

Progesterone Receptor Status Significantly Improves Outcome Prediction Over Estrogen Receptor Status Alone for Adjuvant Endocrine Therapy in Two Large Breast Cancer Databases

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Purpose: To determine whether progesterone receptor (PgR) status provides additional value to estrogen receptor (ER) status and improves prediction of benefit from endocrine treatment among patients with primary breast cancer.

Patients and Methods: Clinical outcomes of patients in two large databases were analyzed as a function of steroid receptor status. The first database (PP), contained 3,739 patients who did not receive any systemic adjuvant therapy and 1,688 patients who received adjuvant endocrine therapy but no chemotherapy. The second database (SPORE), contained 10,444 patients who received adjuvant endocrine therapy but no chemotherapy. Biochemical ER and PgR assays were identically performed in two different central laboratories.

Results: In univariate and multivariate analyses, the prognostic significance of PgR status among systemically untreated patients is modest. Among endocrine-treated patients, however, multivariate analyses, including lymph-node involvement, tumor size, and age, demonstrate that PgR status is independently associated with disease-free

and overall survival. For recurrence, the reduction in relative risk (RR) was 25% for ER-positive/PgR-negative patients and 53% for ER-positive/PgR-positive patients, compared with ER-negative/PgR-negative patients ($P < .0001$, PP patients). Patients with ER-positive/PgR-negative tumors have a reduction in RR of death of 30% (SPORE patients) and 38% (PP patients), compared with patients with ER-negative/PgR-negative tumors ($P < .0001$). For ER-positive/PgR-positive tumors, the reduction of the risk of death was greater than 46% in SPORE patients and 58% in PP patients, indicating that ER-positive/PgR-positive patients derive more benefit from endocrine therapy ($P < .0001$).

Conclusion: When accurately measured, PgR status is an independent predictive factor for benefit from adjuvant endocrine therapy. Therefore, PgR status should be taken into account when discussing RR reductions expected from endocrine treatment with individual patients.

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ONLY ABOUT one half of patients with early breast cancer are cured by local therapy alone.¹ Therefore, it is important to be able to identify in which patients the disease is destined to recur and which patients are likely to benefit from systemic therapy.

Estrogen receptor (ER) and progesterone receptor (PgR) status has been used since the mid-1970s in the clinical management of breast cancer both as an indicator of endocrine responsiveness and as a prognostic factor for early recurrence. Although the predictive value of ER level in predicting response to hormone therapy in early breast cancer patients is undisputed, the prognostic value of ER and PgR is still debated, as is the value of PgR. Many studies that have evaluated the prognostic role of ER or PgR in primary breast cancer have included patients who received adjuvant endocrine therapy as well as patients who did not receive any adjuvant therapy. These inclusion criteria make it difficult to separate the prognostic role of these biomarkers from the predictive value. In addition, small sample size, short follow-up, differences in clinical features of patients, and exclusion from statistical analyses of pathobiologic or clinical variables relevant for breast cancer natural history may have contributed to different conclusions regarding the prognostic impact of steroid receptor content.

In comparison, the role of ER content as a predictor of response to endocrine treatment in early breast cancer patients has been better studied and consistently recognized.^{2,3} A recent update of a meta-analysis of all tamoxifen trials⁴ shows that

women with ER-positive tumors derive significant benefit from 5 years of tamoxifen in reducing the odds of recurrence and death, whereas women with ER-negative tumors do not. This benefit is directly proportional to the level of ER, with patients with higher tumor ER levels deriving the greatest benefit from therapy.

Despite this clearly demonstrated benefit, a substantial portion of ER-positive patients fail to respond to hormone therapy. Because of this, additional markers are needed to improve the ability to predict response. In the 1970s, it was first hypothesized that PgR might provide additional information to more accurately predict which patients will respond to hormonal therapy because the presence of PgR should serve as an indicator of a functionally intact estrogen response pathway.⁵ Unlike the advanced-disease setting in which several small retrospective

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studies and one relatively large prospective study have confirmed the importance of PgR in predicting response to hormonal therapy,^{6,7} the value of PgR in combination with ER for predicting clinical benefit from hormone therapy in the adjuvant setting has not been as well studied. Results from the Oxford overview⁴ indicated that knowledge of PgR status did not provide any additional information in assessing the benefit of adjuvant therapy in ER-positive patients. Because of the technical difficulty in performing PgR assay, these results may be a result of inaccuracies in measuring PgR content rather than lack of clinical or biologic significance of the receptor.

The objective of this study was to assess the prognostic utility of PgR in addition to ER in a large sample of patients with primary breast cancer who received no systemic adjuvant therapy for their breast cancer. Most importantly, the clinical outcome of patients who received only adjuvant hormonal therapy was evaluated to determine whether PgR status independently provided clinically useful information for identifying patients with a greater likelihood of benefiting from adjuvant hormonal therapy. All assays were performed at central laboratories with stringent quality control.

PATIENTS AND METHODS

Study Population

The Breast Center at Baylor College of Medicine (Houston, TX) maintains two databases of breast cancer patients whose biopsy or mastectomy specimens were sent to central laboratories for steroid receptor assays. The first database was funded by the National Cancer Institute (Bethesda, MD) as part of a Program Project grant and is designated the PP database. All steroid receptor assays were performed in a central laboratory at the University of Texas Health Science Center at San Antonio. The second database was funded by the National Cancer Institute as part of a Breast Cancer Specialized Program of Research Excellence grant and is designated the SPORE database. Steroid receptor assays for this database were performed by identical methods at Nichols Institute (San Juan Capistrano, CA). Histologic diagnoses for both databases were made by pathologists at community hospitals and were not reviewed centrally. Patients who received adjuvant chemotherapy, either alone or in combination with endocrine therapy, were excluded from all analyses because the focus of this study was to evaluate the clinical utility of steroid receptor status both for prognosis in systemically untreated patients and for predicting response to endocrine therapy.

The PP database contains information about 9,859 patients with early breast cancer who were diagnosed and treated between 1970 and 1998. Information about adjuvant therapy, disease recurrence, and death was obtained primarily from physicians who were involved in the management of the patients' breast cancer. External validation against the Surveillance, Epidemiology and End Results Registry and other data sources indicates that this information has been reliably ascertained. The primary surgical treatment was mastectomy (86.2%) or lumpectomy (13.8%) with axillary lymph-node dissection; 19.2% of patients received radiotherapy. A total of 3,739 patients (69%) received no systemic adjuvant therapy and 1,688 patients received adjuvant endocrine treatment after local treatment, with tamoxifen accounting for 97% of these treatments.

The SPORE database contains 49,023 patients with early breast cancer who were diagnosed and treated between 1970 and 1999 from hospitals throughout the United States. Follow-up information was obtained primarily from tumor registries. External validation indicates that death has been reliably ascertained; however, administration of adjuvant therapy and determination of disease recurrence were often underascertained. For these reasons, only overall survival was used as an end point in this data set and only those patients known to have received endocrine therapy ($n = 10,444$;

tamoxifen accounting for 95% of the endocrine therapy) were analyzed. The primary treatment was mastectomy (83.6%) or lumpectomy (16.4%) with axillary lymph node dissection; 24.0% of patients received radiotherapy.

Steroid Receptor Determination

ER levels were measured by the dextran-coated charcoal method, as previously described.⁸ From 1970 to 1984, [³H]estradiol was used as labeled ligand. During the same time period, PgR levels were measured by sucrose density gradient.⁹ In 1985, the standard multipoint dextran-coated charcoal assay was modified to incorporate iodine-125-labeled estradiol and [³H]R5020 in a single assay, allowing the simultaneous determination of both ER and PgR.¹⁰ Levels of 3 fmol/mg of protein or greater were considered positive for ER, and levels of 5 fmol/mg of protein or greater were considered positive for PgR.

Statistical Methods

Distributions of steroid receptor status and other categorical variables were compared using standard χ^2 tests. The disease-free interval was calculated from the date of diagnosis. First recurrence or first metastasis (local or distant) was scored as an event, and patients without recurrence were censored at the time of last follow-up or death. Overall survival was calculated from the date of diagnosis, with death from any cause being scored as an event. Patients who were alive at last follow-up were censored at the last follow-up date. For graphical presentation, follow-up was truncated at 120 months.

Survival curves were derived from Kaplan-Meier estimates,¹¹ and the curves were compared by log-rank tests.¹² Tumors were stratified according to their receptor status into the following four groups: ER-positive/PgR-positive, ER-positive/PgR-negative, ER-negative/PgR-positive, and ER-negative/PgR-negative. The influence of receptor status, adjusted for other prognostic factors, was assessed in multivariate analyses by Cox proportional hazards models.¹³ Confounding variables with k subgroups were coded from 0 for the group with the best prognosis to $k - 1$ for the worst prognostic group. These models assume log-linear relationships of relative risks (RRs) between two subsequent subgroups when k is greater than 2. Separate analyses were performed for treated and untreated patients. Tests of interactions between receptor status and administration of adjuvant hormone therapy were adjusted for axillary lymph-node status, tumor size, and patient age. Patients in the PP database who received no systemic adjuvant therapy were analyzed to evaluate the prognostic significance of steroid receptor status for disease-free and overall survival. Patients in the PP database who received adjuvant hormonal therapy were included in analyses of both disease-free and overall survival to determine whether steroid receptor status is predictive of a clinical benefit from endocrine therapy, whereas patients in the SPORE database who were known to have received adjuvant hormonal therapy were analyzed only for overall survival for the reasons previously discussed.

All statistical tests were two-sided at the 5% level of significance and were performed using SAS Version 8.0 (SAS Institute, Cary, NC). Survival rates and RRs are presented with their 95% confidence intervals (CIs).

RESULTS

Patient and Tumor Characteristics

Patient and tumor characteristics for the women in each database are listed in Table 1. Patients who received adjuvant endocrine therapy were more likely to be older than 50 years of age (86.7%) compared with patients who received no adjuvant therapy (76.4%; PP database). The median age was 61 years (range, 24 to 102 years) for PP untreated patients, 65 years (range, 29 to 98 years) for PP treated patients, and 68 years (range, 23 to 104 years) for SPORE treated patients. Significantly more untreated patients were node negative (79.6%) compared with treated patients (51.2%, PP database; and 60.8%,

Table 1. Clinical and Tumor Characteristics in PP and SPORE Databases

Characteristic	PP						P
	No Treatment		Endocrine Therapy		SPORE Endocrine Therapy		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Age, years							
< 50	883	23.6	225	13.3	731	7.0	< .001
≥ 50	2854	76.4	1462	86.7	9713	93.0	
Axillary lymph nodes							
None	2974	79.6	866	51.2	5741	60.8	< .0001
1-3	483	12.9	458	27.2	2476	26.2	
≥ 4	282	7.5	364	21.6	1231	13.0	
Tumor size, cm							
≤ 2	1722	49.0	766	47.5	5618	55.7	< .0001
> 2 to ≤ 5	1524	43.3	710	44.0	3993	39.6	
> 5	270	7.7	137	8.5	470	4.7	
Steroid-receptor status							
ER+/PgR+	1872	50.1	1107	65.6	7368	70.5	< .0001
ER+/PgR-	939	25.1	474	28.1	2520	24.1	
ER-/PgR+	99	2.6	14	0.8	185	1.8	
ER-/PgR-	829	22.2	93	5.5	371	3.6	

Abbreviations: PP, Program Project (first) database; SPORE, Breast Cancer Specialized Program of Research Excellence (second) database; ER+, estrogen receptor-positive; ER-, estrogen receptor-negative; PgR+, progesterone receptor-positive; PgR-, progesterone receptor-negative.

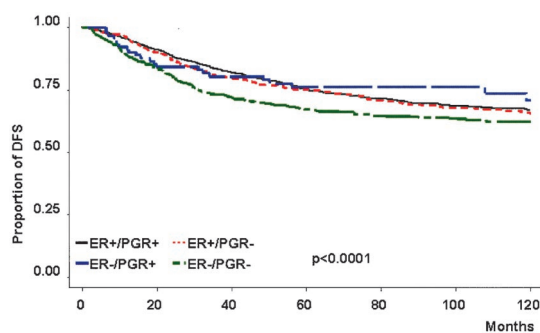
SPORE database). The distributions of tumor size, although statistically significantly different, were relatively comparable between the groups. As expected, the frequency of ER-negative/PgR-negative tumors was much higher among untreated patients (22.2%) compared with treated patients (5.5% and 3.6% for PP and SPORE databases, respectively). The median follow-up of patients still alive at the time of analysis was 64 months (range, 0 to 267 months), 53 months (range, 0 to 261 months), and 85 months (range, 0 to 179 months) for PP untreated, PP treated, and SPORE treated patients, respectively.

Prognostic Significance of Steroid Receptor Status in Untreated Patients

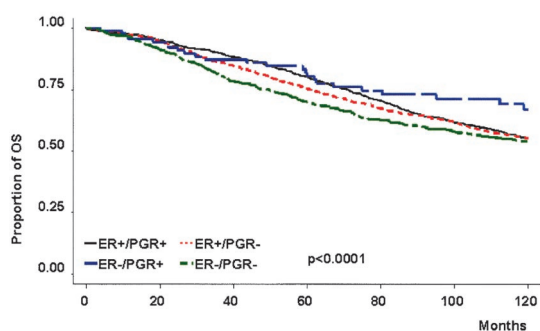
The prognostic significance of ER and PgR status was first evaluated using the untreated PP patients (Fig 1A and 1B). In multivariate analyses, the RRs of recurrence were 0.78 (95% CI, 0.66 to 0.92), 0.81 (95% CI, 0.67 to 0.98), and 0.65 (95% CI, 0.41 to 1.03) for ER-positive/PgR-positive, ER-positive/PgR-negative, and ER-negative/PgR-positive patients, respectively, compared with ER-negative/PgR-negative patients ($P < .0001$). The RRs of death were 0.78 (95% CI, 0.67 to 0.90), 0.80 (95% CI, 0.67 to 0.95), and 0.69 (95% CI, 0.44 to 1.06) for ER-positive/PgR-positive, ER-positive/PgR-negative, and ER-negative/PgR-positive patients, respectively, compared with ER-negative/PgR-negative patients ($P = .0005$; Table 2). Thus, patients with ER-positive/PgR-positive and ER-positive/PgR-negative breast cancer had significantly better prognoses than patients with ER-negative/PgR-negative disease. Patients with ER-positive/PgR-negative tumors tended to have slightly worse disease-free and overall survival than patients with ER-positive/PgR-positive tumors, but the differences did not achieve statistical significance ($P > .05$). Thus, the purely prognostic significance of PgR among ER-positive patients is extremely modest.

Predictive Significance of Steroid Receptor Status in Endocrine-Treated Patients

Separate analyses were performed using patients from the PP and SPORE databases who received adjuvant endocrine therapy.



A



B

Fig 1. (A) Disease-free survival and (B) overall survival according to estrogen receptor/progesterone receptor status, in the first database Program Project patients who received no systemic adjuvant therapy. ER+, estrogen receptor-positive; ER-, estrogen receptor-negative; PgR+, progesterone receptor-positive; PgR-, progesterone receptor-negative.

Table 2. Multivariate Analyses of Disease-Free and Overall Survival in PP Patients Who Received No System Adjuvant Therapy

Factor	DFS			OS		
	RR	95% CI	P	RR	95% CI	P
Axillary lymph nodes						
None	1			1		
1-3	1.57	1.30 to 1.90	< .0001	1.78	1.51 to 2.10	< .0001
≥ 4	3.52	2.87 to 4.32		3.93	3.30 to 4.69	
Tumor size, cm						
≤ 2	1			1		
> 2 to ≤ 5	1.29	1.11 to 1.49	< .0001	1.28	1.12 to 1.45	< .0001
> 5	1.29	1.11 to 1.49		1.92	1.57 to 2.35	
Age, years						
< 50	1			1		
≥ 50	1.26	1.08 to 1.46	.004	1.46	1.25 to 1.71	< .0001
Steroid-receptor status						
ER-/PgR-	1			1		
ER-/PgR+	0.65	0.41 to 1.03	< .0001	0.69	0.44 to 1.06	.0005
ER+/PgR-	0.81	0.67 to 0.98		0.80	0.67 to 0.95	
ER+/PgR+	0.78	0.66 to 0.92		0.78	0.67 to 0.90	

Abbreviations: PP, Program Project (first) database; DFS, disease-free survival; OS, overall survival; RR, relative risk; CI, confidence interval; ER-, estrogen receptor-negative; ER+, estrogen receptor-positive; PgR-, progesterone receptor-negative; PgR+, progesterone receptor-positive.

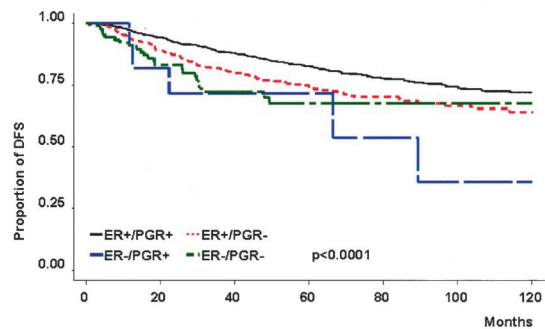
In univariate analyses, PP patients who were ER-positive/PgR-positive had the best 5-year disease-free survival (82.5%; 95% CI, 79.9% to 85.1%), compared with ER-positive/PgR-negative patients (73.8%; 95% CI, 69.0% to 78.6%), ER-negative/PgR-positive patients (71.6%; 95% CI, 44.2% to 99.0%), or ER-negative/PgR-negative patients (67.7%; 95% CI, 56.4% to 79.1%; $P < .0001$). The same patterns were observed for 5-year overall survival: the rates were 81.2% (95% CI, 78.5% to 84.0%) for ER-positive/PgR-positive patients, compared with 71.6% (95% CI, 66.7% to 76.5%) for ER-positive/PgR-negative patients, 48.0 (95% CI, 15.7% to 80.1%) for ER-negative/PgR-positive patients, and 62.0% (95% CI, 50.6% to 73.4%) for ER-negative/PgR-negative patients ($P < .0001$; Fig 2A and 2B).

Similar results were observed among SPORE patients, where the 5-year overall survival rates were 80.2% (95% CI, 79.2% to 81.1%) for ER-positive/PgR-positive patients, compared with 73.4% (95% CI, 71.6% to 75.2%) for ER-positive/PgR-negative patients, 72.1% (95% CI, 65.4% to 78.9%) for ER-negative/PgR-positive patients, and 63.9% (95% CI, 58.7% to 69.0%) for ER-negative/PgR-negative patients ($P < .0001$; Fig 3).

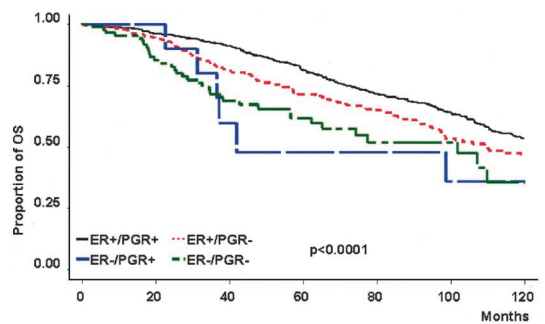
In the PP data set, multivariate analyses confirmed that both ER and PgR are independent significant predictors of disease-free and overall survival among patients who received adjuvant endocrine therapy (Tables 3 and 4). The reduction in RR of recurrence was 53% for ER-positive/PgR-positive patients and 25% for ER-positive/PgR-negative patients ($P < .0001$).

Patients whose tumors are positive for both receptors have the greatest reduction of RR of death compared with patients whose tumors are ER-negative and PgR-negative. Indeed, the reduction in RR of death in the ER-positive/PgR-positive data set of patients is 47% in the SPORE database ($P < .0001$) and 58% in the PP database ($P < .0001$). If the tumors are ER-positive but PgR-negative, the reduction in the RR of death decreases to 32% for the SPORE patients ($P < .0001$) and 38% for the PP patients ($P < .0001$). No meaningful conclusion for the ER-negative/PgR-positive subset was possible because number of events in this subset was too small.

The quantitative level of ER in the tumor is directly related to benefit from endocrine therapy and also to PgR. Therefore, to further investigate whether PgR status was predictive of benefit independent of quantitative ER, we also performed multivariate



A



B

Fig 2. (A) Disease-free survival and (B) overall survival according to estrogen receptor/progesterone receptor status, in the first database Program Project patients who received systemic endocrine therapy. ER+, estrogen receptor-positive; ER-, estrogen receptor-negative; PgR+, progesterone receptor-positive; PgR-, progesterone receptor-negative.

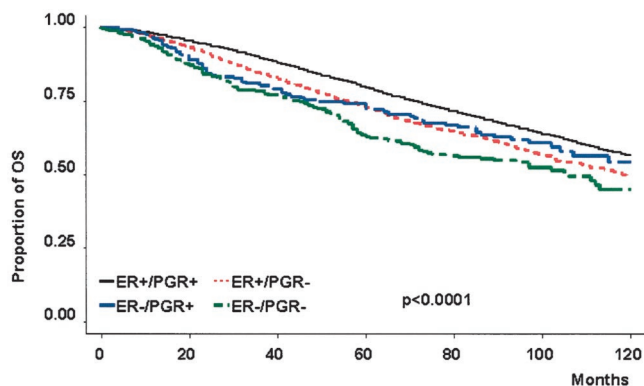


Fig 3. Overall survival according to estrogen receptor/progesterone receptor status in the second database Specialized Program of Research Excellence patients who received systemic endocrine therapy. ER+, estrogen receptor-positive; ER-, estrogen receptor-negative; PGR+, progesterone receptor-positive; PGR-, progesterone receptor-negative.

analyses with ER as a continuous variable and PgR as a dichotomous variable. ER was included in the models as log (quantitative ER plus 1). For disease-free survival in the endocrine-treated PP database, RR for patients with PgR-positive tumors was 0.63 (95% CI, 0.50 to 0.80; $P = .0003$). For overall survival in the endocrine-treated PP and SPORE databases, patients with PgR-positive tumors had a RR of 0.64 (95% CI, 0.53 to 0.79) and 0.73 (95% CI, 0.66 to 0.82), respectively ($P < .0001$). Thus, PgR status yielded predictive information independent of quantitative ER level.

Ideally, the predictive significance of steroid receptor status would be evaluated by testing the interaction between receptor status and treatment using patients who were randomly assigned to receive either adjuvant endocrine therapy or no therapy. Because the steroid receptor assays in this study were performed to help select therapy, some of the patient and tumor characteristics differed between treatment groups. To adjust these imbal-

Table 3. Multivariate Analysis of Disease-Free Survival in PP Patients Who Received Endocrine Adjuvant Treatment

Factor	PP		
	RR	95% CI	P
Axillary lymph nodes			
None	1		
1-3	1.64	1.22 to 2.22	
≥ 4	3.30	2.49 to 4.37	< .0001
Tumor size, cm			
≤ 2	1		
>2 to ≤ 5 cm	1.48	1.14 to 1.92	
> 5	2.41	1.70 to 3.43	< .0001
Steroid-receptor status			
ER-/PgR-	1		
ER-/PgR+	1.08	0.37 to 3.12	
ER+/PgR-	0.75	0.47 to 1.18	< .0001
ER+/PgR+	0.47	0.30 to 0.78	

Abbreviations: PP, Program Project (first) database; RR, relative risk; CI, confidence interval; ER-, estrogen receptor-negative; ER+, estrogen receptor-positive; PGR-, progesterone receptor-negative; PGR+, progesterone receptor-positive.

ances and test whether PgR status adds information to ER status in predicting endocrine therapy benefit, a multivariate analysis was performed comparing PgR-positive versus PgR-negative patients in endocrine-treated, ER-positive patients, after adjusting for axillary lymph-node status, tumor size, and patient age. Results from this analysis are presented in Table 5. This analysis confirms the predictive significance of PgR status among ER-positive patients.

DISCUSSION

This is the largest study assessing the clinical utility of steroid hormone receptors in breast cancer. Women with systemically untreated ER-positive/PgR-positive tumors have better clinical outcomes compared with women with ER-negative/PgR-negative tumors, affirming the prognostic significance of the receptor-positive phenotype. Treatment with hormone therapy broadens this difference, which is consistent with treatment effect.

In addition, in the untreated group of patients, there was a trend toward a worse overall survival and disease-free survival for women with ER-positive/PgR-negative tumors compared to women with ER-positive/PgR-positive tumors, although not to an extent that is clinically significant in most circumstances.

There is general agreement that the presence of ER is a favorable prognostic factor, although not a strong one. Growing evidence indicates, however, that this improved prognosis may not be sustained with longer follow-up.¹⁴⁻¹⁷

Among endocrine-treated patients, two previous reports^{18,19} also showed that the presence of both ER and PgR was a stronger marker for the benefit of adjuvant endocrine therapy than ER alone. In the Ferno et al¹⁸ study involving early-stage breast cancer, patients with ER-positive/PgR-positive tumors had a significant improvement in prognosis after treatment with adjuvant tamoxifen, either for 2 or 5 years, compared with patients with ER-positive/PgR-negative tumors. Similarly, Ellis et al¹⁹ showed a trend among letrozole-treated patients for a better response rate in ER-positive/PgR-positive tumors compared with ER-positive/PgR-negative tumors. Therefore, PgR status added to ER status significantly improves the accuracy of predicting endocrine responsiveness of the primary tumor.

In the Oxford overview,⁴ the recurrence reduction for patients with ER-positive/PgR-negative tumors after adjuvant tamoxifen was similar to the corresponding reduction among patients with ER-positive/PgR-positive tumors. One of the reasons for discordance between the overview results and our results could be the technical difficulty in measuring PgR in some of the earlier reports.²⁰ Some of the patients included in the overview analyses could have been misclassified as PgR-negative, even though their tumors might actually have been PgR-positive and vice versa. It is possible that the lack of difference in risk reduction between tamoxifen-treated ER-positive/PgR-positive and ER-positive/PgR-negative subgroups in the meta-analysis is a result of this misclassification of PgR status because analyses were performed in different laboratories around the world with different levels of experience.

Because the presence of PgR reflects a functional ER pathway, smaller benefit from tamoxifen for ER-positive/PgR-negative

Table 4. Multivariate Analyses of Overall Survival in PP and SPORE Patients Who Received Endocrine Adjuvant Treatment

Factor	PP			SPORE		
	RR	95% CI	P	RR	95% CI	P
Axillary lymph nodes						
None	1			1		
1-3	1.83	1.43 to 2.34		1.58	1.45 to 1.73	
≥ 4	3.15	2.48 to 4.01	< .0001	2.55	2.31 to 2.82	< .0001
Tumor size, cm						
≤ 2	1			1		
> 2 to ≤ 5	1.36	1.09 to 1.68		1.58	1.46 to 1.71	
> 5	2.19	1.63 to 2.95	< .0001	2.18	1.88 to 2.53	< .0001
Age, years						
< 50	1			1		
≥ 50	1.79	1.30 to 2.47	.0004	2.27	1.81 to 2.85	< .0001
Steroid-receptor status						
ER-/PgR-	1			1		
ER-/PgR+	0.87	0.34 to 2.23		0.74	0.54 to 1.02	
ER+/PgR-	0.62	0.43 to 0.91	< .0001	0.68	0.57 to 0.82	< .0001
ER+/PgR+	0.42	0.29 to 0.60		0.53	0.44 to 0.63	

Abbreviations: PP, Program Project (first) database; SPORE, Breast Cancer Specialized Program of Research Excellence (second) database; RR, relative risk; CI, confidence interval; ER-, estrogen receptor-negative; ER+, estrogen receptor-positive; PgR-, progesterone receptor-negative; PgR+, progesterone receptor-positive.

tumors compared with ER-positive/PgR-positive tumors would be expected. PgR is synthesized by tumor cells that are stimulated by estrogens through an interaction with ER.²¹ In theory, the presence of PgR might be a better indicator of hormonal dependence than ER because ER may be present but not functional in some patients. The natural history of ER-negative/PgR-positive tumors and their responsiveness to hormone therapy is still controversial. The presence of ER is considered to be a prerequisite for PgR positivity,²² and ER-negative/PgR-positive tumors could reflect methodologic problems with ER analysis resulting in an occasional false-negative ER assay. Alternatively, ER may be present but at levels beneath the level of detectability of the assay. Another possibility is that certain variant ERs might be unable to bind the hormone or be recognized by monoclonal antibodies but might still be functional in stimulating the estrogen-responsive PgR.^{23,24} In the Oxford overview,⁴ evidence indicates that a positive PgR assay identifies a more tamoxifen-responsive subgroup of patients even when patients have ER-negative tumors.⁴ From our data ER-negative/PgR-positive tumors do not seem to be as sensitive to endocrine therapy as ER-positive/PgR-positive or ER-posi-

tive/PgR-negative tumors, although the number of events is too small to draw any firm conclusion about the ER-negative/PgR-positive uncommon tumor phenotype.

Although this report is a retrospective study, the PP and SPORE database are the two largest data sets of early breast cancer patients in which steroid receptor status is collated with adjuvant endocrine therapy. Furthermore, the analysis of the same variables in two different populations, and the measurement of ER and PgR status by central pathology laboratories with extensive experience, assay standardization, and quality-control procedures enhance the reliability of these data. Additional studies will have to be performed to extend these results to other types of steroid receptor assays.^{25,26}

Our study supports the concept of a modest prognostic value of both ER and PgR over the initial 3 years of follow-up, although the prognostic significance may decrease over time. Results from this analysis validate the predictive roles of ER and PgR in the identification of subsets of patients with high, intermediate, or low benefit from adjuvant hormone therapy. Patients with ER-positive and PgR-positive tumors derive the greatest benefit from adjuvant hormone therapy. If only one

Table 5. Multivariate Analysis to Test PgR Predictive Value on DFS and OS Among Endocrine-Treated ER+ Patients After Adjusting for Nodal Status, Tumor Size, and Age

Database	DFS			OS		
	HR	95% CI	P	HR	95% CI	P
PP						
PgR-	1			1		
PgR+	0.62	0.49 to 0.80	< .0002	0.67	0.54 to 0.82	< .0002
SPORE						
PgR-				1		
PgR+				0.78	0.71 to 0.85	< .0001

Abbreviations: PgR-, progesterone receptor-negative; PgR+, progesterone receptor-positive; ER+, estrogen receptor-positive; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; PP, Program Project (first) database; SPORE, Breast Cancer Specialized Program of Research Excellence (second) database.

receptor is present, either ER or PgR, this benefit decreases by almost half or more. Evidence from this study and others^{18,19} indicates that patients with ER-positive/PgR-negative tumors have less benefit from adjuvant endocrine therapy, so additional or better treatments for the ER-positive/PgR-negative subset may be needed. When adjuvant treatment decisions are made with individual patients, especially when endocrine therapy alone or endocrine therapy combined with chemotherapy is considered, PgR status may be an important additional consid-

eration. Patients with ER-positive/PgR-negative tumors may want to more strongly consider the addition of chemotherapy given the reduced benefit expected from hormone therapy alone. This may be especially true for patients with small- or intermediate-size, node-negative cancers, an increasingly common subset. In this group, the additional overall benefits of chemotherapy are modest at best, and the patient's and physician's analysis of risk and benefits should be used in deciding on therapy.²⁷

REFERENCES

- McGuire WL: Prognostic factors for recurrence and survival in human breast cancer. *Breast Cancer Res Treat* 10:5-9, 1987
- Breast Cancer Trials Committee: Adjuvant tamoxifen in the management of operable breast cancer: The Scottish Trial—Report from the Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. *Lancet* 2:171-175, 1987
- Fisher ER, Sass R, Fisher B, et al: Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6): II. Relation of local breast recurrence to multicentricity. *Cancer* 57:1717-1724, 1986
- Early Breast Cancer Trialists' Collaborative Group: Tamoxifen for early breast cancer: An overview of the randomised trials—Early Breast Cancer Trialists' Collaborative Group. *Lancet* 351:1451-1467, 1998
- Horwitz KB, McGuire WL: Specific progesterone receptors in human breast cancer. *Steroids* 25:497-505, 1975
- Elledge RM, Green S, Pugh R, et al: Estrogen receptor (ER) and progesterone receptor (PgR), by ligand-binding assay compared with ER, PgR and pS2, by immuno-histochemistry in predicting response to tamoxifen in metastatic breast cancer: A Southwest Oncology Group Study. *Int J Cancer* 89:111-117, 2000
- Ravdin PM, Green S, Dorr TM, et al: Prognostic significance of progesterone receptor levels in estrogen receptor-positive patients with metastatic breast cancer treated with tamoxifen: Results of a prospective Southwest Oncology Group study. *J Clin Oncol* 10:1284-1291, 1992
- McGuire WL, De La Garza M, Chamness GC: Evaluation of estrogen receptor assays in human breast cancer tissue. *Cancer Res* 37:637-639, 1977
- Powell B, Garola RE, Chamness GC, et al: Measurement of progesterone receptor in human breast cancer biopsies. *Cancer Res* 39:1678-1682, 1979
- Dressler LG, Seamer LC, Owens MA, et al: DNA flow cytometry and prognostic factors in 1331 frozen breast cancer specimens. *Cancer* 61:420-427, 1988
- Kaplan EL, Meier P: Non-parametric estimation for incomplete observation. *J Am Stat Assoc* 53:457-471, 1958
- Peto R, Peto J: Asymptotically efficient rank invariant test procedures. *J R Stat Soc A* 135:185-207, 1972
- Cox DR: Regression models and life table (with discussion). *J R Stat Soc A* 34:187-202, 1972
- Aamdal S, Borner O, Jorgensen O, et al: Estrogen receptors and long-term prognosis in breast cancer. *Cancer* 53:2525-2529, 1984
- Hahnel R, Woodings T, Vivian AB: Prognostic value of estrogen receptors in primary breast cancer. *Cancer* 44:671-675, 1979
- Hilsenbeck SG, Ravdin PM, de Moor CA, et al: Time-dependence of hazard ratios for prognostic factors in primary breast cancer. *Breast Cancer Res Treat* 52:227-237, 1998
- Coradini D, Daidone MG, Boracchi P, et al: Time-dependent relevance of steroid receptors in breast cancer. *J Clin Oncol* 18:2702-2709, 2000
- Ferno M, Stal O, Baldetorp B, et al: Results of two or five years of adjuvant tamoxifen correlated to steroid receptor and S-phase levels: South Sweden Breast Cancer Group, and South-East Sweden Breast Cancer Group. *Breast Cancer Res Treat* 59:69-76, 2000
- Ellis MJ, Coop A, Singh B, et al: Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial. *J Clin Oncol* 19:3808-3816, 2001
- Rutqvist LE, Cedermark B, Fornander T, et al: The relationship between hormone receptor content and the effect of adjuvant tamoxifen in operable breast cancer. *J Clin Oncol* 7:1474-1484, 1989
- Arafah BM, Finegan HM, Roe J, et al: Hormone dependency in N-nitrosomethylurea-induced rat mammary tumors. *Endocrinology* 111:584-588, 1982
- Horwitz KB, McGuire WL, Pearson OH, et al: Predicting response to endocrine therapy in human breast cancer. *Science* 189:726-727, 1975
- McGuire WL: Breast cancer prognostic factors: Evaluation guidelines. *J Natl Cancer Inst* 83:154-155, 1991
- Fuqua SA, Fitzgerald SD, Chamness GC, et al: Variant human breast tumor estrogen receptor with constitutive transcriptional activity. *Cancer Res* 51:105-109, 1991
- Harvey JM, Clark GM, Osborne CK, et al: Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol* 17:1474-1481, 1999
- Allred DC, Harvey JM, Berardo M, et al: Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol* 11:155-168, 1998
- National Institutes of Health: NIH Consensus Development Conference on Adjuvant Therapy for Breast Cancer. Bethesda, MD, National Institutes of Health, 2000