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EDITORIAL

Standardisation of PSMA images interpretation: why do we need it?

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The contribution of molecular imaging in prostate cancer (PCa) is increasing, especially for positive emission tomography (PET). While several radiopharmaceuticals (including ^{11}C-choline or ^{18}F-choline, ^{18}F-fluciclovine and ^{11}C-acetate among the others) have been proposed for investigating PCa and its metastatic sites over the last decade, highly successful approaches to measure the expression of the prostate-specific membrane antigen (PSMA) have been introduced recently [1]. Small, highly specific, urea-based inhibitors have been developed to target the catalytic site of PSMA in extracellular domain. The first radiopharmaceutical released (PSMA-HBED-CC) was labelled with ^{68}Ga (^{68}Ga-PSMA-11) and quickly evolved to the most commonly used radiotracer for PSMA-based PET imaging [1, 2]. ^{68}Ga-PSMA-11 is currently undergoing extensive clinical evaluations and initial results attested a high accuracy for disease detection compared to conventional radiology or other nuclear medicine procedures [2]. Prospective clinical trials designed to determine whether PSMA PET can improve outcome in PCa patients are still on-going (e.g., NCT03582774 UCLA-IRB#18-00484). Hence, the diagnostic performance of PSMA PET (either PET/CT or PET/MRI) has been tested so far in retrospective analysis or in single-centre prospective registry study. Despite this limitation, level 2b evidence for superior detection rates in the early stage of biochemical recurrence after radical surgery led to a Grade A recommendation for PSMA-ligand PET/CT by the European Association of Urology [3].

The clinical relevance of PSMA PET for investigating PCa includes a high signal–background ratio for improved tumour detection, especially, but not exclusively, in the recurrence setting. Furthermore, the favourable PSMA biodistribution usually makes images easier to read and interpret. Despite high performance, PSMA PET imaging is not exempt from false-positive findings and pitfalls. The physiological PSMA uptake in pre-sacral, coeliac and stellar ganglion might represent a difficult challenge for readers with low level of expertise. While, PSMA uptake in inflammatory processes, benign osseous processes or tumour neovasculature of non-prostate malignancies can lead to incorrect interpretation of the images [1]. It is interesting to note that, despite PSMA PET already proved its accuracy to detect systemic visceral metastasis, uncommon metastatic sites are usually interpreted as false positive [4]. The preconception that soft tissue or organ metastases are rare in PCa (especially in early stages of recurrence) might explain the reason why these findings are usually misinterpreted.

As a consequence, consensus of images interpretation is necessary to provide comparability between clinical trials and to meet upcoming clinical diagnostic needs. While research reporting tools need to be reproducible and accurately allow for stratification of patient cohorts or to provide the structure for pooling of data, clinical diagnostic reporting tools need to be simple and adaptable to specific clinical situations. Harmonisation of PSMA PET images interpretation is also needed to communicate the exact locations of findings to referring physicians, to support clinician therapeutic management decisions, as happens for metastasis-directed therapy. Thus, interobserver agreement is an important aspect of clinical applicability.

Two studies regarding the development of standardised image interpretation for ^{68}Ga-PSMA PET/CT were recently published [5, 6]. Both studies involved centres with significant prior experience with PCa imaging in general and, specifically, with experience of ^{68}Ga-PSMA PET/CT. The first study published was promoted and funded by European Association of Nuclear Medicine (EANM) [5]. Rather than producing a consensus statement based on opinion, Fanti et al. [5] applied the Delphi approach recruiting the expertise of seven international PET facilities. This approach enabled the development of harmonised

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guidelines for the interpretation of abnormalities identified by ^{68}Ga-PSMA-11 PET/CT. The results during the Delphi process suggested that most cases of disagreement between readers were related either to extremely subtle abnormalities of uncertain significance or differing interpretation of the nomenclature appropriate for describing the abnormalities observed. Accordingly, expert readers are more likely to provide reliable and reproducible advice in their report conclusion regarding the presence of significant abnormality that would either guide treatment or direct further investigation. The prostate was the most challenging site for interpretation, especially in case of anatomic changes related to radical surgery or radiotherapy. Readers also agreed that the presence of radioactive urine in the urethrovesical anastomosis or in the base of the bladder is one of the potential limitations of ^{68}Ga-PSMA-11 PET/CT. However, observers agreed substantially or almost perfectly in the detection of nodal or systemic metastases. Similar results have been described by Fendler et al. [6]. Authors evaluated prospectively the interobserver agreement for ^{68}Ga-PSMA-11 PET/CT interpretations and compared findings among readers with various levels of experience. Notably, in all cases, a standard of reference to validate PSMA PET findings has been provided (50% of cases had histologic verification). This study demonstrated that readings are highly reproducible for high-experienced and intermediate-experienced observers. Conversely, low-experienced observers provided highly reproducible reads for bone metastases but achieved lower agreement for local tumour, lymph node, and organ metastasis assessments. However, both visual and semiquantitative ^{68}Ga-PSMA-11 PET/CT interpretations in prostate cancer patients are highly reproducible among observers with intermediate and high experience. According to the results proposed in this study, initial training is required to achieve an acceptable reader performance.

Considering the potential applications of PSMA ligands in the management of PCa, the precise description and classification of PSMA PET/CT findings are crucial both for clinical needing (e.g., definition of disease extension, tailoring therapy or assessing the response to systemic therapy) and research purposes (e.g., facilitating pool of data in multicentre clinical trials, comparison of performance characteristics between two studies or performing meta-analysis). In this context, the clinical–pathological TNM classification of malignant tumours is the most widely used PCa staging system, while the Reporting and Data System (RADS) is a quality assurance tool applied to pre-therapy initial diagnosis of primary prostate cancer, generally applied to magnetic resonance imaging (MRI).

Recently, two studies proposed different approaches to facilitate PCa reporting and classification, incorporating PSMA PET into two existing systems of tumour diagnosis and staging classifications. These studies are identified as PSMA-RADS (authors incorporated PSMA findings into RADS) [7] and molecular imaging TNM (miTNM) (authors incorporated PSMA findings into TNM classification) [8]. PSMA-RADS proposes a standardised method to allow for an accurate and efficient means of relaying findings to referring providers and facilitate the collection of data for large prospective trials. The study proposes reporting a reader level of certainty regarding PSMA PET findings using a 5-point scale (PSMA-RADS-1, benign; PSMA-RADS-2, likely benign; PSMA-RADS-3, equivocal; PSMA-RADS-4, prostate cancer highly likely; PSMA-RADS-5, prostate cancer almost certainly). PSMA-RADS is proposed for categorization of findings outside the prostate in pelvic or distant metastatic disease and does not address primary prostate cancer [7]. miTNM serves to provide standardised reporting of the presence, location, and extent of local PCa and pelvic diffusion; the presence, location, extent, and distribution pattern of extrapelvic metastases; the PSMA expression level of tumour lesions; the diagnostic confidence about reported findings. To support acceptance, implementation, and correlation, definitions for the PSMA PET miTNM framework were designed in analogy with the clinic–pathologic TNM classification. miTNM organises the staging of whole-body prostate cancer by including information on exact location, pattern of disease distribution, PSMA expression, and level of certainty. Thus, miTNM aims to aid information exchange by unifying clinical and research reporting of PSMA-ligand imaging [8]. The main advantage of these classifications is related to the incorporation of these reporting system into multi-centre prospective clinical trials aimed to evaluate the efficacy of PSMA PET imaging in PCa. While miTNM addresses the anatomic regional definition of primary disease and recurrence, PSMA-RADS delineates the observer level of certainty regarding PSMA PET findings for metastatic disease.

The development of consensus guidelines regarding the interpretation of PSMA PET images may contribute to provide more consistent clinical reports in clinical practice. The standardisation of PSMA images interpretation may also contribute to increase the data reproducibility within clinical trials and improve on the comparison between PSMA PET with other imaging modalities. Defined criteria for interpreting PSMA PET images would help in improving accuracy, precision and repeatability of this diagnostic procedure, thus increasing its chance to have a leading role in oncology guidelines and in the clinical management of PCa patients.

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest. Authors contributed equally to the conception discussion and writing of this paper. This paper does not report studies on human subjects or animals performed by the authors.

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