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# Survival prediction in high-grade gliomas using CT perfusion imaging

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**Abstract** Patients with high-grade gliomas usually have heterogeneous response to surgery and chemoirradiation. The objectives of this study were (1) to evaluate serial changes in tumor volume and perfusion imaging parameters and (2) to determine the value of these data in predicting overall survival (OS). Twenty-nine patients with World Health Organization grades III and IV gliomas underwent magnetic resonance (MR) and computed tomography (CT) perfusion examinations before surgery, and 1, 3, 6, 9, and 12 months after radiotherapy. Serial measurements of tumor volumes and perfusion parameters were evaluated by receiver operating characteristic analysis, Cox proportional hazards regression, and Kaplan–Meier survival analysis to determine their values in predicting OS. Higher trends in blood flow (BF), blood volume (BV), and

permeability-surface area product in the contrast-enhancing lesions (CEL) and the non-enhancing lesions (NEL) were found in patients with OS < 18 months compared to those with OS ≥ 18 months, and these values were significant at selected time points ( $P < 0.05$ ). Only CT perfusion parameters yielded sensitivities and specificities of ≥70 % in predicting 18 and 24 months OS. Pre-surgery BF in the NEL and BV in the CEL and NEL 3 months after radiotherapy had sensitivities and specificities >80 % in predicting 24 months OS in patients with grade IV gliomas. Our study indicated that CT perfusion parameters were predictive of survival and could be useful in assessing early response and in selecting adjuvant treatment to prolong survival if verified in a larger cohort of patients.

**Keywords** High-grade gliomas · Glioblastoma multiforme · Computed tomography · CT perfusion · Overall survival

A complete list of the members of the PERNO study group appears in the “Appendix”.

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## Introduction

High-grade gliomas account for over 70 % of all malignant brain tumors, and survival remains dismal even after maximal safe resection, radiotherapy, and temozolomide chemotherapy. The median survival is typically 12–15 months and 2–5 years for patients with World Health Organization (WHO) grade IV and grade III gliomas, respectively [1]. However, there is considerable heterogeneity in patients' treatment response. At present, widely accepted prognostic factors of survival in high-grade gliomas are WHO grade, extent of surgical resection, age, and performance status [2]. Molecular biomarkers, such as isocitrate dehydrogenase 1 (IDH1) mutation status, O6-methylguanine-DNA-methyltransferase (MGMT) methylation status and 1p19q loss of heterozygosity are also recognized as prognostic biomarkers in these patients [3].

Magnetic resonance (MR) is the standard imaging method for assessing high-grade gliomas [4]. For radiographic assessment, the typical MR protocol includes a T2-weighted or fluid-attenuated inversion recovery (FLAIR) MR and a gadolinium-enhanced T1-weighted MR [5]. The gadolinium-enhanced T1-weighted MR images depict the contrast-enhancing lesion (CEL) with disrupted blood–brain barrier. The T2-weighted or FLAIR MR images detect regions of T2 hyperintensity that are suspicious of tumor infiltration and vasogenic edema. This T2 hyperintense region is the non-enhancing lesion (NEL).

In addition to anatomical imaging, functional imaging, such as perfusion imaging, provides quantitative information regarding tumor biology that may be related to patient prognosis [6]. Measurements of tumor blood flow (BF), blood volume (BV), and permeability obtained by perfusion imaging have been shown to correlate with WHO grade [7, 8], histopathologic marker of tumor angiogenesis (e.g. microvessel density) [9,10], and outcome [11–13]. Most perfusion imaging studies that evaluated the relationships between tumor perfusion parameters and overall survival (OS) have focused on MR perfusion imaging at a single time point [14] or two time points [15]. CT perfusion has not been studied extensively despite the ubiquity of CT scanners [16]. However, CT perfusion can help distinguish between high and low grade gliomas [7, 17–19] and between tumor recurrence and radiation necrosis [20, 21]. Therefore, CT perfusion should be considered as a potentially valuable perfusion imaging modality in neuro-oncology. To our knowledge this study is the first to investigate serial changes in tumor BF, BV, and permeability-surface area (PS) in the CEL and NEL of patients with high-grade gliomas for up to a year after radiotherapy. In this analysis, we used these data to evaluate the prognostic value of CT perfusion imaging in predicting OS of these patients.

## Materials and methods

### Patient population

This study was conducted in compliance with the institutional research ethics committee, and informed consent was obtained from patients. Patients with suspected WHO grade III and IV gliomas were prospectively recruited prior to surgery. Exclusion criteria were (1) prior diagnosis or therapy of a brain lesion, (2) clinically unstable, (3) contraindications to contrast materials, and (4) contraindications to MR imaging such as metallic implants, claustrophobia, and obesity. Our study included 29 patients with high-grade gliomas. The median age at diagnosis was 61 (range 31–81) years. Patients underwent serial MR and CT perfusion examinations prior to surgery and one, three, six, nine, and 12 months after radiotherapy. After surgery, genomic DNA was extracted from formalin-fixed paraffin-embedded tissue samples using a DNA extraction kit (Qiagen, Germany) after micro-dissection. MGMT promoter methylation status was determined for WHO grade IV glioma patients by methylation specific polymerase chain reaction after prior DNA bisulfite modification [22]. For WHO grade III glioma patients, IDH1 mutation was assessed by exon 4 direct DNA sequencing [23]. Primer extension sequencing was performed with the use of the Big Dye Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA). Sequences were determined using the ABI PRISM 310 Genetic Analyzer (Applied Biosystems) and the Sequencing analysis 5.2 software (Applied Biosystems).

All patients underwent surgery followed by radiotherapy (60 Gy in 30 fractions,  $N = 28$ ; 45 Gy in 15 fractions with stereotactic boost of 24 Gy in 3 fractions,  $N = 1$ ). Twenty-six patients received concurrent and adjuvant temozolomide chemotherapy. Six patients underwent second surgical resection after radiotherapy, and corticosteroids were administered to patients before the second surgery. WHO grade IV patients were also given Fotemustine at the time of progression. The median follow-up was 18.2 (range, 4.7–60.4) months.

### MR and CT perfusion examinations

MR images were acquired with a 1.5 T Signa HDXT (GE Healthcare, Milwaukee, WI) or a 1.5 T Achieva scanner (Philips Medical Systems, Best, The Netherlands). The MR protocol included the following sequences: axial T1-weighted spin-echo, axial T2-weighted spin-echo or axial FLAIR, coronal FLAIR, and post-gadolinium axial T1-weighted spin echo.

All CT perfusion studies were performed using a multidetector-row CT scanner (Lightspeed VCT, GE) that

covered eight 5-mm sections of tissue. Ten patients were imaged with a one-phase CT perfusion protocol while 19 patients were imaged with a two-phase CT perfusion protocol. For the one-phase protocol, a bolus of non-ionic contrast (Iomeron, Bracco Imaging, Konstanz, Germany; 350 mg I/ml, 40 ml) was injected at a rate of 4 mL/s. A cine scan of 50 s duration was initiated at 5 s after the injection (100 mA, 80 kV, 1 rotation/s), and the images were reconstructed at 0.5 s intervals. For the two-phase protocol, images were reconstructed at 0.5 s intervals in the initial 44 s cine scan, followed by eight additional axial images at 15 s intervals for another 105 s. The total scan duration was 150 s.

### Image analysis

Maps of BF, BV, and PS were computed using CT Perfusion 4D (GE Healthcare) [24, 25]. Averaged CT images were produced by averaging the cine CT images of the same sections. MR images were rigidly registered to the averaged CT images using 3D Slicer [26]. A radiologist with 8 years of experience delineated the entire contrast-enhancing lesion (CEL) and the entire non-enhancing lesion (NEL). The NEL was the peritumoral T2 hyperintense region outside the CEL, central necrosis, and surgical cavity. Thus, the NEL included peritumoral edema and post-radiation T2 changes around the CEL. Mean volume, BF, BV, and PS in both the CEL and NEL were used for analysis.

### Statistical analysis

Statistical analysis was performed using SPSS (IBM® SPSS®, version 21.0, Chicago, IL) and R (<http://www.r-project.org/>) to evaluate whether the imaging parameters were candidate biomarkers of OS. Patients were stratified by their OS using 12, 18, and 24 months OS as endpoints. Patients were designated as “long-term survivors” (OS  $\geq$  18 months) or “short-term survivors” (OS < 18 months) based on the 18 months OS endpoint. The imaging parameters in patients with short-term versus long-term OS were examined longitudinally. The Friedman test followed by the Wilcoxon signed-rank test were used for longitudinal comparisons within-group, and the Mann–Whitney U test examined the differences between groups. Only imaging data from pre-surgery, one, three, and 6 months post-radiotherapy were included for analysis due to patient dropouts resulting from deaths or complete regression of tumors at nine and 12 months post-radiotherapy.

For the entire cohort of 29 patients, receiver operating characteristic analyses were performed to consider all possible cut points to differentiate patients with long-term

and short-term OS. The optimal cut point for each imaging parameter was selected for use in Cox proportional hazards regression and Kaplan–Meier survival analyses. Cox proportional hazards regression analyses were performed to determine the relationships between OS and the imaging parameters. A separate Cox proportional hazards regression model was computed for each imaging parameter at each time point while adjusting for age, Karnofsky performance status, extent of surgical resection, and WHO grade. The hazard ratios (HR) and their 95 % confidence intervals (CI) were computed. IDH1 mutation status was not adjusted in the Cox proportional hazards regression due to the small number of WHO grade III patients ( $N = 5$ ). Kaplan–Meier survival analysis and log-rank test compared the OS of patients with high versus low values of imaging parameters.

For patients with grade IV gliomas ( $N = 24$ ), Cox proportional hazards regression and Kaplan–Meier survival analysis were repeated. MGMT promoter status, age, Karnofsky performance status, and the extent of resection were also included in the Cox proportional hazards regression. A  $P \leq 0.05$  was considered statistically significant. Lastly, joint modeling of OS and the longitudinal covariates was performed to evaluate whether changes in these imaging parameters correlate with OS [27].

## Results

### Patient characteristics and outcomes

A total of 150 CT perfusion and 150 MR examinations were acquired, and 109 CT perfusion and 109 MR scans from the first 4 time points were analyzed. Twenty-two patients had imaging studies available from the first four time points while seven patients had imaging studies available from the first three time points. No radiation-induced side effects (e.g. skin erythema) from the serial CT perfusion scans was noted. The median OS was 18 months (range, 5–60 months) with three patients alive at the end of the study. Table 1 summarizes patient characteristics and the corresponding OS data. In univariate analyses, gender, extent of surgical resection, Karnofsky performance status, re-operation, and second-line Fotemustine were not significant predictors of OS. Older patients ( $\geq 50$  years) had worse OS than younger patients, but this was marginally significant ( $P = 0.06$ ). WHO grade IV was associated with worse OS when compared to grade III ( $P = 0.04$ ), while patients with unmethylated MGMT promoter status was associated with worse OS compared to patients with methylated MGMT promoter ( $P < 0.001$ ). IDH1 mutation could be associated with OS ( $P = 0.05$ ), but the sample size was too small to be conclusive (wild-type  $N = 1$ ).

**Table 1** Patient characteristics, percentages of patients living beyond 12, 18, and 24 months, and median OS

Demographics	<i>n</i>	12 Months OS (%)	18 Months OS (%)	24 Months OS (%)	Median OS in months (95 % CI)	<i>P</i> value*
<b>Age</b>						
<50	5	100	100	75	32.7 (20.7–44.7)	0.06
≥50	24	63	38	23	16.6 (10.1–23.1)	
<b>Gender</b>						
Female	11	55	45	27	16.7 (9.4–24.0)	0.58
Male	18	78	50	33	18.2 (9.8–26.6)	
<b>WHO Grade</b>						
III <sup>#</sup>	5	100	100	67	29.7 (13.0–46.4)	0.04
IV	24	63	38	26	16.6 (10.1–23.1)	
<b>Extent of resection</b>						
Total	18	89	56	38	22.3 (12.5–32.1)	0.37
Subtotal	11	36	36	20	11.4 (10.0–12.8)	
<b>Karnofsky perfusion status</b>						
≤80	18	61	39	28	16.4 (7.9–24.9)	0.70
>80	11	82	64	38	24.4 (16.9–31.9)	
<b>MGMT status (Grade IV patients only)</b>						
Methylated	14	93	57	38	18.2 (8.7–27.7)	<0.001
Unmethylated	10	20	20	10	10.4 (7.5–13.3)	
<b>IDH status (Grade III patient only)</b>						
Mutated	4	100	100	100	29.7 (not available)	0.05
Wild-type	1	100	100	0	18.2 (not available)	
<b>Re-operation</b>						
Yes	6	83	50	0	16.7 (12.2–21.2)	0.40
No	23	65	52	38	22.3 (12.3–32.3)	
<b>Second-line fotemustine chemotherapy (WHO Grade IV patients only)</b>						
Yes	18	61	33	12	16.4 (8.1–24.7)	0.24
No	6	67	67	67	28.8 (3.8–53.8)	

OS Overall survival, CI Confidence interval, WHO World Health Organization

\* Log-rank *P* value comparing OS for the demographic factor

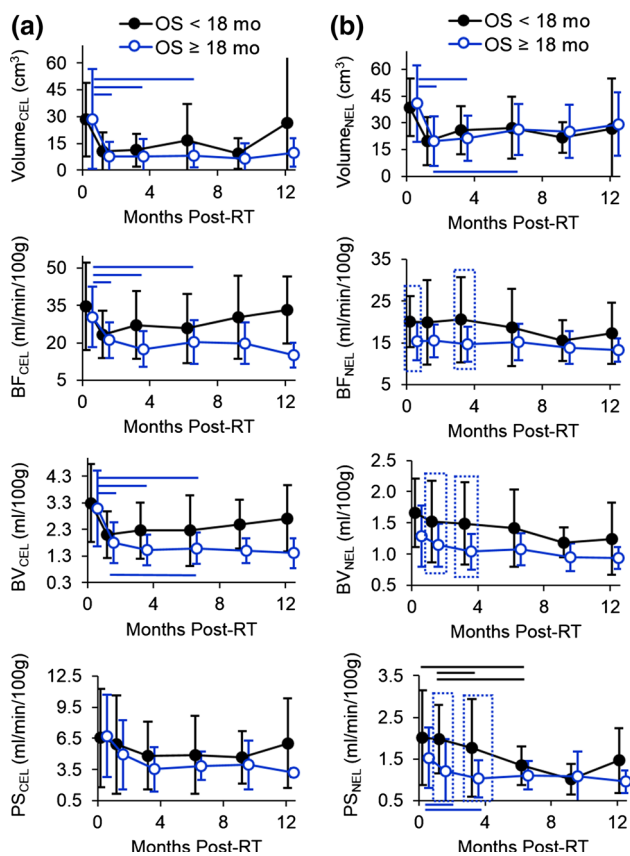
<sup>#</sup> Anaplastic oligodendroglioma

## Serial analysis

Figure 1a shows the serial changes in the CEL of patients stratified by 18 months OS. Patients appeared to show a reduction in CEL volumes after surgery and radiotherapy compared to baseline, and this was significant for long-term survivors (OS ≥ 18 months) ( $P < 0.04$ ). There were also decreasing trends in BF, BV, and PS in the CEL after surgery and radiotherapy. These trends were significant for BF and BV in long-term survivors ( $P < 0.05$  and  $P < 0.03$ , respectively). In general, CEL volumes, BF, BV, and PS appeared to be higher in short-term survivors (OS < 18 months) compared to long-term survivors. Serial changes in these patients stratified by 12 and 24 months OS are provided in Fig. S1.

Figure 1b illustrates the serial changes in the NEL of patients stratified by 18 months OS. NEL volumes

decreased after surgery and radiotherapy. The change in NEL volume (compared to baseline) was significant for long-term survivors ( $P < 0.03$ ). However, there was no between-group difference in NEL volumes in long-term versus short-term survivors. BF values in the NEL before surgery were significantly higher in short-term survivors ( $P = 0.003$ ) compared with long-term survivors, and they were also significantly higher at 3 months post-radiotherapy ( $P = 0.05$ ) in short-term survivors compared to long-term survivors. BV values in the NEL were significantly higher at 1 and 3 months post-radiotherapy in short-term survivors ( $P = 0.04$  and  $P = 0.02$ , respectively) when compared to long-term survivors. PS values in the NEL significantly decreased after surgery and radiotherapy in long-term survivors ( $P < 0.01$  and  $P \leq 0.03$ , respectively), and also in short-term survivors ( $P < 0.04$ ). PS values in the NEL at one and three months post-



**Fig. 1** Serial changes in **a** the contrast-enhancing lesion (CEL) and **b** the non-enhancing lesion (NEL) of patients stratified by 18 months (mo) overall survival (OS) for volume (*top row*), blood flow (BF, *second row*), blood volume (BV, *third row*), and permeability-surface area product (PS, *last row*). *Horizontal line* connects significant changes between two time points of the same group. *Dotted box* encloses a significant difference between the groups at a particular time point. *Error bar* represents 1 SD

radiotherapy were significantly higher in short-term survivors when compared to long-term survivors ( $P < 0.01$  and  $P = 0.02$ , respectively). Figure S2 shows these serial changes in patients stratified by 12 and 24 months OS.

**Survival analysis**

For the entire cohort of patients ( $N = 29$ ), the Cox proportional hazards regression model of the “classical” prognostic factors (i.e. age, performance status, extent of resection, and WHO grade) showed that higher WHO grade ( $HR = 49.6$ ,  $95\% \text{ CI} = 5.1\text{--}483.2$ ,  $P < 0.001$ ) and lower extent of resection ( $HR = 19.0$ ,  $95\% \text{ CI} = 3.6\text{--}99.5$ ,  $P < 0.001$ ) were associated with significant hazards of death. Cox proportional hazards regression models of the imaging parameters were evaluated while adjusting for age, performance status, extent of resection and WHO grade. Figure 2 illustrates imaging parameters with cut points that

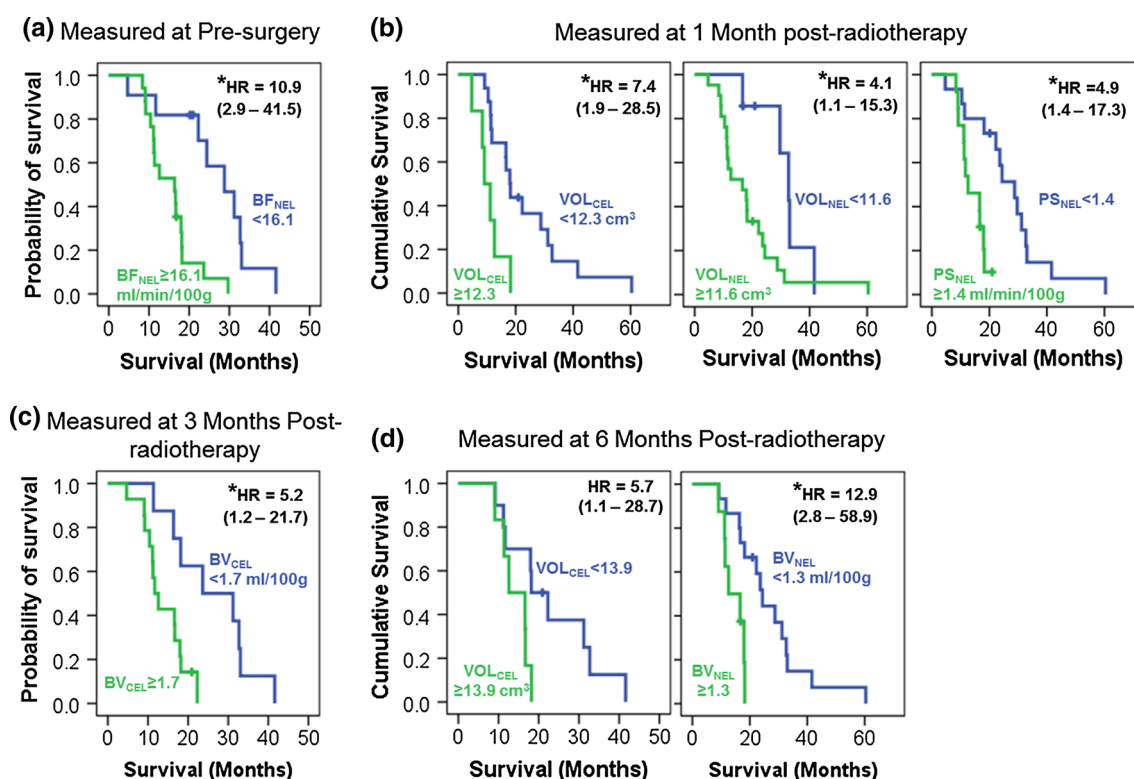
were associated with both significant HRs and significant differences in OS for all 29 patients.

For WHO grade IV glioma patients, Cox proportional hazards regression of MGMT promoter status, age, extent of resection, and performance status showed methylated MGMT promoter status was associated with better OS ( $HR = 0.28$ ,  $95\% \text{ CI} = 0.09\text{--}9.85$ ,  $P = 0.02$ ). With the exception of CEL volume at 6 months post-radiotherapy, the Kaplan–Meier analysis results presented in Fig. 2 were also significant for patients with grade IV gliomas and the Cox proportional hazards regression results were significant even with the adjustment for MGMT status, age, extent of resection, and performance status ( $P \leq 0.05$ ). In addition, grade IV glioma patients with high BV in the NEL 3 months post-radiotherapy had significantly shorter OS (BV  $\geq 1.1$  ml/100 g, median OS = 11.4,  $95\% \text{ CI} = 9.8\text{--}13.0$  months) than those with low BV (BV  $< 1.1$  ml/100 g, median OS = 23.6,  $95\% \text{ CI} = 20.3\text{--}26.9$ , log-rank  $P = 0.01$ ), and this was associated with a significant HR 7.4 ( $95\% \text{ CI} 1.6\text{--}34.6$ ,  $P = 0.01$ ). Joint modeling of longitudinal covariates and OS showed that changes in any of the imaging parameters did not affect survival.

Table 2 shows the sensitivities and specificities of imaging parameters that are  $\geq 70\%$  in stratifying OS of grade IV glioma patients. BF in the NEL at pre-surgery could stratify patients by 18 and 24 months OS with sensitivities and specificities  $\geq 80\%$ . Similarly, BV in the CEL and NEL 3 months post-radiotherapy could stratify patients by 24 months OS with sensitivities and specificities  $\geq 80\%$ . It is important to note that volumes of NEL and CEL could not stratify OS with sensitivities and specificities  $\geq 70\%$ . The extent of resection could predict 12 months OS with 100% sensitivity and 78% specificity, but failed to achieve a specificity of  $>50\%$  when predicting 18 and 24 months OS. MGMT promoter status could predict 12 months OS with 87% sensitivity and 89% specificity, but specificities fell below 60% when predicting 18 and 24 months OS. Figure 3 illustrates representative pre-surgery CT perfusion and MR images of two patients with different survival (16.7 vs. 41.6 months). Higher BF, BV, and PS in the NEL can be seen in the patient with shorter survival.

**Discussion**

In our analysis of patients treated for malignant gliomas, we found that CT perfusion parameters could potentially identify patients with favorable outcomes based on pre-treatment parameters as well as at early time points post-treatment. Based on our findings, we suggest CT perfusion could potentially serve as a valuable imaging biomarker that is complementary to conventional MR imaging.



**Fig. 2** Kaplan–Meier survival plots of **a** blood flow in the non-enhancing lesion ( $BF_{NEL}$ ) measured at pre-surgery, **b** volume of the contrast-enhancing lesion ( $VOL_{CEL}$ ), volume in the NEL ( $VOL_{NEL}$ ), permeability-surface area product in the NEL ( $PS_{NEL}$ ) measured at 1 month post-radiotherapy, **c** blood volume in the CEL ( $BV_{CEL}$ ) measured at 3 months post-radiotherapy, and **d**  $VOL_{CEL}$  and  $BV$  in the NEL ( $BV_{NEL}$ ) measured at 6 months post-radiotherapy for all patients ( $N = 29$ ). Higher values in these parameters were associated with worse overall survival (log-rank  $P < 0.05$  for all comparisons).

We first investigated the serial changes in volume, BF, BV, and PS. The initial decline of all imaging parameters in the CEL after surgery and radiotherapy could be attributed to surgical debulking of the tumor and therapeutic effect of radiotherapy and chemotherapy. After stratifying patients based on OS, all three perfusion parameters in the CEL started to diverge as early as 3 months after radiotherapy with elevated BF, BV, and PS seen in patients with shorter OS. BF, BV, and PS in the NEL were also higher in patients with shorter OS. Although statistical differences were identified only at selected time points, our data provided corroborating evidence that the variation in tumor perfusion characteristics in the CEL and NEL were associated with differences in OS. This variation in perfusion characteristics reflects differences in angiogenesis and vascularity (and by extension differences in aggressiveness and treatment response) between patients. Angiogenesis leads to an increase in tumor microvessel area that facilitates tumor growth, and it is an active target in cancer therapies [28]. It has been shown to correlate with tumor

These parameters were associated with significant hazard ratios (HR) after adjusting for tumor grade, age, Karnofsky performance status, and extent of surgical resection ( $P \leq 0.05$ ). Numbers in parentheses are the 95 % confidence interval (CI) of the HR. Asterisk represents significant HR and significantly different OS when considering only grade IV glioma patients with adjustments for MGMT promoter status, age, extent of resection, and Karnofsky performance status in the Cox proportional hazard regression

BV and patient survival [10]. More recently, vasculogenesis, a process by which bone marrow-derived cells are recruited to form new tumor blood vessels, has been shown to govern tumor recurrence after radiotherapy [29]. Given that recurrence occurs within 2 cm of the irradiated volume [30], it is critical to assess perfusion parameters in both the CEL and NEL. In fact, we found perfusion parameters in the CEL and NEL to be prognostic of OS. The importance of perfusion parameters in the NEL reflect the limitation of conventional contrast-enhanced MR where enhancement may be more reflective of changes in vessel architecture and permeability (i.e. breakdown of the blood–brain barrier) rather than reflecting the overall vascular supply to the tumor.

None of the imaging measurements made in the CEL before surgery showed a significant association with OS. This could be because total resection of the tumor (mostly CEL) is a stronger predictor of OS. Over 60 % of patients underwent total resection, and it showed a significant association with OS. Prediction of survival using pre-surgery



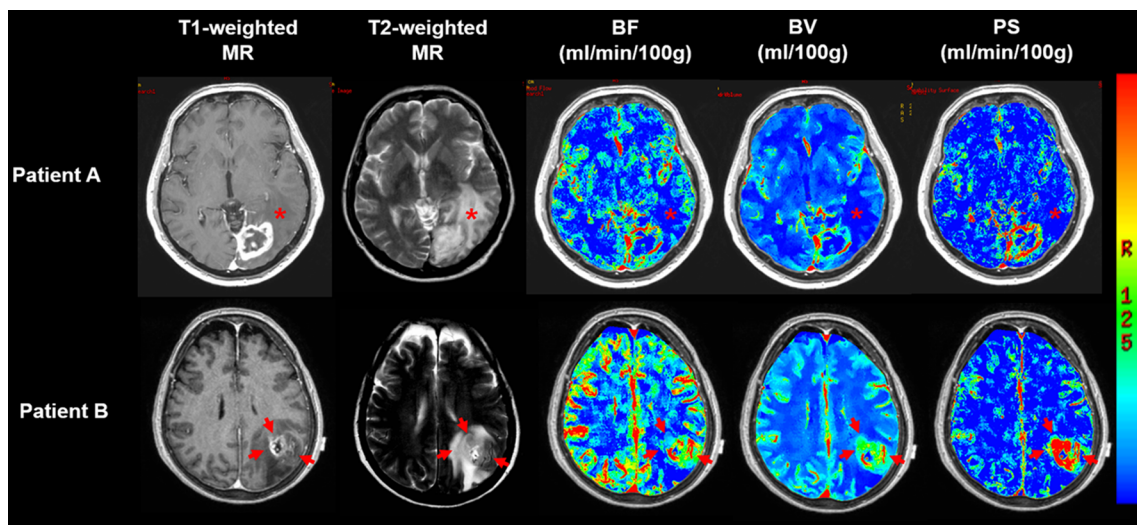
**Table 2** Receiver operating characteristic analysis of imaging parameters with sensitivities and specificities  $\geq 70\%$  in stratifying overall survival (OS) for patients with grade IV gliomas only

Imaging Time	Cut-point selected based on	Region	Parameter cut point	AUC	Sensitivity (%)	Specificity (%)
Pre-surgery	18 mo OS <sup>a</sup>	NEL	BF $\geq 16.8$ ml/min/100g	0.93	80	100
	24 mo OS <sup>b</sup>	NEL	BF $\geq 16.1$ ml/min/100g	0.95	82	100
1 month post-radiotherapy	18 mo OS <sup>a</sup>	NEL	PS $\geq 1.3$ ml/min/100g	0.86	79	89
	24 mo OS <sup>a</sup>	CEL	PS $\geq 2.3$ ml/min/100g	0.82	93	75
	24 mo OS	NEL	BV $\geq 1.1$ ml/100g	0.80	75	83
3 months post-radiotherapy	12 mo OS	NEL	BF $\geq 14.8$ ml/min/100g	0.67	78	71
	12 mo OS	NEL	BV $\geq 1.1$ ml/100g	0.73	78	71
	18 mo OS	CEL	BV $\geq 1.7$ ml/100g	0.76	86	71
	18 mo OS	NEL	BF $\geq 14.8$ ml/min/100g	0.79	71	89
	18 mo OS	NEL	BV $\geq 1.1$ ml/100g	0.81	71	89
	24 mo OS <sup>b</sup>	CEL	BV $\geq 1.7$ ml/100g	0.84	81	100
	24 mo OS	NEL	BF $\geq 14.4$ ml/min/100g	0.73	75	83
	24 mo OS	NEL	BV $\geq 1.0$ ml/100g	0.84	81	83
	6 months post-radiotherapy	12 mo OS	NEL	BV $\geq 1.2$ ml/100g	0.76	83

*NEL* non-enhancing lesion, *CEL* contrast-enhancing lesion; *mo* months, *OS* overall survival, *BF* blood flow, *BV* blood volume, *PS* permeability-surface area product, *AUC* area under the receiver operating characteristic curve

<sup>a</sup> Parameters with sensitivities and specificities  $\geq 70\%$  in stratifying OS when considering both grade III and IV glioma patients

<sup>b</sup> Parameters with sensitivities and specificities  $\geq 80\%$  in stratifying OS when considering both grade III and IV glioma patients



**Fig. 3** Illustrative pre-surgery CT perfusion and MR images of patients with WHO grade IV gliomas. Both patients presented with a contrast-enhancing lesion on post-gadolinium T1-weighted MR images, which also had elevated blood flow (BF), blood volume (BV), and permeability-surface area product (PS). Patient A presented

with low BF, BV, and PS in the non-enhancing lesion (NEL, red asterisks). However, Patient B presented with regions of elevated BF, BV, and PS in the NEL (red arrows). The survival for patient A was 41.6 months, and patient B was 16.7 months. Identical window and level were used for the color maps

CT perfusion parameters in the CEL may be more appropriate for patients who are not candidates for total resection. For example, pre-surgery tumor BV is a predictor of survival in a study with a mixture of patients that received biopsy, subtotal resection, and total resection [11]. However, pre-surgery measurement of BF in the NEL proved to be useful in predicting OS in this study. This result points

to the significance of tumor burden in the T2 hyperintense lesion that is not typically removed by surgery.

Although a larger sample size is required to show consistent associations between OS and CT perfusion parameters across all time points, our results are consistent with previous reports that higher BV and PS are associated with poor outcomes [11, 12, 20, 31, 32]. It is also

noteworthy that while we showed significant hazards of death associated with both volumetric and CT perfusion parameters, only CT perfusion parameters resulted in sensitivities and specificities  $\geq 70\%$  in stratifying OS while volumetric parameters did not. Volume of the CEL may not be a reliable predictor of outcome because the volume of contrast-enhancement may be affected by many nontumoral processes including inflammation, postsurgical changes, pseudoprogression, and treatment-induced necrosis [33–36]. Similarly, the volume of the NEL encompasses many causes of T2 hyperintensity such as vasogenic edema, gliosis, cystic changes, inflammation, and tumor infiltration [37–39]. It is evident from Fig. 3 that tumors can have regions of high BF, BV, and PS that are bigger than the CEL. These regions can potentially lead to future sites of recurrence. Although this is hypothesis-generating, there is preliminary evidence to suggest that there could be better spatial concordance between CT perfusion parameters with the site of future recurrence than the concordance between CEL and the site of future recurrence [24].

Some limitations must be noted. Firstly, a one-phase rather than two-phase CT perfusion protocol was used in one-third of the patients. Although a shorter scan duration of the CT perfusion protocol can affect measurements of PS, the effects on BF and BV are smaller [25]. The identified predictors of OS are unlikely to change, but the cut points of these predictors could change with a larger cohort of patients studied with a uniform two-phase protocol. It is important to use a two-phase CT perfusion protocol in future studies. Secondly, we could not adjust for the effect of IDH1 mutation status in our regression models due to a small number of WHO grade III glioma patients. Finally, a CT perfusion scan at the time point of pre-radiotherapy but post-surgery could be a better baseline scan than a pre-surgery perfusion imaging scan. The prognostic importance of CT perfusion parameters obtained pre-radiotherapy compared to post-radiotherapy remains to be demonstrated.

## Conclusions

BF, BV, and PS are potential biomarkers of OS in patients with high-grade gliomas treated with multi-modality therapies (surgery, radiotherapy, chemotherapy) even after adjustments for age, WHO grade, Karnofsky performance status, the extent of resection, and MGMT promoter status. The results of this study, if verified in a larger cohort of patients, could establish CT perfusion imaging as a reliable early predictor of survival.

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## Appendix

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