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Prognostic Value of Estrogen and Progesterone Receptors in Primary Infiltrating Ductal Breast Cancer

A Sequential Multivariate Analysis of 1262 Patients

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Abstract—*Nine prognostic variables were evaluated for their significance in predicting the overall survival (OS), the length of disease-free survival (DFS) and the length of metastasis-free survival (MFS) of 1262 patients with primary breast cancer. The variables studied were: UICC clinical stage; menopausal status; histologic grade; number of involved nodes; anatomic tumor size; estrogen and progesterone receptors; local and adjuvant therapies. Three sequential multivariate analyses, at 2, 5 and 10 years, using the Cox proportional hazard regression model, were carried out to identify those variables most highly related to the criteria studied (overall, disease-free, metastasis-free survivals) and especially to fully evaluate the effects of hormonal receptors on prognosis and their stability over time. Our results showed that number of involved nodes and histologic grade were the most significant prognostic factors for all periods of time and whatever the criterion studied; ER had no predictive value while PR was an independent prognostic factor for metastasis-free survival at 2 years (P = 0.01) and 5 years (P = 0.02) but lost its significance at 10 years (P = 0.06).*

In the subgroup of 261 patients who received prolonged post-operative adjuvant chemotherapies, PR was the main prognostic factor for MFS at 2 years (P = 0.03) and the second at 5 years (P = 0.05) just after number of involved nodes.

In the 1001 patients who did not receive prolonged post-operative adjuvant chemotherapies ER was significant for MFS at 5 and 10 years.

The present data urge the need for a periodic redefinition of prognostic factors in primary breast cancer.

INTRODUCTION

THE IMPORTANCE of estrogen and progesterone receptors as prognostic indicators in breast cancer remains controversial. Several authors conclude that patients with ER positive tumors have longer overall and disease-free survival than ER negative patients [1–9]. However, other studies with longer follow-up suggest that the beneficial effect of ER positivity on tumor recurrence gradually diminishes over time [10–13]. In addition, relatively few studies compare both ER and PR; and at present controversy also exists as to which hormonal receptor actually conveys the favorable prognosis [12–28]. Another limitation is that only four of these studies use a multivariate analysis to assess the effect of these hormone receptors on prognosis [17, 24, 25, 28], while all others rely solely on univariate analysis. An additional problem with published results is that the end point of the analysis is often only disease-free survival [1–3, 6, 8, 12–14, 16–18, 21, 25, 26, 28]. This end point fails to differentiate local from distal recurrences, a distinction which may affect prognosis and overall survival [29].

To clarify the relative effect of ER and PR on prognosis, we analyzed a large group of breast cancer patients who had both hormone receptors assayed and assessed with seven other factors of potential prognostic importance. We employed sequential multivariate analysis to evaluate the relative prognostic importance of ER and PR at various follow-up times (2, 5 and 10 years) with respect to DFS, metastasis-free survival (MFS) (distant DFS), and overall survival (OS). This approach allowed us to isolate the significance of various prognostic

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factors over time. Furthermore and unlike many other studies, all patients were followed at one institution under standard conditions, and all receptor studies were performed from primary tumors, in the same laboratory using identical methodology.

MATERIALS AND METHODS

(a) Patients

Clinical histories of all patients at our Center were entered on a computerized database and updated regularly. Patients for this study were treated at the Centre René Huguenin between December 1975 and February 1986.

All patients were staged at the time of their initial surgery according to the UICC classification of TNM [30]. Histological tumor grading was performed according to the method of Scarff, Bloom and Richardson (SBR) [31].

ER and PR studies were performed on the primary breast carcinoma in our laboratory in 2162 patients. Of these, 1262 who met the following criteria were selected retrospectively: (1) primary non-metastatic, unilateral breast cancer (disease confined to breast and axillary lymph nodes); (2) ductal carcinoma, (3) interpretable ER and PR assays on the primary tumor; (4) no prior therapy; (5) no second primary cancer (including breast) at any time; (6) full follow-up history available at CRH. These 1262 patients had complete clinical, histological and biological information sufficient to allow additional multivariate prognostic analysis. They had an identical distribution of age, histological grade, menopausal, TNM (by UICC classification) and hormone receptor status compared to the original 2162 patients. Several reasons explain the loss of patients for the multivariate analysis: first, the absence of one of the nine factors; second, patients lost to follow-up; third, carcinomas other than infiltrating ductal carcinomas.

Surgery was performed as primary therapy in all patients: 858 patients (68%) underwent modified radical mastectomy, and 404 (32%) a partial mastectomy with inferior axillary lymph node clearance. Six hundred and fifty-four patients had postoperative irradiation as part of locoregional treatment; 50–55 Grays with either a cobalt-60 or electron beam source to the breast (with partial mastectomy) and to the internal mammary, supraclavicular and axillary lymph nodes (if axillary lymph nodes were involved). Sixty-three patients with partial mastectomy also received perioperative bradytherapy. All patients received adjuvant perioperative chemotherapy consisting of 40–50 mg Thiotepa intravenously.

Two hundred and sixty-one patients (21%) also received prolonged post operative adjuvant treatment due to the following high risk factors for recurrence: if more than three axillary lymph nodes were involved; or if at least one involved axillary lymph node was present and the tumor was histologic Grade III or the patient was under age 35.

Three consecutive adjuvant chemotherapy protocols were employed during that period:

Period 1 from 1975 to 1978 ($n = 8$), 18 monthly cycles of VCMF (vincristine, 1 mg; cyclophosphamide, 500 mg; methotrexate, 15 mg; 5-fluorouracil, 500 mg).

Period 2 from 1978 to 1981 ($n = 99$), 12 cycles of FAC (J1 and J8: 5-fluorouracil, 400 mg/m^2; J1: Adriamycin®, 40 mg/m^2; cyclophosphamide, 400 mg/m^2).

Period 3 from 1981 to 1985 ($n = 154$), six cycles FAC followed by six cycles CMF (J1 and J8: 5-fluorouracil 600 mg/m^2, methotrexate 40 mg/m^2; J1–14: cyclophosphamide 100 mg/m^2/24 h).

In addition, over approximately the same periods, 164 patients (13%) also received endocrine manipulation as part of adjuvant treatment:

Period 1 ($n = 5$): surgical or radiocastration for pre-menopausal women;

Period 2 ($n = 61$): surgical or radiocastration and Tamoxifen for 3 years for postmenopausal;

Period 3 ($n = 98$): the same as Period 2 but selected on the basis of positive hormone receptors. PR− patients received no hormonal manipulation.

The mean and median follow-up period was 42 months (maximum 120). Most of the patients were entered between 1981 and 1985; this explains the relatively short median follow-up. The mean time to relapse 27 months (maximum 108); 631 patients had passed the median follow-up period with 315 patients followed longer than 5 years (60–120 months).

All the patients were followed post-operatively at the CRH. Physical examination, routine chest X-ray, multichemistry panels and CEA levels were performed every 3 months for 2 years, then yearly. Ultrasonographic liver scans and mammograms were performed yearly.

The disease-free survival was defined as the time from mastectomy to the first detection of local recurrence or distant metastasis, or the end of the study. Metastasis-free survival was the length of time to distant metastasis.

(b) Estrogen and progesterone receptor assays

Both ER and PR assays were performed in the same laboratory using a dextran-coated charcoal method, described by the EORTC [32], on tumors frozen and stored in liquid nitrogen. The detection limit was set at 10 fmol/mg proteins. Quality control was assured by frequent testing with both internal controls [33] and EORTC standards.

(c) *Statistical methods*

Tests for differences in distribution between hormone receptors and any of the studied patient characteristics were carried out by using chi-square tests. For the prognostic study, the criteria analyzed were the overall survival (OS), the disease-free survival (DFS) and the metastasis-free survival (MFS). Nine potential prognostic factors were analyzed in a multivariate analysis using Cox's proportional hazards regression model [34].

Menopausal status, UICC stage, histologic grade, local and adjuvant therapies were variables coded from zero to their respective maximum modalities minus one. All other variables were continuously expressed as: hormone receptor (fmol/mg), number of involved nodes (count) and anatomic tumor size (mm).

To detect the influence of prognostic factors during different time periods, sequential analyses were performed at 2, 5 and 10 years. The total follow-up period with an amplitude of 10 years was split into three observation phases represented by three successive time phases as follows: phase I had a maximum follow-up of 2 years from the study entry ($t = 0$); phase II had a maximum follow-up of 5 years, and phase III 10 years, both beginning with $t = 0$. An example is a patient with a 4-year follow-up where a distal metastasis was found 3 years after study entry; in phase I, her follow-up would be reduced to 2 years and be considered as not having a metastasis. For phases II and III, she would have a follow-up of 4 years with metastasis recorded at 3 years. Patients initial categorization remained unchanged.

RESULTS

A strong association was found between hormone receptors and histologic grade ($P < 10-6$) and nodal status ($P < 0.01$). ER− tumors had significantly ($P = 0.0003$) more involved lymph nodes than ER+ tumors. The significance was less important with PR ($P = 0.002$). Post menopausal women were more frequently ER+ ($P < 0.0001$), but PR status had no association with menopause.

Table 1 shows the characteristics of the 1262 patients entering the Cox analysis; 918 (71%) had ER+ tumors, and 700 (54%) had PR+ tumors. The mean concentration of ER was 86 fmol/mg protein, and of PR 92 fmol/mg protein.

Table 1. Characteristics of the 1262 patients entering the prognostic study

Variables	n(%)
Age	
Median 57 years	
Range 26–92	
UICC stage	
I	205 (16%)
II	846 (67%)
III	211 (17%)
Histological grading of Scarff, Bloom, Richardson	
I	143 (11%)
II	696 (55%)
III	423 (34%)
Axillary lymph node status	
0	654 (52%)
1–3	403 (32%)
>3	205 (16%)
Anatomic tumor size	
<15 mm	191 (15%)
15–29 mm	699 (55%)
≥ 30 mm	372 (30%)
Menopausal status	
Pre	499 (40%)
Post	763 (60%)
ER level	
<10 fm/mg (ER−)	344 (29%)
≥10 fm/mg (ER+)	918 (71%)
PR level	
<10 fm/mg (PR−)	562 (46%)
≥10 fm/mg (PR+)	700 (54%)
Adjuvant treatment	
Yes	261 (21%)
No	1001 (79%)
Local treatment	
MRM*	606 (48%)
MRM + RT†	252 (20%)
PM‡ + RT	404 (32%)
Total	1262

*Modified radical mastectomy.
†Radiation therapy.
‡Partial mastectomy.

Multivariate analysis with the Cox model in the 1,262 patients

Tables 2A, B, C presents all statistically important factors in the analysis for OS, DFS and MFS at the three follow-up phases.

With one exception (OS at 2 years), number of involved lymph nodes and grade were the most important factors for all time periods and type of survival studied, while ER did not appear as a significant prognostic factor.

Overall survival. In all cases, lymph node status had the highest prognostic power. Over the short term (2 years), the stage increased the predictability of death; over the long term, grade, tumor size and menopausal status were found to be prognostic factors.

Disease-free survival. For all time periods, number of involved lymph nodes, grade and stage are important prognostic factors. Hormone receptors (ER and PR) are not significant prognostic variables.

Table 2A. Results of the multivariate analysis in 1262 patients at 2 years follow-up

Variables	Coefficient	S.E.	*P* value
OS (70 deaths)			
Nodes	0.086	0.018	<0.000001
Stage	0.845	0.217	0.0001
DFS (138 events)			
Nodes	0.085	0.013	<0.0000001
Grade	0.516	0.149	0.00006
Stage	0.486	0.155	0.001
MFS (108 metastases)			
Nodes	0.094	0.014	<0.000000001
Grade	0.481	0.172	0.0001
Stage	0.459	0.177	0.01
PR	−0.002	0.001	0.01

Table 2B. Results of the multivariate analysis in 1262 patients at 5 years follow-up

Variables	Coefficient	S.E.	*P* value
OS (156 deaths)			
Nodes	0.071	0.014	<0.00000001
Grade	0.547	0.142	0.00001
Size	0.019	0.005	0.0008
Menopause	0.394	0.172	0.02
DFS (256 events)			
Nodes	0.078	0.010	<0.000000001
Grade	0.389	0.106	0.00003
Stage	0.339	0.112	0.002
MFS (199 metastases)			
Nodes	0.085	0.011	<0.00000001
Grade	0.400	0.124	0.00005
PR	−0.001	0.001	0.02
Size	0.012	0.005	0.03

Table 2C. Results of the multivariate analysis of 1262 patients at 10 years follow-up

Variables	Coefficient	S.E.	*P* value
OS (190 deaths)			
Nodes	0.069	0.013	<0.000000001
Grade	0.493	0.129	0.00001
Size	0.020	0.005	0.0002
Menopause	0.472	0.158	0.002
DFS (281 events)			
Nodes	0.076	0.009	<0.000000001
Grade	0.395	0.101	0.00001
Stage	0.293	0.107	0.006
MFS (217 metastases)			
Nodes	0.08163	0.01097	<0.000000001
Grade	0.44872	0.11766	0.00003
Size	0.01125	0.00523	0.038

A positive coefficient indicates that the presence of that factor correlates with decreased survival.

Metastasis-free survival. The main prognostic factors were the number of involved lymph nodes and histologic grade at the three phases of follow-up. Stage and PR were significant at 2 years. Tumor size and PR at 5 and 10 years (borderline at 10 years for PR).

As there have been varying results in the literature as to the relative importance of receptor studies in treated and non-treated patients, analyses were performed in relation to adjuvant chemotherapy.

Multivariate prognostic analysis with the Cox model in relation to prolonged post-operative adjuvant chemotherapies

In the 1001 patients who received only perioperative adjuvant chemotherapy, OS and DFS showed no difference for significant factors with ER the first factor dropped in the analysis (results not shown). For MSF, number of involved lymph nodes, grade, ER ($P = 0.004$) and tumor size were important in decreasing order, with PR the first factor dropped in analysis. At 10 years, ER still showed an effect upon MFS ($P = 0.002$) (Table 3).

In the 261 patients receiving adjuvant chemotherapy PR, not ER, appeared as the important receptor for prognosis if considered as a qualitative (but not quantitative) variable (Table 3). At short follow-up (2 years) it is even more important ($P = 0.03$) than nodal status, but this effect is lost over time.

DISCUSSION

Given the often contradictory findings in the literature with regard to the prognostic value of hormone receptors [1–28], we have attempted to better delineate the relative predictive accuracies of ER and PR in patients with primary operable breast cancer. Our patient population was found to have similar percentages of ER and PR as those previously reported. Also the relationship of these receptors with other prognostic factors appear similar to those other studies [35].

Sequential analyses were performed using the Cox model at three observation periods (2, 5 and 10 years) to evaluate the independent prognostic accuracy over time of nine factors including both hormone receptors. This multivariate analysis of our 1262 patients revealed nodal status and histologic grade as the most important factors for all types of survival at all time periods. Our study confirms other research [36–38] where histologic grade was the second important prognostic factor (after nodal status) in the multivariate equation. In none of the above studies, however, was hormonal receptor status considered in the analysis.

Since histologic grade is not always considered as a prognostic factor in multivariate studies, we excluded this factor from one of our models and still found no improvement in the contribution of the

Table 3. P *values of the multivariate analysis (metastasis-free survival) in relation to adjuvant chemotherapies*

Variable	Adjuvant chemotherapy $n = 261$	Number of metastases	No adjuvant chemotherapy $n = 1001$	Number of metastases
Phase I (2 years)		36		72
Nodal status	0.06		$<10^{-9}$	
Grade	N.S.		0.0003	
Tumor size	N.S.		0.009	
ER qualitative	N.S.		N.S.	
quantitative	N.S.		N.S.	
PR qualitative	0.03		N.S.	
quantitative	N.S.		N.S.	
Phase II (5 years)		71		128
Nodal status	0.003		$<10^{-9}$	
Grade	N.S.		0.00003	
Tumor size	N.S.		0.001	
ER qualitative	N.S.		0.002	
quantitative	N.S.		0.004	
PR qualitative	0.05		N.S.	
quantitative	N.S.		N.S.	
Phase III (10 years)		79		138
Nodal status	0.002		$<10^{-9}$	
Grade	0.014		0.0001	
Tumor size	N.S.		0.004	
ER qualitative	N.S.		0.01	
quantitative	N.S.		0.02	
PR qualitative	0.09		N.S.	
quantitative	N.S.		N.S.	

hormonal receptors to the prognostic equation (results not shown).

Our study may be criticized in that our entire patient group did not receive identical surgical and adjuvant treatments. It has to be noted that this is the case in most published studies. The administration of adjuvant chemotherapy (considered as a variable in our model) does not appear to be an important prognostic factor. It is possible, however, that certain subgroups may have benefited from adjuvant chemotherapy; however, axillary lymph node status remains a very strong prognostic factor in patients receiving prolonged adjuvant chemotherapy. This is not different from several other publications where adjuvant chemotherapy was not effective in patients with more than three involved lymph nodes [39–41]. If, according to our results, nodal status and grade are present throughout the period of observation, on the contrary, hormonal receptors are not consistently present except in metastasis-free survival where PR had a maximum effect on MFS up to 5 years and thereafter decreased with time. ER was found to have no prognostic value. These results are essentially similar to another large multivariate study [24] which demonstrated an almost identical prognostic value for PR at 10 years follow-up ($P = 0.05$).

In contrast, another Cox analysis of prognostic factors failed to show any significance for either ER or PR with a mean follow-up of 49 months [25]. In both studies, nodal status was again the most important prognostic factor. The conflicting results observed in the literature regarding the potential prognostic value of hormone receptors might have been biased because some patients received adjuvant chemotherapies. In our population, it was then interesting to compare the results obtained in patients receiving adjuvant chemotherapy to those obtained in patients who did not. In the subgroup not treated with chemotherapy, ER was important instead of PR for metastasis-free survival at 5 and 10 years, although of less importance than nodal status or grade. For the 261 patients treated by different protocols of chemotherapy, PR was the most important prognostic factor, particularly at short follow-up times, but only when PR was considered as a qualitative and not quantitative variable. This has been very recently observed by Raemaekers *et al.* in 82 patients treated by CMF [42]. McGuire *et al.* [24] observed that PR was a

prognostic factor in stage II breast cancer patients treated by adjuvant chemotherapy, while ER was more important in stage I patients. Therefore, the apparent lack of consensus on the prognostic significance of PR disappears if adjuvant treatments are taken into account. PR has no prognostic influence in patients who did not receive adjuvant chemotherapy, while it shows an important prognostic significance in patients receiving adjuvant chemotherapy or in patient populations including those who received adjuvant chemotherapy. Padmanabhan *et al.* [43] also observed this situation in pre-menopausal women and postulated that adjuvant chemotherapy could act primarily through an endocrine effect secondary to ovarian ablation induced by chemotherapy. Most patients with PR positive tumors receiving adjuvant chemotherapy have also received hormonal therapy, and it may be postulated that patients who respond to hormonal therapy (mainly PR+) also have a longer response to chemotherapy. This has been noted in patients with metastatic disease [44] and may play a similar delaying role in adjuvant studies.

The multivariate model as performed in this study is a demonstration of one method dealing with the interrelationships existing between prognostic variables in breast cancer and illustrates the limitations of the univariate analysis. Our patient population when studied by the log-rank test showed an important prognostic value for ER and PR for OS, DFS and MFS (results not shown). In multivariate analysis, however, variables differ widely from one study to another, leading to difficulties in comparing the results. Available reported analyses are also difficult to compare because of the differences in size and characteristics of patient population, receptor determination and cut-off points as well as differences in treatment and follow-up periods.

Several conclusions may result from our findings.

1. Nodal status and histological grade are major prognostic factors for all periods of time and type of survival studied.
2. The prognostic influence of hormone receptors, as already stated by others [24], appears to correlate not with the likelihood but with the timing of metastasis and they appear less important than nodal status and histological grade.
3. The interaction which appears from some recent studies between the effect of adjuvant chemotherapy and the presence of progesterone receptors emphasizes the need to take into account adjuvant treatments in the reappraisal of hormone receptor status primary breast cancer patients.

Prognostic factors should be periodically redefined to better identify patients who should receive further and/or more intensive therapy. Furthermore, newer prognostic factors such as tumor DNA content [45, 46] or oncogenes [47, 48] may lead to more critical selection of patient populations based on other biological characteristics.

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