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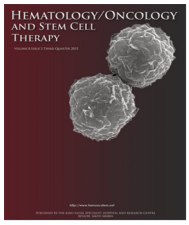

ORIGINAL RESEARCH REPORT

Relevance of progesterone receptor immunohistochemical staining to Oncotype DX recurrence score

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Abstract

Objective/Background: Progesterone-receptor negativity (PR−) is predictive of adverse outcomes in estrogen receptor-positive (ER+) breast cancer. The Oncotype DX assay provides risk stratification for hormone receptor-positive (HR+) invasive breast cancer; however, the association of PR status and Oncotype DX recurrence scores (RSs) is less clear.

Methods: We designed an analysis to determine whether a significant difference exists in the RS for ER+/PR− tumors when compared with ER+/PR+ breast cancer. Three hundred and fifty patients with HR+ invasive breast cancer who underwent Oncotype DX testing at our institution from December 2006 to October 2013 were included. We also examined the concordance in the HR status reported by immunohistochemical (IHC) and reverse transcriptase-polymerase chain reaction (RT-PCR) analyses. The data were analyzed by analysis of variance, *F* test, *t* test, and chi-square tests. Multivariate linear regression was used to determine significant predictors of Oncotype DX RS.

Results: A total of 301 patients had ER+/PR+ tumors and 47 patients had ER+/PR− tumors by IHC. PR− tumors had a significantly higher RS than PR+ tumors (24.7 ± 8.53 vs. 17.3 ± 7.38; $p < .001$), predicting a greater 10-year risk of distant recurrence. Multivariate linear regression showed PR status and tumor grade to be significant predictors of Oncotype DX RS ($p < .0001$). A

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total of 284 patients had HR status reported by Oncotype DX assay. Concordance between IHC and RT-PCR was 99.3% for ER and 88.7% for PR.

Conclusion: Our study shows that ER+/PR− breast cancer tumors are associated with a significantly higher Oncotype DX scores; this interprets into a higher risk of recurrence. Our data also show that the concordance between IHC and RT-PCR was 99.3% for ER and lower at 88.7% for PR.

Introduction

The management of breast cancer has advanced significantly with recognition of its molecular subtypes. Current approaches merge clinical, pathological, and molecular understanding of this tumor with a better grasp of therapeutic efficacy and outcomes. Estrogen and the estrogen receptor (ER) play key roles in normal breast development and the development of breast cancer. The progesterone receptor (PR) is present in both normal and malignant cells in the breast and its synthesis is dependent on both estrogen and the ER. Approximately 75% of primary breast cancers express ER, whereas more than half of these cancers also express PR [1]. However, within the group of ER+ tumors is the ER+/PR− subtype, which is now recognized as a distinct biological and clinical entity associated with a less favorable outcome. Recent studies have shown that the absence of PR is an independent predictor of poor response to antiestrogen therapy, and is associated with higher recurrence rates and shorter survival time [2].

Risk assessment is crucial to avoid overtreatment of patients with primary breast cancer. Gene expression profiling has emerged as a useful tool for assessing the risk of distant disease recurrence in patients with early stage breast cancer as it provides additional information to the traditional clinicopathological factors and biomarkers in clinical decision making [3—8]. The 21-gene Oncotype DX assay is a validated genomic test that quantifies the risk of distant recurrence at 10 years from diagnosis and the potential benefit of chemotherapy in early stage ER+ breast cancer [9—11].

In contrast to ER+/PR+ breast tumors, ER+/PR− tumors display greater genomic instability that may explain, in part, their poorer prognosis than ER+/PR+ tumors [12]. However, the association of PR− status per se with Oncotype DX recurrence scores (RSs) has not been extensively reviewed. We, therefore, conducted a retrospective study to evaluate the association of PR− tumors with Oncotype DX RSs with the primary objective to assess whether a significant difference exists in the RS for PR− tumors when compared with PR+ tumors. Since 2008, the Oncotype DX reports have also included ER, PR, and HER2 qualitative and quantitative results. Our secondary objective was to compare the results of ER and PR determination by traditional immunohistochemical (IHC) methods with the result of ER and PR determination by the Oncotype DX assay which employs a reverse transcriptase-polymerase chain reaction (RT-PCR) assay to quantitate hormone receptor (HR) status of breast tumors. This objective sought to determine the level of concordance in the status of hormone receptors reported by the two methods.

Methods

Patient population and data collection

A retrospective review analysis was performed to determine whether the Oncotype DX RSs differ between ER+/PR+ and ER+/PR− tumors. A total of 350 patients with hormone receptor-positive, node-negative invasive breast cancer who underwent Oncotype DX testing at our institution between December 2006 and October 2013 were included in our study. We identified 284 patients in whom the Oncotype DX assay also included an analysis of hormone receptor status in addition to the RS. Additional patient data collected included age, menstrual status, tumor pathology (i.e., histology, grade, and receptor status), breast cancer stage, and treatments received including surgery, radiation, chemotherapy, and endocrine therapy. The study was approved by the Institutional Review Board and the Protocol Review and Monitoring Committee of the Medical College of Wisconsin, WI, USA.

IHC analysis of the primary tumor

ERs and PRs were evaluated by IHC on formalin-fixed paraffin-embedded tissue using clone 1 D5 for ER and clone PgR 636 for PR (Dako, Carpinteria, CA, USA). In 2008, our institution switched to clone SP1 for ER and clone SP2 for PR (Ventana, Tucson, AZ, USA). Detection utilized a monoclonal polymer. Prior to 2012, appropriate nuclear staining in $\geqslant$10% of the cells of interest was considered positive, whereas <10% was considered negative for the ER or PR. In 2012, the nuclear staining criteria were revised to consider any nuclear staining in $\geqslant$1% of the malignant cells to be positive and <1% to be considered negative for the ER or PR.

Oncotype DX assay

The Oncotype DX RS is reported to represent the likelihood of breast cancer relapse within 10 years in patients treated with tamoxifen for 5 years [7,11]. Patients at low, intermediate, and high risk for relapse are defined as having an RS of 0—17, 18—30, and 31—100, respectively [7]. The Oncotype DX assay uses the following expression units criteria for hormone receptor and HER2 expression: ER negative <6.5, ER positive $\geqslant$6.5, PR negative <5.5, PR positive $\geqslant$5.5,

HER2 negative <10.7, HER2 equivocal ⩾10.7—11.4, and HER2 positive ⩾11.5.

Statistical analysis

Continuous variables were compared using *t* tests. Wilcoxon rank-sum test was used for ordinal data. Multivariate linear regression was used to determine significant predictors of Oncotype DX scores. Covariates included in the regression model were age, menopausal status, tumor size, tumor histology, grade, ER status, and PR status. Chi-square test was used to analyze the discrepancies between the two methods to assess concordance of HR results. All statistical tests with two-sided $p < .05$ were considered statistically significant. Statistical analysis was completed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

This study included 350 patients. The mean age at diagnosis was 58 years (58 ± 10.1 mean ± standard deviation [SD]). Of the 350 patients, 301 had PR + disease and 47 patients had PR− tumors by IHC. Receptor information was missing for two patients, and they were not included in the analysis. Most patients were postmenopausal (70%) and had invasive ductal carcinoma (84%). As much as 60% of patients had Grade 2 tumors, and 57% of patients had T1c tumors. All patients had tumors that were ER+ by IHC and node negative. Other patient characteristics relative to hormone receptor status are presented in Table 1.

Table 1 Patient characteristics relative to hormone receptor status.

Variables	ER+/PR+ *N* = 303 (%)	ER+/PR− *N* = 47 (%)	*p*
Age at DX			.542*
Mean ± standard deviation	58.1 ± 10.2	59.1 ± 9.5	
Menstrual status			.041**
Menopausal	207 (68.3)	39 (83.0)	
Premenopausal	96 (31.7)	8 (17.0)	
Histology			.424**
Invasive ductal carcinoma	248 (82.4)	44 (93.6)	
Invasive lobular carcinoma	50 (16.6)	3 (6.4)	
Grade			.183***
1	103 (34.1)	11 (23.4)	
2	176 (58.3)	32 (68.1)	
3	23 (7.6)	4 (8.5)	
Stage			
T1a	2 (0.7)	2 (4.2)	
T1b	49 (16.2)	9 (19.1)	
T1c	174 (57.5)	25 (53.3)	
T2	74 (24.5)	11 (23.4)	
T3	2 (0.7)	0 (0.0)	
Surgery			.056**
Lumpectomy	198 (65.6)	30 (63.8)	
Mastectomy	102 (33.8)	17 (36.1)	
None	3 (0.6)	0 (0.0)	
Chemotherapy			
Yes	93 (30.4)	32 (68.1)	
No	210 (69.6)	15 (31.9)	
Endo tx			
AI	167 (55.4)	30 (65.2)	
Tam	89 (29.2)	9 (19.5)	
Switch AI and Tam	36 (10.9)	4 (8.8)	
Luteinizing hormone releasing hormone agonists	2 (0.6)	0 (0.0)	
None	7 (2.3)	3 (6.5)	

AI = aromatase inhibitor; ER = estrogen receptor; PR = progesterone receptor; Tam = tamoxifen.
* *t* test.
** Chi-square test.
*** Wilcoxon rank-sum test.

PR status and Oncotype DX RS

Univariate analysis showed that PR− tumor status was associated with significantly higher Oncotype DX scores when compared with PR+ tumors (mean ± SD, 24.7 ± 8.53 vs. 17.3 ± 7.38; $p < .001$), thereby predicting a greater 10-year risk of distant recurrence. Most of the patients with PR− tumors had intermediate or high Oncotype DX RSs [53.2% ($n = 25$) and 27.7% ($n = 13$), respectively], compared with PR+ tumors, which were associated more with low and intermediate RSs [53.5% ($n = 161$) and 41.2% ($n = 124$), respectively]. Only 5.3% ($n = 16$) of patients with ER+/PR + tumors had a high Oncotype DX RS as shown in Table 2.

Grade and Oncotype DX RS

Higher tumor grade was associated with a higher Oncotype DX score when compared with intermediate- and low-grade tumors (18.9 ± 8.6 vs. 16.2 ± 6.7; $p = .024$) and (23.3 ± 9.6 vs. 16.2 ± 6.7; mean ± SD; $p < .0001$), respectively, as shown in Fig. 1.

Histology and Oncotype DX RS

We also evaluated the association of histology, that is, invasive lobular breast cancer versus invasive ductal breast cancer, with Oncotype DX scores. No significant difference in Oncotype DX scores was seen based on histology of breast cancer ($p = .23$).

IHC clone and Oncotype DX RS

Our institution used clone 1 D5 for ER and clone PgR 636 for PR (Dako) IHC staining until 2008 when we switched to clone SP1 for ER and clone SP2 for PR (Ventana). There was no significant difference in the Oncotype DX scores based on the different clones and staining criteria used (18.6 ± 6.55 vs. 17.9 ± 8.86; mean ± SD, $p = .75$).

Multivariate linear regression analysis

PR status was a significant predictor of Oncotype DX RS ($p < .0001$). Higher tumor grade was also associated with a higher Oncotype DX score ($p < .0001$). Age, menstrual

Table 2 Association of PR status with Oncotype DX recurrence scores.

Variables	ER+/PR+ *N* (%)	ER+/PR− *N* (%)	*p*
Recurrence score			<0.001*
N	301	47	
Mean ± standard deviation	17.3 ± 7.38	24.7 ± 8.53	
Recurrence score			<0.001**
Low	161 (53.5)	9 (19.1)	
Intermediate	124 (41.2)	25 (53.2)	
High	16 (5.3)	13 (27.7)	

ER = estrogen receptor; PR = progesterone receptor.
* *t* test.
** Chi-square test.

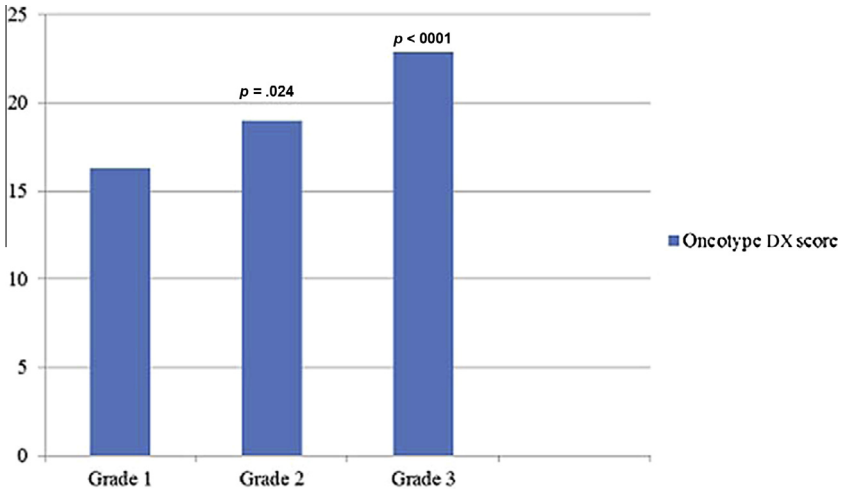

Fig. 1 Association of tumor grade with Oncotype DX score.

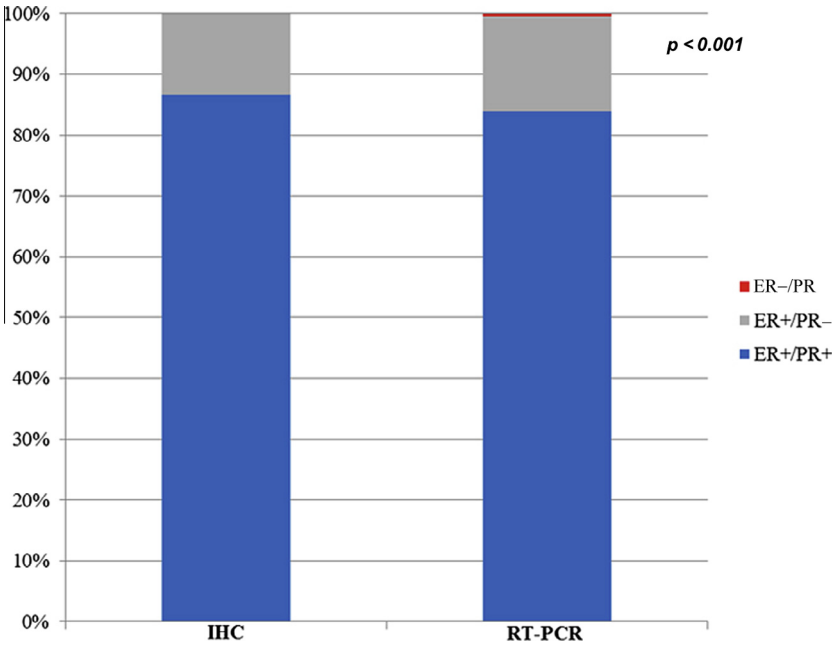

Fig. 2 Concordance between immunohistochemistry (IHC) and reverse transcriptase-polymerase chain reaction (RT-PCR). ER = estrogen receptor; PR = progesterone receptor.

status, tumor histology, and size were not significant predictors of Oncotype DX RS.

Concordance in hormone receptor assessment by IHC and RT-PCR

A total of 284 patients in our study had hormone receptor status reported by Oncotype DX assay. When comparing IHC and Oncotype DX assay, 20 patients (8.1%) who were ER+/PR+ by IHC were found to have ER+/PR− tumors by RT-PCR. Of the ER+/PR− cases identified by IHC, 12 (31.6%) patients were ER+/PR+ and two (5.3%) patients were ER−/PR− by RT-PCR ($p < .001$), as shown in Fig. 2 and Table 3. ER was concordant between IHC and RT-PCR in 99.3% of cases. However, the concordance for PR between the two methods was lower at 88.7%.

Table 3 Concordance between IHC and Oncotype DX hormone receptor results.

RT-PCR	IHC		*p*
	ER+/PR+ *N* (%)	ER+/PR− *N* (%)	
ER+/PR+	226 (91.9)	12 (31.6)	<0.001*
ER+/PR−	20 (8.1)	24 (63.2)	
ER-/PR−	0 (0.0)	2 (5.3)	

ER = estrogen receptor; IHC = immunohistochemistry; PR = progesterone receptor; RT-PCR = reverse transcriptase polymerase chain reaction.
* Chi-square test.

Discussion

Tremendous progress has been made in the treatment of breast cancer. A wealth of knowledge acquired in the last decade in the field of molecular endocrinology, tumor biology, and genomic medicine has led to substantial improvements in the efficacy of cancer treatment and prevention. Determining ER, PR, and HER2 status is crucial to optimizing treatment outcomes in breast cancer patients. Loss of PR is associated with a more aggressive tumor phenotype and earlier tamoxifen resistance. Retrospective analysis from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial showed that patients with ER+ PR− tumors derived less benefit from tamoxifen therapy when compared to anastrozole [13]. This benefit was not seen in the TransATAC analysis, although PR expression continued to be a significant predictor of outcome for both anastrozole and tamoxifen therapy, leading to the conclusion that the expression of PR has an intrinsic prognostic effect [14]. Rakha et al. [2] demonstrated that ER+/PR− tumors are more frequently seen in elderly postmenopausal women and that the absence of PR was an independent predictor of recurrence and shorter survival. Other studies have also shown that ER+/PR− tumors were larger in size, more likely to be higher grade, and to display HER2 gene amplification [15,16].

The Oncotype DX assay developed by Genomic Health (Redwood City, CA, USA) offers additional prognostic and predictive information to ER+ lymph node-negative breast cancer patients as well as ER+ lymph node-positive postmenopausal patients [9,10]. Although a number of studies have shown the value of Oncotype DX RS in assisting clinical decision making for breast cancer management [10,11,17–20], only a few studies have focused on the

relationship between established clinicopathological variables and the RS. Clark et al. [21] in their quality assurance study of 1074 cases reported that a higher PR expression was associated with a lower Oncotype DX RS and this inverse relationship was independent of tumor grade. Auerbach et al. [22] analyzed the relationship between RS and components of routine pathologic assessment in lymph node-negative, ER+ invasive breast cancer patients ($N = 138$). In their study, 13/138 cases had a high RS, of which 10 were PR− and three were PR+ but with a high Nottingham Grade of 3. All other cases that were either PR− or had Grade 3 tumors had at least an intermediate-risk RS. In another study of 77 cases of invasive breast cancers in which the vast majority were ER+/PR+, all six PR− cases had intermediate-risk or high-risk RS [23].

Our study provides further validation to the inverse relationship between PR receptor status and Oncotype DX RS. Oncotype DX RS is predictive of patient's benefit from adjuvant chemotherapy in both the low and high RS categories based on the rate of distant recurrence at 10 years. However, the data and suggested treatment strategy for intermediate RS patients are less clear and will likely remain so until the results from the Trial Assigning IndividuaLized Options for Treatment (TAILORx) trial become available [24]. When weighing the treatment options for the patients in the intermediate RS category, the PR status may be an important factor to consider in clinical decision making. PR− breast cancer likely represents a luminal B subtype that is associated with a more aggressive disease course and a greater likelihood of endocrine resistance when compared with PR+ tumors. Thus, patients with ER+/PR− breast cancers may be considered for adjuvant chemotherapy if they belong to the intermediate-risk category.

ER and PR status is an important factor in determining whether a patient will benefit from antiestrogen therapy. According to the American Society of Clinical Oncology/College of American Pathologists, validated techniques to assess these biomarkers are IHC and fluorescence *in situ* hybridization [25,26]. Since 2008, the qualitative and quantitative results for ER, PR, and HER2 have been included in the Oncotype DX report. With supplemental reporting of these biomarkers, there has been growing interest in molecular testing by RT-PCR. Conflicting views on the utility of Oncotype DX as a test to accurately measure these biomarkers have been recently published [27–30]. Badve et al. [29] compared central IHC analysis results for ER and PR with Oncotype DX RT-PCR assay for 776 cases from the Eastern Cooperative Oncology Group (ECOG) 2197 trial. For ER, the concordance between central IHC and RT-PCR was 93%, whereas for PR the concordance was 88%. Park et al. [24] reported 98.9% concordance for ER and 91.3% concordance for PR when IHC and RT-PCR were compared in 265 breast cancer patients. In another study of 464 breast cancer cases, comparison of hormone receptor status reported by IHC and RT-PCR showed a good concordance of 98.9% for ER and 94.2% for PR status [28]. The authors also concluded that IHC was slightly more sensitive at determining the ER and PR expression. Similar to the previously published data, our study showed good concordance of 99.3% for ER status when comparing IHC with RT-PCR. However, the concordance for PR status was lower at 88.7%. This is comparable with the results published by Badve et al. [29]; however, it is much lower than other published studies. One of the hypotheses for the lower concordance for PR status was the change in the clones used to generate the ER and PR antibodies used for IHC and the staining criteria within the period of our study at our institution. However, our analysis and group-wise comparisons did not show any significant difference in Oncotype DX scores and concordance rates between the different clones used and the staining criteria.

Some limitations of our study are the relatively small number of patients and retrospective design. Nonetheless, our findings appear to be plausible and warrant confirmation in further studies with larger number of patients. Such studies would help elucidate the value of PR expression in recurrence risk determination and would assist clinicians in therapeutic decision making and avoidance of undertreatment or overtreatment of early stage breast cancer.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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