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Progesterone and Estrogen Receptors as Prognostic Variables in Breast Cancer[1]

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ABSTRACT

Estrogen receptor (ER) and progesterone receptor (PR) levels have been measured in 374 tumors from patients with primary breast cancer and compared with axillary nodal status and other patient variables to determine their relationship to prognosis. Nodal status reliably predicted disease-free interval and overall survival, and both ER and PR status predicted overall survival both individually and within node-positive and node-negative subgroups. PR but not ER status was also able to predict disease-free survival both overall and in the node-positive subgroup. When the two receptor measurements were used in combination, a group of receptor-negative, (ER- and PR-negative), node-negative patients were identified with a significantly worse survival than that for an ER- and PR-positive group of node-positive patients. It is apparent that receptor status provides useful prognostic information in patients with early breast cancer and that ER and PR assays used in combination identify a subgroup of node-negative patients with poor prognosis who are likely to benefit from adjuvant therapy following mastectomy.

INTRODUCTION

There is a continuing search for methods to identify patients at risk of developing recurrent breast cancer following mastectomy. Accurate estimation of prognosis is of particular importance when considering the necessity for adjuvant therapy after initial breast surgery. If prognosis could be determined more precisely than at present, unnecessary treatment would be avoided in favorable subgroups, and appropriate prophylactic therapy would be reserved for high-risk patients. It has become clear that tumor size (10) and grade (2) and, in particular, axillary nodal status (10) are important prognostic indicators. Recently, a number of groups have analyzed ER[2] status as a further prognostic variable in early breast cancer. The presence of receptors in the primary tumor has been shown to either improve (3, 4, 6, 8, 15, 16) or not influence (1, 11, 12, 20) prognosis. A study of PR suggested that PR-positive patients had fewer metastases than did PR-negative patients but a similar number of local recurrences (19).

In the present study, both ER and PR content of primary breast tumors have been measured and analyzed in an effort to improve the assessment of prognosis. Other prognostic indicators have also been assessed in relation to receptor data in an effort to determine whether receptor measurements provide additional information complementing existing methods of predicting disease outcome.

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[2] The abbreviations used are: ER, estrogen receptor; PR, progesterone receptor.

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MATERIALS AND METHODS

Auckland, New Zealand had a population of 797,000 in 1976 and a population of 829,000 in 1981. On the average, 280 new cases of breast cancer are diagnosed each year. Data on all new cases of breast cancer presenting between September 1976 and September 1980 were recorded by the Auckland Breast Cancer Study Group on a PDP11 computer disc file. Follow-up records are updated every 9 months. The frequency of clinical examinations and diagnostic procedures is at the discretion of individual clinicians, but clinical assessments are usually made quarterly for 1 year, semi-annually for the next 2 years, and then annually. Patients lost to follow-up, whose cause of death was unknown, or in whom death was not due to breast carcinoma were included in the present study but were recorded as only being on study up to the time of last contact. Follow-up records to within 6 months of the analysis were obtained in 97% of all other patients.

ER and PR were measured in tumor tissue by a dextran-charcoal method as described previously (13). In the present study, ER levels were considered negative at <5 fmol/mg, since the response of patients with advanced breast cancer to endocrine therapy was very low when tumor receptor levels were below this value (14). A significant concentration of PR was arbitrarily defined as 1 fmol/mg or greater for actuarial life-table analyses. Significant values for PR were arbitrarily defined as either ≥1, ≥3, or ≥5 fmol/mg in the Cox's life-table regression analysis.

All patients, except 63, had a modified radical mastectomy or a simple mastectomy with axillary clearance. The remaining 63 patients had local tumor biopsies before proceeding directly to radiotherapy and are included only in Chart 1.

Statistical Methods. Actuarial life-table analysis (17) was made using either date of first recurrence or death as end points, and the results were analyzed using the generalized Wilcoxon statistic (9). Intervals of 1 month were used in the life-table analysis. When comparing the interaction of receptor and nodal status, Cox's life-table regression model was used, as implemented in the COXREGR procedure of the statistical package SAS (5). These computations were performed on an IBM4341 computer.

RESULTS

Over the period 1976 to 1980, 1136 new breast cancer cases were recorded in Auckland. Measurements of both ER and PR were made in 437 tumors (39%). Median follow-up time of these patients from date of diagnosis to date of death or last contact was 2.6 years. In 231 tumors (20%), only ER was measured, because the amount of tissue available was too small to permit analysis of both receptors. Tissue was not received for receptor assay from 467 patients (41%). The absence of these patients, however, did not appear to bias the study series. Thus, similar proportions were contributed from the various hospitals, they were of the same average age (59 years), and a similar proportion were node positive (1:1.5) compared to the total group.

To date, 10 patients have died from causes other than breast cancer. The cause of death was unknown in 2 patients, and 9 patients have been lost to follow-up. The following analysis is

restricted to those patients for whom both receptors were measured. The pathological status of the axillary nodes was reported in all cases and confirmed by histology in 374 of the 437 patients. Pathology reports did not always state the number of nodes observed, although all reports state that nodes were found and examined. In the node-negative group, 54% of the reports gave the number of nodes examined, with a median of 9 nodes.

Various possible prognostic factors are compared with the receptor and nodal status of the patient group in Table 1. There were significantly more large tumors in the node-positive compared to the node-negative group ($p < 0.005$). Other variables, including menopausal status, tumor grade, and receptor status had the same distribution in both nodal groups. As expected, menopausal status ($p < 0.01$) and tumor histological grade ($p < 0.005$) had a significantly different distribution between ER-positive and ER-negative groups.

In addition, PR status was clearly related to ER status, as described previously (13). The 3 variables, menopausal status, tumor size, and grade, are evenly distributed between PR-positive and -negative groups. Surgical adjuvant chemotherapy (alkeran) was received by 38% of the node-positive group (57 patients). These patients are not significantly associated with a particular receptor group.

The disease-free interval and survival time of patients grouped by receptor status are shown in Chart 1. There is a significant relationship between ER status and survival ($p < 0.0001$), and both disease-free interval ($p < 0.001$) and survival ($p < 0.0001$) were significantly related to PR status.

The disease-free interval and survival time of patients related to either ER and nodal status or PR and nodal status combined are shown in Charts 2 and 3, respectively. It is clear that of the 2 variables, nodal status was the main determinant of disease-free interval, although PR status had a significant additional influence restricted to node-positive patients ($p < 0.05$). Overall survival, however, was significantly influenced by ER status in both node-positive ($p < 0.005$) and node-negative ($p < 0.05$) groups. PR status was significantly related to survival only in node-positive patients ($p < 0.05$).

The relationship between different combinations of ER, PR, and nodal status and either disease-free interval or survival is shown in Charts 4 and 5. There was a significant difference in disease-free interval between ER-negative/PR-negative and ER-positive/PR-positive patients within both node-positive and node-negative subgroups ($p < 0.05$; Chart 4). Survival was similary influenced by receptor status in both node-positive and node-negative groups ($p < 0.05$; Chart 5). Importantly, a subgroup of node-negative patients (node-negative/ER-negative/PR-negative) had a significantly ($p < 0.05$) worse survival than a node-positive (node-positive/ER-positive/PR-positive) subgroup (Chart 5).

The influence of receptor and nodal status on prognosis was also analyzed by an alternative method to the actuarial-life table technique. The interaction between ER, PR, and nodal status with time to first recurrence or length of survival was studied using Cox's life-table regression. As with the actuarial analysis, ER status was not significantly related to time of first recurrence

Table 1
Distribution of patient variables

	Axillary nodes				Estrogen receptors				Progesterone receptors			
	Tumor present		Tumor absent		≥5 fmol/mg		<5 fmol/mg		≥3 fmol/mg		<3 fmol/mg	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Menses					[a]							
Pre- and intramenopausal	51	41	73	59	62	50	62	50	71	57	53	43
Postmenopausal	96	39	148	61	156	64	88	36	110	45	134	55
Unknown	3		3		6				4		2	
Tumor size	[a]											
≤5 cm	120	37	208	63	196	60	132	40	164	50	164	50
>5 cm	28	65	14	35	25	58	17	42	18	43	24	57
Unknown	2		2		3		1		3		1	
Tumor grade					[a]							
1	3	25	9	75	6	50	6	50	6	50	6	50
2	27	37	45	63	55	76	17	24	32	44	40	56
3	19	40	29	60	22	46	26	54	16	33	32	66
Unknown	101	42	141	58	141		101		131		111	
Estrogen receptors									[a]			
≥5 fmol/mg	92	41	132	59					141	63	83	37
<5 fmol/mg	58	39	92	61					44	29	106	72
Progesterone receptors					[a]							
≥3 fmol/mg	71	38	114	62	141	76	44	24				
<3 fmol/mg	79	42	110	58	83	44	106	56				
Axillary nodes												
Tumor present					92	61	58	39	71	47	79	53
Tumor absent					132	59	92	41	114	51	110	49
Adjuvant therapy												
Alkeran	57	100			33	58	24	42	24	42	33	58
Hormonal	6	75	2	25	2	25	6	75	4	50	4	50
Radiotherapy	3	75	1	25	3	75	1	25	4	100		
Chemotherapy	1	100					1	100	1	100		
No therapy	83	27	221	73	186	61	118	39	152	50	152	50

[a] Significant difference between groups within cell ($p < 0.01$).

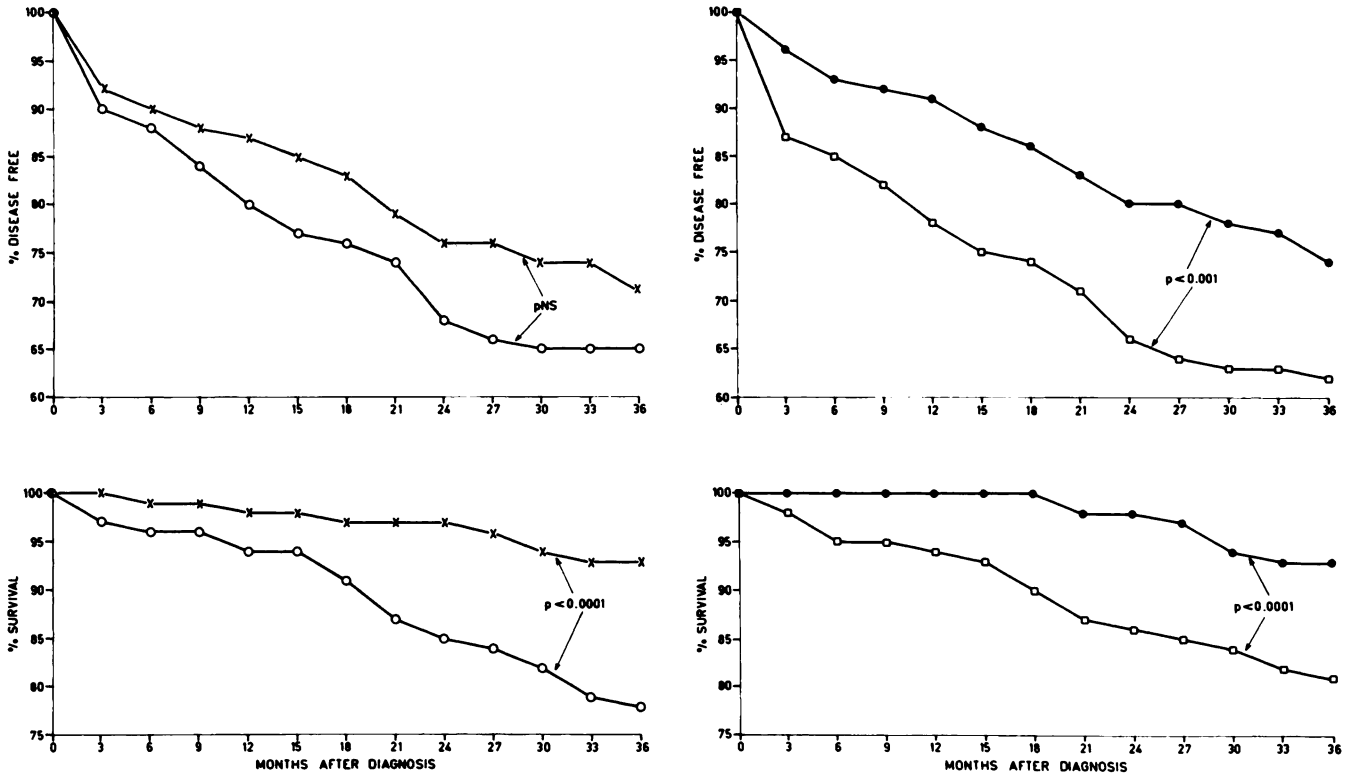

Chart 1. Actuarial analysis of disease-free survival and overall survival of breast cancer patients according to the presence of tumor ERs and PRs. ×, ER-positive, $n = 252$; O, ER-negative, $n = 185$; ●, PR-positive, $n = 213$; □, PR-negative, $n = 224$.

but, unlike the actuarial results, PR status also failed to correlate significantly with disease-free interval (Table 2). This result was not altered if a positive level of PR was redefined as ≥3 or ≥5 fmol/mg. ER and PR, however, each added significantly to nodal status when determining the duration of survival (Table 3). As the level of definition of a positive PR concentration was increased from ≥1 to ≥3 to ≥5 fmol/mg, the value of PR status as a prognostic indicator increased. Thus, when a positive PR level was defined as ≥3 fmol/mg, the addition of PR status to nodal and ER status led to a significant improvement in assessment of survival. Neither receptor was superior to the other in assessing survival time.

Tumor size and grade were also studied as prognostic factors in relation to nodal and receptor status. Tumor size did not further influence survival when nodal status was known (Cox's life-table regression model), although there was a significant improvement if only receptor status was known ($p < 0.05$). The addition of tumor grade to ER or PR results did not significantly add to the assessment of survival.

DISCUSSION

The identification of breast cancer patients at risk of tumor recurrence following initial surgery has become increasingly important in view of adjuvant therapies known to delay the appearance of metastases (7) or improve survival (18). Currently, the status of the axillary nodes at surgery is considered the most important variable in predicting tumor recurrence, although attention has been drawn to the possibility that receptor assays may provide additional information (7).

The present study provides further support for a role for receptor status in assessing prognosis in breast cancer. Only PR status appeared to relate to time to first recurrence when assessed by actuarial analysis either alone or in node-positive patients (Charts 1 and 3). The usefulness of PR status for determining time to recurrence (Charts 1, 3, and 4) was not, however, confirmed by Cox's life-table analysis (Table 2). In contrast, ER status was not significantly related to disease-free interval when analyzed by either actuarial life-table analysis (Charts 1 and 2) or Cox's life-table regression analysis (Table 2). A number of other groups have also found ER status unhelpful in assessing disease-free interval (1, 11, 12, 20, 21). Pichon *et al.* (19) found PR status to be more important than ER status in determining prognosis in early breast cancer. However, a number of groups have found that ER status helps to predict disease-free interval both in isolation (3–5, 8, 16) and within nodal groups (3, 4, 16). Currently, there seems to be no resolution of these divergent results and, clearly, longer follow-up of carefully categorized patient groups is required.

By comparison with results comparing receptor status to time to first recurrence, it seems clear from the present study that receptor levels are clearly important when assessing overall survival time. Thus, either ER or PR status identified patients with significantly prolonged survival (Charts 1 to 3 and 5). When patients were grouped according to nodal status, receptor levels still indicated subdivisions with significantly longer survival (Table 3; Charts 2 and 3). These findings are in agreement with other reports in the literature (6, 8).

Knowledge of nodal status and levels of both ER and PR enabled survival to be further categorized within patient subgroups (Chart 5). In particular, analysis of both receptors identified a group of node-negative patients (ER-negative, PR-negative) with a significantly worse survival than a node-positive subgroup (ER-positive, PR-positive). This type of information

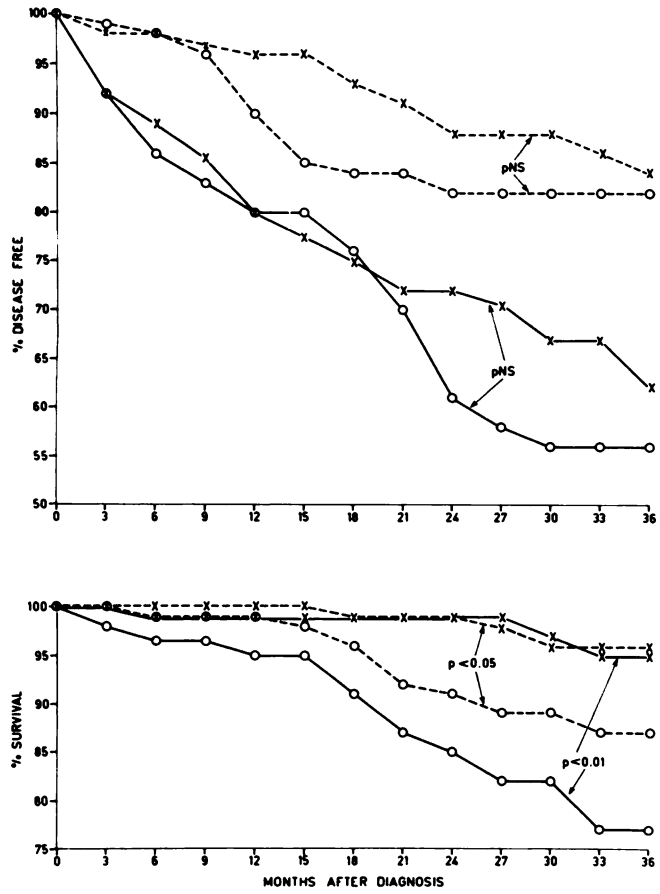

Chart 2. Actuarial analysis of disease-free survival and overall survival of breast cancer patients according to the presence of tumor ERs and axillary nodal status. - - - -, node-negative tumors (×, ER-positive, n = 130; O, ER-negative, n = 94); ——, node-positive tumors (×, ER-positive, n = 91; O, ER-negative, n = 59).

could be of considerable importance when planning strategies for adjuvant therapy in high-risk groups following mastectomy.

From the present data, it could be questioned whether analysis of PR provides useful information on early breast cancer over and above that obtained with ER assays. In general, either receptor when used alone or together with nodal status has provided similar data (Charts 2 and 3). However, the combination of ER and PR results appears to provide useful additional information in a subset of patients (Chart 5), although whether this information will provide clinically usable patient stratification awaits formal testing in suitable prospective trials of adjuvant therapy.

In this type of analysis, it is obviously of importance to consider what tissue level of receptor should be considered biologically significant. The present ER assay has been validated against response of patients with advanced disease to endocrine therapy, and an ER level of ≥5 fmol/mg appears biologically "positive" (14). It is, however, more difficult to describe a similar biologically significant PR level. We have chosen to classify any PR level of 1 or more fmol/mg as "positive" (Charts 1 and 3–5). If, however, positive levels are redefined as ≥3 or ≥5 fmol/mg, the results are essentially unchanged, although there is a trend to increasing significance of PR as a prognostic indicator at the higher cutoff levels.

When assessing receptor levels as prognostic indicators in breast cancer, it is important to consider other variables known to influence prognosis which could relate to receptor status. A number of such factors have been considered in the present study (Table 1) and do not appear to have influenced the current

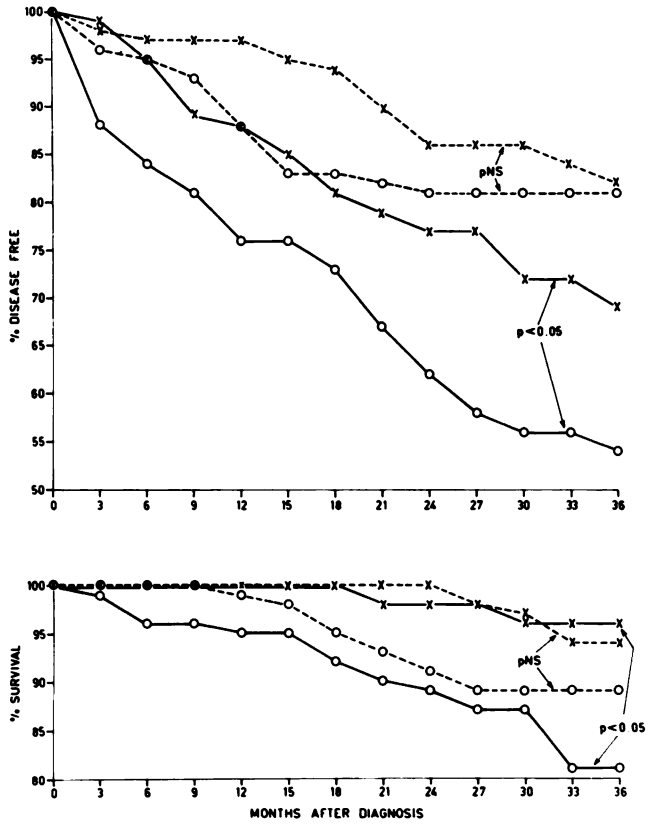

Chart 3. Actuarial analysis of disease-free survival and overall survival of breast cancer patients according to the presence of tumor PRs and axillary nodal status. - - - -, node-negative tumors (×, PR-positive, n = 118; O, PR-negative, n = 106); ——, node-positive tumors (×, PR-positive, n = 74; O, PR-negative, n = 76).

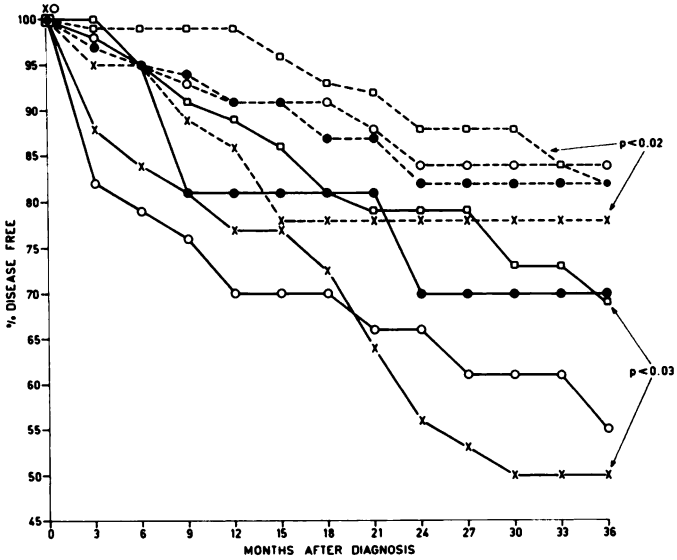

Chart 4. Actuarial analysis of disease-free survival of breast cancer patients according to the presence of tumor ERs and PRs and axillary nodal status. - - - -, node-negative tumors (□, ER-positive/PR-positive, n = 86; O, ER-positive/PR-negative, n = 44; ●, ER-negative/PR-positive, n = 32; ×, ER-negative/PR-negative, n = 62); ——, node-positive tumors (□, ER-positive/PR-positive, n = 58; O, ER-positive/PR-negative, n = 33; ●, ER-negative/PR-positive, n = 16; ×, ER-negative/PR-negative, n = 43).

Table 2

Cox's life-table regression analysis of interaction between time to first recurrence and receptor and nodal status

Variable[a]	No. positive	No. negative	χ^{2b}	p	d.f.	χ^2 difference	p
Axillary nodes	150	224	30.34	<0.001	1		
PR[c]	185	189	3.02	NS[d]	1		
ER	224	150	0.95	NS	1		
Nodes and PR			32.94		2	2.60	NS
Nodes and ER			31.34		2	1.00	NS
Nodes, PR, and ER			33.15		3	0.21	NS

[a] Independent variables. Note: dependent variable = disease-free interval.
[b] Based on log likelihood.
[c] PR positive = level of 3 fmol/mg or greater.
[d] NS, not significant.

Table 3

Cox's life-table regression analysis of interaction between patient survival and receptor and nodal status

Variable[a]	No. positive	No. negative	χ^{2b}	p	d.f.	χ^2 difference	p
Axillary nodes	150	224	14.18	<0.001	1		
PR[c]	185	189	10.24	<0.005	1		
ER	224	150	8.84	<0.01	1		
Nodes and PR			23.29		2	9.11	<0.01
Nodes and ER			23.65		2	9.47	<0.01
Nodes, PR and ER			27.70		3	4.05	<0.05

[a] Independent variables. Note: dependent variable = survival.
[b] Based on log likelihood.
[c] PR positive = level of 3 fmol/mg or greater.

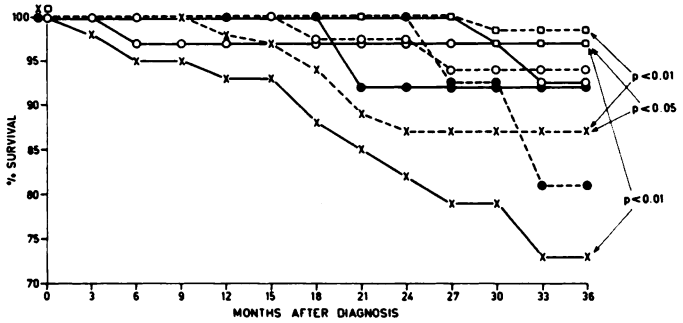

Chart 5. Actuarial analysis of overall survival of breast cancer patients according to the presence of tumor ERs and PRs and axillary nodal status. Symbols and patient numbers as for Chart 4.

results. Many reports of receptor status in early breast cancer have failed to identify the patient group in whom receptor studies were performed and to account for possible patient bias. In the present series, the group under study represented only 39% of the total population developing breast cancer over the survey period. It does not, however, appear that bias was introduced by this selection, although study of a greater proportion of the total breast cancer group would have been preferable.

In the present study, an interaction was observed between receptor status and tumor histological grade (Table 1). Tumor grade measures the differentiation of tumor cells and, since the breast is a hormone-responsive organ, it is very likely that the presence or absence of hormone receptors in tumor cells also reflects differentiation. It is of interest that although receptor measurements and nodal status were both bound to be significant prognostic variables, both measurements are distributed independently of one another within the patient group (Table 1). These findings are similar to those already reported (1, 4). This suggests that the 2 variables reflect different biological mechanisms in patient survival, and it could thus be desirable to combine both types of prognostic measure when considering patient management.

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