Extent of resection of peritumoural DTI abnormality as a predictor of survival in adult glioblastoma patients

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Running title:
Extent of DTI resection in glioblastoma

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ABSTRACT

Object. Diffusion tensor imaging (DTI) has been shown to detect tumor invasion in glioblastoma patients and has been applied in surgical planning. However, the clinical value of the extent of resection based on DTI is unclear. Therefore we retrospectively reviewed the correlation between the extent of resection of DTI abnormalities and patients' outcome.

Methods. We reviewed 31 newly diagnosed supratentorial glioblastoma patients who underwent standard 5-ALA aided surgery with the aim of maximal resection of the enhancing tumour component. All patients received presurgical MR including volumetric T1 post contrast, DTI and FLAIR. Postsurgical anatomical MR images were obtained within 72 hours after resection. The diffusion tensor was split into an isotropic (p) and anisotropic (q) component. The extent of resection was measured for the abnormal area on the p, q, FLAIR and T1 post contrast map. Data were analyzed in relation to patients' outcome using univariate and multivariate Cox regression models controlling for possible confounding factors including age, MGMT-methylation status and IDH-1 mutation.

Results. Complete resection of T1 contrast enhancing tumor was achieved in 24 out of 31 patients (77%). The mean extent of resection of the abnormal p, q and FLAIR area were 57%, 83% and 59%, respectively. Increased resection of the abnormal p and q areas correlated positively with progression free survival ($p = 0.009$ and $p = 0.006$, respectively). Additionally, a larger residual q volume predicted significantly shorter time to progression ($p = 0.008$). More extensive resection of the abnormal q and T1 contrast area improved overall survival ($p = 0.041$ and $p = 0.050$, respectively).

Conclusion. Longer progression free survival and overall survival were seen in glioblastoma patients in which more DTI abnormality was resected, previously shown to represent infiltrative tumor. This highlights potential usefulness and the importance of an extended resection based on DTI-derived maps.

Key words: glioblastoma, extent of resection, diffusion tensor imaging, volumetric study, progression free survival

INTRODUCTION

Glioblastoma is the most prevalent malignant primary brain tumors and one of the leading cancers in terms of years of life lost.[15] Standard treatment against this highly malignant disease includes maximal safe resection followed by concomitant chemoradiotherapy (CCRT) and adjuvant chemotherapy with temozolomide. However, the prognosis remains poor with two and five-year survival only 27% and 9.8%, respectively.[27]

The main factors influencing prognosis are age, performing status, tumor molecular type and extent of resection, of which the former three are fixed while the latter can be changed. Therefore, many efforts have been put on the extent of maximal tumor resection while preserving normal brain tissue and function. Resection of a larger fraction of the tumor results in a longer life expectancy.[6,7,12] In order to achieve maximal tumor resection, intraoperative neuronavigation, 5-aminolevulinic acid (5-ALA) and other imaging techniques (e.g. intraoperative MR or ultrasound) have been introduced. Utilization of 5-ALA increased the extent of resection to 65% of the total contrast enhancing area and prolong the progression free survival.[24] Contrast-enhanced T_1-weighted signal has many limitations in accuracy of the delineation of tumor margin.[19] Consequently, the clinical benefit of resection outside the contrast enhanced area has been investigated.[13] Recently it has been shown that extending the resection to the peritumoral high T2 areas beyond the T1 contrast enhancing can provide longer survival than less extensive resections.[13] This is thought to be due to tumor infiltration beyond the contrast enhancing area.[20] However high T2 is not specific for tumor infiltration, as it is also caused by edema.

Diffusion tensor imaging (DTI) is able to detect tumor extent beyond the contrast enhancing area due to subtle white mater change.[17] By decomposing the diffusion tensor into an isotropic component (p) and anisotropic component (q),[16] white matter that is infiltrated or disrupted by the glioblastoma can be identified.[17] Radiotherapy treatment plans based on peritumoral abnormal DTI areas were able to achieve a large reduction of 15 - 35% in planning target dose

and 50% of clinical target volume, which minimized radiation complication without affecting the survival.[1,8] In addition, DTI changes especially, p map, can be used for evaluate early treatment response after temozolomide chemotherapy in glioma patients.[2] However, to date there are no studies showing a clinical benefit of resecting the abnormal peritumoral DTI area. This prompted our study to aim at analyzing the influences of the extent of resection of abnormal peritumoral DTI areas on patients' outcome.

METHODS

Patient Population

We included 31 glioblastoma patients (mean age 56 years, range 31-68; 19 males) from our consecutive cohort. All patients were with a Karnofsky performance score ≥70 and with presurgical MR scans that also had follow-up MR available after tumor resection. Patients were deemed suitable to undergo complete resection of the contrast enhancing tumor by one senior author neurosurgeon (SJP) and all subsequently underwent tumor resection under neuronavigation (StealthStation, Medtronic, Minnesota, USA) and 5-ALA fluorescence guidance with the aim of maximal tumor resection. The presurgical images were acquired on average one day (range 0-9) before surgery. Follow-up MR scans were obtained as soon as possible after surgery and no later than 72 hours. Exclusion criteria were previous cranial surgery, previous cerebral radiotherapy or a known other primary tumor. All patients received standard concomitant and adjuvant temozolomide chemoradiotherapy[27] about one month after surgical resection. MGMT is done with pyrosequencing of the DMR2 region. IDH is measured using immunohistochemistry for R132H mutation. Survival data were extracted from the medical records. Tumor eloquence was classified as described previously.[22,12]

The study was approved by the local Institutional Review Board (10/H0308/23) and informed written consent was obtained from all patients.

MR data acquisition

Presurgical imaging was performed on a 3.0 T MR Magnetom system (Siemens Healthcare, Munich, Germany) with a standard 12-channel head coil. Imaging included a T1-weighted imaging after contrast, T2-weighted fluid attenuated inversion recovery (FLAIR) sequence and DTI. A 3D T1-weighted scan with fat suppression was acquired after the intravenous injection of 9 mL gadolinium (Gadovist, Bayer Schering Pharma, Berlin, Germany) (TR/TE/TI 2300/2.98/900 ms; flip angle 9°, FOV 256 × 240 mm; 176-192 slices; no slice gap; voxel size of 1 × 1 × 1 mm). A 2D FLAIR sequence was performed (TR/TE/TI 7840-8420/95/2500 ms; flip angle 150°; FOV 250 x 200 mm; 25-27 slices; 1 mm slice gap; voxel size 0.78125 x 0.78125 x 4 mm). DTI data was acquired using a single-shot echo-planar sequence (TR/TE 8300/98 ms; flip angle 90°; FOV 192 x 192 mm; 63 slices; no slice gap; voxel size 2 x 2 x 2 mm) with multiple b-values (0, 350, 650, 1000, 1300 and 1600 s/mm2) scanned in 13 directions.

Direct postsurgical images were acquired on a 1.5 T GE Optima, a 1.5 or 3.0 T GE Signa or a 3.0 T GE Discovery (General Electric Company, Little Chalfont, United Kingdom) with standard head coil. Imaging included a T1-weighted anatomical sequence after the intravenous injection of 9 mL gadolinium (Gadovist, Bayer Schering Pharma, Berlin, Germany). This was performed as a 2D T1-weighted sequence (TR/TE 460-700/11-21 ms, flip angle 90°, FOV 220-260 x 220-260 mm; 20-85 slices; 0-1 mm slice gap; voxel size 0.429-0.5079 x 0.429-0.5079 x 2-6 mm) or a 2D T1 inversion recovery sequence (TR/TE/TI 2508-2600/12-42/780-920 ms; flip angle 90-110°, FOV 220 × 220 mm; 20-22 slices; 1-3.5 mm slice gap; voxel size of 0.4297 x 0.4297 x 6 mm).

Image processing

DTI images were processed using tools from the FMRIB Software Library (FSL) version 5.0.0 (fsl.fmrib.ox.ac.uk/fsl/fslwiki). DTI images were realigned to the b0-image to compensate for eddy currents and motion.[10] We calculated the isotropic (p) and anisotropic (q) component after eigenvalues were calculated on multiple fiber directions at each voxel in the DTI data as described previously described.[16] For each subject, presurgical DTI and FLAIR images were

coregistered with presurgical post contrast T1 weighted images by a linear transformation using the default FLIRT functions provided by FSL.[10]

Coregistration between postsurgical and presurgical images was done by a semi-automatic co-registration methods (AH and JLY).. All images were fit into presurgical volumetric contrast-enhanced T1-weighted images. Firstly, we used automatic brain extracted images,[9] which were manually corrected. Then we calculated the transformation between presurgical tumor and postsurgical resection cavity by using the linear FLIRT co-registration of the lesion, ventricle and the external mask of the brain between presurgical and postsurgical images. These transformation were then used as input transformation matrix for a non-linear FNIRT coregistration to coregister the brain.

Tumor Volume and EOR Data analysis

Extent of resection was determined by the surgical resection cavity in the coregistered postsurgical T1 post contrast (Figure 1, blue outline) by an author (JLY) blinded to the outcome at the moment with the agreement of the second author (AH). The 3D peritumoral abnormal FLAIR, p and q regions of interest were manually selected on the coregistered presurgical MR images (Figure 1B, 1C and 1D, respectively). The interobserver correlation was done between the first author (JLY) and senior author (SJP) with fair agreement. The coregistered resected region was extracted from the total abnormal presurgical region for each sequence using Matlab (MathWorks Inc., Natick, MA, USA). The resected volumes were calculated for the p, q and FLAIR regions by multiplying all voxels of interests with the slice thickness in Matlab.

Statistical Analysis

Data was analyzed using SPSS version 22 (IBM Inc., New York, USA). Cox regression model was used to estimate the influence of the extent of resection based on p, q, FLAIR and T1 post contrast images on progression free survival and overall survival. Multivariate analysis includes the covariates age, O^6-methylguanin-DNA-methyltransferase (MGMT) methylation status,

isocitrate dehydrogenase (IDH)-1 mutation, presurgical tumor volume based on T1 post contrast, tumor location based on eloquence and midline shift. These covariates were tested individually with resection ratio of p, q, FLAIR, T1 contrast enhancing area and residual tumor volume based on different MR images. Subgroup analysis was done for a group with a low and high q resection ratio by splitting the patient based on the median of the whole group. Patients' characteristics comparisons in different groups were calculated by using t-test for continuous data as they showed a normal distribution tested by D'Agostino-Pearson normality test and the chi-square for dichotomous data. Chi square test with Yate's correction was used for small number contingency categorical analysis. A two-sided *p*-value of 0.05 was used throughout.

RESULTS

Patients' Characteristics

Patients' clinical characteristics are shown in Table 1. Complete resection based on T1 post contrast was achieved in 24 patients (77% out of 31). Ten patients had the tumor located within an eloquent area which included primary motor or sensory cortex, speech center, internal capsule and basal ganglia. Ten patients had tumor located in near eloquent area which included supplementary motor area, near calcarine fissure, near speech center, corpus callosum. The mean midline shift was 3.3 mm (SD ± 3.7; range 0-11.9). Mean presurgical T1 enhancing tumor volume was 46 mL (± 30; range 8-119 mL). Size of resection area was 53 mL (± 31; range 10-131), which was significantly larger than the presurgical tumor ($p = 0.001$). A total of 57% of the p area, 83% of the q area and 59% of the FLAIR area were resected. Residual tumor volume based on p, q, FLAIR and T1 contrast enhanced images were 38.4 mL (± 30.2; range 4.4-129.4), 8 mL (± 9.7; range 0-36), 40.7 mL (± 32.7; range 0.4-127.9), and 2.7 mL (± 6.8; range 0-26.6), respectively. All patients did not have major postsurgical neurologic deficit and decrease KPS under 70 which is our condition to enter the following temozolomide chemoradiotherapy.

Extent of Resection and Patient Outcome

Univariate Cox regression models for each variable showed a significant correlation of progression free survival with the extent of resection of p (p = 0.030), complete resection of T1 contrast enhancing lesion (p = 0.004) and MGMT methylation status (p = 0.041). Multivariate analysis was used to test extent of resection with other covariables (Table 2). The results showed that resection of the more abnormal p was a protective predictor of tumor progression (HR = 0.911, p = 0.009). The extent of resection of q areas was also significant correlate with progression free survival in the multivariate analysis (HR = 0.935, p = 0.006). The extent of resection of FLAIR showed no association with progression free survival in both univariate and multivariate analysis (p = 0.994 and p = 0.799, respectively). Presence of MGMT methylation was found to be a significant predictor of progression free survival in the multivariate models for p (HR = 4.626, p = 0.009), q (HR = 6.716, p = 0.006) and FLAIR (HR = 95.941, p = 0.001).

For overall survival, multivariate analysis was performed after controlling for the age, MGMT-methylation status, IDH-1 mutation status, presurgical tumor volume, tumor eloquence and midline shift. Extent of resection based on q and T1 contrast were identified as predictors for overall survival (HR = 0.965, p = 0.041 and HR = 9.946, p = 0.050, respectively). The MGMT methylation status was significantly associated to overall survival in the multivariate models for p (HR = 3.737, p = 0.043), q (HR = 4.932, p = 0.012) and FLAIR (HR = 10.274, p = 0.009). Besides, presurgical tumor volume based on T1 post contrast was found to be a covariable that increase the hazard in extent of resection on q (HR = 1.039, p = 0.024) and T1 contrast (HR = 1.037, p = 0.040).

As previous results indicated the importance of the extent of resection especially q abnormality on outcome, we explored this in more detail. Classifying patients into two groups by using the median of the extent of q resection, resulted in a resection cut-off of 89% of the q abnormality. Patients with a resection over 89% of the q abnormality had a significantly longer progression free survival (421 ± 311 days) than those with under 89% (257 ± 214 days; p = 0.034) and

better overall survival (621.9± 389.0 versus 518.13 ± 264.7; p = 0.011; Figure 2). With this two subgroups, there was no statistical difference in age, gender, tumor location, number of patients receiving a gross-total resection, MGMT methylation or IDH-1 mutation status (Table 3). Similar result can be seen while subgrouping patient with median extent of p resection, longer progression free survival was shown in patients received over 60% of resection on p abnormal area. (421 ± 311 versus 258 ± 176, p = 0.046).

In our study, 26 patients (83.9%) had tumor recurrence within 2 cm adjacent to the resection cavity. Three patients (9.7%) had distal recurrence more than 2 cm from the original resection cavity, and 2 had recurrence both locally and distally. All solely distal recurrence patients received complete resection of T1 contrast enhancing lesion and a higher extent of resection of q abnormal area (97.7%) versus the others (87.4%) and two of them were MGMT methylated. Progression free survival (721 ± 270 days) and overall survival (954 ± 461 days) were also longer in distal recurrent patients.

Residual Tumor Volume and Patient Outcome

The correlation of patients' outcome and residual tumor volume based on different MR images are summarized in Table 4. A larger residual volume of DTI showed a decrease in progression free survival, which was statistically significant for the q abnormality (HR = 1.118, p = 0.008), while residual volume of p was not significant (HR = 1.28, p = 0.074). Residual FLAIR was not correlated to progression free survival. Overall survival was not influenced by the residual p, q or T1 contrast volume. Residual FLAIR volume decreased the hazard ratio of overall survival (HR = 0.942, p = 0.008).

DISCUSSION

In this study, we retrospectively review the correlation between the extent of resection based on DTI and patients' outcome. Although the intention of initial surgical resection is based on 5-ALA rather than on any DTI parameter, this study showed a significant correlation between the extent of resection based on both the p map, and q map with progression free survival using a multivariate Cox regression model. Furthermore a favorable overall survival can be seen in patients received more resection of the q map and T1 contrast enhancement. Thus, by resecting more abnormal DTI areas, most importantly the q area, the infiltrating tumor burden decreases leading to better outcome.

The significance of resecting more T1 contrast enhanced lesion has been shown clearly to correlate with patient survival. Sanai and colleagues showed improved overall survival begins starting at a resection of 78% and continue to increase with more tumor resection of the contrast enhancing area.[21] A non-volumetric studies of high grade glioma has also shown a longer overall survival in complete resection than in incomplete resection (16.7 versus 11.8 months. $p < 0.001$).[25] Others also showed the synergic clinical benefit of the extent of resection and concomitant chemoradiotherapy.[23] Moreover, the benefit of reduced tumor burden was also shown on the efficacy of1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU) of where a lower concentration is needed to achieve 90% of growth inhibition in low tumor burden groups.[14] In patients receiving BCNU wafers during surgery, longer median survival is also noted in the complete resection group compared to in subtotal resected patients.[26] Therefore, reduction of enhancing tumor burden is an important prognostic factor for patient outcome.

However, to date, most studies have defined extent of resection using the contrast enhancing area only. But, a false negative rate of 16% can be found in normal appearing areas on T1,[17] and tumor cells often extend beyond the contrast enhancing area. We have previously shown that specific DTI signatures can predict this microscopic tumor invasion.[17,18] In particular, regions with >10% increase of the p (isotropic) component signified white matter infiltration by tumor, whilst regions with >12% decrease in q (anisotropic) component showed white matter

disruption by cancer. Therefore, using DTI can better delineate actual tumor margin and show the invasive area of tumor. Although, we have not performed a histological correlation in this study, previous research has validated a correlation between DTI and viable tumor cells.[4]

A previously conducted tumor resection treatment bias study showed that complete resection more often achieved in younger patients and tumors in non-eloquent tumor location.[25] We tested our result by using median q extent of resection 89% as the cut-off to stratify patients into two group. In these two groups, a longer progression free survival can be seen in those receiving more than 89% of q resection, but other variables including age, tumor eloquence, MGMT-methylation status, IDH-mutation, midline shift, presurgical tumor size and complete T1 contrast resection rate were all comparable (Table 3). A bias could therefore not be identified, which strengthens our results indicating the importance of the extent of resection based on DTI.

Specifically looking at the distal recurrence patients, previous study showed a correlation between extended resection and recurrence pattern with a better prognosis in those with distal recurrence[3]. In our study, all three distal recurrent patients received a higher extent of resection on DTI abnormality (EOR of q > 97%) beyond contrast enhanced area. Although the number in our study is small, this finding may indicate that distal recurrence occurs in those with a better local control based on DTI and consequently resulted in a better prognosis.

We also examined the residual tumor volume based on different MR sequences. The more q volume left after surgery can significantly increase the risk of progression and marginally decrease overall survival. Grabowski and colleagues showed that residual contrast enhanced lesion volume more than 2 cm^3 after surgical resection was a strong unfavorable predictor to overall survival.[5] Furthermore, others also concluded that a smaller residual contrast enhanced tumor under 10 cm^3 can lead to both prolonged time to progression and survival.[11] In our results

only marginal significance in progression free survival was noted based on T1 post contrast. This may be due to the limited numbers of patients in our study. Regardless of the limited numbers, we clearly displayed the advantage of the q map, which according to a previous biopsy studies, represents regions of tumor cells.[17] Thus a smaller residual abnormality on the q region indicated a lower tumor load and a better prognosis.

CONCLUSION

In summary, with the expanding application of DTI in brain tumor patients, it can not only demonstrate the possible tumor invasion but also provide a guide for surgeons. Our results underscore the importance of abnormal DTI area, especially of abnormal q area, that in patients received more extent of resection and with less residual abnormal DTI had better patients' progression free survival and overall survival. Further prospective studies is needed to clarify the clinical benefit of incorporating DTI into surgical planning.

DISCLOSURE

None of the authors have financial of other conflict of interest related to the work presented in this paper.

TABLE 1 - Patient Characteristics

Total number of patients	31
Male	19
Female	12
Age (years)	56 ± 11
Tumor location	
Eloquent	10
Near eloquent	12
Non eloquent	9
Midline shift (mm)	3.3 ± 3.7
Presurgical tumor size (mL)	
T1 contras enhanced	46 ± 30
FLAIR	84 ± 44
Isotropic (p) DTI	83 ± 44
Isotropic (q) DTI	51 ± 23
Extent of resection (%)	
T1 post contrast	136 ± 71
FLAIR	58 ± 21
Isotropic (p) DTI	57 ± 18
Isotropic (q) DTI	83 ± 20
Residual tumor size (mL)	
T1 post contrast	2.7 ± 6.7
FLAIR	41 ± 32
Isotropic (p) DTI	38 ± 30
Isotropic (q) DTI	8 ± 9.6
GTR (based on contrast)	24
STR (based on contrast)	7
IDH-1 positive	3
MGMT methylation positive	10
Progression free survival (days)	367 ± 263
Overall survival (days)	559 ± 292

Numbers or mean values and standards deviation are presented for the main patient characteristics. Abbreviations: DTI = diffusion tensor imaging; FLAIR = fluid attenuated

inversion recovery; GTR = gross total resection; IDH-1 = Isocitrate dehydrogenase-1; MGMT = O^6-methylguanin-DNA-methyltransferase; STR = subtotal resection.

TABLE 2 - Extent of Resection and Patients' Outcome

	Progression Free Survival			Overall Survival		
	p-value	HR	CI (95%)	*p*-value	HR	CI (95%)
EOR of p	0.009*	0.911	0.850-0.977	0.795	0.993	0.940-1.049
EOR of q	0.006*	0.935	0.891-0.980	0.041*	0.965	0.934-0.999
EOR FLAIR	0.799	0.997	0.926-1.061	0.052	1.062	1.999-1.129
EOR of T1C	0.094	6.499	0.727-58.069	0.050*	9.946	1.005-98.464

Multivariate analysis results showing age, MGMT methylation status, IDH-1 mutation status, presurgical tumor volume based on T1 post contrast, midline shift and tumor eloquent location as covariates. An * indicates a statistically significant *p*-value. Abbreviations: CI = confidence interval; EOR = extent of resection; T1C= T1 post contrast; FLAIR = fluid attenuated inversion recovery; HR = hazard ratio

TABLE 3 - Patient characteristics for the subgroups of q resection area

	q EOR < 89%	q EOR > 89%	*p*-value
Male	9	10	1
Female	6	6	
Age (years)	53.67 ± 13.16	58.68 ± 8.8	0.4168
Tumor location			0.1298
Eloquent	5	5	
Near eloquent	8	4	
Non eloquent	2	7	
Midline shift (mm)	3.33 ± 3.90	3.65 ± 3.63	0.8138
Presurgical tumor size (mL)			
T1 post contrast	35.9 ± 18.4	53.3 ± 30.6	0.0682
FLAIR	81.1 ± 37.8	95.8 ± 52.2	0.3888
Isotropic (p) DTI	80.1 ± 38.1	90.9 ± 48.2	0.4948
Isotropic (q) DTI	48.8 ± 14.3	54.5 ± 30.8	0.5147
GTR (based on contrast)	9	15	0.0693
STR (based on contrast)	6	1	
IDH-1 positive	2	1	0.5050
MGMT methylation positive	5	5	0.9013
Progression free survival (days)	257 ± 214	421 ± 311	0.034*
Overall survival (days)	518.13 ± 264.7	621.9± 389.0	0.011*

T1C = T1 post contrast.

Patients' characteristics are displayed for the subgroup of patient with an extent of resection (EOR) over or below 89%. Progression free survival and overall survival comparison were analyzed by multivariate Cox regression model. Number or mean and standard deviation are displayed. An * indicates a statistically significant *p*-value. See table 1 for abbreviations.

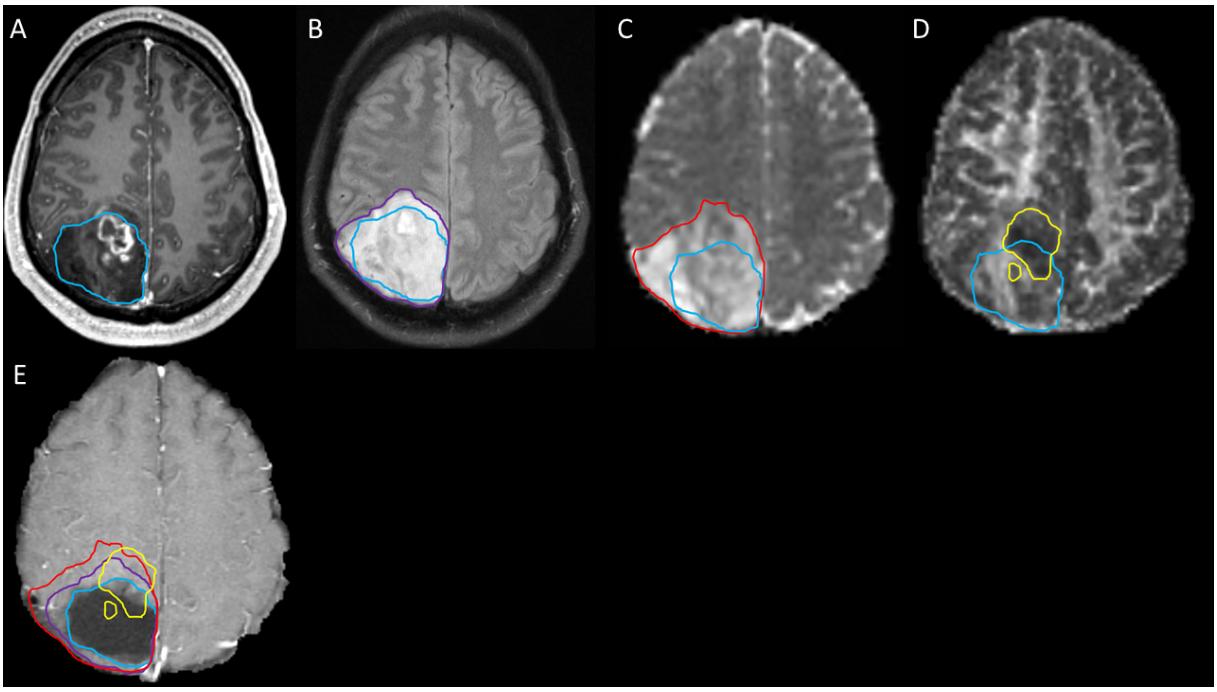
Table 4 - Residual Tumor Volume and Patients' Outcome

	Progression Free Survival			Overall Survival		
	p-value	HR	CI (95%)	*p*-value	HR	CI (95%)
Residual T1 contrast	0.060	1.393	0.986-1.969	0.401	1.140	0.840-1.549
Residual p	0.074	1.028	0.997-1.059	0.942	0.999	0.970-1.029
Residual q	0.008*	1.118	1.029-1.215	0.080	1.053	0.994-1.116
Residual FLAIR	0.882	1.003	0.968-1.038	0.008*	0.939	0.897-0.983

Multivariate analysis results showing age, MGMT methylation status, IDH-1 mutation status, presurgical tumor volume based on T1 contrast imaging, midline shift and tumor eloquent location as covariates. Abbreviation and annotations as in table 2.

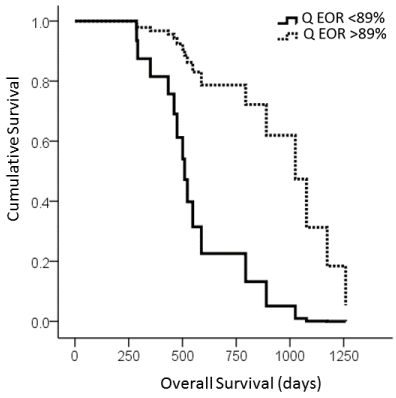
Figure Legends

FIGURE 1 - Regions of interest and extent of resection



Presurgical T1 post contrast (A), FLAIR (B) and DTI (C-D) are shown with the resected area contoured on top in blue (A-D) in a representative example of one patient. The abnormal FLAIR region (B, purple), the isotropic (p) abnormality (C, red) and the anisotropic (q) abnormality (C, yellow) is outlined. In figure 1-E summarize above regions of interests in postsurgical T1 post contrast image.

FIGURE 2 - Patient overall survival according to q resection ratio



Cox regression survival analysis showed that, patients received q resection ratio more than 89% had a better overall survival than those received less than 89% of q resection (p = 0.011).

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