RESEARCH ARTICLE

Comparison between MR Perfusion and 18F-FDG PET in Differentiating Tumor Recurrence from Nonneoplastic Contrast-enhancing Tissue

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Abstract

Objective: Comparison of the accuracy of MR perfusion and 18-FDG-PET for differentiating tumor progression from nonneoplastic contrast-enhancing tissue. **Methods and Materials:** Retrospective review of MR perfusion and 18-FDG-PET in 23 cases of primary brain tumors (17 high grade and 6 low grade glial neoplasms) and 5 cases of metastatic lesions with enhancing lesions on post-treatment MRI was performed. The accuracy of MR perfusion versus 18-FDG-PET for distinguishing between nonneoplastic contrast-enhancing tissue and tumor recurrence was assessed. **Results:** Both CBV ($p<0.004$) and SUV ($p<0.02$) are higher in recurrent tumors than necrosis. MR perfusion has an accuracy of 94.5% for differentiating between tumor recurrence and necrosis, while 18-FDG-PET has an accuracy of 85.1% for differentiating between tumor recurrence and nonneoplastic contrast-enhancing tissue. **Conclusion:** Overall, recurrent tumor demonstrates significantly higher CBV and SUV than nonneoplastic contrast-enhancing tissue. However, MR perfusion appears to be more accurate than FDG PET for distinguishing the two entities.

Keywords: Radiation necrosis- MR perfusion- PET-CT- FDG

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Introduction

Nonneoplastic contrast-enhancing tissue after irradiation for malignant brain tumors is not uncommon (Valk et al., 1991). However, differentiating between recurrent tumor and nonneoplastic contrast-enhancing tissue is often challenging with conventional MRI (Dooms et al., 1986; Mullins et al., 2005). In general, both tumor progression and nonneoplastic contrast-enhancing tissue should be considered possibilities for focal enhancement that appears in the irradiated area. Consequently, it is often necessary to perform follow up imaging or biopsy. However, with the growing desire for prompt and non-invasive management, there is a strong impetus to establish and validate more accurate imaging biomarkers that can acutely discriminate between tumor recurrence and nonneoplastic contrast-enhancing tissue.

Dynamic susceptibility contrast (DSC) MR perfusion is a surrogate marker for angiogenesis and has been used to assess brain tumor treatment response with high sensitivity for distinguishing residual/recurrent neoplasm from radiation brain injury. In particular, CBV values are potentially useful for differentiating treatment-related effects from recurrent tumor, whereby it has been reported that CBV values decrease by an average of 41% in pseudoprogression as opposed to an increase by an average of 12% with tumor progression from pretreatment to post-treatment scans (Mangla et al., 2010). CBV has also been found to be significantly higher in the recurrent intra-axial metastatic tumor than gamma knife-induced radiation necrosis (Barajas et al., 2009).

18F-fluorodeoxyglucose positron emission tomography (FDG PET) has served a role in pretherapeutic baseline studies for monitoring the effect of a therapy, mapping of hypermetabolic regions before surgery or biopsy, mapping of hypermetabolic regions before radiotherapy, postsurgical evaluation for residual tumor, assessment of the malignancy of a mass as a substitute for biopsy, and distinguishing between radiation necrosis and recurrent tumor (Deshmukh et al., 1996). In general, there is focal hypometabolism in the area of necrosis as opposed to hypermetabolism associated with the residual/recurrent tumor. However, both false-positive and false-negative PET scan results yield a sensitivity of 73% and a specificity of 56% for discriminating between primary central nervous system tumor and radiation necrosis using contralateral grey matter as a reference (Ricci et al., 1998). Another study that included both primary central nervous system tumors and metastases in the analysis reported a sensitivity of 75% and specificity of 81% for FDG PET

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in diagnosing recurrent tumor (Chao et al., 2001). In particular, for brain metastasis with MRI co-registration, FDG PET had a sensitivity of 86% and specificity of 80%. MRI co-registration appears to improve the sensitivity of FDG PET (Chao et al., 2001). Although for metastases FDG PET significantly improved the diagnostic accuracy in the subgroup of patients with positive and non-diagnostic MRI, it provided no additional value in the MRI-negative subgroup (Sugahara et al., 2000).

The purpose of this study was to compare the accuracy of DSC MR perfusion to 18F-FDG PET for differentiating between recurrent tumor and nonneoplastic contrast-enhancing tissue.

Materials and Methods

IRB approval was obtained for a retrospective review of all cases referred with a request to differentiate between recurrent tumor and nonneoplastic contrast-enhancing tissue between July 2013- June 2015. The final diagnosis of treatment induced necrosis was decided by histology or follow-up imaging. On imaging, lesions that increased on at least two subsequent MR examinations were considered to represent recurrence, while those that remained stable or decreased in size on two consecutive scans were considered to represent nonneoplastic contrast-enhancing tissue (Figure 1 and 2).

Imaging was performed on a 1.5T GE LX scanner (GE Medical systems, Milwaukee, Wisconsin). Conventional sequences included axial T2-FLAIR, T1-FSE, GRE, T2-FSE and post contrast T1 weighted images in three planes. Dynamic susceptibility contrast (DSC) imaging was performed using a gradient-recalled T2*-weighted echo-planar imaging sequence. Parameters used were TR/TE of 1500/50 ms, flip angle of 800, number of excitation (NEX) =1, matrix size = 128x96, and 6 mm slice thickness (with no gap). A total of 60 image volumes were acquired, in which the first 10 acquisitions were executed before starting the contrast agent injection to establish a pre-contrast baseline. At the end of the 10th image volume acquisition, Gadopentate dimeglumine was injected through an 18- or 20-gauge intravenous catheter using a power injector at a rate of 5 mL/sec, immediately followed by a bolus injection of saline (total of 20 mL at 5 mL/sec).

Twelve contiguous axial section levels were chosen for the analysis. The selection was based on lesion extent as determined on the pre-contrast T2-FLAIR images. No contrast agent was administered prior to DSC perfusion MR imaging. Raw perfusion-weighted MR data were processed with implementation of LUPE, a correction algorithm for T1 effects related to blood brain barrier leakage. The CBV values of the lesions were normalized to the unaffected contralateral white matter to establish a CBV ratio. Multiple ROIs of size 30-40 mm^2 were placed over hot spots within the region of interest and the maximum CBV of all ROI's was selected. This method has been described to yield greater inter- and intraobserver agreement (Wetzel et al., 2002). For the normalization, a ROI of approx 80-100 mm2 was placed in the contralateral, normal appearing white matter, carefully avoiding inclusion of grey matter.

The amount of 18F-FDG injected was related to age, and weight, and prior to injection, the blood-glucose level was measured. An emission scan of the head was acquired 45 minutes after the injection. Emission data were then corrected for signal attenuation using a transmission scan which allows for relative (not absolute) quantitative measurements. Activity cou

nts in the ROIs were normalized to injected dose per kilogram of patient body weight (standardized uptake value [SUV]). For semiquantitative image analysis, MRI scans were also visually inspected and ROIs were manually drawn on PET scans. Multiple ROIs of size 30-40 mm2 were placed within the regions of hot spots and maximum SUV was chosen. The images were analyzed by calculating lesion-to-normal ratio (l/n).

The Statistical Package for Social Sciences (SPSS) was used for statistical analysis. Two-tail t-test with equal variance not assumed was used to determine the difference between recurrence and necrosis. 18F-FDG and perfusion parameters were compared using the Wilcox nonparametric test. Receiver-operating-characteristic (ROC) curve analysis was used to determine the optimal index of CBV and PET (SUV) and cutoff values for differentiation between tumor recurrence and nonneoplastic contrast-enhancing tissue.

Results

There were 36 patients treated for primary glial tumors or metastatic brain lesions with suspected tumor recurrence for which both MR perfusion and FDG PET examinations were performed within 6 weeks of each other. Five patients were excluded due to treatment changes during the interval between the two examinations. Another 3 patients were excluded due to inadequate follow-up. Consequently, 28 patients with MR perfusion and FDG PET studies performed within 6 weeks of one another and where no treatment had been changed between the two examinations were available for this study. There were 30 lesions in the 28 patients who had undergone both MR perfusion and FDG-PET. Among the 28 patients (mean age-45.2

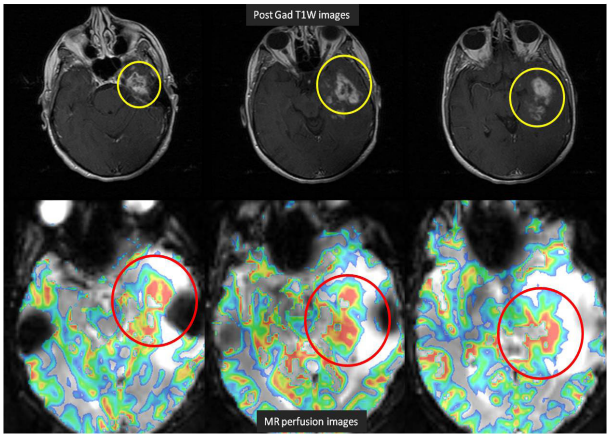

Figure 1. Panel of Axial Post-Contrast T1 MR Images (Top) and Corresponding MR Perfusion Images (Bottom) Show Elevated Perfusion (Red Circles) in the Heterogeneously Enhancing (Yellow Circles) Left Temporal Lobe Lesion. This was a Case of Residual Glioblastoma Multiforme

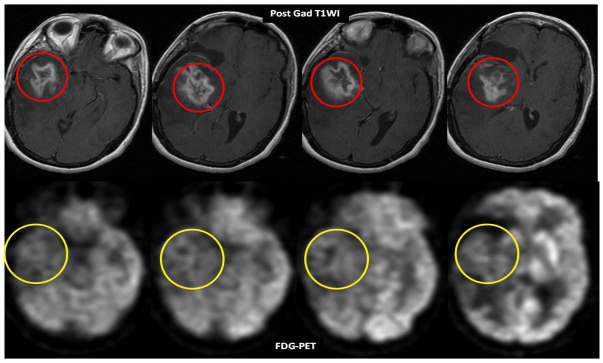

Figure 2. Panel of Axial Post-Contrast T1 MR Images (Top) and Corresponding FDG-PET Images (Bottom) Show Hypometabolism (Yellow Circle) in the Enhancing Lesion (Red Circle). This was a Case of Right Temporal Lobe High Grade Astrocytoma

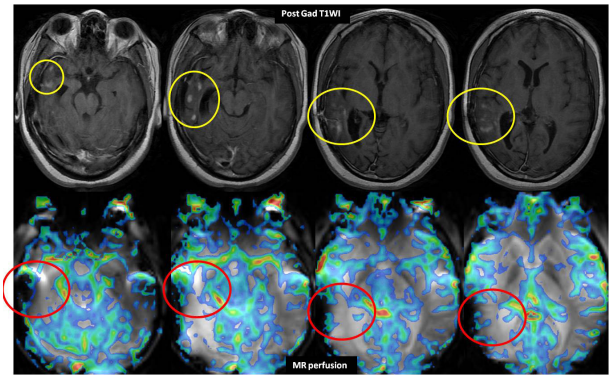

Figure 3. False Negative MR Perfusion. Panel of Axial Post-Contrast T1 MR Images (Top) and Corresponding MR Perfusion Images (Bottom) Show Areas of Enhancement Without Corresponding Elevated CBV. This was a Case of Enhancing Malignant Tissue

years, age range 6-65 years, 18 males, and 10 females), there were 23 cases (23 lesions) of primary brain tumors (17 high grade and 6 low grade glial tumors) and 5 cases (7 lesions) of metastatic lesions (Table 1). The primary diagnosis was histopathologically proven in all cases.

The average interval between the FDG-PET and MR perfusion examinations was 15 days. MR perfusion was non-diagnostic in 3 lesions (10%) due to susceptibility artifacts, including intra-tumoral hemorrhage in two cases and posterior fossa susceptibility artifact in one case. Thus, there were 27 lesions were included in the MR perfusion evaluation and 30 cases were included for FDG-PET. Subsequent biopsies for recurrence versus necrosis were performed in 10 cases. The remaining 18 cases (20 lesions) were characterized based upon the appearance on follow-up imaging. All lesions had a minimum follow-up of 6 months. The diagnosis in 6 cases of the tumor recurrence and 4 cases of the nonneoplastic contrast-enhancing tissue were confirmed by pathologic

Table 1. CBV Ratios for Recurrent Tumor and Necrosis (27 Lesions)

Group	N	Mean (p 0<.004)	Standard Deviation	Standard Error
Recurrence	15	3.41	2.40	0.642
Necrosis	12	1.03	0.73	0.21

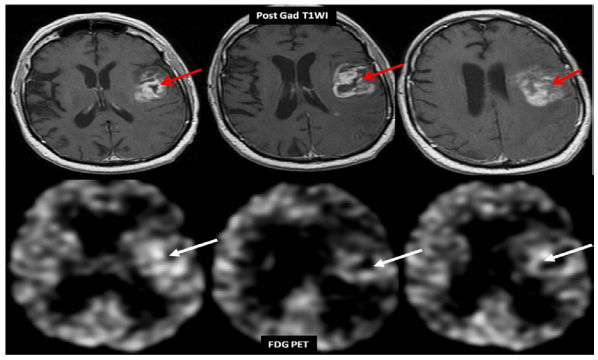

Figure 4. False Positive FDG PET. Panel of Axial Post-Contrast T1 MR Images (Top) and Corresponding FDG-PET Images (Bottom) Show Hypermetabolism (Arrows) in the Area with Corresponding Enhancement. This was a Case of Enhancing Non-Neoplastic Tissue

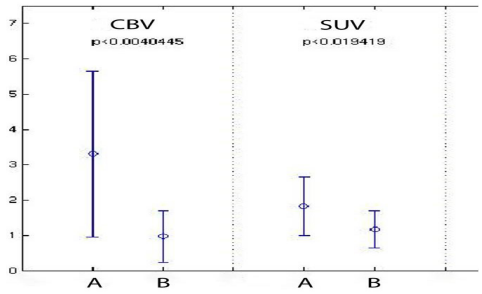

Figure 5. Plot Shows the Mean and Standard Deviation of Normalized CBV and SUV Values for Tumor Recurrence (A) and Nonneoplastic Contrast-Enhancing Tissue (B)

examination.

Recurrent tumor demonstrated statistically significant higher CBV ratios ($p<0.004$) and SUV ratios ($p<.02$) than nonneoplastic contrast-enhancing tissue (Tables 1 and 2). In 11 cases both MR perfusion and FDG-PET were positive, in 9 cases both were negative, in 9 cases there was discordance between the two modalities, in which perfusion correctly diagnosed 6 cases and

Table 2. SUV Ratios for Recurrent Tumor and Necrosis (30 Lesions)

Group	N	Mean (p <0.02)	Standard Deviation	Standard Error
Recurrence	16	1.88	0.82	0.213
Necrosis	14	1.14	0.50	0.13

Table 3. Number of Cases Considered Positive or Negative for Tumor Recurrence on MR Perfusion and FDG-PET

Outcome	Reference Positive	Reference Negative
CBV Positive	13 (5)	1 (0)
CBV Negative	2 (0)	11 (3)

Outcome	Reference Positive	Reference Negative
SUV Positive	12 (3)	2 (1)
SUV Negative	4(2)	12 (2)

The values in parenthesis represent the cases confirmed by pathology

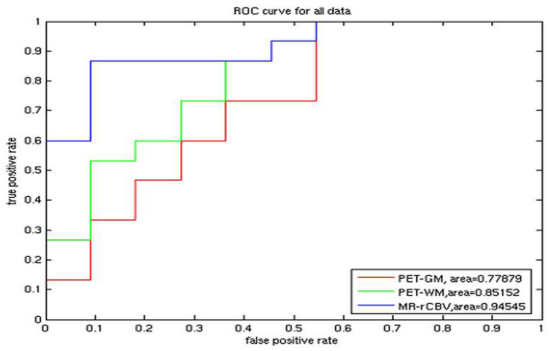

Figure 6. ROC Curve Shows a Higher Accuracy for MR Perfusion than FDG-PET in Differentiating Tumor Recurrence from Nonneoplastic Contrast-Enhancing Tissue

PET correctly diagnosed 3 cases. Among the 3 cases in which MR perfusion was non-diagnostic due to artifacts, PET correctly diagnosed 2 cases and one case was false positive (Table 3 and Figure 3). Examples of false negative and false positive studies are depicted in Figure 4 and Figure 5. ROC analysis showed that the accuracy of CBV ratio and FDG-PET was 94.5% and 85.1% in differentiating between tumor recurrence and nonneoplastic contrast-enhancing tissue, respectively (Figure 6).

Discussion

This study constitutes an intra-individual comparison of MR perfusion and FDG-PET imaging to distinguish between brain tumor recurrence and nonneoplastic contrast-enhancing tissue following treatment. Necrosis is known to occur after chemotherapy although more commonly after radiation (5%–24% overall). Imaging evaluation based on contrast-enhanced MRI at a single time point is not very helpful for differentiating between tumor recurrence and nonneoplastic contrast-enhancing tissue. It has been shown that MR perfusion and FDG PET are complementary to anatomic conventional MR imaging when differentiation between tumor recurrence and nonneoplastic contrast-enhancing tissue is clinically relevant (Kim et al 1992; Di Chiro et al 1988; Belohlavek et al 2003). The results in this study show that nonneoplastic contrast-enhancing tissue has lower CBV and SUV ratios. Furthermore, ROC analyses showed that CBV-ratio had a better sensitivity and specificity than FDG-PET in differentiating between recurrence and nonneoplastic contrast-enhancing tissue.

The findings show the utility of MR perfusion imaging, by means of CBV evaluation, for the follow-up of treatment in these patients allowing for earlier detection of tumor recurrence and to avoid unnecessary re-operation or change of treatment in cases of nonneoplastic contrast-enhancing tissue. Other studies of glioma grading have found CBV to correlate with tumor grade (Shin et al 2002; Hakyemez et al 2005). Other studies have also evaluated the role of CBV in differentiating between late nonneoplastic contrast-enhancing tissue and tumor recurrence (Sugahara et al 2000). Hu et al found a sensitivity of 91.7% and a specificity of 100% in histopathologic proven recurrence or necrosis by choosing a CBV-ratio threshold of 0.71 (Hu et al., 2009). Our threshold is higher than that found in their study due to their use of grey matter as the internal reference, while we used normal appearing white matter in the contralateral hemisphere.

Histopathologic examination is still considered the gold standard to determine recurrence. However, this is often obtained by biopsy and may represent only a small part of the enhancing lesion, predisposing to under-sampling errors. Histologically, neoplasms show mainly neo-angiogenesis, which is described as an irregular meshwork of newly formed vessels arising from the co-existing vessels, while nonneoplastic contrast-enhancing tissue show extensive vascular injury and tissue ischemia with vascular endothelial damage, hyalinization of vessels, thrombosis and increased permeability (Grossman et al., 1998). This increased permeability and the vascular injury can lead to a more pronounced increase in contrast medium leakage through a defective blood brain barrier. This treatment induced necrosis/leakage can manifest as an enlarging, enhancing mass lesion on conventional MRI. The BBB leakage corrected CBV evaluation used in this study allows us to better assess the microscopic vascular density.

The results regarding FDG-PET in this study are comparable to other studies that have shown an overlap in elevated 18F-FDG uptake between recurrent tumors and nonneoplastic contrast-enhancing tissue (Usuda et al., 2016). Even high-grade recurrent tumors can demonstrate uptake similar to or slightly above that of normal white matter and the uptake in necrosis can be higher than that of normal white matter (Ricci et al., 1998). Factors that can contribute to false-negative FDG-PET results include recent radiation therapy, low histologic grade, and small tumor volume (Spence et al., 2004). FDG PET may result in false positive interpretations due to the intrinsically high glucose metabolism in the brain, which results in high background activity, inflammatory processes, and seizure activity (Brandsma et al., 2008).

Limitations of this study include its retrospective design, relatively small sample size, heterogeneity of tumor histology and form of treatment, and the lack of pathology to confirm the diagnosis in some cases. Additional investigation of the relative merits of MR perfusion versus FDG-PET is therefore warranted.

In most cases, both 18F-FDG and MR perfusion were able to distinguish between treatment necrosis/pseudoprogression and tumor recurrence. However, MR perfusion was more accurate than 18F-FDG-PET.

Statement conflict of interest

None

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