Original Article

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Correlations Between Oncotype DX Recurrence Score and Classic Risk Factors in Early Breast Cancer: Results of A Prospective Multicenter Study in Turkey

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ABSTRACT

Objective: Breast cancer is the most common malignancy among Turkish women and the rate of early stage disease is increasing. The Oncotype DX 21-gene assay is predictive of distant recurrence in ER-positive, HER2-negative early breast cancer. We aimed to evaluate the correlations between Recurrence Score (RS) and routine risk factors.

Materials and Methods: Ten academic centers across Turkey participated in this prospective trial. Consecutive patients with breast cancer who had pT1-3, pN0-N1mic, ER-positive, and HER2-negative tumors were identified at tumor conferences. Both pre- and post-RS treatment decisions and physician perceptions were recorded on questionnaire forms. Correlations between RS and classic risk factors were evaluated using univariate and multivariate analyses.

Results: Ten centers enrolled a total of 165 patients. The median tumor size was 2 cm. Of the 165 patients, 57% had low RS, 35% had intermediate RS, and 8% had high RS, respectively. Multivariate analysis indicated that progesterone receptor (PR) and Ki67 scores were significantly related to RS.

Conclusion: Oncotype DX Recurrence Score does not seem to have a significant correlation with the majority of classic risk factors, but it may have a correlation with PR score and Ki67 score.

Keywords: Oncotype DX, pathology, hormone receptors, Ki67, correlation

Introduction

Invasive breast carcinoma is the most commonly seen malignancy and the leading cause of cancer-related death in Turkish women, both in premenopausal and postmenopausal age groups. Forty-five percent of all patients with breast cancer are premenopausal because of the larger young population in Turkey (1). The incidence of breast cancer has been observed to be gradually increasing in Turkey, and this has been attributed to westernized lifestyle, population growth, and aging, and most importantly, the successful implementation of nation-wide opportunistic screening programs in newly- opened cancer screening centers. The latter contributed to a higher proportion of earlier stage disease reported in recent decades (2). According to the Turkish Ministry of Health, nearly half of all breast cancer cases across the country were diagnosed at an early stage in 2011 (3). A recent analysis of 13,240 patients in the National Breast Cancer Database established within the Turkish Federation of Breast Diseases Societies showed that 50% of patients had pN0 disease, and 27% of all patients' breast cancer was diagnosed as stage I disease. Overall, 62% of patients had pathologic characteristics of luminal A- type breast cancer (1).

The prognostic features most commonly used in adjuvant treatment decisions for patients who are node-negative include patient age, menopausal status, tumor size, tumor grade, Ki67 score, HER2 status, and strength of estrogen receptor (ER)/progesterone receptor (PR)

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expression. Although the treatment decision is easier for patients with unequivocal features, it becomes challenging to personalize therapy for those with early-stage breast cancer who have less clearly defined features, especially when they are young. Occasionally, agreeing on a treatment plan may be difficult in tumor conference even for tumors with the luminal A-like phenotype, which are believed to be less responsive to chemotherapy (4, 5).

With an increasing breast cancer incidence and with nearly half of new breast cancer cases presenting as stage pN0 in Turkey, overtreatment is gaining significance as a health care and medical ethics issue facing Turkish physicians and patients, as well as the national health insurance system, which provides extensive coverage for cancer treatment and treatment-related toxicities.

There is increasing evidence that molecular tests may have a role in individualizing therapy. The Oncotype DX 21-gene assay quantifies the likelihood of distant recurrence in women with ER-positive, lymph node-negative breast cancer treated with adjuvant tamoxifen, and it has been validated to predict benefit from chemotherapy in this population (6, 7). It has been incorporated into commonly accepted guidelines including the National Comprehensive Cancer Network (NCCN) (8), the American Society of Clinical Oncology (ASCO) (9), the European Society of Medical Oncology (ESMO) (10), and St Gallen Consensus guidelines (4). The analysis of women in the lowest risk group of the recently-reported TAILORx trial (clinicaltrials.gov identifier NCT00310180) provided prospective evidence that this low-risk group (Oncotype DX Recurrence Score 0-10) may potentially be spared chemotherapy, with 5-year rates of distant relapse-free survival of 99%, invasive disease-free survival of 94%, and of overall survival of 98% with hormonal therapy alone (11). It should be noted that in the original Oncotype DX studies, the cut-off level of RS 18 or lower was indicative of lower risk with a 10-year risk of distant recurrence of 6.8% (95% confidence interval (CI):[4.0 to 9.6]), which was significantly lower than in the high-risk group (RS 31 or higher) whose 10-year distant recurrence risk was 30.5% (95%:[23.6 to 37.4]) (6). Similar data defined the current practice of using RS 18 or lower as an indicator of low risk of recurrence.

The Oncotype DX 21-gene assay is not considered feasible by many Turkish physicians owing to its cost; it is not currently reimbursed by the Turkish Social Security Administration. We designed a prospective multicenter study that aimed to assess the impact of the Oncotype DX Recurrence Score result (RS) on treatment decisions, and the physicians' perceptions regarding influence of RS results on their final treatment recommendations. We also analyzed the correlation between RS and routine pathologic risk factors used at our tumor conference discussions.

Materials and Methods

Patients and Study Design

Ten academic centers in seven Turkish cities that routinely discuss all new cases of breast cancer at weekly multidisciplinary tumor conference participated in this prospective trial. The study was approved by a central Ethics Committee, as well as by each Institutional Review Board. Consecutive patients with breast cancer who had pT1-3, pN0-N1mic, M0, ER (+), and HER2 (-) tumors were identified. Tumors with ≥1% positively-stained cells for ER and PR were considered ER- and PR-positive, respectively. "Luminal subtypes" were defined based on PR and Ki67 evaluation as follows: luminal A = PR score ≥20 and Ki-67 <20%; luminal B = PR <20% or Ki67 >20%. Adjuvant treatment decisions were made with careful consideration of clinical and pathologic information by all of the tumor conference members. This initial treatment decision (pre-RS assay decision) was recorded on a questionnaire form by site investigators, and baseline pathologic characteristics were recorded in an enrollment form. The patients identified at tumor conference were individually contacted. The pre-RS assay decision was conveyed and informed consent was obtained. Formalin-fixed paraffin-embedded (FFPE) tissue blocks were sent to the central laboratory (Genomic Health, Inc.; California, USA). Cases were discussed at tumor conference again when the RS became available and investigators filled the post-RS assay questionnaire forms with their final decision. The pre- and post-RS assay questionnaires also contained questions aimed to capture how strongly the investigator believed that the RS assay result would contribute, and did contribute to the final treatment decision, respectively.

Statistical analysis

Statistical analyses on the Oncotype-DX RS were conducted using both nominal data based on the actual RS score, and an ordinal scale with three RS categories (<18, 18-30, >30). Integrated evaluation by multivariable analysis was performed to study the association between RS (dependent variable) and all clinicopathologic risk factors (predictors) using linear regression models. The risk factors (independent variables) included in the multivariable regression analysis were age, tumor size, tumor grade, ER score, PR score, Ki67 score, and HER2 score (per immunohistochemistry). The cut-off for p value was taken as less than 0.05 for statistical significance in all analyses performed.

Results

Patient and Tumor Characteristics

In total, 165 patients were enrolled from 10 centers across Turkey. The median age was 49 years (range, 26-76 years). Table 1 outlines the patient and tumor characteristics at the time of surgery. One hundred eight (65.5%) patients had pT1 tumors and the median tumor size was 2 cm (range, 0.6-8.0 cm). Only 11 (6.7%) patients had micrometastasis in axillary lymph nodes (pN1mic). The majority of patients had modified Scarff-Bloom-Richardson grade 2 tumors (n=108, 65.5%). Overall, 76 (53.5%) patients had a Ki67 score of <20%, including 60 patients whose Ki67 scores were less than 14%. Based on PR and Ki67 scores, 90 (60.4%) patients were considered to have characteristics of luminal B molecular subtype.

Associations between RS and Clinicopathologic Features

When age groups were analyzed with three different cut-off values (age < or ≥ 40, 45 or 50 years), age was not found a significant predictor of RS in either univariate or multivariable analysis (Mantel-Haenszel test for univariate and regression model for multivariable analysis; p= 0.297, table not included). Among patients who were aged less than 40 years, 52.2% had a low RS, 30.4% had an intermediate RS, and only 17.4% had a high RS. For patients aged over 50 years, these ratios were 54.8%, 31.0%, and 12.1%, respectively.

In the univariate analysis, grade (p=0.002), Ki67 score (14% and 20% cut-offs; p<0.001 for both groups) and PR score (cut-off 20%; p<0.001) were the only risk factors that significantly correlated with RS, whereas tumor size, LN status (presence of micrometastasis), and ER score were not found significant predictors of RS (Mantel-Haenszel test; table not included). Among patients with luminal A-molecular subtype as per their PR and Ki67 scores, the vast majority

(81.4%) had a low RS and only 1.7% had a high RS. In contrast, only 41.1% of patients with luminal B tumors had a low RS and 13.3% had a high RS (Mantel-Haenszel test, p<0.001).

Multivariable analysis of all risk factors including Ki67, age, tumor size, ER score, PR score, and HER2 score (0 vs +1) showed that the combination of all these numeric variables constituted a statistically significant regression model for predicting RS (R= 0.671, R^2= 0.450, p<0.001). When each variable was examined, Ki67 and PR scores were the only variables that seemed to significantly contribute to estimating the RS (Table 2). The seven predictors included in the regression model shown in Table 2 constituted a group of variables that, in combination, could predict the Oncotype DX score, whereas when they were tested individually in the multivariate analysis, it was seen that RS decreased as Ki67 increased (Beta=0.424, p<0.001), and RS decreased as PR increased (Beta= -0.381, p<0.001), but the other variables in the model did not significantly predict RS independently.

Discussion and Conclusion

Although our results suggest correlation with some pathologic features, the RS result made a significant impact in clinical practice despite rigorous pathologic evaluation at our academic centers, as reported separately (12). The significant predictors in our multivariate analysis included the Ki67 score, which is also considered to be important in predicting luminal subtype. It should be noted that significant inter-laboratory variability is a notable concern when interpreting Ki67 score, especially in grade 2 tumors (13). Our multivariable analysis also suggests that the PR score may have a predictive value in estimating the risk group, also as reported in earlier literature (14). As in interpretation of the Ki67 score, variability in immunohistochemistry results could potentially influence physician confidence in PR score while planning treatment. The strength of PR expression may help identify those patients who could require more careful evaluation of prognostic parameters, and potentially molecular testing.

Aside from the limitations inherent in Ki67 testing in general, another main limitation of our study was the sample size, which was restricted because of the high cost of the test and the limitations of the academic grant. While providing valuable information as the largest national study within our country, reaching more patients could help us draw

Table 1. Patient and Tumor Characteristics (n=165)

		n (%)
Age	<40 years	23 (14.0)
	40-49 years	70 (42.4)
	≥50 years	72 (43.6)
Tumor size	≤1 cm	19 (11.5)
	1-2 cm	89 (53.9)
	>2 cm	57 (34.5)
LN Status	pN0	154 (93.3)
	pN1 mic	11 (6.7)
Grade	1	28 (17.0)
	2	108 (65.5)
	3	26 (15.8)
ER score	≤10%	6 (3.6)
	11-30%	4 (2.4)
	31-50%	6 (3.6)
	51-70%	14 (8.5)
	>%70	135 (81.8)
PR score	≤20%	54 (32.7)
	>%20	111 (67.3)
Ki67 score	<20%	76 (53.5)
	≥%20	66 (46.5)
Luminal Subtype (n=145)*	Luminal-A	59 (39.5)
	Luminal-B	90 (60.4)

"Luminal subtypes*" were defined based on PR and Ki67 evaluation as follows: Luminal A= PR score ≥20 and Ki-67 <20%; Luminal B= PR <20% or Ki67 >20%. Sixteen patients had missing Ki67 data and therefore a subtype could not be assigned.

ER: estrogen receptor; PR: progesterone receptor

Table 2. Correlation between RS and clinicopathologic factors, multivariate regression analysis

R	R2	Corrected R2	SE	p
0.671	0.450	0.421	7.961	<0.001
Variables	**B**	**SE**	**Beta**	**p**
Fixed	23.066	4.816		<0.001
Ki-67 score (%)	0.286	0.047	0.424	<0.001
PR score (%)	-0.111	0.019	-0.381	<0.001
Age (years)	-0.104	0.066	-0.106	0.118
Grade	1.576	1.308	0.084	0.231
HER-2 (0 or +1)	0.985	0.937	0.069	0.295
Tumor size (cm)	-0.733	0.706	-0.068	0.301
ER score (%)	-0.027	0.030	-0.059	0.374

ER: estrogen receptor; PR: progesterone receptor; RS: recurrence score

clearer conclusions that are more reflective of the Turkish population, given our ever-growing population size and the genetic/ethnic variability in our population.

Some groups have argued that results of a careful pathologic examination negate the need for Oncotype DX testing and routine pathologic parameters, or composite indexes created using these parameters can predict Oncotype DX assay results (15-18). On the other hand, despite the predictive value of a careful pathologic evaluation, breast oncologists tend to overestimate the recurrence risk in a considerable number of patients (19). The comfort level in sparing a patient from chemotherapy may be even lower in regions with less experience of using molecular testing in routine practice. Moreover, patients with equivocal pathologic features, most of whom have luminal-B subtype tumors, may be conflicted about the treatment recommendation. According to their most recent consensus report, the St Gallen Expert Panel did not believe chemotherapy should be recommended in all patients with luminal B-like disease and that it could be omitted in cases with low scores on Oncotype DX.

Oncotype DX may provide additional information to improve personalize therapy in a significant proportion of patients with early stage breast cancer. More frequent use in carefully selected patients may help spare patients from chemotherapy, and in some rare instances, it may help correctly identify high-risk patients who would otherwise be recommended hormonal therapy alone. Moreover, when used with careful consideration, it may increase confidence levels in treatment recommendations. Among pathologic parameters, Ki67 score and PR score seem to correlate with RS, which would be expected, because these parameters are included among the 16 cancer-related genes in the score.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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