Nuclear Medicine Applications in

Metastatic Prostate Cancer

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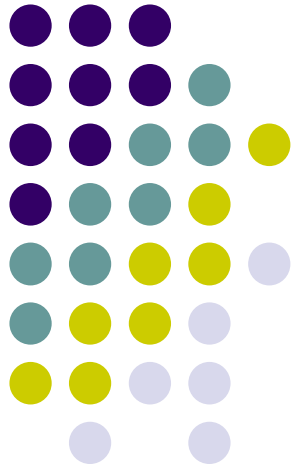
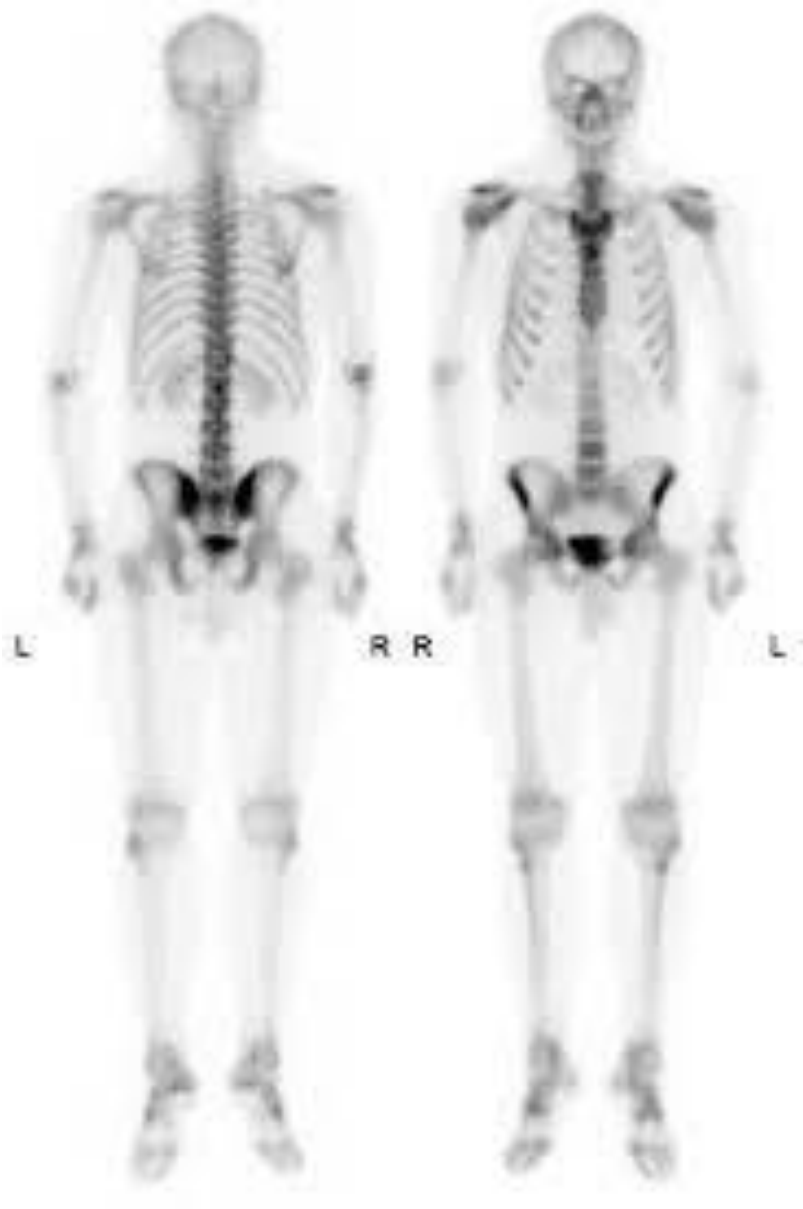


Conventional Nuclear Medicine (Bone Scan)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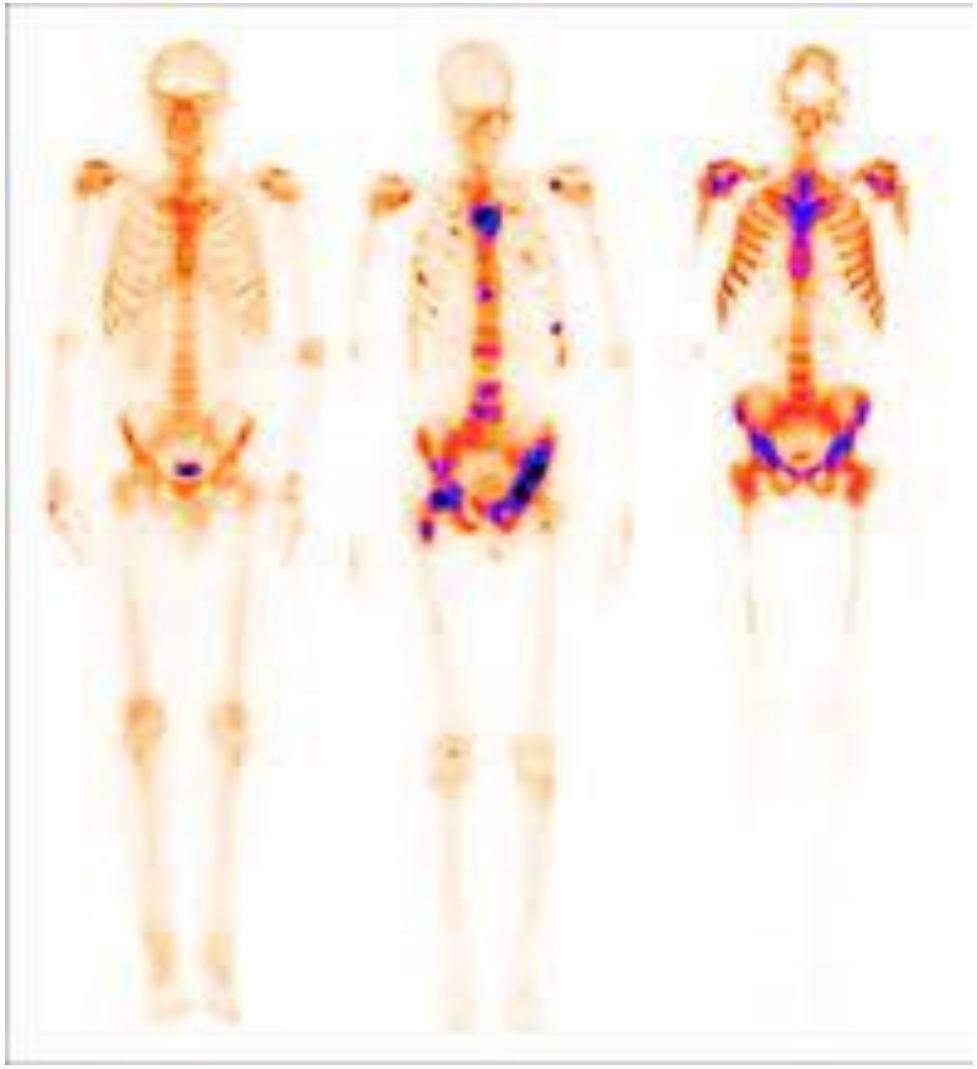


Background

General

• Prostate cancer is the most common cancer in men, other than skin cancer. It's also the second-leading cause of cancer death (after lung cancer)
• It is diagnosed in 30%–70% of autopsies in patients older than 60 years who died because of other causes
• Metastatic disease as the initial presentation of prostate cancer declined from >70% to <30% after the global prostate-specific antigen (PSA) screening was started because of early detection of primary disease in the prostate gland

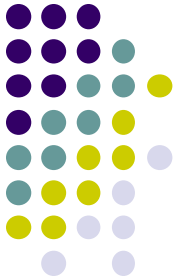
Early Clinical Symptoms

- There are no signs or symptoms in the early stages
- In the advanced stages, symptoms include pelvic discomfort/pain, dysuria, nocturia, hematuria, and renal insufficiency caused by upper tract obstruction
- Bone pain and skeletal-related events are seen in metastatic disease

Primary Diagnostic Procedure

- PSA testing
- Digital rectal examination
- Sonography
- Transrectal biopsy

Standard Treatment



The standard treatment is usually considered for patients with life expectancy >10 years

- Low-risk prostate cancer: active surveillance/watchful waiting,radical prostatectomy, radiation therapy, brachytherapy, focal therapy, clinical trials
- Intermediate-risk prostate cancer: radical prostatectomy, radiation therapy + short-term androgen deprivation therapy, brachytherapy, clinical trials
- High-risk prostate cancer: radical prostatectomy, radiation therapy + long-term androgen deprivation therapy, brachytherapy, clinical trials
- Metastatic disease: androgen deprivation therapy + chemotherapy, androgen deprivation therapy alone, management of metastasis,RLT

Prognostic Factors

- Gleason score
- PSA
- Clinical and pathologic stage
- Surgical margins
- Tumor volume
- Gene profiles

Five-Year Survival

- Local disease (cancer confined to prostate gland) ~100%
- Regional disease (cancer with local invasion/pelvic lymph node metastases) ~100%
- Distant disease (distant lymph node and organ involvement) ~28%

Histopathology

- Adenocarcinoma >95%
- Others (mucinous/signet ring cell and adenoid cystic carcinomas, neuroendocrine tumors, large prostatic duct carcinoma, small-cell undifferentiated cancers) <5%

Cancer Distribution

- Peripheral zone: 75%–85%
- Transitional zone: ≤25%
- Central zone: 1%

Common Pattern of Spread

Lymph Nodes

- Regional pelvic lymph nodes
- Distant extrapelvic lymph nodes

Distant Metastasis

- Most common sites:
- Bone (90%)
- Lung (46%)
- Liver (25%)
- Pleura (21%)
- Adrenal glands (13%)

Clinical Guidelines for Using PET/CT

Primary Staging

• PET/CT is not recommended by the EAU, European Society for Medical Oncology, and National comprehensive Cancer Network (NCCN)

However, in the large study of 130 patients with intermediate-to high-risk prostate cancer prior to radical prostatectomy and lymph node dissection, the sensitivity and specificity of 68Ga PMSA PET were 66 and 99%, respectively, compared to 44 and 85% for morphologic imaging

Recurrent Disease

• **EAU**: Choline PET/CT is not recommended in patients with biochemical recurrence and a PSA level <1 ng/mL

• **NCCN**: 68Ga PMSA and Choline PET/CT are indicated in the evaluation of patients with biochemical recurrence after radical prostatectomy or radiation therapy, as well as in the evaluation of distant metastases and workup of patients scheduled for local treatment

EAU Risk Groups for Biochemical Recurrence of Localised and Locally Advanced Prostate Cancer

	Low-risk	Intermediate-risk	High-risk	
Definition	PSA < 10 ng/mL and GS < 7 and cT1–2a	PSA 10–20 ng/mL or GS 7 or cT2b	PSA > 20 ng/mL or GS > 7 or cT2c	any PSA any GS cT3–4 or cN+
	Localised			Locally advanced

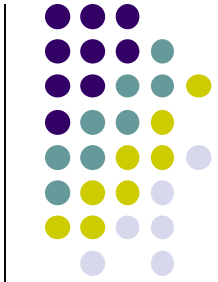
TABLE 1

Risk classification of localized prostate cancer according to D'Amico (6)

Risk group	Parameters
Low risk	PSA ≤ 10 ng/mL and Gleason score 6 (Gleason grade group I) and cT category 1c, 2a
Intermediate risk	PSA > 10 to ≤ 20 ng/mL or Gleason score 7 (Gleason grade groups II and III) or cT category 2b
High risk	PSA > 20 ng/mL or Gleason score ≥ 8 (Gleason grade groups IV and V) or cT category 2c

PSA, Prostate-specific antigen

PET radiotracers, such as 11C- and 18F-choline and 11C-acetate, seem to be promising in staging of high-risk prostate cancer. They showed a good performance in the therapy monitoring of patients with metastatic prostate cancer. On the other hand, 68Ga-PSMA PET/CT is more sensitive than CT or MRI for the detection of metastatic disease in patients with intermediate-to high-risk prostate cancer, even at low serum prostate-specific antigen values.



• Fludeoxyglucose (FDG) PET/CT is not useful in the evaluation of initial or early recurrent prostate cancer. However, FDG PET/CT provides prognostic value and may be beneficial for therapy monitoring in castrate-resistant metastatic disease with poorly differentiated tumor.

• 68Ga-prostate-specific membrane antigen (PSMA) PET/CT is more sensitive than CT or MRI for the detection of metastatic disease in patients with intermediate- to high-risk prostate cancer, even at low serum PSA values. Thus, although current knowledge is still limited and derived mostly from retrospective series, 68Ga-PSMA based imaging holds great promise to improve prostate cancer management

PMSA is a transmembrane protein that is expressed in the apical epithelium of the secretory ducts in benign prostatic tissue. Prostatic malignancy results in upregulation and migration of PMSA to the plasma membrane, particularly during the transition to hormone refractory disease. PMSA expression in prostate cancer cell membranes is 100- to 1000-fold that in normal cells. Increased PMSA expression is associated with higher grade and increased risk of tumor progression. The most studied ligand is gallium-68 (68Ga)

- 18F-NaF PET/CT is superior to conventional bone scintigraphy and provides excellent performance in the assessment of bone metastasis

68Ga-Prostate-Specific Membrane Antigen PET/CT

PSMA is a cell membrane protein with enzymatic activity that is highly expressed in prostate cancer cells but not on normal prostate tissue or benign lesions.

It is noteworthy that the detection rate of 68Ga-PSMA PET/CT may reach 100% even in patients with serum PSA levels >2.2 ng/mL. This rate is approximately 60% at PSA levels of <2.2 ng/mL. In a study on 112 cases with this modality to detect cancer, a sensitivity and specificity of 92%, and a PPV and NPV of 96% and 85%, were calculated, respectively

In a meta-analysis, 68Ga-PMSA PET was positive in 76% of patients with biochemical recurrence

The rate of positivity increased with shorter PSA doubling time. For PSA levels of 0 to 0.2, 0.2 to 1, 1 to 2, and greater than 2 ng/mL, the positive scan rates were 42, 58, 76, and 95%, respectively. Shorter PSA doubling time also increased positivity

One report indicates that the optimal cutoff values for performing PMSA PET are a PSA of 0.83 ng/mL and a PSA doubling time of 6.5 months

In a prospective comparison of 18F-fluoromethycholine and 68Ga-PMSA PET,at PSA levels of less than 0.5, 0.5 to 2, and greater than 2 ng/mL, the detection rates for fluoromethylcholine PET were 12.5, 31, and 57%, respectively,and 50, 69, and 86%, respectively, for PMSA PET.

Clinical Point of View

The following statements are of clinical relevance to define imaging of choice in the assessment of patients with prostate cancer:

- Detection of intraprostatic prostate cancer lesions for initial diagnosis
- Initial staging after the diagnosis to rule in or out lymph node or distant metastasis before treatment with curative intent
- Staging at the time point of biochemical recurrence to rule in or out local recurrence, regional recurrence to lymph nodes, or distant recurrence
- Detection of intraprostatic prostate cancer lesions when suspecting local recurrence after radiotherapy or ablative treatments
- Monitoring of treatment response in patients treated for metastatic prostate cancer
- Information about cancer size/volume
- Number of metastatic lesions
- Location/organ of metastatic lesion
- Quantification of tracer intensity
- Use of test in the correct clinical setting and when result will change treatment strategies

Pitfalls

False Positive

• Inflammation and infections, such as prostatitis
• Benign conditions, such as prostatic hyperplasia (BPH)
• Reactive lymph nodes

False Negative

• Neuroendocrine neoplasia in the prostate (except for neuroendocrine tumor-specific tracers)
• Low metabolic cancer tissue
• Poorly differentiated cancer on non-FDG tracers
• Micrometastases in the locoregional lymph node
• Common false negative in all cancers: early-stage malignancy,small lesions (<8 mm

- Studies have reported that this modality is able to detect cancer lesions even in patients with serum PSA levels of as low as 0.5 ng/mL

- In a large-cohort study of 319 patients with recurrent prostate cancer, PSMA PET/CT revealed a sensitivity, specificity, PPV, and NPV of approximately 77%, 100%, 100%, and 91%, respectively, on a lesion-based analysis. However, in patient-based analysis, the sensitivity reached 88%

Considering the high level of PSMA on metastatic lesions from prostate cancer, investigators tried to use radiolabeled PSMA for endoradiotherapeutic purposes. The efforts resulted in the production of 177Lu-PSMA for the treatment of patients with metastatic and castration-resistant prostate cancer

18F-Sodium Fluoride PET/CT

99mTc-methylene diphosphonate (MDP) whole-body bone scan is a widely available and relatively inexpensive imaging method with reasonable sensitivity for detecting prostate cancer bone metastases. However, this test suffers from a relatively low specificity. 18F-NaF as an old bone-seeking positron emitter has been reintroduced to PET clinics mainly because of its excellent performance and more availability of PET/CT scanners. The mechanism of action is not quite clear but is most likely by chemisorption to hydroxyapatite at the bone turnover site. Overall, it is indicated in the detection of primary and secondary bone cancers, therapy monitoring, and clarification of equivocal findings of other imaging tools, such as plain radiography or CT. Review of correlated sensitivity and specificity of 18F-NaF PET/CT in the medical literature shows different results

Even-Sapir and colleagues calculated a sensitivity and specificity of 100%, whereas Poulsen and colleagues reported a high sensitivity of 93% but surprisingly low specificity of only 54%, most likely because of a large number of false-positive lesions associated with degenerative or inflammatory changes in older patients

Table 1 Indications for PSMA-ligand PET/CT

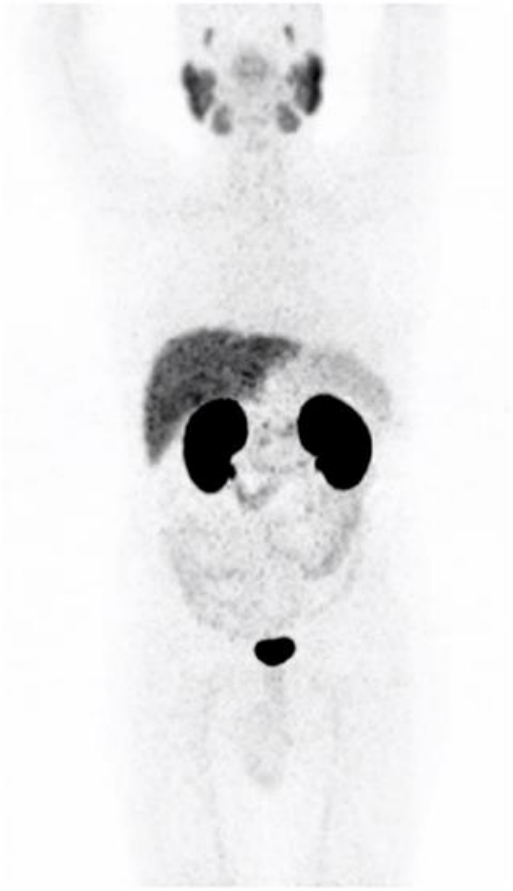
Routine clinical use
Initial staging of prostate cancer
Localization of recurrent (BCR) or persistent (BCP) prostate cancer
Localization of prostate cancer which is non-metastatic by conventional imaging (nmCRPC)
Staging before PSMA-directed radioligand therapy
Potential clinical applications
Guidance of prostate biopsy
Imaging metastatic prostate cancer
Monitoring of systemic treatment for metastatic prostate cancer

Potential indications for ^{68}Ga-PSMA ligand PET/CT

From: ^{68}Ga-PSMA ligand PET/CT in patients with prostate cancer: How we review and report

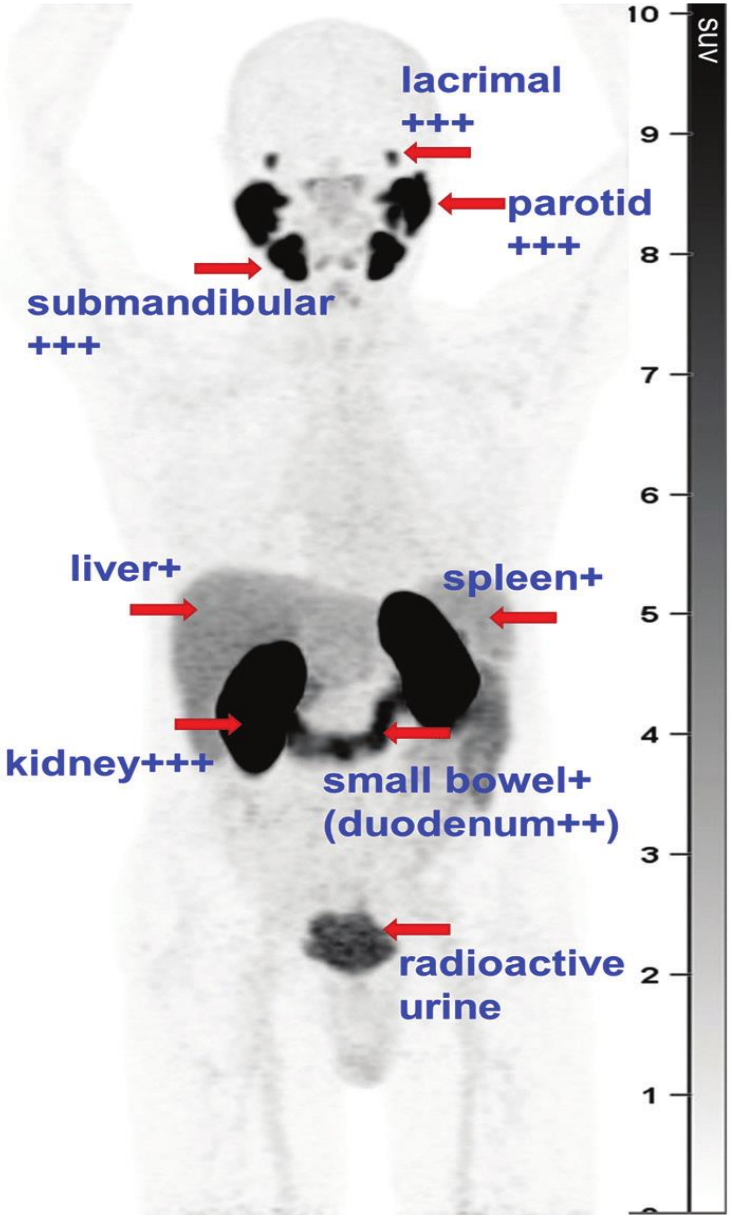
Benefit using ^{68}Ga-PSMA ligand PET/CT	Patient group
High estimated benefit/diagnostic gain	• Primary staging in high-risk disease according to D'Amico classification • Biochemical recurrence with low PSA-values (0.2 ng/ml to 10 ng/ml)[a]
Low estimated benefit/diagnostic gain	• Primary staging in low-risk (and intermediate-risk) disease according to D'Amico classification
Potential application with promising preliminary data	• Biopsy targeting after previous negative biopsy, but high suspicion of PC (esp. in combination with multiparametric MRI using PET/MRI)
Potential application with current lack of published data	• Monitoring of systemic treatment in metastatic CRPC[b] • Monitoring of systemic treatment in metastatic castration-sensitive PC[b] • Active surveillance (esp. in combination with multiparametric MRI using PET/MRI) • Treatment monitoring in metastatic castration-resistant PC undergoing radioligand therapy targeting PSMA (e.g. ^{177}Lu-PSMA-ligand)

Normal 68Ga-PSMA PET Scan



The most intense activity is appreciated in the kidneys with subsequent urinary excretion (ureters and urinary bladder) as well as lacrimal and salivary glands. The high-grade uptake in small bowel, particularly the duodenum, is likely attributed to the dietary uptake of folates in this region and thus increased PSMA expression. Relatively low-grade activity is appreciated in the liver and spleen, and this activity should be uniform in distribution

Maximal intensity projection image(MIP),
showing the normal biodistribution of Ga68-PSMA.


lacrimal
+++
parotid
+++
submandibular
+++
liver+
spleen+
kidney+++
small bowel+
(duodenum++)
radioactive
urine
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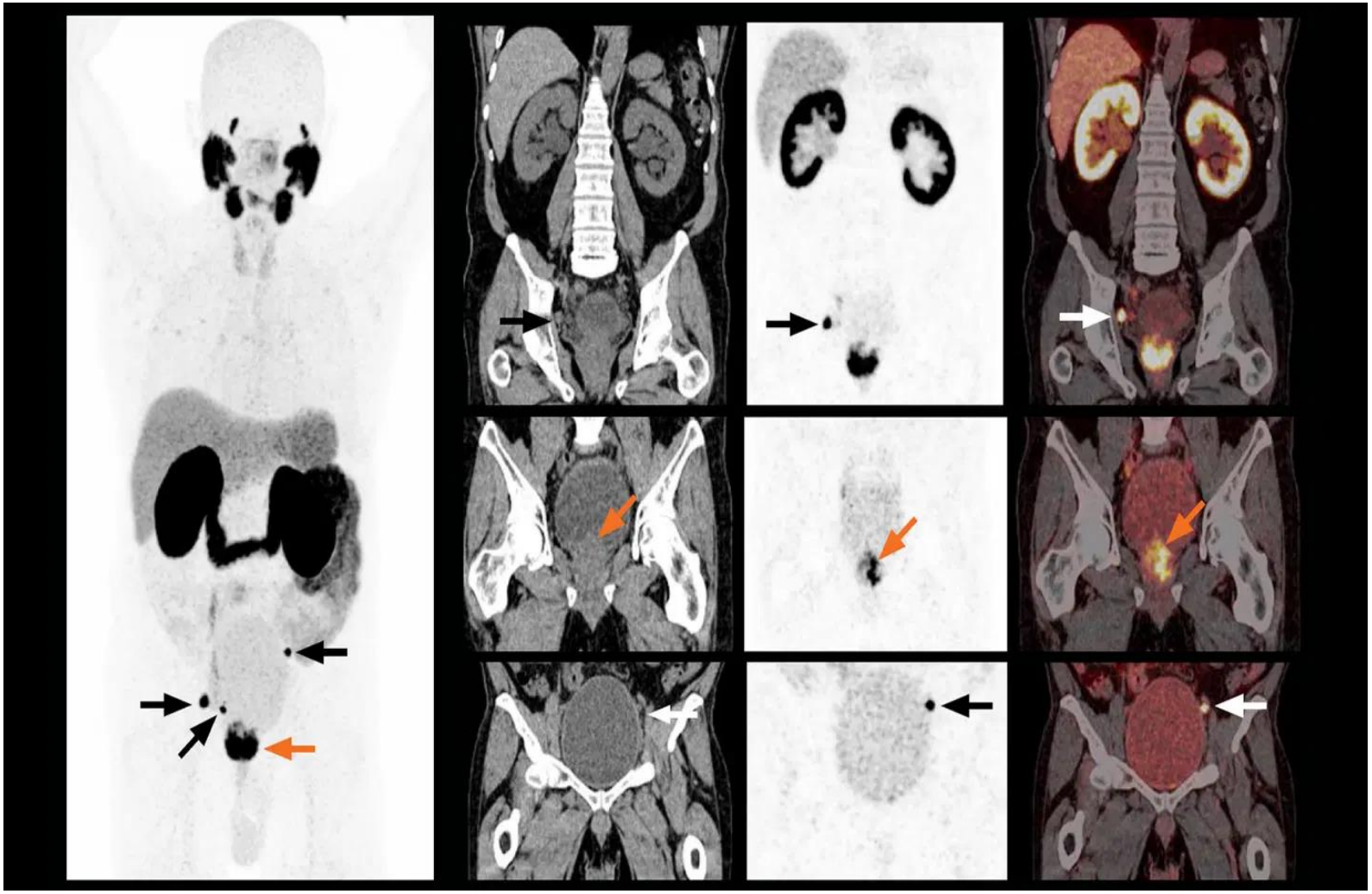
ROC analysis revealed:

An optimal prostate lesion SUVmax and SUVmean cut-off of 6.94 and 3.89 for discrimination of pathological prostate lesions from normal prostate tissue

SUVmax of 4.25 and SUVmean of 2.32 were the optimal cut-off values for distinguishing pathological bone lesion from physiological iliac bone

SUVmax of 4.72 and SUVmean of 3.11 were the optimal cut-off values for distinguishing pathological lymph node

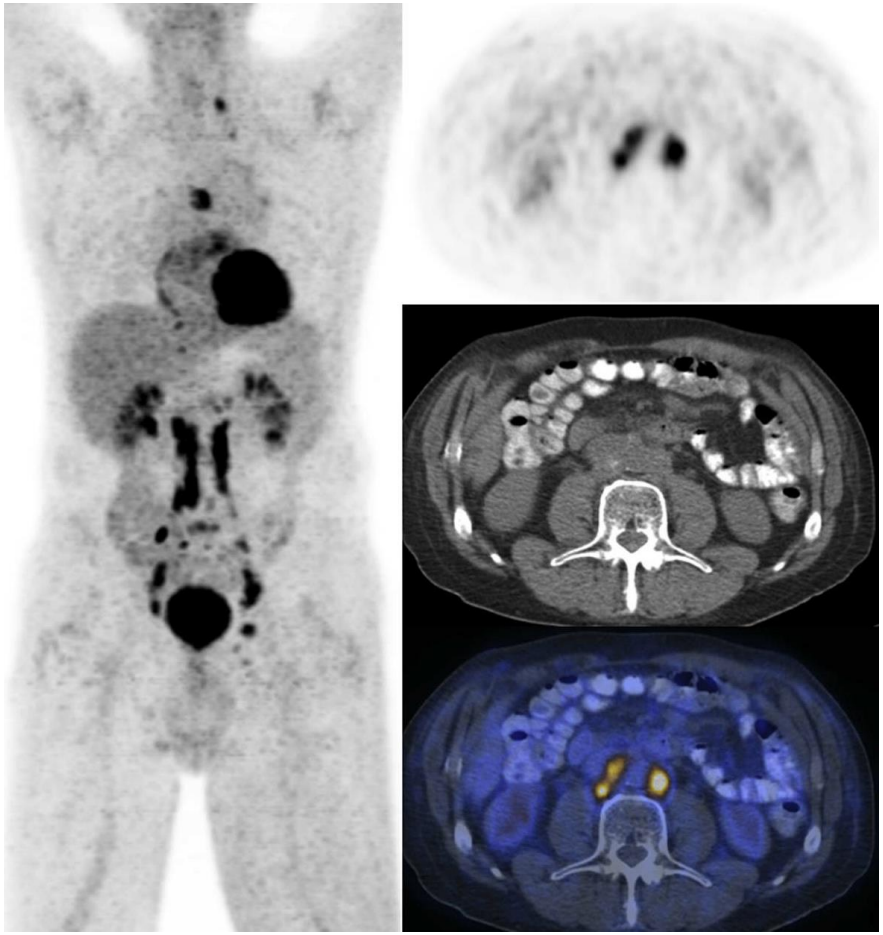


68Ga PSMA PET/CT shows primary prostate cancer involving the majority of the enlarged prostate gland measuring nearly 3 cm in all dimensions with invasion into the bladder neck and external urinary sphincter), with resulting bladder outflow obstruction. The PET/CT also revealed three highly tracer-avid pelvic lymph node metastases in the right meso-rectal, right external iliac and left common iliac nodes. No distant metastases were visualized.

Case 1: FDG PET/CT—Staging

Findings

A 75-year-old male with high-risk prostate cancer, PSA = 8 ng/mL and GS = 10. FDG PET/CT shows tracer-avid cervical, mediastinal, and retroperitoneal lymph node metastases



Teaching points

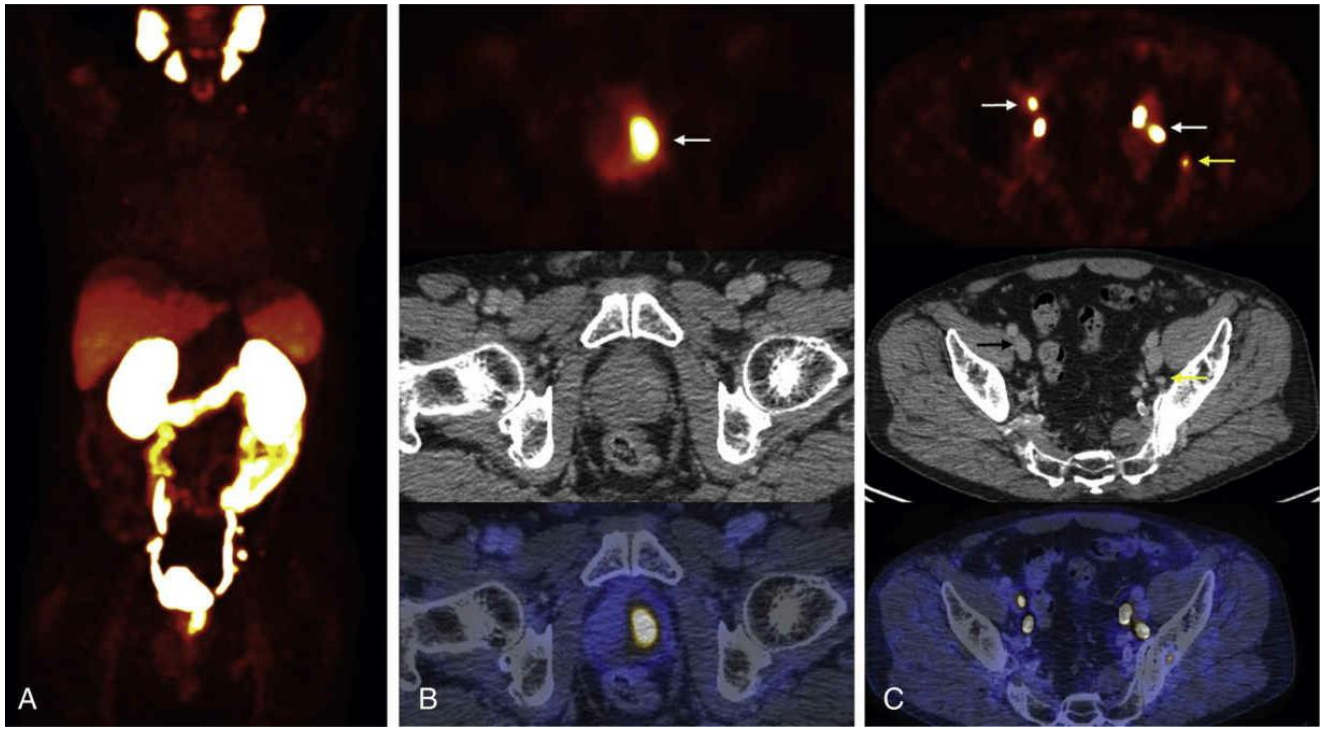
• FDG PET/CT has limited sensitivity for the assessment of prostate cancer. However, it could be positive in high-grade prostatic cancers. These patients have poorer prognosis compared with patients with FDG-negative malignancies

• In patients with disseminated lymph node involvement, further evaluation should be performed to exclude lymphoma or sarcoidosis

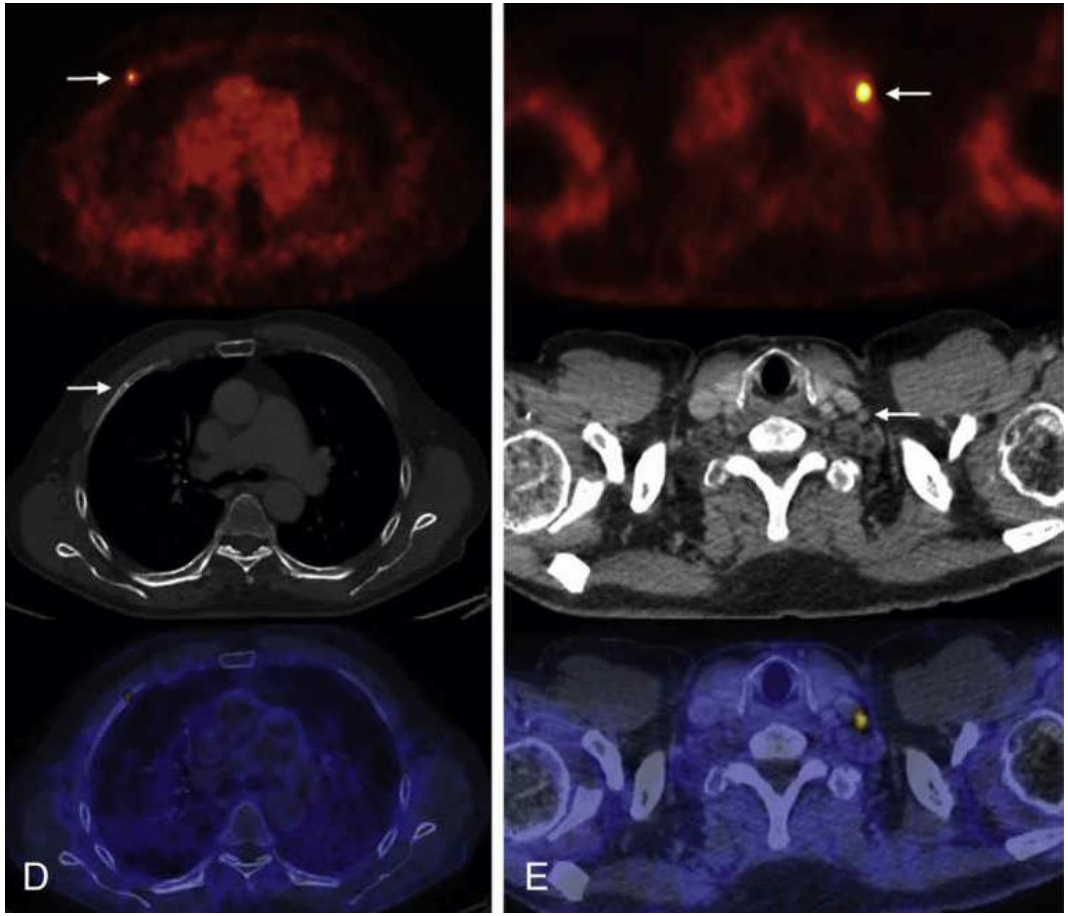
Case 2: ^{68}Ga-PSMA PET/CT—Staging

Findings

An 80-year-old male with high-risk prostate cancer, PSA = 55 ng/mL and GS = 9. ^{68}Ga-PSMA PET/CT shows tracer-avid primary prostate cancer (B, arrow) and multiple pelvic lymph nodes (C, white arrows), as well as a focal uptake in the left iliac bone (C, yellow arrow)….



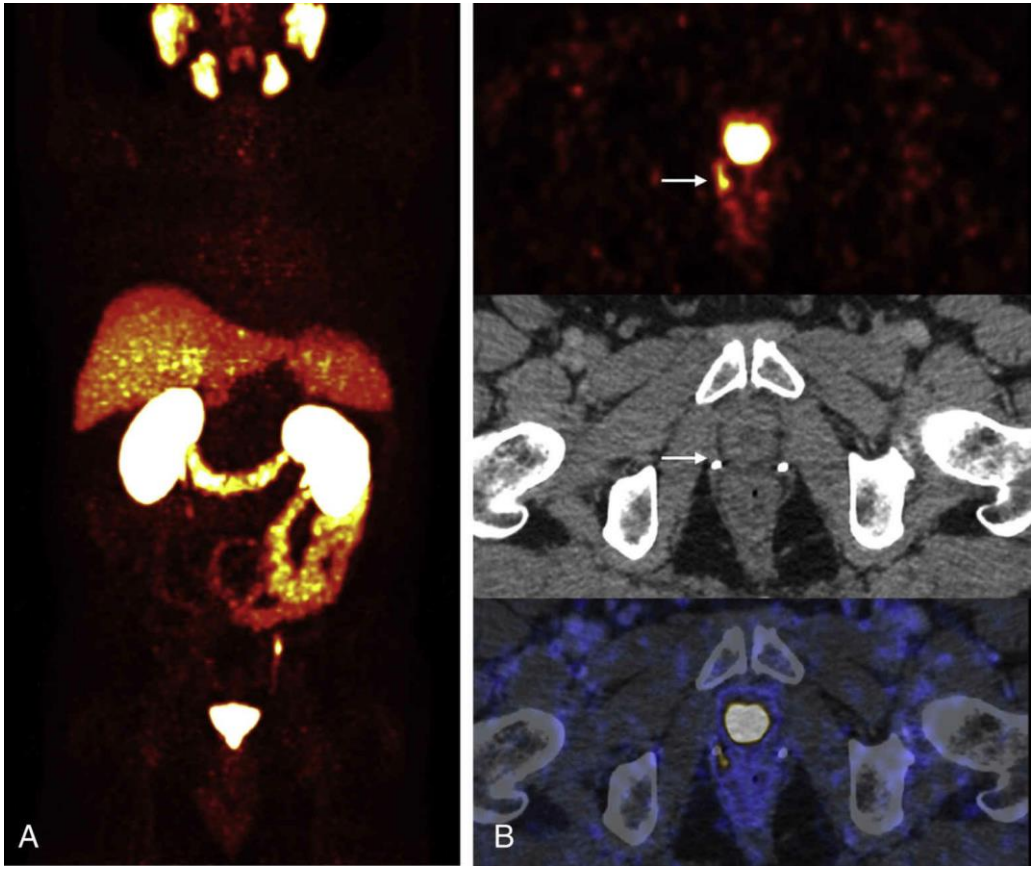
and left supraclavicular lymph node (E,arrow).
Of incidental note is a focal uptake in the right rib (D,arrow)



Case 3: ^{68}Ga-PSMA PET/CT—Biochemical Recurrence

Findings

A 63-year-old male with biochemical recurrence of high-risk prostate cancer, initial PSA = 10.2 ng/mL and GS = 8, PSA at the time of recurrence = 0.33 ng/mL. ^{68}Ga-PSMA PET/CT shows focal uptake in the right prostate bed (B, arrow), suggestive of malignancy recurrence



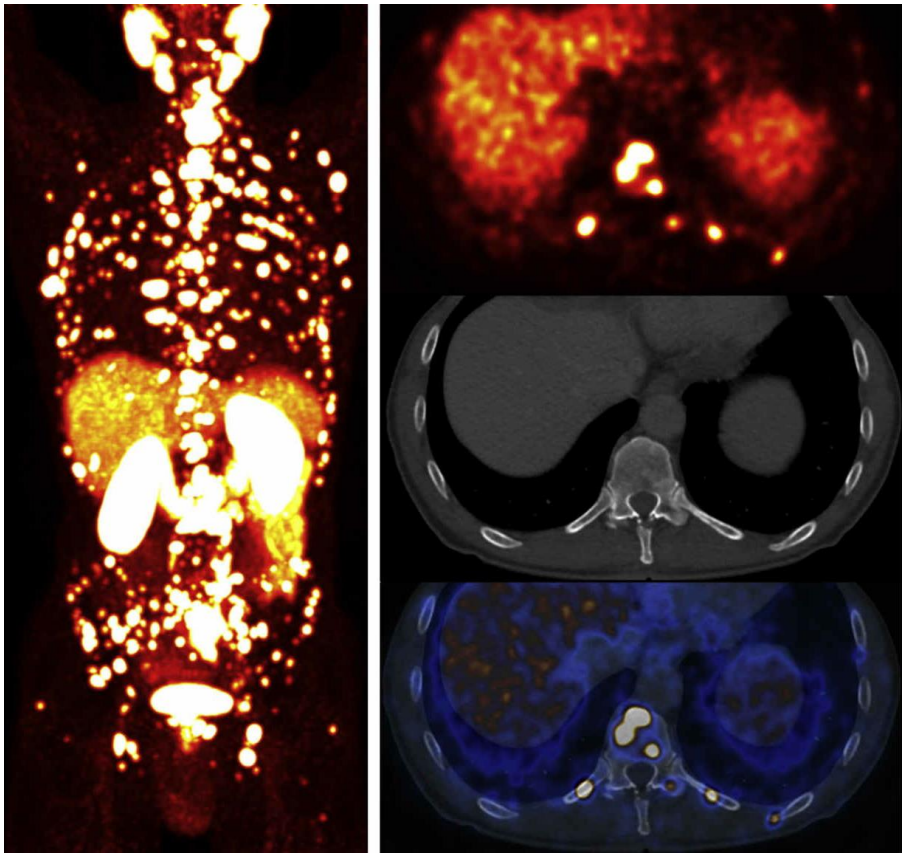
Teaching points

• 68Ga-PSMA PET/CT is a promising modality for the assessment of recurrent prostate cancer with excellent sensitivity and high tumor to background ratio
• It provides useful information even at low PSA levels (i.e.,<1 ng/mL)

Case 4: ^{68}Ga-PSMA PET/CT, Extensive Recurrent Metastatic Disease

Findings

A 68-year-old male with biochemical recurrence of primary intermediate-risk prostate cancer, initial PSA = 10.6 ng/mL and GS = 7. ^{68}Ga-PSMA PET/CT shows generalized bone marrow metastases without significant CT correlation



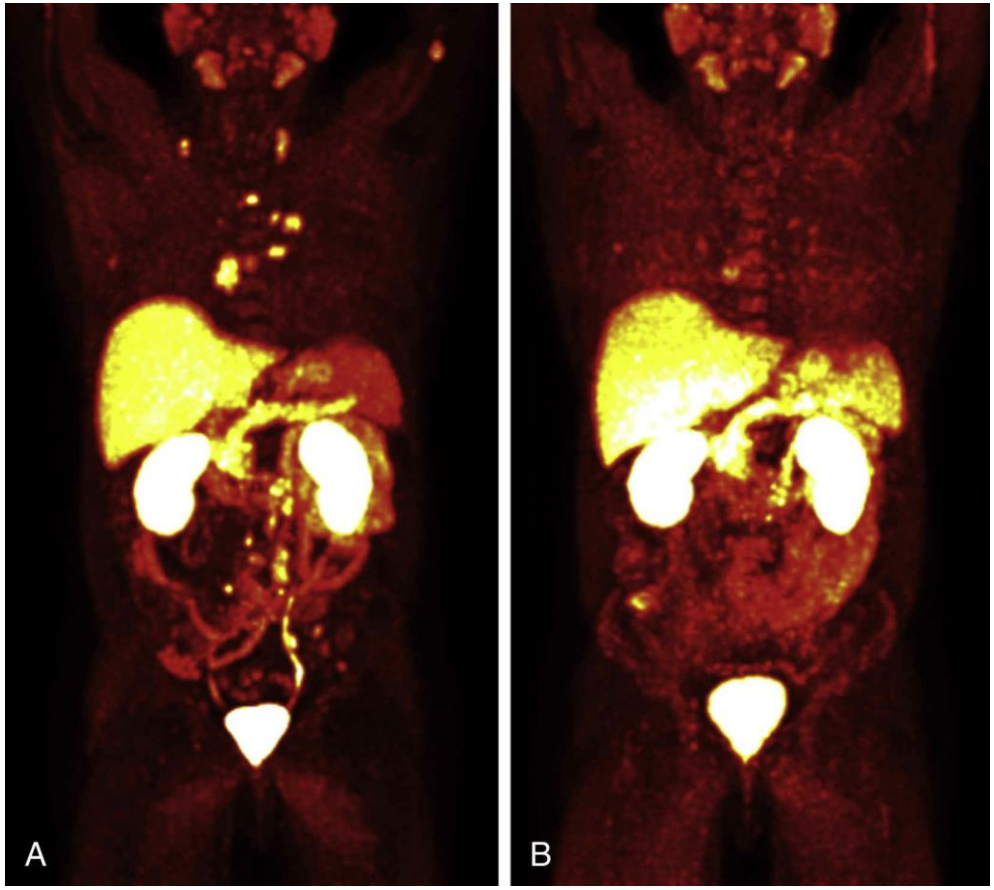
Teaching points

• Functional imaging modalities, such as 68Ga-PSMA and 18Fcholine PET/CT, are able to detect early bone marrow metastases before morphologic changes are evident
• PET/CT is a feasible modality for examining the whole body in one acquisition
• Specific targets, such as PSMA, can be used for both diagnostic and therapeutic (transonic) purposes

Case 5: ^{18}F-Choline PET/CT—Therapy Monitoring

Findings

A 58-year-old male with high-risk prostate cancer, initial PSA = 18.2 ng/mL and GS = 9. 18F-choline PET/CT shows tracer-avid bone metastases and cervical, mediastinal, and retroperitoneal lymph node involvement (A). A follow-up scan shows an excellent metabolic response to therapy (B)



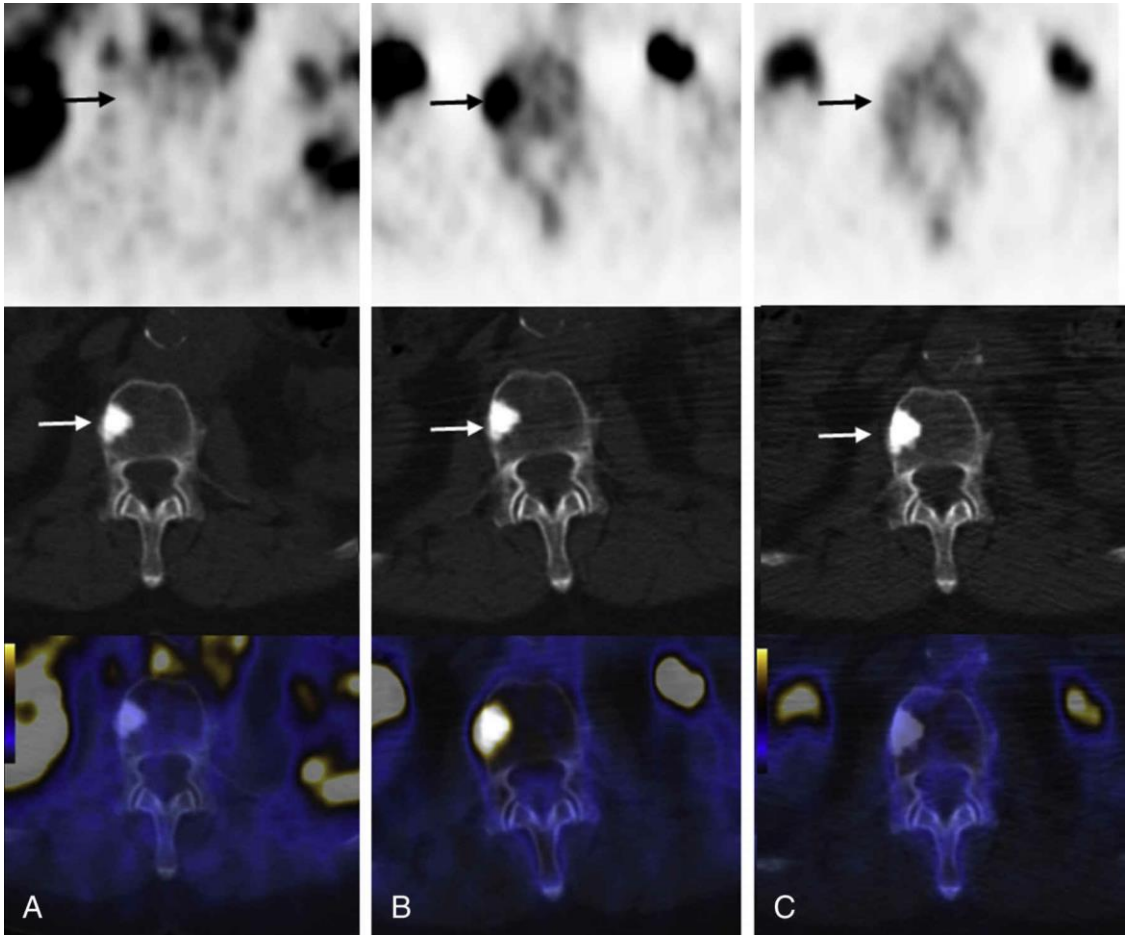
Teaching points

- 18F-choline PET/CT is a useful modality in the evaluation of therapy monitoring in patients with prostate cancer
- It may have limited value in the assessment of therapy response in densely sclerotic bone metastases
- If the uptake of 18F-choline is negative in densely sclerotic lesions (i.e., Hounsfield unit >800), additional evaluation with a bone-screening agent imaging (e.g., 18F-NaF PET/CT) is recommended

Case 6: Bone Metastases—Functional Versus Anatomic Imaging

Findings

An 85-year-old male with prostate cancer, PSA = 12.8 ng/mL, referred for imaging after therapy. Follow-up PET/CT imaging shows sclerotic lesions on CT, which are negative on 18F-choline (A, arrow), positive on initial 18F-NaF (B, arrow), and negative on post therapy 18F-NaF PET/CT (C, arrow)



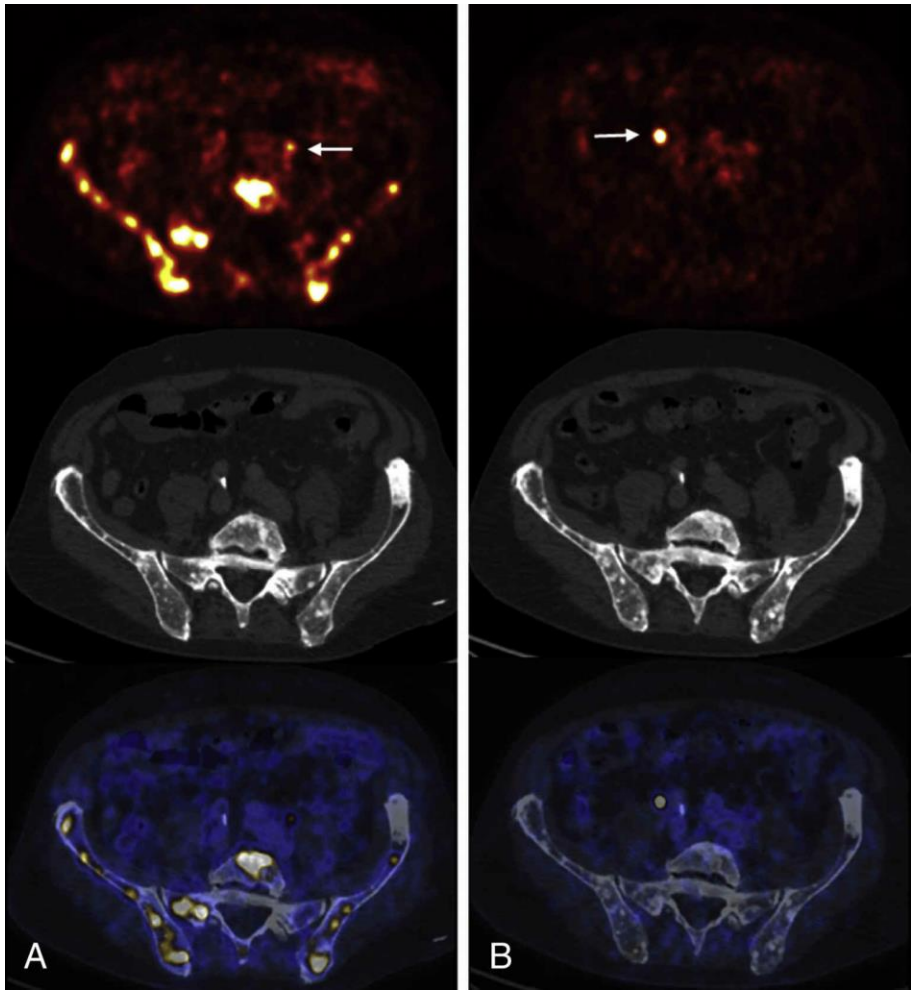
Teaching points

- A small tumor volume and low perfusion may limit the accuracy of 11C- and/or 18F-choline PET/CT in the assessment of densely sclerotic lesions
- Although CT shows stability or progression of disease, functional imaging proved nonviable sclerotic lesions (e.g., complete metabolic remission). It shows the superiority of functional over anatomic imaging in the assessment of prostate cancer
- In the case of 18F-choline-negative sclerotic lesions, further evaluation with a bone-screening agent imaging (e.g., 18F-NaF PET/CT) is recommended

Case 7 ^{68}Ga-PSMA PET/CT—Metastatic Bone Disease

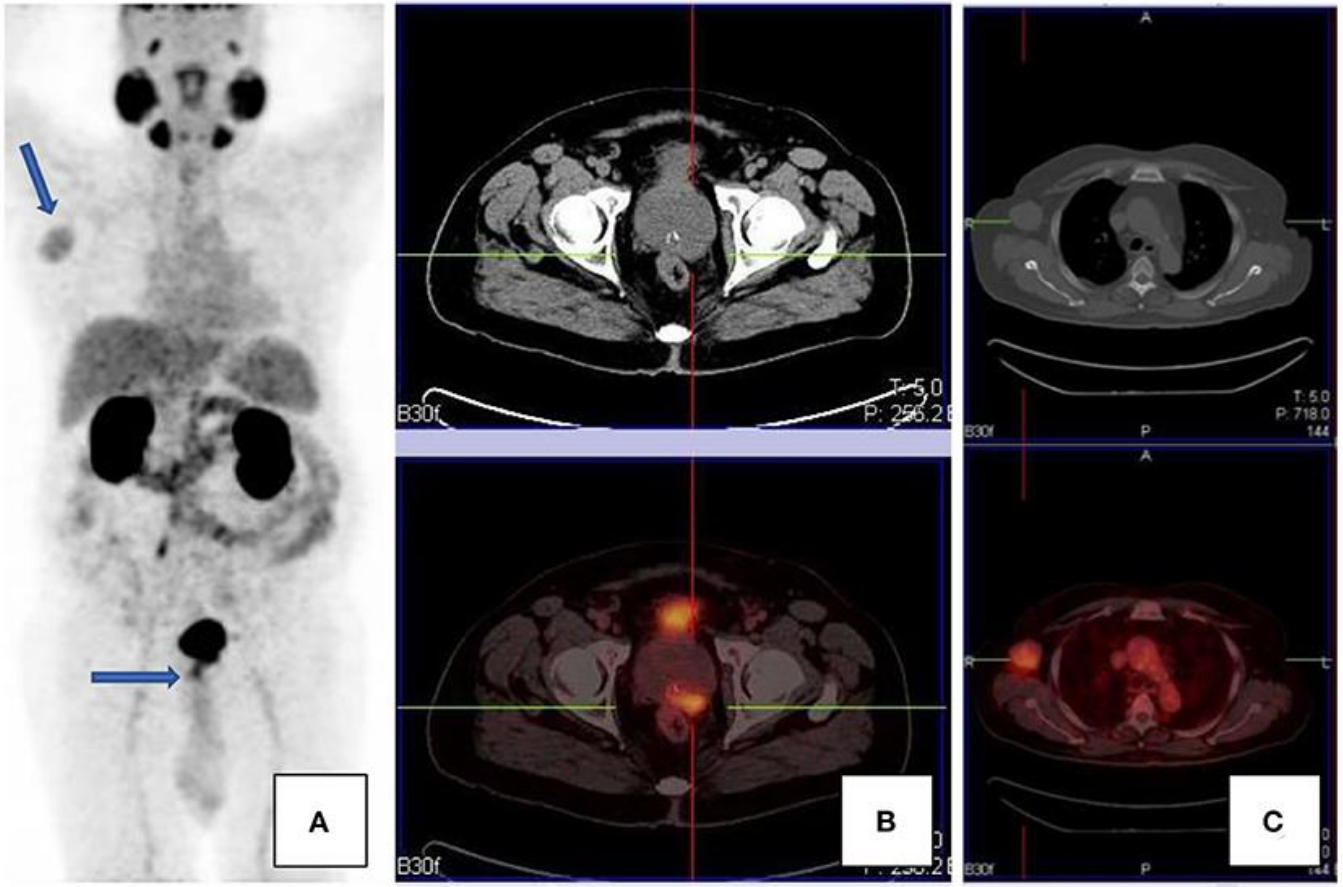
Findings

A 70-year-old male with primary low-risk prostate cancer, initial PSA = 9.2 ng/mL and GS = 5. 68Ga-PSMA PET/CT shows disseminated tracer-avid bone metastases (A) with an excellent response to therapy (B)



Teaching points

• In spite of a constant or progressive pattern of bone metastases on CT, complete remission is evident by metabolic imaging using 68Ga-PSMA, which emphasizes again on the value of functional imaging for the evaluation of response to therapy



A patient with confirmed prostate carcinoma, with focal uptake in the prostate gland [transaxial CT and fused PET/CT images, (B)], as well as an avid right axillary nodal mass [transaxial CT and fused PET/CT images, (C)]. Maximal intensity projection images are shown in (A). The axillary mass was an unlikely site of metastases, given the paucity of other metastases. The mass was excised and histology confirmed Hodgkin's lymphoma.

Teaching points

• 68Ga-PSMA seems to be superior to 18F-choline PET/CT for the evaluation of metastatic prostate cancer to skeleton and lymph nodes
• 68Ga-PSMA PET/CT seems to be superior to 18F-NaF PET/CT, with a higher sensitivity for the early detection of bone marrow–based metastatic lesions
• Metastases can have characteristics different from those of the primary tumor, with a different pattern of response to therapy
• PET/CT using different specific tracers may provide the most accurate statement regarding response to therapy.

Teaching points

PSMA expression is not specific to prostate cells. This includes tumors of the central nervous system, i.e., gliomas, thyroid cancer, breast, lung, lymphoma, neuroendocrine tumors, colorectal tumors, primary bone tumors, and many others

Radioligand Therapy (RLT)

177Lu: 177Lutetium is a medium-energy β-emitter. The electron energies (including β-particles and internal conversion electrons) are mean/max 147 keV/497 keV and correspond to ranges of approx. 0.28 mm/1.8 mm in soft tissue. Its physical half-life is 6.65 days. Gamma coemissions at 208 keV (emission probability 10.4%) and 113 keV (6.2%) enables detection of contaminations and scintigraphy

177Lu-PSMA

225Actinium-PSMA

In this guideline, the term *radioligand therapy* (RLT) is used for the low-molecular-weight (<10 kDa),Glu-urea-based, PSMA-targeting ligands PSMA-617and PSMA-I&T, whenever the commentary is generic

CRPC: Briefly, castration-resistant prostate cancer, either metastatic (m-prefix) or non-metastatic (nmprefix) by imaging, is defined by two consecutive PSA progressions (min. 2 weeks apart) to a 25% increase,or appearance of new lesions on imaging, despite hormonal manipulation leading to testosterone serum levels < 50 ng/dl (< 1.7 nmol/l)

INDICATIONS:

1. Patients with PSMA-positive mCRPC, who progressed under at least one novel androgen-axis drug (e.g., enzalutamide or abiraterone) and at least one taxane regimen (and are unfit for or refuse a second taxane regimen). Strong recommendation according to highest level of evidence: For this setting, the international phase-3 RCT VISION demonstrated superiority of [177Lu]LuPSMA-617 over the best standard-of-care (defined by physician's choice) regarding safety, efficacy, and quality-of-life

2. Patients with PSMA-positive mCRPC who progressed under at least one novel androgen-axis drug (e.g., enzalutamide or abiraterone) and docetaxel, but would still be possible candidates to receive cabazitaxel: strong recommendation based on a high level of evidence—for this setting, the 11 center phase-2b RCT TheraP demonstrated higher response rates (biochemical, imaging),longer progression free survival at an equal median overall survival, an increased number of long-term responders at 12 months, better patient-reported outcome in multiple domains, and a reduced number of grade 3/4 toxicities of 177Lu-PSMA-617compared to cabazitaxel

3. Patients with PSMA-positive but taxane-naïve mCRPC who progressed under at least one novel androgen axis drug (e.g., enzalutamide or biraterone)

4. Currently, various clinical situations are being evaluated in ongoing phase 2/3 RCTs and physicians are encouraged to refer patients to RCTs whenever available. If no option to participate in an RCT exists and alternative treatment options have been exhausted or are contra-indicated, it is reasonable and ethically warranted (Article 37 of Helsinki Declaration) to offer 177Lu-PSMA-RLT on an individual patient basis or in a compassionate care setting; but national regulations have to be considered

Relative Contra-indications:

Absolute: As 177Lu-PSMA-RLT is indicated for life-threatening, malignant disease, it is not reasonable to define absolute contra-indications. In general, the chances to improve should outweigh the risks of harming a patient. Therefore, the indication to treat patients with high-grade myelosuppression should be established with caution, and infrastructure to adequately deal with complications should be available

Relative Contra-indications:

Table 1 Relative contra-indications against ^{177}Lu-PSMA-RLT

Relative contra-indication	Comment
Life expectancy < 3 months	Except the main purpose is palliative (treatment of tumor-related symptoms)
ECOG ≥ 3	High radiation burden to caregivers and relatives, while most likely only prolonging suffering but not quality-life-time
Unmanageable urinary incontinence	A urinary catheter alone is no contra-indication; it should eventually be even considered to improve radiation protection
Acute urinary tract obstruction or hydronephrosis	Patients with diagnosed or risk of urinary retention, [^{99m}Tc]Tc-MAG3 or -DTPA renal scintigraphy should be considered a baseline exam [83]
Unmanageable psychiatric comorbidities	Patient unable to be isolated on a nuclear medicine therapy unit (if requested by local radiation protection regulations)
Other severe (e.g., cardiovascular) comorbidities	e.g., patient must be able to tolerate increased hydration
Progressive deterioration of organ function/risk of multiorgan failure	e.g., GFR < 30 ml/min, creatinine > twofold ULN, liver enzymes > fivefold ULN
Acute infections	–
Myelosuppression[a]	WBC < 2.5/nl ANC < 1.5/nl PLT < 75/nl

In non-compromised patients, the approved treatment regimen for [177Lu]Lu-PSMA-617 is 7.4 GBq (200 mCi) per cycle at 6 w (±1 w) interval for a maximum of 6 cycles. In clinical practice, safety and antitumor activity of [177Lu]Lu-PSMA-617 and [177Lu] Lu-PSMA-I&T have successfully been demonstrated for a range of 6–9.3 GBq per treatment and for treatment intervals of 4–10 weeks

Any toxicity that is considered unacceptable by the patient, any life-threatening toxicity that does not resolve within 4 weeks, GFR loss to<30 ml/min, or unexpected liver toxicity (AST or ALT>fivefold upper-limit of normal): Discontinue 177Lu-PSMA-RLT