Reappraisal of the Baseline Bone Scan in Breast Cancer

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Baseline staging bone scans in 1,267 consecutive women with breast cancer attending a single clinic between 1980 and 1986 were reviewed. 0.3% of patients with T1, 3% with T2, 8% with T3, 13% with T4 tumors and none of those with Stage 1, 3% with Stage 2, 7% with Stage 3, and 47% with Stage 4 disease had a positive scan due to bone metastases. Two hundred eighty-nine (23%) had bone scan abnormalities secondary to radiologically confirmed benign bone disease. In 20 patients, no cause for a bone scan abnormality could be found after a median follow-up of 3.50 yr, a false-positive frequency of 1.6%. The false-negative rate was 0.08%. It is concluded that patients with tumors <2 cm are most unlikely to have a positive scan. In this instance, scans are not required routinely. However, we recommend a baseline scan in all patients with Stage 2, 3, or 4 disease.

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Radionuclide bone scanning with technetium-99m-(^{99m}Tc) labeled diphosponate enables detailed imaging of the skeleton and the detection of focal pathology at an early stage of development, usually before changes on plain radiographs are visible (*1*). With the introduction of the [^{99m}Tc]phosphate scanning agents, a large number of reports appeared in the literature on bone scanning at the time of presentation in clinically early breast cancer (*2–7*). The frequency of a positive baseline bone scan varied from 0–18% in Stage 1 disease and 0–41% in Stage 2 disease (*8*). Despite the wide variation in results, bone scanning became a routine part of preoperative staging of breast cancer. However, in recent years the value of this has been questioned (*9–13*). Some authors have concluded that the low frequency of a positive bone scan in early breast cancer is a poor return for the time and money invested, whereas others consider it an important baseline for future comparison which, when positive for metastatic disease, will influence clinical management (*14–16*).

This unit treats a large number of patients with breast cancer and has a policy of performing baseline bone scans in all new patients. Baseline scans (1,267) performed between 1980 and 1986 have been reviewed. The frequency of a positive bone scan has been determined and related to tumor size and clinical stage.

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METHODS

New patients presenting to this unit for the first time between Jan. 1, 1980 and Mar. 31, 1986 were reviewed. Patients referred from other hospitals for a second opinion, treatment for advanced disease, or diagnosed elsewhere were excluded. Patients were included if at presentation either tumour size or clinical stage had been accurately recorded. Clinical staging was performed by specialized breast surgeons.

Patients had a preoperative baseline bone scan performed 3–4 hr after injection of ^{99m}Tc-labeled methylene diphosphonate. All scans were reported by a nuclear medicine consultant. Plain radiographs were taken of areas of increased tracer uptake. Occasionally, localized computerized tomography (CT) was performed to investigate abnormalities, which were suspicious of metastatic disease when the plain radiographs were normal. The bone scan was considered positive for metastatic disease if, either at the time of the scan or subsequently, bone metastases were confirmed on plain radiographs or CT of the site of scan abnormality.

Operable breast cancer was treated either by modified radical mastectomy or conservation surgery with interstitial and external beam radiotherapy. Inoperable disease was treated by external beam radiotherapy. Patients had indefinite regular follow-up, and the time and site of any relapse was recorded. There was a minimum follow-up of 1 yr with a median follow-up time of 3.50 yr. The TNM system for clinical staging and tumor size (T) was used (*17*).

RESULTS

We reviewed 1,267 women with newly diagnosed breast cancer. T size was recorded in 1,155, clinical

TABLE 1
Frequency of Positive Baseline Scan and Subsequent Relapse in Relation to Tumor Size

Prognostic group	No.	Relapse at any site	First relapse in bone	Bone relapse within 1 yr	Bone relapse at any time	Positive baseline scan
T0	57	6 [11]	2 [4]	2 [4]	3 [5]	0 [0]
T1	251	52 [21]	12 [5]	3 [1]	23 [9]	1 [0.3]
T2	582	187 [32]	60 [10]	27 [5]	106 [18]	17 [3]
T3	122	57 [47]	13 [11]	11 [9]	36 [30]	10 [8]
T4	143	89 [62]	22 [15]	21 [15]	52 [36]	18 [13]
Total	1155	391 [34]	109 [9]	64 [6]	220 [19]	46 [4]

[ ]: Percentage of total number in prognostic group.
T0: lump not palpable.
T1: <2 cm lump.
T2: 2-5cm lump.
T3: >5 cm lump.
T4: Any size + skin infiltration/ulceration/peau d'orange/satellite nodules.

stage in 1,074. Table 1 shows the data for T size. The number of positive baseline scans is shown in addition to the number of patients developing a recurrence, recurring first in bone, developing bone metastases within 1 yr of diagnosis, and the total number who have developed a recurrence in the skeleton to date. Forty-six patients (4%) had a positive baseline scan: none of T0, 1 (0.3%) of T1, 17 (3%) of T2, 10 (8%) of T3, and 18 (13%) of T4.

The data are shown in the same format for clinical stage in Table 2. None of the patients with Stage 1, 18 (3%) of Stage 2, 13 (7%) of Stage 3, and 15 (47%) of Stage 4 had a positive baseline scan.

All 46 patients with a true-positive baseline scan developed radiologic evidence of metastases within 1 yr. Of 70 patients (6.5%) developing bone metastases within 1 yr of diagnosis, 46 (65%) were identified on the baseline bone scan. This included 1/3 with T2 and 17/27 (63%) with T2 tumors.

An additional 289 patients (23%) had an abnormal baseline bone scan. These were considered to represent degenerative disease in 233 (18%), trauma in 14 (1.1%), Paget's disease in 17 (1.3%), and other benign pathologies in 5 (0.3%). Plain radiographs provided confirmation with no subsequent evidence of metastases at these sites appearing during a minimum of 12 mo of follow-up. In 20 patients (1.6%), no cause for bone scan abnormality could be found and to date there has been no radiologic evidence of bone metastases at these sites. These scans are considered to be false-positives.

The diagnosis of metastatic bone disease was identified on plain radiographs before the development of an abnormal bone in only one patient. In this patient, the plain radiographs showed diffuse sclerotic disease. Re-

TABLE 2
Frequency of Positive Baseline Bone Scan and Subsequent Relapse in Relation to Clinical Stage

Prognostic group	No.	Relapse at any site	First relapse in bone	Bone relapse within 1 yr	Bone relapse at any time	Positive baseline scan
Stage 1	271	47 [17]	9 [3]	0 [0]	18 [7]	0 [0]
Stage 2	593	201 [34]	71 [12]	27 [5]	119 [20]	18 [3]
Stage 3	179	123 [69]	31 [17]	24 [13]	64 [36]	13 [7]
Stage 4	32	32 [100]	12 [38]	20 [63]	22 [69]	15 [47]
Total	1074	402 [37]	123 [11]	70 [7]	222 [21]	46 [4]

[ ]: Percentage of total number in prognostic group.
Stage 1: T0, 1; N0; M0.
Stage 2: T2; N0; M0, or T0, 1, 2; N1; M0.
Stage 3: T3, 4; N0, 1, 2, 3; M0, or T0, 1, 2; N2, 3; M0.
Stage 4: Any T; any N; M1 (metastases detected or suspected on clinical examination).

view of the bone scan showed that diffusely increased tracer uptake had been missed, a false-negative rate of 0.08%.

DISCUSSION

The prognosis of breast cancer is extremely variable, and metastatic disease, which may be microscopic and clinically undetectable, is often present at the time of initial diagnosis. Despite effective local control of the primary tumor, relapse may occur at any time, occasionally within months but often many years after presentation. A number of clinical, pathologic, and biologic features are known to influence the probability of relapse—size of the primary tumor, clinical stage, axillary lymph node status, and histologic grade being the most important (*18*). The optimum treatment for a woman with breast cancer depends on these prognostic features with the clinical findings, baseline investigations, and operative staging suggesting the appropriate local treatment and indicating the need for adjuvant systemic therapy.

The introduction of the ^{99m}Tc-labeled phosphates with their sensitivity for the identification of skeletal disease led to bone scanning becoming part of routine preoperative staging of breast cancer (*19*). The superiority of bone scanning over plain radiography for lesion detection is well established (*1*) and has recently been reviewed (*20*). However, over recent years there has been disagreement on the value of bone scanning in routine staging. Several authors have argued against routine scanning on the basis that it is not cost-effective because of the low pick-up rate in early disease (*8–11*). They have recommended that baseline scans should be restricted to patients with breast cancer who have Stage 3 or 4 disease. This advice may represent an overswing away from the bone scan and underestimate the value of a baseline scan.

This large review of baseline bone scans performed on all patients seen at a single center addresses several of the points at issue. All patients were carefully staged by experienced breast surgeons, all scans were performed with ^{99m}Tc-labeled MDP, and reported by a nuclear medicine consultant with radiologic backup. In 1,267 patients, the frequency of a positive baseline bone scan was 4% with as expected a rise in the positive rate with increasing tumor size and clinical stage. Only one patient (0.3%) with a T1 tumor or clinical Stage 1, 3% of T2 and Stage 2, and 8% of T3 patients had a positive baseline scan. These figures are lower than those quoted in many of the earlier studies that have been reviewed by McKillop (*8*), but are similar to several more recent studies (*12,21–22*).

Although the incidence of skeletal metastases is low in patients with apparently operable breast cancer, the value to those patients in whom needless mastectomy was avoided should not be underestimated. Only eight of the 28 patients with potentially operable tumors (T1, T2, and T3) and a positive baseline scan had surgery. Further investigation of these patients did not confirm metastases at that time. In the others, confirmation of metastatic disease resulted in alternative treatments being selected.

The positive scan rate was higher in patients with inoperable locally advanced or clinical Stage 4 disease, rising to 47% in those presenting with Stage 4 disease. The influence of a positive scan on initial management in these patients was paradoxically less. The optimum treatment of these patients is radiotherapy for local control and systemic treatment for the almost inevitable metastatic or micrometastatic disease. A positive scan did not usually influence this; although it did indicate specific bony sites for observation with follow-up radiographs in an attempt to preempt pathologic fracture or spinal cord compression.

The prognostic value of the baseline scan has been studied. Some authors have found the bone scan to be a poor predictor of subsequent skeletal relapse (*11,23*), much less than other factors including axillary lymph node status. McNeil (*14*) and Wickerham et al. (*16*) have remarked on the poor prognosis of patients with a positive scan. In this study, however, the baseline bone scan did reflect prognosis and identified more than half of the patients with recurring bone metastases within 12 mo. In our experience, a positive bone scan indicates a poor prognosis with a median survival of 24 mo (*24*).

The probability that further patients with an abnormal baseline scan will develop radiologic confirmation of metastatic disease is small after a minimum follow-up of 1 yr and median of 3.50 yr (*25*). It is more likely that these bone scans are false-positives. Some authors have quoted a high 70% false-positive rate (*23*). In this study, it was 1.6%, similar to other reports (*9,13*). The false-positive rate is clearly dependent on a number of factors including the scanning technique and equipment, reporting expertise, and subsequent investigation of focal lesions.

Many abnormalities can be confidently attributed to benign pathology, particularly when the scan is reported in conjunction with plain radiographs. The distribution and pattern of uptake in Paget's disease, trauma, and degenerative disease is usually different from those seen with metastatic disease (*26*). The ability to confirm metastatic involvement will depend on the quality of plain radiographs, complemented when necessary by CT or plain tomography, and reporting the films in conjunction with the scan results.

Our false-negative rate was low, similar to Bishop's report (*9*). In our series, 1/46 (2%) of patients developing metastatic bone disease was missed on the bone

scan in marked contrast to the 12/45 (27%) cases reported by Moneypenny et al. (*12*). The exquisite sensitivity of the bone scan for lesion detection is well accepted, and we are unable to explain the high false-negative rate in the Moneypenny series. We have seen individual lesions on radiographs that fail to produce a significant osteoblastic response and are not seen on the bone scan but other lesions, which are visible on the bone scan, were present. However, to our knowledge none of our patients with bone metastases from breast cancer have had a normal bone scan (Coleman RE and Rubens RD, personal communications).

In addition to the opinion that routine scanning is not cost-effective, several authors (*9,27*) also consider that a positive bone scan is of little value because early detection of relapse does not influence prognosis. Although premature death from metastatic disease is accepted as inevitable despite present treatments, there are no studies reported that either support or refute this opinion. Adjuvant systemic therapy for patients with axillary lymph node involvement, however, does prolong survival (*28*). It seems logical that if the prognosis of undetectable micrometastatic disease is influenced by treatment, then a small tumor burden, detected by sensitive imaging tests, could respond similarly.

The cost-effectiveness of an investigation is difficult to define in financial terms. Ultimately a decision on whether to perform routine baseline scans must lie with the individual physician or surgeon and reflect his available financial and technical resources. We agree that patients with tumors <2 cm are most unlikely to have a positive scan, and here scans are only of value as a baseline reference and for identifying other bone pathologies. It is recognized that routine bone scanning in this population may be inappropriate for many centers. However, the pick-up rate in larger tumors is significant, and it is probably worth trying to identify the 5% of patients with T2 tumors who will recur in bone within 1 yr.

CONCLUSION

Any center, conducting clinical trials in breast cancer, needs accurate staging to ensure patients assigned to different treatments are comparable and can be monitored accurately to identify relapse. For this reason, we continue to perform baseline scans. We consider the influence of a positive scan on clinical management in Stage 2 disease and having a baseline reference for all patients to have sufficient value.

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