Detection of Bone Metastases in Breast Cancer by ^{18}FDG PET: Differing Metabolic Activity in Osteoblastic and Osteolytic Lesions

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Purpose: **^{99m}Technetium methylene diphosphonate (^{99m}Tc MDP) bone scintigraphy is currently the method of choice for the detection of bone metastases, but ^{18}F-fluoro-deoxy-D-glucose positron emission tomography (^{18}FDG PET) offers superior spatial resolution and improved sensitivity. We have compared ^{18}FDG PET with ^{99m}Tc MDP bone scintigraphy in patients with skeletal metastases from breast cancer and have analyzed the data in subgroups based on radiographic characteristics of lesions.**

Patients and Methods: **Twenty-three women with breast cancer and confirmed bone metastases were studied with both ^{99m}Tc MDP bone scintigraphy and ^{18}FDG PET, and the number of lesions detected and the quantitation of uptake (standardized uptake values [SUVs]) of ^{18}FDG in osteolytic and osteoblastic metastases were compared. Survival was compared for both lytic and blastic bone metastases and for patients with high and low accumulation of ^{18}FDG.**

Results: **^{18}FDG PET detected more lesions than ^{99m}Tc MDP scintigraphy (mean, 14.1 and 7.8 lesions, respectively; $P < .01$). However, ^{18}FDG detected fewer bone metastases compared with ^{99m}Tc MDP scintigraphy in a subgroup of patients with osteoblastic disease ($P < .05$). Higher SUVs were observed for osteolytic than osteoblastic disease (mean, 6.77 and 0.95, respectively; $P < .01$). Survival was lower in patients with osteolytic disease compared with the remainder ($P = .01$). A difference in survival was not found for those patients with high SUVs (> 3.6; $P = .4$).**

Conclusion: **^{18}FDG PET is superior to bone scintigraphy in the detection of osteolytic breast cancer metastases, which led to a poorer prognosis. In contrast, osteoblastic metastases show lower metabolic activity and are frequently undetectable by PET. The biologic explanation for this observation remains to be elucidated.**

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BREAST CANCER is common; women in the United Kingdom have a lifetime probability of 1 in 12 to develop this disease. In the UK population, the annual incidence is 25,000 new cases, but the prevalence is estimated at 105,000.[1] The skeleton is the most common distant site to which breast cancer spreads. Bone metastases affect 8% of all patients who develop breast cancer, but this increases to 70% in those with advanced disease. Secondary tumors in bone cause much of the morbidity and disability of this disease because of the potentially prolonged clinical course (median survival of 24 months for those in whom disease remains confined to the skeleton).[2] Complications include pain, pathologic fracture, hypercalcemia, myelosuppression, spinal cord compression, and nerve root lesions, and 20% of the patients remain alive at 5 years. The costs of treating bone metastases and associated complications make a major demand on health care resources.[3]

Skeletal damage results from increased bone resorption caused by stimulation of osteoclasts by tumor-derived humoral mediators that include growth factors and cytokines.[4] It is the central role of increased osteoclast activation in skeletal metastases that has led to the development of newer treatments, such as the bisphosphonates that inhibit osteoclast activity and reduce skeletal morbidity.[5] Techniques are required that may help identify at an earlier stage those patients who may benefit most from these interventions.

Deoxyglucose, an analogue of glucose, is labeled with the positron emitter ^{18}F-fluoride and is taken up into cells by the same carrier-mediated transport system as glucose. 2-[F-18]-fluoro-2-deoxy-D-glucose (^{18}FDG) positron emission tomography (PET) shows malignant tissue with great sensitivity because of enhanced glycolysis in many cancers,[6] with the ability to detect small volumes of disease before morphologic changes appear. In addition, the degree of uptake has been correlated with prognosis and grade of malignancy in some tumors, which includes breast cancer.[7,8] PET has advantages over conventional single-photon nuclear medicine techniques in improved spatial resolution and the acquisition of tomographic data as a routine.

^{18}FDG PET is sensitive for the detection of breast cancer, which includes skeletal metastases.[9,10] In contrast, the results for ^{18}FDG PET in the detection of carcinoma of the prostate have been disappointing, particularly in the detection of bone metastases that are most often osteoblastic, and ^{99m}technetium methylene diphosphonate (^{99m}Tc MDP) bone

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scintigraphy remains more sensitive.[11] This raises the question of whether avidity of ^{18}FDG is related to morphologic appearances of bone metastases or whether it is intrinsic to the tumor type.

We studied 23 women with both osteolytic and osteoblastic metastases from carcinoma of the breast with ^{18}FDG PET to correlate findings with radiologic appearances and to assess the sensitivity of this technique in the detection of osseous metastases compared with ^{99m}Tc MDP bone scintigraphy.

PATIENTS AND METHODS

Twenty-three women (mean age, 52 years; range, 29 to 70 years) with a history of breast cancer who had been referred for bone scintigraphy that showed evidence of bone metastases were included. All patients had at least one other method of confirmation that bone scan findings were caused by metastatic disease, which included plain film radiography (n = 17), computed tomography (CT; n = 10), magnetic resonance imaging (n = 6), or bone biopsy (n = 2). Patients were categorized with lytic, sclerotic, or mixed metastatic bone disease by two independent observers at the original diagnosis of bone metastases from either original plain films (n = 16) or CT scans (n = 4) that were performed before subsequent systemic treatment had been started. Three patients remained unclassifiable because bone metastases were only visible with bone scintigraphy and magnetic resonance imaging.

Twenty-one of the 23 women had evidence of progressive metastatic disease during the study period. Two patients had stable disease and were currently not receiving specific anticancer treatment; both had stopped hormone manipulation treatment 5 and 12 months previously without a documented response to therapy.

Ten patients received hormone manipulation therapy, which ended between 1 and 48 months (mean, 18.2 months) before PET scanning, and three patients were currently receiving this treatment, but all 13 patients had progressive disease despite this. Five patients had previously received chemotherapy between 7 and 13 months (mean, 10.3 months) and four patients had previously received treatment with bisphosphonates between 11 and 84 months (mean, 34.5 months) before PET scans. Two patients had received prior palliative radiotherapy to bone metastases.

Imaging

In all but one patient, ^{99m}Tc MDP bone scans and ^{18}FDG PET scans were performed within 8 weeks of each other (mean, 2.9 weeks). One patient was included in whom the bone scan appearances had not changed from 9 months before to 5 months after the PET scan.

Patients fasted for 6 hours before the PET scan. Half-body (above the knees to midbrain) emission and localized emission/transmission scans were performed 1 hour after the injection of 350 MBq of ^{18}FDG. Sixteen patients had both half-body emission and localized emission/transmission scans; the remainder had localized scans only. Standardized uptake values (SUVs) were calculated from attenuation-corrected data for bone lesions within the localized field of view and were corrected for partial volume effects. SUV = [activity in region of interest [ROI]/volume of ROI)/(injected activity/weight of patient)]. For those patients with more than one lesion within the attenuation-corrected, localized views, the mean SUV for identified lesions was used. The included lesions had remained radiographically stable in type from pretreatment classification to the time of the study.

Bone scans were performed after the injection of 550 MBq of ^{99m}Tc MDP that used high-resolution collimation on a twin-headed gamma camera.

Metastatic bone scan and PET bone lesions were counted at different sittings by an observer blinded to all patient details.

Survival curves[12] were plotted that compared survival in groups with sclerotic, mixed, and lytic disease and in two groups separated by a median SUV value of 3.6.

RESULTS

All patients had bone scan evidence of metastatic disease confirmed by at least one other imaging technique or, in two patients, by bone biopsy. Of the 16 patients who had half-body PET scans, between 1 and 38 (mean, 7.8) ^{99m}Tc MDP bone scan lesions were identified. The corresponding results for these 16 patients with ^{18}FDG PET were between 0 and 61 (mean, 14.1) bone lesions ($P < .01$, Wilcoxon's signed rank-sum test).

Twenty patients had radiologically classifiable disease. Of these, six patients had sclerotic disease, five patients had mixed disease, and nine patients had lytic disease. The mean SUVs for these groups were 0.95, 3.64, and 6.77, respectively (Table 1; $P < .01$, Kruskal Wallis test).

Of the 16 patients who had half-body PET scans, three patients had sclerotic disease, three patients had mixed disease, eight patients had lytic disease, and two patients were not classified. In two of three patients with sclerotic disease, ^{18}FDG PET showed fewer lesions than ^{99m}Tc MDP bone scan in contrast to those with lytic disease, in whom no patients had fewer and seven of eight patients had more lesions identified with ^{18}FDG PET. Overall, ^{18}FDG PET detected fewer lesions than bone scans in the subgroup with osteoblastic disease compared with those with purely lytic disease ($P < .05$, Wilcoxon's signed rank-sum test).

Survival Data

When survival curves are plotted for sclerotic, mixed, and lytic disease from the time of diagnosis of bone metastases, a significant difference is found in survival between each group ($P = .04$, χ^2), and if patients with lytic disease are compared with patients with sclerotic and mixed disease as a combined group, a more significant difference in survival is found ($P = .01$, χ^2; Fig 1). When length of survival from the diagnosis of bone metastases in those patients with an SUV

Table 1. Differences Between Type of Bone Metastasis With Regard to Behavior With ^{18}FDG PET

	Bone Scan Lesions			FDG PET Lesions			SUV		
	No.	Mean	Range	No.	Mean	Range	No.	Mean	Range
Sclerotic	3	3.7	1-8	3	2.7	0-8	6	0.95	0-3.9
Mixed	3	5.0	3-8	3	13.3	3-31	5	3.64	2.5-5.0
Lytic	8	11.9	2-38	8	21.8	2-61	9	6.77	2.1-11.6

NOTE. Lesion counts are compared in 14 patients who had half-body PET studies performed and who had classifiable disease. SUV comparison is in 20 patients in whom metastases were classifiable.

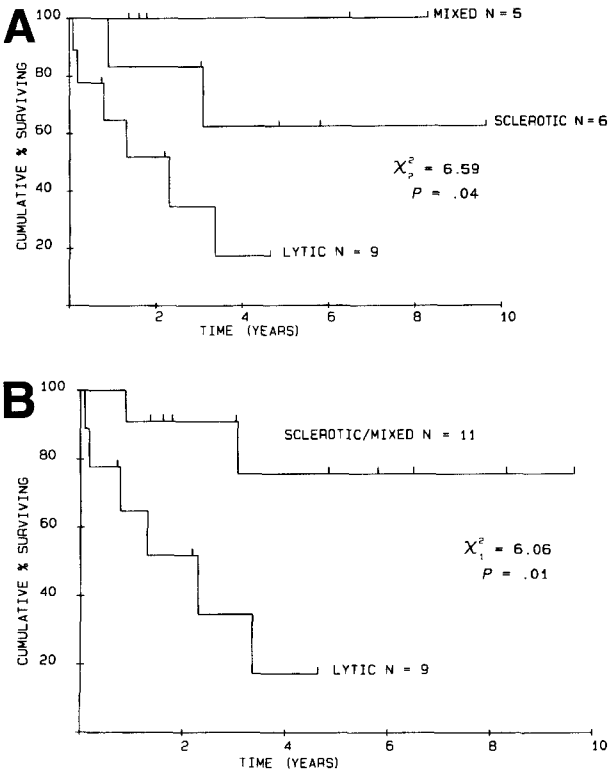

Fig 1. Kaplan-Meier survival plots. (A) Survival from diagnosis of bone metastases in patients with lytic, mixed, and sclerotic disease; and (B) in patients with mixed and sclerotic disease compared with those with lytic disease.

greater than the median (3.6) is compared with patients with an SUV less than the median, a difference in survival is not found ($P = .40$, χ^2).

DISCUSSION

A difference in the avidity of accumulation of ^{18}FDG has been found between sclerotic, mixed, and lytic metastases from breast cancer ($P < .01$; Figs 2 and 3). ^{18}FDG PET shows a higher sensitivity for the detection of lytic bone lesions than ^{99m}Tc MDP bone scans, but it is less sensitive for sclerotic metastases. This lack of sensitivity in the detection of bone metastases in patients with sclerotic metastases has also been observed in patients with prostate cancer[11] and may, therefore, be a feature of this type of skeletal metastasis, rather than tumor type. Furthermore, a lower survival from the time of diagnosis of bone metastases in those with purely lytic disease compared with a group with either sclerotic or mixed metastases is found ($P = .01$). No difference in survival is found in those patients with higher SUVs.

The reason for greater avidity for FDG in lytic metastases is unknown, but may reflect a higher glycolytic rate in this type of metastasis. Sclerotic metastases are relatively acellular, however,[13] and as such, lower volumes of viable tumor tissue within individual lesions may influence the degree of uptake of ^{18}FDG. In addition, more aggressive, lytic disease might be expected to outstrip its blood supply, which renders the tumor relatively hypoxic compared with sclerotic disease. Hypoxia increases FDG uptake in some cell lines,[14] and this may be an additional factor in osseous metastasis accumulation.

A change in radiologic appearance of metastases from lytic to sclerotic as a result of treatment does not explain our observations because each patient was classified before the treatment of bone metastases, and lesions that had changed type radiographically were not included in the quantitative analysis. Lesions in only two patients showed a change from lytic to sclerotic. This occurred after local radiotherapy, and these bones were excluded from the quantitative analysis. A number of patients had received systemic treatment before ^{99m}Tc MDP bone and ^{18}FDG PET scanning, and it is not possible to exclude delayed disease modification that may have influenced scan appearances; however, the majority (21

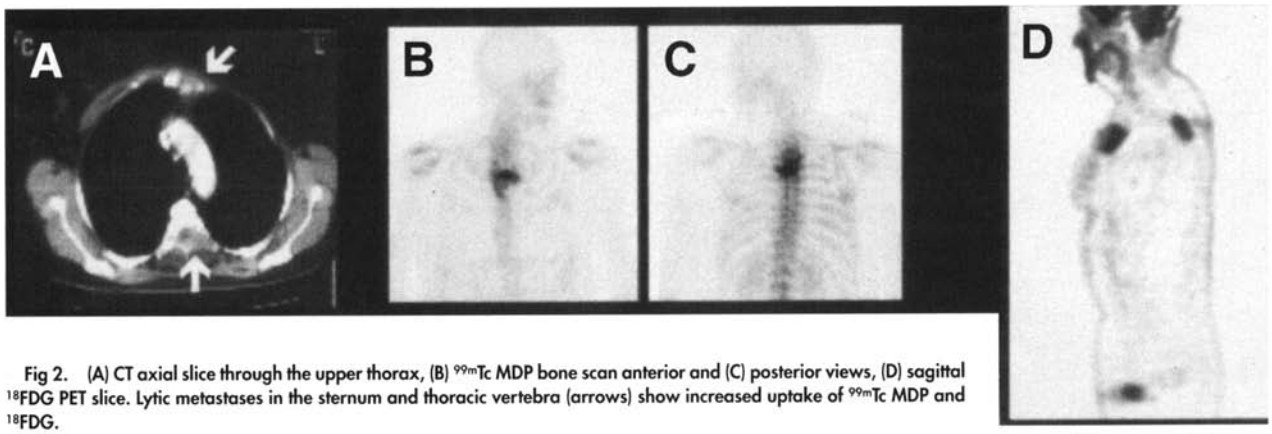

Fig 2. (A) CT axial slice through the upper thorax, (B) ^{99m}Tc MDP bone scan anterior and (C) posterior views, (D) sagittal ^{18}FDG PET slice. Lytic metastases in the sternum and thoracic vertebra (arrows) show increased uptake of ^{99m}Tc MDP and ^{18}FDG.

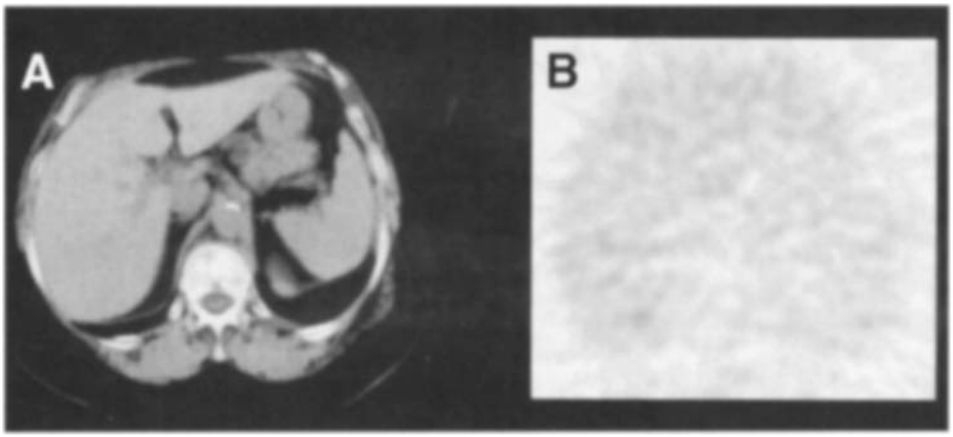

Fig 3. (A) CT axial slice through the upper abdomen, (B) axial ^{18}FDG PET slice at the same level. Sclerotic deposits in the vertebral body show no associated increase in uptake of ^{18}FDG.

of 23 patients) had progressive disease at the time of the study.

There are a number of reasons why ^{18}FDG PET may show an increase in sensitivity for the detection of osseous metastases compared with ^{99m}Tc MDP bone scintigraphy. PET is a method that intrinsically has a higher spatial resolution than gamma camera imaging and also routinely includes tomography. Tomography was not performed in this study on ^{99m}Tc MDP bone scans. In addition, ^{18}FDG PET and bone scintigraphy exploit different mechanisms to detect tumor involvement. ^{99m}Tc MDP bone scintigraphy relies on an osteoblastic bone response to tumor, whereas ^{18}FDG PET measures glucose uptake into the tumor itself. ^{18}FDG PET is therefore more likely to detect metastases at an early stage, perhaps when they are confined to bone marrow.

A correlation of FDG uptake into soft tissue metastases from breast carcinoma has previously been shown with tumor grade and prognosis,[7,8] but this study has not shown a difference in survival dependent on SUV measurement.

There is no obvious explanation for the difference in behavior of osteoblastic and osteolytic metastases, but the actions of growth factors on both tumor growth and bone metabolism may also be involved. A variety of growth factors, which includes transforming growth factors (TGFs), appear to regulate breast cancer cell growth.[15] These same factors are known to regulate bone remodeling. For example, TGF-α and related peptides stimulate the growth of human breast cancer cells. TGF-α is also a potent stimulator of osteoclastic bone resorption.[16]

Conversely, TGF-β and related peptides are a family of inhibitory growth factors found in normal breast epithelium. TGF-β inhibits breast cancer cell growth and is induced by tamoxifen.[17] TGF-β is an inhibitor of osteoclastic bone resorption that stimulates osteoblasts to form new bone[18,19] and many of the events involved in bone formation, which include chemotaxis of osteoblast precursors, mitogenesis of osteoblast precursors, and differentiated function in committed osteoblasts.[20]

It is possible that those patients who develop an osteoblastic response (sclerotic metastases) induced in part by TGF-β, which in turn has an inhibitory effect on tumor cells, may show improved survival and lower accumulation of ^{18}FDG compared with those with lytic metastases.

Irrespective of the underlying molecular mechanisms, ^{18}FDG PET detects more bone lesions than ^{99m}Tc MDP bone scintigraphy in patients with osteolytic metastases. These patients experience the most skeletal morbidity and have a reduced survival. Earlier detection of those patients who have a more aggressive clinical course and poorer survival may help identify a group who could benefit from the early introduction of newer systemic treatments, such as the bisphosphonates.

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