and favoring accumulation of mutations and thus evolution in glioma with a more aggressive behavior.

In the near future, one could conceive that novel targeted therapies and immunotherapy involving the mutated IDH protein could improve patient outcomes in selected cases.

The primary goal of this study was to identify factors pertinent to surgical neurooncological management of patients with iLGGs. While extensive neuropsychological testing was not routinely employed for all patients in this study we now recognize the importance of this for future studies in this patient population.

Nonetheless, all of our iLGG patients were classified as having a general level of performance within the normal range; however, this did not necessarily consider borderline performance.[23] Fortunately, part of the sample included in the present multicenter investigation did receive postoperative neuropsychological assessment.[43] This testing showed proficient performance overall, allowing patients to resume a professional activity in 97% of cases.[44] Furthermore, we reported that most patients were cognitively preserved except for mild difficulties in a few, detected during the postsurgical neurological assessment.

Taken together these results demonstrate that a return to a normal life is not hampered by early surgery for iLGGs.

## Conclusions

This multicenter study, integrating objective tumor volumetric data with surgical outcomes, confirms that early surgery is of clinical importance for iLGG management. These results are in accordance with and significantly strengthen the limited literature available in this field. Our findings, the result of homogeneous data collection in the largest multicenter case series of iLGGs studies to date, will pave the way for future studies with larger cohorts, longer postoperative follow-up, and enriched analysis of novel prognostic molecular and genetic biomarkers. Early surgery is safe and is emerging as the best clinical option to improve survival prognosis for asymptomatic patients harboring iLGGs.

## Keywords

brain mapping | extent of resection | incidental findings | low-grade gliomas | molecular pattern

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