# Role of 1p/19q Codeletion in Diffuse Low-grade Glioma Tumour Prognosis

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**Abstract.** *Background/Aim: In the latest 2021 WHO classification of central nervous system tumours (CNS), gliomas that present isocitrate dehydrogenase (IDH) mutations are defined as diffuse low-grade gliomas (DLGGs). IDH mutations are commonly observed in this tumour type. The Extent of Resection (EOR) positively influence survival; however, it is still debated whether the predictive value of EOR is independent of the 1p/19q co-deletion. We carried out a retrospective analysis on patients operated on for DLGG at the Sant'Andrea University Hospital Sapienza University of Rome, correlating the outcome with the presence of 1p/19q co-deletion and EOR. Patients and Methods: The study examined 66 patients with DLGG who had undergone surgery for tumour resection between 2008 and 2018. Patients with DLGG were divided into two groups; diffuse astrocytoma (DA) in which 1p/19q codeletion is absent and oligodendroglioma (OG) in which 1p/19q codeletion is present. According to EOR, both groups were divided into two subgroups: subtotal resection (STR) and gross total resection (GTR). Three end-point variables were considered: overall survival (OS), progression-free survival (PFS) and time to malignant transformation (TMT). Results: In the DA group, the GTR subgroup had an average OS of 81.6 months, an average PFS of 45.9 months and an average TMT of 63.6 months. After surgery, these patients had an average Karnofsky Performance Score (KPS) of 83.4. The STR subgroup had an average OS of 60.4 months, PFS was 38.7 months, and TMT was 46.4 months, post-operative KPS was 83.4. In contrast, in the OG group, the GTR averagely had 101.7 months of OS, 64.9 months of PFS, 80.3 months of TMT and an average post-operative KPS of 84.2, and the STR subgroup had an average of OS of 73.3 months, PFS of 48.2 months, TMT of 57.3 and an average postoperative KPS of 96.2. Conclusion: In patients affected by DLGGs, 1p/19q codeletion is significantly associated with prolonged survival and longer time-to-malignant transformation (TMT) compared to the absence of 1p/19q codeletion. Also, the extent of surgical resection (EOR) in DLGG patients has been confirmed as one of the main prognostic factors. However, its predictive value is substantially influenced by the presence of the 1p/19q codeletion.*

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*Key Words:* Diffuse low-grade glioma, extent of resection, overall survival, molecular markers, intraoperative magnetic resonance imaging.

The incidence of gliomas in the central nervous system (CNS) is estimated at 7.3 per 100,000 people per year, and diffuse low-grade gliomas (DLGG) represents 12.8% of them (1). Surgery is the treatment of choice for these types of tumours; it results in being safe and effective (2, 3);

considering the rarity of such conditions, its role in treating DLGG is fundamental but still lacks efficacy and DLGG management remains controversial (4). Extensive resection improves survival and delays tumour progression. Also, supramarginal resections can delay the time-to-malignant transformation (TMT) and increase overall survival (OS) (5). More than 80% of DLGG cases are associated with isocitrate dehydrogenase (IDH) 1 or IDH2 missense mutations (6). DLGG oligodendroglioma also shows the presence of the codeletion of chromosome arms 1p and 19q (7).

The World Health Organization (WHO) 2021 classification of CNS tumours is genotype-centred; for diagnosis and treatment selection the genetic profile is taken more into consideration than histological features in cases where the histology and molecular features are not comparable. It defines diffuse astrocytoma as a DLG IDH-mutant, and oligodendroglioma as a DLG IDH mutant with the 1p/19q codeletion (8). Three DLGGs have been identified: astrocytoma IDH-mutant, oligodendroglioma IDH-mutant and 1p/19q- co-deleted, and glioblastoma IDH-wildtype.

The "not otherwise specified (NOS) DLGG" category will likely increase in this classification. This designation is used for genotyped tumours that do not fall into the new, more strictly defined categories. For this reason, another essential Classification has been proposed, which includes IDH mutations, 1p/19q codeletions and telomerase reverse transcriptase promoter (TERTp) mutations. Patients affected by DLGG triple-positive defined by 1p/19q codeletion, TERT mutation, and IDH mutation have the most favourable clinical outcomes (9). Other mutations, such as TP53 mutations, are associated with significantly poorer survival among patients with DLGGs and disease progression in the secondary glioblastoma (GBM) (10).

This study aimed to clarify the role of 1p/19q-codeletion as a clinical outcome factor in DLGG patients. as clinical outcome. We performed a long-term follow-up of these patients and were able to evaluate whether this mutation impacts survival regardless of the degree of the surgical resection of the tumour.

## Patients and Methods

*Study cohort and inclusion criteria.* The inclusion criteria for this study were satisfied for 66 patients, including adult patients (≥18 years) who underwent DLGG surgery from December 2008 to December 2018 at the Sant'Andrea Hospital University of Rome, with a confirmed diagnosis of DLGG IDH mutated. The presence of 1p/19q codeletion was confirmed, and patients without definitive molecular profiling were excluded. Selected patients received regular clinical and neuroradiological follow-up.

Patients were divided in two groups based on the presence of 1p/19q codeletion: 37 patients presented to DLGG with IDH-mutated without codeletion 1p/19q (DA group) and 29 patients presented to DLGG with IDH-mutated with codeletion 1p/19q (OG group). The DA Group included 37 patients, and the observed histological and molecular characteristics are summarized in Figure 1.

A total of 29 patients showed a DLGG IDH mutation with 1p/19q codeletion and were included in the OG Group. In Figure 2, their histological and molecular features are shown. Both groups underwent surgery using intraoperative magnetic resonance imaging (Io-MRI) and were further divided into subgroups based on extent of resection (EOR), subtotal resection (STR), and gross total resection (GTR).

TP53 mutation and Epidermal growth factor receptor (EGFR) amplification/EGFR variant III mutation and their predictive value was investigated in both groups. The data analysis methodology is consistent with the one used by Salvati *et al*. (11).

*Molecular analysis.* Formalin-fixed paraffin-embedded (FFPE) 3-mm-thick sections from tissue samples were cut and stained with haematoxylin and eosin (HE) with a pre-step of deparaffination with xylol. An immunohistochemical panel including GFAP, ATRX, P53, IDH1 R132H was used. Immunohistochemistry (IHC) was performed by Leica Bond RXm™ automated staining processor (Leica Biosystems, Buffalo Grove, IL, USA). Tissue sections were cut at 5 μm, dried at 70°C for 30 min and then dewaxed. Antigen retrieval was performed in the Bond Rx system with Epitope Retrieval Solution 1 (pH 6) for 30 min. Sections were incubated for 30 minutes with GFAP (Novocastra – Leica Biosystems clone GA5, mouse monoclonal, 1:400 dilution), ATRX (NBP1-83077, rabbit polyclonal, 1:1,000 dilution; Novus Biologicals, Centennial, CO, USA), p53 (NCL-L-p53-DO7, mouse polyclonal, 0.875 μg/ml; Leica Novocastra), IDH1 R132H (DIA H09, mouse monoclonal antibody, Dianova, Hamburg, Germany).

The presence or absence of 1p deletion was detected by the fluorescence in situ hybridisation (FISH) technique, using the Vysis LSI 1p36 orange/1q25 green Dual-Color Probe kit (Abbott, Abbott Park, IL, USA). Moreover, the presence or absence of 19q deletion was found by FISH using the Vysis LSI 19q13 orange/19p13 green Dual-Color Probe kit (Abbott). When 30% of neoplastic nuclei exhibited 1O/2G signals for both 1p36/1q25 and 19q13/19p13, they are considered positive for 1p/19q co-deletion.

*Neuroradiology protocol.* The preoperative study included a neurological examination with evaluation of the KPS score and a radiological study performed with MRI 1.5T after administering gadolinium and fluid-attenuated inversion recovery (FLAIR) with the integration of diffusion-weighted imaging (DWI), Perfusion-weighted imaging (PWI) sequences and spectroscopy. A functional MRI was performed in patients with a lesion in the eloquent area, the brain area controlling the speech. All patients performed one or more Io-MRI with gadolinium and FLAIR after removing the tumour to verify that they had reached the target. Pre and postoperative tumour volumes were assessed in a semiautomatic fashion using the Smart Brush tool in Brainlab Elements (version 2.1.0.15) on the T2w-FLAIR sequence for volumetric multiplanar reconstruction (MPR) whenever possible. The EOR was determined by comparing early contrast-enhanced MRI images (with T2w-FLAIR sequence) acquired within 24hrs after surgical treatment with the preoperative ones and calculated with the ABC/2 method. The residual volume (RV) which is recorded in $cm^3$ is defined as the post resection residual tumour volume. The radiological criteria used to define EOR and RV are hyperintense regions on T2w-FLAIR MRI axial images, and therefore can only be determined by comparing preoperative and postoperative tumour volumes on MRI (12). We define a GTR as the absence of residual disease in axial
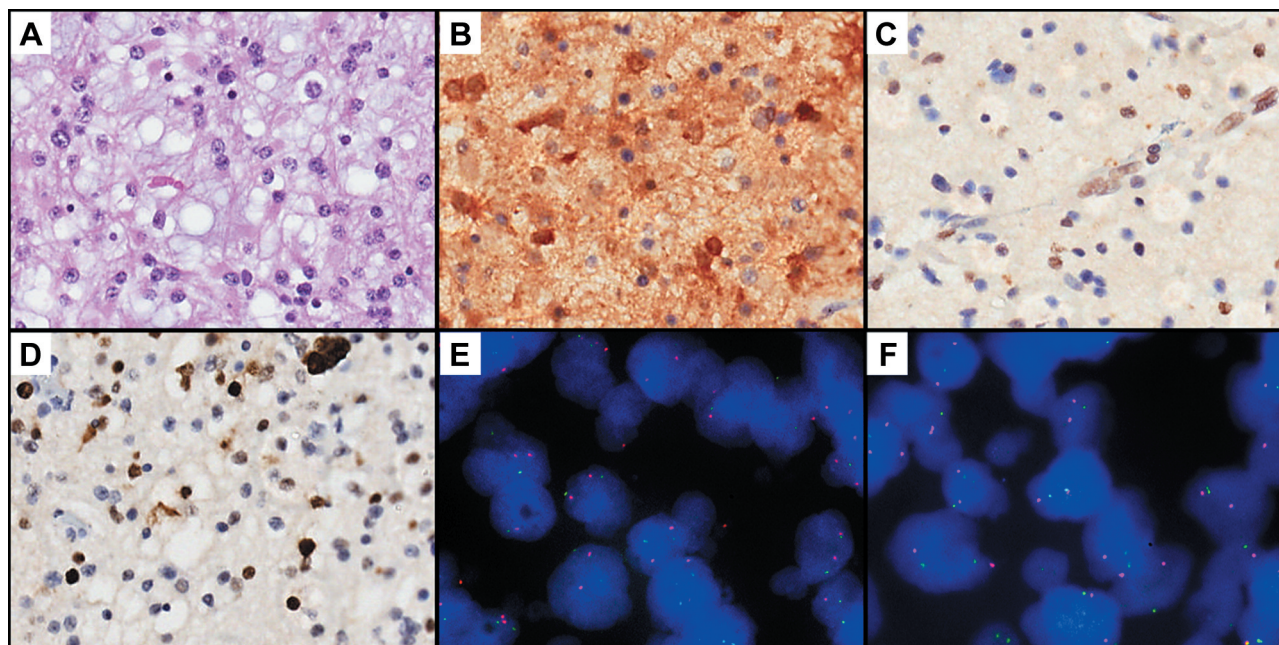
Figure 1. *Results of the diffuse astrocytoma (DA) group are illustrated. (A) An infiltrating astrocytic glioma of low cellularity with mild nuclear atypia, fibrillar background with mild oedema haematoxylin and eosin (H&E, 20×). (B) Immunohistochemistry for isocitrate dehydrogenase (IDH1 R132H) demonstrating strong cytoplasmic reactivity in neoplastic cells (20×). (C) Immunohistochemistry for ATRX Chromatin Remodeler revealing loss of nuclear staining in neoplastic cells (20×). (D) Immunohistochemistry for p53, showing strong nuclear staining in neoplastic cells. (E) Absence of 1p deletion in astrocytic glioma detected by fluorescence in situ hybridization (FISH) using the Vysis LSI 1p36 orange/1q25 green Dual-Color Probe kit (100×). (F) Absence of 19q deletion detected by FISH using the Vysis LSI 19q13 orange/19p13 green Dual-Color Probe kit (100×). Sample is considered negative for 1p/19q co-deletion.*

T2w-FLAIR MRI images. At the same time, we consider STR to be an EOR >90%. The study did not include partial resections (resection <90%) and biopsies.

*Surgical management.* The surgical strategy aimed to maximise the extension of the resection of the T2w-FLAIR MRI signal, preserving the eloquent areas to avoid neurological deficits. Surgical procedures of 93.8% of patients suffering from DLLG involving the eloquent area were performed under cortical and subcortical white matter intraoperative electrical stimulation (IES), intraoperative neuromonitoring (IoN), cortical mapping through direct stimulation. A neuronavigational system (BrainLab, Vector Vision) was used in all cases. A Diffusion tensor imaging (DTI) fibre tracking was carried out to investigate the anatomical relationship between the lesions and the cortico-spinal tract (CST) and arcuate fascicles (AF). Patients with lesions involving eloquent cortical and subcortical structures underwent awake surgery procedures (AS) with the "Asleep-Awake-Asleep" anaesthetic technique. AS was performed on 32 patients (48.4%) presenting lesions involving eloquent areas, and 11 patients had lesions in the somatosensory area and the dominant temporal lobe, premotor lobe, and insula lobe. Similarly, five patients affected by lesions involving non-dominant supplementary and primary motor areas and non-dominant insular lobes were treated in AS, in which cortical and subcortical IES enabled the detection of corticospinal lesions. Electrocardiography and electroencephalography were routinely added to the standard

monitoring setup throughout the procedure to monitor the occurrence of intraoperative seizures. Cortical brain mapping required a maximum of 4 mA of current intensity and subcortical brain mapping required 6 mA of simulation (Figure 3). Language abilities were evaluated using standard stimuli, such as counting, picture naming, and reading tasks.

*Neuro-oncology follow-up.* OS was recorded in months and measured from the date of diagnosis to the date of death or date of the last contact, if alive. KPS was globally evaluated at the final follow-up endpoint and was subject to changes during therapeutic and rehabilitative treatment. Clinical and demographic information was obtained from the digital database of our institution, whereas OS data were obtained by telephone interview. A neuroimaging follow-up was performed on all patients. They received their first brain MRI within 24 h of surgery. In addition, they received a brain MRI 30 days after surgery for the radiation treatment planning, three months after surgery, and at the end of the adjuvant treatment. A multidisciplinary team that worked for integrated care discussed and evaluated all the cases. In case of malignant transformation of the tumour, adjuvant treatment and surgical indication followed the European Federation of Neurological Societies (EFNS) international guidelines for high-grade glioma (HGG) management.

MRI scans are used for diagnosis of malignant transformation. The criteria include the following: neo-angiogenesis and microvascular proliferation is a necessary step in the malignant transformation of
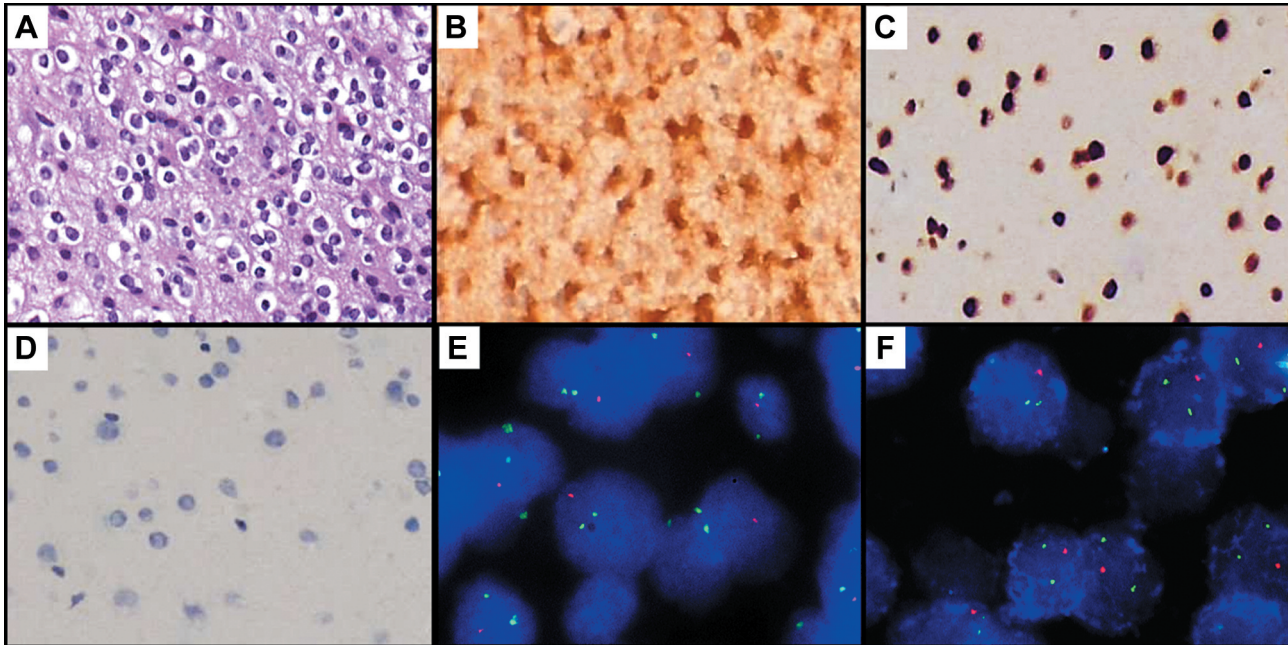
Figure 2. *Results of the oligodendroglioma (OG) group are illustrated. (A) A glial tumour with uniformly round nuclei slightly larger than normal oligodendrocytes, with increase in chromatin density and perinuclear halo [haematoxylin and eosin (H&E 20×)]. (B) Immunohistochemistry for isocitrate dehydrogenase (IDH1 R132H) demonstrating strong cytoplasmic reactivity in neoplastic cells (20×). (C) Immunohistochemistry for ATRX Chromatin Remodeler revealing nuclear stain in neoplastic cells (20×). (D) Negative stain for p53 immunostain. (E) 1p deletion detected by fluorescence in situ hybridization (FISH) using the Vysis LSI 1p36 orange/1q25 green Dual-Color Probe kit (100×). (F) 19q deletion detected by FISH using the Vysis LSI 19q13 orange/19p13 green Dual-Color Probe kit (100×). Samples are considered positive for 1p/19q co-deletion.*
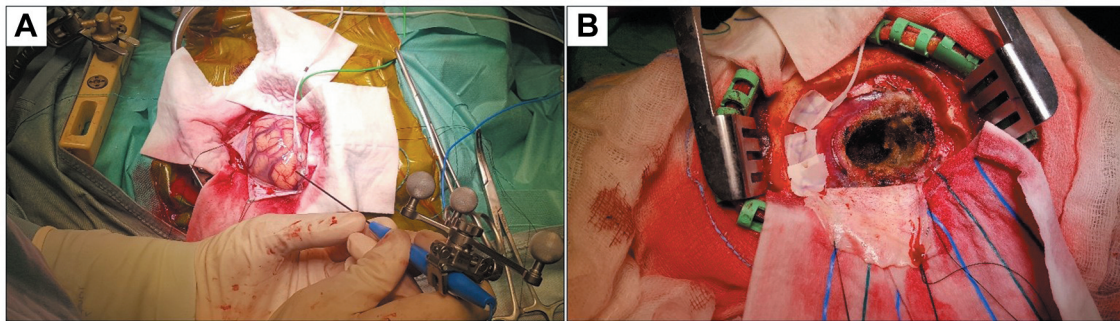


Figure 3. *Intraoperative magnetic resonance imaging-guided diffuse low-grade gliomas (DLGGs) surgery with the asleep-awake-asleep anaesthetic technique and intraoperative functional mapping and monitoring: (A) Brain mapping with preoperative functional magnetic resonance imaging (fMRI) and intraoperative diffusion tensor imaging (DTI); (B) Safe gross total resection (GTR) of isocitrate dehydrogenase (IDH)-mutated diffuse astrocytoma in the eloquent area of the brain.*

DLGG and may be detectable by perfusion imaging and rCBV >1.75 time to progression (12); to identify malignant transformation, a multivariate model has been used that incorporates choline (Cho)/creatine (Cr), cho/N-acetyl aspartate (NAA), and NAA/Cr ratios (13); the presence of contrast enhancement in previously non-enhancing tumours is thought to be indicative of advance grade progression.

Those patients who did not complete the follow-up at our institution were excluded from this study.

*Adjuvant treatment.* Adjuvant treatment consisted of low dose conformal radiotherapy immediately postoperatively (45-54 Gy/30 fractions) for up to six weeks. The chemotherapy was administered after progression to malignant transformation and treatment with TMZ (75 mg/m$^2$/day) for up to six weeks followed by maintenance therapy with a standard TMZ (150-200 mg/m$^2$ five days, every 28, for 12 cycles) (14). Some patients with high risk, according to RTOG (age <40 years; subtotal resection), were

Table I. *Demographic characteristics of the diffuse astrocytoma isocitrate dehydrogenase (IDH)-mutant group vs. the oligodendroglioma IDH-mutant and 1p/19q-codeleted group.*

| | DA Group<br>Diffuse astrocytoma (DA) IDH-mutant<br>and 1p/19q-codeletion absent | OG Group<br>Oligodendroglioma (OG)<br>IDH-mutant with 1p/19q-codeletion |
|---|---|---|
| Sex, N. (%) | | |
| Male | 21 (56.7) | 18 (62.1) |
| Female | 16 (43.2) | 11 (37.9) |
| Age (SD) | 55.2 (19.1) | 49.2 (11.1) |
| Eloquent location, N. (%) | | |
| Not | 19 (51.3) | 14 (48.2) |
| Motor | 9 (24.3) | 7 (24.1) |
| Language | 5 (13.5) | 3 (10.3) |
| Motor and language | 4 (10.8) | 5 (17.2) |
| Tumours side, N. (%) | | |
| Frontal | 16 (43.2) | 11(37.9) |
| Parietal | 7 (18.9) | 5 (17.2) |
| Temporal | 11(29.7) | 7 (24.1) |
| Occipital | 6 (16.2) | 5 (17.2) |
| Insular | 3 (8) | 1 (3.4) |
| Laterality, N. (%) | | |
| Left | 19 (51.3) | 17 (58.6) |
| Right | 18 (48.6) | 12 (41.3) |
| Surgery type, N. (%) | | |
| GTR | 18 (48.6) | 13 (44.8) |
| STR | 19 (51.3) | 16 (55.1) |
| Awake | 9 (24.3) | 7 (24.1) |
| Neurophysiological monitoring | 14 (37.8) | 10 (34.4) |
| Intraoperative ultrasound | 17 (45.9) | 13 (44.8) |
| Radiation dose | | |
| Total doses Gy (SD) | 53.6 (3.2) | 52.8 (7.3) |
| Fractions (SD) | 28.9 (1.4) | 28.5 (5.7) |
| Residual tumour, cm$^3$ (SD) | 3.21 (1.9) | 2.97 (3.07) |
| Median follow-up, Months (SD) | 51.2 (12.8) | 76.6 (14.7) |
| Recurrent surgery N. (%) | | |
| 0-2 Years | 4 (10.8) | 1 (3.4) |
| 2-5 Years | 14 (37.8) | 7 (24.1) |
| >5 Years | 19 (51.3) | 21 (72.4) |

SD: Standard deviation; STR: subtotal resection; GTR: gross total resection.

treated with Procarbazine, Lomustine and Vincristine combination chemotherapy (PCV).

*Statistical analysis.* Univariate analyses were performed within the single subgroups for sex, age, EOR, radiotherapy dose and fraction, IDH1 mutations status, EGFR amplification/EGFR variant-III mutation and TP53 mutation. The different subgroups were analysed regarding OS and PFS using Kaplan–Meier survival curves with log-rank tests. We conducted a contemporary parametric ANOVA multivariate regression analysis using the F-test. Independent variables used were sex, age, EOR (GTR, STR), radiotherapy dose, radiotherapy fraction, EGFR amplification/EGFR variant-III mutation and TP53 mutation. The dependent variables and endpoint variables were OS, PFS, and postoperative KPS. We performed a simultaneous regression model in which all the independent variables are simultaneously introduced into the regression equation. The analyses were conducted using IBM SPSS 25 statistics software.

*Institutional Review Board statement.* The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Sapienza University of Rome.

*Informed consent statement.* Informed consent was obtained from all subjects involved in the study, and written informed consent was obtained from the patients to publish this paper.

## Results

We retrospectively analysed a cohort of 66 patients and assigned them to the DA and OG Groups, based on their 1p/19q codeletion status, characterised by histological and molecular features summarised in Figure 1 and Figure 2. The two groups were divided into two subgroups, STR and GTR. The main features of enrolled patients are presented in Table I.

*DA Group*. In the DA group, the average OS was 71.3 months, PFS was 42.8 months, and TMT was 55.2 months, with an average KPS score of 85.5 and cumulative 5-year survival of 88.7%. For this group, the average follow-up period was 51.2 months. In the GTR subgroup, Average OS and TMT were longer (81.6 months and 63.6 months) than in OS and TMT values observed in STR group. Patients presented an average postoperative survival rate of 85.5. In the STR subgroup, the median OS was 60.4 months, with a PFS and a TMT average of 38.7 and 46.4 months, respectively. Patients of this subgroup, the average postoperative KPS was 92.4. We found significant differences between the subgroups for the following dependent variables: OS (*p*=0.012), PFS (*p*=0.003), time to malignant transformation (TMT) (*p*=0.001) and postoperative KPS (*p*=0.03). These data confirm that the GTR has an advantage in terms of OS, PFS, and TMT, as also shown in Figure 4, and that the result is strictly related to RV.

A total of 27 patients in the DA group received an adjuvant radio with irradiation ranging between 40 and 60 Gy (52.1±7.28 Gy) in averagely 27.2±6.4 fractions. The average volume of the right ventricle in the DA group was 3.3 cm$^3$; such parameter was further codified as a three-step ordinal variable, thus obtaining three subgroups of patients: RV <2 cm$^3$, 3 cm$^3$> RV ≥2 cm$^3$ and RV ≥3 cm$^3$. According to Figure 4, patients with RV <2 cm$^3$ have a significantly higher OS, PFS, and an advantage of TMT. The PFS of patients with RV <2 cm$^3$ is significantly higher than the other subgroups. Therefore, in the STR subgroup, the presence of a lower RV has a significant advantage in terms of PFS.

TP53 mutation was present in 6.4% of patients in the DA group. This mutation disclosed a statistically significant negative association with OS (r=–0.513; *p*=0.018; standard error (SE=0.159) and with PFS (r=–0.519; *p*=0.016; SE=0.161). 9.2% of these patients presented also an EGFR amplification/EGFRvIII mutation, negatively related with OS (r=–0.544; *p*=0.011; SE=0.162) and PFS (r=–0.561; *p*=0.008; SE=0.162). This analysis of correlation is reported in Table II. The EGFR amplification/EGFRvIII mutation is already an adverse prognostic factor for both OS and PFS in glioma after TMT.

*OG Group*. The OG group comprised 29 patients presenting an average OS of 87.9 months, a PFS of 56.3 months, a TMT of 69.1 months, and a KPS of 89.8 months. This group was followed by a medium follow-up period of 76.6 months. Overall, the OG group has a greater advantage in terms of OS, PFS, and TMT compared to the DA group (Table III). Thirteen patients in this group received a GTR and 16 received a STR. GTR subgroup reported an averaged 101.7 months OS, 64.9 months PFS, 80.3 months TMT and an average KPS of 84.2. This subgroup did not receive adjuvant chemotherapy or radiotherapy. The GTR subgroup of OG has a more extensive OS, PFS, and TMT than the GTR subgroup

Table II. *Correlation between overall survival (OS)/progression free survival (PFS) and mutations; TP53 mutation and epidermal growth factor receptor (EGFR amplification/EGFRvIII) mutation in the diffuse astrocytoma isocitrate dehydrogenase (IDH)-mutant group.*

|  | Overall survival | |
| --- | --- | --- |
| Correlation of Pearson | TP53 | EGFR |
| r | –0.513 | –0.544 |
| *p*-Value | 0.018 | 0.011 |
| Bootstrap | | |
|   Distortion | 0.012 | 0.002 |
|   Standard error | 0.159 | 0.162 |
|   Confidence interval 95% | | |
|     Inf | –0.780 | –0.817 |
|     Sup | –0.143 | –0.173 |

|  | Progression-free survival | |
| --- | --- | --- |
| Correlation of Pearson | TP53 | EGFR |
| R | –0.519 | –0.561 |
| *p*-Value | 0.016 | 0.008 |
| Bootstrap | | |
|   Distortion | 0.008 | 0.004 |
|   Standard error | 0.161 | 0.162 |
|   Confidence interval 95% | | |
|     Inf | –0.784 | –0.830 |
|     Sup | –0.151 | –0.186 |

Inf: Infimum; Sup: supremum.

of DA. The difference is also significant in terms of TMT as reported in Table III.

The STR subgroup had an average OS of 73.3 months, PFS of 48.2 months, TMT of 57.3, and the average postoperative KPS was 96.2 (Table III). In this subgroup, the average RV was 3 cm$^3$ (Figure 5). The following dependent variables showed a statistically significant difference between GTR and STR subgroups: OS (*p*=0.0001), PFS (*p*=0.002), and TMT (*p*=0.001). The results are summarised in Table III and their differences are illustrated in Figure 5. Compared to the DA subgroup, the STR subgroup of OG has a larger OS, PFS, and TMT. Although RV differences are less significant than DA's STR subgroup, as shown in Figure 5.

Table III summarises the results of the two groups of patients with their subgroups in terms of OS, PFS, 5-year survival (months), KPS, and TMT.

## Discussion

Low-grade gliomas are classified using molecular markers instead of histological and morphological characteristics. The DLGGs with 1p/19q codeletion show lower immune cell infiltration and lower expression of immune checkpoint genes than the non-codeletion cases (15). The 1p/19q co-deletion
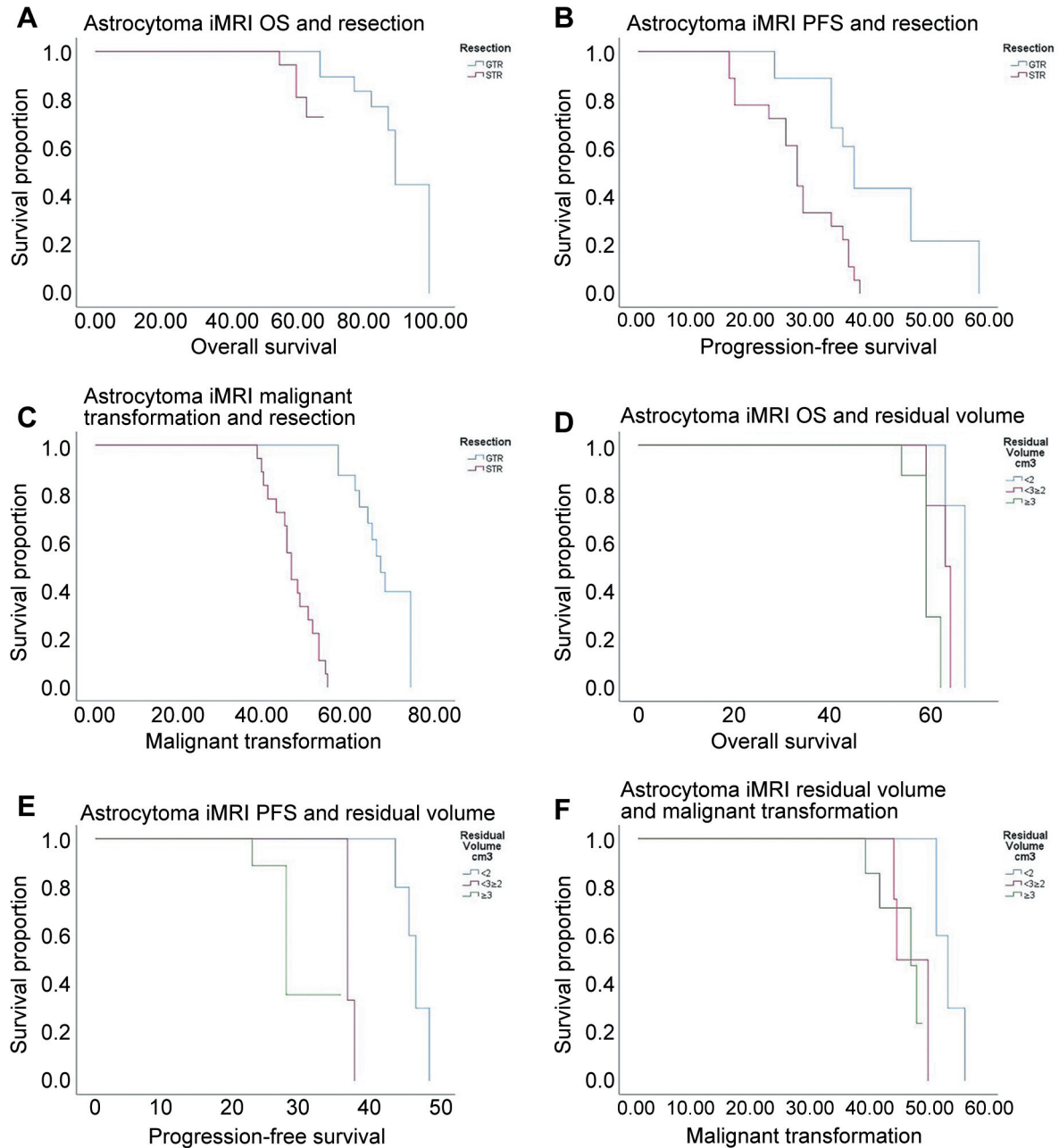
Figure 4. *Kaplan–Meier curves for the comparison in the diffuse astrocytoma isocitrate dehydrogenase (IDH)-mutant group. (A) Overall survival (months) comparison between subgroup gross total resection (GTR in blue) and sub-total resection (STR) (in red). (B) Progression-free survival (PFS) (months) between subgroups GTR (blue) and STR (red). (C) Malignant transformation (months) between subgroup GTR (blue) and STR (red). (D) Overall survival (months) comparison between the different subgroups with residual tumour volume (RV) less than 2 cm³ (blue), between 2 and 3 cm³ subgroup (red) and RV above 3 cm³ subgroup (green). (E) PFS (months) and RV (cm³) are compared between subgroups with RV <2 cm³ (blue), subgroup with RV between 2 and 3 cm³ (red) and subgroup with RV ≥3 (green). (F) Malignant transformation (months) and RV (cm³) between subgroups regarding RV <2 cm³ (blue), subgroup with RV between 2 and 3 cm³ (red) and subgroup with RV ≥3 cm³ (green).*

status reflects distinct tumour-associated macrophages (TAM) infiltration in gliomas, which is likely mediated by macrophage colony-stimulating factor (M-CSF) and transforming growth factor beta 1 (TGF1) signalling (16).

The presence of 1p/19q codeletion can be a discriminative feature for the diagnosis of DLGG and these would need to be analysed for 1p/19q codeletion status to meet 2021 WHO Classification of tumours of the CNS diagnostic requirements.
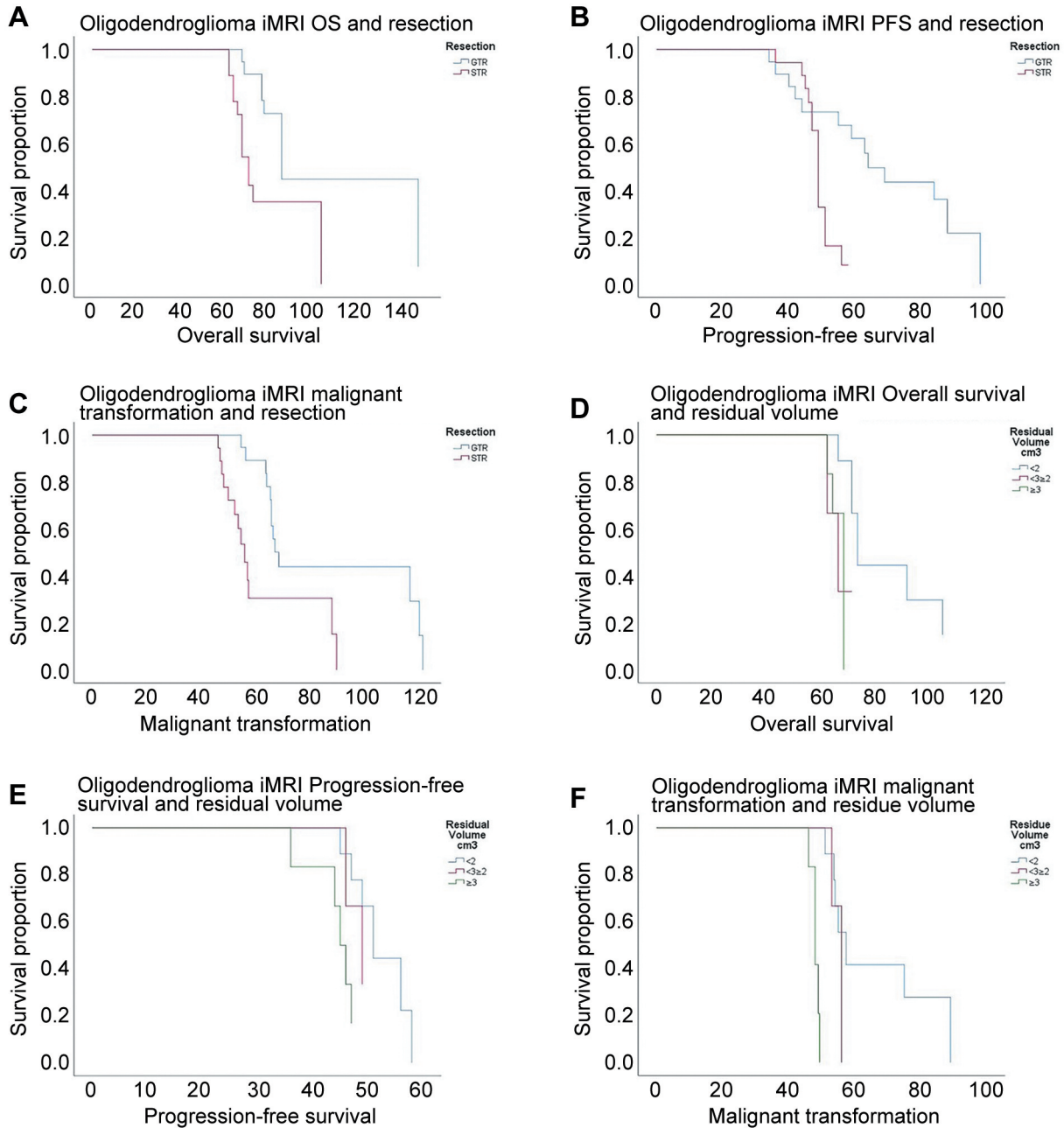
Figure 5. *The Kaplan-Meier curves are used to compare the oligodendroglioma isocitrate dehydrogenase (IDH)-mutated and 1p/19q codeleted group. (A) The overall survival (OS months) of the subgroup gross total resection (GTR in blue) and sub-total resection (STR) (in red). (B) Progression-free survival (PFS months) between Subgroup GTR (blue) and STR (red). (C) Malignant transformation (months) between subgroup GTR (blue) and STR (red). (D) OS comparison between different subgroups; with residual volume (RV) <2 cm³ (blue), with RV between 2 and 3 cm³ (red) and with RV ≥3 (green). (E) PFS (months) confront between subgroups with RV <2 cm³ (blue), subgroup with RV between 2 and 3 cm³ (red) and subgroup with RV ≥3 cm³ (green). (F) Malignant transformation (months) and residual volume (cm³) confront the subgroup with RV <2 cm³ (blue), subgroup with 2 ≤ RV <3 (red) and subgroup with RV ≥3 (green).*

In fact, a diffuse glioma that is histologically astrocytic, 1p/19q codeleted and IDH mutation need to be diagnosed as an oligodendroglioma (16, 17). The study aimed to investigate the impact of 1p/19q codeletion on prognosis, on long-term outcomes of patients and verify their independence from EOR. The specific objective of the authors study is to examine survival parameters (OS, PFS and TMT) in a cohort of patients affected by DLGG with accurate and distinct genetic patterns.

Table III. *Overall survival (OS), progression-free survival (PFS), Karnofsky Performance Status (KPS), and time to malignant transformation (TMT) in diffuse astrocytoma (DA) isocitrate dehydrogenase (IDH)-mutant and the oligodendroglioma IDH-mutant with 1p/19q codeletion.*

| Tumour type | N° | OS (STD) | PFS (STD) | 5-year survival rate (STD) | KPS (STD) | TMT (STD) |
|---|---|---|---|---|---|---|
| Diffuse astrocytoma IDH-Mutant (DA group) | 37 | 71.3 (12.6) | 42.8 (6.8) | 88.7% | 85.5 (15.5) | 55.3 (10.8) |
| GTR | 16 | 81.6 (8.3) | 45.9 (8.3) | 93.1% | 83.4 (6.8) | 63.6 (7.5) |
| STR | 21 | 60.4 (4.5) | 38.7 (7.8) | 75.5% | 92.4 (4.9) | 46.4 (5.2) |
| *p*-Value GTR *vs*. STR | | <0.012 | <0.003 | | 0.03 | <0.001 |
| | | | | | | |
| Oligodendroglioma IDH-Mutant and 1p/19q Codeleted (OG group) | 29 | 87.9 (28.8) | 56.3 (15.9) | 91.1% | 89.8 (10) | 69.1 (23.8) |
| GTR | 13 | 101.7 (32.9) | 64.9 (21.4) | 98.7% | 84.2 (11.8) | 80.3 (26.4) |
| STR | 16 | 73.3 (12.9) | 48.2 (4.8) | 80.9% | 96.2 (5) | 57.3 (12.9) |
| *p*-Value GTR *vs*. STR | | 0.0001 | <0.002 | | | 0.001 |

STD: Standard deviation; STR: subtotal resection; GTR: gross total resection.

All patients had undergone surgery between December 2008 and December 2018, using the Io-MRI from Sant'Andrea University Hospital of Rome. In addition, all included patients received a homogeneous schedule of adjuvant treatments and underwent the same neuro-radiological follow-up protocol. The selected patients were divided into two groups based on the presence of 1p/19q codeletion. Within the two groups, two subgroups were identified based on EOR (GTR and STR). We were able to compare the results with the same EOR grades. In our cohort, the maximal safe resection preserved neurological functions. Awake Surgery and Brain Mapping are the gold standards for safely maximising the resection of lesions affecting the eloquent areas. High safety and effectiveness profiles for resection lesions in the eloquent areas are guaranteed through the integrated use of these technologies and techniques (19). Several studies have strongly suggested that Io-MRI extends survival due to a greater EOR (20-22). Since neurological deficits have been associated with a poor oncologic prognosis as independent factors, we performed an appropriate approach to maximise the resection without compromising neurological function therefore reducing the risk of brain shift in neuronavigation after dural opening. (23-25).

Several trials studied the impact of treatment on survival and surgery compared to conservative treatments resulted in improving survival (26). According to our data, the first-line treatment depends on the markers analysed (27). Alternatively, Cordier asserts that the resection positively impacts survival, independent of the molecular markers. He reports a large cohort of DLGGs where higher EOR was not related to a better molecular prognosis (28). Our results demonstrate that the EOR and 1p-19q codeletion are two OS-independent prognostic factors. This molecular marker is mainly related to the TMT, and also related to the PFS. The comparison of the outcome of the subgroups GTR and STR shows that 1p/19q codeletion predicts an improved OS and a longer TMT.

The results of our study do not support the hypothesis proposed by Cordier *et al*., which states that longer survival of DLGG patients who benefited from a maximal EOR could be attributable to a favourable genetic profile (28).

Similarly to Scherer *et al*. (29), our data demonstrate that a lower RV <2 cm$^3$ is related to a better prognosis in terms of OS and PFS in both the examined patients. GTR group produced a statistically significant survival advantage compared to those associated with STR in the OG group (101.7 *vs*. 73.3 months, *p*=0.0001). Similar findings were confirmed in patients affected by DA (81.6 *vs*. 60.4 *p*=0.012), despite the globally shorter survival. Our data show that GTR is more significant, in terms of survival, in both the patient's group we examined. However, the patients who present this codeletion have an overall greater survival and its prognostic value results independent of EOR. Patients with DLGG IDH-mutated and 1p/19q codeletion have significantly greater survival than the patient without the codeletion. The presence of 1p/19q codeletion is associated with a longer PFS, and the most significant difference is related to a larger TMT. Regarding the EOR in surgery for DLGG, resection size is more strongly connected to PFS than OS (30-34). We found that patients with a GTR had a longer average PFS, independent of their molecular patterns. A significant PFS difference was observed in patients suffering from DA undergoing STR: an R <2 cm$^3$ was associated with a significantly longer PFS. A significantly longer TMT interval was observed in patients with 1p/19q codeletion. However, we found a significantly shorter TMT interval when the RV was greater than 3 cm$^3$ in this group of patients. We report that there is a strong statistical difference in TMT within the OG group between patients with RV less than 2 cm$^3$ *versus* those with RV greater than

3 cm$^3$. The higher the number of residual oncological cells, the greater the probability of malignant transformation.

The p53 positivity in >10% predicts TP53 mutations and Amplification/EGFRvIII mutation has already been reported as a negative prognostic factor for both OS and PFS in glioma after TMT (32). These mutations are commonly found in inactivating mutations in ATRX in IDH-mutated DLGGs. The suitability of death receptor 6 (DR6) as a prognostic marker was tested since it is up-regulated in gliomas and shows an aberrant signalling network. The effect of DR6 as a prognostic marker, playing an opposing role in primary and relapsed DLGG, is an interesting candidate for further studies (35).

In our study, the presence of a TP53 mutation and an EGFR amplification/EGFRvIII mutation in the DA group was associated with a shorter OS and PFS. These mutations were associated with a higher grade of glioma development.

## Conclusion

This study demonstrated that the EOR and 1p-19q codeletion are two independent prognostic factors on overall survival and do not support the hypothesis that longer survival of DLGG patients which benefited from a maximal EOR could be attributable to the presence of the 1p-19 codeletion. Furthermore, we investigated the role of the 1p/19q codeletion in DLGGs and presented the findings of 1p/19q codeletion as an independent prognostic factor associated with a prolonged survival and a longer TMT. We found that EOR maintains its role as a prognostic factor in managing DLGG treatment, especially when the residual volume is less than 2 cm$^3$, and that progression-free survival is longer for patients with DA IDH-mutated DLGG. TMT interval was significantly shorter in OG IDH-mutated and 1p/19q codeleted DLGG patients with RV less than 2 cm$^3$, compared to those with RV greater than 3 cm$^3$.

Patients who present with 1p/19q codeletion have an extended survival, independent of the surgical extent of resection. TP53 mutation and EGFR amplification/EGFRvIII mutation in DLGG are negatively correlated with OS and PFS.

## Conflicts of Interest

The Authors declare no conflicts of interest.

## Authors' Contributions

Conceptualisation, P.B., P.L., P.F. and G.D.A.; methodology, P.B. and P.F.; software, P.B. and P.F.; validation, G.D.A., A.S., F.A. and M.S.; formal analysis, P.F., A.D. and P.B.; investigation, P.B., G.C., A.P. and V.P.; resources, G.C. and V.P.; data curation, P.B, P.L., and A.D..; writing – original draft preparation, P.F., A.D., A.P. and P.L.; writing – review and editing, P.F., P.L., A.D. and M.R.; visualisation, M.S., A.F. and A.S.; supervision, P.F., P.L., G.D.A.,

A.S., F.A. and M.S.; project administration, P.B. and G.D.A.; funding acquisition, M.R. All Authors have read and agreed to the published version of the manuscript.

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