Nonspecific Uptake of ^{68}Ga-Prostate-Specific Membrane Antigen in Diseases other than Prostate Malignancy on Positron Emission Tomography/Computed Tomography Imaging: A Pictorial Assay and Review of Literature

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Abstract

^{68}Ga-labeled prostate-specific membrane antigen (PSMA) ligand positron emission tomography/computed tomography imaging (PET/CT) is a rapidly evolving imaging modality for prostate cancer. Many studies have proved its superiority in staging, restaging, and detecting the recurrent prostate cancer. However, case reports describing the incidental tracer uptake in benign and nonprostatic malignancies are also reported in the literature, thus questioning the specificity of the tracer. This pictorial assay illustrates the nonspecific tracer uptake encountered during PSMA PET/CT imaging, knowledge of which can increase the confidence of interpreting physicians and may also open a new path for peptide receptor radionuclide therapy in nonprostatic malignancies.

Keywords: *^{68}Ga-labeled prostate-specific membrane antigen positron emission tomography/computed tomography imaging, nonprostatic malignancies, prostate cancer, rectal adenocarcinoma, renal cell cancer, thyroid cancer*

Introduction

Prostate-specific membrane antigen (PSMA) a type II transmembrane glycoprotein is overexpressed in prostate cancer which further increases manifold with tumor grade and stage.[1] The level of PSMA expression increases with tumor dedifferentiation, metastatic disease, and hormone resistance.[2] PSMA was initially detected in the prostate gland, hence the name. However, eventual histopathological studies have shown its expression in salivary glands, duodenal epithelium, lacrimal glands, proximal tubule cells in the kidney, and tumor-associated vascular endothelium.[3,4] It is known that PSMA participates in matrix degradation and facilitates integrin signaling and p21-activated kinase activation causing tumor invasion. Role of PSMA in regulating angiogenesis has been postulated; however, its exact mechanism is unknown.[5]

The development of PSMA-targeted small molecule labeled with ^{68}Ga has allowed the molecular imaging of prostate cancer by positron emission tomography (PET). ^{68}Ga-labeled PSMA (also known as ^{68}Ga-PSMA-HBED-CC) since its introduction in the year 2011 has revolutionized the imaging and management of prostate cancer.[6] It is now being increasingly used for whole-body primary staging of intermediate- or high-risk prostate cancer or restaging after biochemical evidence of recurrence (rising prostate-specific antigen levels) in patients with prior radical prostatectomy and/or after radical external beam radiation.[7,8] Perera *et al*. in a meta-analysis showed that ^{68}Ga-labeled PSMA PET/computed tomography (CT) in advanced prostate cancer had a sensitivity of 80% and specificity of 97% on per lesion analysis.[9] For overall bone involvement in patients with prostate cancer, the sensitivity and specificity have been found to be 99%–100% and 88%–100%, respectively.[10] However, with increasing experience of imaging with PSMA-labeled radiotracers, expression of PSMA has been demonstrated in various nonprostatic malignant and nonmalignant conditions leading to potential pitfalls in the interpretation of PSMA-targeted imaging.

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Nevertheless, this drawback may prove beneficial in imaging and therapeutic target for other nonprostatic conditions. Here, we present a few cases showing PSMA expression in unexpected sites encountered during ^{68}Ga-labeled PSMA PET/CT imaging.

Benign Diseases

Meningioma

^{68}Ga-labeled PSMA normally does not show tracer uptake in the normal brain parenchyma providing high precision for the detection of brain metastasis from prostate cancer.[6] Focal ^{68}Ga-PSMA avidity has been reported in few isolated case reports in meningiomas in the past. This tracer uptake may be either due to the PSMA expression in the tumor vasculature or due to the blood pool effect.[11] Although brain metastases from prostate cancer is a rare occurrence, ^{68}Ga-PSMA uptake in the brain should be interpreted with caution and should be correlated with CT/magnetic resonance imaging findings [Figure 1].

Cerebral infarct/hemorrhage

^{68}Ga-labeled PSMA PET/CT provides excellent diagnostic value in the detection of brain metastasis and primary brain tumors, as normal brain parenchyma essentially shows no PSMA tracer uptake in the presence of an intact blood–brain barrier.[12] However, breach in blood–brain barrier may lead to nonspecific tracer accumulation in infarct/hemorrhage site due to increased permeability of tracer as well as the simultaneous occurrence of reparative processes (characterized by neovascularization) at these sites.[13] Hence, visualization of tracer avidity in subacute cerebral infarction on PSMA PET/CT may potentially mimic the brain metastasis [Figure 2].

Lung consolidation

^{68}Ga-PSMA uptake in lung parenchyma has been documented in metastases from prostate cancer and nonprostate malignancies, primary lung cancer, and benign etiologies such as tuberculosis, sarcoidosis, anthracosilicosis, benign lung opacities, and bronchiectasis.[14-18] Although tracer uptake in the nonprostatic malignancies has been attributed to PSMA expression in the tumor neovasculature endothelial cells, uptake in the benign pathologies is likely due to increased capillary permeability caused by infection or inflammation leading to tracer accumulation in the interstitial space. Thus, cautious interpretation of the scan is required, especially in India where infective pathologies such as tuberculosis are endemic which may lead to over staging of the disease [Figure 3].

Gynecomastia

Androgen deprivation therapy is therapeutic treatment for asymptomatic high risk, locally advanced prostate cancer given in isolation or combined with external beam radiotherapy. Androgen deprivation either by medical or surgical castration is known to cause gynecomastia with an incidence as high as 75%. Gynecomastia is the result of an imbalance between estrogens and androgens in breast tissue with a high level of estrogen causing the growth of the breast tissue.[19,20] Although localization of ^{68}Ga-labeled PSMA in the breast parenchyma has been well documented in the neovasculature of breast cancer, it is essential to know that PSMA expression is also seen in gynecomastia [Figure 4].[21,22]

Inferior vena cava thrombus

Prostate cancer is associated with increased risk of thromboembolic disease. The risk of thromboembolic disease increases exponentially with age, and the

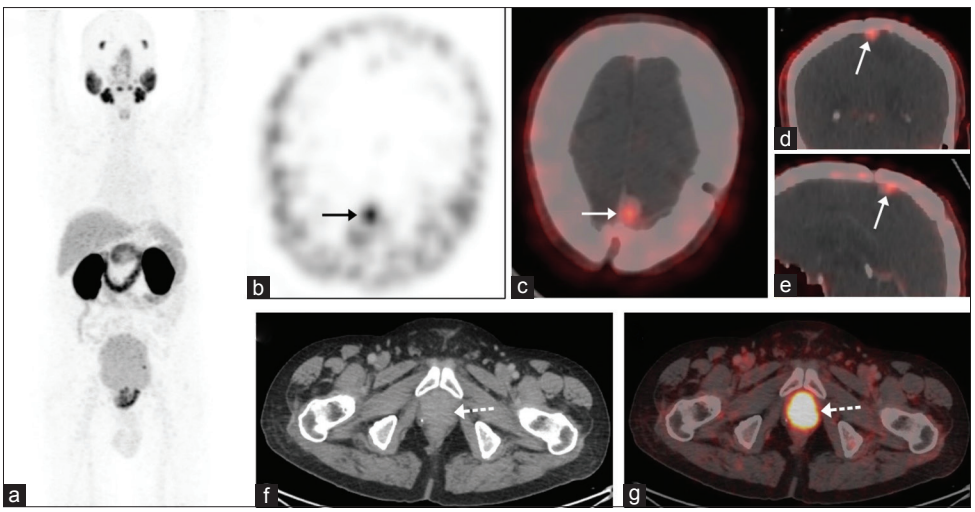

Figure 1: Meningioma: A 75-year-old man a case of adenocarcinoma prostate with raised prostate-specific antigen level (72.1 ng/ml) underwent ^{68}Ga-labeled prostate-specific membrane antigen positron emission tomography/computed tomography imaging (maximum intensity projection image; a) which shows tracer avid (SUVmax 4.1) well-defined dural-based enhancing lesion (~ 1 cm × 0.9 cm) in the parasagittal region in the left parietal cortex (b-e; arrow) suggestive of meningioma. In addition, diffuse increased tracer uptake (SUVmax 27.7) is noted in the enlarged prostate gland from base to apex (f and g; dotted arrow) suggestive of prostate cancer

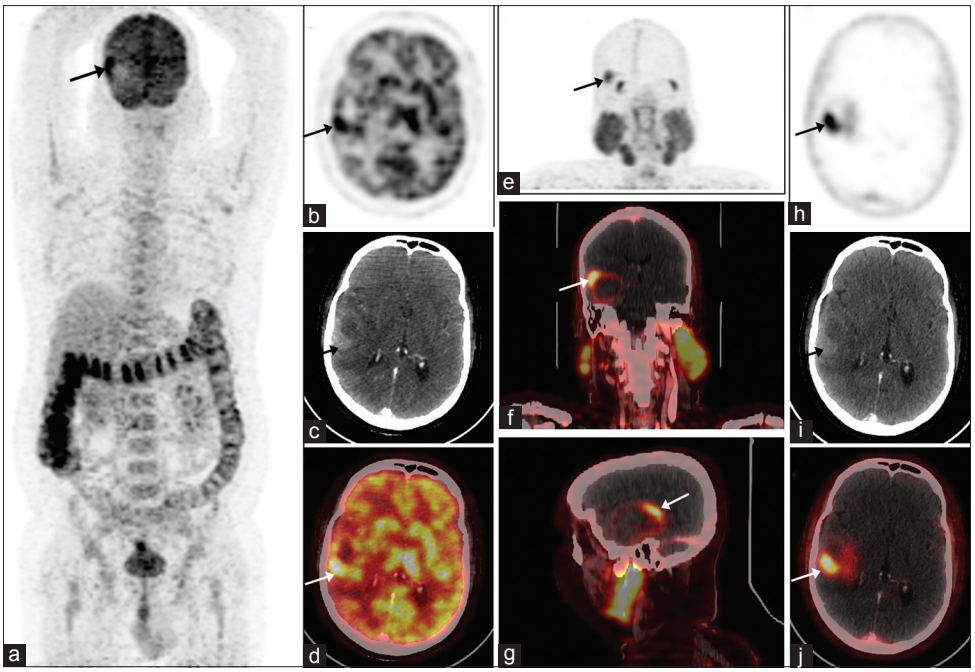

Figure 2: Cerebral infarct/hemorrhage: A 52-year-old male underwent fluorodeoxyglucose positron emission tomography/computed tomography imaging (maximum intensity projection; a) which shows peripherally fluorodeoxyglucose-avid space-occupying lesion in the right temporoparietal region (b-d; arrow). To ascertain the nature of lesion, ^{68}Ga-labeled prostate-specific membrane antigen positron emission tomography/computed tomography imaging (e) was done which shows increased tracer uptake (SUVmax. 8.1) in the enhancing periphery of a ring-enhancing lesion in the right parietal cortex (f-j; arrow) suggestive of metastasis. However, a detailed clinical history of the patient and subsequent magnetic resonance imaging brain localized the tracer uptake to cerebral infarct following intracranial hemorrhage

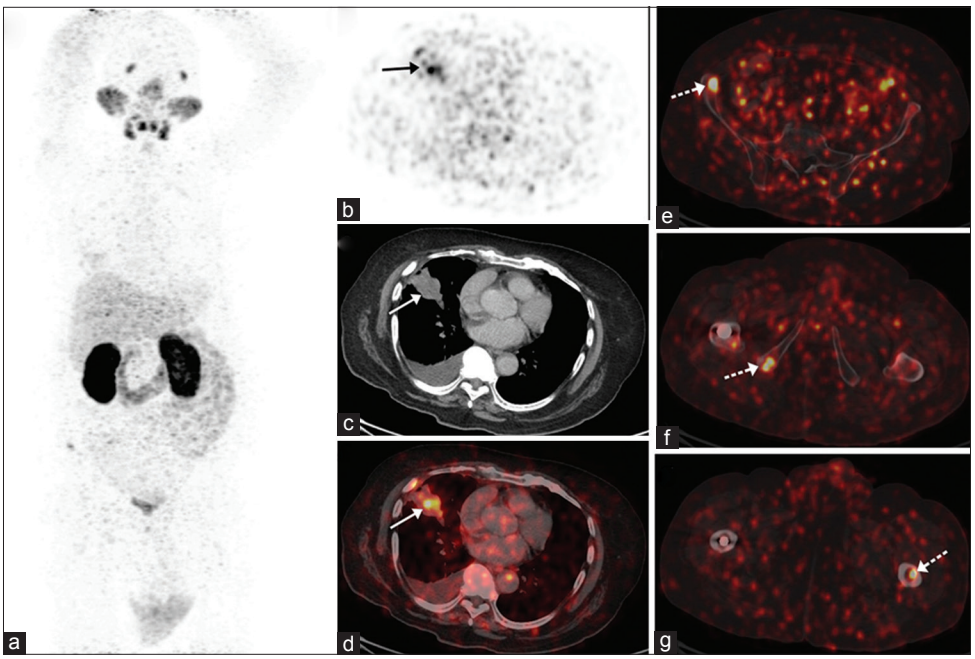

Figure 3: Lung consolidation: ^{68}Ga-labeled prostate-specific membrane antigen positron emission tomography/computed tomography imaging (maximum intensity projection; a) was done in a 73-year-old man, and adenocarcinoma prostate postradiotherapy for disease assessment shows increased tracer uptake (SUVmax 8.1) in a pleural-based consolidation in the right middle lobe (b-d; arrow). Note is made of nontracer avid moderate right pleural effusion. In addition, multiple tracer avid skeleton lesions were also noted suggestive of skeletal metastasis (e-g; dotted arrow)

patient on hormonal therapy has the highest risk of the thromboembolic event.[23] PSMA uptake in thrombi are likely caused by nonspecific tracer binding and are in the part of noise related [Figure 5].[24]

The rapidly expanding role of ^{68}Ga-labeled PSMA PET/CT in prostate cancer needs careful evaluation as its specificity is limited by some false-positive findings as enumerated in the present article [Table 1].[25-43] Knowledge of these

limitations can decrease the potential diagnostic pitfalls and increase the confidence of interpreting physicians.

Malignant Diseases

With the rapid evolution of PET from a pure research tool to an imaging modality with enormous clinical potential, especially in oncology, ^{18}F-fluorodeoxyglucose (FDG) an analog of glucose metabolism has been increasingly used for the staging and restaging of most of the solid tumors. Although most of the solid tumors are FDG avidity, some tumors such as prostate cancer, well-differentiated neuroendocrine tumor, renal cell carcinoma (RCC), hepatocellular carcinoma, and low-grade lymphoma shows low FDG avidity.[44] More clinical research led to the development of various other non-FDG avid tracers. ^{68}Ga easily available from Ge-68/Ga-68 generator was labeled with various peptides and used for imaging of neuroendocrine tumors and prostate cancer, etc. ^{68}Ga-labeled PSMA PET/CT is now considered as the reference standard for prostate cancer imaging.[9,10] As the experience with ^{68}Ga-labeled PSMA PET/CT for prostate imaging is increasing its nonspecific uptake at the other malignancies apart from prostate cancer are being reported. Several isolated case reports have shown incidental PSMA avidity in high-grade gliomas, lung cancer, breast cancer, multiple myeloma, and malignant melanoma, etc. [Table 2].[21,45-66] The ^{68}Ga-labeled PSMA avidity in these various nonprostatic malignancies has been ascribed to the PSMA expression in the endothelial cells of the tumor neovasculature.

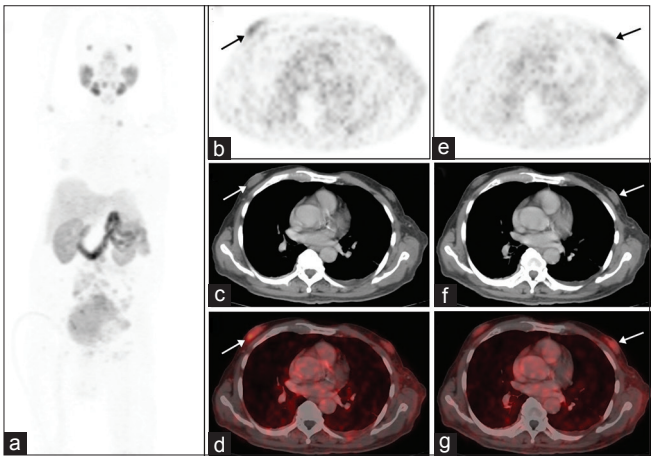

Figure 4: Gynecomastia: A 66-year-old man a known case of adenocarcinoma prostate on hormonal therapy (abiraterone acetate) underwent ^{68}Ga-labeled prostate-specific membrane antigen positron emission tomography/computed tomography imaging (maximum intensity projection; a). Transaxial images (b-g; arrow) showed mild tracer uptake in the bilateral enlarged breast tissue suggestive of gynecomastia

Focal PSMA accumulation at unexpected places needs careful evaluation, as observed in the present series, incidental focal PSMA avidity in the rectum [Figure 6], and

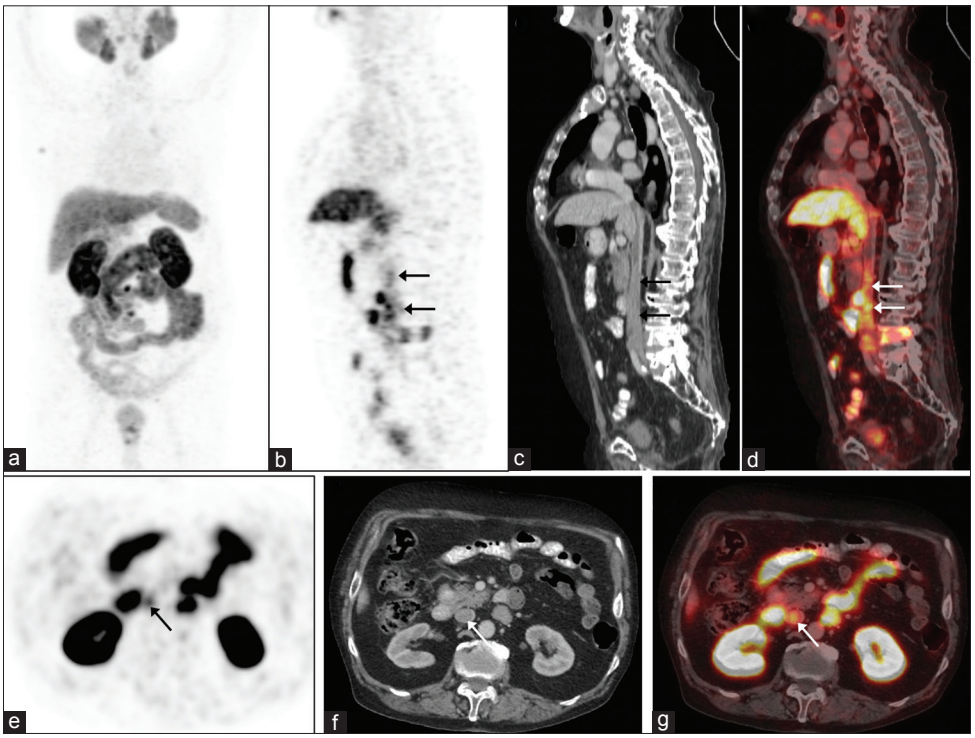

Figure 5: Inferior vena cava thrombus: ^{68}Ga-labeled prostate-specific membrane antigen positron emission tomography/computed tomography imaging (maximum intensity projection; a) in a 71-year-old, a case of adenocarcinoma prostate postradiotherapy, on hormonal therapy with rising prostate-specific antigen level (22 ng/ml) shows tracer avid (SUVmax. 5.3) filling defect in the inferior vena cava (sagittal positron emission tomography, computed tomography imaging, and hybrid positron emission tomography/computed tomography imaging; b-d, arrow). Transaxial positron emission tomography, computed tomography, and hybrid positron emission tomography/computed tomography imaging (e-g; arrow) showing tracer avid filling defect in the infrarenal part of inferior vena cava

thyroid gland [Figure 7]. Histopathological examination of these lesions revealed adenocarcinoma of the rectum and papillary thyroid cancer, respectively. The authors have already reported few other malignancies such as radioactive iodine-refractory thyroid cancer, gastroesophageal carcinoma, signet ring cell, and urinary bladder carcinoma showing PSMA avidity.[51,53]

Among nonprostate cancers studied by ^{68}Ga-labeled PSMA PET/CT, RCC is by far the most abundant entity. Of the published isolated case reports, ^{68}Ga-labeled PSMA PET/CT is found to be superior in terms of lesion detection in comparison to FDG PET/CT and conventional imaging.[67] Moreover, PSMA provides a definite advantage over FDG in the detection of brain metastasis due to the absence of tracer uptake in normal brain parenchyma [Figure 8]. The finding of PSMA expression in these malignancies provides interesting diagnostic and radioligand-based therapeutic options.

Conclusion

^{68}Ga-labeled PSMA PET/CT is generally considered to be highly sensitive and specific for the prostate cancer, but PSMA, as publicized earlier, is not an exclusive marker of prostate cancer. A growing number of reports and present pictorial assay indicate the possibility of false-positive PSMA accumulation in various nonprostatic benign and malignant pathologies. Knowledge of the false-positive tracer uptake of ^{68}Ga-labeled PSMA helps in improving the reporting of ^{68}Ga-PSMA for prostate cancer imaging. Despite the reports on false-positive tracer uptake in nonprostate conditions, ^{68}Ga-labeled PSMA is the most accurate tracer available for imaging prostate cancer. This nonexclusivity of PSMA avidity opens a window to utilize the variety of accessible radioactive PSMA ligands for imaging and possibility of nuclear theranostic in a few other nonprostate malignancies.

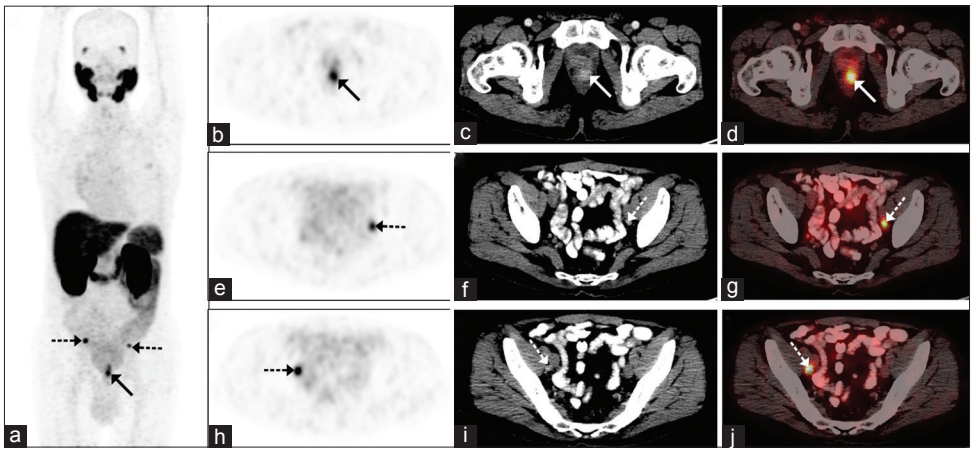

Figure 6: Adenocarcinoma rectum: ^{68}Ga-labeled prostate-specific membrane antigen positron emission tomography/computed tomography imaging images (maximum intensity projection; a) of a 73-year-old man a case of carcinoma prostate (postradical prostatectomy) showing intense tracer uptake in a soft-tissue lesion at 3 o'clock position (b-d; arrow) in the rectum (atypical site for prostate cancer metastasis). In addition, tracer avid external iliac lymph nodes (e-j; dotted arrow) were also noted. Histopathology of the tissue from rectal lesion revealed primary rectal adenocarcinoma

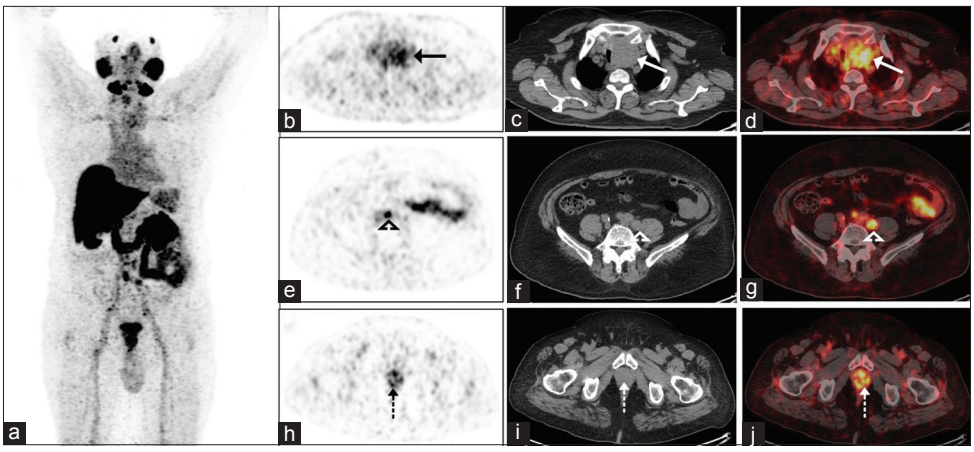

Figure 7: Papillary carcinoma thyroid: ^{68}Ga-labeled prostate-specific membrane antigen positron emission tomography/computed tomography imaging images and maximum intensity projection (a) and transaxial images (b-d; arrow), of a 66-year-old man, a case of adenocarcinoma prostate, showing tracer uptake in the left lobe of thyroid gland. Intense tracer uptake was also seen in a few subcentimetric paraaortic (e-g; arrowhead) and tracer avid lesion in the left peripheral zone of prostate (h-j; dotted arrow) suggestive of carcinoma prostate with nodal metastases. Fine-needle aspiration from thyroid lesion revealed papillary cancer (classical variant)

Table 1: Summary of incidental detection of ^{68}Ga-labelled prostate-specific membrane antigen avidity in nonprostatic benign disease

Author	Tissue origin	Diagnosis
Jain *et al*.[25]	Brain	Meningioma
Noto *et al*.[26]		Cerebral infarction
Vadi *et al*.[27]		Neurocysticercosis
Kanthan *et al*.[28]	Thyroid	Follicular adenoma
Elri *et al*.[29]	Lung	Anthracosis
Bouchelouche and Vendelbo[17]		Benign lung opacities and bronchiectasis
Pyka *et al*.[30]		Reactivated tuberculosis
Malik *et al*.[31]	Breast	Pseudo-angiomatous stromal hyperplasia of breast
Sasikumar *et al*.[22]		Gynaecomastia
Bhardwaj *et al*.[32]	Liver	Haemangioma
Hermann *et al*.[33]		Sarcoidosis
Chan *et al*.[34]	Pancreas	Pancreatic serous cystadenoma
Kobe *et al*.[35]	Spleen	Sarcoidosis
Law *et al*.[36]	Adrenal	Lipid rich adrenal adenoma
Froehner *et al*.[37]	Bone	Paget's disease
De Coster *et al*.[38]		Benign fibrous dysplasia
Vamadevan *et al*.[39]		Vertebral body fracture
Kanthan *et al*.[40]	Miscellaneous	Desmoid tumor
Zacho *et al*.[41]		Intramuscular myxoma
Malik *et al*.[42]		Liposarcoma: Well-differentiated
Vamadevan *et al*.[43]		Peripheral nerve sheath tumor

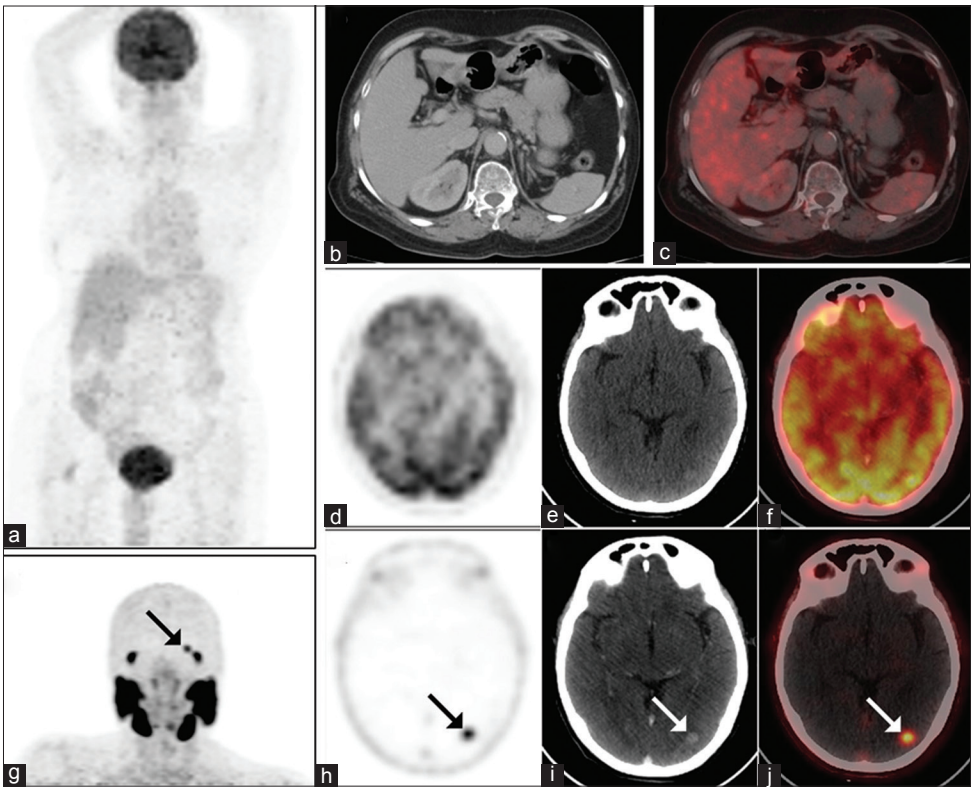

Figure 8: Renal cell carcinoma: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography images (a- maximum intensity projection, b- transaxial CT and c-transaxial fused PET/CT at kidneys level) in a 64-year-old woman with renal cell carcinoma (renal cell carcinoma; postnephrectomy) for surveillance purpose, revealed non-fluorodeoxyglucose-avid suspicious lesion in the left parieto-occipital cortex (d-f). To characterize the lesion, prostate-specific membrane antigen positron emission tomography/computed tomography imaging brain (g) was performed, which revealed a tracer avid lesion in the left parietooccipital cortex (h-j; arrow) suggestive of metastatic disease recurrence

Table 2: Summary of ^{68}Ga-labelled prostate-specific membrane antigen avidity in various non-prostatic malignant disease

Author	Tissue origin	Diagnosis
Salas Fragomani *et al.*[45]	Brain	High grade gliomas
Sasikumar *et al.*[12]		CNS lymphoma
Sager *et al.*[46]	Thyroid	Follicular carcinoma of thyroid
Jena *et al.*[47]		Papillary thyroid carcinoma
Arora *et al.*[48]		Medullary thyroid cancer
Krishnaraju *et al.*[49]	Thymus	Thymoma type B2
Pyka *et al.*[30]	Lung	Primary lung cancer
Shetty *et al.*[50]		Non-small cell lung cancer
Sathekge *et al.*[21]	Breast	Breast carcinoma
Malik *et al.*[51]	Gastrointestinal Tract	GE junction adenocarcinoma
Noto *et al.*[52]		Gastrointestinal stromal tumor
Malik *et al.*[53]		Signet-ring cell carcinoma
Stoykow *et al.*[54]		Rectal adenocarcinoma
Sasikumar *et al.*[55]	Liver	Hepatocellular carcinoma
Alipour *et al.*[56]		Hepatocellular cholangiocarcinoma
Vamadevan *et al.*[57]	Pancreas	Pancreatic neuroendocrine tumor
Arora *et al.*[58]	Adrenal	Adrenocortical carcinoma
Rhee *et al.*[59]	Renal	Clear cell RCC
Sawicki *et al.*[60]		Papillary RCC
Roy *et al.*[61]	Urinary bladder	Adenocarcinoma
Sasikumar *et al.*[62]	Bone	Osteosarcoma
Osman *et al.*[63]	Lymphatic	Lymphoma
Rauscher *et al.*[64]		Multiple myeloma
Anconina *et al.*[65]	Miscellaneous	Malignant melanoma
Froehner *et al.*[66]		Squamous cell carcinoma of penis

RCC: Renal cell carcinoma

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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