Henry Ford Hospital Medical Journal

Volume 38 | Number 1 Article 21

3-1990

Evaluation of the Predictive Power of Progesterone Receptor Levels in Primary Breast Cancer: A Comparison with Other Criteria in 559 Cases with a Mean Follow-up of 74.8 Months

Robert A. Huseby

Helen E. Ownby

Sam Brooks

Jose Russo

Evaluation of the Predictive Power of Progesterone Receptor Levels in Primary Breast Cancer: A Comparison with Other Criteria in 559 Cases with a Mean Follow-up of 74.8 Months

Robert A. Huseby, MD,* Helen E. Ownby, PhD,† Sam Brooks, PhD,‡ Jose Russo, MD,‡ and the Breast Cancer Prognostic Study Associates‡

A total of 559 women with primary breast cancer treated by modified radical mastectomy were followed for a mean of 74.8 months to evaluate the relationship of sex hormone receptor content in the tumor with time to first recurrence and to death due to breast cancer. The prognostic significance of progesterone receptor (PgR) status was evaluated in terms of estrogen receptor (ER) status, age (≤ 49 years, ≥ 50 years), extent of lymph node involvement, tumor size, and morphologic characteristics. Overall, patients with PgR positive (> 9 femtomoles/10 mg wet weight tissue) tumors experienced a significantly longer period to both first recurrence and death due to breast cancer, but this advantage was restricted to those whose cancer had metastasized to their axillary lymph nodes. For women with nodal involvement, the extent of this involvement and the size of the primary lesion had the greatest predictive value followed by nuclear grade and PgR status. In these node-positive patients, PgR positivity, although strongly associated with ER positivity, had a greater predictive value than that of the estrogen receptor per se. (Henry Ford Hosp Med J 1990;38:79-84)

Relatively soon after a satisfactory method had been devised for quantifying high affinity progesterone-specific receptors (PgR) in cytosolic preparations from human breast cancer specimens, the value of such determinations in predicting response to endocrine therapy for tumor metastases was established (1,2). The predictive power of PgR quantitation for estimating prognosis after primary treatment of early breast cancer has also been evaluated, but interpretation of the results is unclear. Many studies include too few cases or the patients have been followed for too short a time to yield definitive conclusions when the well-established prognostic criteria are considered concurrently (3-12). Combining results is difficult because of various methodologic and end-point differences employed. Three large reports encompass fairly homogeneous cases. Fisher et al (13) published the results of a large number of axillary node-positive cases, all treated by radical mastectomy (standard or modified) followed by adjuvant cytotoxic chemotherapy. As a group those patients whose cancer contained quantifiable PgR experienced a statistically significantly longer disease-free interval and survival than did those whose neoplasm had very low or nondetectable quantities of this receptor. Furthermore, higher levels of PgR were associated with the best prognosis. In a large series of node-negative cases treated by total mastectomy and axillary sampling (n = 600), PgR positivity was of some value in predicting recurrence for the 154 patients under 50 years of age but of no significance in the larger group of older women (14). In another series of node-negative cases (15), all of whom had had axillary dissection along with varying treatment for control of the primary lesion, PgR status was not statistically significantly associated with disease-free survival in either age group. However, overall survival was statistically significantly better at five years in women ≤ 49 years of age whose cancers were PgR positive. This was not true for the older group.

In the present study we examined the significance of PgR status to prognosis, analyzing concurrently tumor size, nodal involvement, estrogen receptor (ER), patient age, and tumor histology. The long period of follow-up, mean 74.8 months, enabled us to obtain meaningful data relative to survivorship as well as to time to first recurrence.

Materials and Methods

All cases entered in the Breast Cancer Prognostic Study at the Michigan Cancer Foundation between December 1978 and April 1983 were included in this study provided tumor material was sufficient for both ER and PgR assays (n = 559). Each patient was diagnosed as having primary breast cancer, with no metastases beyond the axillary nodes demonstrated at the time of surgery and no history of cancer within the previous five years. The initial therapy was modified radical mastectomy and

Submitted for publication: February 2, 1990.
Accepted for publication: May 22, 1990.
*Formerly Department of Oncology, Henry Ford Hospital. Currently Department of Biochemistry, Loma Linda University, Loma Linda, CA.
†American Red Cross, Detroit.
‡Michigan Cancer Foundation, Detroit.
Address correspondence to Dr. Ownby, American Red Cross, Southeastern Michigan Chapter and Blood Services, 100 Mack Ave, Box 33351, Detroit, MI 48232.

Table 1
Association of Progesterone Receptor Content of Breast Tumors and Other Prognostic Indicators

	n	%ER+	%ER-	%LN_0	LN_{1-3}	LN4+	$T_{\leq 1}$	$T_{1.1-2}$	$T_{2.1-5}$	$T_{>5}$	NG_{1+2}	NG_3	Not Graded
PgR ≤ 9	334	52.6	47.3	48.2	24	27.8	8.9	29.6	48.8	12.6	51.4	43.6	12.8
PgR > 9	225	90.7	9.3	52.4	28	19.6	9.3	28	55.1	7.6	69.5	30.5	7.1
Total	559												
χ^2			89.1		5.1			4.4				8.9	
P-value			< 0.0001		> 0.07			> 0.2				< 0.003	

PgR = progesterone receptor, ER = estrogen receptor, LN = lymph node, T = tumor size, NG = nuclear grade.

all axillary nodes found in the specimen were examined histopathologically for evidence of metastatic disease. In node-negative patients (a mean of 17 nodes per axilla examined), some form of adjuvant treatment (local irradiation, hormonal alteration, or cytotoxic chemotherapy) was instituted in 16% prior to the appearance of metastatic disease while 78% of those with nodal metastases received such therapy. Patients were grouped according to age at the time of primary surgical therapy (≤ 49 years and ≥ 50 years).

Follow-up information was obtained by a nurse-coordinator at four-month intervals by means of patient interview and/or review of the medical record. Breast cancer recurrence status and usually the cause of death were determined by personal physicians. Confirmation and cause of death were verified from death certificates available on computer tape in the Michigan Cancer Foundation's Metropolitan Detroit Cancer Surveillance System. Only deaths confirmed as due to breast cancer were considered in the survival analysis; deaths due to other causes were treated as if the patient were lost to follow-up at the time of death. The mean time of follow-up for all living, study-eligible patients (n = 365) was 74.8 months.

Specimens were collected by pathologists at 12 metropolitan Detroit area hospitals. Immediately after the diameter of each lesion had been measured, a portion of the tumor was placed on ice for transfer to the Foundation. After a total elapsed time of no more than two hours, a portion of the specimen weighing at least 200 mg was immediately frozen at −70°C for subsequent receptor analysis. The two directly adjacent segments were taken for detailed histopathologic evaluation, and only cases in which both of these tissue fragments contained the neoplasm were included in this analysis.

The preparation of cytosols and details of the dextran-coated charcoal protocol employed for receptor quantitation have been detailed elsewhere (10). Significant for this report is that a short incubation with isotope was employed in all assays, ie, two hours at 0°C to 4°C. The binding capacity and dissociation constant were determined by Scatchard plot, and a linear regression was performed on each data set. For the ER analyses, the five data points so plotted routinely yielded a correlation coefficient (R value) better than −0.90. Greater variability was encountered in the PgR analyses. For the purpose of this presentation, only cytosols that yielded plot points with an R value greater than −0.75, giving a binding capacity of more than 9 femtomoles/10 mg tissue, were considered positive for this receptor. Samples binding ≥ 3 fmol of E_2/10 mg of tissue were considered positive for ER. A comparative study of 1,000 samples showed that expressing results as positive either at the level of 3 fmol/10 mg of tissue or at 5 fmol/mg of cytosol protein was similar in 99% of cases (16).

Histologic evaluation of the primary neoplasms was carried out by a panel of Foundation pathologists (17). The more undifferentiated portions of the sections were graded and, as suggested by Fisher et al (18), morphologically less infiltrative tumors termed "lobular," "medullary," or "pure tubular" were not graded. Only nuclear grade (NG) was used as an indicator of tumor differentiation. This parameter yields the best distribution of cases between more (NG1 + NG2) and less (NG3) differentiation and was employed by Fisher et al (13,15) in evaluating National Surgical Adjuvant Breast and Bowel Project Protocol (NSABP) data.

The chi-square test (continuity uncorrected) was used to test for association between PgR and other putative prognostic parameters. Life table analysis (19) was used to compare both time to disease recurrence and death due to breast cancer for the various patient groups over time. Significance levels for the life table analyses were computed by Breslow's generalized Kruskal-Wallis Analysis (20). Cox proportional hazards models were used to estimate the relative hazard of low PgR levels compared to patients with levels higher than 9 fmol/10 mg wet weight using BMDP program 2L. Estimates were computed using maximum likelihood methods, and 95% confidence intervals for each estimate were computed using the Wald method (21). Similar estimates were obtained for the other covariates mentioned above, and the analyses were adjusted for age and tumor size. Likelihood ratio statistics were used to test significance of categorical variables with more than two groups (22). All covariates were tested individually by means of time-dependent covariates to assess any departures from the proportional hazards (23). Covariates violating the proportionality assumptions were included in the model by means of stratification.

Results

The correlations between tumor PgR and several established prognostic indicators of outcome of primary therapy listed in Table 1 are similar to those reported in other studies. There is a significant correlation with ER status in that the great majority

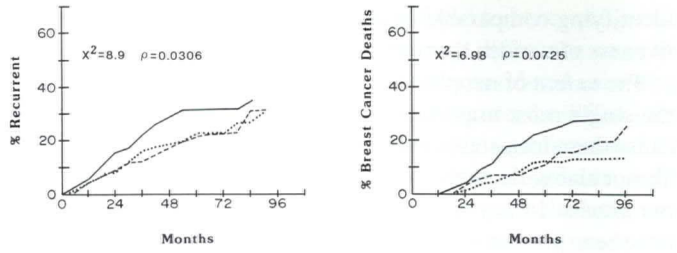

Fig 1A—Time to recurrence and breast cancer death in lymph node negative patients based on progesterone (PgR) and estrogen receptor (E_2R) status (the solid line indicates PgR– E_2R– [n = 83], the dashed line indicates PgR– E_2R+ [n = 78], and the dotted line indicates PgR+ E_2R+ [n = 105]).

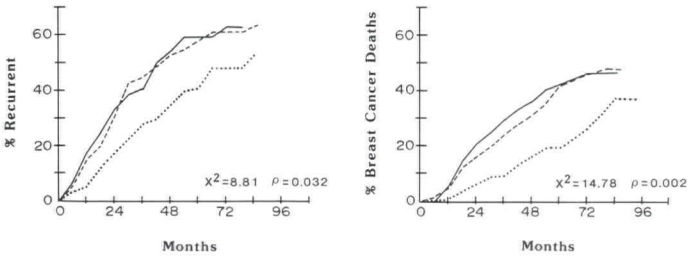

Fig 1B—Time to recurrence and breast cancer death in lymph node positive patients based on progesterone (PgR) and estrogen receptor (E_2R) status (the solid line indicates PgR– E_2R– [n = 75], the dashed line indicates PgR– E_2R+ [n = 98], and the dotted line indicates PgR+ E_2R+ [n = 99]).

of neoplasms containing quantifiable levels of PgR also have significant concentrations of ER, and only a small percent of PgR positive tumors have an ER level below that considered "positive." Nuclear pleomorphism also correlated with PgR levels but to a lesser degree (24), ie, a significantly greater proportion of the less pleomorphic tumors possessed quantifiable amounts of PgR. On the other hand, there was no statistically significant correlation between PgR and either the size of the primary lesion or the number of axillary lymph nodes involved with metastastic disease (24,25). Although the data are not given in Table 1, there was also no relationship between PgR positivity and age (24,25).

Considering all patients, PgR status of the primary tumor as a single variable was a significant indicator of both the frequency of recurrent disease (P = 0.016) and occurrence of death due to breast cancer (P < 0.001). In this study there was no apparent difference between those PgR positive cases with values above 50 fmol/10 mg tissue and those with lower values.

Life table analyses of recurrences and deaths due to breast cancer combining PgR and ER status are shown in Fig 1. Analyses of patients in the ER– and PgR+ category are not given since the total number of such individuals was small (n = 21), making analysis unreliable. It seems enigmatic that for both end points the clinical course of the ER+ PgR– group in relation to the two other major categories was quite different for the node-negative patients than for those whose axillary nodes were involved with cancer. Because of this dichotomy, PgR status had significant predictive value in node-positive patients but was of little or no value in those with uninvolved axillary nodes (see Tables 2 and 3).

Recurrence and mortality data plotted in Fig 2 combine PgR status with the degree of nodal involvement. PgR status had little influence on the clinical course of patients whose cancer had not spread to the axillary lymph nodes, although the late mortality figures for patients with PgR+ tumors appear slightly better (P = 0.17). The predictive value of this index is clearly evident in those patients with positive axillary nodes. The differences in the rate of diagnosis of recurrence were greater in those patients who had four or more nodes involved at the time of surgery, although the magnitude of these differences is somewhat less when considering mortality.

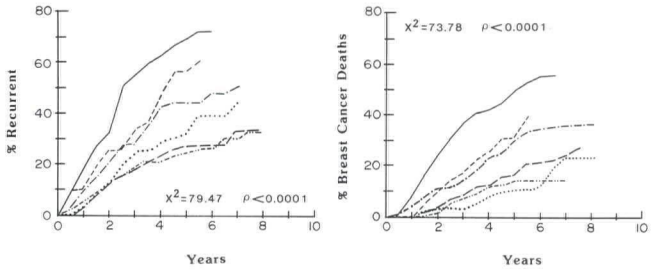

Fig 2—Time to recurrence and breast cancer death based on combined progesterone receptor (PgR) and lymph node (LN) status (the solid line indicates PgR– LN_{4+} [n = 93], the dashed line indicates PgR+ LN_{4+} [n = 44], the dash/dot/dash/dot line indicates PgR– LN_{1-3+} [n = 80], the dotted line indicates PgR+ LN_{1-3+} [n = 63], the dot/dash/dash/dot line indicates PgR– LN_0 [n = 161], and the dash/dot/dot/dash line indicates PgR+ LN_0 [n = 118]).

The results of applying Cox multivariant analysis to these data are given in Tables 2 and 3. Excluded in these analyses were 43 patients whose tumors were morphologically less infiltrative, as well as 53 cases in whom the primary tumor had not been graded histopathologically. A clear difference in predictive power of tumor PgR content is demonstrated between patients whose breast cancer had spread to the axillary lymph nodes and those with a negative axilla. In neither group did the ER status, independent of PgR status, have statistical significance as a predictor of outcome. The degree to which the axillary nodes were involved with cancer was clearly the most important prognostic variable tested followed by tumor size and nuclear grade.

Discussion

The success or failure of initial therapeutic procedures employed to "cure" a carcinoma of the breast depends on the tu-

Table 2
Estimated Relative Risks for 211 Patients Whose Axillary Nodes were not Involved with Cancer

	Number of Patients	Relative Hazard*	95% Confidence Interval	P-Value
Disease-Free Survival:				
Age				0.725
≤ 49 years	67	1.00		
≥ 50 years	144	0.91	0.54, 1.53	
PgR				0.595
≤ 9 fmol	113	0.86		
> 9 fmol	98	1.00	0.50, 1.49	
ER				0.130
≤ 3 fmol	65	1.55		
> 3 fmol	146	1.00	0.88, 2.71	
Tumor size				0.056
≤ 2.0 cm	94	1.00		
2.1–5.0 cm	110	1.85	1.10, 3.07	
> 5.0 cm	7	1.33	0.32, 5.73	
Nuclear grade				0.069
1 or 2	138	1.00		
3	73	1.60	0.97, 2.63	
Survival:				
Age				0.850
≤ 49 years	67	1.00	0.51, 1.75	
≥ 50 years	144	0.94		
PgR				0.167
≤ 9 fmol	113	1.61		
> 9 fmol	98	1.00	0.81, 3.17	
ER				0.201
≤ 3 fmol	65	1.53		
> 3 fmol	148	1.00	0.79, 3.01	
Tumor size				0.005
≤ 2.0 cm	94	1.00		
2.1–5.0 cm	110	2.88	1.45, 5.61	
> 5.0 cm	7	2.98	0.65, 13.48	
Nuclear grade				0.168
1 or 2	138	1.00		
3	73	1.55	0.84, 2.86	

*Adjusted for all variables in the model.

mor's biologic aggressiveness, ie, how readily its neoplastic cells invade the vasculature and form emboli, the proclivity of these emboli to establish distant metastases, and the period of time these processes have been operating before the institution of therapy. The time course of the process may be altered by other biologic factors or by therapeutic interventions to suppress tumor cell proliferation and eradicate established micrometastases. Features of the primary neoplasm that reflect the described variables are useful in predicting the outcome of therapy. Although no combination of available prognostic criteria can predict the outcome, they can indicate the probability of success and identify those patients likely to benefit from adjuvant therapy. In addition, features of the primary tumor are utilized in identifying comparable treatment groups to evaluate the effectiveness of various therapeutic regimens.

The extent of neoplastic invasion of axillary lymph nodes is the single most important indicator of prognosis probably because these metastases indicate the biologic variables described. Tumor size reflects the "opportunity" for viable distant micrometastasis. In any series of cases the larger tumors generally have been present longer than the smaller ones and have invaded more surrounding tissues, increasing the probability of neoplastic emboli via vascular channels. Thus, tumor size was the most significant prognostic indicator among node-negative patients in this series (Table 2), even in those patients whose axillary nodes were already the site of metastatic deposits (Table 3). Other recent publications have established tumor size as an important prognostic indicator independent of nodal status (26-28). Undifferentiated histologic characteristics are also correlated with biologic aggressiveness. Nuclear pleomorphism was an important prognostic indicator for this group of patients (for survival relative hazard = 1.86, 95% confidence level 1.35 to 2.57), although due to sample size this level of statistical significance was not achieved when the node-negative and node-positive cases were analyzed separately. In larger series of cases this morphologic feature had statistical significance in both groups of patients (13,15,17).

According to present dogma, the sex hormone receptor proteins influence the response of the neoplasm to endogenous steroids as well as to therapeutic hormonal alterations. However, such factors must have only a secondary role, considering the natural course of the disease. ER positivity, which should permit a response by the neoplastic cells' estrogen, actually portends a better prognosis if it is the sole steroid receptor demonstrated. The significance of both ER and PgR as prognostic indicators, therefore, must derive from their relationship to cellular differentiation and biologic aggressiveness. The reason for the difference in predictive power of PgR positivity in node-positive versus node-negative patients is unclear. As a single indicator, PgR is superior to ER in node-positive cases but has no additional value in node-negative cases (28).

Nonetheless, combining two or more independent variables yields a much more reliable prediction. Thus, in node-negative patients, combining both nuclear grade and ER status with tumor size permits more precise prognostic prediction (29) than does combining tumor size with either nuclear grade or ER status alone (unpublished data). In the present patient population, nodal status was of the greatest prognostic importance. However, in terms of overall survival, the N 1–3-positive group whose tumors were PgR+ did as well as those patients whose axillary nodes were uninvolved. The size of the primary lesion, which has great importance to the outcome of therapy, is the only variable that can be influenced favorably by the patient and the physician. This important variable has rarely been used in evaluating the results of clinical trials, either of adjuvant or primary therapeutic regimens.

Our results agree in general with other reports. Differences are encountered when recurrence and/or survival rates are related to sex hormone receptor status and compared in different series of node-negative cases. Considering all age groups, in five

of the large series ER positivity was related to better prognosis (15,27-30) while no statistically significant difference was evident in two (14,28-31). When results were considered according to the age of the patients (≤ 49 versus ≥ 50 years) the differences in disease-free survival were not statistically significant in four series (15,29,30,32) but were of considerable magnitude in the two European studies (14,31). For older women in the latter two reports, ER status made no significant difference in disease-free survival. However, in three of the four studies from this country, both recurrence rates and survivorship were superior in ER positive patients. Fewer data are available regarding PgR as a prognostic indicator. PgR status is considered to be a significant prognostic feature in node-positive cases, often more significant than ER status alone, but its importance in node-negative cases seems minimal. In the Danish series (14) better disease-free survival was found for women ≤ 49 years of age but not for older patients with PgR positive tumors. A small but not statistically significant improvement in disease-free survival is seen in the NSABP data (15); however, the difference in five-year survivorship had statistical significance for the ≤ 49-year-old patients but not for the older group of women.

In summary, sex hormone receptor quantitation is useful in predicting the outcome of primary therapy in breast cancer. However, the importance of receptor data is less than that of axillary node involvement, tumor size, and morphologic evidence of abnormal differentiation. Still, knowledge of hormone receptor status is essential for designing randomizations and for interpreting the results of comparative adjuvant regimens. Such information is also important when planning therapy for recurrent disease and may be of importance in selecting appropriate adjuvant treatment.

Table 3
Estimated Relative Risks for 252 Patients Whose Axillary Nodes were Involved with Cancer

	Number of Patients	Relative Hazard*	95% Confidence Interval	P-Value
Disease-Free Survival:				
Age				0.173
≤ 49 years	78	1.00		
≥ 50 years	174	1.25	0.85, 1.83	
PgR				0.048
≤ 9 fmol	152	1.45		
> 9 fmol	100	1.00	1.00, 2.22	
ER				0.662
≤ 3 fmol	67	0.94		
> 3 fmol	185	1.00	0.60, 1.38	
Tumor size				0.038
≤ 2.0 cm	76	1.00		
2.1–5.0 cm	136	1.39	0.91, 2.12	
> 5.0 cm	40	2.01	1.19, 3.40	
Nuclear grade				0.358
1 or 2	147	1.00		
3	105	1.21	0.85, 1.72	
Number of positive nodes				0.001
1–3	130	1.00		
> 3	122	1.78	1.23, 2.56	
Survival:				
Age				0.676
≤ 49 years	78	1.00		
≥ 50 years	174	1.10	0.71, 1.70	
PgR				0.052
≤ 9 fmol	152	1.59		
> 9 fmol	100	1.00	0.99, 2.55	
ER				0.780
≤ 3 fmol	67	0.93		
> 3 fmol	185	1.00	0.58, 1.51	
Tumor size				0.009
≤ 2.0 cm	76	1.00		
2.1–5.0 cm	136	2.12	1.23, 3.68	
> 5.0 cm	40	2.34	1.20, 4.56	
Nuclear grade				0.006
1 or 2	147	1.00		
3	105	1.80	1.19, 2.72	
Number of positive nodes				0.005
1–3	130	1.00		
> 3	122	1.85	1.20, 2.86	

*Adjusted for all variables in the model.

Acknowledgments

We thank Renee McCune, RN, OCN, for patient follow-up, and Mary DuPuis, MS, and Paul Juneau, MS, for statistical analysis.

This study was supported by the Suzanne Korman Morton Laboratory and PHS grant CA-22453 from the Division of Extramural Activities, National Cancer Institute.

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