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Influence and Significance of Certain Prognostic Factors on Survival in Breast Cancer*

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Abstract—*Prognostic factors documented at presentation of patients with breast cancer are usually studied by dividing all patients diagnosed as having breast cancer into prognostic factor subgroups and analysing their respective survivals. This method assumes that the biological nature of the disease in each group is similar, an assumption which may not be valid. In order to examine these presenting prognostic factors as they apply to patients with disease of proven distant metastatic potential, we analysed their influence on the survival of 896 patients who presented with breast cancer at our hospital and developed distant metastases during 1971–1980. We also analysed, in the traditional way, these prognostic factors as they affected the survival from primary treatment of 3084 patients who presented with breast cancer at our hospital during 1971–1980. As has been reported many times previously, survival from primary treatment of all patients with breast cancer was influenced by clinical stage at presentation, pathological axillary node status and oestrogen receptor level of the primary tumour. This influence was also seen in the distant metastasis-free period when only patients who developed distant metastases were analysed. In contrast, of the three prognostic factors studied, only the presenting level of oestrogen receptor was shown to influence the course of the disease after the development of first distant metastasis. These results suggest that the oestrogen receptor level of the primary tumour is a biological prognostic factor exerting an influence throughout the course of the disease, whereas clinical stage and pathological axillary node status reflect more the age of the tumour than its intrinsic biological properties. Our study provides support for basing adjuvant therapeutic protocols as much on the oestrogen receptor level of the primary tumour as on the presence or absence of disease in the axillary nodes.*

INTRODUCTION

THREE of the most commonly used prognostic factors in primary breast cancer are clinical stage, pathological axillary node status and, recently, oestrogen receptor levels. These prognostic variables are often loosely considered to indicate the chances of a patient developing a recurrence and as such are clinically valuable. Their real meaning in the context of breast cancer as a disease is obscure. Are these factors predominantly biological, reflecting growth characteristics of the disease process, or are they predominantly chronological, indicating the age of the disease from inception to diagnosis?

The traditional way of analysing survival by prognostic factors in breast cancer has been to divide all patients presenting with lesions diagnosed as 'breast cancer' into subgroups by, for example, clinical stage, and then graphing the proportion of each subgroup of patients who survive over a period of time. This form of presentation of results, while clinically valuable, tells us little about the nature of the prognostic factors, since the underlying assumption in presentations of this kind is that the nature of the disease in each subgroup is similar whichever prognostic factor is

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examined. It is assumed that patients who do not recur have been cured by their treatment, and had they not been treated their disease would have progressed in an orderly fashion with the development of metastases and ultimately death. An alternative interpretation is that the biological nature of the disease in patients who do not recur differs to the disease from which patients develop metastases and die. The curious difficulty of showing any major change in mortality rates over many decades, despite the introduction of improved treatment techniques and diagnostic facilities and an increased public awareness, at least suggests that this alternative interpretation merits some consideration.

Variations of the theory of 'biological predeterminism' have been proposed to explain some difficult data [1, 2]. This theory suggests that so-called early breast cancer may well be biologically indolent cancer rather than chronologically early, and that high cure rates in early breast cancer reflect the favourable biology of the disease rather than any beneficial effect of early treatment. Baum, in discussing therapeutic strategies, proposed that breast cancer may be divided into several subgroups based on the biological and metastatic potential of the tumour; these groups were not reliably established by clinical stage and nodal status at presentation, and in order to classify patients satisfactorily, greater refinement and understanding of prognostic indicators was required [3]. In contrast, the more conventional assumption of orderly progression of disease proposes that the risk of dying from disease due to dissemination of metastases increases as the cancer grows and the benefits of early diagnosis and treatment are considerable in saving life [4].

In this paper we elected to analyse prognostic factors not only in the conventional way, with survival of all patients diagnosed as having breast cancer, but also by examining these prognostic factors as they apply only to patients who have developed distant metastases. Patients who have recurred only locally or regionally and to date have not developed distant metastases were excluded from the study; this means we are dealing only with patients who have disease of proven distant metastatic potential and the results therefore do not include patients in whom the ultimate biological nature of the disease is unknown. Local and regional recurrence rates are dependent on the particular locoregional treatment employed and their significance in relation to eventual survival is uncertain [5], so that a less treatment-dependent point in the disease course, such as time of diagnosis of first distant metastasis, seems preferable for this kind of survival analysis. While not ideal as a point of reference (since diagnostic criteria and diligence of follow-up for first distant recurrence do vary and, recently, adjuvant chemotherapy has increased disease-free survival), at least the time of first distant metastasis has the advantage of being a clinically and biologically significant event, since the vast majority of patients will then go on to die of their disease. Many forms of local recurrence are an expression of disease of eventual distant metastatic potential [6], and therefore by excluding these patients from the analysis, results may be skewed if patients who have only a local recurrence were drawn from one particular stage or nodal grouping rather than equally from all groups. Therefore this selection of patients (performed in order to achieve a uniform grouping of patients with proven distant metastatic potential) will influence the interpretation of the results: unequivocal conclusions applicable to all patients with breast cancer on the nature of the prognostic factors discussed will not be possible, since our follow-up time spans only one decade.

In order to explore at a preliminary level the influence and significance of certain presenting prognostic factors on the survival of patients who suffer an early recurrence, we studied a population of patients who presented with breast cancer since 1971. We examined three commonly used prognostic factors in patients presenting with primary breast cancer: clinical stage, pathological axillary node status and oestrogen receptor levels. We investigated the influence of these factors on overall survival and survival after development of a distant recurrence.

MATERIALS AND METHODS

Clinical and pathological data on 3084 female breast cancer patients from northern Alberta, all of whom were registered at the Cross Cancer Institute, Edmonton, were entered prospectively onto a computer between 1971 and 1980 [7]. Three thousand and fifty-five (99%) of these patients presented with primary breast cancer during 1971–1980; 29 patients (1%) who developed metastases but who had their primaries diagnosed prior to 1971 were also entered in the early years of the computerised breast registry. This latter practice was stopped in 1972.

Locoregional recurrence was defined as limited recurrence occurring in the chest wall,

ipsilateral regional nodes (axillary, supraclavicular, infraclavicular or internal mammary) or, in those patients who received treatment other than a mastectomy, recurrence in the ipsilateral breast. Distant metastasis was defined as recurrence in sites other than those identified under locoregional recurrence.

Clinical stage was defined according to the UICC classification [8]. Axillary node status was determined from the result of a histological examination of lymph nodes removed at the time of primary treatment. Oestrogen receptor (ER) status of the primary tumour, determined by dextran-coated charcoal single-point competitive inhibition assay [9], was available only for patients presenting since late 1976. A level of oestrogen binding of less than 3.0 fmol/mg protein was classified as an ER-negative tumour (242 patients); a level of greater than 7.0 fmol/mg protein was recorded as an ER-positive tumour (383 patients). Values falling in the range of 3.0–7.0 fmol/mg protein were classified as 'borderline' (100 patients). The level of 7 fmol/mg protein was used as the lower limit of oestrogen receptor positivity because our laboratory employed this range until recently.

Clinical stage at presentation, pathological axillary node status and oestrogen receptor levels of the primary tumour were correlated with survival from primary treatment in all presenting patients; in patients who went on to develop distant metastases, survival from presentation, metastasis-free survival and survival from diagnosis of first distant metastasis were analysed. The number of patients used in any particular analysis varied depending upon the completeness of information available for each patient; for example, when the axillary node status of patients was unknown due to the patient having had limited surgery with no nodes available for examination, those patients were excluded from analyses of node status.

All censored survival curves were calculated by the method of Kaplan and Meier [10] and the difference between pairs of curves was tested for statistical significance using a modified Wilcoxon test [11]. Survival data were also analysed using the log rank test [12] for simultaneous comparisons of several groups of patients, and the chi-square statistic was used to assess significance.

RESULTS

Three thousand and eighty-four patients presenting with carcinoma of the breast formed the population base from which analyses of survival by clinical stage at presentation, axillary node status and oestrogen receptor levels were performed.

Of the 3084 patients, 1046 (33.9%) have had recurrent disease. Of these 1046 recurrences, 150 (14.3%) patients had recurred in locoregional sites only and 896 (85.7%) patients developed distant metastases. These 896 patients (29.1% of the entire population) formed the population-based sample for analysis of survival after first distant metastasis by clinical stage, axillary node status and oestrogen receptor levels. The total number of patients in each analysis depended on the availability of information for each prognostic factor.

1. *Survival of all patients with and without distant metastases*

Survival by clinical stage at presentation (*Fig.* 1). This analysis showed the expected decrease in survival as clinical stage at presentation became more advanced. There was a statistically significant difference in survival for any paired comparison of stages ($P < 0.001$).

Survival by axillary node status at presentation (*Fig.* 2). Pathological axillary node status at presentation correlated significantly with overall survival in the expected manner ($P < 0.001$ for both node-positive categories compared to node-negative).

Survival by oestrogen receptor levels (*Fig.* 3). Although patients who had an oestrogen receptor analysis performed on their primary tumour have been followed for a shorter period of time, patients with ER-positive tumours survived significantly longer than patients with ER-negative tumours ($P < 0.004$). Patients with ER-borderline tumours had an intermediate survival.

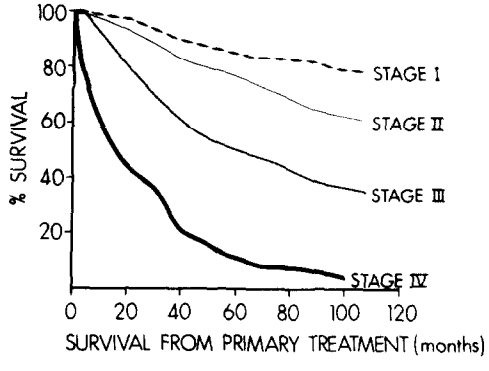

Fig. 1. *Overall survival by clinical stage at presentation. Stage I,* 630 *patients; stage II,* 982; *stage III,* 463; *stage IV,* 186. $P < 0.001$ *for any paired comparison of stages. Patients in whom the clinical stage at presentation was unknown (i.e. patients who were referred post-operatively to our institute) have been excluded from the analysis* (823 *patients*).

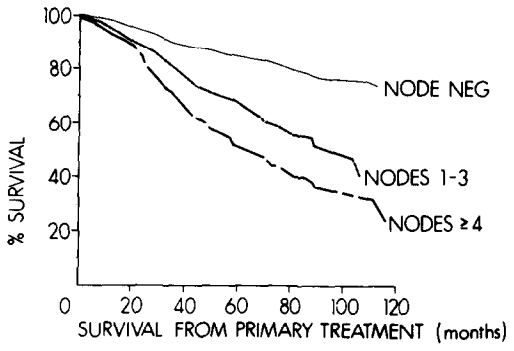

Fig. 2. Overall survival by pathological axillary node status at presentation. Node-negative patients, 1144; 1–3 nodes positive, 566; ≥4 nodes positive, 291. P < 0.001 for both node-positive categories compared to the node-negative group. The 1083 patients who did not have an axillary dissection have been excluded from this analysis.

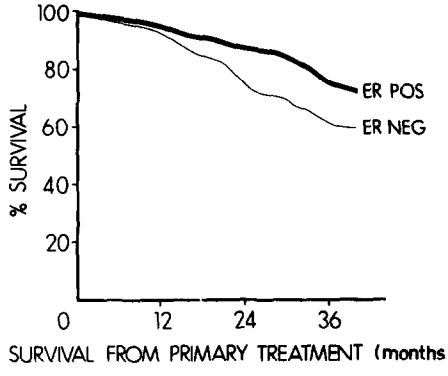

Fig. 3. Overall survival by oestrogen receptor status of primary tumour. The 383 patients with a positive ER survived significantly longer than the 240 patients with a negative ER. Statistically significant at P < 0.004.

2. *Survival of patients who developed distant metastases*

Survival from primary treatment of those who developed distance metastases. Overall survival is a composite of the metastasis-free period and the survival after metastases for patients who have at some point developed distant metastases. Since we were interested in analysing the behaviour of the disease in patients who developed distant metastases we examined the survival from primary treatment by clinical stage in these patients (Table 1). The survival from primary treatment of patients who developed distant metastases differed by clinical stage at presentation, patients with stages I and II disease surviving significantly longer than patients with stage III disease ($P < 0.05$). The presumably reflects the longer metastasis-free period in patients with earlier stages of disease.

Length of distant metastasis-free period by clinical stage, node status and oestrogen receptor levels in patients who developed distant metastases. Table 2 summarises the relationship of clinical stage, pathological node status and ER levels to the duration of the distant metastasis-free period for those patients who developed distant metastases. Patients with clinical stage III disease at diagnosis demonstrated a shorter median metastasis-free period than patients with clinical stages I and II disease. Similarly, the pathological node status was found to influence the metastasis-free period, with node-positive patients recurring significantly earlier than node-negative patients ($P < 0.001$). Patients with ER-negative tumours demonstrated a higher rate of relapse than patients with ER-positive tumours. After excluding those patients who presented with distant metastases (i.e. excluding stage IV patients), patients with ER-negative tumours showed a significantly shorter metastasis-free period than patients with ER-positive tumours ($P < 0.03$). The difference between median survival times was only five months; however, this difference should become more pronounced as the proportion of metastatic patients increases and follow-up time lengthens.

Survival after first distant metastasis by clinical stage, node status and oestrogen receptor levels at presentation. Clinical stage at diagnosis, in contrast to its relationship to overall survival, was found to be unrelated to survival after the onset of distant metastasis (Fig. 4). Paired comparisons of the curves showed no

Table 1. Overall survival from primary treatment by clinical stage at presentation for breast cancer patients with metastases

Stage at presentation	Total No. of patients with primary breast cancer	No. developing metastasis (%)	Survival of patients developing distant metastases: Median survival (months)	Three-year survival (%)	Five-year survival (%)
Stage I	630	75 (12%)	47	66	38
Stage II	982	240 (24%)	45	59	38
Stage III	463	218 (47%)	32	46	30
Stage IV	186	186(100%)	15	25	10

Table 2. Relationship of prognostic factors to duration of metastasis-free period in breast cancer

	Total No. of patients who presented with primary breast cancer	No. developing metastasis (%) but not presenting with metastasis*	Median metastasis-free period (months)	Statistical significance	
Stage I	630	75 (12%)	24	I vs II	NS
Stage II	982	240 (24%)	23	I vs III	$P < 0.001$
Stage III	463	218 (47%)	15	II vs III	$P < 0.01$
0 Nodes	1144	46 (13%)	24	0 vs 1–3	$P < 0.05$
1–3 Nodes	566	167 (30%)	20	0 vs ≥4	$P < 0.001$
≥4 Nodes	291	147 (51%)	17	1–3 vs ≥4	NS
ER-negative	240	53 (22%)	11	$P < 0.03$	
ER-positive	383	33 (9%)	16		

*Patients presenting with distant metastases at time of diagnosis were excluded from this analysis, i.e. excluded were 186 stage IV patients, 5 patients with zero nodes, 17 with 1–3 nodes and 7 with ≥4 nodes, 8 patients with ER-negative tumours and 28 with ER-positive tumours.

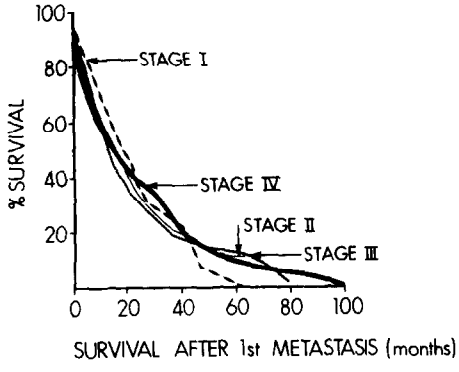

Fig. 4. Survival after first distant metastasis by clinical stage at presentation. Stage I, 75 patients; stage II, 240: stage III, 218: stage IV, 186. No significant differences.

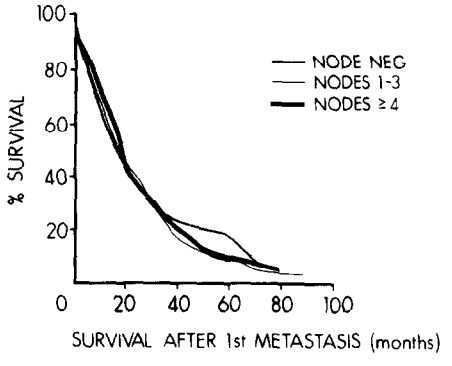

Fig. 5. Survival after first distant metastasis by node status at presentation. Node-negative patients, 151; 1–3 nodes positive, 184; ≥4 nodes positive, 156. No significant differences.

significant difference between the groups, and the maximum spread between the median survival times for all stages was only four months. Likewise, survival after first metastasis was independent of pathological node status at presentation (Fig. 5). In contrast, ER status was found to be of prognostic value in predicting survival after first metastasis (Fig. 6). Patients with ER-positive tumours survived significantly longer than those with ER-negative tumours, while patients with ER-borderline tumours had an intermediate survival ($P < 0.02$).

Of the three variables analysed, all of which were measured at the time of primary diagnosis, only the ER status proved to be of prognostic value for survival of patients after diagnosis of first distant metastasis.

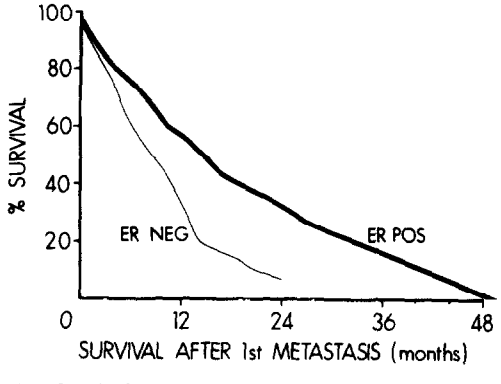

Fig. 6. Survival after first distant metastasis by oestrogen receptor status of primary tumour. ER-positive, 61 patients; ER-negative, 61 patients. Statistically significant (P < 0.02).

DISCUSSION

Few clinical researchers have examined prognostic factors as they apply only to patients who have developed metastases; most have preferred to examine these variables in all cases which a pathologist diagnoses as 'breast cancer'. We suggest that by focusing on distant metastatic cases we can observe these factors exerting their influence on patients with disease of proven distant metastatic potential.

This paper presents data on patients who have recurred up to ten years after primary treatment; this is still a short follow-up period and our conclusions are therefore derived from patients who have had a relatively early recurrence of breast cancer.

Of the three prognostic factors examined at presentation of patients with breast cancer, only the presenting level of oestrogen receptor was shown to influence the course of the disease after the development of distant metastases, suggesting that the ER level is a strong biological prognostic factor exerting its influence long after it has been measured in the primary tumour. In contrast, clinical stage and pathological node status at presentation exerted little or no effect on the disease process after diagnosis of first distant metastasis. They are therefore either prognostic factors of a different kind to the oestrogen receptor analysis, or their influence on the disease after first metastasis is of a quite different order and this influence could not be detected in our study. The data on the distant metastasis-free period for both clinical stage and pathological axillary node status showed that there is a significant delay to first distant metastasis for node-negative patients compared to node-positive patients, and for stage I patients compared to stage III patients. These results, taken together with the lack of influence of these factors on survival after first distant metastasis, suggest that in the group of patients analysed these prognostic factors do not exert their influence on the disease process *per se* but are chronological prognostic factors indicating the age of the tumour from inception to diagnosis.

Our interpretation of these results is speculative and several alternative explanations are possible. It is quite possible that some node-negative cancers are biologically indolent and we are observing a poor prognosis group, the malignant cells of which, for one reason or another, are lymphophobic; nevertheless, in those patients who have had an early recurrence no effect on survival after first distant metastasis was observed with clinical stage or node status at presentation. Similarly, it cannot be refuted that in node-positive patients there may well be some patients in whom node-positivity marks the extremities of the cancer's invasion (for example, a proportion of the 25% of node-positive patients who survive ten years after primary treatment and in whom no distant metastases will ever become evident). These patients obfuscate our attempts to understand prognostic factors as they relate to breast cancer as a systemic disease. Presumably, in these patients node status and clinical stage at presentation reflect as much the inherent growth characteristics of the cancer as they do its age.

Recently, Pater *et al.* [13] studied 456 patients with recurrent breast cancer and found that while pathological node status exerted no effect on survival from diagnosis or first relapse, clinical stage seemed to exert an effect, although this was predominantly an effect of tumour size. He concluded that clinical stage at presentation reflects as much the biology of the tumour as it does the age of the tumour. This view tends to support the earlier reports of Devitt [2], who claimed that clinical stage not only influenced survival after metastasis but also the site of disease recurrence. These reports and others [14] support the concept of 'biological predeterminism' in breast cancer. Our own results cannot confirm this view and suggest that, at least for patients who have had an early recurrence after primary treatment, clinical stage and axillary node status at presentation reflect more the age of the tumour than its intrinsic biological properties. This viewpoint does not exclude the possibility that a proportion of smaller lesions are biologically indolent and vice versa.

There are several clinical implications which may be derived from this study. Firstly, if the level of oestrogen receptor is the major biological prognostic factor at presentation of primary breast cancer, then its measurement should not only influence the kind of adjuvant systemic therapy given but it should also be incorporated into future trials of limited surgery in breast cancer. Secondly, since studies of long-term follow-up of patients with breast cancer show that some 70–85% of patients, irrespective of clinical stage or pathological nodal status, will die of their disease [15, 16], and we have shown that the level of oestrogen receptor is the single most important biological prognostic factor, then it becomes logical to offer oestrogen receptor-negative patients some form of adjuvant chemotherapeutic programme within a clinical trial setting irrespective of pathological axillary node status. Conversely, clinical trials should be established along the lines of the recently activated NSABP trial B-14 [17], re-examining the role of adjuvant hormone therapy in oestrogen receptor-positive patients.

Our findings suggest that in patients who recur early, clinical stage and pathological axillary node status reflect the age of the tumour from inception to diagnosis, whereas oestrogen receptor levels are of biological significance,

exerting their influence on the disease long after they have been measured in the primary tumour. Our analysis gives important information on the nature of the various prognostic factors in breast cancer and should be repeated by study groups capable of analysing a range of different variables, such as histology, tumour size and the progesterone receptor. It is vital that this information be collected prospectively over as long a follow-up time as possible.

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