Is FLAIRectomy Directly Correlated with Prolonged Survival in Glioblastoma? A Prospective National Multicenter Study on Correlation Between Extent of Tumor Resection and Clinical Outcome

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BACKGROUND AND OBJECTIVES: Several articles have demonstrated a positive correlation between glioblastoma supramarginal resection, based on MRI fluid-attenuated inversion-recovery (FLAIR) sequences (ie, FLAIRectomy), and prolonged survival. This study analyses the efficacy, safety, and reliability of FLAIRectomy in a multicentric cohort of patients, correlating the extent of FLAIR resection (EOFR) with clinical outcome and survival.

METHODS: One hundred fifty glioblastoma or grade IV astrocytoma patients (82 men), with a mean age of 58.2 years (range 36-82 years), from 3 neurosurgical centers were included. In all cases, supramarginal resection was deemed feasible preoperatively; multicentric neoplasms or tumors with enhancing nodule involving eloquent areas were excluded. Analysis of EOFR was based on comparison between preoperative and postoperative 3-dimensional FLAIR images. EOFR was compared with extent of tumor resection (EOTR) based on gadolinium-enhanced T1 sequences; theses data were also statistically correlated with survival parameters as well as with clinical and biomolecular data.

RESULTS: EOFR rate was 78.8% in the entire cohort, whereas EOTR based on T1 sequences was 98.3%. Mean progression free survival (PFS) and overall survival (OS) were 16.33 and 28.4 months, respectively. Adjusted Cox-regression models showed that a higher EOTR based on T1 sequences and EOFR were both associated with improved OS in individuals with either isocytrate dehydrogenase-1 wild-type or isocytrate dehydrogenase-1 mutated tumors. After adjustment, only the EOFR retained a statistically significant association with OS. Specifically, the risk of mortality decreased by 6.8% and 12.1% with each one-unit increase in EOFR, respectively. Further analysis based on artificial intelligence demonstrated that the cluster of patients with higher values of PFS and OS received greater rate of FLAIRectomy.

CONCLUSION: This multicenter study demonstrates that EOFR is a more reliable predictor of PFS and OS than extent of resection based on gadolinium-enhanced T1 sequences, if supramarginal resection is performed according to specific preoperative planning. 3-dimensional FLAIR navigation-guided resection may represent the optimal strategy to achieve a real FLAIRectomy.

KEY WORDS: FLAIR, FLAIRectomy, Glioblastoma, Supramarginal resection, Extent of resection, Survival

ABBREVIATIONS: 5-ALA, 5-aminolevulinic acid; **AI,** artificial intelligence; **ANOVA,** Analysis of Variance; **EOFR,** extent of FLAIR resection; **EOR,** extent of resection; **EOTR,** extent of tumor resection; **HGG,** high-grade gliomas; **HR,** hazard ratios; **IDH1,** isocytrate dehydrogenase-1; **KPS,** Karnofsky Performance Score; **OS,** overall survival.

The strategy for surgical treatment of glioblastoma (GBM) remains controversial.[1-7] Several articles demonstrated that extent of resection (EOR) is correlated with improvement in overall survival (OS) and progression free survival (PFS).[8-14] Recently, the idea that tumor resection should be extended beyond the tumor boundaries contoured on magnetic resonance T1 gadolinium-enhanced images has been applied with encouraging results.[15-22] The use of 5-aminolevulinic acid (5-ALA)[23] and other fluorophores (fluorescein, combined fluorophores, etc)[24] has proved to be effective in guiding GBM resection, with high sensitivity and specificity.[23] Nevertheless, the widespread application of fluorescence-guided surgery highlighted some inherent limitations of the technique.[25,26]

Previous studies investigated the feasibility of FLAIRectomy, based on the possibility to plan and extend the GBM resection to fluid-attenuated inversion-recovery (FLAIR) positive areas surrounding the gadolinium-enhancing tumor.[16,27-31] Intuitively, resection of FLAIR positive areas is strictly related to the respect of functional integrity.[7,10,13]

This is a prospective multicenter study demonstrating the effect of FLAIR-based supramarginal resection (FLAIRectomy) on patients' outcome.

METHODS

Patient Population and Inclusion Criteria

Three neurosurgical centers were involved. One hundred fifty GBM patients (82 men), with a mean age of 58.2 years (range 36-82 years), were prospectively included. Demographic data are summarized in Table 1. The 3 different centers were named: Site A, Site B, and Site C. Data were prospectively collected. The research protocol has been approved by the Institutional Ethical Committee of Site A, in the preliminary phase of the study. Subsequently, local Ethical Committees of Sites B and C adopted the same protocol. A specific part of the informed consent form focusing on the research goals (hence different from the consent form used for surgery) was always presented to all patients enrolled. The research consent form includes a specific section explaining potential benefits associated with supramarginal surgery and potential increased risks of related neurological sequelae.

Radiological evaluation of preoperative MRI was performed before inclusion, and all included patients were deemed suitable candidates to receive complete enhancing tumor resection. Inclusion and exclusion criteria are summarized in Table 2.

Preoperative Radiological Evaluation and Planning

Preoperative radiological evaluation included volumetric T1-weighted, with and without gadolinium, volumetric FLAIR, T2-weighted, and diffusion-weighted imaging sequences. Volumetric evaluation of preoperative MRI was performed both on gadolinium-enhanced 3-dimensional (3D) T1-weighted sequences and on 3D FLAIR sequences, using a manual segmentation method. Segmentation of FLAIR positive areas constantly included the enhancing tumor on T1 gadolinium-enhanced sequences. Therefore, 2 different volumes were preoperatively calculated for each patient: one volume based on the enhancing tumor contoured on T1 gadolinium-enhancing volumetric sequences and the other one based on FLAIR positive areas including enhancing tumor and the surrounding infiltrated white matter. The contouring of presumed tumor infiltration on FLAIR images was made by identification of differences in signal intensity found in the peritumoral areas[32,33] (Figure 1). The 2 final volumes (of both the enhancing tumor and FLAIR positive tumor) were the average of values identified by the 2 surgeons. After that, the relationships between FLAIR tumor-positive and eloquent cortical/subcortical areas were evaluated, and an extension of FLAIR resection (EOFR) was preoperatively calculated and planned accordingly, before starting surgery. We performed a grading of functional location of all tumors according to the article by Sawaya et al[34] in 1998. In cases of gadolinium-enhancing, grades II (near-eloquent) and I (noneloquent) tumors, a different extension of surrounding FLAIR positive regions, contoured as tumor-infiltrated areas, was identified preoperatively (in some grades I and II tumors, the surrounding abnormal FLAIR extended as far as to eloquent or near-eloquent areas).

Both 3D sequences (volumetric T1-Gad and volumetric FLAIR) were also made available for neuronavigation (Figure 2).

Intraoperative Fluorescence Guidance

Ninety-three of 150 patients underwent 5-ALA fluorescence-guided surgery. Dosage 5-ALA hydrochloride (5-ALA HCL, Gliolan, Medac GmbH) was 20 mg per kilogram (20 mg/Kg) of body weight administered orally 3 hours before anesthesia. The presence of 5-ALA positive brain areas in FLAIR positive zone was confirmed by neuronavigation, and the resection of all 5-ALA positive areas in noneloquent brain was performed.

Neuromonitoring and Neurological Evaluation

Intraoperative monitoring was used in 103/150 cases, according to the preoperative evaluation of tumor location (contoured on FLAIR sequences) and its relationship with eloquent cortical or subcortical areas. The standard neuromonitoring protocol included somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) recording as well as direct cortical and subcortical electrical stimulation. Eleven patients underwent awake surgery. The results and the role of intraoperative

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TABLE 1. Demographic and Clinical Characteristics of Patients Included in the Study

Characteristics	Mean/value (range) or frequency (%)
Patients enrolled	150
Patients/centers	
Site A	80
Site B	18
Site C	52
Age, y	62.7 (22-84)
Male	86 (57.3%)
Female	64 (42.7%)
MGMT methylation	71 (47.3%)
IDH1 mutation	63 (42.0%)
Preoperative tumor volume on T1-weighted, gadolinium-enhancing, MRI sequences	41.1 (0.6-106.6)
Preoperative tumor volume on FLAIR sequences	81.3 (5.5-227.7)
Postoperative radiation dose	61.3 (32-64)
Postoperative temozolomide cycles	6.1 (2-10)
EOR	98.3% (37.7-100)
EOFR	78.8% (22.7-100)
OS, mo	28.4 (8-57)
PFS, mo	16.3 (2-40)

EOFR, extent of FLAIR resection; EOR, extent of resection; FLAIR, fluid-attenuated inversion-recovery; IDH1, isocytrate dehydrogenase-1; MGMT, O^6-methylguanine-DNA methyltransferase; OS, overall survival; PFS, progression free survival.

TABLE 2. Inclusion and Exclusion Criteria Considered for Patients' Enrollment

Inclusion criteria	Exclusion criteria
MRI spectroscopy suggesting high-grade glioma	Recurrent tumors
	Gadolinium-enhancing nodule involving eloquent areas
Complete resection of enhancing tumor preoperatively deemed feasible	Patients already treated with biopsy or partial resections
	Pediatric patients
	Multifocal disease
	Pathological findings not compatible with glioblastoma or grade IV astrocytoma (postsurgery exclusion)

neuromonitoring are summarized in Table 3. Preoperative neurological status and postoperative neurological outcome are summarized in Table 4.

Intraoperative Neuronavigation

Gadolinium-enhanced, T1-weighted, 3D sequences and FLAIR 3D sequences were used for intraoperative navigation. The 2 data sets were merged before patient registration. T1 sequences were used as reference images, and either optic or electromagnetic surface tracer was used for patient registration.

Postoperative Radiological Evaluation

Postoperative MRI was obtained within 48 h after surgery in all patients, including volumetric T1-weighted, with and without gadolinium, volumetric 3D FLAIR sequences, T2-weighted and diffusion-weighted imaging. T1-weighted images before and after gadolinium infusion were compared with visualize hyperintense areas in the surgical cavity, differentiating blood clots (hyperintense both on images with and without gadolinium) from residual tumor (hyperintense only in gadolinium-enhanced sequences). Volumetric measurement of residual tumor was made using the same method described above for preoperative assessment on T1-weighted, gadolinium-enhancing, and FLAIR images (Figure 2). Extent of tumor resection (EOTR) analysis was then performed by calculating the rate of tumor resection, considering the values of preoperative and postoperative tumor volumes on T1-weighted gadolinium-enhancing and FLAIR sequences, according to the following formula[29]:

$$[(\text{Preoperative tumor volume} - \text{postoperative tumor volume}) / \text{preoperative tumor volume}] \times 100.$$

Thus, for each patient, 2 different EOR were obtained: EOTR on T1-Gad and extent of FLAIR resection (EOFR).

Analysis of O^6-Methylguanine-DNA Methyltransferase Promoter Methylation and Isocytrate Dehydrogenase-1 Mutation

O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status and isocytrate dehydrogenase-1 (IDH1) mutations were analyzed in all patients. Both MGMT and IDH1 were extracted form DNA amplified, purified, and then sequenced.

Survival Data and Statistical Analysis

Survival parameters were extracted from oncological charts and, in case of missing data, from telephone interview. Response Assessment in Neuro-Oncology criteria[35] were used to assess tumor progression. Follow-up scheme included brain MRI performed every 3 months. Karnofsky Performance Score (KPS) was used to assess patients' clinical status. Statistical analysis was made using the SPSS 22.0 software (IBM). The Analysis of Variance (ANOVA) test was used to determine statistical homogeneity between the 3

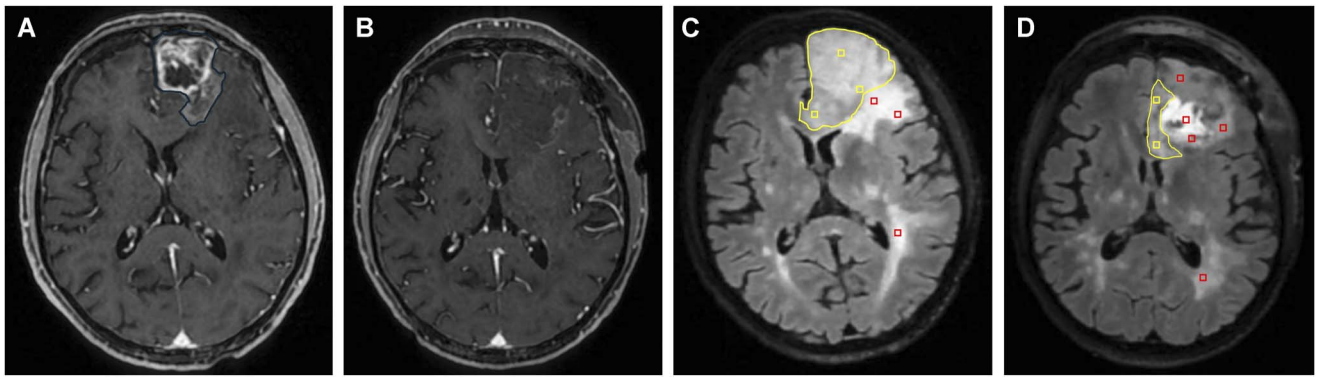

FIGURE 1. **A** *and* **B**, *Manual segmentation based on T1 gad and* **C** *and* **D**, *FLAIR sequences for volumetric evaluation of high-grade gliomas. Contouring of presumed tumor infiltration on FLAIR images was performed by identifying differences in signal intensity found in the peritumoral areas, involving the placement of ROIs in regions with different signal intensities. As it is known, the brain area surrounding the contrast-enhancing tumor exhibits lower signal intensity compared with the more distant white matter, which displays a FLAIR signal intensity similar to the oedema observed in noninfiltrating tumors (ie, meningioma, metastases). Based on these imaging features and after confirming the different signal intensities using multiple ROIs, manual segmentation of the tumor edges was conducted independently by 2 neurosurgeons at each center, both with specific experience in neuro-oncology.* **C**, *In this case, the yellow ROIs revealed a lower hyperintensity value than 3 red ROIs peripherically placed. This allows to differentiate tumor (yellow ROIs), included in segmented areas, from edema (red ROIs) excluded from segmented lesion.* **D**, *Same method described above (multiple ROIs analysis of hyperintense areas) has also been applied to the postoperative FLAIR images. Hyperintense areas surrounding the surgical cavity are often extended beyond the margins of the preoperative FLAIR-positive areas due to the effects of vascular damage or surgical manipulation. However, in all these cases, the hyperintense signal is similar to that of oedema; therefore, these areas have been excluded from volumetric evaluation. FLAIR, fluid-attenuated inversion-recovery; ROI, region of interest.*

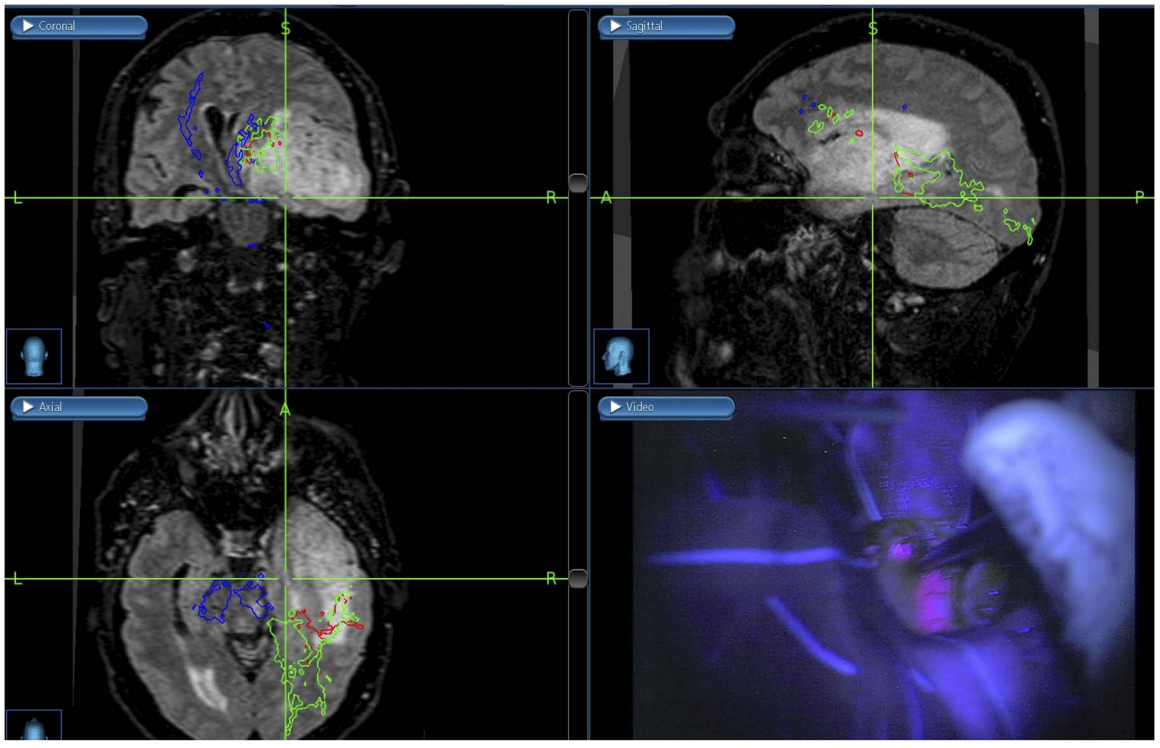

FIGURE 2. *Navigation of 3-dimensional fluid-attenuated inversion-recovery sequences and simultaneous use of 5-aminolevulinic acid in peritumoral areas is shown.*

TABLE 3. Results of Intraoperative Neuromonitoring

Characteristic	Value
Patients operated with neuromonitoring	109
Under general anesthesia	98
Awake surgery	11
MEPs	
Stable during surgery	88
Reduction of amplitude during surgery	21
SSEPs	
Stable during surgery	87
Reduction of amplitude during surgery	22
FLAIRectomy halted for positive neuromonitoring response (cortical/subcortical direct stimulation)	
Under general anesthesia	89
Awake surgery	3

FLAIR, fluid-attenuated inversion-recovery; MEP, motor evoked potentials; SSEPs, somatosensory evoked potentials.

TABLE 4. Preoperative Neurological Status and Postoperative Neurological Outcome

Characteristic	Value
Preoperative neurological status	
No deficits	28/150
Seizures	33/150
Headache	87/150
Neuropsychological impairment	43/150
Language deficit	22/150
Motor deficits	12/150
Neurological outcome (IONM worsened during surgery)	
Transient worsening (recover within 30 d)	12/150
Permanent deficits	9/150
Neurological outcome (IONM stable during surgery)	
Transient worsening (recover within 30 d)	5/150
Permanent deficits	1/150
Karnofsky performance status	
Preoperative	78.3
Postoperative (5 d after surgery)	64.8
Postoperative (last follow-up visit)	76.6

IONM, intraoperative neuromonitoring.

groups included in this study. The Student *t*-test was used to verify the presence of statistically significant differences between preoperative tumor volumes measured on T1 and FLAIR sequences.

Correlations between independent variables were tested using the Spearman correlation coefficient (ρ) to identify potential multicollinearity. Univariate analyses (Kaplan-Meier method and log-rank test) were conducted to compare OS and PFS among distinct groups. Unadjusted Cox regression analyses explored the individual associations of OS and PFS with each independent variable. Variables significantly associated with OS or PFS in the unadjusted analyses were incorporated into the adjusted multivariable Cox regression model. The findings are presented as hazard ratios (HR) and their corresponding 95% CI.

A further analysis has been performed, including all these clinical, radiological, and biological features in a data analysis software based on artificial intelligence (AI) to investigate the effect of these variables on OS and PFS, with the aim to find a role of EOFR as predictor of survival. A dimensionality reduction algorithm has been used for the AI data analysis.[36] Uniform manifold approximation and projection, a nonlinear dimensionality reduction technique, has been used. The goal of this analysis is to transform data from a high-dimensional space into a low-dimensional space to clean the data set and highlight only meaningful properties of the original data. The presence of a cluster distribution in graphical representation of uniform manifold approximation and projection confirms the presence of a common feature affecting OS and PFS in patients' cohort.

RESULTS

Patients' Selection

Enrollment of patients started in January 2020 and ended in November 2022. In total, 192 patients were screened. Thirty-eight were excluded before signing informed consent as they did not meet inclusion criteria. Four patients were excluded after surgery as histological examination revealed a diagnosis different from GBM. The enrollment was stopped when the goal of 150 patients included was reached. Patients' selection process is summarized in Figure 3.

Histopathological and Clinical Data

Histological examination confirmed the diagnosis of GBM or grade IV astrocytoma in all patients included in this study. MGMT promoter methylation was found in 71 of 150 patients (47.3%), whereas IDH1 mutated was detected in 63 of 150 patients (42%): All IDH1 mutated tumors were histologically classified as grade IV astrocytomas. KPS varied from a mean preoperative value of 78.3 to a mean postoperative value of 64.8. The mean KPS variation (KPS delta) was 15.6. PFS and overall survival were 16.33 (range 2-40) and 28.4 (8-57) months, respectively. In 138 of 150 (92 %) patients, progression was radiologically documented according to Response Assessment in Neuro-Oncology criteria[35] at the last follow-up magnetic resonance. The mean temozolomide cycle was 6.07 (range 2-10), and the mean radiation dose was 61.27 Gy (range 32-64). We did not observe statistically significant differences in complication rate

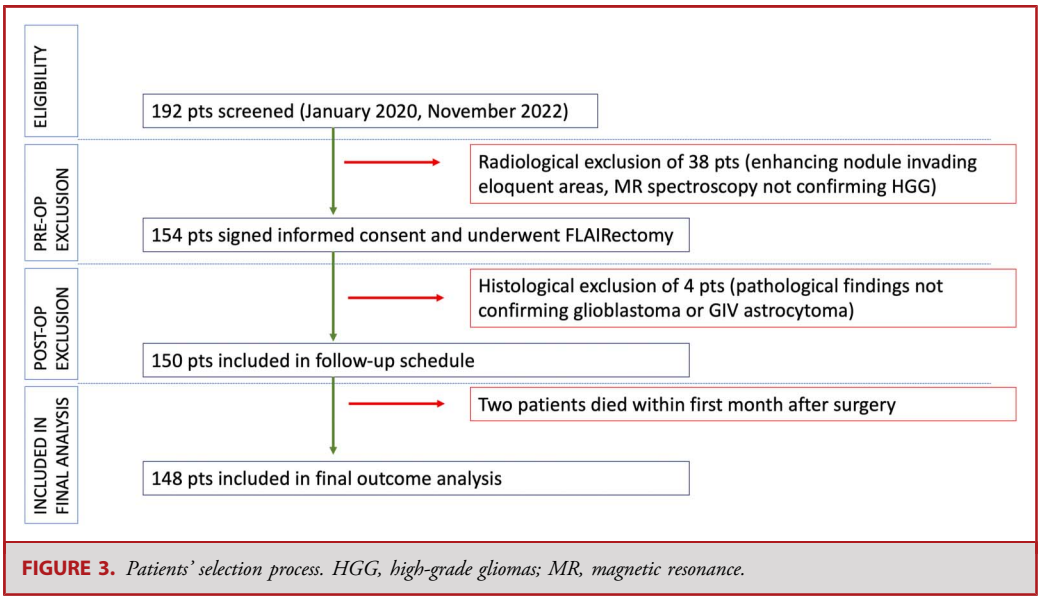

FIGURE 3. *Patients' selection process. HGG, high-grade gliomas; MR, magnetic resonance.*

comparing the 3 group of patients (ANOVA test, $P < .01$). Two patients (1.33%) died within the first month after surgery and could not receive adjuvant therapies. Both patients were excluded from survival and statistical analysis.

Intraoperative Neuromonitoring Findings and Neurological Outcome

Intraoperative changes of MEPs and SSEPs were recorded in 22 of 150 patients. In 10/22, worsening of evoked potentials recovered before the end of surgery and patients did not experience neurological deficits. In remaining 12 cases, intraoperative modifications of MEPs and SSEPs persisted at final stimulation: In all these patients, a postoperative neurological worsening was observed (Table 3) In 5 of 12 cases, neurological deficits recovered within 1 month after surgery; in remaining 9 cases, neurological worsening was permanent (vascular damage). Six patients without changes in intraoperative neuromonitoring recording experienced postoperative neurological worsening (Table 4).

TABLE 5. Summary of Volumetric Evaluation of Extent of Resection Based on Gadolinium-Enhanced T1 and FLAIR Sequences of MR Images

	T1-Gad	FLAIR	
Tumor volume (cc)			
Mean	58.7	75.9	[a]
Range	23.4-97.7	41.5-103.8	
Residual tumor volume (cc)			
Mean	1.9	4.2	[a]
Range	0.4-2.1	0.7-9.8	
Extent of resection (%)			
Mean	98.3	78.8	[a]
Range	37-100	22.7-100	

FLAIR, fluid-attenuated inversion-recovery.
[a]Statistically significant differences ($P < .05$).

5-ALA/FLAIR Correlation

After completing resection of gadolinium-enhancing nodule and verifying with navigation that FLAIR tumor-positive areas have been reached, 5-ALA fluorescence combined with neuromonitoring was used to safely perform supramarginal resection. We constantly found the presence of fluorescent tissue (usually not lava-like fluorescence) in FLAIR tumor-positive areas. Correlation between FLAIR-positive areas and FLAIR-positive regions was performed using neuronavigation in the different steps of fluorescence-guided microsurgical resection (Figure 2).

EOR Analysis

Grade III tumors according to Sawaya classification[34] were excluded. Sixty-four tumors have been classified as near-eloquent (grade II) and 86 as noneloquent (grade I).

The mean preoperative tumor volume on T1 gadolinium-enhancing, MRI sequences was 58.7 cc (range 23.4-97.7 cc); the mean preoperative tumor volume on FLAIR sequences was 75.9 cc (range 41.5-103.8 cc). The paired Student *t*-test revealed statistically significant differences between the 2 series of data ($P < .05$). According to the method previously described, EOTR was 98.3% (range 37%-100%) and EOFR was 78.8% (range 22.7%-

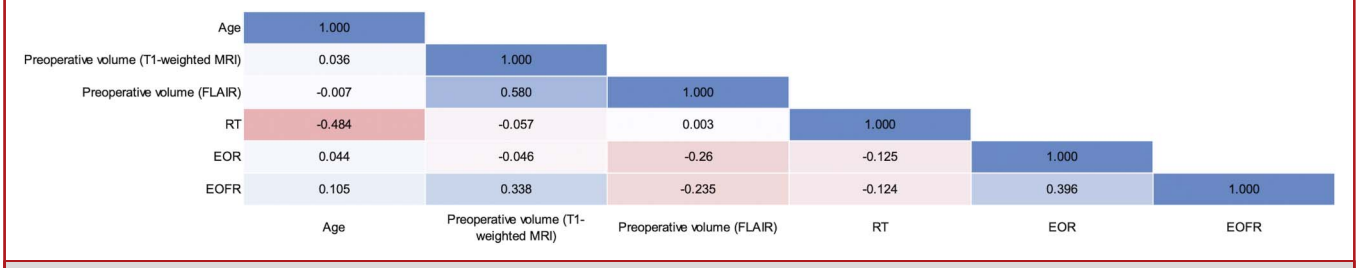

FIGURE 4. *Correlation analysis between different independent variables and survival parameters. EOR, extent of resection; EOFR, extent of FLAIR resection; FLAIR, fluid-attenuated inversion-recovery; RT, residual tumor.*

100%). Volumetric analysis of residual tumor was also made. We found a mean residual T1-weighted enhancing tumor of 1.9 cc (range 0.4-2.1 cc) and a mean residual FLAIR positive tumor of 4.2 cc (range 0.7-9.8 cc). Statistically significant differences in postoperative residual tumor volumes measured with the 2 different techniques were found according to the paired Student t-test ($P < .05$, Table 5).

In cases of gadolinium-enhancing, grades II (near-eloquent) and I (noneloquent) tumors, a different extension of surrounding FLAIR positive regions, contoured as tumor-infiltrated areas, was identified preoperatively. In 109 of 105 cases of grades I and II tumors, the surrounding abnormal FLAIR extended as far as to eloquent or near-eloquent areas. In all these cases, to maintain high level of surgical safety, intraoperative neuromonitoring was used to assist the resection of surrounding FLAIR tumor-positive areas in proximity of eloquent regions.

Statistical and Artificial Intelligence Data Analysis

We conducted an initial examination of potential correlations among the independent variables to mitigate the risk of multicollinearity biasing the analysis of predictors for both OS and PFS (Figure 4). No strong correlation among the examined variables was evident. EOFR showed moderately weak correlations with the volume based on the enhancing tumor contoured on T1 gadolinium-enhancing sequences ($\rho = 0.338$, $P < .001$), as well as with the volume based on FLAIR-positive areas, including enhancing tumor and the surrounding infiltrated white matter ($\rho = -0.235$, $P = .004$), and with EOR based on T1 gadolinium sequences ($\rho = 0.396$, $P < .001$).

For OS and PFS, univariate analyses did not reveal statistically significant differences between the 2 genders and according to the MGMT methylation status. On the contrary, the presence of IDH1 mutation was associated with longer OS (median = 33.0 months; 95% CI = 27.2-38.8) and PFS (median = 18.0 months, 95% CI = 16.5-19.6) compared with individuals with the IDH1 wild-type GBM (median OS = 23.0 months, 95% CI = 20.4-25.6; median PFS = 12.0 months, 95% CI = 9.3-14.7) (Figure 5).

The unadjusted Cox regression analysis confirmed the association of IDH1 mutation with improved OS and PFS. Specifically, HR for OS was 0.435 (95% CI = 0.310-0.611, $P = .001$), and the HR for PFS was 0.546 (95% CI = 0.392-0.760, $P < .001$). We stratified the subsequent analyses by IDH1 status. In the unadjusted Cox regression models, a higher EOR based on T1 sequences and EOFR were both associated with improved OS in

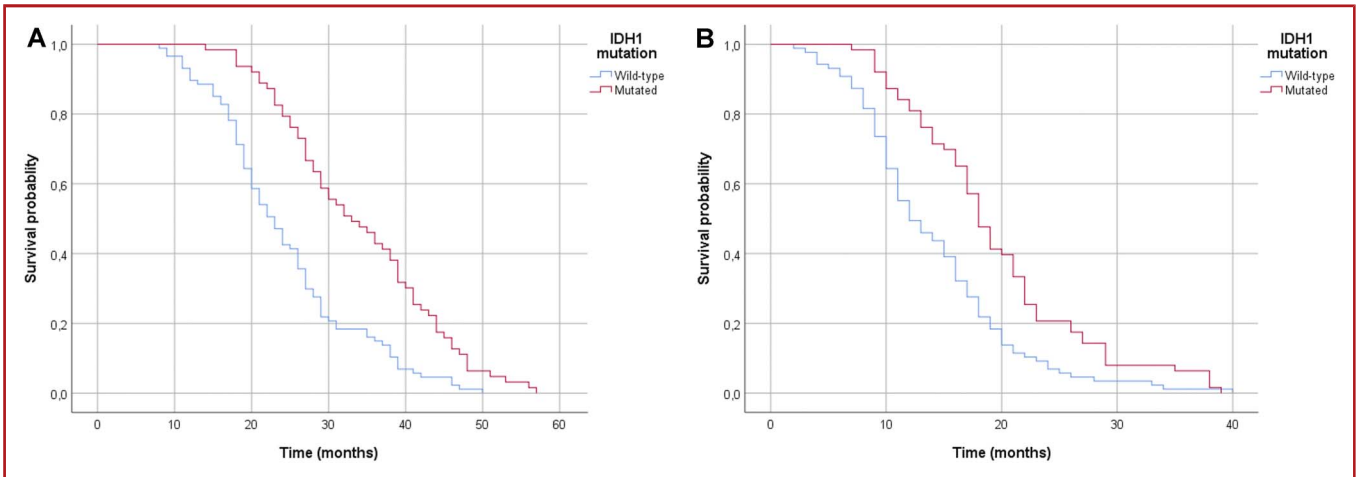

FIGURE 5. *Survival analysis according to IDH1 mutational status (A, overall survival and B, progression free survival). IDH1, isocytrate dehydrogenase-1.*

TABLE 6. Survival Analysis of Predictors Influencing Overall Survival

	Unadjusted model		Adjusted model[a]	
Characteristics	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
IDH1 wild-type				
Age[b]	0.986 (0.968-1.004)	.136	—	
Sex (male vs female)	1.060 (0.683-1.645)	.795	—	
MGMT methylation (yes vs no)	0.804 (0.518-1.249)	.332	—	
Postoperative radiation dose[b]	0.991 (0.952-1.030)	.637	—	
Postoperative TMZ cycles[b]	0.990 (0.971-1.009)	.301	—	
EOR[b]	0.981 (0.964-0.998)	.030	1.007 (0.985-1.029)	.549
EOFR[b]	0.933 (0.919-0.947)	<.001	0.932 (0.919-0.947)	<.001
IDH1 mutated				
Age[b]	0.990 (0.970-1.010)	.336	—	
Sex (male vs female)	0.939 (0.567-1.554)	.805	—	
MGMT methylation (yes vs no)	0.871 (0.521-1.458)	.600	—	
Postoperative radiation dose[b]	1.006 (0.985-1.029)	.571	—	
Postoperative TMZ cycles[b]	0.812 (0.597-1.105)	.185	—	
EOR[b]	0.652 (0.447-0.951)	.027	0.827 (0.555-1.231)	.349
EOFR[b]	0.879 (0.848-0.910)	<.001	0.879 (0.849-0.910)	<.001

EOFR, extent of FLAIR resection; EOR, extent of resection; IDH1, isocytrate dehydrogenase-1; HR, hazard ratios; MGMT, O^6-methylguanine-DNA methyltransferase; OS, overall survival; TMZ, temozolomide.

[a]The adjusted model incorporates independent variables that demonstrated associations with OS in the unadjusted models.

[b]Results are presented as HR along with their corresponding 95% CI for each one-unit increase in the independent variable.

individuals with either IDH1 wild-type or IDH1-mutated tumors. However, after adjustment, only the EOFR retained a statistically significant association with OS. Specifically, the risk of mortality decreased by 6.8% and 12.1% with each one-unit increase in EOFR, respectively (Table 6).

In IDH1 wild-type patients, the unadjusted Cox regression analysis revealed that a higher number of postoperative temozolomide cycles and a higher EOFR were associated with improved PFS. However, after adjustment, only EOFR maintained a statistically significant association with PFS. In IDH1-mutated patients, both a higher EOR based on T1 sequences and a higher EOFR were associated with improved PFS in the unadjusted analyses. After adjustment, only the EOFR remained significantly associated, reducing the risk of disease progression by 5.2% with each one-unit increase (Table 7).

The AI data analysis has been performed including 8 different variables (Figure 6) correlated with OS and PFS. The pattern of distribution of patients demonstrated that patients harboring higher rate of EOFR and IDH 1 mutation were had better clinical outcomes, with OS and PFS constantly higher than average value of the entire cohort.

DISCUSSION

EOR and Survival in High-Grade Gliomas

EOTR is a survival predictor in brain glioma surgery.[8-14] High-grade gliomas (HGG), often identified as the most infiltrating and aggressive brain tumors, should be considered as the manifestation of a complex tumorigenesis process involving not only the "visible" tumor but also the peritumoral areas.[3,4,16,35]

For years, GBM peritumoral areas have been considered as regions of tumor infiltration, where tumor cells could be found intermingled with normal brain tissue.[3,4,19,37]

In routine neurosurgical practice, resection of HGG aims to safely remove all visible tumor while respecting neurological functions. However, strategies aiming to increase EOTR (ie, 5-ALA and intraoperative imaging tools)[23,24,31] have the potential risk to mistakenly facilitate resection of eloquent brain, particularly in peritumoral infiltrated areas.

FLAIRectomy in HGG

In 2015, Li et al[18] published the results of a retrospective analysis on a cohort of patients who underwent surgery for HGG. They

TABLE 7. Survival Analysis of Predictors Influencing Progression-Free Survival

	Unadjusted model		Adjusted model[a]	
Characteristics	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
IDH1 wild-type				
Age[b]	0.990 (0.972-1.009)	.313	—	
Sex (male vs female)	1.044 (0.674-1.618)	.847	—	
MGMT methylation (yes vs no)	0.823 (0.536-1.262)	.371	—	
Postoperative radiation dose[b]	0.996 (0.958-1.034)	.818	—	
Postoperative TMZ cycles[b]	0.514 (0.301-0.879)	.015	0.637 (0.438-0.928)	.019
EOR[b]	0.997 (0.978-1.016)	.725	—	
EOFR[b]	0.949 (0.937-0.962)	<.001	0.950 (0.938-0.963)	<.001
IDH1 mutated				
Age[b]	0.999 (0.980-1.018)	.885	—	
Sex (male vs female)	1.357 (0.818-2.251)	.237	—	
MGMT methylation (yes vs no)	0.918 (0.555-1.519)	.739	—	
Postoperative radiation dose[b]	1.012 (0.989-1.036)	.312	—	
Postoperative TMZ cycles[b]	1.086 (0.802-1.470)	.594	—	
EOR[b]	0.632 (0.433-0.921)	.017	1.010 (0.988-1.032)	.392
EOFR[b]	0.886 (0.857-0.916)	<.001	0.948 (0.936-0.961)	<.001

EOFR, extent of FLAIR resection; EOR, extent of resection; IDH1, isocytrate dehydrogenase-1; HR, hazard ratios; MGMT, O^6-methylguanine-DNA methyltransferase; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide.
[a]The adjusted model incorporates independent variables that demonstrated associations with PFS in the unadjusted models.
[b]Results are presented as HR along with their corresponding 95% CI for each one-unit increase in the independent variable.

performed a review of 1229 operated cases and found that complete resection of T1-weighted, contrast-enhancing, tumor had been achieved in 71% of cases. A subgroup of these patients received a resection of ≥53.21% of the abnormal FLAIR area beyond the 100% T1-weighted, contrast-enhancing resection. In this subgroup, a significant survival prolongation, compared with that observed after resection of the enhancing tumor only, was documented (15.2 vs 9.8 months). The article by Li et al is the first to propose the idea to extend resection in abnormal FLAIR area surrounding T1-weighted, contrast-enhancing tumor. However, that study is retrospective and lacks a volumetric evaluation of EOFR. In modern neuro-oncology, volumetric assessment of resection is considered the most accurate method to objectively evaluate EOTR and it should be applied not only for research purposes but also for routine clinical use.[38] For this reason, in 2021, the idea to plan and perform "FLAIRectomy" has been introduced.[16]

Interpretation of Results

Our results, although limited to 150 patients only, demonstrate a direct and constant correlation between a more extended tumor resection (ie, supramarginal resection-flairectomy), which also includes FLAIR infiltrated areas around the T1-weighted, contrast-enhancing ones, and survival, confirming the results of the first monocentric study. In particular, analyzing this multicentric cohort, we found that a higher rate of FLAIR-based EOTR is associated with a prolonged OS. This also confirm the positive effect of our surgical multimodal protocol, aiming at supramarginal EOTR, on clinical outcome. The statistical analysis and the analysis based on AI demonstrated that higher rate of FLAIRectomy is constantly related to a better clinical outcome.

As demonstrated by Grabowski et al,[39] residual tumor is a survival negative predictor factor in GBM and a residual tumor volume smaller than 2 cm^3 can guarantee a significant improvement in clinical outcome. We performed a volumetric analysis of residual tumor both on T1 gadolinium-enhanced and on FLAIR sequences. We did not find a statistically significant correlation between residual tumor measured on T1-weighted, gadolinium-enhancing, or FLAIR sequences and survival.

A recent pooled meta-analysis highlighted the lack of consensus on the role of FLAIRectomy on survival.[40] Moreover, the

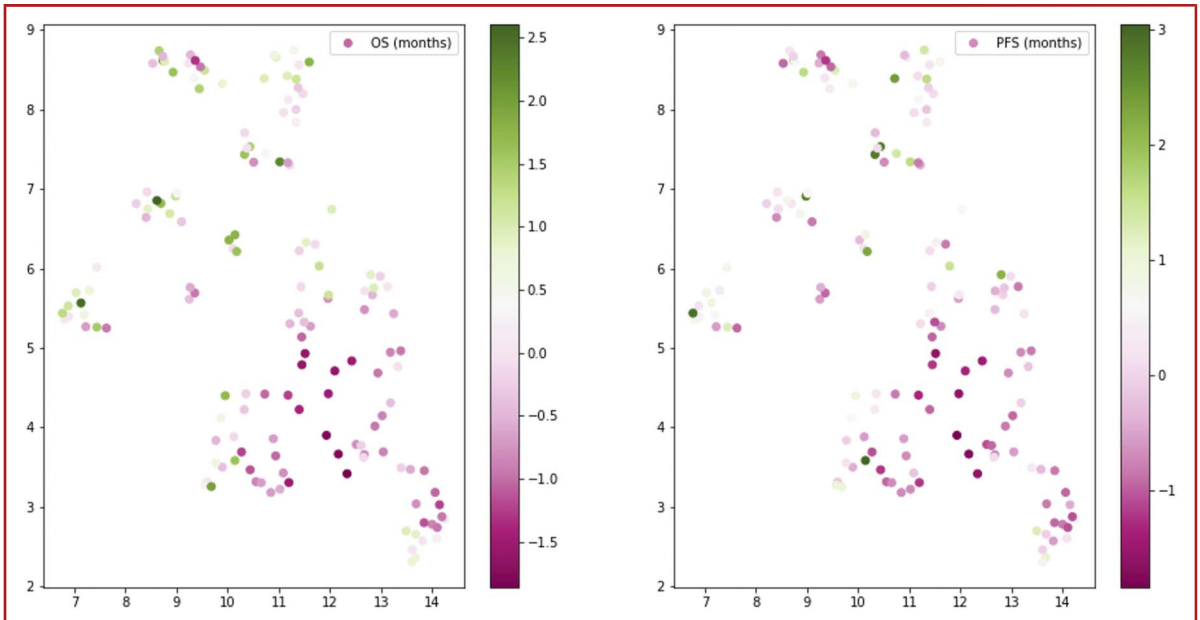

FIGURE 6. *Artificial intelligence analysis: the color intensity of each point is chosen according to the corresponding value of OS (left panel) and PFS (right panel), properly renormalized so that green points represent patients with higher-than-average OS/PFS and purple ones represent patients with lower-than-average OS/PFS. As can be seen, in both plots' points are roughly distributed following a gradient of color, going from purple (bottom-right corner) to green (top-left corner): this means that the information contained in the 10 variables used is sufficient to identify and separate 2 main clusters of patients using UMAP. Goal of this analysis is to transform data from a high-dimensional space into a low-dimensional space with the aim to clean the dataset and highlight only meaningful properties of the original data. Presence of a cluster distribution in graphical representation of UMAP confirms the presence of a common feature impacting OS and PFS in patients' cohort. OS, overall survival; PFS, progression free survival; UMAP, uniform manifold approximation and projection.*

demonstration that a cutoff value of resection must be reached to obtain a survival advantage has been reported only in few studies, without strong level of evidence.[18,19,41,42] The main limits of all studies on FLAIRectomy are related to the difficult interpretation of the hyperintense areas in FLAIR images and the lack of volumetric evaluation of FLAIR-based resection. The method used in this study to evaluate FLAIRectomy has the advantage to introduce a reproducible criterion to quantify supramarginal resection.

Limitations

This study has some limitations: The sample size is relatively small and patients' follow-up is still ongoing, as 21 of 150 patients are alive and under follow-up. As known, in several studies on GBM treatment, the homogeneity of surgical protocol is often not guaranteed. Conversely, in this study, we adopted a rigorous and standardized surgical protocol, which was applied to a small, but still homogeneous cohort of patients.

CONCLUSION

Evaluation of HGG EOTR based only on MRI T1-weighted, contrast-enhancing, tissue does not correspond to the real tumor extension and to its EOR. FLAIR MRI sequences could be more accurate and reliable in identifying both the tumor nodule and the surrounding areas infiltrated by tumor cells.

Resection of HGG based on altered FLAIR sequences, when feasible according to the eloquence of the involved brain, could enhance the cytoreductive role of surgery, allowing a wider EOTR.

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COMMENTS

Glioblastoma (GBM) remains one of the most aggressive primary brain tumors, with a poor prognosis despite advances in multimodal

therapy. The standard of care includes maximal safe resection followed by radiotherapy and temozolomide, achieving a median overall survival (OS) of approximately 15 months.[1a] The extent of resection (EOR) is a well-established prognostic factor, but conventional gross total resection (GTR) does not account for GBM's infiltrative nature. Recently, supramarginal resection (SMR) has gained attention, involving the removal of peritumoral tissue beyond the contrast-enhancing lesion. A specific approach, FLAIRectomy, targets hyperintense regions on FLAIR-MRI sequences, as these areas may harbor infiltrating tumor cells.[2a]

Several studies support SMR and FLAIRectomy as viable strategies. A meta-analysis found that SMR improved progression-free survival (PFS) by 8.44 months compared to GTR, without increasing postoperative complications.[3a] Another meta-analysis reported a median OS of 25 months in SMR patients.[4a] Since GBM recurrences typically occur within 2 cm of the resection margin, extending resection beyond contrast-enhancing regions appears justified.[3a]

The present study provides data reinforcing the benefits of FLAIRectomy. The authors demonstrate that the extent of FLAIR resection (EOFR) is a stronger predictor of survival than the extent of contrast-enhancing tumor resection (EOTR). Each 1% increase in EOFR correlates with a 6.8% reduction in mortality risk for IDH-wildtype patients and 12.1% for IDH-mutant patients. These findings align with research indicating that IDH-mutant gliomas, which exhibit a diffuse infiltrative pattern, benefit from extensive resection.[3a] Despite strengths, challenges remain. Neurological safety is a key concern, as excessive FLAIR resection may increase functional impairment risk. The heterogeneity of FLAIR hyperintensity complicates planning, as not all FLAIR-positive areas contain tumor cells. Advanced imaging techniques, such as 11C-methionine PET, may improve surgical accuracy.[5a] Additionally, intraoperative fluorescent markers and confocal laser endomicroscopy (CLE) have emerged as promising tools for real-time tumor visualization, aiding differentiation of infiltrating tumor cells and enhancing FLAIRectomy-guided resections.[6a]

In conclusion, this study provides compelling evidence that FLAIRectomy improves GBM outcomes. To establish it as standard, multicenter trials with molecular and radiomic profiling are needed. Future research should refine patient selection, optimize intraoperative guidance, and assess long-term effects.

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