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Oestrogen Receptors, Sites of Metastatic Disease and Survival in Recurrent Breast Cancer

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Abstract—*Two hundred and seventy eight patients with advanced breast cancer who had oestrogen receptor (ER) analyses performed on primary or recurrent tumours were studied. Oestrogen receptor (ER) positive (ER* ≥ 5 fmole *receptor/*mg *cytosol protein) tumours recurred significantly more commonly in bone and ER negative (ER* < 5 fmole *receptor/*mg *cytosol protein) tumours recurred significantly more often in liver and brain. Patients with ER positive tumours had a significantly better survival after relapse. ER analysis of either primary or recurrent tumour gives some indication of the natural history of breast cancer.*

INTRODUCTION

THE RESPONSE of advanced breast cancer to endocrine treatment varies according to the site of metastases. Visceral disease responds less often than does osseous or soft tissue disease [1–3]. Additionally, responsiveness to endocrine treatment correlates with the presence of oestrogen receptors [4, 5]. A possible explanation for the observation that endocrine sensitivity varies with sites of recurrence is that receptor status can influence the pattern of metastasis, with receptor-rich tumours spreading to soft tissues and bone, and receptor-poor tumours spreading to visceral sites. Before the commencement of hormonal therapy it is not always possible to determine oestrogen receptor values from each site of disease, but an attempt to correlate metastatic site with the receptor values of either the primary or recurrent tumour can be made. It is uncommon for oestrogen receptor status to change from rich to poor or *vice versa* during the course of the disease, and values measured on biopsy material taken from different sites are usually similar [6, 7].

In this paper we report the association between receptor status and distribution of metastatic disease as well as the effect of receptor status on survival in advanced breast cancer.

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MATERIALS AND METHODS

Patients

The case histories of all patients with breast cancer of known oestrogen receptor status who had relapsed were reviewed. Patients were regarded as ineligible if:

(i) Bilateral primary breast cancers had occurred without receptor information on *both* tumours (33 patients);
(ii) There was a history of a previous malignancy elsewhere (2 patients);
(iii) There was no histological proof that receptor analysis had been performed on tumour tissue (2 patients).

There were 278 eligible patients.

Information was obtained about:

(a) Stage of disease on presentation;
(b) Oestrogen receptor content of tumour;
(c) Site of the biopsy for oestrogen receptor assay;
(d) Menopausal status both at presentation and relapse;
(e) Treatment of the tumour at presentation and on relapse;
(f) Sites of initial and subsequent relapses;
(g) Survival from the time of diagnosis and from the time of first recurrence.

The TNM staging [8] was used except that patients with tumours greater than 5 cm in diameter but regarded as operable (T3, NO, NI, MO) were included with the stage 2 group.

For the purpose of this analysis, patients with tumours that were disseminated at first presentation are not included when tabulating sites of initial relapse and length of survival from relapse but are included when tabulating all sites of metastatic disease and survival from presentation.

Menopausal status both at presentation and at relapse was defined as follows:

pre menopausal—menstrual period within 6 months of date of presentation or relapse;

early post menopausal—last menstrual period greater than 6 months and less than 2 years from date of presentation or relapse;

late post menopausal—patients with last menstrual period greater than 2 years from date of presentation or relapse.

Oestrogen receptor analysis

Oestrogen receptor analysis was carried out by the method of King *et al.* [7] An oestrogen receptor value of less than 5 fmole receptor/mg cytosol protein was regarded as negative. Any value greater than this was regarded as positive and receptor positive values were arbitrarily sub-divided into less than 15 fmole, equal to or greater than 15 and less than 100 fmole, and greater than or equal to 100 fmole receptor/mg cytosol protein.

Statistical methods

The significance of differences between the binary variables, oestrogen receptor status and metastatic sites was calculated by the Chi-squared test for 1 degree of freedom. Survival was analysed by the log rank method [9].

Two hundred and forty-four patients were treated by a single surgical and medical team in one institution from the time of diagnosis. The remaining thirty-four patients were referred after treatment elsewhere. Treatment for patients, both with early and advanced disease, was given in the context of several clinical trials. Radiotherapy was given for localized relapse, while more generalized disease was managed by endocrine treatment with chemotherapy being reserved for subsequent treatment after failure of endocrine therapy. Patients were followed up at regular intervals, usually monthly or three monthly, and chest radiographs, bone scintiscans and biochemical screens performed. A physical examination was done at each clinic visit. If relapse was suspected, histological confirmation was obtained if possible, and a chest X-ray, biochemical screen, bone scintiscan and full blood count were obtained. Liver and brain scans were performed if otherwise indicated.

RESULTS

Table 1 shows the distribution of oestrogen receptor status and initial stage of patients. Preliminary analysis showed no significant difference in sites of metastatic disease in any sub-group of oestrogen receptor positive patients, so for correlation with sites of recurrence all sub-groups of tumours with ER value of ≥ 5 fmole/mg cytosol protein were pooled (as a single oestrogen receptor-positive group). As there was a minor difference in survival of the various sub-groups of oestrogen receptor-positive tumours, survival data are presented separately for each sub-group. Other patient characteristics are outlined in Table 2. Table 3 shows sites of initial relapse and oestrogen receptor content of tumours. There were no significant differences in initial sites of relapse between patients with ER-positive and ER-negative tumours. Table 4 shows sites of metastases for all stages of initial presentation. Brain metastases are more common in patients with ER-negative tumours and this difference is most marked for tumours that are Stage I at presentation. Patients with ER-negative tumours more frequently develop hepatic involvement.

Osseous involvement is more frequent in ER-positive patients and this difference is most marked for tumours that are Stages I and II at presentation.

Soft tissue and lung pleural involvement does not significantly vary with receptor status.

Table 1. *Patient population, showing initial stage and tumour oestrogen receptor content*

	Oestrogen receptor content (fmole/mg cytosol protein)				Total number of patients in each stage
	<5	5–14	15–99	≥100	
Stage I	25	5	29	19	78
Stage II	34	12	42	28	116
Stage III	22	11	24	8	65
Stage IV	6	0	6	7	19
Total number of patients in each ER subgroup	87	28	101	62	

Figures refer to number of patients.

Table 2. Patient characteristics

	Receptor status	
	ER negative	ER positive
Number of patients	87	191
Mean age (years)	53	56
Age range (years)	26–83	32–79
Menopausal status (number of patients)		
(a) At presentation		
Premenopausal	39	54
Early post-menopausal	5	9
Late post-menopausal	43	118
(b) At relapse*		
Premenopausal	32	44
Early post-menopausal	4	7
Late post-menopausal	45	127
(c) Site of receptor analysis		
Primary	42	90
Recurrence	37	82
Primary + recurrence	6	15
Not stated	2	4

*Stage IV tumours excluded.

Table 3. Site of initial recurrence and oestrogen receptor status of tumour

Site	Receptor status: Negative ($N=81$)	Receptor status: Positive ($N=178$)	P value
Soft tissue	60	123	0.50
Bone	17	55	0.10
Liver	8	9	0.30
Lung + pleura	14	31	0.98
Brain	0	3	0.10

Tumours that were Stage IV at presentation are excluded from this table.

Survival

Of the 278 patients, 100 were alive at the time of analysis (January 1980). Median survival from diagnosis was 50 months, and, in Stages I–III tumours, median survival from relapse was 28 months. In this selected group of patients with recurrent disease, the importance of oestrogen receptor status on overall survival was seen for all stages of tumour at presentation (Table 5). ER-negative tumours had a poorer survival for all stages than ER-positive tumours. In patients with Stage I disease a survival advantage was only seen if the ER content was equal to or exceeded 15 fmole/mg cytosol protein.

Survival from relapse was independent of stage at presentation (Fig. 1) but dependent on oestrogen receptor status (Fig. 2).

Table 5. Median survival from diagnosis, stage at presentation and oestrogen receptor content of tumour

Stage at presentation	ER in fmole/mg protein: <5	5–14	15–99	≧100	P values	χ^2
I	44	43	86	66	0.01	10.6
II	38	103	58	57	0.03	9.01
III	22	55	41	256	0.007	11.97
IV	13	—	37	22	0.025	7.4

Figures refer to median survival in months. Numbers of patients in each group are shown in Table 1.

DISCUSSION

These results suggest that oestrogen receptor analysis can provide information about the natural history of breast cancer. Oestrogen

Table 4. Distribution of sites of metastases for all stages at presentation and oestrogen receptor status

Stage at presentation	I		II		III		IV		All	
	78		116		65		19		278	
ER status	ER⁻ 25	ER⁺ 53	ER⁻ 34	ER⁺ 82	ER⁻ 22	ER⁺ 43	ER⁻ 6	ER⁺ 13	ER⁻ 87	ER⁺ 191
Sites involved										
Soft tissue	19	43	26	64	18	39	5	12	68	158
Bone	11	35*	15	56‡	9	23	2	10	37	124§
Liver	5	12	17	15	8	9	3	4	33	40‡
Lung + pleura	13	19	15	33	10	19	3	5	41	76
Brain	5	1†	5	3	3	3	1	0	13	5§

Results expressed as numbers of patients.
*$P<0.05$.
†$P<0.02$.
‡$P<0.01$.
§$P<0.001$.

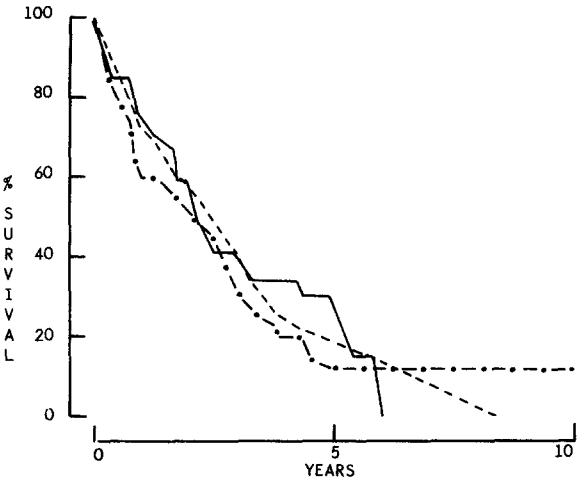

Fig. 1. Survival from relapse and stage at presentation. Key: —— *Stage* I ($N=77$); — — *Stage* II ($N=117$); —·—. *Stage* III ($N=65$).

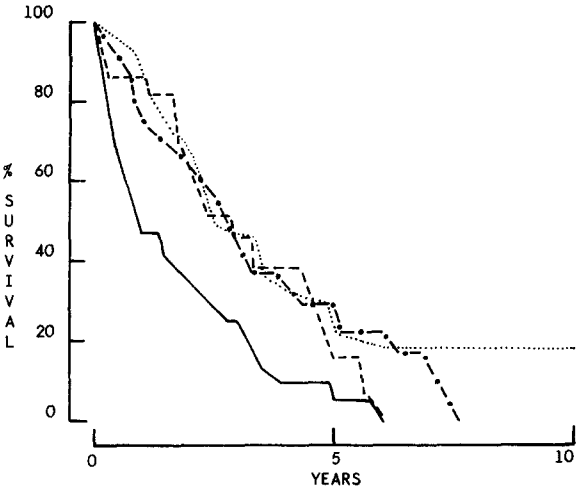

Fig. 2. Survival from relapse and ER content of tumour. Key: ER content in fmole/mg *protein;* —— <5 ($N=81$); — — ≥ 5 *and* <15 ($N=28$); —·— ≥ 15 *and* <100 ($N=95$); ..... ≥ 100 ($N=55$). *ER negative vs ER positive* <0.001.

receptor-positive tumours have a longer disease-free survival and total survival than oestrogen receptor-negative tumours [10, 11]. Hahnel *et al.* [10] reported that patients with operable tumours that were oestrogen receptor-positive had an increased survival from recurrence. Our data confirm this finding for a larger group of patients, including those who have advanced local disease at presentation. Length of survival from recurrence does not increase with increasing ER content, rather the important difference being whether tumours are oestrogen receptor-positive or negative as defined by a cut-off point of 5 fmole/mg protein.

There is disagreement in the literature on whether ER status can influence sites of metastases [10, 12, 13]. Our data show that brain and liver metastases are more frequent in patients with ER-negative tumours and bone metastases more common in patients with ER-positive tumours. Soft tissue and lung metastases do not appear to be influenced by ER status. Our data would thus complement that of Singhakowinta *et al.* [13] and give additional information about the association of ER status with brain metastases. As with survival, the essential difference again is whether a tumour is ER-positive or negative. In ER-positive tumours the absolute amount of receptor present does not appear to relate to the site of metastases. Although there are significant differences in sites of metastases between ER-positive and ER-negative tumours, an individual tumour can still metastasize to any site. A possible explanation for this is that tumours have mixed populations of ER-positive and negative cells present [14].

A single ER measurement on tissue from one site can serve only as an indirect measurement for the ER status of metastases at other sites, but multiple biopsies especially from visceral deposits are hard to justify in view of the inaccessibility of some organs and the hazards involved in their biopsy.

There is a correlation between different sites of metastatic disease and survival in advanced breast cancer [15]. Our results suggest that receptor status is related to the length of survival from relapse indirectly via the site of metastatic disease. Additionally, ER-positive tumours are more commonly hormone responsive and this could lead to improved survival.

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