Role of Ga68 Prostate-Specific Membrane Antigen Positron Emission Tomography-Computed Tomography in Prostate Cancer Imaging

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Abstract

The introduction of prostate-specific membrane antigen (PSMA) in clinical practice has revolutionized the evaluation of biochemical recurrence (BCR) of prostate cancer after curative-intent treatment. The high expression of this glycoprotein in prostate cancer cells makes PSMA imaging superior to the current conventional staging methods, namely bone scanning and computed tomography. The high capability of PSMA imaging for identifying very small previously undetected lesions has been widely demonstrated in the literature, leading to a rethinking of patient management by treating physicians. The usual and predictable patterns of spread in prostate cancer are still more prevalent, such as spread to pelvic lymph nodes and bone metastasis, but different patterns of disease spread are becoming more commonly recognized with higher reliability because PSMA imaging allows the detection of more usual and unusual lesions than conventional imaging. The expanding use of PSMA positron emission tomography (PET) has also revealed PSMA ligand uptake in diverse non-prostatic diseases, which raised questions about the specificity of this imaging modality. It is important for the reading physician to recognize and understand the usual disease spread, the most prevalent unusual sites of relapse, and the nonprostatic conditions which are PSMA avid not only to heighten the relevancy of reports but also to improve imaging consultancy in multispecialty oncologic practice. This article aims to brief the role of PSMA PET in the initial staging of multitude of clinical scenarios, BCR, castration-resistant prostate cancer, usual and unusual patterns of recurrence and metastatic spread diagnosed with PSMA PET, normal variants, pitfalls, and nonprostatic disorders showing PSMA expression.

Keywords

► 68Ga-PSMA
► positron emission tomography
► prostate cancer

Introduction

Prostate cancer is primarily a disease of the elderly, with more than three-quarters of the cases occurring in men above 65 years of age. Epidemiologic studies show that prostate cancer is the second most frequently diagnosed cancer in men worldwide and the fifth most common cancer overall.1 It is also the sixth leading cause of cancer deaths in men.2 Preliminary data point to an increase in the incidence of aggressive, high-risk, and metastatic prostate cancer cases.

It can range in severity and aggressiveness from indolent, very low-risk, localized prostate cancer to life-threatening,
very high-risk, metastatic prostate cancer. Accurate assessment of disease extent (e.g., metastatic versus localized prostate cancer) is critical for making treatment decisions. Imaging is crucial in the assessment, which has traditionally been done using bone scan (Tc99m-MDP) and computed tomography (CT) in men at high risk for metastatic disease. Other more sensitive imaging techniques for detecting the extent of disease include positron emission tomography (PET) combined with CT using different types of radiopharmaceuticals. Despite its applicability across cancer types, 18F-fluorodeoxyglucose (18F-FDG) PET has had limited use in prostate cancer staging. Newer radiopharmaceuticals, such as 18F-fluciclovine and choline PET, are used more frequently in the biochemical recurrence (BCR) setting, but their specificity is limited.

**Prostate-Specific Membrane Antigen Positron Emission Tomography**

The increasing utilization of radiopharmaceuticals targeting the prostate-specific membrane antigen (PSMA) is based on growing scientific evidence that supports their favorable imaging performance. Two of the many PSMA-targeting imaging agents that the U.S. Food and Drug Administration currently approved are 18F-DCFPyL and 68Ga-PSMA-11. Although there may be minor differences between both, there is no evidence to specify that one has improved diagnostic characteristics compared with the other.

**Prostate-Specific Membrane Antigen Positron Emission Tomography Protocols and Reporting**

The protocols for 68Ga-PSMA-11 and 18F-DCFPyL image acquisition are similar. The administered activity is 3 to 7 mCi, and the uptake time is 45 to 60 minutes. This document will treat all PSMA PET radiotracers as equivalent and refer to Ga68 PSMA PET-CT as a standard. Delayed imaging is of value in patients with high bladder urine activity in selected cases. Using iodinated contrast in the urogram phase may benefit some cases, particularly for separating ureteric activity from minor nodal abnormalities and characterizing local recurrence. PSMA PET is usually performed with PET-whole-body CT (with or without iodinated contrast). Additional multiparametric magnetic resonance imaging (mpMRI) of the pelvis can be fused with the PET-CT for more definite anatomic characterization and localization. The added value of PET/whole-body MRI is yet to be elucidated. Overall, PSMA PET imaging with PET/whole-body CT is optimal for proper disease staging, with a possible improvement in local disease evaluation with PET/MRI. The CT protocol can be designed to meet clinical needs, and it can include low-dose CT (for anatomical correlation and attenuation correction) or diagnostic-dose CT with or without intravenous and/or oral contrast agents.

A well-trained nuclear medicine physician should be able to appreciate standard patterns, pitfalls, and usual and unusual patterns of disease spread.

**Prostate-Specific Membrane Antigen Positron Emission Tomography-Computed Tomography versus Conventional Imaging**

PSMA PET-CT has superior diagnostic accuracy for detecting pelvic nodal or distant metastases to conventional imaging with CT and bone scanning. PSMA PET-CT demonstrated 92% accuracy compared with 65% accuracy for conventional imaging (area under the curve difference 27%, 95% confidence interval 23–31%; p < 0.0001). Conventional imaging showed lower sensitivity and specificity than PSMA PET-CT (38 vs. 85% and 91 vs. 98%, respectively). In patient subgroup analyses, PSMA PET-CT was superior to conventional imaging in men with pelvic nodal metastases (91 vs. 59%) and distant metastases (95 vs. 74%). Uncertain results in the identification of any metastatic disease were more common for conventional imaging (23% of men) than for PSMA PET-CT (7% of men).

**Prostate-Specific Membrane Antigen Positron Emission Tomography and Stage Migration**

In total, 28% of men undergoing PSMA PET-CT had their treatment plans changed after the scans compared with 15% after conventional imaging. Specifically, for first-line PSMA PET-CT, the management of 14% of men was changed from curative to palliative therapy and 14% underwent a different radiotherapy (7%) or surgical technique (7%). In men who crossed over to second-line imaging, conventional imaging had a high or medium effect on management in 5% of men versus 27% for PSMA PET-CT. Radiation exposure from first-line conventional imaging was 10.9 mSv higher than that from PSMA PET-CT. PSMA PET-CT demonstrated 92% accuracy compared with 65% accuracy for conventional imaging.

**Role of Prostate-Specific Membrane Antigen Positron Emission Tomography in Oligometastatic Disease**

The term “oligometastatic disease” refers to disease with few metastatic sites and locations, with consensus publications recommending a maximum of three or five lesions in up to two organ types. The improved specificity of PSMA PET can reclassify some oligometastatic bone scan findings as false positive and downstage to MO.

The advent of molecular imaging (with tracers recommended by the National Comprehensive Cancer Network [NCCN]) has allowed patients in BCR to be reclassified as PET oligometastatic. The more sensitive and specific PSMA PET has introduced a lead-time bias known as the “Will Rogers phenomenon.” This phenomenon occurs when the disease is reclassified using more sensitive tools. Metastasis-directed therapy (MDT), often ablative-dose radiation, has been used to delay systemic therapy by detecting metastatic disease earlier. Recently developed randomized phase III trials such as ECOG-ACRIN 8191 (NCT04423211), VA STARPORT NCT04787744, PEACE-V (STORM, NCT03569241),
Prostate-Specific Membrane Antigen Positron Emission Tomography and Androgen Deprivation Therapy

Treatments that inhibit the androgen receptor (AR) influence PSMA expression. AR inhibition may rapidly reduce PSMA expression in patients with hormone-sensitive metastatic prostate cancer. AR blockers, such as bicalutamide and enzalutamide, may increase PSMA expression in patients with hormone-resistant disease. The use of PSMA PET imaging to evaluate therapy response in ADT is poorly defined due to the complex modulation of PSMA expression. Accordingly, the uptake intensity alone should be used cautiously during treatment response assessment.

Prostate-Specific Membrane Antigen-Targeted Radioligand Therapy Trials that Impact the Use of Prostate-Specific Membrane Antigen Positron Emission Tomography

Currently, the primary indications for PSMA PET are detecting metastatic disease during initial staging and at the time of BCR. PSMA PET can screen patients for PSMA-targeted radioligand therapy (RLT). The results of the VISION trial (NCT03511664) and the TheraP trial, as well as the approval of 177Lu-PSMA-617, support the use of PSMA in patients with metastatic castration-resistant prostate cancer (mCRPC) for patient selection. Uptake greater than background liver is commonly used and is the only criterion used in a randomized trial demonstrating overall survival benefit. 18F-FDG PET/CT may help identify disease sites that are 18F-FDG positive but PSMA negative.

Initial Staging

PSMA PET imaging is more accurate than conventional imaging (Bone scan and CT) in the initial staging of men with newly diagnosed prostate cancer. PSMA PET had a 27% higher accuracy than the conventional imaging for staging of men with high-risk prostate cancer, according to the multicenter randomized ProPSMA trial. Another study found that 18F-DCFPyL-PET/CT had a high specificity (median 97.9%) for detecting pelvic lymph node metastasis but only a 40% sensitivity. These data support the utility of PSMA PET imaging in facilitating accurate risk stratification of newly diagnosed high-risk prostate cancer.

Scenario 1: Suspected prostate cancer patients (e.g., abnormal digital rectal examination results, high/rising prostate-specific antigen [PSA] levels) may be considered for targeted biopsy and detection of intraprostatic tumor.

There are some scenarios when MRI results are inconclusive or biopsy results are negative, in which the use of PSMA PET may be of help. PRIMARY is an ongoing, multicenter, prospective, cross-sectional clinical trial that will provide additional evidence on the added value of PSMA PET to mpMRI in detecting clinically significant prostate cancer in men undergoing initial biopsy for suspected prostate cancer.

Scenario 2: Patients with very low, low, and favorable intermediate-risk prostate cancer—not routinely recommended.

The NCCN guidelines for prostate cancer stratify the initial risk for clinically localized disease as very low, low, intermediate (favorable and unfavorable), high, and very high based on several clinical and pathological features. Imaging is generally not indicated for very low, low, and intermediate (favorable) risk diseases and may be considered only in certain circumstances. Per the NCCN guidelines and due to the lack of relevant evidence and the morbidity and financial cost associated with screening for clinically insignificant prostate cancer, PSMA PET is considered rarely appropriate in this clinical scenario.

Scenario 3: Newly diagnosed unfavorable intermediate, high-risk, or very high-risk prostate cancer—highly recommended.

In this clinical setting, there is evidence that PSMA PET is more informative than conventional imaging and may be considered the “new” conventional imaging. Prospective trials have shown that PSMA PET has a 40% sensitivity for detecting pelvic node metastasis when compared with pathology at the time of radical prostatectomy and pelvic node dissection. Furthermore, in the ProPSMA randomized trial, PSMA PET was compared with conventional imaging for staging high-risk prostate cancer before curative intent surgery or radiotherapy. PSMA PET imaging was more accurate than conventional imaging, with fewer ambiguous imaging results, less radiation exposure to the patient, and a more significant treatment impact (Fig. 1). Acquiring pelvic mpMRI and fusion with PSMA PET adds incremental value to local disease characterization by giving information about the capsular breach and neurovascular bundle infiltration (Fig. 2). Furthermore, an analysis of the cost per accurate diagnosis revealed that PSMA PET/CT was less expensive than conventional imaging for detecting disease spread.

Scenario 4: Newly diagnosed unfavorable intermediate, high-risk, or very high-risk prostate cancer with negative/equivocal or oligometastatic disease on conventional imaging—highly recommended.

Randomized trials such as ProPSMA have demonstrated the superiority of PSMA PET over conventional imaging in staging high-risk localized prostate cancer. PSMA PET may show sites of disease that are not identified or are equivocal on conventional imaging. Moreover, because PSMA PET has a higher sensitivity, metastatic disease will be detected earlier. Furthermore, oligometastatic disease seen on conventional imaging may be polymetastatic, which can influence subsequent clinical
management decisions (e.g., systemic therapy vs. MDT)\textsuperscript{30,31} (\textsuperscript{\textcircled{3}} Fig. 3). In keeping with the supportive evidence in this clinical space, PSMA PET is recommended as appropriate in this clinical scenario.

Scenario 5: Newly diagnosed prostate cancer with widespread metastatic disease on conventional imaging—may be appropriate.

PSMA PET adds little additional value in the setting of known widespread metastatic disease identified on conventional imaging, given that detecting other disease sites will likely have no significant clinical management implications. However, PSMA PET will be of immense value in assessing response to treatment in this clinical scenario. Early progression and neuroendocrine dedifferentiation of the disease can be identified much earlier than with conventional imaging. PSMA PET may be appropriate for this clinical scenario.

\textbf{Biochemical Recurrence}

BCR is experienced by approximately 40% of patients who undergo local definitive therapy within 10 years of surgery.\textsuperscript{32} The PSA level is expected to fall to undetectable levels after a successful radical prostatectomy; otherwise, the condition is known as PSA persistence. BCR after prostatectomy is defined as a PSA rise of 0.2 ng/mL measured 6 to 13 weeks after surgery and confirmed by a second PSA level of $>0.2$ ng/mL.\textsuperscript{33} BCR is defined in patients who received definitive radiation therapy as a PSA rise of 2 above the nadir achieved after radiotherapy, regardless of ADT.\textsuperscript{34} BCR signals locally recurrent disease, metastatic disease, or both. Sensitivity of conventional imaging in localizing disease in many patients is limited, with either false-negative findings or underestimation of disease burden. Prospective studies with 68Ga-PSMA-11\textsuperscript{35,36} and 18F-DCFPyL,\textsuperscript{37} which demonstrated high patient-level detection rates, positive predictive values, and sensitivities for disease localization in the setting of BCR after definitive therapy, provide strong evidence for the utility of PSMA PET in the background of BCR.

Scenario 6: PSA persistence or PSA rise from undetectable level after radical prostatectomy—appropriate.

PSMA PET should be used to localize disease in patients with BCR or persistence after radical prostatectomy. Salvage treatments are often used at PSA values below the standard American Urological Association definition of BCR.\textsuperscript{33} PSMA PET has
been shown to localize recurrent disease at lower PSA levels with high sensitivity, thereby significantly affecting clinical management.\textsuperscript{38–40} PSMA PET is appropriate in this clinical scenario based on high-quality, supportive evidence.

Scenario 7: PSA rises above nadir after definitive radiotherapy—appropriate.

This scenario’s supporting evidence is similar to Scenario 6. The utility of PSMA PET should not be limited to only BCR as per definition\textsuperscript{34} because the treatment of patients frequently occurs before the BCR threshold criteria are met. PSA doubling time (PSADT) and other patient-specific factors should be considered besides the PSA level. PSMA PET is indicated in this clinical scenario based on high-quality supporting evidence.

Castration-Resistant Prostate Cancer

CRPC is defined as disease progression despite low levels of serum testosterone. Bone scans are available to assess
skeletal metastases, and CT/MRI is used to determine nodal, soft tissue, and visceral metastases. 18F-FDG PET scans are not recommended for staging prostate cancer by NCCN. In addition to serum PSA levels, conventional imaging is used when symptoms change, when systemic therapy is adjusted to establish a new baseline or assess treatment response.\textsuperscript{41,42}

Many life-prolonging therapies have been approved in CRPC (discussion of which is beyond the scope of this article). Given that these therapies are systemic, the role of imaging is to evaluate progression rather than localize metastatic disease.

Scenario 8: Non-mCRPC (M0) on conventional imaging—appropriate

PSMA PET has been studied in the M0 CRPC population. Nearly all patients categorized as M0 CRPC based on conventional imaging had PSMA-positive disease, and 55% were classified as M1 by PSMA PET.\textsuperscript{43} Apart from drugs approved in this clinical setting, external beam radiation is used to treat patients with oligo-mCRPC, with some preliminary data on its effectiveness\textsuperscript{44}; therefore, PSMA PET is essential for correctly characterizing disease in these patients. On this basis, PSMA PET can be considered appropriate in this clinical scenario.

Scenario 9: Evaluation of eligibility for patients being considered for PSMA-targeted RLT—appropriate

The VISION trial, which randomized PSMA RLT (radionuclide ligand therapy) to the best standard of care, showed that radiographic PFS was improved to 8.7 months with PSMA RLT versus 3.4 months for standard of care (hazard ratio 0.40) with an associated improvement in overall survival (15.3 vs. 11.3 months, respectively, hazard ratio 0.62).\textsuperscript{45} The TheraP trial (PSMA RLT vs. cabazitaxel) demonstrated that PSMA RLT was associated with higher PSA response, longer PFS, and fewer grade 3 or 4 adverse events.
than cabazitaxel. With the recent FDA approval of 177Lu PSMA-617, PSMA PET should be used to evaluate eligibility for PSMA-targeted RLT. Eligibility for PSMA RLT in the VISION trial used uptake in disease more significant than the liver, and no measurable disease with uptake less than the liver. Eligibility in the TheraP study used SUV ≥ 20 at one disease site, SUV ≥ 10 at soft tissue measurable sites, and no FDG-positive PSMA-negative disease sites. PSMA PET uptake may be used as a criterion to weigh various treatment options.

Scenario 10: Evaluation of response to therapy—appropriate

With the approval of PSMA-based RLTs, PSMA PET has a vital role in assessing response to various therapies that target the androgen axis. PSMA PET is considered appropriate for this clinical scenario as a good response biomarker [23,46] (Fig. 4).

Usual and Unusual Patterns of Recurrence and Metastatic Spread Diagnosed with Prostate-Specific Membrane Antigen Positron Emission Tomography

The mainstays of curative-intent prostate cancer treatment are currently radical prostatectomy and radiation therapy. Unfortunately, prostate cancer recurrence after curative-intent treatment is not rare, affecting 30 to 50% of patients in the first 10 years after initial therapy. BCR, that is, rising serum level of PSA, is the first landmark of prostate cancer recurrence. It occurs before clinical (imaging-detectable) recurrence by months or years owing to the higher accuracy of this laboratory biomarker. However, PSA-based detection is not site-specific and does not allow precise differentiation among local, regional, and systemic ( nodal, bone, or visceral) recurrence, which is critical information for further appropriate management.

![Fig. 4](image-url) 74-year-old male; Gleason 4 + 5; Ga68 PSMA PET-CT images include posttreatment scan (top row), axial CT (left panel), fused axial PET/CT (middle panel), and maximum intensity projection (MIP) PET image (right panel), pretreatment scan (bottom row) - axial CT (left panel), fused axial PET/CT (middle panel) and maximum intensity projection (MIP) PET image (right panel). PET/CT images show PSMA avid primary lesion in the peripheral zone of the prostate with multiple pelvic, retroperitoneal, and mediastinal lymph nodes in the pretreatment scan and complete resolution and response to treatment in the post-treatment scan.
Imaging provides valuable data in this setting, particularly allowing the identification of localized recurrence and guiding specific therapeutic approaches. Conventional prostate cancer imaging based on MRI, bone scanning, and CT has shown low sensitivity for BCR, especially at low PSA levels (e.g., <1.0–1.5 ng/mL). Multiparametric MRI and, more recently, fluorine 18 (18F) or carbon 11 (11C) choline PET/CT improve the detection of local-regional and distant relapse, but at low PSA levels, unmet needs remain. PSMA PET, due to its unique characteristics (allowing assessment of a critical molecular phenotype with higher sensitivity, specificity, and target-to-background ratio), provides better diagnostic accuracy than previously used modalities for prostate cancer recurrence, particularly in cases of BCR.\(^{53-55}\) PSMA PET positivity increases with PSA level, with a detection rate of 57.9% for PSA level of 0.2 to 0.5 ng/mL, 72.7% for PSA level of 0.5 to 1.0 ng/mL, 93.1% for PSA level of 1.0 to 2.0 ng/mL, and 96.8% for PSA level higher than 2.0 ng/mL.\(^{55}\)

The current literature has shown that abdominopelvic lymph nodes are the most prevalent site of metastases in the BCR scenario (approximately 50% of cases), followed by local recurrence and bone metastases (approximately 35%). Less frequent sites are supradiaphragmatic lymph nodes and visceral metastases (approximately 5%). A mixed pattern of these locations may occur in approximately 30% of patients.\(^{55}\) Therefore, PSMA PET offers the potential to reduce the critical gap between PSA level-only and imaging-detectable recurrence and a new way of looking at disease spread.

In terms of imaging, a more accurate assessment of BCR with PSMA PET has revealed previously unknown patterns of disease spread and recurrence behavior in prostate cancer. Thus, practitioners have faced new imaging features, many of which have not been previously imaged.\(^{56,57}\) Prostate cancer recurrence imaging from the perspective of PSMA PET, emphasizing usual and unusual patterns and its implication on clinical management, are discussed further.

### Patterns of Recurrence

#### Local Recurrence

Prostate cancer relapse in the prostate bed region after local curative-intent treatment is considered local recurrence. For clinical and imaging purposes, it is important to distinguish between two types of local recurrence: recurrence outside the gland (after radical prostatectomy) and recurrence within the gland (after radiation therapy).

1. **Postoperative recurrence**

   The most typical site of postoperative local recurrence, accounting for 57 to 62% of relapse cases, is the vesicourethral anastomosis, which comprises the membranous urethra, bladder neck, and surrounding soft tissue.\(^{58}\) Other typical local relapse sites are the lateral surgical margins (seminal vesicle bed) or remnant ducti deferentia, accounting for 25 to 27% of cases\(^{59}\) and the retrovesical region (topography of rectoprostatic/Denon Villiers fascia) in 8 to 21% of cases.\(^{58}\)

   At PSMA PET/CT, local recurrence appears more often as focal ill-defined hypodense soft tissue with moderate PSMA uptake but can also simply appear as focal unilateral radiotracer uptake within the fibrotic tissue (\(\text{Fig. 5}\)). Because of the known lack of soft-tissue contrast in the pelvic region at CT, most cases of postoperative local recurrence rely solely on the PET component of the hybrid imaging.\(^{55}\) Although the PSMA component has a high lesion-to-background ratio, the prostate bed is the most difficult site to analyze because of the regional high radiotracer activity in urinary bladder. To overcome this interference, it is recommended to administer an intravenous diuretic (e.g., furosemide) before image acquisition and request preimaging voiding to reduce interference from physiologic urinary activity as much as possible, allowing neoplastic lesion uptake to be highlighted.\(^{9,60}\)

   Potential complementary diagnostic information can be obtained when imaging the prostate bed with simultaneous PET/MRI after radical prostatectomy as opposed to PET/CT, as the MRI can aid in lesion detection and increase the combined imaging detection rate.\(^{61}\) Anterior portions of urethra (bulbar and penile segments) are considered uncommon sites of relapse.\(^{52}\)

   Another unusual site of local prostate cancer recurrence is the bladder wall, which is located far from the anastomotic area. The posterior bladder wall has a higher risk for tumor relapse because it is near the resection area.\(^{62}\) Urethral and bladder recurrence can manifest as focal or segmental wall thickening with moderate-to-high PSMA uptake (\(\text{Fig. 6}\)). The morphologic appearance is indistinguishable from that of urothelial cancer, which must be considered the main differential diagnosis. Rectum represents another possible location of unusual local recurrence.\(^{64}\) Main aspects of rectal involvement include an anterior mass/irregular wall thickening and annular wall infiltration with or without stricture,\(^{65-67}\) showing varying degrees of PSMA uptake.

2. **Recurrence after radiation therapy**

   The detection rate of local recurrence in the prostate with PSMA PET after radiation therapy is 48 to 63.5%.\(^{68,69}\) Tumor recurrence appears as focal tracer uptake in the prostate or even in the seminal vesicles (\(\text{Fig. 7}\)). Relapse tends to occur at the same gland location as the primary lesion before treatment.\(^{70}\) Atypical local recurrence after radiation therapy is similar to the postoperative scenario.

#### Nodal Recurrence

Lymph node metastases are frequent in patients with prostate cancer, with rates ranging from 37 to 63%.\(^{71,72}\) Conventional imaging methods such as CT and MRI have known limitations for nodal assessment, as parameters such as size, shape, contour, and location lack specificity and often fail to allow distinction of benign from malignant lymph nodes.\(^{73-75}\) The classic pattern of lymphatic spread is from the pelvic stations to the retroperitoneum across the common iliac nodes. Metastatic nodes below the bifurcation of common iliac arteries are classified as regional nodal disease (N1), whereas patients with involvement of common iliac
nodes and more cranial sites are staged as having distant disease (M1a).76–78

1. Usual appearance of nodal recurrence

The most common sites of nodal spread from prostate cancer in pretreatment patients or those who have not undergone lymphadenectomy, in descending order of importance, are as follows: obturator fossae, external iliac, internal iliac, common iliac, and retroperitoneal chains.54,78–81 (Fig. 8). The obturator fossae and external iliac stations account for up to 88.8% and the internal iliac and common iliac stations for up to 44.4% of patients.81,82 In most patients who have undergone prostatectomy with lymph node dissection, the predictable pelvic lymphatic spread is no longer present. Rauscher et al.83 showed that, in PSMA-positive nodes resected in salvage lymphadenectomy, there is a tendency for more equal prevalence of metastases among pelvic nodal stations including the presacral/mesorectal nodes. Retroperitoneal nodal involvement is usually encountered in patients with positive common iliac nodes78,80 and is considered as distant metastatic disease.76,84 Recent studies83,85–87 have shown that even diminutive nodal metastases (as small as 5 mm) broadly missed with conventional imaging are precisely
identified with PSMA PET/CT although there is still a considerable false-negative rate for lesions smaller than 5 mm.

1. Unusual appearance of nodal recurrence

Exclusive involvement of retroperitoneal nodes with sparing of pelvic chains is unusual and likely due to hematogenous dissemination, with the frequency increasing after nodal dissection or irradiation. These interventions disrupt the normal lymphatic network and allow different routes of spread. Another drainage pathway is spread through gonadal vessels to para-aortic and paracaval nodes.

Another unusual site is the mesorectum. The advent of PSMA PET has shown mesorectal metastases to be far more prevalent (in up to 15% of patients) than previously thought. These nodes had reportedly been missed with conventional imaging and omitted from treatment, as local primary and salvage surgery and radiation therapy do not encompass this region as a standard. Other rare pelvic lymph node stations that can be seen are inguinal, perivesical regions, and ischiorectal fossa (Fig. 9).

Distant Recurrence

Conventional imaging with limited/regional CT and bone scanning, as recommended by the guidelines, consistently demonstrated tumor burden predominantly confined to the bones and lymph nodes, and only rarely at other sites. Unusual sites often were missed or were not considered important as related to prostate cancer. PSMA PET dramatically altered imaging analysis of metastatic disease, increasing the accuracy by including an increased number of typical metastatic lesions (including those without any morphologic changes, such as normal-sized lymph nodes) and revealing atypical sites of metastatic lesions with high specificity.

1. Usual appearance

Classic hematogenous dissemination through the vena cava and reverse spread through the veins from the prostate

Fig. 6 Case of posterior urinary bladder wall recurrence after radical prostatectomy. 68-year-old male; PSA 66.1; Gleason 4 + 5; Ga68 PSMA PET-CT images include axial CT (top left panel), fused axial PET/CT (top right panel), axial PET (bottom left panel), and maximum intensity projection (MIP) PET image (bottom right panel). PET/CT images show focal abnormal PSMA uptake in the right posterior wall of the urinary bladder adjacent to but not involving the right vesicoureteric junction suggestive of local recurrence. MIP image also shows multiple sites of metastatic skeletal disease.
to the spine (Batson venous plexus) usually occur first. This phenomenon explains the bone-seeking behavior of prostate cancer, in which approximately 90% of patients have bone lesions, representing the most common site of metastasis. Other usual sites are the distant lymph nodes, liver, and thorax (including lungs and pleura). A nonnegligible number of patients (approximately 15%) present with visceral metastases without skeletal involvement, more often in the distant lymph nodes, liver, and thorax (lung and pleura).

The CT appearance of skeletal lesions is variable, but osteoblastic metastases are far more common. In a recent study, 51.9% of detected metastases were osteoblastic, 19.5% were bone marrow lesions (with no CT changes), 14.9% had a mixed pattern, and 13.6% were osteolytic (Fig. 10). The general assumption that prostate cancer bone lesions are almost exclusively osteoblastic can be changed with the ability of PSMA to demonstrate nonsclerotic metastases. F18 Sodium fluoride (NaF) bone scan has high sensitivity and low specificity for the detection of bone metastases because of tracer uptake in many nonspecific and benign conditions. Metastases in distant lymph nodes may occur at any location with variable prevalence, including (in descending order) the retroperitoneal, mediastinal, cervical/supraclavicular, inguinal, mesenteric, and axillary nodes, with the most common site being the para-aortic region. Careful evaluation can help differentiate malignant from nonneoplastic uptake, which can be frequent in these nodes. Such cases demonstrate faint PSMA uptake and normal appearance. Lung and liver lesions usually occur later during the clinical course of the disease, often simultaneously with bone metastases.

Metastatic involvement of left supraclavicular (Virchow) nodes must be highlighted. The ascending lymphatic spread of prostate cancer mentioned earlier continues from retroperitoneal nodes to the cisterna chyli and thoracic duct,
which is the gateway to the systemic circulation owing to its junction with the left subclavian vein. Left supraclavicular nodes are closer to this junction, and it is thought that cancer cells can reach them via retrograde lymphatic spread. Although rare, supraclavicular lymphadenopathy can be the first clinical manifestation of metastatic prostate cancer. As a whole-body imaging technique, PSMA PET allows easy detection of supraclavicular nodal involvement by prostate cancer.

1. Unusual appearance

Rarer metastatic sites of prostate cancer occur in less than 5% of patients and may be observed in any organ, including the brain/meninges, thyroid gland, adrenal glands (►Fig. 11), peritoneum (►Fig. 12), gastrointestinal tract, urinary tract (ureter, urethra, and kidney), spleen, or pancreas. Even more rarely, atypical metastases may arise in the penis (►Fig. 13), testicles, soft tissue/skin, breast, pleura (►Fig. 14) or heart.

Recently, it was reported that unusual sites of PSMA uptake are more often related to benign changes, supporting the additional role of CT or MRI in morphologically characterizing the findings to increase specificity. It is noteworthy that unusual metastases from prostate cancer appeared to be more frequent than a second primary malignancy. The proposed explanation for PSMA uptake by nonprostatic malignancy is related to PSMA protein expression in the tumor neovasculature. On the basis of several case reports, PSMA uptake by second primary tumors is in general not as high as PSMA uptake by prostate cancer metastases. Although this may increase the reliability of suspicion for metastases, a lesion with an atypical imaging pattern at PSMA PET/CT prompts further histologic assessment, especially in an oligometastatic scenario, where it can change treatment management.

Normal PSMA uptake is seen in the following structures, with descending avidity: kidneys, submandibular glands, parotid glands, descending duodenum, lacrimal glands, spleen, descending colon, Waldeyer ring in the neck, vocal cords, liver, and rectum.

An important consideration is the small proportion of reportedly negative PSMA PET-CT in the context of raised PSA (e.g., PSA > 10 ng/mL), where negative PSMA PET-CT was 4%. Such negative PSMA PET-CT scans show hepatic and pulmonary metastatic lesions which are Ga68 PSMA (tracer).
According to the literature, almost all prostatic adenocarcinomas will express PSMA; however, there is a subpopulation that lacks strong PSMA tracer uptake, including men with intraductal prostatic adenocarcinoma and neuroendocrine histology/differentiation. Those men with advanced, castration-resistant disease, may have areas of dedifferentiation, predominantly of neuroendocrine histology and loss of PSMA expression (►Figs. 15 and 16). False negatives are also more common in patients with lower serum PSA values or slower PSA kinetics. For purely intraductal adenocarcinoma, which represents around 0.3% of all prostate cancers, the sensitivity of PSMA PET-CT has been questioned. Intraductal prostatic adenocarcinoma has been shown to have a lower PSA expression by 30% and thus may make detecting intraductal prostatic adenocarcinoma more difficult. No specific studies have reviewed the efficacy of PSMA PET-CT in intraductal prostatic adenocarcinoma; however, several articles express concerns over their accuracy and suggest the addition of FDG PET (►Figs. 17 and 18) or mpMRI (►Figs. 19 and 20) to more accurately stage and monitor these patients.

Despite its misleading name, PSMA is surely not a PSMA as previously thought. An increasing number of nonprostatic disorders have shown PSMA expression, including inflammatory/infectious diseases (►Fig. 21), vascular conditions, benign neoplasms (►Fig. 22), and other malignancies. Awareness of these findings appears mandatory to prevent misinterpretation.

The evidence that PSMA is overexpressed in the endothelium surface of the neoangiogenic vessels in several solid tumors has been largely demonstrated (►Fig. 23). In the most recent years, there is an increased interest in the potential application of PSMA ligand imaging in nonprostate neoplasms, with encouraging results in renal cell carcinoma and gliomas, while less favorable evidence for thyroid and gastroenteric neoplasms exists.

Few data are available about the mechanism of PSMA expression by immune cells. It is possible that neovascularization also plays a role in this scenario, as well as an increased availability of PSMA ligands to the site of inflammation/infection due to an increase in regional blood flow/vascular permeability. As a rule, PSMA PET demonstrates intense uptake in neoplastic lesions, in contrast to faint accumulation in inflammatory processes.

A spectrum of nonprostatic causes of PSMA expression is summarized in ►Table 1.

### Comparison of Prostate-Specific Membrane Antigen Positron Emission Tomography with Other Imaging Modalities

#### Nodal Metastases
Numerous studies have demonstrated that PSMA PET outperforms other imaging modalities in regard to nodal staging. Standard imaging techniques are insufficient...
for reliable detection of nodal metastases in prostate cancer because they depend on nonspecific morphologic parameters with poor sensitivity. Furthermore, PSMA PET has greatly increased the detection of atypical lymph node metastases missed with traditional imaging methods because of their unusual locations, often not included in the field of view of traditional modalities. For detection of local recurrence, MRI has higher sensitivity, while PSMA PET has higher specificity, raising the possibility of use of PET/MRI, especially after surgery for prostate cancer but also after radiation therapy.

**Bone Metastases**
With regard to detection of bone metastases, studies have shown that PSMA PET is capable of accurate assessment of skeletal involvement, reducing the need for additional investigations routinely demanded to elucidate ambiguous findings with 18F NaF PET and technetium 99m SPECT. PSMA PET is more sensitive and specific than bone scintigraphy, while 18F-NaF PET/CT appears to be more sensitive but less specific on account of high uptake of the tracer by benign processes, such as degenerative and posttraumatic changes. Lytic and bone marrow metastases, often overlooked, may be found in, respectively, 13.6 and 19.5% of patients with bone involvement at PSMA PET.

**Visceral Metastases**
With respect to visceral disease, data suggest that PSMA PET is superior to conventional imaging, namely CT and multiparametric MRI, including diffusion-weighted whole-body MRI. PSMA PET has increased diagnostic accuracy by revealing metastatic lesions without any morphologic changes and at atypical sites with high specificity as discussed earlier.

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*Fig. 10* 80-year-old male; Gleason 3+4; postradical prostatectomy; on follow-up surveillance found to have increased serum PSA; Ga68 PSMA PET-CT images include coronal and axial CT (top row), fused coronal and axial PET/CT (bottom row), and maximum intensity projection (MIP) PET image (extreme right panel). PET/CT images show small foci of PSMA avid (red circle) sclerotic lesion in the left pedicle of D1 vertebra and a marrow lesion in proximal third shaft of left femur, not demonstrated by conventional imaging.
Clinical Impact of Imaging Findings

Several treatment options are available for relapsed prostate cancer, including surgery, radiation therapy, androgen deprivation therapy, chemotherapy, and nuclide therapy. Given the different patterns of prostate cancer recurrence, the protracted time course of the disease, and the naturally extended survival in many cases, patients usually undergo several treatments with the evolution of the disease. Optimizing and sequencing local, local-regional, and systemic treatments for relapsed prostate cancer is not an easy task and depends on factors such as disease localization, extension, clinicopathologic features, potential toxic effects, comorbidities, costs, and best evidence. PSMA PET can be a valuable imaging tool for characterizing usual and unusual patterns of disease spread with a precision that has not been previously achieved, thus bringing clinicians closer to achieving the goal of personalized medicine: “the right treatment to the right patient at the right time.” Advantages include changes in radiation therapy planning (i.e., better target volume delineation by depicting atypical patterns or unsuspected localization) and better accuracy for excluding pelvic nodal or extra pelvic disease. In cases of regional (pelvic) nodal oligometastatic recurrence, PSMA PET can be a powerful tool in guiding SBRT, not only by depicting more lesions earlier but also by helping better delineate the target volume and serving as a baseline imaging method for subsequent response assessment. In case of salvage lymph node dissection, surgeons must be aware in advance of atypical nodal disease that may require changes to the surgical plan, such as disease of the mesorectum and

Fig. 11 Case of metastatic CRPC; 72-year-old male; PSA 198; initial Gleason 4 + 4; Ga68 PSMA PET-CT images include axial CT (top left panel), fused axial PET/CT (top right panel), axial PET (bottom left panel), and maximum intensity projection (MIP) PET image (bottom right panel). PET/CT images show an abnormal PSMA avid nodular lesion in the left adrenal gland (red circle) suggestive of metastatic disease. MIP image shows extensive PSMA avid skeletal metastatic disease.
Fig. 12  Case of newly diagnosed carcinoma prostate with peritoneal metastasis; 71 year old male; PSA 15.4; Gleason 4+4; Ga68 PSMA PET-CT images include axial CT (top left panel), fused axial PET/CT (top right panel), axial PET (bottom left panel), and maximum intensity projection (MIP) PET image (bottom right panel). PET/CT images show PSMA avid primary lesion in the prostate and a metastatic peritoneal deposit in the right paracolic gutter. MIP image also shows PSMA avid nodule in the right lobe of the thyroid.
Fig. 13  Case of carcinoma prostate, staging workup. 56-year-old male; PSA 38; Gleason 4 + 5; Ga68 PSMA PET-CT images include sagittal, coronal, and axial CT (Top row), fused sagittal, coronal, and axial PET/CT (bottom row) and maximum intensity projection (MIP) PET image (extreme right panel). PET/CT images show PSMA avid primary lesion in both lobes of the prostate with PSMA tracer avid unusual metastatic deposit in proximal shaft of the penis (red circle), left inguinal node, and marrow lesion in manubrium sternum (not evident on conventional imaging).

Fig. 14  Case of newly diagnosed carcinoma prostate with pleural metastases; 58-year-old male; PSA 38; Gleason 4 + 4; Ga68 PSMA PET-CT images include axial CT (top left panel), fused axial PET/CT (top right panel), axial PET (bottom left panel), and maximum intensity projection (MIP) PET image (bottom right panel). PET/CT images show abnormal PSMA avid primary lesion in the right peripheral zone of prostate and left pleural nodular thickening (red circle). Biopsy was suggestive of metastatic adenocarcinoma from the prostate. MIP image also shows a discrete PSMA avid metastatic left supraclavicular node and a subcutaneous nodule in the left lower chest wall on the lateral aspect.
Fig. 15  Case of metastatic CRPC on ADT; 84-year-old male; PSA 38; initial Gleason 4 + 5; Images include Ga68 PSMA PET MIP image (left panel) and F18 FDG PET MIP image (right panel). Ga68 PSMA PET MIP image shows multiple sites of PSMA avid skeletal metastases. Faint foci of abnormal PSMA uptake seen in the liver (red circle). F18 FDG PET MIP image shows foci of intensely FDG avid lesions in both lobes of liver. Biopsy of liver lesion was suggestive of neuroendocrine differentiation of prostate carcinoma. However, the PSMA avid skeletal lesions were showing only low-grade FDG avidity, demonstrating tumor heterogeneity.

Fig. 16  Case of metastatic CRPC on ADT; 84-year-old male; PSA 38; initial Gleason 4 + 5; images include axial CT (left panel), fused axial PET/CT (right panel), F18 FDG PET-CT (top row), and Ga68 PSMA PET-CT (bottom row). Images show intense FDG uptake and only faint PSMA avidity in the hypodense lesions in segment 8 of the liver. Biopsy of liver lesion was suggestive of neuroendocrine differentiation of prostate carcinoma.
Fig. 17 Case of metastatic CRPC on docetaxel chemotherapy; 81-year-old male; PSA 16; initial Gleason 4+5; Images include Ga68 PSMA PET MIP image (left panel) and F18 FDG PET MIP image (right panel). Ga68 PSMA PET MIP image shows multiple sites of mild-to-moderately PSMA avid skeletal metastases. F18 FDG PET MIP image shows intense FDG avidity in few of the lesions (right scapula and right iliac bone—marked with green arrow). Biopsy of scapular lesion was suggestive of neuroendocrine differentiation of prostate carcinoma. However, other PSMA avid skeletal lesions were showing comparatively less FDG avidity—demonstrating tumor heterogeneity.

Fig. 18 Case of metastatic CRPC on Docetaxel chemotherapy; 81-year-old male; PSA 16; initial Gleason 4+5; images include corresponding similar plane axial fused Ga68 PSMA PET/CT (left panel) and axial fused F18 FDG PET/CT (right panel). Images show intense FDG uptake and only low-grade PSMA avidity in the right scapular lesion. Biopsy of the lesion was suggestive of neuroendocrine differentiation of prostate carcinoma. Discordant FDG avid and PSMA nonavid lesions are demonstrated in the left iliac bone, left sacral ala, and left supraclavicular lymph node suggesting neuroendocrine differentiation.
retroperitoneal para-aortic nodes, which is more commonly identified in the PSMA era. The incremental value of PSMA PET in polymetastatic recurrence is that it can serve as a reliable baseline parameter for future systemic response assessment or, more interestingly, as a theranostic selector for radionuclide PSMA-based therapy.

Conclusion

In summary, PSMA PET-CT is now routinely used in the evaluation of prostate cancer in the context of primary staging and suspected tumor recurrence. More specific PET radiopharmaceuticals improve both assessments and provide additional benefits in theranostics. Treated prostate cancer can exhibit two different patterns of disease recurrence before clinical manifestation. First, recurrence can be biochemically identified by rising the PSA level, which generally occurs without any corresponding clinical imaging findings. Second, recurrence can be clearly identified with imaging. The pre-PSMA era relied mainly on information from CT and MRI and molecular data from bone scanning, each with certain limitations and often identifying disease only in advanced stages. The current PSMA era has decreased the gap between biochemical and imaging recurrence and now allows disease to be detected at earlier stages. Thus, treatment decisions can be individually tailored, possibly improving patient outcomes. Recognition of different patterns of spread of prostate cancer with PSMA PET enables the reading physician to increase diagnostic accuracy, allowing proper identification of usual and unusual disease manifestations at local, regional, and distant sites. As mentioned earlier, PSMA is not exclusively expressed on prostatic tissue and can be identified in other malignant and nonmalignant processes.

Fig. 19 Case of intraductal prostatic adenocarcinoma; 62-year-old male; PSA 6; Gleason 5 + 4; for staging workup. Ga68 PSMA PET-CT images include axial CT (top left panel), fused axial PET/CT (top right panel), axial PET (bottom left panel), and maximum intensity projection (MIP) PET image (bottom right panel). PET/CT images show no abnormal PSMA uptake in the ill-defined nodular lesion in the prostate (red circle) sparing the left peripheral zone. Biopsy from the lesion suggestive of intraductal prostatic adenocarcinoma.
Fig. 20 Case of intraductal prostatic adenocarcinoma; 62-year-old male; PSA 6; Gleason 5 + 4; for staging workup. Images include axial T2 weighted MRI (left first panel), fused axial PET/T2W MRI (right first panel), axial diffusion restriction sequence (left middle row), and fused axial PET/diffusion restriction sequence (right middle row), ADC (left bottom row), and fused axial PET/ADC (right bottom row). PET/MRI fusion images show a T2W hypointense lesion with diffusion restriction and low ADC values involving almost the entire prostate gland with sparing of the left peripheral zone.
Furthermore, radio-theranostics (use of radioligands like Lutetium 177 and Actinium 225 PSMA-617 with specific uptake targeting PSMA receptor) are being used to treat advanced metastatic castration-resistant prostate carcinoma. These new radioligands deliver $\beta$ and $\alpha$ particle radiation selectively to PSMA-positive cells and their direct microenvironment without causing harm to surrounding tissue and increase the overall survival from 11.3 to 15.3 months.

**Fig. 21** Case of adenocarcinoma prostate (Gleason 4 + 3), serum PSA—26.0. Ga68 PSMA PET-CT images include axial CT (first column), fused axial PET/CT (second column) at the level of the pelvis (top three rows), mediastinum (bottom row), and maximum intensity projection (MIP) PET image (extreme right panel). PET/CT images show abnormal Ga68 PSMA avid lesions involving the central and transition zone regions of the prostate. Heterogenous Ga68—PSMA avidity is also seen in the bilateral peripheral zones, Ga68—PSMA avid metastatic left external iliac and right inguinal nodes, Ga68—PSMA avid mediastinal and bilateral hilar lymph nodes seen (MIP image). A larger subcarinal node is seen with foci of calcification (bottom row images)—representing inflammatory/granulomatous etiology.

**Fig. 22** Case of acinar adenocarcinoma prostate; Gleason 3 + 4; postradical prostatectomy; PSA 0.1; Ga68 PSMA PET-CT images include axial CT (left panel), fused axial PET/CT (middle panel), and axial PET (right panel). PET/CT images show mildly Ga68—PSMA avid well-defined extra axial dural-based lesion in the right frontal convexity region—suggestive of meningioma. Meningioma was later confirmed with MRI brain correlation.
(p < 0.001), decrease the PSA level by 50 to 80%, and delay imaging-based progression, as elucidated by VISION trial.

**Conflict of Interest**

None declared.

**References**


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**Table 1** A spectrum of nonprostatic causes of PSMA expression is summarized in the table

<table>
<thead>
<tr>
<th>Region</th>
<th>Benign conditions</th>
<th>Malignant conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>Adrenals or adrenal adenoma, diverticulosis, and hepatic hemangioma</td>
<td>Adrenocortical malignancy, bladder cancer, colon cancer, gastrointestinal stromal tumor, hepatocellular carcinoma, cholangiocarcinoma, neuroendocrine tumor, prostate cancer, renal cell carcinoma (clear cell, papillary, chromophobe), and urothelial cancer</td>
</tr>
<tr>
<td>Bone</td>
<td>Fibrous dysplasia, fracture, osteoid osteoma, osteoarthritis, Paget’s disease, polycythemia rubra vera, Schmorl’s node, and vertebral hemangioma</td>
<td>Multiple myeloma, plasmacytoma, and osteosarcoma</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Parathyroid adenoma and follicular thyroid adenoma</td>
<td>Adenoid cystic carcinoma, squamous cell carcinoma of tongue, and various types of thyroid carcinoma</td>
</tr>
<tr>
<td>Muscular, cutaneous and vascular</td>
<td>Angiolipoma, intramuscular myxoma, neurofibromatosis, subcutaneous hemangioma, and synovitis</td>
<td>Hemangioepicytoma, liposarcoma, and melanoma</td>
</tr>
<tr>
<td>CNS</td>
<td>Meningioma, Neurocysticercosis, and subacute brain infarcts</td>
<td>Atypical meningioma, glioma (grade 2 to 4), and primary CNS lymphoma</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>Neurofibromatosis, peripheral nerve sheath tumor, and sympathetic ganglia</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Amyloidosis, sarcoidosis, and tuberculosis</td>
<td>Lymphoma (diffuse large B cell and follicular)</td>
</tr>
<tr>
<td>Thorax</td>
<td>Bronchiectasis, gynecomastia, pneumonia, lung atelectasis, pleural inflammation, and stromal hyperplasia of breast</td>
<td>Breast cancer, gastroesophageal junction, lung adenocarcinoma, and thymoma (types AB, B2, and C)</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; PSMA, prostate-specific membrane antigen.
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107 Malik D, Kumar R, Mittal BR, Singh H, Bhattacharya A, Singh SK. 68Ga-labeled PSMA uptake in nonprostatic malignancies: has the time come to remove "PS" from PSMA? Clin Nucl Med 2018;43(07):529–532
108 Rizzo A, Dall’Armellina S, Pizzuto DA, et al. PSMA radioligand uptake as a biomarker of neoangiogenesis in solid tumours: diagnostic or theragnostic factor? Cancers (Basel) 2022;14(16):4039
111 Gorin MA, Rowe SP, Denmeade SR. Clinical applications of molecular imaging in the management of prostate cancer. PET Clin 2017;12(02):185–192