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The Influence of Hormone Receptors and Hormonal Adjuvant Therapy on Disease-free Survival in Breast Cancer: a Multifactorial Analysis*

LEONARDO CALDAROLA,†‡ PIETRO VOLTERRANI,† BEATRICE CALDAROLA,† MARIO LAI,† AUGUSTO JAYME§ and PIERO GAGLIA†

†*Istituto di Oncologia, Cattedra di Oncologia Chirurgica dell'Università di Torino, via Cavour* 31, 10123 *Torino, Italy and* §*Centro di Calcolo Molinette, Ospedale S. Giovanni, corso Bramante* 88/90, 10126 *Torino, Italy*

Abstract—*The prognostic value of estrogen (ER) and progesterone (PgR) receptor status and the influence of hormonal adjuvant therapy on disease-free survival (DFS) in breast cancer were evaluated in* 680 *women after radical and modified radical mastectomy. The effect of* 17 *variables, including clinical data, TNM, hormone receptor status, histology and adjuvant therapy, on the DFS observed was analyzed, using a multivariate proportional hazard model. Multifactorial analysis revealed that DFS was strongly related to the number of positive axillary nodes* ($P < 0.001$) *and the histological grade of the tumor* ($P = 0.05$). *Moreover, the DFS of ER-positive patients with node involvement was significantly improved by hormonal adjuvant therapy (tamoxifen). Combination of adjuvant chemotherapy with hormonal therapy did not enhance its effectiveness. Recurrence rates of either node-negative or ER-negative patients were not affected by either adjuvant therapy. When no systemic therapy was given, no significant relationship between ER or PgR content of the tumor and the DFS was observed. These findings suggest that hormone receptor status is not an independent prognostic factor but provides reliable information on responsiveness to adjuvant hormonal therapy which is very effective in patients selected on the basis of ER assay.*

INTRODUCTION

THE USE of estrogen (ER) and progesterone (PgR) receptor assays in early breast cancer to identify subsets of patients with high risk of recurrence after surgery is still a matter of debate. Several reports suggest that patients whose tumors lack ER and/or PgR have earlier recurrence and shorter survival [1–9], but no general consensus on this point has yet emerged [10–15].

Conflicting findings can be ascribed to differences in patient selection standards and treatment of the primary tumor, the administration of adjuvant therapy in some trials, and the timing of follow-up.

Many parameters influence the survival of breast cancer patients. Multifactorial analysis alone can indicate their prognostic significance in predicting outcome. It was used in this trial to investigate the prognostic value of ER and PgR status and the influence of hormonal adjuvant therapy on disease-free survival (DFS) after mastectomy for infiltrating breast carcinoma.

MATERIALS AND METHODS

Six hundred and eighty women subjected to radical or modified radical mastectomy for primary breast cancer at the Department of Oncology, University of Turin, between July 1976 and August 1984 were studied.

All tumors were staged according to the TNM system. Eligible patients had: (a) histological diagnosis of infiltrating breast carcinoma; (b) complete axillary node clearance; (c) no clinical evidence of distant metastases; and (d) assays for ER and PgR performed on samples from the primary lesion.

Tumor ER and PgR content was assayed with a dextran-coated charcoal technique. A total specific hormone binding capacity of 10 or more fmol/mg of cytosol protein was classified as positive, from 3 to 9 fmol/mg as borderline and less than 3 fmol/mg as negative. The histological grade of the tumor was measured by the method of Bloom and Richardson [16].

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‡To whom requests for reprints should be addressed.

Neither chemotherapy, radiation nor hormonal therapy was given before surgery. After mastectomy, 119 patients received chemotherapy (CMF, six cycles), 323 received hormonal adjuvant therapy (tamoxifen, 20 mg daily for 2 yr or more) and 390 were irradiated. These adjuvant therapies were variously combined. Follow-up ranged from 4 to 100 months (median, 49 months).

The effect of multiple variables on DFS was evaluated with a stepwise proportional hazard analysis. The association of putative prognostic factors with DFS was estimated in a multifactorial analysis, using Cox's proportional hazard survival regression models [17]. Recurrence curves were calculated from the product-limit estimate of Kaplan and Meier [18]. Statistical significance between curves was assessed using the Mantel–Cox test [19]. All data were processed with the BMDP programs elaborated by Health Science Computing Facility, UCLA.

RESULTS

Table 1 lists the 17 putative prognostic factors and their distribution.

The multifactorial analysis data for the whole series are shown in Table 2. Several factors seemed to affect DFS when examined singularly without reference to other factors (step 0). The prognostic value of a single factor is indeed affected by other parameters. In the subsequent steps, the reciprocal influences of single parameters were eliminated to give the dominant factors affecting DFS (final step): number of positive nodes ($P < 0.001$); administration of hormonal adjuvant therapy ($P = 0.005$); and histological grade ($P = 0.05$).

ER level was no longer significant after stepwise regression, showing that this parameter cannot be regarded as an independent prognostic factor. PgR showed no influence on DFS at any step. However, given the low rate of positive and borderline PgR cases in our series, further evaluation after a longer time of follow-up is necessary.

These results are confirmed by the multifactorial analysis on the 284 patients who did not receive systemic treatment after surgery (Table 3). Neither ER nor PgR status was associated with freedom from recurrence. Recurrence rates curves for ER $<$ 3 and ER $\geq$ 3 tumors in homogeneous subsets of patients not given systemic therapy are shown in Figs 1 and 2. The difference in recurrence rates between ER $<$ 3 and ER $\geq$ 3 was not significant in either pT1a2a pN0 ($P = 0.42$) or pT1a2a pN1 patients ($P = 0.50$).

Hormonal adjuvant therapy was a dominant prognostic factor and its possible relation with ER status, node status, histological grade of the tumor and menopausal status were therefore investigated. Patients with locally advanced cancer were excluded; pT1a2a tumors were stratified according to their node status and ER level. The influence of radiotherapy, chemotherapy and hormonal therapy on DFS was evaluated.

Multifactorial analysis did not show a significant relationship between the DFS of pT1a2a pN0 patients and any postoperative therapy (Table 4). In the pT1a2a pN1 subset, DFS was affected by

Table 1. *Variables examined by multifactorial analysis (No. of cases in parentheses)*

Age	range 27–90 yrs; mean 57.3 yrs
Menopausal status	premenopausal = last period $<$ 2 yr (233)
	postmenopausal = last period $\geq$ 2 yr (447)
Tumor size (pT)	pT1 (284); pT2 (289); pT3 (11); pT4 (96)
Tumor size (diameter)	range 2–80 mm; mean 25.6 mm
Node status (pN)	pN0 (344); pN1 (336)
No. of positive nodes	range 0–44; mean 3.1
ER status	negative $<$3 fmol/mg (236)
	borderline 3–9 fmol/mg (70)
	positive $\geq$10 fmol/mg (374)
ER level	range 0–681 fmol/mg; mean 42.2 fmol/mg
PgR status	negative $<$3 fmol/mg (568)
	borderline 3–9 fmol/mg (51)
	positive $\geq$10 fmol/mg (61)
PgR level	range 0–520 fmol/mg; mean 5.5 fmol/mg
Histotype	NOS infiltrating carcinoma (408)
	ductal infiltrating carcinoma (162)
	lobular infiltrating carcinoma (62)
	other infiltrating carcinoma (48)
Multicentricity	absent (518); present (162)
Vascular invasion	absent (617); present (63)
Histological grade	G1 (65); G2 (277); G3 (102); not evaluated (236)
Adjuvant radiotherapy	administered (390); not administered (290)
Adjuvant chemotherapy	CMF 6 cycles (119); not administered (561)
Adjuvant hormonal therapy	tamoxifen 20 mg daily (323); not administered (357)

Table 2. Multifactorial analysis (680 patients)

Single factors affecting DFS unaccounted for by other factors (step 0)	
Factors examined	*P* value
Age	N.S.*
Menopausal status	N.S.
Tumor size (pT)	0.003
Tumor size (diameter)	0.035
Node status (pN)	0.001
No. of positive nodes	<0.001
ER status	N.S.
ER level	0.021
PgR status	N.S.
PgR level	N.S.
Histotype	N.S.
Multicentricity	N.S.
Vascular invasion	N.S.
Histological grade	0.003
Adjuvant radiotherapy	N.S.
Adjuvant chemotherapy	0.006
Adjuvant hormonal therapy	0.031
Dominant factors affecting DFS after all other factors were accounted for (final step)	
Dominant factors	*P* value
No. of positive nodes	<0.001
Adjuvant hormonal therapy	0.005
Histological grade	0.05

*N.S. = not significant ($P > 0.05$).

Table 3. Multifactorial analysis of 284 patients who did not receive systemic adjuvant therapy

Single factors affecting DFS unaccounted for by other factors (step 0)	
Factors examined	*P* value
Age	N.S.*
Menopausal status	0.048
Tumor size (pT)	N.S.
Tumor size (diameter)	N.S.
Node status (pN)	0.004
No. of positive nodes	0.001
ER status	N.S.
ER level	N.S.
PgR status	N.S.
PgR level	N.S.
Histotype	N.S.
Multicentricity	N.S.
Vascular invasion	N.S.
Histological grade	0.048
Dominant factors affecting DFS after all other factors were accounted for (final step)	
Dominant factors	*P* value
No. of positive nodes	0.001

*N.S. = not significant ($P > 0.05$).

tamoxifen when the ER level was ≥3 fmol/mg. No other adjuvant therapy had any influence on DFS (Table 5).

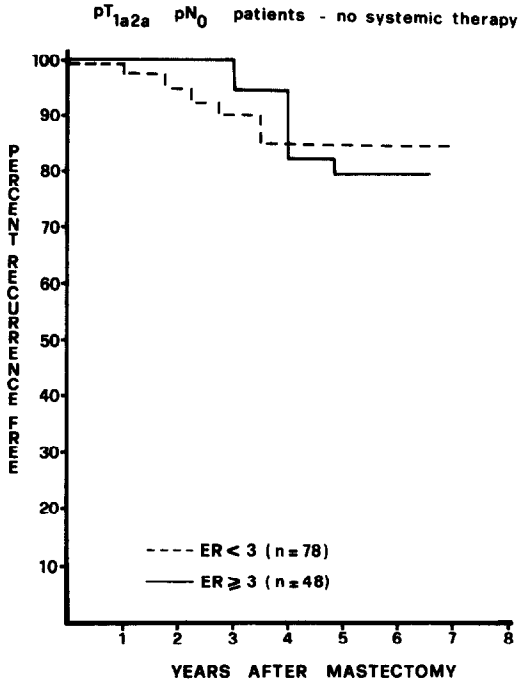

Fig. 1. Recurrence curves for pT1a2a pN0 patients (no systemic adjuvant treatment) divided according to ER level. The Mantel–Cox test indicates no significant difference between them (P = 0.42).

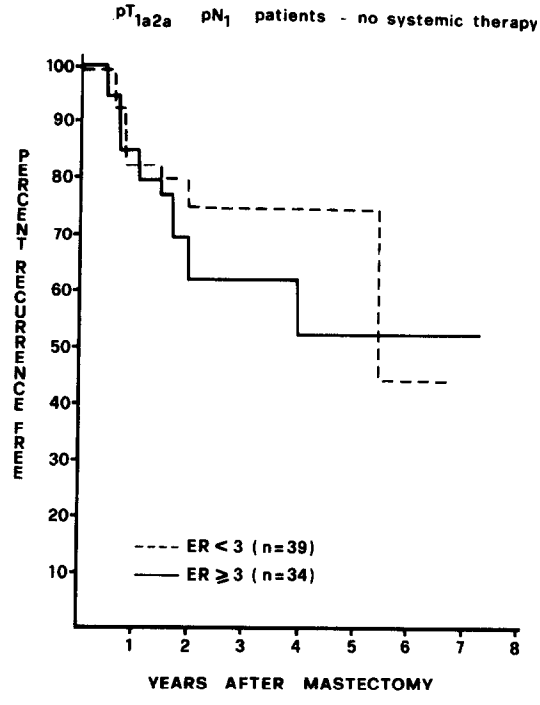

Fig. 2. Recurrence curves for pT1a2a pN1 patients (no systemic adjuvant treatment) divided according to ER level. The Mantel–Cox test indicates no significant difference between them (P = 0.50).

Figure 3 shows the recurrence curves for pT1a2a pN1 ER ≥3 patients grouped by function of the systemic adjuvant treatment administered. In each group listed in Fig. 3 a similar percentage of patients was also given radiotherapy (group A: 19/26; group B: 54/70; group C: 27/34; group D: 8/10). Patients who received tamoxifen alone or in

combination with CMF had a significantly lower recurrence rate than those who did not receive antiestrogens ($P < 0.05$). Furthermore, addition of chemotherapy did not improve DFS ($P = 0.44$).

Multifactorial analysis was then performed in tamoxifen-responsive patients (pT1a2a pN1 ER ≥3), stratified according to their number of positive nodes, menopausal status and histological tumor grade (Table 6). Tamoxifen affected DFS when less than four nodes were involved, and to a lesser extent above this figure ($P = 0.066$). There was no correlation between response to hormonal adjuvant therapy and menopausal status: $P = 0.048$ in premenopausal and $P = 0.026$ in postmenopausal patients. Only grade 1 and 2 ER ≥ 3 tumors were responsive to tamoxifen.

DISCUSSION

Conflicting data have been reported on the prognostic value of ER and PgR assay in breast cancer. In this work, 17 variables potentially influencing DFS of patients subjected to mastectomy were assayed by multifactorial analysis. This is a highly reliable technique since the relative importance of each factor is examined and the contribution of all the other factors is simultaneously accounted for.

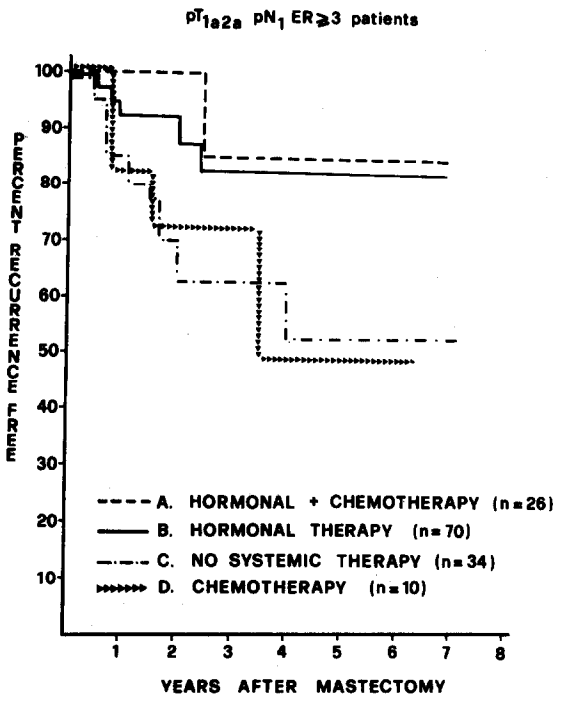

Fig. 3. Recurrence curves for pT1a2a pN1 ER ≥ 3 patients divided according to adjuvant treatment. The Mantel–Cox test indicates a significant difference between A and C (P = 0.019), *A and D* (P = 0.041), *B and C* (P = 0.023) *and B and D* (P = 0.048), *and no significant difference between A and B* (P = 0.44) *and C and D* (P = 0.69).

Table 4. Multifactorial analysis of 291 pT1a2a pN0 patients: factors (adjuvant treatments) affecting DFS (final step)

Factors	*P* value		
	ER < 3	3 ≤ ER < 10	ER ≥ 10
Radiotherapy	N.S.	N.S.	N.S.
Chemotherapy	N.S.	N.S.	N.S.
Hormonal therapy	N.S.	N.S.	N.S.

Table 5. Multifactorial analysis of 248 pT1a2a pN1 patients: factors (adjuvant treatments) affecting DFS (final step)

Factors	*P* value		
	ER < 3	3 ≤ ER < 10	ER ≥ 10
Radiotherapy	N.S.	N.S.	N.S.
Chemotherapy	N.S.	N.S.	N.S.
Hormonal therapy	N.S.	0.035	0.019

ER was shown not to be an independent factor in our series. In addition, the recurrence rates of ER-positive and -negative patients in homogeneous subsets (pT1a2a pN0 and pT1a2a pN1) did not differ when no systemic adjuvant treatment was administered.

By contrast, the analysis showed that administration of hormonal adjuvant therapy (tamoxifen) improves DFS. The favorable effect of tamoxifen was related to ER level, node status and histological grade of the tumor, but not to menopausal status. Only patients with node involvement and ER ≥ 3 had an improved DFS when hormonal therapy was given. The improvement was more

Table 6. Multifactorial analysis of 140 pT1a2a pN1 ER ≥ 3 patients stratified according to No. of positive nodes, menopausal status and histological grade: factors (adjuvant treatments) affecting DFS (final step)

Factors	*P* value					
	1–3 positive nodes	≥4 positive nodes	Pre-menopausal	Post-menopausal	Grades 1 and 2	Grade 3
Radiotherapy	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Chemotherapy	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Hormonal therapy	0.027	N.S. (0.066)	0.048	0.026	0.026	N.S.

significant when either less than four nodes were positive or the grade of the tumor was 1 or 2. Hormonal therapy was the only effective treatment and its combination with CMF did not give better results.

These findings are not new. The Nolvadex Adjuvant Trial Organisation showed that tamoxifen after surgery was followed by a better DFS irrespective of ER, node and menopausal status [20]. The control group received no systemic adjuvant therapy. Fisher and other NSABP investigators [21] and Pearson and co-workers [22] found that tamoxifen plus polychemotherapy (L-PAM plus 5-FU and CMF respectively) only decreases the number of recurrences at 5 yr in ER-positive (cut-off 10 and 3 fmol/mg respectively) patients with four or more involved nodes, and (Fisher) older than 50 yr.

Our data show that tamoxifen is a very effective adjuvant treatment in selected patients. They also suggest that hormonal therapy should be considered in the design of all adjuvant trials.

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