Clinical and Translational Imaging (2019) 7:377–379
https://doi.org/10.1007/s40336-019-00348-x

EDITORIAL

PSMA-PET/CT imaging in prostate cancer: why and when

Francesco Ceci[1] · **Stefano Fanti**[2]

Published online: 15 November 2019

Keywords PSMA prostate · PSMA-PET/CT · PSMA nomogram · Radioligand therapy · PSMA radiotherapy

Prostate-specific membrane antigen (PSMA) is considered, at present, one of the most successful targets for imaging and therapy in nuclear medicine. PSMA is a glycoprotein, a membrane-bound metallo-peptidase, encoded by FOLH1 gene on chromosome 11. The protein acts as a glutamate carboxypeptidase on different alternative substrates, including the nutrient folate and the neuropeptide *N*-acetyl-L-aspartyl-L-glutamate (NAAG), and is expressed in a number of organs including the prostate and kidneys, as well as the nervous system [1]. PSMA is upregulated in prostate cancerous cells and is used as an effective diagnostic and prognostic biomarker of prostate cancer (PCa). It has been shown that this overexpression is present in 90–100% of PCa cells, making PSMA a reliable tissue biomarker for PCa functional imaging. PSMA expression levels increase according to the stage and tumor grade as well as to aneuploidy and biochemical recurrence. More important PSMA expression is upregulated when tumor becomes androgen independent, and during anti-androgen therapy (ADT) [2]. This characteristic makes PSMA expression assessment particularly attractive, potentially useful as an early indicator of progression and tumor heterogeneity in castration-resistant prostate cancer (CRPC).

The localization of the catalytic site of PSMA in the extracellular domain has allowed the development of very small and very specific urea-based PSMA inhibitors that, once radioactively labeled, can be used as radiopharmaceuticals for Positron Emission Tomography (PET) imaging [1]. Considering all these biological and biochemical favorable characteristics, PSMA-based PET/CT imaging holds a key role among the new-generation imaging techniques [3].

The most updated guideline released by the European Association of Urology (EAU) [3] suggests the use of PSMA-PET/CT imaging in any case of biochemical recurrence, i.e., PSA > 0.2 ng/mL, after radical prostatectomy. This recommendation reaches a strong level of evidence, namely when PSMA-PET/CT scan allows the optimization of the treatment strategy. Thus, the assessment of possible recurrence after radical therapy is the main field of application of PSMA imaging. In this scenario, the superior diagnostic accuracy of PSMA-PET/CT compared to "direct competitors", such as Choline-PET/CT has already been proven [1, 3]. The main advantage of a receptor-based radiopharmaceutical, such as PSMA, compared to a metabolic one, such as choline or fluciclovine, is related to the higher target-to-background ratio in PSMA-PET/CT scans, which results in superior sensitivity and high inter-reader agreement [4, 5]. These considerations were highlighted in a recently published prospective study, comparing fluciclovine-PET/CT and PSMA-PET/CT, that allowed to demonstrate a significantly higher accuracy of PSMA-PET/CT vs. fluciclovine-PET/CT in PCa patients in the first biochemical recurrence after surgery, thus suitable for salvage therapy [5]. However, even though PSMA-PET/CT allows detecting sites of recurrence earlier than fluciclovine-PET/CT, the implications on the oncological outcomes and the real cost-effectiveness of this imaging procedure is still unknown. Also whether or not PET/CT-positive metastasis-directed therapy improves progression-free or overall survival remains unclear [5]. Randomized clinical trials of standard salvage radiotherapy vs. PSMA-PET/CT-based salvage radiotherapy (NCT03582774) and fluciclovine-PET/CT-based vs. PSMA-PET/CT-based

Francesco Ceci and Stefano Fanti contributed equally to writing and editing this paper.

✉ Francesco Ceci
francesco.ceci@unito.it

[1] Nuclear Medicine Unit, AOU Città della Salute e della Scienza di Torino, Department of Medical Sciences, University of Turin, Corso AM Dogliotti, 14, 10126 Turin, Italy

[2] Metropolitan Nuclear Medicine, S.Orsola-Malpighi University Hospital, University of Bologna, Bologna, Italy

salvage radiotherapy (NCT03762759), both powered for outcome, are ongoing.

However, despite optimal performance to detect PCa metastatic location(s), PSMA-PET/CT imaging is not exempt from false-negative results. In the very early stage of biochemical recurrence, roughly half of the scans may be negative [4, 6].

PCa hormone-sensitive patients at their first PSA relapse after radical therapy represent a very challenging population, mostly composed by subjects with oligo-metastatic disease and with a non-negligible incidence of micro-metastatic disease undetectable by any imaging procedures. This is a key point since men with recurrent disease represent a highly heterogeneous population, carrying different prognosis and different profiles of disease aggressiveness. Therefore, selecting the most suitable candidates for PSMA-PET/CT imaging is critical to optimize its use and to avoid expensive and potentially unnecessary staging procedures in low-risk patients. In this scenario, predictive nomograms may represent comprehensive useful tools for the most appropriate use of PSMA-PET/CT. To this end, an accurate comprehensive model that includes pathologic variables (ISUP grade), biochemical features (PSA, PSA kinetics, ongoing ADT, time to relapse) and different clinical settings of PSA relapse has been proposed [7]. By allowing to identify patients with high probability of being positive at a PSMA-PET/CT scanning, this nomogram might help physicians to identify suspicious PCa recurrence(s) and also to adjust subsequent treatment strategies. Conversely, expensive procedures, often unable to provide definite answers regarding the presence of recurrence, may be avoided when the likelihood of positive PSMA-PET/CT is low. According to this statistical model, patients receiving a score corresponding to a likelihood $\geq 40\%$ (nomogram best cut-off value) may benefit from PSMA-PET/CT imaging, revealing clinical net benefit across the entire range of threshold probabilities. On the contrary, patients with likelihood $< 40\%$ should be counseled to avoid PSMA-PET/CT imaging. The use of this statistical model (based on PSA, PSA kinetics and ISUP grade) allows identifying those subjects that are more likely to be affected by a more aggressive disease and higher tumor burden and that are likely to receive a beneficial impact on treatment by a PSMA-PET/CT scan.

Patients with biochemical disease persistence (PSA > 0.1 at 6 weeks after surgery) represent a subpopulation with residual malignant tissue after the primary therapy. These patients generally have a worst outcome compared to patients who have undetectable PSA levels after surgery. In this context, it has been shown that PSMA-PET/CT has a favorable performance regardless of the PSA absolute value, and that PCa metastatic location(s) can be detected in approximately two-thirds of patients with high-risk features and PSA persistence after prostatectomy [4, 7, 8]. As a consequence, biochemical persistence is a condition that should be carefully investigated with new-generation imaging procedures, in view of the high probability to detect the residual disease and the possibility of using a wide range of salvage therapies.

The residual disease after radical prostatectomy might be related to an initial underestimation during the staging procedures prior to surgery and, although EAU guidelines do not suggest at present the use of PSMA-PET/CT in this setting [3], new-generation imaging procedures might positively impact the management of intermediate- and high-risk PCa patients, namely in the evaluation of nodal involvement. Recently, Ferraro et al. [9] proposed a model to predict lymph node metastases in intermediate or high-risk PCa and to assess the added value of PSMA-PET/CT in comparison with current clinical nomograms for risk assessment of nodal disease. The results of this study indicate that risk prediction of nodal metastases obtained using PSMA-PET/CT scanning information has the potential to improve patient selection for extended pelvic lymph node dissection (ePLND). Accordingly, at least high-risk PCa patients might be counseled to undergo PSMA-PET/CT imaging for staging prior to primary treatment.

Finally, one of the most interesting fields of application of PSMA-PET/CT is that of advanced PCa. When CRPC condition occurs, patients are usually staged with conventional imaging (such as contrast-enhanced CT or bone scintigraphy) to differentiate between non-metastatic (nmCRPC) vs. metastatic CRPC (mCRPC) since treatment strategy differs in these two conditions. New androgen-receptor-targeted therapies (e.g., abiraterone acetate, enzalutamide, apalutamide, darolutamide) are generally allowed in mCRPC only. However, as recently pointed out by Fendler et al. [10], PSMA-PET/CT allows detecting metastatic lesions in nearly all nmCRPC patients negative at conventional imaging and, in their patient-series, systemic disease (bone or visceral) was detected in the majority of patients previously diagnosed with nmCRPC.

Furthermore, like other receptor-targeting radiopharmaceuticals, PSMA is an excellent theragnostic agent [10, 11] offering the possibility to highlight PCa lesions by PET/CT imaging, and subsequently to irradiate metastatic sites with personalized doses by use of high-energy beta or alpha particle emitters (radioligand therapy [RLT]). The PSMA extracellular domain contains an internalization motif resulting in its internalization and endosomal recycling which increases the deposition of binding substrates leading to enhanced tumor uptake and retention and a high local dose for therapeutic applications. Promising results of PSMA-RLT have been shown already, mainly obtained in academic, non-commercial research setting in the USA and Europe; these results have recently been translated into clinical practice through the courage and efforts of treating physicians and

their patients. At present, a worldwide industry-sponsored phase III trial is ongoing (NCT03511664) and these results will hopefully clarify whether or not this new-generation treatment can be implemented in the pipeline of drugs available for advanced-stage PCa patients.

In conclusion, PSMA-based PET/CT imaging should be the procedure of choice in case of biochemical recurrence, namely when PSMA-PET/CT scanning allows the optimization of the treatment strategy. However, to avoid a high incidence of false-negative scan, prediction nomograms might guide physician in selecting the most suitable candidates for PSMA-PET/CT imaging and to optimize its use. Patients with biochemical persistence after radical surgery represent an interesting subset, considering both the presence of residual disease and the high performance of PSMA-PET/CT in this setting. To reduce the incidence of residual disease after surgery, PSMA-PET/CT should be considered also in patients with intermediate- and high-risk PCa prior to radical prostatectomy. Finally, PSMA is an excellent theragnostic agent offering the possibility to highlight PCa lesions by PET/CT imaging, and subsequently to irradiate metastatic sites with beta or alpha particle emitters.

Compliance with ethical standards

Conflict of interest Francesco Ceci declares that he has no conflict of interest. Stefano Fanti declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Fendler WP, Eiber M, Beheshti M et al (2017) (68) Ga-PSMA PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging 44(6):1014–1024
2. Emmett L, Yin C, Crumbaker M et al (2019) Rapid modulation of PSMA expression by androgen deprivation: serial (68) Ga-PSMA-11 PET in men with hormone-sensitive and castrate-resistant prostate cancer commencing androgen blockade. J Nucl Med 60(7):950–954
3. Mottet N, van der Bergh RCN, Briers E, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. EAU Guidelines. Edn.In: presented at the EAU Annual Congress Barcelona 2019. ISBN 978-94-92671-04-2
4. Ceci F, Castellucci P, Graziani T et al (2019) (68)Ga-PSMA-11 PET/CT in recurrent prostate cancer: efficacy in different clinical stages of PSA failure after radical therapy. Eur J Nucl Med Mol Imaging. 46(1):31–39
5. Calais J, Ceci F, Eiber M (2019) (18)F-fluciclovine PET-CT and (68)Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol. 20(9):1286–1294
6. Farolfi A, Ceci F, Castellucci P et al (2019) (68)Ga-PSMA-11 PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy and PSA < 0.5 ng/ml. efficacy and impact on treatment strategy. Eur J Nucl Med Mol Imaging 46(1):11–19
7. Ceci F, Bianchi L, Borghesi M et al (2019) Prediction nomogram for (68)Ga-PSMA-11 PET/CT in different clinical settings of PSA failure after radical treatment for prostate cancer. Eur J Nucl Med Mol Imaging. https://doi.org/10.1007/s00259-019-04505-2 **[Epub ahead of print]**
8. Farolfi A, Gafita A, Calais J et al (2019) (68)Ga-PSMA-11 Positron emission tomography detects residual prostate cancer after prostatectomy in a multicenter retrospective study. J Urol. https://doi.org/10.1097/JU.0000000000000417
9. Ferraro DA, Muehlematter UJ, Garcia Schüler HI et al (2019) (68)Ga-PSMA-11 PET has the potential to improve patient selection for extended pelvic lymph node dissection in intermediate to high-risk prostate cancer. Eur J Nucl Med Mol Imaging. https://doi.org/10.1007/s00259-019-04511-4 **[Epub ahead of print]**
10. Fendler WP, Weber M, Iravani A et al (2019) Prostate-specific membrane antigen ligand positron emission tomography in men with nonmetastatic castration-resistant prostate cancer. Clin Cancer Res. https://doi.org/10.1158/1078-0432.ccr-19-1050 **[Epub ahead of print]**
11. Ceci F, Herrmann K, Hadaschik B, Castellucci P, Fanti S (2017) Therapy assessment in prostate cancer using choline and PSMA PET/CT. Eur J Nucl Med Mol Imaging. 44(Suppl 1):78–83