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The Prognostic Role of Progesterone Receptor Status and Age in Relation to Axillary Node Status in Breast Cancer Patients

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Abstract—*The prognostic role of axillary lymph node status, progesterone receptor (PgR) status, age of the patient at operation, oestrogen receptor (ER) status and tumour diameter was studied in 443 breast cancer patients treated by modified radical mastectomy. Logistic and proportional hazard regression analyses were used to estimate the prognosis from the time of operation up to 60 months. We also estimated the prognosis from 36 to 60 months for those who had survived 36 months (conditional analysis).*

PgR and age gave significant information in each node class, old age and PgR negativity being disadvantages. PgR status relative to node status was more important for estimating early (24 months) prognosis, while age was of more importance later (60 months).

Node status and age were the only variables giving significant information in the conditional analyses. It is thus of importance to consider the time dependency of the prognostic variables when predicting survival in breast cancer patients. No effect was found for ER status or tumour diameter.

INTRODUCTION

EVALUATION of oestrogen receptor (ER) status in breast cancer is well established in clinical practice, while progesterone receptor (PgR) status has been less studied. PgR positive tumours have been found to be associated with later recurrence and prolonged survival or less metastatic occurence. The trend is strong in node positive patients, but less obvious in the node negative [1–7].

There is considerable uncertainty as to the prognostic role of age in breast cancer patients. Most works focus on young women. Some have reported that young women have a prognosis worse than older ones [8, 9], while others have found survival in young patients to be comparable to that of old patients [10, 11]. Younger women have also been reported to have a better prognosis than older ones [12, 13].

Most survival analyses in breast cancer concentrate on estimating survival from the time of operation. The clinician, however, also needs estimates for those who have survived a certain period. If the patients have not developed symptoms of distant metastases, the clinician is left with the information gathered at the time of operation.

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This work studies the prognostic effect of node status, PgR status, age at operation, ER status and tumour diameter, and in addition also tests their importance later in the course of the disease.

MATERIALS AND METHODS

This study is based on a consecutive series of 443 breast cancer patients treated by modified radical mastectomy with axillary node dissection. The specimens were received at this Institute between January 1976 and November 1984. No preoperative treatment had been given. All histological types were included. Node metastases were present in 195 (44%) and absent in 248 (56%) patients. A mean of 8.5 lymph nodes (range 1–30) were examined in the total material. In the node positive group a mean of 3.6 out of 9 lymph nodes were positive.

The patients were followed up via data from the Norwegian Cancer Registry to their death or to October 1985. No information was available on antihormonal treatment. Choice of treatment, however, was based on ER status only, PgR status not being taken into consideration.

The proportional hazard regression and logistic regression methods were used as programmed in BMDP2L and BMDPLR, respectively [14].

The proportional hazard regression method assesses the relation between a prognostic variable

and the time to death or the last follow-up. The strength of this relationship is indicated by the estimated regression coefficient. Variables with significant regression coefficients (log likelihood ratio tests, $P < 0.05$) are included in a model which estimates the death rates for groups of patients. The significance of the variable can be judged from the regression coefficient and its standard error. The ratio between the two should not drop below 2.0. This is also the case in the logistic regression method.

The proportional hazard regression method relies on the assumption that the ratio of the death rates in subgroups of patients given by the levels of a variable, does not change with time. This proportionality assumption was checked for each variable using plots of the log minus log survival function [14]. For variables that violated the assumption, stratified analyses were carried out as recommended by Kalbfleisch and Prentice [15].

A total of 443 patients was included in the proportional hazard regression analyses. Deaths from all causes were included. Patients dying of causes other than breast cancer were censored at the time of death, i.e. treated as living to the time of death and then excluded. We also estimated the prognosis of the 253 patients who survived 36 months (conditional analysis).

The logistic regression method was evaluated for its ability to predict the outcome of the disease as death or survival at 24, 36, 48 and 60 months after the operation. These analyses were based on 343, 287, 233 and 198 patients respectively. All patients included in the analyses had a follow-up longer than the cut off level for survival time. Patients dying of causes other than breast cancer were excluded. The outcome of the disease before 60 months was also tested on 163 patients who survived 36 months (conditional analysis) and had a follow-up longer than 60 months.

A model consisting of the significant variables (log likelihood ratio tests, $P < 0.05$) predicts the probability of dying (P) in subgroups of patients. The odds for dying is given by $P/1-P$. The odds ratio, i.e. the ratio between the odds for dying in two groups of patients as given by the levels of a prognostic variable, indicates the strength of the variable, and can be found by exponentiation of its regression coefficient. Tests were examined to make certain that models fitted the data adequately. The method was used in a backward manner in order not to miss possible interactions between the variables.

Age was included in the proportional hazard regression analysis as 50 years and younger (young), between 50 and 70 years (middle aged), and older than 70 years (old), being the 25th and 75th percentiles of the age distribution. In order to make the survival plots more readable, only patients 50 years and younger and those older than 70 years were included. In the logistic regression analyses age(1) describes the distinction between middle aged and young patients, age(2) that between old and young patients, while age(2) minus age(1) gives the distinction between old and middle aged ones.

The PgR and ER receptor content was measured by the dextran-coated charcoal technique [16]. The Breslow and Mantel–Cox chi-square tests [15] were used to find the cut-off level for PgR and ER status and tumour diameter. An optimal prognostic discrimination was obtained when PgR and ER negativity was defined as 15 fmol/mg or less tumour cytosol protein. The optimal cut off level for tumour diameter was 2.5 cm or less vs. those larger.

RESULTS

Proportional hazard regression

Log minus log plots indicated violation of the proportionality assumption for node status, while age and PgR status seemed acceptable for inclusion in the analyses as prognostic variables. The prognostic strength of node status, thus, seems to be time dependent.

Analyses stratified on node status (Table 1) showed PgR status and age to be significant variables, PgR status being the strongest one. ER status and tumour diameter were acceptable as prognostic variables, but they gave no additional information to that of PgR and age ($P > 0.17$).

Figure 1 shows how age modifies the prognostic effect of PgR status in both node groups, young patients with PgR negative tumours having a prognostic development similar to old patients with PgR positive tumours. Thus PgR negativity and old age are of prognostic disadvantage in both node groups.

Predicting prognosis for those who survived 36 months (conditional), log minus log plots indicated time dependency for age and PgR status. Logistic regression was therefore used for further analyses of the change in prognostic strength with time for age, PgR and node status.

Logistic regression analyses

Prediction of 24 months survival (Table 2) showed node status and PgR status to be significant

Table 1. Estimated regression coefficients, standard errors and the ratio between the regression coefficient and its standard error for node status, PgR status and age using proportional hazard regression

Variables	Regression coefficient	S.E.	Regression coefficient/S.E.
PgR	−1.02	0.27	−3.7
Age	+0.46	0.19	+2.4

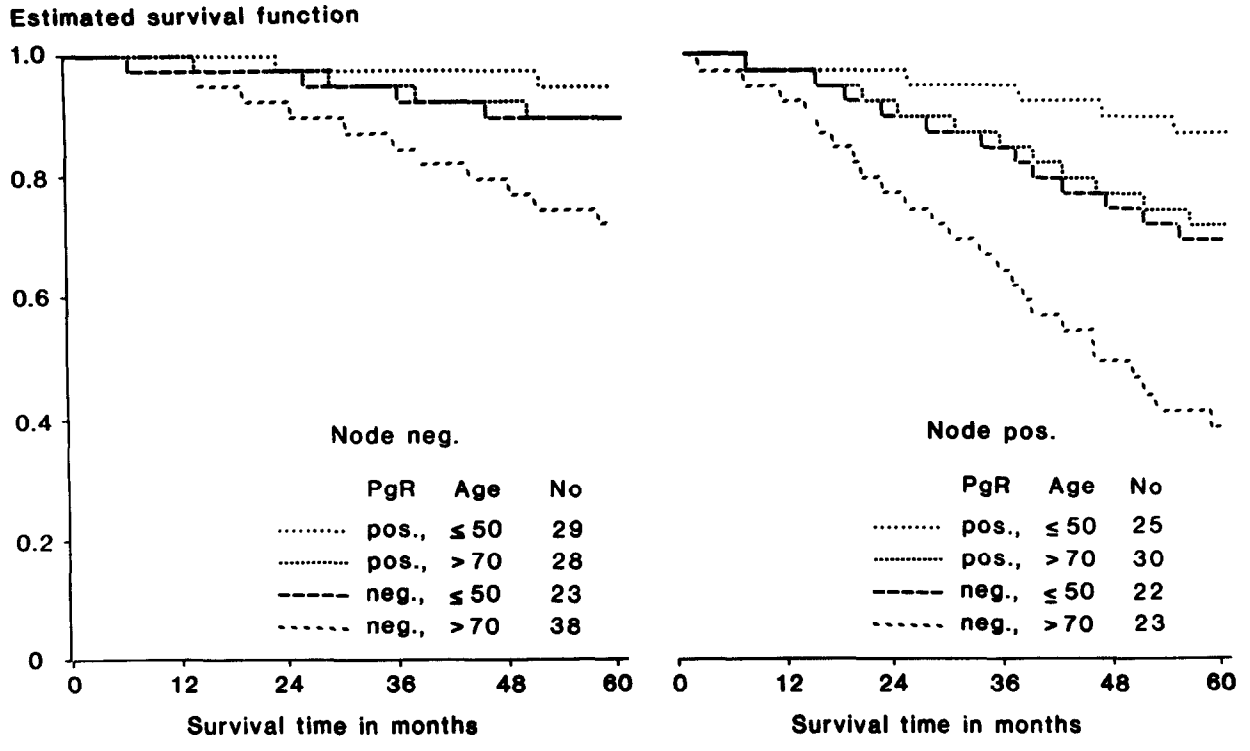

Fig. 1. The plot of the estimated survival function for the four subgroups given by progesterone receptor status and young and old patients in both node groups using proportional hazard regression. The number of patients in each subgroup is shown.

Table 2. Estimated regression coefficients, standard errors and the ratio between the regression coefficient and its standard error for node status, PgR status and age at 24, 36, 48 and 60 months after the operation using logistic regression

Months	Variables	Regression coefficient	S.E.	Regression coefficient/S.E.
24	Node	+1.09	0.42	+2.6
	PgR	−1.63	0.52	−3.1
	Age(1)	+0.70	0.59	+1.2
	Age(2)	+1.13	0.65	+1.7
	Constant	−3.15	0.61	−5.2
36	Node	+1.13	0.38	+3.0
	PgR	−1.36	0.43	−3.2
	Age(1)	+0.32	0.48	+0.7
	Age(2)	+1.29	0.54	+2.4
	Constant	−2.47	0.49	−5.0
48	Node	+1.25	0.36	+3.4
	PgR	−1.34	0.40	−3.3
	Age(1)	+0.60	0.48	+1.2
	Age(2)	+1.58	0.55	+2.9
	Constant	−2.22	0.49	−4.5
60	Node	+1.53	0.39	+4.0
	PgR	−0.94	0.40	−2.3
	Age(1)	+0.88	0.49	+1.8
	Age(2)	+2.22	0.58	+3.8
	Constant	−2.49	0.51	−4.9

variables. Age(2) was as strong as node status, but its high standard error precluded its reaching significance.

The model consisting of node status and PgR status fits the data adequately ($P = 0.12$) and predicted the outcome of the disease correctly in 78% of the patients.

Node status, PgR status and age(2) were significant variables when predicting 36, 48 and 60 months prognosis (Table 2). The models fit the data well ($P > 0.40$). The outcome of the disease was correctly predicted in 86% of the patients at 36 months, in 80% at 48 months and in 78% at 60 months respectively.

The odds ratio for node status increased from 3.0 at 24 months to 6.2 at 60 months (Fig. 2) indicating increasing prognostic strength with increasing prediction time. For PgR status the odds ratio decreased from 5.1 at 24 months to 2.6 at 60 months showing decreasing prognostic strength with time.

The odds ratios for age (Fig. 3) increased with time. Old patients had 3.1 higher odds for dying than young ones at 24 months and 9.1 higher at 60 months. The same pattern were found between the other age groups, the differences, though, being smaller. Thus the prognostic strength of age increases with increasing prediction time.

Predicting 60 months prognosis (Table 3) for those who had survived 36 months after the operation (conditional analysis), showed node status and age(2) to be significant variables. PgR status gave no additional information ($P > 0.8$). The model fitted the data poorly ($P = 0.03$), but predicted the outcome of the disease correctly in 89.5% of the patients.

The odds ratio for node status (Fig. 2) was 6.2 from 36 to 60 months, two times higher than from 0 to 36 months. The odds ratio for old vs. young patients (Fig. 3) was 6.8 from 36 to 60 months, nearly two times higher than in the period from 0 to 36 months. The differences between the other age groups were smaller. Thus node status and age discriminate more effectively from 36 to 60 months than from 0 to 36 months.

In *summary* the analyses showed PgR status and age to add prognostic information to that reached by node status, old age and PgR negativity being of disadvantage. The power of the variables, however, varied with time. Node status and age were relatively more important for prediction of late (60 months) prognosis, while PgR status gave relatively more information predicting early (24 months) prognosis. Only node status and age gave significant prognostic information for patients who had survived 36 months.

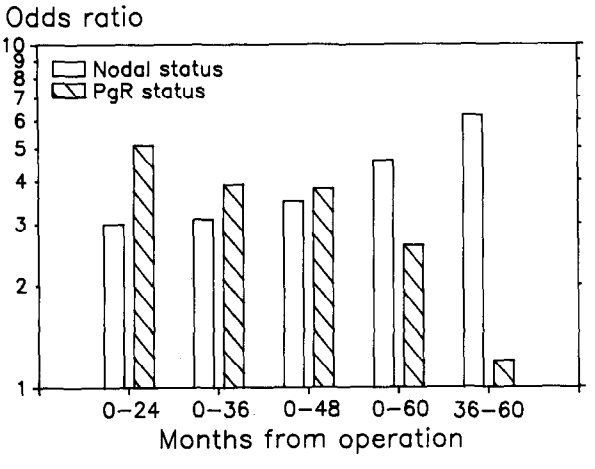

Fig. 2. Odds ratios for node status and PgR status as derived from the logistic regression analyses.

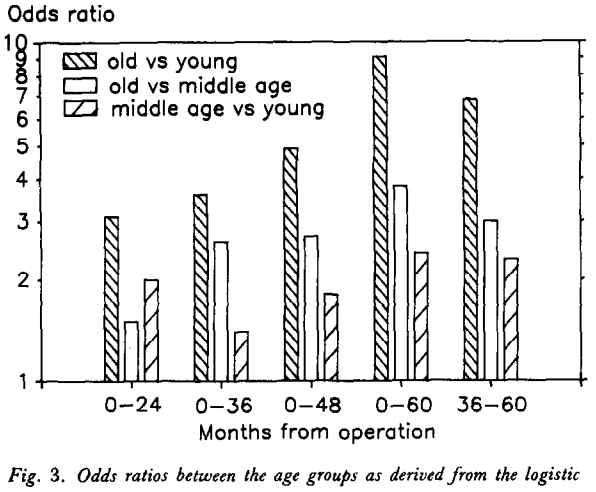

Fig. 3. Odds ratios between the age groups as derived from the logistic regression analyses.

DISCUSSION

The present results are in basic agreement with those of Saez *et al.* and Pichon *et al.* [1–3], showing the ability of PgR status to predict survival or metastatic occurence during the first 3–5 years in node positive patients. However, they did not find significant discrimination in node negative patients. In addition our results show that the prognostic advantage of PgR positivity is present in both node

Table 3. Estimated regression coefficients, standard errors and the ratio between the regression coefficient and its standard error for node status, PgR status and age. 60 months prognosis is predicted for those who have survived 36 months using logistic regression (conditional analysis)

Variables	Regression coefficient	S.E.	Regression coefficient/S.E.
Node	+1.79	0.71	+2.5
PgR	−0.14	0.65	−0.2
Age(1)	+0.83	0.86	+1.0
Age(2)	+1.90	0.95	+2.0
Constant	−4.43	0.97	−4.5

groups. This has also been reported by Mason *et al.* [6]. Node negative patients with PgR negative tumours have a prognosis similar to node positive patients with PgR positive tumours.

Saez *et al.* [2] showed that node positive patients with PgR positive tumours do not have more recurrences than node negative ones. They did not, however, find significant effect for PgR in the node negative group. This may be due to the use of different cut off levels for PgR status. Mason *et al.* [6] found increased prognostic power of PgR when increasing cut-off levels from 1 to 5 fmol/mg. In our material all cut-off levels from 0 to 40 fmol/mg gave significant discrimination in node positive patients, while in node negative patients significant effect was seen only when 15 or 20 fmol/mg were used. This illustrates that the cut-off level for PgR status determines its prognostic power, especially in node negative patients.

The PgR status has been shown to be more important than the ER status [17], while others have reported that the ER status indicates time to recurrence and survival more strongly [7]. Our results showed that once node status and PgR status were known, no additional information could be reached by ER status. This is in accordance with McGuire and Clark [17] who reported that ER status gave no additional information once the number of positive nodes and the PgR status were known. PgR status has been shown to result from oestrogen action on ER status [17], and is thus highly associated with ER. This may explain why ER gives no additional information.

Our results are in accordance with those showing old age to be of prognostic disadvantage in both node groups [12, 13]. Age also added prognostic information to that of PgR status in both node groups. Age is known to be closely associated with ER status [18, 19], while no such relation is found beween age and PgR [17]. Thus, age and PgR seem to reflect different biological constellations in breast cancer.

Tumours from old patients have been shown to have a lower proliferative rate than those from young patients [20]. A low proliferative rate may indicate a long preclinical period. Thus old patients have more time to develop distant metastases. This may explain why more breast cancer deaths are seen among old patients than young ones.

Our results show that old patients have an increasing risk of dying of breast cancer relative to young ones, old patients having more than three times greater chance of dying than young ones before 36 months and nine times before 60 months. This is in accordance with Adami *et al.* [13] who showed that the annual hazard rate remains high in old patients after 60 months, while that of younger patients decreases.

Node status and age also gave significant prognostic information when estimating 60 month survival for those who have survived 36 months, while no information was added by PgR status. Stenkvist *et al.* [21] showed axillary metastization to be a strong prognostic factor for the first 2.5 years, but considerably weaker for the next 2.5 years. In contrast, our results showed node positive patients to have three times higher chance for dying than node negative patients before 36 months. In the second period, after 36 months, node positive patients had a six times higher chance of dying than node negative patients. The corresponding odds ratios for age were three in the first period and six in the second. Thus both variables discriminate more strongly in the second than in the first period.

In proportional hazard regression analyses the patients can be included independent of survival time or length of follow-up. Patients dying of causes other than breast cancer may also be included. The method, however, assumes proportionality of the hazard rates, and, thus, no time dependency of the variables. This assumption was violated by node status, while age and PgR status seemed acceptable prognostic variables. The conditional proportional hazard regression analyses, however, indicated time dependency for these variables also. Logistic regression analysis does not assume proportionality between the death rates. The analyses, though, demand a minimum follow up longer than the cut off for survival time regardless of the survival status of the patient [22]. In addition only deaths of breast cancer can be included. In this work, these limitations to logistic regression reduce the number of patients significantly. Caution is therefore needed in the judgement of the results in the logistic regression analysis with the longest follow up. Thus both methods have their limitations.

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