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Oestrogen Receptors, Clinical Features and Prognosis in Stage III Breast Cancer

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Abstract—*One hundred and twenty-four patients with stage III breast cancer who had oestrogen receptor analyses (ER) performed on primary tumour were studied. For operable disease (T_{3a}, $N_{0,1}$, M_0), patients with ER-negative (ER <5 fmol/mg cytosol protein) tumours had a shorter duration of symptoms, but no other differences were observed at presentation. In patients with inoperable ($T_{3b,4}$, $N_{0,1}$, M_0 or any T, $N_{2,3}$, M_0) tumours there were no differences in the clinical characteristics that rendered the primary tumour inoperable between those with ER+ or ER- tumours. The median disease-free interval (DFI) in patients with operable tumours and uninvolved axillary nodes was significantly longer in those with ER+ tumours* ($P<0.05$). *Median survival was significantly longer in patients with ER+ tumours than in those with ER- tumours* (50 *vs* 27.5 months, $P<0.05$), *and when survival was analysed according to various methods of initial treatment, it was significantly prolonged in patients with operable (T_{3a}, $N_{0,1}$, M_0) ER+ tumours compared to those with operable ER- tumours. In patients with inoperable tumours no effect of ER status on prognosis was demonstrated. These results suggest that oestrogen receptor content may be a prognostic variable in patients with operable stage III breast cancer, but further studies of patients with similar methods of initial treatment are needed to confirm this. Patients with operable stage III tumours should be considered separately from those with locally advanced inoperable tumours in view of the significant differences in their survival prospects.*

INTRODUCTION

STAGE III carcinoma of the breast (TMN classification) is characterised by one or more of the following features: large size of primary tumour (>5 cm in greatest dimension: T_{3a}), involvement of the overlying skin, satellite skin nodules, peau d'orange, attachment to deep structures, adherence or fixation of axillary lymph nodes and/or involvement of supraclavicular lymph nodes ($T_{3b,4}$, any N, M_0 or any T, $N_{2,3}$, M_0). Generally, these features indicate inoperability (except for T_{3a} tumours) and the preferred treatment is radiotherapy.

In a previous report, duration of symptoms, deep fixation or diffuseness of primary tumour and response to radiotherapy were found to correlate with prognosis [1]. In this early series of patients data on oestrogen receptor status were not available but, in view of the prognostic value of this information in early [2] and disseminated [3] breast cancer, it is of interest to study the relevance of it to stage III disease.

In this paper we report on the association between clinical features, prognosis and primary tumour oestrogen receptor status in patients with locally advanced breast cancer.

MATERIALS AND METHODS

Patients

One hundred and twenty-four patients with stage III breast cancer who had oestrogen receptor analyses performed on primary tumour are the subject of this report. Stage III is defined using the TNM classification as either $T_{3,4}$, $N_{0,1}$, M_0 or any T, $N_{2,3}$, M_0 [4]. Accrual to this study was from March 1975 to October 1981.

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Clinical features studied included: (a) menopausal status at diagnosis (premenopausal, last period <6 months previously, postmenopausal, last period $\geqslant 6$ months previously); (b) age at diagnosis; and (c) duration of symptoms.

In the 53 patients with T_{3a}, $N_{0,1}$, M_0 tumours treated by radical mastectomy, information was also collected about: (a) size of primary tumour (largest dimension); and (b) incidence of pathologically involved axillary nodes, whilst in 71 patients with inoperable $T_{3b,4}$, $N_{0,1}$, M_0 or any T, $N_{2,3}$, M_0 tumours, information was collected about: (a) size of primary tumour ($\leqslant 5$ cm, >5 cm in largest dimension); (b) skin involvement (fungation, infiltration of skin overlying primary, satellite skin nodules over the breast, peau d'orange); (c) fixation to deep structures; and (d) clinical node involvement ($N_{2,3}$) according to the TNM classification.

In patients with T_{3a}, $N_{0,1}$, M_0 tumours, disease-free interval (DFI) was dated from time of radical mastectomy to time of first recurrence.

In the 62 patients with $T_{3b,4}$, $N_{0,1}$, M_0 or any T, $N_{2,3}$, M_0 tumours who had radiotherapy as part of their initial treatment, assessment of complete response was by UICC criteria, namely complete disappearance of all visible and palpable disease [5]. Duration of complete response was dated from the time of commencement of radiotherapy to the date of documentation of progressive disease.

Disease-free interval (DFI), duration of complete response and survival were analysed by the log rank method [6]. Differences between proportions were evaluated by the χ^2 test.

Oestrogen receptor analysis was performed by the method of King *et al.* [7]. An oestrogen receptor value of $\geqslant 5$ fmol/mg cytosol protein was regarded as positive (ER+) and any value less than this was regarded as negative (ER-).

Treatment

Details of patient treatment are summarised in Table 1.

The 53 patients with T_{3a}, $N_{0,1}$, M_0 tumours were each treated with a radical mastectomy. Patients with pathologically involved axillary nodes, as part of several clinical trials of adjuvant therapy, received either no adjuvant therapy (24 patients) or melphalan 6 mg/m^2 p.o. (max. 10 mg) on days 1–5 in a 6-week cycle for 16 cycles (7 patients), adjuvant CMF [cyclophosphamide 100 mg/m^2 p.o. on days 1–14, max. 150 mg, methotrexate 30 mg/m^2, max. 50 mg (patients $\geqslant 60$ yr 20 mg/m^2, max. 40 mg) i.v. on days 1 and 8, and 5-fluorouracil, 600 mg/m^2 (patients $\geqslant 60$ yr 400 mg/m^2) i.v. on days 1 and 8], the cycle being repeated at 4-weekly intervals for 12 courses (1 patient), tamoxifen 10 mg b.d. p.o. (1 patient), or adjuvant radiotherapy, 3000 cGy in 3 weeks to ipsilateral local gland fields at 250 kV (4 patients). One patient with uninvolved axillary nodes received radiotherapy as above, the remaining 15 patients receiving no additional treatment.

For $T_{3b,4}$, any N, M_0 or any T, $N_{2,3}$, M_0 tumours, treatment policy at this unit varied during the time of this analysis but included: (a) radiotherapy alone, 36–40 Gy in 3–3½ weeks by tangential fields to the chest wall by a 4-MeV linear accelerator with skin bolus (15 fractions), followed by 30 Gy in two weeks to the ipsilateral local gland fields at 250 kV (26 patients); (b) radiotherapy, 40 Gy in 4 weeks to the breast and ipsilateral local gland fields by a 4-MeV linear accelerator in 10 fractions, followed by a further 3 Gy × 3–4 in daily fractions by a direct field with 250 kV X-rays of ^{137}caesium gamma-rays to residual palpable disease. In addition, these patients were given 4 courses of adriamycin, 70 mg/m^2 (max. 120 mg) (60 mg/m^2 in patients aged $\geqslant 60$ yr) i.v. on day 1, and vincristine, 1.4 mg/m^2 (max. 2 mg) i.v. on days 1 and 8 (AV). This cycle was repeated every 3 weeks for 4 courses. This was either completed 3 weeks before the start of radiotherapy (9 patients) or started after radiotherapy was completed (7 patients) [8]. All these patients then received 8 cycles of CMF as above; (c) radiotherapy to 46 Gy, given 23 fractions over 5 weeks by a 4-MeV linear accelerator to the breast and ipsilateral local gland fields, followed by a further 2 Gy × 7 to sites of initial palpable disease, to a maximum of 60 Gy tumour dose (6 patients). In addition, some patients were randomly allocated to receive adjuvant systemic treatment (EORTC protocol 10792). One premenopausal patient received ovarian irradiation (1500 cGy central dose in 5 consecutive days by opposed fields) plus prednisolone 2.5 mg t.d. starting on the first day of ovarian irradiation (O + P). Three postmenopausal patients received tamoxifen 10 mg b.d. Six patients received chemotherapy with CMF for 12 courses. The doses and scheduling were identical to (b) above. Four patients received chemotherapy with CMF as above, plus endocrine therapy, either tamoxifen 10 mg b.d. (3 patients) or (O + P) (one patient). In addition, 4 patients were treated with palliative mastectomy and one of these received additional CMF. Three patients received tamoxifen 10 mg b.d. only, one patient received 8 cycles of AV [as in (b) above] and one patient with an ER- tumour received no treatment.

RESULTS

Table 2 shows the characteristics of these patients at presentation. Apart from a significantly longer mean duration of symptoms (23 vs 13

Table 1. *Details of patient treatment*

	ER+ (≥ 5 fmol/mg cytosol protein)	ER− (< 5 fmol/mg cytosol protein)
(A) T_{3a}, $N_{0,1}$, M_0 tumours		
No. of patients	32	21
No axillary node metastases (N−)	7	9
Radical mastectomy only	6	9
+ radiotherapy	1	0
Axillary node metastases (N+)	25	12
Radical mastectomy only	19	5
+ melphalan	2	5
+ CMF	1	0
+ radiotherapy	3	1
+ tamoxifen	0	1
(B) $T_{3b,4}$, $N_{0,1}$, M_0 and any T, $N_{2,3}$, M_0 tumours		
No. of patients	47	24
Radiotherapy only (3600–4000 rad)	21	5
(4600 rad + boost)	1	5
+ AV + CMF	9	7
+ endocrine treatment	4	0
+ CMF	6	0
+ endocrine treatment + CMF	3	1
Palliative mastectomy	0	3
+ CMF	1	0
AV chemotherapy only	1	0
Endocrine therapy only	1	2
No treatment	0	1

Table 2. *Clinical and pathological characteristics of patients with stage III breast tumours*

	ER+ (≥ 5 fmol/mg cytosol protein)	ER− (< 5 fmol/mg cytosol protein)
No. of patients	79	45
Mean age at presentation (yr)	58	56
Age range (yr)	25–83	29–80
Mean length of history (weeks)	23	13
Range (weeks)	1–150	1–100
Menopausal status at presentation		
Premenopausal	22	12
Postmenopausal	57	33
T_{3a}, $N_{0,1}$, M_0 tumours		
No. of patients	32	21
Mean tumour size (cm)	6.5	6.9
Uninvolved axillary nodes (N−)	7	9
Involved axillary nodes (N+)	25	12
$T_{3b,4}$, $N_{0,1}$, M_0 or any T, $N_{2,3}$, M_0 tumours		
No. of patients	47	24
Clinical features:		
(i) >5 cm in size	33 (70%)	19 (80%)
(ii) diffuse tumour	1 (2%)	3 (13%)
(iii) fixation to chest wall	7 (15%)	4 (17%)
(iv) oedema, infiltration or ulceration of skin of breast (including peau d'orange) or satellite skin nodules	38 (81%)	21 (88%)
(v) clinically involved supraclavicular nodes	5 (11%)	1 (4%)
(vi) Fixed homolateral axillary lymph nodes	9 (19%)	4 (17%)

weeks, $P < 0.05$) in patients with ER+ tumours, there were no other differences between patients with ER+ and ER- tumours at presentation.

In Table 3, numbers of complete responses to initial therapy are shown for patients with $T_{3b,4}$, $N_{0,1}$, M_0 or any T, $N_{2,3}$, M_0 tumours. In patients whose initial therapy included radiotherapy, 37/44 (84%) with ER+ tumours had a complete response compared to only 11/18 (61%) with ER- tumours, but this difference was not significant.

In patients with operable (T_{3a}, $N_{0,1}$, M_0) tumours and uninvolved axillary nodes at mastectomy, those with ER+ tumours had a significantly prolonged DFI compared to those with ER- tumours ($P < 0.05$; Fig. 1). When analysis for DFI in this group was restricted to those patients treated by radical mastectomy only, a longer median DFI in patients with ER+ tumours (not reached) compared to those with ER- tumours (27 months) was again seen, though this was no longer significant. However, in patients with operable tumours and involved axillary nodes there was a trend for a longer median DFI in patients with ER- tumours (ER-, not reached, ER+ 17 months), but this was not statistically significant.

In patients with inoperable ($T_{3b,4}$, $N_{0,1}$, M_0 or any T, $N_{2,3}$, M_0) tumours treated with radiotherapy only, median duration of complete response was no different in patients with ER+ tumours (11.5 months) or ER- tumours (8 months). Similarly, in those receiving radiotherapy + chemotherapy there was no difference in median duration of complete response between patients with ER+ (34 months) or ER- (17 months) tumours.

Median survival was significantly longer in patients with T_{3a}, $N_{0,1}$, M_0 tumours compared to those with $T_{3b,4}$, $N_{0,1}$, M_0 or any T, $N_{2,3}$, M_0 tumours (72 vs 30 months, $P < 0.001$; Fig. 2). In addition, for all patients with stage III tumours, those with ER+ tumours had a significantly prolonged survival compared to those with ER- tumours (median 50 vs 27.5 months, $P < 0.05$; Fig. 3).

In patients with operable stage III tumours, survival was significantly prolonged ($P < 0.025$) in those with ER+ tumours compared to those with ER- tumours (Fig. 4). This was most marked in those with uninvolved axillary nodes (Fig. 5), although, again, when this analysis was restricted to those patients treated by radical mastectomy only, no significant difference emerged (ER+ vs ER-, not reached vs 27 months). In those patients with operable tumours and axillary nodal

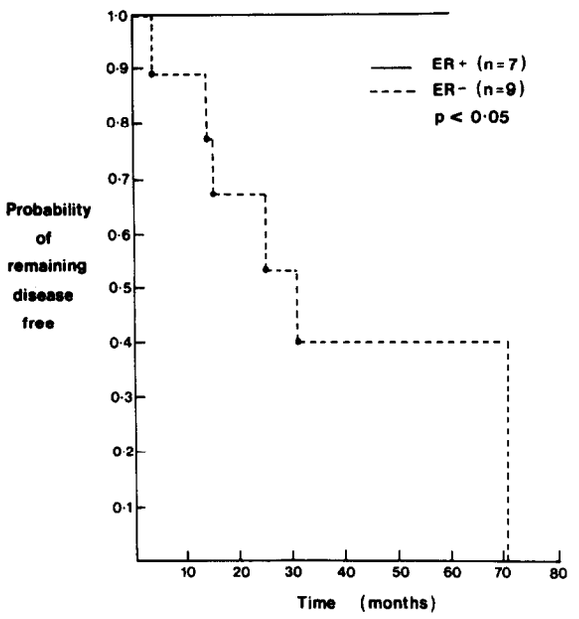

Fig. 1. Disease-free interval in patients with operable (T_{3a}, $N_{0,1}$, M_0) tumours and uninvolved axillary nodes at mastectomy according to tumor ER content.

Table 3. Number of complete responses in patients with $T_{3b,4}$, $N_{0,1}$, M_0 or any T, $N_{2,3}$, M_0 tumours treated with radiotherapy ± adjuvant endocrine or chemotherapy

Treatment	ER+ (≥5 fmol/mg cytosol protein)	ER- (<5 fmol/mg cytosol protein)
Radiotherapy only	19/22*	7/10
+ chemotherapy	12/15	4/7
+ endocrine therapy	3/4	0/0
+ chemotherapy + endocrine therapy	3/3	0/1
Total receiving radiotherapy	37/44	11/18
Not treated with radiotherapy		
Hormonal therapy only	0/1	0/2
Chemotherapy only	1/1	0/0

*Numerator = No. of responses; denominator = No. of treatments.

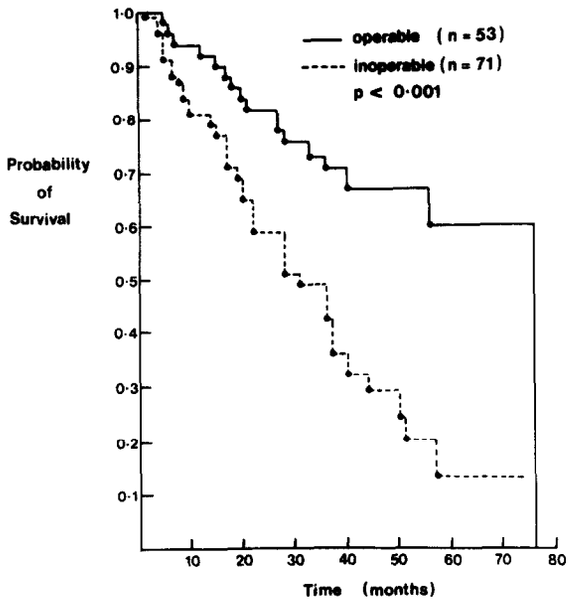

Fig. 2. Survival in patients with operable and inoperable stage III tumours.

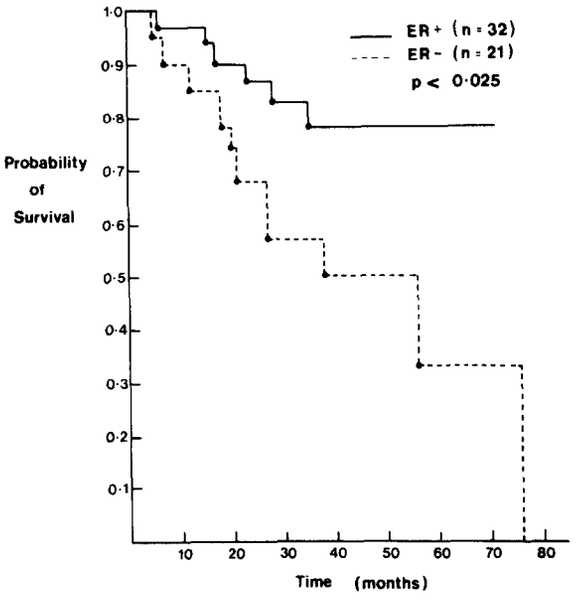

Fig. 4. Survival in patients with operable stage III tumours according to tumour ER content.

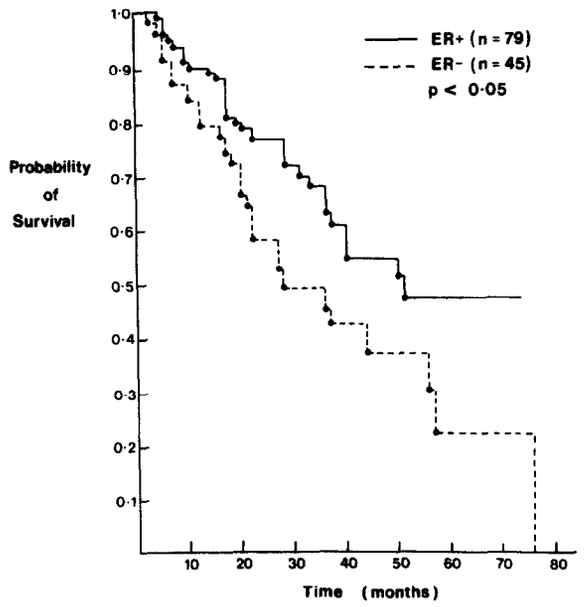

Fig. 3. Survival in patients with stage III tumours according to tumour ER content.

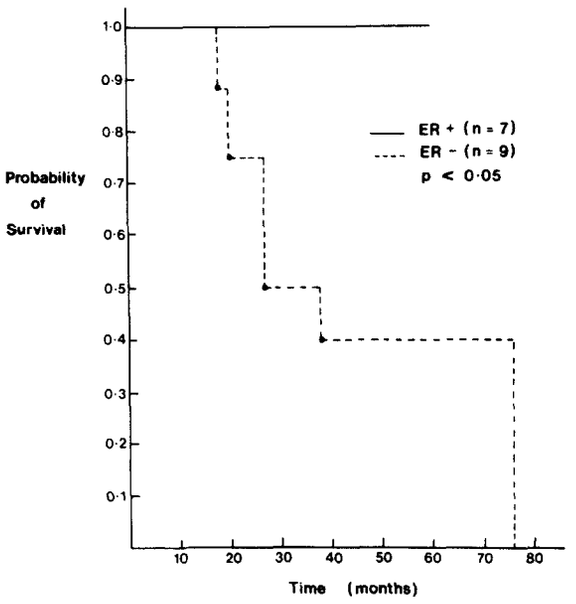

Fig. 5. Survival in patients with operable stage III tumours and uninvolved axillary nodes at mastectomy according to tumour ER content.

metastases there was no difference in survival between those with ER+ or ER- tumours (median survival ER+ not reached, ER- 30 months).

There were no significant differences in survival between patients with inoperable ER+ or ER- tumours receiving radiotherapy only (29 vs 28 months) or radiotherapy + chemotherapy (37 vs 25 months). In all these groups there were, however, only small numbers of patients.

DISCUSSION

This analysis suggests that in stage III carcinoma of the breast presence of oestrogen receptors in the primary tumour may be a prognostic guide. In inoperable tumours oestrogen receptor content is independent of clinical features at presentation, in particular incidence of deep fixation (respectively 15% in ER+ tumours and 17% in ER- tumours), previously noted to be

a prognostic factor [1]. In patients with ER– tumours there was a shorter duration of symptoms and a lower response rate to radiotherapy, both factors previously being shown to adversely affect prognosis [1].

In patients with stage III tumours the presence of oestrogen receptors affected survival significantly, but because of the marked difference in survival ($P < 0.001$) between those with operable and inoperable tumours these two groups should be analysed separately. Because of the number of different treatment modalities employed, further analysis was restricted to small numbers of patients, although in those with operable tumours and uninvolved axillary nodes the presence of tumour ER indicated a prolonged DFI and survival compared to those patients whose tumours were ER–. In patients with inoperable stage III tumours receiving comparable therapies the presence or absence of tumour ER did not influence prognosis, but a more definitive statement about the prognostic importance of ER in stage III breast cancer must await analysis of larger numbers of patients receiving similar therapy. However, these preliminary results suggest that any effect of tumour ER on the prognosis of patients with stage III tumours is limited to those with operable tumours only.

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