Eur J Cancer Clin Oncol, Vol. 18, No. 7, pp. 629–636, 1982.
Printed in Great Britain.

0277-5379/82/070629-08$03.00/0

What do Early Bone Scans Tell about Breast Cancer Patients?*

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Abstract—*In* 1978, 1012 *out of a total of* 1888 *Danish breast cancer patients registered for a nationwide therapeutical trial were bone-scanned to find osseous metastases. A re-reading group (N.R., O.M. and S.P.N.) interpreted* 842 *of the scans produced in the twelve participating hospitals. Specific criteria were used for grading the scintiscans. Of the* 842 *scans* 682 *were performed within* 30 *days of the operation and were defined as initial. The re-reading group found* 50 (7%) *of these scans to be equivocal and* 46 (7%) *to be indicative of bone metastases at the time of operation. The number of X-ray-verified bone metastases was only* 5 (0.6%). *The frequency of positive bone scans correlated with the age of the patients and tumor size, but not with clinical staging at the time of operation, number of positive axillary lymph nodes or degree of tumor anaplasia. Recurrences and death rates during a 2-yr follow-up period correlated significantly with initial clinical staging. In the clinical low-risk group a positive initial bone scan worsened the prognosis, but this was not statistically significant for all patients grouped together. Although the prognostic value of the initial bone scan* per se *is dubious, it serves as a guidance for elective X-ray examination and as a basis for comparing subsequent scans.*

INTRODUCTION

SINCE 1978 about 90% of all primary breast cancer patients in Denmark have been registered in the Danish Breast Cancer Cooperative Group, DBCG. The patients were operated at 80 surgical departments. They entered coordinated randomized adjuvant therapy protocols according to their clinical and menopausal stage [1]. The main reasons for exclusion from the protocols were advanced disease (i.e., distant metastases), old age, other primary cancers, and the wish of the patients not to participate.

The surgical departments were encouraged to have the patients bone-scanned initially and thereafter twice a year. Negative scans were taken to exclude bone metastases. Positive scans resulted in elective X-ray examination for verification. The purpose of the present study was (1) to standardize the reading of the scintiphotos; (2) to compare the initial abnormal bone scans with skeletal roentgenograms; and (3) to correlate the results of the initial scans with age, tumor size, axillary lymph node involvement and the degree of tumor anaplasia. Furthermore, the results of the initial bone scans were related to recurrences and death rates in a 30-month follow-up period.

MATERIALS AND METHODS

Table 1 shows the clinical characteristics of the 1888 operated patients who were registered in DBCG in 1978. Protocolled patients in group I had a breast cancer of ≤ 5 cm, no invasion in the chest wall, no histological evidence of invasion in the skin or profound resection line,

Accepted 5 February 1982.

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*This work was carried out on behalf of the Danish Breast Cancer Cooperative Group.

Table 1. Patient category

	No. of patients	Bone scans No.	%
In protocol			
Group I. Mastectomy only	619	428	69
Group. II. Mastectomy and adjuvant therapy	466	368	79
Not in protocol			
Metastases; previous cancer	255	55	22
Medical contra-indications	163	30	18
Fixation to skin	135	68	50
Operation deviating from protocol	168	24	14
Other deviations from protocol	73	36	49
Patients refusal of participation	9	3	33
Total	1888	1012	54

In protocol: Group I: low-risk patients (see text).
In protocol: Group II: high-risk patients.

and no lymph node metastases, i.e. presumably they belonged to the prognostically favourable group. Protocolled patients in group II belonged to the prognostically inferior group, and did not meet the above-mentioned requirements [2].

The bone scans were primarily evaluated at 12 local hospitals. The 1012 initial scans were subsequently re-read 'blind' jointly by three of the authors (N.R., O.M. and S.P.N.). We characterized each scintiphoto according to the following standardized grading:

Grade 0: no abnormal finding.
Grade 1: one or more foci visible together with knowledge of benign bone-joint disorder involving the suspect region/regions: benign pathology most likely, but malignancy cannot be excluded with certainty.
Grade 2: one or more foci visible and at least one of them in the axial skeleton together with scintigraphic signs of and/or knowledge of a benign bone-joint disorder as a possible cause of the foci in question: malignant pathology most likely, but benign cause cannot be excluded.
Grade 3: one of more foci visible and at least one of them in the axial skeleton. Bening disorders in the regions concerned unlikely according to provided data. Scintigraphic findings compatible with metastases: malignant cause almost certain.

This grading was subsequently recommended as a standard to all participating departments. The scintigraphic technique employed by the participating departments varied as shown in Table 2. The radiopharmaceuticals used were [^{99m}Tc]-labelled polyphosphate, pyrophosphate, and in more than half of the cases, methyl diphosphonate. The doses were 15–20 mCi. Scanning took place 2–3 hr after i.v. injection. All scans reached from the skull to at least the femoral shafts. Parallel collimators were standard.

RESULTS

Evaluations of the method

A test to compare the recurrence rate between patients in protocol who had an initial scan at the time of operation and patients in protocol who had not yielded, P = 50%, i.e. for patients in protocol the scanned population was representative for the 1978 cohort.

Out of the 1012 scans, 170 had to be disregarded either because they were not available for re-reading or because of technically unsatisfactory scans.

Table 3 compares the initial grading of the 842 evaluable scintiphotos performed at the local department with that of the re-reading group. It is seen that the number of suspicious scans (grade 2) was reduced from 166 to 65, out of which 63 were solitary lesions. The number of definitely positive scans were raised by the re-reading group from 44 to 60, out of which 5 showed solitary foci. The number of definitely positive findings (grade 3) increased from 44 as judged locally to 60 found by the re-reading group. As to the localisation of the 'hot spots' in the 60 scans classified as indicative of bone metastases, all but 3 (95%) were in the axial

Table 2. The scintigraphic technique employed by the participating twelve departments. AP = antero-posterior projection. PA = postero-anterior projection

Equipment	Projection	Bone scans	
		No.	%
Rectilinear scanner	AP + PA	87	9
Scanning gammacamera	AP + PA	647	64
Stationary gammacamera	AP + PA	166	16
Stationary gammacamera	PA	42	4
Combinations	AP + PA	70	7
Total		1012	100

Table 3. Interpretation of scintigrams by performing department as compared with that of the re-reading group

Grading (local)	Grading (re-reading group)				
	0	1	2	3	Total
0	501	44	8	7	560
1	38	22	10	2	72
2	50	50	41	25	166
3	6	6	6	26	44
Total	595	122	65	60	842

skeleton including the cranium. No 'hot spots' on the operated side of the chest wall were of grade 2 or 3. Four of the 60 positive scans would have been missed if only posterior views had been obtained, while 20 would have been missed if only anterior projection had been used.

Table 4 shows the relation between the scintigraphic grading of the re-reading group and the applied technique in the 842 scintigrams. With scanning gammacameras there was a significantly lower proportion of grade 2 and 3 and a correspondingly higher proportion of grade 0 and 1 scans.

Table 5 shows a comparison of the results of the local grading and the grading of the re-reading group. Grade 2 and 3 are pooled as they indicate equivocal and positive scans respectively. Grade 0 and 1 are considered to indicate negative diagnoses. The discrepancies between the results of the two readings were analysed according to Koran [3]. The observed agreement between the two readings was 0.83. The expected chance agreement is 0.68.

Table 4. Evaluable scintigrams performed with either scanning, stationary gammacamera or other modalities related to scintigraphic grading by the re-reading group

	Scintigraphic grading					
	0 and 1		2 and 3		Total	
	No.	%	No.	%	No.	%
Scanning gammacamera	532	87	79	13	611	100
Stationary gammacamera	135	80	33	20	168	100
Other modalities	50	79	13	21	63	100
Total	717	85	125	15	842	100

$\chi^2 = 6.5$; d.f. = 2; $P < 0.05$.

Table 5. Comparison between the results of the local grading and the grading of the re-reading group

Grading (local)	Grading (re-reading group) 0 and 1	2 and 3	Total
0 and 1	605	27	632
2 and 3	112	98	210
Total	717	125	842

Observed agreement = (98 + 605/842) = 0.83.
Expected chance agreement = (125/842) × (210/842) + (717/842) × (632/842) = 0.68.
Kappa = (0.83 − 0.68/1.00 − 0.68) = 0.47.

Therefore the observed agreement not accounted for by chance (0.83–0.68) divided by the possible agreement not accounted for by chance (1.00–0.68) is 0.47 (kappa).

Evaluation of the clinical value

For the evaluation of the clinical value of the initial bone scans their number had to be reduced from 842 evaluable primary scans to 682, since only those were the patients who had been scanned less than 30 days before or after the operation. The excluded 160 patients were scanned at a later date.

Table 6 shows that 13% of the patients entered postoperative therapy protocols as belonging to group I and the same percentage entered group II in spite of having scintiphotos of grade 2 or 3, i.e. these 69 patients showed no bone metastases at roentgenograms. Only 5 out of 682 patients had X-ray-verified bone metastases, and they all except one were among 48 patients with multiple foci. Four out of 9 patients with other initial metastases had positive scintiphotos, although their X-ray photo was without signs of bone metastases.

The prognostic value of the initial bone scan can be evaluated from Table 7. After 30 months of observation of the 1978 cohort a total of 33 out of 530 patients had developed X-ray-visible bone metastases (6,2%). Only 2 of these had initial bone scans of grade 2 and another 2 patients had scans of grade 3. Out of the 33 patients developing bone metastases, 6 were among the 283 patients with supposedly good prognosis (2.1%) and 27 were among the prognostically inferior group of 247 patients (10.9%). X-ray-visible bone metastases arose during the observation period randomly among the patients, independent of the grade of the initial bone scans and without relationship to the number of 'hot spots' in the cases of positive scans. The recurrence rate outside the skeleton was statistically significantly higher in low-risk patients (group I patients) with grade 2 and 3 scintiscans than in those with non-suspicious scans ($P < 0.05$). The death rate at 30 months showed the same trend. But in the high-risk group the early scintigrams did not add to the distinction. When referring to Table 7 it should be mentioned that the recorded osseous recurrences add up only to a minimum value. This is because bone metastases were not recorded when they occurred after the patients went off study for other reasons.

Table 8 shows that there was a highly significant positive correlation between the age of the patients and the number of positive initial scans.

Table 6. Scintigraphic grading and patient category

Patient category	Grading (re-reading group) 0	1	2	3	Total	Percentage 2+3 of total*
In protocol						
Group I	210	37	21	15	283	13
Group II	185	29	20	13	247	13
Not in protocol						
X-ray-verified bone metastases	0	0	0	5	5	100
Other metastases	4	1	2	2	9	44
Other reasons	98	22	7	11	138	13
Total	497	89	50	46	682	14

*Patients with initial bone scans grade 2+3 in percentage of the total number of patients in the group. Scintigraphic grading by the re-reading group of the initial scan compared with inclusion and exclusion from protocols according to official clinical criteria (Table 1).

Table 7. Bone recurrences, total recurrences and deaths among 530 patients after 30 months of observation

		Scintigraphic grading						
		Protocol group I			Protocol group II			Group I+II
		0+1	2+3	Total	0+1	2+3	Total	Total
No. of patients		247	36	283	214	33	247	530
X-ray bone	No.	4	2	6	25	2	27	33
recurrences	%	2	6	2	12	6	11	6
Total	No.	44	14	58	66	8	74	132
recurrences	%	18	39	20	31	24	30	25
		$P < 0.05$						
Deaths	No.	10	5	15	42	5	47	62
	%	4	14	5	20	15	19	12
		$P < 0.05$						

Table 8. Age and scintigraphic grading (re-reading group)

	Grading					
	0 and 1		2 and 3		Total	
Age	No.	%	No.	%	No.	%
≤ 49	166	97	6	3	172	100
50–59	149	87	23	13	172	100
60–69	158	84	31	16	189	100
≥ 70	113	76	36	24	149	100
Total	586	86	96	14	682	100

$\chi^2 = 29.4$; d.f. = 3; $P \ll 0.001$.

Table 9 shows that initially, 12% of the patients with breast tumors of less than 5 cm were scintigraphic grades 2 and 3, whereas 21% of the patients with larger tumors belonged to these groups ($P = 0.05$).

There was no correlation between axillary lymph node involvement and initial scintigraphic grading (Table 10) or between the degree of tumor anaplasia as assessed according to WHO's recommendations [4] and the results of the initial bone scans (Table 11).

DISCUSSION

Radioisotope bone scanning for staging and control of breast cancer patients has been advocated by some [5–15] and discouraged by others [16–21]. The present nationwide and representative material is in many ways comparable to that published in 1978 by The British Breast Group on bone scanning [22]. The frequency with which the 8 participating British centres observed initial positive bone scans

Table 9. Tumor size and scintigraphic grading (re-reading group)

	Grading					
	0 and 1		2 and 3		Total	
Size of tumor	No.	%	No.	%	No.	%
≤ 5 cm	473	88	65	12	538	100
> 5 cm	61	79	16	21	77	100
Total	534	87	81	13	615	100

$\chi^2 = 3.5$; d.f. = 1; $P = 0.05$.
In 67 patients the tumor size was not recorded.

Table 10. Axillary lymph node involvement and scintigraphic grading (re-reading group) in 545 patients

No. of tumor-positive lymph nodes	Grading 0 and 1		2 and 3		Total	
	No.	%	No.	%	No.	%
0	264	85	45	15	309	100
1-3	143	87	22	13	165	100
≥ 4	60	85	11	15	71	100
Total	467	86	78	14	545	100

In 137 patients no information was available as to the axillary lymph node status.

Table 11. Tumor anaplasia (WHO) and scintigraphic grading (re-reading group)

Anaplasia	Grading 0 and 1		2 and 3		Total	
	No.	%	No.	%	No.	%
I	165	84	32	16	197	100
II	245	86	40	14	285	100
III	56	87	8	13	64	100
Total	466	85	80	15	546	00

In 136 patients the grade of anaplasia was not recorded.

had a surprisingly large variation, ranging from 1.9% to 20.2%. The re-reading procedure carried through in the present work to a certain extent allows an explanation of this discrepancy, namely that local criteria of interpretation will vary if not coordinated. Still, the difference between the 12 Danish centres, and between the centres and the re-reading group did not amount to that of the British group by far. Nevertheless, the discordance between the local departments and the re-reading group was unsatisfactory, and shows that the technique and the evaluation must be standardized and optimized if bone scans shall be useful and not mistrusted. Even when these demands are fulfilled, this study leaves some puzzling questions as to what are the reliable criteria for osseous metastases and what are the clinical consequences of using such 'true' criteria.

The material does not allow calculation of the false-negative rate. The problem is with the rate of unspecific scans which cannot be calculated. At time of surgery, 5 had X-ray-verified bone metastases among the 46 with grade 3 scans. The scans were compared with roentgenograms since bone biopsies were not obtainable for obvious reasons. This comparison, however, yields too high figures for false-positive scans considering that bone X-rays may reveal osseous involvement much later than bone scans [6], and only when as much as 50% of the mineral content has been displaced by the malignant tissue. Furthermore, considering that about 1/4 of all breast cancer patients [23, 24] and most of all those with positive regional lymph nodes [25, 26] have distant metastases, with the skeleton being the most frequent site of location, it is remarkable that only 5 patients out of 682 had initial positive roentgenograms. In view of the finding of others [14, 15] that 20% of breast cancer patients develop positive bone scans during the first 2 years following operation, it is also remarkable—and presumably not reflecting reality—that only 6% went off study due to X-ray-verified bone metastases during a 30-month observation period. All this suggests that bone scanning may overestimate the number of bone metastases, while routine roentgenograms may underestimate it. It might be argued that bone metastases might have been X-ray-verified in some of the 99 patients (132–33; Table 7) after they went off study due to recurrences in other anatomical sites specified by the clinician at a questionnaire at the off-study card. This introduces a bias that cannot be overcome due to the design of the clinical study. Table 4 indicates that the scan-

ning gammacamera yields positive scans at a lower and maybe more probable frequency than do other scanning devices. The 7% grade 2 and 7% grade 3 initial bone scans found in this study (Table 6) may thus be too many, but the figures fit with data from more recent reports [8–11, 13, 14, 17, 18] stating initial positive bone scan frequencies between 2.3 and 6%. These figures are much smaller than those first reported, indicating that about 1/4 of all patients had bone metastases at the time of operation [5, 6].

It is remarkable that the initial bone scan correlated significantly only to the age of the patients and the tumor size, and not to other data registered at the time of operation. The initial bone scans might seem of less prognostic value with respect to disease progression in soft tissue and life expectancy than the clinical staging at the time of operation. However, this is not quite so. A more profound interpretation of Table 7 might be that the patients which by other parameters were judged to belong to the low-risk group fared no better than the high-risk group when their grade 2 or 3 initial scan was taken into consideration.

The reason why others have found a much stronger correlation between bone scans and prognosis than we have might be that our study covers a completely unselected 1/4–1/3 of the nation's patients. Others judge from a smaller and possibly more selected material. In favour of this explanation is the fact that, for example, Galasko [6] shows a good relationship between bone scan and prognosis, although as many as 12 out of his 50 patients had initial bone lesions.

In spite of the shortcomings mentioned above, a good-quality and correctly interpreted initial bone scan is of value in the primary staging of the patients as a guidance for elective X-ray examination of suspicious sites with refined techniques. It is also of value for comparison with follow-up scans performed at regular intervals [12, 14] or for clinical reasons [27], since a change from a normal initial to an abnormal later bone scan may be indicative of osseous metastases, when the clinical history does not suggest other types of skeletal affection.

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