The Added Prognostic Value of Metabolic Tumor Size on FDG-PET at First Suspected Recurrence of Glioblastoma Multiforme

Gloria C. Chiang, Naveen Galla, Richard Ferraro, Ilhami Kovanlikaya
From the Department of Radiology, Division of Neuroradiology, Weill Cornell Medical College, NewYork-Presbyterian Hospital, New York, NY.

ABSTRACT

BACKGROUND AND PURPOSE: Patients with glioblastoma multiforme (GBM) face a dismal prognosis, with an average survival of 6–7 months after recurrence. There remains no consensus for managing these patients due to the heterogeneity of these tumors. Imaging may affect treatment decisions by helping to stratify patient prognosis. The purpose of this analysis was to evaluate the added utility of 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) over magnetic resonance (MR) imaging metrics in predicting survival.

METHODS: Forty-four consecutive patients who underwent FDG-PET for first recurrence of GBM were included in this analysis. Tumor sizes, using cross products, and volumes on FDG-PET and MRI, maximum standardized uptake value (SUV), minimum apparent diffusion coefficient (ADC) value, presence of satellite lesions, presence of multifocal lesions, and presence of bilateral tumor were considered as prognostic variables. Survival was assessed using Cox hazard and logistic regression models based on the time interval between the PET scan and the patient’s date of death.

RESULTS: Tumor volumes on FDG-PET (P = .046), tumor cross products on FDG-PET (P = .017), and tumor cross products on MRI (P = .031) were significant prognostic variables, adjusting for the extent of the initial resection. Enhancing tumor volume, tumor cross product on a T2-weighted MRI sequence, maximum SUV on FDG-PET, minimum ADC value, presence of satellites, multifocality, and bilaterality were not prognostic (P > .5). Prognostic accuracy of predicting short survival increased from 58% with tumor cross product on MRI alone to 74% after including tumor cross product from PET.

CONCLUSIONS: Tumor size on FDG-PET adds prognostic information to enhancing tumor size on MRI at first suspected recurrence of GBM.

Keywords: Brain tumor, PET, imaging.

Acceptance: Received May 18, 2016, and in revised form July 11, 2016. Accepted for publication July 12, 2016.

Correspondence: Address correspondence to Gloria C. Chiang, MD, Department of Radiology, Division of Neuroradiology, Weill Cornell Medical College, NewYork-Presbyterian Hospital, 525 East 68th Street, Starr Pavilion, Box 141, New York, NY 10065. E-mail: gcc8004@med.cornell.edu

Acknowledgments and Disclosure: The authors have no financial conflicts-of-interest relevant to this work.

We would like to thank Paul Christos, DrPH, MS, for statistical assistance and Jeffrey Edwards, MD, MA, MAS for proofreading our manuscript for grammatical errors.

J Neuroimaging 2016;00:1-5.
DOI: 10.1111/jon.12386

Introduction

Patients newly diagnosed with glioblastoma multiforme (GBM) face a dismal prognosis with a median overall survival of slightly more than 1 year.1,2 Survival after recurrent GBM is even more dismal, with a median of approximately 6–7 months.3 In the last decade, numerous clinical trials have failed to significantly prolong patient survival,4 and one potential reason is the heterogeneity within and among these tumors. Molecular subgroups of gliomas have garnered interest in stratifying prognosis among gliomas, particularly mutations in isocitrate dehydrogenase and codeletions of chromosome 1p and 19q.5,6 However, these molecular subgroups do not stratify survival among GBM patients.5

Imaging may provide an alternative means to stratifying patients with GBM in terms of prognosis and potential therapies. Current standard-of-care clinical practice involves monitoring tumor growth on conventional magnetic resonance imaging (MRI) sequences, with the addition of advanced MR imaging sequences and/or 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) to better differentiate between tumor progression and radiation necrosis. However, whether these additional MR and PET images aid in stratifying prognosis at the time of recurrence is unclear. FDG-avidity, often reported using a visual grading scale, has been shown to be prognostic in mixed cohorts of low- and high-grade gliomas.7–10 Low apparent diffusion coefficient (ADC) values on the diffusion-weighted sequence may serve as a proxy for tumor cellularity and is reportedly associated with prognosis of GBM before bevacizumab therapy.11–13 However, to our knowledge, no one has considered the prognostic utility of both PET and MRI in a posttreatment cohort of recurrent GBM.

Therefore, the purpose of our analysis was to determine the added value of semiquantitative PET imaging metrics to conventional MRI in predicting prognosis in a cohort of GBM patients at first suspected recurrence.

Methods

Subjects
This retrospective study was approved by the institutional review board and is compliant with the Health Insurance Portability and Accountability Act. At our institution, GBM patients are...
monitoring by MRI every 1–3 months, and an FDG-PET scan is performed when tumor progression is suspected due to interval tumor growth or development of a new mass. Forty-four consecutive patients with pathologically-proven GBM who underwent FDG-PET for first suspected recurrence at our institution between February 2007 and August 2013 were included in this analysis. All patients underwent surgical resection followed by concomitant radiotherapy and temozolomide therapy. Some patients also underwent repeat resection, as delineated in Table 1. All patients were followed clinically until the date of death.

MR Image Acquisition and Analysis

MR images were obtained on a 1.5 or 3 T clinical MR system (GE Signa HDxt) using a standardized brain tumor protocol. The protocol included axial T1 pre- and postcontrast sequences (TR 400, TE 20, matrix size 320 × 224, FOV 24 × 24 cm², 5 mm slice thickness) and an axial T2 FLAIR sequence (TR 10,000, TE 140, matrix size 256 × 192, FOV 24 × 24 cm², 5 mm slice thickness). Diffusion-weighted imaging data were acquired using a single-shot echo-planar imaging sequence with parallel imaging (FOV 24 × 24 cm², b = 0, 1,000 s/mm², 5 mm slice thickness).

A board-certified neuroradiologist with subspecialty certification (GCC) and 13 years of experience with MR imaging analysis performed the imaging measurements, blinded to all clinical information, including treatment course and duration of survival. To obtain the region of the tumor with the minimum ADC value, multiple small circular regions-of-interest (ROI) measuring approximately 10–15 mm² were placed on the enhancing and nonenhancing portions of the tumor on the ADC map, taking care to avoid areas of necrosis or hemorrhage (Fig 1). This method has been found to be the most accurate and reproducible way to perform these measurements. The ROI with the lowest ADC value was included in the analysis and considered the minimum ADC. The minimum ADC was then normalized, using an ROI of the same size that was drawn in the contralateral normal-appearing white matter. To determine the reproducibility of ROI placement, the ROI analysis was repeated 3 months after the first analysis, blinded to the first set of measurements, and the intraclass correlation was found to be .93.

Enhancing tumor volumes were obtained using FDA-approved software (Olea Sphere 2.3; Olea Medical Solutions, La Ciotat, France). 3-Dimensional volumes were created by selecting a seed voxel at the center of the enhancing portions of the tumors and expanding the ROI to include surrounding voxels of similar signal intensities. Areas of hemorrhage or necrosis were excluded, and manual editing was performed to include or exclude voxels as necessary. Enhancing tumor size was calculated using the cross product of the longest anteroposterior and transverse dimensions of the enhancing portion of the tumor on an axial MR image, again excluding portions of necrosis or hemorrhage. Nnonenhancing tumor size was calculated using the cross product of the longest anteroposterior and transverse dimensions of the T2 hyperintense portion of the tumor on axial MR images, including areas that also had contrast enhancement, but excluding markedly T2-hyperintense areas that likely reflected radiation change. Satellite nodules of tumor were considered present if enhancing nodules were identified in contiguous areas of T2 hyperintensity, as previously defined in the literature. Multifocal tumor was considered present if enhancing nodules were identified, separated by normal-appearing white matter. Finally, a tumor was considered “bilateral” if enhancing or nonenhancing tumor involved both cerebral hemispheres or crossed the genu or splenium of the corpus callosum.

PET Image Acquisition and Analysis

The FDG PET images were obtained using an integrated PET/CT scanner (Discovery LS, GE Medical Systems) with a four-slice LightSpeed CT, tube voltage of 140 kVp and tube current of 100–160 mA. FDG was administered intravenously, and patients were then kept at rest in a quiet, dimly lit room for at least 45 minutes to avoid muscle uptake of FDG. Attenuation-corrected images were constructed using the CT scan. The standard uptake values (SUVs) were reported as maximum values within an ROI, expressed in grams per milliliter.

Image processing was performed on a General Electric Advantage Workstation server, Version 2.0, GE Healthcare. Small circular ROIs of approximately 10–15 mm² were placed on the portion of the tumor with the peak tumor activity by visual inspection to obtain the maximum SUV, as described previously. The maximum SUV was normalized by dividing by the mean SUV obtained from an ROI of a similar size that was placed on the contralateral normal-appearing cortex on the same slice at the same level of the brain. ROI placement was repeated 3 months after the first analysis, and the intraclass correlation was found to be .96.

Metabolic tumor volumes were obtained using the segmentation tools provided in the GE Advantage Workstation toolbox. All images were first thresholded using an SUV cutoff of 4–8 to include voxels of hypermetabolic tumor and exclude normal cortex. The paint tool was then used to manually include or exclude voxels that were considered hypermetabolic tumor by visual assessment. Metabolic tumor size was calculated using the cross product of the longest anteroposterior and transverse dimensions of the FDG-avid portion of the tumor based on visual assessment.

Statistical Analysis

All statistical analyses were programmed in STATA version 13 (StataCorp, College Station, TX). Comparisons of baseline
variables among groups were performed using the Wilcoxon rank-sum test and Fisher exact test depending on the variable type.

We first tested whether enhancing tumor size and volume, metabolic tumor size and volume, nonenhancing tumor size, normalized maximum SUV, normalized minimum ADC, satellite lesions, multifocality, or bilaterality were individually associated with survival using Cox regression analyses. Significant associations remained significant after adjusting for whether or not the gross total or partial surgical resection was performed.

We then dichotomized survival into “short,” less than 6 months, and “long,” equal to or greater than 6 months, following the PET scan. We determined the accuracy of the imaging variables, individually and combined, in predicting short survival, using area under the receiver operating characteristic (AUROC) curves and logistic regressions.

**Results**

Baseline subject characteristics are presented in Table 1, grouped by whether they survived less than or greater than 6 months following the PET. A total of 44 patients were included in our study based on inclusion criteria—29 (66%) were male and 15 (34%) were female. All patients were followed until the time of death. Fifteen (34%) patients underwent repeat resection after PET to document histopathological confirmation of recurrence, 12 of which were within 6 weeks of PET. The mean overall survival in our cohort was 12.9 months (median 8.8 months, ranging from 0.6 to 49 months). PET was performed a mean of 9.6 months after initial surgical resection (median 5.8 months, ranging from 2.4 to 43.7 months). PET was performed a mean of 7.0 months after completion of concurrent radiation therapy and temozolomide therapy (median 2.9 months, ranging from 1 week before completion to 41.2 months after completion). The mean age at the time of FDG-PET was 59 years (median 59 years, ranging from 29 to 81 years). The mean tumor size using gadolinium-enhanced MRI was 7.0 cm$^2$ (median 3.8 cm$^2$, ranging from 0.9 to 37.3 cm$^2$). The metabolic tumor size by FDG PET was 4.6 cm$^2$ (median 1.8 cm$^2$, ranging from 0.35 to 32.3 cm$^2$). The mean tumor volume using gadolinium-enhanced MRI was 15.7 cm$^3$ (median 9.7 cm$^3$, ranging from 1.7 to 75.7 cm$^3$). The mean tumor volume using FDG PET was 4.1 cm$^3$ (median 1.2 cm$^3$, ranging from 0.07 to 41.8 cm$^3$). The mean maximum SUV of the enhancing tumor was 9.9 (median 8.9, ranging from 4 to 20). The mean normalized maximum SUV, normalized by normal contralateral cortex, was 1.04 (median 1.02, ranging from 0.54 to 2.24).

Adjusting for extent of surgical resection, the tumor cross product on MRI (hazard ratio = 1.05, 95% confidence interval 1.004-1.09, $P = .031$), tumor cross product on PET
The finding that tumor cross products and volumes at first recurrence are predictive of survival is consistent with the literature. Initial surgical intervention is considered standard-of-care for glioblastomas, with maximum safe resection reportedly prolonging survival. Our analysis contributes to these prior reports by demonstrating that, even after adjusting for whether or not a patient underwent gross total or partial resection, posttreatment tumor size at recurrence remains predictive of survival. Furthermore, we found that tumor size and volume on FDG-PET added prognostic value compared to enhancing tumor size on a posttreatment MRI scan, suggesting that PET may better pinpoint viable tumor on the background of treatment-related changes. Since our measurement of nonenhancing tumor size may have included areas of T2 hyperintensity representing both viable infiltrative tumor and treatment-related changes, it is not surprising that this variable was not prognostic. Finally, we found that other morphological features seen on the MRI at the time of recurrence, such as bilaterality, satellite lesions, and multifocality, did not appear to add prognostic value, despite one prior report of their utility.

We also found that normalized minimum ADC values were not useful in the posttreatment period in predicting prognosis. The role of ADC in the predicting prognosis among glioma patients has been most extensively studied in the pretreatment period. The literature, including a meta-analysis, suggests that low ADC values significantly predict survival possibly because they serve as a proxy for tumor cellularity. In the posttreatment period, ADC histograms have been shown to be useful in the prognosis of glioblastomas imminently undergoing bevacizumab therapy, although not those undergoing subsequent chemotherapy. The finding that minimum ADC value did not demonstrate prognostic utility may reflect the heterogeneity of our cohort, with some receiving bevacizumab therapy and some not.

The finding that normalized maximum SUV values from an FDG-PET scan were not associated with survival differs from prior papers that reported that FDG-PET is prognostically useful. This could be because many of the prior papers included mixed cohorts of low- and high-grade tumors, inclusion of tumors of oligodendroglial etiology, varied initial treatment protocols, and different imaging time points, such as the pretreatment period or during concomitant radiotherapy and chemotherapy. It is thus conceivable that the utility of FDG-PET lies primarily in differentiating low-grade tumors from higher grade tumors.

Finally, we found that incorporating clinical variables, such as the number of repeat resections and age, did not significantly improve prognostic accuracy. Although one prior paper demonstrated improved survival with resection of glioblastoma recurrence, whether or not a second resection improves patient outcomes remains controversial. We also noted that age was not found to be prognostic, contradicting prior literature; this suggests that including PET and MR imaging variables may have overpowered the prognostic power of age in these models.

The strengths of our study include our multivariate analysis of both PET and MR imaging variables, using a semiquantitative approach that may be less prone to bias than grading.

**Discussion**

The major finding of our analysis was that, at the time of first recurrence, tumor cross products on both PET and MRI and metabolic tumor volume on PET were significantly associated with survival. Furthermore, adding tumor cross product from PET to enhancing tumor cross product from MRI significantly increased accuracy of predicting a short survival of less than 6 months from 58% to 74%. Other imaging metrics, including enhancing tumor volume, tumor cross product on T2-weighted imaging, normalized minimum ADC value on MRI, normalized maximum SUV on FDG-PET, satellite lesions, and multifocal tumor were not significantly associated with overall survival in this setting.

![Fig 2. Receiver operating characteristic (ROC) curves demonstrating prognostic accuracy of tumor cross products from MRI alone (dotted line) and after inclusion of tumor cross products from 18F-fluorodeoxyglucose PET (solid line). The area under the ROC curve increased from .58 with MRI alone to .74 after combining MRI and PET.](image-url)
Newer PET agents, such as MRI may not be fully generalizable. Our findings in patients who did undergo both FDG-PET and MRI have shown to be prognostic.11 Newer PET agents, such as amino acid tracers, also were not included in this analysis, since they are not yet standard-of-care agents and are not widely used clinically. Finally, not all patients in our Brain Tumor Center undergo FDG-PET for tumor surveillance for varying reasons, including scheduling feasibility or billing reasons. As a result, we did not include MR perfusion metrics, since many of our patients did not undergo MR perfusion, although these have also been shown to be prognostic.11

Conclusion
Metabolic tumor size on FDG-PET adds prognostic information to enhancing tumor size on MRI alone at first recurrence of GBM, probably by better identifying viable tumor on a background of treatment-related changes.

References