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# Current and emerging clinical applications of PSMA-PET diagnostic imaging for prostate cancer

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**ABSTRACT**

Prostate-specific membrane antigen (PSMA) is highly expressed on most prostate cancer (PCa) cells and several PSMA ligands for PET imaging (PSMA-PET) are now available worldwide. $^{68}$Ga-PSMA-11 has already received American Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval, and PSMA-PET is currently suggested by several international guidelines to investigate PCa in different clinical settings. In primary PCa, PSMA-PET has been shown to be superior to cross-sectional imaging for the detection of pelvic lymph nodes and distant metastases with subsequent clinical management changes. Additionally, it might also have a role in intraprostatic tumor localization, especially when combined with multiparametric MRI. In a setting of PCa recurrency higher detection rates were observed when compared to all other available imaging techniques, especially at low PSA values. Furthermore, PSMA-PET consistently led to a shift in clinical management, thus increasing the proportion of radiotherapy, surgery, or other focal therapies at the expense of systemic options and/or no treatment. In oligometastatic disease after radical surgery, PSMA-PET may be relevant in guiding a metastases-directed therapy approach, as preliminary data seem to suggest a benefit in terms of progression-free survival after treatment of PSMA-PET positive lesions. As a staging and gatekeeping technique, it represents a reliable whole-body imaging procedure in combination with second-line therapy of castration-resistant PCa (CRPC) as well as pivotal when assessing patients eligible for radioligand therapy such as $^{177}$Lu-PSMA. This critical review aims at providing a comprehensive overview of the latest literature on the current (or emerging) main indications as well as a general outlook of the recommended interpretation criteria while reading PSMA-PET imaging.

## INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in men, and is associated with high morbidity and mortality rates [1]. MRI and different PET radiotracers have been extensively employed to improve the accuracy of Conventional Imaging (CI), namely CT and Bone Scintigraphy, at all times during the natural history of PCa. Choline, labelled either with $^{11}C$ or $^{18}F$, and $^{18}F$-fluciclovine are still broadly employed as metabolic PET tracers in clinical practice and their role for imaging biochemical recurrence and their impact on therapeutic management has been demonstrated in clinical trials [2–5]. Other PET tracers, such as gastrin-releasing polypeptide receptors (GRPR)-targeting radiopharmaceuticals, show promising results at various stages of PCa, and data from prospective trials are awaited before translate these tracers into clinical practice [6]. The emerging data suggest that novel prostate-specific membrane antigen (PSMA)-based radioligands carry the highest diagnostic value in the imaging of PCa [7]. PSMA is overexpressed in most of PCa cells and it is associated with higher PSA values and ISUP grade at diagnosis as well as with a worse overall survival. However, it showed a marked inter- and intra-patient heterogeneity [8]. The nuclear medicine community has come a long way since the first in-human applications of $^{68}Ga$-PSMA-11, which dated back to 2012. Its approval by EMA and FDA at production sites only in late 2020 marks an important step towards its wide acceptance, but it will not represent an endpoint to its further use in the molecular imaging of PCa [9]. Prospective, randomized clinical trials incorporating PSMA imaging will be probably published in the next future, their results needed to provide even more robust evidence of its role in improving patient outcome. Several PSMA-ligands have been synthetized, based on both small urea-based molecules and antibodies, bound with Gallium-68 rather than Fluorine-18 or other isotopes, using both positron or single-photon emission tomography [10–16] while more radio-labelled PSMA ligands are expected in the future (Table 1). A detailed analysis of the different diagnostic performances of PSMA radiopharmaceuticals goes however beyond the scope of this review. The aim of this critical review is to highlight the already established or currently emerging diagnostic applications of PSMA compounds during the natural history of PCa.

## INTRAPROSTATIC CANCER DETECTION

The detection, characterization, and better definition of intraprostatic foci of PCa are among the most relevant emerging applications of PSMA-PET imaging. In association with multi-parametric MRI (mpMRI), PSMA-PET may be used to detect the need of and subsequently guide a targeted biopsy in patients presenting with a clinical suspect of PCa. Furthermore, it might improve the accuracy of segmentation prior to radiation therapy (RT) or other localized treatments as well as offering a non-invasive characterization of unclear findings and providing prognostic information.

*Biopsy guidance*

MpMRI should be performed in all subjects presenting with a clinical suspect of PCa before any biopsy attempt in order to guide the biopsy to significant foci in accordance with the most recent recommendations [17]. In this setting, PSMA-PET might increase the accuracy of mpMRI, mostly in patients with high clinical suspect where mpMRI resulted negative (PIRADS 1-2) or inconclusive (PIRADS 3). Bodar *et al.* mapped foci of increased PSMA uptake within the prostate gland in 30 patients, prospectively studied with $^{18}$F-DCFPyL PET/CT before radical prostatectomy [18]. The targeting of PSMA-PET findings on a later biopsy showed positive (PCa) lesions in 28/30 patients (93%). However, considering all the intraprostatic cancer lesions, sensitivity and specificity for PSMA-PET were 61.4% and 88.3%, respectively. Chen *et al.* (2019) used PSMA-PET and mpMRI alone or in a hybrid setting (PET/MRI) to improve the detection of clinically significant PCa in 54 men studied before radical prostatectomy, maintaining the final histopathology results as standard of reference [19]. Sixty-six lesions were retrospectively considered clinically significant. The combination of PET/MRI showed a significantly better accuracy than mpMRI alone: sensitivity was 89% vs. 76% ($P < 0.01$) while specificity was 96% vs. 88% ($P > 0.05$). This was particularly evident when clinically significant lesions occurred within the context of a PIRADS scoring of 3.

In conclusion, from the limited literature data available, the use of PSMA-PET could add diagnostic accuracy in patients with inconclusive MRI. However, in consideration of the large number of patients who could benefit from a PSMA-PET and the still limited availability of this method, an extensive application of PSMA-PET for this purpose appears not easily feasible. On the contrary, studies on highly selected populations could in the future clarify the role and the added value of PSMA-PET in this context. The ongoing prospective multicenter PRIMARY clinical trial will measure and compare sensitivity, specificity, positive predictive value and negative predictive value of both mpMRI and PSMA-PET versus targeted prostrate biopsy [20]. The results will be used to determine the proportion of men who could safely avoid biopsy without compromising detection of clinically significant PCa.

*Segmentation for RT or other focal therapies guidance*

Batterman *et al.* showed a better accuracy for PSMA-PET in comparison with mpMRI for intraprostatic gross tumor volume (GTV) delineation. The authors prospectively performed PSMA-PET and mpMRI in 17 patients candidate to radical prostatectomy [21]. GTVs contours for mpMRI and PSMA-PET were drawn and compared with final GTV drawn on histopathology. Median tumor volumes were 10.4 mL for GTV drowned on histology; 10.8 mL for GTV drowned on PSMA-PET and 4.5 mL for mpMRI. Sensitivity and specificity were 86% and 87% for PSMA-PET, 58% and 94% for mpMRI and 91% and 84% for the combination of both techniques.

*Characterization of intraprostatic findings and prognostic information*

Using a similar study design, Scheltema *et al.* retrospectively enrolled 56 patients who underwent mpMRI and PSMA-PET before radical prostatectomy (RP) [22]. PSMA-PET was accurate in detecting prostate segments containing ISUP grade 2-3, if compared with mpMRI and it may have a role in diagnosing or monitoring PCa. Roberts *et al.* retrospectively enrolled 71 patients with MRI-guided, biopsy-proven PCa and PSMA-PET performed before surgery [23]. PSMA uptake in the prostate has been correlated with adverse pathology outcomes and progression free survival, with a minimum follow up of 24 months. PSMA-PET provided reliable prognostic information especially in patients with biopsy-proven Gleason 3+4 potentially suitable for active surveillance or focal therapy.

Summarizing, based on the available literature, and considering the anticipated widespread use of highly sensitive PET tomographs, it is reasonable to think that in the next future PSMA-PET will be routinely part of the diagnostic flow-chart in many PCa patients before biopsy or primary therapy.

**STAGING**

A correct assessment of the tumor extension at onset is crucial to establish the correct therapeutic strategy after primary staging. In this setting PSMA-PET for lymph node (LN) and bone spread detection has shown high specificity and positive predictive values (PPV) but a sub-optimal sensitivity, which remains however significantly higher than that of CI [7]. In the most recently published meta-analysis the results of 11 studies, including 904 intermediate or high-risk patients, were grouped: pooled sensitivity and specificity on a patient basis were 63% (95% CI: 0.46–0.78) and 93% (95% CI: 0.88–0.96) [24]. On a lymph-node basis, they were 70% (95% CI: 0.49–0.85) and 99% (95% CI: 0.96–1.00). The pooled PPV and negative predictive value (NPV) were above 80% whether on a per-patient or a per-node analysis. The recently published results of the proPSMA study are a game changer in staging high-risk PCa patients [25]. The proPSMA study is the first multicentric, two-arm, randomized study aimed at investigating whether PSMA-PET may show an improved accuracy when compared to CI or if it may end up replacing CI as the only imaging method to perform in high-risk PCa patients at disease presentation. In the study, 302 high-risk patients were included: 152 patients have been randomly assigned to CI diagnostic flow chart, 150 to PSMA-PET only. Results were validated by a composite reference standard including histopathology, imaging, and laboratory data. At final diagnosis 30% of the patients showed local or distant metastatic disease. PSMA-PET showed greater accuracy compared to CI, 92 % vs. 65%, respectively, better sensitivity, 85% vs. 38%, higher impact on clinical decisions 28% vs. 15% and lower number of indeterminate findings 7% vs. 23%. The authors conclude that PSMA-PET may replace CI when staging high-risk patients. Nevertheless, the main drawback is that in men having radiotherapy histological confirmation of nodal disease was not performed, and some patients might have had microscopic disease that was missed by either CI or

PSMA-PET. Wondergem *et al.* studied 160 high-risk patients at presentation with a fluorinated PSMA compound ($^{18}$F-DCFPyL) [26]. PSMA-PET correctly identified 81/90 (90%) patients with local or distant metastatic spread at final diagnosis. PSMA-PET detected additional LN metastases in almost all patients (41 out of 42) in which CT was already positive in at least one LN. PSMA-PET determined a significant shift in patient management in 17% of the population. In accordance with the proPSMA study, the authors conclude that PSMA-PET might be considered the first-line imaging modality for high-risk PCa at presentation, with no need for further diagnostics (Supplemental Figure 1). In a recent prospective multicenter single-arm open-label phase 3 trial the accuracy of PSMA-PET in the detection of N1 status was assessed in 277 intermediate or high-risk patients at presentation [27]. At final diagnosis 27% of the patients were N1 at histopathology. On a region-based analysis, sensitivity, and specificity for PSMA-PET in N1 detection were 40% and 95%, respectively. Higher PSA values and larger nodes were correlated with increased sensitivity by PSMA-PET. According to the available data and the foreseeable increase in PSMA-PET use before primary treatment, it stands to reason to expect a future inclusion of PSMA-PET within the main international guidelines at least in a setting of high-risk PCa at disease presentation. Moreover, a cost-effectiveness analysis developed using data from the proPSMA study demonstrated greater accuracy and lower direct comparative costs for PSMA-PET compared to conventional imaging, namely CT and bone scan [28].

**BIOCHEMICAL RECURRENCE**

Imaging in PSA persistence/recurrence after radical treatment aims at treatment changes and thus possibly to a better clinical outcome. PSMA-PET demonstrated higher sensitivity than 11C-choline- and/or 18F-fluciclovine-PET in this setting [29,30] and scan positivity increases with higher PSA values [7]. A common limitation of PSMA-PET for this purpose is the lack of robust validation of PSMA-PET positive findings as well as the accurate evaluation of its impact on outcome since most of the data are retrospective and/or with short median follow-up time. However, a large amount of data confirms a significant impact of PSMA-PET at least on clinical management. A meta-analysis investigating the impact of PSMA-PET on management of BCR patients (11 studies, 908 patients) reported changes in 54% of patients, although substantial heterogeneity among the included studies was noted, i.e. differences in clinical settings, types of initial definitive treatment and baseline characteristics [31]. Between 5% and 20% of men, continue to have detectable PSA after RP (most often defined as PSA ≥ 0.1-0.2ng/mL within 4–8 weeks from surgery). This condition is often associated with poor prognosis. In this setting of patients retrospective studies report a PSMA-PET positivity rate ranging from 67 to 70% [32–34]. According to the EAU guidelines, PSMA-PET is the most sensitive imaging modality to detect metastasis in this setting of patients and should be offered in patients with PSA > 0.2 ng/mL after RP [35] (Table 2). In a large single-arm multicenter prospective

study, 635 patients with BCR after RP (41%), RT (27%), or both (32%) were enrolled, with the main aim of evaluating the PPV and the detection rate of PSMA-PET [36]. PSMA-PET showed recurrent PCa in 75% of patients. PPV was 0.84 in the 87 patients validated by histopathology and 0.92 in the 217 patients validated by the composite reference standard. As expected PSMA-PET detection rate was associated with increased PSA values, ranging from 38% in patients with PSA <0.5 ng/mL to 97% in those with PSA >5.0 ng/mL. These data confirm that higher serum PSA levels are associated with PSMA positivity in BCR. Careful patient selection employing nomograms has been proposed to maximize the probability of a positive PSMA-PET, implementing clinical parameters such as ISUP grades, current androgen-deprivation therapy (ADT), time to BCR, clinical stage and PSA kinetics, with areas under the ROC curve ranging from 0.69 to 0.76 [37,38]. In detail, Rauscher *et al.* included 272 hormone-sensitive patients with previous RP and PSA values at time of PSMA-PET between 0.2 and 1.0ng/mL [37]. Among those, about 10% were on ADT at the time of the PSMA-PET scan. In a multivariable regression model ADT administration and PSA values were identified as most relevant predictors of positive PSMA-PET. Similarly, Ceci *et al.* included 703 patients with PSA failure after RP, stratified according to different clinical settings, i.e. first-biochemical recurrence, recurrence after salvage-treatment, PSA persistence after radical surgery and advanced-stage of PCa before second-line systemic therapy [38]. At multivariable regression model, ISUP grade, PSA values, PSA doubling time and clinical setting were independent predictors of a positive PSMA-PET. In conclusion, besides PSA values at time of PSMA-PET, concurrent ADT and PSA kinetics were identified as most relevant predictors of a positive scan in BCR patients. Nevertheless, in clinical daily practice, despite the high detection rates and accurate patient selection, a not negligible number of patients will have a negative PSMA-PET. A prospective multicenter study aimed to evaluate the predictive value of PSMA-PET in 260 men with BCR (PSA of 0.26ng/mL; follow-up of 38 months), candidate to salvage radiotherapy (S-RT). Overall, free from progression after 3 years was statistically significant longer in patients with negative PSMA-PET or were PSMA-PET showed disease confined to the prostatic fossa, in comparison with patients showing extra prostatic disease ($p < 0.0001$). It is interesting to point out that in the same population; PSA values were not able to stratify patients with the same statistically significant accuracy.

**SALVAGE RADIOTHERAPY PLANNING**

Salvage radiotherapy (SRT) after RP is associated with PSA control in about 50% of patients. International guidelines suggest performing SRT when serum PSA levels are lower than 0.5/1.0 ng/mL [35]. At this PSA levels CI demonstrated very low sensitivity to detect sites of recurrence. For this reason, GTVs are usually drawn without imaging guidance. PSMA-PET performed in patients eligible for SRT may improve the likelihood of PSA response and it is suggested by the main international

guidelines (Table 2)[35,39]. Calais *et al.* enrolled 270 patients after prostatectomy and before SRT who underwent PSMA-PET at a PSA level < 1 ng/mL (median 0.48 ng/mL) [40]. PSMA-PET was positive in 49% of patients and showed the presence of at least one lesion out of the planned GTV in 19% (52/270 patients), mostly localized in the bones or in peri-rectal lymph nodes. PSMA-PET findings lead thus to a major change in management in 19% of the patients (Figure 1). In a randomized phase 3 trial aimed to evaluate success rate of SRT with and without RT planning based on PSMA-PET findings, the primary endpoint was the SRT success rate at 5 years among patients who actually received SRT measured as biochemical progression-free survival [41,42]. Enrollment is complete: 83 patients in the control arm proceed with standard SRT, while 102 patients in the investigational arm underwent PSMA-PET prior to SRT planning. Patients in the control group were staged heterogeneously using fluciclovine PET (33%), CT (36%), bone scan (17%), MRI (27%), or fluorodeoxyglucose (FDG) PET (1%), while 34% had no imaging. In the intervention group, PSMA-PET was positive in 37% of patients with 9% positive outside the pelvis (M1). This large prospective study will provide useful information's about on the added value of PSMA-PET performed in patients candidate to SRT and whether the impact of PSMA-PET on SRT planning would translate into better patient outcomes.

**METASTASIS-DIRECTED THERAPIES AFTER RADICAL TREATMENT**

The oligometastatic state is proposed as intermediate stage of cancer spread between localized and systemic disease, enabling potential opportunity for metastasis-directed therapies (MDT) to delay the emergence of polymetastatic disease [43]. Disease volume and distribution have prognostic implications for patients' management, quality of life and survival, and thus prompt recognition of oligometastatic PCa is desirable [44]. However, the type of imaging that best defines oligometastatic PCa for the purpose of MDT is debated [45]. PSMA-based literature on this topic is mostly retrospective and the randomized phase 2 ORIOLE (Observation vs. Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer) study is the first clinical trial on PSMA-PET-directed salvage therapy [46]. Thirty-six patients with hormone-sensitive oligo-metastatic PCa underwent CI and were randomized to receive SBRT vs. observation alone. Baseline PSMA-PET was performed with $^{18}$F-DCFPyL and PSMA-PET results were not used for SBRT treatment planning. Sixteen of 36 (44.4%) patients treated with SBRT showed positive findings at baseline PSMA-PET that were not included in the prescribed treatment fields. Post-hoc analysis of progression-free survival based on extent of untreated disease appreciable by PSMA-PET, found improved progression-free survival and distant metastases-free survival advantages among men who received consolidation of all PSMA-avid disease (HR0.26;95% CI:0.09-0.76; p=0.006). This means that PSMA-PET should be considered for MDT to maximize patient benefit in oligo-metastatic PCa and consolidation of PET-PSMA positivity might improve progression-free survival.

## CASTRATE-RESISTANT PROSTATE CANCER

In castration-resistant PCa (CRPC), the number of available treatments is steadily rising over ADT, ranging from novel androgen receptor targeted therapy (abiraterone, enzalutamide, or apalutamide) to anti–programmed cell death protein 1 and radionuclide therapy. In this setting, CI is recommended [35] despite PSMA-PET is emerging as an accurate imaging modality for evaluating CRPC patients. A multicenter retrospective study including 200 patients with PSA > 2.0 ng/mL, negative CI and high risk for metastasis, (i.e. PSAdt ≤10 months and/or Gleason score ≥8) aimed to assess the performance of PSMA-PET in non-metastatic CRPC [47]. PSMA-PET was positive in 196/200 (98%) of patients. Overall PSMA-PET showed pelvic diseases in 44%, including 24% with local prostate bed recurrence and distant metastasis in 55% despite negative CI (Supplemental Figure 2). The overall accuracy of PSMA-PET was 95 % for osseous lesions and 60% for soft-tissue lesions. PSMA-PET demonstrated also a shift in 30% of patients for per-patient PCWG3 clinical subtype in comparison with CI and a major concordance with CI in a multicenter retrospective analysis of 67 CRPC patients imaged with PSMA-PET and CT plus bone scintigraphy or whole-body MRI [48]. According to these results, it stands to reason that PSMA-PET leads to an earlier detection of metastasis compared with CI and a change of clinical subtype, which may trigger earlier or different treatments. However, if and how this could impact on patient outcome in terms of overall survival and quality of life has yet to be determined and further studies are warranted. Additionally, PSMA-PET might be useful to select patients for the most appropriate treatment. In a retrospective analysis of 80 advanced CRPC patients treated with $^{223}$Ra-dichloride the final outcome was significantly better in the group of patients studied with PSMA-PET before treatment in comparison whit those only staged with CI [49]. Moreover, assessing PSMA expression is essential for the inclusion criteria in all PSMA-based radio-ligand therapy (RLT) trials, since some patients may show low or absent PSMA expression, posing a contraindication for RLT. Experience derived from $^{177}$Lu-PSMA, suggests a dual tarcer approach employing both PSMA and FDG for patients selection before treatment [50,51]. FDG-avid disease represents sites of aggressive disease that cannot efficiently targeted with RLT. However, an optimal threshold for defining low PSMA expression on PSMA-PET has not been defined and validated yet. Further prospective trials are required to elucidate the role of PSMA-PET in response assessment and survival prediction. In a retrospective study on PSMA-PET before and after 3 cycles of docetaxel, 16 mCRPC patients were evaluated [52]. Authors compared PSA decline with the responses on PSMA-PET and CT. PSMA-PET was a better predictor of response (56% of the cases) while CT correctly predicted response in 33%. In another retrospective study, 43 mCRPC patients underwent PSMA-PET before and after systemic therapies [53]. PSMA-PET parameters, as well as the RECIST 1.1 [54], were significantly associated with PSA response. However, neither the investigated PET parameters nor PSA level or RECIST 1.1 criteria were associated with overall survival. This could

be explained by the design of the study and the heterogeneity of treatments, but also by the lack of standardized criteria to assess response (or progression) at PSMA-PET. In this regard the PSMA PET Progression Criteria (PPP) were proposed to define disease progression [55], since the criteria of the Prostate Cancer Clinical Trials Working Group (PCWG3) include only laboratory parameters and CI but no molecular imaging [56]. The proposal who defines PSMA-PET progression in mCRPC are reported in Supplemental Table 1.

**ANTI-ANDROGEN MODULATION OF PSMA**

PSMA-PET is routinely performed in many patients who have received or are receiving ADT at the time of investigation, thus the potential interaction of ADT on PSMA expression should be fully investigated, with implications for image interpretation and PSMA-RLT timing. In vitro studies evaluating the effect of ADT on PSMA expression were firstly published by Wright [57]. Two elements regulate PSMA expression: PSMA promoter and PSMA enhancer (PSME), located within the third intron of FOLH1. FOLH1 gene expression is down-regulated by androgens that reduce transcription of PSMA mRNA. On the other hand, anti-androgens administration up-regulates the FOLH1 gene causing an increased PSMA expression. In vivo studies showed that the PSMA expression is increased after ADT while the tumor size is decreased after administration of enzalutamide [58]. Therefore, theoretically, the effect of ADT on images may cause an increased PSMA expression before reduction in tumor size. Summarizing, ADT administration may lead to an increased PSMA uptake due to androgen receptor inhibition, but androgen receptor inhibitors may also lead to a reduction of tumor mass with a consequent PCa cell death. Hope *et al.* showed that PSMA uptake significantly increased in one hormonal naïve patient imaged with PSMA-PET before and after four weeks of ADT (single administration of 7.5-mg leuprolide and 50 mg of bicalutamide/die), in contrast with the significant reduction of PSA levels who dropped down from 66ng/mL to 9ng/mL [59]. Moreover, some authors have postulated that PSMA expression after ADT is differently modulated depending on the status of the patient: CRPC or castrate sensitive (CSPC). In this regard, Emmett and colleagues studied with sequential PSMA-PET eight CSPC patients at baseline and after 9, 18 and 28 days from ADT administration (LHRH plus bicalutamide) [60]. They also enrolled seven CRPC patients studied with PSMA-PET at the same time points after administration of abiraterone or enzalutamide. After 9 days, LHRH plus bicalutamide stimulation caused a median 30% PSMA uptake reduction in CSPC patients while in CRPC patients, abiraternone/enzalutamide administration caused a median 45% PSMA increased expression. According to these data it could be postulated that PSMA expression after ADT stimulation is different depending on the patient status. Authors conclude that there is a rapid dichotomous response to ADT depending on the presence of a CSPC or CRPC phenotype. If this hypothesis is correct, PSMA-PET could be used in the future to early classify patients after few days

of hormonal treatment. In a prospective clinical trial aimed to understand if ADT administration may improve the performance of PSMA-PET in PCa patients at presentation, nine treatment naive patients were enrolled [61]. PSMA-PET/MRI has been performed at baseline and three times after administration of ADT in a range course of 1-8 weeks. Authors observed a heterogeneous increase in PSMA uptake after 3-4 weeks of ADT administration, while in lesions showing deceased PSMA uptake after ADT, none disappeared. It is interesting to point out that this finding was more evident in bone metastases. According to these data, the optimal imaging time point to perform a second PSMA-PET might be 3 to 4 weeks post-ADT administration. Finally, Afshar-Oromieh *et al.* studied the effect of long-term ADT (mean 7 months) in ten CSPC [62]. PSMA uptake decreased in about 75% of the lesions, while in a small proportion of lesions (13%) PSMA uptake increased despite a complete or partial PSA response. Authors postulated that the lesions who showed an increased uptake, despite clinical and PSA response, might be correlate with those cell clones that become castration-resistant first. Summing up briefly, considering the paucity of literature about this topic, we can assume that probably a short duration of ADT administration may increase PSMA expression, while long-term ADT might have the opposite effect in CSPC patients, even if probably able to early detect those lesions at risk to become castrate resistant. In conclusion, there are still many un-answered questions, and first of all the optimal time point between ADT administration and PSMA imaging in order to reduce or increase (depending on the clinical needs) the effect of ADT on PSMA expression [63]. In addition, further prospective studies are needed to clarify the influence of ADT administration on PSMA expression and its impact on PET imaging.

## STANDARDIZED REPORTING AND INTERPRETATION

With the increasing diffusion of PSMA-PET imaging worldwide, the application of standardized, unique methods to read and interpret images has become mandatory, in order to collect reproducible data and increase the accuracy of PSMA-PET. Several criteria have been already proposed and Table 3 summarizes the key features.

### *PROMISE criteria*

PROMISE is a suggested standardization for PSMA-PET either for reading (based on the intensity of the expression of PSMA: miPSMA) and/or for the interpretation of the images and staging of the disease (miTNM) [64]. miPSMA categories were defined in relation to mean PSMA uptake in the blood pool, the liver and the parotid gland, ranging from 0 to 3. However, authors recommend that the interpretation of the images and the conclusion regarding the extension of the disease (miTNM) have to be performed within the clinical context and the extent and the location of PET findings. miTNM could be used as a guide for a standardize report taking into consideration: presence, location and

extent of local PCa and pattern of metastases, PSMA expression level of tumor lesions and diagnostic confidence of reported findings.

*PSMA RADS*

PSMA-RADS is a classification of PSMA-PET findings into categories that reflect the likelihood of the presence of PCa [65]. Like for other radiological RADS criteria the goal of the PSMA-RADS is to score the level of confidence of the reader on the presence of PCa and the potential need for any additional work-up. The scores for PSMA-RADS range from 1 to 5, with higher numbers indicating a greater probability of PCa. In addition, the authors also recommend to collect a complete clinical history for each patient, reporting the current and previous PSA levels, the findings of other imaging modalities, the type and duration of previous therapies or other known malignancies.

*E-PSMA*

The E-PSMA are comprehensive guidelines supported by the European Association of Nuclear Medicine (EANM) and aims to develop a structured report for PSMA-PET images and to harmonize diagnostic interpretation criteria [66]. In the suggested structured E-PSMA report the visual description should relate PSMA uptake to background uptake in blood pool, liver and salivary glands on a visual scale 0-3. For images interpretation Panelists suggest a five-point scale of confidence. The document also suggests the use of a standardized terminology in reporting PSMA-PET findings and the adoption of a structured report.

**CONCLUSION**

PSMA ligands for PET-imaging have been adopted at an unprecedented rate, resulting in a tremendous increase of published studies and trials. Most importantly, PSMA-PET is now part of the diagnostic flow-chart of prostate cancer in international guidelines and received first regulatory approval. Several PSMA radiotracers are now available, while many more are under investigation, thus increasing the availability of PSMA-PET imaging worldwide. Currently, the challenge lies in understanding the mechanisms behind PSMA expression and its influencing factors, either endogenous or exogenous. Furthermore, nuclear medicine physicians will have to familiarize themselves with a standardized reporting system, while a strict collaboration with the clinician remains vital for an effective implementation of the PSMA-PET imaging results. In short, from now on what we need is the production of reliable data on patient outcome at dedicated endpoints.

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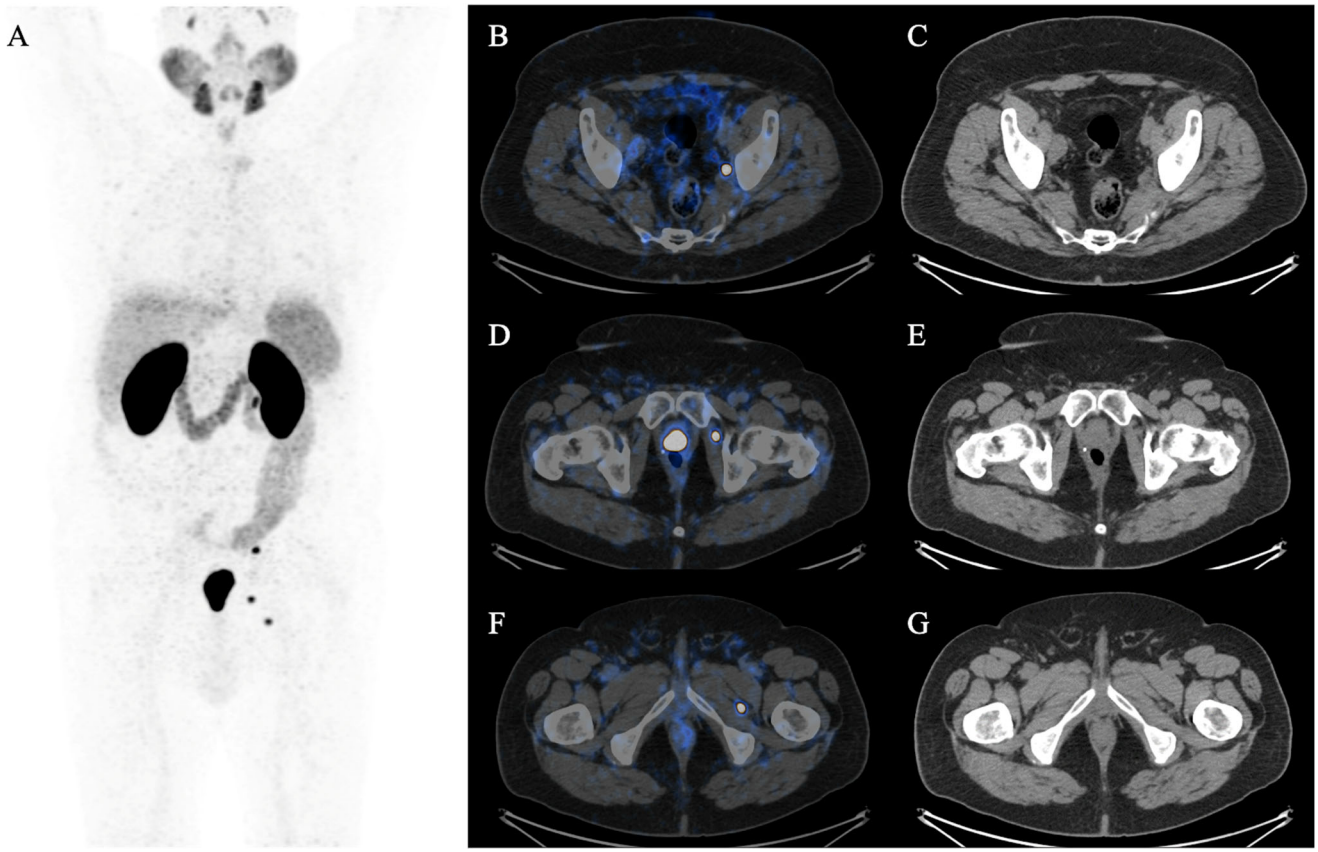



**Figure 1. PSMA-guided salvage treatment.** 69 years old, iPSA 5.1 ng/mL, RALP and lymph node dissection for adenocarcinoma with neuroendocrine phenotype, ISUP 4, pT3a pN0 (0/11), R0. PSA persistence 4 weeks after surgery 0.73 ng/mL. Referred for PSMA-PET before scheduled SRT. PSA at time of the scan 0.92 ng/mL, PSA doubling time 5.2 months. A: PSMA-PET MIP projection; B, C, D, E, F, G: PSMA-PET/CT fused images and CT images showing one right obturatory lymph. Node with PSMA uptake (B, C) and two intramuscular lymph nodes with PSMA-uptake (D, E, F, G). The patient was treated with SRT and simultaneous integrated boosts with complete PSA response 9 months after treatment.

## TABLES

### Table 1. PSMA ligands commonly used in the clinical practice for Imaging and Therapy.

| Ligand | Label | Imaging and/or Therapy | Advantages | Disadvantages |
|---|---|---|---|---|
| PSMA-11 (PSMA-HBED-CC) [12] | $^{68}$Ga | Imaging | Most widely employed in literature EMA and FDA approval | $^{68}$Ga-related disadvantages<br>High accumulation in the urinary tract |
| PSMA-617 [13] | $^{68}$Ga | Imaging and Therapy | Reduced kidney uptake compared to PSMA-11 | $^{68}$Ga-related disadvantages<br>Slightly slower tracer kinetics than for PSMA-11<br>High accumulation in the urinary tract |
| PSMA-I&T [14] | $^{68}$Ga | Imaging and Therapy | Lower hepatic uptake compared to PSMA-11 | $^{68}$Ga-related disadvantages<br>Lower lesion binding and higher background than PSMA-11 |
| DCFPyL [11] | $^{18}$F | Imaging | Low hepatic uptake | High accumulation in the urinary tract |
| PSMA-1007 [15] | $^{18}$F | Imaging | Low accumulation in the urinary tract | High hepatic uptake<br>Higher number of PSMA positive lesions attributed to benign origin * |
| rhPSMA-7 [16] | $^{18}$F, $^{68}$Ga | Imaging and Therapy | Radio-hybrid concept<br>Low accumulation in the urinary tract with $^{18}$F | Higher number of PSMA positive lesions attributed to benign origin * |

**Notes:** * compared to $^{68}$Ga-PSMA-11 (e.g. ganglia, unspecific bone lesions, unspecific lymph nodes)

**Table 2.** Recommendation on the use of PSMA-PET or Next-Generation Imaging, i.e. PET/CT, PET/MRI and whole-body MRI, by EAU-EANM-ESTRO-ESUR-SIOG 2020 [56] and ASCO Guidelines (52).

| Clinical stage | EAU-EANM-ESTRO-ESUR-SIOG 2020 [17,35] | Strength rating | ASCO 2020 [39] | Strength rating |
|---|---|---|---|---|
| Diagnosis | Not recommended | | Not recommended | |
| Staging | PSMA-PET<br>Not recommended<br><br>Perform at least cross-sectional Imaging for intermediate and high-risk patients | | When CI is negative in patients with a high risk of metastatic disease, NGI may add clinical benefit, although prospective data are limited<br>When CI is suspicious or equivocal, NGI may be offered to patients for clarification of equivocal findings or detection of additional sites of disease, which could potentially alter management, although prospective data are limited | weak |
| BCR | Perform PSMA PET/CT if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions. | Weak | The goal of therapy and the potential use of salvage local therapies in these scenarios should guide the choice of imaging | moderate |
| PSA persistence | Offer PSMA PET to men with a persistent PSA > 0.2 ng/mL to exclude metastatic disease. | Weak | or men for whom salvage local or regional therapy is contemplated, there is evidence supporting NGI for detection of local and/or distant sites of disease. | moderate |
| Before S-RT | Perform PSMA PET/CT (if available) or fluciclovine or choline in patients fit for curative salvage treatment. | strong | For men for whom salvage radiotherapy is contemplated PSMA imaging should be offered [or NGI) as they have superior disease detection performance characteristics and may alter patient management | high |
| nmCRPC | With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are expected to be diagnosed with early mCRPC | NR | For men with nm CRPC, NGI can be offered only if a change in the clinical care is contemplated | moderate |
| mCRPC | The use of choline or PSMA PET/CT scans for progressing CRPC is unclear and most likely not as beneficial as for patients with BCR or hormone-naïve disease | NR | The use of NGI in this cohort is unclear, with a paucity of prospective data. When a change in clinical care is contemplated and there is a high clinical suspicion of subclinical metastasis despite negative conventional imaging, the use of NGI could be contemplated In in clear evidence of radiographic progression on CI, NGI should not be routinely offered. NGI may play a role if performed at baseline to facilitate comparison of imaging findings/extent of progression of disease | insufficient |

Notes: NGI = next-generation imaging, i.e. PET/CT, PET/MRI and whole-body MRI; NR = not reported; nmCRPC = non-metastatic castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer.

**Table 3.** Proposed reading and interpretation criteria by PSMA-RADS [56] E-PSMA [66] and PROMISE [55] for PSMA-PET.

| | PSMA RADS [65] | E-PSMA [66] | PROMISE [64] |
|---|---|---|---|
| PSMA-PET reading score | | E-PSMA scores *: 0 to 3<br>0: uptake < blood pool<br>1 uptake > blood pool and < liver<br>2 uptake > liver and < parotid glands<br>3 uptake > parotid glands. | miPSMA scores † : 0 to 3<br><br>0: uptake < blood pool<br>1 uptake > blood pool and < liver<br>2 uptake > liver and < parotid glands<br>3 uptake > parotid glands. |
| PSMA-PET interpretation | 1A Benign lesion without abnormal uptake;<br>1B Benign lesion with abnormal uptake;<br>2- Likely benign;<br>3- Equivocal:<br>3A Equivocal uptake in soft-tissue site typical of PCa involvement;<br>3B Equivocal uptake in bone lesion not definitive but also not atypical of PCa on anatomic imaging;<br>3C Intense uptake in site highly atypical of all but advanced stages of PCa;<br>3D Lesion suggestive of malignancy on anatomic imaging but lacking uptake;<br>4- PCa highly likely Intense uptake in site typical of PCa but lacking definitive findings on conventional imaging;<br>5- PCa almost certainly present. | 1- Benign lesion without abnormal PSMA uptake<br>2- Probably benign lesion: faint PSMA uptake in a site atypical for PCa<br>3- Equivocal finding: faint uptake in a site typical for prostate cancer or intense uptake in a site atypical for PCa<br>4- Probably prostate cancer: intense uptake in typical site of PCa, but without definitive findings on CT<br>5- Definitive evidence of prostate cancer: intense uptake in typical site typical of PCa, with definitive findings on CT | Scores 2 and 3 should be considered PCa lesions, depending on the clinical context, the extent and the location of the findings. |

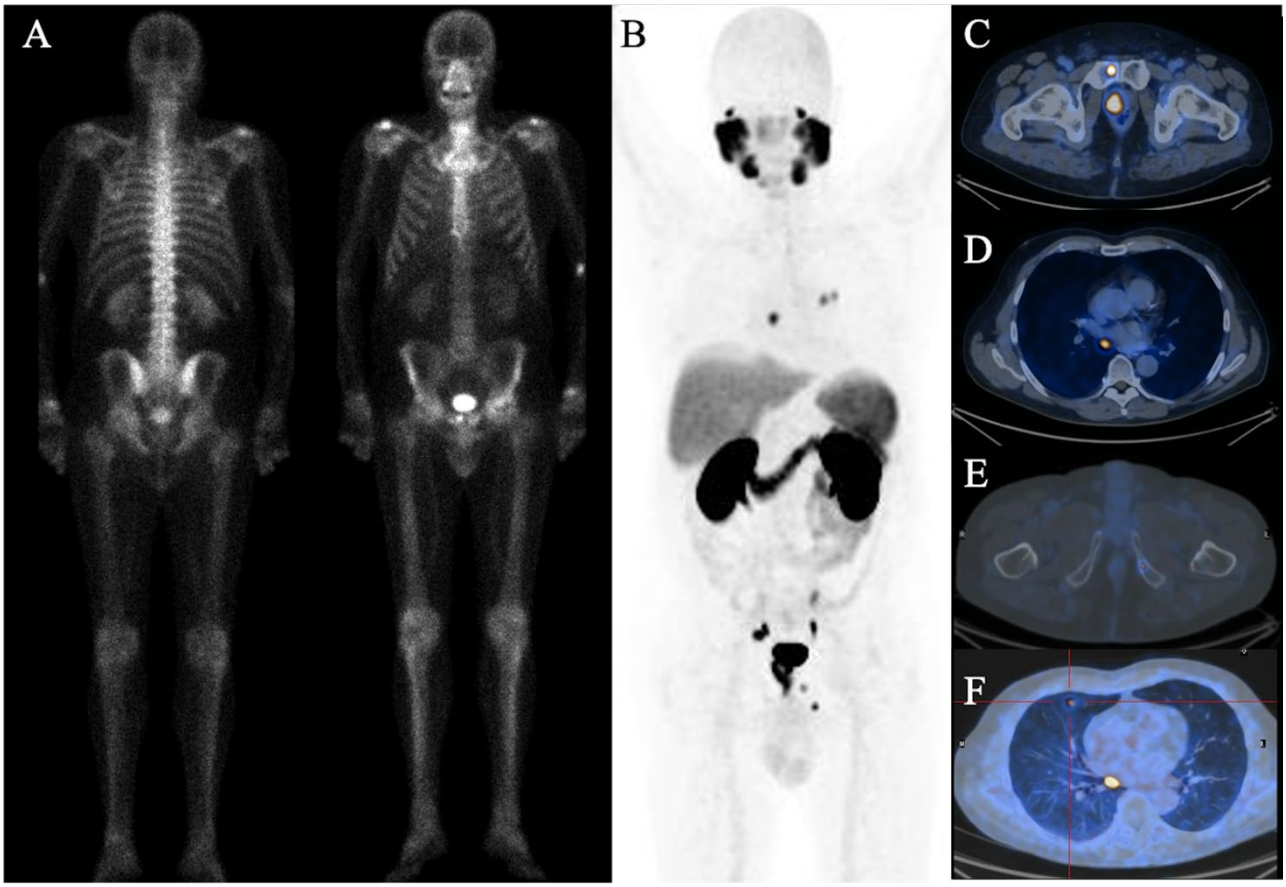
**Notes:** * designed for the most extensively employed PSMA-ligands, i.e. $^{68}$Ga-PSMA-11, $^{18}$F-DCFPyL and $^{18}$F-PSMA-1007; **†** designed mainly for $^{68}$Ga-PSMA-11, for PSMA-ligands with liver-dominant excretion spleen is recommended as reference organ instead of liver

**SUPPLEMENTAL MATERIAL**

**Supplemental Table 1.** Summary of the reading and interpretation criteria of PCWG3 (*56*), RECIST 1.1 (*54*) and PPP (*55*) For the definition of progressive disease in mCRPC.

| | **PCWG3** (*56*) | **RECIST 1.1** (*54*) | **PPP** (*55*) |
|---|---|---|---|
| **Reading criteria** | Development of new lesions or growth of preexisting lesions | 1- Appearance of new lesions<br><br>2- ≥20% increase in the sum of length diameters of target lesions,<br><br>3- Un-equivocal increase of non-target lesions. | 1- Appearance of 2 new PSMA positive lesions<br><br>2- Appearance of 1 new lesion + clinical and laboratory data.<br><br>3- Increased by at least 30% in size or uptake + clinical and laboratory data. |
| **Images** | CT or MRI plus Bone Scintigraphy | CT, MRI | PSMA-PET |

**Supplemental Figure 1. Primary staging before treatment.** 64 years old, bioptic ISUP 5; iPSA 10 ng/ml; mpMRI: cT3b N1 M0, PI-RADS 5, referred for primary staging before scheduled RP. According to PSMA-PET findings the patient has been addressed to systemic therapy. PROMISE stage was T1N1M1b for conventional imaging and T1N1M1abc for PSMA-PET. Bone Scan showing small focal uptake in the right pubic bone (A) and PSMA-PET MIP projection (B) and fused images (C, D, E, F) showing multiple lesions involving the prostate and right pubic bone (C), mediastinal lymph nodes (D), one left ischiatic bone (E), and right lung nodule (F).



**Supplemental Figure 2. Shift from CI nmCRPC to PSMA mCRPC.** 71 years old, ISUP 4, iPSA 12 ng/ml; pelvic MRI PI-RADS 4: pT3aN1M0; RP in 2015; PSA nadir 0,2 ng/ml. Increased PSA values during ADT, up to PSA 2,2 ng/ml with PSA doubling time 8 months at the time of PSMA-PET. CT and Bone Scan negative and condition of nmCRPC. PSMA-PET MIP projection (A), fused images (B) and CT part only (C) showing bone metastases (B) and small distant lymph nodes (C).