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Contemporary assessment of extent of resection in molecularly defined categories of diffuse low-grade glioma: a volumetric analysis

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Abstract

OBJECTIVE—While the effect of increased extent of resection (EOR) on survival in diffuse infiltrating low-grade glioma (LGG) patients is well established, there is still uncertainty about the influence of the new WHO molecular subtypes. The authors designed a retrospective analysis to assess the interplay between EOR and molecular classes.

METHODS—The authors retrospectively reviewed the records of 326 patients treated surgically for hemispheric WHO grade II LGG at Brigham and Women's Hospital and Massachusetts General Hospital (2000–2017). EOR was calculated volumetrically and Cox proportional hazards models were built to assess for predictive factors of overall survival (OS), progression-free survival (PFS), and malignant progression-free survival (MPFS).

RESULTS—There were 43 deaths (13.2%; median follow-up 5.4 years) among 326 LGG patients. Median preoperative tumor volume was 31.2 cm^3 (IQR 12.9–66.0), and median postoperative residual tumor volume was 5.8 cm^3 (IQR 1.1–20.5). On multivariable Cox

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regression, increasing postoperative volume was associated with worse OS (HR 1.02 per cm^3; 95% CI 1.00–1.03; p = 0.016), PFS (HR 1.01 per cm^3; 95% CI 1.00–1.02; p = 0.001), and MPFS (HR 1.01 per cm^3; 95% CI 1.00–1.02; p = 0.035). This result was more pronounced in the worse prognosis subtypes of IDH-mutant and IDH-wildtype astrocytoma, for which differences in survival manifested in cases with residual tumor volume of only 1 cm^3. In oligodendroglioma patients, postoperative residuals impacted survival when exceeding 8 cm^3. Other significant predictors of OS were age at diagnosis, IDH-mutant and IDH-wildtype astrocytoma classes, adjuvant radiotherapy, and increasing preoperative volume.

CONCLUSIONS—The results corroborate the role of EOR in survival and malignant transformation across all molecular subtypes of diffuse LGG. IDH-mutant and IDH-wildtype astrocytomas are affected even by minimal postoperative residuals and patients could potentially benefit from a more aggressive surgical approach.

Keywords

low-grade glioma; oligodendroglioma; astrocytoma; extent of resection; volumetric analysis; oncology

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Diffuse infiltrative low-grade gliomas (LGGs) are intraaxial WHO grade II neoplasms, accounting for < 5% of all primary brain tumors in adults.[27] LGGs grow slowly and diffusely in the brain parenchyma and, despite multimodal standard of care management, inexorably transform to higher grades, a process leading to neurological impairment and ultimately death.

Due to the indolent nature of LGGs, treatment for these tumors has long been controversial, especially with regard to the role of surgery.[1,4,7,9] Because prospective studies for diffuse LGGs are largely precluded by a lack of clinical equipoise, guidelines about the timing of surgery and extent of resection (EOR) rely on retrospective observational data and currently recommend upfront surgery with the goal of maximal safe resection.[26]

While there have been numerous studies documenting a beneficial effect of higher EOR on survival in LGG patients,[12,17,21,33] these small cohorts have often been limited by the imprecise methods for assessing EOR, with the majority of studies relying on neurosurgeons' intraoperative or neuroradiologists' postoperative impressions. Importantly, the diagnosis and management of diffuse LGGs have been transformed by the revised 2016 WHO classification of CNS tumors,[23,24] which for the first time incorporated molecular information to classify diffuse LGG into the following subtypes, in order of worsening prognosis: WHO grade II, IDH-mutant, 1p/19q-codeleted oligodendrogliomas; IDH-mutant astrocytomas; and IDH-wildtype astrocytomas. By aggregating these prognostically diverse subtypes, the results of key studies of EOR in diffuse LGG were complicated by multiple confounders. Therefore, investigating the interplay between accurately assessed EOR and molecular groups in diffuse LGG is of paramount clinical importance.

To address these knowledge gaps, we designed a study to examine the effects of volumetrically calculated EOR on survival outcomes in the different molecular subtypes

of adult hemispheric diffuse LGG, and to identify predictive factors of malignant transformation and survival.

Methods

Data Sources

Under Partners Healthcare Institutional Review Board approval (2015P002352), we retrospectively identified all patients who were histopathologically diagnosed with supratentorial WHO grade II diffusely infiltrating LGG at Brigham and Women's Hospital or Massachusetts General Hospital departments of neurosurgery from January 2000 to September 2017. Patients were eligible for inclusion if they had available preoperative and immediately postoperative MRI studies, as well as molecular data that would enable assignment to one of the 2016 WHO diagnostic categories (i.e., *IDH1/2* mutation status, 1p/19q codeletion status, *ATRX,* and/or *p53* mutation status). Exclusion criteria were age < 18 years, craniotomy performed for diagnostic biopsy but not resection, and administration of neoadjuvant therapy.

Patient demographics and primary tumor characteristics were collected, including date of initial diagnosis of LGG, presenting symptom(s), tumor location including involvement of eloquent areas, and relevant molecular markers. Classification as eloquent cortex was based on available functional MRI data or, absent that, on localization in one of the presumed eloquent areas as previously described.[11] The date of craniotomy and use of intraoperative MRI (iMRI), in addition to type and date of adjuvant therapy (if present), were recorded for each patient. A qualitative measure of EOR as gross-total resection (GTR), near-total resection (NTR), or subtotal resection (STR), based on the neurosurgeon's intraoperative impression, was also extracted (surgeon-assigned EOR).

We assessed the following survival outcomes: overall survival (OS), progression-free survival (PFS), and malignant progression-free survival (MPFS). OS was calculated from the initial date of surgery to the date of last follow-up or death. PFS was defined as the time between initial surgery and disease progression according to the treating physician's assessment and the initiation of a new therapeutic intervention. MPFS was calculated from the date of initial surgery to the date of resection or biopsy with pathology demonstrating transformation to grade III or higher. Patients who did not reach an endpoint were censored at last follow-up.

Volumetric Analysis

Manual segmentation and volumetric assessment were performed independently by two of the authors using 3D Slicer software (v. 4.8.1). Interrater agreement was then calculated (Bland-Altman plot, Supplementary Fig. 1), and discrepant cases were referred to a neuroradiologist with 6 years of radiology experience. For postoperative imaging, the first available scan within 48 hours after surgery was used. Segmentation was performed on FLAIR sequences, unless unavailable, in which case a T2 sequence was employed. Volumetric EOR (%) was calculated as follows: [(preoperative volume – postoperative volume)/preoperative volume] × 100.

Volumetric assessment was made without any knowledge of clinical outcomes.

Classification by Molecular Groups

Integrated histological and molecular WHO CNS 2016 diagnoses were rendered as follows. First, a determination of *IDH* mutational status was made based on immunohistochemistry (IHC) for the common *IDH1* Arg132His (R132H) mutation. In case of positivity, 1p/19q codeletion status was then ascertained through fluorescence in situ hybridization (FISH) or array comparative genomic hybridization (aCGH) techniques. If *IDH* status was negative by IHC, possible noncanonical mutations were assessed by targeted next-generation sequencing assays (i.e., Onco-Panel or SNaPshot).[14,16] The presence of both *IDH* gene mutation and combined whole-arm losses of 1p and 19q led to designation as an oligodendroglioma. The presence of *IDH* mutation and absence of 1p/19q codeletion signified a diagnosis of IDH-mutant astrocytoma. Absent 1p/19q status, *ATRX* loss, or mutant *p53* by IHC in a diffuse glioma with astrocytic histology also led to designation as an astrocytoma, consistent with the recommendations of the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Official WHO (cIMPACT-NOW).[22] The wildtype status of *IDH1/2* defined the IDH-wildtype astrocytoma class.

Statistical Analysis

All analyses were done using Stata software (v. 15.1, StataCorp). The statistical significance level was set at 0.05. All tests were two-sided. Categorical variables were compared with the chi-square or Fisher's exact test, as appropriate. Comparisons of continuous nonparametric variables in multiple subgroups were done with the Kruskal-Wallis test. The Kaplan-Meier method was used for time-to-event analyses and compared by log-rank tests. Cox proportional hazards (CPH) regression models were fit for all survival outcomes: OS, PFS, and MPFS. We used postoperative residual volume as the measure of tumor burden for our analyses. For multivariable modeling, we incorporated all variables with p values less than 0.1 in univariate analyses. Additionally, age at diagnosis, molecular class, eloquent location, and postoperative residual volume were included in all models since they are known prognostic factors. Scaled Schoenfeld residuals were used to test whether the proportionality assumption held, and goodness of ht was assessed using Cox-Snell residuals. A multiple linear regression model was used to assess for predictors of postoperative volume. The dependent variable was log transformed due to its right-skewed distribution.

Results

A total of 326 patients with histopathologically diagnosed supratentorial LGG met inclusion criteria. Clinical characteristics and survival information are shown in Table 1. Median follow-up was 5.4 years (IQR 2.6–9.5). Median time from radiological diagnosis to surgical resection was 4 weeks (IQR 1.3–13.6). There was a slight preponderance of men (n = 178, 54.6%), and the median age at diagnosis was 36 years (IQR 30–46). Seizures were the predominant presenting symptom (n = 176, 53.9%). Baseline characteristics were comparable between the different molecular groups. A notable difference was that oligodendroglioma patients presented at an older age compared to astrocytoma patients (median 41 vs 33 years for IDH-mutant and 38 years for IDH-wildtype astrocytoma; p <

0.0001). Interestingly, IDH-wildtype astrocytomas were more often located in the temporal lobe (n = 17 [53.1%] vs 14 [10.0%] and 39 [25.3%] for oligodendroglioma and IDH-mutant astrocytoma patients, respectively), and most of these tumors involved the paralimbic areas.

There was a statistically significant difference in the median preoperative tumor volume between diffuse LGG subtypes (p = 0.0002), with oligodendrogliomas having the largest volume (36.4 cm^3, IQR 20.0–75.3), followed by IDH-mutant astrocytomas (30.6 cm^3, IQR 11.9–56.1) and IDH-wildtype tumors (6.7 cm^3, IQR 2.5–44.9). Postoperative residual volume was also significantly higher in oligodendrogliomas than in IDH-mutant and IDH-wildtype astrocytomas (median 8.3 [IQR 1.9–26.4] vs 4.5 [IQR 0.8–14.2] and 2.4 cm^3 [IQR 0.1–10.6], respectively; p = 0.002, Supplementary Fig. 2). Neurosurgeons' assessments of EOR as GTR, NTR, or STR were associated with increasing postoperative volumetric residuals (median 0.79 vs 1.9 vs 19.6 cm^3, respectively; p = 0.0001, Supplementary Fig. 3). Adjuvant therapy was administered to 38.6% of the cohort (n = 126) in the form of chemotherapy (13.2%), radiotherapy (6.13%), or combined chemoradiotherapy (19.3%). Median time from resection to initiation of adjuvant therapy was 9.6 weeks (IQR 6.1–14.5). Of the 176 (53.9%) patients who experienced progression, initial salvage therapy was in the form of reoperation in 117 (35.9%), radiotherapy in 34 (10.4%), and chemotherapy in 12 (3.7%) patients.

Survival Outcomes

At the time of analysis, there were 43 (13.2%) deaths in the cohort. Five- and 10-year OS rates were 88.3% (95% CI 83.0–92.1) and 70.1% (95% CI 60.9–78.7), respectively. After stratification by molecular subtype, oligodendroglioma patients had the longest OS, with 5- and 10-year rates of 96.9% (95% CI 88.2–99.2) and 84.1% (95% CI 62.0–93.9), respectively, whereas IDH-wildtype patients had the shortest OS, with 5- and 10-year rates of 65.4% (95% CI 40.9–81.8) and 36.3% (95% CI 8.8–65.7), respectively. Figure 1 presents Kaplan-Meier curves of OS for the different molecular subgroups.

In univariable analysis, postoperative volume was significantly associated with worse OS (HR 1.02 per cm^3, 95% CI 1.01–1.03, p < 0.0001), and this association was consistent across all molecular classes (oligodendroglioma HR 1.05 per cm^3, 95% CI 1.0–1.09, p = 0.025; IDH-mutant astrocytoma HR 1.02 per cm^3, 95% CI 1.01–1.03, p < 0.0001; and IDH-wildtype HR 1.03 per cm^3, 95% CI 1.01–1.05, p = 0.001). After stratification of postoperative volume in subgroupings as previously defined (< 0.1 cm^3, 0.1–5.0 cm^3, 5.1–15.0 cm^3, > 15.0 cm^3),[34] it was evident that even small residuals of 0.1–5.0 cm^3 had a negative OS impact in both IDH-mutant and IDH-wildtype astrocytomas. Regarding oligodendroglioma patients, it was not until postoperative volume reached levels of 15 cm^3 that OS was significantly divergent (Fig. 2A–D). To more granularly explore the presence of a specific residual volume cutoff, we compared survival curves of dichotomized postoperative volumes at 1-cm^3 increments, from 0 to 30 cm^3. The data show a similar picture of significantly worse OS for IDH-mutant and IDH-wildtype tumors even from small residuals of 1 cm^3. For oligodendrogliomas, a value of 8 cm^3 seems to be the volume above which differences in OS start to become evident (Table 2 and Supplementary Figs. 4 and 5).

In a multivariable CPH model (Table 3), significant predictors of worse OS were age at diagnosis (HR 1.06 per year, 95% CI 1.03–1.09, $p < 0.001$) and male sex (reference female: HR 2.02,95% CI 1.03–3.99, $p = 0.042$); IDH-mutant (reference oligodendroglioma: HR 7.76, 95% CI 2.95–20.4, $p < 0.001$) or IDH-wildtype (reference oligodendroglioma: HR 20.6, 95% CI 6.79–62.4, $p < 0.001$) astrocytoma class; increasing preoperative volume (HR 1.01 per cm^3, 95% CI 1.0–1.02, $p = 0.014$) and postoperative residual volume (HR 1.02 per cm^3, 95% CI 1.0–1.03, $p = 0.004$); and provision of adjuvant radiotherapy (reference no radiotherapy: HR 2.99, 95% CI 1.52–5.88, $p = 0.001$). The ht was satisfactory and the bootstrap-corrected c-index was 0.87 (95% CI 0.81–0.92). These results persisted after adjusting for the interaction of adjuvant chemotherapy and postoperative volume.

Malignant progression was documented in 24.5% (n = 80) of the cohort, with an almost even split between progression to grade III (n = 41) and grade IV (n = 39). Prognostic factors associated with worse MPFS in a multivariable CPH model were age at diagnosis (HR 1.02 per year, 95% CI 1.00–1.04, $p = 0.033$); IDH-mutant (reference oligodendroglioma: HR 5.12, 95% CI 2.83–9.26, $p < 0.001$) or IDH-wildtype (reference oligodendroglioma: HR 4.44, 95% CI 1.91–10.3, $p = 0.001$) molecular groups; presence of contrast enhancement (HR 2.04, 95% CI 1.08–3.87, $p = 0.029$); and increasing preoperative volume (HR 1.01 per cm^3, 95% CI 1.0–1.01, $p = 0.001$) and postoperative residual volume (HR 1.01 per cm^3, 95% CI 1.0–1.02, $p = 0.029$).

Postoperative Volume Predictors

To assess for predictive factors of EOR, we implemented a multiple linear regression model with postoperative volume as the dependent variable (Table 4). The model showed that preoperative volume ($p < 0.0001$; Fig. 3), insular and temporal locations ($p < 0.0001$ and $p = 0.03$, respectively), and increasing age ($p = 0.014$) are associated with higher postoperative volumes. On the other hand, use of iMRI ($p = 0.002$) and IDH-mutant ($p = 0.009$) and IDH-wildtype astrocytomas ($p = 0.03$) were associated with lower residual volumes postoperatively.

Discussion

The optimal timing and aggressiveness of surgery in patients with diffuse LGG have historically been a matter of much controversy.[20] Recent data from pseudorandomized analyses have shown that upfront maximal resection should be the preferred treatment approach, rather than watchful waiting.[19,30] On the topic of EOR, multiple studies have demonstrated the importance of pursuing a more aggressive resection for achieving better oncological control.[31] However, many of these studies were hampered by the subjective nature of assessing EOR, most commonly relying on the neurosurgeon's intraoperative interpretation. Volumetric studies have corroborated the prognostic significance of EOR for survival outcomes but have not addressed the interaction with the new WHO 2016 integrated molecular and histological diagnoses.[8,18,34]

Our data suggest that higher postoperative tumor residuals are associated with worse OS, PFS, and MPFS across all molecular subtypes. The effect is particularly pronounced in the more aggressive subtypes, namely IDH-mutant and IDH-wildtype astrocytomas, but is also

evident in oligodendrogliomas. In the former 2 groups, postoperative residual volumes as little as 1 cm^3 lead to significantly worse OS. On the other hand, in oligodendroglioma patients, postoperative residuals only start becoming significantly predictive of worse survival after reaching values of > 8 cm^3. A possible explanation is that astrocytomas are inherently more prone to progress to higher grades and this negatively impacts survival even with minimal residuals, while oligodendrogliomas are more indolent and small residuals may not affect survival considerably. Moreover, 1p/19q codeletion imparts higher sensitivity to chemotherapeutic regimens,[35] further lowering the risk of progression in oligodendrogliomas. Taken together, these findings indicate that pursuing a more radical EOR, for example, with a multistage resection strategy, may be more advantageous in astrocytic than in oligodendroglial tumors, for which small remnants could be acceptable when the risk of iatrogenic neurological deficits is high.

Our results are in line with those of a recent study[36] that also focused on the prognostic significance of EOR for the different molecular subtypes of LGG. However, this study was limited to conclusions for IDH-wildtype astrocytomas due to a small sample size. Additionally, the IDH-wildtype group seemed to be preferentially treated with biopsy alone (n = 19, 82.6%), further precluding any meaningful assessment of the effect of EOR in this particular subtype. IDH-wildtype astrocytomas are admittedly rare tumors, complicating attempts at clearly delineating optimal treatment. Although IDH-wildtype astrocytomas were previously thought to invariably confer a dismal prognosis,[6] hence the designation “GBM-like,” recent work has shed light on the remarkable molecular heterogeneity within this subtype.[2,29] Our results suggest that a more aggressive surgical approach is particularly benehcial, especially in the worse prognosis IDH-wildtype cases. A recent meta-analysis of 22 studies[15] confirmed the survival variability of IDH-wildtype tumors as well as the favorable effect of increasing EOR. Additional investigations are needed to elucidate the clinical characteristics of IDH-wildtype tumors, possibly by pooling data from multiple institutions, given the rarity of these cases.

Although the notion of PFS has less significance for a tumor that will inexorably progress, MPFS is a clinically important measure since it is often a harbinger of new neurological deficits and ultimately death. Numerous studies[8,10,34] have shown that postoperative residual volume is a predictor of malignant transformation. Our multivariable CPH model confirms the role of postoperative residual volume, as well as that of preoperative volume, in predicting malignant transformation. Interestingly, contrast enhancement was also significantly associated with transformation, consistent with a known[28] tendency for contrast-enhancing tumors to exhibit increasingly malignant behavior.

We further show that preoperative volume is a significant predictor of EOR, with greater preoperative volumes associated with lower EOR, as previously demonstrated.[25] Not surprisingly, insular location, a notoriously challenging site to access surgically,[32] is associated with higher postoperative residuals. Moreover, both IDH-wildtype and IDH-mutant astrocytomas were predictive of higher EOR in this cohort. Despite the unclear significance of this finding, it further supports the results of our survival analysis, since these subtypes had worse survival outcomes despite significantly higher achieved EOR. This

could temper concerns that tumors amenable to wider resection tend to have more favorable mutational prohles, e.g., IDH-mutant tumors.

Low- or high-held iMRI has been used in glioma surgery to facilitate real-time updates of neuronavigational models with the goal of maximizing EOR. In diffuse LOG patients, evidence from retrospective studies points to a positive impact of iMRI in achieving GTR,[13] but data are conflicting regarding survival outcomes. In our cohort, use of iMRI was significantly associated with a lower postoperative residual volume in a multiple regression model, but this effect did not translate into a survival advantage in multivariable CPH models. Further data from prospective studies are needed to elucidate the roles of the various intraoperative imaging modalities in helping guide surgical strategies.

Limitations

Our investigation is limited by biases inherent to all retrospective analyses—most importantly selection bias. Patient follow-up was short, considering the long survival prospects of diffuse LGG patients. This is something with which all retrospective studies of LGG have to contend, especially considering that routine classification by molecular subtypes is a recent phenomenon. In addition, there were very few deaths in the oligodendroglioma subtype. This, coupled with the limited follow-up, makes interpretations of findings challenging. It is conceivable that longer follow-up times could have unveiled a detrimental effect of small residuals for this subtype as well as the IDH-wildtype and IDH-mutant astrocytoma subtypes. Another limitation pertains to the timing of postoperative imaging. We elected to preferentially use early (< 48 hours) postoperative scans according to current National Comprehensive Cancer Network (NCCN) guidelines.[26] We acknowledge the reported risk of overestimation of residual volumes,[3 5] and to address this concern during our workflow, we utilized both diffusion-weighted sequences (to localize areas of postoperative ischemia) and cross-referencing to follow-up scans (to ensure that only true residual tumor was calculated). Finally, some patients received parts of their neurosurgical or oncological treatment at other institutions, introducing an element of heterogeneity with regard to imaging and surgical techniques, as well as chemo- and radiotherapy regimens employed. Despite these limitations, this study is, to our knowledge, the largest single-institution analysis of EOR in different molecular subtypes of diffuse LGG using the volumetric approach.

Conclusions

In a large diffuse LGG cohort, we corroborated the prognostic significance of increasing EOR across all molecular subtypes. The association was more pronounced in IDH-mutant astrocytomas and, importantly, in IDH-wildtype astrocytomas, for which there are limited data in the current literature. In oligodendrogliomas, a significant survival benefit is observed even up to a residual volume of 8 cm^3, which may reflect the more indolent nature of these tumors. These results provide further evidence in support of current recommendations for maximal resection in hemispheric diffuse LGGs, as part of an individualized management plan to achieve onco-functional balance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

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ABBREVIATIONS

CPH	Cox proportional hazards
EOR	extent of resection
GTR	gross-total resection
iMRI	intraoperative MRI
LGG	low-grade glioma
MPFS	malignant progression-free survival
NTR	near-total resection
OS	overall survival
PFS	progression-free survival
STR	subtotal resection

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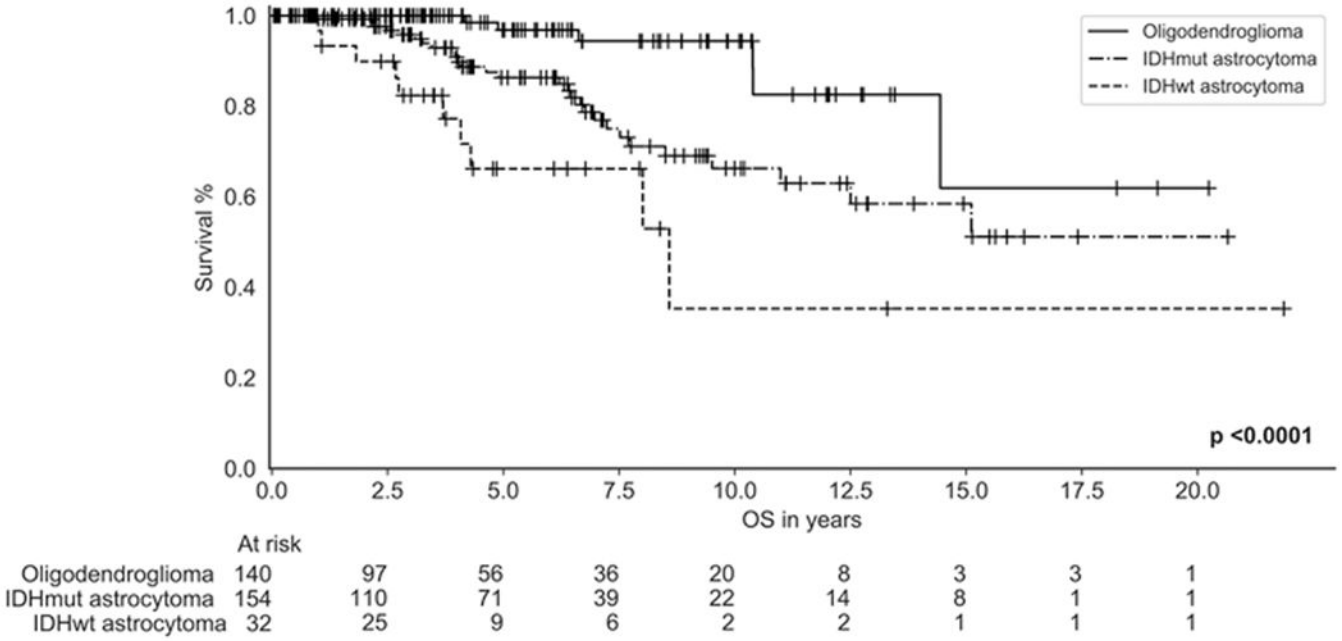

FIG. 1.

Kaplan-Meier curves of OS stratified by molecular group. IDHmut = IDH mutant; IDHwt = IDH wildtype.

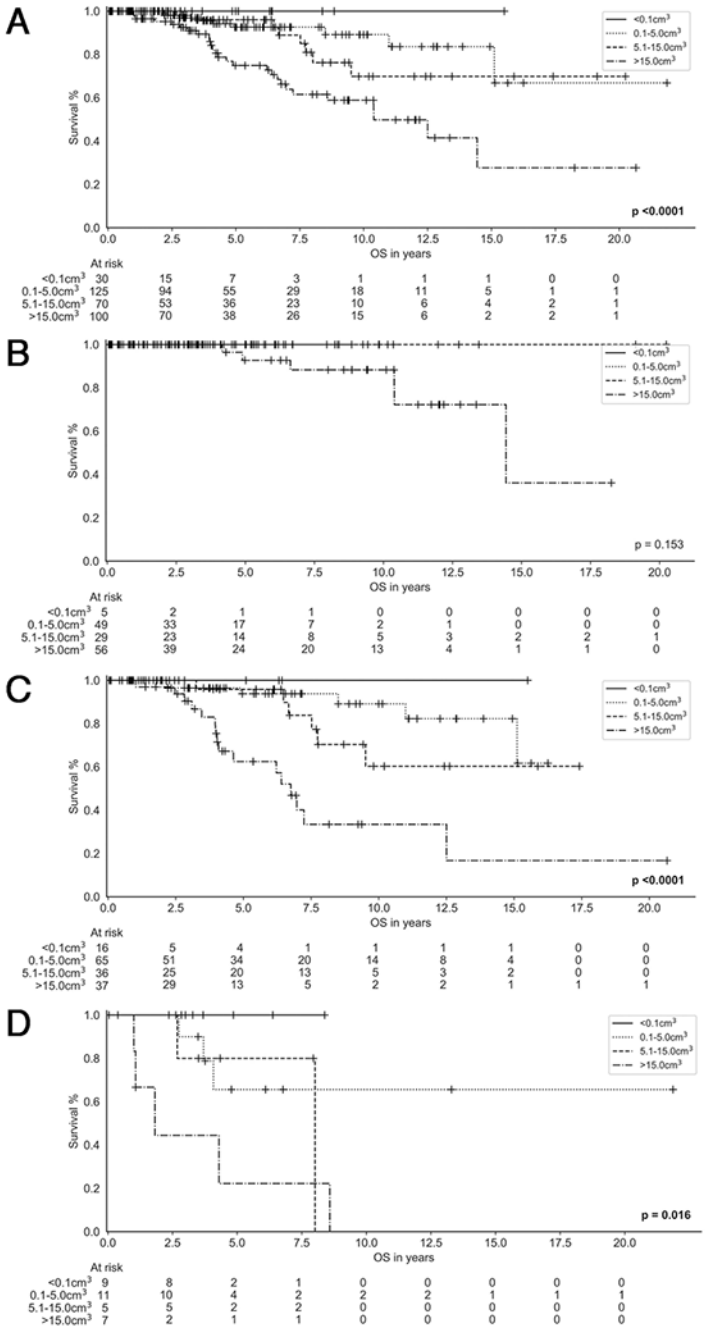

FIG. 2.

Kaplan-Meier curves of OS stratified by categories of increasing postoperative residuals in all patients (**A**), oligodendroglioma patients (**B**), IDH-mutant astrocytoma patients (**C**), and IDH-wildtype astrocytoma patients (**D**). p values are log-rank across the 4 categories.

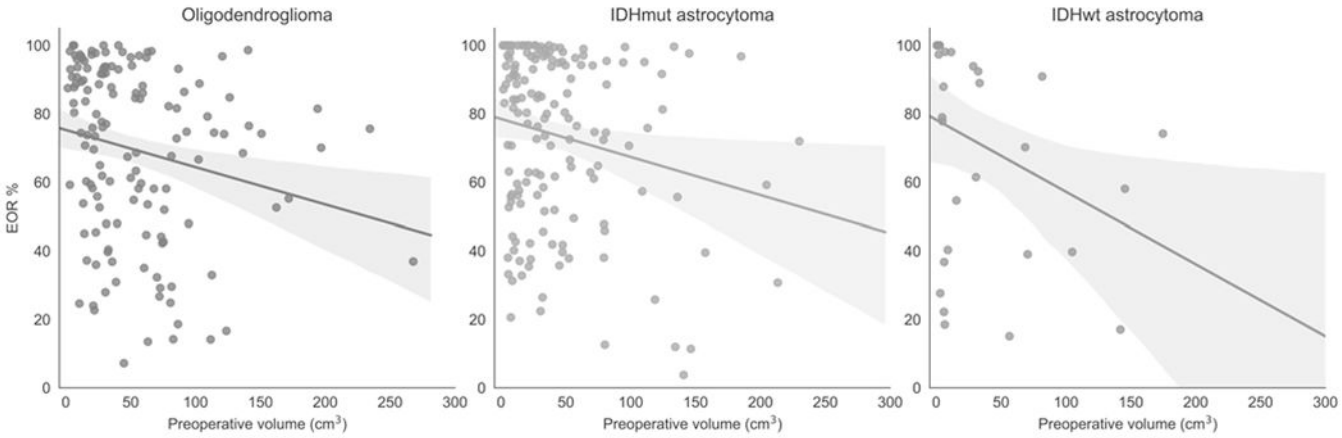

FIG. 3.

Scatterplot and estimated regression line (translucent bands represent 95% CIs) demonstrating the significant association of preoperative tumor volume with achieved **EOR** across molecular subtypes.

TABLE 1.

Clinical and tumor characteristics of diffuse LGG patients stratified by molecular class

	All Patients	IDHmut 1p/19q-Codeleted ODG	IDHmut AC	IDHwt AC	p Value
Total no. of patients	326	140	154	32	
Sex					0.757 *
Female	148 (45.4)	65 (46.4)	67 (43.5)	16 (50)	
Male	178 (54.6)	75 (53.6)	87 (56.5)	16 (50)	
Age at diagnosis, yrs					**<0.001** †
<40	200 (61.3)	63 (45)	119 (77.3)	18 (56.2)	
40–59	99 (30.4)	64 (45.7)	27 (17.5)	8 (25)	
≥60	27 (8.3)	13 (9.3)	8 (5.2)	6 (18.8)	
Median [IQR]	36 [30–46]	41 [33–51]	33 [28–39]	38 [29–55.5]	
Presentation					0.651 *
Seizures	176 (53.9)	80 (57.1)	80 (51.9)	16 (50)	
Headaches	57 (17.5)	18 (12.9)	32 (20.8)	7 (21.9)	
Incidental	37 (11.3)	15 (10.7)	18 (11.7)	4 (12.5)	
Other	56 (17.1)	27 (19.3)	24 (15.6)	5 (15.6)	
Tumor laterality					0.930 *
Right	174 (53.4)	75 (53.6)	81 (52.6)	18 (56.2)	
Left	152 (46.6)	65 (46.4)	73 (47.4)	14 (43.8)	
Location					
Frontal	187 (57.4)	98 (70)	82 (53.3)	7 (21.9)	
Temporal	70 (21.5)	14 (10)	39 (25.3)	17 (53.1)	
Parietal	39 (11.9)	15 (10.7)	20 (13)	4 (12.6)	
Occipital	5 (1.5)	2 (1.4)	2 (1.3)	1 (3.1)	
Insular	22 (6.7)	9 (6.4)	11 (7.1)	2 (6.2)	
Other	3 (1)	2 (1.5)	0 (0)	1 (3.1)	
Eloquent	61 (18.9)	28 (20)	28 (18.5)	5 (15.6)	0.841 *
iMRI	98 (34)	46 (36.2)	43 (33.1)	9 (29)	0.716 *

	All Patients	IDHmut 1p/19q-Codeleted ODG	IDHmut AC	IDHwt AC	p Value
Contrast enhancement	36 (11)	20 (14.3)	11 (7.1)	5 (15.6)	0.102 *
Preop vol, cm^3					**<0.001** †
<25	130 (39.9)	46 (32.9)	64 (41.6)	20 (62.5)	
25–49	79 (24.2)	31 (22.1)	44 (28.6)	4 (12.5)	
50–99	75 (23)	42 (30)	29 (18.8)	4 (12.5)	
100–249	40 (12.3)	19 (13.6)	17 (11)	4 (12.5)	
≥250	2 (0.6)	2 (1.4)	0 (0)	0 (0)	
Median [IQR]	31.2 [12.9–66]	36.4 [20–75.3]	30.6 [11.9–56.1]	6.7 [2.5–44.9]	
Postop vol, cm^3					**0.002** †
0.0	28 (8.6)	4 (2.9)	16 (10.4)	8 (25)	
0.1–4.9	127 (38.9)	50 (35.7)	65 (42.2)	12 (37.5)	
5.0–14.9	70 (21.5)	29 (20.7)	36 (23.4)	5 (15.6)	
≥15.0	101 (31)	57 (40.7)	37 (24)	7 (21.9)	
Median [IQR]	5.8 [1.1–20.5]	8.3 [1.9–26.4]	4.5 [0.8–14.2]	2.4 [0.1–10.6]	
Volumetric EOR					0.145 †
0–39	52 (16)	23 (16.5)	21 (13.6)	8 (25)	
40–69	77 (23.7)	37 (26.6)	36 (23.4)	4 (12.5)	
70–89	85 (26.2)	41 (29.5)	38 (24.7)	6 (18.7)	
90–99	83 (25.5)	34 (24.5)	43 (27.9)	6 (18.7)	
100	28 (8.6)	4 (2.9)	16 (10.4)	8 (25)	
Median [IQR]	77.8 [53.8–94.1]	74.7 [52.6–91.7]	80.3 [56.1–95.9]	83.4 [40–99]	
Surgeon-assigned EOR					0.187 *
STR	156 (47.8)	74 (52.8)	69 (44.8)	13 (40.6)	
NTR	35 (10.7)	18 (12.8)	14 (9.1)	3 (9.4)	
GTR	122 (37.4)	42 (30.0)	65 (42.2)	15 (46.9)	
NA	13 (3.9)	6 (4.2)	6 (3.9)	1 (3–1)	
Adjuvant therapy					**0.032** *
Radiotherapy	20 (6.1)	4 (2.8)	13 (8.4)	3 (9.4)	

	All Patients	IDHmut 1p/19q-Codeleted ODG	IDHmut AC	IDHwt AC	p Value
Chemotherapy	43 (13.2)	27 (19.3)	15 (9.7)	1 (3–1)	
Chemoradiotherapy	63 (19.3)	28 (20)	30 (19.5)	5 (15.6)	
Time to adjuvant therapy in wks	9.6 [6.1–14.5]	10.8 [7.4–15.1]	8.6 [6.1–13.2]	9.6 [5.4–17]	0.314 †
Salvage therapy					**0.012** *
Radiotherapy	34 (10.4)	16 (11.4)	18 (11.7)	0 (0.0)	
Chemotherapy	12 (3.7)	7 (5.0)	3 (1.9)	2 (6.2)	
Resection	117 (35.9)	32 (22.8)	76 (49.3)	9 (28.1)	
Time to reop in yrs	3.5 [2.5–5.9]	3.6 [2.6–5.9]	3.5 [2.5–6.0]	2.6 [1.5–6.3]	0.612 †
Survival outcomes					
OS					
5 yr	88.3 (83.0–92.1)	96.9 (88.2–99.2)	86.3 (77.9–91.7)	65.4 (40.9–81.8)	
10 yr	70.1 (60.9–78.7)	84.1 (62.0–93.9)	66.8 (53.6–76.9)	36.3 (8.8–65.7)	
PFS					
5 yr	30.0 (23.6–36.7)	38.5 (27.6–49.4)	19.3 (12.2–27.7)	57.6 (32.5–76.3)	
10 yr	12.7 (7.2–19.8)	24.1 (12.8–37.4)	3.2 (0.6–9.5)	28.8 (1.9–67.6)	
MPFS					
5 yr	72.8 (65.9–78.5)	87.6 (77.1–93.5)	63.8 (53.6–72.4)	59.4 (34.0–77.8)	
10 yr	42.2 (31.9–52.1)	70.9 (51.3–83.8)	26.0 (15.3–38.1)	46.2 (17.7–70.9)	
Follow-up in yrs	5.4 [2.6–9.5]	4.7 [2.6–8.9]	5.9 [2.5–9.9]	6.5 [3.4–9.1]	

AC = astrocytoma; IDHmut = IDH mutant; IDHwt = IDH wildtype; NA = not assessed; ODG = oligodendroglioma.

Values are presented as number of patients (%), median [IQR], or mean (95% CI). Boldface type indicates statistical significance.

*Pearson chi-square test

†Kruskal-Wallis test.

TABLE 2.

Results of log-rank tests comparing the survivor functions of LGG patients at increasing postoperative residual thresholds for OS and MPFS, stratified by molecular class

	Log-Rank p Value	
Postop Vol, cm^3	**OS**	**MPFS**
ODG		
<0.1 vs ≥0.1	0.762	0.537
<1 vs ≥1	0.508	0.162
2 vs ≥2	0.423	0.084
3 vs ≥3	0.303	**0.031**
4 vs ≥4	0.291	**0.026**
5 vs ≥5	0.234	**0.011**
6 vs ≥6	0.086	**0.018**
7 vs ≥7	0.067	**0.007**
8 vs ≥8	0.059	**0.004**
9 vs ≥9	**0.048**	**0.002**
10 vs ≥10	**0.047**	**0.002**
12 vs ≥12	**0.042**	**0.001**
15 vs ≥15	**0.021**	**0.004**
20 vs ≥20	**0.001**	**<0.001**
30 vs ≥30	**0.005**	**0.001**
IDHmut AC		
0.1 vs ≥0.1	0.264	0.349
1 vs≥1	**0.019**	0.134
2 vs ≥2	**0.003**	**0.038**
3 vs ≥3	**0.001**	0.075
4 vs ≥4	**0.001**	**0.009**
5 vs ≥5	**<0.001**	**0.003**
6 vs ≥6	**<0.001**	**<0.001**
7 vs ≥7	**<0.001**	**<0.001**
8 vs ≥8	**<0.001**	**<0.001**
9 vs ≥9	**<0.001**	**<0.001**
10 vs ≥10	**<0.001**	**<0.001**
12 vs ≥12	**<0.001**	**<0.001**
15 vs ≥15	**<0.001**	**<0.001**
20 vs ≥20	**<0.001**	**<0.001**
30 vs ≥30	**<0.001**	**<0.001**
IDHwtAC		
0.1 vs ≥0.1	0.070	0.055
1 vs≥1	**0.017**	**0.020**

	Log-Rank p Value	
Postop Vol, cm^3	**OS**	**MPFS**
2 vs ≥2	**0.036**	**0.038**
3 vs ≥3	0.065	0.076
4 vs ≥4	**0.033**	**0.034**
5 vs ≥5	**0.014**	**0.015**
6 vs ≥6	**0.002**	**0.002**
7 vs ≥7	**0.002**	**0.002**
8 vs ≥8	**0.003**	**0.004**
9 vs ≥9	**0.003**	**0.004**
10 vs ≥10	**<0.001**	**<0.001**
12 vs ≥12	**0.003**	**0.001**
15 vs ≥15	**0.003**	**0.001**
20 vs ≥20	**0.003**	**0.001**
30 vs ≥30	**0.003**	**0.001**

Boldface type indicates statistical significance.

TABLE 3.

Multivariable CPH models for all survival outcomes

	OS			PFS			MPFS		
Variable	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Age (per yr)	1.06	1.03–1.09	**<0.001**	0.99	0.98–1.01	0.955	1.02	1.00–1.04	**0.033**
Male sex (female is ref)	2.02	1.03–3.99	**0.042**	*	*	*	*	*	*
Molecular group (ODG is ref)									
IDHmut AC	7.76	2.95–20.4	**<0.001**	1.98	1.36–2.87	**<0.001**	5.12	2.83–9.26	**<0.001**
IDHwtAC	20.6	6.79–62.4	**<0.001**	0.83	0.41–1.68	0.605	4.44	1.91–10.3	**0.001**
Eloquent	2.21	0.97–5.02	**0.058**	1.26	0.83–1.92	0.271	1.51	0.83–2.74	0.172
iMRI	*	*	*	1.69	1.16–2.49	**0.007**	*	*	*
Contrast enhancement	1.29	0.54–3.07	0.566	*	*	*	2.04	1.08–3.87	**0.029**
Preop vol (per cm^3)	1.01	1.0–1.02	**0.016**	1.00	1.00–1.01	**0.009**	1.01	1.00–1.01	**0.001**
Postop vol (per cm^3)	1.02	1.0–1.03	**0.016**	1.01	1.00–1.02	**0.001**	1.01	1.00–1.02	**0.035**
Adjuvant RT	2.99	1.52–5.88	**0.001**	0.41	0.26–0.64	**<0.001**	1.47	0.89–2.43	0.125
Adjuvant CT	1.23	0.57–2.63	0.598	*	*	*	*	*	*

CT = chemotherapy; ref = reference; RT = radiotherapy. Boldface type indicates statistical significance.

*Variable not included in this model.

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TABLE 4.

Multiple linear regression model of factors predictive of postoperative residual volume

Variable	Coefficient	SE	p Value
Intercept	0.288	0.104	**0.006**
Age (per yr)	0.005	0.002	**0.014**
Male sex (female is ref)	0.042	0.049	0.398
Molecular group (ODG is ref)			
IDHmut AC	−0.144	0.054	**0.008**
IDHwtAC	−0.195	0.088	*0.028*
Location (frontal is ref)			
Temporal	0.148	0.067	**0.028**
Parietal	0.041	0.077	0.598
Occipital	−0.694	0.208	0.739
Insular	0.494	0.103	**<0.001**
Other	0.104	0.240	0.666
Eloquent	−0.011	0.063	0.861
iMRI	−0.165	0.053	**0.002**
Preop vol (per cm^3)	0.008	0.104	**<0.001**

Boldface type indicates statistical significance.