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Relation Between Estrogen Receptor Concentration and Clinical and Histological Factors: Their Relative Prognostic Importance After Radical Mastectomy for Primary Breast Cancer

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Abstract—*After modified radical mastectomy, 490 primary breast cancer patients were followed for a median of 75 months. Bloom grade was measured in 340 patients and ER status in 341. Follow-up of these patients has yielded the following results:*
(*a*) *The value of traditional indices has been reaffirmed. (Cox's multivariate analysis identified, in order of decreasing importance, the number of invaded lymph nodes, the initial tumor size and the histological grade. Other variables were found to be of lesser importance and were correlated with the three main indices.)*
(*b*) *The value of ER status disappeared after more than 3 years of follow-up.*
(*c*) *ER positive patients fared better after recurrence. This was interpreted as being a consequence of their responsiveness to hormonal treatment.*

INTRODUCTION

ALTHOUGH operable primary cancer of the breast gives the apparent impression of being a homogeneous entity, it does in fact encompass a wide variety of diseases. Due to the impossibility of being able to determine at the first clinical evaluation a patient's prognosis, such patients have invariably received an almost uniform treatment. As has been pointed out in recent reviews [1, 2], this probably accounts for the lack of therapeutic effectiveness and poor improvement in survival in this field over the last few decades. The aim of every medical team concerned with breast cancer is to be able to identify each type of tumor and determine the probable natural course of a patient's disease. To help reach this goal, several parameters have been defined, each of which appears to be correlated with the disease's pattern of evolution. The most frequently cited prognostic factors are: the clinical staging, the menopausal status, the number of invaded lymph nodes in the dissected axilla, the histological grading and estrogen receptors (ER) in the cytoplasm of tumor cells [1–4]. The relationship between these factors and their relative importance in predicting the course of the illness brings up the subject of the validity of some of these factors in predicting the course of the disease. Moreover, this also queries the choice of which adjuvant therapy will be the most efficient in improving the disease-free interval and duration of survival [2, 3, 5–12]. We have aimed to establish the correlations existing between these factors and have tried to determine their relative predictive values. In particular, special emphasis has been given to the value of the ER concentration as a prognostic factor and its relationships with the other variables under study.

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MATERIALS AND METHODS

Patients under study

From May 1969 to December 1977, 490 primary breast cancer patients underwent a modified radical mastectomy, as initial treatment, in our institution. All mastectomies were carried out by a single surgical team according to the technique described by Madden [13]. Twelve patients treated for bilateral breast tumors which occured within 5 years after mastectomy were excluded from this study.

Clinical staging was carried out according to the TNM classification [14]. Fresh surgical specimens from the different axillary levels (inferior, middle, superior) were screened for lymph nodes by palpation and by serial systematic sections. All nodes were embedded in paraffin and stained with hematoxylin and eosin. Based on histological examination the number of invaded lymph nodes was recorded.

The ER concentration in the cytosolic portion of 341 tumors, expressed as fentomoles (10 exp −15 moles) per milligram of tissue protein, was determined by the method described by Leclercq *et al.* [15]. A tumor containing an ER concentration superior to 10 fmoles was considered 'ER positive'. Using the classification criteria delineated by Bloom and Richardson [16] and Scarff and Torloni [17], a team of two pathologists, unaware of the tumor's ER content, reviewed 448 available slides in order to determine the tumor's histological grading.

After mastectomy, patients were followed monthly for the first 3 months, every 3 months until 1 year, and every 6 months thereafter. Initially, baseline chest X-rays, bone scintiscans and biochemical screens were performed to serve as a control for follow up examinations. Initial sites of recurrence were recorded and since not all investigations were necessarily carried out at the same moment, multiple sites were considered as simultaneous if no more than 2 months elapsed between their confirmation.

The disease-free interval (DFI) was defined as the time elapsing between the mastectomy and the confirmation of the first recurrence, either local or distant.

As is often the case in retrospective studies, various modalities of adjuvant treatment were employed according to the current practice at the time the patient was initially treated: from May 1969 to June 1976, patients with more than three invaded axillary lymph nodes received axillo-thoracic radiotherapy after surgery; as of July 1976, for patients with invaded lymph nodes, this treatment practice was replaced by a policy of adjuvant chemotherapy in combination with a less extensive irradiation which was restricted to the internal mammary lymph nodes (see Table 1 for more details). Doses and schedules have been reported elsewhere [18]. The 15 patients with T3 or T4 tumors who received a pre-operative treatment in order to reduce the extension of the local lesion [19] were not considered to be evaluable for analysis of the histopathology or the ER concentration.

Details of treatments received after first recurrence, which took each individual patient's characteristics into account, are summarized in Table 2.

Statistical methods

Actuarial survival curves and disease-free interval (DFI) curves were calculated according to the Kaplan–Meier technique [20]. These curves give the probability that the patient has not died or relapsed yet at different time points after surgery. Two patients who died within 1 month after surgery were excluded from the disease-free interval analysis but included in the survival curves; one patient with no follow-up has been excluded from both analyses. Differences between curves have been tested for significance using the log-rank test and the Breslow test (this one gives more weight to early differences between the curves) [21]. For ordered variables, the log-rank test for trend [22] was used. The prognostic importance of one variable with regard to another categorical variable has been assessed by means of retrospective stratification using the adjusted log-rank test [22].

Table 1. Adjuvant radiotherapy and chemotherapy according to type received

Radiotherapy	Chemotherapy None	CMF	TCHAC	Other	Total
None	190	8	7	4	209
Axillo-thoracic 4000–4500 rads	181	4	1	2	188
Internal mammary lymph nodes 4000 rads	8	63	7	2	80
Other radiotherapy	10	1	2	0	13
Total	389	76	17	8	490

CMF: cyclophosphamide, methotrexate, 5-fluorouracil [19]; TCHAC: tamoxifen, cyclophosphamide, methotrexate, 5-fluorouracil, adriamycin, vincristine [19].

Table 2. *Treatments for first recurrence*

Local recurrences	23
local resection	19
external radiation	2
hormonotherapy	2
Distant metastasis	202
ovariectomy	19
adrenalectomy	2
external radiation	30
chemotherapy	23
hormonotherapy	25
combined chemo- and hormonotherapies	36
combined radiations and chemo and/or hormonotherapies	11
more complex combinations of treatments	38
no treatment	20

The joint effects of the prognostic variables and their relative importance with respect to a patient's duration of survival or disease-free interval was examined using Cox's proportional hazards regression model for censored data [23]. In this manner it was possible to identify a subset of variables which 'best' predicts or explains the patient's duration of survival or disease free interval. Kendall's Tau B and Tau C have been used to test for correlation betwen two ordered categorical variables [24, 25].

The prognostic importance of each of the following factors on the disease-free interval and survival was examined: T and N classifications, number of microscopically invaded axillary nodes (three groups were considered: 0, 1–3 and 4 or more invaded nodes), histological tumor type and grade, ER concentration, menopausal status and age.

RESULTS

The principal characteristics of the population are: median age was 57 years (range 27–92), 60% of the women were postmenopausal, ER positive tumors comprised 72% of the total of 341 tumors analyzed.

The median follow-up was 75 months, 101 months for 264 patients last known to be alive and 37 months for 226 who have died.

Disease-free interval and survival: the main factors of prognostic significance for both the DFI and the duration of survival, presented in order of importance, were found to be: the number of invaded lymph nodes in the axilla, the tumor size (T) at presentation and the G grade for the infiltrating duct carcinomas ($P < 0.001$) (Figs. 1–3). For the special histological forms, it was noted that cribriform, lobular and papillary tumors had a DFI similar to that of G1 duct carcinomas while apocrine and medullary tumors resembled more closely the G3.

On the other hand, the ER concentration was not of prognostic significance (log-rank and Breslow test give $P = 0.63$ and $P = 0.20$ respectively) with respect to disease-free interval (Fig. 4). For survival, however, the curves initially show a better outcome

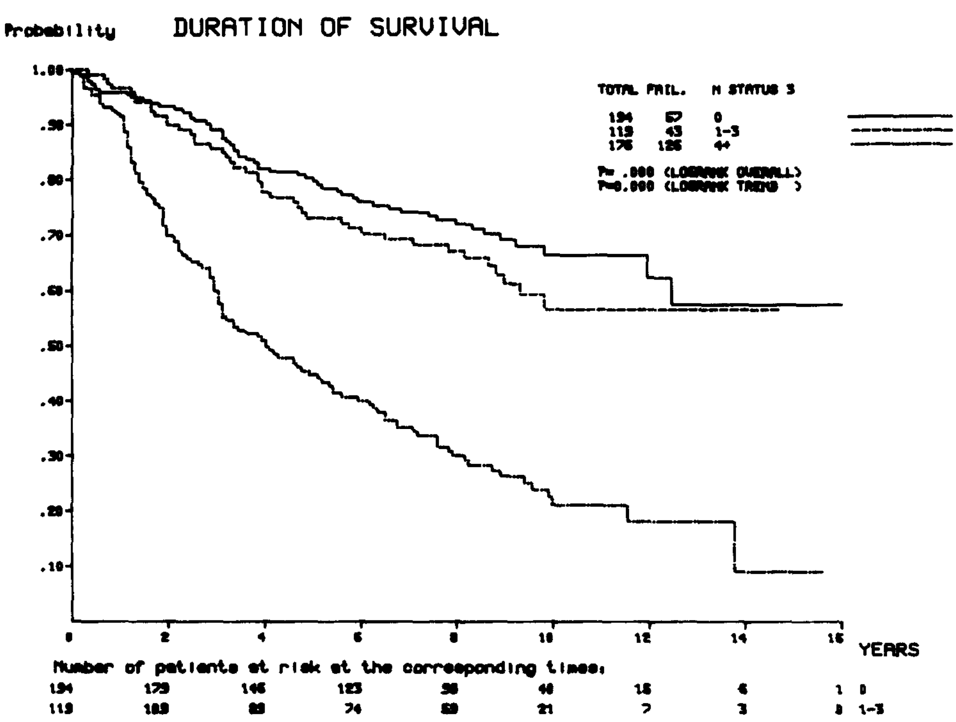

Fig. 1. *Survival after mastectomy according to the nodal involvement in the axilla.*

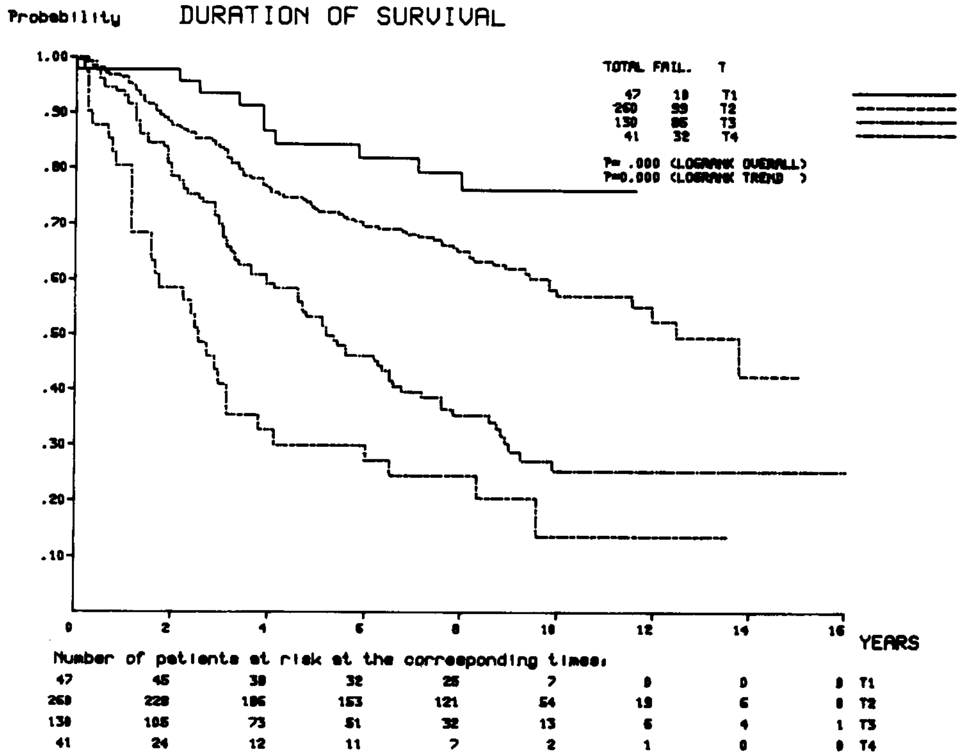

Fig. 2. Survival after mastectomy according to the T stage of the tumor at presentation.

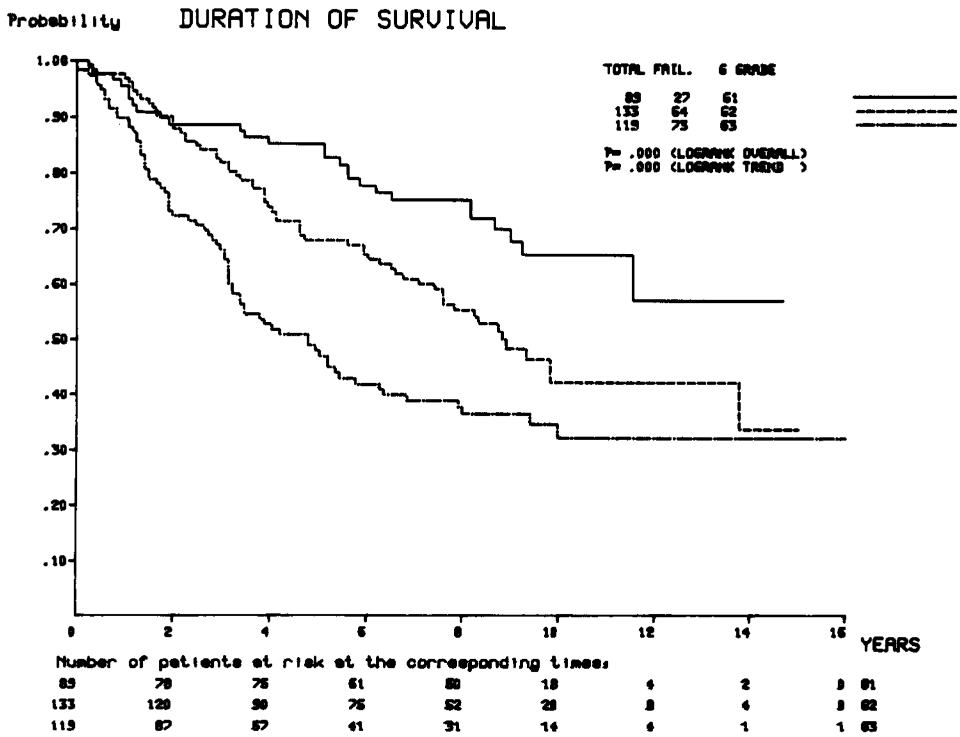

Fig. 3. Survival after mastectomy according to the G grade of the tumor.

for ER+ patients but they eventually converge (Fig. 5) (log-rank and Breslow tests give $P = 0.60$ and $P = 0.08$ respectively). Considering the group of patients who did not receive adjuvant chemotherapy (i.e. patients without nodal involvement), there was no difference either in DFI or in survival according to their ER content; the same is true in the group of patients with four (or more) involved nodes. As there was no significant difference between N0 and N1–3 groups, Figs. 6 and 7 give

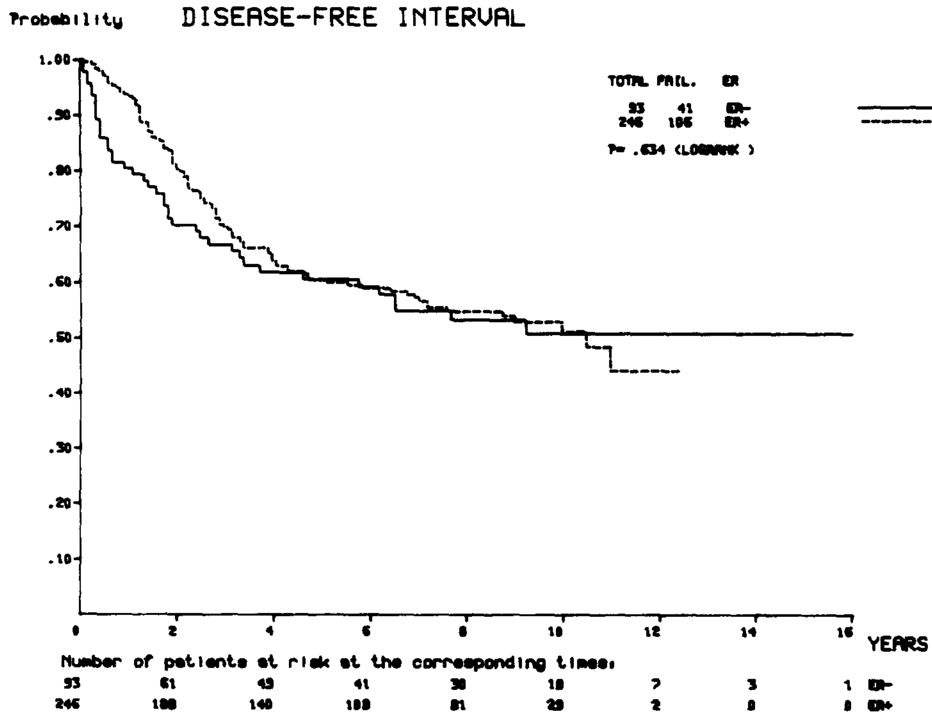

Fig. 4. Disease-free interval from mastectomy according to the ER content (ER+ vs. ER−) of the tumor.

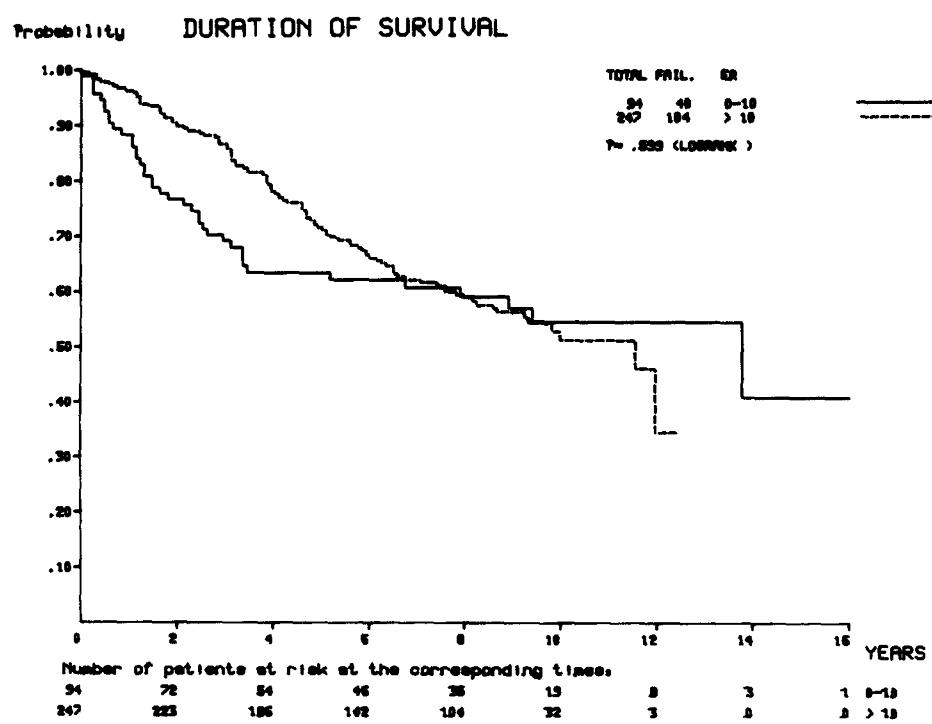

Fig. 5. Survival after mastectomy according to the ER content (ER+ vs. ER−) of the tumor.

the DFI and the survival according to the ER and the nodal status (0–3 or 4+). Thus there was no difference in long term prognosis between ER− and ER+ once the nodal status was taken into account. The patient's menopausal status was significant ($P = 0.02$) with the premenopausal patients having a longer DFI and survival than the postmenopausal.

Age was found to be of significance for predicting survival. The survival duration for patients older than 70 years (median 40 months) was shorter than

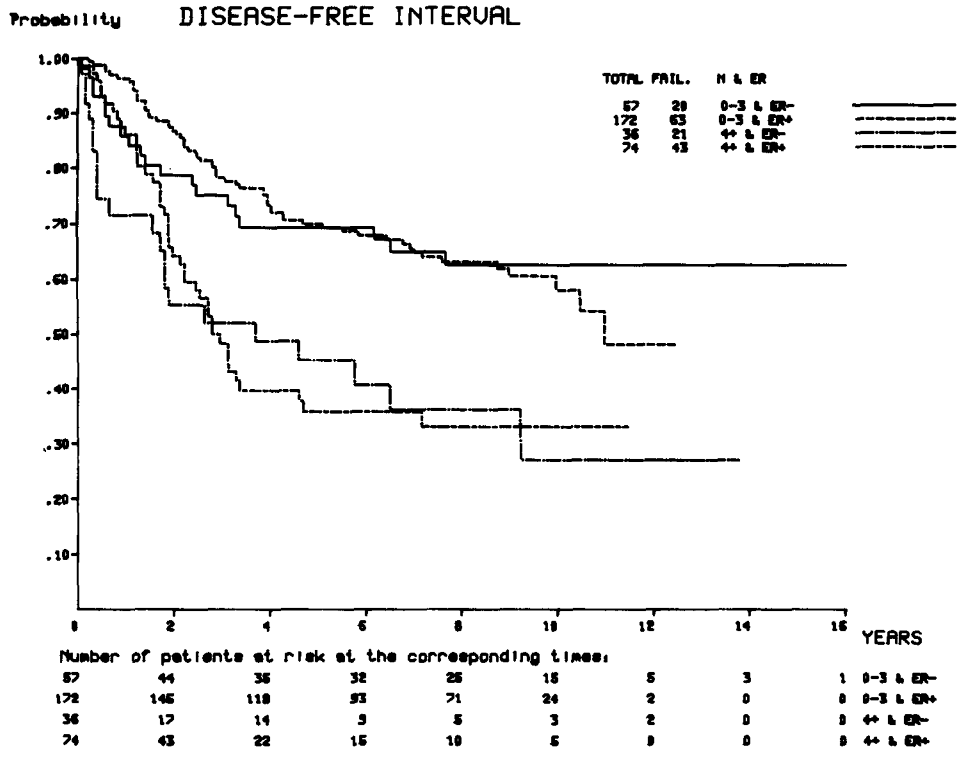

Fig. 6. Disease-free interval from mastectomy according to the ER content in two subgroups defined by nodal invasion (the curves relating to patients without involvement and to those with 1–3 nodes involved are surimposed for these two groups and, therefore, appear as only one curve).

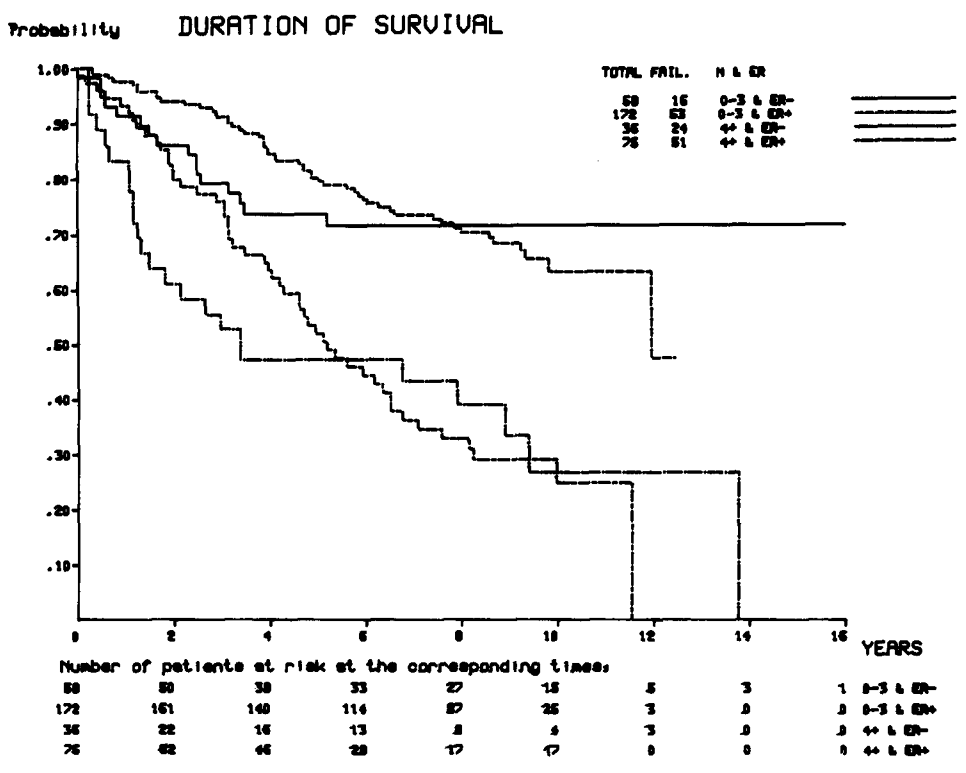

Fig. 7. Survival after mastectomy according to the ER content in two subgroups defined by nodal invasion (same remark as for Fig. 6).

for the other age groups (median 146 months) ($P < 0.0001$).

Duration of survival after the first relapse is better for patients whose tumors are initially ER+ than for those who are ER− (Fig. 8, $P = 0.002$). The prognostic impact of the ER concentration on post relapse survival is important mainly for patients who recurred within 2 years after the initial treatment ($P = 0.001$, log-rank) but disappears for those who recurred later ($P = 0.42$, log-rank).

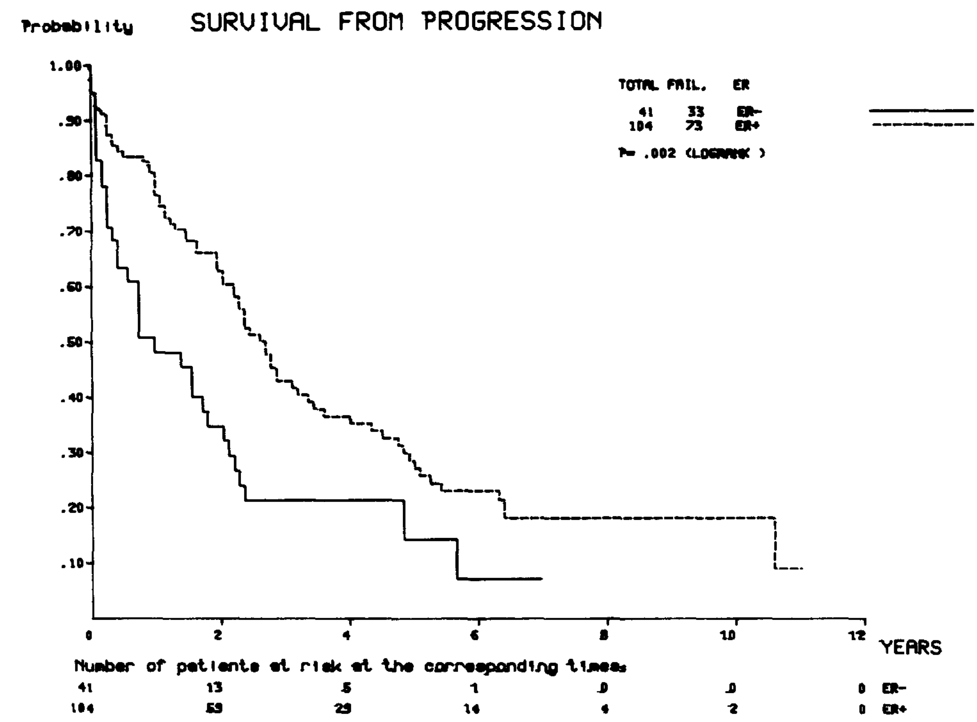

Fig. 8. Survival after first recurrence according to the ER content of the tumor.

Correlation between patient characteristics: significant correlations were detected among many of the variables of potential prognostic importance. Correlations, significant at $P \leq 0.01$ using Kendall's test, were observed as follows:

1. The T classification with the following factors: the N classification, the number of invaded axillary lymph nodes, the G grade and the menopausal status.
2. The number of invaded axillary nodes with the G grade.
3. The ER concentration with the grading and histological type and with the menopausal status (Table 3).

In general, patients with a poor prognosis with respect to one variable exhibited a poor prognosis with respect to the other variables as well. For example, larger tumors were associated with a worse N, a greater number of invaded lymph nodes with a lesser degree of tumor differentiation. It was also found that postmenopausal patients had larger tumors but possessed a higher ER concentration.

The ER concentration was uniformly distributed among the various levels of the T and N clinical classifications and according to the number of microscopically involved axillary lymph nodes. Table 3 shows however that postmenopausal patients tend to possess higher levels of ER.

To take into account the distribution of the menopausal status, the prognostic significance of ER content was again assessed after adjustment for menopausal status: no modification in the prognostic importance of the ER status was disclosed, neither for DFI nor for survival.

Relative importance of prognostic factors: due to the correlation of the prognostic factors with one another, a Cox's proportional hazards model was used in order to determine the set of variables which best explains the DFI and survival. Applying a step up procedure it was found that the number of invaded lymph nodes was the single most important factor with respect to the duration of DFI and survival. After adjustment for this variable, the T classification and then the G grade were the only additional variables to be retained as being highly significant ($P < 0.001$) by each model. In contrast to the G grade, the ER concentration was of no prognostic importance in predicting the DFI either

Table 3. Distribution of estrogen concentration by menopausal status

Menopausal status	Receptor concentration (fmoles) 0–10	11–100	101–2000	Total
Pre	38 (34%)	54 (49%)	19 (17%)	111 (35%)
Post (natural)	51 (25%)	55 (26%)	102 (49%)	208 (65%)
Total	89 (28%)	109 (34%)	121 (38%)	319

by itself or once the lymph node status, the T classification, or both have been considered. The other variables could be omitted (except age for duration of survival) due to their correlation with the three variables actually retained.

DISCUSSION

Our results reaffirm the pre-eminent value of the number of pathologic nodes, the traditional staging method and the grading system with respect to the disease-free interval and the duration of survival [1, 4, 26, 27]. The independence of both the clinical staging system and the number of invaded lymph nodes with the ER content [27–31] along with the predominance of ER positive tumors among postmenopausal patients [3, 6, 10, 27, 28, 32, 33] and those aged over 55 years [34–37] is in agreement with the literature.

However, we did not observe the favorable effect of positive ER on the recurrence rate (Fig. 4) reported by some authors [27–29, 31, 35, 38–56]. This has been a matter of debate for years with others reporting series like ours, where ER+ tumors do not fare significantly better with regard to DFI [37, 57–68]. One would assume that these heterogeneous results are mainly due to differences in length of follow-up and also to differences in the distribution of various prognostic factors in the patients analyzed. Indeed, if only shorter periods of follow-up had been taken into account, the initial separation of the curves (Fig. 4) would have led to preliminary conclusions in favor of ER+ patients. This has been well documented by Raemaeckers *et al.* [69] in a recent review of papers dealing with this subject.

In our series, as in others, there exists a initial trend in favor ER+ patients, as may be seen in Figs. 4 and 5, and as is suggested by the fact that the Breslow test gives lower *P*-values than the log-rank test. Nevertheless, the long term outcome is similar between ER− and ER+ patients. The apparently poorer prognosis of the ER− patients during the first 3 years following mastectomy may be explained by the higher fraction of poorly differentiated tumors (i.e. histologic grade 3) belonging to this group. The univariate and multivariate analyses revealed that the histological grading has a greater prognostic influence than the ER concentration and the two parameters are significantly correlated: the less differentiated tumors had, in general, a lower ER content, as was already suggested by Heuson [70], Maynard *et al.* [71] and Thorensen *et al.* [72].

The importance of the ER content is unquestioned when selecting the recurrent breast cancer patients who would benefit from hormonal treatments [2, 3, 5, 6, 10–12, 59, 73–78]. ER positive patients have a better survival after relapse than the ER negative ones (Fig. 8), a reflection of the efficacy of hormonal treatment in this subgroup of patients [65, 69, 79]. However this beneficial effect does not significantly improve the overall survival curves of the ER+ patients when compared to the ER− ones (Fig. 5). The hormonal treatment of recurrences seems to be beneficial mainly for ER+ patients who recurred within the first 2 years after the initial treatment. This may explain the more pronounced initial divergence of the survival curves (ER+ vs. ER− patients, Fig. 5) as compared to those for the DFI (Fig. 4).

We conclude that the histologic grade as defined by Bloom and Richardson [16] and Scarff and Torloni [17] should be part of the initial criteria to be taken into consideration for any further treatment after modified radical mastectomy.

Adjuvant treatments should not be chosen based on the ER content only. Other factors such as lymph node involvement, tumor size, histologic type and grade, age and menopausal status should be given priority.

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