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Prostate-specific membrane antigen expression in intracranial lesions — a review of the primary, metastatic, and nonneoplastic lesions

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Abstract

Prostate-specific membrane antigen (PSMA) is a membrane protein originally discovered in prostate cancer cells. It is widely used at all stages of prostate cancer diagnosis. Several studies have highlighted its possible wide application in other cancers. This review discusses the potential use of positron emission tomography with labelled PSMA for the diagnosis or differentiation of intracranial lesions. Given the numerous reports on the usefulness of PSMA in the diagnosis of brain tumours of glial origin, the focus is on lesions of a different aetiology.

KEYwords: PET/CT; PSMA; glial tumours; GBM; brain metastases; intracranial lesions

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Introduction

Tumours located intracranially, and even more particularly those located in brain tissue, can cause serious consequences, such as impaired consciousness, epilepsy, paresis, or even death [1, 2]. Brain tumours can be divided into primary and metastatic. Among primary brain tumours, gliomas account for 45–50% of all lesions [3]. Brain metastatic changes are most common from lung cancer (45%), breast cancer (15%), melanoma (10%), and colorectal carcinoma (less than 2%) [4]. Due to its location in the brain tissue, invasive diagnostic methods are severely limited and can cause significant side effects. Non-invasive imaging methods also have some limitations, which is why improvements in current methods or new imaging possibilities are needed. Among the methods of classical radiology, the most commonly used are magnetic resonance imaging (MRI) and computed tomography (CT) [3]; recently, positron emission tomography/computed tomography (PET/CT) with various markers has increasingly been used [5–7]. Of these, prostate-specific membrane antigen (PSMA) seems to be very promising. This review considers its use in the case of intracranial lesions.

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Prostate-specific membrane antigen

Prostate-specific membrane antigen or glutamate carboxypeptidase II is a membrane protein [8]. It is widely used for the diagnosis of prostate cancer (PC) to search for the primary focus, staging, restaging, recurrence, and metastasis diagnosis with the highest sensitivity for PC recurrence among the available imaging methods [9]. A study by Malik et al. [10] points out that PSMA can be used in malignant pathologies other than PC, such as urinary bladder carcinoma, breast cancer, oligodendroglioma, or thyroid cancer. Recently, an increasing number of studies have shown various possibilities for using PSMA in non-prostatic indication, and the focus will be put on intracranial lesions. Due to its structure and numerous synthesized derivatives, it can be labelled with various radiotracers, such as ^{18}F, ^{68}Ga [11], ^{99m}Tc [12], or even ^{89}Zr [13]. This makes PSMA a universal marker and widely available both in places with access to cyclotron or generator-made radioisotopes.

Gliomas

A glioma is a tumour of glial cells of the brain or the spine origin. They account for only a third of all brain tumours but approximately 80% of malignant tumours [14]. According to the 5th edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System, they are a heterogeneous group of tumours divided not only by histopathological features but also by changes in markers or genetic mutations [15]. Histopathologically, they could be divided into low-grade (LGG) and high-grade tumours (HGG), which correspond to the WHO classification G2 *vs.* G3 and G4. HGGs are characterized by a high propensity for infiltration and significant vascularization [16]. Distant metastases from glial tumours are extremely rare, with an incidence ratio of 0.5% [17]. In terms of survival, HGGs have an unfavourable prognosis and a high mortality rate, in contrast to LGGs, which have a better prognosis [18]. MRI is the standard method used to diagnose tumours of glial origin, but new diagnostic methods such as PET/CT are being sought owing to the limited potential of MRI.

Although a review [19] and systematic reviews [20, 21] on the use of PSMA for tumours of glial origin have already been published and proved the usefulness of PSMA, this review includes the most important aspects of glioma diagnosis.

Immunohistochemical PSMA staining

The study by Holzgreve et al. [22] analysed immunohistochemical staining for PSMA in patients with initially diagnosed glioblastoma (GBM) and at relapse. Positive staining was found in both native tumours and in recurrence. PSMA staining was shown in glioblastoma multiforme vessels [23, 24]. However, there are conflicting data on the impact on survival time, in one study the intensity of staining in the vascular compartment correlated negatively with the survival time of patients, in another study no such impact has been noticed [25]. Saffar et al. [26] found a statistically significant association between PSMA staining and tumour grade. The immunohistochemical staining of PSMA in the vessel compartment corresponds with the accumulation of PSMA tracers in PET studies [27].

Glioma suspicions and differentiation

Apart from MRI and other tracers focused on glucose, carbohydrate or cell membrane metabolism, radiolabelled amino acids, or nucleoside analogues, PSMA is considered a potential diagnostic marker in the differentiation of primary brain lesions [28]. In a prospective study of 38 patients with suspected glial tumours, Akgun et al. [29] confirmed statistically significant differences in quantitative parameters of [^{68}Ga]Ga-PSMA PET/MR between WHO G2 and G3 *vs.* G4 tumours [29]. Verma et al. [30] presented a study on the differentiation between HGG and LGG with a [^{68}Ga]Ga-PSMA-11 PET/CT scan. They recruited 10 patients with suspicion of glial tumour in MRI, which was histopathologically proven. PSMA expression was significantly higher in HGG than in LGG. Vallejo-Armenta et al. [31] presented a study with [^{99m}Tc]Tc-iPSMA SPECT brain imaging as a potential specific diagnosis of HGG and brain metastases. They confirmed accumulation in HGG and metastases but not in LGG and benign lesions. The PSMA targeted imaging with [^{18}F]DCFPyL PET/CT was positive in three patients with findings on MRI highly suggestive of glioblastoma multiforme and the final histopathological diagnosis confirmed HGG [32].

Glioma recurrence

A recent systematic review and meta-analysis published by Ninatti et al. [33] demonstrated the usefulness of various markers, mainly ^{11}C-fluoro-ethyl-tyrosine ([^{11}C]FET) and ^{11}C-methionine ([^{11}C]MET), in the diagnosis of GBM recurrence. Despite the inclusion of only one study with PSMA [34], attention was drawn to its potential in future studies. Increased PSMA accumulation has been shown in several studies of HGG recurrence. Kumar et al. [34] presented a prospective study including 30 patients with evidence of HGG recurrence in MRI. The [^{68}Ga]Ga-PSMA-11 PET/CT showed uptake in all found lesions, while the radiation necrosis found on MRI showed no tracer accumulation. Kunikowska et al. [35, 36] and Sasikumar et al. [37] confirmed [^{68}Ga]Ga-PSMA-11 tracer accumulation in the PET/CT study in all lesions of tumour recurrence, which was confirmed by histopathological examination or by radiological follow-up. Sasikumar et al. [37] confirmed the comparability of [^{18}F]FDG and [^{68}Ga]Ga-PSMA-11 in the detection of recurrence, with better tracer accumulation in the lesion compared to the background for PSMA. A single case of glioblastoma recurrence with positive lesions on both [^{18}F]FDG and [^{18}F]FPSMA-1007 scans has been described [38]. A positive lesion with a recurrence of HGG was also noted in PET/CT with [^{89}Zr]Zr-Df-IAB2M anti-PSMA minibody [39]. Examples of glial tumours are shown in Figure 1.

Single cases of PSMA in tumours of glial origin

Other interesting cases can also be found in the literature. In one of those described, high [^{68}Ga]Ga-PSMA-11 uptake was found in the case of gliosarcoma [40]. Another author described an oligodendroglioma with a high accumulation of [^{68}Ga]Ga-PSMA-11 and [^{18}F]Fluciclovine in PET/CT [41]. Finally, a case of pseudoprogression in [^{68}Ga]Ga-PSMA-11 PET/CT has been published [42].

Brain metastases from other malignancies

As mentioned earlier, brain metastases are often diagnosed as pathology in the case of intracranial lesions. Numerous PET/CT studies have been published in patients with PC, and many cases of intracranial metastases of this cancer have been described. According to the frequency of metastases, the literature also reports cases of lung cancer, breast cancer, melanoma, and other less frequent metastases [4]. Due to the indications for PET/CT with PSMA, it should be remembered that for some cancers, these will be accidental findings, and future studies are necessary to assess the usefulness of PSMA in those tumours.

Prostate cancer brain metastases

Typical sites for PC metastases are the bones and lymph nodes, followed by the liver and lungs. The brain is one of the rarer metastatic sites for PC. In the literature are found a few retrospective summaries of the occurrence of such metastases, as well

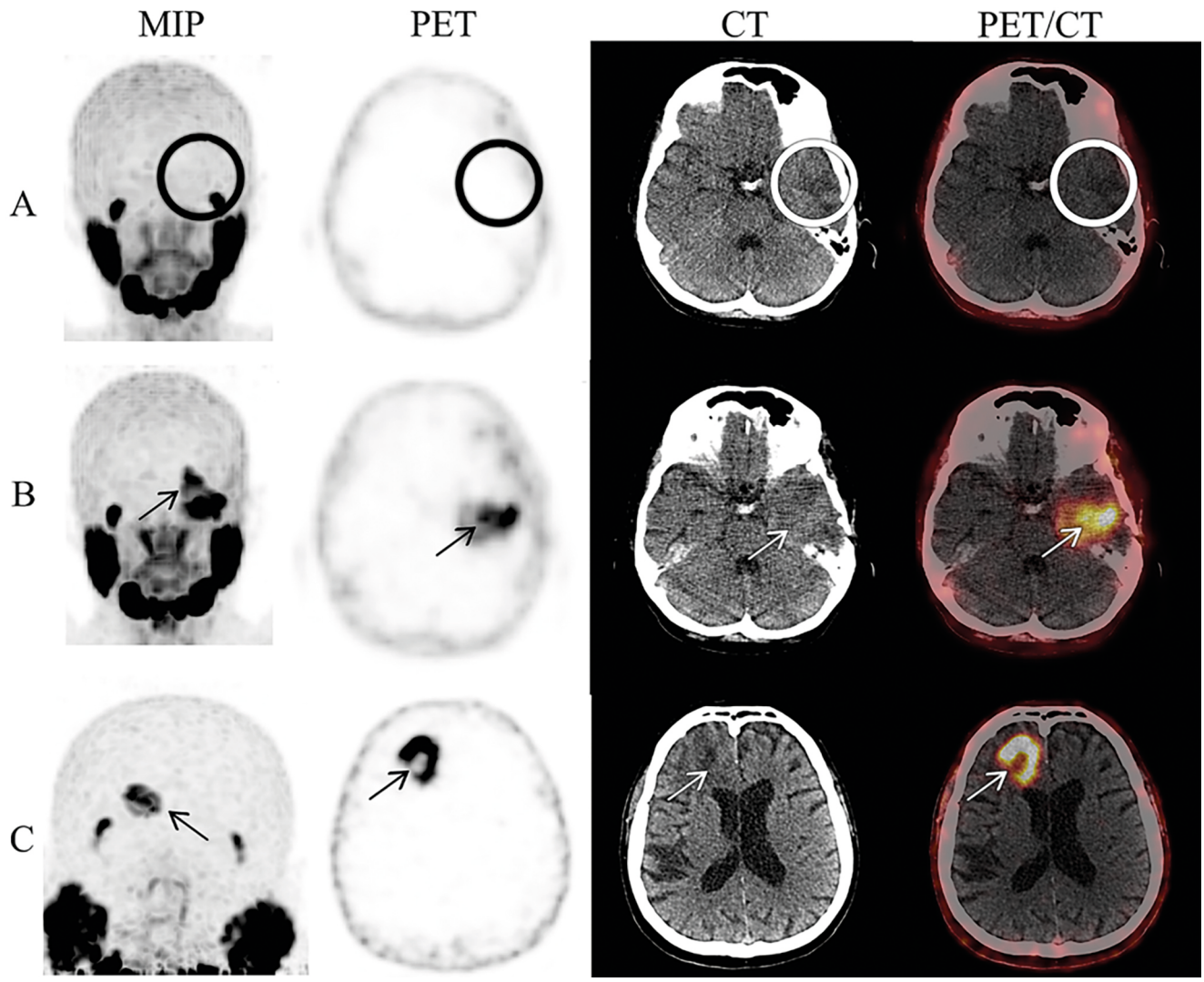

Figure 1. The example images of glial tumours. MIP — maximum intensity projection; PET — positron emission tomography; CT — computed tomography; PET/CT — fused images of PET and CT (authors' own images); **A, B** — 53-years-old woman; **A** — with a primary diagnosis of astrocytoma, IDH-wildtype NEC WHO 2/3 in the left temporal lobe — without accumulation of [^{68}Ga]Ga-PSMA-11 in PET scans (MIP, PET, CT, PET/CT — circles); **B** — after 11 months, with recurrence of glial tumour — glioblastoma, IDH-wildtype WHO 4 in left temporal lobe, with accumulation of [^{68}Ga]Ga-PSMA-11 in PET scans (MIP, PET, CT, PET/CT — arrows); **C** — 72-years-old man with glioblastoma, IDH-wildtype WHO 4 in right frontal lobe, with accumulation of [^{68}Ga]Ga-PSMA-11 in PET scans (MIP, PET, CT, PET/CT — arrows)

as several clinical case descriptions of lesions that turned out to be metastases.

Hatzoglou et al. [43] presented a retrospective analysis of patients with PC seen at their institution between 2000 and 2010. Within 13 547 patients screened *via* MRI, they identified 21 with brain metastases, which led to an incidence of 0.16%. Notably, most of these patients had bone (95%), lymph node (86%), or liver/lung (76%) metastases. McBean et al. [44] obtained similar results in a retrospective analysis of [^{68}Ga]Ga-PSMA PET/CT studies carried out between 2014 and 2020 [44]. The incidence was 0.18% — 8 patients from 4 341 screened — all had extensive metastatic disease. McLaughin [45] presented the latest analysis of [^{68}Ga]Ga-PSMA-11 or [^{18}F]F-DCFPyL PET/CT. They found 44 brain lesions, of which 33 were PSMA positive. The lesions were identified as PC metastases in 14 pts (10 intraparenchymal and 4 dural-based metastases), meningiomas in 16 pts, pituitary macroadenomas in 2 pts, and one with an epidermal inclusion cyst. At the time of parenchymal brain metastasis detection, 57% of patients had no concurrent extracranial disease, 14% had localized prostate disease only, and 29% had extracranial metastases.

In the literature, at least 4 cases of single asymptomatic brain metastases can be found [46–50]. Two cases report present multilocal brain PC metastases of a patient undergoing initial evaluation for newly diagnosed PC who had few brain lesions, apart from primary localization and lymph nodes and bone metastases [51], and one of asymptomatic PC recurrence in the form only of brain metastases [52]. There are two cases of cerebellar metastases with only mild neurological symptoms [53, 54]. One patient with trigeminal neuralgia and no previous history of malignancy had been found to have PC metastases in the brain [55]. Two patients were described with a very rare metastatic site, the orbital location [47], and orbital and brain metastases [56].

In one study, [^{18}F]FDCFPyL PET/CT was used to distinguish radiation necrosis from tumour recurrence after the surgery and radiotherapy of a PC brain metastasis, within the unclear result of the MRI image [57]. The [^{18}F]FDCFPyL PET/CT confirmed recurrence and it was used for monitoring of the brain metastases treatment. It confirmed a good response to the treatment of PC brain metastases after [^{225}Ac]Ac-PSMA-617 treatment [58] and a combination of [^{177}Lu]Lu-PSMA-617 and external radiotherapy [59] in castration-resistant PC patients.

However, it is important to be aware of other brain lesions that can accumulate PSMA in patients with PC. For the two case descriptions of patients with suspension of brain metastases of PC, the final histopathology confirmed lesions of a different origin, a meningioma [60] and a GBM [61].

Lung cancer

Lung cancer is a common cancer that causes distant metastases, including brain metastases [62]. Pei et al. [63] investigated the clinical application of [^{68}Ga]Ga-PSMA-11 PET/CT in 7 patients with lung carcinoma. The study confirmed a traced accumulation in all patients in the primary site and brain metastases, with significantly higher accumulation in metastases. Immunohistochemical staining confirmed intense staining in vessels. One case report presents a man with a synchronous diagnosis of prostate cancer and lung adenocarcinoma who underwent both [^{18}F]FPSMA-1007 and [^{18}F]FDG PET/CT [64]. [^{18}F]FPSMA-1007 PET/CT showed accumulation in a PC, lung, and brain lesion; finally, the brain lesion was interpreted as a lung metastasis. An example of brain metastasis of lung cancer is shown in Figure 2.

Breast cancer

Breast cancer was the most common cancer in 2022 among women in the USA [65]. Despite the existence of recommended preventive examinations, many patients are diagnosed at a more advanced stage of the disease. The occurrence of brain metastases is a poor prognostic parameter [66]. Several publications presented PSMA expression in immunohistochemical staining in a large cohort of breast cancer patients [67–69].

For PET studies, only a few cases confirm PSMA accumulation in brain metastases of breast cancer. A single case of ineffective treatment of brain metastasis of breast cancer presented intense [^{68}Ga]Ga-PSMA PET/CT brain uptake in the supratentorial lesion. Biopsy documented disease progression despite treatment [70]. Marafi et al. [71] presented a case of brain metastasis recurrence in [^{18}F]FDG and [^{18}F]FPSMA-1007 PET/CT in a woman with triple-negative breast cancer. PSMA accumulation was found in the site of recurrence and two suspicious, ambiguous lesions were seen on MRI. Another single case of brain metastasis recurrence of triple-negative breast cancer with low uptake of [^{18}F]FDG and high uptake of [^{68}Ga]Ga-PSMA-11 PET/CT was presented [72].

Melanoma

Hod N. et al. [73] present a case of a man who had a [^{68}Ga]Ga-PSMA PET/CT due to the rising PSA marker of a known PC. They had found a lesion in an area of nonspecific gliotic brain changes, which occurred to be a location of the tumour operated on 2 years earlier. It was a melanoma recurrence.

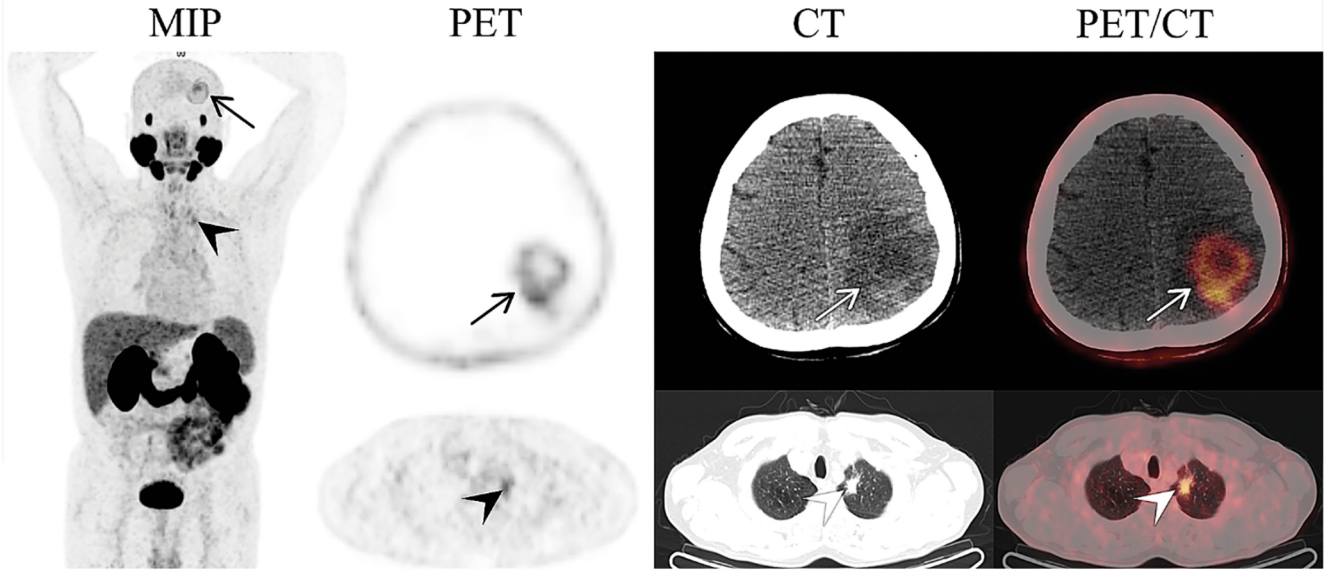

Figure 2. Example images of lung brain metastasis. MIP — maximum intensity projection; PET — positron emission tomography; CT — computed tomography; PET/CT — fused images of PET and CT (authors' own images); A 59-years-old man with lung adenocarcinoma, who was referred for brain surgery due to the suspicious of glial tumour in brain and neurological symptoms. There is a clearly visible focus of [^{68}Ga]Ga-PSMA-11 accumulation in the brain (MIP, PET, CT, PET/CT — arrows), and in the lung tumour (MIP, PET, CT, PET/CT — arrowheads)

Renal cell carcinoma

Renal cell carcinoma (RCC) is the most common primary malignancy of the kidney with various histopathological manifestations [74]. Rowe et al. [75] performed a study with [^{18}F]DCFPyL in 5 patients with clear cell RCC. Within all multisite metastases, one patient had a visible lesion in the brain, which occurred in addition to lymph nodes, lungs, and bones. One case report of a man with RCC who underwent [^{18}F]FPSMA and [^{18}F]FDG PET/CT for restaging after radical nephrectomy showed a cerebellar lesion with increased expression of both tracers, which was confirmed in MRI as a metastatic lesion [76]. One case of a [^{68}Ga]Ga-PSMA PET/CT used to differentiate the recurrence of brain metastasis from radiation necrosis after radiotherapy of RCC brain lesions was presented [77]. Yin et al. [78] performed [^{18}F]DCFPyL PET/CT in 8 patients with metastatic nonclear cell RCC. One patient with unclassified RCC had 3 brain metastases, of which only one demonstrated definitive tracer uptake.

Thyroid carcinoma

Papillary carcinoma is the most common subtype of thyroid cancer. Typically, whole-body iodine scintigraphy is used to diagnose metastasis in the case of rising thyroglobulin levels. Taywade et al. [79] present a case of rising thyroglobulin and negative ^{131}I whole-body scan in a 50-year-old man who was previously treated with surgery and an ablative dose of radioiodine. The [^{68}Ga]Ga-PSMA-11 PET/CT showed multiple lesions in the lymph nodes, lung nodules, bones, and brain. The [^{18}F]FDG scan performed confirmed the location of the lesions but only showed 1 of the 5 foci visible in the previous [^{68}Ga]Ga-PSMA-11 PET/CT scan in the brain.

Gastric carcinoma

Kesim et al. [80] present a case of a man with gastric adenocarcinoma who was referred to [^{68}Ga]Ga–PSMA PET/CT for restaging due to biochemical recurrence of PC. Tracer accumulation has been found in prostate, lymph, and bone metastases. There was also a brain lesion, which was later confirmed on biopsy to be a metastasis of gastric carcinoma.

Dermoid cyst

Dermoid cysts are slow-growing, cystic masses usually diagnosed under the skin of the periorbital location in the paediatric population. Hod et al. [81] presented a rare case of an intracranial lesion with a high accumulation of [^{18}F]FPSMA in a PET/CT of a 68-year-old man who was referred for staging of a newly diagnosed prostate adenocarcinoma. The final diagnosis was a dermoid cyst with long-term asymptomatic survival.

Meningioma

Meningiomas are the most common nonglial tumours and can be diagnosed due to their characteristic appearance on MRI [82]. Usually, they are diagnosed after the 5th decade of life and are often asymptomatic. In the literature, there have been accidental findings during the PET/CT examination with PSMA in the primary staging of PC [83] and in the diagnostic test for recurrence [84] and were also reported in the study by McLaughlin et al. [45]. Similar findings with PSMA-positive meningiomas have been reported by other authors [85–87].

Primary juvenile nasal angiofibroma

Juvenile nasal angiofibroma is a rare benign tumour that can be locally aggressive. Sakthivel et al. [88] presented a pilot study in which [^{68}Ga]Ga-PSMA-11 PET/CT scans were performed in a consecutive series of 25 patients. During this study, all patients had increased tracer accumulation, even in areas of intracranial infiltration. Similarly, previously published case reports had PSMA uptake in intracranial extension [89]. However, in one case, the recurrence of this tumour was negative on PSMA PET/CT [90].

Parotid adenoid cystic carcinoma

Parotid adenoid cystic carcinoma is the most common malignant secretory gland tumour in the head and neck region. The tumour is characterized by an indolent growth rate, locoregional recurrence, and distant metastasis, usually in the lungs. A study of a consecutive group of 9 patients was performed [91]. The [^{68}Ga]Ga-PSMA-11 PET/CT was able to visualize local recurrence and/or distant metastases in all cases. In one case, nasopharyngeal recurrence and leptomeningeal metastasis were confirmed. Gupta et al. [92] present a case of a woman with known adenoid cystic carcinoma with metastases in the lungs. After another line of treatment, PET/CT with [^{18}F]FDG indicated metastases in the lungs; however, [^{68}Ga]Ga-PSMA PET/CT revealed additional focal uptake in the right cerebellum, which was then confirmed as metastases by MRI.

Other non-malignant lesions

In the literature, there are also case reports showing the accumulation of PSMA in the case of noncancerous lesions located intracranial. They are extremely rare, but they should be taken into consideration when differentiating an incidentally found lesion.

Stroke/infarction

A stroke is a medical condition in which poor blood flow caused by a lack of blood flow or bleeding causes brain cell death. In the literature can be found a few case reports of positive PSMA accumulation in areas affected by infractions. Chan et al. [93] reported a case of an 85-year-old man with a high-risk PC who was referred for staging in [^{68}Ga]Ga-PSMA-11 PET/CT. Apart from focal uptake in the prostate, an additional focus of PSMA uptake was seen in the left cerebral hemisphere, which was verified in MRI as a subacute infarct of an embolic nature. Noto et al. [94] showed a case of a man with disseminated bone metastases of prostate cancer who was referred for [^{68}Ga]Ga-PSMA-11 PET/CT to exclude visceral metastases before treatment of bone metastases with ^{223}Ra-dichloride. The [^{68}Ga]Ga-PSMA-11 PET study revealed focal cerebral tracer uptake in the right frontal lobe, which was finally diagnosed as a cerebral infarction due to the patient's history of infarction 14 days before imaging. Oh et al. [95] showed a case of right cerebral hemisphere subacute infarction with [^{68}Ga]Ga-PSMA-11 uptake in patients with

PC local recurrence. The site corresponded to the infraction shown on the MRI of the brain performed 35 days previously.

Neurocysticercosis

Neurocysticercosis is a form of the infectious parasitic disease cysticercosis that is caused by a brain infection with Taenia solium. Vadi et al. [96] present a case of a 56-year-old man with PC who was referred for [^{68}Ga]Ga-PSMA PET/CT for restaging. In the study, multiple cystic lesions with enhancing peripheries with tracer accumulation were noticed in the brain [96]. The CT re-elevated the presence of an eccentrically located hyperdense nodule representing the scolex. It was recognized as neurocysticercosis.

Tuberculosis

Tuberculosis is an infectious disease usually caused by *Mycobacterium tuberculosis* bacteria, which affects the lungs, but it can also affect other regions. A case of a man referred for a [^{68}Ga]Ga-PSMA-11 PET/CT scan for suspected PC recurrence was presented by Wong et al. [97]. The study revealed dura-based hyperdense lesions with tracer accumulation in the brain. A biopsy was performed on suspicion of metastatic PC, which demonstrated the presence of acid-fast bacilli — *Mycobacterium tuberculosis*.

Conclusion

As numerous studies have shown, PSMA is becoming an increasingly widely used tracer, not only for lesions originating from the prostate gland. Studies show its usefulness in the primary diagnosis of brain tumours of glial origin, their recurrence after treatment, as part of staging differentiation, or after radiation necrosis. Among intracranial lesions, tumour metastases of prostate cancer, lung cancer, breast cancer, melanoma or gastric cancer have been described. PET/CT with radiolabelled PSMA showed increased accumulation in head and neck tumours such as meningioma, dermoid cyst, juvenile nasal angiofibroma, or parotid adenoid cystic carcinoma. In differentiating the lesions found, it is also important to consider noncancerous lesions such as poststroke lesions or caused by parasites or bacteria. Descriptions of single cases of tracer-accumulating lesions with PSMA are increasingly reported in the literature. This may result in further studies, which may translate into the establishment of wider indications for PET studies with this 'prostate-specific' tracer.

Article information and declarations

Author contributions

The study conception and design were done by Kacper Pełka and Jolanta Kunikowska. Material preparation, data collection and were performed by Kacper Pełka and Aleksandra Bodys-Pełka. The first draft of the manuscript was written by Kacper Pełka and Aleksandra Bodys-Pełka. All authors commented on all versions of the manuscript, read, and approved the final manuscript.

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Conflicts of interest

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Supplementary material

None.

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