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Molecular imaging and therapy of prostate cancer using PSMA ligands

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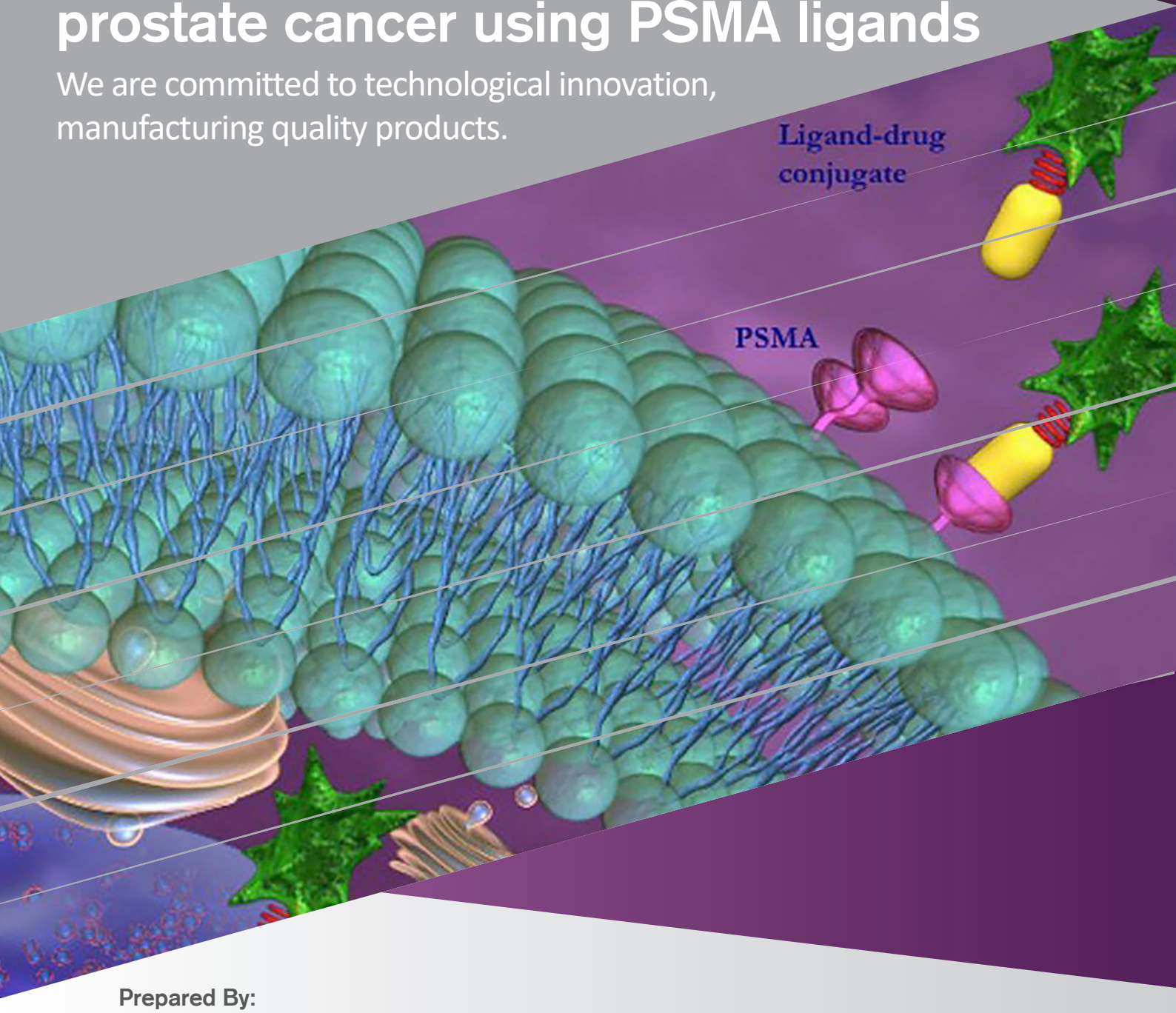

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Introduction

Prostate Cancer is the most frequently diagnosed malignancy in males and the third commonest cause of cancer related death in men. Treatment strategy varies from surgery, radiotherapy, chemotherapy and palliative care. The institution of appropriate and effective treatment depends on disease status.
A current clinical model includes five progressive state for prostate cancer: initial prostate evaluation prior to diagnosis, clinically localized disease, rising prostate-specific antigen (PSA) after treatment, non-castrate recurrent disease and castrate recurrent disease.
Effective treatment relies in part on accurate imaging. In early states, the focus is on assessing disease extent and prognostication, while late states emphasize determining biological profile and assessment of response to systemic treatment. Molecular imaging techniques offer an opportunity for increased timely detection of prostate cancer, its recurrence, as well as metastatic disease.

^{68}Ga-PSMA PET/CT in Prostate Cancer, A non-invasive diagnostic technique to image prostate cancerr

Prostate Specific Membrane Antigen (PSMA) is a transmembrane protein primarily present in all prostatic tissues. Increased PSMA expression is seen in a variety of malignancies, however, most notably in prostate cancer. PSMA is highly overexpressed (100- to 1,000-fold) on almost all PC tumors. Nearly all adenocarcinomas of the prostate demonstrate PSMA expression in the majority of primary and metastatic lesions with this in mind that only 5-10% of prostate adenocarcinomas are PSMA negative (1).
PET/CT hybrid imaging combines functional imaging using Positon Emission tomography (PET) with anatomical imaging using computed tomography (CT) and has revolutionized medical imaging in many eras. In the field of prostate cancer, ^{68}Ga isotope complexation with PSMA and use of PET/CT hybrid cameras allow for an accurate non-invasive visual and quantitative assessment of PSMA expression throughout the body (2).

Clinical applications of ^{68}Ga-PSMA PET/CT

1- Targeted biopsy after previous negative biopsy in patients with high suspicion of prostate cancer

Initial data indicate ^{68}Ga-PSMA PET may be valuable for guidance of repeated biopsy in patients with high suspicion of prostate cancer and prior negative biopsies as it has been shown to add in localization of primary prostate cancer. However, preferably, ^{68}Ga-PSMA PET should be combined with multi-parametric MRI for this application (3).

2- Primary staging in high-risk disease before surgical procedures or planning external beam radiation

In patients with high-risk disease (Gleason score >7, PSA >20 ng/mL, clinical stage T2c – 3a) the likelihood of lymph node and bone metastases is increased. Several studies demonstrate the superiority of ^{68}Ga-PSMA PET/CT as compared to conventional modalities for detection of nodal and skeletal metastases (4,5) ^{68}Ga-PSMA PET/CT can replace abdomino-pelvic CT for detection of lymph node metastases:

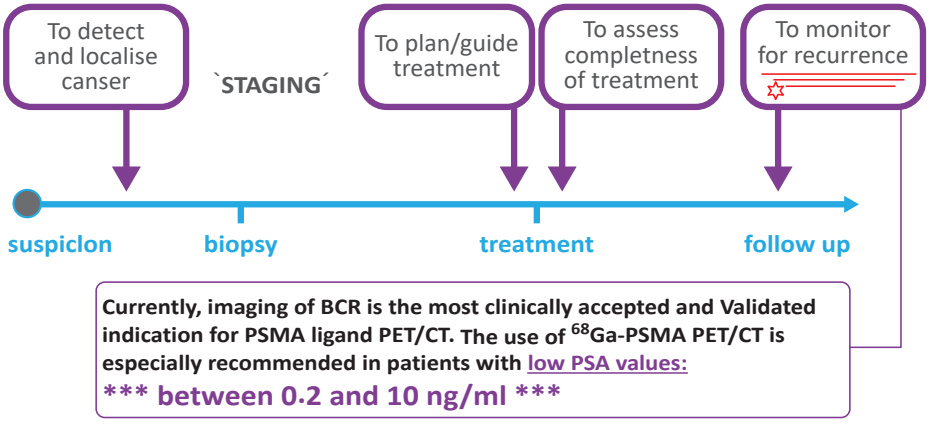
	Overall Sensitivity	Overall Specificity	Overall accuracy
^{68}Ga-PSMA PET/CT	68 %	99%	95%
Morphologic imaging	27%	97%	87%

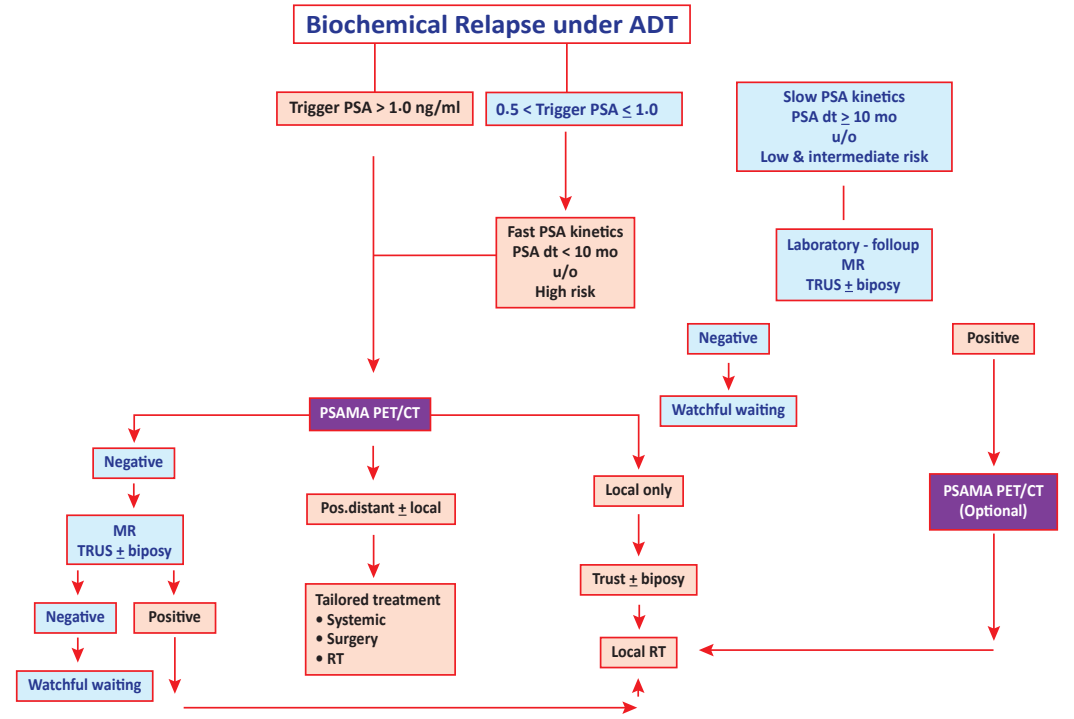
	Low Risk	Moderate Risk	High Risk
Primary Tumor, cT	cT2/1a	cT2b	cT2c[1]/3
	and	or	or
PSA Value (ng/ml)	≤10	>10≤20	>20
	and	or	or
Gleason Score	≤6	7	>8
Further Diagnostics	None	Bone Scintigraphy (Optionally)	MRI or CT of Pelvis Bone Scintigraphy Other Symptom-Oriented Diagnostics

Guidelines recommend initial staging with ^{68}Ga-PSMA PET/CT in high risk patients

3- Localization of tumor tissue in recurrent prostate cancer

After primary treatment, biochemical recurrence (BCR) occurs in approximately 30%–40% of patients. In BCR, accurate restaging is crucial because site and extent of disease (local versus systemic disease) substantially influences further treatment management. Currently, imaging of BCR is the most clinically accepted and validated indication for PSMA ligand PET/CT. The use of ^{68}Ga-PSMA PET/CT is especially recommended in patients with low PSA values between 0.2 and 10 ng/mL (6).





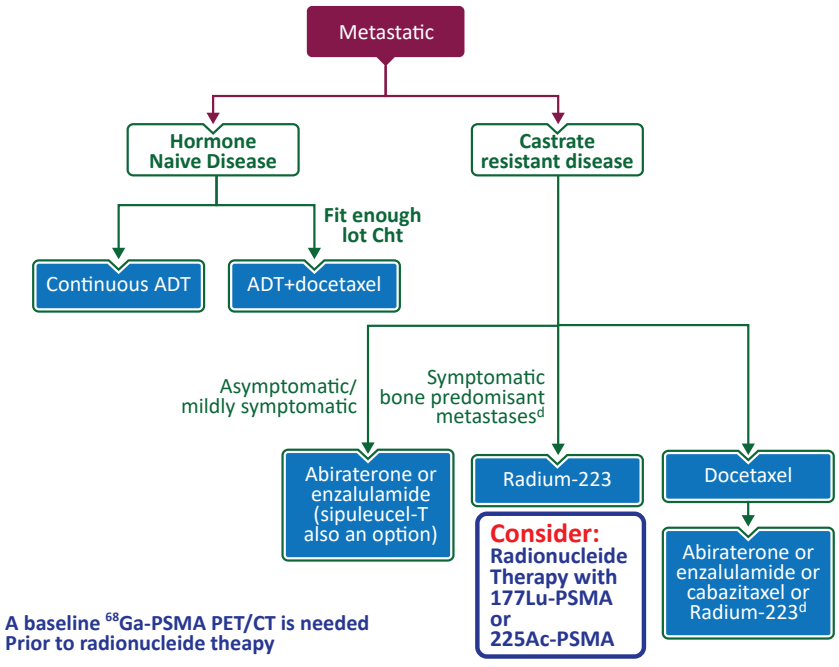
A Schematic Model for Appropriate Use of ^{68}Ga-PSMA PET/CT In Biochemical Relapse

4- Monitoring of systemic treatment in metastatic prostate cancer

RECIST 1.1 is limited by the high prevalence of non-measurable lymph node and bone metastases. Bone scan is limited by a potential flare phenomenon. Monitoring of systemic disease might become a potential application for ^{68}Ga- PSMA PET/CT. With these mind, PSMA ligand PET/CT might overcome many of the limitations of standard-of-care imaging (CT, MRI and bone scan).

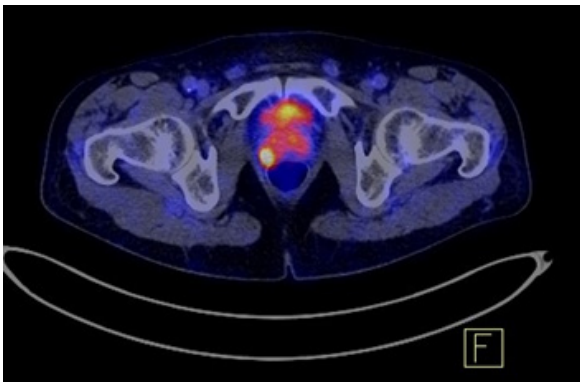
5- Staging before and during PSMA-directed radionuclide therapy

Imaging before PSMA-directed therapy (e.g. radioligand therapy) is crucial to determine the presence and intensity of target expression. Low PSMA expression in target lesions poses a contraindication for radioligand therapy.
Of note, ^{68}Ga-PSMA PET can produce false negatives in up to 5% of patients with prostate cancer. In addition, it has been reported that in advanced metastatic castration-resistant prostate cancer, metastases (mainly in the liver) can lose PSMA expression, possibly due to therapy induced neuroendocrine differentiation of the malignancy.

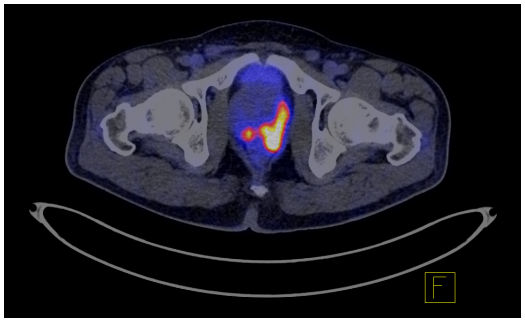


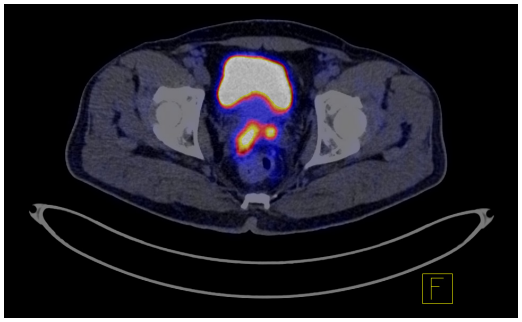
Case Presentation

A focal PSMA activity in right prostate lobe base, is the most appropriate biopsy site in a patient with high clinical suspicion for prostate adenocarcinoma.

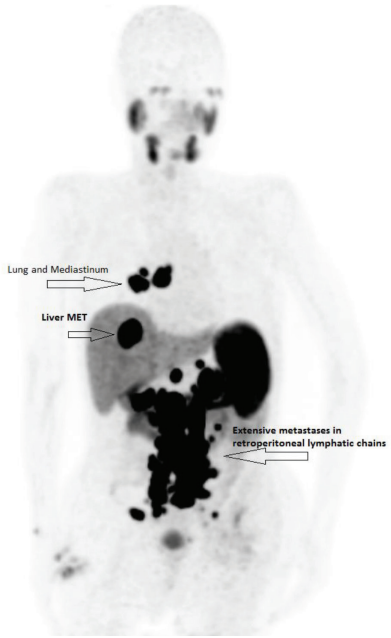


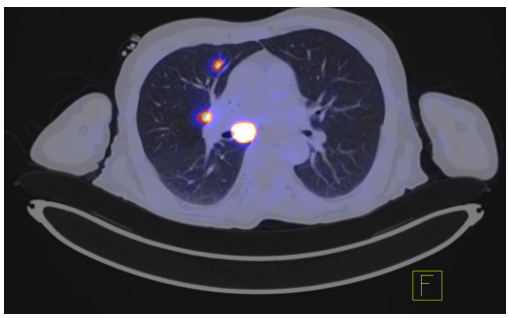
Local staging of a recently biopsy high risk proven prostate cancer, shows the primary malignancy in the left prostate base with local invasion to bilateral seminal vesicles and anterior rectal wall.

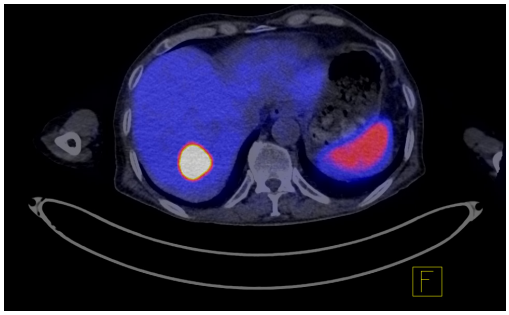




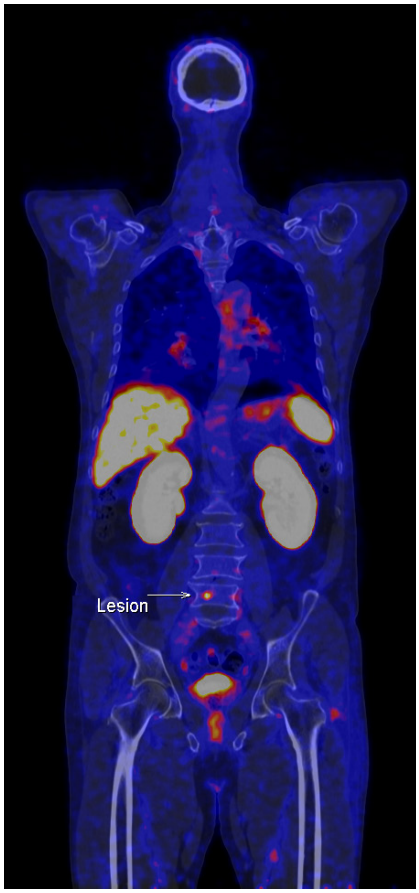
Superiority of Ga-PSMA PET/CT in distant staging over CT scan and whole body bone scan. Multiple PSMA positive metastatic lymph nodes are seen. Most of them are not sizable and not detected on CT scan. The left lateral 5th rib lesion was not reported on whole body bone scan.

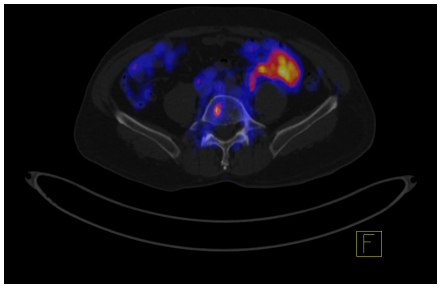


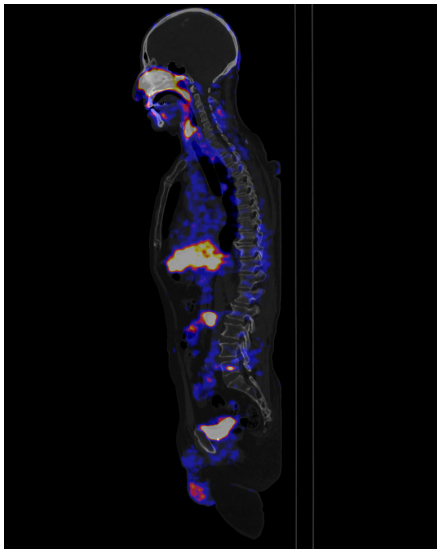




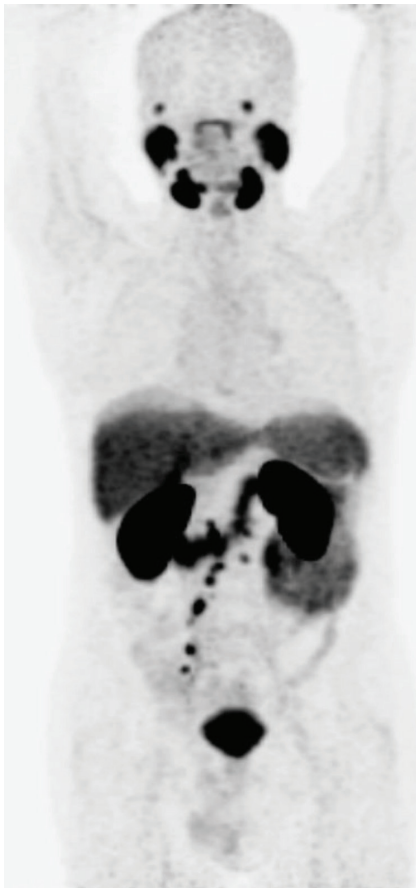
The patient is status post radical prostatectomy and is referred for evaluation of suspicious recurrence due to elevated serum PSA level. ^{68}Ga-PSMA PET/CT study is compatible with PSMA positive sclerotic bone metastasis within L5 vertebral body. The lesion was not detected in planar whole body bone scan.

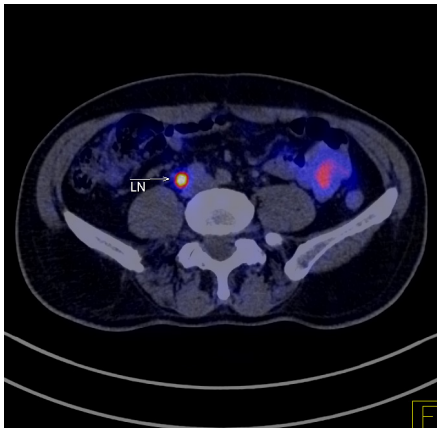


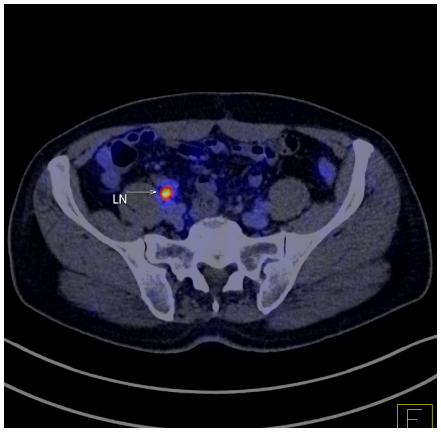




There are several small sized (insignificant based on anatomical CT imaging) pelvic and retroperitoneal lymph nodes showing intense PSMA uptake, **compatible with nodal metastatic** disease as a source for elevated serum PSA in a patient who is referred for evaluation of biochemical recurrence.

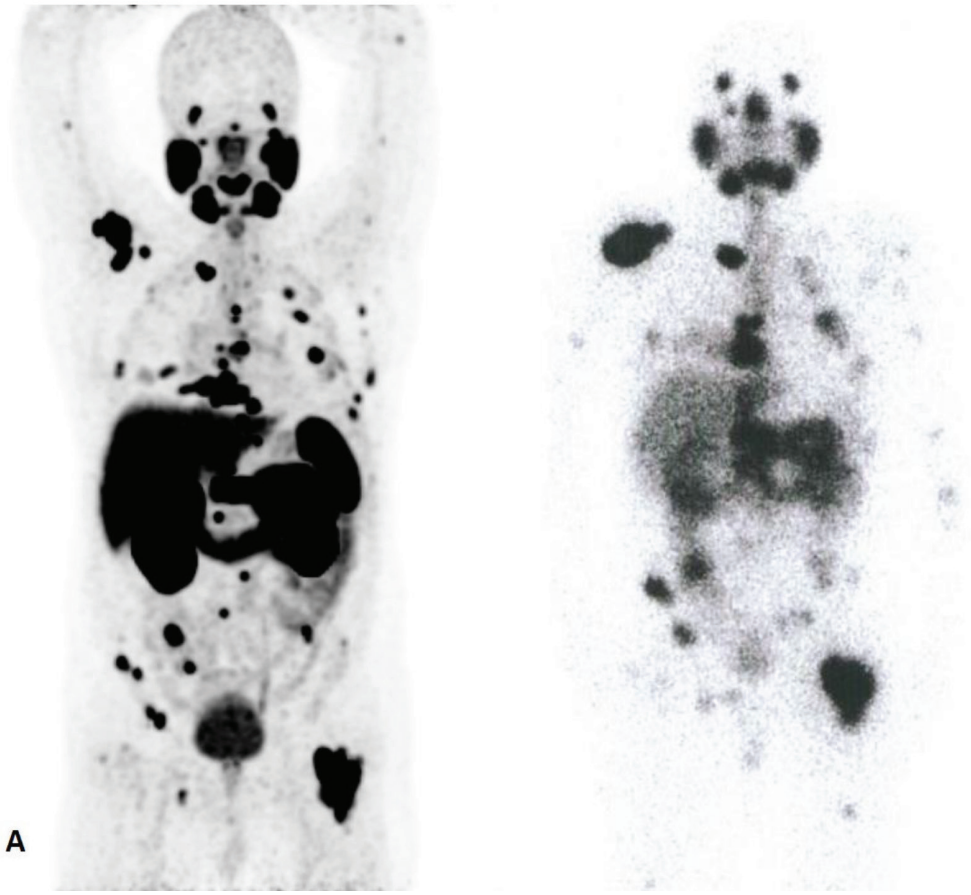






Target evaluation with ^{68}Ga-PSMA, prior to treatment with ^{177}Lu in patient with metastatic castration resistant prostate cancer (mCRPC). The metastatic skeletal lesions are intensely PSMA positive and the patient is candidate for therapy (A). Anterior post therapy whole body ^{177}Lu-PSMA scan of the same patient is concordant (B).

THERANOSTICS



Diagnostic
Ga-68 PSMA PET/CT

Therapy
Lu-177 PSMA scan

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