Ga-68 PSMA PET-CT – Reporting Document

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Chapter 1: Introduction

Prostate cancer is the most commonly diagnosed cancer and the second most common cause of cancer related deaths in men. Prostate cancer ranges from slowly growing, indolent intraprostatic tumors to rapidly progressive metastasizing and therapy-resistant clones. The 5-year overall survival is 100% for localized and regional disease at primary diagnosis; but only 30% in patients with multiple distant metastases. Hence accurate staging is essential and imaging plays an important role in the staging of prostate cancer. Initial diagnosis and T staging are usually done with transrectal ultrasound guided biopsy and multiparametric magnetic resonance imaging (mpMRI). However, when staging for extraprostatic locoregional / distant metastatic disease, conventional morphological imaging like computed tomography (CT) has limited sensitivity.

Molecular imaging particularly F-18 Flourodeoxyglucose (FDG) positron emission tomography (PET)/CT has become an essential imaging modality in the evaluation of most of cancers in last two decades. FDG PET/CT is of only limited value in the management of prostate cancer because of it's poor sensitivity owing to low glucose metabolism of well differentiated prostate cancer. There is also overlap of FDG uptake in normal prostate, benign prostate hyperplasia, prostatic inflammation (prostatitis and abscess) and prostate cancer, leading to poor specificity. In addition there is interference by high urinary tracer (FDG) activity in bladder. Hence various radiotracers (Table 1) have been tried in the evaluation of prostate cancer.

Table 1. Radiotracers tried for the evaluation of prostate cancer

S. No	Mechanism of uptake	Radiotracer(s)
1.	Glucose metabolism	F-18 FDG
2.	Cell membrane synthesis	C-11 choline/ F-18 fluorocholine
3.	Fatty acid synthesis	C-11 acetate/ F-18 fluoroacetate
4.	Amino acid metabolism/ transport	F-18 FACBC (fluciclovine), C-11 methionine, C -11 5-hydroxytryptophan (HTP)
5.	Cell proliferation	F-18 fluorothymidine (F-18 FLT)/ F-18 fluoro-methyl-arabinofuranosyluracil (F-18 FMAU)
6.	Androgen Receptor binding	F-18 16β-fluoro-5α-dihydrotestosterone (F-18 FDHT)
7.	Gastrin-releasing peptide receptor (mammalian bombesin) binding	Ga-68 GRP antogonist (Ga-68 RM2)
8	Prostate-Specific Membrane Antigen (PSMA) binding	Monoclonal antibodies: 89Zr - J591/ In-111 capromab pendetide (Prostascint) Ligands/Inhibitors: Ga-68 PSMA(PSMA-11/ PSMA-617/ PSMA-I&T), F-18 PSMA 1007, F-18 DCFBC/ F-18 DCFPyL
9	Bone Matrix imaging	F-18 Sodium fluoride (F-18 NaF)/ Tc- 99m methylene diphosphonate (Tc-99m MDP)

Of these Ga-68 labelled PSMA PET ligands have shown most encouraging results in terms of sensitivity and are widely used in patients with prostate cancer. PSMA, also known as glutamate carboxypeptidase II is a type II transmembrane glycoprotein, encoded by the folate hydrolase 1 (*FOLH1*) gene. This is expressed in normal prostate tissue and is overexpressed in prostate cancer. PSMA ligands are small molecules that bind to the extracellular active centre of PSMA and have the advantage of higher binding affinity, internalization and rapid plasma clearance, leading to high tumor to background ratio compared to other PET agents.

- Monitoring of systemic treatment in metastatic prostate cancer.
- Imaging before PSMA radioligand therapy (mainly in metastatic castration-resistant prostate cancer) and its response assessment
- Before radiotherapy planning of prostate cancer
- Guiding focal therapy (such as ablation by radiofrequency, laser, cryotherapy and electroporation etc.)

Chapter 2: Indications

- Detection of disease sites in prostate cancer patients with biochemical recurrence (even with serum PSA level of 0.2 ng/ml).
- Primary staging of patients with high-risk prostate cancer (Gleason score >7, PSA >20 ng/mL, clinical stage T2c – 3a) in whom the likelihood of lymph node and bone metastases is increased.
- Targeted biopsy after previous negative biopsy in patients with high suspicion of prostate cancer.

In addition to prostate cancer, PSMA is overexpressed in neovasculature of various non prostatic malignancies. Hence it may be useful in following malignancies where FDG has limited role.

- Hepatocellular carcinoma
- Renal cell carcinoma (clear cell variant)
- Recurrence evaluation of gliomas

Chapter 3: Reporting Essentials

3.1 Clinical Details

1. Diagnosis: Type of prostate cancer (acinar adenocarcinoma/ poorly differentiated carcinoma / carcinoma with neuroendocrine differentiation/ small cell carcinoma etc)
2. Indication for imaging study: Primary staging /Detection disease sites in biochemical recurrence/ treatment response assessment/ Guiding appropriate biopsy site for diagnosis/ evaluation to plan PSMA radioligand therapy
3. Gleason score
4. Serum Prostate specific antigen (PSA) levels - including PSA kinetics
5. Previous treatment history - e.g. prostatectomy, external beam radiation therapy, androgen deprivation therapy (ADT) or other androgen receptor (AR)-targeted treatments, chemotherapy, bone pain palliation with beta emitters , radium-223 or PSMA-targeted radioligand therapy.
6. Relevant symptoms (bone pain, frequent urination, nocturia, hematuria, dysuria, impotence, erectile dysfunction or painful ejaculation)
7. Previous imaging findings (for comparison/ correlation)
8. Relevant co-morbidities (Non-prostate malignancies, Allergies and Renal failure)
9. Serum creatinine/ estimated glomerular filtration rate (if intravenous contrast is used)

3.2 Procedure Details:

1. Radiopharmaceutical:
2. Dose: MBq / mCi
3. Site and route of Injection:
4. Duration between time of injection to Imaging: _____ minutes
5. Regions Scanned:
6. Scanner used:
7. Usage of contrast: Oral/ intravenous/ rectal:
8. Usage of any Diuretics
9. Delayed imaging if any
10. Reconstruction and attenuation correction methods used:

11. Any allergic/ adverse events encountered during the study period.

3.3 Findings:

1. Identification of scan: by recognizing physiological tracer distribution (high-intensity Ga-68 PSMA uptake is seen in the lacrimal, parotid and sub mandibular glands as well as small intestine, primarily in duodenum. Moderate-intensity uptake is seen in the liver and spleen).
2. Quality checking: Check whether the quality of scan is adequate and interpretable. Suspected radiopharmaceutical impurity or various artefacts such as motion, halo (due to high activity in the urinary system), truncation and attenuation artefacts if any, should be reported.
3. Mention site of abnormal increased PSMA uptake and intensity (including standardized uptake value - SUV)
4. Corresponding abnormalities in CT (including size of the lesion) and further characterization and extent of disease site, if contrast enhanced CT was performed
5. Primary site: Location of tumor in prostate (apex, mid zone or base and whether it involves peripheral zone or central zone etc); involvement of adjacent structures like seminal vesicles, urinary bladder, rectum etc.
6. Lymph nodal metastases: Location and size of lymph nodes and intensity of uptake. Any changes like necrosis/ calcification to be noted. Perinodal fat standing/ adjacent structure involvement if any to be noted.
7. Visceral metastases: Liver, lungs etc - number, location and size of lesions with intensity of uptake.
8. Bone metastases: Sites and intensity of abnormal uptake with corresponding changes on CT (sclerotic/ lytic/ mixed lytic and sclerotic/ no abnormality). Any pathological fracture of bones/ collapse of vertebrae/ associated soft tissue component/ compression on important structures like brain or spinal cord if any should be reported.
9. Reporting of incidental findings (PSMA avid as well as PSMA non avid), likely unrelated to prostate cancer should be mentioned.

3.4 Conclusion:

1. PSMA avidity and extent of primary / recurrent lesion in the prostate/ prostatic bed.

2. PSMA avidity and location of metastatic lymph nodes.
3. PSMA avidity, number (approximate; solitary, few or multiple) and location of visceral (lung/ liver etc) metastases.
4. PSMA avidity, number (approximate; solitary, few or multiple) and location of bone metastases along with pathological fracture/compression of vital structures if any.
5. Mention the incidental but important findings if any and also suggest should there any further investigation be needed.
6. If there are previous images available for comparison, it should be compared and opined.
7. If there is any uncertainty of nature of a lesion / alternate diagnosis is suspected, suggest appropriate (laboratory/ imaging/ histopathological) investigations.

Chapter 4: Artefacts and Pitfalls

4.1 Normal Variants

Normal variants in Ga-68 PSMA PET-CT are:

1. Ganglia uptake
2. Gall bladder uptake
3. Gynaecomastia
4. Uptake in calcified choroid plexus

4.2 False Positive Findings:

Common false positive ^{68}Ga-PSMA PET/CT findings in prostate cancer are:

1. In spite of the term "prostate specific" PSMA is expressed in a variety of normal tissues, neovasculature, inflammation/ infection and other tumor types, both benign and malignant which might result in false positivity.
2. Excreted urinary tracer activity might interfere in the evaluation of prostate/ prostatic bed lesions or pelvic lymph nodes (Further imaging after infusion of normal saline and/or administration of diuretics may be useful in such cases)
3. Physiological PSMA uptake in various organs (eg; celiac/ presacral ganglionic uptake may be mistaken as lymph nodal metastases)
4. Treatment (radiotherapy / surgery) related inflammatory changes
5. Flare phenomenon following androgen deprivation therapy can lead to false positives.
6. Various artefacts like misregistration artefact, partial volume effect, attenuation correction artefact and truncation artefact can result in false positives.

4.3 False Negative Findings:

Common false negative ^{68}Ga-PSMA PET-CT findings in prostate cancer are:

1. PSMA PET CT may be falsely negative in a small number of prostate cancer patients such as poorly differentiated type with neuroendocrine differentiation or small cell carcinoma.
2. Even though it detects many sub-centimetric lesions, very tiny lesions/ lymph nodes may be falsely negative.

3. Certain visceral metastases (eg; liver) may be obscured due to relatively high background activity as well possible low PSMA expression in advanced metastatic disease
4. Halo effect around organs with intense tracer activity (eg; kidneys/ urinary bladder) may obscure adjacent lesions.
5. Artefacts like misregistration artefact can lead to falsely low uptake.

It should be noted that SUV values in PSMA PET/CT has not yet been validated for treatment response monitoring in prostate cancer patients. Changes in size of lesions as well as extent and intensity of PSMA uptake should carefully be interpreted along with clinical and biochemical parameters. Other factors such as flare phenomenon and tumor sink effect (in the context of decreasing PSMA uptake in previously seen dominant avid lesions) have to be kept in mind while interpreting apparently new small lesions on PSMA PET during treatment response evaluation.

Causes of the false negative and false positive imaging are summarized in table 2:

Table 2: Cause of false negative and false positive ^{68}Ga-PSMA PET/CT in prostate carcinoma

False Negative	False Positive
• Low PSMA expression • Poorly differentiated prostatic carcinoma • Partial volume effect due to small size • High activity in the background (liver or urinary bladder) • Certain visceral metastases (eg; liver) • Halo effect around organs with intense tracer activity.	• Prostatitis • Paget's disease • Sarcoidosis • Tuberculosis • Wegener's granulomatosis • Bone fractures • Subacute stroke • Urinary activity • Fascitis

Normal physiological distribution of Ga-68 PSMA on a PET-CT is shown in figure 1.

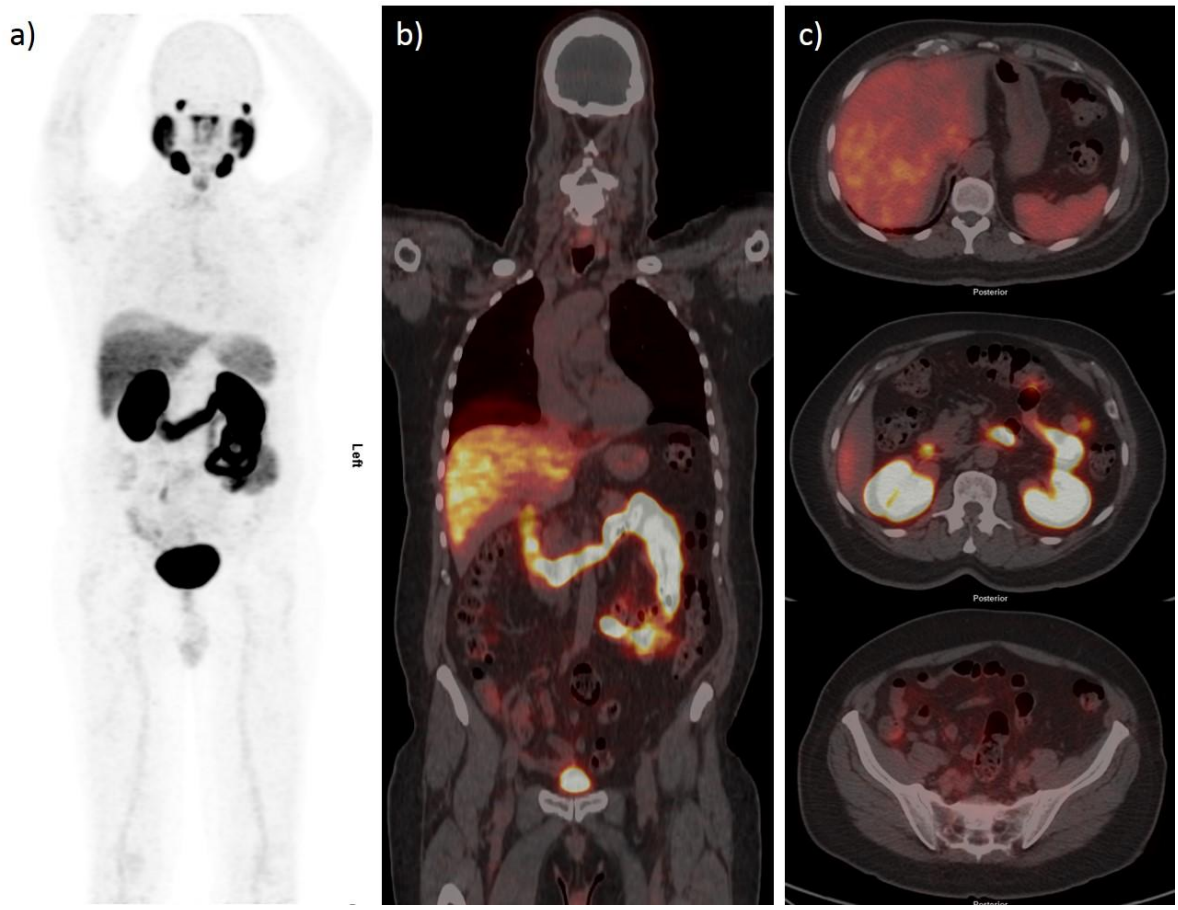
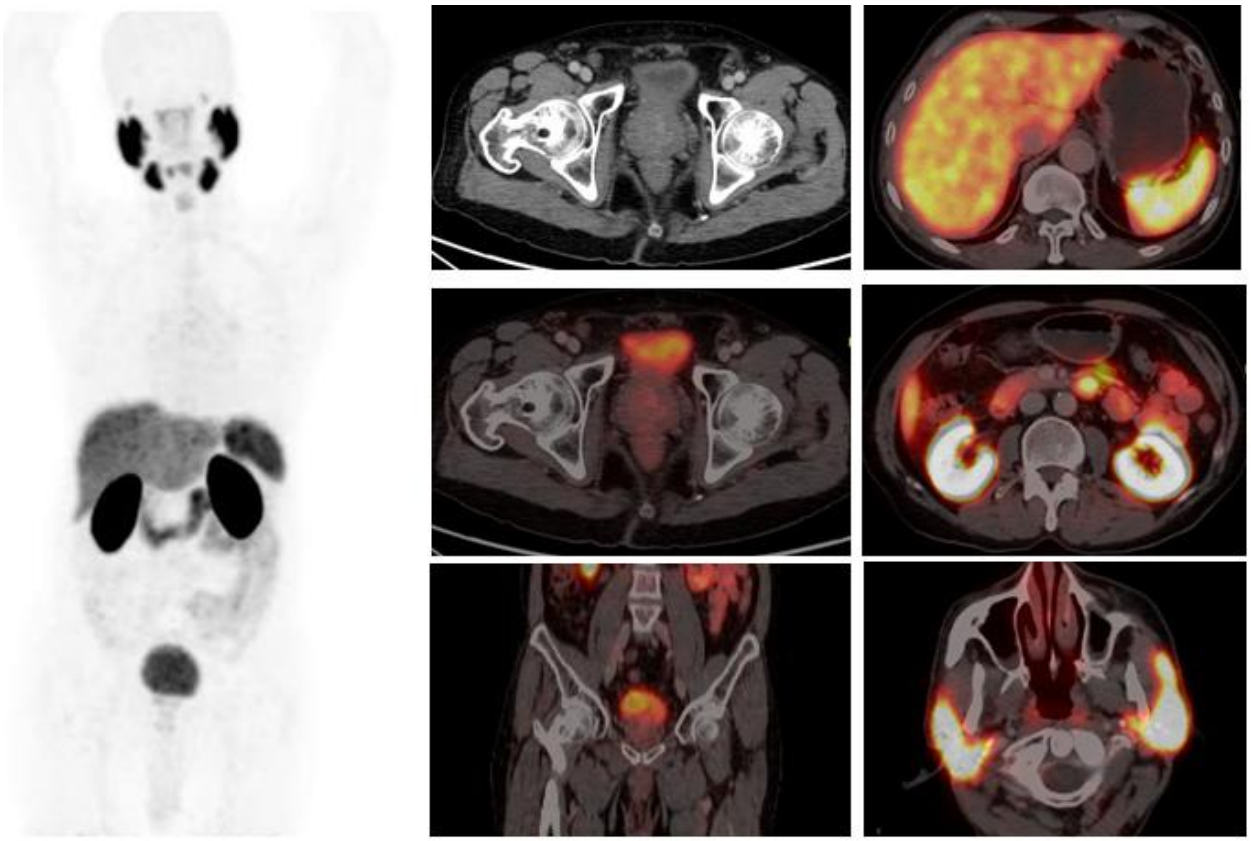


Figure 1: A 74-year-old male is a known case of prostate cancer with Gleason score 7 (4+3) treated with prostatectomy 2years back. Now complaining of back pain with slow rising PSA 0.24ng/ml.^{68}Ga-PSMA-11 PET-CT performed after injection of 3.6 mCi ^{68}Ga-PSMA-11. a) Anterior MIP b) Coronal c) Transaxial fused PET-CT images show physiological activity within the lacrimal glands, the parotid and submandibular glands, the nasal region, the kidneys and the urinary bladder. A mild to moderate tracer localization is noted at the duodenum and the small bowel representing physiological uptake. No abnormal tracer localization seen. Findings are negative for any disease recurrence.

Chapter 5: Sample Reports:

5.1 Sample Report No. 1:



Clinical details:

A 65-year-old male had lower urinary tract symptoms for 6 months duration with elevated serum prostate specific antigen (PSA) level (7.2 ng/ml). Multiparametric MRI showed PIRADS -3 lesions in peripheral zones of prostate on both sides. Core biopsy of prostate was negative for malignancy. Had rising S. PSA level (9.3 ng/ml) 3 months later. The patient was referred for Ga-68 PSMA PET CT to look for possible site for prostatic primary malignancy.

Procedure:

Whole body PET scan (vertex to mid-thigh) with contrast (oral and intravenous) enhanced CT was performed using a PET CT scanner 60 minutes after intravenous injection of 5 mCi of ^{68}Ga PSMA. Attenuation correction of PET images was performed. The standardized uptake value (SUV) was calculated based on body weight and expressed in g/ml.

Findings:

No abnormal increased PSMA uptake is seen in the bulky prostate, which shows heterogeneous enhancement on CT.

No abnormal PSMA avid lymph nodes are seen.

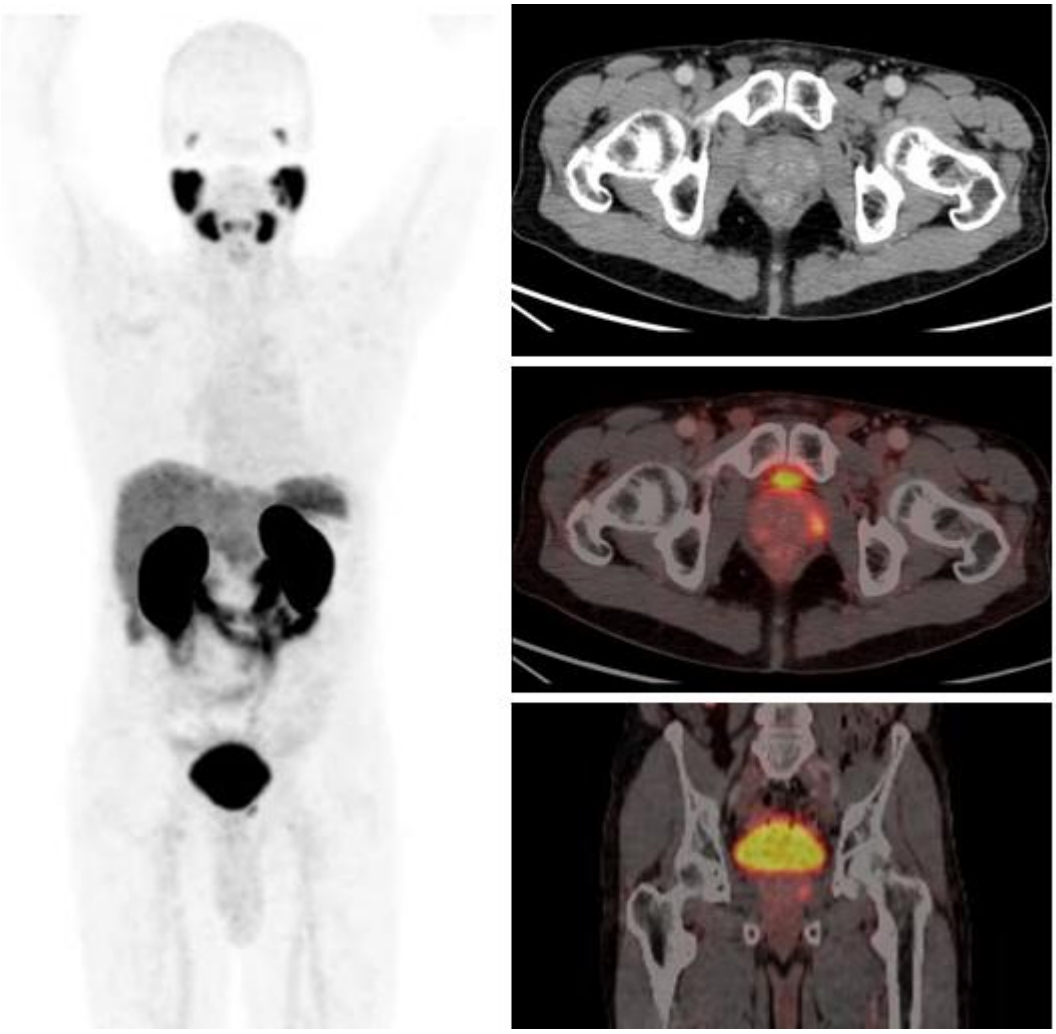
Physiological tracer distribution is seen in bilateral lacrimal, parotid and sub mandibular glands, kidneys, small intestine, spleen and liver.

No abnormal increased PSMA uptake/ lesion identified elsewhere in the whole body survey, particularly in liver, lungs and bones.

Conclusion:

- No evidence of PSMA avid lesion in the bulky prostate.
- No abnormal PSMA avid lesion identified in the whole-body survey.

5.2 Sample Report No. 2:



Clinical details:

A 63-year-old male presented with increased frequency of micturition for 3 months duration and elevated serum prostate specific antigen level (8.25 ng/ml). Biopsy of prostate showed prostatic adenocarcinoma (Gleason's score of 4 + 3=7/10) in left lobe. The patient was referred to Ga-68 PSMA PET CT for staging.

Procedure:

Whole body PET scan (vertex to mid-thigh) with contrast (oral and intravenous) enhanced CT was performed using a PET CT scanner 60 minutes after intravenous injection of 5 mCi of 68Ga PSMA. Attenuation correction of PET images was performed. The standardized uptake value (SUV) was calculated based on body weight and expressed in g/ml.

Findings:

Focal PSMA avid enhancing lesion measuring 15 x 8mm with SUV Max: 5.7 is seen in left posterolateral aspect of prostate gland at mid zone.

No abnormal PSMA avid lymph nodes are seen.

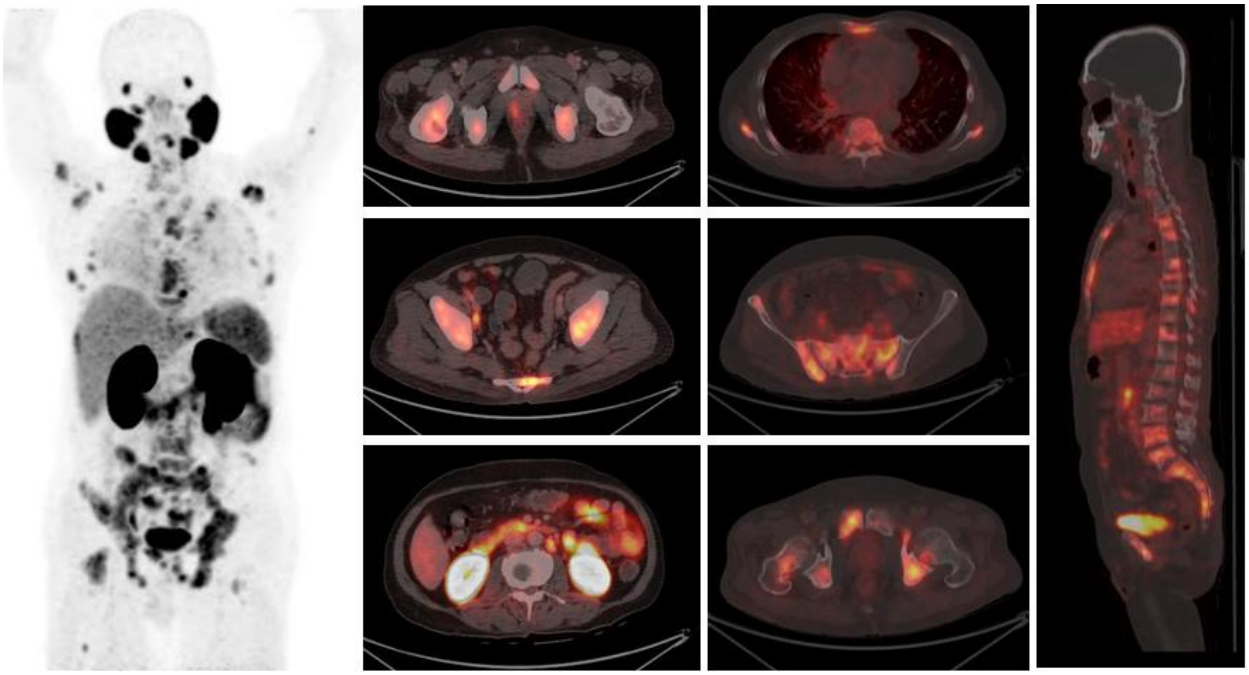
Physiological tracer distribution is seen in bilateral lacrimal, parotid and sub mandibular glands, kidneys, small intestine, spleen and liver.

No abnormal increased PSMA uptake/ lesion identified elsewhere in the whole body survey, particularly in liver, lungs and bones.

Conclusion:

- Focal PSMA avid enhancing lesion in left posterolateral aspect of prostate gland at mid zone – primary malignancy.
- No evidence of PSMA avid lymph nodal or distant metastases in the whole-body survey.

5.3 Sample Report 3:



Clinical details:

A 58-year-old male diagnosed to have prostatic adenocarcinoma (Gleason's score of 4 + 3=7/10). Serum prostate specific antigen level was 210 ng/ml. The patient was referred to Ga-68 PSMA PET CT for staging.

Procedure:

Whole body PET scan (vertex to mid-thigh) with contrast (oral and intravenous) enhanced CT was performed using a PET CT scanner 60 minutes after intravenous injection of 5 mCi of 68Ga PSMA. Attenuation correction of PET images was performed. The standardized uptake value (SUV) was calculated based on body weight and expressed in g/ml.

Findings:

Focal increased PSMA uptake (SUV Max: 4.4) is seen in right posterolateral aspect of prostate gland at apex.

Multiple PSMA avid enlarged lymph nodes are seen in paraaortic, aortocaval, pericaval, bilateral common & internal iliac as well as right external iliac regions; largest lymph node measuring 23 x 19mm with SUV Max: 7.4 in right external iliac region.

Multiple PSMA avid sclerotic lesions are seen in following bones;

Skull base (SUV Max: 8.0 near right occipital condyle).

Multiple cervical, thoracic & lumbar vertebrae (with collapse of D2, D7, D8 & L2 vertebrae; SUV Max: 5.1 in D3 vertebra).

Multiple bilateral ribs (SUV Max: 5.2 in right 8th rib).

Sternum (SUV Max: 8.6) & bilateral scapulae (SUV Max: 7.5 on left side).

Sacrum (SUV Max: 9.0) & multiple pelvic bones (SUV Max: 8.2 in left ischium).

Bilateral humeri (SUV Max: 5.0 on right side) & bilateral femora (SUV Max: 6.7 on right side).

Physiological tracer distribution is seen in bilateral lacrimal, parotid and sub mandibular glands, kidneys, small intestine, spleen and liver.

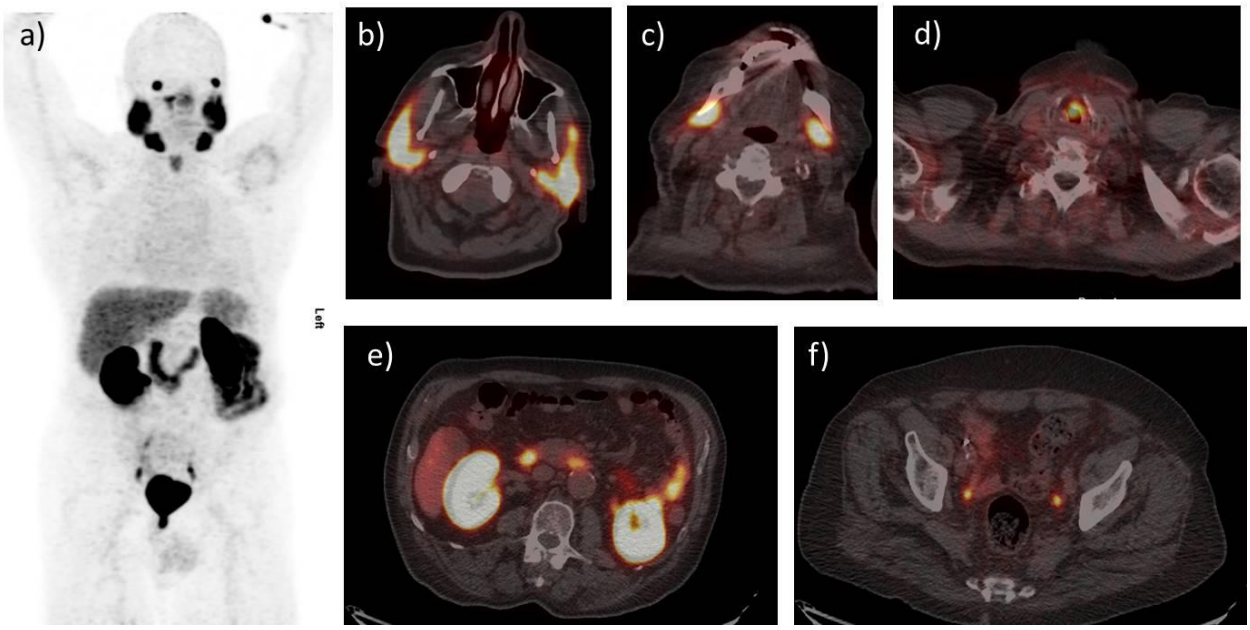
No abnormal increased PSMA uptake/ lesion identified elsewhere in the whole body survey.

Conclusion:

- Focal increased PSMA uptake in right posterolateral aspect of prostate gland at apex –primary malignancy.
- Multiple PSMA avid enlarged lymph nodes in paraaortic, aortocaval, pericaval, bilateral common & internal iliac as well as right external iliac regions – metastases.
- Multiple PSMA avid sclerotic lesions involving both axial and appendicular skeleton as described above (with collapse of D2, D7, D8 & L2 vertebrae) – extensive metastases.
- No other abnormal PSMA avid disease identified in the whole-body survey.

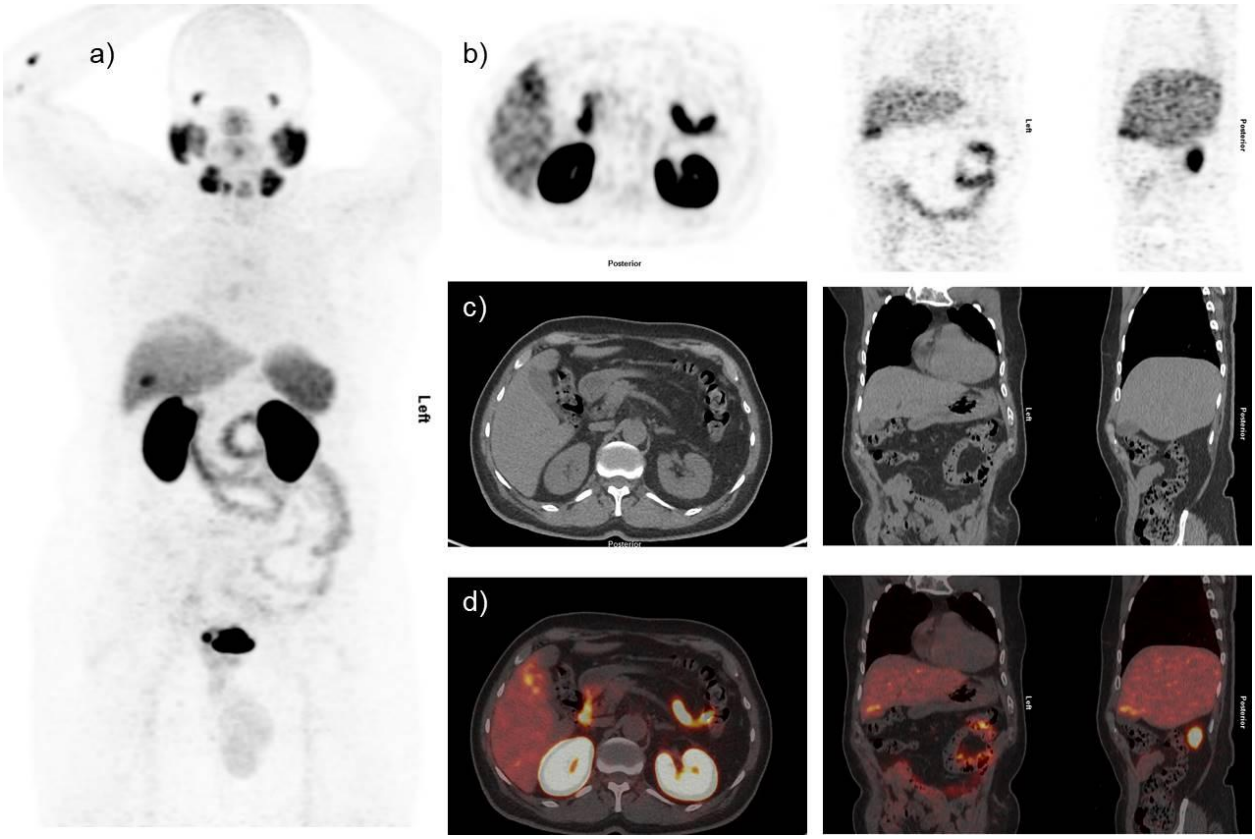
Chapter 6: Image Gallery:

6.1 Case 1:



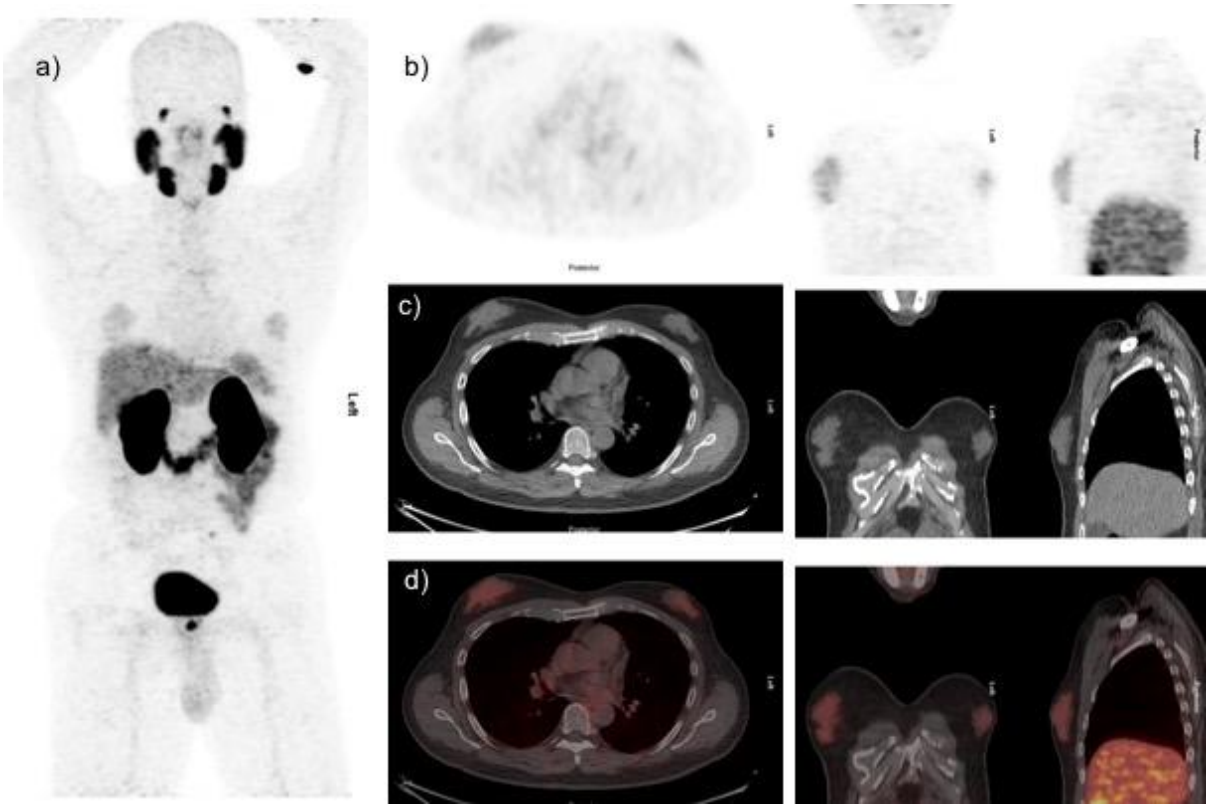
An 85-year-old male with prostate cancer treated with radical prostatectomy in 1998. Recently presented with mild rise in PSA 0.12 ng/ml. ^{68}Ga-PSMA-11 PET/CT is performed after intravenous injection of 2.47 mCi of ^{68}Ga-PSMA-11. a) MIP images of ^{68}Ga-PSMA-11. Physiological activity identified within the lacrimal glands, the parotid (b) submandibular glands, larynx (d), the nasal region, the kidneys and the urinary bladder (e-f). A mild to moderate tracer localization is noted at the duodenum and the small bowel.

6.2 Case 2:



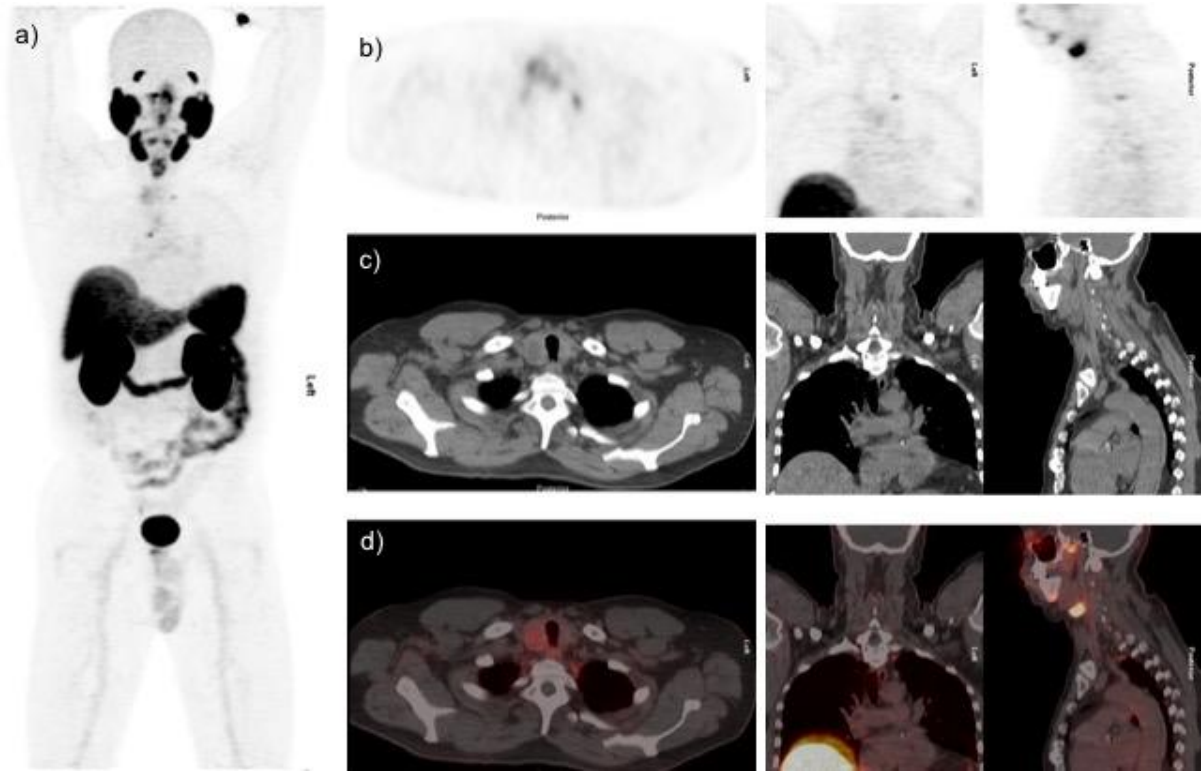
A 63-year-old male is a known case of prostate cancer. ^{68}Ga-PSMA-11 PET-CT is performed after intravenous injection of 2.8 mCi of ^{68}Ga-PSMA-11 for assessing the prostate tumor expression. MIP images of 68-Ga PSMA show focal area of increase tracer uptake at gallbladder fossa. Findings are due to normal variant uptake in the gallbladder.

6.3 Case 3:



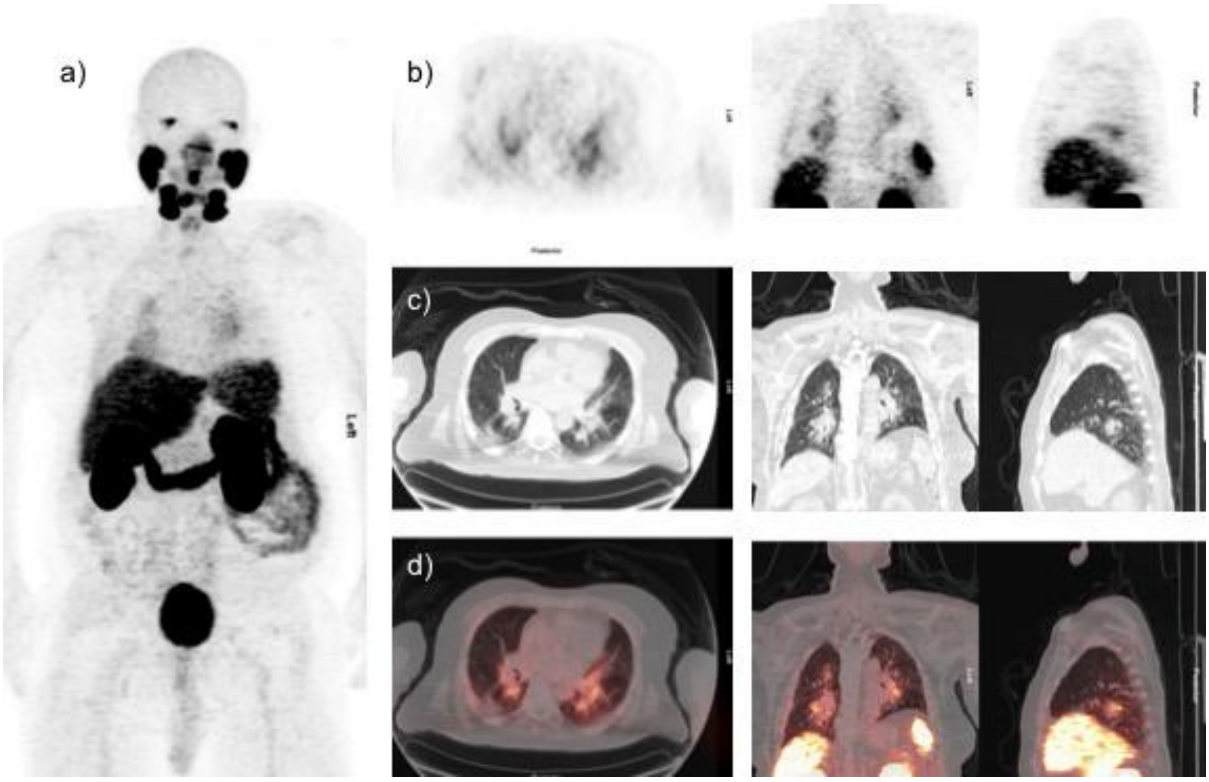
A 69-year-old male with prostate cancer on hormonal therapy since 6years. Recent PSA is 1.12 ng/ml. a) ^{68}Ga-PSMA-11 MIP image shows mild diffuse increase tracer uptake in the bilateral chest region. b-d) There is hyperdense soft tissue density with mild activity noted at bilateral breast which is likely related to hormonal imbalance caused by castration treatment (gynecomastia).

6.4 Case 4:



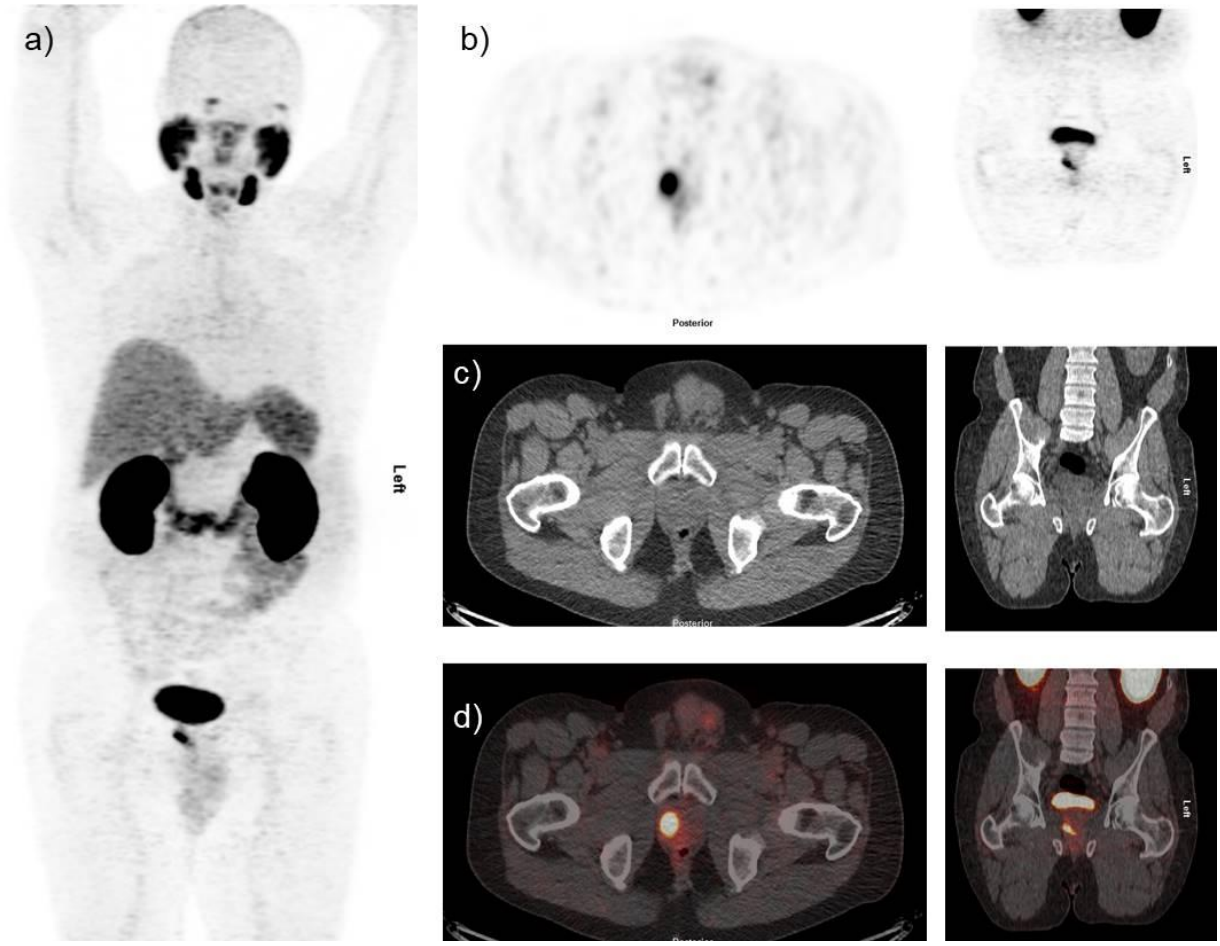
A 65-year-old male is case of prostate cancer with Gleason score of (4+3). PSA is 7.4ng/ml. a) MIP images of ^{68}Ga-PSMA-11 b-d) Increased uptake of SUV max 3.0 are seen at bilateral thoracic inlet region at D1 level, likely uptake at cervicothoracic, stellate ganglia and D4 vertebral level with SUV max 5.7. Uptake at D1 and D4 vertebral region are likely due to normal variant uptake at sympathetic ganglia. Advised follow-up scan.

6.5 Case 5:



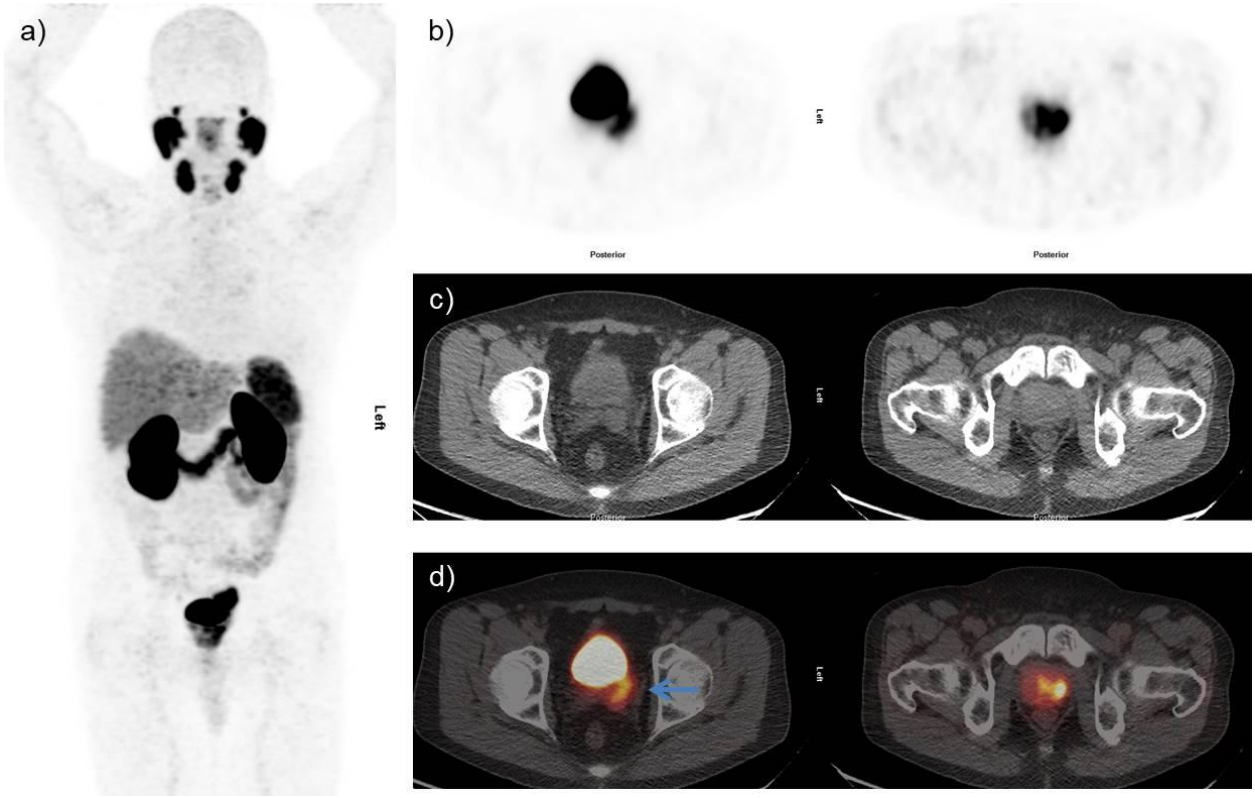
A 72-year-old male with prostate cancer, with slow rising PSA 0.04ng/ml. ^{68}Ga-PSMA-11 PET-CT is performed after intravenous injection of 2.55 mCi of ^{68}Ga-PSMA-11. a) MIP PET images of ^{68}Ga-PSMA-11 show diffuse increase tracer uptake also noted in the bilateral hilar and chest region. b-d) ^{68}Ga-PSMA-11 PET-CT show increase tracer uptake at bilateral hillar and inferior bronchial region, corresponding show diffuse infiltration and atelactatic bands. Findings are likely due to infective process.

6.6 Case 6:



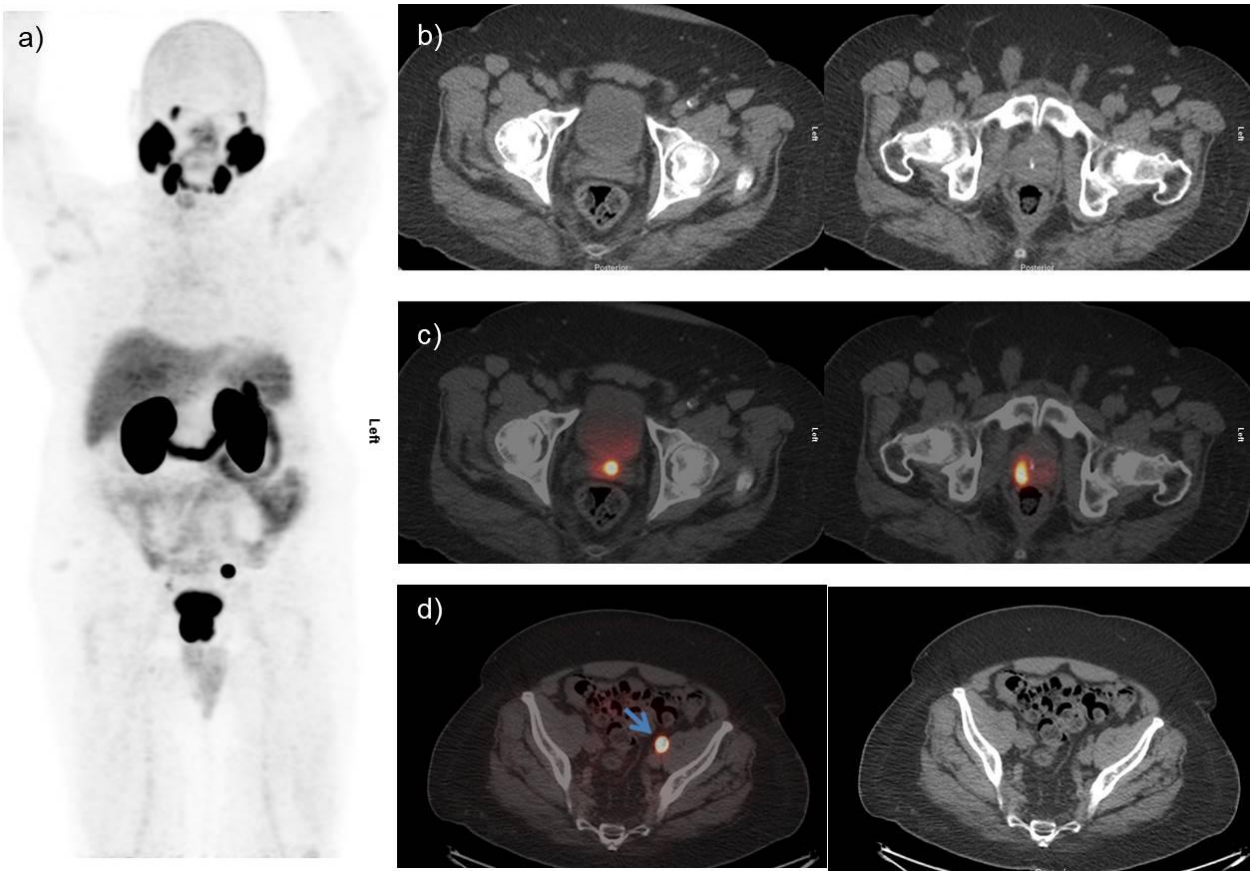
A 63-year-old male is a new case of prostate cancer with Gleason score of (4+4). PSA is 13 ng/ml. a) ^{68}Ga-PSMA MIP and b-d) PET-CT images show increase tracer uptake of SUV max 18.0 in the right posterior peripheral zone of prostate gland. Increased PSMA expression is seen at primary prostate lesion with no distant metastatic lesion.

6.7 Case 7:



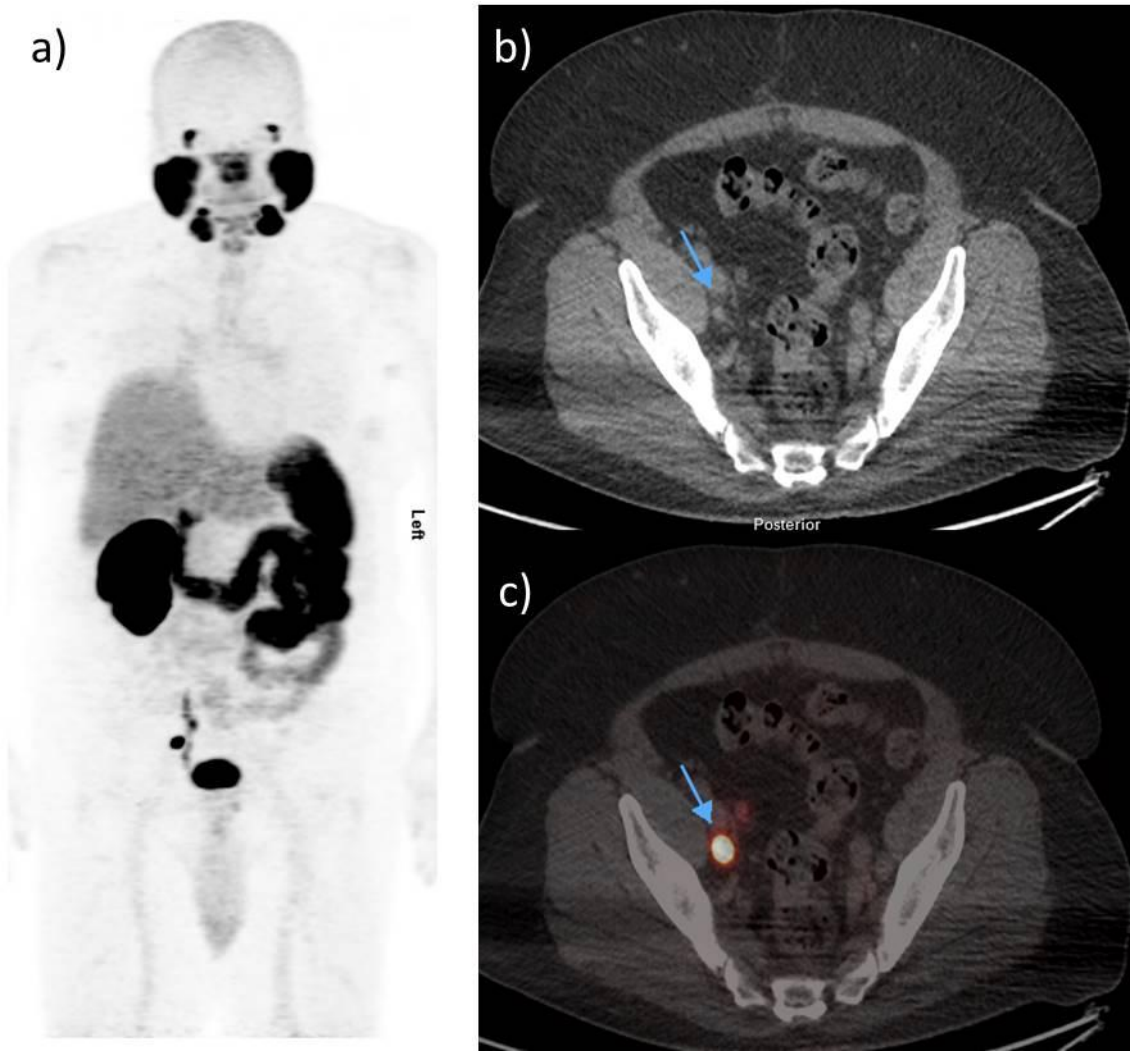
A 66-year-old male is a new case of high-risk prostate cancer. a) ^{68}Ga-PSMA MIP and b-d) PET-CT images demonstrate increase uptake of SUV max 30.5 at left peripheral zone of prostate gland extending to left seminal vesicle with SUV max 8.9 (arrow). Increased PSMA expressions seen at primary prostate lesion with possible extension to left seminal vesicle. There is no evidence of distant metastases.

6.8 Case 8:



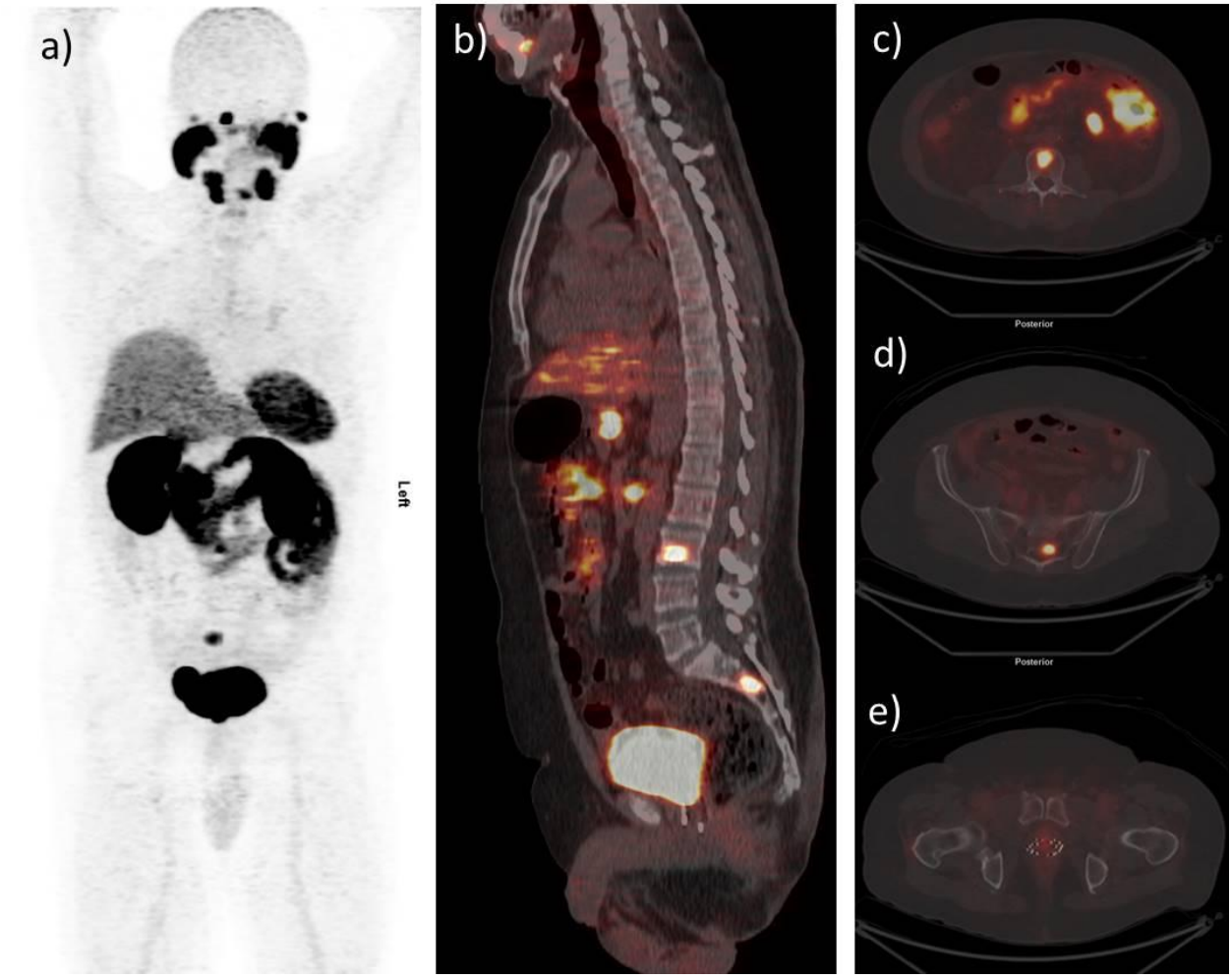
A 70-year-old male is a new case of prostate cancer with Gleason score of (4+4). PSA is 71.3 ng/ml. a) ^{68}Ga-PSMA-11 MIP image b-d) PET-CT images show increase uptake of SUV max 25.4 at right peripheral zone of prostate gland. Seminal vesicle show focal intense uptake of SUV max 16.8. Increase tracer uptake is also noted at left external iliac lymph node (arrow). Increased PSMA expressions are seen at primary prostate lesion, with local extension to seminal vesicle. ^{68}Ga-PSMA-11 avid left external iliac lymph node is consistent with lymph node metastasis.

6.9 Case 9:



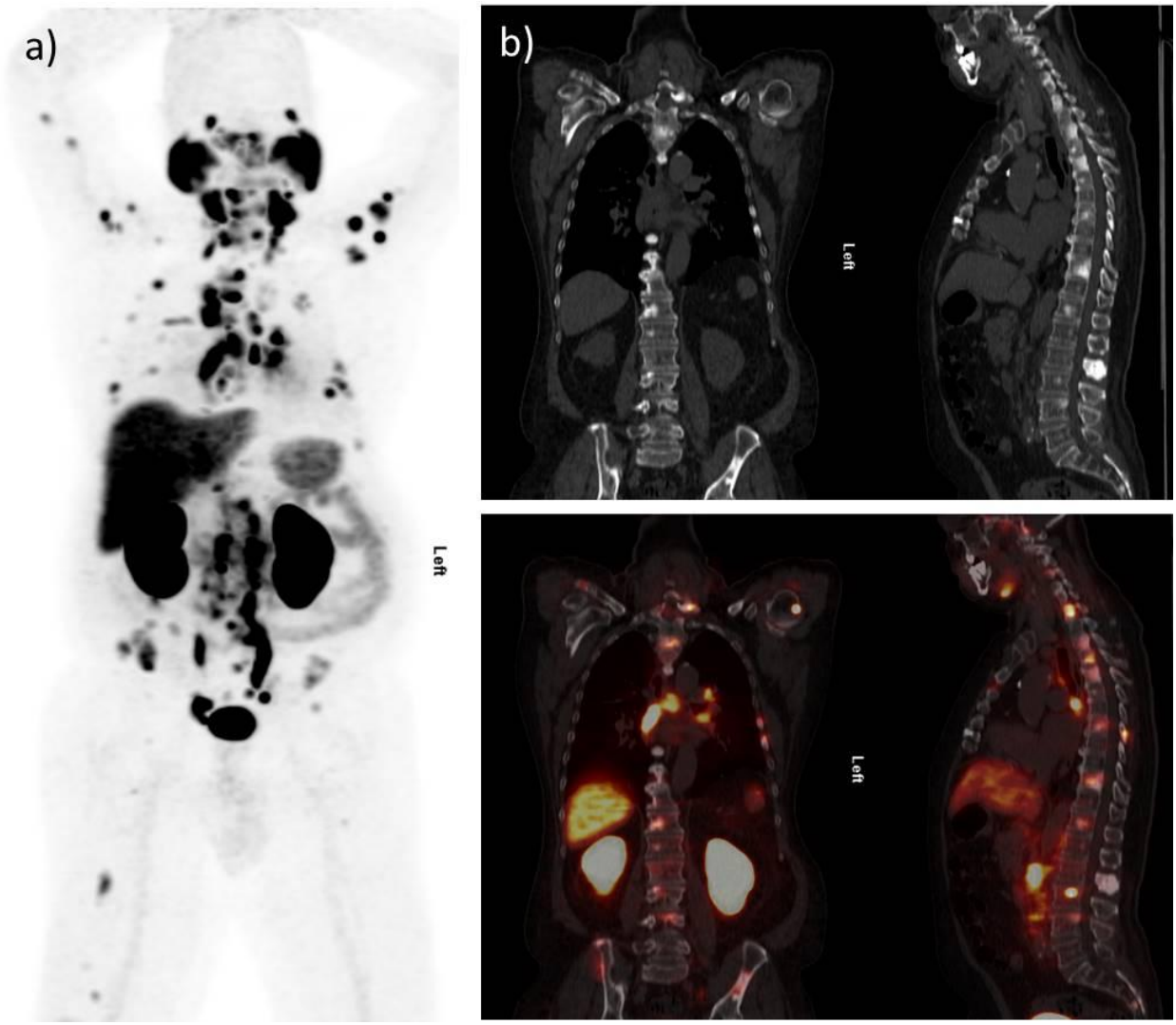
A 58-year-old male is case of prostate cancer treated with radiotherapy in 2011. Now presented with rising PSA 2.71ng/ml. a) ^{68}Ga-PSMA-11 MIP b-c) PET-CT images show increased tracer uptake of SUV max 46.7 at subcentimeter right iliac lymph node (arrow). Increased PSMA expression is seen at metastatic right iliac lymph node.

6.10 Case 10:



A 59-year-old male is case of hormonal refractory prostate cancer with rising PSA 1.95ng/ml. ^{68}Ga-PSMA-11 MIP image b-d) PET-CT images show PSMA avid bone lesions at L3 vertebral body and sacrum with SUV max 10.5. e) No abnormal tracer uptake is seen at the prostate bed. Findings are consistent with ^{68}Ga-PSMA-11 avid bone metastases.

6.11 Case 11:



A 73-year-old male is case of progressive metastatic castration resistant refractory prostate cancer with rising PSA 19.9ng/ml referred for ^{68}Ga-PSMA-11 PET-CT for lesion characterization before Lu-177 PSMA radionuclide therapy. Ga-68 PSMA MIP b) PET-CT images shows multiple PSMA avid bone lesions at axial and proximal appendicular skeleton.