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Estrogen Receptor as an Independent Prognostic Factor for Early Recurrence in Breast Cancer[1]

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SUMMARY

The usefulness of estrogen receptor measurements in primary breast tumors in the prediction of early recurrence was examined in a series of 145 patients. The absence of estrogen receptor in such tumors was associated with early recurrence independent of other known prognostic factors such as axillary lymph node status and tumor size.

INTRODUCTION

It is now established that patients with metastatic breast cancer are more likely to respond to endocrine therapy if their tumors contain ER+[3] (4). In addition, a survival advantage has been reported for those patients with ER+ tumors (7). We therefore inquired whether this survival advantage might be reflected in a longer interval between primary mastectomy and first recurrence. We now report that those breast cancer patients whose tumors are determined to be ER− at the time of primary mastectomy recur early and constitute a very high risk group.

MATERIALS AND METHODS

From September 1973 until September 1976, 145 women underwent modified or radical mastectomy for potentially curable breast cancer. All patients were operated on by the same group of San Antonio surgeons and had their tumors analyzed for ER by a Dextran-coated charcoal assay in the same laboratory (5). Tumors with levels less than 10 fmoles/mg cytosol protein were considered ER−; those with greater than 10 fmoles were ER+. Clinical information was obtained from the patient records and pathology reports. Recurrence of disease was documented by liver, bone, and brain scans; chest X-rays, and biopsy, if lesions were accessible. Statistical significance between groups was determined by the χ^2 test.

RESULTS

Chart 1 presents the recurrence data in 145 breast cancer patients. We found a statistically significant increase in early recurrence in those patients with ER− primary tumors. The median follow-up was 16 months in ER− and 18 months in ER+ patients.

We next considered whether the early recurrence in ER− patients might be due to a maldistribution of patients with positive axillary nodes, tumor size or location, etc. Table 1 presents the patient characteristics, ER distribution, and recurrence rate at 18 months. The majority of the patients were over 50 years old; these were less frequently ER−. However, regardless of age, early recurrence was more frequent in the ER− group.

ER− tumors were distributed evenly in all categories of axillary node status. Recurrence was clearly related to ER− status in each case, although only in the group of 4 or more positive nodes were the results statistically significant at $p < 0.05$. The higher overall recurrence rate among positive-node patients emphasizes the predominance of ER− recurrences, as seen in Chart 2. Some positive-node patients received additional postoperative radiotherapy and/or a variety of adjuvant therapies including chemotherapy and endocrine therapy. ER− tumors were distributed similarly in these groups, and again the recurrences were found predominantly in the ER− patients. Tumor size and location of the primary lesion are also considered in Table 1. Although ER− tumors were equally distributed among these subgroups, recurrences once again predominated in the ER− patients.

DISCUSSION

Walt *et al.* (7) have reported that ER− patients are more likely to develop visceral metastases and have a shorter survival. We have examined the prognostic implication of an ER− tumor determined at primary mastectomy and have found that recurrence is higher in ER− patients regardless of primary size, location of the tumor, number of involved axillary nodes, age, or adjuvant therapy.

The distribution of ER− tumors was similar in all of the above groups, except for age, wherein a significantly larger percentage of ER− patients were under 50 years old, and as a group ER− patients had a median age that was 9 years younger than that of ER+ patients. Nevertheless, within both age groups recurrence was higher in ER− patients.

Meyer and Bauer (6) have reported that primary breast tumors with a high growth fraction, as represented by a high thymidine-labeling index, are more subject to early recurrence, and it has been suggested that such tumors

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[3] The abbreviation used is: ER, estrogen receptor.

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Table 1
Prognostic factors, estrogen receptors, and recurrences in breast cancer patients

	No. of patients	ER distribution (% ER−)	% recurrence at 18 mos. ER−	ER+
Total no. of patients	145	37 (54)[a]	34 (14)	14 (13)[b]
Age				
<50	48	48 (23)	35 (8)	8 (2)[c]
>50	97	32 (31)	36 (11)	17 (11)[c]
Tumor-infiltrated axillary nodes				
0	71	35 (25)	12 (3)	6.5 (3)
1-3	24	33 (8)	38 (3)	12.5 (2)
≥4	50	42 (21)	62 (13)	27 (8)[c]
Postoperative radiation	57	40 (23)	43 (10)	21 (7)
Adjuvant therapies[d]	41	34 (14)	43 (6)	19 (5)
No adjuvant therapy[d]	33	46 (15)	67 (10)	28 (5)[c]
Size of tumor				
<2 cm	27	33 (9)	33 (3)	0 (0)[b]
2-5 cm	79	37 (29)	31 (9)	14 (7)
Location of tumor				
Inner and central	28	32 (9)	56 (5)	26 (5)
Outer	79	41 (32)	28 (9)	4 (2)[b]

[a] Numbers in parentheses, number of patients in each group.
[b] Horizontal comparison, $p = 0.01$.
[c] Horizontal comparison, $p = 0.05$.
[d] Node-positive patients only.

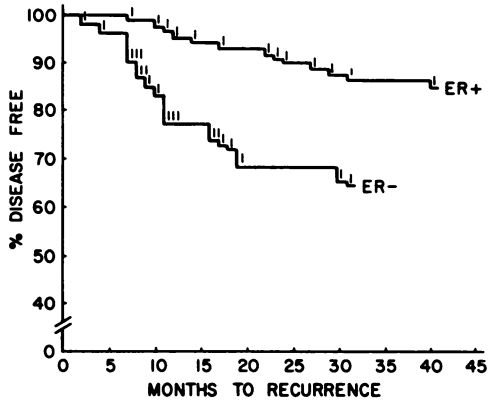

Chart 1. ER and recurrence in all patients.

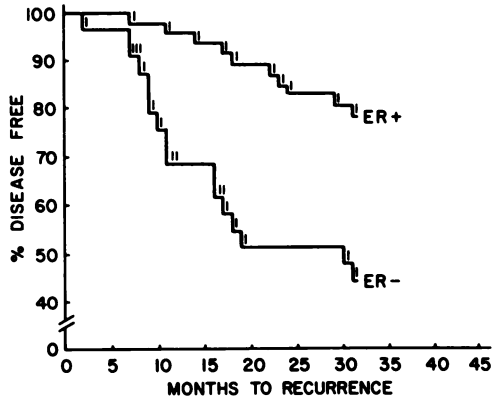

Chart 2. ER and recurrence in axillary node-positive patients.

are also more likely to respond to chemotherapy (3). Since we find ER− tumors with their associated early recurrence to be more common in premenopausal patients, this may explain why recurrence time is more affected by chemotherapy in these patients than in the postmenopausal group (1, 2). It may be that ER− will serve as a useful predictor of favorable response to adjuvant chemotherapy, while ER+ tumors, with more probability of a low growth fraction and a delayed recurrence, would be correspondingly less likely to benefit from this therapy. The present data do not permit a test of this hypothesis due to the relatively small numbers and the variety of adjuvant therapies used, but a prospective randomized trial of adjuvant chemotherapy incorporating ER data seems indicated.

In conclusion, we have identified a subgroup of primary breast cancer patients (ER−, node positive) who have a recurrence rate of 50% at 18 months. These patients should be treated aggressively with combination chemotherapy. ER determinations in primary tumors may be of help in the design of future adjuvant trials.

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