Preoperative assessment and staging of breast cancer: preliminary communication[1]

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Summary: A prospective study has been carried out in 172 women to determine the sensitivity of methods to detect occult metastatic disease in the skeleton and liver. With the exception of bone scintiscans, the results of these tests bore little relationship to recurrence rates. On the other hand, knowledge of the histopathology of the lower axillary (pectoral) lymph nodes is of value in this respect.

A follow-up study is also reported which confirms the importance of accurate measurements of the primary tumour clinical node status and oestrogen receptor contact of the tumour in defining prognostic groups. Elastosis (estimated in 165 tumours) did not prove to be a useful prognostic index.

Introduction

It is now recognized that when a patient with breast cancer first presents for treatment, the disease is frequently already systemic. So also is it accepted that in the future, systemic treatment, by endocrine or chemotherapeutic means, may become routine in the primary management of the disease. Therefore it is increasingly important to detect which patients presenting with primary disease have already got systemic metastases and therefore disease which is likely soon to recur.

In this paper we present an update of our study to evaluate methods of detecting occult metastatic disease (Cant *et al.* 1977, Forrest *et al.* 1979); and also some preliminary data on a study of other prognostic factors.

Edinburgh superstaging study

In 1974 a prospective study was set up to determine whether those investigations then available for the detection of abnormalities in the skeleton or liver increased the sensitivity of detecting occult metastatic disease in these sites. We included consecutive patients treated on our unit, with operable breast cancer (UICC stages I, II, and operable III) and with negative chest and pelvic X-rays. Following confirmation of the diagnosis by Tru-cut needle biopsy, patients were admitted to an assessment unit for four days for investigation by a standard regime. This included, for the detection of bone metastases, a skeletal scintiscan with ^{99m}Tc-hydroxyethylidene disodium phosphate or ^{99m}Tc disodium etidronate stannous chloride and a NE mark IV gamma camera; 24-hour outputs of urinary hydroxyproline while taking a gelatin-free diet and estimations of serum alkaline phosphatase and, if abnormal, its bone isoenzyme. For the detection of liver metastases we used hepatic scintigraphy with ^{99m}Tc-sulphur colloid, estimates of serum gamma glutamyl transpeptidase (gamma-GT) alkaline phosphatase and, if abnormal, its liver enzyme. Details of these tests have been fully described elsewhere (Cant *et al.* 1977, Forrest *et al.* 1979).

When a scan was reported as abnormal this was reviewed by two of the original investigators along with appropriate skeletal X-rays. Abnormal values for the other tests were defined by studying normal women of similar age (Cant 1979). These were set for urinary hydroxyproline

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at $\geqslant 33.0$ mg total output per 24 hours and/or $\geqslant 31.0$ mg per gram creatinine; for gamma-GT at $\geqslant 35$ units per litre and for alkaline phosphatase at > 100 units per litre.

The standard treatment for all patients were total mastectomy and axillary node sampling supplemented by radiotherapy if positive nodes was identified. One-hundred-and-sixty-eight of the first 172 patients were treated in this way; on account of age the remaining 4 patients were treated either by local excision of the tumour (3) or by radiotherapy alone (1). Axillary node sampling was an important part of the staging procedure. On original reporting, nodes were identified for histology only in 148 patients, 75 of whom had involved, and 73 non-involved lower axillary (pectoral) nodes. Nodes were not identified by surgeon or pathologist in 24 cases. Patients have been followed up at a special clinic where they were seen by one of us at intervals of four months for two years and then at six-monthly intervals.

This report is of the first 172 patients investigated between October 1973 and December 1977 and now followed up for at least two years. A review of the records of these 172 patients has been carried out (Black *et al.* 1980). The results of all tests have been checked and the progress of all patients at their most recent follow-up appointments have been reviewed to December 1979. A detailed study of lymph node histology was one of the objectives of this review and sections of those lymph nodes which were sampled were seen by one of us (RBB) in all but 8 cases. It was then confirmed that 73 patients had proven lymph node involvement and 67 had histologically negative nodes. There remained 32 patients in whom nodes had not been identified at operation or on histopathology.

In the 73 patients with proven lymph node involvement, the degree of metastatic infiltration was assessed as being 20% or more of the gland involved (gross metastases), and less than 20% of the gland involved (micrometastases). This accounted for 60 and 13 patients respectively.

Results

The recent review confirmed our previous report (Forrest *et al.* 1979) that 53 (31%) of these 172 patients had at least one test positive and therefore suspected occult metastatic disease. In 40 (23%) the abnormality suggested the possibility of bone disease, and in 21 (12%) the possibility of liver disease. Recurrence and death rates continue to be the same in these two groups (Table 1).

Table 1. Comparison of recurrence and mortality in those patients with suspected metastatic disease at the time of primary treatment and those whose tests were negative

		Recurrence			
	No. of patients	Local only	Disseminated ±local	Total	Died with recurrence
Suspected metastatic disease in bone, liver, or both	53	6	13	19 (36%)	12 (23%)
Metastases not suspected	119	6	35	41 (34%)	26 (22%)

The results of the individual tests are related to recurrence in Table 2, which gives details of site-related as well as total recurrences. The only tests of predictive consequence were the skeletal scintiscans and the biochemical detection of alkaline phosphatase of bone origin. However, the proportion of patients in whom these tests indicated an abnormality was small.

In our initial report (Forrest *et al.* 1979) we indicated that the results of these tests contributed little additional information over that derived from knowledge of node status. Thus only an additional 14% of patients (over the 44% with proven positive nodes) were suspected to have disease of bad prognosis. Table 3 gives the results of the recent review of histological lymph node status related to the incidence of recurrent disease. Substantial involvement of the lower axillary (pectoral) nodes at the time of primary treatment is of sinister prognosis and a better indicator of 'bad' disease than are results of the superstaging investigations. Conversely, involvement of nodes to less than 20% of their volume did not have an adverse effect on short-term recurrence.

Table 2. Incidence of site-related and total recurrence in those patients whose investigations at the time of primary treatment were suspicious of bone or liver metastases

	Suspicion of bone metastases			Suspicion of liver metastases		
		Recurrence			Recurrence	
	No.	Bone	Total	No.	Liver	Total
Nuclear scan:						
Positive	12	6	7 (58%)	11	1	4 (36%)
Negative	160	22	53 (33%)	161	19	56 (35%)
Alkaline phosphatase:						
Positive	10	3	5 (50%)	5	1	2 (40%)
Negative	162	25	55 (34%)	167	19	58 (35%)
Urinary hydroxyproline:						
Positive	26	5	8 (31%)			
Negative	144	23	52 (36%)			
Glutamyl transpeptidase:						
Positive				13	1	4 (31%)
Negative				158	19	56 (35%)

Table 3. Results of the review of axillary node histology in 172 patients related to the incidence of recurrent disease

		Recurrence		
Histology of pectoral nodes	No.	Local	Disseminated ± local	Total
Nodes not involved	67	4	7	11 (16%)
Nodes involved:				
Micrometastases	13	0	2	2 (15%)
Gross metastases	60	4	31	35 (58%)
Node state unknown	32	4	8	12 (38%)

Other prognostic indices

During the past year, a follow-up study has been carried out by one of us (VH) on 243 patients treated for primary cancer of the breast in this unit between December 1973 and December 1977; these included the 172 patients in the above study. All patients had 'operable disease' defined as TNM stages I, II and operable III. The staging of each patient by the 1974 TNM system was initially carried out by two observers, with measurements of tumour size by caliper. The TNM stage was further checked in all patients by one of us (HJS). When there was lack of agreement the findings represent the highest (most severe) stage.

All patients were treated by mastectomy and pectoral node sampling within the Edinburgh Breast Cancer Trials (Duncan *et al.* 1975) and have been followed up regularly by us. The date of first onset of recurrent disease (either local or systemic) has been recorded.

In all patients the tumour was assayed for oestrogen receptor activity. This was measured by a standard saturation analysis using dextran-coated charcoal separation and Scatchard analysis of the six-point assay. At that time our standard dividing point between receptor positive and negative tumours was 0.1 fmol/mg wet weight (Hawkins *et al.* 1975). One-hundred-and-sixty-five of these 243 tumours also had the extent of focal elastosis in their tumour graded by the simple 3-point system previously described (Masters *et al.* 1978).

Results

The results of this study are to be reported in full (Humeniuk *et al.* 1980*a*,*b*, in preparation). Some preliminary results are given in Figures 1–6. These show first that careful clinical

examination by more than one observer to include a measure of tumour size (Figure 1), and palpation of the axilla for enlarged nodes (Figure 2), does provide useful information of the time of recurrence and therefore of prognosis. Those patients with tumours greater than 2 cm in diameter and with palpably enlarged nodes have on average significantly shorter 'disease-free intervals' than those with small tumours and non-palpable nodes.

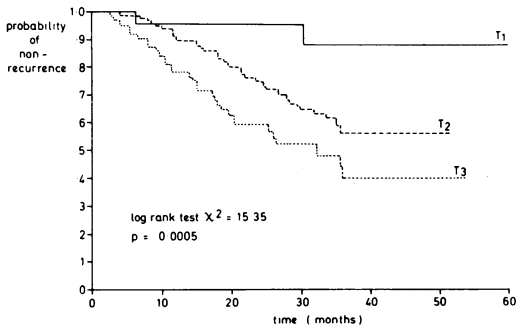

Figure 1. Relationship between freedom from recurrence (disease-free interval) and size of primary tumour in 243 patients with primary breast cancer

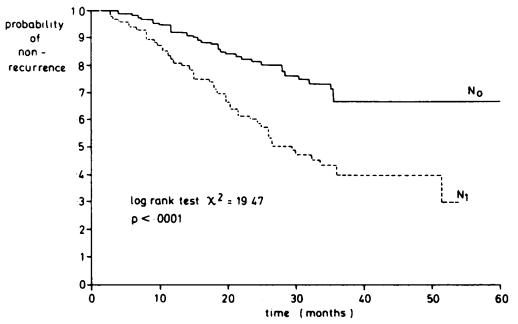

Figure 2. Relationship between disease-free interval and palpability of axillary lymph nodes in 243 patients with primary breast cancer

The relationship between oestrogen receptor activity and the disease-free interval is shown in Figure 3. This confirms that receptor-positive tumours have on average a better prognosis than those which are receptor negative. Our data also confirm that receptor activity is an independent prognostic variable to the histology of the axillary nodes (Figure 4). Thus the disease-free interval in patients with receptor-negative tumours which are not associated with histological evidence of node involvement is similar to that of those with receptor-positive tumours associated with histologically involved nodes. Patients with receptor-negative tumours and involved nodes have an uncommonly poor prognosis.

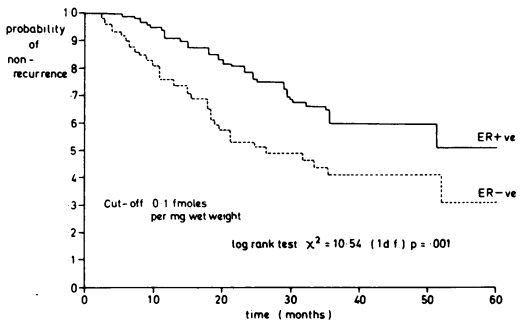

Figure 3. Relationship between tumour oestrogen receptor activity with primary breast cancer and freedom from recurrence of disease in 243 patients

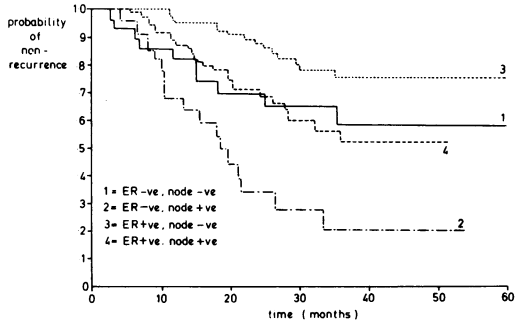

Figure 4. Relationship between oestrogen receptor activity, histological node status and freedom from recurrence in 243 patients with primary breast cancer

The relationship between receptor status and prognosis is not simple. By moving the 'cut-off point' separating receptor rich (positive) from receptor poor (negative) tumours from 0.1 to 0.5 fmol/mg wet weight, its prognostic value can be eliminated (Figure 5).

The relationship between elastosis and recurrence is shown in Figure 6. Only those tumours without elastosis (and this is a small proportion) show a trend towards more rapid recurrence. This trend was not statistically significant.

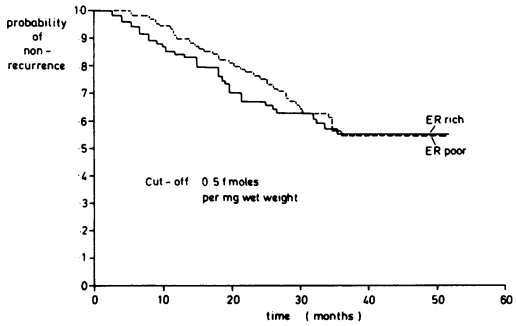

Figure 5. The effect of altering the 'cut-off point' between oestrogen receptor negative and oestrogen receptor positive tumours from 0.1 to 0.5 fmol/mg wet weight

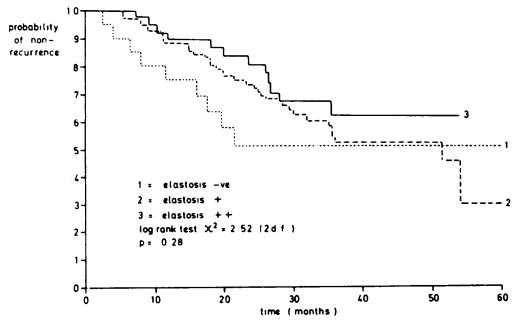

Figure 6. Relationship between the degree of elastosis in 165 breast tumours and freedom from recurrence following treatment for primary breast cancer

Discussion

The most common preoperative assessment of a patient with primary breast cancer is by the International TNM system. This was not designed as a method of determining the prognosis of the disease; its main objective was to facilitate the conveying of clinical experience to others without ambiguity (TNM 1978). Nevertheless, our studies confirm that a careful assessment of TNM stage by trained observers, with the measurement of tumour size and an estimate of the palpability of the axillary nodes, are significant prognostic indices.

At the same time, clinical staging has two main drawbacks. Firstly, the palpability of axillary nodes is an inaccurate guide to their involvement in about one third of cases (Wallace & Champion 1972). Secondly, clinical examination and radiology are not sufficiently sensitive to detect the small visceral or skeletal metastatic deposits which may be present. The introduction of pathological lymph node staging has largely counteracted the first; the second is still under study.

It was expected that the evolution of more sensitive methods of imaging and better biochemical tests would improve the detection of these small occult metastatic deposits, and so predict those patients destined to develop recurrence soon after primary treatment. Our findings in 172 patients who were fully investigated by a series of such tests suggests that this is not so. Only a positive skeletal scintiscan and a raised alkaline phosphatase have proved of value in detecting occult bone disease. However, the small proportion of patients in which these tests proved to be positive contrasts strikingly with the knowledge that 50% of patients with breast cancer have evidence of bone involvement at death (Willis 1948). Because of its low sensitivity, even a bone scan would not appear to be worthwhile as a preoperative investigation. This conclusion has also been reached by Bishop *et al.* (1979) and by Burkett *et al.* (1979). Further, the variability of interpretation of bone scans between centres is high (British Breast Group 1978).

Although it is suggested that better methods of imaging, e.g. with CT scans, may improve detection rates for occult metastatic disease, we have not found this to be so as far as CT brain scans are concerned. None of a consecutive series of 40 patients with primary operable breast cancer, or 8 patients with locally advanced disease without cerebral symptoms, had an abnormal scan even when contrast enhancement was used (Lewi *et al.* 1980).

It has now been shown that sequential biochemical testing of patients following primary treatment for tumour 'markers' may give a few months lead time on the clinical detection of metastatic disease (Coombes *et al.* 1980). However, better discrimination at the time of primary treatment must still be our aim; and attention is also turning to tumour characteristics.

Histological and nuclear grade, contour, the degree of lymphocytic infiltration and of reactive hyperplasia in the regional lymph nodes are well established biological determinants of prognosis. Two of recent interest are oestrogen receptor status (Walt *et al.* 1976, Knight *et al.* 1977, Kiang *et al.* 1978, Maynard *et al.* 1978, Cooke *et al.* 1979) and elastosis (Shivas &

Douglas 1972). Our results confirm the importance of oestrogen receptor status as a prognostic indicator and its independent relationship to node status (Cooke *et al.* 1979). The effect of varying the cut-off point between receptor-positive and negative tumours is, however, a matter for concern.

These various tumour relationships are complex and all may be but estimates of functional and morphological differentiation. Thus, correlations between oestrogen receptor activity, tumour grade and elastosis have been described (Maynard *et al.* 1978, Masters *et al.* 1978). Whether they will prove of value in determining the treatment of an individual patient is still uncertain.

In the meantime it would appear that the most valuable and simplest guide to the prognosis of primary breast cancer is the histological state of the axillary lymph nodes. Determination of this parameter is now an essential part of the investigation of all patients with early disease.

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