Breast Cancer Research and Treatment 6: 123–130, 1985

Report

Disease-free interval and estrogen receptor activity in tumor tissue of patients with primary breast cancer: analysis after long-term follow-up.

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Key words: breast cancer, disease-free interval, estrogen receptor, prognostic factors

Summary

Specific estrogen receptor activity (ER) was found in 115 of 175 (66%) tumors of patients treated for primary breast cancer in the period 1974–1981; 60 patients had ER-negative tumors. All patients were under observation for at least 48 months (median 76 months). The 24 patients who received adjuvant chemotherapy as part of their initial treatment, were excluded from the analysis of the disease-free interval (DFI). Groups of patients with ER-positive or ER-negative tumors did not differ significantly in clinical characteristics. Patients with ER-positive tumors had a significantly longer DFI than those with ER-negative tumors only in the first year after initial treatment. After prolonged observation a significant difference in recurrence rates was no longer found. In premenopausal women, the DFI was not different for those with ER-positive compared to those with ER-negative tumors, not even in the first year of observation. However, in postmenopausal women, those with ER-positive tumors had a significantly longer DFI up to 3 years after initial treatment but not thereafter. There was no difference in DFI between the ER-positive and ER-negative groups when the tumor stage was taken into account. It is concluded that the ER status of the primary tumor affects prognosis only on the short term.

Introduction

The prognostic significance of measurement of estrogen receptor (ER) content in tumor tissue of patients with primary breast cancer with regard to recurrence rate is still under debate at this time. Most studies, with a short follow-up period, indicate a more favourable prognosis for patients with ER-positive tumors (1–27). However, in most of these studies the estimated disease-free intervals (DFI) were calculated on relatively few recurrences, which makes statistical analyses less reliable. Studies with more prolonged follow-up suggest that the favourable effect of ER positivity on recurrence rate diminishes gradually in time (28–32). Here we present our data on recurrence rates in a group of 175 patients with primary breast cancer related to the ER status of the primary tumor and the tumor stage, all under protocol follow-up for at least 48 months.

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Patients and methods

In the period 1974–1981, ER activity was assessed in the tumor tissue of 175 patients with primary breast cancer who underwent surgery in this center. In none of these patients was there evidence of distant metastases. The surgery consisted of modified radical mastectomy, simple mastectomy, or excisional biopsy. Most patients received postsurgical radiotherapy (71%). Only 24 patients received adjuvant chemotherapy consisting of the combination of 5-fluorouracil, methotrexate, and cyclophosphamide. All patients were followed at regular intervals, at the minimum twice yearly in the first two years and at least yearly thereafter. Evidence of recurrent disease was confirmed by biopsy, whenever possible. For the purpose of this study the follow-up of the patients ended July 1st, 1984. None of the patients was lost to follow-up. The 9 patients (ER+, n = 4; ER−, n = 5) who died in the disease-free interval of causes unrelated to breast cancer, are included as 'disease-free' in the analysis. The DFI was defined as the period between date of surgery and date of first relapse. The diameter of the primary tumor was measured by mammography or by pathologic examination and classified according to the U.I.C.C. (1978) (33). On the basis of diameter of the primary tumor and lymph node invasion (N_0 = no invasion, N_+ = invasion, and $N_?$ = invasion unknown), the patients were classified into three subgroups:

i) patients with good prognosis: $T_1T_2N_0$ (n = 49)
ii) patients with poor prognosis: T_3T_4 irrespective of N status or N_+ irrespective of T status (n = 89)
iii) patients with unknown prognosis: $T_1T_2N_?$ (n = 37).

The menopausal state was defined as postmenopausal when menses had ceased at least 12 months (n = 93) or after previous ovariectomy (n = 2) or when patients were older than 55 years and had a hysterectomy in the past (n = 4). The two patients who were younger than 55 years and underwent hysterectomy were to be classified as menopausal state 'unknown'. Thus, the remaining 74 patients were premenopausal. The ER assays were performed using the dextran-coated charcoal method as described earlier (34). ER levels ≥5 fmol/mg protein are considered ER positive.

Statistical methods

Analysis of the expected disease-free interval was carried out by the Kaplan-Meier method (35). Statistical comparisons between the relapse functions were made using the Gehan-Mantel non-parametric test (P denoted by p) (36, 37). Further statistical analysis was performed using Fisher's Chi Square test (P denoted by p*) and Wilcoxon's two-sample test (P denoted by p**).

Results

Clinical characteristics and ER status (Table 1)

Clinical characteristics of the 175 patients studied are shown in Table 1. One hundred and fifteen of these patients (66%) had an ER-positive tumor. There were no significant differences in any of the clinical characteristics between the groups of patients with ER positive and ER negative tumors. The validity of our classification based on tumor extension and lymph node staging is clearly illustrated by the differences in expected DFI between the groups with good and poor prognosis (Fig. 1).

Disease-free interval (Table 2)

Analysis of the DFI is restricted to those patients who did not receive adjuvant chemotherapy as part of their initial treatment (n = 151). All these were observed for at least 48 months with a longest follow-up period of 130 months. No relapse was observed in 84 of the 151 patients (55.6%) after a median follow-up time of 76 months. Of the 67 patients who relapsed (44.4%), the shortest interval to recurrence was 2 months and the longest 99 months (Table 2).

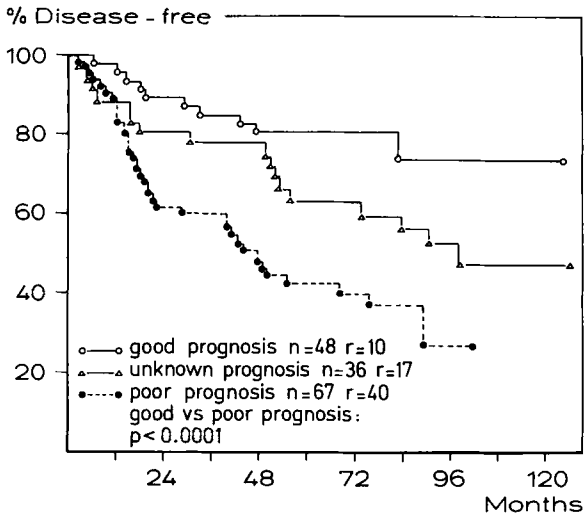

Fig. 1. Estimated disease-free interval and staging according to tumor extension and lymph node invasion. n = number of patients; r = number of recurrences.

DFI, ER status, and menopausal state (Table 2, Figs. 2 and 3)

Table 2 shows that in the group of patients with ER-positive tumors (n = 96), recurring disease developed in 44 patients (46%) whereas in the ER-negative tumor group (n = 55), metastases developed in 23 patients (42%) ($p^* > 0.1$). However, the mean duration to recurrence was significantly longer for the patients with ER-positive tumors than for those with ER negative tumors: 37 vs 20 months ($p^{**} < 0.01$).

Analysing the DFI 1 year after initial treatment of each patient, there was a significant difference in DFI in favour of the group of patients with ER-positive tumors ($p<0.05$). After 24 and 36 months the differences in DFI between the two groups are merely indicative ($0.05<p<0.1$). However, analysing the data after 48 months, a significant difference in DFI between the two groups was no longer found ($p>0.1$). Accordingly, as shown in Fig. 2 after a median follow-up of 76 months, no significant difference was present between the two groups ($p>0.1$).

With regard to the menopausal state, in the premenopausal women no statistically significant difference in recurrence rate was found between the ER-positive and ER-negative group at any time of observation, not even in the first year (data not shown). The recurrence rate in the ER-positive group of postmenopausal women is significantly

Table 1. Clinical characteristics of the 175 patients with primary breast cancer and the ER status of the tumor tissue.

	ER-positive n = 115 (66%)	ER-negative n = 60 (34%)
- Age (years)		
mean	56	54
± S.D.	12	13
range	29–86	31–81
- Menopausal state		
premenopausal	46 (40)	28 (46)
postmenopausal	67 (58)	32 (54)
unknown	2 (2)	-
- T.N.M. classification		
$T_1T_2N_0$: 'good' prognosis	33 (29)	16 (27)
T_3T_4 or N_+: 'poor' prognosis	62 (54)	27 (45)
$T_1T_2N_0$: 'unknown' prognosis	20 (17)	17 (28)
- Surgical treatment		
modified radical mastectomy	59 (51)	25 (41)
ablation	40 (35)	23 (39)
excisional biopsy	16 (14)	12 (20)
- Radiotherapy	81 (71)	46 (77)
- Adjuvant chemotherapy (C.M.F.).	19 (16)	5 (8)

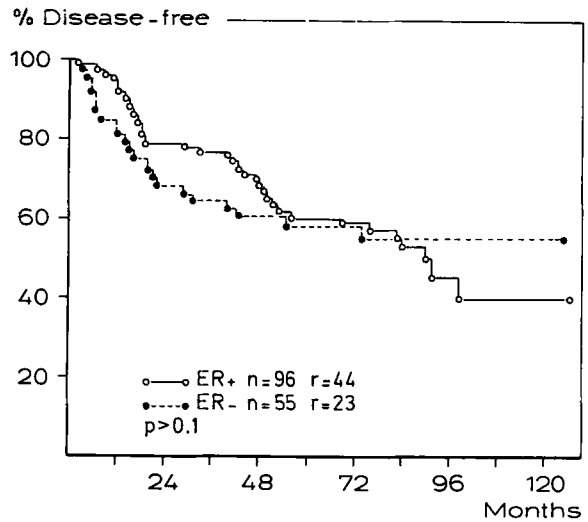

Fig. 2. Estimated disease-free interval and ER status of the primary tumor.

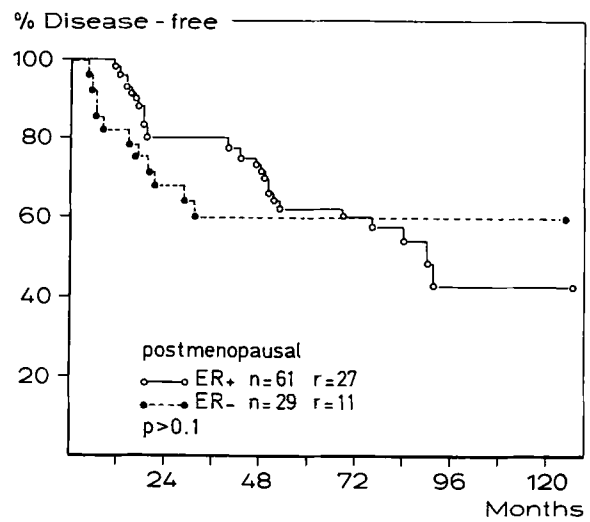

Fig. 3. Estimated disease-free interval and ER status of the primary tumor in postmenopausal patients.

lower after 12 ($p<0.02$), 24 ($p=0.05$), and still after 36 months ($p<0.05$). At longer follow-up this difference in recurrence rate had disappeared: after 5 years of observation 63% of the post-menopausal group of patients with ER-positive tumors and 61% of the ER-negative group was expected to be disease-free ($p>0.1$) (Fig. 3). The patterns of Figures 2 and 3 suggest that when patients with ER-negative primary breast cancer develop metastases, they tend to do so mainly in the first 3 years after initial treatment. After 3 years the number of recurrences in the ER-negative group decreases: only 4 of 35 patients with ER-negative tumors who were disease-free for more than 3 years relapsed thereafter, whereas in the ER-positive group 22 of 73 developed metastases ($0.05<p^*<0.1$).

DFI and prognostic staging based on tumor extension and lymph node status (Table 1, Fig. 1)

As expected, the patients with good prognosis had a significantly longer DFI than the patients with poor prognosis as shown in Fig. 1. At any duration of follow-up patients with poor prognosis have indeed a significantly higher recurrence rate than the patients with good prognosis. The patients with unknown prognosis had an intermediate risk of relapse at any time of follow-up, as was expected since this group of patients ($n=36$) is composed of patients with and without axillary lymph node involvement. In none of the three defined subgroups was a difference in DFI found between the groups of patients with ER-positive and ER-negative tumors (data not shown).

Table 2. Recurrence and ER status of the primary tumor (adjuvant chemotherapy excluded).

	Total number of patients (n = 151)	ER+ (n = 96)	ER− (n = 55)
Recurrence (n)	67	44	23
Time to recurrence (months)			
median	20	36	15
mean ± SD	32 ± 25	37 ± 26*	20 ± 18*
range	2–99	2–99	3–74

* $p^{**}<0.01$

Table 3. Review of literature on disease free interval and ER status of the tumor in patients with primary breast cancer.

Author	Number of patients n	ER+ %	Follow-up months	Comments
A. Significant difference in favour of ER+				
Knight (1)	145	63	median: 17	only N ≥4
Rich (2)	285	43	max.: 21	
Maynard (3)	232	56	max.: 36	only N+
Allegra (4)	182	57	median: 23	
Cooke (5)	286	51	mean: 19	
Kern (6)	53	49	range: 9–40	
Osborne (7)	281	73	not stated	
Pichon (8)	105	90	max.: 48	only postmenopausal
Westerberg (9)	270	74	mean: 22	
Hawkins (10)	233	not stated	not stated	
Cheix (11)	148	78	median:18	only N+
Blamey (12)	206	54	min.: 30	only N+
Rainer (13)	188	59	max.:34	only N+; postmenopausal
Gapinsky (14)	274	13 rich	median: 22	
Hartveit (15)	150	63	mean: 30	
Valagussa (16)	464	70	median: 36	only N_o; premenopausal
Bertuzzi (17)	99	78	range: 18–42	
Samaan (18)	198	58	mean: 36	only premenopausal
Kinne (19)	1034	47	median: 14	only N≥4
Godolphin (20)	583	71	max.: 60	
Crowe (21)	510	74	median: 51	only N_o
Raemaekers (22)	176	66	median: 34	only postmenopausal
Neifeld (23)	132	45	median: 25	ER+ ≥200 fmol/gr tissue
Paterson (24)	623	61	not stated	
Logan (25)	134	39	not stated	only premenopausal
Pascual (26)	136	54	all: 18	
Clark (27)	189	76	median: 41	only stage II
B. No significant difference in favour of ER+				
Hilf (38)	111	55	median: 52	
Bloom (39)	110	58	range: 6–24	first 6 months ER+ worse
Skinner (40)	98	57	mean: 19	
Kaufman (41)	95	66	max.: 22	
Stewart (42)	53	60	max.: 70	only stage III
Stewart (43)	390	74	max.: 70	stage I and II
Ciatto (44)	283	64	range: 10–42	
Mason (45)	437	58	median: 30	
Caldarola (46)	208	61	range: 30–72	
Howell (47)	508	70	median: 36	
Alanko (48)	263	61	mean: 41	
Aamdal (49)	233	71	median: 108	
Parl (50)	121	76	range: 60–144	
C. Significant difference in favour of ER+ only after short follow-up, but no longer after prolonged observation				
Hähnel (28)	335	53	range: 12–60	N.S. after 5 yr
Furmanski (29)	422	52	max.: 40	N.S. after 30 months
v. Maillot (30)	222	50	median: 46	N.S. after 7 yr
Howat (31)	175	58	median: 29	N.S. after 3 yr
Saez (32)	148	67	range: 36–102	N.S. after 4 yr

N = number of lymph nodes involved; N.S. = not significant

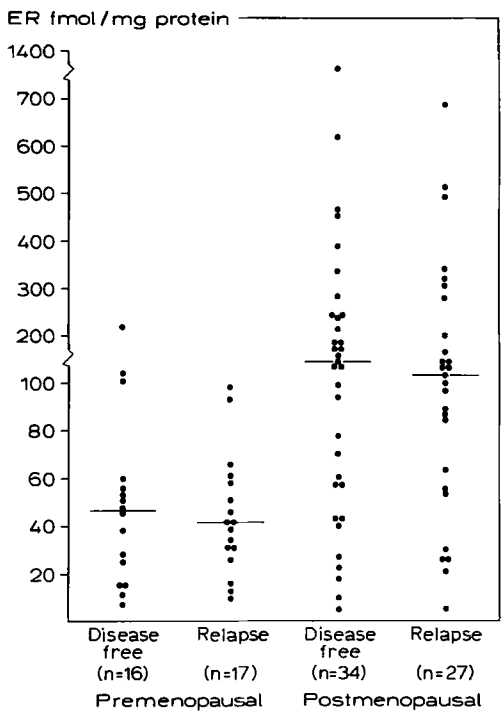

Fig. 4. Absolute ER values of the ER-positive tumors of those patients who relapsed and those who remained disease-free, related to menopausal state. n = number of patients.

DFI and quantitative ER activity

There were no significant differences in absolute ER levels between the patients with ER-positive tumors who relapsed and those who did not. As depicted in Fig. 4, this holds true in the premenopausal as well as in the postmenopausal patients. The median ER level in the premenopausal group of patients who did not relapse was 47 fmol/mg protein and for those who relapsed 42 fmol/mg protein. In the postmenopausal group of patients, the median values were 145 and 120 fmol/mg protein respectively.

Discussion

Earlier, we reported that patients with ER-positive primary breast cancer have a significantly longer estimated disease-free interval than patients with ER-negative tumors, although the difference was only significant in the postmenopausal group of patients (22). Those results were based on actuarial analysis of recurrence after a median follow-up of 34 months. The present study analysed the recurrence rate of primary breast cancer related to the ER status of the tumor on the strength of the recurrences in a rather large number of patients who were all under observation for at least 4 years, with the median follow-up of the whole group being 76 months. Our analysis shows that the prognosis in primary breast cancer in the short term is affected indeed by the ER status. However, for the patients with ER-positive tumors there seems to be a gradual but sustained risk of relapse throughout full length of follow-up, whereas patients with ER-negative tumors seem to develop metastases mainly in the first 3 years after initial treatment. This is substantiated by our finding that the mean disease-free interval of the patients who relapsed was significantly longer for the ER-positive than for the ER-negative group.

In the literature, most authors have reported a significantly longer estimated disease-free interval for the patients with ER-positive tumors, based on estimations of recurrence rates after a relatively short follow-up (Table 3A) (1–27). Knight et al. (1), Maynard et al. (3), Blamey et al. (12), Kinne et al. (19), and Clark et al. (27) found significant differences only in the group of patients with lymph node invasion, whereas Valagussa et al. (16) and Crowe et al. (21) established significant differences only in the lymph-node negative groups. Samaan et al. (18), Valagussa et al. (16), and Logan (25) found significant differences only in the premenopausal patients, whereas Pichon et al. (8), Rainer et al. (13), and Raemaekers et al. (22) stated that there was only a significant difference in the postmenopausal patients. A second group of authors (Table 3B) (38–50) found no difference at all between the ER-positive and ER-negative groups of patients, either after relatively short follow-up (Bloom et al. (39), Skinner et al. (40), Kaufman et al. (41), Stewart et al. (42 and 43), Ciatto et al. (44), Mason et al. (45), Howell et al. (47)) or after more prolonged follow-up (Hilf et al. (38), Caldarola et al. (46), Alanko et al. (48), Aamdal et al. (49) and Parl et al. (50)). Our data are in accordance with

those of Hähnel et al. (28), Furmanski et al. (29), v. Maillot et al. (30), Howat et al. (31), and Saez et al. (32) (Table 3C). These authors found significant differences in relapse rates only in the short term.

Our data indicate that patients with ER-positive breast cancer on long-term follow-up have no lower risk of recurring disease than those with ER-negative tumors, unlike the results of analysis on short-term follow-up which are indicative of fewer recurrences in the ER-positive group, at least in postmenopausal women.

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