THERAPEUTIC ADVANCES in
Medical Oncology

Review

Current role of PSMA-PET imaging in the clinical management of prostate cancer

Ther Adv Med Oncol

2023, Vol. 15: 1–10

DOI: 10.1177/17588359231208960

Alexander Georgakopoulos, Aristotle Bamias and Sophia Chatziioannou

***Abstract*:** Despite the developments of the last few years, metastatic castration-resistant prostate cancer (PC) remains a deadly disease. Until recently, almost all guidelines recommended magnetic resonance imaging (MRI) or computed tomography (CT) for the initial staging and local/systematic recurrence. Positron emission tomography/computed tomography (PET/CT) with prostate-specific membrane antigen (PSMA) at the present stage, emerged as a promising diagnostic imaging tool for PC. PSMA PET/CT alone or in combination with multiparametric magnetic resonance imaging (mpMRI) can improve the detection of clinically significant PC, especially for Prostate Imaging Reporting & Data System (PI-RADS) = 3 lesions. In addition, PSMA PET/CT is more accurate than CT and bone scan for intermediate to high-risk disease at the initial staging. Contrariwise, a negative PET is not useful for surgeons to avoid a pelvic nodal dissection. PET-PSMA imaging is appropriate for prostate-specific antigen (PSA) persistence or PSA rise from undetectable level after radical prostatectomy or for PSA rise above nadir after definitive radiotherapy. Also, it is recommended for patients fit for curative salvage treatment. It should be noted that in patients, candidates for radionuclide therapy with Lutetium-177 (^{117}Lu), a PSMA strong expression from PET/CT at baseline is considered necessary. This review summarizes the evolution of PSMA PET/CT and its current role in the management of PC.

Keywords: nuclear medicine, PET, PSMA, prostate cancer

Received: 4 June 2023; revised manuscript accepted: 2 October 2023.

Correspondence to:
Aristotle Bamias
2nd Propaedeutic Department of Internal Medicine, University General Hospital 'Attikon', Rimini 1, Athens 12462, Greece
abamias@med.uoa.gr

Alexander Georgakopoulos
2nd Radiology Department, Nuclear Medicine Section, University General Hospital 'Attikon', Athens, Greece

Sophia Chatziioannou
2nd Radiology Department, Nuclear Medicine Section, University General Hospital 'Attikon', Athens, Greece

PET/CT Department, Biomedical Research Foundation Academy of Athens, Athens, Greece

Introduction

Prostate cancer (PC) is the second most commonly diagnosed cancer in men with the incidence of its diagnosis to vary widely between different geographic areas.[1] Despite improvements in survival rate, many men with PC still present with advanced disease either at initial diagnosis or following recurrence.[2] Surgery and radiotherapy are the proposed treatments in localized disease and androgen-deprivation therapy (ADT), androgen signaling inhibition (ARSI), and chemotherapy in recurrent or metastatic disease.[3] However, the majority of cases will progress to castration resistance. Although there have been many developments in the last few years, metastatic castration-resistant PC (mCRPC) remains a deadly disease.

Several imaging modalities, such as transrectal ultrasound (TRUS) and TRUS-guided prostate gland biopsy, magnetic resonance imaging (MRI), computed tomography (CT), ^{99m}Tc-methylene diphosphonate bone scan (99mTc-MDP bone scan), and positron emission tomography/computed tomography (PET/CT), have an important role for initial staging and recurrence of PC. Until recently, almost all guidelines recommended MRI or CT for staging, detecting lymph node metastases, and local recurrence. PET/CT, at the present stage, emerged as a promising diagnostic imaging tool for PC. Several radiolabeled tracers were used for disease detection in various clinical scenarios.[4]

^{18}F-fluorodeoxyglucose (FDG) has low sensitivity for the detection of PC due to low glucose

metabolism.[5] In recent years, radiolabeled choline tracers (F-choline and ^{11}C-choline) were the most commonly used, mainly for the detection of biochemical relapse.[6] Fluorine 18 (^{18}F) fluciclovine (anti-1-amino-3–^{18}F-fluorocyclobutane-1-carboxylic acid [FACBC]) is a radiolabeled amino acid analog. Its use is based on the increased amino acid transport in PC cells. Its major advantage is the minimal or no activity during the acquisition in the bladder, while the pathologic activity in PC and nodal metastatic disease peaks rapidly, between 4 and 10 min, after the radiotracer injection.[7]

Rationale for the use of PSMA in PC imaging

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein (glutamate carboxypeptidase II or N-acetyl-L-aspartyl-L-glutamate peptidase I). Physiological PSMA expression is detected in salivary and lacrimal glands, normal prostate epithelium, sympathetic ganglia, duodenum and colon, and the proximal tubules of the kidneys.

Significant pathological overexpression of PSMA is found in the primary and metastasized PC. It is also expressed by a wide range of different tumors and their metastases due to neovascularization. In addition, PSMA uptake can be detected in various benign granulomatous or inflammatory diseases.[8] All tracers of PSMA can be labeled for diagnostic single photon emission computerized tomography (SPECT/CT) with Tc-99m or Gallium-68 (^{68}GA), fluorine-18 (^{18}F) for PET/CT, and some of them with Lutetium-177 (^{117}Lu) or actinium-225 (^{225}Ac) for theragnostic use.[9] Tc-99m PSMA is generally recommended when ^{68}GaPSMA is not available.[10] There is no evidence to date that one specific radiopharmaceutical has better diagnostic accuracy compared with another, and this is probably due to the fact there are small differences between each tracer.^{68}Ga has a half-life of 68 min and is usually produced from a germanium–gallium generator in contrary to ^{18}F which has 120 min half-life so an on-site cyclotron is not required.

Physiologic biodistribution of PET PSMA tracers includes lacrimal and salivary glands, kidneys, ureters, bladder with moderate intensity in the duodenum, small intestines, liver, and spleen.

Table 1. Four-point scale (visual score) of PSMA expression.[11]

Visual score	Grade of PSMA expression
0	Below blood pool
1	Equal or to above the blood pool and lower than the liver
2	Equal or to above the liver and lower than the parotid gland
3	Equal or to the above parotid gland

PSMA, prostate-specific membrane antigen.

Imaging protocols and reporting

The proposed activities are 111–259 MBq (3–7 mCi) for 68Ga-PSMA-11 with an uptake time of 50–100 min and 296–370 MBq (8–10 mCi) for 18F-DCFPyL with an uptake time of 60 min. Delayed images are optional in patients with high bladder urine activity. PET-PSMA can be combined either with CT (PET/CT) or with magnetic resonance imaging (PET/MRI).[11]

The description of PSMA uptake in either prostate bed, or metastases should include both qualitative and quantitative descriptions. Visual description compares PSMA uptake to background uptake in the blood, liver, and salivary glands on a visual scale of 0–3 (Table 1). Quantitative description related to SUVmax or a tumor-to-background ratio. Also, reports should include Tumor-Node-Metastasis (TNM) classification and a five-point scale, classifying individual findings, depending on the probability of disease presentation[12] (Table 2).

The total effective dose of 18F-DCFPyL per mCi is similar to that of 68Ga-PSMA-11 per mCi (0.011 mSv/MBq). The highest exposure organ for 18F-DCFPyL is the kidney, with a dose of 0.123 mGy/MBq.[11]

The role of ADT

ADT therapy could be associated with increased PSMA expression. Although PSMA PET is routinely performed on patients who have received or are receiving ADT, there is no optimal duration of ADT administration and PSMA imaging. It seems that a short duration of ADT administration may

Table 2. Five-point scale for interpretation of PSMA PET/CT findings.[12]

Score	Findings
1	Benign lesion without PSMA uptake
2	Probably benign (faint PSMA uptake in a site atypical for PC)
3	Equivocal finding (faint PSMA uptake in a site typical for PC or intense uptake in a site atypical for PC)
4	Probably PC (intense uptake in a site typical for prostate cancer but without definitive findings on CT)
5	PC (intense uptake in a site typical for prostate cancer, with definitive findings on CT)

PC, prostate cancer; PET/CT, positron emission tomography/computed tomography; PSMA, prostate-specific membrane antigen.

increase PSMA expression, whereas long-term ADT might have the opposite effect.[13,14]

Gallium *versus* fluorine PSMA tracers

^{68}Ga-PSMA 11 is the most widely used tracer for imaging PC with European Medicines Agency and Food and Drug Administration (FDA) approval. PSMA-617 can be used with both ^{68}Ga for imaging and ^{117}Lu for therapy but presents disadvantages of slightly slower tracer kinetics than PSMA-11 and high accumulation in the urinary tract.[15] The same diagnostic and therapeutic properties also have the PSMA I&T with lower lesion binding and higher background than PSMA-11.[16] Gallium tracers, overall, have a higher urinary excretion, limiting the assessment of the prostatic fossa and surrounding pelvic lymph nodes.[17] Regarding ^{18}F-labeled tracers, although we have less published data compared with ^{68}Ga-PSMA 11, there is an increasing interest due to their physical characteristics and availability, with the two most well-known being PSMA-1007 and DCPyL. ^{18}F-PSMA 1007 has low accumulation in the urinary tract and is superior to gallium tracers for the evaluation of prostatic fossa recurrence but, on the other hand, presents a high rate of false-positive findings in the skeletal system and also has a higher excretion *via* the liver and bile ducts, making the evaluation of visceral organs of the upper abdomen difficult.[18,19]

On the contrary, ^{18}F-DCPyL showed fewer equivocal skeletal lesions with higher inter-reader agreement.[20]

It should be emphasized that in any case, the current data demonstrated similar outcomes for ^{18}F or ^{68}Ga PSMA compounds but head-to-head comparison studies are lacking and precise definitive conclusions cannot be exported.[19]

Staging

T-staging

Multiparametric MRI (mpMRI), which combines T2-weighted imaging, diffusion-weighted imaging, and a dynamic contrast-enhanced sequence, is still the recommended imaging modality for the diagnosis of PC, predominantly to aid the selection of patients who will benefit from a prostate biopsy. PRECISION trial and several other prospective trials found that MRI-targeted biopsy had superior levels of detecting PC with International Society of Urological Pathology (ISUP) grading $\geqslant$2 compared to the systematic biopsy approach or MRI alone. Despite its advantages, accurate interpretation for Prostate Imaging Reporting & Data System (PI-RADS) = 3 lesions as well as of very large hyperplastic transitional zones remains difficult. Several retrospective studies have compared the accuracy of PSMA PET/CT to mpMRI or evaluated the combined diagnostic accuracy of both.[8]

^{68}Ga-PSMA PET/CT alone or in combination with mpMRI can improve the detection of clinically significant PC, especially for PI-RADS 3 lesions.[21] Pepe *et al.* compared ^{68}Ga PSMA PET/CT with mpMRI in the diagnosis of high-risk PC. The study revealed that ^{68}Ga-PSMA PET/CT demonstrated good diagnostic accuracy and that it could be proposed in this group of patients to perform diagnosis (targeted biopsy), improving the cost–benefit ratio as a single procedure.[22]

A multicenter prospective clinical trial determined whether the combination of PSMA plus MRI was superior to MRI in diagnostic performance for detecting PC. A total of 296 men underwent MRI, pelvic-only PSMA, and systematic $\pm$ targeted biopsy. The combination of pMRI plus PSMA PET reduced false negatives for clinically significant PCa compared with pMRI alone, potentially allowing a reduction in the number of prostate biopsies required.[23]

A recent meta-analysis including seven studies (389 patients) reported a pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for the initial diagnosis of PC using ^{68}Ga-PSMA PET/CT of 0.97 (95% CI, 0.90–0.99), 0.66 (95% CI, 0.52–0.78), 2.86 (95% CI, 1.95–4.20), and 0.05 (95% CI, 0.01–0.15), respectively. The authors concluded that this method is a potential rule-out test for these patients.[24]

PSMA PET/CT-guided prostate biopsies may improve diagnostic accuracy in patients with previous negative ultrasound or MRI-guided biopsies.[8] A recent trial assessed the possibility of intraoperative quantification of PSMA PET/CT uptake in core biopsies as an instant confirmation for accurate lesion sampling. They concluded that the technique could improve confidence in imaging-based biopsy guidance and reduce the need for saturation biopsy.[25] A study by Donato *et al.* reported that ^{68}Ga-PSMA-PET/CT had better detection rates for multifocal and bilateral disease compared to mpMRI.[26] In the evaluation of extraprostatic disease, PSMA PET/CT has better diagnostic accuracy compared to mpMRI to reveal seminal vesicle invasion with higher inter-reader agreement.[27,28] Another series of patients demonstrated that ^{68}Ga-PSMA-PET/CT-targeted biopsy has good accuracy in the diagnosis of clinically significant PC, which was not inferior to mPMRI-targeted biopsy, improving the detection rate for cancer of systematic biopsy.[29]

Regarding the prognostic value of standardized uptake value (SUV), a study with 160 patients showed that ^{68}Ga-PSMA-PET/CT is correlated with the aggressiveness of PC. In detail, an SUVmax cutoff of 8 demonstrates 100% accuracy in the diagnosis of grade group $\geq$3 PC.[30]

According to the aforementioned, the combination of structural, multiparametric functional, and molecular information of PSMA PET/MRI would be a challenge for the primary diagnosis of PC. In a recent meta-analysis including seven studies with 225 patients, PET/MRI and PET/CT with 68Ga-PSMA were compared. The overall discrepancy in PET-positive findings between PET/CT and PET/MRI was very low, and agreement between the two methods was high, in the range of 71% to 95%. PET/MRI has 80% lower exposure to radiation than PET/CT but the acquisition time is much longer (60 *versus* 20 min) due to the inclusion of a mpMRI of the prostatic fossa. The latter improves significantly the resolution of prostate scans.[31] One major limitation of PET/MRI up to date is its limited application with major availability only in academic centers.

The above findings need to be validated in prospective studies. Available information up to now suggests that PSMA PET/CT and mpMRI can complement each other in primary T-staging.[8]

N- and T-staging

According to the PC Guidelines Panel and recent ESMO clinical practice guidelines for diagnosis, treatment, and follow-up of PC, PSMA PET/CT is more accurate for staging than CT and bone scan for high-risk disease but to date no outcome data exist to inform subsequent management.[32,33] On the other hand according to the appropriate use criteria (AUC) document for PET-PSMA imaging and EAU-EANM Consensus Statements on the role of PSMA PET/CT in patients with PC, the latter is appropriate for newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk PC with negative/equivocal or oligometastatic disease on conventional imaging.[11,34]

The proPsma trial, a multicenter, two-arm, randomized study, conducted at 10 hospitals in Australia, included men with biopsy-proven high-risk PC, who underwent conventional imaging with CT and bone scanning or ^{68}Ga-PSMA PET-CT. The latter had a 27% greater accuracy than that of the conventional imaging (92% *versus* 65% $p < 0.0001$). Subgroup analyses revealed the superiority of PSMA PET-CT (91% *versus* 59%) for patients with pelvic nodal metastases and 95% *versus* 74% for patients with distant metastases. Conventional imaging had more equivocal findings (23% *versus* 7%) than PSMA PET-CT. Also, radiation exposure was 10.9 mSv higher for conventional imaging. In addition, conventional second-line imaging resulted in changes in clinical management only in 5% of patients *versus* 27% for those who followed PSMA PET-CT.[35]

In another prospective trial (OSPREY) designed to determine the diagnostic accuracy of ^{18}F-DCFPyL PET/CT, the latter presented high specificity (median 97.9%) but limited sensitivity (40%) for the detection of pelvic lymph node metastases. Also, the authors concluded that positive lesions are likely to represent disease, supporting the potential utility of ^{18}F-DCFPyL-PET/

CT to stage men with high-risk PC for nodal or distant metastases.[36]

A prospective validation study of PSMA PET-CT in patients with intermediate- to high-risk PC reported that it can detect lymph node metastases with high specificity and moderate sensitivity, leading to a treatment change in 12.6% of patients.[37] In addition, a systematic review and meta-analysis (13 studies, 1597 patients) compared PSMA PET-CT and MRI for staging of lymph node metastases. ^{68}Ga-PSMA PET had a higher sensitivity and a slightly different specificity when compared with MRI for staging preoperative lymph nodes in intermediate- and high-risk PC.[38] In addition, a prospective study with 26 patients with high-risk PC compared PSMA PET-CT and mpMRI. Ga-PSMA PET/CT detected higher numbers of patients with regional and nonregional lymph nodes in comparison with MRI.[39]

A systematic review with 18 clinical trials and 969 patients revealed a median sensitivity of 59% and a specificity of 93% for primary lymph node staging in PC. Four studies compared PSMA PET with anatomical imaging (CT or MRI) with all reporting superior sensitivity and specificity for PSMA PET.[40] In addition, a multicenter, prospective, phase III imaging trial, assessed the accuracy of PSMA PET imaging for the detection of pelvic nodal metastases compared with histopathology at the time of radical prostatectomy and pelvic lymph node dissection. The sensitivity and specificity of ^{68}Ga-PSMA were 0.40 and 0.95, respectively. The authors noted that 20% of patients who underwent prostatectomy with a negative PET will have nodes on pathology. For this reason, it is important to mention that a negative PET should not discourage pelvic nodal dissection.[41]

Regarding the impact on the management of the disease, a prospective Australian multicenter study assessed whether ^{68}Ga-PSMA PET/CT imaging affects management intent in patients with primary or recurrent PC. Overall, ^{68}Ga-PSMA PET/CT scanning led to a change in planned management in 51% of patients, with 21% in those undergoing primary staging.[42] In any case when we use PSMA PET or whole-body MRI to increase sensitivity, we should be aware of the lack of outcome data of subsequent treatment changes.[32]

Oligometastatic disease is defined as limited metastatic locations (3–5 lesions in up to 2 organ types).[35] A post hoc retrospective cohort study of patients with intermediate-risk and high-risk PC who underwent PSMA PET/CT demonstrated that the latter may detect and rule out more metastatic lesions, which could prove valuable in guiding treatment, downstaging patients with these findings to M0.[43]

Almost all relevant studies revealed the superiority of PSMA PET/CT *versus* the bone scan for the detection of bone metastases. Also, a systematic metanalysis with 1858 patients supported the superior sensitivity and specificity of PSMA PET.[44] PSMA PET/CT is potentially useful for screening castration-resistant PC. A multicenter retrospective study investigated the impact of PSMA PET on Prostate Cancer Clinical Trials Working Group 3 (PCWG3) clinical subtype classification when compared with conventional imaging. Authors reported that PSMA PET demonstrated superior reproducibility and accuracy especially for non-metastatic castration-resistant PC, despite 70% concordance with conventional imaging and should be implemented in future clinical trial entry procedures.[45]

Biochemical recurrence

Biochemical recurrence (BCR) represents the first application of PSMA PET/CT in patients with PC. There is strong evidence supporting the superiority of PSMA tracers *versus* choline either with 18F or 11C for BCR, especially for prostate-specific antigen (PSA) levels <1 ng/mL.[46] According to the AUC document for PET-PSMA imaging, EAU-EANM Consensus Statements, and ESMO clinical practice guidelines for PC, the use of PSMA PET/CT is strongly recommended in cases of BCR, especially for PSA persistence or PSA rise from undetectable level after radical prostatectomy or for PSA rise above nadir after definitive radiotherapy.[11,33,34]

Without particularly differentiating the PC Guidelines Panel for PSA recurrence after radical prostatectomy, there is a strong recommendation to perform PSMA PET/CT in patients fit for curative salvage treatment.[11] A recent meta-analysis for the utility of ^{68}Ga-PSMA PET in biochemically recurrent disease highlights the improvement of detection of metastases, particularly at low pre-PET PSA levels of >0.2 ng/mL

(33%) and 0.2–0.5 ng/mL (45%; micrometastatic disease). Also, they mentioned that significant differences in positivity after biochemical recurrence in the prostate bed were noted between radical prostatectomy (22%) and radiotherapy (52%) patients.[47]

PSMA PET/CT studies showed that a significant proportion of recurrences after radical prostatectomy were located outside the prostatic fossa even at low PSA levels. Combining PSMA PET and MRI may improve the detection of disease. Based on the above, some studies have found that PET/MRI was more accurate than PET/CT in detecting local recurrences, thereby improving the detection rate for lower PSA levels.[31,32]

For patients with BCR in the absence of distant metastases, salvage radiation is a potential treatment option. The potential role of PSMA PET/CT on salvage radiotherapy planning has been assessed in several studies. A post hoc analysis of 270 patients who underwent ^{68}Ga-PSMA-11 PET/CT at four institutions for BCR after prostatectomy without prior radiotherapy at a PSA level of less than 1 ng/mL, demonstrated a major impact on salvage radiotherapy planning in 19% of patients.[48] However, the impact of PET PSMA on the overall survival of PC undergoing salvage radiotherapy patients is yet to be determined.

Higher serum PSA levels are associated with PSMA positivity in BCR. A single-arm prospective trial of 635 patients with biochemically recurrent PC after prostatectomy, radiation therapy, or both who underwent ^{68}Ga-PSMA-11 PET revealed that detection rates significantly increased with PSA: 38% for <0.5 ng/mL, 57% for 0.5 to <1.0 ng/mL, 84% for 1.0 to <2.0 ng/mL, 86% for 2.0 to <5.0 ng/mL, and 97% for ≥ 5.0 ng/mL. Parameters that show strong statistical correlation in the vast majority of studies are ISUP grading, PSA values, PSA doubling time, and clinical setting which are independent predictors of a positive PSMA PET result.[49]

PSMA radionuclide therapy

In mCRPC, which is characterized by disease progression despite ADT, PSMA radionuclide therapy is proposed as a therapeutic option. The VISION, an open-label, phase III trial evaluated ^{177}Lu-PSMA-617 in patients who had metastatic castration-resistant PC previously treated with at least one androgen-receptor–pathway inhibitor and one or two taxane regimens. Patients were randomly assigned to two groups (2:1 ratio). The first received ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks for four to six cycles) plus standard of care, while the second received standard of care alone. ^{177}Lu-PSMA significantly prolonged both imaging-based progression-free survival (PFS) (median, 8.7 *versus* 3.4 months) and overall survival (OS) (median, 15.3 *versus* 11.3 months).[50] After the above results, ^{177}Lu-PSMA-617 was approved by the FDA for the treatment of patients with metastatic castration-resistant PC in March of 2022.

Another randomized phase II trial (Thera-P) compared the activity and safety of cabazitaxel chemotherapy *versus* ^{177} Lu-PSMA-617 therapy in the treatment of men with mCRPC. The group of ^{177} Lu-PSMA-617 was associated with a higher PSA response rate, longer PFS, and fewer severe adverse events.[51]

Both above-mentioned studies took into consideration PSMA expression, assessed with PET/CT at baseline for patients' selection. Patients with tumor uptake greater than the liver were suitable for the VISION study.[50] Physiologic liver uptake is higher with ^{18}F-PSMA 1007 and this affects patient eligibility for radioligand therapy. Instead, the Thera-P trial used quantitative criteria to overcome this limitation. More specifically, patients underwent a screening of PSMA and FDG-PET/CT to confirm high PSMA expression at all sites of disease. Significant PSMA avidity is defined as a minimum uptake of SUVmax >20 at a site of disease, and SUVmax >10 at all other measurable sites of metastatic disease. In addition, patients with sites of disease with FDG intensity $>$ ^{68}Ga-PSMA activity were excluded.[51]

Moreover, according to the report of the Advanced PC Consensus Conference (APCCC) of 2022, PSMA PET/CT was recommended to select patients for radioligand therapy, with the same PSMA threshold as in the VISION trial. Only one-third of panelists proposed FDG PET/CT for PSMA-negative lesions but the majority of them suggested a correlation of PSMA PET findings with the results of contrast-enhanced CT.[52]

Regarding the role of PSMA PET/CT as a prognostic biomarker, a retrospective multicenter cohort study on 301 patients with metastatic castration-resistant PC treated with ^{177}Lu-PSMA

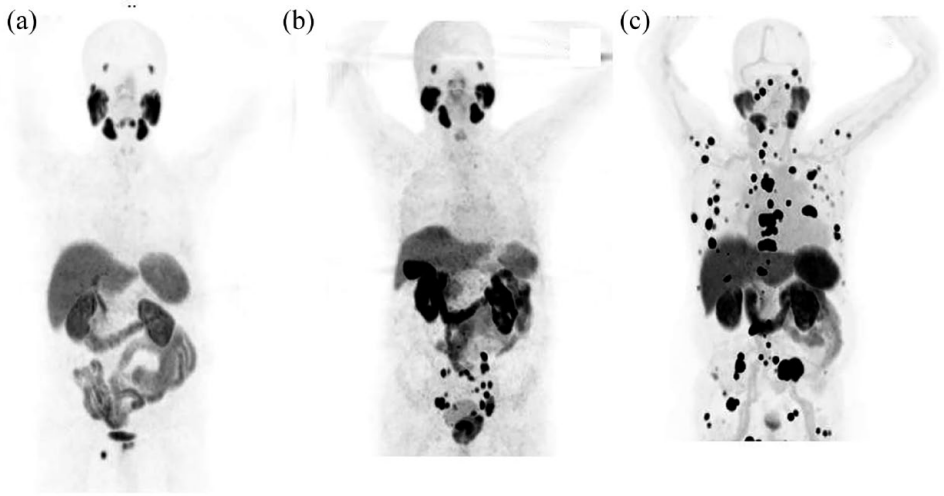

Figure 1. Three cases of ^{18}F-PSMA PET/CT (MIP) for staging of PC. (a) Increased radiotracer uptake at the left side of the prostatic bed (PC) and in a right inguinal lymph node (metastatic lesion). (b) Increased radiotracer uptake in the prostatic bed (PC) and multiple abdominal and pelvic lymph nodes (metastatic disease). (c) Increased radiotracer uptake in multiple bone lesions (metastatic disease).
^{18}F-PSMA, fluorine-18 prostate-specific membrane antigen; MIP, maximum intensity projection; PC, prostate cancer; PET/CT, positron emission tomography/computed tomography.

reported that those who had PSMA PET/CT screen failure by VISION Criteria had a poor outcome after therapy.[53] In a substudy of the Thera-P trial, authors concluded that PSMA SUVmean was predictive of a higher likelihood of favorable response to ^{177}Lu-PSMA-617 therapy than cabazitaxel, which provides guidance for optimal radioligand therapy use. Also, in the same trial, higher FDG metabolic tumor volume was associated with lower responses.[54] On the same topic, several studies report that PSMA total tumor volume is associated with OS and/or PSA response during ^{177}Lu-PSMA-617 therapy while tumor-to-liver ratio independently can predict PFS of this treatment modality.[55]

Conclusion – Key messages

- Although mpMRI is still the 'gold standard' imaging modality for the diagnosis of PC, the addition of PSMA PET/CT imaging can improve the detection of clinically significant PC, especially for PI-RADS 3 lesions.
- PSMA PET/CT is more accurate than CT and bone scan for the initial staging of intermediate-risk to high-risk PC (Figure 1).
- A negative PET-PSMA should not result in the omission of pelvic nodal dissection.
- The increasing use of PSMA PET/CT at the initial staging increases sensitivity, but there is a lack of outcome data of subsequent treatment changes.
- PET-PSMA imaging is appropriate for PSA persistence or PSA rise from an undetectable level after radical prostatectomy or for PSA rise above nadir after definitive radiotherapy.
- ^{177}Lu-PSMA therapy has enriched our armamentarium for the treatment of mCRPC
- Candidates for ^{177}Lu-PSMA therapy should be selected based on strong PSMA expression, as detected by PET/CT at baseline.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Alexander Georgakopoulos: Conceptualization; Data curation; Writing – original draft; Writing – review & editing.

Aristotle Bamias: Conceptualization; Writing – original draft; Writing – review & editing.

Sophia Chatziioannou: Conceptualization; Data curation; Supervision; Writing – original draft; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
All authors made a substantial contribution to the concept or design of the work, acquisition, analysis and interpretation of data, approved the version to be published, and participated sufficiently in the work to take public responsibility for appropriate portions of the content. AG and SC drafted the article and AB revised it critically for important intellectual content. The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

ORCID iD
Aristotle Bamias https://orcid.org/0000-0002-5996-7262

References

1. Kimura T, Sato S, Takahashi H, *et al*. Global trends of latent prostate cancer in autopsy studies. *Cancers (Basel)* 2021; 19; 13: 359.
2. Ferlay J, Parkin DM and Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010; 46: 765–781
3. Posdzich P, Darr C, Hilser T, *et al*. Metastatic prostate cancer – a review of current treatment options and promising new approaches. *Cancers* 2023; 15: 461.
4. Li R, Ravizzini GC, Gorin MA, *et al*. The use of PET/CT in prostate cancer. *Prostate Cancer Prostatic Dis* 2018; 21: 4–21.
5. Calais J, Ceci F, Eiber M, *et al*. (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* 2019; 20: 1286–1294.
6. Schwarzenbock S, Souvatzoglou M and Krause BJ. Choline PET and PET/CT in primary diagnosis and staging of prostate cancer. *Theranostics* 2012; 2: 318–330.
7. Gusman M, Aminsharifi JA, Peacock JG, *et al*. Review of ^{18}F-Fluciclovine PET for Detection of recurrent prostate cancer. *Radiographics* 2019; 39: 822–841.
8. Lisney AR, Leitsmann C, Strauß A, *et al*. The role of PSMA PET/CT in the primary diagnosis and follow-up of prostate cancer—a practical clinical review. *Cancers*. 2022; 14:3638.
9. Kopka K, Benesova M, Barinka C, *et al*. Glu-Ureido–Based inhibitors of prostate-specific membrane antigen: lessons learned during the development of a novel class of low-molecular-weight theranostic radiotracers. *J Nucl Med* 2017; 58: 17S–26S.
10. Moghadam SZ, Askari E and Aryana K. ^{99m}Tc-PSMA left behind: a call for collaboration. *Nucl Med Mol Imaging* 2022; 56: 218–219.
11. Jadvar H, Calais J, Fanti S, *et al*. Appropriate use criteria for prostate-specific membrane antigen PET imaging. *J Nucl Med* 2022; 63: 59–68.
12. Ceci F, Oprea-Lager DE, Emmett L, *et al*. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. *Eur J Nucl Med Mol Imaging* 2021; 48: 1626–1638.
13. Hope TA, Truillet C, Ehman EC, *et al*. 68Ga-PSMA-11 PET imaging of response to androgen receptor inhibition: first human experience. *J Nucl Med* 2017; 58: 81–84.
14. Afshar-Oromieh A, Debus N, Uhrig M, *et al*. Impact of long-term androgen deprivation therapy on PSMA ligand PET/CT in patients with castration-sensitive prostate cancer. *Eur J Nucl Med Mol Imaging* 2018; 45: 2045–2054.
15. Afshar-Oromieh A, Malcher A, Eder M, *et al*. PET imaging with a [68Ga] gallium labeled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. *Eur J Nucl Med Mol Imaging* 2013; 40: 486–495.
16. Farolfi A, Calderoni L, Mattana F, *et al*. Current and emerging clinical applications of PSMA PET diagnostic imaging for prostate cancer. *J Nucl Med* 2021; 10; 62: 596–604.
17. Strauss DS, Sachpekidis C, Kopka K, *et al*. Pharmacokinetic studies of [68Ga]Ga-PSMA-11 in patients with biochemical recurrence of prostate cancer: Detection, differences in temporal distribution and kinetic modelling by tissue type. *Eur J Nucl Med Mol Imaging* 2021; 48: 4472–4482.

18. Anttinen M, Ettala O, Malaspina S, *et al*. A prospective comparison of 18F-prostate-specific membrane antigen-1007 positron emission tomography computed tomography, whole-body 1.5 T magnetic resonance imaging with diffusion-weighted imaging, and single-photon emission computed tomography/computed tomography with traditional imaging in primary distant metastasis staging of prostate cancer (PROSTAGE). *Eur Urol Oncol* 2021; 4: 635–644.
19. Evangelista L, Maurer T, van der Poel H, *et al*. [^{68}Ga]Ga-PSMA versus [^{18}F]PSMA positron emission tomography/computed tomography in the staging of primary and recurrent Prostate cancer. A systematic review of the literature. *Eur Urol Oncol* 2022; 5: 273–282.
20. Wondergem M, van der Zant FM, Broos WAM, *et al*. Matched-pair comparison of 18F-DCFPyL PET/CT and 18F-PSMA-1007 PET/CT in 240 prostate cancer patients; Inter-reader agreement and lesion detection rate of suspected lesions. *J Nucl Med* 2021;62:1422–9.
21. Chen M, Zhang Q, Zhang C, *et al*. Combination of ^{68}Ga-PSMA PET/CT and multiparametric MRI improves the detection of clinically significant prostate cancer: a lesion-by-lesion analysis. *J Nucl Med* 2019;60:944-9.
22. Pepe P and Pennisi M. Targeted biopsy in men high risk for prostate cancer: 68Ga-PSMA PET/CT versus mpMRI. *Clin Genitourin Cancer* 2023;S1558-7673(23)00146-5. doi: 10.1016/j.clgc.2023.06.007. Epub ahead of print. PMID:37394379.
23. Emmett L, Buteau J, Papa N, *et al*. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentrestudy. *Eur Urol* 2021; 80: 682–689.
24. Satapathy S, Singh H, Kumar R, *et al*. Diagnostic accuracy of 68Ga-PSMA PET/CT for initial detection in patients with suspected prostate cancer: a systematic review and meta-analysis. *Am J Roentgenol* 2021; 216: 599–607.
25. Ferraro DA, Laudicella R, Zeimpekis K, *et al*. Hot needles can confirm accurate lesion sampling intraoperatively using [18F]PSMA-1007 PET/CT-guided biopsy in patients with suspected prostate cancer. *Eur J Nucl Med Mol Imaging* 2022;49:1721–1730.
26. Donato P, Roberts MJ, Morton A, *et al*. Improved specificity with 68Ga PSMA PET/CT to detect clinically significant lesions "invisible" on multiparametric MRI of the prostate: a single institution comparative analysis with radical prostatectomy histology. *Eur J Nucl Med Mol Imaging* 2019; 46: 20–30.
27. Privé BM, Israël B, Schilham MGM, *et al*. Evaluating F-18-PSMA-1007-PET in primary prostate cancer and comparing it to multi-parametric MRI and histopathology. *Prostate Cancer Prostatic Dis* 2021; 24: 423–430.
28. Laudicella R, Skawran S, Ferraro DA, *et al*. Quantitative imaging parameters to predict the local staging of prostate cancer in intermediate- to high-risk patients. *Insights Imaging* 2022;13:75.
29. Pepe P, Pepe L, Tamburo M, *et al*. Targeted prostate biopsy: 68Ga-PSMA PET/CT vs. mpMRI in the diagnosis of prostate cancer. *Arch Ital Urol Androl* 2022; 94: 274–277.
30. Pepe P, Pepe L, Tamburo M, *et al*. 68Ga-PSMA PET/CT and prostate cancer diagnosis: which SUVmax value? *In Vivo* 2023; 37: 1318–1322.
31. Evangelista L, Zattoni F, Cassarino G, *et al*. PET/MRI in prostate cancer: a systematic review and meta-analysis. *Eur J Nucl Med and Mol Imaging* 2021; 48: 859–873.
32. Mottet N, Cornford P, van den Bergh RCN, *et al*. *EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer*. European Association of Urology, 2022. http://uroweb.org/guideline/prostate-cancer/
33. Parker C, Castro E, Fizazi K, *et al*. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020; 31: 1119–1134.
34. Fanti S, Briganti A, Emmett L, *et al*. EAU-EANM consensus statements on the role of prostate-specific membrane antigen positron emission tomography/computed tomography in patients with prostate cancer and with respect to [^{177}Lu]Lu-PSMA radioligand therapy. *Eur Urol Oncol* 2022; 5: 530–536.
35. Hofman MS, Lawrentschuk N, Francis RJ, *et al*. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet* 2020; 395: 1208–1216.
36. Pienta KJ, Gorin MA, Rowe SP, *et al*. A phase 2/3 prospective multicenter studyof the diagnostic accuracy of prostate specific membrane antigen PET/CT with 18F-DCFPyL in prostate cancer patients (OSPREY). *J Urol* 2021; 206: 52–61.
37. van Kalmthout LWM, van Melick HHE, Lavalaye J, *et al*. Prospective validation of gallium-68 prostate specific membrane antigen-positron emission tomography/computerized

tomography in primary staging of patients with prostate cancer. *J Urol* 2020; 203: 537–545.

38. Wu H, Xu T, Wang X, *et al.* Diagnostic performance of (68)Gallium labelled prostate-specific membrane antigen positron emission tomography/computed tomography and magnetic resonance imaging for staging the prostate cancer with intermediate or high risk prior to radical prostatectomy: a systematic review and meta-analysis. *World J Mens Health* 2020; 38: 208–219.
39. Tulsyan S, Das CJ, Tripathi M, *et al.* Comparison of 68Ga-PSMA PET/CT and multiparametric MRI for staging of high-risk prostate cancer 68Ga-PSMA PET and MRI in prostate cancer. *Nucl Med Commun* 2017; 38: 1094–1102.
40. Petersen LJ and Zacho HD. PSMA PET for primary lymph node staging of intermediate and high-risk prostate cancer: an expedited systematic review. *Cancer Imaging* 2020; 20: 10–19.
41. Hope TA, Eiber M, Armstrong WR, *et al.* Diagnostic accuracy of 68Ga-PSMA-11 PET for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: a multicenter prospective phase 3 imaging trial. *JAMA Oncol* 2021; 7: 1635–42.
42. Roach PJ, Francis R, Emmett L, *et al.* The impact of ^{68}Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study. *J NuclMed* 2018; 59: 82–88.
43. Lenis AT, Pooli A, Lec PM, *et al.* Prostate-specific membrane antigen positron emission tomography/computed tomography compared with conventional imaging for initial staging of treatment-naïve intermediate- and high-risk prostate cancer: a retrospective Single-center study. *Eur Urol Oncol* 2022; 5: 544–552.
44. Zacho HD, Nielsen JB, Haberkorn U, *et al.* 68Ga-PSMA PET/CT for the detection of bone metastasesin prostate cancer: a systematic review of the published literature. *Clin Physiol Funct Imaging* 2018;38:911–22.
45. Farolfi A, Hirmas N, Gafita A, *et al.* Identification of PCWG3 target populations is more accurate and reproducible with PSMA PET than with conventional imaging: a multicenter retrospective study. *J Nucl Med* 2021; 62: 675–678.
46. Afshar-Oromieh A, Zechmann CM, Malcher A, *et al.* Comparison of PET imaging with a (68) Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2014; 41: 11–20.
47. Perera M, Papa N, Roberts M, *et al.* Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer-updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. *Eur Urol* 2020; 77: 403–417.
48. Calais J, Czernin J, Cao M, *et al.* (68) Ga-PSMA-11 PET/CT mapping of prostate cancer biochemical recurrence after radical prostatectomy in 270 patients with a PSA level of less than 1.0 ng/mL: Impact on salvage radiotherapy planning. *J Nucl Med* 2018; 59: 230–237.
49. Fendler WP, Calais J, Eiber M, *et al.* Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. *JAMA Oncol* 2019; 5: 856–863.
50. Sartor O, de Bono J, Chi KN, *et al.* Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med* 2021; 385: 1091–1103.
51. Hofman MS, Emmett L, Sandhu S, *et al.* [(177) Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet* 2021; 397: 797–804.
52. Gillessen S, Bossi A, Davis ID, *et al.* Management of patients with advanced prostate cancer-metastatic and/or castration-resistant prostate cancer: report of the advanced prostate cancer consensus conference (APCCC) 2022. *Eur J Cancer* 2023; 185: 178–215.
53. Hotta M, Gafita A, Czernin J, *et al.* Outcome of patients with PSMA-PET/CT screen failure by VISION criteria and treated with (177)Lu-PSMA therapy: a multicenter retrospective analysis. *J Nucl Med* 2022; 63: 1484–1488.
54. Buteau JP, Martin AJ, Emmett L, *et al.* PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [^{177}Lu] Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): a biomarker analysis from a randomised, open-label, phase 2 trial. *Lancet Oncol* 2022; 23: 1389–1397.
55. Heidegger I, Kesch C, Kretschmer A, *et al.* Biomarkers to personalize treatment with 177Lu-PSMA-617 in men with metastatic castration-resistant prostate cancer – a state of the art review. *Ther Adv Med Oncol* 2022; 14: 17588359221081922.