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ORIGINAL ARTICLE

Correlation between clinicopathologic factors and recurrence score according to TAILOR x risk category in patients with hormone receptor positive early-stage breast cancer

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Summary

Purpose: *Oncotype DX 21 gene recurrence score (RS) is commonly used to determine prognosis and the adjuvant therapy decision for patients with estrogen-receptor (ER)-positive, human epidermal growth factor 2(HER 2)-negative, early-stage breast cancer, especially in western countries. The use of this test is limited in Turkey due to its high cost, and the therapy decision is rather made based on clinicopathologic factors. In this study, we aimed to classify Oncotype DX RS according to the TAILOR x risk category in patients with early-stage breast cancer and to demonstrate its correlation with clinicopathologic characteristics.*

Methods: *Oncotype DX RS was classified according to the TAILOR x risk categorization and retrospectively compared in terms of clinicopathologic characteristics in 196 patients with estrogen-receptor (ER)-positive, HER-2 negative, early-stage breast cancer.*

Results: *Oncotype DX RS was found as ≥ 11 in 81.6% of the patients. Out of the patients with low recurrence scores (< 11), 75% had Luminal A and 25% had Luminal B molecular subtypes. The univariate analysis showed a significant correlation between young age (<50 years), low progesterone receptor (PR) immunoreactivity (≤20%), high Ki-67 (≥14) values, and high RS (≥11) and the multivariate analysis found a correlation between high RS (≥11), young age, and low PR immunoreactivity. There was significantly reverse correlation between age and RS.*

Conclusions: *A significant correlation was identified between 11 and above according to the TAILOR x risk categorization and low PR immunoreactivity (≤20%) and young age (<50 years) as classic clinicopathologic factors. Certain clinicopathologic parameters may not be sufficient alone to determine the treatment decision in cases where the Oncotype DX test is not accessible; however, they may have a supportive role.*

Key words: *early-stage breast cancer, clinicopathologic characteristics, oncotype DX recurrence score, TAILOR x risk categorization*

Introduction

In Turkey, approximately 20 000 new breast cancer diagnoses are made every year, and 27% are stage I (pT1N0), while 45% are stage II (pT1-2N0-1) breast cancers [1]. Nearly half of early-stage patients constitute the estrogen-receptor (ER)-positive, human epidermal growth factor re-

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ceptor-2 (HER-2)-negative group. Identifying the most appropriate treatment for this group is one of the most important challenges in the management of breast cancer. Most patients have a good prognosis with adjuvant endocrine treatment and recurrence is seen in only 15% despite endocrine treatment [2] and the added systemic chemotherapy reduces the recurrence risk by 2-10% [3,4]. If patient selection is not performed correctly, patients may be subjected to the risks of adjuvant chemotherapy without having its benefits [2]. It is difficult to determine the group of patients who may benefit from chemotherapy. Traditionally speaking, patient characteristics such as age and comorbidities as well as histopathologic characteristics and markers such as lymph node status are used to determine recurrence risk and making the decision on adjuvant chemotherapy [5,6]. However, methods that are more sophisticated are needed to predict treatment response and determine the patients' prognosis. The 21-gene assay Oncotype DX (Genomic Health, Redwood City, CA, USA) test, one of the tests developed for this purpose that assesses the genetic composition of tumor, is more commonly used [7]. Oncotype DX is a reverse transcription polymerase chain reaction (RT-PCR)-based assay that analyzes 16 cancer-related and 5 reference genes to provide a recurrence score (RS) [2,8]. Its benefit in determining the prognosis in patients with ER-positive, HER-2-negative early-stage breast cancer, identifying the clinical benefit of adjuvant chemotherapy, and evaluating the 10-year distant recurrence risk was validated in previous studies [2,9-13]. Oncotype DX is subdivided into three risk categories: low (<18), intermediate (18-30) and high (>30) scores (2), and the distant recurrence risk is 6.8%, 14.3%, and 30%, respectively [11]. Although patients with high RS benefit from chemotherapy, this benefit is very low for patients with low RS. The potential benefit obtained from chemotherapy is unclear for patients in the intermediate risk group. The study titled 'Trial Assigning Individualized Options for Treatment' (TAILOR x) was designed to help the treatment decision for patients in the intermediate-risk group [14] and differentiated risk categories according to the Oncotype Dx RS (low risk, RS <11; intermediate risk, RS 11-25; high risk, RS > 25) [14]. To minimize the risk for patients to be undertreated, the low-risk group was classified as <11. The 5-year results of that study have been announced and the 5-year distant relapse-free survival was 99%, invasive disease-free survival 94%, and overall survival 98% with hormone therapy only in the patient group with RS <11 [15].

Our essential aims in this study were to group the Oncotype DS RS we obtained according to the newly defined TAILOR x risk categorization, to evaluate the association between this information and clinical and pathologic risk factors, and to identify parameters that may provide guidance in making decisions on adjuvant therapy in cases where the test is not accessible.

Methods

The study included 196 female patients aged 18-75 years with ER-positive, HER-2-negative early-stage breast cancer (pT1-3, pN0-N1mic) who consented to take part in the study at 10 oncology centers in different regions of Turkey, and whose data was accessible. The 21-gene recurrence scores were studied in formalin-fixed, paraffin-embedded tissue sections collected from patients at a central laboratory. The clinicopathologic characteristics of patients were recorded (age, tumor diameter, histologic grade, ER and PR status (%), HER-2 status, Ki-67, lymph node status) (Table 1). ER and/or PR were considered positive if there was moderate-to-strong nuclear staining in ≥1% of the tumor cells [16]. HER-2/neu overexpression was assessed in all patients via immunohistochemistry, and fluorescence in situ hybridization (FISH) was used in patients who were borderline HER-2/neu (2+). No patients with completed FISH analyses were identified as having gene amplification. The Nottingham combined histologic grade (Elston-Ellis modification of the Scarff-Bloom-Richardson grading system) was determined for all tumors [17]. The Ki-67 score was defined as the percentage of positively stained cells among the total number of malignant cells that were scored. A staining level of <14% was defined as Ki-67 low, and ≥14% was considered as Ki-67 high [18,19]. For patients whose Ki-67 score was <14 or those who did not have their Ki-67 evaluated, patients with a PR immunoreactivity >20% were considered as Luminal A and those with Ki-67 ≥14 or PR immunoreactivity ≤ 20 were considered as Luminal B. The clinicopathologic features of carcinomas with recurrence score <11 vs. ≥11 were compared.

The study protocol was approved by the ethics committee of Istanbul Bilim University.

Statistics

For the descriptive statistics of the data, the mean, standard deviation, median, lowest, highest, frequency, and ratio values were used. The distribution of variables was measured using the Kolmogorov-Smirnov test. For the analysis of quantitative data, the Mann-Whitney U test and independent samples t-test were used. X^2 was used for the analysis of qualitative data, and in cases where the conditions for x^2 could not be fulfilled, the Fischer test was used. The quantitative impact level was investigated using univariate and multivariate logistic regression analyses. An integrated evaluation by multivariate analysis was performed to study the association between RS (dependent variable) and all clinicopathologic risk factors (predictors) using linear regression mod-

els. The risk factors (independent variables) included in the multivariate regression analysis were age, tumor size, tumor grade, ER score, PR score, Ki-67 score, and HER2 score (per immunohistochemistry). The cut-off p value for statistical significance was <0.05 in all analyses performed. SPSS version 22.0 was used for the analysis of clinical and histopathologic data.

Results

Table 1 shows the patient and tumor characteristics at the time of surgery. The mean age of the 196 patients was 50.11 years (range, 26-75). The histopathology results of patients were as follows: 82.1% (n=161) invasive ductal, 11.7% (n=23) invasive lobular and 6.12% other rare results (mucinous (n=3), metaplastic (n=1), micropapillary (n=2), cribriform (n=4), and papillary (n=2)). Breast-conserving surgery was performed on 152 patients (77.55%) and mastectomy on 44 patients (22.44%). Sentinel lymph node biopsy (SLNB) was performed in all of the patients. SLNB was deemed sufficient for 166 patients (84.69%) with conclusive negative paraffin results, and axillary lymph node dissection (ALND) was performed on 30 patients (15.30%) who had positive or suspected diagnosis from their frozen sections. Micrometastasis (pN1mic) was identified in 11 patients (5.6%) and isolated tumor cells (pN0(i+) were identified in 5 patients (2.55%) (Table 1). The majority of patients had histological grade 2 (n=132, 67.34%). The number of patients with a Ki-67 score <14 was 70 (35.71%), and the number of patients with a Ki-67 score ≥14 was 88 (44.89%). The Ki-67 score of 38 patients (19.38%) was not known.

In the univariate analysis, young age (<50 years), low PR positivity (cut-off: 20%), Ki-67 score (cut-off: ≥14%), and high RS (≥11) were identified as significantly correlated (p=0.011, p=0.002, p=0.005, respectively). No significant correlations were identified between tumor diameter, lymph node status (micrometastasis, isolated tumor cell), ER score, grade, and RS (Table 2). Among the patients, (95 patients, 48.4%) had Luminal A and 51.5% (101 patients) had Luminal B molecular subtypes. The RS was <11 in 26 patients (27.36%) with Luminal A subtype, and in 9 (8.91%) with Luminal B sub-

Table 1. Patient characteristics sorted by the recurrence score

	RS <11		*RS ≥11*		*p*
	Mean ±SD / n (%)	*Med*	*Mean ±SD / n (%)*	*Med*	
Age	53.8±10.6	51.5	49.2±9.6	48.0	0.019[b]
Age, years					0.009
<50	13 (36.1)		96 (60.0)		
≥50	23 (63.9)		64 (40.0)		
Tumor diameter (cm)	18.2±7.7	17.0	19.7±8.7	18.0	0.327[b]
Tumor size (cm)					0.559[a]
<1	2 (5.6)		11 (6.9)		
1-2	20 (55.6)		73 (45.6)		
>2	14 (38.9)		76 (47.5)		
Stage					0.639[a]
1a	0 (0.0)		2 (1.3)		
1b	5 (13.9)		20 (12.5)		
1c	19 (52.8)		78 (48.8)		
Stage 2	12 (33.3)		60 (37.5)		
Histologic grade					0.173[a]
I	5 (13.9)		21 (13.1)		
II	28 (77.8)		104 (65.0)		
III	3 (8.3)		35 (21.9)		
ER (%) positivity	84.0±22.9	90.0	84.0±19.8	90.0	0.603[b]
PR (%) positivity	68.2±29.7	80.0	47.0±35.7	50.0	0.001[b]
Ki-67 (%)	12.0±9.4	10.0	21.1±16.1	18.0	0.001[b]
Lymph node count	4.3±5.6	2.0	4.4±5.7	2.0	0.476[b]
Isolated tumor cells	-		5		
Micrometastasis	2		9		

[a]Mann-Whitney U test, [b]x^2 test

type. The multivariate analysis, which included all histopathologic parameters, identified a significant correlation between young age (<50 years), low PR level, and the patient group with RS ≥11 (p=0.001, p=0.001, respectively) (Table 2).

When the RS value of TAILORx was taken as the thresholds value of 16, 21, and 26, Ki-67 and PR loss were found to be statistically significantly higher in the higher RS group than in the lower RS group.

We compared the changes in different risk groups with x^2 by dividing them into different age groups (35, 40 and 50 years). When RS 11 was considered, the number of patients over the age of 50 was higher in the groups below RS 11 than 11 and above.When RS 21 was considered, the number of patients over 40 years of age was higher in patients below RS 21 than 21 and above. When RS 26 was considered, the number of patients both over 40 and 35 years was higher in the below groups of RS 26 than 26 and above.No age group of 35, 40 and 50 years was affected from threshold for RS 16.

In multivariate analysis,from the adjusted factors [NPI score, LI (+/-), Vİ(+/-), PR(+/-), Ki-67 (≤20% vs >20%), LN (-/ith/mi +), histology (idc/NOS), PR % (≤20% vs >20%), stage (1,2/3), tumor diameter (≤2 vs >2 cm), age (≤50 vs >50, ≤40/40, ≤ 35 vs >35 years) age 50 and PR for RS 11and RS 16, age 40, PR, ER and NPI score for RS 21 and RS 26 were independent factors (Table 3).

There was significantly reverse correlation between age and RS (p<0.001) (Figure 1).

Discussion

A risk exists for the development of serious adverse effects during adjuvant chemotherapy for early-stage breast cancer [20] because the benefit from chemotherapy can only be obtained in patients with hormone-receptor-positive, early-stage breast cancer, therefore, the treatment decision should be

Table 2. Univariate and multivariate analyses of the association between clinicopathologic parameters and recurrence score

	Univariate model			*Multivariate model*		
	OR	*95% CI*	*p*	*OR*	*95% CI*	*p*
Age (<50)	0.38	0.18-0.80	0.011	0.27	0.12-0.60	0.001
TM diameter	1.02	0.98-1.07	0.327			
Pathologic stage	1.06	0.64-1.78	0.813			
Histologic grade	1.56	0.82-2.99	0.174			
NPI score	1.52	0.84-2.74	0.164			
ER	1.00	0.98-1.02	0.993			
PR	0.98	0.97-0.99	0.002	0.98	0.97-0.99	0.001
Ki-67	1.07	1.02-1.13	0.005			

Table 3. Multivariate logistic regression adjusted from univariate analysis

		Multivariate model		
	RS	*OR*	*95% CI*	*p*
Age (≤ 50 vs >50)		0.277	0.124-0.619	0.002
PR (≤20% vs >20%)	<11/ ≥11	0.196	0.063-0.602	0.005
Age (≤ 50 vs >50)		0.378	0.198-0.721	0.003
PR (≤20% vs >20%)	<16/ ≥16	0.266	0.128-0.552	<0.001
Age, years (≤ 40 vs >40)		0.325	0.125-0.862	0.025
NPI score		2.932	1.553-5.570	0.001
ER (≤50% vs >50%)	<21/ ≥21	0.222	0.055-0.932	0.035
PR (≤20% vs >20%)		0.128	0.058-0.278	<0.001
Age (≤ 40 vs 40)		0.216	0.047-0.990	0.049
NPI score		2.600	1.304-5.183	0.007
ER (≤50% vs >50%)	<26/ ≥26	0.127	0.032-0.500	0.003
PR (≤20% vs >20%)		0.143	0.066-0.359	<0.001

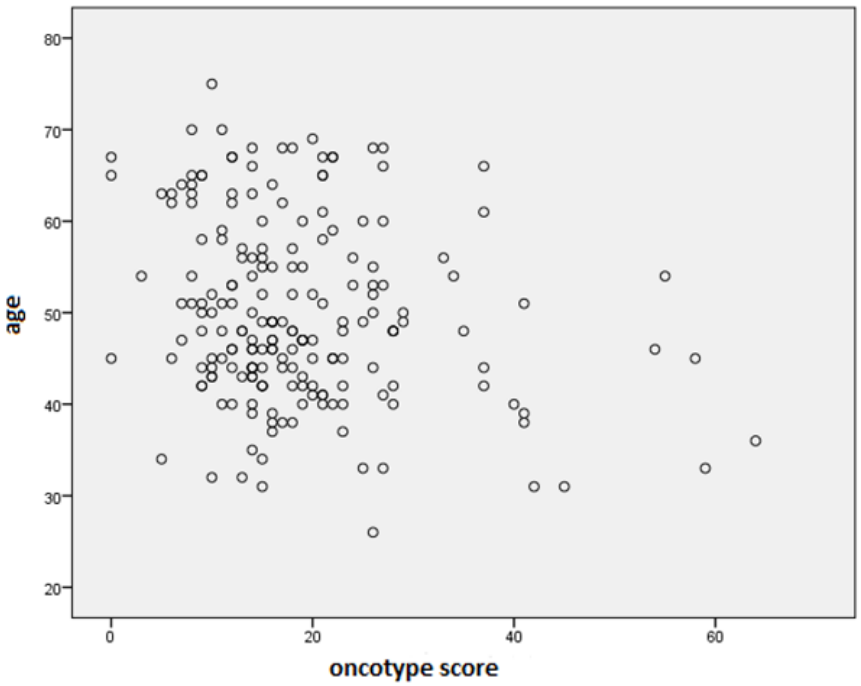

Figure 1. Reverse correlation between age and RS (p>0.01). The older the patients, the lower the recurrence scores.

made very carefully and overtreatment should be avoided [21]. The decision for adjuvant chemotherapy taken by oncologists is shaped by taking clinicopathologic parameters such as age, tumor diameter, histology results and receptor status into account; however, more detailed analyses are required to ensure standardization in treatment approaches [22].

Several gene-expression tests have been developed to assess the potential benefit of treatment and the mean distant recurrence risk [26] such as Mammaprint (Agendia BV, Amsterdam, The Netherlands), a microarray-based assay that assesses the expression of 70 genes (23); Mammostrat (Clarient, Aliso Viejo, CA, USA) [24]; EndoPredict, a 12-gene test [25]; and Oncotype DX (Genomic Health, Inc., Redwood City, CA), a 21-gene-expression test [2]. Among these, Oncotype DX is the most frequently used and various studies have proven that it changes the adjuvant treatment decision by a minimum of 30% [27-29]. However, there are difficulties in accessing this test in Turkey due to its high cost; therefore, the treatment decision is generally taken based on classic risk factors. Several studies identified a correlation between Oncotype DX RS and some clinicopathologic parameters, and these parameters have been used in taking the treatment decision in cases where accessing the test is not possible [15,30-33].

Ingoldsby et al conducted a study in which they assessed Oncotype DX and TAILOR x risk categories along with histopathologic markers and identified a significant correlation between nuclear pleomorphism, PR negativity, and high Ki-67 level, and intermediate and high RS, whereas no correlations were identified between lymphovascular invasion and tumor diameter [30]. Clark et al proved that there was a correlation between PR expression and Oncotype DX recurrence score in their study [31]. Ozmen et al identified a significant correlation between PR immunoreactivity, Ki-67 level, and RS in their study that included 165 patients [34].

In the study conducted by Sparano et al, RS was found as <11 in 15.9% of patients and a significant difference was identified between grade, age, and PR expression in comparison with the patient group with RS ≥11. The ratios of high grade, young age, and low PR expression were significantly higher in the patient group with RS ≥11 [15]. In our study, 18.3% of our patients were in the RS <11 group, and 81.6% were in the RS≥11 group. In the univariate analysis, a significant correlation was identified between young age (<50 years), low PR immunoreactivity (≤20), and high Ki-67 level (≥14) and RS ≥11. In the multivariate analysis, there continued to be a correlation between age and PR and the significance for the level of Ki-67 was lost. Parallel relations between Ki-67 level and RS could not be demonstrated because no central pathologic analyses were performed in our study due to the lack of conformity among laboratories for the assessment of this parameter.

In this study, we compared the patients according to the with different RS thresholds [11,16,21, 26] similar to those in the TAILOR x study. We

observed that higher Ki-67 level and PR loss were lower in older patients than in younger ones. We found a significant inverse correlation between age and RS score (p <0.001). It is known that patients under 51 years of age with a RS cutoff of 21 and above in subgroups according to TAILOR x have 6.5% greater distant metastasis-free survival with chemotherapy than patients 51 and above. Although this study did not include survival analysis, it showed that in the younger patient group (≤ 35 vs > 35 years) there was a significant difference in the RS 26 threshold value, whereas in the advanced age group (≤ 50 vs > 50 years) there was a significant difference in the RS 11 threshold value. Combining the data of TAILORx with this study, the higher rate of RS patients in the younger age group was more prominent, but the contribution of chemotherapy was more independent of age.

Several studies have emphasized that parameters such as the PR expression level, grade, Ki-67 proliferative index and age are correlated with Oncotype DX RS in ER-positive, node-negative, early-stage breast cancer and assist in determining the treatment decisions in cases where the test is not accessible [32,33, 35,36,37]. PR negativity and low immunoreactivity were especially identified as being significantly correlated with high RS [32,33]. Rakha et al found a significant correlation between PR negativity and recurrence risk and short survival time in their study [38]. The reason for this situation may be that patients who are PR-negative are more refractory to endocrine treatment and have a more aggressive progression in comparison with those who are PR-positive [39]. The most significant characteristic of the Luminal B molecular subtype is a high level of Ki-67 and low PR immunoreactivity or negativity; the St. Gallen International Expert Consensus supports the addition of adjuvant chemotherapy to hormone therapy in this group of patients, which has a high risk of recurrence [40].

In conclusion, the Oncotype DX test is important in determining the treatment decision for patients with ER-positive, node-negative early-stage breast cancer, independently from clinicopathologic parameters, and it has become widely used in recent years. According to the TAILORx risk category, endocrine treatment alone is deemed sufficient in the group of patients with RS <11.

When we compared the RS <11 patient group with the group of patients with ≥11 according to the TAILORx categorization, some data indicated that certain clinicopathologic markers such as age and PR receptor may aid in determining patients with RS <11. There was a significant inverse correlation between age and RS score (p<0.001).

This situation may be important in terms of taking the decision for adjuvant treatment when genomic tests cannot be accessed in societies with more limited healthcare resources. However, the most important challenge in using the pathologic markers in early-stage breast cancer to determine the adjuvant treatment decision is the difficulty in ensuring consistency among centers where analyses are conducted. To amend this situation, diligent training efforts supported by nation-wide branch associations are required. Furthermore, the results of comparative, prospective, and randomized studies where genomic and pathologic analyses are conducted at a single center should be awaited to confidently base the adjuvant treatment decision for patients at intermediate-risk solely on pathologic studies.

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Conflict of interests

The authors declare no conflict of interests.

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