Association Between Number and Sites of New Bone Scan Abnormalities and Presence of Skeletal Metastases in Patients With Breast Cancer

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Review of 1,441 bone scans performed on 242 breast cancer patients without known skeletal metastases identified 239 scans with new abnormalities. Findings on 54 of these 239 scans (23%) represented bone metastases. The proportion of scans reflecting metastases, grouped by the number of new abnormalities, was: (1) 20/182 (11%); (2) 9/26 (35%); (3) 4/9 (45%); (4) 1/2 (50%); ≥5 — 20/20 (100%). When metastatic disease presented as a bone scan with 1-4 new abnormalities, the spine was the most common site of involvement (18 of 34 (53%)), followed by the skull (5/34;15%), extremities and sternum (each 4/34; 12%). Rib lesions were the most common new findings on scans with <5 new abnormalities (seen on 76 of 219 scans (35%)) but only infrequently represented metastases (n = 2). Considering as indicative of malignancy only, those bone scans which demonstrated either (a) ≥5 new abnormalities, (b) initial radiographic correlation suggestive of metastases, or (c) thoracic spine lesions with normal correlative radiographs, the presence of skeletal metastatic disease could be predicted with a sensitivity of 0.80 and a specificity of 0.94.

J Nucl Med 1990; 31:387-392

Bone scintigraphy is a sensitive method for detecting the skeletal metastases of breast carcinoma, often providing the first evidence of distant malignant spread (*1-4*). However, a limitation of the technique is its nonspecificity (*5-10*), particularly when used in routine follow-up of patients without known metastatic disease. Any individual bone scan abnormality can be due to either a benign or malignant process, and it is only the presence of multiple new abnormalities without evidence for a benign etiology that can be considered characteristic of metastatic involvement (*11,12*). While the prevalence of metastases in solitary bone scan abnormalities has been examined by several groups (*13-18*), a rigorous investigation of the association between the number and sites of scan abnormalities and the likelihood of metastatic disease has not been described.

We retrospectively identified all new abnormalities on the serial skeletal scintigrams of a group of breast cancer patients followed on a regular basis after entrance into an adjuvant chemotherapy protocol (*19,20*). From available scintigraphic, radiologic, and clinical follow-up, the presence or absence of metastatic disease at each new abnormal site was ascertained. The prevalence of bone metastases as a function of the number of new scan abnormalities was then determined, and the anatomic distributions and correlative radiologic findings for benign and malignant lesions were compared.

MATERIALS AND METHODS

Patient Population

Six hundred and sixty-one breast carcinoma patients, all clinical Stage I, II, or III at diagnosis (*21*), were entered into an adjuvant chemotherapy protocol at our institution between 1974 and 1985 (*19,20*). Requirements for protocol entry included a bone scan with no evidence of metastatic disease prior to initiation of chemotherapy. Recommended follow-up at conclusion of chemotherapy included a bone scan every 6 mo for the first three years and annually thereafter. Two hundred fifty-eight protocol participants identified on nuclear medicine records as having had at least two bone scans at our institution form the initial patient population examined for this report.

Image Review

A total of 1,741 bone scans performed on the 258 patients were available for review. All scans were performed 2–4 hr following i.v. injection of 555–925 MBq (15–25 mCi) of

Received May 8, 1989; revision accepted Nov. 1, 1989.

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technetium-99m- (^{99m}Tc) labeled diphosphonate compounds. Three baseline studies performed in 1974 employed a rectilinear scanner. Gamma camera studies employed large field-of-view cameras with low-energy, high-resolution collimators. From 1974 to 1982, scans were acquired using a moving table format (22 cm/min) to produce whole-body images in the anterior and posterior projections, with selected stationary views obtained of abnormal sites. Studies performed after 1982 utilized overlapping stationary views exclusively. In virtually all cases, the entire skeletal system was imaged.

A flow chart summarizing the imaging and clinical review processes is presented in Figure 1. Briefly, a nuclear medicine physician (AFJ) read the written reports for each patient's scintigraphic studies, and guided by these reports, examined the following scans:

1. The first scan for which the report mentioned a new abnormality.
2. The study which immediately preceded the one in which the new abnormality was described, to determine if the "new" abnormality could be retrospectively identified.
3. All subsequent scans for a minimum of 18 mo.

For scans with four or fewer new lesions, the reviewer recorded the anatomic location of each new abnormality and the lesion intensity relative to adjacent bone, scored as 1+ (minimal to mildly increased), 2+ (moderately increased), or 3+ (markedly increased). For scans with five or more new lesions, only the total number of new findings was recorded; detailed tabulations of these lesions were performed only if suspected malignancy was not confirmed on subsequent data review. Cases in which the reviewer disagreed with the written report regarding the presence of an abnormality, its anatomic location, or its relative intensity, were submitted to a second nuclear medicine physician (WDK) for examination, and a final interpretation was achieved by consensus.

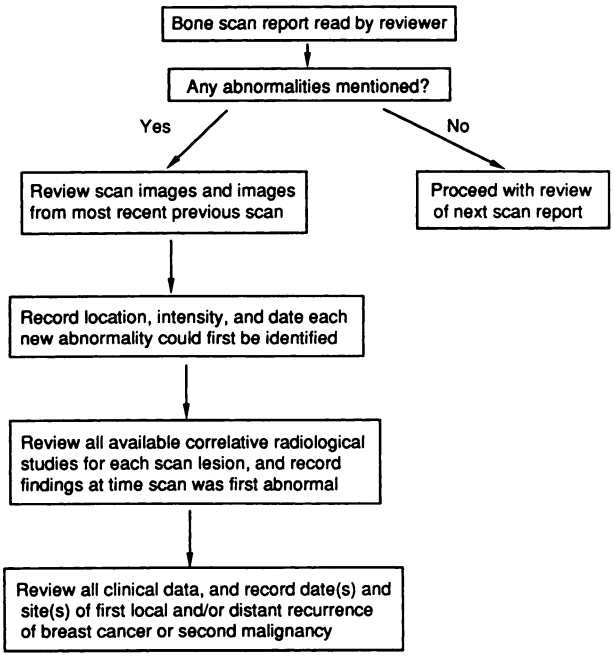

FIGURE 1
Flow chart summarizing the review process used to identify and characterize new bone scintigraphic abnormalities.

The reports of all radiologic examinations (plain films, fluoroscopy, trispiral, and computed tomography (CT)) of areas abnormal on bone scan were reviewed. Initial radiologic correlation was categorized as either: 1) negative (RN); 2) benign (RB); 3) suggestive of metastasis (RS); 4) consistent with metastasis (RM); or 5) no correlative study performed within 30 days of the bone scan (R0). Radiographic studies originally reported as showing a finding of uncertain significance were blindly reread by a radiologist (PCS or MSJ) and classified as either RN, RB, RS, or RM. Radiographs originally reported as RS and RN or RB films of scan lesions eventually proven to be bone metastases, were also reexamined to confirm the initial interpretations.

Recurrence Status

Clinical records through June 30, 1987 were reviewed to identify those patients who:

1. Developed local or distant nonosseous recurrence of breast cancer.
2. Had a documented second malignancy.
3. Developed new malignant involvement whose etiology (new primary versus breast or other metastasis) was uncertain.

Bone was considered a site of initial distant relapse if metastases were either detected there first or were identified within 30 days following confirmation of a nonosseous site of recurrence. An individual scan lesion was established as a bone metastasis by either:

1. Radiographic or tomographic images showing a typical blastic or lytic lesion and changes on follow-up radiographic and/or scintigraphic studies consistent with progression or healing in response to therapy.
2. Progression on a follow-up bone scan, with an increase in lesion intensity and appearance of at least two additional new lesions without evidence for a benign etiology.
3. Positive tissue diagnosis at autopsy.

The earliest scintigraphic abnormality, which on follow-up proved to be a metastasis, was recorded as the initial site of bone involvement, even if verification of this finding did not occur until after other nonosseous metastatic sites had been documented. A scintigraphic abnormality which remained stable or decreased in intensity on at least one follow-up scan was considered nonmalignant if the patient had no objective evidence of recurrence in bone during the 18 mo after the original scan date, or at autopsy.

Data Tabulation

Following scan and clinical review, 16 patients were excluded from analysis. These included 12 patients with recurrent breast cancer and evidence of metastatic disease prior to or on their first scan at our institution, and 4 who did not have two scans prior to developing either a second malignancy or new neoplasm of uncertain histologic type.

For the remaining 242 patients, data were tabulated from all scans of those patients without distant recurrence, and from scans up to the time of first distant recurrence (osseous or nonosseous) of breast cancer or a second malignancy in the other patients. The following findings were excluded:

1. All lesions on the earliest available scan for each patient.
2. Two or more adjacent, aligned rib lesions in a pattern indicative of trauma.
3. Polyarticular increased uptake in the joints of the extremities.
4. Diffuse or focal increased uptake in the appendicular skeleton at sites of documented trauma.
5. Increased uptake in the maxilla or mandible indicative of dental pathology.
6. Abnormalities without sufficient follow-up to establish their etiologies.

Each scan abnormality was classified in terms of anatomic location, initial scintigraphic intensity, and results of correlative radiographs. Nine anatomic regions were defined: skull, cervical spine, thoracic spine, lumbar spine, sternum, shoulder girdle (scapula and clavicle), ribs, pelvis, and extremities. Chi-square statistics were used for comparisons between different groups of scan findings. Sensitivity and specificity for detection of metastases using selected criteria were calculated.

RESULTS

A total of 1,441 scans met the inclusion criteria for analysis, 1,032 from the 152 patients without distant recurrence (Table 1) (range 2 to 18 scans/patient, mean 6.8) (Fig. 2A), and 409, including the first scans with evidence of metastatic breast cancer, in the other 90 patients (range 2 to 14 scans/patient, mean 4.5) (Fig. 2B). Two hundred thirty-nine of the 1,199 follow-up scans (20%) had new abnormalities, involving 117 patients (48% of the study population).

Fifty-five patients had bone as a site of initial distant recurrence (Table 1), with bone metastases first identified on a follow-up scan in 54 patients and on radiographs at a time no scan was performed in one patient. Metastatic disease was confirmed by: positive radiographs with subsequent radiographic and/or scintigraphic progression (n = 50); scintigraphic progression (n = 4); autopsy (n = 1). The number of new abnormalities on the 54 initial positive scans ranged from 1 to 24, with the prevalence of metastases increasing from 11% (20/182) for solitary new abnormalities to 100% (20/20) for scans with five or more new lesions (Table 2). The interscan interval during which bone metastases first appeared was the same regardless of the number of new lesions, with means of 10.1 (± 4.5) (1 s.d.), 10.1 (± 6.1), and 10.6 (± 6.4) mo for scans with 1, 2, and ≥3 new abnormalities, respectively.

The anatomic distribution for the 182 new solitary bone scan abnormalities is shown in Table 3. Benign solitary lesions were most common in the ribs (n = 58), while solitary metastases were most frequent in the thoracic spine (n = 8). There was no statistical difference between the prevalence of metastases for lesions of different scintigraphic intensity (1+: 10/111 (9%); 2+: 9/66 (14%); 3+: 1/5 (20%) (p = ns)).

Initial radiologic correlation was available for 162 of the 182 solitary lesions (Table 3). The majority of both benign and malignant lesions were RN, 59% and 53%,

TABLE 1
Follow-Up of 242 Breast Cancer Patients

Clinical status	Number of patients
Distant recurrence	
Bone involvement at recurrence	55
No bone involvement at recurrence	27
Local recurrence only	12
Second malignancy without metastases	15
New neoplastic involvement of uncertain histologic type	8
No recurrence	125
Total	242

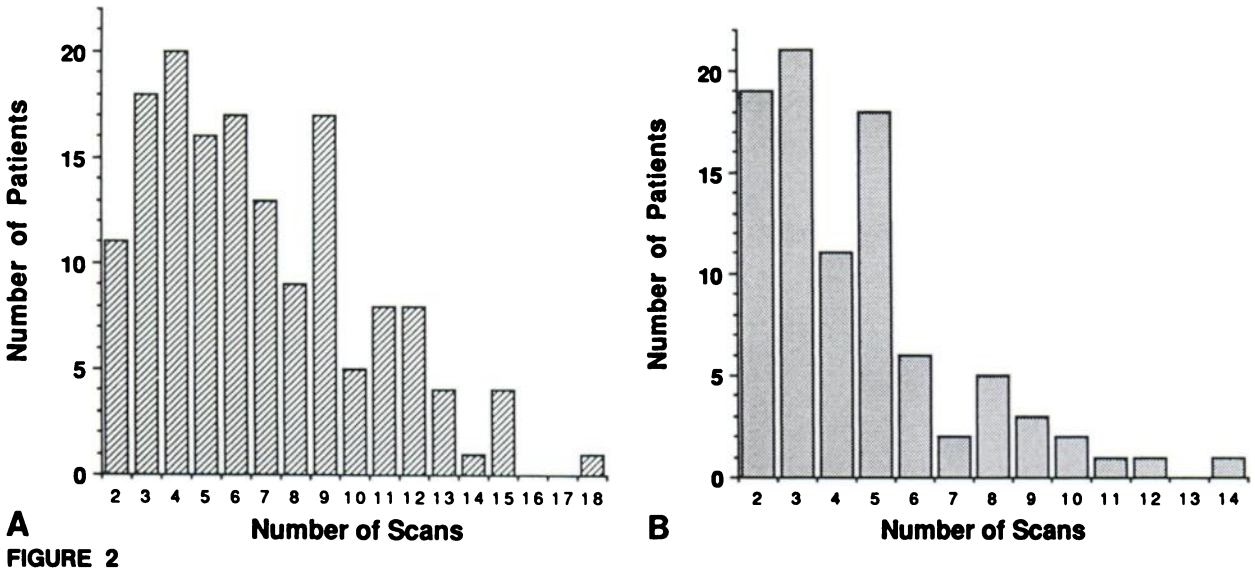

FIGURE 2
Number of serial bone scans reviewed in 242 breast cancer patients. (A) 152 patients without distant recurrence and (B) 90 patients with either distant recurrence of breast cancer (n = 82) or new neoplasm of uncertain histologic type (n = 8).

TABLE 2
Occurrence of Metastases as a Function of Number of New Abnormalities on Bone Scintigraphy

Number of new bone scan abnormalities	Number of occurrences	Number with metastases*
1	182	20 (11%)
2	26	9 (35%)
3	9	4 (45%)
4	2	1 (50%)
5	4	4 (100%)
6	2	2 (100%)
>6	14	14 (100%)
Total	239	54 (23%)

* Percentage with metastases in parentheses.

respectively. One metastasis (in the thoracic spine) had initial radiographs interpreted as RB, while one rib lesion reported as RM and one extremity and three rib abnormalities interpreted as RS proved to be benign on follow-up.

The sites of the 24 confirmed metastases on bone scans with 2–4 new abnormalities were: thoracic spine, 7; pelvis, 4; extremities, 4; lumbar spine, 3; skull, 3; sternum, 2; ribs, 1. Radiographic results for these metastases were: RN: 13 (54%); RM: 5 (21%); RS: 4 (17%); RB: 1 (4%); R0: 1 (4%). Of the 10 other abnormalities on these 14 scans, 2 were benign, and for the other 8, follow-up was insufficient to establish an etiology. Overall, only 6 of the 14 scans (43%) had at least one RM or RS lesion.

Of the 34 bone scans with metastatic disease presenting as <5 new abnormalities, 53% showed malignant involvement of the spine, 38% in the thoracic spine (Table 4). There were no RS or RM findings for any lesions on 21 of these scans (62%).

Sensitivity and specificity for identification of metastases on bone scans with new abnormalities were 0.37 (20/54) and 1.00 (185/185), respectively, if only scans with five or more lesions were considered to reflect the presence of metastases. Inclusion of initial radiologic correlation (thus excluding the 20 solitary new abnormalities (three metastases) for which initial radiographs were not obtained), with RS lesions considered as metastases, resulted in sensitivity of 0.65 (33/51) and specificity of 0.97 (163/168). As RN lesions in the thoracic spine proved to be metastases on 8 of 13 scans (62%) (Tables 3 and 4), categorizing all such lesions as metastases resulted in sensitivity of 0.80 (41/51) and specificity of 0.94 (158/168).

DISCUSSION

Bone scintigraphy is the most sensitive method for identifying skeletal metastates in breast carcinoma (*1–4,12*). However, uncertainty concerning the etiology of many bone scan abnormalities has caused the utility of the technique to be questioned in the routine follow-up of clinically disease-free patients (*6,7,10,22–24*). Unexplained new scan abnormalities, namely those with normal correlative radiographs, represent a diagnostic dilemma for the clinician, who must decide how aggressively to pursue the possibility of new distant relapse. Although some early bone metastases, particularly in the spine, can be detected by CT before they are evident on plain radiographs (*25*), bone biopsy may be the only method capable of establishing the etiology of a scan finding in other cases (*26–29*).

In the present study, a bone scan with five or more new abnormalities always reflected the presence of metastatic disease, but this pattern was seen in only 20 of 54 patients (37%) with scintigraphic evidence of initial distant recurrence in bone. Twenty other patients (37%) had only a solitary new abnormality as the first indication of recurrence in bone, a scan finding eight times more likely to be benign than malignant (162/20 = 8.1). In contrast to solitary scan findings, there was a better than one in three likelihood that a scan with 2–4 new lesions reflected bone metastases. The low likelihood of malignancy for solitary new abnormalities allowed attainment of a high specificity (0.94) simply by considering as malignant only scans with ≥5 new abnormalities, lesions with positive (RM or RS) radiographs, and RN lesions in the thoracic spine, the latter included because of the increased frequency of such findings proving to be metastases (Table 4). While the sensitivity of 0.80 achieved using these criteria would be unacceptably low, this example does demonstrate that the specificity of bone scintigraphy can be improved through careful examination of patterns of scan findings.

Only new abnormalities which (a) developed in the interval between two consecutive bone scans, and (b) did not represent obvious trauma or degenerative disease were included in this review; this allowed us to focus on findings of the greatest clinical relevance. The presence or absence of malignancy at a scan positive site was judged based upon imaging and clinical follow-up of 18 mo or longer (except in instances of patient death). Although biopsy or autopsy confirmation of lesion etiology was rarely available, almost all patients with bone metastases showed obvious progression to widely disseminated disease. Most nonmalignant scan abnormalities either resolved or had eventual radiologic demonstration of a benign cause.

Considering scans with less than five new metastatic lesions to reflect early distant recurrence, the most common site of involvement for this stage of disease was the spine. This is consistent with the common involvement of the spine in breast cancer patients with widely disseminated bone metastases (*11,30–32*). Although rib abnormalities were the most common

TABLE 3
Anatomic Distribution and Initial Radiographic Correlation for 182 Solitary New Bone Scan Abnormalities

Scan findings			Initial correlative radiograph[†]				
Site	Intensity	No.[*]	RN	RB	RS	RM	RO
Skull	1+	8 (1)	4	3	0	0	1 (1)
	2+	6 (1)	5 (1)	0	0	0	1
Sternum	1+	3 (1)	2	0	0	1 (1)	0
	2+	2 (1)	1	0	0	1 (1)	0
Ribs	1+	31	22	7	1	1	0
	2+	25 (1)	16 (1)	6	2	0	1
	3+	3	2	1	0	0	0
Shoulder girdle	1+	11	5	3	0	0	3
	2+	7	6	0	0	0	1
Cervical spine	1+	6	1	4	0	0	1
	2+	5 (1)	0	4	0	1 (1)	0
Thoracic spine	1+	18 (4)	7 (3)	7	0	0	4 (1)
	2+	4 (3)	1 (1)	1 (1)	1 (1)	0	0
	3+	1 (1)	0	0	1 (1)	0	0
Lumbar spine	1+	12 (2)	5 (1)	6	1 (1)	0	0
	2+	6 (1)	1 (1)	4	0	0	1
Pelvis	1+	10 (1)	5	3	0	0	2 (1)
	2+	5	3	2	0	0	0
	3+	1	0	0	0	0	1
Extremities	1+	12 (1)	7 (1)	3	0	0	2
	2+	7 (1)	1	2	1	1 (1)	2
Totals	1+	111 (10)	58 (5)	36	2 (1)	2 (1)	13 (3)
	2+	66 (9)	34 (4)	19 (1)	4 (1)	3 (3)	6
	3+	5 (1)	2	1	1 (1)	0	1
		182 (20)	94 (9)	56 (1)	7 (3)	5 (4)	20 (3)

[*] Number of metastases in parentheses.
[†] Key: RN = normal; RB = benign; RS = suggestive of metastasis; RM = consistent with metastasis; and RO = not done.

TABLE 4
Sites of Metastatic Involvement in 34 Patients with Initial Scan Presentation of Less Than Five New Abnormalities

Anatomic site	Number of scans with metastases[*†]	Number of scans with only RN[‡] lesions
Thoracic spine	13 (38%)	8
Lumbar spine	6 (18%)	3
Skull	5 (15%)	2
Sternum	4 (12%)	2
Extremities	4 (12%)	2
Pelvis	3 (9%)	1
Ribs	2 (6%)	1
Cervical spine	1 (3%)	0

[*] Percentage of scans in parentheses.
[†] Column total exceeds 34 because of metastates in more than one anatomic site on four scans: thoracic + lumbar spine (2); thoracic spine + skull (1); lumbar spine + skull (1).
[‡] RN: initial correlative radiograph negative.

new findings on all scans with 1-4 new lesions (76/219; 35%), they represented metastatic disease on only two scans.

Bone scan abnormalities are commonly evaluated in conjunction with correlative radiographs (*4,10,25,33, 34*). Although such correlation can be helpful even when the pattern of scan abnormalities strongly suggests either a benign or malignant explanation, its major impact is on cases where the scan shows a finding of uncertain clinical relevance such as a solitary new lesion. Our finding that 58% of such abnormalities were RN demonstrates that correlative x-rays alone cannot adequately deal with the problem of unexplained new scintigraphic lesions, and underscores the value of knowing the relative likelihood of a lesion being a metastasis based upon its skeletal location.

The results of the present review indicate that the number, sites, and radiologic appearance of new bone

scan abnormalities in patients with breast cancer can be helpful in predicting the likelihood that skeletal metastases are present. Although staging bone scans have a low yield for identifying unsuspected metastatic disease, particularly for clinical Stage I and II patients (*10,22,23,35,36*), they do provide baseline information which allows the determination of whether abnormalities seen on subsequent scans are new, thereby aiding in the prediction of lesion etiology. While bone scintigraphy in conjunction with selected radiographs remains the most efficacious means for identifying early skeletal metastases, isolated new RN lesions in sites such as the thoracic and lumbar spine warrant further investigation by means such as CT (*9,25*), MRI (*37,38*), or bone biopsy (*27,29*).

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