Clinical parameters outweigh diffusion- and perfusion-derived MRI parameters in predicting survival in newly diagnosed glioblastoma

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Background. The purpose of this study was to determine the relevance of clinical data, apparent diffusion coefficient (ADC), and relative cerebral blood volume (rCBV) from dynamic susceptibility contrast (DSC) perfusion and the volume transfer constant \( k_{\text{trans}} \) from dynamic contrast-enhanced (DCE) perfusion for predicting overall survival (OS) and progression-free survival (PFS) in newly diagnosed treatment-naive glioblastoma patients.

Methods. Preoperative MR scans including standardized contrast-enhanced T1 (cT1), T2 - fluid-attenuated inversion recovery (FLAIR), ADC, DSC, and DCE of 125 patients with subsequent histopathologically confirmed glioblastoma were performed on a 3 Tesla MRI scanner. ADC, DSC, and DCE parameters were analyzed in semiautomatically segmented tumor volumes on contrast-enhanced (CE) cT1 and hyperintense signal changes on T2 FLAIR (ED). Univariate and multivariable Cox regression analyses including age, sex, extent of resection (EOR), and KPS were performed to assess the influence of each parameter on OS and PFS.

Results. Univariate Cox regression analysis demonstrated a significant association of age, KPS, and EOR with PFS and age, KPS, EOR, lower ADC, and higher rCBV with OS. Multivariable analysis showed independent significance of male sex, KPS, EOR, and increased rCBV_{CE} for PFS, and age, sex, KPS, and EOR for OS.

Conclusions. MRI parameters help to predict OS in a univariate Cox regression analysis, and increased rCBV_{CE} is associated with shorter PFS in the multivariable model. In summary, however, our findings suggest that the relevance of MRI parameters is outperformed by clinical parameters in a multivariable analysis, which limits their prognostic value for survival prediction at the time of initial diagnosis.

Keywords: diffusion, glioblastoma, MRI, perfusion, survival.
outcome, which is commonly attributed to the fact that tumor-induced angiogenesis causes increased blood flow, hence marking aggressive tumor growth. A combination of diffusion- and perfusion-imaging also allows identifying different growth patterns associated with prognosis.

DCE MR perfusion-derived $k^{\text{trans}}$, the volume transfer constant of contrast agent from a plasma space to an extravascular extracellular space, reflects both flow and vascular permeability within brain tissue. It has shown to correlate with glioma grade and allows distinguishing recurrent glioma from radiation necrosis. While one study reported that low $k^{\text{trans}}$ predicts worse outcome in glioblastoma patients, other studies stated that elevated $k^{\text{trans}}$ values are associated with worse outcome.

In line with the recently published consensus recommendations for brain tumor imaging protocols, our institution routinely includes all of the above-mentioned MRI-sequences in patients with suspected intra-axial lesions. Therefore, if proven useful, they will be readily available as potential biomarkers for every patient in the future.

Our aim was to examine a large and homogenous patient collective of exclusively newly diagnosed glioblastoma patients and thus provide a comprehensive analysis of clinical and imaging parameters that are suggested as predictors of outcome in glioblastoma patients at the time of diagnosis.

Materials and Methods

Patients

This retrospective study was approved by our local ethics committee (ethics approval number, 5-320/2012). By screening our database from July 2009 to August 2014, we identified 85 patients who had received an MRI examination including T1, T2, DSC, and DCE perfusion MRI and diffusion (ADC) sequences prior to surgery (median 3 [0–23] days) and were thereafter diagnosed with primary glioblastoma (IDH-wild-type). Another 48 patients with primary glioblastoma had received all sequences except for DCE perfusion. Eight patients had to be excluded after postprocessing due to insufficient image quality or motion artifacts, yielding a total of 125 patients who were enrolled in our analysis. We obtained data about the age at diagnosis, sex, extent of tumor resection (EOR, defined as gross total resection, subtotal resection, or biopsy on postoperative MRI within 72 hours after surgery), adjuvant therapy regimen, KPS closest to surgery, and MGMT-promoter status (available for 51 patients). Overall survival (OS) was calculated as the time from surgery to death or date of inquiry at the registration office where the patient was reported to be alive. Progression-free survival (PFS) was determined as the time from surgery to death, progress according to RANO criteria, and/or clinical progress as reported in follow-up visits. At the date of the last inquiry on October 1, 2014, 42 patients were still alive, and 19 patients had not experienced progression of their disease and were therefore censored.

Magnetic Resonance Imaging

All patients were examined a median of 3 days prior to surgery in a 3 Tesla MRI scanner according to the standardized tumor protocol at our institution (TrioTIM or VERIO, Siemens Healthcare) as described previously. A 12-channel head matrix coil was used. First, ADC-maps based on DWI were obtained (TR = 5300 ms, TE = 90 ms, b = 0 and b = 1200 with isotropic gradients, pixel size 1.769 mm/1.769 mm, image matrix 130 × 130, slice thickness 5 mm, flip angle 90°, FoV 229 × 229 mm), together with a FLAIR sequence (TR = 8500 ms, TE = 85 ms, inversion time = 2400 ms, slice thickness 5 mm; intersection gap 5%). DCE-MRI was performed in 85 of 125 patients (68%) as a 3D fast low-angle shot (FLASH) volume-interpolated gradient-echo (VIBE) sequence (TR = 5.28 ms, TE = 2.4 ms, pixel size 0.898 mm/0.898 mm, image matrix 256 × 192, slice thickness 5 mm, flip angle 10°, FoV 172 × 256 mm). Thereby, 22 dynamic acquisitions, each including 26 slices were obtained every 13.34s, resulting in a total measurement time of 4:53 minutes. After the third dynamic acquisition, a standard dose (0.1 mmol/kg body weight) of gadoterate meglumine (Gd-DOTA, Dotarem) was injected as a bolus through a pneumatically driven injection pump at an injection rate of 5 mL/s. After completion of the DCE-MRI sequence, another standard dose (0.1 mmol/kg body weight) of contrast agent was administered and followed by acquisition of DSC-MRI, obtained as a 2D-multislice, T2*-weighted gradient-echo EPI sequence (TR = 2220 ms, TE = 36 ms, pixel size 1.797 mm/1.797 mm, image matrix 128 × 128, slice thickness 5 mm, flip angle 90°, FoV 240 × 240 mm) as described previously. Subsequently, a postcontrast T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (cT1) sequence was performed with TR = 1710 ms, TE = 4.04 ms, pixel size 0.5 mm/0.5 mm, image matrix 512 × 512, slice thickness 1.3 mm, flip angle 15°, FoV 256 × 256 mm, and inversion time 1100 ms.

Postprocessing

Postprocessing of DSC and DCE-MRI data and generation of rCBV and $k^{\text{trans}}$ maps were performed with dedicated software (Olea Sphere v2.3, Olea Medical) as described previously. Next, image registration was performed with the FMRIB software library (FSL, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) as described previously. First, brain voxels were isolated by generating a binary brain mask from the T1-volume using the brain extraction tool and transferred to all other imaging volumes (cT1, FLAIR, DWI, ADC map, first temporal volume of DSC-MRI raw data, rCBV map) for each patient. These image volumes were then registered to the brain-extracted T1-volume as the reference sequence (slice thickness 1.3 mm) using the linear image registration tool with a mutual information algorithm and a 6 degree of freedom transformation. T1 subtraction volumes (subT1) were generated by voxel-wise subtraction of the T1 from the cT1 volume. Tumor segmentation was then performed semi-automatically (by S.B. [doctoral candidate with 2 years of experience in neuroradiologic research] and checked by P.K. [neuroradiologist with 4 years of experience] and D.B. [board-certified radiologist and neuroradiologist with 15 years of experience in image processing]) on the cT1 and subT1 images to select the contrast-enhancing part (CE) and on FLAIR images to select the nonenhancing part (ED, defined as FLAIR hyperintense abnormality excluding the contrast-enhancing and necrotic tumor portion as well as...
obvious leukoaraiosis (ie, presence of bilaterally symmetrical, patchy, or confluent periventricular white matter hyperintensities) using a region-growing segmentation algorithm implemented in ITK-SNAP (www.itksnap.org) as described previously (for illustration please compare Fig. 1).39-42 The presurgical tumor volume was defined as all hyperintense tumor parts on FLAIR images including CE, ED, and necrotic parts.

Extraction of rCBV, $k_{\text{trans}}$ and ADC values from the CE- and ED-VOI was performed with customized in-house software implemented in Matlab as described previously.39,42 The first volumes of the DWI and DSC-MRI raw data were thresholded to determine regions of prohibitive signal loss near susceptibility interfaces such as the skull base, and the tumor segmentations were modified by removal of low-signal regions. Gaussian normalization of rCBV, $k_{\text{trans}}$, and ADC maps was performed with voxel-wise division of the corresponding map through the standard deviation of the normal-appearing brain volume (derived from the inverted FLAIR-hyperintense tumor segmentations)39 prior to calculation of appropriate percentiles (10th and 90th) from the Gaussian-normalized rCBV, $k_{\text{trans}}$, and ADC histograms of the CE and ED-VOI.

**Statistical Analysis**

All statistical analyses were performed in R (Version 3.2.3). $P$ values \( \leq 0.05 \) were considered significant. Model assumptions for the Cox regression analysis were checked.

Univariate Cox regression analysis was performed for PFS and OS with the following variables: age, KPS, sex, presurgical tumor volume, EOR, 10th percentile ADC, 90th percentile rCBV, 90th percentile $k_{\text{trans}}$ in contrast enhancement (CE), and peritumoral edema (ED). Hazard ratios and corresponding 95% confidence intervals were calculated.

For the multivariable Cox regression analysis, we included age, KPS, sex, presurgical tumor volume, EOR, 10th percentile ADC, 90th percentile rCBV in CE, and ED. As there were about 38% missing data in $k_{\text{trans}}$ values, we refrained from including this variable in the multivariable analysis. Again, hazard ratios for each regressor and corresponding 95% confidence intervals were calculated. Moreover, we used the Gönen & Heller concordance probability estimate (CPE)48 to evaluate the predictive power of our multivariable Cox proportional hazards models.

**Results**

**Clinical Data**

Overall, 125 patients were included in the analysis. There were 50 female and 75 male patients with a median age of 63 (37–71) years. Median OS was 10.7 months (95% CI: 8.9–13.3), 42 patients still alive and thus censored, and mean PFS was 4.8 months (95% CI: 4.1–6.3; 19 patients censored). Patients underwent surgical intervention as follows: 41% gross total resection (GTR), 38% subtotal resection (STR), and 21% biopsy (B). The tumor was most often localized in the frontal lobe (28%), followed by temporal lobe (26%), multifocally (2 or more lobes affected; 18%), parietal lobe (15%), occipital lobe (7%), or centrally in the basal ganglia/thalamus (6%).

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**Fig. 1.** Semiautomatic segmentation of the volumes of interest in a 74-year-old female patient with a glioblastoma. A, contrast enhancement volume of interest on the cT1 image (red area); B, nonenhancing peritumoral edema volume of interest (blue area) on the FLAIR image; C, both volumes of interest displayed in 3D for the whole tumor. The segmentation masks were then transferred to D, apparent diffusion coefficient, from diffuse weighted imaging; E, relative cerebral blood flow from dynamic susceptibility contrast perfusion MRI, and F, $k_{\text{trans}}$ map from dynamic contrast-enhanced perfusion MRI for the readout of histograms.
The adjuvant therapy regimen consisted of radiotherapy plus temozolomide in 51% of patients; in another 12% of patients, a drug within a clinical study was added to this scheme. 8% in another 12% of patients received temozolomide only, 21% received radiotherapy only, and 6% received palliative care. The adjuvant therapy regimen was not documented for 2 patients. The median KPS was 80 (20–100) points. Fifty-one patients had their KPS score documented prior to surgery, and postoperative KPS was available for 74 patients (median = 7 ± 5 days after surgery). O6-methyl-guanine DNA methyltransferase (MGMT)-promoter status was documented in 42% of patients (N = 53), of whom 47% were hypermethylated. Median ki67 was 20 (5;80)%.

### Cox Regression Models

Model assumptions for the Cox regression analysis were checked by testing the proportional hazard assumption and the linear relationship between covariates and log hazard. As expected, the proportional hazard assumption was violated by the covariate “age” in both multivariable analyses, with its hazard increasing steadily over time. However, the proportional hazard assumption for the whole models remained fulfilled. Linearity assumption of all covariates was confirmed for OS and PFS.

In the univariate Cox regression model, age (HR = 1.03, P < .01), KPS (HR = 0.85, P < .01), and EOR (GTR vs B; HR = 2.04, P < .01) were significant for PFS, while EOR (GTR versus STR; HR = 1.54, P = .05), and rCBV\(_{CE}\) (HR = 1.12, P = .08) showed a tendency towards significance (Table 1).

For OS, age (HR = 1.05, P < .01), KPS (HR = 0.80, P < .01), EOR (GTR vs STR, HR = 1.77, P = .02, and GTR vs B, HR = 2.23, P = .01), 10th percentile ADC\(_{CE}\) (HR = 0.64, P = .01), 10th percentile ADC\(_{ED}\) (HR = 0.62, P = .01), 90th percentile rCBV\(_{CE}\) (HR = 1.19, P = .01), and 90th percentile rCBV\(_{ED}\) (HR = 1.38, P < .01) were significant (Table 1).

### Discussion

A principal finding of this study is that MRI parameters help to predict OS in a univariate Cox regression analysis, while their relevance is outperformed by clinical parameters when included in a multivariable Cox regression analysis. Increased rCBV\(_{CE}\) was a predictive marker only for PFS.

In looking at the clinical parameters, a somewhat surprising effect is that females had a longer PFS and OS in our multivariable analysis. While age, KPS, EOR, and adjuvant therapy do not differ significantly in our cohort between the sexes, 80% of females for whom an MGMT-promoter status was documented (N = 20) were hypermethylated, while only 27% of males were hypermethylated (N = 35). Since MGMT-promoter hypermethylation is associated with better response to chemotherapy, this might be the reason why the females in our cohort had a better outcome. Unfortunately, MGMT-promoter status was only documented for 42% of patients, but its uneven distribution among the sexes might be a possible explanation for the effect of sex on survival.
Concerning the MRI parameters, low ADC values and high rCBV values in contrast enhancement and peritumoral edema were associated with shorter OS in our univariate Cox regression analysis. Increased rCBVCE was also associated with shorter PFS in the multivariable model. This is in accordance with many studies that found decreased ADC values and high rCBV values in contrast enhancement and peritumoral edema to be predictive of OS (in a univariate analysis) in one study.

While there is a variety of studies looking at MR characteristics to predict survival following resection,10 radiochemotherapy,11 or at the time of recurrence,39 there are only 4 studies that have included both diffusion and perfusion parameters for a survival analysis in astrocytic brain tumors before surgery or treatment.6-8 Summarizing their findings, rCBV was found to be predictive of OS (in a univariate analysis) in one study.12 Four studies found diffusion-derived MRI parameters to be significant for OS even if included in a multivariable analysis.6-8 In our multivariable analysis, rCBVED trended towards significance for OS, and rCBVCE was the only significant MRI parameter for PFS. Diffusion-derived MRI parameters did not predict survival. The main reason why our results differ from previously published multivariable analyses is probably the implementation of other methodical and statistical approaches with which we hoped to overcome some of the limitations of the previously mentioned works.

First, with 125 primary (IDH-wildtype) WHO IV glioblastoma patients, our study is among those with the largest and most homogenous patient collective. Hence, we avoid including gliomas of different grades with varying biological properties.

Second, we chose to perform a histogram analysis based on a manually controlled, semiautomatic segmentation of the whole tumor volume as opposed to placing singular regions of interest in visually abnormal areas of the functional MRI maps. We consider this to be an observer-independent, reproducible, and well-established method in this context.7-10,17,28,49 Even though MRI cannot account for the microscopic heterogeneity inherent in all glioblastomas, we are confident that our approach is the most reliable for noninvasive characterization of glioblastoma to date.

Third, the use of continuous variables rather than binary variables, both as regressors and endpoints in a multivariable regression approach, will yield unbiased estimators that are adjusted for potential effects of the other covariates. Together with varying selections of clinical and imaging parameters that were entered into the analysis, we consider this to be the main explanation why our results differ from previously published works.

Limitations of our study are its retrospective design, censored data, and some missing values when patient records were incomplete or patients had been referred to other institutions. The concordance indices of our multivariable models indicated an acceptable predictive ability. They could have probably been improved by including the received therapy regimens in the model. We chose not to do so because this information would not have been available for predicting survival at the time of diagnosis. We also refrained from retrospectively selecting patients with uniform adjuvant therapy regimens because that might have excluded those with particularly good or poor survival who were allocated to nonstandardized treatment regimens.

While age, performance status, and extent of resection remain the relevant prognostic markers at the time of diagnosis when measured against singular physiologic MRI parameters, the next step would be to investigate enhanced methodical approaches such as radiomics50,51 (preferably in longitudinal studies). Additionally, a combination of radiological and histopathological/molecular features in the emerging field of radiogenomics52,53 might help to establish markers that complement clinical information.
Conclusion

The presented volume of interest-based histogram analysis of 125 patients with glioblastoma showed that MRI parameters help to predict OS in a univariate regression analysis and that increased rCBV_CE is associated with shorter PFS in the multivariable model. In summary, however, our findings suggest that the relevance of MRI parameters is outperformed by clinical parameters in a multivariable analysis, which limits their prognostic value for survival prediction at the time of initial diagnosis.

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References


