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Cancers and Benign Processes on ^{68}Ga PSMA PET-CT Imaging Other than Prostate Cancer

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Abstract

Background Imaging plays an important role in the evaluation of prostate cancer patients. In recent years, much attention has been focused on gallium 68 prostate-specific membrane antigen positron emission tomography-computed tomography (^{68}Ga PSMA PET-CT) in prostate cancer patients and has been widely used for staging, restaging, and therapy response for these patients. The aim of this study was to report ^{68}Ga PSMA PET-CT in other cancers and benign processes incidentally detected on ^{68}Ga PSMA PET-CT in patients with prostate cancer.

Materials and Methods A total of 600 ^{68}Ga PSMA PET-CT scans were performed for initial staging, restaging, detection of suspected recurrence, and therapy response in prostate cancer patients between December 2018 and June 2020. A total of 38 patients with histopathologically proven prostate cancer were included in the current study with other malignancies and benign processes. Mainly histopathology in most of cases and clinical and radiological follow-up in few cases after PET/CT scanning served as the standard of reference.

Results A total of 38 patients (age range: 52–85 years; mean age: 68.6) with prostate cancer final histopathology results were included in the study. A total of 51 lesion sites were evaluated in 38 patients. Forty-one lesion regions of these 51 regions were based on histopathological diagnosis, whereas 10 of them were based on clinical follow-up and conventional radiological follow-up as differential criteria. Thirty of 51 lesion regions were evaluated as malignant and 21 were benign lesions. The most common ^{68}Ga PSMA ligand avid malignancy was lung adenocarcinoma (6/38).

Keywords
- ^{68}Ga PSMA PET-CT
- benign processes
- other malignancies
- lung cancer
- colon cancer
- gastric tumor
- multiple myeloma

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Conclusions Prostate-specific membrane antigen (PSMA) is a cell surface glycoprotein and mainly expressed in prostate epithelium. ^{68}Ga PSMA PET-CT imaging is very sensitive and specific imaging modality in prostate cancer patients. However, other malignancies and some benign processes may also have ^{68}Ga PSMA ligand avidity and some prostate cancer metastases may imitate other malignancies.

Introduction

^{68}Gallium prostate-specific membrane antigen positron emission tomography-computed tomography (^{68}Ga PSMA PET-CT) imaging is the most exciting used imaging modality in prostate cancer patient in recent years. PSMA is a cell surface glycoprotein. It is not only expressed in prostate epithelium, but also additional three tissues of the body, including the proximal tubules of the kidney, the jejunal brush border of the small intestine, and ganglia of the nervous system.[1,2] Additionally, it may be seen in lacrimal and saliva glands and neovascularization areas of other tumors.[3] While there is a prominent ^{68}Ga PSMA ligand uptake in liver, thyroid gland uptake is variable. The highest ^{68}Ga PSMA ligand activity occurs in the kidneys and bladder. Radiopharmaceutical uptake may be heterogenous and variable in the prostate gland. Cancers other than prostate cancer and also some benign processes may express PSMA. In ^{68}Ga PSMA PET-CT studies conducted in our center for staging, restaging, or therapeutic response in patients with prostate cancer, we observed variable ^{68}Ga PSMA ligand uptake in some benign processes and some malignancies other than prostate cancer. There are few case reports on this subject in the literature. The aim of this study was to report ^{68}Ga PSMA PET-CT in other cancers and benign processes incidentally detected on ^{68}Ga PSMA PET-CT in patients with prostate cancer.

Materials and Methods

Imaging Protocol

^{68}Ga is obtained using a germanium-68-gallium-68 (^{68}Ge/^{68}Ga) radionuclide generator for labeling PSMA. ^{68}Ga PSMA-11 ligand was used. An Agilent 1260 Infinity HPLC system (including dual pump, degasser and UV detector, Agilent Technologies, Santa Clara, CA, United States) equipped with an ACE-5-C18 column (150 × 3 mm, affinity capillary electrophoresis [ACE]) and a NaI radiodetector (Type: B-FC-3500, Eckert & Ziegler) was used to determine the radiochemical purity. 0.02 mL sample is used to determine the percentage of [^{68}Ga] PSMA. The elution was monitored both by detecting UV (at 220 nm) and radioactivity signals. Water, acetonitrile, and trifluoroacetic acid (78/22/0,1 v/v/v) mixture was used as the mobile phase and flow rate was maintained at 0,6 mL/min. Radiochemical purity was <97%. ^{68}Ga PET/CT scans were obtained 45 to 60 minutes after injection of 185 MBq (5 mCi) ^{68}Ga PSMA using an integrated scanner (Siemens, Biograph True Point 6 PET/CT, Germany). A whole-body CT scan was performed without intravenous contrast administration with 120 kV, 30 to 413 mAs, a pitch of 0.8, a section thickness of 3 mm, and a field of view of 78 cm. A PET scan was performed immediately after an unenhanced CT scan, and acquired from the skull base to the upper thigh with a 2-minute acquisition per bed position using a three-dimensional acquisition mode. Any unusual PSMA uptake was documented, and followed up.

All patients fasted for at least 4 to 6 hours before fluorodeoxyglucose (FDG) injection of 370MBq (10 mCi). PET/CT scans were obtained 60 minutes after injection using an integrated scanner (Siemens, Biograph True Point 6 PET/CT, Germany). A whole-body CT scan was performed without intravenous contrast administration with 130 kV, 50 mAs, a pitch of 1.5, a section thickness of 5 mm, and a field of view of 70 cm. A PET scan was performed immediately after an unenhanced CT scan, and acquired from the skull base to the upper thigh with a 2-minute acquisition per bed position using a three-dimensional acquisition mode. Any unusual FDG uptake was documented, and followed up. FDG PET-CT images were comparatively evaluated with Ga-68 PSMA PET-CT images.

Diagnostic Criteria for Malign and Benign Processes

Mainly histopathology in most of cases and clinical and radiological follow-up in same cases after PET/CT scanning served as the standard of reference.

Image Analysis

PET/CT images were viewed in the coronal, axial, and sagittal sections. Maximum standard uptake value (SUVmax) of lesions were calculated on PET/CT by using region of interest (ROI) included at least two-thirds of the nodular lesions. Partial volume effect was minimized by this way. The regions were drawn by generating sphere circles. The quantitative uptake values of ^{68}Ga (SUVmax) in the lesions ROIs were semiautomatically calculated using workstations (Siemens).

Results

Patients' data diagnosed with biopsy proven prostate cancer and underwent ^{68}Ga PSMA PET-CT were selected retrospectively. A total of 600 ^{68}Ga PSMA PET-CT scans were performed in a total of 480 patients for initial staging, restaging, detection of suspected recurrence, and therapy response in prostate cancer patients between December 2018 and June 2020. A total of 38 patients of 480 patients with histopathologically proven prostate cancer were included in the study with other malignancies, suspected other malignancies, and benign processes. The patients included in the current study consisted of patients who had a

Table 1 Malign lesions with ^{68}Ga PSMA-positive cases detected on ^{68}Ga PSMA PET-CT imaging

Age	Malignant lesions	Histopathological or follow-up result	^{68}Ga ligand uptake	FDG ligand uptake
68	Gastric tumor, perigastric LAP	Adenocarcinoma	+	+
73	Lung mass, mediastinal LAP, synchronous nodules	Neuroendocrine tumor	+	+
63	Intraabdominal LAP	Gastric adenocarcinoma metastasis	+	+
57	Expansive masses in ribs	Multiple myeloma	+	+
63	Colon mass	Adenocarcinoma	+	+++
	Lung mass	Adenocarcinoma	+	+
75	Cervical, supraclavicular LAP	[a]Prostate cancer metastasis	+	+
77	Lung mass, synchronous nodules	NSCLC	+	+
58	Liver mass	[b]Prostate cancer metastasis	+	+
59	Lung mass	Adenocarcinoma	+	+
71	Soft tissue masses	[c]Prostate cancer metastasis	+	N/A
72	Lung mass, mediastinal LAP, synchronous nodules	Adenocarcinoma	+	+
70	Lung nodule	[d]Prostate cancer metastasis	+	+
70	Lung nodule	[d]Prostate cancer metastasis	+	+
85	Pleural effusion	Multiple myeloma	+	N/A
62	Bladder mass	Urothelial carcinoma	+	+
75	Pleural thickening	Small cell lung cancer	+	+
52	Lytic bone lesions	HCC metastasis	+	+
80	Colon mass	Colon cancer	+	+

Abbreviations: FDG, fluorodeoxyglucose; ^{68}Ga PSMA PET-CT, gallium 68 prostate-specific membrane antigen positron emission tomography-computed tomography; HCC, hepatobiliary cancer; LAP, laparoscopic perigastric; N/A, not available; NSCLC, non-small cell lung cancer.
[a]Suspected lymphoma.
[b]Suspected hepatobiliary malignancy.
[c]Suspected soft tissue malignancy.
[d]Suspected lung malignancy.

pathological diagnosis of prostate cancer and who had non-prostate malignancy or benign lesions on ^{68}Ga PSMA PET-CT imaging. Mean age of patients was 68.6 (range: 52–85) years. ^{68}Ga PSMA studies were performed for initial staging in 11 patients, treatment response in 9 patients, and restaging in 18 patients. A total of 51 lesion sites were evaluated in 38 patients. Forty-one lesion regions of these 51 regions were based on histopathological diagnosis, whereas 10 of them were based on clinical follow-up and conventional radiological follow-up as differential criteria. Thirty of 51 lesion regions were evaluated as malignant and 21 were benign lesions. In ►**Tables 1** and **2**, all patients with malignant and benign lesions were summarized.

Table 2 Benign processes ^{68}Ga PSMA positive cases detected on ^{68}Ga PSMA PET-CT imaging

Age	Benign lesions	Histopathological or follow-up result	^{68}Ga ligand uptake	FDG ligand uptake
57	Mediastinal, intraabdominal, cervical and axillary LAP	Lymphadenitis	+	+
62	Mandibular bone uptake	Osteomyelitis	+	+
71	Retroareolar breast nodule	Gynecomastia	+	N/A
70	Pleural plaque	Asbestosis and inflammation	+	N/A
75	Head nodule	Benign	+	N/A
72	Rectal polyp	Rectal tubular adenoma	+	N/A

Abbreviations: FDG, fluorodeoxyglucose; ^{68}Ga PSMA PET-CT, gallium 68 prostate-specific membrane antigen positron emission tomography-computed tomography; LAP, laparoscopic perigastric; N/A, not available.

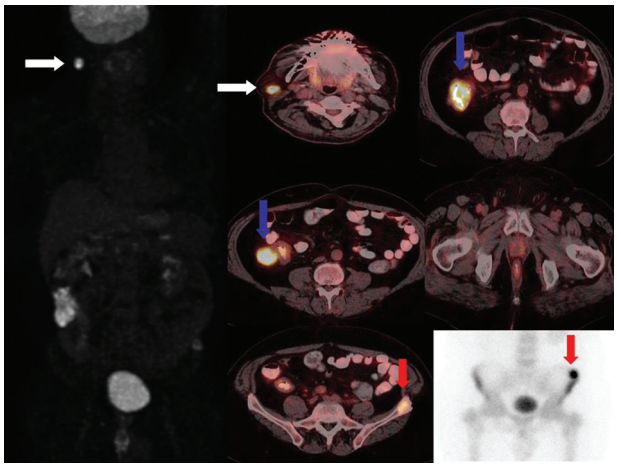

Fig. 1 Fluorodeoxyglucose positron emission tomography computed tomography (FDG PET-CT) images of a 63-year-old prostate cancer patient. Maximum intensity projection image, axial fusion PET-CT images, and pelvic static image of bone scintigraphy demonstrates Wharton tumor with intense FDG ligand uptake (maximum standard uptake value [SUVmax]: 45) in right parotid region (*white arrow*), $77 \times 47 \times 41$ mm right colon mass (SUVmax: 34.7) demonstrated with blue arrow, and left iliac bone metastases (SUVmax: 13.9—*red arrow*).

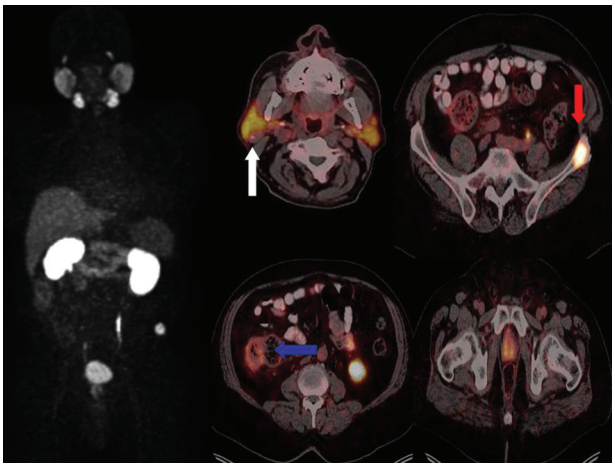

Fig. 2 Gallium 68 prostate-specific membrane antigen positron emission tomography-computed tomography (^{68}Ga PSMA PET-CT) images of the same patient shown in ►**Fig. 1** (prostate-specific antigen [PSA]: 10). The patient was followed with Gleason score: 6 (3 + 3) prostate cancer for few years and ^{68}Ga PSMA PET-CT was performed for restaging because of PSA progression and suspected recurrence. Maximum intensity projection image and axial fusion PET-CT images demonstrate Wharton tumor without ^{68}Ga PSMA ligand uptake in right parotid region (*white arrow*), right colon mass with middle ^{68}Ga ligand uptake (maximum standard uptake value [SUVmax]: 13.64) (*blue arrow*), and left iliac bone metastases high ^{68}Ga ligand uptake (SUVmax: 41.13—*red arrow*).

In our study group including malign lesions, colon adenocarcinoma, gastric adenocarcinoma, lung neuroendocrine tumor, adenocarcinoma, bladder cancer, hepatobiliary cancer (HCC), and non-small cell lung cancer (NSCLC) showed high ligand uptake. Multiple myeloma showed moderate ^{68}Ga PSMA ligand uptake (►**Table 1**). However, one renal cell cancer (RCC) metastases, one skin basal cell cancer (BCC), one skin squamous cell cancer (SCC), and one lung adenocarcinoma nodule showed no ^{68}Ga PSMA ligand uptake or low uptake.

In our study group including benign lesions, one lymphangioma hemangioma, one Wharton tumor, one liver hemangioma, two liver and spleen cysts, one bone lesion, one benign fibrous pleuritis, two thymoma, four lung nodules had no or low ligand uptake with ^{68}Ga PSMA, whereas gynecomastia, lymphadenitis, osteomyelitis, asbestosis, rectal tubular adenoma, and inflammation had moderate or high ^{68}Ga PSMA ligand uptake (►**Table 2**).

Right colon adenocarcinoma mass with high FDG ligand uptake, moderate ^{68}Ga PSMA ligand uptake, Wharton tumor with high FDG ligand uptake, no ^{68}Ga PSMA ligand uptake and prostate cancer bone metastases with moderate FDG ligand uptake, and high ^{68}Ga PSMA ligand uptake were demonstrated in ►**Figs. 1** and **2** in a 63-year-old prostate cancer patient with PSA progression and suspected recurrence.

^{68}Ga PSMA and FDG PET-CT images of a 57-year-old patient with prostate cancer and multiple myeloma (PSA:9) were demonstrated in ►**Fig. 3**.

Maximum intensity projection images and axial fusion images of a 71-year-old patient with prostate cancer and lung cancer (Gleason score 7: (4 + 3)-PSA:13) in ►**Figs. 4** and **5**.

Discussion

In recent years, with the use of ^{68}Ga PSMA PET/CT imaging in prostate cancer staging, there have been serious improvements in the evaluation of these patients. ^{68}Ga PSMA PET-CT imaging is a very sensitive and specific imaging modality in prostate cancer patients. PSMA is a cell surface glycoprotein. It is mainly expressed in prostate epithelium. PSMA is expressed in both benign and malignant prostate pathologies. PSMA is

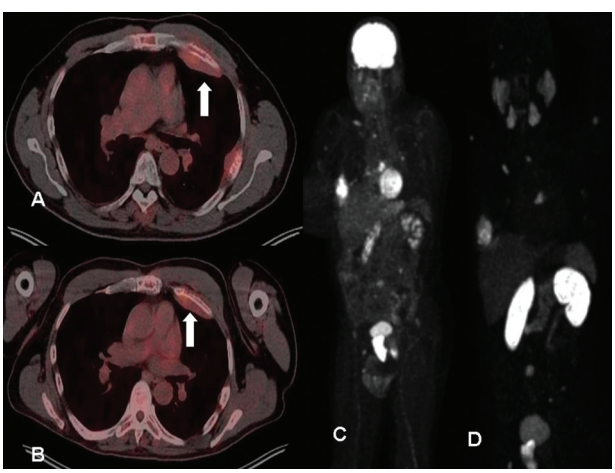

Fig. 3 Gallium 68 (^{68}Ga) and fluorodeoxyglucose positron emission tomography computed tomography (FDG PET-CT) images of a 57-year-old patient with prostate cancer and multiple myeloma (prostate-specific antigen:9). Biopsy of expansile rib lesions was compatible with multiple myeloma, whereas pelvic bone metastases were because of prostate cancer in the same patient. Axial fusion image demonstrates expansile bone lesions in ribs on ^{68}Ga (**A**) and FDG (**B**) (*white arrows*) PET/CT with maximum standard uptake value 10.8 and 8.23, respectively, for ^{68}Ga and FDG ligands. Maximum intensity projection images belonging to FDG PET-CT (**C**) and ^{68}Ga prostate-specific membrane antigen (**D**) in the same patient 1 year later demonstrate progression.

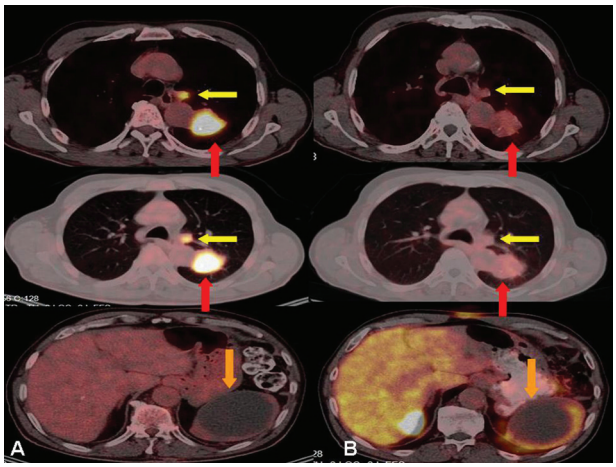

Fig. 4 Gallium 68 prostate-specific membrane antigen (^{68}Ga PSMA) and fluorodeoxyglucose positron emission tomography computed tomography (FDG PET-CT) images of a 71-year-old patient with prostate cancer and lung cancer (Gleason score 7: (4 + 3)-prostate-specific antigen:13). Biopsy of the 4.5 × 4 cm lung mass (FDG maximum standard uptake value [SUVmax]: 24.42/ ^{68}Ga PSMA SUVmax: 5.06) was compatible with adenocarcinoma. Axial fusion images demonstrate lung mass with *red arrows*, left perihilar and aortopulmonary lymphadenopathies (FDG SUVmax: 14.94) with *yellow arrows*, and 9 × 7 cm cystic mass with mild peripheral uptake with *orange arrows* in FDG (**A**) and ^{68}Ga PSMA (**B**).

expressed over 100- to 1000-fold in prostate cancer cell membranes compared with normal prostate cell membranes. In addition to prostate, various other normal and pathological tissues also take up PSMA tracers. An intense uptake of ^{68}Ga PSMA ligand has been shown in several malignant and benign soft-tissue lesions such as desmoid tumors, nodular fasciitis, dermatofibroma, acrochordon, and subcutaneous capillary hemangioma.[4] Moreover, PSMA is expressed in other cancers as well, more specifically in the neovasculature associated with these cancers.[5] However, other malignancies and some benign processes may also have ^{68}Ga PSMA ligand avidity and some prostate cancer metastases may imitate other malignancies.

Physiological intense ^{68}Ga PSMA ligand uptake may be seen in lacrimal and salivary glands, kidneys, vocal cords, and urinary bladder. Mildly and moderately increased PSMA ligand uptake may be seen pancreatic head, Waldeyer ring, liver, spleen, proximal small bowel, and fossa of Rosenmüller.

Mild nonspecific ^{68}Ga PSMA ligand uptake may be seen in distant lymph nodes such as axillary and hilar stations that are unusual for prostate cancer metastases. Reactive etiology, lymphoma, or granulomatous disease needs to be considered in such conditions.[6] A follicular lymphoma showing avid ^{68}Ga PSMA ligand uptake has been reported in a recent case report.[7]

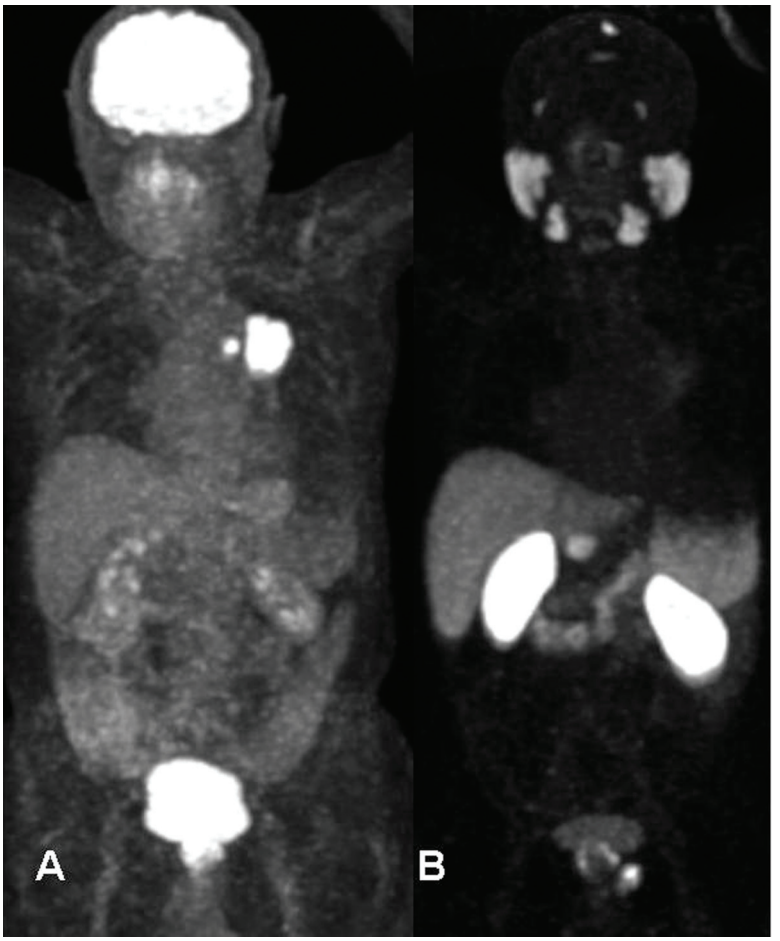

Fig. 5 Maximum intensity projection images belonging to fluorodeoxyglucose positron emission tomography computed tomography (FDG PET-CT) (**A**) and gallium 68 prostate-specific membrane antigen (^{68}Ga PSMA) (**B**) in the same patient demonstrate high FDG avid lung mass, whereas low ^{68}Ga PSMA avidity. Mild peripheral FDG and ^{68}Ga PSMA avidity was seen in a spleen cyst located in the upper part of spleen.

Inflammation, infection, or some benign conditions may show ^{68}Ga PSMA ligand uptake mimicking malignancy. Law et al demonstrated ^{68}Ga PSMA ligand uptake in a patient in adrenal adenoma in a case of the month.[8] Benign processes such as gynecomastia, lymphadenitis, rectal tubular adenoma, osteomyelitis, asbestosis, and inflammation demonstrated ^{68}Ga PSMA avidity in our study. ^{68}Ga PSMA ligand uptake was identified in lung infection, atelectasis, and pleural plaques atherosclerotic arteries in a research article by Shetty et.al.[6]

^{68}Ga PSMA ligand uptake in thyroid gland, lung metastasis, gastric and colonic malignancies, RCC, neuroendocrine tumor, glioma, breast cancer, gynecological malignancies, and HCC was reported in literature.[5,9–17] Parathyroid adenoma was included in the differential diagnosis of focal tracer uptake in a report by Pfob et al.[18] In the current study, the most common ^{68}Ga PSMA ligand avid malignancy was lung adenocarcinoma. In addition, malignancies such as gastric adenocarcinoma, multiple myeloma, lung neuroendocrine tumor, urothelial carcinoma, HCC, colon adenocarcinoma, NSCLC showed ^{68}Ga PSMA ligand avidity. However, many benign lesions such as liver cysts and hemangioma, spleen cyst, lymphangiohemangioma, Wharton tumor, benign fibrous pleuritis, thymoma and malignant lesions such as BCC, SCC, RCC had no or low ligand uptake with ^{68}Ga PSMA. Brain, liver, and penis are uncommonly involved sites in prostate cancer patients. Dureja et al demonstrated these rare sites of metastases in a case series.[19] Some prostate cancer metastases imitated other primary malignancies in our study. However, these suspicious lesions were histopathologically proven to be prostate cancer metastases. In our study, a 71-year-old patient with multiple soft tissue masses and prostate cancer diagnosis was suspected for second primary malignancy such as soft tissue malignancy. While soft tissue metastasis is a rare condition in prostate cancer patients, soft tissue second primary malignancy was suspected. However, biopsy of these soft tissue lesions was compatible with prostate cancer metastases.

Conclusions

^{68}Ga PSMA PET-CT imaging is very sensitive and specific imaging modality in prostate cancer patients. However, other malignancies and some benign processes may also have ^{68}Ga PSMA ligand avidity and some prostate cancer metastases may imitate other malignancies. While evaluating the images, every lesion showing ^{68}Ga PSMA ligand avidity should not be perceived as prostate cancer metastasis. Further studies are needed for evaluation of use of ^{68}Ga PSMA PET-CT imaging in nonprostate cancers.

Funding
None.

Conflict of Interest
None declared.

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