Pearls and pitfalls in clinical interpretation of prostate-specific membrane antigen (PSMA)-targeted PET imaging

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Abstract

Background The rapidly expanding clinical adaptation of prostate-specific membrane antigen (PSMA)-targeted PET imaging in the evaluation of patients with prostate cancer has placed an increasing onus on understanding both the potential pearls of interpretation as well as limitations of this new technique. As with any new molecular imaging modality, accurate characterization of abnormalities on PSMA-targeted PET imaging can be accomplished only if one is aware of the normal distribution pattern, physiological variants of radiotracer uptake, and potential sources of false-positive and false-negative imaging findings. In recent years, a growing number of reports have come to light describing incidental non-prostatic benign or malignant pathologies with high uptake on PSMA-targeted PET imaging. In this review, we have summarized the published literature regarding the potential pearls and technical and interpretive pitfalls of this imaging modality. Knowledge of these limitations can increase the confidence of interpreting physicians and thus improve patient care.

Conclusions As PSMA-targeted PET is expected to be evaluated in larger prospective trials, the dissemination of potential diagnostic pitfalls and the biologic underpinning of those findings will be of increased importance.

Keywords Prostate-specific membrane antigen · PSMA · PET/CT · Prostate cancer · Pearls and pitfalls

Background

Prostate cancer (PCa) is the most common non-cutaneous malignancy in men, with an estimated 1.4 million incident cases diagnosed worldwide in 2013 [1]. At the present time, PCa diagnosis and staging relies largely on morphologic imaging with CT and magnetic resonance imaging, as well as evaluation of bone metabolism with 99mTc-methylene diphosphonate scintigraphy [2, 3]. Recently, diagnostic imaging in the work-up of PCa has begun to evolve from dependence on morphological imaging to use of advanced hybrid molecular imaging techniques such as positron emission tomography (PET) [2, 4, 5]. Various radiotracers have been investigated for molecular imaging of PCa including those targeting lipid metabolism (11C-choline, 18F-fluorocholine, and 11C-acetate), amino-acid transporters (anti-L-amino-3,16F-fluorocyclobutane-L-carboxylic acid), 18F—sodium fluoride and prostate-specific membrane antigen (PSMA) expression [6–8].

PSMA has been shown to be a promising target for both imaging and therapeutic interventions in PCa [8–10]. To date, several studies have demonstrated superb diagnostic performance of PSMA-based PET in disease staging and the detection of recurrent PCa [10–16]. Perhaps the greatest utility of
PSMA-targeted PET imaging is in the evaluation of men with biochemically recurrent PCa, who by definition do not have evidence of disease on conventional imaging, and especially in patients with low PSA levels [8, 10, 17]. In addition, PSMA-targeted imaging can dictate a change in therapeutic management of up to 54% of PCa patients and can help in individualizing the radio-therapeutic plan in appropriately selected patients by adjusting pelvic lymphatic irradiation field or dose-escalation to sub-volumes of PCa [4, 15, 18–20].

As with any new molecular imaging modality, accurate characterization of abnormalities on PSMA-targeted PET can be accomplished only if one is aware of the normal distribution pattern, physiological variants of radiotracer uptake, and potential sources of false-positive and false-negative findings. With more extensive clinical use of this imaging modality, potential interpretative pitfalls are beginning to be recognized.

In this review, we summarize the published literature regarding the pearls and potential technical and interpretive pitfalls of PSMA-targeted PET imaging. Knowledge of these limitations can decrease the potential for false imaging findings and thus improve patient care by interpreting physicians.

**Review criteria**

A comprehensive literature review of PubMed/Medline was performed using a combination of following keywords: “prostate specific membrane antigen”, “PSMA”, “PET”, and “positron emission tomography”. No date limit or language restrictions were applied, and the search included articles published online up through May 31, 2017. A total of 484 records including 76 review articles and 106 case reports/short case series were identified. The identified records were reviewed, and the most pertinent articles are discussed herein.

**Mechanisms of PSMA-radiotracer uptake, bio-distribution, and imaging protocols**

PSMA is a type II transmembrane protein with glutamate carboxypeptidase/folate hydrolase activity [21]. Human PSMA is a zinc containing metalloenzyme (750 amino acids) with a unique 3-part structure composed of a large extracellular domain, a trans-membrane portion, and an intracellular component. PSMA is expressed in the apical side of the prostatic ducts [22] and is upregulated by PCa cells [21]. In fact, PSMA expression is associated with PCa aggressiveness and has been shown to have prognostic relevance [23, 24].

Binding of the PSMA ligand to its anchored-cell membrane target mediates internalization through clathrin-dependent endocytosis [21, 25]. This leads to enhanced retention of conjugated radionuclides into the cells even in small volume sites of disease, which in turn enables high quality image acquisition for diagnostic procedures and high local dose for therapeutic applications [8, 21]. In recent years, several antibodies, as well as small molecules with high affinity to the extra-cellular domain of PSMA have been developed [8, 26]. Among them, the urea-based small molecule inhibitors of PSMA are the most promising due to their pharmacokinetic features and rapid blood clearance that results in low background activity [27–39]. To date, several bio-distribution studies have attempted to optimize the protocols for imaging with these small molecules.

**68Ga-PSMA-11 PET imaging**

68Ga-PSMA-11 (also known as 68Ga-PSMA-HBED, 68Ga-PSMA-HBED-CC, and 68Ga-PSMA-Glu-urea-Lys(Alx)-HBED-CC) was introduced by the German Cancer Research Centre (Heidelberg, Germany) [40] in May 2011 [11, 41]. This radiotracer has since become the most widely used agent for PSMA-targeted imaging, particularly in Europe and Asia. The human bio-distribution of 68Ga-PSMA-11 has been well described in several studies [11, 42–44]. In normal organs, high 68Ga-PSMA-11 uptake (maximum standardized uptake values [SUVmax] >10) was observed in the kidney cortex, duodenum, parotid and submandibular salivary glands followed by moderate uptake (SUVmax > 3) in the spleen, lacrimal glands and liver [11, 42, 44, 45].

Biodistribution studies on dynamic 68Ga-PSMA-11 PET imaging demonstrated sufficiently high radiotracer uptake in tumor lesions as early as 5 min post injection (p.i.). The lesion-to-background ratios and the SUVmax of primary tumors and lymph node and bone metastases were shown to significantly increase over time, mediated by PSMA internalization [45, 46]. Sahlman et al. and Afshar-oromieh et al. compared the 68Ga-PSMA-11 PET images obtained at 1 h p.i. and 3 h p.i. and suggested that a second time-point (i.e. 3 h p.i.) can improve the characterization of tumor lesions regarded as equivocal on early imaging (1 h p.i.). In addition, this modified imaging protocol can help identify additional lesions since 68Ga-PSMA-11 uptake increases over time in tumor lesions as compared to benign tissue [45, 47, 48]. Although imaging at 3 h p.i. appears to be superior to 1 h p.i. [45, 47], the optimal imaging timing for 68Ga-PSMA-11 PET/CT and the incremental clinical value of second-time point imaging need to be evaluated in larger patient cohorts.

One potential limitation of 68Ga-PSMA-11 and most current PSMA ligands for PET-imaging includes the detection of lesions around the prostate gland. This is related to high levels of radiotracer excretion and urinary bladder activity that may mask small local recurrences in this vicinity [25, 45, 46]. Kabaskal et al. suggested that early pelvic imaging (5 min p.i.), obtained before radiotracer accumulation within the urinary bladder, may help in better evaluation of lesions in this region [46]. Recent studies have indicated that sufficient hydration and administration of diuretics prior to late scan time
point (i.e. 3 h p.i.) can reduce the radioactivity and help optimize the visibility of lesions around the structures of urinary tract [45, 47].

18F–PSMA-targeted PET imaging

The first in the class of 18F-labeled PSMA ligands, 18F–DCFB, was initially introduced in 2008 by researchers from the Johns Hopkins University [49]. In 2012, the first-in-human clinical study of 18F–DCFBC demonstrated the feasibility of this radiopharmaceutical agent for accurate delineation of bone and soft tissue metastases in men with PCa [13]. For the detection of primary PCa, 18F–DCFBC PET allowed for localization of clinically significant high grade primary tumors [50].

Further studies support higher detection rate and sensitivity of 18F–DCFBC PET compared to conventional imaging in hormone-naïve and castration-resistant metastatic PCa [7, 51]. Rowe et al. suggested that late time point imaging (approximately 2.5 to 3 h p.i.) with 18F–DCFBC can optimize image quality by both improving tumor uptake and decreasing background distribution [7]. An important limitation of 18F–DCFBC is the relatively persistent blood-pool radioactivity, possibly due to binding of the radiotracer to plasma proteins [52].

To address the potential pitfalls and improve the pharmacokinetics of 18F–DCFBC, a second generation 18F–labeled PSMA ligand, 18F–DCFPyL, was developed [53]. Initial data on the bio-distribution and radiation dosimetry of 18F–DCFPyL showed a more rapid renal excretion, higher tumor-to-blood and tumor-to-muscle ratios, and lower uptake in liver [52]. Compared to 18F–DCFBC, 18F–DCFPyL showed more than five times greater affinity for PSMA with corresponding higher uptake in presumed primary and metastatic foci of PCa. These features significantly improved the visualization of suspected metastatic PCa lesions.

Similar to 68Ga-PSMA-11 and possibly all other small molecule PSMA ligands, 18F–DCFPyL uptake is seen by the salivary glands, lacrimal glands, kidneys, liver, spleen, small intestine, and urinary collecting system (Fig. 1) [53]. Bio-distribution studies on dynamic 18F–DCFPyL PET imaging demonstrated a significant trend toward increasing tumor uptake and decreasing background uptake between approximately 1 h and 2 h p.i. Thus, delayed imaging at 2 h p.i. appeared to lead to the better diagnostic performance [54].

Rowe et al. suggested that 18F–DCFPyL PET can detect multiple sites of recurrent disease that were occult or equivocal on conventional imaging modalities. This is particularly important in the evaluation of pelvic/peri-prostatic tissues and subcentimeter lymph node lesions (Fig. 2). Similarly, 18F–DCFPyL PET was found to be superior to conventional imaging modalities in detection of primary infiltrative or lytic bone lesions (that may be visually occult on contrast enhanced CT and with low uptake on bone scan) [54] (Fig. 3).

18F–DCFPyL is a significant breakthrough for 18F–labeled PSMA radiotracers and is a highly promising alternative to 68Ga-labeled compounds while offering important advantages related to 18F–labeling. These include a longer half-life, higher production capacity, improved image resolution related to lower energy positron emissions, and potentially improved lesion detectability [55, 56].

Two recent publications compared the performance of PSMA-targeted PET/CT imaging with the 68Ga-PSMA-11 (150 MBq, 1 h p.i) and 18F–DCFPyL (250 MBq, 2 h p.i) in a cohort of 25 patients with recurrent PCa [57, 58]. Pairwise comparison of matched PET scans showed highly concordant radiotracer distribution pattern [57]. Compared with 68Ga-

Fig. 1 Whole-body maximum intensity projection (MIP) image from an 18F–DCFPyL PET/CT of a post-prostatectomy patient presenting for evaluation of biochemical recurrence. This image demonstrates the normal biodistribution of the radiotracer, which is quite similar to other urea-based small molecule agents that target PSMA. Organs with uptake include the lacrimal glands, the salivary glands, liver, spleen, kidneys, bowel (variable, proximal intestines as well as parts of the colon), ureters (variable, as seen here), and urinary bladder.
PSMA-11, 18F–DCFPyL was found to provide at least comparable tumor/background contrast and detected additional suspicious lesions in 36% (four out of 11) of 68Ga-PSMA-11 positive scans [57]. While these studies suggested a possible improved sensitivity of 18F–DCFPyL, the lack of harmonized acquisition protocols, different injected radiotracer doses, and different time windows after injection significantly limited the comparison. Further in-depth clinical studies with standardized acquisition protocols and histological validation are needed to establish the comparative performance of these two radiotracers.

Recently, another promising 18F–labeled agent, 18F–PSMA-1007, has been reported [59, 60]. This compound also takes advantage of the intrinsic positive characteristics of 18F and has been found to identify very small sites of PCa, while also having relatively low urinary excretion, which may aid visualization of intraprostatic or locally recurrent disease [61, 62].

**General pitfalls and interpretation issues of PSMA-targeted PET imaging**

Although PSMA expression was first confirmed in PCa, the expression of this molecule has been documented in a range of normal tissues, as well as other benign and malignant pathologies [63, 64]. In contrast to the predominantly epithelial expression of PSMA in PCa, PSMA expression in non-prostatic solid malignancies is mainly associated with the tumor neovasculation [51, 64]. PSMA is also selectively expressed in the endothelium of some benign proliferative tissues such as keloids, granulation tissue from heart valves, pleura, and endometrium [21, 65]. With the rapid clinical adoption of PSMA-targeted PET imaging of PCa, several reports have come to light questioning the specificity of PSMA for PCa. In the last few years, an expanding number of case reports and case series have been published describing incidental non-prostatic benign or malignant lesions with high PSMA-radiotracer uptake. To expand our knowledge base, we have reviewed and summarized all published clinical case reports/short case series on this topic herein.

**Lymph node involvement**

Lymph node and bone are among the most common metastatic sites in PCa. Early detection of nodal recurrence and
oligometastatic disease is paramount for selecting the optimal mode of therapy for these patients [66]. The performance of conventional imaging (CT and MRI) in nodal staging of PCa are limited primarily based on lymph node size. PSMA-targeted PET has superior specificity in the assessment of nodal recurrence, particularly in the detection of small volume metastases (longest diameter less than 1 cm) [8, 17]. A recent meta-analysis demonstrated high sensitivity (80%) and specificity (97%) for 68Ga-PSMA-11 PET/CT for the assessment of lymph node metastases compared to histopathology after salvage lymph node dissection [9]. PSMA-targeted PET imaging can improve lymph node metastases mapping by detecting subtle sites of disease in unrecognized locations including mesorectal, posterior pelvic, and supraclavicular nodes [17, 67–69]. This is particularly important as the mesorectum/posterior pelvic region would usually not be included in the standard pelvic lymph node dissection or radiation field unless lymph node involvement is known [67].

A potential limitation of PSMA-targeted PET imaging is in the detection of lesions below the spatial resolution of PET cameras (5 mm) [70]. To detect these lesions, intense background ratios are required to overcome partial volume effects. Van Leeuwen et al. observed intense radiotracer uptake in 60% of lymph node metastases measuring 2 to 4.9 mm, based on histopathology. Remarkably, they showed that almost all false negative lymph node metastases were less than 5 mm in diameter (median 2.7 mm) [68].

An important observed diagnostic pitfall of PSMA-targeted PET imaging is non-specific physiological radiotracer uptake in sympathetic chain, cervical, coeliac, and sacral ganglia [44, 71, 72]. This finding can easily be misinterpreted as metastases to non-regional lymph nodes. Krohn et al. observed apparent radiotracer uptake in the coeliac ganglia of 41% of PCa patients with no lymph node metastases on restaging 68Ga-PSMA-11 PET/CT [44]. This finding can potentially result in misdiagnosis of metastatic disease (non-regional lymph node involvement(stage cM1a) in a patient with localized primary PCa [44, 71].

In a recent case series, Beheshti et al. demonstrated 68Ga-PSMA-11 uptake in cervicothoracic/stellate ganglia (located at the level of C6-C7 inferior to the subclavian artery) [71]. At least one coeliac ganglia with intense 68Ga-PSMA-11 uptake was identified in up to 94.0% of PCa patients with PET/CT [44, 72]. Immunohistochemical staining confirmed high PSMA expression in coeliac ganglia [44]. Another study of 308 patients with 68Ga-PSMA-11 PET showed that uptake in coeliac ganglia (average SUVmax 2.9) is higher compared to the cervical (average SUVmax 2.6) and sacral (average SUVmax 1.9) ganglia [72]. Accurate anatomic localization of ganglia, along with the pattern and degree of radiotracer uptake, can be used to differentiate this normal variant from lymph node metastases (Figs. 4 and 5).

### Benign pathologies mimicking prostate cancer

High uptake of PSMA-targeted PET radiotracers has been shown in various benign pathologies including granulomatous diseases such as sarcoidosis [43, 73–78]; benign bone pathologies such as Paget’s disease of the bone [79–85], fibrous dysplasia [86], and healing bone fracture [87, 88]; hemangiomas [89–91]; benign soft tissue lesions [92–97]; tumors of neurogenic origin such as meningiomas [98, 99], schwannomas [100, 101], peripheral nerve sheath tumor [102]; senile amyloidosis [103]; adenomas [104–107]; and cerebral infarction [108, 109]. Radiotracer uptake by these benign/inflammatory pathologies could cause false-positive findings and mimic lymph node or distant metastasis from PCa. Thus, the results of a PSMA-targeted PET/CT in patients with a history of or clinical concern for one of these conditions must be interpreted with caution. A detailed summary of published reports on benign entities that show uptake on PSMA-targeted PET imaging is provided in Table 1.

#### Granulomatous diseases

Thus far, several case studies demonstrated increased 68Ga-PSMA-11 uptake in benign granulomatous lesions [43, 73–78]. Sarcoidosis is a chronic multi-system granulomatous inflammatory disorder, which predominantly involves the lungs and thoracic lymph nodes [120]. However, the disease can also involve other organs which can mimic cancer metastases [120]. Several studies have suggested that PSMA-radiotracer uptake can be seen in patients with known or active sarcoidosis [75–78]. In a recent report, bilateral 68Ga-PSMA-11 uptake was observed in the mediastinal and hilar lymph nodes of two PCa patients. Endobronchial ultrasound-guided biopsy showed non-necrotizing granulomata compatible with active sarcoidosis [75]. Sarcoioid lesions have also been reported in the spleen and liver of two patients referred for restaging of PCa [76, 77].

68Ga-PSMA-11 uptake has also been described in a case of Wegener’s granulomatous (SUVmax = 3.2) [43], as well as other benign inflammatory conditions of the lung including active tuberculosis [73], anthracosis [74], and bronchiectasis [111]. Molecular mechanisms of uptake of PSMA-targeted radiotracers in granulomatous diseases are not yet well understood.

#### Benign bone disease

Benign bone diseases such as Paget’s disease [79–85, 113], healing fractures (Figs. 6 and 7) [87, 88], and fibrous dysplasia [86] have been reported occasionally to exhibit increased radiotracer uptake on PSMA-targeted imaging. These pathologies are potential pitfalls being that should
be considered in clinical interpretation of PSMA-targeted PET imaging, as it may lead to false diagnosis of metastatic disease (Stage cM1b/bone involvement) and alter the subsequent management.

Paget’s disease has recently been suggested as a potential clinical mimicker of bone metastases on PSMA-targeted PET imaging. Paget’s disease is a chronic, localized skeletal disorder that is relatively common in elderly men [84, 121]. The disease is characterized by increased osteoclastic bone resorption followed by disorganized bone formation and increased bone vascularity [121]. So far, several case reports have demonstrated increased uptake within the sacrum, ischial tuberosity, iliac bone, pubic bone, humeral head, and phalanx in patients with conventional imaging or pathological findings compatible with Paget’s disease [79–85, 113]. Fig. 6 includes an example of uptake of 18F–DCFPyL agent in a patient with Paget’s disease of the right iliac bone.

Bone metastasis is the most common site for distant PCa metastasis [122]. Falsely positive radiotracer uptake in benign bone processes may relate to bone remodeling and increased vascularity [84, 87]. Thus, correlation of finding with conventional imaging techniques is necessary for accurate differentiation of benign bone pathologies. This includes diffusely increased uptake on bone scintigraphy along with areas of altered bone structure such as coarsened trabeculae, thickened cortices and bone hypertrophy on cross-sectional CT or MRI in Paget’s disease [121].

**Benign neurogenic tumors**

In addition to non-specific PSMA ligand uptake in sympathetic chain ganglia (“Lymph Node Involvement” section) [44], PSMA expression has been reported in some benign tumors of neurogenic origin including meningiomas, schwannomas, and peripheral nerve sheath tumor [98–100, 102, 123]. So far, incidental increased 68Ga-PSMA-11 uptake with corresponding MRI findings consistent with meningiomas have been reported in two case reports of patients with PCa [98, 99]. Leptomeningeal metastases are an infrequent finding in genitourinary cancers including PCa, in contrast to lung and breast cancer [124, 125]. Given the rarity of meningeal metastases from PCa, further imaging (e.g. MRI) can be considered in the presence of meningeal PSMA-radiotracer uptake to differentiate reliably metastases from meningioma.

It is worth noting that meningioma can potentially be a host tumor for brain metastases from extra-cranial carcinomas.
Table 1  Summary of the published reports on incidental detection of non-prostatic benign PSMA-avid lesions in the staging/restaging work-up of prostate cancer (false-positive findings)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>PSA level</th>
<th>Imaging finding</th>
<th>Diagnosis</th>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dias et al.</td>
<td>&gt; 0.3 &amp; 17 μg/L</td>
<td>Staging/Restaging 68Ga-PSMA: symmetrical bilateral uptake in mediastinal and hilar LNs (Two patients)</td>
<td>Sarcoïdosis</td>
<td>Pathology (biopsy)</td>
</tr>
<tr>
<td>Hermann et al.</td>
<td>1.4 ng/mL</td>
<td>Restaging 68Ga-PSMA: Avid area in the liver segment VIII CE Ultrasound: No pathological area or tumor in the liver</td>
<td>Sarcoïdosis</td>
<td>2-year FU, PMH sarcoïdosis</td>
</tr>
<tr>
<td>Kobe et al.</td>
<td>0.2 ng/mL</td>
<td>Restaging 68Ga-PSMA: Intense uptake in spleen MRI: Hypo intense lesion (T2-weighted); not specific for a benign splenic lesion</td>
<td>Sarcoïdosis</td>
<td>Pathology (biopsy)</td>
</tr>
<tr>
<td>Ardies et al.</td>
<td>elevated</td>
<td>Staging 68Ga-PSMA: Uptake in numerous thoracic and intra-abdominal LNs</td>
<td>Sarcoïdosis</td>
<td>History of sarcoïdosis, remained stable on CT imaging over 50 years</td>
</tr>
<tr>
<td>Pyka et al.</td>
<td>NR</td>
<td>68Ga-PSMA: Uptake in lung lesions (Two patients) (SUVmax: 7.8 and 2.5)</td>
<td>Reactivated tuberculosis</td>
<td>Sputum analysis</td>
</tr>
<tr>
<td>Bouchelouche and Vendelbo</td>
<td>23.7 ng/mL</td>
<td>Staging 68Ga-PSMA: Opacities and bronchiectasis, airway wall thickening with moderate uptake</td>
<td>Benign lung opacities and bronchiectasis</td>
<td>Endoscopic bronchoalveolar lavage, FU CT in 3 months</td>
</tr>
<tr>
<td>Elri et al.</td>
<td>21.4 ng/mL</td>
<td>Restaging 68Ga-PSMA: Intense uptake in hilar mass in the left lung and accompanying mediastinal lymphadenopathy (in addition to liver and bone metastases)</td>
<td>Anthracosis</td>
<td>Pathology (bronchoscopic biopsy)</td>
</tr>
<tr>
<td>Froehner et al.</td>
<td>6.7 ng/mL</td>
<td>Staging 68Ga-PSMA: Moderate uptake in left pubic bone</td>
<td>Paget’s disease</td>
<td>Pathology (biopsy)</td>
</tr>
<tr>
<td>Sasikumar et al.</td>
<td>0.5 ng/mL</td>
<td>Staging 68Ga-PSMA: Heterogeneous moderate to intense uptake in sclerotic changes in the left iliac bone</td>
<td>Paget’s disease</td>
<td>Pathology (biopsy)</td>
</tr>
<tr>
<td>Derlin et al.</td>
<td>1.1 ng/mL</td>
<td>Restaging 68Ga-PSMA: Intense uptake in the right iliac bone and in multiple LNs</td>
<td>Paget’s disease</td>
<td>Imaging correlate, PMH Paget’s disease</td>
</tr>
<tr>
<td>Blazak and Thomas</td>
<td>elevated</td>
<td>68Ga-PSMA: Intense uptake within the left ischial tuberosity and the posterior right inferior pubic ramus</td>
<td>Paget’s disease</td>
<td>Bone scan/SPECT/CT</td>
</tr>
<tr>
<td>Artigas et al.</td>
<td>rising</td>
<td>Restaging 68Ga-PSMA: Uptake in the proximal phalanx of the finger</td>
<td>Paget’s disease</td>
<td>Bone scan and X-ray</td>
</tr>
<tr>
<td>Bourgeois et al.</td>
<td>6.5 ng/mL</td>
<td>Restaging 68Ga-PSMA: Intense uptake in left humeral head, several LNs</td>
<td>Paget’s disease</td>
<td>Imaging correlate (CT, stable appearance over 8 yrs) contrast-enhanced CT, bone scan, and pelvic MRI</td>
</tr>
<tr>
<td>Rowe et al.</td>
<td>0.3 ng/mL</td>
<td>Restaging 18F-DCFPPyL: Diffuse uptake in sacrum (SUVmax 4.6)</td>
<td>Paget’s disease</td>
<td>Imaging correlate (CT, history of fall)</td>
</tr>
<tr>
<td>Vamadevan et al.</td>
<td>8.9 μg/L</td>
<td>Staging 68Ga-PSMA: tracer uptake localized to an undisplaced transverse fracture of the L1 vertebral body (SUVmax, 6.3)</td>
<td>Vertebral body fracture</td>
<td>Imaging correlate (MRI, history of fall)</td>
</tr>
<tr>
<td>Gykiere et al.</td>
<td>1.8 μg/L</td>
<td>Restaging 68Ga-PSMA: Moderately and diffuse tracer uptake in the sacrum</td>
<td>Healing Sacral Fracture</td>
<td>Imaging correlate (MRI, history of fall)</td>
</tr>
<tr>
<td>De Coster et al.</td>
<td>5.7 ng/mL</td>
<td>Staging 68Ga-PSMA: Mild focal uptake in the posterior arch of the sixth right rib</td>
<td>Benign fibrous dysplasia</td>
<td>Pathology (surgical resection)</td>
</tr>
<tr>
<td>Kanthan et al.</td>
<td>6.9 μg/L</td>
<td>Staging 68Ga-PSMA: Avid right pelvic mass anterior to the sacrum (SUVmax:4)</td>
<td>Schwannoma</td>
<td>Pathology (Surgical resection), MRI</td>
</tr>
<tr>
<td>Rischpfler et al.</td>
<td>11.3 ng/ml</td>
<td>68Ga-PSMA: Intense uptake right paravertebral soft-tissue mass</td>
<td>Schwannoma</td>
<td>MRI</td>
</tr>
<tr>
<td>Bilgin et al.</td>
<td>16.4 ng/mL</td>
<td>Restaging 68Ga-PSMA: Moderate uptake in left orbitofrontal region (SUVmax:3.1)</td>
<td>Meningioma</td>
<td>Imaging correlate (FU MRI)</td>
</tr>
<tr>
<td>Jain et al.</td>
<td>NR</td>
<td>Staging 68Ga-PSMA: Uptake in a meningioma</td>
<td>Meningioma</td>
<td>NR</td>
</tr>
<tr>
<td>Author, year</td>
<td>PSA level</td>
<td>Imaging finding</td>
<td>Diagnosis</td>
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<tr>
<td>Vamadevan et al. [88, 102]</td>
<td>7.5 μg/L</td>
<td>Staging 68Ga-PSMA: intense uptake in prostate gland and increased uptake localized to a soft tissue density in the left adductor compartment (SUVmax 4.7)</td>
<td>Peripheral nerve sheath tumor</td>
<td>Pathology (biopsy)</td>
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<td>Hemangiomas and benign soft tissue pathologies</td>
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<tr>
<td>Artigas et al. [90]</td>
<td>2.1 ng/mL</td>
<td>Restaging 68Ga-PSMA: intense uptake in the 12th thoracic vertebra without morphological correlation in CT</td>
<td>Vertebral hemangioma</td>
<td>Spinal MRI and 1-year FU</td>
</tr>
<tr>
<td>Jochumsen et al. [91]</td>
<td>0.5 μg/L</td>
<td>Restaging 68Ga-PSMA: intense uptake in the abdominal wall</td>
<td>Subcutaneous capillary hemangioma</td>
<td>Pathology (resection)</td>
</tr>
<tr>
<td>Bhardwaj et al. [89]</td>
<td>NR</td>
<td>Staging 68Ga-PSMA: intense uptake in hepatic segment IVa (SUVmax: 20.6)</td>
<td>Benign liver hemangioma</td>
<td>Imaging FU (CT, MRI; no growth over 3 months)</td>
</tr>
<tr>
<td>Zacho et al. [96, 118]</td>
<td>0.2 ng/mL</td>
<td>Restaging 68Ga-PSMA: uptake in left vastus medialis muscle (SUVmax: 3)</td>
<td>Intramuscular myxoma</td>
<td>Pathology (surgical resection)</td>
</tr>
<tr>
<td>Daglia Gorur et al. [97]</td>
<td>19.62 ng/mL</td>
<td>Staging 68Ga-PSMA: moderate uptake in a protruded lesion left lower quadrant of abdomen (SUVmax: 20.6)</td>
<td>Acrochordon</td>
<td>Consistent with history and physical exam</td>
</tr>
<tr>
<td>Aydin et al. [94]</td>
<td>elevated</td>
<td>Restaging 68Ga-PSMA: uptake in subcutaneous masses in the frontal region of the cranium, abdomen, thigh and trunk (SUVmax: 12.8)</td>
<td>Dermatofibroma</td>
<td>Pathology (excisional biopsy)</td>
</tr>
<tr>
<td>Malik et al. [95]</td>
<td>18.2 μg/L</td>
<td>Staging 68Ga-PSMA: Focal increased uptake in left chest (SUVmax: 3.1)</td>
<td>Pseudo-angiomatous stromal hyperplasia of breast</td>
<td>Pathology (breast biopsy)</td>
</tr>
<tr>
<td>Kantham et al. [92, 100, 104, 117]</td>
<td>6.9 μg/L</td>
<td>Staging 68Ga-PSMA: large intensely avid soft tissue mass in the right pelvis abutting the cecum and terminal ileum (SUVmax: 15.9)</td>
<td>Desmoid tumor</td>
<td>Pathology (Surgical resection)</td>
</tr>
<tr>
<td>Henninger et al. [93]</td>
<td>19.86 ng/mL</td>
<td>Staging 68Ga-PSMA: intense uptake in soft-tissue mass in the left rectus femoris muscle (PET/MRI)</td>
<td>Fasciitis nodularis</td>
<td>Pathology (biopsy)</td>
</tr>
<tr>
<td>Other benign pathologies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al. [119]</td>
<td>NR</td>
<td>Staging 68Ga-PSMA: Focal uptake in the pancreatic head (SUVmax: 10.1)</td>
<td>Pancreatic serous cystadenoma</td>
<td>1-year clinical and imaging FU (MRI)</td>
</tr>
<tr>
<td>Kantham et al. [92, 100, 104, 117]</td>
<td>rising</td>
<td>Restaging 68Ga-PSMA: intense uptake in a mixed density nodule in the left lower pole of the thyroid (SUVmax: 25.3)</td>
<td>Follicular thyroid adenoma</td>
<td>Pathology (left hemi thyroidectomy)</td>
</tr>
<tr>
<td>Derlin et al. [105]</td>
<td>NR</td>
<td>Restaging 68Ga-PSMA: uptake in thyroid lesion (SUVpeak: 2.9)</td>
<td>Follicular thyroid adenoma</td>
<td>Pathology (surgical resection)</td>
</tr>
<tr>
<td>Law et al. [107]</td>
<td>1.3 μg/L</td>
<td>Restaging 68Ga-PSMA: mild-to-moderate tracer uptake in the left adrenal gland</td>
<td>Lipid-rich adrenal adenoma</td>
<td>Stable lesion on CT for 9 years</td>
</tr>
<tr>
<td>Malik D, 2017</td>
<td>6.6 ng/mL</td>
<td>Restaging 68Ga-PSMA: intense uptake in a soft tissue lesion at the base of the urinary bladder (SUVmax 15.3- local recurrence), intense uptake in the left hemithorax (SUVmax 15.5)</td>
<td>Hemiated spleen</td>
<td>99mTc-labeled sulfur colloid scintigraphy, history of congenital hiatal hernia</td>
</tr>
<tr>
<td>Stephens et al. [103]</td>
<td>NR</td>
<td>Staging 68Ga-PSMA: Symmetrical intense uptake in the seminal vesicles bilaterally</td>
<td>Senile seminal vesicle amyloidosis</td>
<td>Pathology (surgical resection)</td>
</tr>
<tr>
<td>Noto et al. [109]</td>
<td>NR</td>
<td>Restaging 68Ga-PSMA: Focal cerebral tracer uptake in the right frontal lobe (SUVmax 1.2)</td>
<td>Cerebral infarction</td>
<td>MRI, 6-month FU, consistent with history</td>
</tr>
<tr>
<td>Chan et al. [106]</td>
<td>NR</td>
<td>Restaging 68Ga-PSMA: additional focus of uptake in the left cerebral hemisphere</td>
<td>Acute cortical Infarct of embolic nature</td>
<td>MRI, consistent with history</td>
</tr>
</tbody>
</table>

FU follow-up; NR, not reported; PMH past medical history
(metastases of one tumor to another) [126, 127]. To date, fewer than 10 cases have been reported in the literature describing PCa metastases to clinically unknown or pre-existing meningiomas [127]. All these patients presented with neurological symptoms and the diagnoses have been made after histological examination of the lesions [127]. Radiological

**Fig. 6** a Coronal CT, b coronal PET, and c coronal PET/CT images from an $^{18}$F--DCFPyL scan in a patient undergoing evaluation for recurrent PSA elevation following prostatectomy. On the CT image, there are the typical findings of Paget’s disease of bone in the right iliac with thickened cortex and trabeculations. Note the subtly increased radiotracer uptake in the right iliac (best appreciated on the PET only image, ) that is most prominent along the iliac crest; this finding has been noted in multiple case reports as a potential false positive for PCa bone metastasis.

**Fig. 7** Two examples of $^{18}$F--DCFPyL uptake in bone fractures, a potential pitfall in PSMA-targeted imaging that could lead to the erroneous assumption of bone metastatic disease in PCa patients. Both patients in this figure were being evaluated for biochemical recurrence after radical prostatectomy. a Sagittal CT, b sagittal PET, and c sagittal PET/CT images from an $^{18}$F--DCFPyL scan in a patient with decreased bone mineralization and multiple prior compression fractures. A new compression deformity had appeared on this scan and was associated with linear radiotracer uptake (red arrows). No suspicious lesion is present on the CT and no lesion has appeared at this site in subsequent follow-up. d Axial CT, e axial PET, and f axial PET/CT images from an $^{18}$F--DCFPyL scan in a different patient with a non-displaced anterior rib fracture with focal radiotracer uptake (red arrows). Again, no suspicious lesion has appeared at this site on follow-up imaging to suggest that this was a pathologic fracture.
diagnosis of coexistence of two tumors are difficult and these lesions are often mimic meningioma. This rare finding should be kept in mind in patients with neurological syndrome and conventional radiographic imaging consistent with meningioma. Increased radiotracer uptake in meningiomas might not necessarily be a false positive finding and may require a definitive tissue diagnosis.

Hemangiomas and other benign soft tissue lesions

Recently, three case reports have appeared describing increased $^{68}$Ga-PSMA-11 uptake associated with hemangioma [89–91]. In these reports, incidental intense $^{68}$Ga-PSMA-11 uptake was observed in the liver, vertebral, and abdominal wall of three-PCa patients who underwent $^{68}$Ga-PSMA-11 PET/CT imaging. Further work-up (imaging and pathology) revealed the presence of benign hepatic, vertebral, and subcutaneous benign lobular capillary hemangioma. The authors hypothesized that increased radiotracer uptake can be associated with the high number of endothelial cells and vascular density in these lesions. Consistently, Derlin et al. showed intense $^{68}$Ga-PSMA I&T radiotracer uptake in a patient diagnosed with malignant epithelioid hemangioendothelioma of the liver [128]. However, a previous in vitro study examining different tissue samples, showed lack of significant PSMA expression in some benign vascular malformations including hemangioma and hemangioendothelioma [129]. Thus, further studies are necessary to determine the expression pattern of PSMA in various subtypes of hemangioma.

Besides, nonprostatic PSMA ligand uptake has been reported in a variety of benign soft tissue pathologies including desmoid tumor [92], fasciitis nodularis [93], intramuscular myxoma [96], acrochordone [97], dermatofibroma [94], and pseudo-angiomatous stromal hyperplasia [95](Table 1).

Malignant PSMA-avid pathologies other than prostate cancer

The detection of malignant tumors other than PCa with PSMA-targeted PET imaging has been the subject of numerous recent publications. A number of case reports have demonstrated the incidental detection of synchronous primary and metastatic lesions from other malignancies on imaging being performed for work-up of PCa. These reports include the detection of follicular lymphoma [117, 130], multiple myeloma [131], papillary and follicular thyroid carcinoma [132–134], pancreatic neuroendocrine tumor [135], gastrointestinal stromal tumor [136], squamous cell carcinoma of the oropharynx.

Fig. 8 a MIP, b axial CT, c axial PET, and d axial fused PET/CT images from $^{68}$Ga-PSMA-11 scan in a patient being evaluated for recurrent prostate cancer. The patient had previously been treated by radical prostatectomy and adjuvant radiation therapy of the prostatic fossa. In addition, a pharyngeal carcinoma had also been diagnosed prior to the PET/CT. $^{68}$Ga-PSMA-11 PET/CT showed intense radiotracer uptake ($SUV_{max}$ 19.9) in the known pharyngeal carcinoma (red arrows)
potential role of PET/CT with 18F
ber of recent case reports and clinical pilot studies support the
carcinoma [113], urothelial carcinoma [139], colorectal
carcinoma [140, 141], hepatocellular carcinoma [142], and
lung cancer [73, 143]. A summary of published reports on
malignant entities that show uptake on PSMA-targeted PET
is provided in Table 2.

PSMA overexpression in neovascular endothelium of
some non-prostatic malignancies could pave the way poten-
tially to expand the theranostic application of PSMA-targeted
radioisotopes. A number of publications have specifically
examined the feasibility of PSMA-targeted PET imaging
for staging/restaging of solid malignancies other than
PCa. These studies demonstrated high PSMA expression
and uptake in RCC (main focus) [114, 116, 145–149], ad-
enocarcinoma of urinary bladder [150], glioblastoma
[151], breast carcinoma [152], gastric and colorectal cancer
(Fig. 9) [144, 153], hepatocellular carcinoma [115], malign-
ant epithelioid hemangioendothelioma of the liver [128],
adenoid cystic carcinoma of the salivary gland [154], mul-
tiple myeloma [155], papillary thyroid carcinomas (and
iodine-131-resistant differentiated thyroid carcinoma
[156, 157]) (Fig. 10), and sarcomatous transformation of
fibrous dysplasia [158]. Further preclinical research and
clinical studies with larger numbers of patients are needed to
validate these findings.

Renal cell carcinoma

The most widely explored non-prostatic tumor with PSMA-
targeted imaging has been RCC [114, 116, 134, 145–149].
The majority of RCC subtypes have shown high PSMA ex-
pression in immunohistochemistry studies; the most diffuse
and intense pattern has been observed in clear cell RCC
(Fig. 11) followed by chromophobe RCC [148, 159]. A num-
ber of recent case reports and clinical pilot studies support
the potential role of PET/CT with 18F–DCFPyL and 68Ga-PSMA-
11 in the diagnostic work-up of advanced RCC, mainly fo-
cused on the clear cell subtype [116, 145–149]. PSMA-
targeted PET/CT has promising utility in accurate staging
of RCC and timely detection of indeterminate or false negative
metastatic lesions on conventional imaging [146, 148]. The
sensitivity of 18F–DCFPyL and 68Ga-PSMA-11 PET/CT ap-
pears to be superior to conventional imaging in identifying
sites of metastatic RCC [146, 148]. One potential limitation
of PSMA-targeted PET/CT imaging of RCC is in the assess-
ment of primary tumors, due to intense radiotracer uptake in
the normal renal parenchyma. In a recent study of six patients
with histologically proven RCC, Sawicki et al. observed vary-
ing avidity of the 68Ga-PSMA-11 radiotracer in primary tu-
mors making them difficult to discern from the normal renal
parenchyma which shows intense radiotracer uptake [149].

Prostate cancer with Neuroendocrine differentiation

Neuroendocrine differentiated PCAs (NEPCa) generally ex-
hibits aggressive behavior and is frequently associated with
rapid progression of disease and visceral metastases [160].
NEPCa rarely arises de novo, often coexisting with prostate
adenocarcinoma, but most commonly arises as a function of
treatment resistance, in patients on prolonged androgen de-
privation therapies (ADT) [161, 162].

The underlying molecular biology of neuroendocrine trans-
formation remains unclear [162]. Studies suggest that NEPCa
do not express the generic prostatic epithelial markers includ-
ing androgen receptor, PSA, PSAP, and PSA [163]. Unlike
conventional PCa, NEPCa cells typically express neuroendo-
docrine tumor markers such as chromogranin A, synaptophysin,
CD56, and NSE [163]. As evidenced by immunohistochem-
istry studies, heterogeneous expression of these markers can
occur in NEPCa [163]. In addition, poorly differentiated PCa
(Gleason score 4 + 5 = 10) can also diffusely express neuro-
endocrine markers [164].

Consequently absent or faint PSMA expression in neuro-
endocrine cells can potentially cause false-negative findings
on PSMA-targeted PET, both for the primary tumor, as well as
its nodal or distant metastases [165–167]. Chakraborty et al.
presented the first case of poorly differentiated NEPCa with
no significant localization of the 68Ga-PSMA-11 radiotracer
either in the prostate or in suspected lymph node and bone
lesions [166]. Tosioan et al., showed highly variable 18F–
DCFPyL uptake in a patient with known PCa (Gleason score
4 + 5) [165]. These authors observed no radiotracer uptake in
liver metastases and moderate uptake in peritoneal metastases.
Lesion specific genomic analysis revealed changes consistent
with neuroendocrine differentiation in the liver lesions with a
mixed neuroendocrine/adenocarcinoma phenotype in the peri-
toneal metastases. Moreover, they revealed a positive correla-
tion between the intensity of radiotracer uptake and PSMA
and androgen receptor expression on immunohistochemistry
[165].

The introduction of potent androgen receptor-targeted treat-
ments has increased the incidence of NEPCa [162]. However,
many NEPCa cases remain unclassified as patients with metasta-
ctic castration resistant PCAs are not routinely biopsied in the
advanced stages of the disease [162]. Developing novel radiotracers
targeting neuroendocrine markers are particularly important in
molecular imaging and therapeutic decision making of this ag-
gressive PCa subtype. 68Ga-DOTATOC and 68Ga-DOTATATE,
targeting somatostatin receptor, are promising additions to the list
of PET radiotracers with the potential to evaluate neuroendocrine
differentiation [167–170]. A recent study on 12 patients with
castration-resistant PCa, demonstrated the potential role of
68Ga-DOTA-TATE PET/CT in assessing the extent of neuroen-
docrine differentiation and early detection of metastatic lymph
node and blastic or lytic bone lesions [168]. This feature may
<table>
<thead>
<tr>
<th>Author, year</th>
<th>PSA level</th>
<th>Imaging finding</th>
<th>Diagnosis</th>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanthan et al. [92, 100, 104, 117]</td>
<td>1.5 μg/L</td>
<td>Restaging 68Ga-PSMA: avid left femoral LN (SUVmax: 5)</td>
<td>Follicular lymphoma</td>
<td>Pathology (core biopsy)</td>
</tr>
<tr>
<td>Vamadevan et al. [130, 135]</td>
<td>1.2 ng/mL</td>
<td>Restaging 68Ga-PSMA: increased uptake in the known enlarged right inguinal LN (SUVmax: 4.7)</td>
<td>Small cleaved B-cell follicular lymphoma</td>
<td>Pathology (core biopsy)</td>
</tr>
<tr>
<td>Sager et al. [132]</td>
<td>NR</td>
<td>Staging 68Ga-PSMA: intense uptake in thyroid nodule in the right thyroid gland</td>
<td>Follicular thyroid carcinoma</td>
<td>Pathology (core biopsy)</td>
</tr>
<tr>
<td>Rauscher et al. [131]</td>
<td>9.98 ng/mL</td>
<td>Staging 68Ga-PSMA: moderate, multifocal uptake in the axial skeleton and proximal extremities, corresponds to an osteolytic lesion in CT</td>
<td>Multiple myeloma</td>
<td>Pathology (bone marrow biopsy), PMH of multiple myeloma</td>
</tr>
<tr>
<td>Jena et al. [133]</td>
<td>Rising</td>
<td>Staging 68Ga-PSMA: focal uptake in thyroid nodule (SUVmax: 5.1)</td>
<td>Papillary thyroid carcinoma + Hurthle cell adenoma</td>
<td>Pathology (thyroidectomy)</td>
</tr>
<tr>
<td>Joshi et al. [134]</td>
<td>9.6 ng/mL</td>
<td>Restaging 68Ga-PSMA: uptake in prostate, right kidney, left thyroid and iliac crest</td>
<td>Gastrointestinal stromal tumor (most probably of gastric origin)</td>
<td>Pathology</td>
</tr>
<tr>
<td>Noto et al. [136]</td>
<td>NR</td>
<td>Staging 68Ga-PSMA: intense uptake in a large soft tissue mass with calcifications in the left upper abdomen (SUVmax = 13.7)</td>
<td>Pancreatic neuroendocrine tumor</td>
<td>Pathology (endoscopic ultrasound biopsy), FU imaging after 6 months</td>
</tr>
<tr>
<td>Sasikumar et al. [82, 114, 115]</td>
<td>17 ng/mL</td>
<td>Staging 68Ga-PSMA: intense tracer accumulation in the liver lesion, mild tracer uptake in the bone lesions and lung lesions</td>
<td>Hepatocellular carcinoma</td>
<td>Pathology (biopsy)</td>
</tr>
<tr>
<td>Huang et al. [144]</td>
<td>NR</td>
<td>Staging 68Ga-PSMA: larger focus of intense abnormal uptake correlated to thickened rectal wall (SUVmax: 8)</td>
<td>Rectal adenocarcinoma</td>
<td>Pathology (surgical resection), MRI, PMH of synchronous PCa and RCa</td>
</tr>
<tr>
<td>Lawkh-Heath et al. [137]</td>
<td>10.7 ng/mL</td>
<td>Staging 68Ga-PSMA: 3.4 cm mass was incidentally found in the right tongue, in addition to prostate uptake</td>
<td>SCC of the oropharynx</td>
<td>Pathology (biopsy), PMH of SCC of unknown primary</td>
</tr>
<tr>
<td>Pyka et al. [73]</td>
<td>NR</td>
<td>Staging/Restaging 68Ga-PSMA: uptake in lung lesions with speculated or irregular configurations (Seven patients) (Mean ± SD SUVmax: 5.5 ± 1.9)</td>
<td>Primary lung cancer</td>
<td>Pathology</td>
</tr>
<tr>
<td>Froehner et al. [85, 113]</td>
<td>NR</td>
<td>68Ga-PSMA: uptake in inguinal, pelvic, and retroperitoneal metastases</td>
<td>Metastatic penile SCC (pelvic lesion and LN)</td>
<td>Pathology (biopsy and IHC), synchronous penile SCC and PCa</td>
</tr>
<tr>
<td>Stoykow et al. [140]</td>
<td>NR</td>
<td>Restaging 68Ga-PSMA: moderate uptake in the liver and strong uptake in rectal primary</td>
<td>Metastatic rectal adenocarcinoma (liver)</td>
<td>Pathology (biopsy), history of RCa and PCa</td>
</tr>
<tr>
<td>Hangaard et al. [141]</td>
<td>Rising</td>
<td>Restaging 68Ga-PSMA: moderate uptake in multiple enlarged lymph nodes and bilateral lung lesions</td>
<td>Metastatic colon adenocarcinoma (LN, lung)</td>
<td>Pathology (biopsy)</td>
</tr>
<tr>
<td>Soydal et al. [142]</td>
<td>Rising</td>
<td>Restaging 68Ga-PSMA: intense uptake in liver lesions, pleural surface and mediastinal LNs</td>
<td>Metastatic hepatocellular carcinoma (liver, pleura)</td>
<td>Pathology (biopsy), PMH of hepatocellular carcinoma</td>
</tr>
<tr>
<td>Shetty et al. [143]</td>
<td>34 μg/L</td>
<td>Staging 68Ga-PSMA: Increased uptake in the left lower lobe lung mass, diffusely increased uptake in an enlarged thyroid gland and bilateral enlarged supravacular LNs, in addition to prostate uptake</td>
<td>Metastatic Non-small cell lung cancer (thyroid, LN)</td>
<td>Pathology (biopsy), PMH of non-small cell lung cancer</td>
</tr>
<tr>
<td>Zacho HD, 2016</td>
<td>0.7 ng/mL</td>
<td>Restaging 68Ga-PSMA: uptake in pelvic and retroperitoneal LN and focal uptake in the thyroid</td>
<td>Metastatic RCC (thyroid and LN)</td>
<td>Pathology (excisional biopsy), PMH of RCC</td>
</tr>
<tr>
<td>Gupta et al. [139]</td>
<td>0.51 ng/mL</td>
<td>Restaging 68Ga-PSMA: intense uptake in the enlarged left supravacular LN</td>
<td>Metastatic urothelial carcinoma of ureter (LN)</td>
<td>Pathology (biopsy) and PMH of urothelial carcinoma</td>
</tr>
<tr>
<td>Einspieler et al. [138]</td>
<td>0.25 ng/mL</td>
<td>Restaging 68Ga-PSMA: intense uptake in mediastinal, retroperitoneal, and iliac LNs</td>
<td>Metastatic RCC (LN)</td>
<td>Pathology (biopsy) and PMH of synchronous PCa and RCC</td>
</tr>
</tbody>
</table>

PMH, past medical history; PCa, prostate cancer; RCa, rectal adenocarcinoma; SCC, squamous cell carcinoma; RCC, renal cell carcinoma; LN, lymph node; NR, not reported; FU, follow-up
Fig. 9  a Axial CT, b axial PET, c and axial fused PET/CT images from a ⁶⁸Ga-PSMA-11 scan in a female patient with rapidly progressive metastatic colorectal cancer. The patient was previously treated with all approved therapeutic modalities and was referred to evaluate a possible PSMA-based radioligand therapy as a last attempt to delay disease progression. The images showed intense radiotracer uptake in the abdominal wall metastasis (SUV$_{max}$ 10.7). The patient was identified eligible for PSMA-targeted radioligand therapy with an $^{131}$I–labeled PSMA agent (MIP-1095).

Fig. 10  a Axial CT, b axial ⁶⁸Ga-PSMA-11 PET, and fused ⁶⁸Ga-PSMA-11 PET/CT images at 1 h p.i. c and 3 h p.i. d in a male patient with initial diagnosis of papillary thyroid carcinoma. Primary thyroid cancer had lost its iodine-avidity due to dedifferentiation, therefore, radioiodine therapies would no longer be expected to have efficacy. ¹⁸F–FDG-PET/CT e showed intense ¹⁸F–FDG uptake in primary thyroid carcinoma. The patient had been referred for ⁶⁸Ga-PSMA-11 PET/CT in order to evaluate the eligibility for possible PSMA-targeted radioligand therapy. Although the patients’ lesions did demonstrate radiotracer uptake (cervical and mediastinal lymph nodes as well as lung metastases), the relatively low degree of ⁶⁸Ga-PSMA-11 uptake (SUV$_{max}$ = 3.5) precluded PSMA-targeted therapy. In this case, the ⁶⁸Ga-PSMA-11 uptake was shown to be decreased over time, from early (1 h p.i.) to late scan (3 h p.i.). This reduced retention of ⁶⁸Ga-PSMA radio ligand in the late scan in thyroid carcinoma may be explained by a difference in internalization.
shed light into the possibility of neuroendocrine-targeted therapies in metastatic castration resistant PCa. Further studies are needed, however, to validate these results.

**PSMA-ligand PET imaging in therapy assessment of prostate cancer**

The latest advances in the development of novel targeted therapeutic agents in PCa have prompted a surge of interest in defining appropriate methods to measure the treatment effects and outcomes in clinical trials [171]. Known response assessment criteria often have limited applicability in PCa, given the relatively low glycolytic rate of PCa cells and infrequent incidence of measurable (non-osseous) disease [171, 172]. The osteoblastic healing flare response can also lead to a false-positive diagnosis of progression on bone scintigraphy [172]. These limitations necessitate more reliable response assessment criteria for optimization and personalization of patients’ management using targeted molecular imaging techniques. Toward this aim, data have been published on the value of PSMA-targeted PET imaging in therapy response assessment of PCa [173–177].

The temporal relationship between PSMA uptake and previous androgen receptor targeted therapies has to be considered in clinical interpretation of PSMA-targeted PET imaging [178]. Initial preclinical experiments suggested that androgen receptor inhibition can significantly increase PSMA expression in both hormone-sensitive and resistant cell lines and animal models [179, 180]. A recent first-in human report by Hope et al., demonstrated an approximately sevenfold increase in $^{68}$Ga-PSMA-11 uptake across all measurable lesions four weeks after the initiation of ADT in a patient with castration-sensitive PCa [178]. Numerous additional lesions were visualized on post-ADT $^{68}$Ga-PSMA-11 PET Imaging [178], indicating that care must be exercised in interpreting PSMA-targeted PET imaging soon after the initiation of ADT.

There have been a dramatic increase in the use of PSMA-targeted theranostics in patients with metastatic PCa who progressed after treatment with other approved therapeutic modalities [10, 173, 175]. In this setting, pre-treatment assessment with PSMA-targeted PET/CT is essential to confirm the PSMA-avidity of target lesions and to quantify the disease burden by standardized uptake value [181]. A number of case series suggested that $^{68}$Ga-PSMA-11 PET/CT outperforms CT in assessing therapy response during or after PSMA-targeted radioligand therapies (e.g., $^{177}$Lu-PSMA) in patients with castration sensitive or resistant metastatic PCa [173, 174, 176].

It should be noted that the inhibition of androgen receptor can theoretically increase the efficacy of PSMA-targeted therapies [178, 182] and potentially improve the sensitivity of PSMA-targeted PET imaging in the detection of progressive disease [15]. Despite these interesting findings, the applicability and potential pitfalls of therapy assessment with PSMA-targeted PET imaging has not yet been systematically evaluated in clinical studies. There is still no consensus on the optimal timing of PSMA-radioligand therapies and appropriate reproducibility criteria (e.g. test-retest) to evaluate response to treatment.

**Conclusions**

The rapidly expanding clinical adaptation of PSMA-targeted PET imaging in the evaluation of patients with PCa is accompanied with the need to understand both the potential pearls and the limitations of this new technique. While PSMA-targeted agents have generally been reported to be highly sensitive and specific, a growing number of reports indicate the possibility of both false positive and false negative findings. As PSMA-targeted PET is expected to be evaluated in larger prospective trials, the dissemination of potential diagnostic pitfalls and the biologic underpinning of those findings will be of increased importance.

**ADT, Androgen deprivation therapy; NEPCa, Neuroendocrine differentiated prostate cancer; PCa, Prostate cancer; PSMA, Prostate specific membrane antigen; RCC, Renal cell carcinoma.**

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Compliance with ethical standards

Conflict of interest  MGP is a co-inventor on a U.S. patent covering 18F-DCFPyL and as such is entitled to a portion of any licensing fees and royalties generated by this technology. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict-of-interest policies. MAG has served as a consultant to Progenics Pharmaceuticals, the licensee of 18F-DCFPyL. KJP, MGP, MAG, and SPR have research funding from Progenics Pharmaceuticals. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References


46. Rowe SP, Macura KJ, Mena E, Blackford AL, Nadal R, Antonarakis ES, et al. PSMA-based [(18)F]DCFPyL PET/CT is superior to conventional imaging for lesion detection in patients


