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Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging of Prostate Cancer: An Update on Important Pitfalls

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The continuing adoption of prostate specific membrane antigen (PSMA)-targeted PET for prostate cancer molecular imaging requires imagers and clinicians alike to be aware of the increasing number of potential interpretive pitfalls that have been reported. This review summarizes and illustrates the spectrum of benign and malignant nonprostatic conditions with high PSMA-radiotracer uptake that may be mistaken for sites of prostate cancer and also discusses potential false negatives. We discuss the recent literature on the effect of androgen deprivation therapy on lesion detection. Furthermore, we briefly review the recently proposed structured reporting systems for the standardized interpretation of PSMA-targeted PET that can guide both imaging specialists and referring clinicians in the appropriate interpretation and work-up of pitfalls.
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Introduction

Prostate-specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II, is a type II transmembrane glycoprotein[1]. PSMA is weakly expressed in normal prostate tissue, overexpressed in prostate cancer, and expression levels are directly associated with prostate cancer aggressiveness.[2] Over the last decade, multiple radiolabeled small molecules, most of which have been based on a urea scaffold, have been developed and have shown high affinity to the extracellular domain active site of PSMA.[3,4] The introduction of ^{68}Ga- and ^{18}F-labeled PSMA-targeted ligands has resulted in a paradigm shift in the imaging of prostate cancer. A number of studies have confirmed the high detection rate and excellent diagnostic performance of PSMA-targeted PET for imaging men with prostate cancer.[5,6]

Despite the improved diagnostic performance of PSMA-targeted agents relative to other methods of imaging prostate cancer, an increasing number of studies have been published describing various benign and nonprostate malignant conditions that may give rise to increased PSMA-radiotracer uptake. Recognition of potential sources of false-positive and false-negative findings is important for accurate interpretation of PSMA-targeted PET imaging studies.[7]

This manuscript aims to update our previous review on the potential interpretative pitfalls of PSMA-targeted PET imaging.[7] A spectrum of benign and malignant nonprostatic PSMA-avid lesions, common sources of false positive and false negative PSMA-targeted PET imaging, and the effect of androgen deprivation therapy on PSMA expression will be discussed. In addition, we will discuss the recently proposed

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structured reporting and data systems in interpretation of PSMA-targeted PET imaging, which provide frameworks through which an interpreting imaging specialist's confidence in a given finding can be communicated.

General Pitfalls in Clinical Interpretation of PSMA-targeted PET Imaging

Physiologic Biodistribution

Currently, ^{68}Ga-PSMA-HBED-CC (also known as 68Ga-PSMA-11 or sometimes simply as ^{68}Ga-PSMA) is the most widely used radiotracer in clinical practice.[8] However, there has been aln increasing interest in the clinical use of ^{18}F-labeled, PSMA-targeted PET imaging agents (eg, ^{18}F-DCFBC, ^{18}F-DCFPyL, ^{18}F-PSMA-1007), due to their favorable physical properties, higher production capacity, and improved imaging characteristics.[9]

Biodistribution studies on ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL-PSMA showed high radiotracer uptake in the renal cortex, duodenum, ileum, parotid, submandibular glands, lacrimal glands, all major salivary glands, liver, and spleen[8,10,11] (Fig. 1). Significant radiotracer accumulation can be observed in the ureters and urinary bladder as these radiotracers have high rates of renal excretion.[11]

Another ^{18}F-labeled PSMA ligand, ^{18}F-PSMA-1007, with primarily hepatobiliary clearance, has been recently introduced.[12] Compared to ^{18}F-DCFPyL, ^{18}F-PSMA-1007 shows significantly lower uptake in the kidneys, urinary bladder, and lacrimal glands and higher uptake in the liver, gallbladder, spleen, pancreas, muscle, submandibular glands, and sublingual glands.[12,13] Nonurinary excretion of ^{18}F-PSMA-1007 might be advantageous for delineation of local recurrence or pelvic lymph node metastases.[13]

Radiopharmaceutical radiolysis causing excessive free ^{68}Ga-citrate has been reported as a rare potential technical pitfall affecting the biodistribution of ^{68}Ga-PSMA.[14] In a recent case report, Hod, et al demonstrated altered biodistribution of ^{68}Ga-PSMA with high vascular activity in large vessels including the aorta, inferior vena cava, subclavian, iliac and femoral vessels and heart due to free 68Ga-citrate.[14]

Benign PSMA-Avid Pathologies on PSMA-Targeted PET Imaging

Lymph Node Involvement and Interpretive Pitfalls

Lymph nodes are the second most common site of metastases in prostate cancer.[15] PSMA-targeted PET imaging is superior to conventional imaging in the assessment of lymph node metastases, even at low prostate specific antigen levels and in the detection of small volume metastases (maximum diameter less than 1 cm).[16] A recent meta-analysis confirmed high sensitivity (80%) and specificity (97%) of ^{68}Ga-PSMA-11 PET/CT in the assessment of lymph node metastases in prostate cancer patients.[5]

Several studies that have demonstrated increased uptake of ^{68}Ga-PSMA-11 or ^{18}F DCFPyL in ganglia of the sympathetic trunk, may serve as a potential source of misinterpretation.[17-21] Approximately 97%-98.5% of patients undergoing PSMA-targeted PET imaging have at least one sympathetic ganglion with visually discernible PSMA uptake above background.[17,20] ^{68}Ga-PSMA-11 uptake in sympathetic ganglia is more frequently observed in cervical ganglia, followed by coeliac, stellate, and sacral ganglia.[20] The pattern of ^{18}F-DCFPyL PSMA-uptake is slightly different with a descending frequency of radiotracer accumulation in lumbar ganglia, followed by cervical, stellate, coeliac, and sacral ganglia[17] (Fig. 2). A detailed summary of these studies is provided in Table 1. Again, these findings can represent an important diagnostic pitfall in the interpretation of PSMA-targeted PET imaging, as they can potentially be misinterpreted as metastases to non-regional lymph nodes.[7] This may lead to the misdiagnosis of metastatic disease in patients with localized primary prostate cancer and could change the therapeutic management from curative surgical treatment to a systemic hormonal and/or chemotherapy.

As the sympathetic trunk runs along the vertebra, benign PSMA uptake in sympathetic ganglia can also be mistaken with bone metastasis, particularly if there is slight

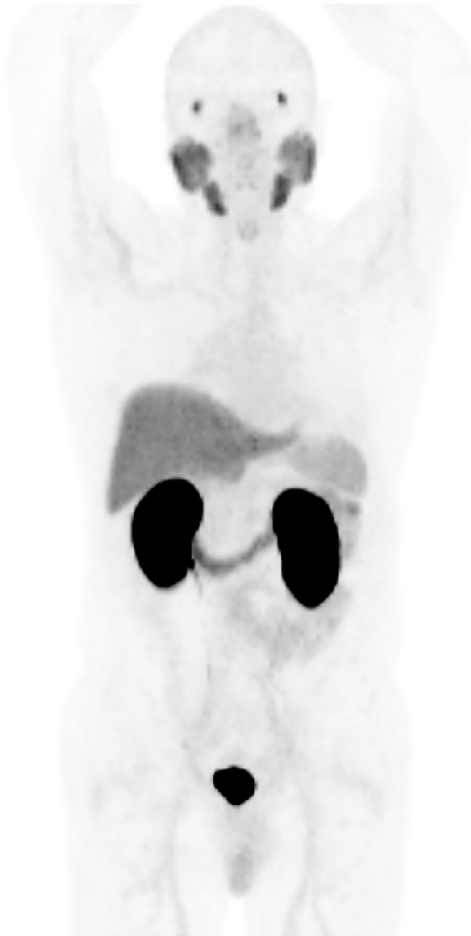

Figure 1 Maximum intensity projection image from a 66-year-old man undergoing restaging for prostate cancer demonstrating the typical biodistribution for most PSMA-targeted radiotracers (in this case, ^{18}F-DCFPyL). Uptake is noted in the lacrimal glands, major salivary glands, liver, spleen, kidneys, bowel, ureters, and urinary bladder.

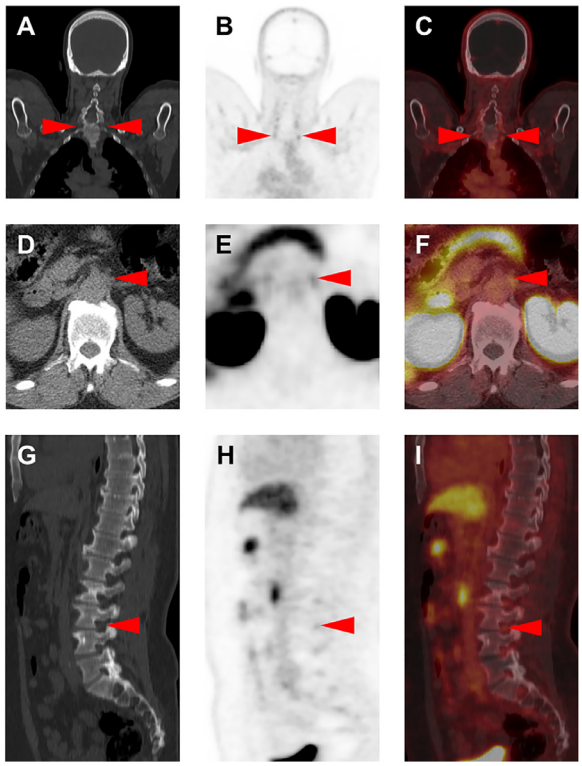

Figure 2 (A) Coronal, attenuation-correction CT, (B) coronal ^{18}F-DCFPyL PET, and (C) coronal ^{18}F-DCFPyL PET/CT images through the neck and upper chest of a 66-year-old man presenting for staging of high-risk prostate cancer and demonstrating radiotracer uptake in the cervical dorsal root ganglia and cervicothoracic/stellate ganglia (red arrowheads). (D) Axial, attenuation-correction CT, (E) axial ^{18}F-DCFPyL PET and (F) axial ^{18}F-DCFPyL PET/CT images through the upper abdomen showing radiotracer uptake in the left celiac ganglion (red arrowheads). (G) Sagittal, attenuation-correction CT, (H) sagittal ^{18}F-DCFPyL PET, and (I) sagittal ^{18}F-DCFPyL PET/CT images to the left of midline demonstrating uptake in lumbar dorsal root ganglia (red arrowhead).

misregistration between the PET and CT acquisitions or if the uptake is distinctly unilateral.[17]

The intensity of PSMA-ligand uptake, localization and configuration of the lesion help to differentiate between the physiologic uptake of sympathetic ganglia and adjacent lymph node metastases. Ganglia predominantly exhibit a band-shaped configuration (71.2%) and rarely have nodular appearance (2%). Lymph node metastases show significantly more intense uptake, more often show teardrop or nodular configuration, and rarely exhibit a band shaped appearance. (1.1%).[20] In addition, patients who exhibit high PSMA-ligand uptake in one ganglion are more likely to have another ganglion with increased uptake.[17,20]

Another recent study suggested that benign PSMA-tracer uptake can be seen in the mediastinal or para-aortic thoracic lymph nodes, as well as lymph nodes with follicular hyperplasia.[22] In contrast to the lymph node metastases in prostate cancer, mediastinal/para-aortic lymph nodes often occur isolated, and usually present with significantly lower radiotracer uptake (Fig. 3), which mostly decreases over time.[22] In a recent study by Afshar-Oromieh, et al, approximately 18.4% and 7.9% of patients without lymph node metastases presented with at least one PSMA-positive mediastinal lymph node at 1 hour p.i., and 3 hours p.i., respectively.[22] The authors recommended conducting additional late scans (eg, at 3 hours p.i) in cases of questionable PSMA-positive lymph nodes, as the majority of lymph node metastases present with increasing radiotracer uptake over time.[22]

Bone Involvement

Bone is the most common site of distant metastasis in prostate cancer and occurs in approximately 70%-84% of patients with advanced prostate cancer.[15] PSMA-targeted PET is an invaluable technique in assessing the extent of bone metastases in men with prostate cancer.[5] PSMA-targeted PET is found to be

Table 1 Pattern of PSMA-Radiotracer Uptake in the Sympathetic Chain Ganglia

Study	Tracer	Number of Patients	At Least One Ganglion With Radiotracer Uptake	Prevalence of Positive Ganglia	SUV_{max} (Mean ± SD)
Rischpler C, 2018	^{68}Ga-PSMA-11	407 prostate cancer	401/407 (98.5%)	>Cervical ganglia (91.8%) >Celiac ganglia (89.4%) >Sacral ganglia (45.5%)	2.4 ± 0.6 2.9 ± 0.8 1.7 ± 0.5
Werner R, 2017	^{18}F-DCFPyL PSMA	76 prostate cancer, 22 RCC	95/98 (96.9%)	>Lumbar ganglia (76.5%) >Cervical ganglia (71.4%) >Stellate ganglia (61.2%) >Celiac ganglia (58.2%) >Sacral ganglia (8.2%)	1.76 ± 0.31 1.82 ± 0.34 1.67 ± 0.47 1.77 ± 0.59 1.91 ± 0.45
Kanthan GL, 2017	^{68}Ga-PSMA-11	100 prostate cancer	Not reported	>Celiac ganglia (45/100 right, 81/ 100 left) >Stellate ganglia (54/100 right, 74/100 left)	2.6 right, 2.7 left 2.2 right, 2.4 left
Krohn T, 2015	^{68}Ga-PSMA-11	86 prostate cancer	76/85 (89.4%)	Coeliac ganglia	2.97 ± 0.88

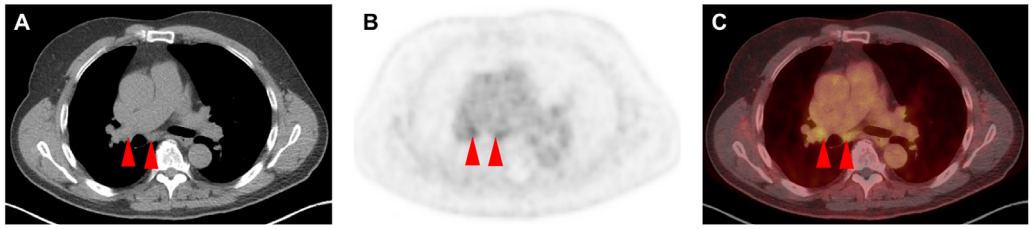

Figure 3 (A) Axial, attenuation-correction CT, (B) axial ^{18}F-DCFPyL PET, and (C) axial ^{18}F-DCFPyL PET/CT images through the chest from a 63-year-old man with low PSA (0.3 ng/mL) biochemical recurrence. Mild radiotracer uptake is seen in right hilar and subcarinal lymph nodes (red arrowheads), most likely reflecting a granulomatous or other inflammatory process and almost certainly not related to patient's underlying prostate cancer.

superior to ^{99m}Tc- bone scintigraphy and anatomic imaging, as it can identify more skeletal lesions, bone marrow seeding and osteolytic metastases, ll of which can be missed by conventional imaging modalities.[23,24]

As discussed in our previous review,[7] increased PSMA-radiotracer uptake has been reported in a number of benign bone pathologies, in the setting of increased vascularity, bone remodeling, and reparative processes[25] (Fig. 4). This can lead to the erroneous identification of metastatic bone disease (Stage cM1b). Correlation with clinical history, the CT portion of the PET/CT, or other advanced imaging usually allows confident differentiation of prostate cancer bone metastases from benign bone abnormalities.[7]

A commonly encountered cause of bone uptake in patients undergoing PSMA-targeted PET is healing bone fractures[7] and degenerative bone changes.[26,27] Several case studies have described increased ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL uptake in healing vertebral body compression fractures, sacral fractures, rib fractures, and distal radius fracture.[28-31]

Paget bone disease has been known to simulate prostate cancer bone metastases in patients undergoing PET imaging with multiple different radiopharmaceuticals including ^{68}Ga-PSMA-11, Na^{18}F, ^{18}F-fluorocholine, and ^{11}C-choline.[32,33] Paget's bone disease, also known as osteitis deformans, is a chronic metabolic bone disease that commonly affects the axial skeleton, and is characterized by increased osseous turnover and disorganized remodeling.[34] The imaging appearance of Paget disease is dependent on the disease stage.[35]

Increased uptake of ^{18}F-DCFPyL and ^{68}Ga-PSMA-11 uptake have been described in cases of Paget disease with involvement of pelvic bones, sacrum, humeral head, and phalanx.[28,33,36-39] On PSMA-targeted PET imaging, Paget disease can demonstrate moderate to intense radiotracer uptake, sometimes with a heterogeneous pattern.

Benign fibrous dysplasia with mild focal ^{68}Ga-PSMA-11 uptake has been described in two case reports in the rib and an iliac bone, with pathology confirmation.[40,41] A recent case report suggested that PSMA-targeted PET has the potential to map tumor neoangiogenesis to differentiate areas of malignant transformation in fibrous dysplasia.[42] In a patient with a history of skull fibrous dysplasia, intense ^{68}Ga-PSMA uptake was observed in the areas of sarcomatous changes, with only minimally increased uptake in the region of benign fibrous dysplasia.[42]

Diffuse ^{68}Ga-PSMA bone uptake has been recently described in a patient with anemia[43] (Fig. 5). Table 2 summarizes the published case reports on benign bone lesions with PSMA-targeted radiotracer uptake.

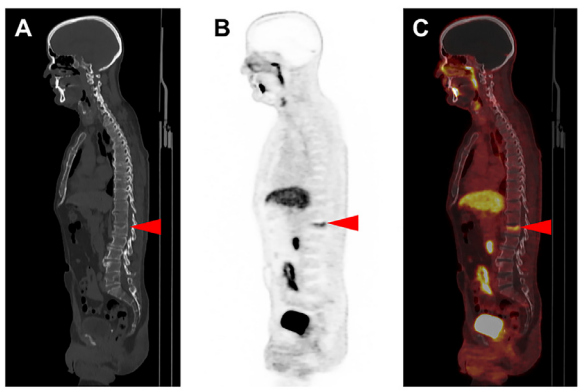

Figure 4 (A) Sagittal, attenuation-correction CT, (B) sagittal ^{18}F-DCFPyL PET and (C) sagittal ^{18}F-DCFPyL PET/CT images at midline in a 62-year-old man presenting for re-staging of prostate cancer. Note the linear radiotracer uptake at a superior endplate L1 compression fracture; the uptake lacks the focality that would be typical for a pathologic fracture.

Pulmonary Involvement

Thoracic metastases are one of the uncommon sites of extranodal metastases in patients with prostate cancer, after bone and liver metastases, although involvement of the lungs can be seen in advanced disease.[15]

Recent studies suggested that there is a high heterogeneity in ^{68}Ga-PSMA radiotracer uptake in pulmonary metastases from prostate cancer.[44] The majority of lung metastases from prostate cancer highly overexpressed PSMA, while a relevant number of metastases showed faint to no PSMA-targeted radiotracer uptake, and therefore are not detected directly by ^{68}Ga-PSMA PET.[44-46]

Several case reports have demonstrated moderate PSMA-targeted radiotracer uptake in benign lung pathologies including pulmonary opacities, bronchiectasis,[47] nonobstructive middle lobe syndrome,[48] pneumoconiosis,[49-51] and granulomatous inflammatory diseases.[52-54] It is therefore not always possible to discriminate reliably between pulmonary metastases from prostate cancer, primary lung carcinoma, and benign pulmonary opacities based only on the SUV analysis of PSMA-targeted PET imaging.[55]

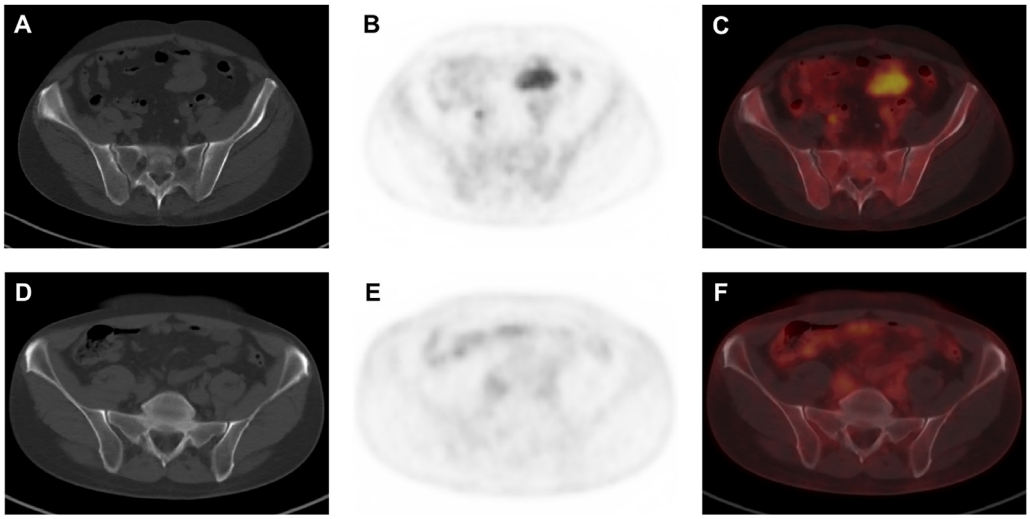

Figure 5 (A) Axial, attenuation-correction CT, (B) axial ^{18}F-DCFPyL PET, and (C) axial ^{18}F-DCFPyL PET/CT images through the pelvis from a 71-year-old man with chronic anemia and activated bone marrow that shows diffuse, mildly increased radiotracer uptake. (A) Axial, attenuation-correction CT, (B) axial ^{18}F-DCFPyL PET, and (C) axial ^{18}F-DCFPyL PET/CT images from the pelvis of a 59-year-old man with normal hemoglobin level and without activated bone marrow. No significant radiotracer uptake is visualized within the bone marrow.

As mentioned above, PSMA radiotracer uptake has been reported in infectious (reactivated tuberculosis as well as tubercular calvarial and lung lesions)[54,55] and noninfectious granulomatous diseases, in patients with known or active mediastinal, pulmonary, or abdominal (spleen, liver lesions) sarcoidosis,[52,53,56,57] and Wegener's granulomatous.[58]

PSMA-uptake in the granulomatous diseases can be in part explained by PSMA expression in neovasculature associated with tissue regeneration and repair.[25] However, the exact mechanism of increased PSMA-radiotracer uptake in benign pulmonary opacities is not yet completely understood. It has been suggested that increased capillary permeability caused by inflammation can result in a higher radiotracer activity in the interstitial space.

Moderate to intense ^{68}Ga-PSMA-11 uptake has been reported in pneumoconiosis, including pulmonary beryllosis, anthracosilicosis, and anthracnosis.[49-51] In a recent report, ^{68}Ga-PSMA uptake was noted in hilar and mediastinal lymphadenopathy (SUVmax up to 44.3), with fibrotic and nodular pulmonary parenchymal changes (SUVmax up to 21.2) that were compatible with chronic beryllium lung disease on histopathology.[51]

Benign Neurogenic Tumors

PSMA-radiotracer uptake has been reported in several benign neurogenic tumors including meningiomas,[59,60] schwannomas[61-66] (Fig. 6), paragangliomas,[67] and neurofibromas.[68] A summary of these studies is provided in Table 2.

Ischemic stroke is another cause of false-positive radiotracer uptake on PSMA-targeted PET imaging, which can potentially mimic brain metastases. Increased ^{68}Ga-PSMA-11 uptake in subacute cerebral and cerebellar infarcts have been described in three case-reports of patients with prostate cancer undergoing restaging PSMA-targeted PET/CT.[69-71] It has been suggested that increased permeability of the blood-brain barrier can lead to higher radiotracer uptake in areas of ischemic stroke.

Increased ^{18}F-DCFPyL-PSMA uptake has been reported in a case of cerebral radionecrosis.[72] Of note, the patient had a history of metastatic castration-resistant prostate cancer with external beam radiation to a dural based lesion 6 years prior to the restaging PSMA-targeted imaging, with ^{18}F-FDG PET/CT, brain CT, and MRI suggestive of cerebral radionecrosis with underlying myelinolysis.[72]

Lack of PSMA-radiotracer uptake in normal brain parenchyma results in excellent visualization of PSMA-avid brain metastases, as it can provide high target-to-background ratios.[73] However, PSMA radiotracer uptake in the brain should be interpreted with caution, as the above benign pathologies,[74,75] as well as gliomas,[73,76] can mimic distant metastases from prostate cancer.

Benign Vascular Tumors and Soft Tissue Lesions

Several case reports have shown the incidental intense PSMA-radiotracer uptake in patients with benign vascular tumors such as benign hepatic and vertebral hemangiomas and a subcutaneous capillary hemangioma.[77,78]

PSMA-targeted radiotracer uptake has also been reported in a variety of benign soft tissue lesions including the desmoid tumor,[79] nodular fascitis,[80] intramuscular myxoma,[81] angiolipoma,[82] acrochordone,[83] dermatofibroma,[84] and pseudoangiomatous stromal hyperplasia.[85]

Mild to moderate PSMA-uptake in the glandular tissue of the breast has been reported in patients with gynecomastia[86,87] (Fig. 7). This pitfall is particularly important as many prostate cancer patients had androgen deprivation either by medical or surgical castration prior to the PSMA-targeted PET imaging which can induce gynecomastia.

Table 2 Spectrum of Reported Benign Pathologies With PSMA-Uptake on PSMA-Targeted PET Imaging, That Can Mimick Prostate Cancer Metastases

	Pathology	Radiotracer
Bone	Paget disease[28,33,36-39]	^{68}Ga-PSMA-11, ^{18}F-DCFPyL
	Fibrous dysplasia[40,41]	^{68}Ga-PSMA-11
	Degenerative changes	^{68}Ga-PSMA-11
	Schmorl's node[27]	
	Lumbar osteophytes)[26]	
	Healing fracture[7,28-31]	^{68}Ga-PSMA-11, ^{18}F-DCFPyL, ^{18}F-PSMA-1007
Lung	Benign lung opacities and bronchiectasis[47]	^{68}Ga-PSMA-11
	Non obstructive middle lobe syndrome[48]	^{68}Ga-PSMA-11
	Granulomatous diseases	^{68}Ga-PSMA-11, ^{18}F-DCFPyL
	Sarcoidosis (mediastinal, pulmonary, or abdominal)[52,53,56,57]	
	Wegner granulomatosis[58]	
	Pneumoconiosis	^{68}Ga-PSMA-11
	Anthracosis, Anthracosilicosis[49,50]	
	Chronic berylliosis[51]	
	Tuberculosis (eg, reactivated tuberculosis, tubercular calvarial and lung lesions)[54,55]	^{68}Ga-PSMA-11
Benign soft tissue lesions	Hemangioma	^{68}Ga-PSMA-11
	Vertebral hemangioma with/without extra osseous extension[77,75]	
	Subcutaneous lobular capillary hemangioma[74]	
	Benign liver hemangioma[78]	
	Intramuscular myxoma[81]	
	Desmoid tumor[79]	^{68}Ga-PSMA-11
	Nodular fasciitis[80]	^{68}Ga-PSMA-11
	Acrochordon[83]	^{68}Ga-PSMA-11
	Dermatofibroma[84]	^{68}Ga-PSMA-11
	Angiolipoma, multiple subcutaneous lesions[82]	^{68}Ga-PSMA-11
	Gynecomastia[86,87]	^{68}Ga-PSMA-11
	Pseudo-angiomatous stromal hyperplasia of breast[85]	^{68}Ga-PSMA-11
Benign neurogenic tumors/pathologies	Benign peripheral nerve sheath tumor (PNST)	^{68}Ga-PSMA-11
	Paravertebral schwannoma[62,65]	
	Pelvic mass-schwannoma[61]	
	Para esophageal Schwannoma[66]	
	PNST, soft tissue density in the left adductor[64]	
	Neurofibromatosis type 1[68]	
	Meningioma[59,60]	^{68}Ga-PSMA-11
	Paraganglioma of the urinary bladder[67]	^{68}Ga-PSMA-11
	Cerebral and cerebellar infarction[69-71]	^{68}Ga-PSMA-11
	Cerebral radionecrosis[72]	^{18}F-DCFPyL
Gastrointestinal	Pancreatic serous cystadenoma[92]	^{68}Ga-PSMA-11
	Intrapancreatic accessory spleen[93]	
	Diverticulum of the sigmoid colon[94]	
	Inflammatory changes in distal esophagus[95]	
	Benign hyperplastic polyp in distal esophagus[95]	
Adrenal	Adrenal adenoma[88,97]	^{68}Ga-PSMA-11, ^{18}F-DCFPyL
	Pheochromocytoma[89]	
	Enlarged adrenal gland without nodular hyperplasia[91]	
Miscellaneous	Senile seminal vesicle amyloidosis[90]	^{68}Ga-PSMA-11
	Follicular thyroid adenoma[96]	^{68}Ga-PSMA-11

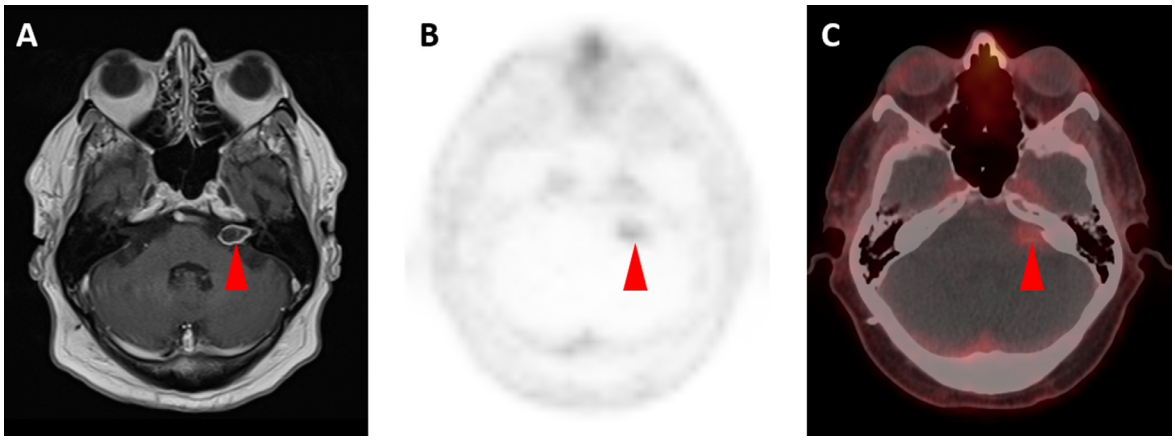

Figure 6 (A) Axial, T1, postcontrast magnetic resonance image of the brain of an 80-year-old man demonstrating a peripherally enhancing, centrally cystic lesion at the left cerebellopontine angle (red arrowhead), consistent with a vestibular schwannoma. This lesion demonstrates PSMA-targeted radiotracer uptake on (B) axial ^{18}F-DCFPyL PET and (C) axial ^{18}F-DCFPyL PET/CT images through the brain (red arrowheads).

A summary of published case reports describing the high PSMA-radiotracer uptake in other benign pathologies is provided in Table 2.[88-97]

Malignant PSMA-Avid Pathologies Other Than Prostate Cancer

PSMA expression in the tumor neovascular of a wide range of nonprostatic malignancies has been shown through numerous immunohistochemistry and clinical studies.[98] With increased clinical use of PSMA-targeted PET in the work up of prostate cancer, an expanding number of case reports has demonstrated the incidental detection of nonprostatic synchronous tumors with high PSMA-uptake.[42,55,73,76,99-142] A summary of published case reports on nonprostatic malignant entities that show uptake on PSMA-ligand PET imaging is provided in Table 3.

The role of PSMA-targeted imaging in nonprostatic cancers has been discussed in detail in a previous review.[98] A number of recent pilot studies support the potential role of PSMA-targeted PET imaging in the work-up of patients with renal cell carcinoma[128,143-147] (Fig. 8), thyroid cancer,[105] breast cancer,[123] and hepatocellular carcinoma.[110] ^{68}Ga-PSMA-11 PET-CT appears to be superior to ^{18}F-FDG PET-CT in imaging patients with HCC (n = 7)[110] and metastatic differentiated thyroid cancer (n = 10).[105] Compared to conventional imaging, the superior performance of ^{18}F-DCFPyL or ^{68}Ga-PSMA-11 PET imaging in the detection of metastases in advanced RCC has been shown in multiple studies.[128,143]

The nonexclusivity of PSMA avidity can potentially pave the way to expand the PSMA theranostic concept outside of prostate cancer.[148] However, further studies with larger numbers of patients are needed to validate these results.

Loss of PSMA Expression in Prostate Cancer

Prostate cancer with neuroendocrine differentiation (NEPC) has been increasingly reported as a common cause of false negative PSMA-targeted PET/CT.[149-152] The use of potent antiandrogens, loss of P53, and lineage plasticity all contribute to the significant suppression of PSMA and increasing prevalence of NEPC.[153-155]

NEPC is most frequently observed in the advanced stages of disease and is associated with frequent visceral metastases.[153] Under androgen deprivation therapy, tumors progress to castration-resistant prostate cancer and can subsequently develop the neuroendocrine phenotype.[155] This phenomenon is associated with significant decline in the expression of

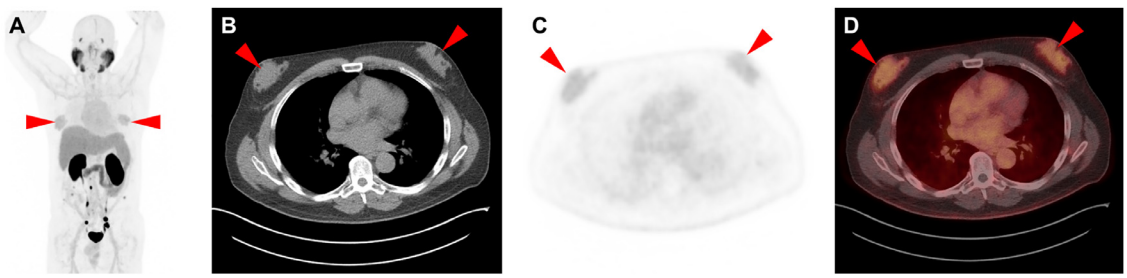

Figure 7 (A) Maximum intensity projection PET image, and (B) axial attenuation-correction CT, (C) axial ^{18}F-DCFPyL PET, and (D) axial ^{18}F-DCFPyL PET/CT images through the chest from a 65-year-old man with recurrent prostate cancer manifest as multiple abdominal and pelvic lymph nodes and peritoneal implants as visualized on the MIP in (A). Note the moderate uptake in gynecomastia (red arrowheads).

Table 3 Summary of Published Case Reports on Nonprostatic Malignant Entities With PSMA-Uptake on PSMA-Targeted PET Imaging

Malignancy	
Hematologic	Follicular lymphoma: increased uptake in lymph nodes[99,100]
	Multiple myeloma[101,112]
Thyroid	Metastatic differentiated thyroid cancer[105]
	Follicular and papillary thyroid carcinoma[102-104,137]
	Medullary thyroid cancer[106]
Gastrointestinal	Gastrointestinal stromal tumor with gastric origin[107,108]
	Signet ring cell gastric carcinoma[118]
	Colorectal adenocarcinoma[114,115,117]
	Metastatic small bowel carcinoid tumor[116]
	Hepatocellular carcinoma[110,111,113]
	Combined hepatocellular cholangiocarcinoma[119]
	Pancreatic neuroendocrine tumor[109,138]
Head and neck	Oropharynx squamous cell carcinoma (tongue)[120]
	Adenoid cystic carcinoma of the maxillary sinus[130]
Breast	Ductal and lobular breast carcinoma[123,139,142]
	Triple-negative bilateral breast carcinoma[140]
Brain	Metastatic Intracranial hemangiopericytoma[131]
	Glioblastoma multiform, anaplastic astrocytoma[76]
	Recurrent gliomas[73]
Genitourinary	Metastatic renal cell carcinoma[125,126,128,143-147]
	Metastatic urothelial carcinoma of ureter[127]
	Urinary bladder adenocarcinoma[129]
	Metastatic penile squamous cell carcinoma[124]
Lung	Primary lung cancer[55,141]
	Metastatic nonsmall cell lung cancer[134]
	Malignant pleural mesothelioma[133]
Miscellaneous	Osteosarcoma[42]
	Metastatic malignant melanoma[132]
	Thymoma[135]
	Liposarcoma[136]
	Metastatic adrenocortical carcinoma[121]

androgen receptor, PSMA, PSA, and also with increased expression of neuroendocrine tumor markers such as somatostatin receptor, chromogranin A, synaptophysin, CD56, and NSE.[156]

Thus far, several case reports have described the loss of PSMA-targeted radiotracer uptake or only faint radiotracer uptake in different subtypes of NEPC including its rare variant small cell carcinoma of the prostate.[149,150,157,158]

Growing number of reports have suggested the alternative use of somatostatin receptor-targeted PET (eg, ^{68}Ga-DOTA-NOC, or ^{68}Ga-DOTATATE), and to a lesser extend ^{18}F-FDG PET, in the restaging and management of patients with NEPC.[151,152,158-160] Imaging surveillance with somatostatin receptor-targeted PET can potentially be considered for early detection of neuroendocrine transformation, particularly in advanced prostate cancer patients being treated with androgen deprivation. Further studies need to evaluate the indications and possibility of somatostatin receptor-targeted radionuclide therapy in patients with NEPC.

Intertumoral heterogeneity of ^{68}Ga-PSMA-11 uptake in sites of prostate cancer metastases (eg, pulmonary metastases) have been reported in a number of studies.[44,150] Interestingly, there have been reports that prostate cancer metastatic lesions can demonstrate metabolic heterogeneity with variable radiotracer uptake on ^{18}F-FDG, somatostatin receptor-targeted, and PSMA-targeted PET imaging.[161,44] This can be at least partially explained in some cases by the degree and extent of neuroendocrine differentiation.

Tosoian et al, showed highly variable ^{18}F-DCFPyL uptake in known sites of prostate cancer metastases, with no radiotracer uptake in liver metastases and moderate uptake in the peritoneal metastases in a patient with NEPC.[150] Lesion-specific genomic and histologic analysis showed neuroendocrine differentiation in the liver lesions with a mixed neuroendocrine/adenocarcinoma phenotype in the peritoneal metastases.[150]

The loss of PSMA expression has been also described in a case of castration resistant acinar prostate adenocarcinoma after docetaxel-based chemotherapy[162] (Fig. 9). In that case, PSMA-targeted PET/CT showed decreased radiotracer uptake in all lesions. Subsequent ^{18}F-FDG-PET/CT revealed a different radiotracer distribution pattern with strongly ^{18}F-FDG-avid new bone and lymph node metastases. Histological analysis showed progressive dedifferentiation with the retention of acinar features. Immunohistochemical analyses confirmed the loss of PSMA expression with no expression of neuroendocrine markers.[162]

Effect of Prior Androgen Deprivation Therapy on Lesion Detection

The temporal relationship between androgen deprivation therapy and PSMA expression has been explored in several recent studies in mouse xenograft models and a limited number of clinical patients with prostate cancer. These studies have suggested that, at least in the short term, inhibition of androgen receptor can increase PSMA expression in prostate cancer metastases.[163,164]

Hope et al reported a 1.5-2-fold increase in PSMA uptake in mouse xenografts bearing androgen sensitive human prostate adenocarcinoma 4 days after treatment with both orchiectomy and antiandrogen therapy with apalutamide. Similarly, ^{68}Ga-PSMA PET/CT imaging 4 weeks after the

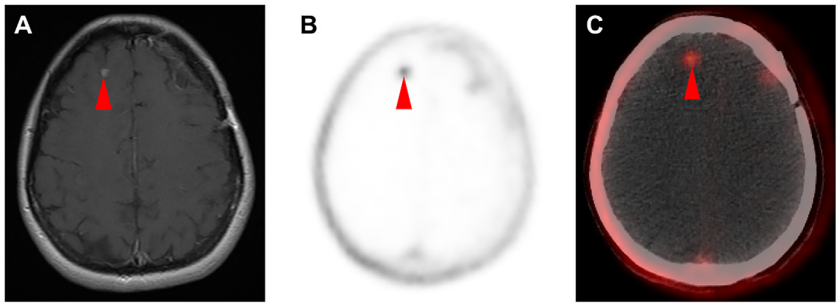

Figure 8 (A) Axial, T1, postcontrast magnetic resonance image, (B) axial ^{18}F-DCFPyL PET and, (C) axial ^{18}F-DCFPyL PET/CT images of the brain from a 40-year-old woman with history of metastatic clear cell renal cell carcinoma. The enhancing focus in the left frontal lobe (red arrowhead in (A)) is consistent with a site of metastatic disease, and this lesion has focal radiotracer uptake (read arrowheads in (B) and (C)). Postsurgical changes from prior left frontal craniotomy for resection of another metastatic lesion are also present.

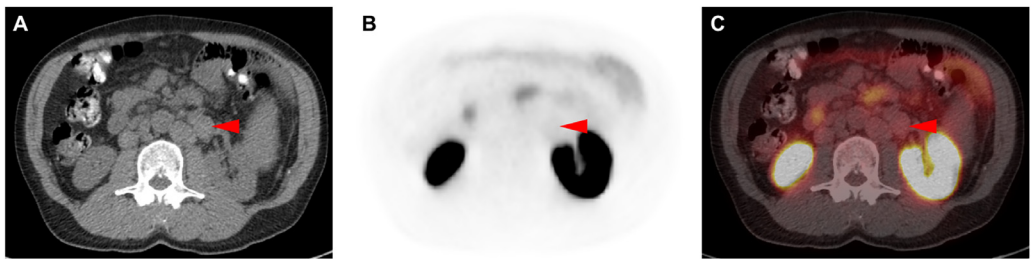

Figure 9 (A) Axial, attenuation-correction CT, (B) axial ^{18}F-DCFPyL PET, and (C) axial ^{18}F-DCFPyL PET/CT images through the abdomen in a 62-year-old man with metastatic prostate cancer demonstrating large retroperitoneal lymph nodes that lack significant radiotracer uptake (red arrowheads). Subsequent biopsy confirmed adenocarcinoma without neuroendocrine differentiation but with relatively little PSMA expression.

initiation of androgen deprivation therapy in a patient with castration-sensitive prostate cancer showed a 7-fold increase in radiotracer uptake of known lesions with visualization of several additional lesions.[164]

Another study on mouse xenografts bearing human castration resistant prostate cancer confirmed the upregulation of PSMA expression in response to androgen deprivation therapy, evident by flow cytometry and ^{68}Ga-PSMA-11 PET imaging. ^{68}Ga-PSMA-11 PET/CT imaging performed on days 23, 29, 34, and 39 postandrogen deprivation therapy with enzalutamide, showed up to 2.3-fold increase in PSMA-targeted radiotracer uptake.[163]

Zacho et al suggested a presence of the bone flare phenomenon to androgen deprivation therapy on ^{68}Ga-PSMA PET/CT in a patient with hormone-sensitive prostate cancer.[165] Imaging 6 weeks after the initiation of androgen deprivation therapy showed complete regression in size and uptake of most PSMA-avid lymph nodes, with increased PSMA-targeted radiotracer uptake in known bone metastases and several new sclerotic bone lesions with moderate to high uptake.[165] A decrease in PSA level and skeletal PSMA-radiotracer uptake were observed 13 weeks after the initiation of androgen deprivation therapy.[165] Similarly, a recent case report showed bone flare phenomenon on 18F DCFPyL PET/CT in a patient with castration-resistant prostate cancer 10 weeks after Enzalutamide therapy (second-generation antiandrogen).[166]

Chemical castration is typically achieved within 3-4 weeks after starting androgen deprivation therapy, however it is highly variable depending on the agent used.[164,167] However, the precise temporal relationship between initiation of androgen deprivation therapy and PSMA upregulation needs to be further investigated. The optimal timing of PSMA-targeted PET to assess therapy response is essential to reduce the false positive uptake of PSMA after androgen deprivation therapy and improve the specificity.

It has been proposed that blocking of the androgen signaling axis may lead to PSMA upregulation and, consequently, more effective PSMA radioligand therapies.[163] A recent study by Lückerath et al compared the efficacy of PSMA-targeted radioligand therapy with ^{177}Lu-PSMA-617 and a combination of androgen antagonism and radioligand therapy with enzalutamide + ^{177}Lu-PSMA617 in prostate cancer mouse xenografts. They showed that enzalutamide-induced PSMA expression does not retard tumor growth more profoundly than ^{177}Lu-PSMA-617 alone, with no significant change in the overall survival of two groups.[163]

Standardized Reporting Systems for Interpretation of PSMA-Targeted Imaging

With increased adoption of PSMA-targeted PET/CT imaging and radioligand therapy in clinical trials, it is crucial to have

Table 4 The Molecular Imaging-RADS Classification Schema

MI-RADS Classification				Work-Up
1	1A	Lesions without radiotracer uptake that are definitively benign (characterized by biopsy or anatomic imaging)	Definitively benign	No PRRT
	1B	Lesions with radiotracer uptake that are definitively benign (characterized by biopsy or anatomic imaging)		No PRRT
2		Low level radiotracer uptake in bone or soft tissue sites that would be Atypical for metastatic prostate cancer/NETs	Likely benign	No PRRT
3	3A	Equivocal radiotracer uptake in soft tissue lesions in a distribution typical for prostate cancer/NETs	Equivocal	Biopsy, Alternatively follow-up imaging*
	3B	Equivocal radiotracer uptake in bone lesions that are not clearly benign		
	3C	High radiotracer uptake in lesions that would be atypical for prostate cancer/NET but may represent a nonprostate cancer/NETs malignancy		
	3D	Lesion without radiotracer uptake but concerning for the presence of malignancy on anatomic imaging		
4		High radiotracer uptake in site typical of prostate cancer/NETs but lack a definitive anatomic abnormality	Highly likely prostate cancer/NETs	Eligible for PRRT
5		High radiotracer uptake in site typical for prostate cancer/NETs with corresponding anatomic findings	Definitively prostate cancer/NETs	Eligible for PRRT

NETs, neuroendocrine tumors; PRRT, peptide receptor radionuclide therapy.

*MI-RADS-3A: Biopsy (if targetable for biopsy). Alternatively, progression on follow-up imaging can confirm the diagnosis (initial follow-up period of 3-6 months).

MI-RADS-3B: Comparison to bone scan, 18F NaF PET, or tumor-protocol MR images may be helpful. Bone biopsy or alternatively follow-up imaging to confirm progression (initial follow-up period of 3-6 months).

MI-RADS-3C and 3D: Biopsy to confirm diagnosis histologically is often preferred, although organ-specific follow-up imaging may be done.

a standardized approach for image interpretation. Over the last 2 years, several standardized framework systems for the interpretation of molecular imaging studies have been proposed. These include the NETPET score for the interpretation of combined somatostatin receptor (SSTR) and ^{18}F-FDG PET/CT in metastatic neuroendocrine tumors (NETs),[168] molecular imaging tumor-node-metastasis system (miTNM) version 1.0,[20] PSMA reporting and data system (PSMA-RADS) version 1.0,[166,169] SSTR-RADS version 1.0,[170] and subsequently molecular imaging reporting and data systems (MI-RADS) for the interpretation of two most commonly used classes of theranostic PET imaging probes, those targeting PSMA and SSTR.[171]

mi-TNM

The miTNM, version 1.0 was proposed by Eiber et al in 2018 as a structured reporting framework for the interpretation of PSMA-ligand PET/CT or PET/MRI.[20] The miTNM classification organizes findings in comprehensible categories based on the TNM classification, that is, the extent of local tumor, involvement of pelvic lymph nodes, and the presence of distant metastases; pattern of disease distribution. The system also incorporates a measure of PSMA expression, the miPSMA score, and conveys a level of certainty.[20]

PSMA expression level is determined visually and in relation to the mean uptake in the blood pool, parotid gland, and liver (or spleen for PSMA ligands with liver-dominant excretion). miPSMA is scored using a 4-point scale, defined as score 0 (uptake below the blood pool), score 1 (uptake equal to or above blood pool and lower than liver), score 2 (uptake equal to or above liver* and lower than parotid gland), score 3 (uptake equal to or above parotid gland), with these levels of uptake corresponding to no, low, intermediate, or high PSMA expression, respectively.[20]

MI-RADS

In 2018, Rowe et al proposed a structured reporting and data system, termed PSMA-RADs, for interpretation of PSMA-targeted PET imaging in prostate cancer.[166,169] Later, SSTR-RADS were proposed for interpretation of SSTR-targeted imaging in NETs.[170] Both classification systems have similar structures and were subsequently combined under the umbrella term of MI-RADS. MI-RADS serve as a standardized assessment for both diagnosis and treatment planning in prostate cancer and NETs.[171] The goal of this structured framework is to avoid the pitfalls described above by assigning a level of certainty to a given finding.

The MI-RADS classification is based on the site of involvement, and the intensity of radiotracer uptake, using a five-point scale with higher numbers indicating a greater probability of prostate cancer/ NETs involvement.[171] Table 4 summarizes the MI-RADS classification schema.

The radiotracer-specific details, normal biodistribution, and common pitfalls of PSMA- and SSTR-targeted imaging were considered to define each category.[171] Thus, this classification can convey the level of confidence of the imaging specialist on the presence of a prostate cancer/NETs lesions and the potential need for any additional work-up.[169,171] A recent study showed an excellent interobserver agreement in interpretation of ^{18}F-DCFPyL PET/CT using the PSMA-RADS classification scheme.[172]

The most complex MI-RADs category, is MI-RADS-3 or indeterminate findings. MI-RADS-3 is divided in to 4 subcategories[171]: MI-RADS-3A and MI-RADS-3B represent soft tissue or bone lesions with equivocal radiotracer uptake with uncertainty whether a given lesion is compatible with prostate cancer/NETs. MI-RADS-3C represents high radiotracer uptake in lesions that would be atypical for Prostate cancer/NET, and may suggest the presence of another PSMA- or SSTR-avid malignancy. Lesions without radiotracer uptake but suspicious for malignancy on anatomic imaging are categorized as MI-RADS-3D. MI-RADS-3D may indicate non-PSMA or SSTR-avid malignancies or aggressive tumors such as NEPC.[171]

Yin, et al followed a series of indeterminate PSMA-RADS-3A and PSMA-RADS-3B lesions to determine how frequently they manifest as true positive prostate cancer malignancy on the follow-up imaging (median follow-up 10 months).[173] Approximately 75.0% of PSMA-RADS-3A lymph node lesions and 21.4% of PSMA-RADS-3B bone lesions demonstrated changes on subsequent imaging compatible with the presence of prostate cancer.[173] The presence of additional definitive sites of prostate cancer (PSMA-RADS-4 and PSMA-RADS-5 lesions), increased the likelihood that indeterminate lesions would manifest as true positive on follow-up.[173]

Conclusions

The continuing adoption of PSMA-targeted PET for prostate cancer molecular imaging requires imagers and clinicians alike to be aware of the increasing number of potential interpretive pitfalls that have been reported. Furthermore, new structured reporting systems will help communicate the level of confidence that sites of uptake represent prostate cancer and will guide the selection of work-up options for indeterminate findings, although more work is necessary to validate such systems. In addition to our previous review on this topic,[7] this update can serve as a valuable reference for known PSMA-targeted PET pitfalls.

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