Prognostic Vascular Imaging Biomarkers in High-Grade Gliomas:

Tumor Permeability as an Adjunct to Blood Volume Estimates

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Rationale and Objectives: Despite recent advances in the treatment of high-grade gliomas, overall survival (OS) remains poor, which underlines the importance of searching for and determining prognostic imaging biomarkers. The purpose of our retrospective study was to correlate patient survival with relative cerebral blood volume (rCBV) and permeability surface area-product (PS) measured using perfusion computed tomography (PCT) in patients with high-grade gliomas.

Methods: This study was composed of 54 patients with high-grade gliomas (World Health Organization [WHO] grade III, $n = 14$; WHO grade IV, $n = 40$) who underwent pretreatment PCT. Kaplan-Meier survival estimates were computed to describe OS for patients with high-versus-low PCT parameters, as well as grade III and IV gliomas.

Results: Differences in OS between high and low rCBV, PS, and rCBV + PS were significant ($P < .001$) for all high-grade gliomas. After adjustment for WHO grade, rCBV ($P = .041$) and rCBV + PS ($P = .013$) estimates remained significant, whereas PS estimates were not ($P = .214$). PS estimates showed a statistically significant difference for OS in the grade III glioma group ($P = .011$), whereas for grade IV gliomas, rCBV estimates were statistically significant ($P = .019$). rCBV + PS was statistically significant for OS in both grade III ($P = .001$) and grade IV ($P = .004$) glioma groups.

Conclusions: Blood volume and permeability estimates measured using PCT can help predict survival in patients with high-grade gliomas. Patients with high PCT parameters showed worse OS compared to the patients with low PCT. Both rCBV and rCBV + PS remained statistically significant even after adjustment for WHO grade, suggesting these may be better predictors of OS than histological grade.

Key Words: High-grade glioma; overall survival; tumor vascular permeability; perfusion CT.

High-grade gliomas are often heterogeneous tumors, which infiltrate the brain parenchyma. As a result, complete cure is nearly impossible and, despite aggressive multimodality treatment approaches, the survival rate for high-grade gliomas remains dismal. Currently, prognostic factors for patients with high-grade gliomas are clinically based, the most important of which include patient age, Karnofsky Performance Status (KPS) score, extent of initial surgical resection, and molecular profile (1,2). The search for prognostic biomarkers, especially in vivo imaging biomarkers, continues with significant improvements in the resolution of clinically available imaging tools. Functional imaging modalities/techniques can provide information about the metabolic (magnetic resonance spectroscopic imaging, positron emission tomography) and physiological (diffusion-weighted imaging, perfusion imaging) aspects of tumor biology, which could not only provide important prognostic information about tumor behavior and aggressiveness but also offer a means of assessing early response to specific treatment regimens by measuring quantifiable parameters. One particular group of parameters being explored is related to tumor perfusion. Although most perfusion imaging studies have focused on blood volume estimates and correlation with survival prediction in mixed populations of gliomas, tumor vascular permeability estimates have not been evaluated in much detail, particularly in relation to survival prediction (3–5). However, tumor blood volume and permeability appear to represent two different aspects of tumor vasculature and angiogenesis (6). Thus, each parameter may provide unique information about the tumor microenvironment. In addition, leaky tumor vasculature is known to be associated with higher tumor grade and increased malignant potential (3–9). Thus, estimating tumor leakiness, in particular, could provide help in quantifying angiogenesis in high-grade gliomas, perhaps serving as an important prognostic biomarker.

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The purpose of this study was to retrospectively assess the prognostic value of both tumor blood volume (relative cerebral blood volume) and permeability surface area-product (PS) estimates obtained using perfusion computed tomography (PCT) in patients with high-grade gliomas.

MATERIALS AND METHODS

Study Population

Our study is Health Insurance Portability and Accountability Act compliant. The first author had control of data and all other information being submitted for publication. Between January 2006 and May 2009, a total of 78 patients with treatment-naïve gliomas underwent PCT as part of our previously published work (6–8). This group included 54 patients who had high-grade gliomas (World Health Organization [WHO] grade III, $n = 14$; WHO grade IV, $n = 40$) that are presented in the present analysis. Mean age was 54.2 years (range, 22–81 years) with 33 men and 21 women. The median follow-up was 18.8 months with a range from 2.6 to 66.5 months.

PCT was performed at 1 to 7 days before surgery. Fifteen (37.5%) of the grade IV patients and 3 (21.5%) of the grade III patients were receiving a stable dose of steroids before the PCT was done. All lesions were confirmed histologically according to WHO criteria by a board-certified neuropathologist who was blinded to the PCT results. All patients underwent surgery (gross total resection, $n = 11$; subtotal resection, $n = 31$; biopsy, $n = 12$), which was followed by adjuvant radiation therapy in 50 patients (external beam radiation therapy, 60 Gy, $n = 48$; intensity-modulated radiation therapy, 60 Gy, $n = 2$). Fifty-three patients received adjuvant chemotherapy (temozolomide [TMZ], $n = 39$; TMZ + cilengitide, $n = 14$). In addition, 34 patients received a second line of chemotherapy (bevacizumab + irinotecan, $n = 18$; bevacizumab + TMZ, $n = 6$; other drug combinations, $n = 10$); 12 received a third line of treatment; and 8 received a fourth line of treatment with various drug combinations.

PCT Studies

Perfusion studies were performed using 64-slice (VCT; GE Medical Systems, Milwaukee, WI) multidetector-row computed tomography (CT) scanners in all the patients using a previously published protocol (7–10). Perfusion maps of cerebral blood volume (CBV) and PS were generated at an Advantage Windows workstation using CT perfusion 3.0 software (General Electric Medical Systems, Milwaukee, WI) and a 2-compartment model in all patients by a neuroradiologist with at least 9 years of experience. Regions of interest (ROIs) were drawn manually on the PCT parametric maps including the whole solid and enhancing lesion on multiple axial images covering the whole lesion. ROIs were drawn with care taken to exclude necrotic/cystic parts or calcified portions of the lesion and to avoid any major cortical vessels. A second ROI was placed over the normal-appearing white matter in the contralateral cerebral hemisphere. Mean absolute values of PS, as well as relative CBV (rCBV) values obtained using normal-appearing white matter as the denominator in each case, were used for the final analysis.

Statistical Analysis

Receiver operating characteristic analyses were made to assess the possible different cut points for rCBV and PS parameters for differentiating between grade III and IV gliomas. We selected values with the highest combination of sensitivity and specificity for use in survival analyses. In addition to the rCBV and PS parameter cut points, a new PCT parameter, which is a combination of these two parameters (rCBV + PS), was considered. rCBV + PS was defined as high when both the rCBV and PS parameters were higher than the respective cut points and low for all other combinations (ie, if either rCBV or PS was lower than respective cut points).

The outcome of interest in the survival analyses was overall survival (OS), which was computed as the time between diagnosis and death or last follow-up. For patients still alive when the analyses were done, their OS rates were censored at the time of their last clinic visit. Kaplan-Meier survival estimates were computed to describe the OS experience for patients with high versus low PCT parameters, as well as grade III and IV gliomas. Median OS in months was also computed from the Kaplan-Meier survival curves. Log rank tests were performed to compare OS for the different groups. Cox proportional hazards regression analyses were performed to adjust for age and prognostic factors of KPS, type of initial surgery, and WHO grade when comparing OS for PCT parameters. Hazard ratios with corresponding 95% confidence intervals and P values were computed for all variables included in the regression models. Separate models were made for each of the three PCT parameters and with and without adjustments for WHO grade. Similar statistical methods were used to assess the association between OS and PCT parameters within the grade III and IV patients, separately. Concordance probability estimates using the method of Gonen and Heller (11) were computed to assess which PCT parameter had the best discriminatory features. The concordance probability estimate is a generalized version of the c-index (a measure of the area under the curve), which takes into account censored data and multiple predictors. Additional survival analyses were performed to compare OS between patients receiving the standard treatment of radiation plus TMZ to patients receiving other treatments. All testing of significance was performed at the .05 level. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

This study was approved by our institutional review board (No. 5156).