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Factors influencing the prognostic role of oestrogen and progesterone receptor levels in breast cancer—results of the analysis of 670 patients with 11 years of follow-up

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Abstract

In the last two decades, the prognostic role of the steroid hormone receptors has been the subject of a myriad of publications. Nevertheless, its relevance after long-term follow-up is still not clear. The confusion about the prognostic value is mainly due to the difficulty in comparing analyses. Despite different study-designs and statistical approaches, oestrogen (ER) and progesterone (PR) receptors are widely accepted as prognostic factors. Data from 670 breast cancer patients with a median follow-up of 11.4 years were analysed retrospectively. ER and PR were measured by the dextran-coated charcoal (DCC) assay. To investigate the time dependence of the prognostic relevance of ER and PR, separate analyses were done for follow-up shorter and longer than 5 years. Special focus was directed at patients $\leqslant 50$ and >50 years, node-negative women, in particular those without adjuvant therapy. Univariate and multivariate analyses were performed. In univariate analysis, ER and PR were associated with a significantly longer overall survival at the cut-off levels 10, 20 or 100 fmol/mg protein. The significant survival benefit occurred in the first 5 years of follow-up and remained unchanged in the following period. In the multivariate analyses, only the PR was of significant prognostic value (for PR $\geqslant 20$ fmol/mg $P=0.036$, for PR $\geqslant 100$ $P=0.01$, Cox analysis). In patients younger than 51 years, only PR was an independent prognosticator at the cut-off level of 100 fmol/mg protein, while in patients >50 years both hormone receptors were not significant. In N0 patients, only the PR reached long-term prognostic independence at a cut-off point of $\geqslant 100$ fmol/mg ($P=0.018$). In addition, in the group of node-negative women $\leqslant 50$ years without adjuvant therapy the PR level reached prognostic significance. The hormone receptor status was a prognostic factor only during the first 5 years of follow-up. Our data suggest that age, lymph node status, length of follow-up and probably the ER/PR assay are important for the evaluation of ER and PR as prognostic variables. In most analyses, PR appeared to be superior to ER in predicting the prognosis of primary breast cancer patients.

Keywords: Breast cancer; Oestrogen receptor; Progesterone receptor; Overall survival; Long-term follow-up; Prognosis

1. Introduction

The prognostic role of the steroid hormone receptors ER and PR in patients with breast cancer has been investigated extensively in the last 20 years. It has been shown that the ER status is age-dependent [1–3], but the exact mechanism of the biological relationship between oestrogen receptor expression and age, menopausal status, fluctuations of endogenous hormone concentrations and ER-synthesis has remained unclear. PR is a product of ER [1,4]. In addition, endogenous hormones—especially in the premenopause—are considered as factors influencing the biochemical oestrogen receptor assay, presumably by binding to ER/PR thus rendering them falsely-negative [5,6]. Despite this knowledge, most authors have not included age and/or menopausal status in their investigations as important discriminators of the prognostic value of the steroid hormone receptors analyses [3,7–18].

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The majority of the available data do not refer to aspects such as receptor content [3,7,8,10–21], both types of receptors [7,11,17,18,21], a possible time-dependent effect [3,7,8,10,12,13,16–18,20,21] and nodal status [3,8,11,12,16,21], due to mostly small patient populations [11,12,20–22] and to short follow-up times [8,16,20,22,23]. Cut-off levels for receptor positivity have also been a matter of debate. For the biochemical dextran-coated charcoal (DCC) assay, various cut-off levels of 5, 10, 15 or 20 fmol/mg protein have been proposed and receptor concentrations higher than 100 fmol/mg protein have been considered as 'extremely high' ER expression.

Therefore, we investigated the prognostic significance in 670 patients with primary breast cancer and a median follow-up of 11.4 years. Prognostic relevance was related to overall survival (OS). The aims of the study were to determine the prognostic relevance of both ER and PR at different cut-off points in relation to age, axillary lymph node status and follow-up time.

2. Patients and methods

The records of 918 patients treated at the University Women's Hospital Heidelberg for primary breast cancer during the years 1978–1983 were reviewed. 112 patients with metastases at the first diagnosis or a previous history of cancer were excluded from analysis. In addition, a further 98 patients were excluded because of unknown causes of death and 38 because hormone receptors had been determined in metastatic lymph nodes, but not in the primary tumor specimen. All remaining 670 patients underwent either a modified-radical mastectomy or conservative breast surgery. 62% of the women received adjuvant chemotherapy and/or hormone therapy. The investigated clinical parameters were: age, menopausal status, tumour size and axillary lymph node status (considered only if at least 10 axillary lymph nodes had been removed) (Table 1).

Oestrogen and progesterone receptor content was measured by the biochemical DCC method [24]. All statistical analyses were done at cut-off levels of 10, 20 and 100 fmol/mg protein. If not otherwise mentioned, the described results relate to 20 fmol/mg protein for both receptors.

The statistical analysis was done with the scientific statistical program of the SAS Institute (SAS Institute Inc., Cary, NC, USA). Life table analyses was performed using the Kaplan–Meier technique and significance was tested by the log-rank test. The multivariate analysis was performed using the Cox proportional hazards regression model [25], including the parameters lymph node status, tumour stage, age, menopausal status and the hormone receptor status. Cox regression analysis was also used to estimate the risk ratio (RR). Patients dying of causes other than breast cancer were treated as censored ($n=58$). Significance was set at the 5% level ($P<0.05$).

Table 1
Clinical characteristics of 670 pts

Factors	Number (%)
Tumour stage	
T1	234 (35)
T2	346 (52)
T3	53 (8)
T4	37 (6)
Nodal status[a]	
N0	268 (45)
N+	325 (55)
Age (years)	
$\leqslant 50$	304 (45)
>50	366 (55)
Menopausal status[b]	
Premenopausal	271 (44)
Postmenopausal	349 (56)
Adjuvant therapy (all pts)	
ER+ (and/or PR+)	240 (65)
ER− and PR−	159 (45)

pts, patients; ER+, oestrogen-receptor-positive; ER− and PR−, oestrogen-receptor-negative and progesterone-receptor-negative.

[a] 77 patients excluded from further analysis, because less than 10 axillary lymph nodes were removed.

[b] in 50 patients, menopausal status were unknown.

To estimate the survival probability, the study design we used included four steps. In the first step, we analysed the total population ($n=670$) for the prognostic significance of the steroid hormone receptors. In the second step, we distinguished between lymph node-positive and lymph node-negative patients. In the third step, we divided the patients into a subgroup of women younger than 51 years ($\leqslant 50$ years) and women older than 50 years (>50 years). The fourth and last step of the calculation included four subgroups: women younger than 51 years either with or without involved nodes as well as women older than 50 years either with lymph node-negative or -positive breast cancer. The analyses are related to three different periods of time: the total follow-up-time, the first 5 years, both analyses including all patients, and the time greater than 5 years, including only women with an overall survival longer than 5 years.

3. Results

The characteristics of patients are shown in Table 1. The median age of the patients was 53 years (range 26–89 years); 55% of all patients were older than 50 years. Tumours in stage T2 were the most common (52%), followed by tumours smaller than 2 cm (35%). 13% of

Table 2
ER and PR in breast cancer - age distribution of various cut-off levels

Receptor status	All patients ($n=670$) n (%)	$\leqslant 50$ years ($n=304$) n (%)	>50 years ($n=366$) n (%)
ER $\geqslant 10$	458 (68)	182 (60)	276 (75)
ER $\geqslant 20$	371 (55)	134 (44)	237 (65)
ER $\geqslant 100$	152 (23)	23 (8)	129 (35)
PR $\geqslant 10$	381 (67)	167 (66)	214 (68)
PR $\geqslant 20$	323 (57)	141 (56)	182 (58)
PR $\geqslant 100$	166 (29)	80 (32)	86 (27)
ER+PR+[a]	238 (42)	90 (36)	148 (47)
ER+PR−[a]	76 (13)	22 (9)	54 (17)
ER−PR+[a]	85 (15)	51 (20)	34 (11)
ER−PR−[a]	168 (30)	90 (36)	78 (25)

ER, oestrogen receptor; PR, progesterone receptor. 10, 20 and 100 are cut-off points for ER and PR in fmol/mg cytosol protein.
[a] Cut-off level = 20 fmol/mg protein for ER and PR.

patients had tumour stages T3 and T4. The nodal status was negative in 268 patients (45%). 65% of the ER+ and/or PR+ patients ($n=240$) received adjuvant therapies compared with only 45% ($n=159$) of the receptor-negative patients. In the ER/PR-positive group, adjuvant therapy consisted of tamoxifen (61%), chemotherapy (23%, mostly cyclophosphamide, methotrexate and 5-fluorouracil (CMF)) or combinations of both (16%). 57% of the treated receptor-negative patients received chemotherapy, 13% tamoxifen and 30% combinations.

ER and PR values according to age are presented in Table 2. Most of the patients younger than 51 years had ER and PR values $\geqslant 10$ fmol/mg protein (60 and 66%, respectively). At the University Women's Hospital Heidelberg, patients were considered ER+ and PR+ only if the receptor content exceeded 19 fmol/mg. Thus, 44% of these patients were ER+ and 56% PR+. When both receptor types were known, 36% of the patients had values $\geqslant 20$ fmol/mg, while the combinations of ER+/PR− or ER−/PR+ accounted for 9 and 20%, respectively. In patients >50 years, 65% had ER values $\geqslant 20$ fmol/mg and 58% PR values $\geqslant 20$ fmol/mg, thus being considered receptor-positive. The most frequent combination of receptors was ER+PR+ in 47% of the cases (both $\geqslant 20$ fmol/mg) in this age group. The median follow-up of the 670 patients was 11.4 years (=137 months).

Kaplan–Meier analysis of the survival of all patients and the corresponding univariate analysis are presented in Fig. 1. Breast cancer patients with ER-positive or PR-positive tumours (i.e. $\geqslant 20$ fmol/mg protein) had a significantly longer overall survival (69 and 68% alive after 10 years) than ER-negative or PR-negative patients (56 and 55%) ($P=0.001$ for ER and $P=0.002$ for PR). When the receptors were combined, 10-year survival was 73% for ER+PR+, 58% for ER+PR− and 55% for ER−PR+ and 54% for ER−PR− ($P=0.0005$). The survival advantage for receptor-positive patients occured during the first 5 years of follow-up and no further increase was noticed during the following period (Fig. 1). Multivariate analysis revealed that only the PR at a cut-off level of 20 and 100 fmol/mg protein was an independent prognostic factor besides nodal status, tumour stage and age.

Median follow-up of 268 node-negative patients was 12.4 years. In this group, 52 of 166 ER-positive patients received adjuvant tamoxifen (34%), while only 6 of 102 (6%) ER-negative patients had adjuvant therapy. Only PR was associated significantly with survival (Fig. 2) and this applied to all cut-off levels. In contrast,

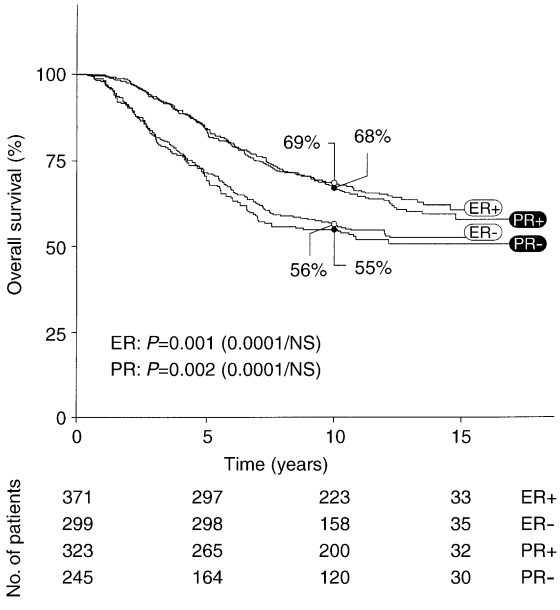

Fig. 1. Kaplan–Meier curves for the survival of all patients ($n=670$) stratified by ER and PR (cut-off point 20 fmol/mg protein). Significance levels in parentheses are related to both intervals $\leqslant 5$ years and >5 years. The numbers of patients below the panels are the numbers at risk. ER, oestrogen receptor; PR, progesterone receptor; No., number, NS, non-significant.

multivariate analysis showed a significance only for high levels of PR ($\geqslant$100 fmol/mg protein).

In order to investigate the prognostic relevance of ER and PR in relation to age, patients were divided in two groups according to the age of 50 years. This age was chosen as an approximation of the menopausal status, thus considering women $\leqslant$50 years premenopausal and women $>$50 years postmenopausal. In the subgroup of patients $\leqslant$50 years, univariate analysis revealed a significantly longer survival for receptor-positive patients at almost all cut-off levels except for the ER at a cut-point of 10 ($P=0.08$) and 100 fmol/mg protein ($P>0.1$) (Fig. 3). Using the Cox proportional hazard model, only PR at a cut-off-level of $\geqslant$100 fmol/mg protein was of independent value for outcome.

In the age group older than 50 years, only the parameters ER+ and ER+PR+ at a cut-off point of 10 and 20 fmol/mg protein reached prognostic significance (Fig. 4). The multivariate analyses revealed no significance of the receptor status after a median follow-up of 11.3 years.

In a subsequent analysis, patients were subdivided in four groups according to age ($\leqslant$50 and $>$50 years) and nodal status (N0 and N+). In the subgroup of node-negative patients $\leqslant$50 years ($n=110$), the probability of long-term survival was equal for ER-positive and ER-negative patients, but significantly different if the PR was considered ($n=87$), independently of the cut-off point. In the Cox regression analysis, the PR at a cut-off point of 20 fmol/mg protein was the only significant independent parameter in the short-term follow-up ($\leqslant$5 years) with a 6 times higher relative risk of dying if the PR was lower than 20 fmol/mg protein ($P=0.038$, RR = 6). In this group, only 4 women received adjuvant

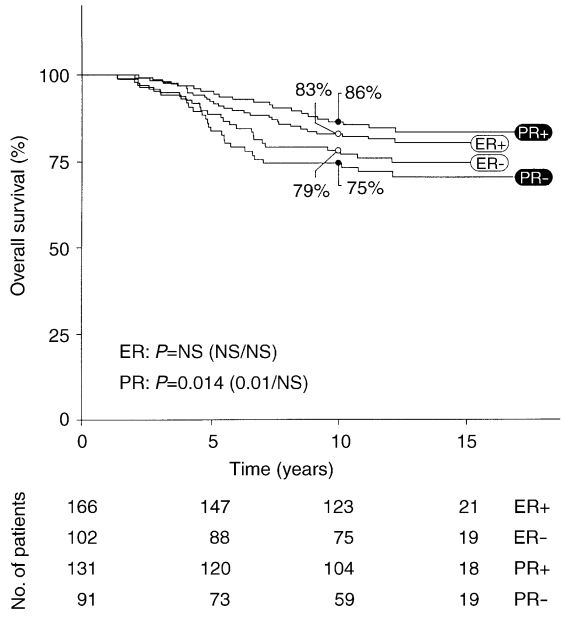

Fig. 2. Kaplan–Meier curves for the survival of node-negative patients ($n=268$) stratified by ER and PR (cut-off point 20 fmol/mg protein). Significance levels in parentheses are related to both intervals $\leqslant$5 years and $>$5 years. The numbers of patients below the panels are the numbers at risk. ER, oestrogen receptor; PR, progesterone receptor; No. number, NS, non-significant.

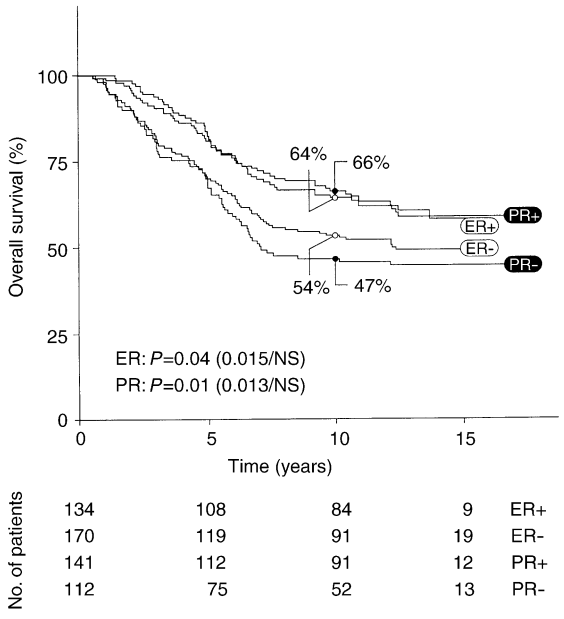

Fig. 3. Kaplan–Meier curves for the survival of patients $\leqslant$50 years ($n=304$) stratified by ER and PR (cut-off point 20 fmol/mg protein). Significance levels in parentheses are related to both intervals $\leqslant$5 years and $>$5 years. The numbers of patients below the panels are the numbers at risk. ER, oestrogen receptor; PR, progesterone receptor; No. number, NS, non-significant.

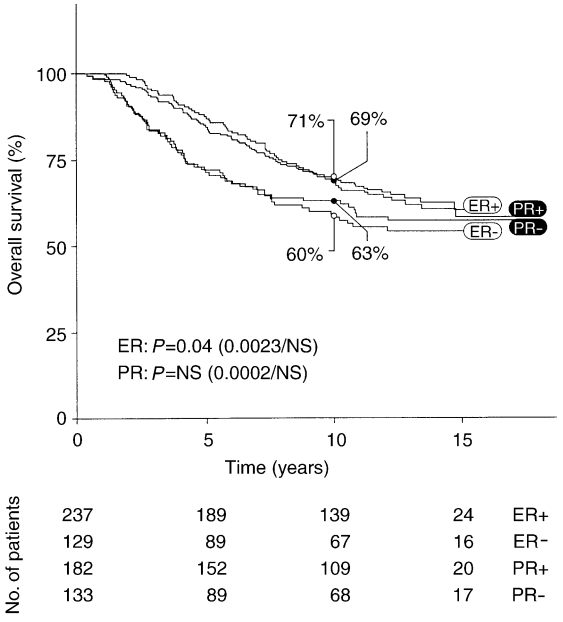

Fig. 4. Kaplan–Meier curves for the survival of patients $>$50 years ($n=366$) stratified by ER and PR (cut-off point 20 fmol/mg protein). Significance levels in parentheses are related to both intervals $\leqslant$5 years and $>$5 years. The numbers of patients below the panels are the numbers at risk. ER, oestrogen receptor; PR, progesterone receptor; No. number, NS, non-significant.

therapy. For node-negative patients older than 50 years, steroid hormone receptors did not correlate significantly with survival.

4. Discussion

In this study, the prognostic relevance of ER and PR was investigated in 670 patients with primary, operable breast cancer with a long median follow-up of 11.4 years. In spite of the huge amount of papers on ER/PR and prognosis, only a few publications have dealt with such high numbers of patients followed-up for more than 9–11 years [3,7,9,14,15,17,19,26,27]. Our data provide evidence for a crucial difference between univariate and multivariate analysis of the prognostic significance of ER and/or PR. If ER and/or PR associations with prognosis are investigated by an univariate method (Kaplan–Meier analysis, log-rank test), several significant results will be found. The multivariate analysis reveals mostly no significance for ER and/or PR, suggesting that they cannot be considered as independent factors.

Some authors [3,19,27] agree that patients with ER-positive breast cancers have longer overall survival than patients with ER-negative tumours, but this is partly restricted either only to specific subgroups [27] or to the first 5 years [9,19]. Our data show a significant longer survival for ER- and/or PR-positive patients only during the first 5 years. After 5 years of follow-up, receptor-positive and -negative patients have nearly the same risk. There might be a strong relationship between the hormone-receptor status and the proliferative capacity [28], nevertheless a coherence between receptor status and rate of metastasis cannot be excluded.

The analysis of the role of adjuvant therapy in our patients is of limited value because the data have been collected retrospectively. However, it is interesting that more ER/PR-positive patients were treated adjuvantly than ER/PR-negative patients. If the benefit of adjuvant tamoxifen as shown by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses [31] is considered, one would expect even more significant differences in favour of the treated, receptor-positive patients. Our data show differences only in the univariate analysis, while a lack of significance in the Cox analysis suggests that neither ER nor PR is independent prognosticators.

If the causes of death were not taken into account, the analysis revealed no significant relationship between ER and prognosis. However, the results become statistically significant if the patients dying of causes other than breast cancer are censored. Only a few authors have used this approach [14,18,19,27], while others leave this point unanswered [7,21]. This could be one reason for the different findings in terms of the prognostic value of ER/PR.

Collett and colleagues found significant results between ER and prognosis only in lymph node-positive patients [19]. Our results confirm these findings, except for a cut-off level $\geqslant 100$ fmol/mg protein. However, the survival analysis stratified by PR revealed significant P values. In node-negative patients, only the PR content of the tumours is significantly related to survival and multivariate analysis, suggesting that PR is an independent prognostic factor in these patients. These results are also found in the group of node-negative women $\leqslant 50$ years independent of adjuvant therapy.

Some authors suggest that the lack of correlation between ER and survival in node-negative patients might be due to the good prognosis, implying low rates of events (relapse and/or death) if the number of patients is low and the follow-up time is short [27,29]. Two decades ago, most of these patients received no adjuvant treatment, and this group of patients appeared to be the most appropriate for the analysis of prognosis because there was no interference from therapeutic effects. In our own analysis of 268 node-negative patients, the median follow-up time is long enough (12.4 years) and the incidence of events (80, i.e. 30% of the patients) warrants statistical power. Despite the fact that 34% of the ER-positive patients received tamoxifen and only 6% of the ER-negative patients had any adjuvant therapy, only PR correlated with survival while ER had no prognostic value in this group. These findings strongly suggest a prognostic role for PR rather than for ER.

Stratification of ER and PR according to age revealed a weak association between ER and survival in patients younger than 51 years (significance only at one cut-off level, namely 20 fmol/mg) mainly due to the merging of the survival curve with longer follow-up. In this subgroup of patients, the Kaplan–Meier analysis resulted in significant P values for PR at all cut-off levels. These results are in agreement with recent findings [22,23,27]. This finding might be due to the biochemical DCC-method since high levels of circulating oestrogens in premenopausal women could hinder receptor binding in the assay. Some authors have suggested that receptor profiles ER−PR+ are falsely-negative for ER, being in fact assay artifacts [5,6]. Theoretically, PR is a product of an intact oestrogen–ER pathway and thus PR positivity is only possible if ER is also expressed. Thus, the constellation ER+PR− might indicate falsely-positive ER levels or inactive/non-functional ER. In a separate analysis of almost 30% of the patients, these receptor combinations were excluded. Interestingly, now ER positivity was associated with a survival benefit, suggesting that the DCC assay interferes with the results in some cases. This methodological shortcoming might be surmounted by determining ER/PR immunohistochemically. As shown by Kinsel and coworkers (1989), comparison between the prognostic relevance of

biochemical and histochemical ER levels revealed significance for ER measured by histochemistry, but not for the DCC method after a follow-up of 6.2 years [11]. The correlation between the two methods was only 0.63.

Interestingly, the PR values appear not to be significantly affected by the receptor-measurement assays [30,11,12]. In patients older than 50 years, ER correlates significantly with survival, while PR loses its significance with longer follow-up. This could be due to a decreased intracellular PR synthesis as a result of a lower circulating oestradiol concentration in postmenopausal women.

In conclusion, our data suggest that age, lymph node status, length of follow-up and probably the ER/PR assay are important for the evaluation of ER and PR as prognostic variables. Statistical analysis should include censoring for the cause of death to assess the prognostic relevance of ER and PR reliably. In most analyses, PR appeared to be superior to ER in predicting the prognosis of primary breast cancer patients.

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