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Positron Emission Tomography and Bone Metastases

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The use of 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in the evaluation and management of patients with malignancy continues to increase. However, its role in the identification of bone metastases is far from clear. FDG has the advantage of demonstrating all metastatic sites, and in the skeleton it is assumed that its uptake is directly into tumor cells. It is probable that for breast and lung carcinoma, FDG-PET has similar sensitivity, although poorer specificity, when compared with the isotope bone scan, although there is conflicting evidence, with several articles suggesting that it is less sensitive than conventional imaging in breast cancer. There is convincing evidence that for prostate cancer, FDG-PET is less sensitive than the bone scan and this may be tumor specific. There is very little data relating to lymphoma, but FDG-PET seems to perform better than the bone scan. There is an increasing body of evidence relating to the valuable role of FDG-PET in myeloma, where it is clearly better than the bone scan, presumably because FDG is identifying marrow-based disease at an early stage. There are, however, several other important variables that should be considered. The morphology of the metastasis itself appears to be relevant. At least in breast cancer, different patterns of FDG uptake have been shown in sclerotic, lytic, or lesions with a mixed pattern, Furthermore, the precise localization of a metastasis in the skeleton may be important with regard to the extent of the metabolic response induced. Previous treatment is highly relevant and it has been found that although the majority of untreated bone metastases are positive on PET scans and have a lytic pattern on computed tomography (CT), after treatment, incongruent CT-positive/PET-negative lesions are significantly more prevalent and generally are blastic, which presumably reflects a direct effect of treatment. Finally, the aggressiveness of the tumor itself may be relevant. The most important question, however, is irrespective of whether a lesion is seen on x-ray, CT, or bone scan and irrespective of lytic of blastic morphology: if the FDG-PET study is negative, what is the clinical relevance of that lesion?
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A wealth of historical data and clinical experience has led to establishment of the isotope bone scan as the reference standard in the search for skeletal metastatic disease. However, in malignancy the bone scan is now used less often and is not considered routine in all cases of breast or prostate cancer. Furthermore, such patients will no longer have automatic annual bone scans, with these studies being generally restricted to higher-risk groups eg, for clinical stage 3 or 4 breast cancer or cases in which the prostate-specific antigen (PSA) is elevated (>20 ng/mL). Essentially, the bone scan currently is used only where there is an issue regarding staging or if a patient has bone symptoms, although several recent studies have revealed only a poor correlation between symptoms and the presence of metastases.[1,2] Although the bone scan is considered to be highly sensitive for pathology, the advent of single-photon emission computed tomography (SPECT) initially surprised and delighted many of us with its undoubted increase in sensitivity for spinal lesions such as facet joint disease, often revealing lesions that were not suspected from the planar studies.[3-5] There is no doubt that SPECT improves lesion detection in the posterior elements of the vertebra but its superiority for pathology in the body of the vertebra is less evident. There have been reports that SPECT increases lesion detection in malignancy[6]; however, although this may be the case, there have been no studies addressing its clinical relevance. Even if SPECT reveals say 32

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lesions in the spine compared with 20 on the planar study, does this matter? To our knowledge, SPECT has not convincingly identified cases of malignancy that were not identified on planar images, although this is implied in reports.[7]

It should be remembered that the bone scan may lead to many false-positive cases, particularly in the elderly, with the most common causes being degenerative disease, Paget's disease, fractures, and inflammatory changes. We believe that an experienced reader will correctly identify all such pathology in most cases, although the bone scan remains nonspecific, and some lesions do require additional investigation. Such problems will arise much more frequently where the reader is less experienced. This invariably adds to physician/patient stress and additional costs. A final point to make is that a positive bone scan occurs because an osteoblastic response has been induced and this persists for some considerable time and the scan therefore remains positive even if there is a successful response to treatment. Thus, the bone scan cannot easily be used to monitor treatment in malignancy and, indeed, if performed too early, eg, in the first few months after successful treatment the appearances can be misleading because of a flare response.[8,9]

Positron Emission Tomography (PET)

In clinical practice, most PET studies are performed with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), and this will be dealt with later, but in the context of the skeleton, ^{18}F is potentially extremely important for imaging. It can also be used for quantitative studies of skeletal kinetics,[10] although only limited data exist on this in the context of malignancy. The more general aspects of this topic cannot be fully covered in such a review. Although there are differences between ^{18}F and ^{99m}Tc-diphosphonate, it is probable that the mechanism of uptake in bone is the same, ie, adsorption onto bony surfaces with predilection for sites of active bone formation.[11] Very few studies have compared ^{18}F and the bone scan, but the limited data suggest that ^{18}F-PET is more sensitive than the conventional bone scan for detecting metastases,[12] although a statistically significant difference could not be shown when compared with ^{99m}Tc-diphosphonate SPECT.[6] Surprisingly, when compared with the conventional planar bone scan, the additional lesions identified by ^{18}F-PET or SPECT were mostly in the spine, yet historically we have always believed that the bone scan performs best in the axial skeleton. In addition to providing beautiful images, ^{18}F should theoretically be better than the bone scan with improved resolution and effortless tomography. There has been the suggestion that ^{18}F could be more cost effective than the bone scan[13] and that a case can be made for ^{18}F replacing the bone scan.[6] Not everyone will be convinced by that argument at the present time, but in a few years, perhaps. A potential problem with ^{18}F is that it is almost too sensitive and one has to learn again how to read a "bone scan," because there are often many lesions present and potentially many false positives due to minor degenerative disease etc. Recently there has been a report of ^{18}F PET CT providing high sensitivity and specificity for the detection of lytic and sclerotic metastases, indicating that PET CT could potentially be invaluable in clarifying benign from malignant disease (Fig. 1).[14]

Although PET is very attractive and currently seems to be the only imaging game in town, the skeleton has been relatively neglected to date, and even with FDG, there are many unanswered questions. Theoretically FDG should be optimal: it is taken up by the tumor itself (conceptually no more problems with degenerative disease), FDG-PET has the advantage of higher resolution than the conventional bone scan, and even if one is primarily interested in bone, it does provide additional information regarding soft tissue disease (Fig. 2). Surely this is the technique that can at long last allow monitoring of treatment and identify "response" in skeletal metastases?

Breast Cancer

Carcinoma of the breast is a common and important condition in which the presence of bone metastases alters both the management and prognosis. However, in this condition the literature is far from clear as to whether FDG-PET is more sensitive than the conventional bone scan in identification of bone metastases (Fig. 3). Lonneux and colleagues[15] studied 39 women with breast cancer who were treated with surgery, both with and without chemotherapy and radiotherapy. Among these, 34 patients had elevated tumor markers whereas 5 had physical symptoms suggesting recurrent disease. In 33 of the 39 patients, 39 sites of recurrence were identified in bone marrow or bone (10), liver (6), lymph nodes (16), lung or pleura (5), peritoneum (1), and axilla (1). Conventional imaging was positive in 6, whereas PET was positive in 31 of the 33 patients. This was not primarily a study of bone but in the discussion the authors state "we observed a high incidence of bone marrow involvement in patients with normal scintigraphy." They concluded that FDG-PET is highly sensitive for the detection of distant breast cancer. Thus in a mixed population, many of whom had received previous treatment, this was a very positive study suggesting that FDG PET was more sensitive than the bone scan in detecting skeletal metastases.

Ohta and colleagues[16] studied 51 patients with breast cancer, but only 9 had bone metastases (which was confirmed by other imaging techniques or biopsy). They found that both FDG-PET and the bone scan had identical sensitivity (77.7%) but that FDG-PET was more specific (97.6% vs. 80.9%). In a further study, Yang and coworkers[17] studied 48 patients with carcinoma of the breast and identified 127 lesions (105 metastases, 22 benign). Patients were followed up for a year, and metastases were confirmed by either histopathology or other imaging techniques. FDG-PET accurately diagnosed 100 metastases and 20 benign lesions whereas the bone scan identified 98 metastases and 2 benign lesions. It was concluded that FDG-PET and the bone scan have similar sensitivity but PET-FDG is more specific than the bone scan. There is a fairly negative paper from Moon and coworkers,[18] who evaluated 57 patients with carcinoma of the breast. Patients were fol-

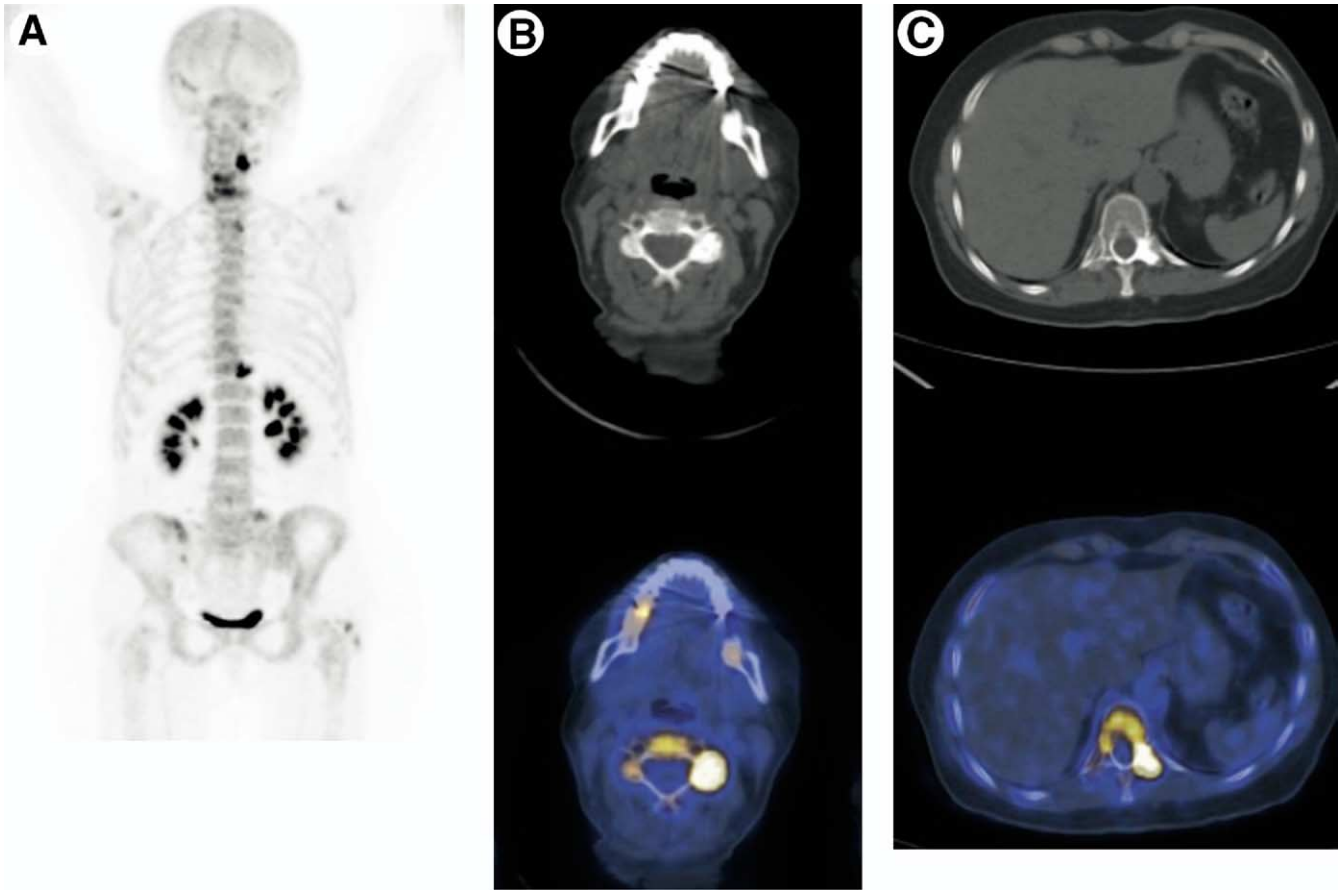

Figure 1 Fluorine-18 imaging of bone lesions in a 67-year-old woman with breast cancer and back pain. (A) Maximal intensity projection (MIP) whole body F-18 PET study indicates the presence of pathological uptake in the cervical, thoracic and lumbar spine, as well as the left hip joint and right pelvis. (B) PET-CT fused images (bottom) and CT (top) transaxial slices at the level of the cervical spine demonstrate the precise localization of the suspicious focus to the left facet joint, consistent with degenerative bone disease. (C) PET/CT fused images (bottom) and CT (top) transaxial slices at the level of the lower thoracic spine indicate the precise localization of the suspicious focus to the left pedicle and posterior elements of the vertebra, consistent with bone metastasis. (Courtesy of Dr. Einat Even-Sapir, Souraski Medical Center, Tel Aviv, Israel).

lowed up for 24 months, and metastatic disease was confirmed by biopsy or other imaging techniques. FDG-PET studies were scored on a basis of 1 to 5 (4/5 being positive) by 3 independent observers. There were 41 sites of recurrent or metastatic disease in 29 patients. On a patient basis, the sensitivity of FDG-PET was 93%, the specificity 79% and on a lesion basis the sensitivity was 85% and specificity 79%. However, the sensitivity for bone lesions was 69% (11 of 16) vs. 96% for nonosseous lesions (24 of 25; $P < 0.05$). The authors therefore concluded that the sensitivity for metastases to bone appears to be lower than that to other organs.

In support of such a conclusion, Gallowitsch and colleagues[19] performed a retrospective analysis of 62 women with breast cancer. Of these, 38 had isotope bone scans in addition to FDG-PET. On a patient basis, there was no difference in sensitivity (92.3%) for either technique but the specificity was better for PET (92 vs. 80%). However on a lesion based analysis, the sensitivity for the isotope bone scan was much higher (89.8 vs. 56.5%) although the specificity was less (74.1 v 88.9%). It was commented on that some lesions were only identified on FDG-PET and there was a pictorial example of one patient who had both FDG PET positive, bone scan negative and bone scan-positive FDG-PET negative lesions. In the total study population, 21 patients had received chemotherapy and 15 antihormonal therapy, but it is not clear what relationship if any prior treatment had to the above findings. The authors concluded that with PET-FDG, fewer bone lesions are detected than with conventional imaging.

To confuse matters further, being aware of the literature with FDG-PET in prostate cancer, we wondered whether the morphological appearance of a metastasis was relevant, ie, if a lesion was sclerotic or otherwise. We went on to study 23 patients with breast cancer with progressive bone metastases.[20] On the basis of their pretreatment bone X-rays, each patient had their metastatic disease classified as being lytic, sclerotic, or a mixed pattern. We found that patients who had either lytic or a mixed pattern of disease had a higher number of lesions identified on FDG-PET than on the isotope bone scan, but for the subgroup with sclerotic lesions, a lower

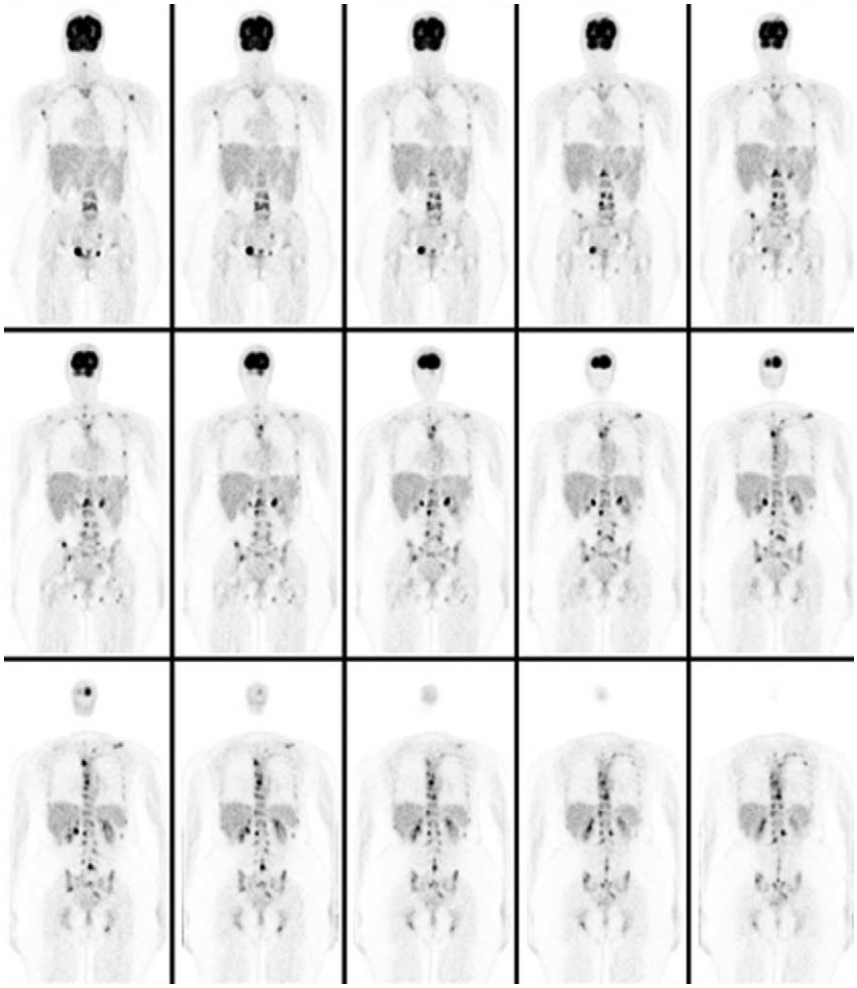

Figure 2 Assessment of skeletal and nodal metastases in a 56-year-old patient with newly diagnosed breast cancer. Coronal PET slices indicate the presence of multiple bone metastases involving the thoracic and lumbar spine, ilium, ischium, and ribs bilaterally. There are additional areas of pathological uptake in the right axilla and the right and left pelvis, consistent with metastatic lymphadenopathy.

number was seen. Furthermore, in those patients in whom FDG uptake could be calculated, sclerotic metastases showed lower uptake of FDG than lytic lesions. In addition the survival of patients with a mixed pattern or sclerotic disease was significantly greater than those with predominantly lytic metastases. This paper is widely quoted and is generally used to make the point that lytic lesions are more FDG avid than sclerotic. There is also a recent case report of a single prostate cancer patient where the bone scan showed more lesions than FDG-PET and a single lung cancer patient on which FDG PET showed more lesions than the bone scan.[21] It now seems to be an established fact and taken for granted that lytic lesions are more FDG avid than sclerotic lesions. This may well be correct in general terms, but the paucity of data are of concern. Renal cell carcinoma could be an exception to this "rule," because there are reports on occasion of the primary tumor being negative when using FDG, and it would be of interest to know whether bone metastases in that situation show FDG avidity or not.

Our study was small with very few patients having purely sclerotic disease. As can be seen even for a specific condition, eg, with breast cancer, there is often some inconsistency in the findings. Studies may report on small numbers of patients and generally do not control for variables, such as the type of lesion and previous treatment. On the assumption that lytic lesions do have greater avidity for FDG, it is interesting to speculate as to why this might be so. Clearly lytic metastases may have a higher glycolytic rate and because of their aggressive nature with rapid growth, could outstrip their blood supply rendering the lesion relatively hypoxic. Hypoxia has been shown in some cell lines to increase FDG uptake.[22] A further factor is that sclerotic metastases are relatively acellular and therefore contain a smaller volume of viable tumor tissue within an individual lesion (Fig. 4).

Few data exist in the literature regarding the use of FDG-PET in monitoring the response of skeletal metastases from breast cancer (or indeed any other cancer) to treatment (Fig. 4). However, Stafford and coworkers[23] studied 24 women with breast cancer and predominantly bony metastases at between 1 and 18 months following cytotoxic and hormonal treatment. There was no standard time interval for the scan, although most were performed

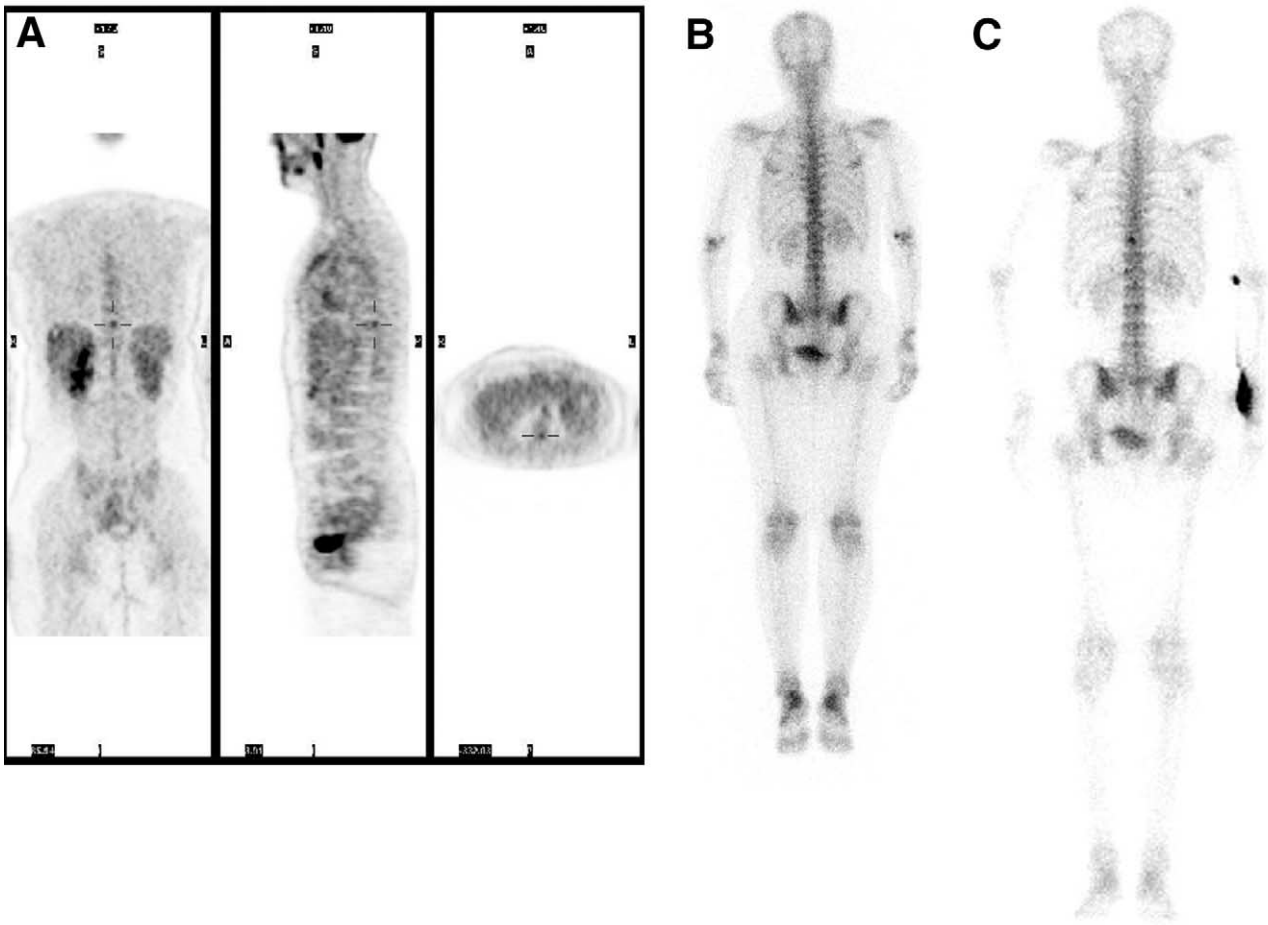

Figure 3 Early detection of bone metastases in a 32-year old woman with breast cancer with known liver metastases. (A) FDG-PET coronal, sagittal, and transaxial slices indicate the presence of a focal area of abnormal uptake in the posterior aspect of the T-10 vertebral body, in addition to the inhomogeneous lesion in the right lobe of the liver. CT with bone windows and (B) Tc99m methylene diphosphonate (MDP) bone scintigraphy is normal. (C) Repeat bone scintigraphy performed 6 months later, at the end of chemotherapy, shows a new focal area of increased Tc99m MDP uptake in the T-10 vertebra.

at between 2 and 4 months and 15 of the patients (63%) were receiving treatment at the time of the baseline scans. They performed quantitative measurements of the response using the maximum SUV of the most prominent (index) lesion. They found a significant association between the change in FDG standardized uptake value (SUV) and the overall classification of response. In a further interesting study, Mortimer and colleagues[24] performed FDG-PET and ^{18}F-labeled estradiol studies in 40 women with breast cancer (ER-positive disease) at 7 to 10 days after the introduction of Tamoxifen therapy. They were able to show that patients who responded to treatment had higher baseline levels of F18 labeled estradiol and showed a significant increase in FDG uptake (28.4%). It was therefore shown that responders had a flare response on FDG-PET although there were only 5 patients with a clinical flare. It is of interest that in this study it was noted that in 4 patients there were discordant results for individual lesions while in the Stafford study[23] it was commented on that there was no discordance between the index and other lesions in individual patients.

Other Conditions

Prostate Cancer

Prostate cancer is now established as the "classic" cancer with false-negative results on FDG-PET. A few studies have looked specifically at the skeleton, and these seem to support the fairly dismal performance of PET. In the study from Yeh and coworkers, only 18% of bone scan lesions were positive on FDG-PET.[25] However, this was a small study, with only 13 patients and only 1 newly diagnosed case, whereas the others received a variety of treatments and were considered to be hormonally resistant. Shreve and coworkers[26] evaluated 34 patients in which PET was compared with the isotope bone scan, computed tomography (CT), and clinical follow up for the presence of skeletal metastases. FDG-PET identified 131 of 202 untreated metastases in 22 patients with a sensitivity of 65%. In that study there were also 6 patients receiving hormonal treatment and 1 studied after orchiectomy, with 131 metastases identified on the bone scan but only 4 seen on FDG-PET! Therefore, on the basis of these 2 studies, one has to conclude that FDG-PET does not perform well in the iden-

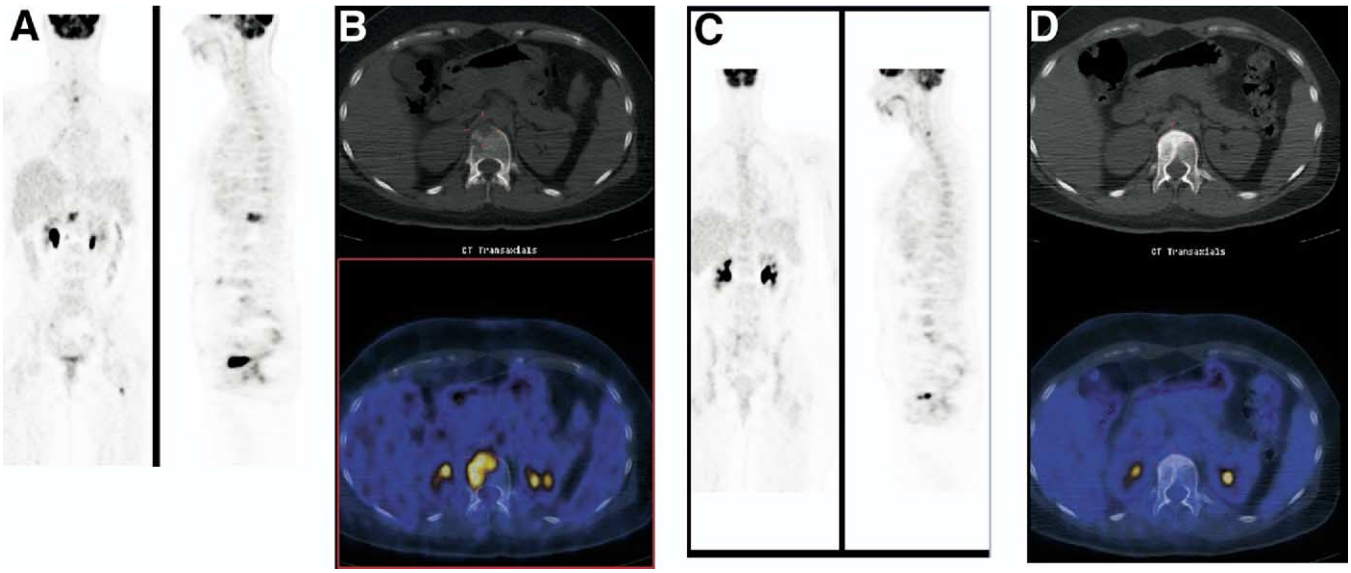

Figure 4 Monitoring response to treatment in a 35-year-old woman with breast cancer. (A) Initial FDG-PET study, coronal and sagittal slices, performed for further evaluation of rising tumor serum markers, indicates the presence of abnormal tracer uptake involving the cervical spine, L-1 vertebra and left proximal femur, consistent with bone metastases. (B) Fused PET/CT transaxial image (bottom) localize the area of pathological uptake in the lumbar spine to a lytic lesion as seen on the corresponding CT component of the study (top). (C) Follow-up FDG-PET performed after 4 months of chemotherapy shows marked improvement with normal tracer uptake in the L-1 vertebra and left femur, and marked decrease in the cervical spine. (D) Follow-up fused PET-CT transaxial image at the level of the lumbar spine (bottom) show no abnormal tracer uptake in the vertebral body, whereas marked osteoblastic reaction is demonstrated on the corresponding CT component of the study (top).

tification of skeletal metastases, even in untreated patients with prostate cancer and, in those who have received treatment, the results may be extremely poor.

However, more recently Morris and colleagues performed a study in 17 patients with progressive metastatic prostate cancer.[27] Progressive disease was carefully documented and defined as a rising PSA level on 3 samples taken at least 1 week apart with a total increase of greater than 50% and progression on the bone scan or CT/MRI within 6 weeks of study entry. Of 134 bone lesions considered to be metastases identified on either FDG-PET or bone scans, 95 were seen on both FDG-PET and bone scan whereas 8 were seen on FDG-PET only and 31 on bone scan only. Therefore, in this population who must have received previous treatment but who had progressive metastatic prostate cancer, FDG-PET had a sensitivity of 77%. The interest in this study was that all but one lesion seen on bone scan alone were "stable" on follow-up when compared with the baseline bone scan, whereas all FDG-PET lesions reflected active disease on subsequent studies. It was concluded that FDG-PET can discriminate active osseous disease from scintigraphically quiescent lesions in patients with progressive metastatic prostate cancer. In the Shreve study,[26] it was stated that only 9 patients (26%) had unequivocally progressive disease. The study by Cook and coworkers[20] in breast cancer also studied patients with progressive disease and these studies suggest an additional important variable when considering FDG PET in the skeleton, ie, whether disease is progressive or not. The Morris study[27] is in many ways tantalizing and raises the question: Are FDG-PET negative, bone scan positive (or indeed CT-positive) lesions clinically relevant? This will surely be a challenge for future studies to resolve.

Lung Cancer

Of the more common malignancies, the situation in lung cancer appears to be less contentious. In a study designed primarily to assess FDG-PET with conventional tests in the staging of nonsmall cell lung cancer Marom and coworkers[28] evaluated 100 patients, of whom 90 had isotope bone scans. Twelve patients had bone metastases (biopsy-proven 4, and 8 with clinical follow-up). FDG-PET identified 11 (92%) patients and in the one case missed, the lesion was in the distal femur, which was not included in the study, whereas only 6(50%) patients were identified by the bone scan. On the basis of their results, the authors stated that PET can eliminate the need for staging bone scintigraphy. Durski and coworkers[29] studied 19 patients with nonsmall cell lung cancer, 12 of whom had bony metastases. Both techniques agreed with the presence or absence of metastases in all cases. Overall, FDG-PET identified more lesions but the bone scan provided more precise localization. The study by Bury and coworkers[30] evaluated 110 consecutive patients with nonsmall cell lung cancer, 43 of whom had metastatic disease. There were 21 patients (19% of the total) who had confirmed bone metastases. Both techniques identified 19 of those patients. FDG PET confirmed the absence of bone metastases in 87 of 89 patients while the bone scan identified 54. Gayed and

coworkers[31] studied 85 patients with lung cancer, 80 non-small cell lung cancer, 4 small cell lung cancer, and 1 bronchoalveolar cancer. On a patient analysis, FDG-PET identified 8 patients with bone metastases while the bone scan identified 10. On a lesion analysis both FDG-PET and the bone scan identified 22 true positives, FDG-PET 58 and bone scan 46 true negatives, FDG-PET 16 and bone scan 27 false positives, and FDG-PET 4 and bone scan 5 false negatives. Both the Bury[30] and Gayed[31] studies reached essentially identical conclusions ie, that both techniques had similar sensitivity for the detection of bone metastases but that FDG PET was more specific. There can be little doubt that FDG PET is more specific for malignancy than the bone scan which is clearly an advantage, but it is difficult to be certain how important this is with expert readers, as most lesions will be accurately classified. Thus when comparing the more recent studies of FDG with the isotope bone scan, the results at the present time appear to be an honorable draw with regard to sensitivity but a points win for PET if specificity is considered.

PET-CT

With the increasing interest in and availability of PET-CT, the possibilities for evaluation of skeletal disease are ever-expanding. Metser and colleagues[32] performed a retrospective review of spinal involvement in 51 patients with metastatic disease. There were a variety of primary sites, including lung (20 patients), lymphoma (12 patients), breast (7 patients), colon (4 patients), melanoma (2 patients), adenocarcinoma with unknown primary (2 patients), and 4 patients with various other tumors. In 26 patients, concordant lesions were seen. In 25 patients discordant or equivocal lesions were identified and in 14 patients, metastatic disease was confirmed by clinical follow up or other imaging modalities. However in 10 patients, metastatic disease was assumed because of the intensity of FDG uptake. On a patient-based analysis, FDG-PET had a sensitivity of 98% compared with 74% for CT and on a lesion-based analysis, FDG-PET had a sensitivity of 96% compared with 68% for CT. In both of these analyses the differences were highly significant ($P < 0.01$ and <0.001, respectively). It was not stated whether patients had received previous treatment but nevertheless in this population with a variety of tumors, it was apparent that FDG-PET was more sensitive than CT alone. With advances in CT, the skeleton is increasingly being evaluated on a routine basis. With 16 slice scanners becoming widely available and with 32 and even higher slice scanners soon to become a reality, it seems inevitable that a large number of additional lesions will be identified and this is a further variable which will have to be taken into account in future studies.

Summary

It is apparent that while FDG-PET is being used extensively in oncological practice, its role in the identification of bone metastases is far from clear. It is probable that for breast and lung carcinoma, FDG-PET has similar sensitivity to the isotope bone scan although there is conflicting evidence in the literature and with several papers adamant that FDG-PET is less sensitive than conventional imaging in breast cancer.[18,19] There is general agreement that FDG-PET has improved specificity and there can be no argument at the present time that the two techniques have a complimentary role if bone metastases are not to be missed. It is much easier to localize lesions in the skeleton on the bone scan, although this is less of an issue with PET-CT becoming increasingly available. There is convincing evidence that for prostate cancer, FDG-PET is less sensitive than the bone scan and this may well be tumor specific rather than reflecting the morphology of the metastases. Few data relating to lymphoma exist, but FDG-PET seems to perform better than the bone scan,[33] and there is an increasing body of evidence relating to the valuable role of FDG-PET in myeloma,[34,35] where it is clearly better than the bone scan (although this is hardly an area where the bone scan shines) and this is presumably because FDG is identifying marrow-based disease at an early stage.

This review highlights some of the differences between individual tumors and is an attempt to summarize the extant data in the literature. However, there are several other important variables that should be kept in mind and which require further research to clarify their relative importance. As has been discussed, the morphology of the metastasis itself appears to be relevant. At least in breast cancer, different patterns of FDG uptake have been shown in sclerotic, lytic or lesions with a mixed pattern. It has been suggested that while there may be differences in the glycolytic rate between these types of metastases, sclerotic lesions have much smaller tumor volume relative to the size of the metastasis and may therefore simply be less likely to be identified. Furthermore the precise localization of a metastasis in the skeleton may be important with regard to the extent of the metabolic response induced. It is possible that small lesions in the cortex of a long bone would induce an intense osteoblastic response and therefore be more likely to be identified on an isotope bone scan, whereas a lesion in trabecular bone in the spine may lead to a lesser osteoblastic response and be more likely to be identified by FDG-PET with uptake of tracer by the tumor itself.

Previous treatment is clearly highly relevant. Israel and coworkers[36] have recently reported that in a population of 131 patients with a variety of cancers, there were 296 malignant bone lesions of which 282 (95%) were CT positive and 172 (58%) PET positive. However, when analyzed on the basis of prior treatment, 69 of 84 (82%) untreated lesions were both CT and PET positive (26 lesions were blastic, and 43 lytic), which contrasts with 114 of 212 (54%) lesions in patients who had received treatment that were CT positive but PET negative (94 lesions were blastic and 20 lytic). It was concluded that although most of untreated lesions are PET positive and have a lytic pattern on CT, after treatment, incongruent CT-positive/PET-negative lesions are significantly more prevalent and these are generally blastic which presumably reflects a direct effect of treatment (Fig. 2). Incidentally, in that study, 5% of lesions were only seen on PET and a

positive PET study guided retrospective detection of a further 14% of lesions on CT.

Finally, the aggressiveness of the tumor itself may be important. There is some evidence to suggest that in the presence of progressive disease, with breast[20] and even prostate cancer,[27] FDG-PET performs somewhat better in the identification of bone metastases than would otherwise be expected even though these patients inevitably will have received extensive treatment previously. However, the studies are based on small numbers of patients and this is an area, which merits close attention in future. Some of these factors could be interrelated, for example following treatment of a lytic lesion that may subsequently become sclerotic due to an intense osteoblastic healing response. The most important question, however, is irrespective of whether a lesion is seen on radiograph, CT or bone scan and irrespective of lytic or blastic morphology: if the FDG-PET study is negative, what is the clinical relevance of that lesion?

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