



# Breast Cancer: Role of SPECT and PET in Imaging Bone Metastases

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Breast cancer is the most common cause of bone metastases in women. Imaging studies are useful to identify bone involvement and associated complications, for follow-up of disease spread and for the assessment of response to therapy. Bone scintigraphy with <sup>99m</sup>Tc-labeled diphosphonates is most widely used, due to its availability, high sensitivity, and low cost, despite the relatively low specificity. The addition of single-photon emission computed tomography and recently single-photon emission computed tomography/computed tomography improves the diagnostic accuracy of this modality. Serial follow-up scans can demonstrate disease progression, but this method is less accurate in determining response to treatment. Positron emission tomography (PET), a tomographic modality with improved resolution shows improved sensitivity and specificity. <sup>18</sup>F-fluorodeoxyglucose (FDG)-PET is the most common clinically used procedure. FDG is taken up by the tumor cells and has therefore the advantage of demonstrating the presence of disease in both bone and soft tissues. FDG-PET is highly sensitive mainly in diagnosis of early metastatic disease, which may still be confined to the bone marrow, as well as for the detection of lytic bone metastases and can be also reliably used to monitor response to therapy. For the detection of sclerotic lesions, however, imaging with a bone-seeking tracer such as <sup>18</sup>F-fluoride, may have a complementary role. As a nonspecific skeletal imaging tracer, <sup>18</sup>F-fluoride has great potential, being more sensitive than bone scintigraphy and when PET/computed tomography is performed it is highly accurate for detection of both lytic and sclerotic lesions and to distinguish benign from malignant skeletal findings. *Semin Nucl Med* 39:408-415 © 2009 Elsevier Inc. All rights reserved.

Breast cancer is the most common cancer in women in the Western world; it was the second leading cause of cancer-related deaths in women with an age adjusted incidence of 126.1 per 100,000 women per year in 2005.<sup>1</sup> The American Cancer Society estimated that 178,480 women were diagnosed with invasive breast cancer and 40,460 women died of breast cancer in 2007.<sup>2</sup> On the basis of data for 2003%-2005%, 12.03% of women (1/8) born today will be diagnosed with breast cancer and 1 in 33 women will die of breast cancer during their lifetime.<sup>2</sup>

Bone is the most common site of breast cancer metastases. Furthermore, breast cancer is the leading cause for skeletal

involvement in women. Bone metastases affect 8% of all patients with breast cancer, but can reach an incidence of 30%-85% in patients with advanced disease.<sup>3-5</sup> Bone metastases impair the quality of life by causing complications, such as bone pain, pathologic fractures, hypercalcemia, and spinal cord compression. Early detection of metastatic disease may prevent these complications, and therefore may improve quality of life as well as survival. Imaging studies are useful to identify bone involvement and associated complications, to guide biopsy for histologic confirmation and to assess response to therapy.<sup>6</sup>

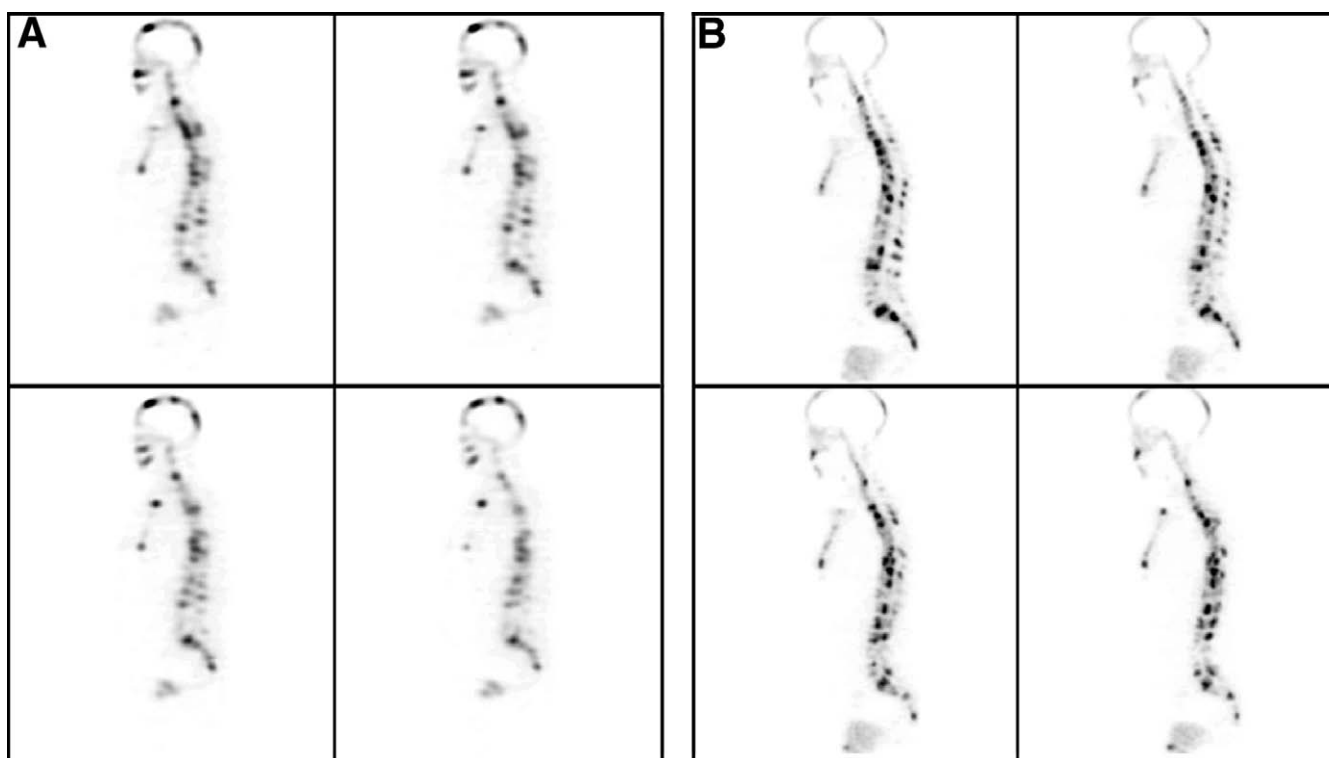
Cortical bone is a thin compact layer comprising 80% of the skeleton. It surrounds the trabecular bone, which also encompasses the bone marrow.<sup>5</sup> Constant remodeling of bone maintains a dynamic balance between bone resorption (by osteoclasts) and bone formation (by osteoblasts). On morphologic imaging studies, bone metastases can present as lytic, sclerotic (blastic), or mixed. Bone metastases spread, as a rule, hematogenously, starting as intramedullary lesions found in more than 90% of cases in the distribution of the red marrow. Skeletal breast cancer metastases are located mainly

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**Figure 1** A 51-year-old woman, 6 months after right breast lumpectomy followed by axillary lymph node dissection (T2N2) was evaluated for restaging purposes after surgery. Whole-body bone SPECT (A) after i.v. injection of 25 mCi  $^{99m}\text{Tc}$ -MDP, acquired at half-standard time (22 min) and processed with ordered-subset expectation-maximization (OSEM) and collimator detector response compensation and  $^{18}\text{F}$ -fluoride PET (B), selected sagittal slices, demonstrate multiple bone metastases.

in the axial skeleton, most commonly in the spine and pelvis, followed by ribs, skull, and femora.<sup>5,6</sup>

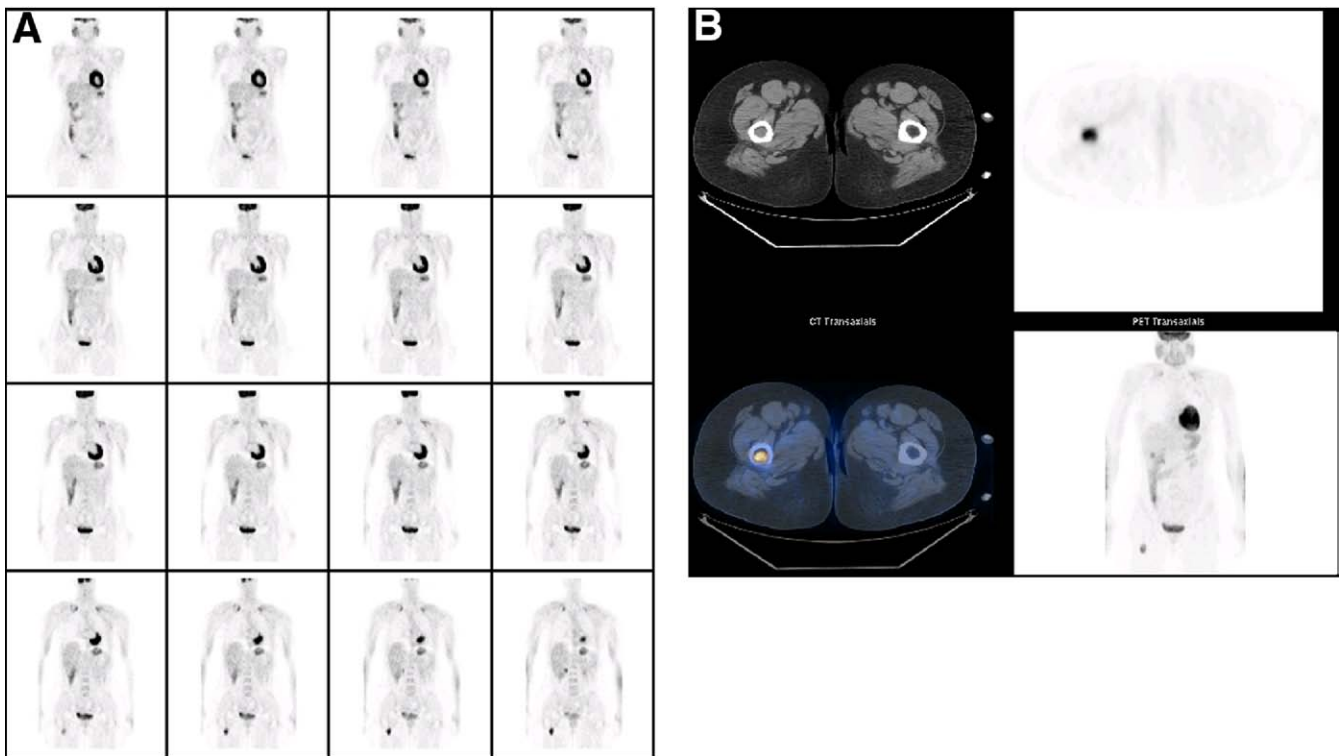
## Bone Scintigraphy

Bone scintigraphy (BS), commonly performed with  $^{99m}\text{Tc}$ -methylene diphosphonate ( $^{99m}\text{Tc}$ -MDP) is a widely used procedure, provides a whole-body skeletal survey at a relatively low cost and is the standard initial imaging modality for assessment of bone metastases.<sup>5,7-9</sup> The uptake of  $^{99m}\text{Tc}$ -MDP on the bone surface reflects increased vascularity and increased osteoblastic activity. Osteolytic lesions also demonstrated secondary bone formation, and therefore even osteolytic metastases can be detected with BS. The reported sensitivity and specificity of BS for the detection of bone metastases in patients with breast range between 62%-100% and 78%-100%, respectively.<sup>5</sup> Although BS is considered overall as very sensitive for detection of bone metastases, comparison with magnetic resonance imaging (MRI) showed underestimation of the extent of metastatic disease.<sup>10-12</sup> False negative results are seen in avascular lesions, in the presence of rapidly growing pure osteolytic metastases with no reactive increased osteoblastic activity, or in lesions with low bone turnover. Specificity of BS is generally lower, due to a known increased blood flow and metabolic reaction of bone to a variety of disease processes, including osteoarthritis, trauma, and inflammation. Therefore, BS is considered diag-

nostic when it shows widespread bone involvement. In other cases, when the scintigraphic pattern is less suspicious, or in the presence of a single focal abnormality, further assessment with other imaging modalities, mainly computed tomography (CT) and MRI, and in some cases histologic confirmation may be required for precise diagnosis.<sup>5,8</sup>

The detection rate of bone metastases by BS in patients with early-stage breast cancer is very low (0.82% and 2.55% in patients with stages I and II, respectively), increasing to 16.75% in patients with stage III disease and 40.52% in patients with stage IV disease. Therefore, routine screening of patients with breast cancer is recommended only in advanced stage disease, whereas in patients with early stages BS should be only performed in symptomatic patients, when there is a clinical suspicion for metastatic bone involvement.<sup>5,13-16</sup>

After treatment, BS can demonstrate disease progression as the appearance of new lesions, or response when there is a decrease in intensity of uptake or in the number of focal abnormalities. However, BS may fail to correctly monitor treatment response due to its inherent low specificity and to the fact that the healing process can be associated with increased bone turnover. Patients showing partial response to therapy may also not be depicted on BS, despite the evidence of clinical improvement and prolonged survival.<sup>5</sup> Patients receiving hormonal therapy may show a "flare phenomenon," characterized by increased tracer uptake during the



**Figure 2** A 39-year-old woman, after left mastectomy and axillary lymph node dissection following neoadjuvant radiochemotherapy, was referred for FDG-PET/CT for restaging and further treatment planning. FDG-PET selected coronal slices (A) show a focal site of abnormal uptake in the right femoral shaft localized intramedullarily, with no evidence of a cortical bone lesion (B), possibly an early bone metastasis. Additional foci of abnormal FDG uptake are seen in the lower pole of the right lobe of the liver, adjacent to the ascending colon, and in the lower lobe of the left lung, consistent with hepatic and pulmonary metastases. Repeat FDG-PET/CT (C) performed 4 months after initiation of chemotherapy demonstrates a significantly larger bone metastasis involving the proximal right femur, as well as local recurrence in the left anterior chest wall, extensive metastatic lymphadenopathy, and multiple lung and liver metastases, consistent with tumor progression.

first few months after initiation of treatment caused by new bone formation during the repair process. Repeat BS performed after 6 months of treatment will demonstrate a gradual decrease in the degree of tracer uptake associated with the flare phenomenon.<sup>17-19</sup>

## Bone SPECT and SPECT/CT

The addition of single-photon emission computed tomography (SPECT) improves the diagnostic accuracy of BS.<sup>6</sup> SPECT enables accurate localization of tracer activity, especially in complex skeletal structures, such as spine, skull, and pelvis, and therefore can improve diagnostic specificity.<sup>20</sup> For example, early metastatic spread to the vertebral column is usually confined to the posterior part of the vertebral body and the pedicle, adjacent to the venous network. Therefore, accurate localization of a suspected lesion on BS to the pedicle or posterior aspect of the vertebral body by SPECT may improve the specificity of this modality.<sup>21-23</sup> The use of SPECT for the assessment of suspicious vertebral lesions on planar BS had a negative predictive value of 98%.<sup>23</sup> SPECT also improved sensitivity and has been shown to detect 20%-50% more vertebral lesions compared to planar BS.<sup>24</sup> The

sensitivity and specificity of bone SPECT for diagnosis of bone metastases are 87%-92% and 91%-93%, respectively.<sup>5,23,25,26</sup> Uematsu et al<sup>27</sup> have studied prospectively 15 breast cancer patients with 144 osteoblastic and 20 osteolytic confirmed metastases and reported sensitivity and specificity of SPECT of 85% and 99%, respectively. Nakai et al<sup>28</sup> have retrospectively assessed 89 patients, including 55 with bone metastases confirmed by bone biopsy or MRI. Bone SPECT was true positive in 49 metastatic lesions, but was false positive in 6 and false negative in 11 sites, for a sensitivity, specificity, and accuracy of 78%, 82%, and 80%, respectively. The degree of osteosclerosis and osteolysis was defined on CT, and based on these findings SPECT was positive in all 18 sclerotic lesions, in 7 of 10 lytic lesions, and in 16 of 19 mixed lesions.<sup>28</sup> Shie et al<sup>9</sup> performed a meta-analysis aiming to assess, among other modalities, BS with or without SPECT for detection of bone metastases in patients with breast cancer. The pooled patient-based sensitivity and specificity for BS was 78% and 79%, respectively, and the pooled lesion-based sensitivity and specificity were 88% and 87%, respectively.<sup>9</sup> The decision to perform single field-of-view SPECT studies has been guided by suspicious findings on planar imaging or localized clinical symptoms. Newly developed

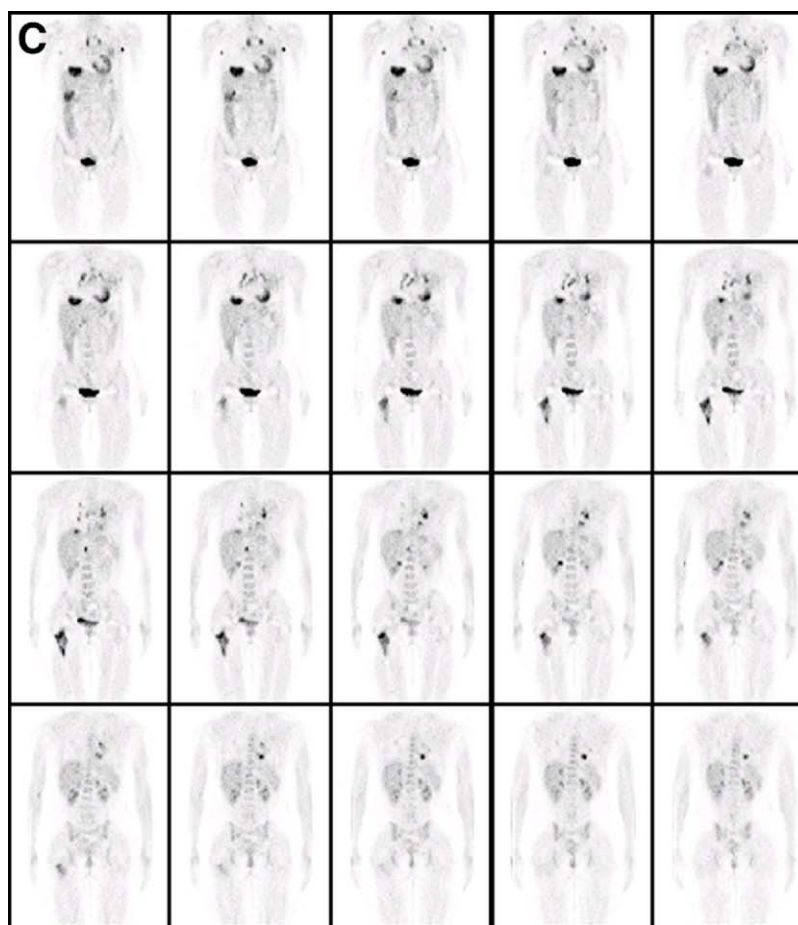


Figure 2 (Continued)

half-time whole-body SPECT protocols provide tomographic assessment of the entire skeleton within an acceptable image acquisition time, with subsequent improvement in sensitivity and an increased detectability rate of asymptomatic small skeletal metastases<sup>29</sup> (Fig. 1).

The use of SPECT enables the correct diagnosis in many cases. However, in patients with advanced disease and high risk for metastatic bone involvement, correlation with high-quality anatomic images, CT, or MRI, may be needed for diagnosis. Hybrid SPECT/CT devices equipped with multislice CT scanners further improve the sensitivity and specificity of BS. CT can assist in the diagnosis of benign skeletal findings, including osteophytes or degenerative changes, hemangiomas, or cysts, causing abnormal tracer activity on BS. Foci of increased tracer activity on BS suspicious as representing malignant bone lesions may not show any morphologic abnormality on CT, and therefore cannot be confirmed as such. Lytic bone lesions with increased tracer activity on BS may only be visualized on CT after they have destroyed 50%-75% of the trabecular bone. Therefore, the lack of anatomic abnormalities suggests medullary disease.<sup>20</sup> In these cases, SPECT/CT imaging is useful and provides the correct diagnosis in a single imaging session. Recently, Utsonomiya et al<sup>30</sup> have performed a retrospective analysis to assess whether hybrid SPECT/CT is useful in the diagnosis of metastatic disease in 45 pa-

tients with various tumors, including breast cancer. They reported an increased diagnostic confidence using fused SPECT/CT images as compared with assessment of separate bone SPECT and CT images in differentiating benign from malignant lesions. Fused images enabled precise localization of abnormal radiotracer activity and increased confidence of lesion characteristics. False-negative SPECT/CT results were due to metastases undetectable on CT and in one case a metastasis adjacent to a facet articulation.<sup>30</sup>

## Positron Emission Tomography

### Detection of Bone Metastases With <sup>18</sup>F-Fluoride and FDG and Comparison With BS

Positron emission tomography (PET) images have higher resolution as well as higher sensitivity and specificity compared with BS with or without SPECT.<sup>31</sup> In addition, PET/CT enables fusion of metabolic function and morphology in a single acquisition, also assisting in a clear differentiation between malignant and benign lesions.<sup>32</sup>

<sup>18</sup>F-labeled sodium fluoride is a nonspecific PET tracer used for assessment of bone metastases.<sup>12,16</sup> <sup>18</sup>F-fluoride diffuses through capillaries into the extracellular fluid followed by a slow exchange of hydroxyl ions in the hydroxyapatite crystal, mainly at the surface of the skeleton, and is therefore

an indicator of bone turnover.<sup>12</sup> The uptake of <sup>18</sup>F-fluoride is approximately two-fold higher and its blood clearance is significantly faster compared with the Tc-labeled agents used for BS, resulting in an increased bone-to-background ratio. In addition, PET offers high sensitivity and high resolution, and therefore enables to perform highly accurate whole-body screening for metastases.<sup>12,16</sup> Even-Sapir et al<sup>33</sup> have assessed the performance of <sup>18</sup>F-fluoride PET and PET/CT in 26 patients with bone metastases from various tumors, including 10 patients with metastatic breast cancer. The overall sensitivity and specificity of <sup>18</sup>F-fluoride PET/CT for the detection of metastases was 99% and 97%, respectively. <sup>18</sup>F-fluoride has higher sensitivity for the detection of bone metastases compared to BS<sup>34</sup> in patients with cancers of prostate, thyroid, and lung. <sup>18</sup>F-fluoride PET had a higher sensitivity compared to BS, showing focally increased uptake in both osteolytic and osteoblastic skeletal metastases. In a prospective study in 34 patients with breast cancer with high risk for metastatic disease, <sup>18</sup>F-fluoride was found to be more sensitive and accurate compared with BS for the detection of sclerotic and lytic metastases, also leading to a change in the clinical management in 4 of the 34 patients.<sup>35</sup> Osteolytic lesions are often seen on <sup>18</sup>F-fluoride PET as photopenic lesions surrounded by a rim of increased activity.<sup>12</sup> <sup>18</sup>F-fluoride is also more sensitive for the detection of benign bone lesions, potentially causing more false-positive findings. However, the superior spatial resolution enables exact anatomic localization and better differentiation between benign and malignant lesions, and therefore better delineation of osteophytes, facet arthropathy, end plate fractures, and serial rib fractures, resulting also in high specificity for <sup>18</sup>F-fluoride PET in the detection of bone metastases<sup>12</sup> (Fig. 1).

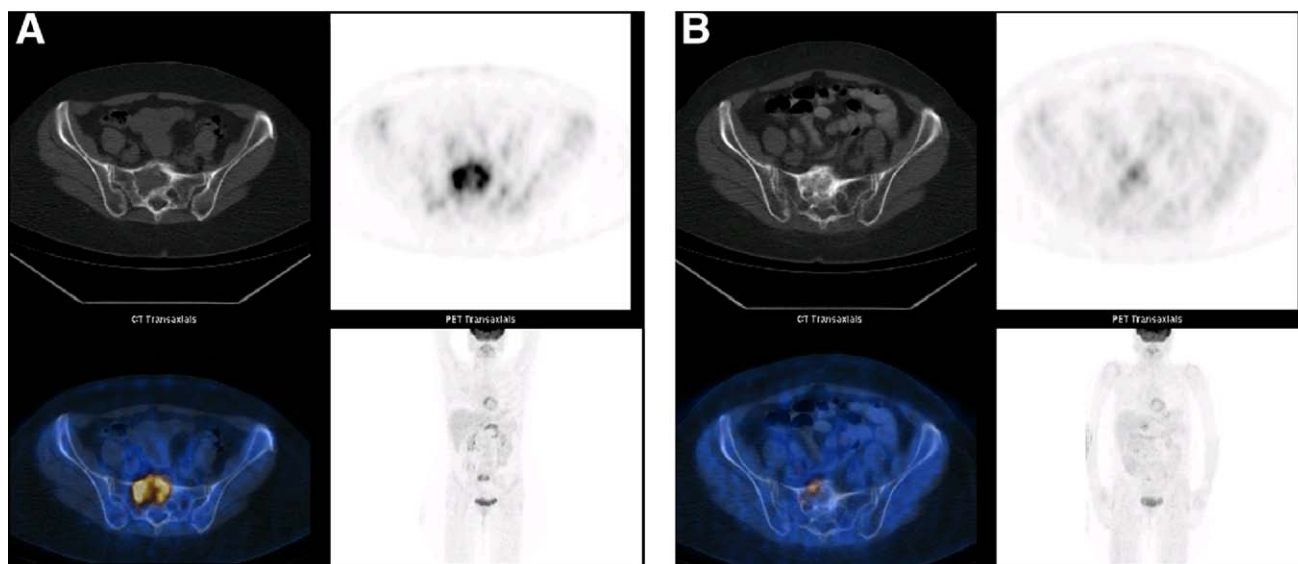
<sup>18</sup>F-fluorodeoxyglucose (FDG) is the most common PET tracer in clinical use. It is transported into tumor cells by the glucose transporter proteins GLUT-1 and GLUT-5 and is phosphorylated by hexokinases to FDG-6-phosphate, which is retained within the malignant cells. In bone metastases, it is assumed that FDG is taken up directly into the tumor cells and not into the surrounding bone. Assessment of <sup>18</sup>F-FDG-PET for detection of skeletal metastases in patients with breast cancer has demonstrated a sensitivity of 56%-100%.<sup>32,36</sup>

Cook et al<sup>4</sup> have compared FDG-PET and planar BS in 23 breast cancer patients with osteoblastic and osteolytic bone metastases. Although overall more metastases were detected by FDG-PET, BS was more sensitive in a subgroup of patients with osteoblastic disease. In addition, mean standard uptake values (SUVs) were approximately seven-fold higher in lytic vs sclerotic metastases, with 0.95 in sclerotic, 3.6 in mixed, and 6.6 in osteolytic lesions.<sup>4</sup> Ohta et al<sup>37</sup> compared the sensitivity and specificity of FDG-PET and BS in 51 patients with breast cancer. Both modalities had similar sensitivity of 78%, but the specificity of FDG-PET was higher than that of BS (98% vs 80%, respectively). In 48 patients with breast cancer and suspected bone metastases, Yang et al<sup>38</sup> reported a sensitivity and accuracy of 93% and 79%, respectively, for BS and 95% and 95%, respectively, for FDG-PET. In a retrospective analysis in 62 patients with suspected recurrent breast

cancer comparing planar BS with FDG-PET in a subgroup of 38 patients with 135 bone lesions, the sensitivity and specificity of PET were 57% and 89%, respectively, compared with 90% and 74%, respectively, for BS.<sup>39</sup> FDG-negative lesions correlated with a sclerotic or mixed sclerotic/lytic morphologic pattern. They were also encountered more often in the skull, masked by the high cerebral uptake of FDG. Mahner et al<sup>40</sup> have retrospectively assessed 119 breast cancer patients with newly diagnosed locally advanced disease or suspected of having distant metastases. BS, FDG-PET, CT, and plain radiographs were performed as part of the assessment protocol. In this study, FDG-PET had a sensitivity of 87% compared with 67% for BS, with specificities of 92% and 99%, respectively. Uematsu et al<sup>27</sup> have compared FDG-PET and BS SPECT in 15 breast cancer patients with known bone metastases, who had 143 osteoblastic and 20 osteolytic lesions. In a lesion-by-lesion analysis, the sensitivity of SPECT was significantly higher than that of PET (85% vs 17%) for similar specificity (99% for SPECT and 100% for PET). Furthermore, the sensitivity of SPECT was 92% for sclerotic (including also mixed lesions) and 35% for osteolytic lesions, compared with sensitivities of 6% and 90%, respectively, for FDG-PET. In 55 breast cancer patients with skeletal metastases, Nakai et al<sup>28</sup> reported a sensitivity of 100% for the detection of lytic skeletal metastases with FDG-PET vs 70% for BS, compared with 56% and 100%, respectively, for sclerotic lesions.

<sup>18</sup>F-FDG-PET/CT provides structural information with respect to the skeletal lesions visualized on the CT component in addition to the assessment of their metabolic activity on PET. Discrepancies between findings on BS and FDG-PET can be explained by the different uptake mechanisms of these tracers. Although uptake of <sup>99m</sup>Tc-MDP uptake is related to the osteoblastic response of the bone to the tumor, uptake of FDG is related to the metabolic activity of the tumor itself. Therefore, FDG is more likely to detect metastases at an earlier stage than BS, when still confined to the bone marrow, before an osteoblastic reaction that can be visualized on BS occurs (Fig. 2). In osteolytic metastases, FDG uptake is higher because of the presence of a larger amount of tumor cells with high glycolytic rate. By contrast, sclerotic metastases contain smaller amounts of viable tumor cells and exhibit therefore less FDG uptake.<sup>4,16</sup> BS SPECT and FDG-PET may therefore play a complementary role in the detection of bone metastases in patients with breast cancer.<sup>12,27</sup>

Few published reports compare <sup>18</sup>F-fluoride with either BS or FDG-PET in patients with breast cancer. Damle et al<sup>41</sup> have recently assessed 72 patients with advanced stage breast cancer and high risk of skeletal metastases, using BS with SPECT, <sup>18</sup>F-fluoride PET/CT, and FDG-PET/CT. The sensitivity of BS, FDG-PET/CT, and <sup>18</sup>F-fluoride PET/CT was 81%, 63%, and 44%, respectively, and specificity was 100%, 100%, and 75%, respectively. The authors suggest that the combined use of <sup>18</sup>F-fluoride PET/CT with a very high sensitivity and negative predictive value and FDG-PET/CT with very high specificity and positive predictive value may be of potential value in the assessment of this group of patients.<sup>41</sup>



**Figure 3** A 62-year-old woman, 14 months after right mastectomy, was referred for FDG-PET/CT with suspected recurrence due to increasing serum Ca 15-3, low back pain, and abnormal tracer uptake at the level of S-1 on bone scintigraphy. FDG-PET/CT demonstrates an area of abnormal, inhomogenous uptake in the midpelvis, corresponding to a large lytic metastasis in the body of the S-1 vertebra (A). Repeat FDG-PET/CT performed 4 months after initiation of bisphosphonate treatment demonstrates significantly reduced intensity of FDG activity and appearance of sclerotic changes in the S-1 vertebra, consistent with a healing process (B).

### Monitoring Response to Therapy

FDG-PET is of value in assessing response to treatment in metastatic breast cancer.<sup>36,42-44</sup> Stafford et al<sup>42</sup> performed FDG-PET/CT in 24 patients with metastatic breast cancer at baseline and 2-4 months after therapy and reported a significant association between changes in SUV and overall response. Du et al<sup>36</sup> assessed sequentially 146 skeletal lesions in 25 patients with suspected recurrence of breast cancer with <sup>18</sup>F-FDG-PET/CT. Prior to treatment, an increased FDG uptake was present in 94% of osteolytic, 82% of mixed, and 61% of osteoblastic lesions, with no corresponding CT morphologic changes in up to 15% of FDG-avid sites. On follow-up after therapy, all CT-negative lesions became FDG negative. After treatment, 81% of the osteolytic FDG-avid lesions became osteoblastic on CT and FDG-negative, suggesting the presence of a healing process, with residual FDG uptake present only in the large lesions. By contrast, of the FDG-avid osteoblastic lesions before treatment, 48% remained <sup>18</sup>F-FDG avid and increased in size on CT, consistent with disease progression.<sup>36</sup> The absence of morphologic changes on the CT component poses a diagnostic dilemma. It is hypothesized that in the early stages of metastatic skeletal disease, metabolic abnormalities detected by increased FDG activity can precede the appearance of morphologic changes depicted on CT.<sup>45</sup> Stafford et al<sup>42</sup> performed FDG-PET/CT in 24 patients with metastatic breast cancer at baseline and 2-4 months after therapy. A significant association was noted between the change in maximum SUV and response. Tateishi et al<sup>44</sup> reviewed FDG-PET/CT of 102 women with metastatic breast cancer, performed before and after treatment. In these patients, increased attenuation on CT and a decrease in SUV of bone metastases after treatment were associated with re-

sponse to therapy. A decrease in SUV of  $\geq 8.5\%$  was a significant predictor for long-term response, whereas a decrease in attenuation and increase in SUV after systemic therapy were associated with a markedly increased risk of disease progression in these patients.<sup>44</sup> Therefore, morphologic and metabolic assessment of skeletal metastatic lesions, both enabled by FDG-PET/CT, may assist in monitoring the response of bone metastases to therapy in patients with metastatic breast cancer (Fig. 3).

### Conclusion

FDG-PET/CT may be less sensitive than BS and <sup>18</sup>F-fluoride PET/CT for the detection of bone metastases in patients with breast cancer, mainly in predominantly sclerotic lesions, with better performance indexes in osteolytic sites. However, compared with studies performed with <sup>99m</sup>Tc-MDP and <sup>18</sup>F-fluoride, FDG-PET/CT is associated with a higher specificity for the assessment of bone lesions and, in addition, enables also accurate evaluation of the primary tumor, as well as soft-tissue metastases in lymph nodes and other viscera. FDG-PET/CT is also useful in monitoring response to treatment in patients with breast cancer metastatic to the bone, and better than BS. Published reports on data regarding the performance of <sup>18</sup>F-fluoride PET/CT for follow-up of patients with bone metastases are not yet available. It may be assumed that being an indicator of bone turnover, similar limitations as with BS using <sup>99m</sup>Tc-MDP may apply. Further studies are needed to determine whether FDG-PET/CT alone or in combination with BS or <sup>18</sup>F-fluoride PET/CT can significantly modify the management of patients with breast cancer and bone metastases.

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