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Seminars in
NUCLEAR
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Prostate Cancer: Role of SPECT and PET in Imaging Bone Metastases

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In prostate cancer, bone is the second most common site of metastatic disease after lymph nodes. This is related to a poor prognosis and is one of the major causes of morbidity and mortality in such patients. Early detection of metastatic bone disease and the definition of its extent, pattern, and aggressiveness are crucial for proper staging and restaging; it is particularly important in high-risk primary disease before initiating radical prostatectomy or radiation therapy. Different patterns of bone metastases, such as early marrow-based involvement, osteoblastic, osteolytic, and mixed changes can be seen. These types of metastases differ in their effect on bone, and consequently, the choice of imaging modalities that best depict the lesions may vary. During the last decades, bone scintigraphy has been used routinely in the evaluation of prostate cancer patients. However, it shows limited sensitivity and specificity. Single-photon emission computed tomography increases the sensitivity and specificity of planar bone scanning, especially for the evaluation of the spine. Positron emission tomography is increasing in popularity for staging newly diagnosed prostate cancer and for assessing response to therapy. Many positron emission tomography tracers have been tested for use in the evaluation of prostate cancer patients based on increased glycolysis (^{18}F-FDG), cell membrane proliferation by radiolabeled phospholipids (^{11}C and ^{18}F choline), fatty acid synthesis (^{11}C acetate), amino acid transport and protein synthesis (^{11}C methionine), androgen receptor expression (^{18}F-FDHT), and osteoblastic activity (^{18}F-fluoride). However, there are presently no accurate imaging modalities to directly, reproducibly, and effectively delineate bone metastases in prostate cancer.

Semin Nucl Med 39:396-407

About 350,000 patients will develop bone metastases (BM) in the United States each year.[1-3] The skeletal system is the third most common site of metastases after the lungs and liver, and 80% of all reported metastatic bone disease is in patients with breast, lung, and prostate cancer. In the United States, prostate cancer is the second leading cause[4] of cancer-related deaths in men (exceeded only by lung cancer) and causes more than 56,000 deaths per year in the European Union.[3,5] Although prostate cancer is one of the few cancers that grow so slowly that it may never be life-threatening, it can show an aggressive pattern that may spread and cause the death of patients mainly due to malignant involvement of bone. This caused an estimated 30,350 deaths in the United States in 2005.[6] The introduction and widespread use of prostate-specific antigen (PSA) testing in the early 1990s is associated with dramatic shifts in the incidence, age, and stage at diagnosis of this cancer. Currently, PSA is the most commonly used screening method for the diagnosis and follow-up in the management of prostate cancer patients, with ultrasound-guided biopsy following in the second place. PSA screening led to a significant drop in the incidence of metastatic disease found at presentation in prostate cancer patients from 20% during 1972-1979 to 5% during 1995-2001.[3] However, using clinical examination alone, staging of prostate cancer will be underestimated, usually in 30%-60% of patients.[7]

Therefore, early diagnosis of metastatic bone involvement in prostate cancer is crucial for selecting appropriate therapy, to assess the patient's prognosis, and to evaluate the efficacy of bone-specific treatments that may reduce future bone-associated morbidity.

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 0001-2998/09/$-see front matter
doi:10.1053/j.semnuclmed.2009.05.003

Bone scanning is the preferred investigation in patients with suspected recurrent disease. Despite the limited sensitivity and specificity of this technique, it provides useful information concerning the localization of bone involvement, prognosis, and effectiveness of treatment.[8,9] However, the diagnostic accuracy of planar scintigraphy can be improved by single-photon emission computed tomography (SPECT), which enhances the performance of the bone scan by providing more accurate anatomic details of individual vertebrae.[10-12]

At present, there are an unprecedented number of novel molecular imaging agents that are potentially available for the assessment of BM in prostate cancer. This article reviews the field of nuclear imaging, concentrating on SPECT and positron emission tomography combined with computed tomography (PET/CT) modalities.

Pattern of BM

In general, hematogenous metastases to bone usually originate in the medullary cavity followed by involvement of the cortex. There are 2 main types of osseous response to a metastasis: bone resorption caused by stimulation of osteoclasts, and bone formation secondary to the activation of osteoblasts. Depending on their pathophysiology, BM are classified as osteolytic, osteoblastic, or mixed (containing both osteolytic and osteblastic elements). These 3 types of BM differ in their effect on bone; consequently, this will affect the imaging modality that best depicts the lesions. Previous studies have shown that prostate cancer cells have an increased affinity for the endothelium of bone marrow in preference to the endothelium of other organs, which is the usual location of osteoblastic lesions.[13-15] In addition, a recent study suggested that PSA plays a crucial role in osteoblastic BM by promoting both osteoblast proliferation and apoptosis of osteoclast precursors.[16] Axial bones are the most common sites of malignant bony infiltration in prostate cancer, which may be due to the presence of the portal vein-like paravertebral venous system in the lumbar spine.[17,18]

Conventional Nuclear Imaging Modalities

Planar Bone Scintigraphy

For several decades, bone scanning has been used extensively for the evaluation of prostate cancer patients. A survey of urologists revealed that 70% of them order a bone scan in cases of increasing PSA levels after radical prostatectomy or radiation therapy.[19] Bone scintigraphy (BS) offers the advantage of providing an instant whole-body examination. The most commonly used tracer for imaging the skeleton in conventional nuclear medicine is methylene diphosphonate (MDP) labeled with ^{99m}technetium (^{99m}Tc). The exact mechanism of this tracer uptake is not fully understood, but it is believed that the compound is chemisorbed onto bone surfaces. Uptake depends on local blood flow and osteoblastic activity and accumulation of this tracer is focal because nearly all BM are accompanied by an osteoblastic reaction. Although ^{99m}Tc-MDP BS has a higher sensitivity than plain-film radiography, false-negative bone scans can result from the absence of reactive changes or slow growing lesions in which reactive bone is not detectable.[20-24] The specificity of BS is also limited because the uptake of the radiotracer is not tumor specific. Moreover, factors such as trauma or surgery, degenerative changes, and infections can result in false-positive bone scans.

Some studies show that the extent of skeletal metastatic disease from prostate cancer can be an independent prognostic marker in patients with an abnormal bone scan.[25-27] Lund and Suciu[28] described the prognostic role of skeletal scintigraphy in prostatic carcinoma; patients found initially to have an abnormal scan had a mortality rate at 2 years of approximately 45% compared with 20% for those with a normal scan.

BS is used routinely to assess high-risk prostate cancer patients. Clinical nomograms, such as PSA levels and Gleason score, can be used to identify patients at high risk of metastatic disease at presentation.[29,30]

For preoperative management, BS is not required in asymptomatic patients or where serum PSA levels are <10 ng/mL. However, in symptomatic patients with bone pain and low or increased PSA levels it will be recommended by urologists.[31] Nevertheless, in a large retrospective analysis, BM were found in $<1\%$ of patients with PSA of <20 ng/mL: among 306 men only 1 (PSA 18.2 ng/mL) had a positive bone scan, yielding a negative predictive value of 99.7%.[32-36]

In postoperative patients, a pattern of increasing PSA levels correlates with a positive bone scan independently of other clinical variables, such as PSA levels and Gleason score.[37]

In addition, bone scan can be used to monitor response to therapy; however, it can be misleading if performed too early[38,39] due to an intense osteoblastic response following successful therapy, the so-called "flare phenomenon." A flare response usually lasts about 6 months after therapy and is associated with a good prognosis.[38]

A number of studies have suggested the use of a bone scan index offering the possibility of semiquantitative evaluation of bone scans.[25,26,40,41] They show that bone scan index can predict the outcome for patients with androgen-independent prostate cancer.

SPECT

The spine is the most common site for metastases arising from several neoplasms. Metastatic spread is the cause of 20%-50% of solitary spine lesions, and 30%-50% of patients with metastatic involvement of the spine are asymptomatic. Therefore, detection of these lesions is very important to determine prognosis and to define optimal therapy, which in turn reduces the risk of pathologic fracture, neurological complications, and other morbidity.

Most spinal metastases occur in the posterior part of vertebra due mainly to the many short secondary (or peripheral) intraosseous arteries, which supply the outer third of the vertebral body.[12,18] The posterolateral "corner" of the verte-

bral body, which lies 3-8 mm off the posterior surface, has the most abundant adjacent periosteal network, and thus the highest frequency of blood-borne metastases.[18]

As the spine is a frequent site for degenerative joint disease, the diagnostic accuracy of planar BS is low, particularly for a single focus of abnormal increased tracer uptake. Many studies show that SPECT can minimize the shortcomings of planar BS in the assessment of the spine.[1,10-12,18,42-45] SPECT has optimized the use of planar BS, with improved sensitivity range of 87%-92% and specificity of about 91%, and a positive predictive value of 82%, negative predictive value of 94%, and an accuracy of 90%.

Recently, Even-Sapir et al[46] performed a novel multi-field-of-view (FOV) SPECT study with 3 or 4 SPECT views of the axial skeleton acquired within 24-32 minutes in 24 high-risk prostate cancer patients.[47] They reported that the sensitivity of BS improved from 69% for planar images to 92% for multi-FOV SPECT in a patient-based analysis and from 39% to 71% in a lesion-based analysis. The performance of multi-FOV SPECT on the entire skeleton was not only useful in the detection of malignant lesions in the lower thoracic and lumbar spine, but also resulted in the detection of BM in other locations, including the skull, upper spine, rib cage, pelvis, and long bones.

Radioimmunoscintigraphy

Over recent years radioimmunotargeting has led to the development of specific agents for applications in both imaging and therapy.[48-51] Capromab pendetide (ProstaScint, EUSA Pharma, Munich, Germany) conjugated to ^{111}Indium is a murine monoclonal antibody, which binds to an intracellular component of the prostate-specific membrane antigen (PSMA). PMSA is a transmembrane glycoprotein on the surface of prostatic epithelial cells with 3 recognized extracellular, transmembrane, and intracellular components. The intracellular component[52] is only available when the membrane is disrupted (eg, dead or dying cells).[53] This is probably responsible for the limited performance of the capromab pendetide scan in detecting metastases accurately, especially in bone lesions. Recently, labeling of monoclonal antibodies to the extracellular component of the PSMA has been attempted as a possible second-generation scan that could improve the accuracy of identifying extraprostatic disease.[54] To improve anatomic localization of revealed lesions, fusion with cross-sectional imaging is gaining increased popularity.[55] PSMA is expressed in almost all prostate cancer cells in the primary, as well as metastatic lesions, and appears to be maximally expressed after withdrawal of androgen.[53,56-58]

The overall sensitivity and specificity of capromab pendetide scan for the detection of prostate cancer cells vary in several studies,[59-64] showing average sensitivities of 60%, specificities of 70%, positive predictive value of 60%, and negative predictive value of 70%.[64]

Availability and cost-effectiveness are major limitations for the wider clinical application of radioimmunoscintigraphy in preoperative staging. Furthermore, due to the presence of PMSA, differentiation of inflammatory changes (after surgery or radiotherapy) from recurrent tumors is also not reliable.

PET and PET/CT Imaging

PET has proved itself as a noninvasive, metabolic imaging modality for diagnosing malignant diseases as well as for assessing new therapies. PET images have higher resolution and provide three-dimensional anatomic information,[65] thus leading to superior sensitivity and specificity compared with conventional planar and SPECT techniques. Despite persisting high costs, PET is used almost routinely in the clinical management of certain cancer patients.[66-68]

New combined in-line PET/CT scanners are providing more detailed and precise CT anatomic localization of tumor lesions, especially in the skeletal system. An unprecedented number of new radiotracers are now available for the assessment of prostate cancer.

^{18}F-fluorodeoxyglucose

It is the increased glycolysis in cancer cells which is directly associated with the accumulation of ^{18}F-fluorodeoxyglucose (FDG) in PET imaging. ^{18}F-FDG is most effectively trapped by tumors with slow or absent dephosphorylation, because malignant lesions have a higher glycolytic rate than normal tissue.[69] Furthermore, ^{18}F-FDG accumulation is increased in tumor hypoxia through activation of the glycolytic pathway.[70] However, in prostate cancer there is no clear relationship between defined biochemical alteration in the glycolysis processes and ^{18}F-FDG uptake.[71,72] Nevertheless, ^{18}F-FDG has been one of the most studied radiotracers in prostate cancer over the last decade.

Early studies with FDG-PET were disappointing because accumulation of FDG was generally demonstrated to be low in prostate cancer cells.[73] Further, unsatisfactory results could occur due to urinary excretion of FDG, increased uptake in benign prostatic hyperplasia, or inflammatory processes. Moreover, in tumors with predominantly sclerotic BM, FDG is also less accurate for the assessment of skeletal involvement,[74,75] and such lesions show lower tracer uptake than lytic metastases as assessed by standardized uptake value.[76] However, FDG uptake is higher in tumors with higher Gleason scores, and close correlation between PSA level and PSA velocity with FDG uptake has been shown in some clinical[77] and in vitro studies.[78,79] Thus, ^{18}F-FDG-PET may be useful for the evaluation of tumor aggressiveness in prostate cancer[78] and might also occasionally be suitable for prostate imaging (Fig. 1) in carefully selected patient groups.[80-83]

Morris et al[84] showed in a study of 17 patients with progressive metastatic prostate cancer that FDG was able to discriminate active from quiescent osseous lesions; in a further study of 22 patients undergoing chemotherapy for castration-resistance metastatic prostate cancer, this group found agreement between PET and PSA in 86% of patients after 4 weeks of chemotherapy.[84] Disease progression was correctly identified by ^{18}F-FDG-PET in 91% of these cases. They also compared PET, PSA, and standard imaging after 12 weeks of chemotherapy and showed that in 94% of cases, PET correctly determined the clinical status of the patients.

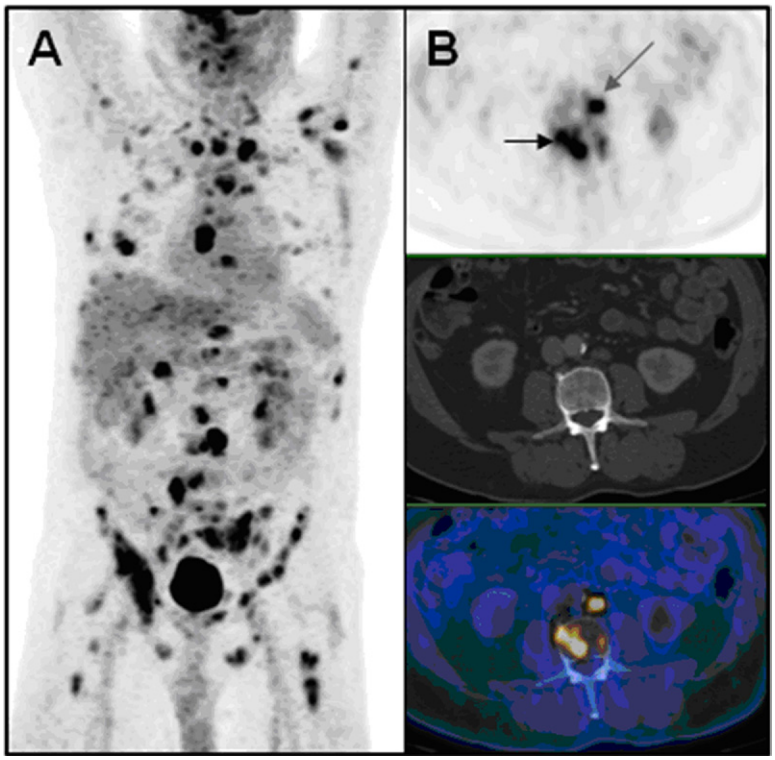

Figure 1 (A) Generalized BM detected by FDG-PET/CT (MIP-Image) from a high-risk prostate cancer patient. (B) Transaxial images from a metastatic bone lesion (black arrow) and a malignant lymph node (gray arrow).

These data suggest that ^{18}F-FDG-PET may be of value in the assessment of therapy, when performed in specific, well-defined clinical stages of prostate cancer.

^{11}C- and ^{18}F-Acetate Derivatives

Many theories as to mechanism by which acetate accumulates in malignant cells have been introduced, but the exact mechanism remains unclear. One approach to the molecular imaging of prostate cancer is to use the malignant transformation of specific citrate metabolism of prostate epithelial cells.[85] The normal human prostate gland produces, accumulates, and secretes extraordinarily high levels of citrate. This is a unique capability, which does not exist in any other soft-tissue cells of the body. Malignant prostate epithelial cells undergo a metabolic transformation from citrate-producing normal cells to citrate-oxidizing malignant cells, leading to an increased turnover of acetate in the prostate cancer. However, Yoshimoto et al[86] suggest that acetate is incorporated into the lipid pool in cancer tissue with low oxidative metabolism and high lipid synthesis.

^{11}C-acetate has also been used for the imaging of prostate cancer during the last few years and shows preferable characteristics for visualizing the pelvis due to its lack of urinary excretion and its acceptable tumor to background contrast.[79,87-90] Shreve et al[88] suggested that ^{11}C-acetate has potential as a suitable tracer for imaging the genitourinary system.

The value of ^{11}C-acetate PET in the detection of prostate cancer recurrence has been assessed in some studies,[89,90] which reported a low sensitivity and discouraging results in postoperative patients, particularly in the case of PSA values < 3 ng/mL.[89] Nevertheless, recent published data show that it might have significant potential for the detection of recurrences and metastases[91] when using more advanced PET/CT equipment (Fig. 2).

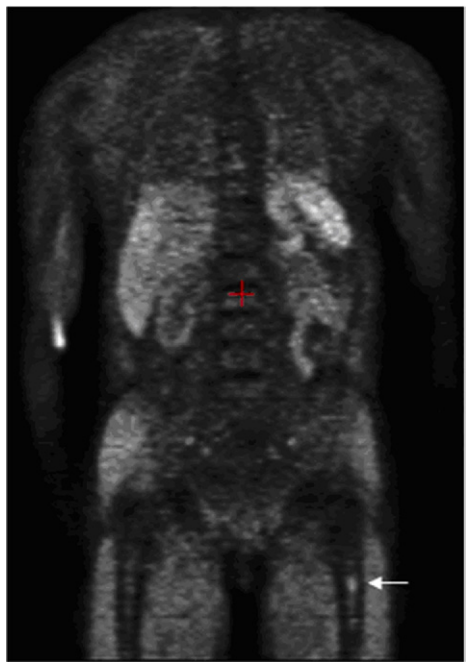

Figure 2 ^{11}C-acetate PET (coronal view): metastatic bone lesion in the proximal part of left femur (white arrow). (Courtesy of Stefan Wachter, MD.)

Recently, ^{18}F-fluoroacetate has been introduced as a possible alternative to ^{11}C-acetate for PET imaging of prostate cancer, especially with respect to its longer half-life.[92,93]

^{11}C- and ^{18}F-Choline Derivatives

The potential advantages of PET using radiolabeled phospholipids, such as ^{11}C- and ^{18}F-labeled choline, in the assessment of prostate cancer patients have recently been emphasized.[94-100]

Two possible mechanisms have been proposed to explain the increased choline uptake in prostate cancer cells.[101] The first is increased cell proliferation in tumors. Choline is a precursor for the biosynthesis of phosphatidylcholine and other phospholipids, which are major components of the cell membrane. Choline uptake seems to be a marker of cell proliferation in prostate cancer, as malignancies are commonly characterized by increased proliferative activity. The second explanation proposed is upregulation of choline kinase in cancer cells: overexpression of choline kinase has been found in cancer cell lines, including human-derived prostate cancer.[102]

^{18}F-fluoromethylcholine (FCH) has the advantage of a longer half-life (110 min), compared with ^{11}C-choline, which has a short half-life (20 min).[103-106] However, urinary excretion of ^{18}F-FCH is comparatively higher than ^{11}C-choline, but can be overcome by performing early dynamic imaging and using coregistered CT data.[107,108]

Cimitan et al[94] examined 100 postoperative prostate cancer patients with persistent increased serum PSA levels, suggestive of local recurrences or distant metastases. ^{18}F-FCH PET/CT correctly detected BM in 21% of patients; also 76% of them were undergoing hormone therapy (HT). In this study, ^{18}F-FCH uptake in bone seems to be highly predictive of skeletal metastases; however, this finding should be interpreted with caution in patients undergoing HT.[109]

Schmid et al[110] studied 19 pre- and postoperative prostate cancer patients and reported that ^{18}F-FCH PET/CT findings were highly suggestive of local recurrences, lymph node involvement, or BM. However, it is difficult to draw a conclusion from this study due to the highly variable clinical status in a small population of patients and the lack of a formal statistical basis for the desired endpoint.[64]

The evaluation of 111 patients (43 patients for staging and 68 patients for restaging), using ^{18}F-FCH PET/CT has been reported by Husarik et al.[111] Pathologic FCH accumulation in osseous structures was seen in about 15% (17/111) of patients, and was subsequently confirmed by bone scan, magnetic resonance imaging, and CT morphology. They concluded that ^{18}F-FCH PET/CT can accurately depict BM in prostate cancer patients.

In a recent prospective study by our group,[112] we examined the capability of ^{18}F-FCH PET/CT for detecting metastatic bone disease in prostate cancer in 70 patients and for the first time have used CT to assess the pattern of metabolic uptake by FCH in relation to morphologic changes in bone. ^{18}F-FCH PET/CT showed a sensitivity, specificity, and accuracy of 79%, 97%, and 84%, respectively, for the detection of BM in prostate cancer patients (Fig. 3). We also observed a

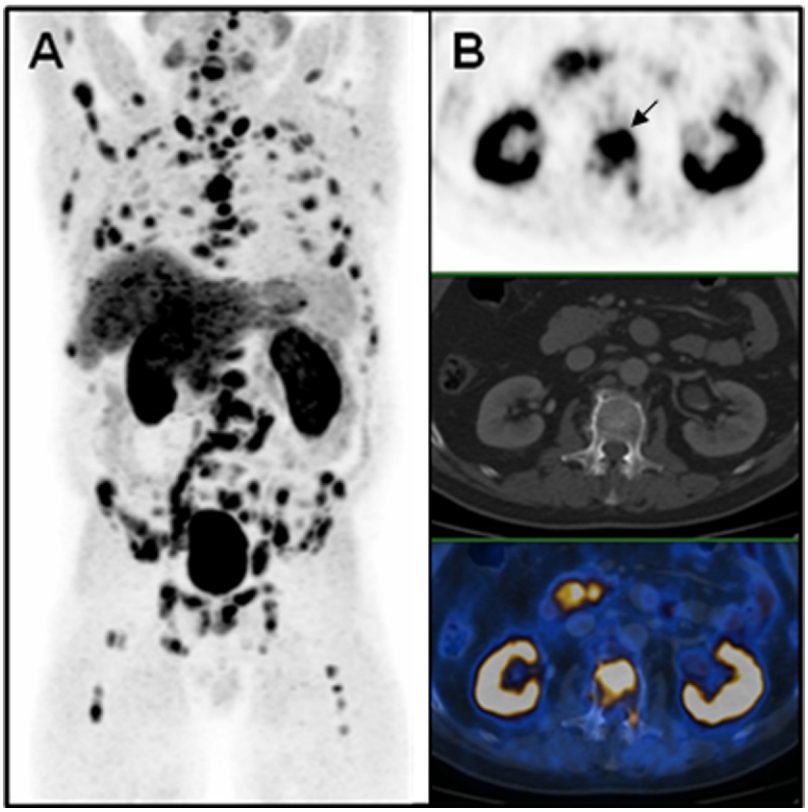

Figure 3 (A) Generalized BM detected by FCH PET/CT (MIP-Image) from a high-risk prostate cancer patient. (B) Transaxial images from a metastatic bone lesion in the thoracic spine (arrow).

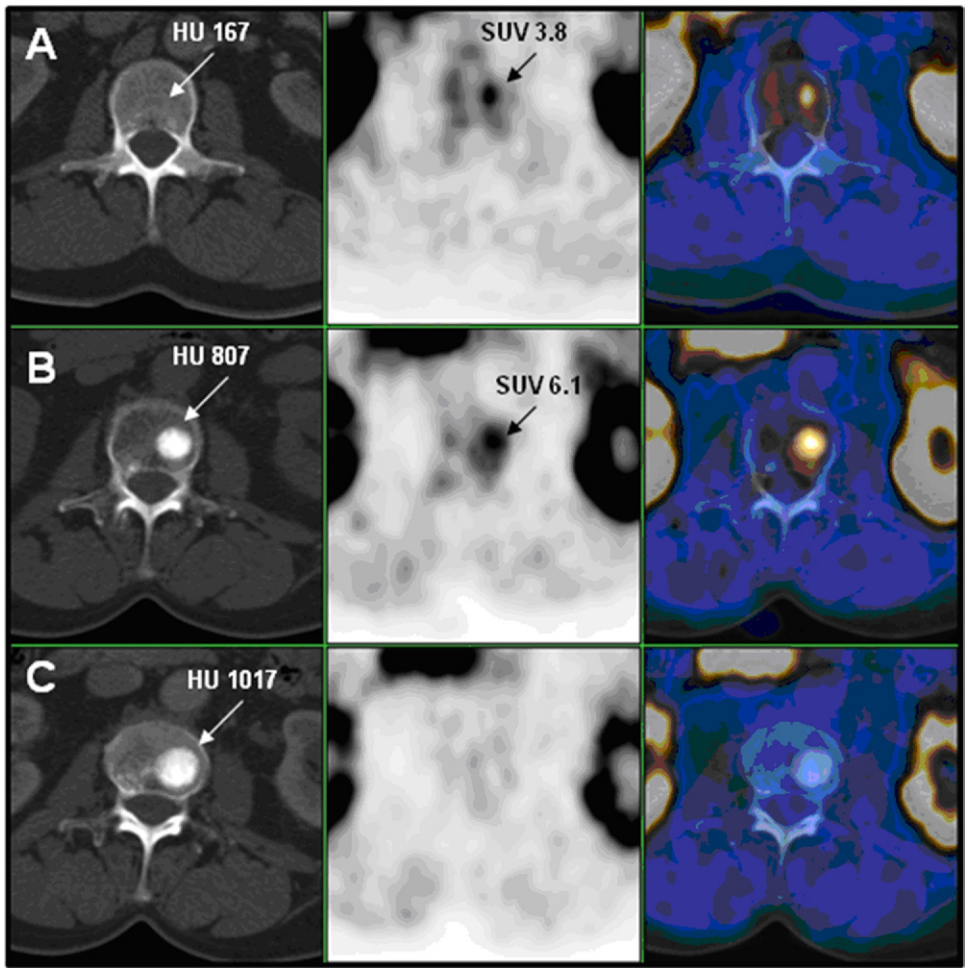

Figure 4 Dynamic pattern of BM detected by ^{18}F-FCH PET/CT. (A) Beginning with bone marrow involvement (FCH-positive, CT-negative), (B) then generally occurring osteoblastic changes (FCH-positive, CT-positive), and (C) finally progressing to densely sclerotic lesions without metabolic activity (FCH-negative, CT-positive). (HU: Hounsfield Unit, SUV: Standardized uptake value.)

dynamic, changing, and progressive pattern of abnormality associated with BM (Figs. 4 and 5), beginning with bone marrow involvement (FCH-positive, CT-negative), then generally osteoblastic but sometimes osteoclastic changes (FCH-positive, CT-positive), and finally progressing to densely sclerotic lesions without metabolic activity (FCH-negative, CT-positive). In addition, FCH PET/CT has shown promising results for early detection of BM (Fig. 6). Furthermore, we have found that a Hounsfield Units level of more than 825 is associated with an absence of metabolic activity with FCH. Almost all the FCH-negative sclerotic lesions were detected in patients who were undergoing HT, and this raises the possibility that these lesions may no longer be viable. Further clarification is needed for such densely sclerotic but metabolically negative lesions.

Finally, in metastatic bone lesions a significant increase in ^{18}F-FCH uptake was seen in the late images (ie, 90 min after injection). This finding confirmed the previous data reported by our group[113-115] as well as other similar studies.[94,111]

^{18}F-Fluoride

For skeletal imaging, ^{18}F-fluoride as a nonspecific bone scanning agent was first described in 1962.[116] With the introduction of gamma cameras it was replaced by ^{99m}Tc-labeled diphosphonates, such as MDP, now the most commonly used bone seeking substance.

With the improvements in new PET scanners, high-resolution imaging of bone has become a reality, thus reintroducing ^{18}F-fluoride for clinical and research investigations.

Although only a few studies compare ^{18}F-fluoride with ^{99m}Tc-MDP for the diagnosis of BM, ^{18}F-fluoride PET seems to be more sensitive than conventional bone scanning,[117] showing a higher contrast between normal and abnormal tissue and with the potential for the detection of additional lesions, especially in the spine.[83,117-121]

Comparative studies by Even-Sapir et al[46] using planar BS, bone scan SPECT, ^{18}F-fluoride PET, and ^{18}F-fluoride PET/CT were performed in patients with either localized high-risk or metastatic prostate cancer. The sensitivity and specificity for detection of BM was 70% and 57% for planar BS, respec-

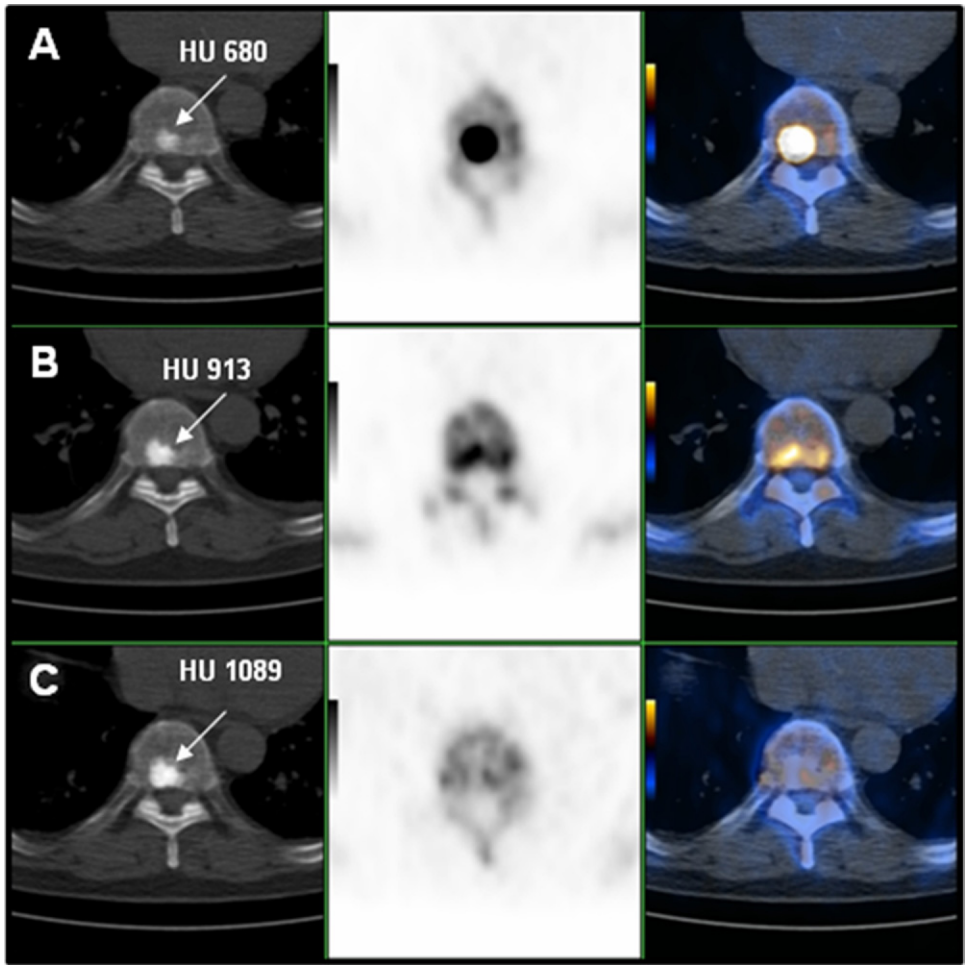

Figure 5 BM detected by ^{18}F-fluoride PET/CT under HT. (A) Osteoblastic changes (fluoride-positive, CT-positive). (B) Increasing density of sclerotic lesion with decreasing intensity of fluoride. (C) Highly dense sclerotic lesion without metabolic activity in fluoride PET study.

tively; 92% and 82% for bone SPECT, respectively; 100% and 62% for ^{18}F-fluoride PET, respectively; and 100% and 100% for ^{18}F-fluoride PET/CT, respectively. ^{18}F-fluoride PET/CT was significantly more sensitive and specific than BS ($P < 0.001$) and more specific than PET alone ($P < 0.001$). They concluded that ^{18}F-fluoride PET/CT is a highly sensitive and specific imaging modality for the detection of BM in high-risk prostate cancer patients.

Another recent comparative study by our own group[122] attempts to determine the value of ^{18}F-fluoride and ^{18}F-FCH for detecting BM in 38 prostate cancer patients. In a lesion-based analysis, the sensitivity and specificity of PET/CT in detection of BM in prostate cancer were 81% and 93% by ^{18}F-fluoride and 74% and 99% by FCH, respectively. In a patient-based analysis, there was good agreement between ^{18}F-FCH and ^{18}F-fluoride PET/CT for the detection of metastatic bone disease in prostate cancer patients ($\kappa = 0.76$). ^{18}F-fluoride PET/CT demonstrated higher sensitivity than ^{18}F-FCH PET/CT for detection of BM; however, it was not statistically significant (Fig. 7).

In conclusion, ^{18}F-FCH PET/CT has proved to be a more specific method than ^{18}F-fluoride PET/CT and has the potential to become a "one stop diagnostic procedure" in the initial assessment of high-risk prostate cancer patients, particularly for the early detection of bone marrow metastases.

However, in patients with FCH negative suspicious sclerotic lesions, a second bone seeking agent (eg, ^{18}F-fluoride) should be performed.

We also noted that HT may be associated with increasing bone mineralization and sclerosis in malignant lesions and that due to such a response to therapy, ^{18}F-fluoride PET could also be negative in highly dense sclerotic lesions.

For the detection of bone abnormalities we predict that ^{18}F-fluoride PET/CT will replace conventional bone imaging with ^{99m}Tc-labeled diphosphonates within the next few years.[83,123]

^{11}C-Methionine

The accumulation of ^{11}C-methionine in tumor cells is attributed to increased amino acid transport and protein synthesis.[124,125] Uptake of ^{11}C-methionine may reflect active tumor proliferation. However, few studies have investigated prostate cancer, using ^{11}C-methionine PET.[126,127]

Nunez et al[126] compared ^{11}C-methionine with ^{18}F-FDG-

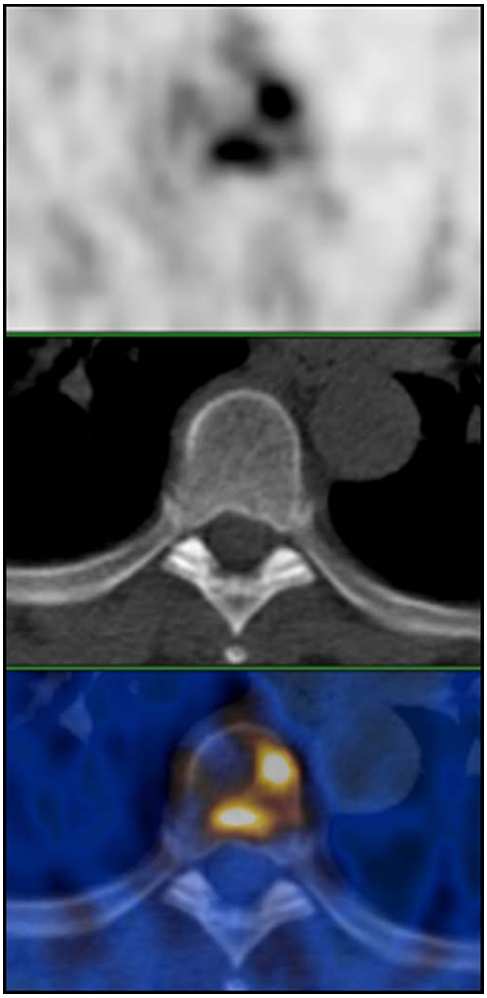

Figure 6 Bone marrow metastases in the thoracic spine detected by FCH PET/CT in preoperative evaluation of a high-risk prostate cancer patient.

PET in 12 metastatic prostate cancer patients. The authors reported that ^{11}C-methionine PET was more effective than ^{18}F-FDG-PET for detecting BM in this patient population. ^{11}C-methionine PET could detect 69.8% of metastatic bone lesions, while ^{18}F-FDG-PET detected 48.3% lesions. The authors assumed that the increased sensitivity of ^{11}C-methionine compared with ^{18}F-FDG-PET may be the result of differences in tumor metabolism between patients, or a time-dependent metabolic cascade in metastatic prostate cancer, with initial uptake of ^{11}C-methionine in dormant sites followed by increased uptake of ^{18}F-FDG during progression of the disease.

^{18}F-Fluoro-5-alpha-dihydrotestosterone PET

A new imaging agent that binds to androgen receptors, ^{18}F-fluoro-5-alpha-dihydrotestosterone (FDHT), has recently been developed.[128] FDHT, an androgen analog, has been shown to accumulate in the prostate gland of nonhuman primates. The androgen receptor is highly functional and plays a major role in tumor growth despite the absence of its ligand dihydrotestosterone, even in castrated patients.[64,129]

In addition to conventional imaging methods, Larson et al[130] used ^{18}F-FDG and ^{18}F-FDHT PET scans to examine 7 patients with progressive clinically metastatic prostate cancer. They studied 59 lesions (10 soft-tissue lesions and 49 bone lesions) seen on standard imaging modalities. ^{18}F-FDG-PET was positive in 57 of 59 lesions (97%), while ^{18}F-FDHT PET was positive in 46 of 59 lesions (78%).

In another study, Dehdashti et al[131] evaluated the feasibility of using ^{18}F-FDHT PET in 19 patients with metastatic prostate cancer. ^{18}F-FDHT PET had a sensitivity of 63% in a patient-based analysis and a lesion detection rate of 86%. They demonstrated a definite reduction in FDHT uptake in all lesions after patients had been treated acutely with an antiandrogen drug. The authors concluded that tumor uptake of FDHT is a receptor-mediated process and positive PET studies are associated with higher PSA levels. ^{18}F-FDHT seems to be promising in the analysis of antigen receptors and their effect on the clinical management of prostate cancer. ^{18}F-FDHT may also be a sensitive agent in the evaluation of therapy response.

Other PET Tracers

The bombesin- or gastrin-releasing peptide receptor is overexpressed in prostate cancer cells and has been a target for imaging of prostate cancer. Rogers et al[132] introduced Cu-64-DOTA-Aoc-bombesin (Aoc is 8-amino-octanoic acid) as the first radiolabeled bombesin analog suitable for PET. MicroPET images showed good tumor localization in a PC-3 xenograft mouse model, but high retention in normal tissues prevented the clinical application of the corresponding radiotracer. Other labeled bombesin derivatives are also under investigation as PET agents for the evaluation of prostate cancer.[133-135]

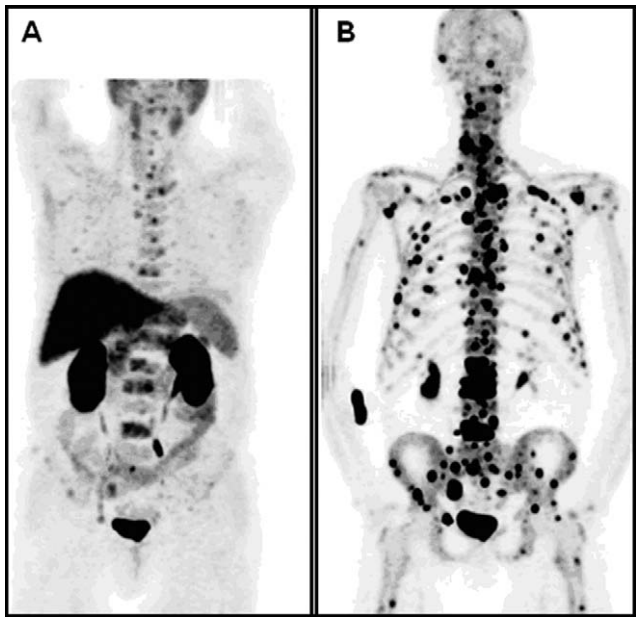

Figure 7 (A) FCH PET (MIP-Image); (B) Fluoride PET (MIP-Image). Fluoride PET demonstrated higher sensitivity than FCH PET for detection of BM (statistically not significant).

One of the other future modalities is imaging of amino acid transport by anti-1-amino-3 ^{18}F-fluorocyclobutane-carboxylic acid (FACBC) PET. ^{18}F-FACBC has shown in vitro uptake within the prostate cancer cell line, DU 145, and orthotopically implanted prostate tumors in nude rats.[136] An early study with ^{18}F-FACBC seems to be promising,[136] but further research is warranted.

Conclusion

Bone imaging is performed for staging of disease, assessment of therapy, and for detecting bone complications in prostate cancer patients. Assessment of BM by imaging modalities is indicated for patients at high risk of bone involvement based on clinical nomograms. Conventional planar BS has been used extensively in detecting bone involvement because it offers the advantage of total body examination, low cost, and higher sensitivity for detection of BM than plain film radiography. However, bone scanning suffers from low specificity.

SPECT scans have improved the sensitivity and specificity of planar bone scanning, particularly for the evaluation of BM in the spine. Multi-FOV SPECT is proposed as a superior method compared with localized SPECT for the evaluation of BM throughout the skeleton.

Recently, PET/CT imaging has shown promising results for the assessment of BM in prostate cancer patients. An unprecedented number of PET tracers have been tested for identifying prostate cancer cells. There is convincing evidence that ^{18}F-FDG-PET is not useful for the evaluation of BM in prostate cancer patients because it is less sensitive than the bone scan, although there are some data to suggest that ^{18}F-FDG-PET may be of value in the assessment of therapy in well-defined clinical groups.

^{11}C- and ^{18}F-acetate may have potential for the detection of recurrences and metastases, but to date, there are not sufficient data for evaluating these agents in the assessment of BM in prostate cancer.

^{18}F-FCH PET/CT shows promising results, especially in the early detection of metastatic bone disease and therapy monitoring, but inconsistent findings in densely sclerotic bone lesions, especially after therapy were seen.

^{18}F-fluoride PET/CT demonstrates higher sensitivity than ^{18}F-FCH PET/CT for detection of BM in prostate cancer patients. However, ^{18}F-FCH PET/CT has been shown to be a more specific method than ^{18}F-fluoride PET/CT and has the potential to become a "one stop diagnostic procedure" in the initial assessment of high-risk prostate cancer patients, particularly, for the early detection of bone marrow metastases.

In patients with FCH negative but suspicious sclerotic lesions, a second bone seeking agent (eg, ^{18}F-fluoride) should be used.

The question "Does negative metabolic imaging (eg, ^{18}F-FCH or ^{18}F-fluoride PET) in CT-positive BM have any clinical relevance?" still remains an issue that should challenge further studies.

Overall there is insufficient data about other PET tracers, such as ^{11}C-methionine, ^{18}F-FDHT, and ^{18}F-FACBC, available to draw conclusions concerning their potential value in the assessment of BM in prostate cancer patients.

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