New perspectives on metabolic imaging in the management of prostate cancer in 2022: A focus on radiolabeled PSMA-PET/CT (Review)

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Abstract. Nuclear medicine is an essential part of prostate cancer management concerning initial staging, patient follow-up and even therapy. Prostate-specific membrane antigen (PSMA) is a glutamate carboxypeptidase II transmembrane glycoprotein expressed by 80% of prostatic cells. The interest in this protein is due to its specificity for prostatic tissue. The use of 68GaPSMA PET/CT in the context of disease staging is thus well-established and recommended, especially for high-risk disease with metastases and lymph node involvement. However, the risk of false positives raises questions regarding its place in the management of patients with prostate cancer. The present study aimed to determine the use of PET-PSMA in the care of patients with prostate cancer but also to assess its limits of use.

Contents

1. Introduction

Prostate cancer is the second most common cancer affecting men worldwide, with 1.41 million cases in 2020 according to the World Health Organization, and is responsible for 375000 deaths every year (1).

Optimal patient care is based on clinical features as well as biological, histological and imaging data. With such information, clinicians are better able to offer suitable therapeutic options to their patient. Nuclear medicine is an essential part of prostate cancer management concerning initial staging, patient's follow-up and even therapy. In fact, developments in metabolic imaging techniques, from bone scintigraphy to positron emission tomography/computed tomography (PET/CT), have led to more accurate initial diagnosis as well as diagnosis of cancer recurrence during patients' follow-up period.

In this article, we will discuss more specifically the interest of prostate-specific membrane antigen (PSMA), a promising radiotracer.

PSMA is a glutamate carboxypeptidase II transmembrane glycoprotein expressed by 80% of prostatic cells (2). Its interest resides in its specificity for prostatic tissue, including carcinoma cells, with the caveat that its fixation to some other non-prostatic malignancies and benign lesions can result in false positives.

In recent years, the potential of prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) has been widely recognized, both as a tool in the diagnosis and follow-up of intermediate and high-risk prostate cancer as well as theranostic applications. However, the risk of false positives raises questions about its place in the management of patients with prostate cancer.

Despite updates on prostate cancer management guidelines from globally influential associations such as the European Association of Urologists or the American Society of Clinical Oncology, the place of PSMA PET/CT in everyday practice remains unclear (3,4).

The aim of this article is to review the contribution of 68Ga-PSMA PET/CT to initial staging and diagnosis, to clarify its use in patients' follow-up and to discuss the theranostic use of 177-Lutetium-PSMA (177Lu-PSMA). Finally, we will consider possible resistance mechanisms and ways to overcome them, along with other new radionuclides associated with PSMA.

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2. Clinical staging and initial management impact

T-staging. Clinical T staging is based initially on digital rectal exam (5,6). In recent years, however, MRI has clearly emerged as a staging tool, including initial staging, due to its high sensitivity for local staging in intermediate and high-risk prostate cancer and excellent negative predictive value in low-risk patients (7). This is an important consideration in the decision-making process with regard to nerve sparing strategies in radical prostatectomy for this group (8).

In a retrospective study assessing the accuracy of 68Ga-PSMA PET/CT compared with multiparametric MRI (mpMRI) in primary prostate cancer lesions, Kalapara *et al* reported no significant difference for the detection of any tumor (94% vs. 95%, P>0.9) and localization of all tumors (91% vs. 89%, P=0.47) (9).

N-staging. 68Ga-PSMA PET/CT has proven its usefulness in lymph node detection for intermediate and high-risk patients in several studies (10).

In a meta-analysis including a total of 1,597 patients, Wu *et al* showed that 68Ga-PSMA had both higher sensitivity and specificity [0.65 (95% CI: 0.49-0.79) and 0.94 (95% CI: 0.88-0.97)] compared with MRI [0.41 (95% CI: 0.26-0.57) and 0.92 (95% CI: 0.86-0.95)] for the detection of lymph node metastases in the staging workup for intermediate or high-risk prostate cancer (11).

Similarly, Herlemann *et al*, comparing the accuracy of 68Ga-PSMA and Computed Tomography (CT) in detecting lymph node metastases, reported higher sensitivity (84% vs. 65%), specificity (82% vs. 76%), positive predictive value (84% vs. 75%), and negative predictive value (82% vs. 67%) with 68Ga-PSMA (12).

However, the implications for patient care are not entirely clear. A multicenter prospective phase 3 imaging trial by Hope *et al* assessing the accuracy of 68Ga-PSMA PET/CT compared with histopathology for the detection of pelvic lymph node metastases in intermediate to high-risk prostate cancer found relatively low sensitivity [0.40 (95% CI: 0.34-0.46)] and high specificity [0.95 (95% CI: 0.92-0.97)] (13).

Given that other studies similarly report low (24.4%) or moderate (41.5%) sensitivity, 68Ga-PSMA-PET/CT cannot replace lymph node dissection in the staging of pelvic lymph nodes (14,15).

M-staging. Distant metastases from prostate cancer are mostly localized in bones. The classic work-up to evaluate the presence of metastatic localizations in prostate cancer is CT and bone scan.

The proPSMA study assessed the impact of 68GaPSMA PET/CT on the diagnosis and management of patients with localized high-risk prostate cancer (16). 68GaPSMA PET/CT clearly improves the accuracy of diagnosis and the staging of the disease, given that PSMA PET-CT showed a 27% (95% CI 23-31) increase in accuracy compared to conventional imaging [92% (88-95) vs. 65% (60-69); P<0.0001].

68GaPSMA PET/CT seems also suited to detect rarer metastatic sites, for example brain metastasis as described in Chakraborty *et al* case report (17).

The use of 68GaPSMA PET/CT in the context of disease staging is thus well-established and recommended, especially for high-risk disease with metastases and lymph node involvement.

But would more accurate staging change our management strategies? And does it have an impact on the survival of our patients?

Management impacts. Using 68Ga-PSMA PET/CT for initial staging could clearly have an impact on the therapeutic management due to changes in the staging of the disease.

Hofman *et al* reported a change of management in 28% vs. 15% (P=0.008) of patients for 68GaPSMA PET/CT and conventional imaging, respectively. Among its advantages, 68GaPSMA PET/CT involves less radiation exposure, produces fewer equivocal findings than conventional imaging and, finally, the cost is lower given that PSMA PET/CT is a single test in addition to being more accurate (16).

The PSMA dRT trial (NCT04457245), a phase 3 multicenter randomized trial, assessed the impact of 68GaPSMA PET/CT on patient selection, radiotherapy planning and improvement in patient outcomes (18).

Preliminary results, as presented at the American Society of Clinical Oncology GU congress, showed a change between the pre-randomization radiotherapy (RT) plan and the delivered RT plan for 28% of patients in the control arm vs. 57% in the PSMA arm (P=0.002). Initial RT was replaced by systematic therapy and/or metastasis-directed RT in 3% vs. 17% (P=0.17), while dose prescription and/or target volume delineation was changed in 3% vs. 26% (P=0.001) of the control and PSMA arms respectively (19).

Calais *et al* reported upstaging by 68Ga-PSMA-PET/CT in 43% of the patients initially diagnosed with localized disease: 9.5% were M1 and 34% were N1, 16.5% had at least 1 positive lesion not covered by either the prostate consensus CTV or the pelvic LN consensus CTV while radiation field required a major change for 32% (20).

Likewise, in a prospective study of 197 patients undergoing scans for various non-classical clinical indications, Sonni *et al* reported that PSMA PET/CT led to a change in the assessment of disease stage in 69% of patients (38% upstaging vs. 30% downstaging) and a change in management for 57% (21).

The ORIOLE study, a phase 2 randomized study, assessed the efficacy of stereotactic ablative radiotherapy (SABR) in men with oligometastatic prostate cancer (22).

This study emphasized the importance of treating lesions detected by 18Ga-PSMA. Indeed, for patients with no untreated lesions median PFS was unreached, as opposed to 11.8 months for untreated lesions [HR 0.26 (95% CI: 0.09-0.76), P=0.006], while the proportion of new metastatic lesions at 180 days was reduced from 62.5 to 15.8%.

However, caution must be taken given the lack of available data concerning a potential improvement in patient outcomes and the risk of false positives (23,24).

68Ga-PSMA: a prognostic factor? Many studies have examined a potential correlation between the clinical parameters of prostate cancer (Gleason score, PSA level, lymph nodes metastasis or distant metastasis) with the intensity of PSMA accumulation in the tumor (25-27). Patients with PSA

>10 ng/ml, Gleason score >7, lymph node metastasis or distant metastasis had significantly higher SUVmax in the primary tumor than their counterparts, for each factor.

Amiel *et al* assessed the predictive value of 68Ga-PSMA PET/CT for surgical response in patients with prostate cancer, prior to radical prostatectomy (28). 68Ga-PSMA PET/CT found extraprostatic disease sites in 14.1% of the patients. Among patients with disease confined to the prostate, 82.9% achieved a surgical response, compared to 28.6% in males with extraprostatic disease identified with 68Ga-PSMA PET/CT (P<0.001). Extraprostatic disease identified with 68Ga-PSMA PET/CT is thus clearly a prognostic factor of poor surgical response (23).

Moreover, outcomes of patients with a positive 68-PSMA PET/CT but who would have been screen failures for the VISION trial was assessed in a multicenter retrospective analysis (29). These patients presented worse outcomes with respect to PSA response rate, PSA-progression free survival and overall survival than patients who were classified as eligible for the VISION trial. Moreover, PSMA average is a better prognosticator of overall survival than PSMAmax (HR: 0.959; P=0.047 vs. HR: 0.992; P=0.231), as reported by Seifert *et al* (30).

3. Monitoring after local treatment

Detecting local recurrence or distant metastases after biochemical recurrence. After local treatment, patients' follow-up is based on clinical examination and PSA levels (3,5,6). In case of biochemical recurrence, it is essential to distinguish between local recurrence and distant metastases, with a corresponding impact on the patient's management. Imaging techniques have a decisive role in this setting.

Most of the time a minor rise in PSA levels does not allow conventional imaging to detect local recurrence or distant metastasis. 68Ga-PSMA PET/CT has demonstrated its superiority in detecting recurrences compared to standard of care and particularly in comparison with choline tracers (31). Because of the poor sensitivity of choline tracers at low PSA levels, Morigi *et al* compared the detection rates of 18F-fluoromethylcholine with those of 68Ga-PSMA following radical prostatectomy and/or radiation treatment in 38 men with rising PSA who were candidates for targeted therapy. Positive scan results were obtained in 26 patients (68%), of which 14 (54%) by 68Ga-PSMA alone, 11 (42%) by 68Ga-PSMA and 18F-fluoromethylcholine, while 18F-fluoromethylcholine alone produced only a false positive (32). At PSA levels of <0.5, 0.5-2 and >2 ng/ml, detection rates for 68Ga-PSMA vs. 18F-fluromethylcholine were respectively 50% vs. 12.5%, 69% vs. 31% and 86% vs. 57%. The detection rate with 68Ga-PSMA it thus significantly higher than with 18F-fluromethylcholine.

A meta-analysis by Hope *et al* assessed the accuracy of 68Ga-PSMA PET/CT for the detection of prostate cancer compared to histopathology. A total of 256 patients with biochemical recurrence were enrolled across 15 studies, of which 233 were reported as true positive lesions (33). The predictive positive value was 0.99 (95% CI 0.96-1.00). The detection rate for 68Ga-PSMA increased with the PSA levels from 0.63 (95% CI 0.55-0.70) with a PSA <2.0 ng/ml to 0.94 (95% CI 0.91-0.96) with a PSA >2.0 ng/ml.

Another study, a multicenter prospective clinical trial by McCarthy *et al* evaluating the diagnostic performances of 68Ga-PSMA PET/CT, focused on patients with biochemical recurrence after local treatment and bone scan and computed tomography (CT) showing no lesions or oligometastatic disease (34). Among patients with no lesions on CT and bone scan, 74% were found to have positive lesions on 68Ga-PSMA PET/CT, with 57% oligometastatic disease. Among patients with oligometastatic disease on the CT and bone scan, 49% were confirmed as oligometastatic and 41% were upstaged to polymetastatic. No notable adverse were observed. This study thus demonstrates that 68Ga-PSMA PET/CT is not only safe, but highly accurate, with a positive predictive value of 0.84 (95% CI, 0.75-0.90) to 0.92 (95% CI, 0.88-0.95), as confirmed by histopathology and the composite reference standard. Furthermore, a PSA drop of 50% or more in 80% of patients has been observed with PET-directed focal therapy (35). 68Ga-PSMA PET/CT is becoming the standard imaging modality for the management of patients with relapsed prostate cancer after local therapy.

However, the specificity of 68Ga-PSMA is not perfect and despite its 'prostate specific' naming, PSMA protein expression can be found in normal tissue (like ganglia of the sympathetic trunk) and in several benign or malignant tumors, leading to potential false positive (36,37).

Management impacts. 68Ga-PSMA PET/CT has a clear impact on the management strategy for patients with biochemical recurrence of prostate cancer.

Several studies, including a prospective survey of physicians, have already shown that information from 68Ga-PSMA PET/CT changes management in more than half of the patients with biochemical recurrence of prostate cancer (38-40).

It has been established that this innovative imaging modality could benefit patients, but randomized prospective trials are needed to determine whether it can really improve outcomes.

More information on patient outcomes will hopefully become available in the near future from studies such as the ongoing randomized prospective phase 3 trial by Calais *et al* which aims to evaluate how PSMA PET/CT findings may affect RT planning and ultimately the success rate of salvage radiotherapy for prostate cancer recurrence after prostatectomy (41).

4. A theranostic approach with 177Lu-PSMA-617 therapy

177Lu-PSMA-617 therapy outcomes. When it disintegrates, 177-Lutetium produces β-radiation, used to induce cells death, and g radiations, used for scintigraphy. This principle can be applied to prostate cancer through PSMA.

The first case report on this innovative technology was published in 2015. The patient presented a metastatic prostate cancer with strong PSMA expression on his PET/CT (42). The patient's radiological response was significant and his PSA level decreased from 38.0 to 4.6 ng/ml. This case report encouraged clinical trials to investigate the potential as a treatment for prostate cancer.

Rahbar *et al* assessed efficacy and safety of 177Lu-PSMA-617 in a retrospective multicenter study with a cohort of

145 patients. Biochemical response, defined as a ≥50% decline in PSA, the primary endpoint of the study, was achieved in 45% of patients, most of whom (58%) after a single cycle. Only 24 grade 3-4 adverse events were reported, most commonly anemia, and no cases of therapy-related death (43).

Likewise, Heck *et al* evaluated the efficacy and safety of 177Lu-PSMA-617 in 100 patients treated with 177Lu-PSMA-617 as a compassionate protocol. Median clinical PFS of 4.1 months and median overall survival of 12.9 months were both extended for the subgroup of patients who achieved a ≥50% decline in PSA. Hematologic grade ¾ toxicities were observed in 19% of patients, but no other grade ¾ toxicities were noted (44).

These findings were confirmed by the LuPSMA trial, a single-arm, single-center, phase 2 trial: 57% of the patients treated with 177Lu-PSMA-617 achieved a PSA decline of at least 50% (45).

Moreover, the benefits of rechallenge with 177Lu-PSMA-617 after progression have been demonstrated in another study on long-term follow-up (46).

Two multicenter, open-label, randomized trials in particular support the use of 177Lu-PSMA as a therapy in advanced metastatic prostate cancer.

In the TheraP trial, as reported by Hofman *et al*, patients with metastatic castration-resistant prostate cancer were randomly assigned to receive either 177Lu-PSMA-617 or cabazitaxel. Treatment with Lu-PSMA-617 resulted in a higher PSA response (66% vs. 44% by treatment received, P=0.0016), fewer grade 3 or 4 adverse events (33% vs. 53%) and no deaths attributed to Lu-PSMA-617 (47).

The efficacy of 177Lu-PSMA-617 compared with standard care (excluding chemotherapy, immunotherapy and radium-223) was assessed by Sartor *et al* in the VISION trial, the primary endpoints of which were progression-free survival (imaging-based) and overall survival. Median PFS was 8.7 months in the 177Lu-PSMA-617 arm (vs. 3.4 months, HR progression/death=0.40, P<0.001) while median overall survival was 15.3 months (vs. 11.3 months; HR death=0.62, P<0.001). A higher incidence of grade-3 adverse events was observed with 177Lu-PSMA-617 (52.7% vs. 38.0%), but did not affect quality of life according to assessments using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory-Short Form (BPI-SF) (48).

Numerous studies to reveal the benefit of 177Lu-PSMA-617 in different scenarios are still under way.

The REALITY study, which also analyzed the efficacy and safety of 177Lu-PSMA in 254 elderly, heavily pretreated patients with late/end-stage disease, found a ≥50% decline in PSA, median PSA-PFS of 5.5 (95% CI 4.4-6.6) months and median OS of 14.5 (95% CI 11.5-17.5) months (49). The most common grade 3/4 adverse events were anemia 8.3% (95% CI 5.5-12.3), fatigue 7.1% (95% CI 4.5-10.9) and thrombocytopenia 4.3% (95% CI 2.4-7.6), with no treatment-related deaths. In keeping with findings by Heck *et al*, early biochemical response again seems to be a significant prognostic factor (44).

The BULLSEYE trial is a multicenter, open-label, randomized controlled trial that aims to prove the benefits of 177Lu-PSMA-617 in oligometastatic hormone sensitive prostate cancer (50).

177Lu-PSMA-617 appears set to take its place in the coming years as an effective, safe treatment for prostate cancer in earlier stages.

Patient selection and resistance mechanisms. 68Ga-PSMA PET/CT parameters can assist in the selection of responder patients.

Erdogan *et al* studied the predictive value of 68Ga-PSMA PET/CT parameters, SUVmax, PSMA TV, TL PSMA, before 177Lu-PSMA with respect to treatment response (51).

The AUC value for SUVmax was significant (AUC=0.677; P<0.001).

From a therapeutic point of view, Peters *et al* found that [68Ga]Ga-PSMA-PET can be used to predict the absorbed dose of [177Lu]Lu-PSMA therapy in organs, and to a lesser extent in lesions, which could help to personalize treatment by maximizing doses without exceeding the threshold for at-risk organs like the kidneys or liver (52).

With these results in mind, heterogeneity of PSMA expression across metastases or within individual lesions could still be detrimental for 177Lu-PSMA efficacy. This issue was raised by Paschalis *et al* with heterogeneity detected between metastases and even within the tumour (53). They reported that 42% of castration-sensitive prostate cancer and 27% of mCRPC tissues sampled had no detectable membranous PSMA. Demonstrating the evolutivity of PSMA expression during the disease and influence by different treatments, Lückerath *et al* have published a preclinical study showing that androgen receptor blockade can increase PSMA expression (54). Based on the evidence of synergistic effects, the Enza-p trial, an ongoing randomized phase 2 trial, assesses the efficacy of the combination of enzalutamide and 177Lu-PSMA (55).

Mutational status seems to have an impact as well on cancer response to radioligand therapy. In addition to its usefulness as a prognostic factor for the development of distant metastases, progression free survival and overall survival in prostate cancer, p53 status could influence the response to 177Lu-PSMA (56). In a preclinical study, Stuparu *et al* reported that p53 loss seems to make prostate cancer resistant to radioligand therapy (57).

Likewise, tumors with defective DNA damage repair had higher mPSMA expression which could incite further investigations.

In the castration-resistant metastatic stage, small cell transformation is possible (58). In order to detect both components of the disease and its aggressiveness, it seems important to use 18F-FDG PET/CT and 68GaPSMA PET/CT. Parghane and Basu reported the usefulness of dual tracer 68GaPSMA PET/CT and 18F-FDG PET/CT in assessing this transformation (59).

Improving responses to 177Lu-PSMA therapy. By knowing and understanding the resistance mechanisms to 177Lu-PSMA therapy, we can find ways to improve patients' response to this treatment.

As mentioned previously, androgen receptor blockage can increase PSMA expression and increase the number of lesions visualized on 68Ga-PSMA PET/CT (60). The Enza-p trial results will provide more data on this subject.

Table I. Place of 68Ga-PSMA PET/CT in the care of patients with prostate cancer.

A, Clinical staging and initial management impact

First author, year	Focus area	Summary of findings	Should we use the 68Ga-PSMA PET/CT in this case?	(Refs.)
Kalapara *et al*, 2020	T-staging	•Digital rectal exam •MRI for local staging in intermediate and high-risk prostate cancer •No significant difference for the detection of tumors between 68Ga-PSMA PET/CT and MRI	•No	(9)
Wu *et al*, 2020; Herlemann *et al*, 2016; Hope *et al*, 2021	N-staging	•68Ga-PSMA PET/CT has proven better accuracy compared with MRI and CT for medium/high risk prostate cancer •68Ga-PSMA-PET/CT cannot replace lymph node dissection	•Yes	(11-13)
Hofman *et al*, 2020	M-staging	•68GaPSMA PET/CT improves the accuracy of metastasis detection for high-risk prostate cancer and metastatic stage	•Yes	(16)
Hofman *et al*, 2020; Calais *et al*, 2021; Calais *et al*, 2021; Calais *et al*, 2018; Phillips *et al*, 2020	Management impacts	•Less radiation exposure, fewer equivocal findings than conventional imaging, lower cost •Leads to a change in the assessment of disease stage in the majority of the patients and therefore to a change in management •Improvement in patient outcomes? Risk of false positives? Prospective studies needed.	•Yes	(16,18-20, 22)
Amiel *et al*, 2021; Hotta *et al*, 2022	68Ga-PSMA: a prognostic factor?	•PSA >10 ng/ml, Gleason >7, lymph node metastasis or distant metastasis: higher SUVmax in the primary tumor •Extraprostatic disease identified with 68Ga-PET/CT: a PSMA prognostic factor of poor surgical response •Worse outcomes for patients with PSMA PET/CT Screen Failure by VISION Criteria and treated with 177Lu-PSMA Therapy	•Yes	(28,29)

Table I. Continued

B, Monitoring after local treatment

First author, year	Focus area	Summary of findings	Should we use the 68Ga-PSMA PET/CT in this case?	(Refs.)
Morigi *et al*, 2015; Hope *et al*, 2019; McCarthy *et al*, 2019	Biochemical recurrence	•68Ga-PSMA PET/CT: a safe and highly accurate way to detect local recurrence or distant metastasis after biochemical recurrence	•Yes	(32-34)
Calais *et al*, 2018; Calais *et al*, 2019	Management impacts	•68Ga-PSMA PET/CT changes management in more than half of the patients with biochemical recurrence •Ongoing randomized phase 3 trial to evaluate how PSMA PET/CT findings may affect patient outcomes	•Maybe	(39,41)

C, 177Lu-PSMA-617 therapy

First author, year	Focus area	Summary of findings	Should we use the 68Ga-PSMA PET/CT in this case?	(Refs.)
Hofman *et al*, 2018; Sartor *et al*, 2021; Khreish *et al*, 2022; Privé *et al*, 2021	Outcomes	•High PSA response and better overall survival rates with few adverse events in patients with metastatic castration-resistant prostate cancer •Ongoing trials for earlier stages of the disease •Demonstrated benefits of rechallenge with 177Lu-PSMA -617 after progression	•Yes for PSMA positive patients	(36,48-50)
Peters *et al*, 2022; Paschalis *et al*, 2019; Rosar *et al*, 2020; Stuparu *et al*, 2021; Nadal *et al*, 2014	Patient selection and resistance mechanisms	•68Ga-PSMA PET/CT parameters can assist in the selection of responder patients •Heterogeneity of PSMA expression across metastases or within individual lesions could be detrimental for 177Lu-PSMA efficacy •Androgen receptor blockade could increase PSMA expression •p53 status could influence the response to 177Lu-PSMA •Small cell transformation after androgen deprivation therapy can lead to a diminution of the tumor's avidity for 68Ga-PSMA: interest of a dual-tracer PET/CT with 18F-FDG?	•Maybe	(52,53, 55,57,58)

Table I. Continued

C, 177Lu-PSMA-617 therapy

First author, year	Focus area	Summary of findings	Should we use the 68Ga-PSMA PET/CT in this case?	(Refs.)
Hope *et al*, 2017	Improving responses to 177Lu-PSMA therapy	Benefit of associating177Lu-PSMA with other therapies as radiation sensitizers?	•Yes	60

D, New PSMA-associated radionuclides

First author, year	Focus area	Summary of findings	Should we use the 68Ga-PSMA PET/CT in this case?	(Refs.)
Schuster *et al*, 2022; Morris *et al*, 2021; Olivier *et al*, 2022; Hoffmann *et al*, 2022	Diagnostic	•Promising 18F-labeled PSMA ligands: 18F-rhPSMA-7.3, 18F-DCFPyl, 18F-PSMA-1007	•Yes	(61,63-65)
Müller *et al*, 2019	Therapy	•161Tb-PSMA: superior *in vitro* and *in vivo* results with respect to tumor cell viability compared to 177Lu-PSMA •225Ac-PSMA-617 undergoing evaluation in a phase 1 study •Further studies needed to support a clinical use		(66)

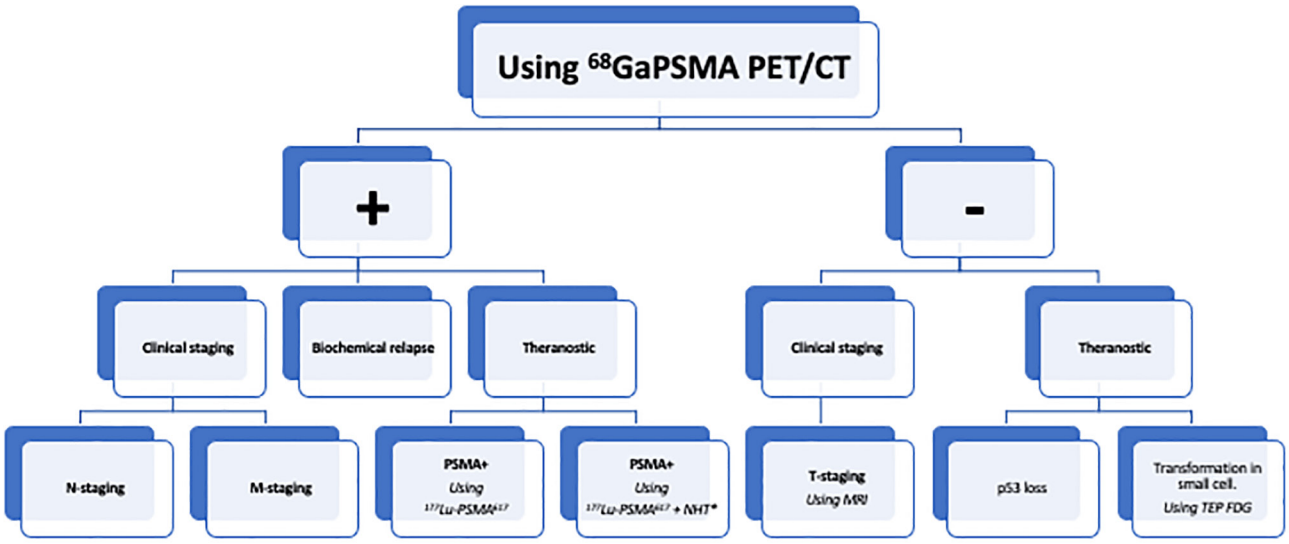

Figure 1. The place of ^{68}GaPSMA PET/CT in the care of patients with prostate cancer. *Trials ongoing. ^{68}GaPSMA PET/CT, ^{68}gallium prostate-specific membrane antigen positron emission tomography/computed tomography; NHT, new hormonal therapy; PSMA PET/CT, prostate-specific membrane antigen positron emission tomography/computed tomography.

Several ongoing trials are testing the benefit of associating 177Lu-PSMA with other therapies as radiation sensitizers: Olaparib for the LuPARP trial (NCT03874884), NOX66 for the LuPIN trial (ACTRN12618001073291), or immunotherapy in different trials like the PRINCE trial (NCT03658447) or the EVOLUTION trial (NCT05150236). The results of these

studies have great potential to help personalize patients' care and improve the response to radioligand therapy, and in particular 177Lu-PSMA-617 therapy.

5. New PSMA-associated radionuclides

The value of PSMA is due largely to its specificity to prostatic cells, but other radionuclides than 68-Gallium and 177-Lutetium are being examined for use in imaging and therapy.

Several 18F-labeled PSMA ligands seem promising in terms of diagnostic techniques.

A phase 3 prospective multicenter study by Schuster *et al* (SPOTLIGHT NCT04186845) assessing detection rate and positive predictive value for 18F-rhPSMA-7.3 PET in 389 patients with suspected prostate cancer recurrence found overall detection and patient-level correct detection rates of 83 and 56.8% respectively over a wide range of PSA levels (median 1.10 ng/ml, range 0.03-134.6). Although PPV, at 59.7% (95% CI 54.7-64.7), did not meet its prespecified threshold, this was attributed to the high proportion of conventional imaging in the composite Standard of Truth, whereas the threshold would have been reached if histopathology alone were taken as Standard of Truth. These findings thus encourage the use of 18F-rhPSMA-7.3 PET/CT in men with recurrent prostate cancer (61).

18F-DCFPyl has also been evaluated through different studies. The OSPREY trial assessed the accuracy of this radiotracer with PET/CT for detecting metastatic prostate cancer. It presented good specificity but a level of sensitivity that did not meet the prespecified endpoint. Nevertheless, the high positive predictive value suggests that 18F-DCFPyl could prove useful in staging high-risk prostate cancers or detecting metastatic recurrences (62).

Another phase 3 prospective multicenter study by Morris *et al* assessing 18F-DCFPyL-PET/CT in patients with suspected biochemical recurrence, CONDOR, reported disease detection rates of 59.1-65.9% and correct localization rates of 84.8-87.0% among three independent readers. Findings obtained by means of 18F-DCFPyL-PET/CT led to a change in management for 64% of patients. Only one grade-3 adverse event was observed, and no grade-4 events or deaths. These results thus confirm the usefulness of 18F-DCFPyL-PET/CT to help detect and localize recurrent prostate cancer (63).

As a last example, 18F-PSMA-1007 has showed a significatively better overall correct detection rate than 18F-fluorocholine PET/CT (0.82 vs. 0.65 or 0.77 vs. 0.57 depending on whether undetermined findings were considered respectively as positive or negative for malignancy) leading to a more adequate management of prostate cancer with biochemical recurrence in a phase 3 prospective randomized multicenter study (64). Hoffmann *et al* showed comparable performance for 18F-PSMA-1007 and 68Ga-PSMA PET/CT in prostate cancer initial staging with a sensitivity, specificity, positive predictive value and accuracy of 62, 85, 92 and 67% respectively for 18F-PSMA-1007 and 54, 91, 93 and 66%% for 68Ga-PSMA (65).

In terms of therapeutic options, Terbium-161 has been tested as a radionuclide associated with PSMA for radioligand therapy. Müller *et al* compared 161Tb-PSMA to 177Lu-PSMA and showed superior *in vitro* and *in vivo* results with respect to tumor cell viability (66). Further studies will be needed to support a clinical use. This is true for 225Ac-PSMA-617 as well, which is currently undergoing evaluation in the AcTION trial, a phase 1 study of 225Ac-PSMA-617 in PSMA-positive prostate cancer with extensive skeletal metastases (NCT04597411).

6. Conclusion

Radiolabeled prostate-specific membrane antigen (PSMA) is a specific radiotracer for prostate cancer. The superiority of 68Ga-PSMA PET/CT in comparison with standard imaging has been demonstrated in detecting metastatic recurrences for patients with biochemical relapse even with very low PSA levels. It also appears to be an excellent imaging modality for initial staging both for nodal lymph nodes and distant metastases in intermediate and high-risk prostate cancer. In both cases, 68Ga-PSMA PET/CT has implications for patients' management. However, its impact on overall survival has yet to be determined (Table I; Fig. 1).

On a therapeutic level, 177Lu-PSMA has proven its benefits for advanced metastatic prostate cancer after ADT and taxane-based chemotherapy with very few adverse events. It could, depending on the results of ongoing studies, take a place in earlier stage prostate cancer sometime in the close future. Many resistance mechanisms to 177Lu-PSMA therapy have not yet been elucidated but some solutions like androgen receptor blockage have already shown great potential in improving responses. New PSMA-associated radioligands are also being tested to enhance the therapeutic and diagnostic arsenal. In sum, radiolabeled PSMA undoubtedly has a promising future ahead of it.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HS, DH, PC and CH contributed to the conception of the work; the acquisition, analysis and interpretation of data; and approved the submitted version. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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