Nuclear Medicine Findings in Prostate Cancer

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92.1 Initial Staging

Bone scintigraphy is a highly sensitive imaging procedure for detecting bone metastases but it is often nonspecific. Positive findings may be related also to degenerative joint disease or to benign bone disease such as skeletal trauma or Paget's disease.

It is particularly important in high-risk primary staging before radical prostatectomy or radiation therapy to assess the patient's burden of the disease to evaluate prognosis and efficacy of specific treatment [1, 2].

Bone Scintigraphy (B.S) offers the advantage of providing whole body examination. The most commonly used tracer for imaging the skeleton is methylene diphosphonate (MDP) labeled with Technetium 99 m (Tc-99 m).

From the early eighties, it was described that patients found initially to have an abnormal bone scan had a mortality rate at 2 years of approximately 45 % compared with 20 % for those with a normal scan. For preoperative management bone scan is not required in asymptomatic patients or where PSA levels are below 10 ng/ml, whereas, in symptomatic patients with bone pain and low or increased PSA the bone scan is recommended. In a large analysis, bone metastases were found in less 1 % at patients with PSA < 20 ng/ml and negative predictive value was 99.7 %. Spine is the most common site for metastases. As the diagnostic accuracy of planar BS is low, SPECT and SPECT/CT procedures are proposed for imaging.

SPECT/CT has optimized the use of planar BS with an improved sensitivity range of 87–92 %, specificity of about 91 %, a positive predictive value of 82 %, a negative predictive value of 94 % and accuracy of 90 %. Recently Even-Sapir [3] with multi field of view (FOV) SPECT reported sensitivity 92 % (over 62 % for planar images) in patient based analysis and from 39 to 71 % in a lesion based analysis (Fig. 92.1a, b).

PET/CT is a modern imaging modality that offers several unique advantages compared with other imaging techniques. The purpose of combining CT and PET systems in a single scanner (PET/CT) offers the precise anatomical localization of regions (and lesions) identified on the PET tracer uptake images. Fluorine-18-Fluorodeoxyglucose (^{18}F FDG) is the most commonly used positron emission tomography (PET) radiotracer for oncology. But ^{18}F FDG is of limited value in Prostate cancer due to low FDG avidity of most Prostate cancer cells, and to the often small volume of the primary tumor (micro carcinoma). In addition urinary activity limits pelvic evaluation and increased uptake in benign prostatic hyperplasia. The majority of primary prostate tumors (81 %) present low FDG uptake [3].

The average SUV (a semiquantitive index) was 4.5 ± 1.4 for prostate cancer, compared to 4.1 ± 1.0 for benign tissue. Nevertheless, the overall clinical experience with ^{18}F FDG in

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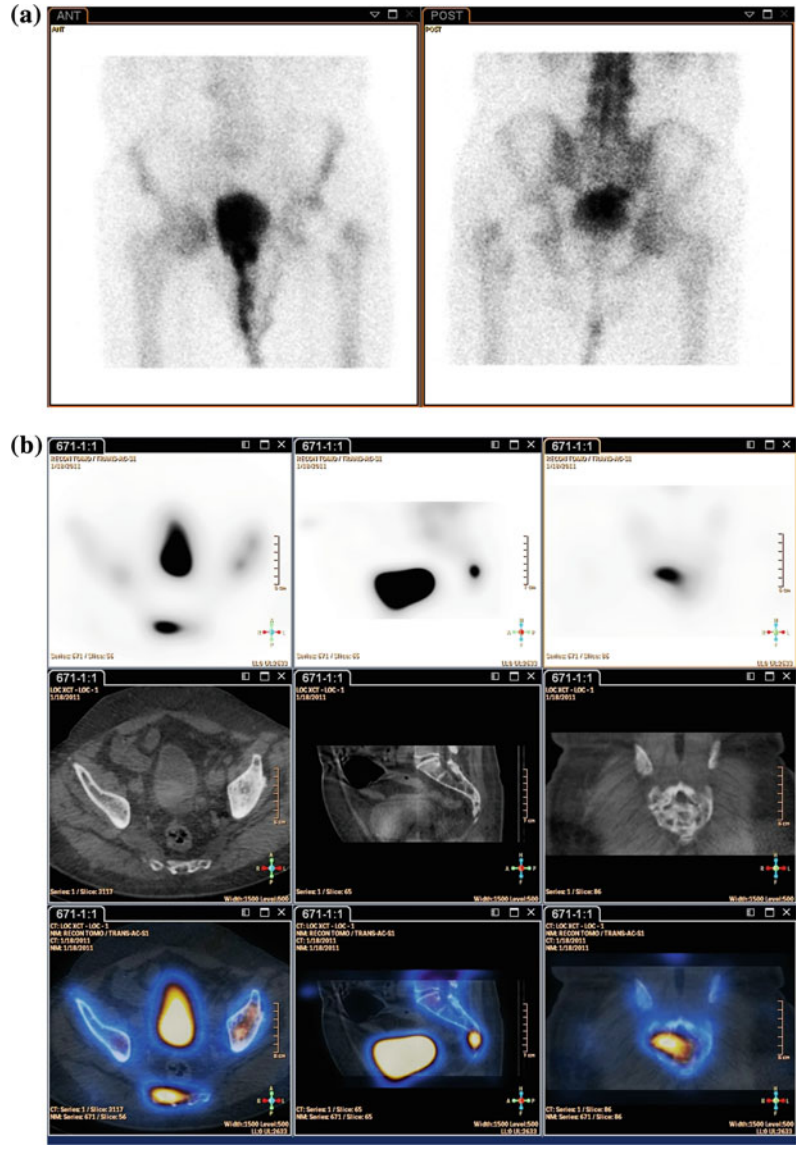

Fig. 92.1 **a** Staging of prostate Ca (Gl = 8, PSA = 55 ng/ml) Tc-99 m MDP—bone scan: Pelvis (*normal static view*) **b** SPECT/CT imaging revealed a bone metastasis in the sacrum

Prostate cancer suffers from heterogeneity in published studies with regard to the clinical phase of the disease, the relatively small numbers of patients and the variability and limitations in the validation criteria.

^{18}F FDG is insensitive for staging pelvic lymph nodes prior surgery and presents lower sensitivity than bone scintigraphy for the detection of active bone metastases. Shreve et al. [4] reported sensitivity only 62 % for bone metastases and a positive predictive value of 98 %. In predominantly sclerotic bone metastases FDG is less accurate and such lesions show lower tracer uptake than lytic bone metastases. FDG uptake is higher in tumors with higher Gleason scores (>7) and close correlation between increased PSA and PSA velocity levels has been shown in some clinical studies [5]. ^{18}F Fluoride a pure bone seeking substance may provide a more sensitive "conventional" bone scan and is superior for FDG non avid tumors. Comparative studies by Even-Sapir [3] were performed in patients with either localized high risk or metastatic Prostate cancer. The sensitivity and specificity of ^{18}F

Fluoride PET/CT was 100 % and 100 %, respectively (versus 70 and 57 % for planar BS) and authors concluded that ^{18}F Fluoride PET/CT is highly sensitive and specific imaging modality for the detection of bone metastases in high risk Prostate cancer patients (with Gleason > 8, PSA >20 ng/ml, or nonspecific sclerotic lesion on CT).

Other PET tracers used to study primary Prostate cancer include ^{11}C and ^{18}F labeled Choline derivative and ^{11}C Acetate. Both Choline and Acetate are key components of the lipid synthesis pathways and Choline uptake seems to be a marker of cell proliferation in Prostate cancer. The major advantage of the two tracers (over FDG) is the negligible renal excretion of tracer for better visualization of the prostate bed and regional pelvic lymph nodes. The major obstacle for routine use is the short life of ^{11}C and the age-related physiologic accumulation of ^{11}C Acetate.

^{18}F Fluoromethyl Choline (FCH) has the advantage of a longer half-life (T½ = 110 min) compared with ^{11}C Choline (T½ = 20 min) and early dynamic imaging by using coregistered CT data can be performed.

But FCH PET/CT imaging seems to have a limited value for initial staging of prostate cancer. Schmid et al. [6] published that FCH is not appropriate for initial T staging due to the limited spatial resolution of PET that does not enable the assessment of capsular infiltration, which in turns defines T3 tumors.

Husarik et al. [7] demonstrated that SUV_{max} values in metastatic lymph nodes (mean 5.04) and in bone metastases (mean 6.3) at initial staging were higher than those of subcutaneous fat (mean 0.2) or physiological uptake in bone of lumbar spine (mean 1.3). The possibility to enhance the detection rate of bone metastases on FCH PET/CT is late imaging at 65–200 min post injection, because the accumulation in bone metastases on late imaging rises compared to early imaging. To note that late imaging has no influence in lymph node metastases uptake.

FCH PET/CT can be helpful to guide biopsy if a patient has persistent elevated PSA levels and the biopsies remain negative for tumor. One major limitation of FCH PET/CT for initial staging is the general inability of PET imaging to detect micrometastases [7]. The identification of occult lymph node metastases appears to have an impact on the outcome of patients with Prostate cancer because these patients show significantly increased risk of recurrence or death (Fig. 92.2).

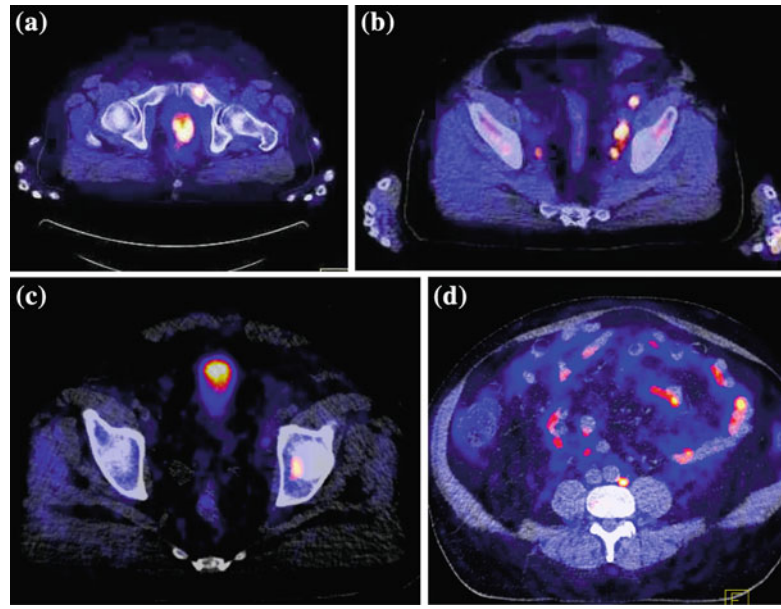

Fig. 92.2 Prostate cancer: (Gl = 7, PSA = 42 ng/ml-) Initial staging 18F FCH: lesion of the prostate (on the *left* SUVmax = 11, 7) Pubic (SUVmax = 10, 5) + L. Acetabulum (SUVmax = 6, 7) bone metastases, Inter + Ext Iliac LN (SUVmax = 11, 0) and paraortic LN (SUVmax = 4) metastases

92.2 Restaging

Bone scans remain the most common examination requested in patients suspected of having new skeletal metastases, usually in the setting of new bone symptoms or increasing PSA levels. The pattern of increasing PSA levels correlates with positive bone scan independently of other clinical variables.

In patients with confirmed metastatic disease, serial scans are often used to assess the extent of bone involvement and the effectiveness of therapy. As patients with prostate cancer with bone metastases often survive for a number of years, the bone scan provides a convenient method to monitor the disease over time.

Caution must be used in early assessment of bone metastases response to treatment due to the flare phenomenon, which is seen in some patients within the first 6 months after hormonal manipulation, whether via administered drugs or orchiectomy, and is associated with good prognosis [8]. It is important than clinicians appreciate that decisions to change or discontinue therapy should not be made until there is convincing clinical radiographic and scintigraphic evidence of metastatic disease progression. Patients with a flare phenomenon seen on bone scan, it might be valuable to exploit the high sensitivity and specificity of ^{18}F Fluoride PET/CT.

In a follow-up study FDG PET/CT has potential value when PSA > 4 ng/ml or increases > 0.2 ng/ml per month, in advanced or untreated cancer, in negative bone/scan and in equivocal pelvic CT findings. It is known that ^{18}F FDG PET/CT has poor accuracy for differencing local recurrence and scar. However is more likely to detect distant metastases (Fig. 92.3).

The detection rate of metastases by FDG PET/CT is highly depended on the level of the serum PSA and on the rate of change of the serum PSA level over time (PSA velocity). FDG PET detected lymph node metastases in 50 % of patients with PSA greater than 4 ng/ml or PSA vel greater than 0.2 ng/ml/month. The low detection rate of metastases by FDG PET/CT in patients with low PSA (or low PSA vel) may indicate that the incidence of metastasis is low in this group of patients. Or it may mean that there exists a small tumors burden which is below the spacial resolution of PET or that the tumor has a low glycolytic rate which is below the metabolic resolution of FDG PET.

Schoder et al. [9] reported sensitivity 79 % and specificity 66 % for PSA levels > 2.4 ng/ml. The same author [10] presented that overall FDG PET detects local or systemic disease in 31 % of patients with PSA relapse. PET/CT is superior to CT but inferior to MRI for detection of recurrence in the prostate bed. ^{11}C Acetate may also be useful in the detection of tumor recurrence in some patients treated previously with prostatectomy or radiation, with lesion dectability of 75 % and false positive rate of up to 15 %.

Choline PET imaging plays a more relevant role in the detection of Prostate relapse. Choline PET shows higher specificity and higher accuracy compared to all conventional imaging

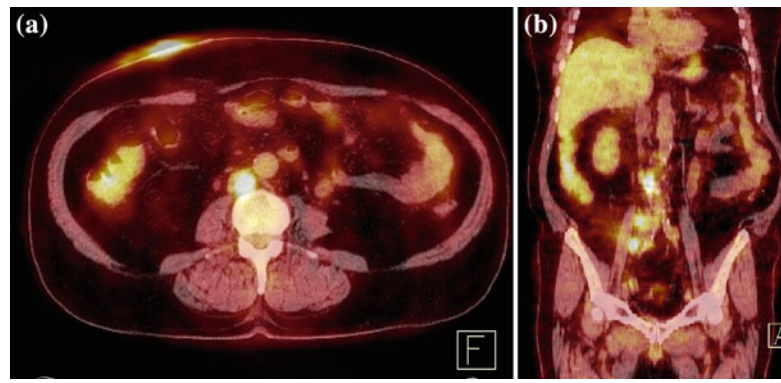

Fig. 92.3 Restaging of prostate cancer, 4y post prostatectomy and hormotherapy (Gl = 8, PSA = 80 ng/ml) ^{18}F FDG PET/CT: shows metastatic paraortic LN (SUVmax = 6, 0)

methods. Choline PET imaging, supplying a whole body tomography exam, has the major advantage of detecting local and distant metastases, within a single session, with a good accuracy. However, patient criteria still have to be defined. The exact threshold of serum PSA, the influence of medication (e.g., testosterone deprivation) and PSA kinetics are important factors on PET/CT detection. In particular, patients with high risk of distant metastases or those susceptible to second surgery and/or radiation therapy could benefit the most from early identification of the site of recurrence. The accuracy of conventional imaging modalities in detecting lymph nodes is low. Molecular imaging, particular Choline PET/CT represents the more accurate exam to stage high risk Prostate cancer and it is useful in staging patients with biochemical relapse, in particular when PSA kinetics is high or PSA levels are more than 2 ngr/ml [11, 12].

In biochemical recurrence imaging with ^{18}F FCH PET/CT seems to be higher among patients with higher PSA at the time of recurrence, shorter PSA dt (PSA duplication time) or higher initial Gleason grade [13].

Cimitan et al. [14] found positive FCH scans in 54 patients examined for rising PSA post radical prostatectomy, radical radiotherapy or while on hormones. All patients with PSA $>$ 4 ng/ml and initial Gleason $>$ 7 had positive scans, but rarely positive (3/38) among patients with PSA $<$ 4 ng/ml. Pelosi et al. [15] noted an overall detection rate of 42.9 % in patients with rising PSA post-prostatectomy and demonstrated an increase in positive ^{18}F FCH scans, with higher PSA at recurrence (20 % at PSA $<$ 1 ng/ml, 44 % at PSA 1–5 ng/ml and 82 % at PSA $>$ 5 ng/ml).

Husarik et al. [7] found FCH imaging reliable for detection of PSA recurrence $>$ 2 ng/ml with good sensitivity 83–87 %, moderate sensitivity (70–75 %) for PSA recurrence $<$ 2 ng/ml and for small lymph mode metastases (<1 cm) with minimal FCH uptake. Langsteger et al. [16] noted the higher specifity of FCH compared with ^{18}F Fluoride (96 vs. 91 %) and the better accuracy levels (95 vs. 98 %).

The overall sensitivity for detecting any recurrence with FCH imaging at PSA levels 2–5 ng/ml seems to be acceptable (>80 %) but the sensitivity decreases for PSA levels $<$ 2–5 ng/ml (about 50 %). Known that insolated local recurrence is more likely at lower PSA levels and these recurrences may be more difficult to detect [17, 18].

92.3 Therapy Response

^{18}F FDG PET may have a limited role in assessing treatment response to chemotherapy in hormone resistant disease and also in monitoring anti androgenic treatment. Early changes in glucose metabolism could enable monitoring metabolic changes in Prostate tumors after treatment in advanced disease with aggressive Prostate cancer [19].

Recently Mc Carthy et al. [20] examined prospectively 26 patients with castrate-resistant Prostate cancer and ^{18}F FCH PET/CT imaging was compared with standard imaging (bone scan or CT) for monitoring treatment. In FCH PET/CT 81 % of the detected lesions are concordant and 19 % are discordant after a 2 years follow-up.

False positive results were related to inflammatory lymph nodes and false negative to sclerotic metastases and iliac metastases post radiation therapy. FCH imaging presented 96 % sensitivity, 96 % specificity, 99 % PPV, 81 % NPV, and 96 % accuracy for the detection of bone and soft tissue metastases in castrate-resistant patients.

Radiotherapy dose escalation to the whole Prostate has been associated with improved disease control and together with higher gastrointestinal and genitourinary toxicity.

^{11}Choline and ^{18}F-FCH PET/CT may be useful for defining dominant intra prostatic lesion (d $>$ 5 mm) for local salvage therapy, for any pelvic lesion in recurrence stage for salvage therapy and also guiding dose escalation [21].

In patients treated with stereotactic body radiation therapy 3 years overall survival was 92 %.

The androgen receptor plays an important role in the growth and proliferation of Prostate cancer as well as modulation of androgen status. ^{18}F FDHT is a radiolabeled analog of dihydrotestosterone. Preliminary studies reported that ^{18}F FDHT may be useful in monitoring treatment response [22].

92.4 Conclusion

In Prostate cancer imaging techniques could be useful for staging of primary disease, restaging after PSA relapse, detection of metastatic lesions and predicting the aggressiveness of the disease.

In Nuclear Medicine imaging common techniques using bone scan with Tc-99 m MDP (planar and SPECT/CT), Positron Emission Tomography imaging added supplementary value with the new agents as ^{18}F FDG and ^{18}F Fluoride.

Advanced technology with coregistiation of CT or MRI images with SPECT or PET, improvements in imaging cameras, image reconstruction algorithms have improved the quality of images. Also development of new tracers as ^{11}C Choline, ^{18}F Choline, and radiolabeled androgen-receptor binding compounds with higher selectivity and rapid localization promise a greater staging, restaging and treatment monitoring of Prostate Cancer.

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