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Clinical study

Survival after reoperation for recurrent glioblastoma

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ABSTRACT

Determining which patients will benefit from reoperation for recurrent glioblastoma remains difficult and the impact of the volume of FLAIR signal hyperintensity is not well known. The primary purpose of this study is to analyze the impact of preoperative volume of FLAIR hyperintensity on prognosis. 37 patients who underwent a reoperation for recurrent glioblastoma after initial gross total resection followed by standard chemoradiation were retrospectively reviewed. Volumetric analysis of preoperative MR images from the initial and second surgery was performed and correlated with clinical data. Survival probabilities were estimated using the Kaplan-Meier method and Cox regression to assess the effect of risk factors on time to reoperation (TTR), progression-free survival (PFS) after reoperation, and overall survival (OS). The volumes of FLAIR signal hyperintensity prior to the initial surgery and reoperation were not associated with prognosis. TTR and OS were significantly affected by the preoperative enhancement volume at the initial surgery, with increasing volumes yielding poorer prognosis. Patients with tumor in critical/eloquent areas were found to have a worse prognosis. Median TTR was 11 months, median PFS after reoperation was 3 months, and OS in patients undergoing a reoperation was 21 months. The results suggest FLAIR signal change seen in patients with glioblastoma does not influence time to reoperation, progression-free survival, or overall survival. These findings suggest the amount of FLAIR signal change should not greatly influence a surgeon's decision to perform a second surgical resection compare to other factors, and when appropriate, aggressive surgical intervention should be considered.

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1. Introduction

Glioblastoma is the most common malignant primary central nervous system tumor, affecting 3 to 4 per 100,000 people in the United States every year [1]. Maximal safe resection followed by temozolamide chemotherapy and fractionated radiotherapy, per the Stupp Trial, has been the standard of care [2]. The 2016 WHO Classification of Tumors of the Central Nervous System identified two subtypes of glioblastoma: IDH-wildtype (~90%) and IDH-mutant (~10%) [3,4]. With standard of care treatment, IDH-mutant tumors carry a better prognosis, with median survival of 31 months compared to only 15 months for IDH-wildtype glioblastomas [5]. In defiance of this treatment, the median time to disease recurrence, or progression-free survival, in recent studies has been found to approach 9 months [6,7].

Contrasted imaging, first with CT and then MRI, has long been used to assess treatment response and evaluate for progression/recurrence of disease. The Macdonald Criteria [8] were proposed, in part, to define a standard way to evaluate this. Progression was defined as at least a 25% increase in the sum of the products of perpendicular diameters of enhancing lesions, any new lesions, or clinical deterioration. The RANO criteria [9] provides an updated method, including significant increases in FLAIR, non-enhancing lesions and recognizing that post-contrast enhancement alone is not sufficient in evaluating radiographic disease due to the infiltrative nature of the disease. FLAIR hyperintensity in glioblastoma is known to be both a marker of vasogenic edema and infiltrative tumor [10].

While there is a standard definition for what constitutes recurrent glioblastoma, there is currently no standard treatment. Second

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line therapies include additional temozolomide, bevacizumab, nitrosoureas, reirradiation, or reoperation [11]. The median survival after a second craniotomy for tumor removal has been found to be between 7 and 12.4 months [6,12,13]. The NIH Recurrent Glioblastoma Scale [14] was devised to help stratify patient outcome in those undergoing repeat surgery and found, even in the best case scenario, median survival was 9.2 months, with the worst group faring only a median of 1.9 months. The scale takes into account Karnofsky performance status, volume of tumor based on enhancing portion of MRI, and involvement of eloquent/ critical brain regions. However, the volume of FLAIR hyperintensity was not included in this scale, coinciding with a paucity of literature analyzing the prognostic significance of increased FLAIR hyperintensity in reoperation for recurrent glioblastoma.

This single center retrospective study attempts to identify the significance of increased FLAIR signal change in patients undergoing a second resection for recurrent glioblastoma. In an effort to predict time to reoperation (TTR), progression-free (PFS) and overall survival (OS), the volume of increased FLAIR signal change is analyzed and compared with the volume of enhancement of MRI. We test the hypothesis that patients with a lower enhancement to FLAIR volume ratio (i.e. increased FLAIR volume) will have a worse prognosis.

2. Patients and methods

2.1. Data source and patient cohort

Following Institutional Review Board approval (IRB No. 201801810), the University of Iowa Holden Comprehensive Cancer Center database was queried for patients with WHO Grade IV glioblastoma who had undergone surgery over a nearly a ten year period from January 2007 to April 2017. Using this institution's electronic medical records and the Cancer Center database, information regarding age, sex, date of initial surgery, location of the tumor, extent of resection, pathological diagnosis, along with postoperative adjuvant treatments were collected for all patients. Extent of resection was determined by the Cancer Center based on information from both the surgeon's report and postoperative MRI. For patients who underwent a second surgery for resection of recurrent disease, IDH mutation status, data on KPS, further chemotherapy and radiation treatments were also collected. From this data, the patients were graded on the NIH Recurrent Glioblastoma Scale. In cases where IDH status was not originally tested, banked brain tumor tissue specimens were immunostained for the most common IDH mutation (IDH1 R132H). The date of death or continued survival (as of February 1, 2018) was recorded for all patients. Critical or eloquent area were defined as: precentral and postcentral gyrus, genu and posterior limb of internal capsule (along with their projection to the peduncle inferiorly and to the corona radiata superiorly), language areas (posterior superior temporal gyrus, pars opercularis and posterior part of the pars triangularis, arcuate and superior longitudinal faisculus in the perirolandic area), basal ganglia, insular cortex), thalamus, hypothalamus, fornix, hippocampus, and brainstem.

MRI studies for patients undergoing a second surgery were reviewed. All MRIs were obtained within 48 h from surgery. Volumes of the enhancing region on post-contrast T1 images and the volumes of FLAIR hyperintensity of the tumors were calculated using the program Vitrea 7 (Vital Images, Inc. Minnetonka, MN, USA) (Fig. 1). This program uses an algorithm to semi-autonomously identify contiguous regions of interest on the MRI sequences and provides a volume and 3D image of the enhancing area of the tumor and the area of FLAIR signal change. The neuroradiologist will highlight the area of interest (margin of enhancement in cystic areas, enhanced tissue, or FLAIR) for the software, and the software will calculate the volume). A ratio of these volumes was then calculated.

2.2. Study protocol

Patient were included in the study if they underwent a reoperation for glioblastoma based on the criteria below: 1) Recurrence or progression based on interval increase in the enhancing portion, confirmed by a perfusion study with a relative cerebral blood volume based on MR perfusion of greater than 1.5, associated with an increase in FLAIR changes, or by the presence of a new lesion; 2) Recurrence or Progression occurred after 6 months; 3) First surgery resulted in > 90% resection (or residual of < 12 ml) of the enhancing portion; 4) The surgeon felt that second surgery will result in greater than 90% resection of the glioblastoma (<12 cc of residual); 5) Patient had a KPS > 80 prior to the second surgery.

Patients who did not undergo a second operation were excluded from the study. Patients did not undergo a second operation due to the following: 1) Patient's wishes; 2) Contraindication or refusal of adjuvant therapies (radiation or chemotherapy); 3) Patient with poor KPS; 4) Recurrence or progression prior to 6-month follow-up; 5) First surgery did not result in > 90% resection; 6) The surgeon estimated that second surgery will not result in > 90% resection. Patients who underwent second surgery, but the pathology returned as pseudoprogression were excluded from the study. In addition, Patient who underwent emergent surgery for clot evacuation or decompression. All patients were discussed in tumor boards, which consisted of the following departments: neuroradiology, neuropathology, radiation oncology, medical oncology and neurosurgery. All patients received standard of care chemoradiation after the first surgery, and chemoradiation with a bevacizumab or temozolomide containing combination- due to the lack of standard of care for recurrence- after the second surgery.

2.3. Statistical analysis

The variables of age, sex, KPS score, NIH Recurrent Glioblastoma Score, postoperative adjuvant treatments, volume of MRI enhancement, and FLAIR signal change were included in the survival analysis.

Survival probabilities were estimated and plotted using the Kaplan-Meier method. Estimates along with 95% confidence intervals are reported. Cox regression was used to assess the effects of clinical and radiographic parameters on time to reoperation (TTR), progression-free survival (PFS) after reoperation and overall survival (OS). For TTR, time was calculated from initial operation to reoperation after disease recurrence. For PFS after reoperation, time was calculated from time of second operation to progression (per RANOs) or death due to any cause. For OS, time was calculated from initial operation to death due to any cause or continued survival (as of February 1, 2008). Estimated effects of predictors are reported as hazard ratios (HR) along with 95% confidence intervals. All statistical testing was two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

The database query returned 403 patients, and of those, 23 patients carried a diagnosis of gliosarcoma, and 4 patients had glioblastoma of the spinal cord. In 144 patients gross total resection was not achieved at the time of the original surgery, and 51 did not undergo chemotherapy and radiation after the first

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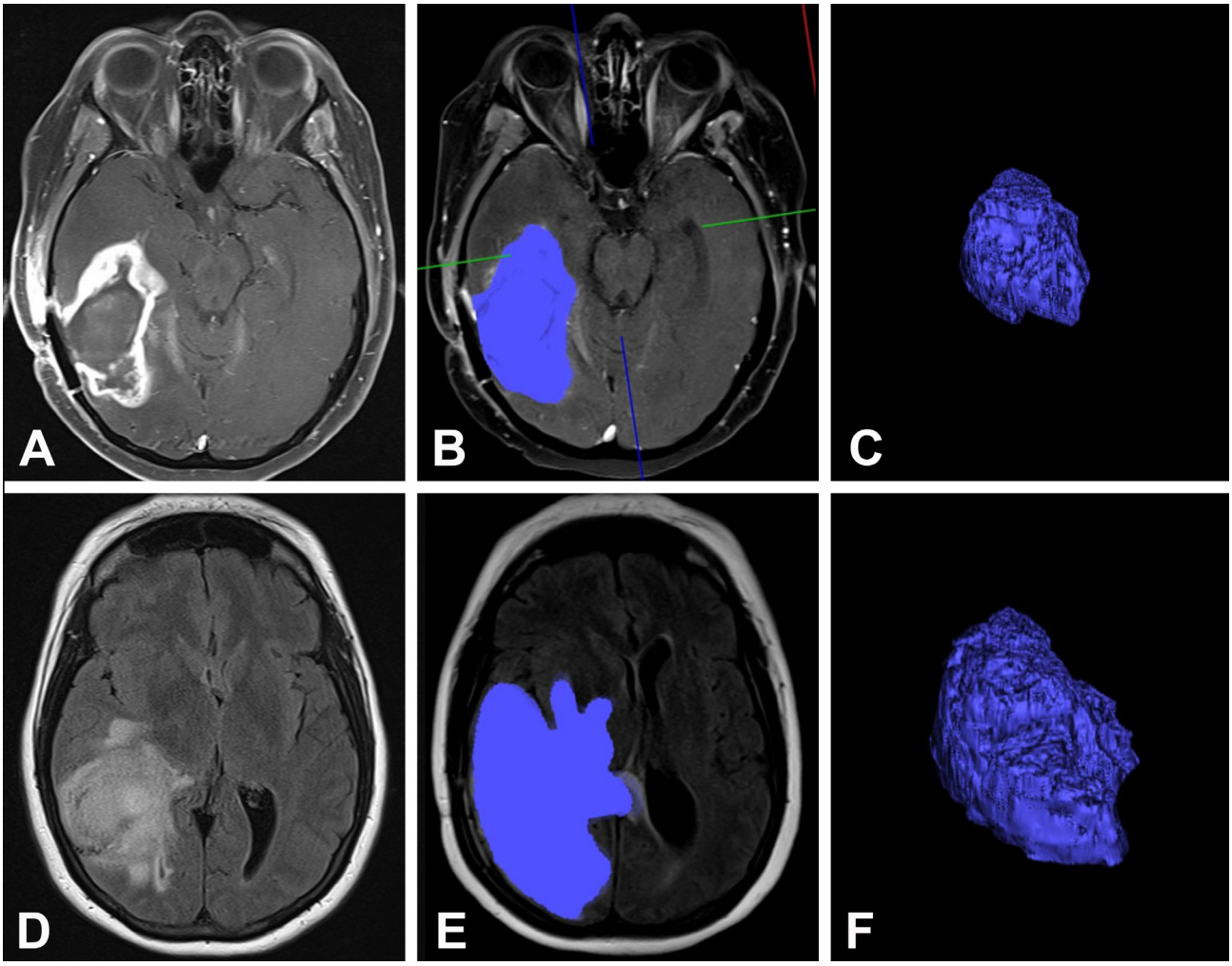

Fig. 1. Representative case using the Vitrea Core software demonstrating volume measurement of a right posterior temporoparietal glioblastoma. A) Axial MRI with contrast. B) 2D measurement of area of enhancement. C) 3D rendering of volume of enhancement. D) Axial MRI FLAIR sequence. E) 2D measurement of area of FLAIR signal change. F) 3D rendering of volume of FLAIR signal change.

resection. Out of the remaining 181 patients who had gross total resection followed by chemoradiation, only 42 had a second surgical procedure. Of the patients that underwent a second resection 5 (11.9%) returned pathology diagnosis of pseudoprogression or radiation necrosis instead of recurrent tumor. Out of 37 patients who underwent resection of histologically confirmed recurrent glioblastoma the median age at initial diagnosis was 56 years (Table 1). The patients were split 19 males vs. 18 females, disease was located in the left hemisphere in 20 patients vs. right hemisphere in 17, and a critical or eloquent area was involved in 19 patients. The average volume of enhancing tissue prior to the first surgery was 38.9 cm^3 compared with an average volume of FLAIR signal change of 115.4 cm^3, which yielded an average enhancement to FLAIR ratio of 0.37 (Table 1).

Median time to reoperation was 11 months (Fig. 2A). Of the 37 patients in our analysis who underwent reoperation, 46% had a KPS of greater than 80 and 84% were considered "good" or "intermediate" candidates based on the NIH Recurrent GBM score (Table 1). The preoperative FLAIR and enhancement volumes at reoperation, interestingly, did not differ greatly from the initial surgery (FLAIR: 115 vs 102 cm^3, enhancement: 38.9 vs 34.5 cm^3, respectively). Likewise, the average enhancement to FLAIR ratio was found to be similar between first (0.37) and second (0.30) surgeries.

Of the potential prognostic variables included in the univariate analysis, only larger enhancement volume prior to initial surgery was significantly associated with shorter TTR ($p = 0.02$; Table 2). The other variables examined for TTR (sex, tumor laterality, critical/eloquent involvement, age, FLAIR volume, and enhancement to FLAIR ratio) were not significantly associated (Table 2).

Median PFS after the second surgery, based on the RANOS criteria, was found to be 3 months (Fig. 2B). Univariate analyses failed to identify factors predictive of progression-free survival after the second surgery (Table 3).

Median OS for the series was 21 months (Fig. 2C). Larger enhancement volume prior to the initial operation was associated with a shorter OS, ($p = 0.04$) (Table 4). Patients with a tumor not in an eloquent or critical region were at 57% decreased risk of death at last follow-up ($p = 0.03$; Table 4). Additionally, Sex, laterality, critical/eloquent involvement, age, initial FLAIR volume (1S), and the ratio of Enhancement to FLAIR (1S) were not significantly associated with OS (Table 4) in univariate analysis. At the time of reoperation (2S), the preoperative FLAIR volume, enhancement volume and their ratio were not significantly associated with OS from the second surgery (Table 4). By comparison, patients who underwent gross total resection followed by chemoradiation without reoperation ($n = 134$) were found to have a median OS of 16 months (Fig. 2D).

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Table 1
Patient characteristics (n = 37 patients).

	n (%)	Mean ± SD
Age, years (median)	56	
Sex		
Males	19 (51%)	
Females	18 (49%)	
Hemisphere		
Left	20 (54%)	
Right	17 (46%)	
Critical/eloquent area	19 (51%)	
Pre-op FLAIR volume, cm^3 (1S)	35	115.4 ± 82.6
Pre-op enhancement volume, cm^3 (1S)	37	38.9 ± 36.5
Enhancement to FLAIR ratio (1S)	35	0.37 ± 0.27
Time to Reoperation, months (median, 95% CI)	37	11 (8–15)
KPS		
>80	15 (41%)	
=<80	20 (54%)	
Unavailable	2 (5%)	
NIH Recurrent Glioblastoma Score		
0	9 (24%)	
1	11 (30%)	
2	11 (30%)	
3	6 (16%)	
Pre-op FLAIR volume, cm^3 (2S)	34	102.1 ± 81.3
Pre-op enhancement volume, cm^3 (2S)	37	34.5 ± 37.6
Enhancement to FLAIR ratio (2S)	34	0.30 ± 0.19
Progression-Free Survival, months (2S) (median, 95% CI)	37	3 (2–4)
Overall Survival, months (median, 95% CI)	37	21 (16–39)

First surgery (1S); second surgery (2S).

4. Discussion

In this study of 37 patients with recurrent glioblastoma who underwent a second resection, we evaluated the impact of volume of FLAIR hyperintensity using a proportional hazards model. Neither the volume of FLAIR hyperintensity nor the ratio of volumes of enhancement to FLAIR hyperintensity were shown to correlate with time to reoperation, progression-free survival, or overall survival.

In glioma patients, hyperintensity on FLAIR sequences is thought to represent both edema and microscopic cancer infiltration [15,16,17]. FLAIR signal changes can also result from other causes including radiation effects, decreased corticosteroid dosing, demyelination, ischemic injury, infection, seizures, and postoperative changes [8]. This can complicate the interpretation of FLAIR signal changes and whether they are indeed due to progression of glioblastoma. While FLAIR is an effective tool in localizing glioblastomas, planning radiation treatment, and post-treatment monitoring, its prognostic value remains unclear. The current study supports the notion that FLAIR hyperintensity is influenced by multiple factors besides disease progression and suggests that the preoperative volume of FLAIR hyperintensity is not able to predict patient outcomes after surgery in recurrent disease. However, it has been shown that post-radiation treatment FLAIR volume was significantly correlated with both PFS and OS [16]. Hence when comparing pretreatment to posttreatment response, the current RANO recommendations for the assessment for high grade gliomas utilize FLAIR signaling to account for the non-enhancing component of the tumor; this is not considered in the older Macdonald Criteria [8,18].

In this study the only prognostic factor significantly associated with a shorter time to reoperation was larger enhancement volume. Higher preoperative enhancement volume prior to the initial procedure was also associated with reduced overall survival. Enhancement volume is one of three variables in the NIH Recurrent GBM scale used to help predict surgical outcomes of a second resection [14]. Park et al. found that patients with a tumor volume greater or equal to 50 cm^3 had significantly worse median survival of 3.9 months compared with 10.3 months for those with smaller tumors [14]. Additionally, enhancement on postoperative MRI has also been effective in showing gross total resection is superior to subtotal resection in patients undergoing repeat surgery with a median OS of 20 months versus 16.6 months respectively [19].

Many prior studies use two-dimensional (2D) measurements and formulas to approximate tumor enhancement volume. Theoretically this provides a sub-optimal level of detail when it comes to analyzing the anatomy of tumors compared with newer 3D volumetric measurements, as performed in this study. Dempsey et al. when comparing single-dimensional (1D), 2D and 3D tumor size in malignant gliomas found that 1D tumor size was not significant, 2D tumor size was significant in univariate analysis but not in multivariate analysis, and 3D tumor size was statistically significant on both univariate and multivariate analysis and a significant predictor of overall survival [20].

Our analysis demonstrates that critical or eloquent cortex involvement is associated with a decrease in overall survival, consistent with prior literature. Awad et al. demonstrated that disease involvement of the critical or eloquent cortex, including motor, sensory, visual and speech areas, significantly decreased survival [21]. Additionally, Park et al. in the NIH Recurrent GBM scale also considers critical or eloquent regions, showing a median OS after reoperation of 1.4 months for patients have those regions affected vs. 9.0 months for those with disease centered in other areas [14]. Frontal lobe involvement, for example, has been shown to have a better prognosis [22]. The impact location has on survival is likely multifaceted. Tumor location greatly influences the ability to achieve gross total resection, as surgeons are less likely to be as aggressive near critical or eloquent cortex. However, this is controlled in this study by analyzing only patients who had an initial GTR, and raises the likelihood that direct disease involvement leading to neurologic deficits places patients at a survival disadvantage. There may also be inherent differences in the disease course as multiple studies have indicated that genetic and epigenetic factors all have the potential to impact location of the tumor [23–25].

Finally, repeat surgery has been shown to significantly improve survival in recurrent glioblastoma [26,27–29]. The findings of this study, showing an improvement in median OS from 16 to 21 months for patients undergoing a repeat resection, is additional support to already existing literature for aggressive surgical management. Interestingly, all but one of the 32 patients who had the testing, were IDH wildtype. This suggests that some characteristic exists regarding primary or "de-novo" GBM that lends them toward undergoing repeat resection, and may not exist in IDH-mutant tumors or "secondary" GBM.

5. Limitations

Interpretation of these results is limited due to the inherent bias attributable to the inclusion criteria for the study. If patients who have a reoperation are different than those who do not, then these results are only generalizable to patients who have had a reoperation. Additionally, since our inclusion criteria were stringent in order to provide the most homogenous population for the study, the sample size is correspondingly small and may have limited the ability to find significance. However, it's not surprising that none of the variables were found to significantly influence PFS after reoperation. With a median PFS of 3 months, a variable would need to demonstrate a quite large difference to have an impact on such a short time period. Finally, due to the time period over which

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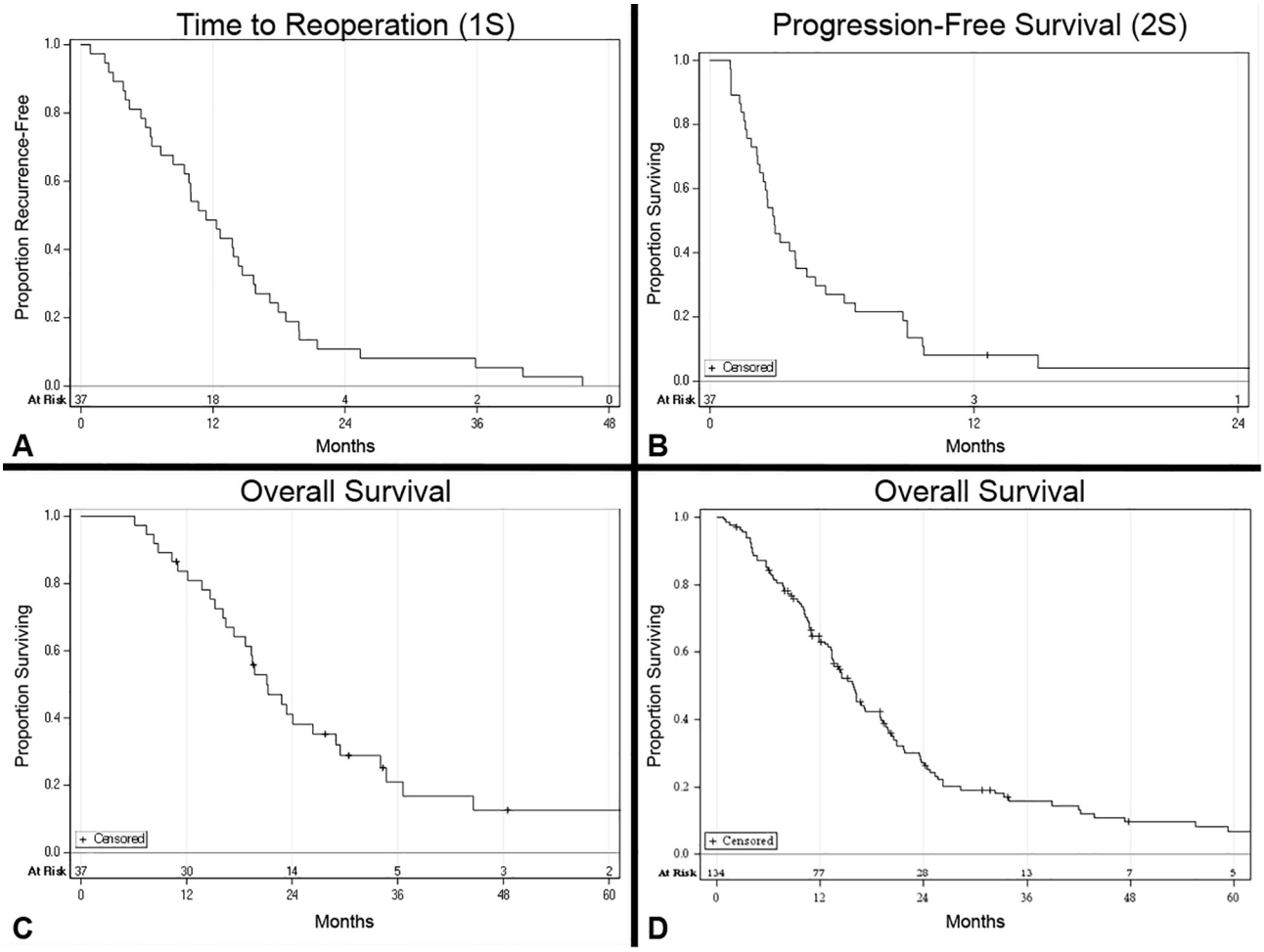

Fig. 2. Kaplan-Meir Survival Plots A) Time to reoperation for recurrence (TTR) B) Progression-free survival after reoperation (PFS) C) Overall survival (OS) for patients undergoing reoperation D) Overall survival (OS) for patients with gross total resection, treated with standard chemoradiation, without reoperation.

Table 2
Time to Reoperation, Univariable Results.

Covariate	n	Hazard Ratio	95% CI	P-value
Sex				
Male	19	0.96	0.48 – 1.91	0.91
Female	18	Ref	–	–
Hemisphere				
Left	20	0.96	0.50–1.87	0.91
Right	17	Ref	–	–
Critical/Eloquent				
No	18	0.54	0.27–1.06	0.07
Yes	19	Ref	–	–
Age at Diagnosis	37	0.99	0.97–1.02	0.60
Pre-op FLAIR Volume (1S)	35	1.00	1.00–1.01	0.13
Pre-op Enhancement Volume (1S)	37	1.01	1.00–1.02	0.02
Enhancement to FLAIR Ratio (1S)	35	2.12	0.71–6.33	0.18

First surgery (1S), Hazard Ratios are for a 1 unit change.

patient data were reviewed for this study and the relatively recent development of molecular and genetic testing, we had 32 out of the 37 patients who were tested for IDH mutation, of which 1 was positive. In addition, 14 of the 37 patients were tested for MGMT status. This did not provide us with enough samples to include the MGMT or IDH status in the analysis. Since we were unable to ascertain MGMT status for the majority of patients, TTR, PFS, and OS need to be qualified as such since those markers are likely to impact prognosis. Given that the majority of these patients received their care prior to the era of molecular tumor marker test, additional data regarding not only MGMT, but also TP53, EGFR, and others was not available. The authors recognize the importance of these markers and in future studies their inclusion will be paramount. Additionally, the authors chose not to include steroid dosage or other adjuvant treatments like bevacizumab and the use of tumor treatment fields due to the fact

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Table 3
Progression-Free Survival, Univariable Results.

Covariate	n	Hazard Ratio	95% CI	P-value
Age at Diagnosis	37	1.01	0.76–1.51	0.71
Sex				
Male	19	1.08	0.31–1.22	0.17
Female	18	Ref	–	–
Hemisphere				
Left	20	0.62	0.31–1.22	0.17
Right	17	Ref	–	–
Critical/Eloquent				
No	18	0.63	0.32–1.23	0.18
Yes	19	Ref	–	–
Pre-2S KPS				
<=80	20	0.97	0.48–1.96	0.94
>80	15	Ref	–	–
NIH Recurrent Glioblastoma Score	37	1.07	0.76 – 1.51	0.71
Pre-op FLAIR Volume (2S)	34	1.00	1.00–1.01	0.88
Pre-op Enhancement Volume (2S)	37	1.00	0.99–1.01	0.96
Enhancement to FLAIR Ratio (2S)	34	0.77	0.71–4.85	0.78
GTR after 2S				
No	8	0.88	0.38–2.04	0.77
Yes	28	Ref	–	–

second surgery (2S); gross total resection (GTR); Karnofsky Performance Scale (KPS), Hazard Ratios are for a 1 unit change.

Table 4
Overall Survival for patients undergoing reoperation, Univariable Results.

Covariate	n	Hazard Ratio	95% CI	P-value
Sex				
Male	19	0.95	0.46–1.97	0.90
Female	18	Ref	–	–
Hemisphere				
Left	20	0.63	0.31–1.29	0.21
Right	17	Ref	–	–
Critical/Eloquent				
No	18	0.43	0.20–0.90	0.03
Yes	19	Ref	–	–
Age at Diagnosis	37	0.99	0.97–1.02	0.70
Pre-op FLAIR Volume (1S)	35	1.00	1.00–1.01	0.62
Pre-op Enhancement Volume (1S)	37	1.01	1.00–1.02	0.04
FLAIR to Enhancement Ratio (1S)	35	2.62	0.71–8.84	0.12
Pre-op FLAIR Volume (2S)	34	1.00	1.00–1.01	0.11
Pre-op Enhancement Volume (2S)	35	1.01	1.00–1.01	0.34
Enhancement to FLAIR Ratio (2S)	34	1.02	0.15–6.94	0.99

First surgery (1S), Hazard Ratios are for a 1 unit change.

the utilization is not standardized and is extremely heterogeneous for a small cohort size such as this and likely representative of the larger population.

6. Conclusion

The primary aim of this study was to determine whether the volume of FLAIR signal change at time of recurrence should greatly influence a surgeon's decision to perform a second surgical resection. This study provides additional evidence showing that the volume of contrast enhancement is associated with worse prognosis in terms of time to reoperation and overall survival. In this study, time to reoperation, progression-free survival after reoperation, or overall survival were more affected by the volume of enhancement rather than the volume of FLAIR signal changes. Other factors that have been well documented such as critical/eloquent area involvement or volume of enhancement continue to play a key role. Future studies should focus on molecular tumor markers, which may have a more significant effect.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.01.009.

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