Molecular imaging with ^{68}Ga-PSMA PET/CT in high grade glioma: A biomarker for tumour neo-angiogenesis

Sharjeel Usmani[1,2], Khulood Al Riyami[3], Shah P Numani[4], Syed Furqan Hashmi[5], Anjali Jain[6], Rashid al Sukaiti[7], Najeeb Ahmed[8], Muhammad Shahzad Shamim[9]

Abstract

There are several promising radiotracers used for both staging and restaging of primary and recurrent brain tumours based on various mechanisms of tracer localization in tumour cells. 68Ga-PSMA PET has extremely low background uptake in normal brain tissue and consequently high tumour-to-brain ratio making it a promising imaging radiotracer for gliomas. 68Ga-PSMA demonstrates utility in evaluating high grade glioma during both initial workup or when suspecting recurrence. Herein the authors evaluate the role of this imaging modality and the potential future it holds in the management of high grade gliomas.

Keywords: ^{68}Ga-PSMA; PET/CT; brain tumors; PET/CT; gliomas; Glioblastoma Multiforme

DOI: https://doi.org/10.47391/JPMA.24-64

Introduction

MRI is the standard method of imaging in the evaluation of gliomas, yet it is often challenging to differentiate between tumour recurrence and radionecrosis. Compared with MRI, PET imaging provides functional information and may add diagnostic value in detecting new lesions and differentiating tumour progression from post-treatment change. ^{18}F-FDG is the most often utilized radiotracer in oncology because cancer cells have a higher metabolism of glucose. However, ^{18}F-FDG PET/CT has a limited role in the detection of brain tumours due to high uptake in normal brain parenchymal tissue.[1] Recent literature shows promising diagnostic value of ^{68}Ga-PSMA PET/CT in evaluation of glioma due to absence of physiological uptake of ^{68}Ga-PSMA in the normal brain parenchyma that results in high tumour to background ratio (TBR) values leading to better visualization of glial neoplasms.[2]

[1,3,5-7]Department of Radiology and Nuclear Medicine1, Sultan Qaboos Comprehensive Cancer Care and Research Center (SQCCCRC), Muscat Oman; [2,8]Hull York Medical School, Hull, UK; 4Department of Radiology, Carl T Hayden VA Medical Center, Phoenix USA; [9]Department of Surgery, Aga Khan University Hospital, Karachi Pakistan.

Correspondence: Muhammad Shahzad Shamim.
e-mail: shahzad.shamim@aku.edu
ORCID ID: 0000-0001-8305-8854

Review of Evidence

Prostate-specific membrane antigen (PSMA) is a type-2 transmembrane glycoprotein and is highly expressed in prostate cancer and is a promising tracer for both staging and detection of biochemical recurrence in prostate cancer.[3] ^{68}Ga-PSMA uptake has also been reported in other solid malignant tumours including glioma, lung, breast cancer and renal cell carcinoma.[4] PSMA is expressed in the endothelium of tumour-associated neovasculature of various solid malignancies possibly due to tumour-associated angiogenic factors and endothelial cell sprouting including gliomas.[5,6] PSMA expression has not been reported in normal vasculature but immuno-histochemical (IHC) analysis show high PSMA expression in neovasculature (identified by CD 31) of high-grade gliomas.[7] Early studies have shown promising results in terms of its ability to detect high grade glioma recurrence, identify tumour grade, extent, guide biopsy and treatment decisions.[8]

68Ga-PSMA PET imaging could be helpful in the detection and localization of gliomas, particularly those with high PSMA expression. It can be used to characterize PSMA expression in gliomas and the degree of ^{68}Ga-PSMA uptake in gliomas seems to correlate well with tumour grade and proliferation index (Ki-67).[1] Verma et al., showed that 68Ga-PSMA PET might help in discriminating high grade gliomas from low grade, on the basis of higher SUV max, and MIB-1 PI tumour-to-background ratio.10 PSMA PET indices like SUV max/mean also seem to show correlation with prognostic parameters (Figure). A recent systemic review also showed PSMA PET/CT to have a pooled sensitivity of 86.5% (95% CI: 73–94%) and specificity 89.2% (95% CI: 71–96.5%) for differentiating high grade and low grade gliomas.[11] Akgun et al., investigated the accuracy of 68Ga-PSMA PET/MRI in grading gliomas tumours and found that the sensitivity and specificity of ^{68}Ga-PSMA PET/MRI were 85.7% for high grade tumours[12] Bertagna et al., in a literature review also suggests that radiolabeled PSMA imaging can be useful in analyzing gliomas and glioblastomas, although the authors recommended large-scale prospective studies are needed to clarify the real clinical and diagnostic role of it.[13]

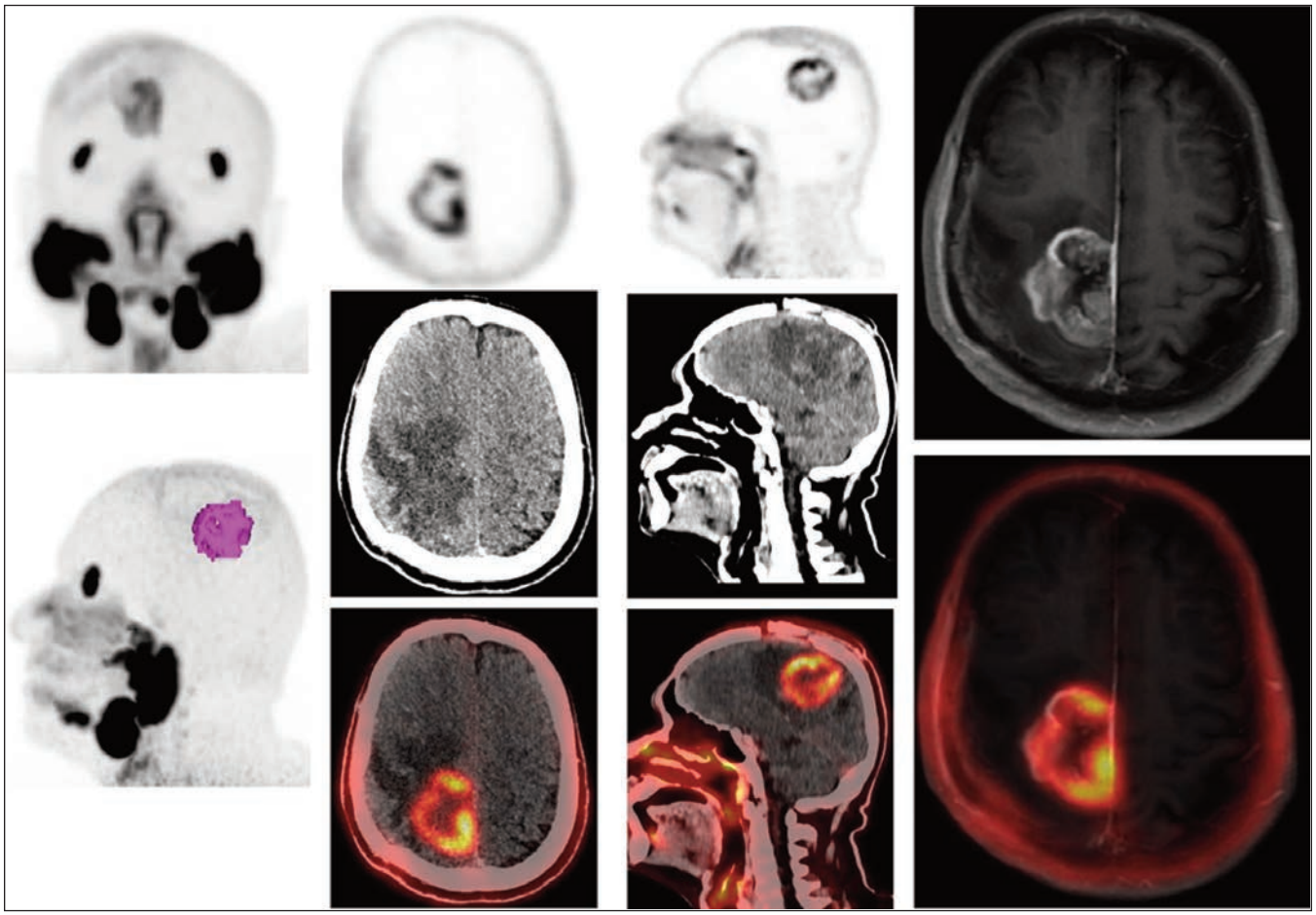

Figure: : A 61-year-old male is a known case of GBM, IDH, not mutant. Post craniotomy. 68Ga-PSMA shows abnormal PSMA expression lesion with SUV max 5.5 at right parietal cortex with central areas of necrosis and cystic degeneration, measuring approximately 3.4 x 4.4 x 4.0 cm along posterior and superior aspects of surgical bed. Quantitative analysis shows metabolic tumour volume (MTV)=21.7cm^3. Findings are consistent with significant active residual tumour characterized by neovascularization in the tumour.

^{68}Ga-PSMA PET/CT may also play an important role in the management of recurrent gliomas. The high tumour-to-brain ratio and exceptionally low background uptake in normal brain tissue makes ^{68}Ga-PSMA PET/CT a promising modality for detection of recurrent disease in high grade glioma patients. ^{68}Ga-PSMA PET is especially beneficial in diagnosing early tumour recurrence as it has been shown to be poorly expressed in treatment-related changes such as radiation necrosis.[14] Kumar et al., recently investigated 68Ga-PSMA in recurrent of high grade gliomas and reported 100% concordance between MRI and PET for patient and lesion-wise detection.[15]

68Ga PSMA PET scans can also be useful in planning radiotherapy for gliomas by identifying the extent of PSMA expression in the tumour. This approach may help customize treatment strategies to better target PSMA expressing cells. A recent study studied ^{68}Ga PSMA PET scans in glial tumours for radiotherapy planning and found that it can accurately outline tumour boundaries and could be useful in defining target volumes particularly during re-irradiation of recurrent tumours.[16]

It is crucial to also consider the potential pitfalls and limitations of this imaging modality. Some studies have indicated that PSMA expression in high grade gliomas can be variable and non-specific, leading to false-positive or false-negative results. This can result in an underestimation or incomplete visualization of tumour extent. Furthermore, pseudoprogression can also be observed on 68Ga-PSMA PET/CT in certain cases of high grade gliomas treated with chemoradiotherapy.[17]

Conclusions

68Ga-PSMA PET appears to be a promising imaging tool for high grade glioma assessment and prognosis. 68Ga-PSMA expression in glioma can also potentially pave the way for PSMA-targeted radioligand therapies. However, the evidence supporting its use is still limited, and larger prospective studies are needed to establish its clinical utility and accuracy.

References

1. Olivero WC, Dulebohn SC, Lister JR. The use of PET in evaluating patients with primary brain tumors: Is it useful? J Neurol Neurosurg Psychiatry. 1995;58:250–252.
2. Sasikumar A, Joy A, Pillai MR, Nanabala R, Anees K M, Jayaprakash PG, et al. Diagnostic Value of 68Ga PSMA-11 PET/CT Imaging of Brain Tumors-Preliminary Analysis. Clin Nucl Med. 2017;42:e41-e48.
3. Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, Lehnert W, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imag. 2017;44:678e88.
4. Usmani S, Sadeq A, Marafi F, Esmail A, Al Kandari F, Ahmed N. 68Ga-PMSA Uptake in the Lung: Metastatic Versus Primary Lung Tumor. Clin Nucl Med. 2020;45:e80-e82.
5 Saffar H, Noohi M, Tavangar SM, Saffar H, Azimi S. Expression of Prostate-Specific Membrane Antigen (PSMA) in Brain Glioma and Its Correlation with Tumor Grade. Iran. J. Pathol. 2018;13:45–53
6 Mahzouni P, Shavakhi M. Prostate-Specific Membrane Antigen expression in neovasculature of glioblastoma multiforme. Adv. Biomed. Res. 2019;8:18
7 Abdel Maguid MS, Saad El Dine MG, Gabal SM, Abou Fandoud SM. Prostate-Specific Membrane Antigen (PSMA) expression in the neovasculature of high grade gliomas (Histopathological and Immunohistochemical Study). Asian Pac J Cancer Prev. 2023;24:1797-1808.
8 Sasikumar A, Kashyap R, Joy A, Charan Patro K, Bhattacharya P, Reddy Pilaka VK, et al. Utility of 68Ga-PSMA-11 PET/CT in Imaging of Glioma-A Pilot Study. Clin Nucl Med. 2018;43:e304-e309.
9 Liu D, Cheng G, Ma X, Wang S, Zhao X, Zhang W, et al. PET/CT using (68) Ga-PSMA-617 versus (18) F-fluorodeoxyglucose to differentiate low- and high-grade gliomas. J. Neuroimaging. 2021;31:733–742.
10 Verma P, Malhotra G, Goel A, Rakshit S, Chandak A, Chedda R, Banerjee S, Asopa RV. Differential uptake of 68Ga-PSMA-HBED-CC (PSMA-11) in low-grade versus high-grade gliomas in treatment-naive patients. Clin Nucl Med. 2019;44:e318-e322.
11 Muoio B, Albano D, Dondi F, Bertagna F, Garibotto V, Kunikowska J, et al. Diagnostic Accuracy of PET/CT or PET/MRI Using PSMA-Targeting Radiopharmaceuticals in High-Grade Gliomas: A Systematic Review and a Bivariate Meta-Analysis. Diagnostics (Basel). 2022;12:1665.
12 Akgun E, Akgun MY, Selçuk HH, Uzan M, Sayman HB. 68Ga PSMA PET/MR in the differentiation of low and high grade gliomas: is 68Ga PSMA PET/MRI useful to detect brain gliomas? Eur. J. Radiol. 2020;130:109199.
13 Bertagna F, Albano D, Cerudelli E, Gazzilli M, Giubbini R, Treglia G. Potential of radiolabeled PSMA PET/CT or PET/MRI diagnostic procedures in gliomas/glioblastomas. Curr Radiopharm. 2020;13:94–98.
14 Kunikowska, J, Kuliński R, Muylle K, Koziara H, Królicki L. 68Ga–Prostate-Specific Membrane Antigen-11 PET/CT: A new imaging option for recurrent glioblastoma multiforme? Clin. Nucl. Med. 2019, 45, 11–18.
15 Kumar A, ArunRaj ST, Bhullar K, Haresh KP, Gupta S, Ballal S, et al. Ga-68 PSMA PET/CT in recurrent high-grade gliomas: evaluating PSMA expression in vivo. Neuroradiology. 2022;64:969-979.
16 Şahin M, Akgun E, Sirolu S, Can G, Sayman HB, Oner Dincbas F. Is there any additional benefit of 68Ga-PSMA PET on radiotherapy target volume definition in patients with glioblastoma? Br J Radiol. 2022;95:20220049.
17 Gupta M, Choudhury PS, Gairola M, Premsagar IC, Rao SA. Pseudoprogression on 68Ga-Prostate-Specific Membrane Antigen-11 PET/CT in a treated glioblastoma. Clin Nucl Med. 2020;45:621-622.