# The Role of Fluorodeoxyglucose, $^{18}$F-Dihydroxyphenylalanine, $^{18}$F-Choline, and $^{18}$F-Fluoride in Bone Imaging with Emphasis on Prostate and Breast

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Diagnostic imaging has played a major role in the evaluation of patients with bone metastases. The imaging modalities have included bone scintigraphy, computed tomography, magnetic resonance imaging, and most recently PET/CT, which can be performed with different tracers, including fluorodeoxyglucose (FDG), $^{18}$F-fluoride, $^{18}$F-choline (FCH), and $^{18}$F-DOPA (dihydroxyphenylalanine). For most tumors the sensitivity of FDG in detecting bone metastases is similar to bone scintigraphy; additionally it can be used to monitor the response to chemotherapy and hormonal therapy. $^{18}$F-Fluoride may provide a more sensitive "conventional" bone scan and is superior for FDG nonavid tumors, but, nevertheless, FDG in "early disease" often has clear advantages over $^{18}$F-fluoride. Although more data need to be obtained, it appears that FCH is highly efficient in preoperative management regarding N and M staging of prostate cancer once metastatic disease is strongly suspected or documented. For neuroendocrine tumors and in particular in medullary thyroid cancer, DOPA is similar to $^{18}$F-fluoride in providing high quality information regarding the skeleton. Nevertheless, prospective studies with large patient groups will be essential to define the exact diagnostic role of FCH and DOPA PET in different clinical settings.
Semin Nucl Med 36:73-92 © 2006 Elsevier Inc. All rights reserved.

P ositron emission tomography (PET) previously regarded as a research procedure has become one of the most important and innovative clinical applications in oncology. In comparison with the established conventional imaging modalities (CIM) such as computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI), PET has important advantages. Tomographic images with PET have substantially higher resolution and provide three-dimensional anatomical information,[1] which leads to superior sensitivity and specificity compared with conventional planar and single photon emission computed tomography (SPECT) techniques. Even with persisting high costs, PET is almost routinely used in the clinical management of certain cancer patients;[2,3] in addition, PET has become an efficient modality for whole-body scanning in a reasonably short time.

With the increasing availability of new combined inline PET/CT machines, the possibility of obtaining more detailed and precise CT anatomic localization of PET directed metabolic abnormalities of tumor lesions, especially in skeletal diseases, has become a clinical reality. In a recent study PET/CT was able to clearly differentiate malignant from benign lesions, even in those cases in which only a low dose CT was provided for anatomic correlation.[4] With the newest CT scanner development (32 and 64 slices) an increasing number of unexpected and additional tumor lesions will be detected and will be more easily visualized.[5]

From the clinical point of view different radiopharmaceuticals for PET imaging may be more suitable in various cancers. $^{18}$F-Fluorodeoxyglucose (FDG) as an agent to image altered tumor metabolism has been proven to be sensitive, specific, and cost effective.[6] In particular, the routine use of $^{18}$F-fluoride as a nonspecific bone tracer is also accepted.[7] Both have potential roles in the management of patients with bone metastases (BM).

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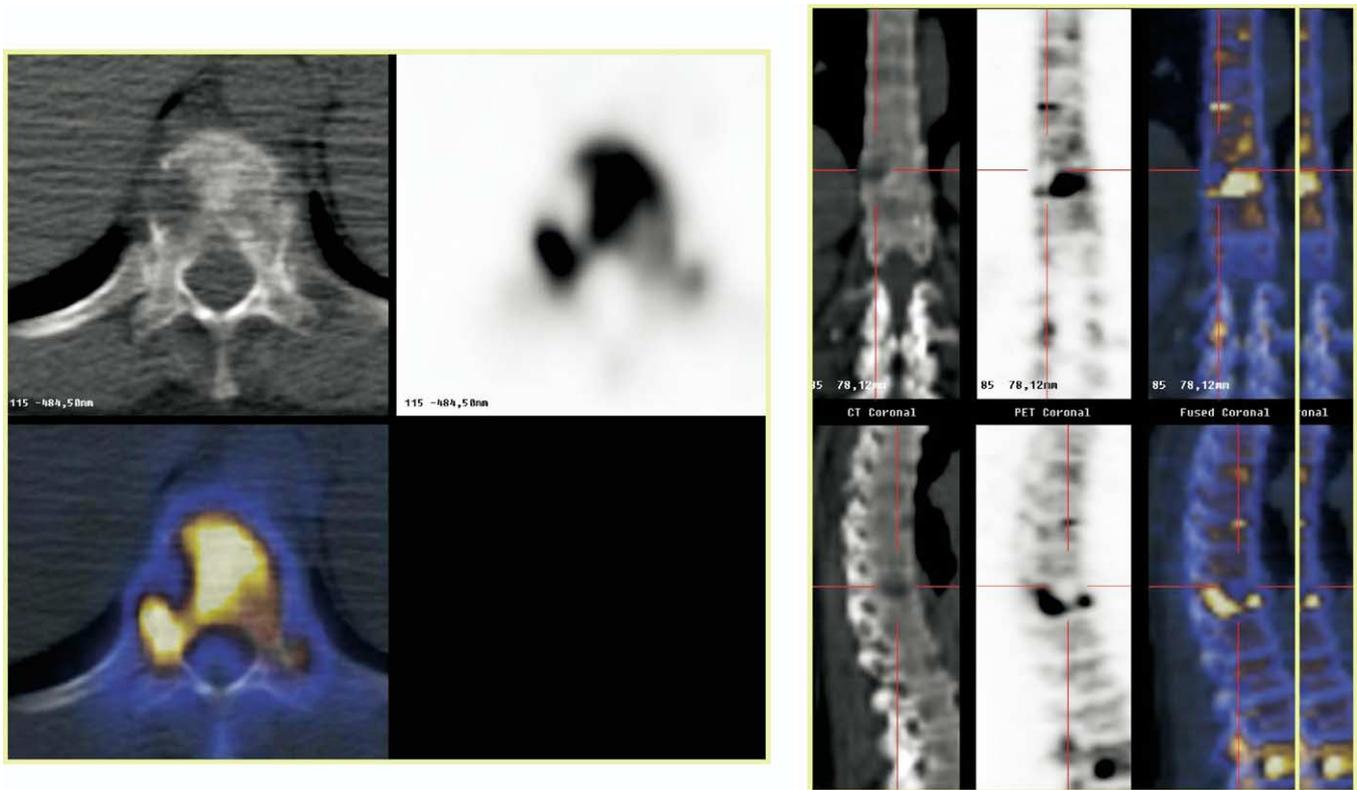
**Figure 1** ^{18}F-Fluoride clearly shows in the coronal, saggital, and axial slices a metastasis in the vertebral body of T11.

[18]F-Choline (methylcholine; FCH) for imaging of prostate cancer and ^{18}F-DOPA (dihydroxyphenylalanine) in the use of neuroendocrine tumors (NET) and medullary thyroid cancer (MTC) patients remain under review.[8]

## Bone Metastases: General Aspects

Bone metastases occur in up to 70% of breast or prostate cancer patients and in about 15 to 30% in other cancer patients (lung, stomach, uterus, bladder, colon, thyroid, kidney, rectum). About 350,000 people in the United States die with BM every year.[9] Patients can have osteolytic, osteoblastic, or mixed lesions containing both elements.

From pathophysiology it is known that in BM, activated osteoclast cells, osteoblast cells, the mineralization process of bone formation, cancer cells, and inflammatory cells coexist. Several factors, including increasing vascularity (in areas of red marrow) as well as tumor cells producing adhesive molecules thus binding them to bone matrix and marrow stromal cells, account for the frequency of BM.[10]

BM not detected in bone scintigraphy (BS) may be explained by the absence of significant reactive changes in patients with slow growing lesions in which reactive bone is not detectable.[11-13] For treatment monitoring BS can be misleading if performed too early,[14,15] due to an intense osteoblastic response following the instigation of successful therapy—the "flare" response.

## Role of Imaging

### Conventional Imaging Modalities

For the characterization of scintigraphic bone lesions, correlation with CT or MRI is the most common approach, visualizing normal and malignant tissues with great detail.[7,16,17] In the day-to-day practice of medicine CT is used to generate images as tomographic slices, with very high sensitivity and specificity.[18-20]

Early stages of disease may not be detected if no associated structural abnormalities are present. Only with disease progression and in the presence of significant structural abnormalities will anatomic imaging techniques be successful. Nevertheless some disorders may never manifest as structural abnormalities throughout the course of certain diseases.[21]

MRI has added a major dimension in the investigation of soft tissue and bone abnormalities, sometimes also associated with multiple organ disorders.[22-25] Today it is accepted as the most accurate and sensitive (97-100%) imaging modality in detecting vertebral metastases,[26,27] distinctly better for imaging the marrow, the spinal cord, and the adjacent soft tissue structure than for examining bone itself.[28] In the spine and pelvis, MRI is more sensitive than planar bone scintigraphy, whereas BS is more sensitive in the skull and ribs.[26,29-31]

Functional MRI is primarily intended for the assessment of physiological phenomena, such as cerebral blood flow and perfusion.[32,33]

**2 min - 180 min pi**     **4 min - 150 min pi**     **8 min – 90 min pi**
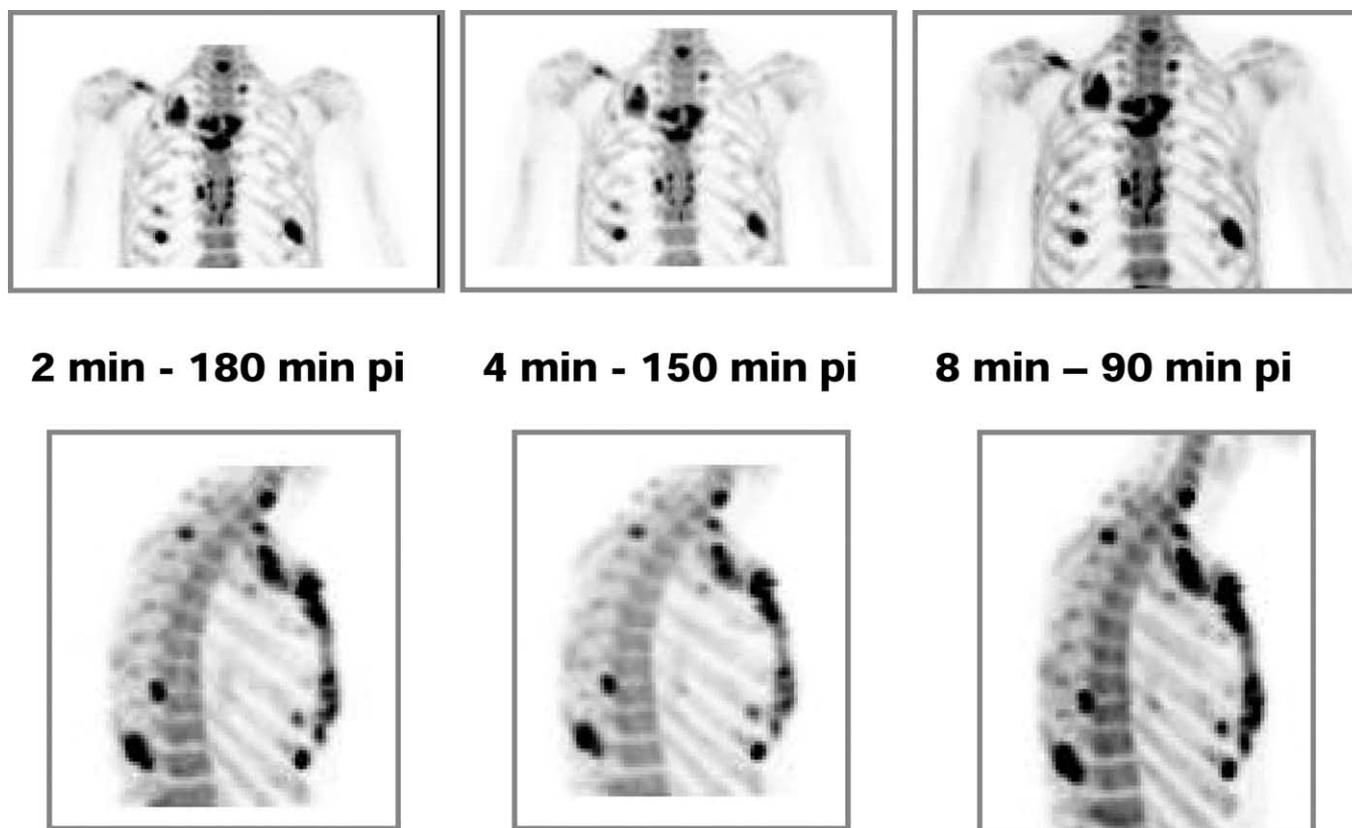
**Figure 2** The quality of $^{18}$F-fluoride imaging is independent from the acquisition time per bed position (2 min 180 min pi versus 4 min 150 min pi versus 8 min 90 min pi).

## Planar and SPECT BS: General Aspects

Although BS is the established reference method for the diagnosis of BM, in daily routine practice it is now less often indicated in breast and prostate cancer patients. Only in high risk groups [eg, prostate cancer with prostate specific antigen (PSA) levels > 20 ng/mL] it is still recommended for preoperative staging as well as for follow-up. Additionally, several studies have shown poor correlation of clinical symptoms and BM;[34,35] therefore BS should generally be performed only in patients with typical bone symptoms.

Due to the fact that conventional planar and SPECT images have limited spatial resolution, quantitative measurements with SPECT are inaccurate. There are also some data showing that SPECT compared with planar scintigraphy was not able to diagnose metastases convincingly.[36] On the other hand studies have shown that the sensitivity of BS could be improved by additional SPECT imaging.[27,37,38] SPECT is superior in the detection of lesions in the posterior vertebral region, but less evident in the body of the vertebra;[39] nevertheless, for that issue, definitive clinically relevant data are not yet published.

The most common false positive scintigraphic findings—especially in elderly patients—are due to other benign bone diseases such as degenerative changes, inflammatory processes, trauma, mechanical stress, and Paget's disease.

In most situations experienced readers will be able to provide a clear cut diagnosis but in a minority of cases additional diagnostic procedures—with additional costs and physician/patient stress—will be required.

We predict that conventional planar gamma camera imaging will be used much less frequently by the end of this decade. Even the role of SPECT as a routine, but still powerful molecular imaging technique will also be questionable at that time.

For the detection of osseous abnormalities we expect that in the coming years conventional bone imaging with $^{99m}$technetium ($^{99m}$Tc)-labeled diphosphonates—performed with nontomographic scanning techniques—will be replaced completely with $^{18}$F-fluoride PET.[21]

## Radiopharmaceuticals

### $^{18}$F-Fluorodeoxyglucose

$^{18}$F-Fluorodexoyglucose (FDG) was first introduced in 1976. FDG is transported in cancer cells by GLUT 1 (glucose transporter protein) and is then phosphorylated by hexokinases (HKII) to FDG-6-phosphate, which is retained within the malignant cells.

Because malignant tumors have a higher glycolytic rate than normal tissue,[40] FDG is most effectively trapped by tumors with slow or absent dephosphorylation. Additionally

**Biopsy GIII**
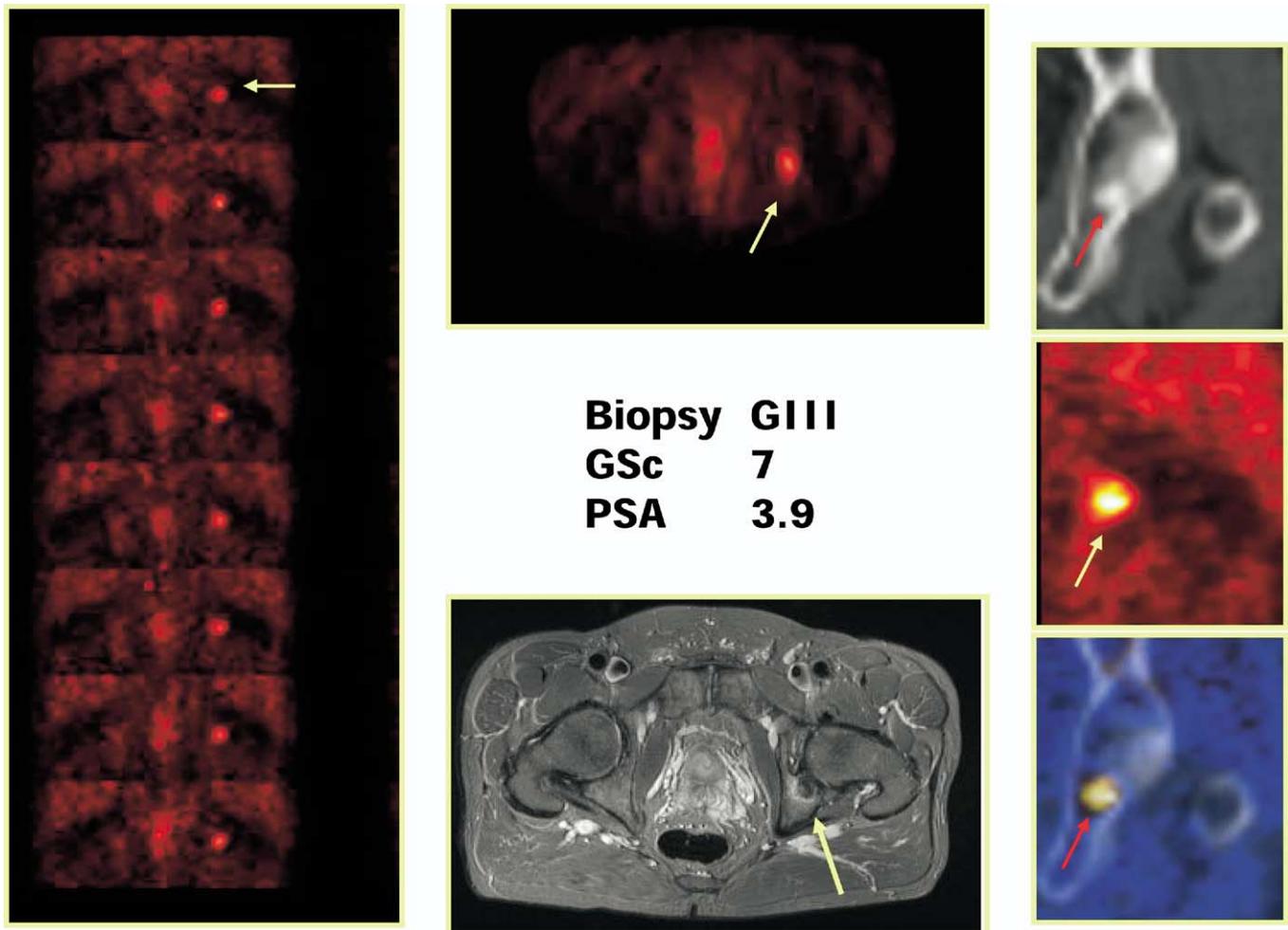**GSc      7**
**PSA      3.9**

**Figure 3** Dynamic images of FCH showing intense focal uptake of FCH in the left acetabulum (1 min pi) with corresponding findings in CT and MRI.

FDG accumulation is increased by tumor hypoxia through activation of the glycolytic pathway.[6]

The role of FDG in the differential diagnosis of benign versus malignant bone tumors is limited because of the high FDG uptake[41] in some benign lesions (eg, giant cell tumors). FDG seems to be highly effective in identifying BM at an earlier stage, when only the bone marrow is involved and before a more generalized bone reaction is visualized. In osteolytic metastases FDG accumulation is higher[42] due to a higher glycolytic rate, whereas sclerotic metastases—being relatively acellular due to the presence of a smaller amount of viable tumor tissue—have lower FDG uptake.[42,43]

In comparison with conventional bone scintigraphy, FDG-PET has higher sensitivity and resolution. In addition it provides more information regarding soft tissue diseases.[5,42]

## Standard Uptake Value

In the clinical setting of FDG-PET scanning the semiquantitative parameter standard uptake value (SUV) is most widely used.[44-46] This measure represents the tissue activity within a region of interest corrected for the injected activity and for patient weight or lean body mass. A transmission scan is required for measuring the true tissue activity in attenuation corrected images.

Due to the FDG uptake, the SUV in tumor cells in general is higher than in benign lesions. In one reported study in breast cancer the mean SUV in FDG visible sclerotic lesions was lower (0.95) compared with 3.6 in mixed and 6.6 in osteolytic metastases.[42] In primary bone tumors, nevertheless, a statistical difference in SUV was seen in benign (2.18 ± 1.52) and malignant (4.34 ± 3.19) lesions.[41] For treatment planning and prognosis SUV measurement of FDG-PET might be useful, due to the fact that a SUV decrease of 30 to 40% is correlated to a chemotherapy response.[47,48]

Despite the potential clinical usefulness, to our knowledge there are no published data that have used SUV for bone metabolism measurement with $^{18}$F-PET.[49]

## $^{18}$F-Fluoride

$^{18}$F-Fluoride, a nonspecific bone tracer, first described in 1962 as a bone-imaging agent, was used for skeletal imaging almost 40 years ago.[50] Diffusion through capillaries into bone extracellular fluid leads to a slow exchange of fluoride ions with hydroxyapatite crystals forming fluoroapatite. Due to
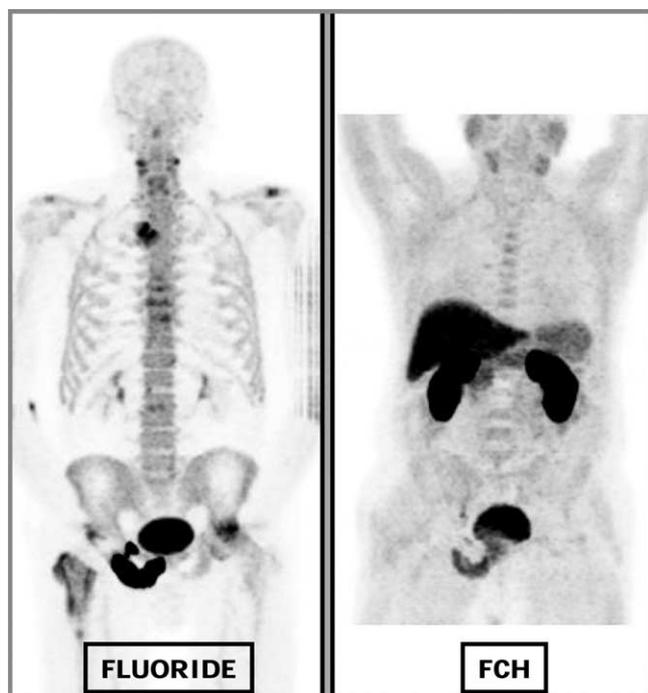
**Figure 4** Comparison of ^{18}F-fluoride and FCH showing metastatic bone disease in the ramus os ischii and the superior and inferior pubic rami.

the fact that remodeling and bone turnover is greatest at the surface, it is mainly stored there.[51-53] The "first-pass" extraction of the smaller ^{18}F from blood through the capillary membrane into the bone is almost 100%,[54,55] in comparison to only 64% of the larger phosphonate complexes.

It is well known that the regional clearance of ^{18}F fluoride from plasma to bone is about three times higher in metastatic lesions than in adjacent "benign" bone tissue.[56] In patients with breast cancer the regional fluoride clearance can increase up to 5 to 10 times in lytic and sclerotic metastases.[7]

With the introduction of gamma camera imaging ^{18}F-fluoride was replaced by ^{99m}Tc–labeled diphosphonates, such as methylene diphosphonate (MDP), which is the most commonly used bone seeking agent and the now "classical" bone imaging tracer.[57] Both tracers, showing almost identical uptake mechanisms,[58] accumulate in osteoblastic lesions, whereas predominantly lytic lesions may show—due to the absence of a reactive osteoblastic reaction—poor or absent tracer uptake.[57]

Following the introduction and subsequent improvements of PET scanners, high resolution imaging of the skeleton became increasingly interesting and reintroduced the use of ^{18}F-fluoride for clinical and research applications (Fig. 1). When ^{18}F-fluoride scanning with 8 to 12 mCi and an acquisition time of 3 min in each bed position and at 45-min postinjection (pi) is performed, excellent image quality with higher spatial resolution[59] than conventional BS is obtained. It is worth mentioning that the quality of ^{18}F-fluoride imaging is extremely high, independent of the acquisition time per bed position (Fig. 2).

Although only a few studies comparing ^{18}F-fluoride and MDP exist, ^{18}F-fluoride PET seems to be more sensitive than conventional BS for the diagnosis of BM;[16] somewhat surprisingly, additional lesions were identified mostly in the spine.[5] Showing a high contrast between normal and abnormal bone ^{18}F-fluoride has potential advantages in sensitivity and specificity;[60] therefore its use in the evaluation of BM is highly recommended.[7,16,56,59,61,62]

A potential problem is that ^{18}F-fluoride PET is very sensitive, and minimal degenerative changes could give false positive findings. Again, PET/CT will provide additional information and should improve the differential diagnosis of benign versus malignant lesions.[4]

Schirrmeister and coworkers[39] in 1999 were one of the first to describe a greater accuracy in detecting BM in breast cancer patients compared with conventional BS, thus changing patient management in >10% of cases; nevertheless no statistically significant data are available.

Some authors[61] have proposed combining FDG and ^{18}F-fluoride to more fully evaluate the distribution of skeletal and soft tissue metastases. This simultaneous administration (two-in-one PET method) for better anatomic localization of lesions in soft tissue and the skeleton by having bone landmarks available is an approach that has not been accepted in routine clinical practice.[61]

As it has been suggested that ^{18}F-fluoride is more cost effective than MDP,[63] we can expect that ^{18}F-fluoride will replace bone scintigraphy completely within several years.[39]

## ^{18}F-DOPA

Neuroendocrine tumors are able to express cell membrane neuroamine uptake mechanism and specific receptors (eg, somatostatin receptors). Diagnostic assessment of this heterogeneous group of tumors involves blood, urine, and biochemical examination as well as imaging modalities.
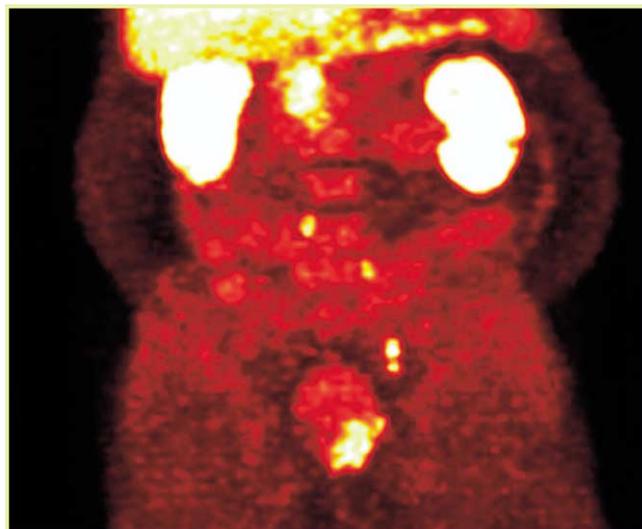


**Figure 5** Pathological high FCH uptake in the prostate (left lobe), multiple retroperitoneal, and iliac lymph node metastases.
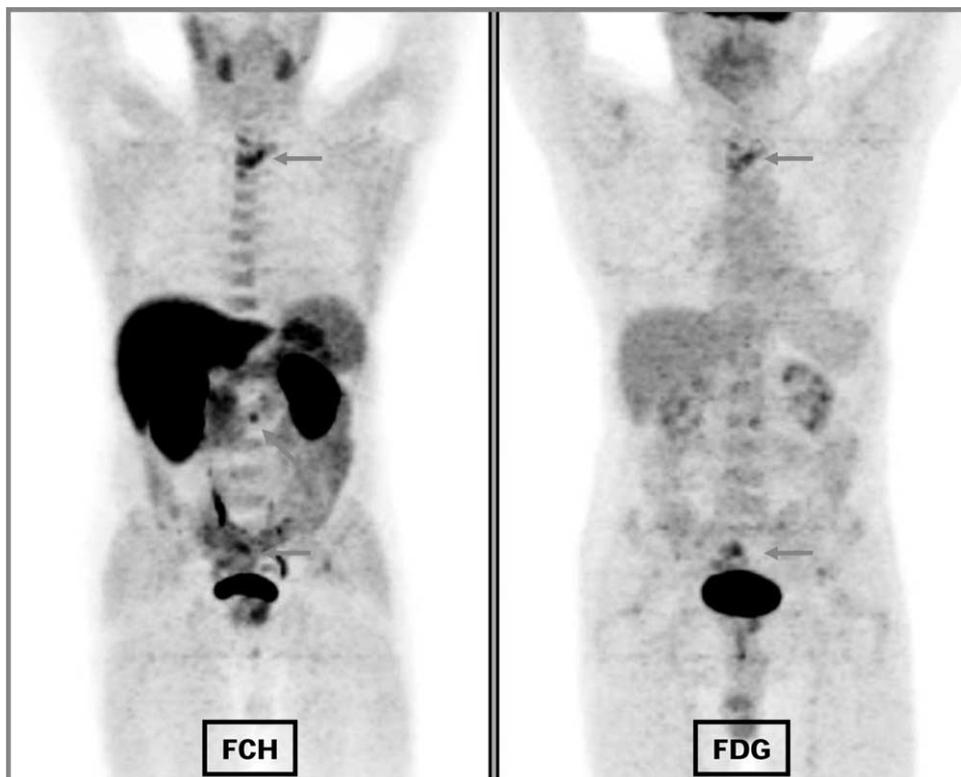
**Figure 6** FCH: Pathological uptakes in the cervical spine, L2, and sacrum due to bone metastases. FDG: Only moderate uptake in the cervical spine and sacrum, no pathological uptake in L2.

For staging of gastroenteropancreatic tumors, CIM (eg, CT, MRI, ultrasonography, angiography, endoscopy) are used for precise localization.[64-66] For metabolic imaging established nuclear medicine techniques with ^{123}I metaiodobenzylguanidine, somatostatin receptor scintigraphy, vasoactive intestinal peptide receptor scintigraphy, and PET have been shown to be most effective. Other PET tracers, such as ^{11}C-dihydroxyphenylalanine (for carcinoids and endocrine pancreatic tumors), ^{11}C-hydroxyephedrine (for phaeochromocytomas), and ^{11}C-metomidate (for adrenal cortical tumors), have been developed and partly introduced as routine procedures.[67] FDG-PET has also been used for diagnostic purposes, but has not yet demonstrated significant uptake in well-differentiated neuroendocrine tissues.[64,65,68]

Fluorinated dihydroxyphenylalanine (^{18}F-DOPA), first synthesized 1992, is a precursor for the neurotransmitter dopamine and is commonly used in the imaging of Parkinson's disease. NETs are capable of taking up amino acids, converting them by means of decarboxylation into biogenic amines, which will be finally stored in cell vesicles; the physiological distribution of DOPA is mostly seen in the gallbladder, bile, and intestine (duodenum, pancreas). To further improve the method, and in particular to reduce the high renal excretion of the tracer producing streaky artifacts in an area of interest, oral premedication by the decarboxylase inhibitor carbidopa was introduced to block the aromatic amino acid decarboxylase enzyme. This led to a six-fold decreased renal excretion while the tumor uptake increased three-fold, hence improving the visualization of these tumors.[65,69]

Many molecular imaging and therapy modalities for NETs are currently under investigation or being developed; nevertheless, no single imaging technique identifies all the metastatic sites of NETs. The best results may be obtained using a combination of functional imaging tests such as PET and SRS and morphologic imaging with CT or MRI. The usefulness of these modalities, however, has to be evaluated by well-designed and multicenter studies.

## ^{18}F-Choline

Although in prostate cancer several imaging methods are available, no single one is able to reliably demonstrate local recurrences, malignant lymph nodes, and skeletal metastases.[70-73]

Recurrences—revealed by a rise in the PSA—are not uncommon after an initial curative therapeutic approach (radical prostatectomy or radiation);[74,75] the velocity of PSA increase is used to distinguish local recurrence from distant metastases.[76,77] Additionally, PET suggests itself as a promising method to localize biochemical recurrence after prostate cancer.

FDG-PET in prostate cancer[43] should only be used in carefully selected patient groups.[78-82] Due to the mostly low FDG uptake in prostate cancer, other radiopharmaceuticals have been studied: ^{11}C-choline;[83] and ^{18}F-labeled choline derivatives, including ^{18}F-fluoroethycholine[84-86] and ^{18}F-fluoromethylcholine (FCH), which show high physiological choline uptake in the liver, pancreas, bowel, and urinary excretion system.
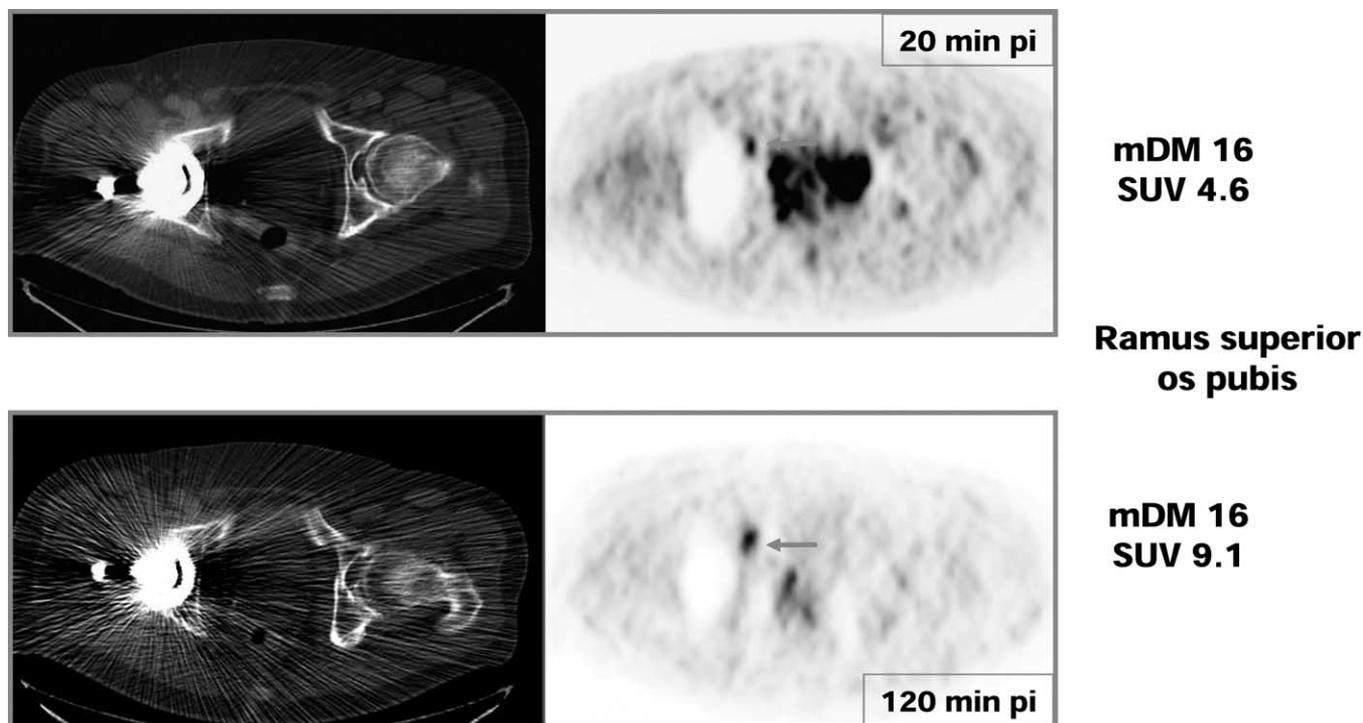
**Figure 7** 20 min and 120 min pi intense focal uptake in the right superior pubic ramus (tumor diameter 16 mm); SUV increased from 4.6 to 9.1.

Choline is transported into cells, phosphorylated, and thus trapped within the cells and used for synthesis of phospholipids. It has be shown that malignant cells have elevated levels of choline and an upregulation of choline kinase activity.[87]

In prostate cancer Hara and coworkers[83,84] compared ^{11}C-choline with ^{18}F-labeled choline and found, in terms of spatial resolution, FCH has a slightly higher image quality than the ^{11}C-labeled tracer; contrary to ^{11}C-choline, FCH is eliminated via the kidneys. The benefit of ^{18}F tracers is a longer half life, which is crucial if a cyclotron is not present on site.

With FCH PET, performing dynamic acquisition (starting 1 min pi) is helpful[88,89] to differentiate focal ureter activity versus pathological lymph nodes in the pelvis: focal FCH uptake from the very beginning (minutes 1-4) has to be interpreted as malignant (lymph nodes and bone), while that occurring in later frames (minutes 5-8) as tracer in the ureter. FCH in the urinary bladder also appears at approximately 5 to 8 min pi.[88,89]

[18]F-Fluoride PET/CT scanning seems to be extremely promising as a follow-up procedure,[4] but nevertheless is only indicated in patients with elevated PSA and suspicious BM.

New generation CT and MRI scanners can visualize lymph node or BM with better resolution, but it still remains to be proven whether this also leads to better diagnostic accuracy in prostate cancer.

# Clinical Impact of PET in Different Malignant Tumors

## Prostate Cancer

Prostate cancer is the most common malignant tumor in men, accounting for approximately one third of all cancer diagnoses; in the United States, 230,000 new cases were diagnosed in 2004.[90] It has a variable biology, ranging from indolent low grade to spreading aggressiveness and finally a tendency to metastasize, killing the patient by bone or bone marrow involvement.

To date PSA is the most commonly used screening method for diagnosis and follow-up management, followed by ultrasound-guided biopsies. Individually, nomograms, including information from PSA and Gleason scores (GsC) at biopsy and clinical stage (at presentation), are used to obtain an early diagnosis (more than 70% of prostate cancers are diagnosed, when the tumor is still confined to the organ). Nevertheless a precise staging in an individual patient cannot always be obtained.[91-93] Using clinical examination alone, staging of prostate cancer is underestimated in 30 to 60% of patients.[94]

### The Impact of Bone Scintigraphy

In prostate cancer with predominantly osteoblastic lesions[95] BS again is the most commonly used follow-up imaging method. To date urologists recommend the use of BS in preoperative management only in patients with PSA levels > 10 to 20 ng/mL. In large retrospective studies in patients with PSA < 20 ng/mL, BM were detected only in
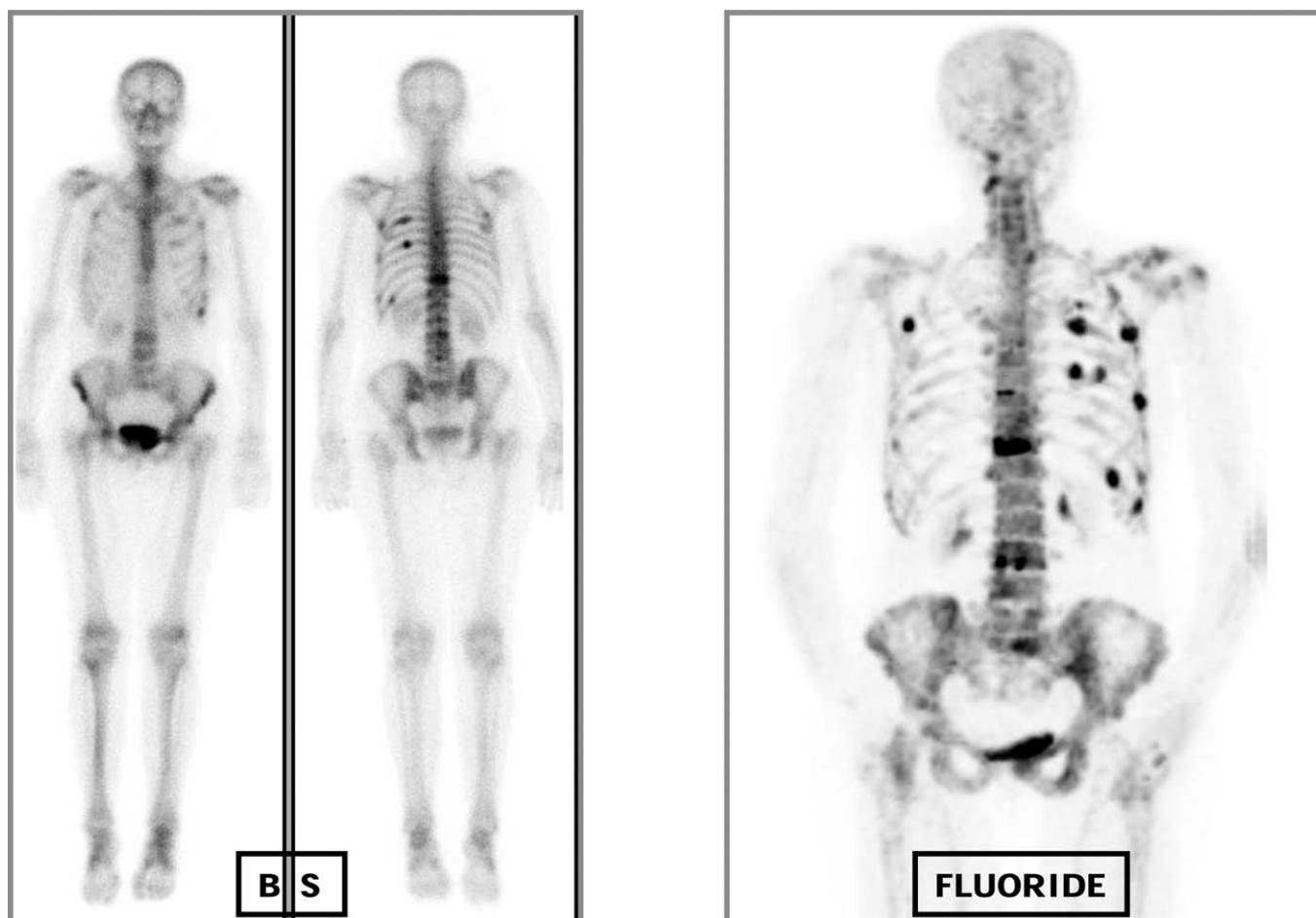
**Figure 8** BS: Intense uptake T11 (suspicious for compression fracture), with pathological uptake in the lumbar spine (L3) and ribs. ^{18}F-Fluoride: Clearly shows extensive metastases.

less than 1%.[96-99] Only one study was able to show a probability of more than 5% for a positive bone scan before PSA increased to 40 to 45 ng/mL.[97] In patients with rising PSA after radical prostatectomy or radiation therapy BS is requested in almost 70% of cases[100] as a follow-up procedure.

Nevertheless, with our recent experience we believe that these recommendations have to be critically reviewed. In several cases we were able to show[101] with ^{18}F-fluoride PET/CT the presence of BM even in patients with low PSA levels (Figs. 3 and 4). Therefore, in high risk patients (GsC > 7 or PSA doubling time < 3 months) we recommend ^{18}F-fluoride PET/CT and not BS as the primary staging procedure.

## ^{18}F-Choline

For preoperative staging in prostate cancer FCH seems to be a very efficient tool. In Linz, FCH PET/CT has been routinely performed in more than 150 patients.

For preoperative staging FCH PET/CT was performed in a high risk group of 49 patients with the following inclusion criteria: GsC > 7 or PSA > 10 ng/mL or PSA doubling time < 3 months. In 4% (2/49)—due to the FCH findings—it was possible to downstage the patient, as suspicious lesions de-

tected formerly in BS could be clearly excluded with FCH PET/CT. In 12% (6/49) of the patients FCH PET led to upstaging with concommitant changes in the therapeutic management: instead of surgery, radiation therapy or hormone therapy (HT) was performed. Four patients were upstaged due to BM and 2 patients (with PSA levels about 12 ng/mL) were upstaged due to multiple lymph node metastases (Fig. 5).

In a small, biopsy-proven, prostate cancer–positive subgroup of 18/49 patients, BM could be visualized in 22% (4/18); in 2 of these (PSA 4.0 and 23.9 ng/mL, respectively) lymph node metastases were also diagnosed as present at the time of initial diagnosis.[89]

In one case with PSA 14 and GsC 8, multiple BM were diagnosed with FCH PET/CT. This case is worth mentioning, as several of the FCH positive bone lesions were also positive on FDG; but FDG uptake was markedly reduced compared with the choline uptake (Fig. 6). In general, in almost all cases with BM there was an increase in the SUV when comparing early and late (approximately 120 min pi) FCH images (Fig. 7).

For follow-up, FCH PET/CT was mostly performed in cases of elevated PSA levels. DeJong and coworkers[102] raised the question whether the use of FCH PET after initial therapy should be restricted to patients with PSA > 5 ng/mL. We
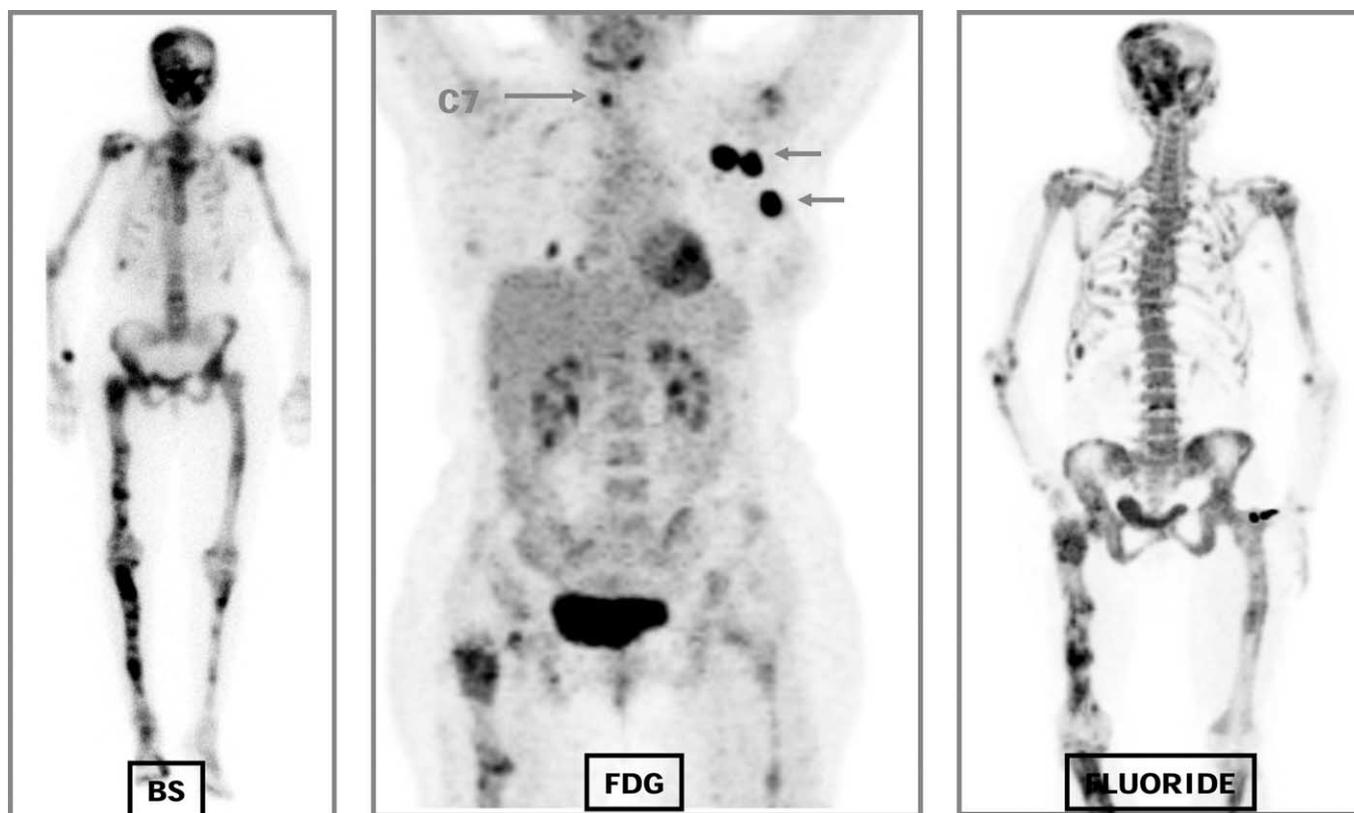
**Figure 9** Comparison BS versus ^{18}F-fluoride versus FDG in breast cancer (left breast and axillary LN) in a patient with known fibrous dysplasia since childhood.
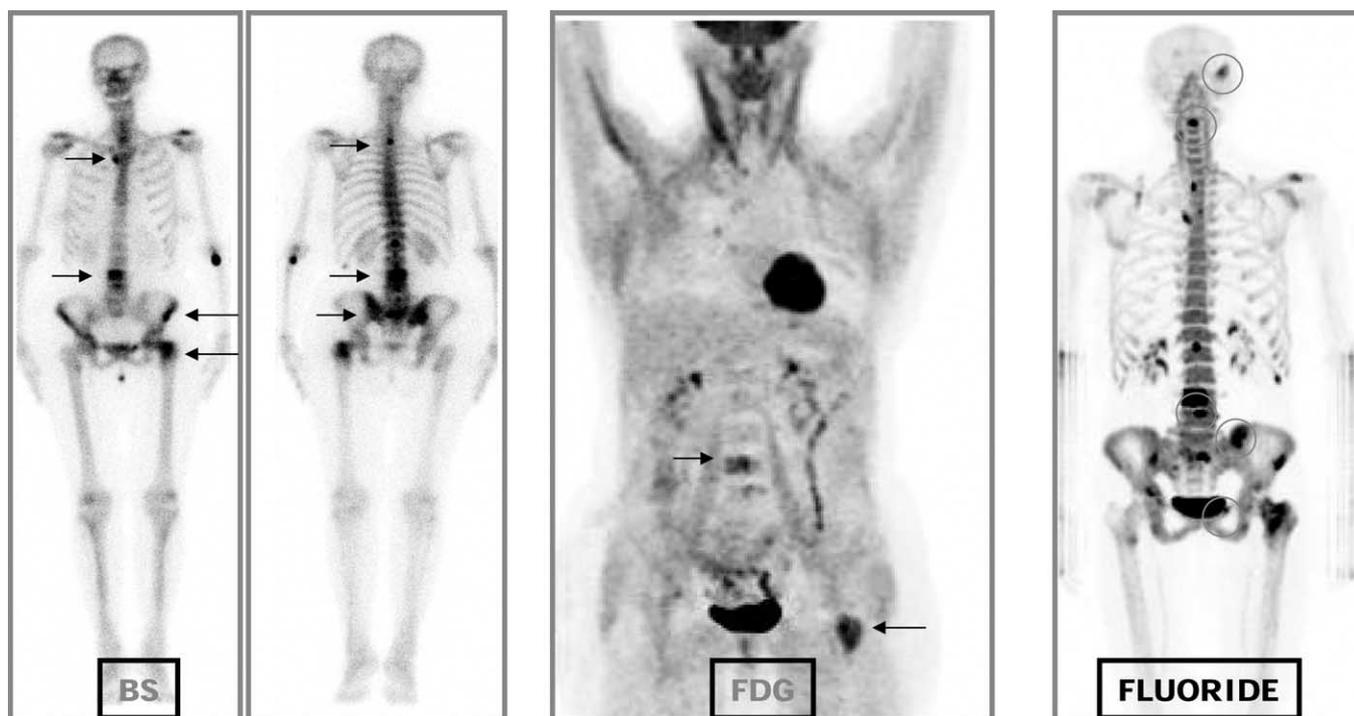


**Figure 10** BS: Bone metastases (cervical and lumbar spine, pelvis, left femur). FDG: Only faint to moderate uptake in a few bone metastases (left femur, lumbar spine); generally reduced FDG uptake due to HT. ^{18}F-Fluoride: Additional bone metastases (not yet seen on bone scan) in the skull, cervical, and lumbar (L5) spine, left os pubis, sacroiliacal left.
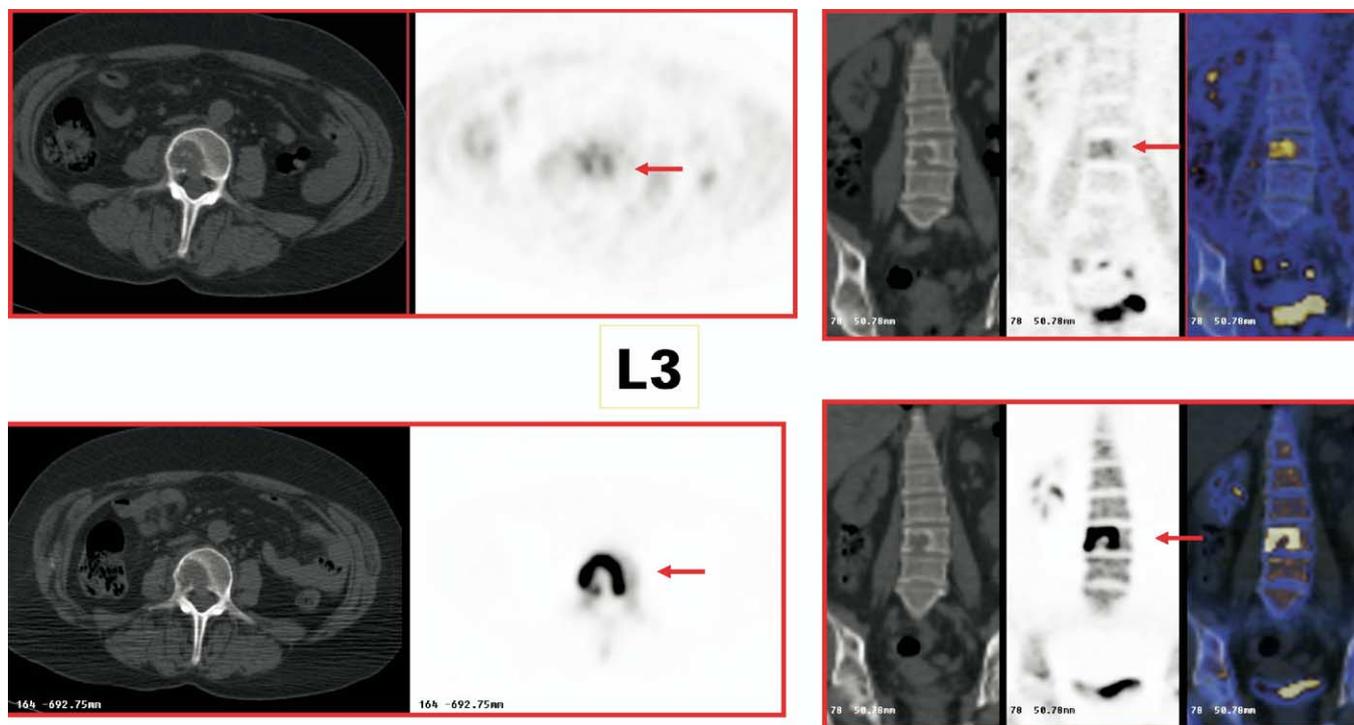
**Figure 11** Bone metastases in the lumbar spine (L3) clearly seen in $^{18}$F-fluoride, with only minimal FDG uptake (axial slices and coronal slices).
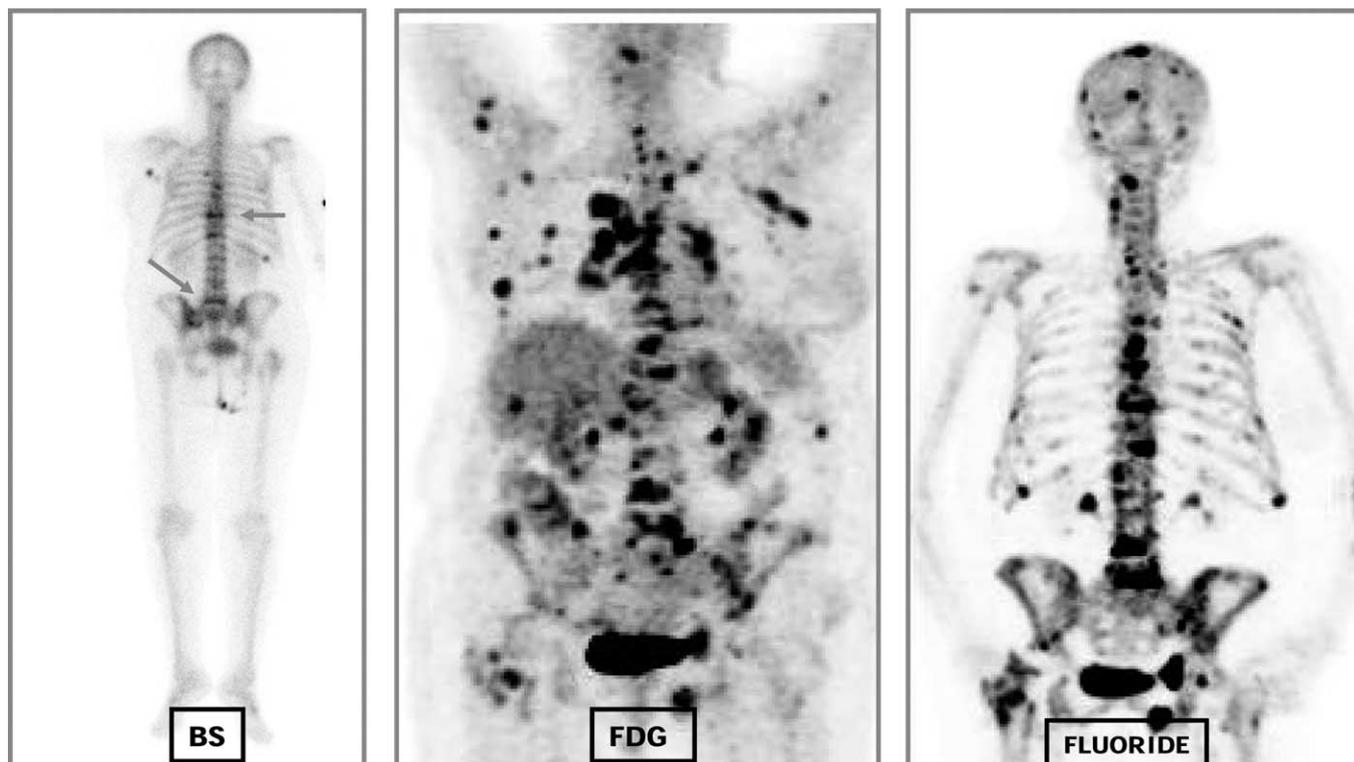


**Figure 12** BS: Pathological compression fracture in lower lumbar spine; metastases in the thoracic spine and in some ribs. FDG and $^{18}$F-fluoride: Multiple bone metastases.

therefore initiated—to our knowledge—the first study to localize with FCH PET/CT recurrences in prostate cancer patients with PSA below 5 ng/mL and have shown that, in 8 of 17 patients with PSA < 5 ng/mL, at least one FCH positive focus could be found, finally confirmed by CT, MRI, biopsy/histology, or the disease follow-up.[103] In one patient, a dedifferentiation of the prostate cancer had apparently occurred: FCH PET-CT showed bone and lymph node metastases, although the PSA level (without any therapy) was as low as 0.03 ng/mL.

As with FDG, the choline uptake during HT (eg, antiandrogen therapy) is also reduced in BM. In patients who have already received HT, the magnitude of the PSA level is likely to be suppressed and may not correlate well with tumor size or metabolism. Moreover, although there are reports of choline uptake decreasing after initiating HT,[104] we do not know whether the influence on choline metabolism and on PSA level occurs in parallel. It cannot be ruled out that the FCH PET signal is influenced less strongly than the PSA level.

In an earlier publication Shreve and coworkers[105] clearly showed in 34 patients that FDG-PET—due to the fact that FDG accumulation in osteolytic metastases is higher[42] than in sclerotic metastases—is less suitable for the detection of BM, in untreated but in particular in patients who had previously received treatment. Morris and coworkers[81] showed in 17 patients with progressive metastatic prostate cancer that FDG was able to discriminate active osseous lesions from quiescent lesions.

## Breast Cancer

In breast cancer (BC) the skeleton is the most common site of distant metastases, and the BS is the most sensitive method of detecting and determining the extent of BM. BC patients have predominantly osteolytic lesions, but 15 to 20% have osteoblastic lesions.[106] Parathyroid hormone–related peptides can be produced by breast cancer cells and other solid tumors, thus stimulating the formation of osteoclasts.[107,108]

In BC a higher number of false negative FDG skeletal lesions compared with nonosseous metastases has been noted[109] and another smaller study also showed a relatively low skeletal sensitivity.[110] These poorer results in BC might be due to the different affinities of simultaneously appearing lytic and sclerotic BM in BC. It is worth commenting that patients with predominantly sclerotic lesions have a longer survival than those with lytic metastases.[42]

Lonneux and coworkers[111] showed in 33 patients with normal bone scintigraphy a high incidence of bone marrow infiltration, concluding that FDG is more sensitive than BS (CIM 6 positive, PET 31 positive BM). Ohta and coworkers[112] compared FDG PET and BS in 51 patients, with a sensitivity of 77.7% for both, whereas FDG specificity was much higher (97.6%) than BS (80.9%). Similar results were also shown by Yang and coworkers[113] who described in 48 patients (1 year follow-up period, 127 lesions overall) an almost identical sensitivity of FDG (95.2%) and BS (93.3%), but a much higher accuracy of FDG with 94.5% versus 78.9% in BS. Stafford and coworkers[114] showed in 24 patients a significant
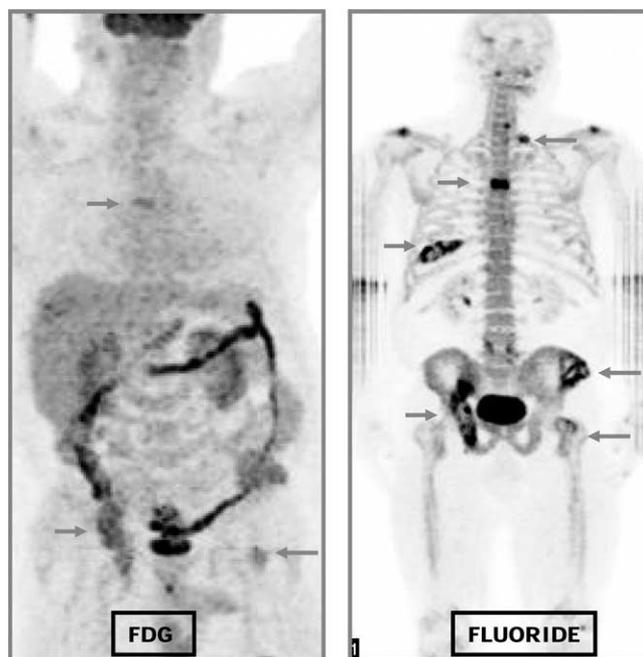


**Figure 13** Only slight FDG uptake in three bone metastases (spine, hip, pelvis), whereas ^{18}F-fluoride clearly showed multiple bone lesions.

association of SUV changes and overall response rate in FDG PET.

[18]F-Fluoride PET seems to have the potential to replace BS in routine studies of metastatic breast cancer staging (Fig. 8). Nevertheless, FDG-PET can often clarify staging in cases of equivocal conventional findings (Fig. 9).

Similar to choline, the FDG uptake under HT (eg, Novaldex) is also reduced in BM (Figs. 10 and 11).

### Comparison FDG and ^{18}F-Fluoride PET/CT

Overall, in Linz we have performed ^{18}F-fluoride PET/CT in more than 100 patients with different malignant tumors or diseases within the last 2 years. In 20 cancer patients (6 breast, 2 MTC, 2 prostate, 2 CUP, 2 anorectal, 2 ovarian, 1 lung, 1 FTC, 1 renal cell, and 1 urinary bladder) both procedures, FDG and ^{18}F-fluoride, were performed, detecting 150 lesions overall (unpublished data).

From these, 72 lesions (group 1) were FDG and ^{18}F-fluoride positive (Fig. 12). Forty-four lesions were FDG positive but ^{18}F-fluoride negative (group 2). Thirty-four lesions were only ^{18}F-fluoride positive (group 3).

In group 2 most lesions were small osteolytic metastases or located in the bone marrow, whereas group 3 consisted of tumors known to have less FDG avidity, eg, MTC, renal cell carcinoma, or thyroid cancer (Fig. 13).

## Lung

In lung cancer BM are already present in 20 to 30% at initial diagnosis and in 35 to 66% at autopsy;[115-117] nonsmall cell lung cancer (NSCLC) without distant metastases is potentially curable. In approximately 20 to 25% of all lung cancer
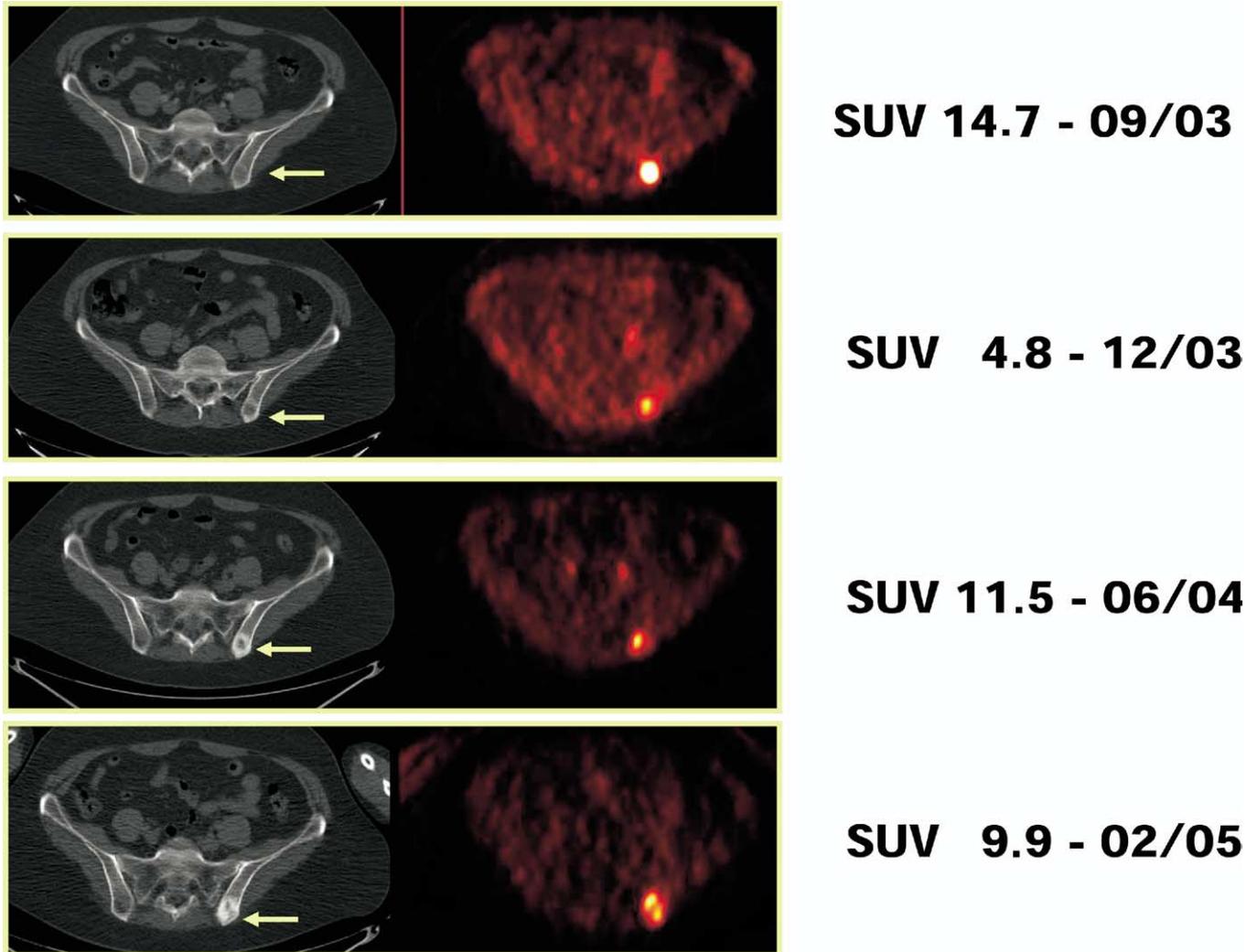
**Figure 14** Comparison of PET/CT and SUV changes (pelvis) from September 2003 until February 2005. September 2003: At initial staging extremly high SUV values (14.7), CT almost normal. December 2003: Peripheral sclerotic bone changes on CT and a marked decrease in SUV (4.8). June 2004 and February 2005: Diffuse but markedly sclerotic increase in the bone metastases on CT, whereas SUV values remained unchanged (9.9-11.5).

cases small cell lung cancer (SCLC) will be seen histologically.

Marom and coworkers[118] showed in 100 patients a sensitivity for FDG of 92 versus 50% for BS, thus concluding that FDG-PET is able to eliminate the need for BS in preoperative tumor staging. Jadvan and coworkers[119] compared FDG and

CT findings and showed a higher sensitivity for FDG (75%) than for CT (50%), with an almost similar specificity of 100% versus 98% for CT.[120,121] In 85 mostly NSCLC patients Gayed and coworkers[122] showed in a retrospective study a higher sensitivity (81%), but lower specificity (78%) for BS than for FDG (sensitivity 73%, specificity 88%). The SUV in BM

**Table 1** Comparison of Metabolic Diameter (mDM) and SUV Over Nearly 2 Years Clearly Showing the Changes in Different Sites of Metastases

| Metastases | DOPA 04/03 | | DOPA 09/03 | | DOPA 12/03 | | DOPA 06/04 | | DOPA 02/05 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | mDM | SUV | mDM | SUV | mDM | SUV | mDM | SUV | mDM | SUV |
| C4 | 10 | 5.0 | 15 | 6.8 | 17 | 9.2 | 17 | 8.5 | 12 | 8.0 (RT) |
| L2 | 10 | 2.8 | 10 | 2.6 | 13 | 7.8 | 13 | 3.8 | 18 | 3.9 |
| Sacrum right | – | – | 16 | 7.9 | 21 | 16.1 | 21 | 3.3 | 30 | 15.1 |
| Spina post left | 15 | 8.2 | 25 | 14.7 | 25 | 4.8 | 25 | 11.5 | 30 | 9.9 |
| Sternum | – | – | – | – | 10 | 3.3 | 10 | 5.1 | 15 | 10.2 |
| T12/L1 | – | – | – | – | – | – | – | – | 11 | 8.8 |

**Table 2** Comparison of mDM and SUV in Fluoride, FDG, and DOPA PET/CT

| Metastases 01/2005 | Fluoride | | FDG | | DOPA | |
|---|---|---|---|---|---|---|
| | mDM | SUV | mDM | SUV | mDM | SUV |
| C4 | 17 | 29.5 | – | – | 12 | 8.0 |
| L2 | 28 | 33.5 | 10 | 3.0 | 18 | 3.9 |
| Sacrum right | 35 | 46.5 | 29 | 5.5 | 30 | 15.1 |
| Spina post left | 40 | 61.9 | 31 | 5.6 | 30 | 9.9 |
| Sternum | 10 | 11.4 | – | – | 15 | 10.2 |
| T12/L1 | – | – | – | – | 11 | 8.8 |

ranged between 1.7 and 14.4 and in false positive lesions between 1.4 to 8.9. The authors concluded that there was significantly higher specificity and negative predictive value for FDG, but no significantly higher sensitivity and positive predictive value for BS.

Similar results were shown by Al Sugair and Coleman[123] in 315 lung patients with a higher sensitivity (84%) and lower specificity (84%) for BS and lower sensitivity (67%) but higher specificity (96%) for FDG-PET. Garcia and coworkers[124] compared lung and prostate cancer, detecting more sclerotic metastases on BS than in FDG (especially prostate cancer), whereas in lung cancer patients PET was superior to BS in lytic metastases.

In a prospective study Schirrmeister and coworkers[39] compared in 53 lung cancer patients the diagnostic accuracy of ^{18}F-fluoride with BS and BS + SPECT at initial staging; in this study 12 patients with SCLC and 41 patients with NSCLC were included. The overall frequency of BM was 23% (12/53).

SPECT increased the sensitivity of BS significantly;[39] compared with ^{18}F-fluoride BS underestimated the extent of BM in 58% (7/12). The clinical management changed in 50% (6/12 patients), which was 11% of all cases.

## Differentiated Thyroid Cancer

In differentiated thyroid cancer about 7% of PTC and 34% of FTC patients already have distant metastases at initial diagnosis; of these 27% in PTC and 59% in FTC are located in the bone.[125]

Schirrmeister and coworkers[126] compared BS, ^{18}F-fluoride, and ^{131}I whole body scans in 35 patients (9 PTC, 26 FTC) showing 83% accuracy for BS alone (64-85% sensitivity, 95-81% specificity), whereas the combination of BS and
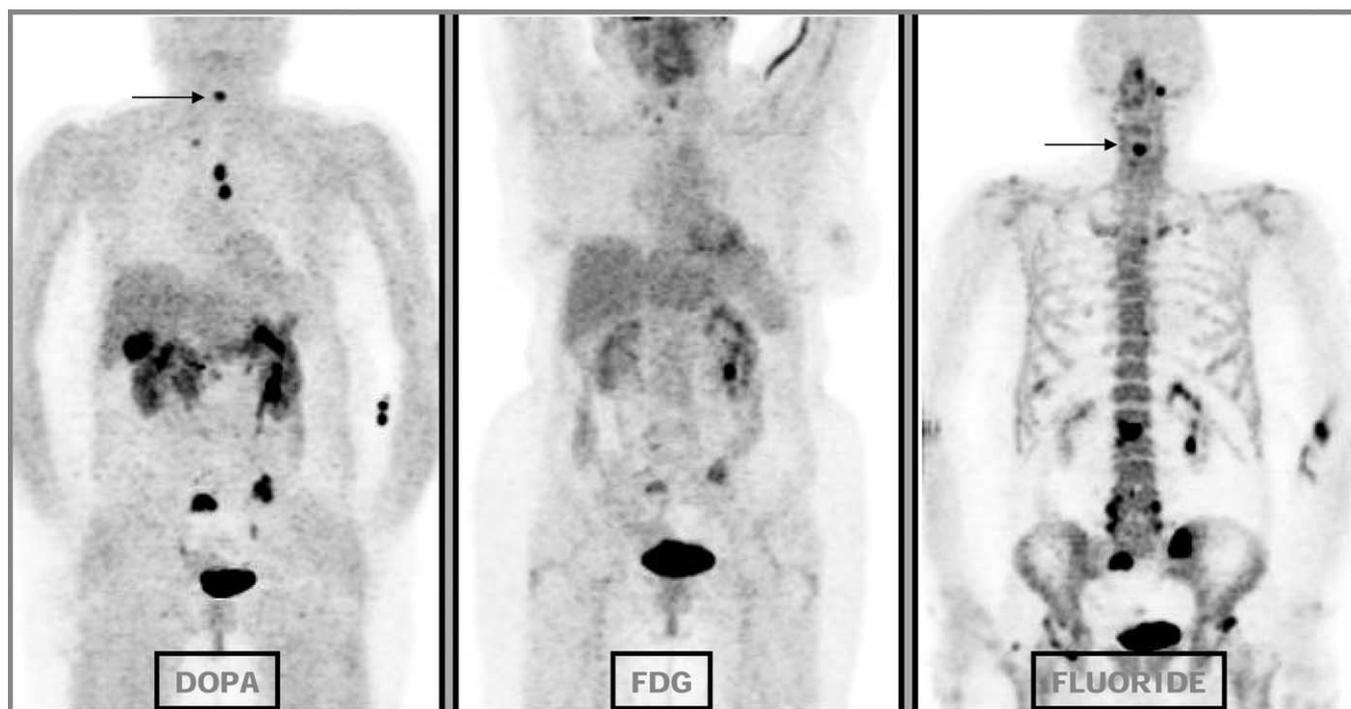


February 3, 2005  January 27, 2005  January 26, 2005

**Figure 15** Comparison DOPA versus FDG versus ^{18}F-fluoride PET/CT: C4 metastasis (FDG negative, DOPA, and ^{18}F-fluoride positive).

**FDG**

**SUV 5.5**

**DOPA**

**SUV 15.1**

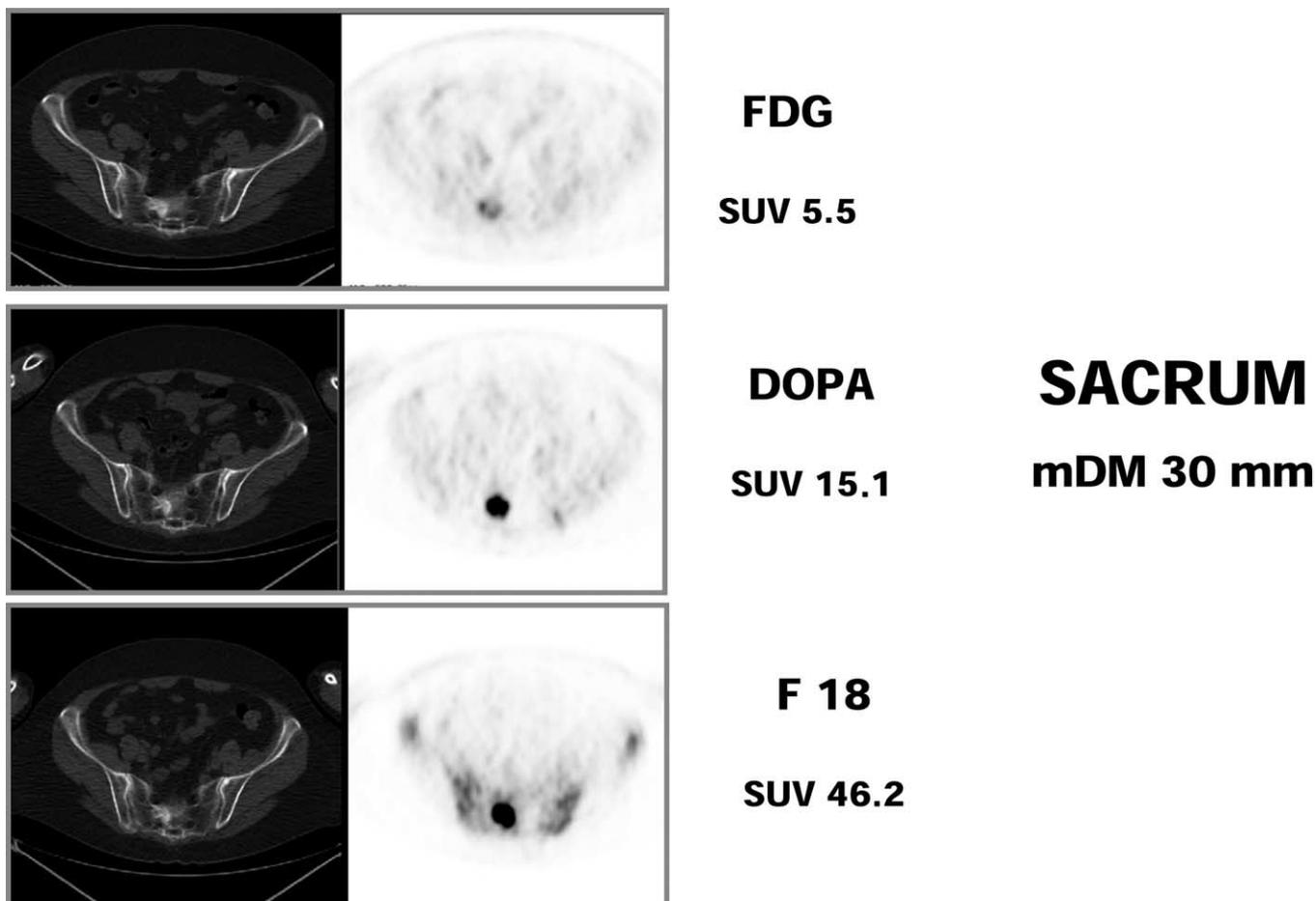**SACRUM**

**mDM 30 mm**

**F 18**

**SUV 46.2**

**Figure 16** Bone metastases in the sacrum (30 mm diameter): Intense uptake in DOPA (SUV 15.1) and ^{18}F-fluoride (SUV 46.2), only faint FDG uptake (SUV 5.5).

[131]I whole body scans had 97% accuracy (100% sensitivity, 95% specificity). Of the BM, 41 were osteolytic, only 2 mixed; 41% of all metastases were located in the vertebral column, 44% in flat bones (pelvis, scull, sternum, ribs). Nevertheless no data were provided in that study about the detection rate of ^{18}F-fluoride.

## MTC

Based on reports in the recent literature DOPA seems also to be useful as a new functional imaging procedure (injected dose 0.08-0.10 mCi/kg) for MTC as well as for NETs, providing better results than SRS and FDG-PET.[8] The authors showed in MTC patients a low sensitivity for FDG (44%), SRS (52%), and DOPA (63%) compared with a sensitivity of CIM with 81%; however all three methods had a very high specificity of more than 90% compared with 67% for CIM.

We have some initial experience with a modified acquisition protocol starting with a dynamic acquisiton at 1 min after DOPA injection and have been able to clearly show that the DOPA uptake in BM could be visualized—similar to choline—within the very first minutes.

During a follow-up period of more than 18 months, the metabolic diameter (mDM) as well as SUV values of the dif-

ferent bone lesions changed markedly, due to morphological changes that could also be seen on the CT (Fig. 14).

Initially tumor metabolism is increasing or relatively high, then, due to peripheral sclerotic changes in the bone structure, SUV and DOPA metabolism decrease markedly. Later, SUV and in particular also mDM increase again, due to diffuse sclerosis of the BM (Table 1). In several lesions, we could observe an increase of greater than 50%; in these lesions morphological changes detected with CT were seen usually some months later. This phenomenon—similar to FDG[42]—could be explained by DOPA accumulation in osteolytic metastases (located in the bone marrow) being visualized earlier than bone structure changes.

We performed FDG and DOPA PET/CT in 11 MTC patients for primary staging and follow-up in cases of suspected recurrence due to elevated calcitonin or CEA levels. With DOPA we could detect 18 lesions, whereas FDG was only able to show 7 pathological lesions. Furthermore, the DOPA uptake was much higher than with FDG[127,128] as shown in Table 2.

In one case, when comparing ^{18}F-fluoride, FDG, and DOPA, we could clearly see in two BM (C4 cervical spine and sacrum) similar tracer uptake and SUV values for DOPA and ^{18}F-fluoride[127,128] whereas FDG showed reduced metabolic activity (Figs. 15 and 16).
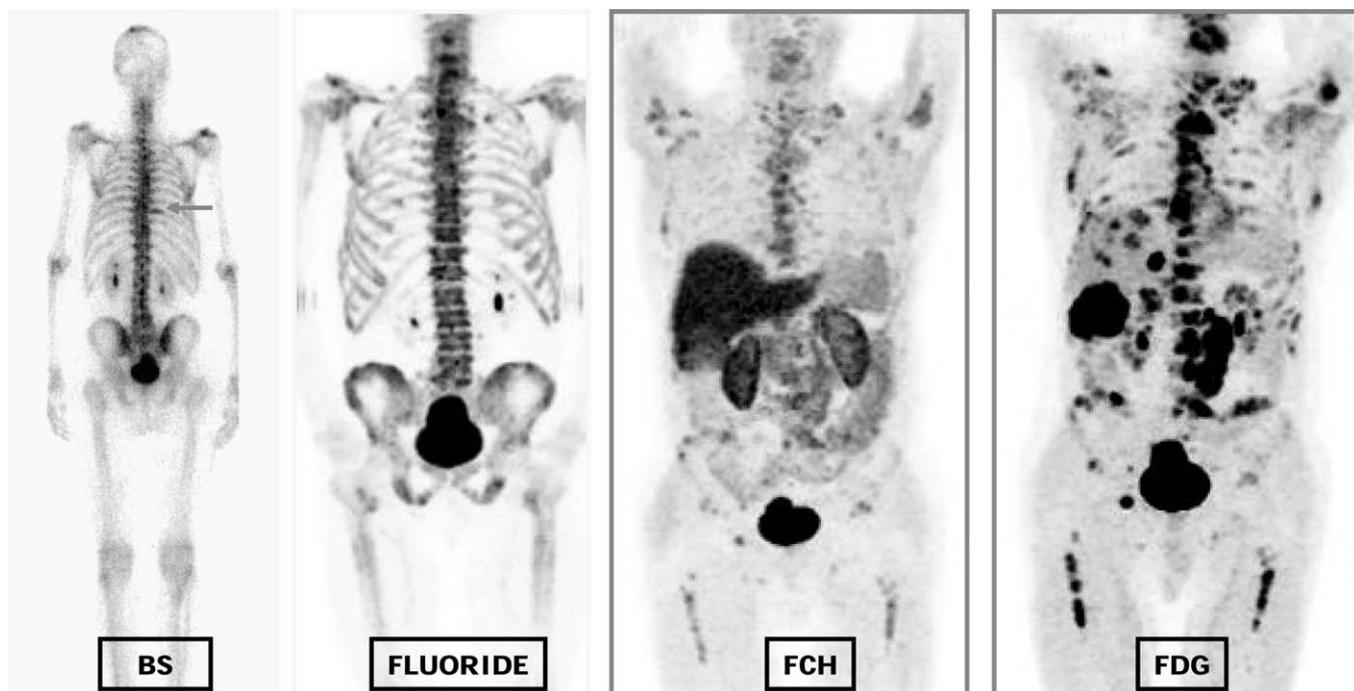
**Figure 17** BS: Only one lesion in the 9th right rib; x-ray negative. $^{18}$F-Fluoride: Multiple bone metastases (spine, ribs, pelvis, femur). FCH: Similar pattern of choline uptake in bone metastases compared with F18 fluoride, slightly reduced uptake due to HT. FDG: intense uptake in multiple bone metastases; additionally multiple liver and lymph node metastases (mediastinum, retroperitonal).

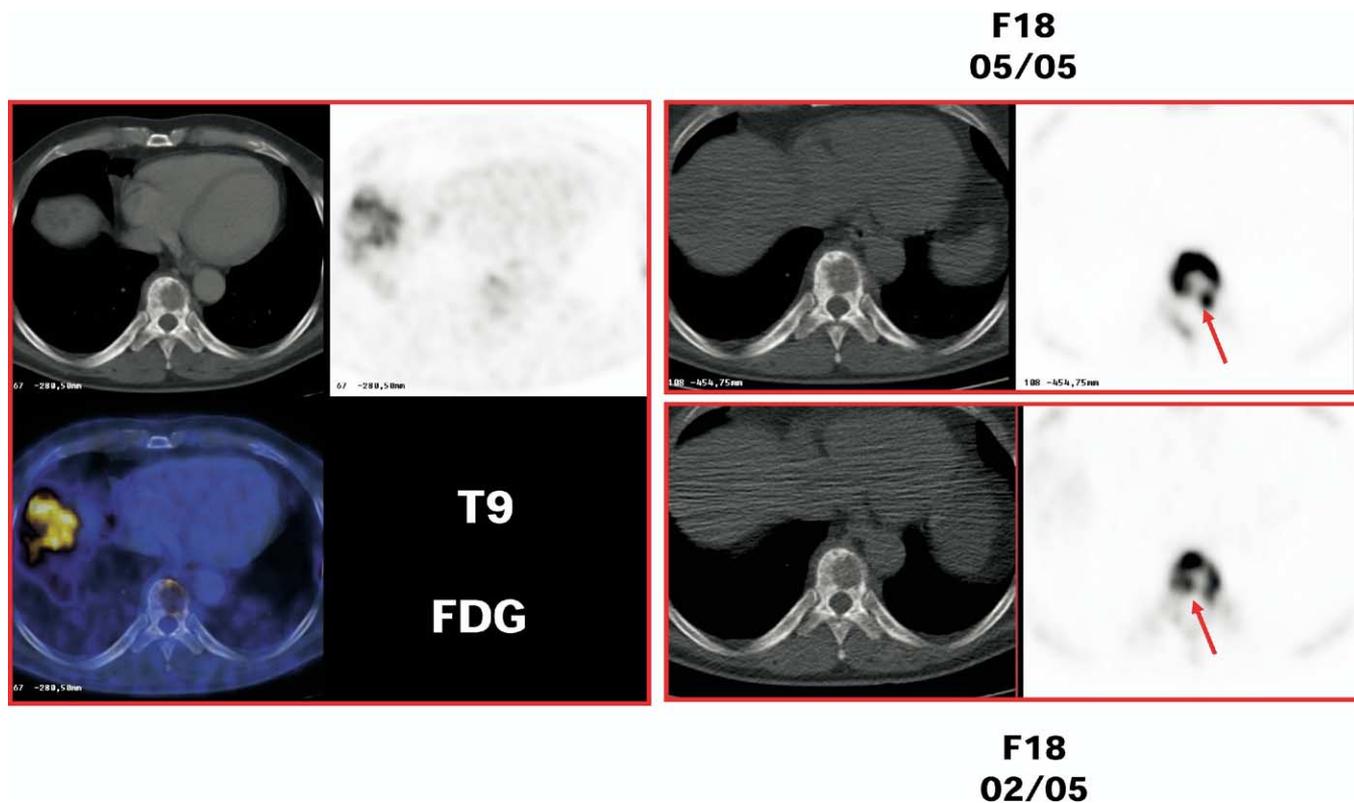

**Figure 18** FDG: No uptake in the thoracic spine (T9), but pathological CT. $^{18}$F-Fluoride: In the preoperative and follow-up images (after 3 months) increased but similar $^{18}$F-fluoride uptake due to bone metastases.
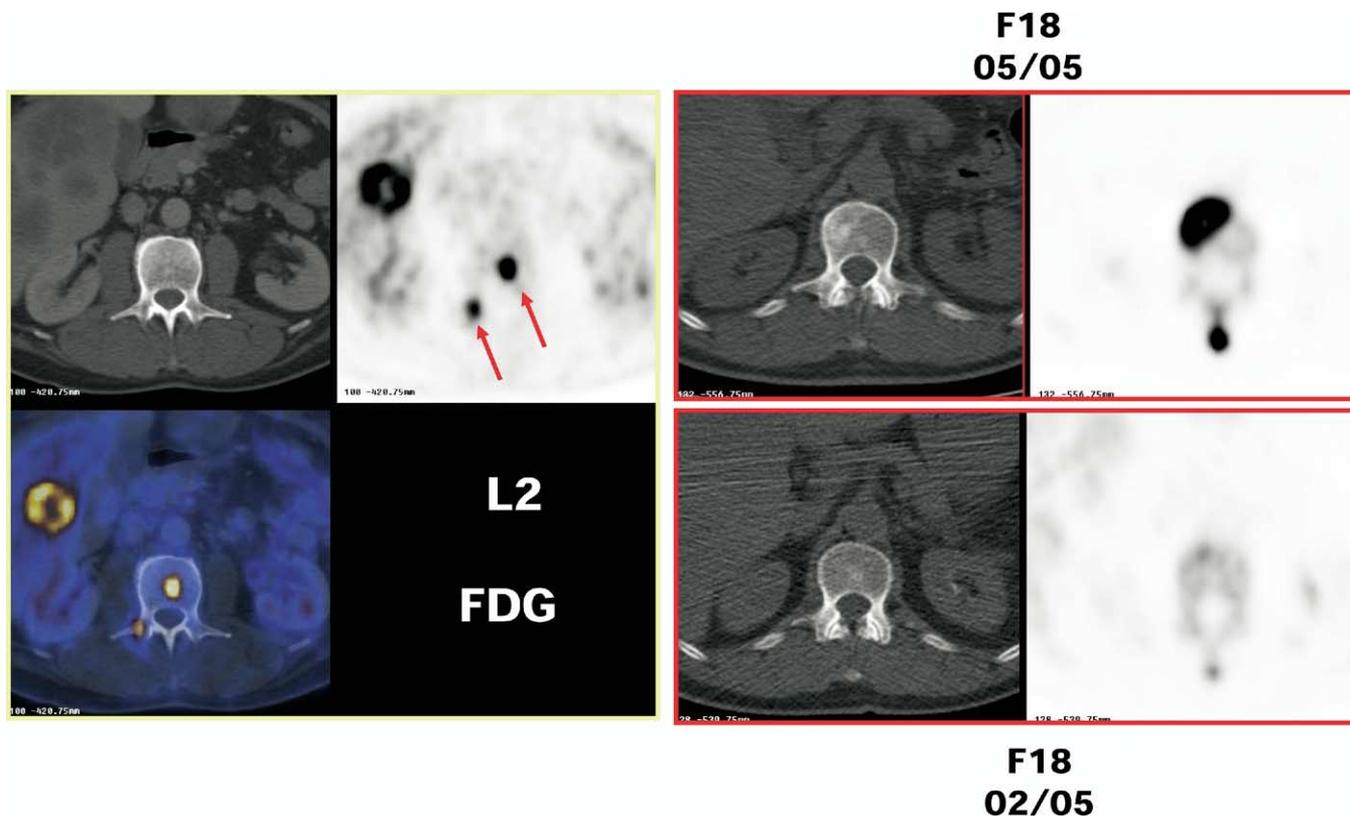
**Figure 19** FDG: Pathological uptakes in the lumbar spine (L2). ^{18}F-Fluoride: In the preoperative staging no pathological ^{18}F-fluoride findings, in the follow-up (3 months later) intense fluoride uptake combined with sclerotic changes on CT.

## Lymphoma

In multiple myeloma, where skeletal metastases are often predominantly marrow based, FDG is more sensitive than conventional BS;[129] clinically in about half of the myeloma cases bone scans are normal despite severe osteolytic bone destruction.[130]

## Osteosarcoma

In osteosarcoma patients the role of FDG remains unclear.[131,132]

## Multitracer Imaging

In rare tumors, eg, NETs, MTC, or highly aggressive breast or prostate tumors, FDG-PET, while very attractive and promising, is not the only imaging "game in town." Other radio-pharmaceuticals, such as fluoride, choline, and DOPA, are very potent procedures providing additional diagnostic information.

In several cases, multitracer imaging will provide insight into the variations of intra- as well as interindividual tumor metabolism (Fig. 15), improving our knowledge about complex tumor metabolism and special pathophysiological mechanisms (Fig. 17).

Not always knowing the ideal "time curve " as to when to perform diagnostic staging and follow-up procedures, early repetition of a diagnostic procedure—due to excessive and

rapid changes in tumor metabolism—may be useful, as shown in Figs. 18 and 19.

A remarkable case of a colorectal cancer could be demonstrated by us showing multiple BM visualized by preoperative FDG staging. At that time ^{18}F-fluoride only visualized two BM in the thoracic spine (T9 and T10). Three months later ^{18}F-fluoride PET/CT also showed a similar pattern to FDG with multiple BM (Fig. 20). To conclude, FDG in "early disease" has clear advantages over ^{18}F-fluoride.

We are tempted to conclude that morphology of metastases (sclerotic, lytic, mixed) is as important as precise localization. Small lesions in long bones show very often an intense osteoblastic response and can therefore easily be diagnosed with ^{18}F-fluoride or BS. On the other hand lesions in the spine may show minimal osteoblastic response and may therefore more easily be diagnosed with FDG.

From the clinical point of view different tracers targeted appropriately should be used for diagnosis and staging of different tumor entities. In breast and lung cancer sensitivity of FDG in detecting BM is similar to BS, although FDG uptake in general is reduced under treatment modalities.

[18]F-Fluoride seems to better visualize BM in FDG negative tumors (renal cell, thyroid) and in FDG avid tumors under therapy (eg, HT in breast cancer patients). The question "do FDG negative and ^{18}F-fluoride, BS or CT positive metastases have any clinical relevance" still remains—an issue that should challenge further studies.
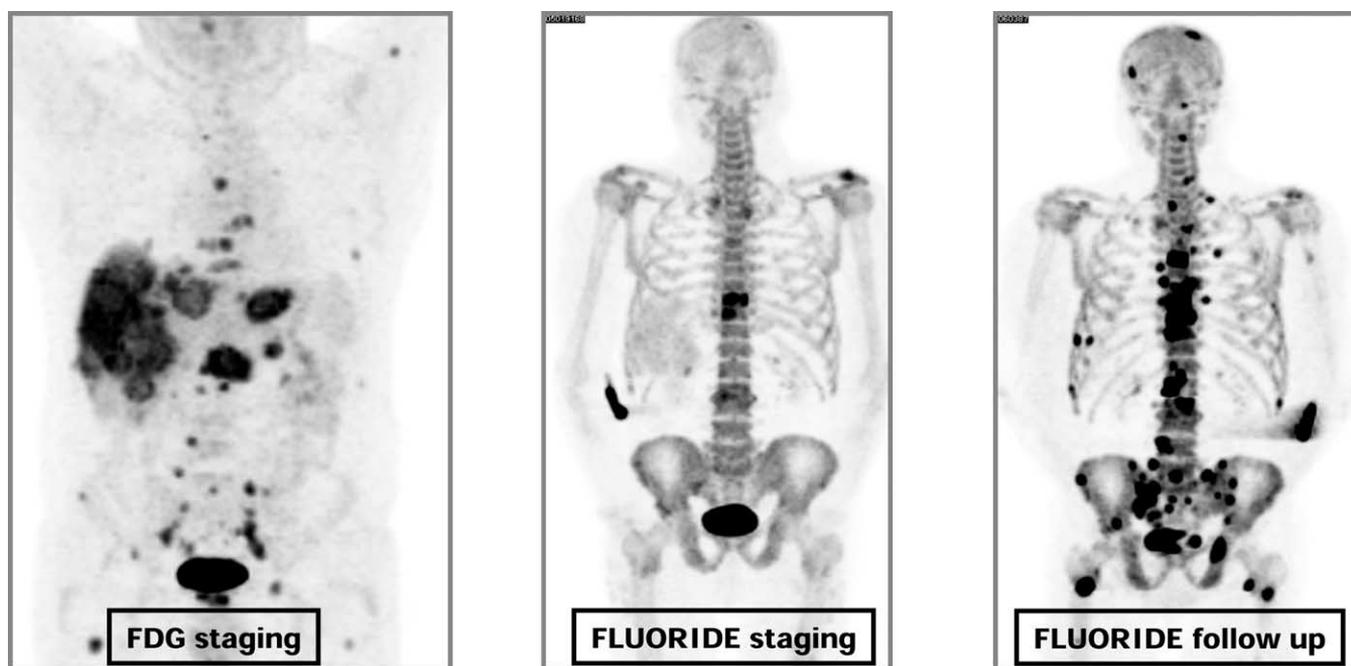
**Figure 20** FDG preoperative staging (February 2005): Multiple metastases in the liver and in the bone (ribs, pelvis, femur, thoracic, and lumbar spine). $^{18}$F-Fluoride preoperative staging (February 2005): Only two bone metastases in the thoracic spine (T9, T10), no more additional bone lesions. $^{18}$F-Fluoride follow-up (May 2005): After 3 months multiple bone metastases.

In MTC patients DOPA is providing more and earlier information than FDG for preoperative staging as well as for follow-up; thus changes in tumor metabolism and SUV may often be seen earlier then with $^{18}$F-fluoride or FDG. In lymphoma and myeloma FDG seems to perform clearly better than bone scintigraphy.

In prostate cancer FDG is less sensitive, but FCH seems to be the tracer of choice for preoperative staging. Dynamic imaging with FCH is almost always valuable in the differential diagnosis between lymph node metastases versus ureter. In most of the cases false positive findings regarding locoregional lymph nodes or bone lesions could be excluded. Nevertheless it is clear that this method is not able to detect micrometastases.

In several cases multitracer imaging or short-term follow-up PET/CT procedures are of great clinical benefit. The value of other PET tracers in BM is still under investigation. Nevertheless, evaluation of cost effectiveness and short- and long-term benefits of PET/CT in clinical decision making and multitracer management has yet to be performed.

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