Diagnostic Value of $^{68}$Ga PSMA-11 PET/CT Imaging of Brain Tumors—Preliminary Analysis

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Objective: To evaluate the feasibility of using $^{68}$Ga PSMA-11 PET/CT for imaging brain lesions and its comparison with $^{18}$F-FDG.

Methods: Ten patients with brain lesions were included in the study. Five patients were treated cases of glioblastoma with suspected recurrence. $^{18}$F-FDG and $^{68}$Ga PSMA-11 brain scans were done for these patients. Five patients were sent for assessing the nature (primary lesion/metastasis) of space occupying lesion in brain. They underwent whole body $^{18}$F-FDG PET/CT scan and a primary site elsewhere in the body was ruled out. Subsequently they underwent $^{68}$Ga PSMA-11 brain PET/CT imaging. Target to background ratios (TBR) for the brain lesions were calculated using contralateral cerebellar uptake as background.

Results: In five treated cases of glioblastoma with suspected recurrence, the findings of $^{68}$Ga PSMA-11 PET/CT showed good correlation with that of $^{18}$F-FDG PET/CT scan. Compared to the $^{18}$F-FDG, $^{68}$Ga PSMA-11 PET/CT showed better visualization of the recurrent lesion (presence/absence) owing to its significantly high TBR. Among the five cases evaluated for lesion characterization glioma and atypical meningioma patients showed higher SUV$_{\text{max}}$ in the lesion with $^{68}$Ga PSMA-11 than with $^{18}$F-FDG and converse in cases of lymphoma. TBR was better with $^{68}$Ga PSMA PET/CT in all cases.

Conclusion: $^{68}$Ga PSMA-11 PET/CT brain imaging is a potentially useful imaging tool in the evaluation of brain lesions. Absence of physiological uptake of $^{68}$Ga PSMA-11 in the normal brain parenchyma results in high TBR values and consequently better visualization of metabolically active disease in brain.

Key Words: brain imaging, glioblastoma, gallium-68, PET/CT, prostate specific membrane antigen, tumor neovascularization

PET/CT (positron emission tomography/computed tomography) imaging using $^{68}$Ga PSMA-11 (prostate specific membrane antigen) first reported in 2013 is now widely used for the detection, staging, therapy response and recurrence evaluation of prostate cancer. The imaging is based on the fact that the transmembrane enzyme, prostate specific membrane antigen is overexpressed in prostate adenocarcinoma. The studies concluded that tumor microvessels of the highly angiogenic grade IV gliomas showed intense PSMA staining. These findings suggest that radiotracers targeting the enzyme PSMA might be useful for targeting neovascularization in brain tumors. In this paper we report the results of $^{68}$Ga PSMA-11 PET/CT imaging in 10 patients having brain lesions.

MATERIALS AND METHODS

Ten patients with brain lesions detected/suspected on magnetic resonance imaging (MRI) referred for $^{18}$F-FDG (fluorodeoxyglucose) PET/CT were included for additional scanning with $^{68}$Ga PSMA-11. Among the 10 patients, 5 patients were glioma cases sent for recurrence evaluation. These patients had high grade glioma and underwent treatment (surgery followed by radiotherapy) and now presented with suspected recurrence on clinical examination. $^{18}$F-FDG PET/CT scan of the brain alone was done for these five patients. Second category included five patients with a space occupying lesion in brain; the nature of which needed to be ascertained (lesion characterization). A whole body $^{18}$F-FDG PET/CT was first done to detect any lesion suggestive of a primary site elsewhere in the body and assess the metabolic nature of the brain lesion. The rationale of doing $^{68}$Ga PSMA-11 brain PET/CT in each case was discussed in detail with the referring physician and an informed consent was taken from each patient for the study. The two imaging studies were done at least with a gap of 24 hours, using a Siemens Biograph 6 Truepoint PET/CT scanner. Table 1 combines the patient data, activity of the two tracers injected as well as the uptake characteristics with both the tracers.

$^{18}$F-FDG PET/CT

Image Acquisition

A dedicated $^{18}$F-FDG brain PET/CT was done for the five high grade glioma patients referred for recurrence evaluation. Patients received 185 ± 38 MBq of $^{18}$F-FDG intravenously and PET/CT scan of the brain was acquired 60 minutes afterwards with the following parameters. PET images: 5 minutes scan duration in a 336 x 336 matrix. CT scan: voltage: 130 Kvp, current: 240 mA and slice thickness of 3 mm. Intrinsically co-registered hybrid PET/CT images were reconstructed in axial, coronal and sagittal orientations with 3 mm image thickness.

For cases referred for lesion characterization, a whole body $^{18}$F-FDG PET/CT was done. Whole body (vertex to mid thigh) image acquisition began 45 minutes post intravenous injection of 262 ± 78 MBq of $^{18}$F-FDG. PET images were acquired with 2 minutes scan duration per bed position, matrix size of 168 x 168. CT scan was acquired with the following parameters; voltage: 10.1097/RLU.0000000000001451

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Informance consent: Informed consent was obtained from all patients.

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110 Kev, current: 160 mA and slice thickness of 3 mm. Intrinsically co-registered hybrid PET/CT images were reconstructed in axial, coronal and sagittal orientations with 3 mm image thickness.

68Ga PSMA PET/CT

Chemistry

68Ga PSMA-11 was prepared by using a 68Ge/68Ga generator and manual synthesis module supplied by ITG, Germany. Typically 5 μg (5.28 nmol) of PSMA-11 (ABX Advanced Biochemical Compounds, Germany) in 1 ml of 0.25 M sodium acetate solution is reacted with 4 ml of 68GaCl3 (370 to 1000 MBq) for about 5 min at 105°C. Purification of the product using a C18 cartridge yielded radiochemical purity greater than 99%. Details of the synthesis are reported elsewhere.

Image Acquisition

Dedicated brain PET/CT images were acquired 60 minutes post injection of 100 ± 19 MBq of 68Ga PSMA-11 tracer. PET images were acquired with 5 minutes scan duration per bed and matrix size 336 × 336. CT scan was acquired with the following parameters; voltage: 130 Kev, current: 240 mA and slice thickness of 3 mm. Intrinsically co-registered hybrid PET/CT images were reconstructed in axial, coronal and sagittal orientations with 3 mm image thickness.

Image Analysis

The PET/CT images were reviewed by two certified nuclear medicine physicians. Any abnormal FDG uptake in the suspicious lesion was taken as significant and maximum standardized uptake value (SUVmax) was calculated for the lesion. SUVmax of the background was calculated using a similar region of interest (ROI) marked in the contralateral uninvolved cerebellum. Target to background ratios (TBR) were calculated using SUVmax of lesion divided by SUVmax of the background. SUVmax of the lesion with both the tracers as well as the background and TBR values are summarized in Table 1.

RESULTS

Category 1: Patients Having Suspected Recurrence

In four out of five cases abnormal tracer uptake was noted with both the tracers in the suspicious lesion detected in the MRI. Visual interpretation showed good concurrence between 18F-FDG PET/CT and 68Ga PSMA PET/CT findings. Figure 1 gives the PET/CT images with 18F-FDG (left), 68Ga PSMA-11 (middle) and MR images (right) of Patient 1. Owing to the absence of physiological tracer uptake in normal brain parenchyma the presence of recurrent lesion is conspicuous and distinctly discernible in 68Ga PSMA-11 PET/CT. The TBR ratios obtained was 0.96 and 12.9 for 18F-FDG and 68Ga PSMA PET/CT respectively. The results of the PET/CT imaging studies for the second and third patients were similar to the first patient (figures not given). Tumor showed an absolute value of SUVmax higher with FDG compared to 68Ga PSMA-11, however owing to significantly low background the TBR was much higher for 68Ga PSMA-11 compared to FDG.

Figure 2 shows the PET/CT images of an 11-year-old boy (Patient 4), who received correspondingly lower dose of 18F-FDG (137 MBq) and 68Ga PSMA (60 MBq). Absence of physiological uptake of 68Ga PSMA helped in the improved visualization of the tumor in this case despite the lower amount of activity injected. The visualization of the tumor in all the four cases was better with 68Ga PSMA-11 as compared to 18F-FDG. All the four patients

<p>| TABLE 1. Patient Data and Analysis of Uptake Characteristics With 18F-FDG and 68Ga PSMA |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Location of Lesion</th>
<th>Activity Injected (MBq)</th>
<th>SUVmax Lesion</th>
<th>SUVmax Background</th>
<th>TBR</th>
<th>Final Diagnosis</th>
</tr>
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<tr>
<td>1</td>
<td>23</td>
<td>M</td>
<td>Right temporal</td>
<td>191</td>
<td>14.83</td>
<td>6.59</td>
<td>0.51</td>
<td>Recurrence</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>F</td>
<td>Left parietal</td>
<td>183</td>
<td>8.59</td>
<td>90</td>
<td>0.97</td>
<td>Recurrence</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>M</td>
<td>Right frontoparietal</td>
<td>329</td>
<td>8.77</td>
<td>90</td>
<td>0.97</td>
<td>Recurrence</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>M</td>
<td>Right temporal</td>
<td>186</td>
<td>10.95</td>
<td>106</td>
<td>0.97</td>
<td>Recurrence</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>M</td>
<td>Left frontoparietal</td>
<td>137</td>
<td>16.54</td>
<td>60</td>
<td>0.97</td>
<td>Recurrence</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>M</td>
<td>Right frontoparietal</td>
<td>231</td>
<td>5.46</td>
<td>109</td>
<td>0.57</td>
<td>Recurrence</td>
</tr>
<tr>
<td>7</td>
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<td>M</td>
<td>Left frontoparietal</td>
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<td>11.62</td>
<td>117</td>
<td>1.11</td>
<td>Recurrence</td>
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<tr>
<td>8</td>
<td>45</td>
<td>F</td>
<td>Right frontoparietal</td>
<td>310</td>
<td>8.45</td>
<td>117</td>
<td>1.11</td>
<td>Recurrence</td>
</tr>
<tr>
<td>9</td>
<td>67</td>
<td>M</td>
<td>Left thalamocapsular region and left cerebellum</td>
<td>320</td>
<td>8.45</td>
<td>116</td>
<td>1.11</td>
<td>Recurrence</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>F</td>
<td>Right temporal</td>
<td>349</td>
<td>8.0</td>
<td>107</td>
<td>0.96</td>
<td>Recurrence</td>
</tr>
</tbody>
</table>

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underwent surgical excision of the recurrent disease and histopathological examination of the excised tissue confirmed recurrence of disease.

The fifth patient in this category referred for recurrence evaluation showed no abnormal tracer uptake in both $^{18}$F-FDG and $^{68}$Ga PSMA-11 PET/CT scans in the doubtful lesion detected in MRI (Fig. 3). The patient was put on follow-up. Repeat MRI at 9 months showed no evidence of disease recurrence. The absence of physiological uptake of the tracer in $^{68}$Ga PSMA PET/CT is advantageous.

**FIGURE 1.** A 23-year-old man (Patient 1) with right temporal recurrent glioblastoma. $^{18}$F-FDG PET/CT images (A and D), $^{68}$Ga PSMA-11 PET/CT images (B and E), and MR images (C and F) taken at the same axis. TBR values: 0.96 (FDG) and 12.9 (PSMA). Lesion is well identified in $^{68}$Ga PSMA-11 PET/CT imaging.

**FIGURE 2.** An 11-year-old boy (Patient 4) with right frontal recurrent glioblastoma. $^{18}$F-FDG PET/CT images (A, B and C) and $^{68}$Ga PSMA-11 PET/CT images (D, E and F). TBR values: 1.79 (FDG) and 4.07 (PSMA). Lesion is well identified in $^{68}$Ga PSMA-11 PET/CT imaging.
in this situation as the absence of lesion could be unequivocally confirmed giving a clear answer to the clinical question posed by the referring physician.

Category 2: Lesion Characterization

This category included five patients with a brain lesion detected in MRI who were referred for $^{18}$F-FDG scan to rule out the possibility of metastasis from a primary elsewhere in the body. Initially they underwent whole body $^{18}$F-FDG PET/CT scan which ruled out the presence of any FDG avid primary site elsewhere in the body. The brain lesions showed variable FDG uptake in each of the cases. All the five cases underwent $^{68}$Ga PSMA-11 scans as an additional study.

The first case (Patient 6) in this category was a 60-year-old man who presented with syncope and persistent headache. MRI showed a globular mass lesion in the deep white matter in the left frontoparietal junction. The imaging findings were suspicious for a primary brain tumor and metastasis as a second differential. $^{18}$F-FDG whole body PET/CT revealed moderate to intense FDG uptake along the periphery of the lesion in the left frontoparietal region. Note was also made of a moderate focal FDG uptake in the right lobe of the thyroid. The thyroid lesion was further evaluated with ultrasound and fine needle aspiration and the results were not suggestive of a primary thyroid malignancy. $^{68}$Ga PSMA-11 scan (Fig. 4) showed intense uptake of the tracer along the periphery of the lesion in left frontoparietal region. Surgical excision of the lesion was done and the final histopathology confirmed it as grade IV glioma.

The second case (Patient 7) in this category was a 45-year-old man with an extra axial mass lesion with destruction of the right frontal calvarium. MRI findings were suspicious of hemangiopericytoma with metastasis as a differential diagnosis. Whole body $^{18}$F-FDG PET/CT scan (Fig. 5) revealed mild heterogeneous FDG uptake in the brain lesion with no focal abnormal FDG concentrating lesion elsewhere in the body. In contrast, $^{68}$Ga PSMA PET/CT showed intense uptake in the lesion. $^{68}$Ga PSMA PET/CT scan provided clear visualization of the lesion. The lesion was surgically excised and histopathology of the surgical specimen confirmed it to be an atypical meningioma.

There were two lymphoma cases included in this study. The case (Patient 8) (Fig. 6) in this category was a 67-year-old woman who presented with complaints of right upper and lower limb weakness. MRI of the brain revealed a suspicious lesion in the left thalamocapsular region extending into midbrain with imaging findings more in favor of lymphoma than glioma. Primary CNS lymphoma was confirmed in histopathological analysis of the biopsy sample obtained from the site. The second case in this category was a 27-year-old woman who presented with suspicious lesion in the brain detected on MRI. She underwent whole body $^{18}$F-FDG PET/CT followed by dedicated $^{68}$Ga PSMA brain study (Fig. 7). Biopsy was done which confirmed it to be lymphoma. The $^{68}$Ga
PSMA uptake characteristics were better than the previous patient with lymphoma.

The last case (Patient 10) in this category was that of a 53-year-old woman with chronic renal failure, detected to have a ring enhancing lesion in the right frontal lobe in MRI. $^{18}$F-FDG PET/CT showed mild uptake of the tracer along the periphery of the lesion with no definitive primary sites detected elsewhere in the body. $^{68}$Ga PSMA PET/CT showed no abnormal tracer concentration in this lesion. The patient was unwilling for stereotactic brain biopsy/surgical excision of the lesion; hence, a final diagnosis could not be reached yet. The patient is under follow-up.

DISCUSSION

Glial tumors constitute approximately 77% of primary malignant brain tumors and are often associated with poor outcomes depending on their grade. Imaging of brain tumors has considerably evolved over the past decade especially with advancements in MRI and PET technologies as well as availability of hybrid PET/MR scanners. Functional imaging with PET provides additional insight beyond MRI into the tumor biology and is potentially useful in lesion characterization, noninvasive grading, prognostication, surgical and radiotherapy treatment planning, assessment of response to treatment and evaluation of suspected recurrence.

A large number of radiotracers having different molecular targeting mechanisms have been found to be useful for imaging brain tumors. These include $^{18}$F-FDG targeting glucose metabolism, $^{18}$F-FLT (fluorothymidine) as a proliferation marker and other tracers such as $^{11}$C-methionine ($^{11}$C]MET), $^{18}$F-fluoroethyl-L-tyrosine ($^{18}$F-FET) and $^{18}$F-fluoro-L-phenylalanine ($^{18}$F-FDOPA) as amino acid transporters.

$^{18}$F-FDG being widely available continues to be the primary tracer in brain tumor imaging, however with the serious disadvantages of non-specificity and very high physiological uptake in brain parenchyma. Amino acid tracers are superior as there is no physiological uptake in the brain; however, their availability is highly restricted. Gallium-68 as a radionuclide for PET/CT imaging had a tremendous growth in the last 10 years, thanks to the availability and easy adaptability of $^{68}$Ge/$^{68}$Ga generators.

Reports on the use of $^{68}$Ga PSMA-11 PET/CT to image non-prostatic malignancies slowly started appearing from several centers. $^{68}$Ga PSMA-11 uptake in most of these cancers is due to the

FIGURE 4. A, a 60-year-old man (Patient 6) having grade IV glioma. The $^{18}$F-FDG PET maximum intensity projection image (B) shows moderate focal uptake in the right lobe of thyroid. $^{18}$F-FDG PET/CT images (D) and $^{68}$Ga PSMA-11 PET/CT images (C, E-G) show uptake of the tracers in the left frontoparietal lesion. TBR values: 1.11 (FDG) and 22.3 (PSMA). Lesion is clearly identified in PSMA scan with very high contrast.
overexpression of PSMA in tumor associated neovasculature. Reports are also appearing on the uptake of $^{68}$Ga PSMA-11 in non-malignant conditions such as Paget’s disease $^{31}$ and healing fractures $^{32}$ indicating the overexpression of PSMA in non-tumor associated angiogenesis as well posing a caution on the interpretation of the PET/CT images.

The overexpression of PSMA in primary gliomas was described by Nomura et al. $^{24}$ Glioblastomas are highly vascularized

**FIGURE 5.** A 45-year-old man (Patient 7) with an extra axial mass lesion with destruction of the right frontal calvarium. Maximum intensity projection images of $^{18}$F-FDG (A) and representative axial sections of $^{18}$F-FDG (B, C) and $^{68}$Ga PSMA-11 PET/CT images (D, E) showing uptake of the tracers. TBR values: 0.74 (FDG) and 29.2 (PSMA). Lesion is clearly identified in PSMA scan with very high contrast. Surgically excised lesion confirmed atypical meningioma.

**FIGURE 6.** A 67-year-old woman (Patient 8) having suspicious lesion in the left thalamocapsular region extending into midbrain with imaging findings more in favor of lymphoma than glioma. $^{18}$F-FDG PET/CT images (A, B and C) and $^{68}$Ga PSMA-11 PET/CT images (D, E and F). TBR values: 4.85 (FDG) and 17 (PSMA). Lesion is well identified in FDG whereas the uptake is mild with PSMA. Primary CNS lymphoma was confirmed in histopathological analysis.
tumors and expansion of nutrient vessels is an important factor in their growth and hence PSMA has been identified as a potential therapeutic target as it is overexpressed in the tumor vasculature of glioblastomas. From the limited data available so far it appears that PSMA expression in brain tumors varies with glioma grade. It has also been identified that metastatic brain tumors can show intense uptake of PSMA targeting tracers owing to the tumor neovascularization.

$^{68}$Ga PSMA PET/CT imaging of primary glioma is already reported. Identifying the ability of the $^{68}$Ga PSMA to image tumor neovascularization, we extended its application from the preoperative setting to assessment of recurrence of glioma and the results are promising. In five cases with suspected recurrence, $^{68}$Ga PSMA-11 PET/CT could accurately identify the recurrent disease in all the four cases of true disease recurrence (confirmed in histopathology). The primary advantage of this modality over $^{18}$F-FDG PET/CT is the ability to get high contrast images due to the absence of physiological tracer uptake in normal brain parenchyma. Similarly high tracer uptake together with low background was seen with atypical meningioma. The uptake of $^{68}$Ga PSMA-11 in absolute terms was higher than $^{18}$F-FDG for Grade IV glioma (patient 6) and atypical meningioma (patient 7). Intense tracer uptake in atypical meningioma and also uptake in metastases show that $^{68}$Ga PSMA-11 is not a specific tracer with regard to the type of malignancy in brain. Uptake of $^{68}$Ga PSMA-11 in primary CNS lymphoma is lower as compared to $^{18}$F-FDG (patients 8 and 9). However, TBR ratio of $^{68}$Ga PSMA-11 is higher than that of $^{18}$F-FDG in all cases.

Many other tracers commonly used in nuclear medicine can also have elevated activity in the brain tumors due to damage of the brain blood barrier (BBB). From the available literature it appears that overexpression of PSMA molecules in tumor neovascularization of brain tumors is a more plausible explanation for the $^{68}$Ga PSMA-11 uptake seen in brain tumors. However, a compounding effect of disruption of BBB to the uptake of $^{68}$Ga PSMA-11 is possible and needs further validation. Over the years, FDG has been used as a successful tracer to image brain lesions despite having a low specificity and high uptake in normal brain parenchyma. In the assessment of nature of brain lesion (lesion characterization), $^{68}$Ga PSMA PET/CT seems to have a complimentary role to $^{18}$F-FDG PET/CT, subject to validation from large-scale studies. The availability of $^{68}$Ga generators in hospital radiopharmacy and the ability to synthesize $^{68}$Ga PSMA-11 economically could eventually enhance the use of this tracer for PET/CT imaging of different brain tumors. Another promising application which appears theoretically feasible is response assessment to treatment with antiangiogenic therapy with temozolomide.

**CONCLUSION**

$^{68}$Ga PSMA-11 brain imaging is definitely a feasible and potentially useful imaging tool in the evaluation of brain lesions. Absence of physiological tracer uptake in the normal brain parenchyma with $^{68}$Ga PSMA-11 offers significantly high TBR in comparison with $^{18}$F-FDG, thus resulting in better visualization of metabolically active disease in the brain. Further larger studies from multiple centers are required to validate the potential clinical applications of $^{68}$Ga PSMA-11 brain PET/CT imaging.

**REFERENCES**


