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Role of Progesterone Receptors in Breast Cancer

By William L. McGuire and Gary M. Clark

It has been demonstrated that progesterone receptor (PR) is at least as valuable as estrogen receptor (ER) for predicting the outcome in breast cancer patients. Retrospective analysis indicates that presence of PR may be the second most critical factor, after the number of positive nodes, in predicting for disease-free survival, with a correlation between length of survival and number of tumor PR. The presence of PR has been shown to be of value for predicting response in both early and advanced breast cancer patients. In studies of assay consistency, major discordance rates were minimal in simultaneous assays but extremely high in sequential assays of tumors that were PR positive in initial assay. The responsible factor was interim endocrine therapy, and it was subsequently determined that prognosis was worse for those patients whose tumors lost PR between assays.

THE POSSIBLE significance of progesterone receptor (PR) in human breast cancer has evoked a great deal of interest in the medical community. What, for example, is its significance in comparison to that of estrogen receptor (ER)? What role does it play in the treatment of early or advanced breast cancer? And finally, how does a change in PR level over the course of the disease affect prognosis and survival?

PROGESTERONE RECEPTOR *V* ESTROGEN RECEPTOR

Dr Charles Hubay and his colleagues in Cleveland, Ohio, conducted a randomized study in which stage II breast cancer patients underwent radical mastectomy followed by chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil alone, or in combination with tamoxifen or tamoxifen plus BCG (a nonspecific immunostimulant). A total of 318 patients made up the study population, of which 311 patients were evaluable. Of those, 189 patients were assayed for both ER and PR.[1]

As has long been recognized, disease-free survival was related to ER status; that is, ER-positive patients had significantly better survival at study points up to 60 months (Fig 1). ER-negative patients have a higher risk of early recurrence than do patients whose tumors are ER positive according to the disease-free survival curves and the significant difference between the two curves. Similarly, the difference between the two curves in PR-positive and PR-negative patients (Fig 2) is also highly significant and again suggests the probability of earlier recurrence of disease for those patients with PR-negative tumors.

The impact of PR on breast cancer patients was then examined in relation to other known prognostic factors, such as the number of positive nodes, size of the primary tumor, type of treatment, and menopausal status. It was determined using univariant analysis that positive nodes ($P < .0001$), size of primary tumor ($P = .0008$), ER ($P = .0008$), and PR ($P < .0001$) are all valuable for predicting disease-free survival.[2] Furthermore, using multivariant analysis techniques, it was possible to assign an order of importance to the factors and thus to determine the impact of each in predicting recurrence in this patient population. As anticipated, the number of positive nodes ($P < .0001$) was the most important factor for predicting early recurrence. Unexpectedly, however, the second most critical factor was PR ($P = .004$). The third factor, of borderline statistical significance, was the size of the primary tumor ($P = .07$). ER was not found to be significant at all. Thus, if the PR value is known, ER status offers no additional prognostic information. The converse, however, is not true; if the ER status is known, useful information is still provided by assessing the PR status. In this particular subset of patients, treatment and menopausal status did not play a role in identifying which patient had recurrences.

If it is accepted that PR is an important biologic variable, it might be anticipated that the number of PR in the tumors would have some impact as well. Disease-free survival was therefore studied with respect to quantitative PR levels. Patients were separated into three groups: those whose tumors contained greater than 50 fmol of PR, those with between 5 and 49 fmol,

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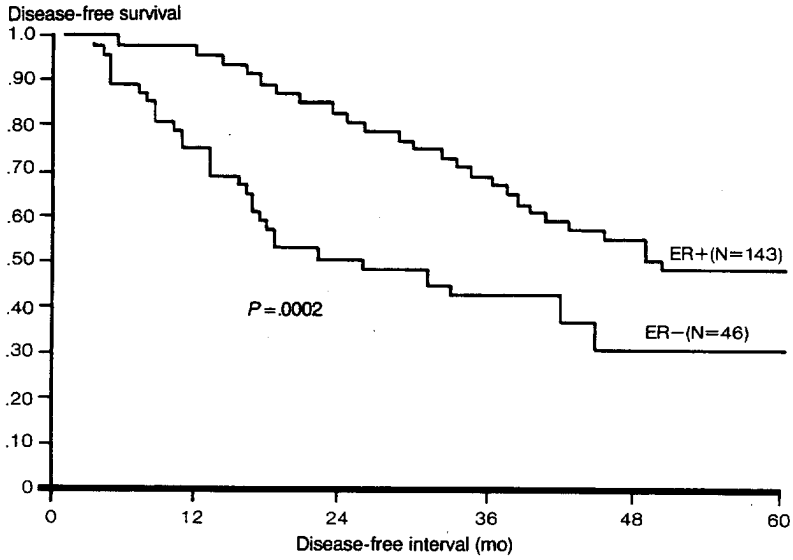

Fig 1. Estrogen receptor (ER) status has long been accepted as a predictive factor in disease-free survival of breast cancer patients (adapted from Clark[2]).

and those with less than 5 fmol. Comparison revealed that disease-free survival improved with increased level of tumor PR.

In summary, the presence of PR was determined to be a more significant prognostic factor for disease-free survival than was the presence of ER. Thus, PR levels should be routinely measured and incorporated into adjuvant therapy trials.

THE VALUE OF PR ANALYSIS IN BREAST CANCER THERAPY

Early Cancer

The most clearcut data regarding the role of PR analysis in planning treatment for early breast cancer come from a National Surgical Adjuvant Breast Project study in which patients with stage II breast cancer were randomized to chemotherapy with L-phenylalanine-mustard plus 5-fluorouracil or chemotherapy plus tamoxifen.[3] Table 1 compares the receptor status, disease-free survival, and absolute survival of patients under 50 years of age who received chemotherapy alone and those who received chemotherapy plus tamoxifen. Results indicate that there were only three categories in which significant differences were evident in patients under 50 years of age: First, in the group of patients lacking both receptors, addition of tamoxifen to the chemotherapy regimen yielded

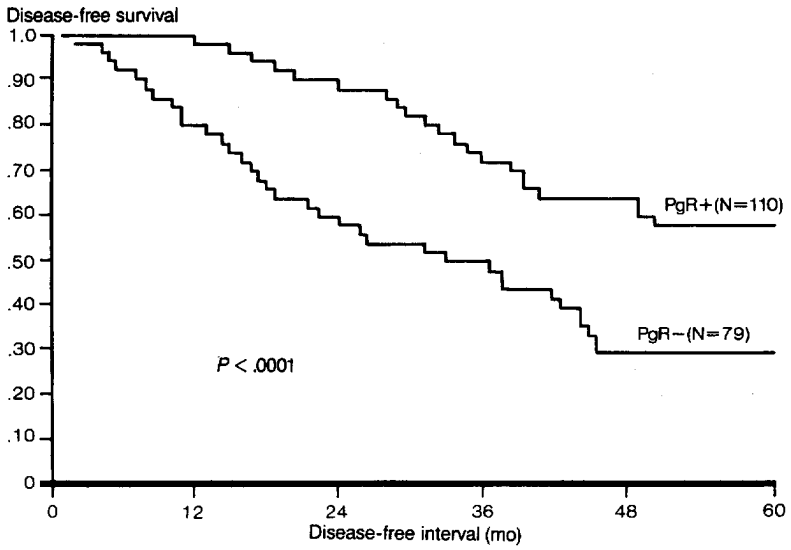

Fig 2. Progesterone receptor (PGR) status appears to be at least as predictive of disease-free survival in breast cancer patients as estrogen receptor status (adapted from Clark[2]).

Table 1. Comparison of Disease-Free and Total Survival in Patients Treated With Chemotherapy Alone and in Combination With Tamoxifen[3]

ER	PR	Treatment	DFS%		S%	
		Age < 50 yr				
–	–	PF	50		86	(.003)
		PFT	47		62	
+	–	PF	76	(.03)	93	(.01)
		PFT	37		70	
+	+	PF	66		86	
		PFT	72		90	
		Age ≥ 50 yr				
–	–	PF	42		64	
		PF	53		70	
+	–	PF	65		84	
		PFT	74		81	
+	+	PF	65	(.004)	90	
		PF	80		94	

Abbrev: ER = Estrogen receptor; PR = Progesterone receptor; DFS = Disease-free survival; S = Absolute survival; PF = L-Phenylalanine mustard and 5-fluorouracil; PFT = Chemotherapy + tamoxifen.

a worse total survival. Second, in those patients who were ER positive but PR negative, the addition of tamoxifen decreased both disease-free and overall survival. It was concluded that the absence of PR in a tumor is predictive of a worse disease-free and overall survival with this combination of therapy.

In the group of patients older than 50 years, the only significant difference between those treated with chemotherapy alone and those treated with chemotherapy plus tamoxifen occurred in the PR-positive tumor patients. Here the disease-free survival rate was improved in those patients who received tamoxifen. Preliminary interpretations of this study indicate that PR is an extremely important factor in identifying which subsets of patients could be expected to improve and which to worsen with the combination of this particular chemotherapy and antiestrogen.

Advanced Cancer

In a retrospective analysis of 345 patients worldwide,[4] overall results showed that absence of both ER and PR in patients with advanced disease was associated with the lowest rate of response, whereas those whose tumors were positive for both ER and PR had the best prognosis (Table 2). A prospective randomized trial of the role of PR in predicting response to endocrine therapy was reported at the 1984 American Society of Clinical Oncology meetings by Cavalli et al.[5] Patients were randomized to receive high-dose or low-dose medroxyprogesterone acetate (MPA). In 91 patients receiving high-dose MPA, the response rate was 70% if PR was present and only 10% if PR was absent. For those patients with unknown PR values, the response rate was 30%, consistent with numerous earlier reports. This study represents an excellent example of the importance of PR for predicting response in advanced breast cancer.

Table 2. Advanced Breast Cancer Retrospective Trials (345 Patients)[4]

		Objective Response
ER–	PR–	11%
ER+	PR–	27%
ER+	PR+	77%

Abbrev: ER = Estrogen receptor; PR = Progesterone receptor.

REPEATED PR ASSAYS

Consistency

The next step was to study the consistency of repeated receptor assays in the same patient. In San Antonio, 283 patients who were biopsied more than once for PR were identified. Of those, 109 patients had simultaneous assays (within the same week) and 174 patients had sequential assays. A positive PR assay was defined as greater than 10 fmol/mg protein in the 8S fraction of sucrose gradient; negative PR values as less than 5 fmol/mg protein, and ± values as between 5 and 10 fmol/mg protein. Patients whose initial biopsies were either positive or negative and remained positive or negative were described as concordant. Discordance was defined in two ways: Major discordance referred to those patients whose biopsy changed from an initial positive or negative to the alternate on later biopsy. Minor discordance described both those patients whose initial assay was either positive or negative but later biopsy was equivocal and those who began as equivocal and changed to positive or negative.

In the group receiving simultaneous assays, the major discordance rate was approximately 14%. The minor discordance rate for the same group was 18%. This result indicates that simultaneous assays for PR are reliable on the same order as assays for ER.

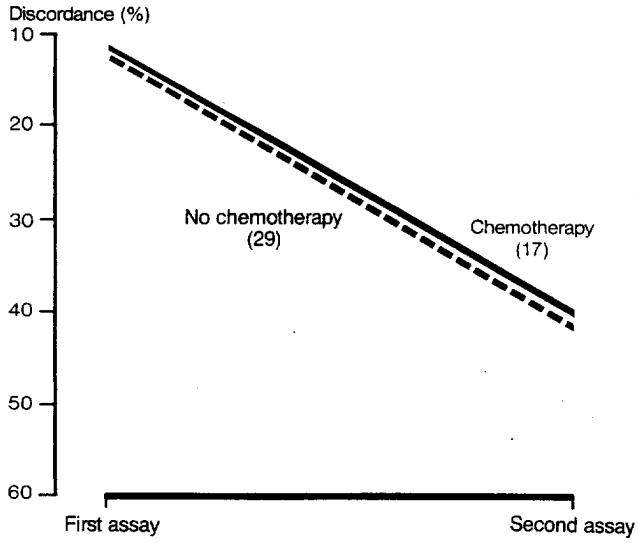

Fig 3. Treatment with chemotherapy had no effect on the major discordance rate (positive to negative) between sequential progesterone receptor assays (adapted from Gross[6]).

In contrast, results of the sequential assays were inconsistent. Although the discordance rate was low for PR-negative tumors (3% and 8% for minor and major discordance, respectively), and for minor discordance in PR-positive tumors (7%), the major discordance rate for PR-positive tumors was 44%, which is high.

In an attempt to explain this high discordance rate, many factors were considered. Tumor size, axillary lymph node status, menopausal status, and the interval between biopsies were not found to be important. Similarly, the discordance rate between the first and second assays was not found to be affected by chemotherapy administered during the interim period (Fig 3). Endocrine therapy, however, appeared to be a likely explanation for the major discordance rate in PR-positive tumor assays. Those patients who did not receive endocrine therapy had a minimal change in their receptor status, whereas a striking change was noted in those patients who did receive endocrine therapy (Fig 4).

Significance of Changes in PR Status

It was subsequently questioned whether there is any biologic or prognostic significance of a change in PR status. To answer this question, survival rates among patients receiving sequential assays were analyzed (Fig 5). Those patients whose tumors were initially PR positive and

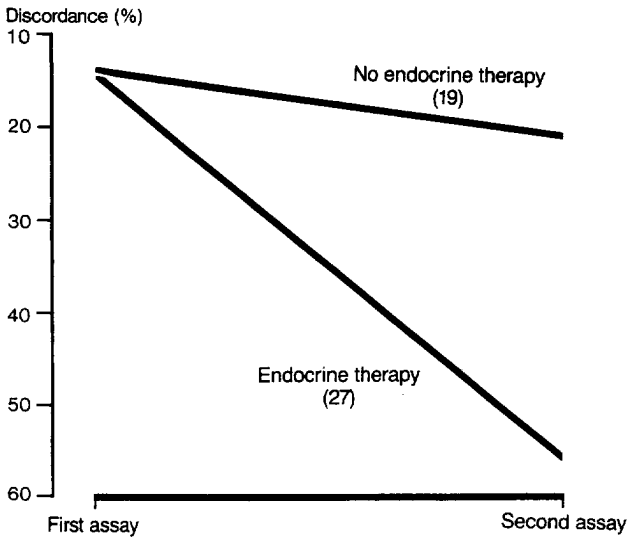

Fig 4. A striking association was found between major discordance (positive to negative) and endocrine therapy in sequential progesterone receptor assayed patients (adapted from Gross[6]).

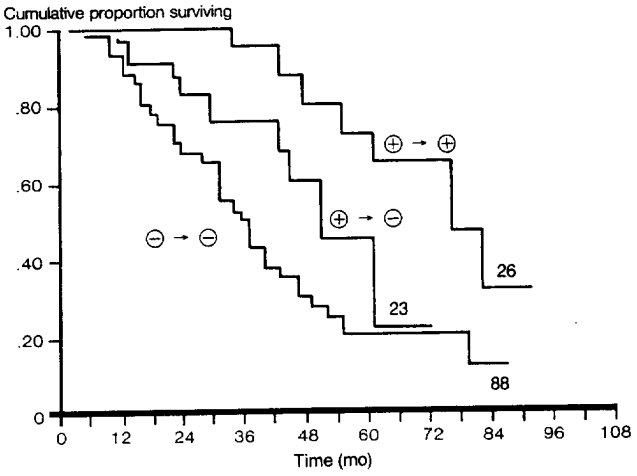

Fig 5. Change in progesterone receptor status was found to play an important role in the prognosis for survival of breast cancer patients (adapted from Gross[6]).

whose tumors were initially PR positive and remained PR positive were clearly shown to have the best prognosis. The worst prognosis was associated with those patients whose tumors were initially PR negative and remained PR negative. The most clinically interesting subset of patients is represented by the middle curve of Figure 5. Their initial biopsy was PR positive, but their second biopsy was PR negative. It is clear that these patients, although initially PR positive, have a worse prognosis than those patients whose tumors remained PR positive. Thus, the loss of PR is an ominous sign.[6]

CONCLUSIONS

PR appears to be an important factor in the prognosis and management of breast cancer. The survival of patients whose tumors lose PR is significantly worse than those retaining PR. Frequent reassessment of PR is therefore recommended to ensure optimal treatment planning for those patients who are initially PR positive.

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