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Bone Metastases in Primary Operable Breast Cancer. The Role of Serial Scintigraphy*

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Abstract—*In* 1978 *and* 1979, 1060 *Danish patients with primary operable breast cancer were bone-scanned for osseous metastases before entering a nationwide therapeutical trial. A re-reading group interpreted the scans produced in* 12 *participating hospitals. As a consequence standardized guide-lines for interpretation were agreed upon from* 1979. *The frequency of positive bone scans suggesting bone metastases fell abruptly from* 1978 *to* 1979, *as read both locally and by the re-reading group. As measured statistically the difference between the interpretation of the local and the re-reading groups remained unchanged. Of the* 1060 *patients* 760 *were followed by repeated pre-scheduled scans* 6 *and* 12 months *after surgery until any kind of recurrence was diagnosed. Only* 37 *of the* 760 *patients* (4.9%) *developed bone metastases verified by radiology or autopsy during the first* 2 yr *after surgery. A single positive scan, especially performed* 6 *or* 12 months *after surgery, as well as two or three scans repeatedly staying or becoming positive increase significantly the risk of developing bone metastases within* 12 months *after the latest scan. In* 13 *of the* 37 *patients with otherwise subsequently proven bone metastases the latest scan(s) were negative. It is concluded that a fixed schedule of repeated bone scans in patients with breast cancer is not warranted.*

INTRODUCTION

PREVIOUSLY we have evaluated the diagnostic and prognostic value of early bone scans performed within 30 days of the operation in breast cancer [1]. On a nationwide basis we found that these initial bone scans showed osseous foci indicative of bone metastasis in 7% of the patients or about 12 times as many as found by radiology. Differences between the interpretation by the participating 12 departments and a central re-reading group indicated that a standardization of the interpretation might lower the frequency of positive scans. It was suggested that the diagnostic value of changes in bone scans with time might be higher than that of an isolated initial scintigram.

The purpose of the current study was (1) to analyse any change in the scan interpretation pattern after performing the already published study [1]; and (2) to analyse the significance of multiple scans in the same patients.

MATERIALS AND METHODS

In 1978 and 1979, 1060 patients with primary operable breast cancer entered nationwide, randomized adjuvant therapy protocols according to their clinical and menopausal state [2] and were bone-scanned at the time of operation. These

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scans were initially evaluated at 12 local hospitals and subsequently re-read 'blind' jointly by a central group. Each scintiphoto was characterized according to a standardized grading defined in the previous study [1] and the grading is summarized here: grade 0: no abnormal finding; grade 1: benign pathology most likely, but malignancy cannot be excluded with certainty; grade 2: malignant pathology most likely, but benign cause cannot be excluded; grade 3: malignant cause almost certain.

The scintigraphic technique employed by the 12 participating departments was the same as in the previous study [1]. If a patient had clinical symptoms of bone metastases and/or a grade 2 or 3 (positive) scan an X-ray of the bone in question was taken.

Bone metastases

Of the 1060 patients 760 had a bone scan 6 and 12 months after surgery when no metastases of any kind were diagnosed before the scheduled scintigraphy. The 760 patients were representative of the 1060 patients with respect to recurrences, mortality or participation in the different protocols. The remaining 300 patients did not have the scheduled bone scans because of failing follow-up. The patients were divided into two groups as follows: patients without and patients with bone metastases diagnosed by radiology or autopsy within 24 months after surgery.

Twenty-four patients died and/or had recurrences (osseous or non osseous) in the first 6 months after presentation. A further 67 patients died or developed recurrences 6–12 months after presentation. Thus a total of 2165 scintigrams (760 at time of operation, 736 at 6 months after presentation and 669 at 12 months after operation) were evaluated and characterized according to the standardized grading. For practical purposes grades 0 and 1 were combined as grade 1 (negative scan).

For statistical analysis both the χ^2 test and Fisher's exact test were used.

RESULTS

Comparison of results of the initial scans of the 1978 and 1979 cohorts

The rate of positive initial scans changed drastically from 1978 to 1979 (Table 1). The scans read as positive locally fell from 124/520 (24%) in 1978 to 36/540 (7%) in 1979. The positive diagnosis rate of the re-reading group fell from 69/520 (13%) to 19/540 (3.5%). The rate of positive scans changed abruptly around the beginning of 1979 for both the local and central reading, whereas the rate did not differ significantly from month to month either through 1978 or 1979.

Table 1. Comparison between the results of the local grading and the grading of the re-reading group before (1978) and after (1979) coordination of interpretation

Grading (local)	Grading (re-reading group) 0 and 1	2 and 3	Total
	1978		
0 and 1	381	15	396
2 and 3	70	54	124
Total	451	69	520
Observed agreement = (54 + 381) / 520 = 0.837			
Expected chance agreement = (69/520) × (124/520) + (451/520) × (396/520) = 0.692			
κ = (0.837 - 0.692) / (1.000 - 0.692) = 0.47			
	1979		
0 and 1	498	6	504
2 and 3	23	13	36
Total	521	19	540
Observed agreement = (13 + 498) / 540 = 0.946			
Expected chance agreement = (19/540) × (36/540) + (521/540) × (504/540) = 0.903			
κ = (0.946 - 0.903) / (1.000 - 0.903) = 0.44			

The agreement between local and central reading of the scans was analysed according to Koran [3]. The kappa values were essentially the same in 1978 and 1979 (Table 1).

The scintigraphy in relation to occurrence of bone metastases

In 37 (4.9%) of the 760 patients bone metastases were diagnosed either radiologically (34 patients) or at autopsy (three patients).

Table 2 shows the initial grading of 760 patients of both the 1978 and 1979 cohorts related to the occurrence of bone metastases during the first 24 months after surgery. An initial positive scan score as compared with a negative scan does not increase the risk of bone metastases development within the first 24 months after surgery ($P > 0.1$).

Table 3 shows the risk of developing bone metastases within 12 months after a bone scan

Table 2. Comparison between scintigraphic grading at time of operation and occurrence of bone metastases during the first and second years after surgery

Grading initial	Total No. of patients	No bone metastases, 1+2 yr	With bone metastases, 1+2 yr
1	701	669	32
2	40	36	4
3	19	18	1
Total	760	723	37
		$P > 0.1$	

Table 3. Comparison between grading of bone scans performed at time of operation (initial) and 6 and 12 months after surgery and the occurrence of bone metastases within 12 months after the bone scan (the 12-month observation period after the 6-month bone scan overlaps with 6 months in the observation period after both the initial and the 12-month bone scans)

Grading	Initial		6 months		12 months	
	No bone metastases	With bone metastases	No bone metastases	With bone metastases	No bone metastases	With bone metastases
1	683	18	649	11	633	2
2	37	3	54	8	25	5
3	18	1	4	10	0	4
Total	738	22	707	29	658	11
	$P > 0.1$		$P < 0.001$		$P < 0.001$	

performed at the time of operation and 6 and 12 months after surgery. It should be noted that one or two previous scans were available when the 6- and 12-month scans were evaluated respectively. A positive scan at 6 and 12 months after surgery indicates a high risk of developing radiologic or histologic bone metastases within 12 months after the bone scan ($P < 0.001$). Thirty-eight per cent (6 months) and 18% (12 months) of the patients who developed bone metastases had a normal scintigram less than 12 months before the metastases were diagnosed. The disagreement between Tables 2 and 3 concerning the number of patients with bone metastases is due to the fact that the follow-up period after the 6-month scintigram is included in the follow-up period for both the initial and the 12-month scintigrams.

Table 4 shows the grading of two repeated scans over the first 6 months after surgery compared to the osseous recurrence rate from 6 to 18 months after surgery. It is obvious that the best skeletal prognosis is when the scintigram is repeatedly negative or changes from positive to negative. It is much worse when repeated positive scans are found or when a positive scan is developed ($P < 0.001$).

Table 4. Comparison between grading at time of operation and 6 months after surgery and the occurrence of bone metastases from 6 to 18 months after surgery

Grading*	Total No.	No bone metastases	With bone metastases
11	625	614	11
21, 31	35	35	0
12, 13	57	43	14
22, 23, 32, 33	19	15	4
Total	736	707	29
		$P < 0.001$	

* 1st digit: the grading of the initial bone scan; 2nd digit: the grading of the bone scan performed 6 months after surgery. For example, 11 is the group with two grade 1 scans; 12, 13 are those patients having an initial grade 1 and a second scan of either grade 2 or 3.

Table 5 shows the grading of three repeated scans over the first 12 months after surgery compared to the occurrence of bone metastases during the second year. The findings are similar to those found after two repeated scans (Table 4).

All 37 patients with otherwise proven bone metastases occurring within 24 months after surgery had a bone scan within 12 months of diagnosis of osseous foci. In 13 of these patients the most recent scan was negative; in eight (61%) this scan had been obtained less than 6 months before metastases were proven radiologically or at autopsy (three had osteolytic metastases, two osteosclerotic and eight mixed). All 24 patients with a positive scan had bone metastases diagnosed by radiology or at autopsy (nine had osteolytic metastases, seven osteosclerotic and

Table 5. Comparison between grading of bone scans performed at the time of operation and 6 and 12 months after surgery and the occurrence of bone metastases in the second year after surgery

Grading*	Total No.	No bone metastases	With bone metastases
111	558	556	2
121, 131	37	37	0
211, 221 231, 311 321, 331	40	40	0
112, 113	22	17	5
122, 123 132, 133	7	4	3
212, 213 312, 313	0	0	0
222, 223 232, 233 322, 323 332, 333	5	4	1
Total	669	658	11
		$P < 0.001$	

* 1st digit: the grading of the initial bone scan; 2nd digit: the grading of the 6-month bone scan; 3rd digit: the grading of the 12-month bone scan. See also footnote to Table 4.

eight mixed) within 12 months after bone scan and in 21 of these (87%) bone metastases were diagnosed within 6 months after the scan.

DISCUSSION

The British Breast Group on bone scanning [4] found a surprisingly large variation of positive initial bone scans among eight participating centres. Although Rossing *et al.* [1] did not find a similar large variation between 12 Danish centres, they explained the differences by the fact that local criteria of interpretation vary unless they are standardized according to the same criteria. Early in 1979 we initiated a coordination of the local interpretation. That resulted in a drastic decline in the frequency of positive bone scans read both locally and by the re-reading group. Whereas a fall in the frequency of positive scans read locally was the intention, it is surprising that the re-reading group also found a lower frequency in 1979 than in 1978 since the group used the same criteria for interpretation through the two years. The decrease is difficult to explain, since the fall was not due to a change in patient attitude and selection and the frequency of bone metastases proven radiologically or histologically was almost the same for the 1978 (5.6%) and 1979 (4.1%) cohorts. Although the observed agreement in evaluating the initial bone scans between the local groups and the re-reading study group improved, the agreement measured by the kappa value was almost unchanged, still at an acceptable level. Thus the effect of issuing standardized guide lines for interpretation was not quite satisfactory. The technique and the evaluation must be better coordinated and optimized than just a simple issue of standardized guide lines.

The clinical value of initial and repeated prescheduled scans should be viewed in the light of the low incidence of bone metastases verified by other techniques: 0.6% at the time of the operation [1] and for primary operable breast cancer patients 4.9% in the following 2-yr period.

The most striking observation of the current study was that the risk of developing bone metastases increases significantly if two or three scans are performed before 12 months after surgery and the scans are unchanged positive or a positive scan is found 6 or 12 months after a negative initial scan. At the same time it is evident that these courses of events are infrequent and that 13 of the 37 patients who developed bone metastases never had a positive scan. The latter cannot be explained by the obvious delay between bone scan and radiology since no significant difference in time between the most recent scan and positive radiology was found in patients with a positive scan and patients with a negative scan. In fact, the majority of patients in both groups had bone metastases diagnosed by radiology or at autopsy within 6 months after the latest scan.

The majority (54 of 59) of the patients with a positive initial bone scan developed no bone metastases during the observation period. According to Citrin [5], this is surprising. However, the specificity of bone scans in relation to bone metastases is low [1] and the current study includes only patients with primary operable breast cancer. Thus patients with radiological or histological bone metastases at the time of operation were not included in the present study.

The use of conventional radiology as the 'true' criterion of bone metastases is not optimal because of its low sensitivity [5]. However, it is nevertheless a matter of fact—at least in this country—that in most cases no change in treatment is done before a positive radiology or histology is demonstrated. Lately it has been shown that conventional X-ray fails to see many bone metastases which on CT scans as well as on bone scans were clearly discernible [6]. Furthermore, application of cytology of bone marrow aspirates using epithelium membrane antigens [7] may result in a further decrease in the number of false positive bone scans.

At one of the participating centres in which the follow-up of all females with breast cancer from that region was centralized similar results as in the current study were found [8].

The data presented suggest that a prescheduled bone scan at 6 and/or 12 months is valuable, despite a large number of false positive scintigrams. However, we believe that a fixed schedule of repeated scans or radiograms in patients with primary operable breast cancer is not warranted, at least within 12 months after surgery, because of the small number of patients developing radiographic bone metastases. This point of view is in agreement with Pauwels *et al.* [9] and Perez *et al.* [10]. The radiograph and the scan are complementary and should be used together in the evaluation of bone metastases.

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