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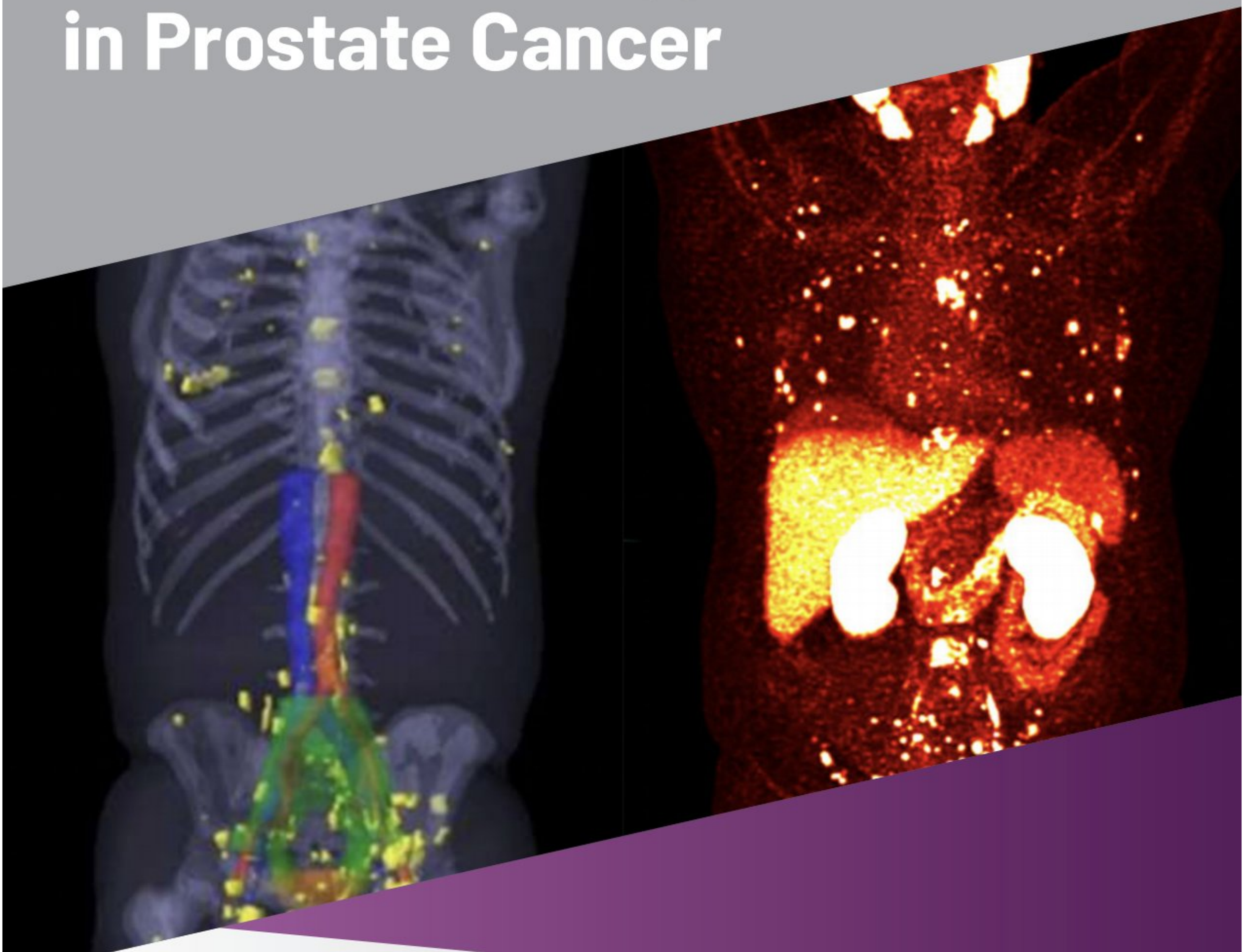
PSMA PET/CT Application in Prostate Cancer



Prepared By:

- Hosseinzadeh.E, MD.IBNM
- Divband.Gh, MD.IBNM

PSMA PET/CT Application in Prostate Cancer

Introduction

Prostate cancer is the second most common cancer in males with three well-established risk factors: increasing age, ethnic origin, and genetic predisposition. (1)

In the majority of cases, early-stage prostate cancer are asymptomatic. It is diagnosed in 80% of men by the age of 80. Sensitive diagnostic procedures are key to improve survival rates. (2)

PSMA-ligand PET/CT is a non-invasive diagnostic technique used to image PSMA positive lesions in individuals with prostate cancer. PSMA is a transmembrane protein expressed highly on the cell surface of prostate cancer cells but is not specific to prostate tissue. Increased PSMA expression is seen in prostate cancer as well as in the neovasculature of other malignancies. Elevated PSMA expression, along with its role in glutamate and folate metabolism, may be associated with a survival advantage for tumor cells. The regulation of PSMA is complex, involving androgen receptor, PI3K/Akt, and DNA damage response pathways. Elevated PSMA expression is linked to advanced metastatic or hormone-refractory prostate cancer, poor disease outcome, and deficient DNA damage repair pathways.(3)

^{68}Ga labeled to PSMA-targeted agents has been extensively studied and successfully used clinically. Also, ^{18}F labeled PSMA radiopharmaceuticals (DCFPyL and PSMA-1007) are under investigation. (4)

[^{99m}Tc]Tc-HYNIC PSMA has lower sensitivity for lesion detection compared to [^{68}Ga]Ga-PSMA PET/CT. Its use is recommended when [^{68}Ga]Ga-PSMA is not available and not recommended in patients with small volume disease.(5)

Indications for PSMA-ligand PET/CT:

Routine clinical use

1-Initial staging of unfavorable intermediate to high-risk prostate cancer:

In patients with risk features (Gleason score 4+3 / ISUP grade 3 or higher, PSA > 20 ng/mL, clinical stage T2c–3a), the likelihood of distant metastases is increased. **PSMA-ligand PET imaging demonstrated higher accuracy for disease localizations compared with CT and bone scan for staging of individuals with initial high-risk prostate cancer.(6)**

[^{18}F]F-DCFPyL and [^{68}Ga]Ga-PSMA-11 PET/CT demonstrated high specificity (≥ 95%) for detection of pelvic lymph node metastases in individuals with intermediate or high-risk prostate cancer undergoing radical prostatectomy. However, due to low sensitivity, a negative PSMA PET scan cannot exclude the presence of pelvic lymph node micrometastases. (3)

2-Localization of biochemical recurrent (BCR) or persistent (BCP) prostate cancer following curative-intent therapy:

BCR is defined as an increase in PSA to ≥ 0.2 ng/mL, measured at 6 to 13 weeks following prostatectomy, and confirmed by a second PSA level > 0.2 ng/mL. BCP is defined as persistently elevated PSA ≥ 0.1 ng/mL more than 6 weeks after prostatectomy.

In patients who have undergone curative-intent radiation therapy, BCR is defined as a rise in PSA of ≥ 2 ng/mL above the nadir achieved after radiotherapy. In these patients, precise tumor localization is critical for subsequent management.

Current evidence underlines the role of PSMA-ligand PET for prostate cancer localization at BCR or BCP and demonstrates superiority over conventional or other forms of molecular imaging.(6, 7)

3- Localization of castrate resistant prostate cancer which is non-metastatic by conventional imaging (nmCRPC):

nmCRPC is characterized by biochemical disease progression despite sufficient ADT. This is defined by the combined occurrence of several conditions: (a) castrate serum testosterone < 50 ng/dL, (b) three consecutive rises in PSA resulting in two 50% increases above the nadir, (c) a PSA>2 ng/mL or a PSA>1 ng/mL, and (d) lack of metastatic spread on conventional imaging.

PSMA-ligand PET/CT detects locoregional only disease in 44% and distant disease in 55% for patients with nmCRPC and risk features. Thus, PSMA-ligand PET/CT detects disease extent in patients with nmCRPC with high accuracy and leads to a considerable stage migration. Accurate localization of disease extent by PSMA-ligand PET/CT may aid patient stratification and adds information for therapy guidance. (8, 9)

4- Staging before PSMA-directed radioligand therapy (RLT) for metastatic prostate cancer:

PSMA-ligand PET/CT is used to confirm eligibility for RLT and assess the likelihood of response to RLT in patients with advanced prostate cancer. Documentation of PSMA expression in metastatic sites is required before initiating RLT. [^{177}Lu]Lu-PSMA-617 RLT was approved by the FDA for the treatment of eligible patients with mCRPC has been shown to improve radiographic progression-free survival and overall survival in patients with mCRPC. Short survival associated with low PSMA expression or the presence of liver metastases on PSMA-ligand PET/CT. (3)

Potential Clinical Applications

1. Guidance of prostate biopsy

PSMA-ligand PET/CT is useful for localizing tumors and guiding repeated biopsies in patients with high suspicion of prostate cancer and prior negative biopsies. PSMA-ligand PET should be combined with multiparametric MRI for biopsy guidance. (3)

2. Imaging metastatic prostate cancer

Imaging for metastatic prostate cancer typically includes bone scan and CT or MRI. Studies have shown that PSMA-ligand PET/CT has high diagnostic performance especially for nmCRPC or visceral metastatic disease, with superior accuracy for bone assessment compared to bone scan. PSMA-ligand PET/CT can accurately identify clinical trial target populations and is useful for guiding treatment in patients with oligometastatic disease. However, its impact on management and patient outcomes needs further assessment.(3)

3. Monitoring of systemic treatment for metastatic prostate cancer

PSMA-ligand PET role in monitoring treatment response is under investigation with promising valuable results. Currently, treatment response is evaluated using conventional imaging.(8)

Summary

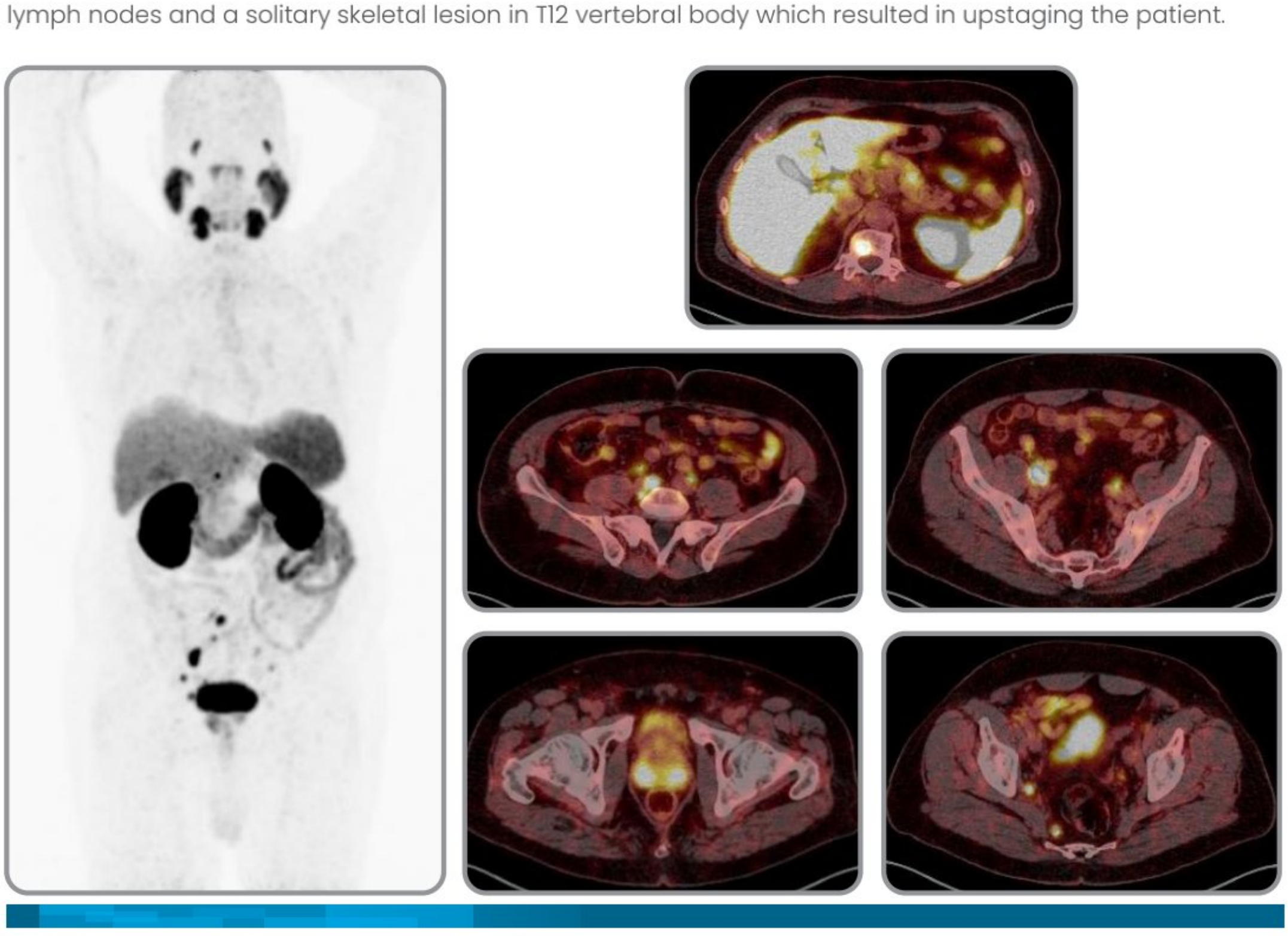
PSMA PET-CT scan is now routinely used in the evaluation of prostate cancer in the context of primary staging, suspected tumor recurrence and selection of appropriate patients for radioligand therapy. More specific PET radiopharmaceuticals may improve both assessments and provide additional benefits in theragnostics.

PET-MR with the ability to perform simultaneous PET and MR acquisitions may be the imaging modality of choice in the future.

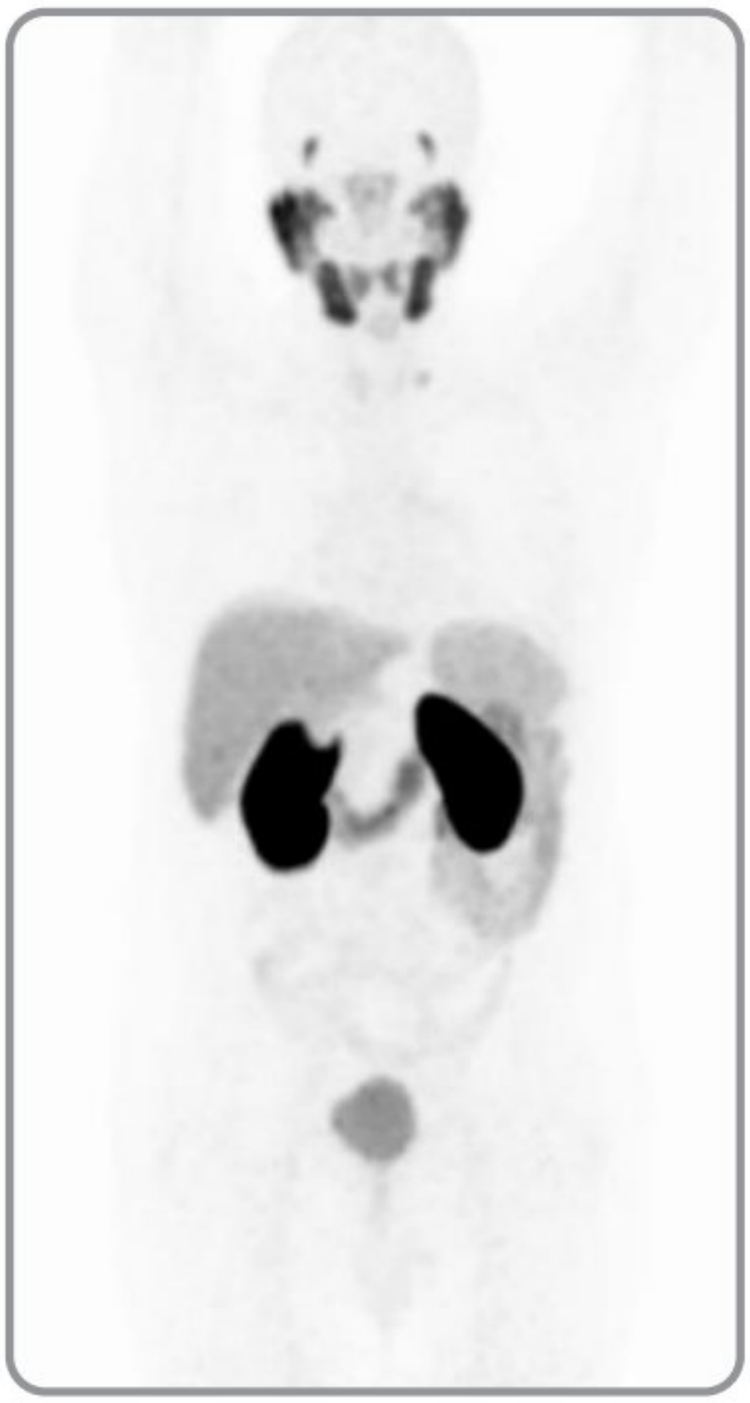
Case Presentations

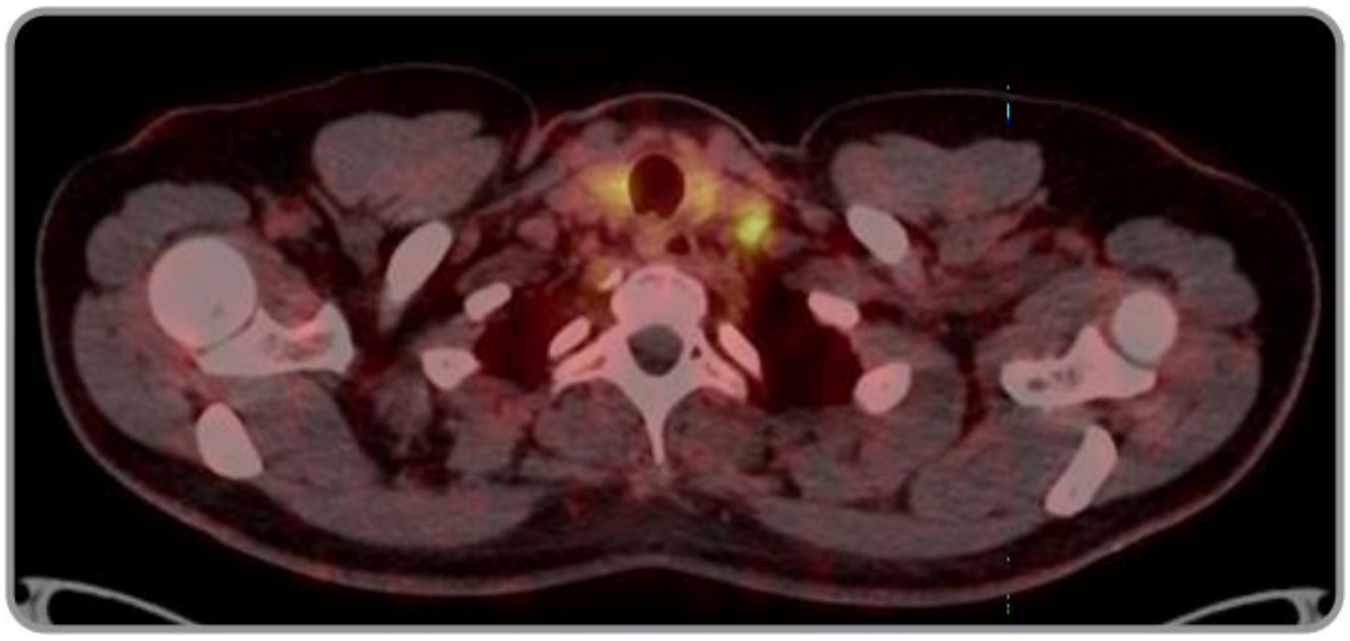
Case 1: A 69 y/o patient with newly diagnosed prostate adenocarcinoma with Gleason score 8 and serum PSA 22.2 ng/dl, was referred for initial staging. Conventional imaging showed prostate mass with metastatic pelvic lymph nodes.

[^{68}Ga]Ga-PSMA PET/CT image detects multiple PSMA-positive soft tissue lesions within prostate gland with invasion to bilateral seminal vesicles along with multiple PSMA-positive retroperitoneal/pelvic metastatic lymph nodes and a solitary skeletal lesion in T12 vertebral body which resulted in upstaging the patient.

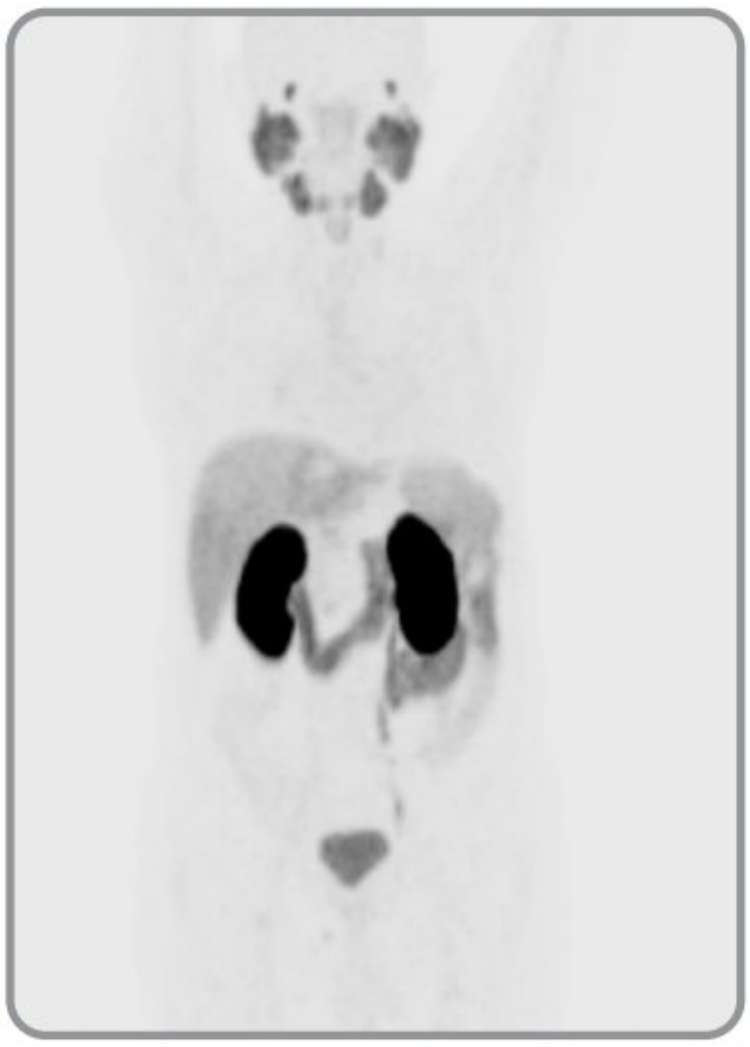


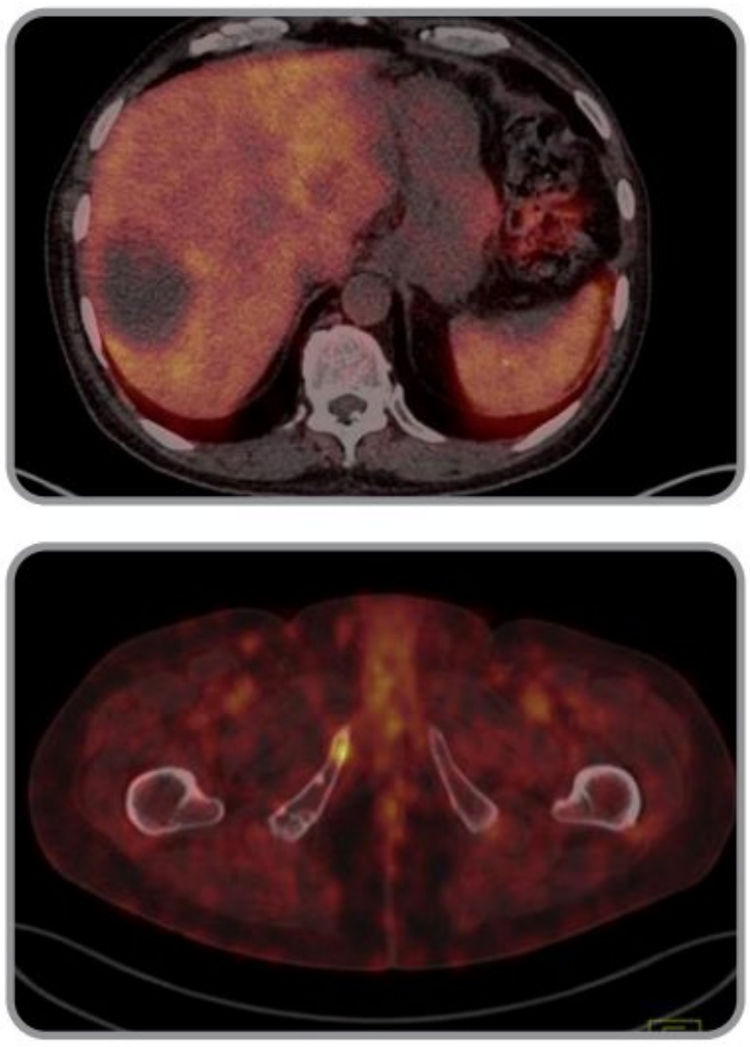
Case 2: [^{68}Ga]Ga-PSMA PET/CT image shows a PSMA-positive left supraclavicular metastatic lymph node (confirmed by biopsy) in a 58 y/o patient with prostate adenocarcinoma; status post prostatectomy, was referred due to suspected biochemical recurrence (PSA=0.5 ng/dl).



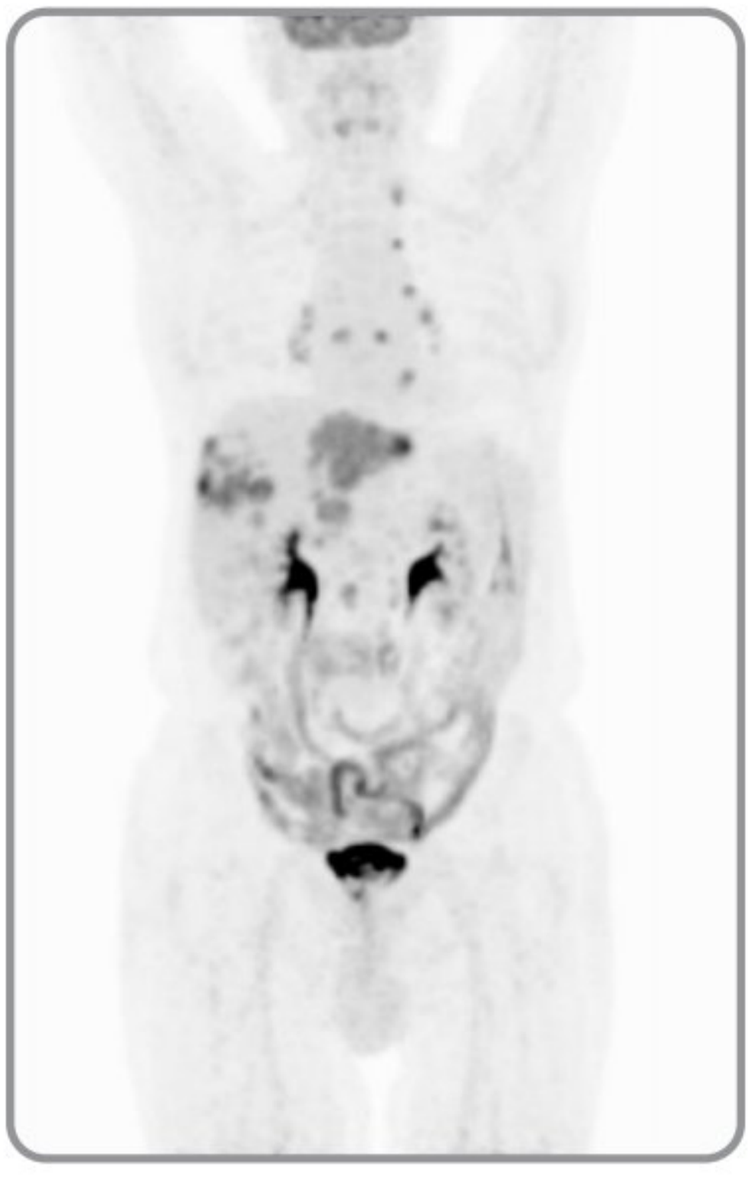


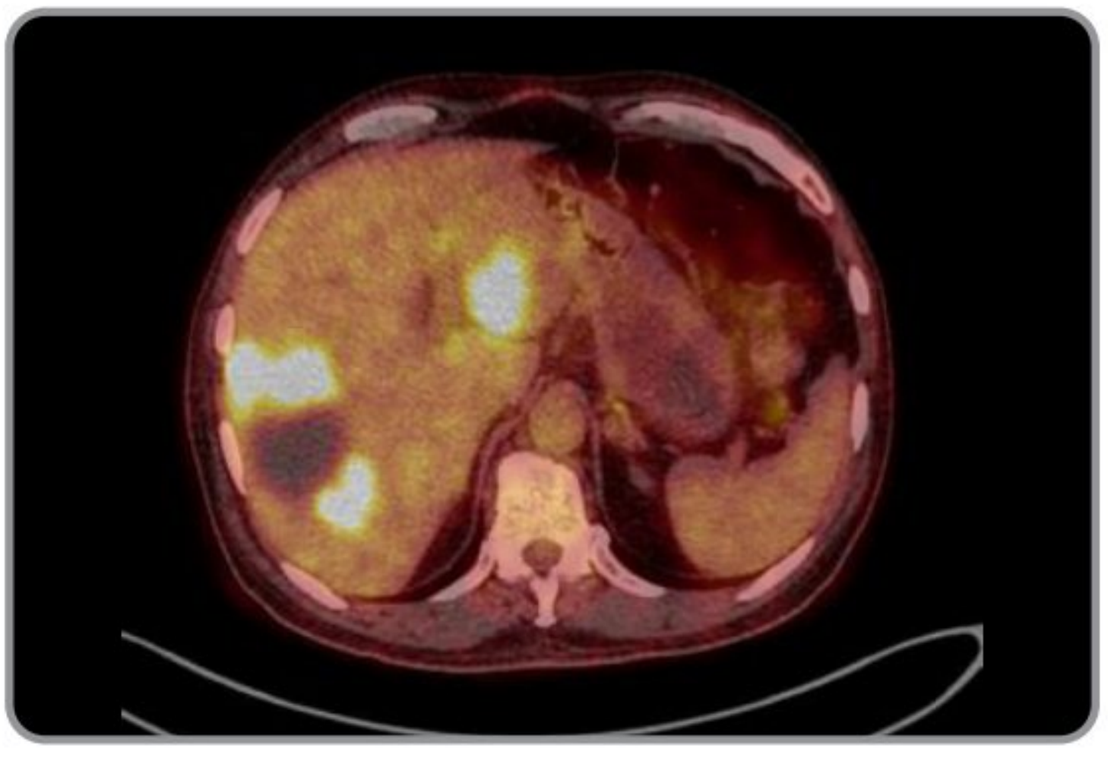
Case 3: [^{68}Ga]Ga-PSMA PET/CT shows PSMA avid right ischio-public sclerotic lesion, few retroperitoneal and left supraclavicular metastatic lymph nodes in a 64 y/o patient with prostate adenocarcinoma, status post prostatectomy, followed by chemotherapy/ADT who is referred for evaluation before [^{177}Lu]Lu-PSMA therapy due to PSA rising.





Case 3, Cont'd: The patient underwent [^{18}F]F-FDG PET/CT scan. There were FDG avid metastases in bilateral liver lobes, several left supraclavicular and multiple abdominal lymph nodes. Dual tracer PET imaging results demonstrated that this case is not suitable for radioligand therapy with [^{177}Lu]Lu-PSMA.





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KHATAM
مرکز پت سی‌تی خاتم
PET/CT CENTER

Khatam PET/CT center, Khatam ol Anbia hospital, Rashid Yasemi St. , Vali- Asr St., Tehran, 1996835911, Iran.
Tel : +98 21 92002202

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