A re-evaluation of isotope screening for skeletal metastases in node-negative breast cancer

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Objective. To determine the accuracy and cost-effectiveness of skeletal scintigraphy in women with early, node-negative ($T_{1-2}N_0M_0$) breast cancer.

Design. Retrospective, where scintigraphic prediction of metastases was compared with the criterion standard of radiological confirmation during a follow-up of 5 - 10 years.

Setting. Tertiary referral breast clinic at Groote Schuur Hospital.

Patients. Six hundred and seventy-three women with clinical $T_{1-2}N_0M_0$ breast cancer who had skeletal scintigraphy between 1974 and 1987, and who had been followed up for more than 5 years.

Interventions. Initial skeletal scintigraphy, annual follow-up with radiological examination of symptomatic areas.

Main outcome measures. Correlation of the sites indicated by scintigraphy with the initial presence or later development of metastases at 1 - 10 years, and the cost.

Results. Five hundred and sixty-one (83.4%) scans were normal, 35 (5.2%) indicated benign processes, and 77 (11.4%) were suggestive or diagnostic of metastatic disease, with radiological confirmation in 3 (initial detection rate 3/673, 0.44%; accuracy rate 3/77, 3.9%). Of the remaining 74 abnormal scans without radiological confirmation of metastases, 62 had a focus at a single site, and 45 were of low intensity and equivocal, with no apparent explanation. The cumulative sensitivity for predicting site of metastases at 1 year was 33% (3/9) and the positive predictive value 4.0% (3/75). At 10 years the sensitivity was 5.0% (3/60) and the positive predictive value 5.0% (3/65). The total cost of screening was calculated to be R323 460.00, suggesting that the cost for each patient in whom metastases were detected was R64 629.00.

Conclusion. While scintigraphy may be of value in symptomatic or more advanced disease, screening of node-negative women had a minimal detection rate, was expensive and cannot be supported.

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Breast cancer is a leading cause of death in women worldwide. Successful management of the disease requires accurate staging, estimation of prognosis and selection of therapy appropriate for stage. Therefore, a detailed knowledge of the extent of the loco-regional disease is necessary together with information whether distant metastases are present or not. The major sites of metastatic spread are the skeleton, lungs, pleura and liver. Skeletal scintigraphy remains the most common screening test for asymptomatic skeletal metastases, and its superiority over radiography is well established.[1] Despite this, after having enjoyed initial enthusiasm and support as a baseline screen,[2-4] scintigraphy has subsequently been criticised for having a low rate of detection.[5-7] Nonetheless, the test remains in use in many academic units, and is used with increasing frequency in the private sector.

The cost of skeletal scintigraphy is rising each year and the cost-effectiveness of using such a test in women with apparently early breast cancer is an important factor for evaluation. This study was therefore designed to determine the sensitivity and specificity of skeletal scintigraphy for the detection and prediction of metastatic disease in women with early breast cancer, as well as to calculate its cost-effectiveness.

Patients and methods

Patient selection

We retrospectively examined the records of 1 168 female patients with histologically proven breast cancer who had been clinically staged as having $T_{1-2}N_0M_0$ disease. These women had presented to the Groote Schuur Hospital breast clinic between January 1974 and December 1987. We excluded 165 as their records were incomplete. Out of the remaining 1 003, skeletal scintigraphy was performed in 673 patients, who constituted this study group. Skeletal scintigraphy had not been performed in certain patients for the following reasons: 131 were older than 65 years (the policy of the clinic was not to perform scans in patients older than 65 years as osteo-arthritis and similar conditions are common in this age group and may give rise to false-positive results); 133 were assessed between 1974 and 1978 when scanning was not performed routinely; 48 patients had skeletal scintiscan taken by a private radiologist before attending and 18 patients declined the investigation.

Skeletal scintigraphy

The skeletal scintiscans were taken pre-operatively and the results evaluated before surgery. Between 1974 and 1979, a rectilinear scanner was used, the views taken being limited to the spine unless otherwise indicated; between 1980 and 1987 patients were scanned with a whole-body Elscint gamma camera that gave anterior and posterior whole-body views. The isotope technetium-99 m (^{99m}Tc) medronate was used in doses of 740 MBq (20 mCi) and the scans were interpreted by the Department of Nuclear Medicine. The diagnostic outcome of the bone scan was evaluated as normal, benign (radiological evidence of a benign lesion), suspicious of metastatic disease (asymmetrical uptake with normal radiographs) or metastatic disease when there was radiological confirmation of this.

Calculations

Possibilities of outcome were analysed on a conventional decision tree. Costs were calculated in South African rands using the 1991 tariffs of the MASA[8] (skeletal scintigraphy R411, radiograph R83, hospital visit R55). MASA tariffs were used as they were felt to be economically more reliable than state-subsidised hospital tariffs. Hidden expenditure such as staff training, equipment maintenance and the use of raw materials are then directly included in the assessment.

Results

The scans were normal in 561 (83.4%) patients, various benign conditions were reported in 35 (5.2%), and metastatic disease suggested in 77 (11.4%) (Table I). There was radiological confirmation of metastases in 3 patients, all of whom had lesions at multiple sites, particularly in the skull, ribs, pelvis and spine. The radiologically confirmed detection rate was therefore 0.44% (3/673) and the accuracy rate was 3.9% (3/77). In 74 patients the scans were abnormal, but lacked radiological confirmation of metastases. The majority of these scans had a focus at a single site, and in 45 instances the focus was of low intensity and equivocal (Table II). There was no explanation for the abnormal scans.

Table I. Initial skeletal scintigraphic result with radiological diagnoses

Normal	561 (83.40%)
Benign	35 (5.2%)
Osteo-arthritis	21
Artefact	5
Paget's disease	2
Trauma	3
Spondylolisthesis	1
Hyperostosis	1
Vascular anomaly	1
Metastases	77 (11.40%)
Total	673

Table II. Subsequent development of metastases over 10 years in the three groups of patients whose scans were reported as normal, suggestive of benign disease or suggestive of skeletal metastases

	Years											
	0	1	2	3	4	5	6	7	8	9	10	Total (%)
Normal	561	4	11	12	8	4	4	5	3	1	2	54 (9.6)
Benign	35	-	1	-	2	-	-	-	-	-	-	3 (8.6)
Metastatic	77	2	1	4	2	-	-	1	-	2	-	12 (16.2)
Total	673	6	13	16	12	4	4	6	3	3	2	69 (8.7)

In addition to the initial 3 patients who had metastases correctly identified by scintigraphy, a further 6 women developed skeletal metastases after 1 year (Table III), having presented with localised pain and having had metastases confirmed by radiography of the area concerned. Four of these had previously had normal scintiscans and 2 had had scintiscans that had reported metastatic disease (but without radiological confirmation of it). In both the latter patients, the bone metastases developed at different sites (right acetabulum, dorsal spine) from the suspicious areas initially reported (left greater trochanter, lumbar spine). Thus at 1 year the test had a cumulative sensitivity of 33% (3/9), a specificity of 89% (592/664) and a positive predictive value of 4.0% (3/75).

Sixty-nine women had developed skeletal metastases by 10 years. Fifty-four of them had had normal scintiscans previously. In a further 3 patients both the scintiscans and radiographs had confirmed benign lesions, and in each case the metastases developed away from that site. Twelve patients had an initial scintiscan that had shown metastatic disease, but without radiological evidence of disease at that time. In 3 instances metastases developed in those areas that were regarded as scintigraphically suspicious. However, in each of these 3 cases there was a diffuse distribution of metastases and the previous localised report of abnormality may have been a coincidence and not a predictive factor. The metastases developed at 2, 3, and 4 years respectively after the initial scintigraphic report of metastatic lesions. Therefore, at 10 years the sensitivity was 5.0% (3/60), the specificity 90.0% (539/601) and the positive predictive value 4.6% (3/65).

A decision tree analysis (Fig. 1) demonstrated that the most common pathway was a normal scan and for no metastases to develop within the first year (probability 0.827). Less common pathways were for the development of metastases with a normal scan (4 patients, probability 0.006), and with an abnormal scan (5 patients, probability 0.16). The total cost of reassurance (path I) was R259 562.00, the cost of missing metastases (path 2) was R2 196.00, the cost of concern (path 3) was R58 743.00. The apparent cost of detecting metastases (path 4) was R2 745.00. Overall, the real cost was R64 692.00 per patient in whom metastases were detected.

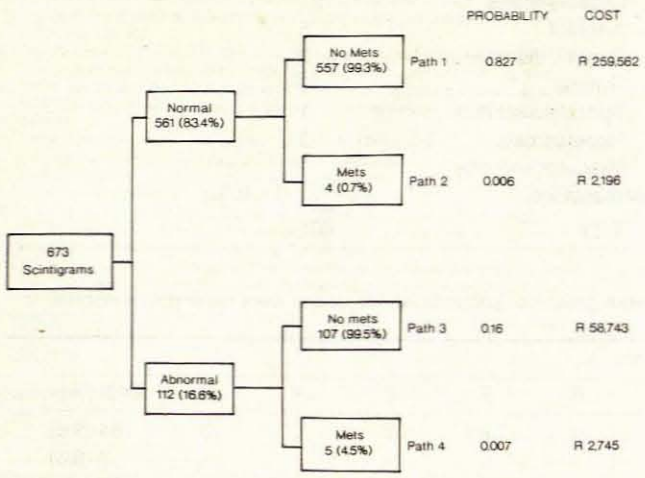

Fig. 1. Decision tree calculating outcome probabilities of bone scan results.

Discussion

We found the detection rate of skeletal metastases by skeletal scintigraphy to be negligible in women with apparent node-negative breast cancer. This has also been the experience of others.[7,9,10] This is partly to be expected, as such women have a true low incidence of metastases, the likelihood of their development being 20% at 10 years.[11] Therefore, even if scintigraphic screening had an absolute sensitivity and specificity for metastases, the frequency of a positive test would be low in any event. We feel that it is unlikely that among those patients excluded because of incomplete records, there could have been some who were scanned and who had metastases detected. No one has been able to confirm Galasko's initial 1974 report[2] of a 24% detection rate of metastatic bone disease in early breast cancer. The Danish Breast Cancer Co-Operative Group[12] and the Scottish Breast Group[13] found higher detection rates than ours — of the order of 5% — but their analyses included stage 2 and operable stage 3 disease. The data from this study have shown not only a low detection rate (sensitivity) for metastatic disease but also a moderate specificity and a very low positive predictive value. Only 3 patients obtained direct diagnostic benefit from the initial screening tests and were spared inappropriate surgery or radiotherapy.

The low specificity and high false-positive diagnostic rate of skeletal scintigraphy present a serious clinical problem. Where there is radiological support for the diagnosis of metastases, appropriate therapeutic decisions may be taken. It is clear, however, that on occasion true metastases may be detected scintigraphically, but be radiologically confirmed. The clinician is therefore faced with the dilemma of regarding a scintigraphic abnormality either as occult metastatic disease (without radiological evidence) or as falsely positive. The latter would seem to be the wise conclusion in the context of screening for metastases in node-negative women.[7]

Constraints are being placed on hospital and medical aid expenditure worldwide. There has been a focus on appropriate and cost-effective spending of limited resources and, in this context, tests that provide results that cause negligible treatment changes are of questionable value.[14] *While we have undertaken a simple costing exercise that used only three components, we feel that it does make a strong point, and may even underestimate the cost.* The high cost of scintigraphy, when calculated for the number of patients in whom metastases were detected, has been pointed out by others.[13] Metastatic screening using skeletal scintigraphy therefore has a very low yield in women with node-negative breast cancer, is very expensive, may adversely affect quality of life and cannot be justified. This does not minimise the value of scintigraphy in more advanced disease (stages 3 and 4) or in patients with unexplained bone pain.

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