

# Impact of 1p/19q Codeletion Status in The Outcome of Patients Affected By Oligodendroglioma and Diffuse Astrocytoma: A Retrospective Single Surgeon Series With 1.5 Io-MRI Guided Surgery

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## Research Article

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# Abstract

**Purpose:** The real impact of the Extent of Resection in respect to the 1p/19q codeletion status in determining the outcomes of Low Grade Glioma (LGG) patients is extensively debated. The aim of this paper is to retrospectively analyze the oncologic outcomes of a homogeneous cohort of LGG patients who underwent surgery by a single operator, first author of the present paper (GDA).

**Methods:** A total of 66 patients suffering LGG who underwent craniotomy for tumor resection were operated on and retrospectively evaluated between 2008 and 2016 in a single center in which the operative theater was equipped with an I-MRI system. We compared a subgroup of 37 patients suffering from Diffuse Astrocytoma to a second subgroup of 29 patients affected by Oligodendroglioma. Volumetric analyses of the Extent of Resection (EOR) were performed, PFS and OS were accurately recorded and used as endpoint variable, as well as the 1p/19q codeletion status of every patient included in the final cohort.

**Results:** GTR produced a statistically significant survival advantage in respect to those associated with STR. This finding is confirmed even in patients suffering from Oligodendrogliomas (in the 1p/19q codeletion group 73.27 versus 101.73 months  $p=0.0001$ ). Similar findings were confirmed for patients affected by Diffuse Astrocytomas (81.63 versus 60.44 months  $p < 0.012$ ), despite the globally shorter survival.

**Conclusions:** We can affirm that the EOR is an independent predictor of survival advantage. The 1p/19q codeletion is an independent prognostic factor significantly associated to a globally longer survival and a longer time to malignant transformation.

## Introduction

### *1.1 Background*

The overall incidence of Central Nervous System (CNS) gliomas is estimated to range around 7.3 cases per 100.000 persons per year. Among them approximately 12.8 % are Low Grade Glioma (LGG) [1]. The new 2016 WHO classification definitively confirms the role played by isocitrate dehydrogenase IDH1 codon 132 or IDH2 codon 172 missense mutations ("IDH mutation") in defining the diffuse astrocytoma as IDH-Mutant and oligodendroglioma as IDH-Mutant and 1p/19q codeleted glioma [2]. Surgery, whenever safe and feasible represent the milestone in the management of LGG [3], nevertheless, evidences concerning its role in the management of the 1p/19q codeleted oligodendrogliomas are still widely lacking, considering the rarity of such a condition.

The present retrospective study analyzes the clinical surgical and oncologic outcomes of an homogeneous cohort of 66 LGG patients operated on by a single surgeon (the senior author of this paper G.D.A.), in the same Intraoperative MRI (I-MRI) equipped surgical theater, with a minimum follow-up of 4 years from their first surgery. Being, for Oligoastrocytomas, a precise molecular, genetic and epigenetic

“fingerprint” substantially absent, they have been canceled as distinct entities from the newest WHO classification [4] and were therefore excluded from the present investigation either. Patients whose lesions were located in critically eloquent areas, such as brainstem, diencephalon and in general every patient whose lesion was addressed with a biopsy or for whom the surgical target was ab initio a partial resection, were a priori excluded from the present investigation.

### *1.1 Objective*

The 1p/19q codeletion associated to IDH mutation, represents a critical positive prognostic factor for LGG surgery, with a better expected chemotherapy response [5]. However there’s still an extremely limited evidence supporting the role of adjuvant chemotherapy in patient diagnosed with IDH mutated, MGMT non methylated grade I and II gliomas, before their malignant transformation. The objective of the present study is therefore to analyze and to compare the outcomes regarding the classical survival (Overall Survival and Progression Free Survival), performance (Karnofsky performance score) and the time to Malignant Transformation endpoint variables in patients who received a Gross Total Resection (GTR) or a Subtotal Resection (STR) in order to understand a possible prognostic impact of an extensive surgical resection in regards to the 1p/19q codeletion.

## **Materials And Methods**

### *Participants and Eligibility*

We have analyzed all patients with LLG treated with lo-MRI surgery at the Sant’Andrea Hospital, University of Rome, since 2008 to 2018. A retrospective analysis was performed on 66 patients with histological diagnosis of LLG and we divided them into two groups: 37 cases of Diffuse astrocytoma IDH-mutant and 29 cases of Oligodendroglioma, IDH-mutant and 1p/19q-codeleted.

Inclusion criteria of this paper are:

- 1) histological diagnosis of WHO grade II of glioma histopathology, Diffuse astrocytoma IDH-mutant and Oligodendroglioma IDH-mutant and 1p/19q-codeleted,
- 2) evidence of surgical intervention with extent of resection (EOR) subtotal resection or gross total resection,
- 3) confirmed 1p/19q status of either absent or present and
- 4) patients  $\geq 18$  years old

No patient received a chemo-radiotherapy treatment before the surgical treatment. All patients and tumor characteristics were separated into two groups based on 1p/19q codeletion status being absent or present. The present retrospective analysis of patients suffering from LGG was performed on lesions

whose diagnoses were obtained on the ground of the WHO 2016 classification. Immunochemical and genetic evaluations were carried out according to the current guidelines.

### *Radiological Protocol*

Preoperative study included an objective neurological examination with evaluation of KPS score and a radiological study performed with MRI 1.5T after the administration of gadolinium and fluid-attenuated inversion recovery (FLAIR) with the integration of DWI, PWI sequences, and spectroscopy. In the case of patients with a lesion in an eloquent area, a functional MRI was performed. All patients carried out one or more lo-MRI with gadolinium and FLAIR after removing the tumor to verify that they had reached the target. Pre- and postoperative tumor volumes were assessed in a semiautomatic fashion using the Smart Brush tool in Brainlab Elements (version 2.1.0.15) and the T2w-FLAIR sequence (volumetric MPR whenever possible) was used for pre- and postoperative volumetric assessment. The EOR was determined by comparing early contrast-enhanced MRI images (with T2w-FLAIR sequence) acquired within 24 h after surgical treatment with the preoperative ones and calculated with the ABC/2 method. The Residual Volume (RV) was thereafter recorder either, in  $\text{cm}^3$ .

### *Surgical Protocol*

The surgical procedures of the 93.8 % of patients with LLG in the eloquent area were conducted under cortical and subcortical white matter intraoperative electrical stimulation (IES). A neuronavigation system (BrainLab, Vector Vision) was used in all cases a DTI Fibertracking[6] was carried out the disclose the anatomical relationship between the lesions and the tract cortico-spinal (CST) and arcuate fasciculus (AF).

Patients harboring lesions involving eloquent cortical and subcortical structures, underwent Awake Surgery procedures (AS) with the aid of Intraoperative Neuromonitoring (IoN), cortical and subcortical mapping through Direct Stimulation. Specifically, the patients underwent an “asleep-awake-asleep” approach employing a combination of propofol-remifentanyl and local analgesia, performed by a bilateral scalp block, at the supraorbital nerve, retro-auricular nerve, great occipital nerve and at the pinsite of the Mayfield head frame using a combination of lidocaine and ropivacaine.

Awake surgery was performed in a total of 32 patients (48.4%) suffering from lesions involving eloquent areas. Eleven patients presenting lesions located in the somatosensory area and in the dominant temporal lobe, premotor lobe and insula. Similarly, 5 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 pathways. All patients remaining awake from the beginning of the procedure with light sedation during skull opening, lo-MRI and closing. Throughout the procedure to monitor the occurrence of intraoperative seizures, Electrocorticography and Electroencephalography in free run mode were routinely added to the standard monitoring setup. The cortical brain mapping needed a maximum of 4 mA of current intensity and subcortical brain mapping of

6 or 8 mA of simulation. The language function was tested with standard stimuli such as counting, picture naming and reading tasks.

### *Clinical and Oncologic Follow Up Program*

Overall Survival was recorded in months; it was measured from date of diagnosis to date of death or date of last contact if alive. Clinical and demographic information was obtained by the digital database of our Institution, whereas OS data, were obtained by telephone-interview. A special focus was on the KPS results: such parameter was considered, as previously observed as associated to Survival. In particular it was recorded in three different moments: 1. Before surgery, 2. At 30 day after surgery and 3. At the end of the adjuvant treatment (the moment of the last outpatient evaluation). A close range dedicated neuro-imaging follow-up program was routinely performed in our Institution. This program included:

- A standard early (maximum 24 hours after surgery) postoperative volumetric brain MRI.
- At approximately one month from surgery (25-35 days) a volumetric brain MRI scan was repeated for a first step follow-up control and to provide information for the radiation treatment planning.
- Depending on the histological diagnoses, a volumetric brain MRI scan was performed every three or six months.

Generally, in case of malignant transformation, the follow-up as well as the adjuvant and surgical indication for further treatments followed the principles of high grade glioma (HGG) management. Malignant transformation is a MRI derived diagnosed including a combination of Perfusion parameters, Spectroscopic parameters change plus the Gadolinium enhancement.

### *Statistical Methods*

Univariate analyses were performed within the single subgroups for sex, age, EOR, radiotherapy dose and fraction, IDH1 mutations status, EGFR, TP53, and Ki-67 expression index, the different subgroups were compared concerning Overall Survival (OS) and Progression Free Survival (PFS) were conducted with Kaplan-Meier survival curves with log-rank tests. Nominal and dichotomous variables were compared  $\chi^2$ , or t-student tests whenever appropriate. Univariate Cox regression analyses and multivariate ANOVA analyses were then carried out with bootstrap regression, conducting different regression analyses on the data. The independent variables used were sex, age, preoperative KPS, EOR (GTR, STR), radiotherapy dose, radiotherapy fraction, EGFR over-expression and TP53 mutation. The dependent and endpoint variables were OS, PFS, and postoperative KPS. The so-called “enter” method was used in all regressions. It corresponds to a simultaneous regression model in which all the independent variables are simultaneously introduced into the regression equation. The analyses were carried out by means of the IBM® SPSS 25 statistics software.

### *Power of the study*

A potential source of bias is expected from exiguity of the sample, which nevertheless, in regards to the endpoints selected, presents an excellent post-hoc statistical estimated power ( $1-\beta = 0.904$  for  $\alpha 0.05$  and effect size “f” = 0.74), thus providing reliable conclusions.

The informed consent was approved by the Institutional Review Board of our Institution. Before surgical procedure, all the patients gave informed written explicit consent after appropriate information. Data reported in the study have been completely anonymized. No treatment randomization has been performed. This study is perfectly consistent with Helsinki declaration of Human Rights.

## Results

We retrospectively analyzed a cohort of 66 patients operated in the Neurosurgical Division of the “Sant’Andrea” University Hospital of Rome, the first center in Italy, availing of a lo-MRI system, and therefore the first center in Italy in using the lo-MRI for the management of LGG. The patients were assigned to the respective subgroup on the ground of the 1p/19q codeletion status (see Materials and Methods for details). The main features of the patients enrolled are summarized in Table 1.

In our cohort the most common histology was the IDH Mutant Diffuse Astrocytoma (56.06%), with 21 males (56.75%) e 16 females (43.25%) with an average age of  $55.22\pm 19.12$  years. In this subgroup GTR was achieved in 18 patients (48.65%) and STR in 19 patients (51.35%).

A total of 48.64% of the Diffuse Astrocytomas involved an eloquent area: in 24.32% it was a motor eloquent area, 13.51% were localized in language eloquent areas, whereas 10.82% involved other eloquent areas and language eloquent areas. Awake Surgery was performed in a total of 9 patients (24.32%), loN were employed in 14 patients (37.83%). Frontal lobe was the most commonly involved (43.25%), followed by temporal (29.72%), parietal (18.92%), occipital (16.12%) and insular (8.01%).

The average OS of patients suffering from IDH-mutant Diffuse Astrocytoma was of  $71.32\pm 12.61$  months, the mean of PFS was  $42.76\pm 6.85$  months, and the average malignant transformation interval was  $55.28\pm 10.82$  months, with an average KPS score of  $85.54\pm 15.53$  and a cumulative 5-years survival of 88.73%.

The OS of IDH-mutant Diffuse Astrocytoma in the GTR subgroup is  $81.63\pm 8.29$  months with a PFS of  $45.94\pm 8.28$  months, the average time to malignant transformation of this subgroups was  $63.65\pm 7.49$  months. These patients presented an average postoperative KPS of  $85.54 \pm 15.53$ .

In the STR subgroup OS was  $60.44\pm 4.47$  months with a PFS of  $38.72\pm 7.85$  months, and average time malignant transformation of  $46.44\pm 5.23$  months. In regards to this subgroup, we found that the patients had an average postoperative KPS of  $92.45\pm 4.86$ .

We found statistically significant differences between the aforementioned subgroups for the following dependent variables: OS ( $p=.012$ ), PFS ( $p=.003$ ), Time to Malignant Transformation ( $p=.001$ ) and postoperative KPS ( $p=.03$ ).

The average Residual Volume recorded was  $3.29 \pm 1.78 \text{ cm}^3$ ; such parameter was further codified as a three step ordinal variable, thus obtaining further 3 subgroups of patients:  $< 2 \text{ cm}^3$ ,  $3 \text{ cm}^3 < \text{RV} < 2 \text{ cm}^3$  and  $\geq 3 \text{ cm}^3$ .

In total, 6.38% of the patients belonging to the Diffuse Astrocytoma subgroup presented TP53 mutation, which disclosed a statistically significant negative association with OS ( $r = -.513$ ;  $p = .018$ ; Standard Error .159) and with PFS ( $r = -.519$ ;  $p = .016$ ; Standard Error .161) and 9.18% of these patients presented also a EGFR amplification/EGFRvIII mutation, negatively correlated with OS ( $r = -.544$ ;  $p = .011$ ; Standard Error .162) e PFS either ( $r = -.561$ ;  $p = .008$ ; Standard Error .162 - Table 2). The EGFR amplification/EGFRvIII mutation is already reported to be a negative prognostic factor for both OS and PFS in glioma after malignant transformation[7].

A total of 29 patients diagnosed up with Oligodendroglioma presented respectively an average OS and PFS of  $87.89 \pm 28.78$  months, and  $56.32 \pm 17.51$  months, with an average Time to Malignant Transformation of  $69.11 \pm 23.77$  and an average postoperative of KPS  $89.79 \pm 9.97$ .

In total, 13 patients were received a GTR and 16 a STR. The GTR subgroup averagely had an age of  $46.58 \pm 7.39$  years,  $101.73 \pm 32.92$  months of OS,  $64.91 \pm 21.4$  months of PFS,  $80.33 \pm 26.45$  months at Malignant Transformation and average KPS of  $84.16 \pm 11.76$ . This subgroup did not receive adjuvant schedules of chemo- or radiotherapy.

The STR subgroup has average age of  $52.77 \pm 13.86$  years, OS of  $73.27 \pm 12.91$  months, PFS of  $48.21 \pm 4.82$  months, Time to Malignant Transformation of  $57.27 \pm 12.91$  and an average postoperative KPS of  $96.19 \pm 4.97$ . The average RV in this subgroup was  $2.97 \pm 3.07 \text{ cm}^3$ . We found a statistically significant difference between these subgroups for the following dependent variables: OS ( $p = .0001$ ), PFS ( $p = .001$ ) and Malignant Transformation ( $p = .001$ ). The aforementioned results are summarized in Table 3, and graphically represented in Figure 1, 2, 3 and 4.

## Discussion

Aim of the present paper is to evaluate the real prognostic impact of surgery in the management of patients suffering from Oligodendrogliomas and Diffuse Astrocytomas with regard to the presence of the 1p/19q codeletion; considering that surgery, in high impact trials, was already reported to improve survival in respect to conservative treatments[8,9] although an histologic and molecular specific comparison of the aforementioned two subgroups of lesion was previously never performed. The specific target is here to examine the classical survival parameters (OS, PFS and Time to malignant transformation) in a series of patients suffering from LGG with precise and distinct genetic patterns, who underwent surgical procedures performed by a single operator (G.D.A). Moreover, as a further cluster of homogeneity of the present series, all the patients were operated on, between 2008 and 2016, with the aid of the lo-MRI of the "Sant'Andrea" University Hospital of Rome, at that time, the only center in Italy being

able to offer this technology. Lastly, all of the included patients received an absolutely homogeneous schedule of adjuvant treatments and underwent exactly the same radiological follow up protocol.

Several authors underline the need to re-appreciate the (impact of surgery in molecularly defined LGG: the investigation performed by Wijnenga supports maximal resection as first-line treatment for molecularly defined LGG[10] whereas Cordier demonstrated that resection positively impacts survival independently from the molecular markers[11]. The author argue that the 1p/19q non-codeletion group would experience a wider survival advantage in respect to patients harboring the 1p/19q codeletion.

In our series, GTR produces a critical and statistically significant survival advantage in respect to those associated with STR. This finding is confirmed even in patients suffering from Oligodendrogliomas (in the 1p/19q codeletion group 73.27 versus 101.73 months  $p=.0001$ ). Similar findings were confirmed for patients affected by Diffuse Astrocytomas (81.63 vs 60.44  $p < 0.012$ ), despite the globally shorter survival.

Several studies focused on the EOR in surgery for LGG, operated on without the aid of the lo-MRI[12,13], concluding that the extent of resection is positively associated with PFS, rather than with OS. Other authors[14,15] report a direct association of *both* the parameters with the EOR. Eseonu[16], reported that the amount of resection is positively associated with the patients' oncologic outcomes.

Scherer et al[17], in a multicentric retrospective trial summarizing the oncologic results of patients operated on with the aid of the lo-MRI, reports a continuous associations between the RV and PFS, confirming that the GTR is superior to incomplete resections in producing a significant survival advantage.

As far as the PFS is concerned, in our series we observed a statistically significant longer average PFS interval in patients who experienced a GTR independently from the molecular patterns (Table 3). Furthermore, in patients undergoing STR, the wider PFS difference was noticed in patients suffering from Diffuse Astrocytomas. A RV of less than 2 cm<sup>3</sup> is associated to a significantly longer PFS (Figure 1). The time to malignant transformation interval is significantly longer in patients presenting 1p/19q codeletion, although the presence of a RV is associated to a statistically significant shortening of this interval, especially when the threshold of 3cm<sup>3</sup> is overcrossed.

The use of lo-MRI increases the EOR, thus prolonging survival[18-22]. Awake Surgery and Brain Mapping are considered to be the gold standard to safely maximize the resection of lesions affecting the eloquent areas[23]. A combined use of such technologies and techniques, demonstrates, in our experience, an high safe and effectiveness profile for the resection of lesions affecting the eloquent areas[23]; it appears to be an appropriate approach to maximize the resection while sparing the neurological functions. Intraoperative Tractography, proved, in our experience, to be a reliable tool, as much as the lo-MRI driven Neuronavigation, after dural opening, dramatically reduces the risk of Brain Shift related Neuronavigation inaccuracies. On the ground of the previously reported findings, the target of our approach is to extend the resection within the limits of the neurological safety, since neurological deficits have been previously

reported as independent factors associated to a poor oncologic prognosis[24], thus matching the concept of pure brain based resection[25] with the concept of lo-MRI driven lesion resection.

### **Limitations of the present Study**

The main limitations of the present investigations are its retrospective nature, although the cohort presents an high homogeneity profile since all the patients enrolled were operated on with the same technologies (lo-MRI) and techniques (Awake Surgery and Brain Mapping), and underwent the same radiological follow-up protocol and superimposable adjuvant treatments schedules. A further possible bias derives from the relative exiguity of the cohort, which nevertheless presents a fair statistical power of the study. Other investigations are recommended to improve the statistical power of the conclusions concerning the association of the EOR and a prolonged survival.

## **Conclusions**

The EOR appears to be the key prognostic factor for OS and PFS in the management of LGG. The 1p/19q codeletion is an independent prognostic factor significantly associated to a globally longer survival and a longer time to malignant transformation. Diffuse Astrocytomas undergoing STR experience a statistically significant longer PFS when the RV is lesser than 2 cm<sup>3</sup>. The use of lo-MRI in surgery for LGG reduces the possibly catastrophic impact of the Brain Shift in the Neuronavigation guided resections, and can be safely and effectively combined with Awake Surgery approaches.

## **Declarations**

### **Compliance with ethical standards**

**Funding:** This study was no funded by any association.

**Conflict of Interest:** We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

### **Informed consent:**

Informed consent was obtained from all individual participants included in the study.

The patient has consented to the submission of this review article to the journal.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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## Tables

**Table 1** - Sex, age, tumor location, surgery type, radiation dose and fractions of patients.

<b><i>Characteristics of Patients</i></b>	<b>Diffuse astrocytoma, IDH-mutant</b>	<b>Oligodendroglioma IDH-mutant and 1p/19q-codeleted</b>
<b>Sex</b>		
<i>M</i>	21 (56.75%)	18 (62.06%)
<i>F</i>	16 (43.25%)	11 (37.94%)
<b>Age</b>		
<i>Average (STD)</i>	55.22 (19.12)	49.24 (11.14)
<b><i>Eloquent location</i></b>		
<i>Not</i>	19 (51.35%)	14 (48.27%)
<i>Motor</i>	9 (24.32%)	7 (24.13%)
<i>Language</i>	5 (13.51%)	3 (10.34%)
<i>Motor and Language</i>	4 (10.81%)	5 (17.24%)
<b><i>Tumor Side</i></b>		
<i>Frontal</i>	16 (43.24%)	11(37.97%)
<i>Parietal</i>	7 (18.91%)	5 (17.24%)
<i>Temporal</i>	11(29.72%)	7 (24.13%)
<i>Occipital</i>	6 (16.21%)	5 (17.24%)
<i>Insular</i>	3 (8.01%)	1 (3.44%)
<b><i>Laterality</i></b>		
<i>Left</i>	19 (51.35%)	17 (58.62%)
<i>Right</i>	18 (48.65%)	12 (41.37%)
<b><i>Surgery Type</i></b>		
<i>GTR</i>	18 (48.65%)	13 (44.82%)
<i>STR</i>	19 (51.35%)	16 (55.18%)
<i>Awake</i>	9 (24.32%)	7 (24.13%)
<i>Neurophysiological monitoring</i>	14 (37.83%)	10 (34.48%)
<i>Intraoperative ultrasound</i>	17 (45.94%)	13 (44.82%)

<b>Radiation Dose</b>		
Total doses of Gy (STD)	53.62 (3.2)	52.8 (7.31)
N° of fractions (STD)	28.96 (1.4)	28.48 (5.72)
<b>Residual Tumor</b>		
Value (STD)	3.21 (1.87)	2.97 (3.07)
GTV (STD)	26.89 (12.46)	23.68 (11.41)
<b>Recurrent surgery</b>		
0-2 Years	4 (10.81%)	1 (3.44%)
2-5 Years	14 (37.83%)	7 (24.13%)
>5 Years	19 (51.35%)	21 (72.41%)

**Table 2.** Correlation of Pearson: **A** Correlation of OS and TP53 mutation and EGFR amplification/EGFRvIII mutation in the Diffuse Astrocytoma IDH-Mutant group **B** Correlation of PFS and and TP53 mutation and EGFR amplification/EGFRvIII mutation in the Diffuse Astrocytoma IDH-Mutant group.

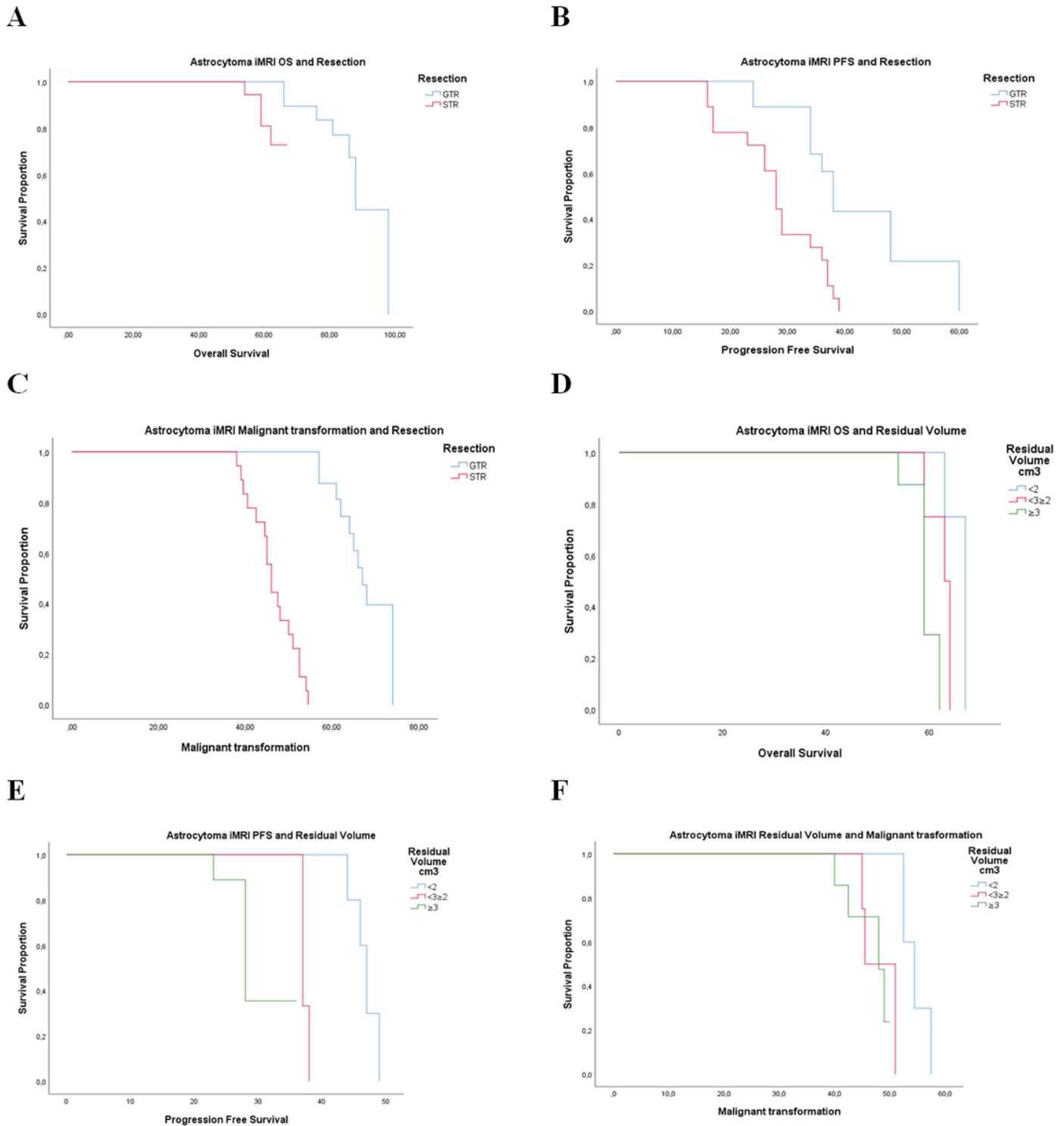
<b>A</b>		P53	EGFR	
<b>OS</b>	Correlation of Pearson	-.513	-.544	
	Pvalue	.018	.011	
Bootstrap	Distortion	.012	.002	
	Standard Error	.159	.162	
	Confidence Interval 95%	Inf	-.780	-.817
		Sup	-.143	-.173

<b>B</b>		P53	EGFR	
<b>PFS</b>	Correlation of Pearson	-.519	-.561	
	Pvalue	.016	.008	
Bootstrap	Distortion	0.008	.004	
	Standard Error	.161	.162	
	Confidence Interval 95%	Infer	-.784	-.830
		Super	-.151	-.186

**Table 3**– <sup>a</sup> Overall Survival (months), <sup>b</sup> Progression Free Survival (months), <sup>c</sup> 5 Years Survival(months), <sup>d</sup>Karnofsky Performance Status, <sup>e</sup>Malignant Transformation (months) in the Diffuse Astrocytoma IDH-Mutant and in the Oligodendroglioma IDH – Mutant and 1p/19q Codeleted

<i>Tumor type</i>	<i>N°</i>	<i>OS<sup>a</sup></i> <i>(STD)</i>	<i>PFS<sup>b</sup></i> <i>(STD)</i>	<i>5-Years</i> <i>S<sup>c</sup></i>	<i>KPS<sup>d</sup></i> <i>(STD)</i>	<i>Malignant</i> <i>Transf.<sup>e</sup>(STD)</i>
Diffuse astrocytoma IDH-Mutant	37	71.32 (12.61)	42.76 (6.85)	88.73%	85.54 (15.53)	55.28 (10.82)
<i>GTR</i>						
<i>STR</i>	16					63.65 (7.49)
Pvalue GTR vs STR	21	81.63 (8.29)	45.94 (8.28)	93.1%	83.38 (6.85)	46.44 (5.23)
		60.44 (4.47)	38.72 (7.85)	75.5%	92.45 (4.86)	< 0.001
		< 0.012	< 0.003			
<i>Oligodendroglioma IDH-Mutant</i> <i>and 1p/19q Codeleted</i>	29	87.89 (28.78)	56.32 (15.97)	91.1%	89.79 (9.97)	69.11 (23.77)
<i>GTR</i>						
<i>STR</i>						
pvalue GTR vs STR	13	101.73 (32.92)	64.91 (21.4)	98.7%	84.16 (11.76)	80.33 (26.45)
	16	73.27 (12.91)	48.21 (4.82)	80.95%	96.19 (4.97)	57.27 (12.91)
		= 0.0001	< 0.002			= 0.001

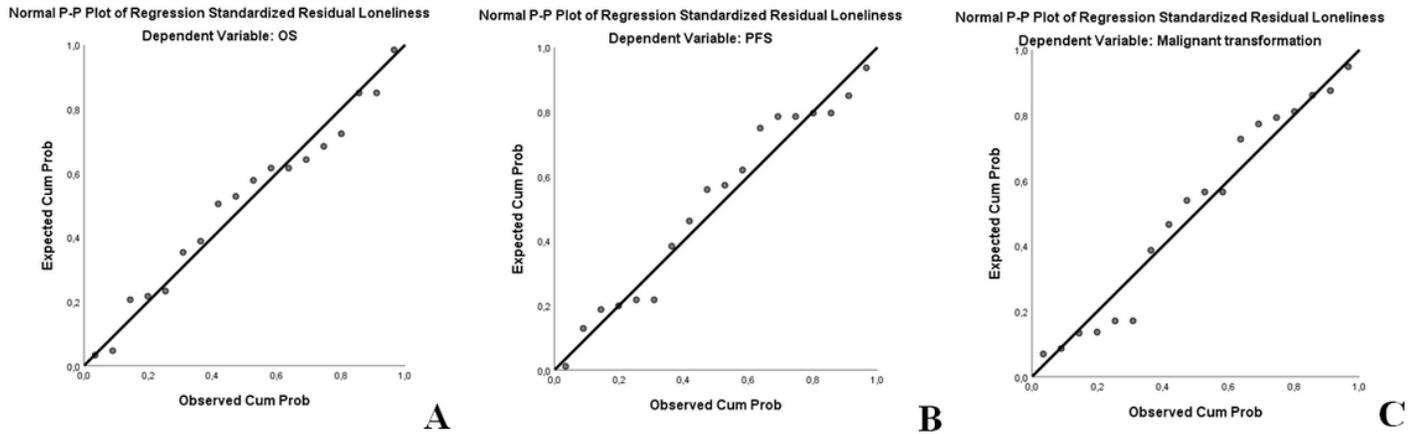
## Figures



**Figure 1**

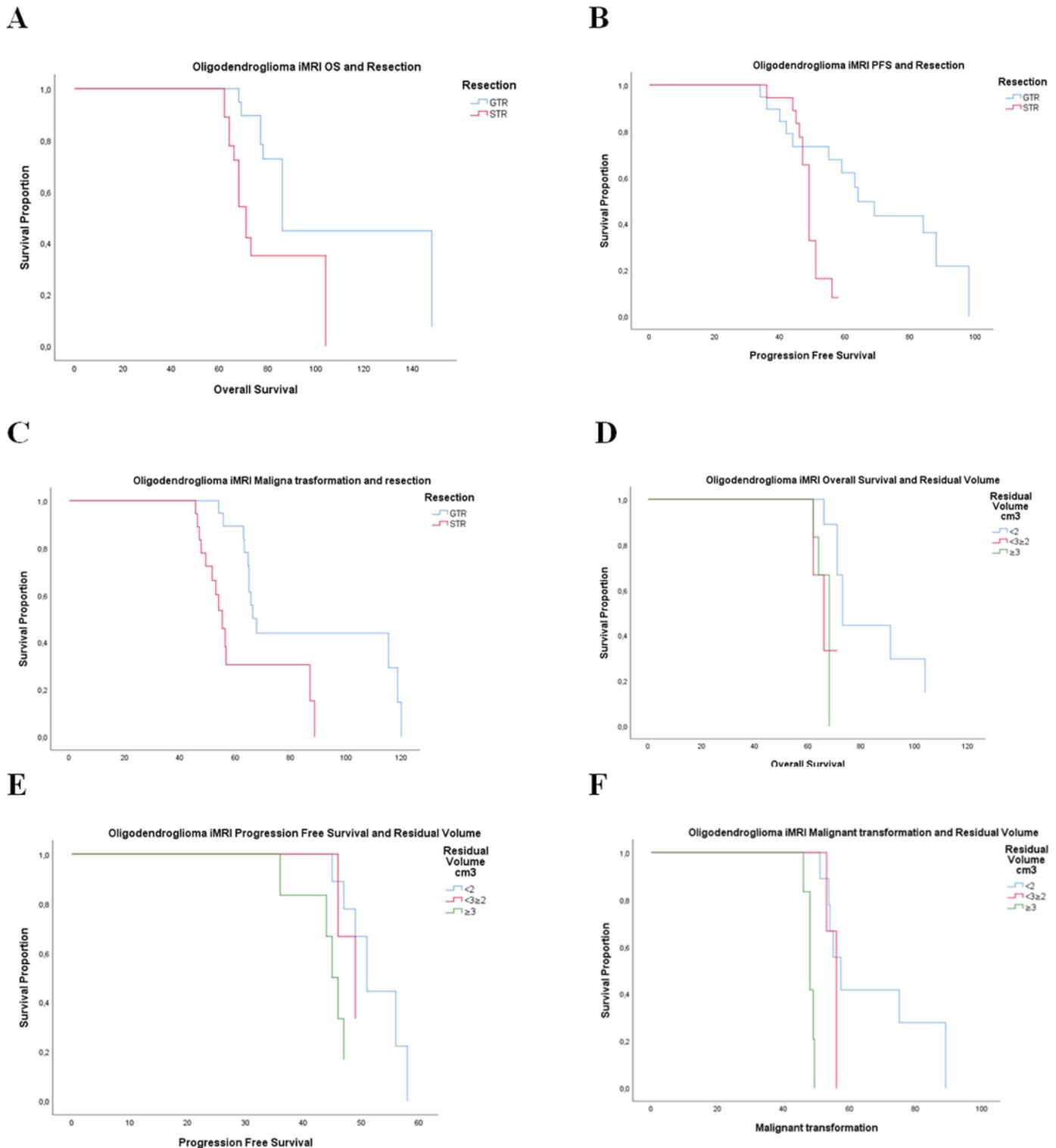
Kaplan–Meier curves for the confront in the Diffuse Astrocytoma IDH-Mutant group: A – Overall Survival (months) confront between subgroup GTR (blue) vs STR (red). B -Progression Free Survival (months) confront between subgroup GTR (blue) vs STR (red). C –Malignant transformation (months) confront between subgroup GTR (blue) vs STR (red). D - Overall Survival (months) and Residual Volume (cm<sup>3</sup>) confront between subgroup with Residual Volume < 2 cm<sup>3</sup> (blue), subgroup with Residual Volume < 3 &  $\geq 2$  (red) and subgroup with Residual Volume  $\geq 3$  (green). E - Progression Free Survival (months) and

Residual Volume (cm<sup>3</sup>) confront between subgroup with Residual Volume < 2 cm<sup>3</sup> (blue), subgroup with Residual Volume < 3 & ≥ 2 (red) and subgroup with Residual Volume ≥ 3 (green). F - Malignant transformation (months) and Residual Volume (cm<sup>3</sup>) confront between subgroup with Residual Volume < 2 cm<sup>3</sup> (blue), subgroup with Residual Volume between 2 cm<sup>3</sup> and 3 cm<sup>3</sup> (red) and subgroup with Residual Volume ≥ 3 cm<sup>3</sup> (green).



**Figure 2**

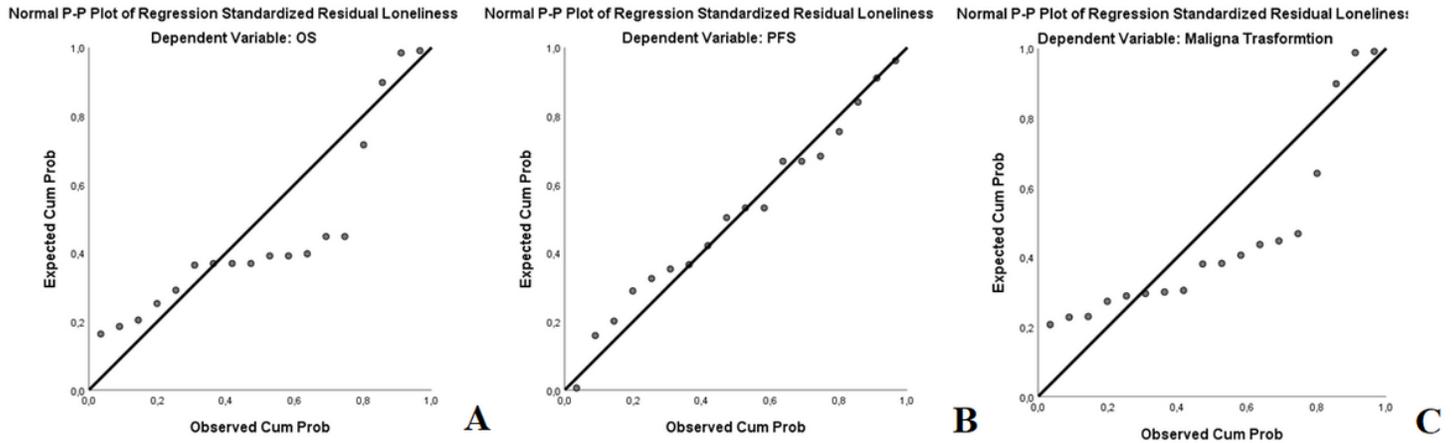
Normal P-P Plot of Regression Standardized Residual Loneliness for the confront in the Diffuse Astrocytoma IDH-Mutant Subtotal Resection Subgroup: A – Overall Survival (months) and Residual Volume (cm<sup>3</sup>) B - Progression Free Survival (months) and Residual Volume (cm<sup>3</sup>) C – Malignant Transformation (months) and Residual Volume (cm<sup>3</sup>).



**Figure 3**

Kaplan–Meier curves for the confront in the Oligodendroglioma IDH-Mutated and 1p/19q codeleted group: A – Overall Survival (months) confront between subgroup GTR (blue) vs STR (red). B -Progression Free Survival (months) confront between subgroup GTR (blue) vs STR (red). C – Malignant transformation (months) confront between subgroup GTR (blue) vs STR (red). D - Overall Survival (months) and Residual Volume (cm<sup>3</sup>) confront between subgroup with Residual Volume < 2 cm<sup>3</sup> (blue),

subgroup with Residual Volume  $< 3$  &  $\geq 2$  (red) and subgroup with Residual Volume  $\geq 3$  (green). E - Progression Free Survival (months) and Residual Volume (cm<sup>3</sup>) confront between subgroup with Residual Volume  $< 2$  cm<sup>3</sup> (blue), subgroup with Residual Volume between 2 cm<sup>3</sup> and 3 cm<sup>3</sup> (red) and subgroup with Residual Volume  $\geq 3$  cm<sup>3</sup> (green). F - Malignant transformation (months) and Residual Volume (cm<sup>3</sup>) confront between subgroup with Residual Volume  $< 2$  cm<sup>3</sup> (blue), subgroup with Residual Volume  $< 3$  &  $\geq 2$  (red) and subgroup with Residual Volume  $\geq 3$  (green).



**Figure 4**

Normal P-P Plot of Regression Standardized Residual Loneliness for the confront in the Oligodendroglioma IDH-Mutant and 1p/19q codeleted Subtotal Resection Subgroup: A – Overall Survival (months) and Residual Volume (cm<sup>3</sup>) B - Progression Free Survival (months) and Residual Volume (cm<sup>3</sup>) C – Malignant Transformation (months) and Residual Volume (cm<sup>3</sup>).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [DATA.xlsx](#)