Prostate-specific Membrane Antigen PET: Clinical Utility in Prostate Cancer, Normal Patterns, Pearls, and Pitfalls

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Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that is overexpressed in prostate cancer. Radiolabeled small molecules that bind with high affinity to its active extracellular center have emerged as a potential new diagnostic standard of reference for prostate cancer, resulting in images with extraordinary tumor-to-background contrast. Currently, gallium 68 (68Ga)–PSMA-11 (or HBED-PSMA) is the most widely used radiotracer for PSMA positron emission tomography (PET)/computed tomography (CT) or PSMA PET/magnetic resonance (MR) imaging. Evolving evidence demonstrates superior sensitivity and specificity of PSMA PET compared to conventional imaging, with frequent identification of subcentimeter prostate cancer lesions. PSMA PET is effective for imaging disease in the prostate, lymph nodes, soft tissue, and bone in a “one-stop–shop” examination. There is emerging evidence for its clinical value in staging of high-risk primary prostate cancer and localization of disease in biochemical recurrence. The high sensitivity provided by PSMA PET, with frequent identification of small-volume disease, is redefining patterns of disease spread compared with those seen at conventional imaging. In metastatic castration-resistant prostate cancer, PSMA PET is frequently used for theranostic selection (eg, lutetium 177–PSMA radionuclide therapy), but its potential use for therapy monitoring is still under debate. However, evidence on its proper use to improve patient-related outcomes, particularly in the setting of early biochemical recurrence and targeted treatment of oligometastatic disease, is still missing. Despite the term prostate specific, PSMA functions as a folate hydrolase and is expressed in a range of normal tissues and in other benign and malignant processes. Knowledge of its physiologic distribution and other causes of uptake is essential to minimize false-positive imaging findings.

Abbreviations: FDG = fluorodeoxyglucose, PI-RADS = Prostate Imaging Reporting and Data System, PSA = prostate-specific antigen, PSMA = prostate-specific membrane antigen, SUV = standardized uptake value

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:
- Describe the characteristics and mechanism of action of the PSMA PET/CT radiotracer.
- Recognize the normal biodistribution of radiolabeled small molecules targeting PSMA on PET images.
- Identify potential causes of false-positive findings at PSMA PET/CT.

See www.rsna.org/education/search/RG.
Introduction
Prostate-specific membrane antigen (PSMA) is expressed on the cell surface in normal prostate tissue and is overexpressed in prostate cancer by several orders of magnitude. It is a type II transmembrane glycoprotein encoded by the folate hydrolase 1 (FOLH1) gene, also referred to as the glutamate carboxypeptidase II (GCPII) gene. PSMA expression appears to be progressively increased in higher-grade tumors, under androgen deprivation, and in hormone-refractory and metastatic disease (1–3). PSMA was recognized as a target in prostate cancer approximately 3 decades ago, when the first antibodies to its intracellular domain were developed (4). An early approach was to radiolabel the antibody capromab with indium 111 (111In). Although this agent was approved by the U.S. Food and Drug Administration (FDA), its utility was limited by low uptake of the antibody and its binding to the intracellular rather than extracellular domain of PSMA, as well as the limited specificity of single photon emission computed tomography (SPECT) for detection of the antibody in hybrid SPECT/computed tomography (CT) (5,6).

In recent times, the landscape of available radiotracers for the imaging of prostate cancer has changed rapidly (7). Of these agents, small molecules that bind to the extracellular active center of PSMA appear to be the most likely to represent a new standard of reference. Compared with antibodies, these have the advantages of higher binding affinity, internalization, and rapid plasma clearance. In 2013, the Heidelberg group in Germany published their first in-human case series of gallium 68 (68Ga)-PSMA-11, which demonstrated high tumor-to-background contrast (8–10). 68Ga-PSMA-11 is variously referred to as 68Ga-PSMA-HBED-CC, 68Ga-HBED-PSMA, and 68Ga-DKFZ-PSMA-11 in the literature and is currently the most-used agent for PSMA positron emission tomography (PET).

68Ga-PSMA-11 is synthesized by labeling the precursor PSMA-11 by using the chelator N,N-bis(2-hydroxybenzyl)ethylenediamine-N,N-diacetic acid (HBED) with 68Ga. This can be performed by using manual, semiautomated, or fully automated techniques. 68Ga is a positron emitter with a short half-life of 68 minutes. It is eluted from a germanium 68 (68Ge)/68Ga generator, a small device with a shelf life of 6–12 months. 68Ga-PSMA-11 is not currently approved for clinical use by the FDA, which limits its use outside of clinical trials. Regulatory rules in some jurisdictions, such as parts of Europe and Australia, allow radiotracers that are compounded extraneously on-site in hospital environments to be used in the clinic.

Other radiotracers for PSMA PET include 68Ga-PSMA-I&T (11), 68Ga-THP-PSMA (12), fluoreline 18 (18F)–DCFPyL (13,14), and 18F-PSMA-1007 (15). These have a similar biodistribution but can differ in their binding affinities and nonspecific uptake, which limits direct comparisons when assessing interval change.

Imaging Procedure, Radiation Dosimetry, and Biodistribution
A weight-adjusted radiotracer dose of 1.8–2.2 MBq/kg of body weight is recommended, subject to variation that may be required owing to variable elution during the lifetime of the 68Ge/68Ga generator. Imaging is performed approximately 45–75 minutes after radiotracer administration. The patient should be well hydrated and should void immediately before commencement of the scan. PET images should be acquired from the pelvis toward the head to minimize misregistration between the CT or magnetic resonance (MR) imaging and PET components of the study due to filling of the bladder during acquisition. CT and MR imaging acquisition protocols vary considerably among institutions. The 68Ga-PSMA-11 is administered in a microgram dose, and no pharmacologic or adverse effects have been reported. Joint European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) procedure guidelines for 68Ga-PSMA-11 PET/CT have recently been published (16). High reporter agreement for 68Ga-PSMA-11 PET/CT has been demonstrated (17,18). The use of 68Ga-PSMA-11 results in relatively low...
Lymph node involvement makes them a potential source of false-positive findings. These ganglia were generally not perceivable at anatomic imaging before the availability of $^{68}$Ga-PSMA-11 PET, but with experience they are now readily identifiable. The frequency of ganglia visualization depends on the type of PET/CT camera and reconstruction method used. The new generation of devices can resolve smaller lesions, especially devices with time-of-flight and point-spread functions, which increase contrast for small structures. In one series, celiac ganglion uptake was visualized in 60% of patients (26).

Clinical Indications in Prostate Cancer

The potential indications for use of $^{68}$Ga-PSMA-11 PET/CT are summarized in the Table.

Primary Staging of Prostate Cancer

Current international guidelines recommend the use of CT, bone scintigraphy, or MR imaging for high-risk patients only (28). There are many approaches to risk assessment. The most common D’Amico classification defines high risk...
as a PSA level greater than 20, a Gleason score greater than 8, or a clinical stage of T2c or T3a. The Gleason score defines five histologic patterns correlating with the degree of differentiation, from most (score of 1) to least (score of 5) differentiated. The score assigns a primary grade to the dominant pattern and a secondary grade to the next most frequent pattern. Recently, a new five-tier Gleason grade grouping with superior prognostic stratification has been adopted (29,30). This separates Gleason score 3+4 (grade group 2) and Gleason score 4+3 (grade group 3) into two separate risk entities. Grades group 3 and above are considered to be high risk. The superior accuracy of PSMA PET over conventional imaging for staging in high-risk patients may allow identification of patients with otherwise occult distant metastatic disease (Fig 3) and could facilitate individualized multimodal treatment concepts, especially in the setting of oligometastatic disease. In some cases, PSMA PET findings may be used to downstage patients who were inaccurately classified as having metastatic disease at conventional imaging (Fig 4).
Several studies have compared $^{68}$Ga-PSMA-11 PET to conventional imaging or histopathologic analysis after pelvic nodal dissection. The results of available retrospective studies vary owing to different risk profiles of the studied patient populations. The largest series to date analyzed 130 patients with intermediate or high-risk prostate cancer and compared $^{68}$Ga-PSMA-11 PET with cross-sectional imaging, with pelvic lymph node dissection results used as the standard of reference (31). In this series, PET had superior sensitivity (66% vs 44%) and specificity (99% vs 85%) compared to cross-sectional imaging. The lymph nodes missed at $^{68}$Ga-PSMA-11 PET were primarily less than 5 mm in size. Two smaller studies of $^{68}$Ga-PSMA-11 PET demonstrated sensitivities of 33% (32) and 91% (33), respectively. A small prospective study of $^{68}$Ga-PSMA-11 PET demonstrated a sensitivity of 64% and a specificity of 94% (34). False-negative findings occurred in lymph nodes with a mean size of 2.7 mm. Because these studies included patients with intermediate-risk disease, the incidence of distant metastatic disease was low, which diminished the opportunity to compare $^{68}$Ga-PSMA-11 PET with other modalities for detection of distant metastatic disease. Evolving experience and literature suggest that $^{68}$Ga-PSMA-11 PET has greater sensitivity and specificity than bone scintigraphy (35). However, in the absence of high-quality data, it is difficult to quantify the incremental accuracy compared with that of conventional imaging. The ProPSMA trial is a multicenter randomized controlled study that has commenced in Australia to establish whether PSMA PET/CT should replace conventional imaging as a first-line study in patients with high-risk prostate cancer before curative-intent surgery or radiation therapy (36).

The greater accuracy provided by $^{68}$Ga-PSMA-11 PET is redefining the patterns of spread of prostate cancer. Lymph nodes within the true pelvis are considered regional nodes, defined as N0 or N1 according to the American Joint Committee on Cancer (AJCC) staging manual (37). Commonly involved nodes include internal and external iliac and obturator nodes. In addition, mesorectal (38) and presacral nodes are frequently visualized at $^{68}$Ga-PSMA-11 PET. The lateralization of nodal involvement usually parallels the dominant side of prostate primary disease. Locating the subcentimeter nodes identified at $^{68}$Ga-PSMA-11 PET during lymph node dissection can be challenging for the surgical oncologist. Use of $^{111}$In or technetium 99m–radiolabeled PSMA with an intraoperative gamma probe to locate lesions has shown potential to facilitate precise surgical localization (39–41).

Nodes outside the true pelvis are classified as nonregional nodes and are designated as M1a. Inferiorly, this includes inguinal nodes, and superiorly, this include common iliac nodes, para-aortic, aortocaval, and retrocrural nodes. In some patients, we have observed drainage to para-aortic nodes in the region of the left renal vein without pelvic nodal involvement, a drainage pathway following the gonadal vessels anterior to the psoas muscle ending in para-aortic and paracaval nodes at the renal hilum (42). Above the diaphragm, there is a high occurrence of supraclavicular nodal involvement visualized at PSMA PET/CT. This can occur even in the absence of upper abdominal nodal involvement and parallels the known lym-

### Potential Indications for Use of PSMA PET/CT

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Indication</th>
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<tbody>
<tr>
<td>High estimated benefit or diagnostic gain</td>
<td>Primary staging in high-risk disease according to the D’Amico classification; biochemical recurrence with low PSA value (0.2–10 ng/mL)</td>
</tr>
<tr>
<td>Low estimated benefit or diagnostic gain</td>
<td>Primary staging in low- and intermediate-risk disease according to the D’Amico classification</td>
</tr>
<tr>
<td>Potential application with promising preliminary data</td>
<td>Biopsy targeting after previous negative biopsy but high suspicion for prostate cancer (especially in combination with multiparametric MR imaging using PET/MR imaging)</td>
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<tr>
<td>Potential application with current lack of published data</td>
<td>Monitoring of systemic treatment in metastatic castration-resistant or metastatic castration-sensitive prostate cancer</td>
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<tr>
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<td>Active surveillance (especially in combination with multiparametric MR imaging using PET/MR imaging)</td>
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<td></td>
<td>Treatment monitoring in patients with metastatic castration-resistant prostate cancer undergoing radioligand therapy targeting PSMA (eg, $^{177}$Lu-PSMA-ligand)</td>
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Note.—Adapted and reprinted under a CC BY 4.0 license from reference 27. $^{177}$Lu = lutetium 177, PSA = prostate-specific antigen.
phatic drainage pathway to the distal left thoracic duct region (the Virchow node).

The most common type of extranodal spread is osseous, designated as M1b. In therapy-naive patients, $^{68}$Ga-PSMA-11 PET–positive osseous lesions often show no corresponding anatomic abnormality at CT. In patients with more indolent well-differentiated disease, sclerotic changes but low-intensity uptake are more frequently seen. Aggressive poorly differentiated disease may even result in lytic osseous changes.

$^{68}$Ga-PSMA-11 PET is also very sensitive for detection of visceral metastatic disease designated as M1c, including metastases to the lung, liver, pleura, adrenal gland, and brain (Fig 5). While some of these organs are not commonly observed

Figure 3. Newly diagnosed Gleason 4+5 prostate adenocarcinoma in a 70-year-old man. Conventional CT and MR imaging of the pelvis and bone scintigraphy (not shown) showed no evidence of metastatic disease. (a) Coronal maximum intensity projection $^{68}$Ga-PSMA-11 PET image shows high tumor-to-background contrast (arrows) at the sites of primary disease and metastases. (b) Axial CT (left) and $^{68}$Ga-PSMA-11 PET/CT (right) images show a metastasis to the rib (top), a subcentimeter right obturator lymph node (middle), and primary prostate disease (bottom). The treatment was changed from radical prostatectomy to hormonal therapy. Follow-up $^{68}$Ga-PSMA-11 PET/CT images obtained 12 months later (not shown) showed resolution of all findings, commensurate with an undetectable PSA level. Although the findings at baseline bone scintigraphy were negative, bone scintigraphy performed at 12 months (not shown) showed an osteoblastic abnormality in the rib, highlighting the limitations in differentiating a healing response from progressive disease at bone scintigraphy.
at anatomic imaging, the visualization of these findings at PSMA PET/CT is consistent with autopsy studies of metastatic patterns of prostate cancer (43). Notably, pulmonary metastases are subject to respiratory movement, which can significantly decrease the apparent intensity of uptake, especially for small lesions. Thus, close review of the anatomic images is required.

**Localization of Intraprostatic Tumor**

An increasing number of studies have investigated the potential of $^{68}$Ga-PSMA-11 for intraprostatic tumor localization. One study showed significantly higher $^{68}$Ga-PSMA-11 uptake in segments with malignancy than in negative segments (maximum SUV [SUV$_{\text{max}}$] of 11.8 vs 4.9) and suggest an SUV$_{\text{max}}$ of 6.5 as an optimal discriminator, with sensitivity of 67% and specificity of 92% for detection of tumor-involved segments (44). In addition, preliminary results indicate that PSMA PET might be complementary to standalone multiparametric MR imaging for intraprostatic tumor localization (Fig 6). Exploiting combined $^{68}$Ga-PSMA-11 PET/MR imaging for direct comparison in 53 intermediate or high-risk patients, the sensitivity of multiparametric MR imaging when using PI-RADS criteria was 43%, compared with 64% for $^{68}$Ga-PSMA-11 PET (45). Simultaneous PET/MR imaging, which combined functional and multiparametric MR imaging data, further improved sensitivity to 76%. Further research is required on how to best integrate PET and MR imaging findings for directed biopsy or active surveillance.

**Biochemical Recurrence**

Despite curative-intent surgery or radiation therapy, there is a significant risk for disease relapse, which is usually detected by a rising PSA level. After radical prostatectomy, this is currently defined as a PSA level of more than 0.2 ng/mL that rises on at least two consecutive measures at least 3 weeks apart. After external beam radiation therapy, a rise of 2.0 ng/mL or more above the nadir PSA that occurs more than 6 weeks after therapy completion is required. However, at these
Figure 5. Subcentimeter visceral metastases in four different patients seen on 68Ga-PSMA-11 PET images (first image in each row), with correlative CT and/or MR images (subsequent images in each row). Images show penile metastasis (arrows) (a), hepatic metastasis (b), pulmonary metastasis (c), and brain metastases (d).

low PSA levels, conventional imaging has a limited ability to depict recurrent disease and therefore is not recommended (46). Following radical prostatectomy, biochemical recurrence is generally empirically treated with salvage radiation therapy to the prostate bed, although this treatment fails in a significant proportion of patients.

There is now a large volume of literature demonstrating the very high sensitivity of PSMA PET/CT in the setting of biochemical recurrence,
even in patients with low PSA levels in whom conventional imaging has very low sensitivity (10,31,47–53) (Fig 7). A meta-analysis of these studies (54) has demonstrated detection rates of 48% at a PSA level of 0.2 ng/mL, increasing to 56% and 70% at levels of 0.5 and 1.0 ng/mL, respectively. These rates are significantly superior to those at choline PET/CT (Fig 8) or conventional imaging. In an intraindividual comparison, \(^{68}\)Ga-PSMA-11 PET/CT had a higher SUV compared with that at choline-11 or \(^{18}\)F-choline PET/CT in 79% of lesions (53). In a prospective series, the detection rate with PSMA PET/CT was 66%, versus 32% with \(^{18}\)F-choline PET/CT (48). PSMA PET is capable of depicting small lymph node metastases, with one study reporting that 78% of PSMA-avid lymph nodes were less than 8 mm in size (50).

PSMA PET has been shown to have a high impact on management in patients with a PSA level from 0.05 to less than 1.0 ng/mL after radical prostatectomy who are candidates for salvage radiation therapy (55). Compared with blind radiation therapy to the prostate bed, \(^{68}\)Ga-PSMA-11 PET changed the management in 29% of patients in this prospective study, as lesions were located in either regional lymph nodes or bones that would not have been included in a conventional salvage radiation therapy field.

Use of PSMA PET in the setting of biochemical recurrence and a low PSA level frequently helps identify patients with oligometastatic disease, which can be potentially targeted with stereotactic radiation therapy or salvage surgery. However, there currently is a lack of high-quality data to indicate improved patient outcomes with use of PSMA PET in this setting (56). Of note, the potential introduction of lead-time bias, with the risk of early treatments causing more harm than good, has been discussed, as the long-term effects on progression-free and overall survival rates are still unclear (Fig 9) (56).

### Restaging of Metastatic Disease and Theranostic Selection

In patients with metastatic prostate carcinoma who are undergoing systemic therapy, conventional imaging, including bone scintigraphy, CT, or MR imaging, combined with the PSA level and clinical presentation is currently used for response assessment. Bone scintigraphy depicts the osteoblastic reaction to a metastasis as a surrogate marker, in contrast to PSMA PET, which depicts prostate cancer directly. In the restaging setting, differentiating treatment response from a healing (flare) response can be challenging. For soft-tissue disease, CT is generally used with the Response Evaluation Criteria in Solid Tumors (RECIST) for formal response assessment. However, subcentimeter target lesions that are visualized with confidence at PSMA PET/CT are not measurable at CT.
Figure 7. Biochemical recurrence in two patients with rising PSA levels (<1.0 ng/mL). Axial CT (left), PET (middle), and PET/CT (right) images in a patient with a prior radical prostatectomy (a) and a patient with prior external beam radiation therapy (b) show localized recurrence (arrows) in the prostate bed. There was no evidence of distant metastatic disease in either patient. The findings were confirmed at biopsy in both cases.

Figure 8 Comparison of $^{68}$Ga-PSMA-11 PET/CT to $^{18}$F-fluorocholine (FCH) PET/CT. (a, b) Axial $^{68}$Ga-PSMA-11 PET/CT image (a) shows high uptake in a presacral node ($\text{SUV}_{\text{max}} = 17$), compared with an $^{18}$F-FCH PET image (b) with an $\text{SUV}_{\text{max}}$ of 3.5. (c, d) Axial $^{68}$Ga-PSMA-11 PET image (c) shows a clearly discernible additional 3-mm node with focal uptake (circle). No visible abnormality (circle) is seen on the axial $^{18}$F-FCH PET image (d).
Nevertheless, well-established criteria such as the Prostate Working Group Criteria (PWGC) (57) for interpretation of response at bone scintigraphy and CT exist. Whole-body diffusion-weighted MR imaging is sensitive for detection of osseous metastases (58), but there is very limited evidence for its use in response assessment.

Because PSMA PET images tumors directly, early experience suggests that PSMA PET may have significant advantages over conventional imaging in treatment response assessment. The ability to evaluate local response in the prostate and in soft-tissue and osseous metastases in a single imaging study is a significant advantage, but further research is needed to define response criteria for PSMA PET/CT. Some caution is also warranted, as we have observed an increase in the intensity of radiotracer uptake early after commencing hormone-deprivation therapy, which may result in a “flare” phenomenon seen on PSMA PET images (Fig 11). This observation is supported by preclinical data demonstrating an increase in PSMA expression following androgen-deprivation therapy (59). PSMA PET may also be useful to evaluate response to taxane-based chemotherapy. A potential limitation in patients with advanced disease is the observation of absent or low PSMA expression at sites of poorly differentiated disease (eg, neuroendocrine differentiated prostate cancer). In these patients, FDG PET/CT may provide complementary information, with a high rather than low SUV that is prognostic for overall survival (60).

PSMA PET/CT has an evolving role in PSMA-targeting treatments in advanced disease (eg, 177Lu-PSMA radioligand therapy) to evaluate target expression and therefore potentially predict response before treatment initiation. High uptake at PSMA PET/CT is a prerequisite in selecting patients who may benefit from PSMA-directed radionuclide therapy. Presently, remarkable treatment responses have been observed in patients with castration-resistant metastatic disease who have failed conventional therapies, such as docetaxel chemotherapy or enzalutamide/abiraterone therapy (61).

**Pitfalls**

PSMA PET/CT is a highly sensitive and specific imaging tool, but imaging specialists must be aware of a variety of physiologic and other pathologic processes that can express PSMA and result in interpretative error. PSMA protein expression was discovered in prostate tissue and prostate cancer and is therefore termed prostate specific. Functionally, PSMA is a folate hydrolase that is expressed in a variety of normal tissues, tissue neovasculature, and other tumor types, both benign and malignant. Most of the non-prostate cancer–related uptake at PSMA PET has low intensity or is nonfocal, in contrast to the focal and usually intense uptake in prostate cancer lesions. Failure to recognize physiologic
uptake, such as in ganglia or urinary activity as detailed earlier, is another potential cause of false-positive findings. An increasing number of case series and reports describe PSMA uptake in benign processes such as osteoblastic activity or in benign tumors with PSMA expression, including hemangiomas, meningiomas, and benign thyroid nodules.

**Benign Conditions with PSMA Expression**

Low-to-moderate PSMA expression is observed in osteoblastic activity, with consequent activity seen in osteoarthritis, degenerative changes (Fig 12), fibrous dysplasia (62), and fractures. After radiation therapy to the pelvis for prostate cancer, sacral insufficiency fractures may also be visualized (Fig 13). Diffuse low-to-moderate uptake is seen in Paget disease (Fig 12), possibly also due to osteoblastic response. Close anatomic correlation usually enables these entities to be characterized with confidence, but uncertainty can arise if no anatomic correlate can be found. In particular, low-grade uptake in a single rib or in several contiguous ribs should be interpreted with caution. If there is uncertainty, ongoing monitoring of the PSA level with follow-up PSMA PET is suggested as the most appropriate strategy. This is preferable to performing further imaging investigations, which are in many instances unlikely to characterize equivocal PSMA PET findings with greater confidence. Moderate uptake can be seen in hemangiomas, including those in cutaneous, vertebral, and hepatic sites. Both acute and chronic inflammation can also be associated with PSMA uptake. As with FDG PET, the pattern of uptake and correlative anatomic findings are important in differentiation of these entities (63).

**PSMA-negative Prostate Cancer**

A small proportion (<10%) of prostate carcinomas exhibit no or minimal uptake at PSMA PET/CT, reflecting low PSMA expression (29). The
significance of PSMA-negative prostate carcinoma is currently uncertain. If the primary tumor is not PSMA avid, the sensitivity for detecting nodal or distant metastatic disease will be lower, and closer attention must be given to anatomic review in this setting. However, if the primary tumor is PSMA avid, the metastasis will usually have a similar phenotype. Therefore, in a patient with a PSMA-avid primary site, an enlarged PSMA-negative node is unlikely to represent prostate carcinoma (Fig 14). Exceptions are patients with advanced castration-resistant metastatic disease, especially after several lines of chemotherapy have failed, where some sites of disease have been observed to lose PSMA expression.

**PSMA PET in Other Malignancies**

PSMA expression has been described in several other tumor types, mainly related to the tumor neovasculature rather than to PSMA expression in the tumor cells themselves (64). High-intensity uptake is seen in several malignant tumor types (Fig 15), including renal cell carcinoma (65), salivary gland ductal carcinoma, pulmonary adenocarcinoma, glioblastoma multiforme, and hepatocellular carcinoma (66). Lower-intensity uptake may be observed in a wide range of tumors; experience continues to evolve, and uptake has been observed in breast carcinoma (67), lymphoma, meningiomas (68), squamous cell carcinoma, and well-differentiated thyroid cancer (69). Nevertheless, very-high-intensity uptake is almost exclusively seen in prostate cancer, and the other tumor types can usually be differentiated by different patterns of spread and correlative anatomic appearances. In a review of 764 PSMA PET/CT studies in patients being evaluated for prostate cancer, identification of
synchronous PSMA-avid malignancies were rare (0.7%) (70).

Conclusion
PSMA PET/CT has rapidly emerged as a potential new reference standard for imaging of prostate cancer, with extraordinary tumor-to-background contrast. Evolving evidence demonstrates superior sensitivity and specificity of this method compared with conventional imaging, with frequent identification of sites of disease less than 10 mm in size. PSMA PET/CT is effective for imaging disease in the prostate, soft tissue, and bone in a “one-stop-shop” examination. There is an emerging strong evidence base for staging of high-risk prostate cancer and localization of disease in the setting of biochemical recurrence. However, evidence regarding proper use of PSMA PET/CT to improve patient-related outcomes, particularly in the setting of early biochemical recurrence and targeted treatment of oligometastatic disease, is still missing. Despite the terminology prostate specific, PSMA that functions as folate hydrolase is expressed in a range of normal tissues and in other benign and malignant processes. Knowledge of the physiologic distribution and benign causes of uptake is essential to minimize

Figure 12. Radiotracer uptake at sites of osteoblastic activity, confirmed with follow-up PSA testing and imaging, in three patients. (a) Axial PSMA PET (left) and CT (right) images show uptake at the site of an anterior spondylolysis (arrows) at the L3-L4 level. (b) Axial PSMA PET (left) and CT (right) images show uptake in a hemangioma (arrows), with a typical polka-dotted appearance at CT (zoomed-in image, inset). (c) Axial PSMA PET (left) and CT (right) images show heterogeneous increased uptake in a man with Paget disease. Comparison with radiographs and CT and MR images obtained 5 years earlier in this patient (not shown) demonstrated changes typical of Paget disease, with no interval change.
Figure 13. Uptake at sites of fractures, confirmed with follow-up PSA testing and imaging. (a) Axial PET/CT image (left) and CT image (right) in a patient with sacral pain and prior salvage radiation therapy show symmetric low-to-moderate uptake in the sacrum. The findings were interpreted as an insufficiency fracture. A follow-up CT image (not shown) demonstrated a fracture line with increased sclerosis and, along with a finding of no elevation of the PSA level, helped confirm the diagnosis. (b) Axial PET/CT image (left) in a patient with local recurrent disease after radiation therapy shows low-to-moderate uptake in a rib. The findings were interpreted as a rib fracture, and a follow-up CT image (right, with magnified view in inset) shows a clear correlate with callus formation.

Figure 14. Primary staging in a patient with a Gleason score of 4+3 and a PSA level of 20 ng/mL. Staging CT (not shown) showed a 14-mm left common iliac node consistent with nonregional nodal metastatic disease (M1a). (a, b) Axial PSMA PET/CT images show high uptake in the prostate primary tumor (a) but no uptake (circle) in the suspected nodal metastasis (b). (c, d) Axial FDG PET/CT images show the opposite phenotype, with no uptake in the prostate (c) but high uptake in the node (d). The differential phenotype suggests a second pathologic condition. Results of nodal biopsy disclosed diffuse large B-cell lymphoma.
false-positive findings. PSMA PET is useful for imaging other PSMA-expressing tumors, with the most experience currently for clear cell renal carcinoma.

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