metoprolol, however, a dissociation between its lipolytic and cardiac actions was noted.

These results indicate therefore differences in the metabolic effects of metoprolol, acebutolol, and propranolol but give no insight into the mechanisms concerned.

Attempts to reduce blood lipid levels in patients with hyperlipaemia with beta-adrenoceptor antagonists have yielded inconsistent results.^{13 14} Carruthers and Taggart¹⁵ have shown, however, that oxprenolol suppresses the rise in free fatty acid concentrations that occurs in response to stress. Prolonged treatment with beta-adrenoceptor antagonists might therefore serve to control lipid metabolism and minimise its atherogenic potential. To investigate this would require long-term studies and, as yet, none have been performed. The findings of this study therefore suggest that, should such a trial be undertaken, acebutolol and propranolol may show a greater therapeutic effect than metoprolol.

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Staging breast cancer: role of bone scanning

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Summary

Bone scans using technetium-99m phosphate complexes and a rectilinear scanner were carried out on 192 women with primary operable breast cancer four to six weeks after operation. The lymph node status of all these patients was assessed histologically from triple node biopsy specimens. Only nine patients had positive scans, although 94 patients had histological evidence that the tumour had already spread beyond the confines of the breast.

Bone scanning, although accurate as a prognostic guide, is helpful only in a very few cases, and serves mainly to confirm prognostic information obtained more simply and less expensively by histological examination of lymph node biopsy specimens.

Introduction

Many women presenting with apparently early "curable" breast cancer die prematurely from their disease.¹ Such women probably have foci of disseminated carcinoma at the time of their primary treatment. There is an urgent need to be able to detect spread of the tumour beyond the confines of the breast, as an essential prerequisite of any plan of treatment is the accurate staging of the disease. If there is evidence of disease beyond the confines of the breast local treatment of any sort is unlikely to influence the outcome with respect to survival.

The study reported here was designed to assess the contribution that bone scanning can make to the original assessment of a patient with apparently early carcinoma of the breast. We attempted to answer the following questions: Does bone scanning help to stage the disease? Is it a reliable prognostic guide? How useful is it compared with that method of staging based on lymph node histology?

Patients and methods

One hundred and ninety-two patients with primary operable breast cancer were studied. They presented over a three-year period at the breast clinic of the university department of surgery in Nottingham. Patients presenting with locally advanced breast cancer for whom mastectomy was thought to be inappropriate were excluded from this series. Although the patients were not staged by the TNM classification, the excluded group broadly corresponded to patients with T3 lesions. Patients who, because of age and tumour site, were treated by a wide local excision of the tumour rather than by mastectomy were also excluded.

The surgical treatment took the form of a standard simple mastectomy with triple node biopsy. After the breast had been removed, lymph nodes were sampled from (a) the low axilla just below the lateral border of pectoralis minor; (b) the apex of the axilla, which was

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approached from below the clavicle by splitting the fibres of pectoralis major and dissecting in the fat adjacent to the axillary vein; and (c) the internal mammary chain, which was usually approached through the second intercostal space. These lymph nodes and the breast were then subjected to histological examination.

All specimens were fixed in 10% phosphate buffered formalin. Paraffin sections were cut at 4-5 μ m and stained with Ehrlich's haematoxylin and eosin. All sections were examined by one pathologist. Lymph nodes containing metastatic tumour were considered to be positive, and nodes were considered to be negative when examination of several sections showed no tumour. The tumours were staged A, B, or C according to the lymph node histology: stage A, tumour confined to the breast; stage B, tumour in low axillary lymph node; stage C, tumour in apical or internal mammary lymph node, or both.

The bone scan and a skeletal survey using conventional radiography were performed within six weeks of mastectomy. The skeletal survey consisted of the following films: chest radiograph; lateral view of skull; anteroposterior and lateral views of cervical, thoracic, and lumbar spine; and pelvis to include upper femora. The scans were done on an Ohio Nuclear 84FD rectilinear scanner using 35L collimators, 5:1 minification, and an information density of 400 counts/cm² in the region of the dorsal spine. The patients were investigated three to four hours after a 10-mCi intravenous injection of technetium-99m-labelled phosphate complex. The first 95 patients received polyphosphate (New England Nuclear) while the remaining 97 patients received diphosphonate (Osteoscan, Procter and Gamble). The presence of an area of increased uptake on a bone scan is not diagnostic of a metastasis.² Other lesions cause areas of increased uptake of the isotope, and conventional radiography may show many of these abnormalities. The scans were therefore initially assessed by one of the consultant radiologists and the medical physicist without knowledge of the skeletal survey and then both used the additional information from the conventional radiographs to produce the final assessment of the scan. These were reported as negative, equivocal, or positive. A positive scan was defined as one where there was a significant increase in activity and where the plain radiographs did not show a benign lesion at the corresponding site. An equivocal scan was diagnosed when a slight variation from normal was detected.

These patients were followed up in the postmastectomy clinic. Patients underwent a full clinical examination every three months and routine blood tests every six months. Additional investigations (blood tests, radiographs) were carried out when they were indicated. A patient was regarded as having a recurrence if she developed symptomatic disease demanding a radical alteration in treatment policy, such as the introduction of deep x-ray therapy, endocrine therapy, or chemotherapy.

Results

All 192 patients studied had histologically confirmed invasive carcinoma of the breast.

Bone scans—Only 9 patients (5%) had positive scans. Fourteen had equivocal scans and the remaining 169 patients had negative scans. The 169 negative scans included five with a grossly abnormal pattern, which was explained by the signs of Paget's disease on conventional radiographs. These scans were therefore regarded as negative. None of the five patients developed evidence of metastatic disease. All the patients were taking part in a study of sequential scanning at various time intervals (this will be the subject of a further report). So far only one of the 14 patients whose original scan was reported to be equivocal has had a subsequent positive scan, so in the following discussion an equivocal scan has been regarded as being negative. With increasing experience fewer scans have been classified as being equivocal.

Lymph node histology—The results of the lymph node biopsies are shown in table I. Almost half (49%) the patients had histological evidence of metastatic tumour in the regional lymph nodes.

TABLE I—Lymph node status and bone scan results in 192 women and results of follow-up

	Histological stage			Bone scan	
	A	B	C	Negative	Positive
No of patients	98	56	38	183*	9
No with recurrence	9	17	24	42	8
No who died	4	6	14	20	4

*Includes 14 women who had equivocal scans (see text).

Follow-up—The patients were followed up for nine months to three years. Fifty patients suffered from major symptomatic recurrent disease. The results of the follow-up studies are shown in table I, where the results of staging by lymph node histology and by bone scanning are compared. Of the nine patients with positive bone scans at the time of mastectomy eight developed symptomatic metastatic disease and four of these patients died. Only one of the nine patients was alive and well without symptomatic evidence of metastatic disease at the time of writing. Follow-up scans on this patient were normal and it seems, therefore, that her original scan was a false-positive. Forty-two of the 183 patients (23%) with negative bone scans also suffered from symptomatic recurrent disease; indeed nine of them had clinical evidence of bone metastases. In contrast, only nine of the 98 patients (9%) with negative findings on lymph node histology experienced a symptomatic recurrence. Evidence of recurrent disease was found with increasing frequency as the degree of lymph node involvement at the time of mastectomy increased—for example, 17 (30%) of the 56 women with stage B histology and 24 (63%) of the 38 with stage C had recurrent disease.

Discussion

Bone scanning is more sensitive than conventional radiology for detecting skeletal metastases.³ Galasko⁴ showed that all his original 12 patients with operable breast cancer and positive bone scans developed metastatic disease within five years of mastectomy. Our results confirm that a positive bone scan accurately predicts an extremely poor prognosis. Galasko⁴ also stated that "skeletal scintigraphy would appear to be the method of choice for staging mammary carcinoma." The usefulness of any staging device, however, depends not only on the accuracy with which it discriminates between various prognostic groups but also on the numbers of patients it is able to separate out into these groups. It should be noted therefore that in Galasko's series 10 out of 38 patients with negative scans at the time of mastectomy also developed disseminated carcinoma within five years. In our series bone scanning identified eight of the 50 patients who suffered from symptomatic recurrent disease. It failed to identify 42 of these patients, nine of whom eventually developed symptoms and signs of bone metastases. It therefore compared badly with the histological method, which predicted 41 out of the 50 cases of symptomatic recurrent disease. Furthermore, if staging by lymph node histology is used as the basis for the formation of a prognostic index incorporating two other simple values—tumour grade and tumour size—an even greater degree of accuracy can be achieved (for publication).

The reported incidence of positive bone scans in patients with early breast cancer has varied greatly.⁵⁻¹⁰ Galasko³ found a 24% incidence of positive scans in a series of patients with T1 and T2 tumours, whereas Green *et al.*⁶ using a similar technique, reported an incidence of positive scans of only 4%. The incidence of positive bone scans in our series is less than that reported by several other workers. But unpublished data from other centres (British Breast Group, October 1976) show results similar to ours. It is unlikely that these differences are accounted for by the use of different techniques. The difference may lie in the selection of cases included in the various series. Some series have included patients referred to several clinicians and they may have been assessed in different ways. Our series consisted of consecutive patients referred to one surgeon. They were assessed and treated in a standard way. The inaccuracies of clinical staging were avoided by using the more accurate method of pathological staging. Only by using such objective methods of staging can series of patients be accurately compared.

In a retrospective study of 321 patients with potentially curable invasive breast cancer¹¹ only 19% showed bone metastases during the 10 years of follow-up. The chance of developing bony metastases was closely related to the patient's histologically assessed lymph node status.

The arguments surrounding the two methods of staging would be superfluous if it were shown that they were identifying different groups of patients. Unfortunately this does not seem

to be the case. The incidence of positive bone scans in the groups of patients classified according to their lymph node status is shown in table II. There was a very low pick up rate among patients with no tumour in the lymph nodes or with tumour confined to the low axilla only, but 16% of the patients with extensive lymph node disease had positive scans. In fact two-thirds of the positive scans were found in patients with stage C tumours. Of the nine patients with positive bone scans, seven also had tumour in the regional lymph nodes and would therefore have been identified histologically as having a poor prognosis. One of the two remaining patients had a false-positive scan (subsequent scans were normal) and the other died. Thus, of the total series of 192 patients, only one patient with a grave prognosis was identified exclusively by bone scanning.

The results of this study cast serious doubts on the value of bone scanning in the initial assessment of patients with apparently early breast cancer. It is an expensive method of

TABLE II—Numbers of positive bone scans according to tumour stage assessed histologically

Stage:	A	B	C
No of patients	98	56	38
No with positive bone scans	2	1	6

confirming information that is more simply obtained by regional lymph node biopsy.

This work was first reported to the British Association for Surgical Oncology in London in December 1976.

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Blood glucose control and glomerular capillary basement membrane thickening in experimental diabetes

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Summary

Glomerular capillary basement membrane thickness (BMT) was measured in 23 rats which had had streptozocin-induced diabetes for 14 months and in 12 age-matched controls. Diabetic rats were randomly allocated to different groups, either receiving no treatment or treated with a low carbohydrate diet or insulin, or both. Control rats were randomly allocated to a normal or low carbohydrate diet.

Among the diabetic rats mean plasma glucose concentrations for the groups ranged from 27.4 mmol/l (494 mg/100 ml) in the untreated rats to 9.8 mmol/l (177 mg/100 ml) in those receiving both a low carbohydrate diet and insulin. A highly significant positive relation was found between BMT and plasma glucose concentration for individual rats. When BMT was corrected for body weight a similar relation was observed.

These data indicate that hyperglycaemia is the main determinant in the development of basement membrane thickening.

Introduction

Despite improvements in health care vascular complications of diabetes mellitus create increasing morbidity and mortality.¹ For example, diabetic retinopathy is the commonest cause of blindness under the age of 65.² Whether or not good diabetic control delays or prevents these complications is a question that remains unanswered. There is evidence that the structural changes in diabetic microangiopathy can result from hyperglycaemia.³ The first detectable lesion in the kidney is thickening of the glomerular basement membrane, which is the forerunner of more advanced disease that eventually leads to renal failure.⁴ Clinical studies have so far failed to determine the effect of diabetic control on the development and progress of nephropathy. Randomised clinical trials in man would be lengthy, expensive, and probably unethical. For these reasons we studied the effects of diabetic control on basement membrane thickening in rats.

Methods

Structure of colony—Male Wistar rats (mean body weight 290 g) were given streptozocin 25 mg/kg intravenously in citrate buffer, pH 4.4, when they were 11 weeks old. Age-matched controls were injected with buffer alone. Eight weeks later capillary blood was taken from these rats in a fed state for measurement of plasma glucose

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