Current Radiopharmaceuticals, 2020, *13*, 94-98

SYSTEMATIC REVIEW ARTICLE

Potential of Radiolabeled PSMA PET/CT or PET/MRI Diagnostic Procedures in Gliomas/Glioblastomas

Francesco Bertagna[1,*], Domenico Albano[1], Elisabetta Cerudelli[1], Maria Gazzilli[1], Raffaele Giubbini[1] and Giorgio Treglia[2,3,4]

[1]*Nuclear Medicine, University of Brescia and Spedali Civili di Brescia, Brescia, Italy;* [2]*Department of Nuclear Medicine and PET/CT Center, Imaging Institute of Southern Switzerland, Bellinzona and Lugano, Switzerland;* [3]*Department of Nuclear Medicine and Molecular Imaging, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;* [4]*Health Technology Assessment Unit, General Directorate, Ente Ospedaliero Cantonale, Bellinzona, Switzerland*

Abstract: ***Background:*** Radiolabeled prostate-specific membrane antigen PSMA-based PET/CT or PET/MRI is a whole-body imaging technique currently performed for the detection of prostate cancer lesions. PSMA has been also demonstrated to be expressed by the neovasculature of many other solid tumors.

Objective: The aim of this review is to evaluate the possible diagnostic role of radiolabeled PSMA PET/CT or PET/MRI in patients with gliomas and glioblastomas, by summarizing the available literature data.

Methods: A comprehensive literature search of the PubMed/MEDLINE, Scopus, Embase and Cochrane library databases was conducted to find relevant published articles about the diagnostic performance of radiolabeled PSMA binding agents in PET/CT or PET/MRI imaging of patients with suspected gliomas or glioblastomas.

Results: Seven case reports or case series and 3 studies enrolling more than 10 patients showed that gliomas and glioblastoma are PSMA-avid tumors.

Conclusion: Radiolabeled PSMA imaging seems to be useful in analyzing glioma/glioblastoma. Further studies enrolling a wider population are needed to clarify the real clinical and diagnostic role of radiolabeled PSMA in this setting and its possible position in the diagnostic flow-chart.

ARTICLE HISTORY

Received: July 17, 2019
Revised: August 29, 2019
Accepted: September 16, 2019

DOI:
10.2174/1874471012666191017093721

Keywords: PSMA, prostate specific membrane antibodies, glioma, glioblastoma, PET, positron emission tomography.

1. INTRODUCTION

Gliomas are the most frequent type of primary brain tumors. The clinical behavior of gliomas is different according to the grade; low grade gliomas are slowly growing, while high grade gliomas are clinically aggressive with poor prognosis. The most frequent and most malignant histological type is the glioblastoma. Gliomas are usually classified on the basis of cellular morphology (oligodendroglioma, oligoastrocytoma, astrocytoma) and according to proliferative features. The WHO classification of central nervous system tumors divides gliomas into grade I–II (low-grade glioma), grade III (anaplastic astrocytoma or oligodendroglioma or oligoastrocytomas) and grade IV (glioblastoma). In a neurological examination, the imaging tests that are commonly used to evaluated gliomas are; magnetic resonance (MR) and computed tomography (CT). Surgery is usually the first step of therapy with the aim to remove the maximum possible the tumor. . Radiation therapy usually follows surgery in the treatment of glioma, especially high-grade gliomas. Chemotherapy is usually used in combination with radiation therapy. The prognosis for patients with gliomas depends on the grade and for patients with high-grade gliomas is generally poor.

Radiolabeled Gallium-68 (^{68}Ga) or Fluorine-18 (^{18}F) prostate specific membrane antigen (PSMA)-based positron emission tomography/computed tomography or magnetic resonance imaging (PET/CT or PET/MRI) are whole-body imaging techniques currently performed for the detection of prostate cancer (PCa) lesions. The main diagnostic application of PSMA-based imaging is the whole body primary

*Address correspondence to this author at the Nuclear Medicine, University of Brescia and Spedali Civili di Brescia, P.le Spedali Civili 1, 25123 Brescia, Italy; Tel: +39-30-3995468; Fax: +39-30-3995420;
E-mail: francesco.bertagna@unibs.it

1874-4729/20 $65.00+.00

staging of intermediate and high risk PCa or restaging after biochemical disease relapse (rising prostate-specific antigen levels) in patients with prior radical external beam radiation or radical prostatectomy [1-3].

PSMA, a type II transmembrane glycoprotein receptor with glutamate carboxypeptidase/folate hydrolase activity. Human PSMA is a zinc containing metalloenzyme (750 amino acids) with a unique 3-part structure composed of a large extracellular domain, a transmembrane portion, and an intracellular component. PSMA has recently emerged as a target for radionuclide imaging and treatment of PCa [4,5]. High expression of PSMA in PCa and upon ligand-binding internalization of PSMA by clathrin-coated pits and subsequent endocytosis makes it a useful target for diagnostic and therapeutic applications in nuclear medicine. PSMA has been demonstrated to be expressed by the neovasculature of many solid tumors (for example colon, gastric, lung, breast, adrenal, bladder, renal cell carcinoma), in some non-neoplastic conditions and also as incidental findings in other organs like thyroid [6-14].

The aim of this review is to evaluate the possible diagnostic role of radiolabelled PSMA PET/CT or PET/MRI in patients with gliomas and glioblastomas, by summarizing the available literature data.

2. METHODS

2.1. Search Strategy

A comprehensive literature search of the PubMed/MEDLINE, Scopus, Embase and Cochrane library databases was conducted to find relevant published articles about the role of radiolabelled PSMA PET/CT or PET/MRI in patients affected by glioma or glioblastoma. We used a search algorithm that was based on a combination of the terms: a) ''PSMA" OR "prostate specific membrane antigen" AND b) "glioma" or "glioblastoma". No beginning date limitation was used; the search was updated until June 30th 2019. Only articles in the English language were selected; pre-clinical or non in-vivo studies, and conference proceedings were excluded. To expand our search, references of the retrieved articles were also screened for additional studies. All literature studies collected were managed using EndNote Web 3.3.

2.2. Study Selection

All articles reporting patients with glioma or glioblastoma evaluated by radiolabeled PSMA PET/CT or PET/MRI in the clinical setting were eligible for inclusion. Two researchers (FB and GT) independently reviewed the titles and abstracts of the retrieved articles. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion.

2.3. Data Abstraction

For each included study, information was collected concerning the basic study (author names, year of publication, country of origin, type of study) and PET device used (PET/CT or PET/MRI), number of patients evaluated, number of patients who underwent further investigations and malignancies detected. The main findings of the articles included in this review are reported in the Results.

3. RESULTS

3.1. Literature Search

The comprehensive computer literature search revealed 127 articles. On reviewing the titles and abstracts, 117 articles were excluded because the reported data were not within the field of interest of this review. 10 articles were selected and retrieved in full-text version [15-24]; no additional studies were found when screening the references of these articles. In total, 10 articles were included in the systematic review [15-24].

3.2. Qualitative Analysis (Systematic Review)

Findings of several studies have shown that radiolabeled PSMA PET imaging may identify gliomas and glioblastomas. The characteristics of the studies and results are briefly presented in Tables **1** and **2**.

Table 1. Clinical Glioma/glioblastoma imaging studies using radiolabeled PSMA binding agents.

First Author	Ref.	Year	N.Pts	Type of Study	Country/Study Type	Device	Radiolabelled agent
Marafi	[15]	2019	1	CR	Kuwait	PET/CT	18F-PSMA 1007
Verma	[16]	2019	10	R	India	PET/CT	68Ga-PSMA-11
Kunikowska	[17]	2018	1	CR	Poland	PET/CT	68Ga-PSMA[§]
Malik	[18]	2018	1/5[$]	CS	India	PET/CT	68Ga-PSMA
Salas Fragomeni	[19]	2018	1	CR	United States	PET/CT	18F-DCFPyL (PSMA-targeted)
Sasikumar	[20]	2018	15^	P	India	PET/CT	68Ga-PSMA-11
Salas Fragomeni	[21]	2017	3	CS	United States	PET MRI[f]	18F-DCFPyL (PSMA-targeted)
Sasikumar	[22]	2017	10^	NA	India	PET/CT	68Ga-PSMA-11
Unterrainer	[23]	2017	1	CR	Germany	PET MRI[f]	68Ga-PSMA-11
Schwenck	[24]	2015	1	CR	Germany	PET/MRI	68Ga-PSMA-11

Ref. = reference; N.Pts = cases examined; R = retrospective; P= prospective; CR = case report; CS= case series; [§]= not better specified; NA = not available; [$]= case series with one patients with brain tumor; [f]= imaging fusion ^=possible partial patients ovelap.

Table 2. Glioma/Glioblastoma PET Imaging Results Using Radiolabeled PSMA Binding Agents.

First Author	Ref.	N.Pts	PET/CT Positive	Final Diagnosis	Gold Standard Final Diagnosis	PET/CT Negative	Final Diagnosis	Gold Standard Final Diagnosis
Marafi	[15]	1	1	GB	histology	/	/	/
Verma	[16]	10	10	5G; 2GBM; 3LG	histology	/	/	/
Kunikowska	[17]	1	1	GBM	histology	/	/	/
Malik	[18]	1/5[$]	1	ODG	histology	/	/	/
Salas Fragomeni	[19]	1	1	Aspecific uptake in radionecrosis	MRI and FU	/	/	/
Sasikumar	[20]	15	13	10GBM; 1ODG; 1 aODG; 1AATGBM;	histology	2	2NS	MRI and FU
Salas Fragomeni	[21]	3	3	2GBM; 1 AA	histology	/	/	/
Sasikumar	[22]	10	8	4GBM; 1HG; 1AM; 2CNSL;	histology	2	1NS; 1NA	MRI and FU
Unterrainer	[23]	1	1	GS	histology	/	/	/
Schwenck	[24]	1	1	GBM	histology	/	/	/

Ref. = reference; N.Pts = cases examined; NA = not available; [$]= case series with one patients with brain tumor; FU= follow-up; GB= glioblastoma; GBM= glioblastoma multiforme; LG= low grade glioma; HG= high grade glioma; ODG= oligodendroglioma; aODG= anaplastic oligodendroglioma; AATGBM= anaplastic astrocytoma with transformation to GBM; NS= negative for disease; [f]= fused; AA= anaplastic astrocytoma; AM= atypical meningioma; CNSL= central nervous system lymphoma; GS= Gliosarcoma.

4. DISCUSSION

Imaging of gliomas/glioblastomas has always been challenging for the nuclear medicine physicians and the radiologists. Functional MRI, [18F]Fluorodeoxyglucose (18F-FDG) and newer tracers like ^{18}F-fluorothymidine (^{18}F-FLT) , ^{11}C-methionine (^{11}C-MET), ^{18}F-fluoroethyl-L-tyrosine(^{18}F-FET), ^{18}F-Fluoro-L-dihydroxyphenylalanine (^{18}F-FDOPA), [11C] Choline/[18F]Fluorocholine and 18F-fluoromisonidazole (18F-FMISO) have also been studied in literature. 18F-FDG (evaluating the upregulation of glycolysis in cancer cells) has shown suboptimal results; in fact, despite 18F-FDG uptake has been demonstrated in gliomas, the high physiological uptake of the normal brain tissue diminishes contrast, particularly in the cortex; as a consequence, tumors and normal brain activity may become indistinguishable. 18F-FLT (a nucleoside radiotracer used to measure and visualize DNA synthesis) uptake is low in the normal brain parenchyma and it has been demonstrated in gliomas but tracer accumulation may also occur in non-neoplastic blood-brain barrier disruption, bone marrow and dural venous sinuses. 11C-MET (radiolabeled amino acid incorporated into proteins synthesis) has been used for brain tumor imaging with good results also due to the low uptake in normal brain but the short half-life (20 minutes) needs on-site cyclotron facilities. 18F-FET (a tyrosine analog radiolabeled tracer that accumulates within tumors without metabolization or incorporation into proteins) has been used with good results in gliomas. 11C- or 18F- Choline (a phospholipid precursor partaking in cell membrane synthesis by phosphorylation by choline kinase) has also been used with good results but its high physiological uptake in non-tumoral structures including choroid plexus, venous sinuses, the pituitary gland and its false positives results in abscesses, inflammatory granulomas, tuberculoma and some demyelinating diseases have limited its specificity. ^{18}F-FDOPA (an amino-acid analog) is approved for the assessment of recurrent brain tumors in Europe and has been increasingly trialled for preoperative glioma characterization. 18F-FMISO has also been used to evaluate gliomas hypoxia being hypoxia a critical component of the glioblastoma microenvironment and has been associated with both poor prognosis and resistance to various therapies.

Therefore, studies using newer tracers like radiolabeled PSMA binding agents warrants study and review.

The PSMA is a type II transmembrane protein physiologically expressed by prostate tissue and significantly overexpressed by most of the PCa cells. However, PSMA is not solely expressed by prostate tissue [6-14]. Importantly, PSMA overexpression also occurs in pathophysiological processes other than PCa, especially in the neovasculature of multiple malignancies. This has important potential implications for PSMA-targeted imaging and possibly also therapies. Tumor specimens analysis and immunohistochemical studies have suggested the presence of PSMA expression of gliomas [25-29]. Only a few studies evaluating PSMA-targeted imaging of gliomas/glioblastomas in clinical practice are currently available. Moreover, most of these studies are case reports or case series [15, 17-19, 21-24] probably because few centers currently use radiolabeled PSMA PET/CT or PET/MRI, thereby reducing the population of patients analyzed globally. As a consequence, considering a very low number of reports and patients analyzed, no high quality evidence could be drawn about the role of radiolabeled PSMA in gliomas/glioblastomas; further, large prospective studies are needed to clarify the real clinical and

diagnostic role of the radiolabeled PSMA in this field and its possible position in the diagnostic flow-chart. Overall, the available literature data demonstrate that gliomas/ glioblastomas are radiolabeled PSMA-avid tumors. These insights, if confirmed, could open up the way to a possible future use of radiolabeled PSMA PET/CT or PET/MRI in this type of brain tumors. In one case only there was a false positive result of the radiolabeled PSMA PET due to radionecrosis [19]. Three studies where more than 10 patients were enrolled showed that gliomas and glioblastoma are PSMA avid tumors; in particular, Verma et al. [16] evaluated 10 patients with ^{68}Ga-PSMA PET/CT, harboring brain lesions that were suspected to be gliomas on MRI; in vivo PSMA expression was seen in all patients with glioma. Of these, 7 patients harboring 8 lesions of glioblastoma (WHO grade IV) showed high-grade PSMA uptake, whereas the remaining 3 patients (3 lesions) of low-grade glioma (WHO grade II) had low-grade PSMA uptake in their respective brain lesions. They concluded that ^{68}Ga-PSMA PET/CT can be used to characterize the PSMA expression in gliomas, high-grade ones demonstrating higher uptake and tumor-to-background ratio than the low-grade ones. Sasikumar et al. [22] evaluated 10 patients with ^{68}Ga PSMA having brain lesions detected on MRI; glioma of 5 patients was evaluated by radiolabeled PSMA PET for suspicious recurrence; five patients were evaluated for characterization of a space-occupying lesion in the brain. In four out of five cases, among the patients referred to recurrence evaluation, abnormal tracer uptake was observed in the suspicious lesion detected by MRI. All the four patients underwent surgical excision of the recurrent disease and histopathological examination of the excised tissue, which confirmed the recurrence of the disease. The fifth patient in this category referred to recurrence evaluation showed no abnormal tracer uptake at ^{68}Ga-PSMA PET/CT scan in the doubtful lesion detected by MRI. The patient was suggested for a follow-up and and an MRI at 9 months showed no evidence of disease recurrence. In the group of five patients with a brain lesion detected by MRI and evaluated by ^{68}Ga-PSMA PET/CT for characterization, one patient had a definitive diagnosis of grade IV glioma, one had an atypical meningioma and two had central nervous system lymphoma; in the last case ^{68}Ga-PSMA PET/CT showed no abnormal tracer uptake. The patient was unwilling for stereotactic brain biopsy/surgical excision of the lesion which hampered to reach a definitive diagnosis.

One year later, the same authors [20], despite a possible partial patients' overlap, published a study in which a total of 15 patients underwent ^{68}Ga-PSMA PET/CT. Indication for doing the scan in majority of the patients (10 patients; 67%) was for a suspected glioma recurrence after surgery and radiotherapy. Two patients (13%) were referred for lesion characterization of space-occupying lesion in the brain and 3 patients (20%) for restaging immediately after surgery. In 13 cases, there was evidence of disease at ^{68}Ga-PSMA PET/CT scan, and the final diagnosis was made on the basis of histopathology. Among the 2 cases where the scan was negative, one was for immediate post-surgery restaging. The subsequent MRI showed no evidence of residual disease, and the patient underwent follow-up with no evidence of disease after 6 months. The other case was followed up clinically, and the repeated MRI scan after 9 months showed no evidence of disease as well.

CONCLUSION

Despite the fact that few studies are currently available, radiolabeled PSMA is not specific for the prostate, as several benign and malignant entities have been reported by imaging and histologic studies to show a relevant expression, especially in tumor-associated endothelial cells. Radiolabeled PSMA imaging seems to be useful in analyzing glioma/ glioblastoma despite further studies enrolling a wider population are needed to clarify the real clinical and diagnostic role of radiolabeled PSMA PET and its possible position in the diagnostic flow-chart.

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA guidelines and methodologies have been followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Treglia, G.; Annunziata, S.; Pizzuto, D.A.; Giovanella, L.; Prior, J.O.; Ceriani, L. Detection rate of ^{18}F-Labeled PSMA PET/CT in biochemical recurrent prostate cancer: a systematic review and a meta-analysis. *Cancers (Basel),* **2019**, *11*(5), E710 http://dx.doi.org/10.3390/cancers11050710 PMID: 31126071

[2] Wu, H.; Xu, T.; Wang, X.; Yu, Y.B.; Fan, Z.Y.; Li, D.X.; Luo, L.; Yang, X.C.; Jiao, W.; Niu, H.T. Diagnostic performance of ^{68}gallium labelled prostate-specific membrane antigen positron emission tomography/computed tomography and magnetic resonance imaging for staging the prostate cancer with intermediate or high risk prior to radical prostatectomy: a systematic review and meta-analysis. *World J. Mens Health,* **2020,** *38*(2),208-219. http://dx.doi.org/10.5534/wjmh.180124 PMID: 31081294

[3] Perera, M.; Papa, N.; Roberts, M.; Williams, M.; Udovicich, C.; Vela, I.; Christidis, D.; Bolton, D.; Hofman, M.S.; Lawrentschuk, N.; Murphy, D.G. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer-updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. *Eur. Urol.,* **2019**, S0302-2838(19)30095-8 http://dx.doi.org/10.1016/j.eururo.2019.01.049 PMID: 30773328

[4] Afshar-Oromieh, A.; Avtzi, E.; Giesel, F.L.; Holland-Letz, T.; Linhart, H.G.; Eder, M.; Eisenhut, M.; Boxler, S.; Hadaschik, B.A.; Kratochwil, C.; Weichert, W.; Kopka, K.; Debus, J.; Haberkorn, U. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur. J. Nucl. Med. Mol. Imaging,* **2015**, *42*(2), 197-209. http://dx.doi.org/10.1007/s00259-014-2949-6 PMID: 25411132

[5] Kratochwil, C.; Giesel, F.L.; Eder, M.; Afshar-Oromieh, A.; Benešová, M.; Mier, W.; Kopka, K.; Haberkorn, U. [^{177}Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur. J. Nucl. Med. Mol. Imaging,* **2015**, *42*(6), 987-988. http://dx.doi.org/10.1007/s00259-014-2978-1 PMID: 25573634

[6] Chang, S.S.; Reuter, V.E.; Heston, W.D.; Bander, N.H.; Grauer, L.S.; Gaudin, P.B. Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. *Cancer Res.,* **1999**, *59*(13), 3192-3198. PMID: 10397265

[7] Haffner, M.C.; Kronberger, I.E.; Ross, J.S.; Sheehan, C.E.; Zitt, M.; Mühlmann, G.; Ofner, D.; Zelger, B.; Ensinger, C.; Yang, X.J.; Geley, S.; Margreiter, R.; Bander, N.H. Prostate-specific membrane antigen expression in the neovasculature of gastric and colorectal cancers. *Hum. Pathol.,* **2009**, *40*(12), 1754-1761. http://dx.doi.org/10.1016/j.humpath.2009.06.003 PMID: 19716160

[8] Kinoshita, Y.; Kuratsukuri, K.; Landas, S.; Imaida, K.; Rovito, P.M., Jr; Wang, C.Y.; Haas, G.P. Expression of prostate-specific membrane antigen in normal and malignant human tissues. *World J. Surg.,* **2006**, *30*(4), 628-636. http://dx.doi.org/10.1007/s00268-005-0544-5 PMID: 16555021

[9] Hofman, M.S.; Hicks, R.J.; Maurer, T.; Eiber, M. Prostate-specific membrane antigen pet: clinical utility in prostate cancer, normal patterns, pearls, and pitfalls. *Radiographics,* **2018**, *38*(1), 200-217. http://dx.doi.org/10.1148/rg.2018170108 PMID: 29320333

[10] Verburg, F.A.; Krohn, T.; Heinzel, A.; Mottaghy, F.M.; Behrendt, F.F. First evidence of PSMA expression in differentiated thyroid cancer using [^{68}Ga]PSMA-HBED-CC PET/CT. *Eur. J. Nucl. Med. Mol. Imaging,* **2015**, *42*(10), 1622-1623. http://dx.doi.org/10.1007/s00259-015-3065-y PMID: 25916744

[11] Taywade, S.K.; Damle, N.A.; Bal, C. PSMA expression in papillary thyroid carcinoma opening a new horizon in Management of Thyroid Cancer? *Clin. Nucl. Med.,* **2016**, *41*(5), e263-e265. http://dx.doi.org/10.1097/RLU.0000000000001148 PMID: 26914556

[12] Noss, K.R.; Wolfe, S.A.; Grimes, S.R. Upregulation of prostate specific membrane antigen/folate hydrolase transcription by an enhancer. *Gene,* **2002**, *285*(1-2), 247-256. http://dx.doi.org/10.1016/S0378-1119(02)00397-9 PMID: 12039052

[13] Bourgeois, S.; Gykiere, P.; Goethals, L.; Everaert, H.; De Geeter, F.W. Aspecific uptake of 68GA-PSMA in paget disease of the bone. *Clin. Nucl. Med.,* **2016**, *41*(11), 877-878. http://dx.doi.org/10.1097/RLU.0000000000001335 PMID: 27556795

[14] Bertagna, F.; Albano, D.; Giovanella, L.; Bonacina, M.; Durmo, R.; Giubbini, R.; Treglia, G. ^{68}Ga-PSMA PET thyroid incidentalomas. *Hormones (Athens),* **2019**, *18*(2), 145-149. http://dx.doi.org/10.1007/s42000-019-00106-8 PMID: 30989578

[15] Marafi, F.; Sasikumar, A.; Fathallah, W.; Esmail, A. 18F-PSMA 1007 brain pet/ct imaging in glioma recurrence. *Clin. Nucl. Med.,* **2020**, 45(1), e61-e62 http://dx.doi.org/10.1097/RLU.0000000000002668 PMID: 31162269

[16] Verma, P.; Malhotra, G.; Goel, A.; Rakshit, S.; Chandak, A.; Chedda, R.; Banerjee, S.; Asopa, R.V. 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*(5), e318-e322. http://dx.doi.org/10.1097/RLU.0000000000002520 PMID: 30829867

[17] Kunikowska, J.; Bartosz, K.; Leszek, K. Glioblastoma multiforme: another potential application for ^{68}Ga-PSMA PET/CT as a guide for targeted therapy. *Eur. J. Nucl. Med. Mol. Imaging,* **2018**, *45*(5), 886-887. http://dx.doi.org/10.1007/s00259-018-3934-2 PMID: 29387926

[18] Malik, D.; Kumar, R.; Mittal, B.R.; Singh, H.; Bhattacharya, A.; Singh, S.K. 68Ga-Labeled PSMA uptake in nonprostatic malignancies: has the time come to remove "PS" from PSMA? *Clin. Nucl. Med.,* **2018**, *43*(7), 529-532. http://dx.doi.org/10.1097/RLU.0000000000002103 PMID: 29688950

[19] Salas Fragomeni, R.A.; Pienta, K.J.; Pomper, M.G.; Gorin, M.A.; Rowe, S.P. Uptake of prostate-specific membrane antigen-targeted 18f-dcfpyl in cerebral radionecrosis: implications for diagnostic imaging of high-grade gliomas. *Clin. Nucl. Med.,* **2018**, *43*(11), e419-e421. http://dx.doi.org/10.1097/RLU.0000000000002280 PMID: 30247210

[20] Sasikumar, A.; Kashyap, R.; Joy, A.; Charan Patro, K.; Bhattacharya, P.; Reddy Pilaka, V.K.; Oommen, K.E.; Pillai, M.R.A. Utility of 68Ga-PSMA-11 PET/CT in imaging of glioma-a pilot study. *Clin. Nucl. Med.,* **2018**, *43*(9), e304-e309. http://dx.doi.org/10.1097/RLU.0000000000002175 PMID: 29939953

[21] Salas Fragomeni, R.A.; Menke, J.R.; Holdhoff, M.; Ferrigno, C.; Laterra, J.J.; Solnes, L.B.; Javadi, M.S.; Szabo, Z.; Pomper, M.G.; Rowe, S.P. Prostate-specific membrane antigen-targeted imaging with [18F]DCFPyL in high-grade gliomas. *Clin. Nucl. Med.,* **2017**, *42*(10), e433-e435. http://dx.doi.org/10.1097/RLU.0000000000001769 PMID: 28737579

[22] Sasikumar, A.; Joy, A.; Pillai, M.R.; Nanabala, R.; Anees K, M.; Jayaprakash, P.G.; Madhavan, J.; Nair, S. Diagnostic value of 68ga psma-11 pet/ct imaging of brain tumors-preliminary analysis. *Clin. Nucl. Med.,* **2017**, *42*(1), e41-e48. http://dx.doi.org/10.1097/RLU.0000000000001451 PMID: 27846000

[23] Unterrainer, M.; Niyazi, M.; Ruf, V.; Bartenstein, P.; Albert, N.L. The endothelial prostate-specific membrane antigen is highly expressed in gliosarcoma and visualized by [68Ga]-PSMA-11 PET: a theranostic outlook for brain tumor patients? *Neuro-oncol.,* **2017**, *19*(12), 1698-1699. http://dx.doi.org/10.1093/neuonc/nox172 PMID: 29045711

[24] Schwenck, J.; Tabatabai, G.; Skardelly, M.; Reischl, G.; Beschorner, R.; Pichler, B.; la Fougère, C. In vivo visualization of prostate-specific membrane antigen in glioblastoma. *Eur. J. Nucl. Med. Mol. Imaging,* **2015**, *42*(1), 170-171. http://dx.doi.org/10.1007/s00259-014-2921-5 PMID: 25293865

[25] Mahzouni, P.; Shavakhi, M. Prostate-specific membrane antigen expression in neovasculature of glioblastoma multiforme. *Adv. Biomed. Res.,* **2019**, *8*, 18. http://dx.doi.org/10.4103/abr.abr_209_18 PMID: 30993088

[26] Matsuda, M.; Ishikawa, E.; Yamamoto, T.; Hatano, K.; Joraku, A.; Iizumi, Y.; Masuda, Y.; Nishiyama, H.; Matsumura, A. Potential use of prostate specific membrane antigen (PSMA) for detecting the tumor neovasculature of brain tumors by PET imaging with ^{89}Zr-Df-IAB2M anti-PSMA minibody. *J. Neurooncol.,* **2018**, *138*(3), 581-589. http://dx.doi.org/10.1007/s11060-018-2825-5 PMID: 29524126

[27] Nomura, N.; Pastorino, S.; Jiang, P.; Lambert, G.; Crawford, J.R.; Gymnopoulos, M.; Piccioni, D.; Juarez, T.; Pingle, S.C.; Makale, M.; Kesari, S. Prostate specific membrane antigen (PSMA) expression in primary gliomas and breast cancer brain metastases. *Cancer Cell Int.,* **2014**, *14*(1), 26. http://dx.doi.org/10.1186/1475-2867-14-26 PMID: 24645697

[28] Saffar, H.; Noohi, M.; Tavangar, S.M.; 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*(1), 45-53. http://dx.doi.org/10.30699/ijp.13.1.45 PMID: 29731795

[29] Wernicke, A.G.; Edgar, M.A.; Lavi, E.; Liu, H.; Salerno, P.; Bander, N.H.; Gutin, P.H. Prostate-specific membrane antigen as a potential novel vascular target for treatment of glioblastoma multiforme. *Arch. Pathol. Lab. Med.,* **2011**, *135*(11), 1486-1489. http://dx.doi.org/10.5858/arpa.2010-0740-OA PMID: 22032578