Oncotype DX RS Correlation with Clinicopathologic Risk Factors and Chemotherapy: Follow up Based on TAILORx Study

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Research Article

Keywords: Breast cancer, Oncotype DX riskscore, TAILORx

Posted Date: June 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-627802/v1

Abstract

Background: Oncotype DX risk score is a clinically validated prognostic and predictive molecular test. It estimates the recurrence and predicts the likelihood of benefit from adjuvant chemotherapy in early ER\PR positive, node-negative breast cancer. Patients are categorized into one of three tiers based on a calculated recurrence score (RS); low (<18), intermediate (18-30), and high (≥31-100) reflecting 10 years distant recurrence likelihood. 2008 NCCN guidelines recommended adjuvant endocrine therapy for low RS and adjuvant chemoendocrine therapy for high RS, but there was no clear recommendation of chemotherapy for intermediate RS (18-30). In 2018 the TAILORx re-established RS categories; a score of less than 11 is low, 11-25 is intermediate and 26-100 is high, and provided evidence to treat patients in intermediate RS category. Reviewing of Oncotype DX RS previous data in reference to TAILORx might support the optimal utility of this test which was suggested by the study.

The Aim of the Study: Look for Oncotype Dx RS correlation, with clinical and pathological risk factors (age, tumor size, tumor grade, ER/PR status, tumor proliferation index) and chemotherapy based on TAILORx RS tier. Study the characteristics of patients who had cancer recurrence.

Method: Retrospective data review of 54 patients who had Oncotype DX test during 2012-2017 at National Cancer Center-Qatar.

Result: Of 54 patients studied 16(29.63%) had low RS, 32(59.26%) had intermediate RS, and 6(11.1%) had high RS. Univariate analysis showed that age ($p<0.014$), tumor grade ($p<0.034$), and Ki67% (cut-off 20%; $p<0.013$) were significantly different among Oncotype DX RS categories. There was no significant difference among Oncotype DX RS categories for tumor size ($p<0.288$) or PR status (cut-off 1%, $p<0.3$). Multivariate analysis showed that none of the clinical/pathological factors significantly predict the Oncotype DX RS. Chemotherapy was given to 1/16 (6.25%) patients with low, 7/32(21.9%) patients with intermediate, and 4/6 (66.7%) patients with high Oncotype DX RS (univariate analysis $p<0.01$). Although Oncotype DX RS had significant association with chemotherapy in univariate analysis, tumor size was the only predictor of adjuvant chemotherapy treatment from all factors including Oncotype DX RS (OR 2.33 CI 0.33 - 3.86, $p<0.020$). The majority (75%) of patients who had disease recurrence belonged to the high intermediate (16-25) Oncotype DX tier, and all were less than 50 years old in age.

Conclusion: Oncotype RS correlates significantly with individual clinical risk factors including age, tumor grade, Ki67%, chemotherapy treatment. Tumor size significantly predicts adjuvant chemotherapy. Breast cancer recurrence was noticed in younger patients with high intermediate RS (16-25), and adjuvant chemotherapy may be a reasonable option for these patients.

Introduction

Oncotype DX risk score, first developed in 2004 by genomic health Inc, is calculated based on characteristics of 21 genes, 16 breast cancer- related genes and 5 reference genes) that define the ER status, Her2 neu status, tumor proliferation, and tumor invasion [1]. The Recurrence Score (RS) is

measured on a scale of 0-100 with a RS of < 18 being low risk; 18 to 30 being intermediate risk, and more than 30 being high risk [1]. It was validated as a prognostic test that estimate the 10 years recurrence of breast cancer on 668 ER-positive, lymph node-negative cases of tamoxifen-only treated breast cancer patients enrolled in the NSABP B-14 [1]. In this study only 6.8% of patients with low RS tumors recurred in 10 years, compared to 14% of patients with intermediate RS, whereas 30.5% of patients with a high RS recurred at 10 years [1, 2]. The risk score also predicted significant benefit from chemotherapy in patients with high RS tumors, whereas those with a low or intermediate RS did not derive significant benefit from chemotherapy as showed in NSABP-B-20 [2, 3].

Based on the previous evidence, ASCO 2007, and National Comprehe- nsive Cancer Network (NCCN) 2008 updated the recommendations for the use of Tumor Markers in Breast Cancer [4,5,6].

The clinical significance of Oncotype DX RS for individualized oncology continued to grow. In 2018 Trial Assigning Individualized Options for Treatment (Rx), also known as TAILORx which involved 10,273 women with hormone-receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, axillary node-negative breast cancer demonstrated that the Oncotype DX Breast Recurrence Score test definitively identifies the vast majority of women with early-stage breast cancer who receive no benefit from chemotherapy, and the important minority of women for whom chemotherapy benefit can be life-saving [7]. The study concluded that, for midrange Oncotype DX score, adjuvant endocrine therapy and chemo-endocrine therapy had similar efficacy in women with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer who had a midrange 21-gene recurrence score, although some benefit of chemotherapy was found in some women 50 years of age or younger with a recurrence score of 16 to 25 [7].

The TAILORx study considered a score of less than 11 as low, 11–25 as intermediate and 26 or more as high. Following the TAILORx study, NCCN in its 2018 guidelines for invasive breast cancer chemotherapy treatment categorized Oncotype DX Breast Recurrence Score® test as the only "preferred" test for chemotherapy treatment decision-making for patients with node-negative early-stage breast cancer [8]. Relooking into Oncotype DX RS previous studies in reference to TAILORx might support the optimal utility of this test which was suggested by this large study.

Materials And Methods

Setting and Design

Retrospective data review of 54 patients who had Oncotype DX test during 2012-2017 at National Cancer Center-Qatar. The medical research committee approved the protocol with reference (MRC-01-18- 128).

Patients

Patients were eligible for the study if they were hormone receptors positive, her2 negative, early breast cancer diagnosed 2012-2017 and had Oncotype DX test in the database of the institute. 54 patients were identified for the study. The patients were categorized based on
TAILORx tier of Oncotype RS. The clinical and pathological parameters to be compared between the risk score groups included age, tumor size, tumor grade, PR status, Ki-67 index, and chemotherapy. The patients who were diagnosed with recurrent tumor had their clinical and pathological differences studied.

Statistical Analysis

The correlation of clinicopathologic factors and chemotherapy with Oncotype DX RS was done using Pearson chi-square for univariate analysis and logistic regression for multivariate analysis. All tests were 2 tailed, p-value ≤0.05 considered to be statistically significant.

Results

Patients and Tumor Description

In total, 54 patients were studied; Table 1 summarizes the patient's characteristics. Of the 54 patients 16 (29.63%) patients had a low score, 32 (59.26%) patients had an intermediate score, and 6 (11.1%) had a high score (Figure 1). The median age of studied patients was 49 years old (range 30-73 years) with 55.6% ≤ 50 years old. The major histology type was invasive ductal carcinoma reaching 90.7%. The median tumor size was 1.7 cm (range 0.6-4.5 cm). 70.4% of patients had tumor size ≤2 cm. 92.6% (n=50/54) of the studied tumors were grade 1/2 by Nottingham grading system, while only7.4% (n=4/54) were grade 3. Overall, 51 (94.4%) patient were PR positive and only 3 (5.6%) were PR negative. Most of the patients (75.9%, 41\54) had tumor with low proliferation index ki67% ≤20. Only one fifth of patients received chemotherapy.

Table 1: Summary of Patients and tumor characteristics for total 54 patients.

Oncotype RS	Low n (%)	Intermediate n (%)	High n (%)	Total n (%)
Age n (%)				
≤50	5 (16.7) (31.3)	23 (76.6) (71.8)	2 (6.7) (33.3)	30 (55.6)
>50	11 (45.8) (68.7)	9 (37.5) (28.2)	4 (16.7) (66.7)	24 (44.4)
Tumor size n (%)				
≤2 cm	9 (23.7) (56.3)	25 (65.8) (78.1)	4 (10.5) (66.7)	38 (70.4)
>2 cm	7 (43.7) (43.7)	7 (43.7) (21.9)	2 (12.6) (33.3)	16 (29.6)
Tumor grade n (%)				
G1\G2	15 (30) (93.7)	31 (62) (96.9)	4 (8) (66.7)	50 (92.6)
G3	1 (25) (6.3)	1 (25) (3.1)	2 (50) (33.3)	4 (7.4)
PR status n (%)				
PR+	16 (31.4) (100)	30 (58.8) (93.7)	5 (9.8) (83.3)	51 (94.4)
PR-	0 (0) (0)	2 (66.7) (6.3)	1 (33.3) (16.7)	3 (5.6)
KI67% n (%)				
≤20	15 (36.6) (93.7)	24 (58.5) (75)	2 (4.9) (33.3)	41 (75.9)
>20	1 (7.7) (6.3)	8 (61.5) (25)	4 (30.8) (66.7)	13 (24.1)
Chemotherapy n (%)				
No	15 (35.6) (93.75)	25 (59.5) (78.1)	2 (4.7) (33.3)	42 (77.8)
Yes	1 (8.3) (6.25)	7 (58.4) (21.9)	4 (33.3) (66.7)	12 (22.2)

Clinicopathologic Factors Correlation with Oncotype DX RS

Three of the studied clinical/pathological risk factors showed significant differences among Oncotype DX RS categories in univariate analysis. The factors included age ($p<0.014$), tumor grade ($p<0.034$), Ki67% (cut-off 20%; $p<0.013$). There were no significant differences among Oncotype DX RS categories for tumor size ($p<0.288$) or PR status (cut- off 1%, $p<0.30$). Patients who are older than 50 comprised the majority in low-risk (68.7%, 11/16) and high risk (66.7%, 4/6) group but young patients formed the bulk in intermediate RS group (71.8%, 23/32 of patients are ≤50). The differences in age among oncotype RS group categories were statistically significant ($p<0.014$).

Tumor grade was one of the three variables that, showed a difference among oncotype DX RS groups with statistical significance (p<0.034). 30% (n 15/50) of all patients who had low-grade tumor (G1\G2) were reported in the low-risk group compared to 62% (31/50) in intermediate and 8% (4/50) in high RS. G1/G2 was a predominant tumor characteristic when looking in each oncotype DX RS category compared to G3 (Table 1). Ki67% differs significantly between Oncotype DX RS groups. It was noticed that 93.7% of patients within low-risk Oncotype DX had Ki67 ≤ 20%, compared to 75% of patients within intermediate and 33.3% within high RS group (p<0.013) (Table 1).

Table 2: Clinicopathologic risk factors correlation with Oncotype DX RS.

	Oncotype RS Low n (%)	Oncotype RS Intermediate n (%)	Oncotype RS High n (%)	Univariate analysis p value	Multivariate analysis p value
Age				0.014	0.116
≤50	5 (16.7)	23 (76.6)	2 (6.7)		
>50	11 (45.8)	9 (37.5)	4 (16.7)		
Tumor size				0.288	0.117
≤2 cm	9 (23.7)	25 (65.8)	4 (10.5)		
>2 cm	7 (43.7)	7 (43.7)	2 (12.6)		
Tumor grade				0.034	0.995
G1\G2	15 (30)	31 (62)	4 (8)		
G3	1 (25)	1 (25)	2 (50)		
PR status				0.304	0.997
PR+	16 (31.4)	30 (58.8)	5 (9.8)		
PR-	0 (0)	2 (66.7)	1 (33.3)		
KI67%				0.013	0.995
≤20	15 (36.6)	24 (58.5)	2 (4.9)		
>20	1 (7.7)	8 (61.5)	4 (30.8)		

The tumor size did not show a significant difference among Oncotype DX RS groups (p<0.288). 56.3% (n 9/16) of tumors within low risk group measured ≤2 cm (T1) compared to 78.1% (n 25/32) within intermediate and 66.7% (n 4/6) within high risk group. Most of patients in RS group categories expressed progesterone receptors positivity but this did not show statistical significance (p<0.30). For Multivariate analysis low risk group was compared to intermediate/high group. The multivariate analysis which considers all factors together at a time did not sub-select any of these as predictive for Oncotype DX RS (Table 2).

Clinicopathologic Factors Correlation with Chemotherapy

Patient age, Tumor size, tumor grade, PR status, and ki67%) show no individual significant correlation with adjuvant chemotherapy treatment in univariate but when all factors were considered collectively in a multivariate analysis, tumor size significantly correlated to chemotherapy p value of < 0.031 (Table 3).

Table 3: Clinicopathologic risk factors correlation with chemotherapy.

	No adjuvant chemotherapy n (%)	Adjuvant chemotherapy n (%)	Univariate analysis p value	Multivariate analysis p value
Total patients	42 (77.8)	12 (22.2)		
Age			0.124	0.063
≤50	21 (50)	9 (75)		
>50	21 (50)	3 (25)		
Tumor size			0.08	OR 6 (CI, 1.2- 30.9) p<0.031
≤2 cm	32 (76.2)	6 (50)		
>2 cm	10 (23.8)	6 (50)		
Tumor grade			0.89	0.924
G1\G2	39 (92.9)	11 (91.7)		
G3	3 (7.1)	1 (8.3)		
PR status			0.634	0.238
PR+	40 (95.2)	11 (91.7)		
PR-	2 (4.8)	1 (8.3)		
KI67%			0.106	0.182
≤20	34 (81)	7 (58.3)		
>20	5 (19)	5 (41.7)		

Oncotype DX RS Correlation with Chemotherapy

Oncotype DX RS strongly correlated with chemotherapy in univariate (p<0.01) but not when considered with other clinical factors (age, tumor size, tumor grade, PR status, and Ki67%) in a multivariate analysis (P< 0.168) (Table 4). Of the total 54 patients, 12 patients (22.2%) received adjuvant chemotherapy. Chemotherapy was given to 1/16 (6.25%) patients with low, 7/32 (21.9%) patients with intermediate, and 4/6 (66.7%) with high Oncotype DX RS. Chemotherapy treatment was given to a patient with low-risk Oncotype DX because of tumor size (4.5 cm). Of the 42 patients who did not receive adjuvant chemotherapy, 35.7 % fall within low-risk group, 59.5% had an intermediate RS, and only 4.8% were high risk.

Table 4: Oncotype DX RS correlation with chemotherapy.

Adjuvant chemotherapy n %	Oncotype RS Low n (%)	Oncotype RS Intermediate n (%)	Oncotype RS High n (%)	Univariate analysis p value	Multivariate analysis p value
No	15 (35.7) (93.75)	25 (59.5) (78.1)	2 (4.8) (33.3)	0.01	0.168
Yes	1 (8.3) (6.25)	7 (58.4) (21.9)	4 (33.3) (66.7)		

Characteristics of Patients Who Had Cancer Recurrence

Total 4 out of 54 patients had cancer recurrence localized to the breast proved on tissue biopsy (Table 5). All were invasive ductal carcinoma. One patient had a low RS (6), three had an intermediate score range (16- 22), and none of them was given chemotherapy at the time of initial treatment. The median time to recurrence was 4 years, range (1.2-6.1 years). The patient with low risk score aged 38 years with tumor size of 4 cm, both are traditional clinical risk factors for breast cancer recurrence, the tumor grade was 2, and ki67 was 5%. The patients with intermediate Oncotype DX RS who had recurrence (3/4) were ranging 33-44 in age, (0.6-1.8 cm) in tumor size (2-3) in grade, and (10-40) in Ki67%.

Table 5: Characteristics of patients who had breast cancer recurrence.

Patients	Date Dx M\Y	Age Y	Size Cm	Grade	Ki67%	Risk Score	Relapse (M\Y)	Time to Relapse (Y)
1	10\2016	38	4	2	5%	6	12\2018	2.17
2	11\2013	44	0.6	2	10%	16	12\2019	6.08
3	10\2012	33	1.4	3	40%	17	07\2018	5.75
4	11\2017	35	1.8	2	25%	22	01\2019	1.16

Discussion

Oncotype DX RS has an impact on the treatment of early node-negative ER + ve breast cancer, as prognostic test of 10 years metastases occurrence and predictive of response to treatment with tamoxifen versus tamoxifen plus chemotherapy [9, 10]. The importance of the test to provide guidance for individualized treatment is growing. The question about how to utilize the score for intermediate risk group is almost answered by the findings of TAILORx. The results of the study gave evidence that at least one of the traditional clinical risk factors (age) can help on deciding how to treat some of the patients, and kept the door open for oncologist to consider traditional clinical risk factors when treating early breast cancer patients.

Our study results suggest that characteristics of age, tumor grade, Ki67%, and chemotherapy differs significantly among the Oncotype DX RS groups on head to head comparison, on the other side none of the clinical risk factors neither chemotherapy showed a predominant clinically significant relation to the risk score when all factors were considered in the comparison. The results of this study are different compared to the results we reached before for the same patients [11].

The patients in this review were categorized based on TAILORx risk score tier (< 11 low, 11–25 intermediate, 26–100 high), while the previously published study considered the standard tier (< 18 low, 18–30 intermediate, > 30 high). Interestingly the influence of traditional clinical factors on patients' treatment was more evident when adopting TAILORx risk score tiers. This re-analysis for the same patients brings up age as significant factor that differs between the RS groups and did not signify the progesterone receptor correlation to Oncotype DX risk; PR status significantly differed among groups in

previous 2018 analysis [11]. The tumor grade and Ki67% showed significant differences among the risk groups in this review as in the previous 2018 analysis [11].

Tumor size was the only factor that correlated with chemotherapy in a multivariate analysis that considered all factors including Oncotype DX RS. This finding might reflect the medical oncologist low threshold to provide chemotherapy treatment to patients with large tumor size regardless of their Oncotype DX RS, and this practice is reasonable as studies of molecular testing did not completely remove the importance of other clinical risk factors, in fact it is the other way around that

Oncologist need to consider molecular testing as well as other alarming clinical factors [12, 13]. Many studies might had showed the evidence to consider clinical risk factors besides molecular testing including for example two of the large studies; Endopredict and TAILORx [7, 14].

Endopredict incorporated genomics, tumor size and node status together into the EPclin score (low < 3.3 high > 3.3) that estimates the 5- and 10- years breast cancer recurrence (low < 10%, high > 10%). The addition of the EP score to Clinico-pathological parameters resulted in improvement of the prognostic performance of the test [14]. TAILORx results showed that there were invasive disease-free survival benefits for chemotherapy given to woman ≤ 50 years age who had intermediate RS 16–25 (P = 0.004) [7].

In our study patient who had recurrence of cancer were noticed to have at least one clear alarming traditional risk factor. Tumor size of 4 cm was striking feature when looking at characteristics of one patient with low oncotype risk score of 6. It was also evident that all 3 patients with intermediate score of 16–22, and were < 50 in age, these patients were similar to TAILORx patients' cohort who had invasive disease-free survival benefit from adding chemotherapy. These observations for our patients who relapsed bring the findings from Endopredict and TAILORx in front of eyes and encourage us not to disregard alarming traditional recurrence risk factors when seeing a low /intermediate score.

Conclusion

Oncotype RS correlates significantly with individual clinical risk factors including age, tumor grade, Ki67%, chemotherapy treatment. Tumor size significantly predicts adjuvant chemotherapy. Breast cancer recurrence was noticed in younger patients with high intermediate RS (16–25), and adjuvant chemotherapy may be a reasonable option for these patients as shown in Endopredict and TAILORx.

Declarations

Acknowledgments

The authors would like to thank the Medical oncology department - Breast cancer team - Department of Pharmacy at National Center for Cancer care and research. The authors also appreciate the extreme cooperation of Medical research center of Hamad Medical Corporation- Qatar.

Ethical Approval

Ethics committee approval was received for this study. Reference (MRC-01-18-128).

Conflicts of Interest

None.

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Figures

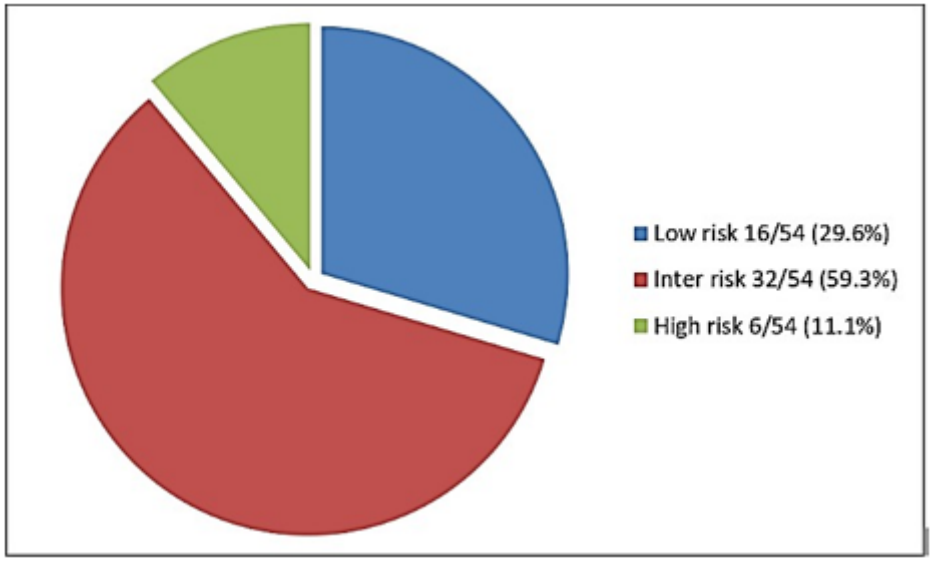

Figure 1

Oncotype DX RS patients' distribution.