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EDITORIAL

A look into the future: the role of PSMA beyond prostate cancer

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Prostate-specific membrane antigen (PSMA) is a transmembrane aminopeptidase with catalytic activity, encoded by the FOLH1 (folate hydrolase 1) gene [1], consisting of a large extracellular domain, a small transmembrane domain, and a short cytoplasmic tail [2]. This protein is physiologically expressed in both prostatic epithelial cells and other healthy tissues, including the renal cortex, duodenum, ileum, salivary and lacrimal glands, coeliac, and stellate ganglia [3]. PSMA is involved in folate and glutamate uptake, metabolism, and signalling, and it plays a role in several processes, including the promotion of excitatory neural transmission in glial cells and the uptake of dietary folates in the duodenum [4]. Nevertheless, the physiological function of PSMA in the prostate is less clear, although it is suggested to contribute to genomic stability [5]. The complex regulation of PSMA involves different molecular pathways including the androgen receptor, DNA damage response, and PI3K/Akt/mTOR signalling pathways [6]. Moreover, PSMA might be involved in cancer-related angiogenesis, playing a role in extracellular matrix degradation, tumor invasion, and integrin signal transduction [7]. Prostate cancer cells have up to 1000-fold higher PSMA expression than benign tissue. Previous studies reported an enhanced PSMA expression in high-grade or metastatic disease, whereas low PSMA levels were found in low-risk disease [3]; in addition, elevated PSMA expression was associated with hormone-refractory prostate cancer [8], poor clinical outcome [9], and the presence of deficient DNA damage repair pathways [5]. These findings promoted theranostic applications of radio-labelled PSMA ligands that reached an established role in the management of prostate cancer [6, 10–12]. Furthermore, increased PSMA expression has also been found in the neovascular endothelial cells of various malignancies, including renal clear cell carcinoma, hepatocarcinoma, salivary gland cancer, and glioblastoma [13], raising the possibility of PSMA-targeting in many other tumors.

In a recent issue of the European Journal of Nuclear Medicine and Molecular Imaging, Souza et al. [14] investigated the role of [^{68} Ga]Ga-PSMA-11 PET/CT imaging for the identification of multiple myeloma (MM) lesions in 20 consecutive patients with the pathologically proven disease. In particular, the authors compared [^{18}F]FDG PET/CT and [^{68} Ga]Ga-PSMA-11 PET/CT image findings in MM patients. They found that [^{18}F]FDG PET/CT and [^{68} Ga]Ga-PSMA-11 PET/CT scans were able to identify a total of 266 lesions in 19 out of 20 patients. [^{18}F]FDG PET/CT scan detected 84% of all lesions in 17 patients, while [^{68} Ga]Ga-PSMA-11 PET/CT scan detected 71% of all lesions in 19 patients. Moreover, a good concordance was found between the number of lesions (ICC = 0.748), the number of soft tissue lesions (ICC = 0.920), and the highest SUVmax values (ICC = 0.782) for the two tracers. This well-designed and elegantly conducted study by Souza et al. [14] provides for the first time systematic data for the application of PSMA imaging in MM patients. In the literature, there were only case reports showing the detection of MM lesions by [^{68} Ga]Ga-PSMA-11 [15–17]. These findings open up new diagnostic and therapeutic perspectives for MM patients. In fact, despite the recent advances in therapeutic strategies, MM is still an incurable disease characterized by markedly heterogeneous biological behavior, with wide inter- and intra-patient variability and different clinical outcomes [18]. Although [^{18}F]FDG PET/CT scan allows the detection of the heterogeneous characteristics of MM lesions by simultaneously providing morphological and metabolic information on the status of the disease [19], image interpretation may be difficult in some patients due to the possible occurrence of false positive or false negative findings [20]. Interestingly, in the study by Souza et al. [14], a [^{68} Ga]Ga-PSMA-11 scan alone was able to detect most bone and soft tissue MM lesions with minimal or no [^{68} Ga]Ga-PSMA-11 uptake in areas of confirmed benign [^{18}F]FDG uptake. Furthermore, the absence of physiological brain uptake of [^{68} Ga]

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Ga-PSMA-11 made it easier to identify MM lesions in the skull as compared to [^{18}F]FDG. In addition, the authors also suggested the possible complementary role of [^{68} Ga] Ga-PSMA-11 PET/CT and [^{18}F]FDG PET/CT scans due to the different uptake mechanisms of the two tracers based on the occurrence of neoplastic angiogenesis for PSMA-ligands and the expression of glycolytic phenotype for [^{18}F]FDG.

Although the authors state that no [^{68} Ga]Ga-PSMA-11 uptake was detected in normal bone marrow, it would be interesting to evaluate whether diffuse bone marrow [^{68} Ga]Ga-PSMA-11 uptake is present in these patients and whether there is a correlation with the plasma cell bone marrow infiltration. In addition to focal lesions, the characterization of diffuse bone marrow involvement may contribute to the staging, evaluation of treatment response, and prognosis of MM patients. Moreover, volumetric PET-based parameters, such as metabolic tumor volume and total lesion glycolysis, that are established [^{18}F]FDG prognostic factors not only in MM patients [21] but also in solid tumors [22, 23], could be calculated on PSMA images to improve the risk and prognostic stratification of MM patients. It would also be interesting to investigate why MM lesions are detected by PSMA imaging. The authors hypothesized that [^{68} Ga]Ga-PSMA-11 uptake in MM lesions is due to neoplastic angiogenesis. However, PSMA also plays an important role in folate metabolism. Malignant plasma cells may be dependent on folate metabolism to comply with their proliferative needs since folate is an important factor in DNA synthesis and methylation [24]. In this respect, plasma cells and other cancer cells show an overexpression of the folate receptor as a consequence of their increased folic acid requirement [25]. Alternative uptake mechanisms of PSMA should be further investigated in the future.

The article by Souza et al. [14] opens new therapeutic perspectives in MM patients due to the theranostic applications of PSMA ligands. In this regard, the choice of the treatment option should take into account the recent clinical introduction of new agents, such as belantamab mafodotin and the more established use of daratumumab targeting specifically plasma cells. Further investigations are needed to identify the clinical context in which PSMA ligands may provide the best therapeutic benefit.

In conclusion, PSMA PET/CT imaging is emerging as a reliable imaging modality not only for prostate cancer patients but also for other solid and lymphoproliferative malignancies. This scenario could lay the foundations for the theranostic applications of PSMA ligands in the management of different malignancies, allowing to achieve more personalized therapies in individual patients.

Declarations

Ethical approval Institutional review board approval was not required because the paper is an editorial.

Consent to participate Not applicable.

Conflict of interest The authors declare no competing interests.

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