Imaging of Hypoxia in recurrent GBM using 18F-fluoromisonidazole PET, MRI and MRSI

Yan Li[1], Laleh Jalilian[1], Youngho Seo[1], Dave Wilson[1], Miguel Pampaloni[1], Henry Vanbrocklin[1], Michael Prados[2], and Sarah J Nelson[1,3]

[1]Department of Radiology and Biomedical Imaging, University of California, San Francisco, California, United States, [2]Department of Neurosurgery, University of California, San Francisco, California, United States, [3]Department of Bioengineering and Therapeutic sciences, University of California, San Francisco, California, United States

Introduction Glioblastoma Multiforme (GBM) represents the highest grade of glioma and is both the most common and the most malignant sub-type, with a median survival of one year. GBMs are highly infiltrative, and recurrence typically occurs in adjacent brain tissue within 2 cm of the original tumor site. GBMs are also characterized by rapidly proliferation, which may cause regional hypoxia due to inadequate vascular supply. Upregulation of vasoactive endothelial growth factor (VEGF) promotes the formation of new blood vessels by the process of angiogenesis. Tumor hypoxia is an important factor in influencing response to radiation therapy (RT), progression-free survival and overall survival. ^{18}F-fluoromisonidazole (^{18}F-FMISO) is a PET tracer that specifically binds to living cells with low pO_2 and can be used to evaluate regional hypoxia in tumors. The purpose of this study was to assess the correlation between ^{18}F-FMISO-PET parameters and those from MR parameters estimated from perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI) and magnetic resonance spectroscopic imaging (MRSI) for patients with GBM in whom progression was suspected.

Methods Three patients diagnosed with GBM by surgery who received RT and temozolomide (TMZ) were studied at the time of suspected progression (~1 month) in order to help in distinguishing true from pseudo-progression. MR data were acquired using a 3T GE scanner. Anatomic images comprised a T1-weighted sagittal scout, axial fluid attenuated inversion recovery (FLAIR), pre- and post-gadolinium T1-weighted spoiled gradient echo (SPGR), DWI and PWI images. The apparent diffusion coefficient (ADC), cerebral blood volume (CBV), percent ΔR2* signal recovery (REC) and heights (PH) were calculated using software developed in our group. The 3D H-1 lactate-editing MRSI data were acquired from patients B and C utilizing a flyback echo-planar gradient trajectory [1]. The 3D spectral array size was 18x18x8 and the nominal spatial resolution was 1cm^3. The choline to NAA index (CNI) was calculated using an in-house automated regression technique. All CT/PET scans were performed on GE PET/CT scanner. The dose (3.7 MBq/kg) of ^{18}F-FMISO was administrated intravenously and a single field-of-view emission scan from 110+/-10 min post-injection was acquired for 20 min. A transmission scan was performed using a low-mA CT scan, followed by the emission scan. During emission tomography, three venous blood samples were obtained at 5 min intervals. Whole blood samples were counted and blood tracer activity was averaged from the three samples, and the decay correction was applied to the injection time. The tissue-to-blood ratio (T/B) was calculated as the tissue activity divided by the averaged blood activity. MRI and PET images were co-registered via the CT image of PET/CT. Regions of interest (ROIs) including the contrast-enhancing lesion (CEL) and non-enhancing lesion (NEL) were defined manually on the MR images.

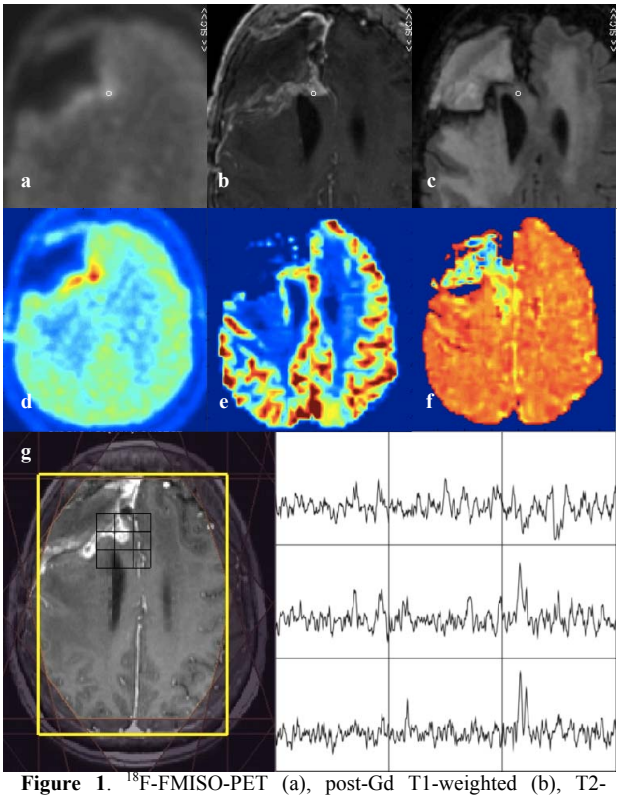

Figure 1. ^{18}F-FMISO-PET (a), post-Gd T1-weighted (b), T2-weighted (c) images, T/B (0-1.1) (d), nCBV (0-3) (e), Rec (0-100) (f) maps and corresponding MRSI (g) acquired from patient B, who were clinically deteriorated in the next month without significant changes on MRI. The region of interest defines where T/B>=1.1.

Results Patient A was confirmed to have progressed by a second surgery, and the other two patients (B and C) were stable based on MRI based upon subsequent clinical follow-up. Although there were no significant changes on MRI for patient B, the patient experienced deterioration based upon clinical criteria. The imaging parameters in the CEL, NEL and regions with T/B>=1.1 are given in Table 1, and an example of PET, MRI images and MRSI is illustrated in Figure 1. The max T/B in the CEL for the 3 patients was 1.03, 1.15 and 0.87. Within the region of T/B>=1.1, relatively low median nADC, high median nCBV and high median nPH were found. No lactate was found in the MRSI data.

ROI	ID	Volume	nADC	10th nADC	nCBV	90th nCBV	nPH	90th nPH	REC	10th REC	Max CNI	Max T/B
CEL	A	6.7	1.58	1.18	1.10	2.00	1.00	1.69	87.3	64.2	-	1.03
	B	11.9	1.53	1.07	1.29	2.66	1.22	2.47	59.2	30.5	1.95	1.15
	C	4.0	1.98	1.41	1.99	3.26	1.70	2.62	73.0	46.0	-0.772*	0.87
NEL	A	101.1	1.54	1.2	0.46	0.91	0.45	0.88	90.0	80.3	-	0.69
	B	117.8	1.59	1.2	0.50	1.06	0.49	1.01	75.7	68.9	2.78	1.00
	C	36.9	1.96	1.28	0.64	1.81	0.58	1.63	80.1	67.2	1.6	0.76
T/B>=1.1	B	0.005	1.41	1.38	1.69	1.80	1.54	1.63	60.89	54.08	-	

Table 1. Percentile, median or max values of PET, MRI and MRSI parameters from 3 patients with GBM. (*only 1 voxel involved)

Discussion MRI is the standard imaging method for the evaluation of patients with brain tumors.^{18}F-FMISO PET has been used in the evaluation of hypoxia. It has been reported that max T/B and hypoxic volume at pre-treatment in newly-diagnosed GBM are strongly correlated with time-to-progression and survival [2], with the hypoxic volumes generally occupying a region straddling the outer edge of the CEL and the T2 abnormality [3]. In this study, we measured the correlation of hypoxia relative to the MRI-defined abnormalities, DWI and PWI parameters. Higher CBV and PH than those in NAWM was found for the patient who had a region with T/B>=1.1. This is lower than the value proposed as a cut-off for hypoxia in the newly-diagnosed patients [4]. There was no lactate in the MRSI data from these subjects. Of note is that the patients in this study had received treatment before the scan, and the biopsy results from patient A are still under the review. Patient B, who had the highest max T/B had stable CEL but deteriorated clinically. Continued follow-up for this patient will be used to differentiate these possibilities. More patients being recruited into the study and will be used to increase the sample size and examine the generality of these findings.

References

1. Park I, et al. Ann Biomed Eng. 39(1):193-204, 20111
2. Spence AM, et al al., Clin Cancer Res. 14(9):2623-30, 2008
3. Swanson KR, et al., J Nucl Med 50:36-44, 2009
4. Rajendran JG, et al., Eur J Nucl Med Mol Imaging 30:695-704, 2003

Acknowledgements The PET scans for this study were supported by a seed grant from the Department of Radiology and Biomedical Imaging. The MR scans and personnel effort were supported by P01CA118816 and a St. Louis Fall Festival Committee American Brain Tumor Association Basic Research Fellowship.