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ORIGINAL RESEARCH REPORT

Prediction of Oncotype Dx recurrence score using clinical parameters: A comparison of available tools and a simple predictor based on grade and progesterone receptor

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Abstract
Objective/Background: The Oncotype Dx test is a genomic test currently used in clinical practice to predict the risk of disease recurrence in estrogen receptor (ER)-positive, HER2-negative breast cancer patients with axillary lymph node-negative or micrometastatic disease. The test is one of several similar genomically based tests available. Although it has a good predictive value, it is expensive and thus constitutes a significant financial burden for health systems. Thus, several attempts have been made to devise low-cost tools that could predict the recurrence score derived from the genomic evaluation using easily obtainable clinical parameters.
Methods: Two previously proposed predictive tools were evaluated in a cohort of 201 patients that had undergone the Oncotype Dx test for their efficacy in predicting the Oncotype Dx Recurrence Score (RS). A simple predictor, named GR-PR, based on two available pathologic parameters, grade and progesterone receptor status was devised and also evaluated.
Results: The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of all three tools were compared and found to be similar for all cutoff points of Oncotype Dx RS. The accuracy of GR-PR was comparable to the best performing of the two other prediction tools for all four cutoff points.

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Conclusion: The simple GR-PR predictor proposed in this study seems to be at least as accurate as more complex tools and should be the preferred tool for the prediction of Oncotype Dx RS from clinicopathologic parameters when the Oncotype Dx test is not available.

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Introduction

Estrogen receptor (ER)-positive, human epidermal growth factor-2 (HER2)-negative carcinoma of the breast represents the most common biologic subset of breast cancer and may portend a good prognosis because of its sensitivity to targeted hormonal treatment. However, some of the cancers with this biologic profile will belong to the so-called luminal B genomic group, which will have a more aggressive clinical course that may be improved with the use of chemotherapy [1,2]. Predicting the clinical course of patients with early ER-positive HER2-negative breast cancer has the dual goal of improving clinical outcomes by adding adjuvant chemotherapy in patients with more aggressive disease while sparing this treatment and the associated toxicity from patients with more indolent disease. Several genomics-based prognostic tools are commercially available for clinical use in patients with early-stage ER-positive, HER2-negative breast cancer for the purpose of predicting its clinical course [3,4]. One of them, Oncotype Dx (Genomic Health Inc., Redwood City, CA, USA), is a 21-gene assay that uses multifold polymerase chain reaction to examine the expression of 16 genes, along with five control genes, in an individual patient's breast cancer tissue. The test provides a recurrence risk score (RS) and a percentage risk of distant disease recurrence at 10 years if hormonal therapy (tamoxifen) alone is used as systemic therapy in the adjuvant setting [5,6]. Oncotype Dx has been validated in ER-positive, HER2-negative, axillary lymph node-negative or micrometastatic patients and has been found to decrease the use of chemotherapy in these patients since its introduction in clinical practice.

Despite its usefulness, the Oncotype Dx test is costly, with a tag price of more than 3000 Canadian dollars in Ontario, Canada. Thus, it would be beneficial from a health system financing point of view if the prognostic information provided by Oncotype Dx could be obtained without the added expense. Attempts to predict the Oncotype Dx score by use of clinicopathologic parameters have been published and claimed some success. In our report, we analyze the correlation of survival predictions of the Oncotype Dx test with predictions obtained with a predictor available online based on clinical parameters (PREDICT) and with two other published predictors of the RS [7,8]. These tools are then additionally compared with a simple, novel tool comprising two pathologic parameters, the percentage of tumor cells with progesterone receptor (PR) positivity and grade of the tumor.

Patients and methods

A cohort of 201 breast cancer patients with ER-positive, HER2-negative, axillary lymph node-negative, or micrometastatic disease, who had undergone the Oncotype Dx test from 2012 to 2017 and had been treated and followed in our Cancer Program was retrospectively analyzed. Baseline demographic patient and disease characteristics were collected. These included age of the patients at diagnosis, menopause status, size, stage, and grade of the tumor, ER, PR, and HER2 receptor status and surgery type (lumpectomy vs. mastectomy). As about 10 variables were to be explored in the analysis as possible clinicopathologic factors affecting the Oncotype Dx score, and given the rule of 10 patients per variable, it was determined that about 100 patients would be required in the cohort to have statistical power to detect clinically significant associations. Detailed results of the Oncotype Dx test were extracted from the genomic reports. Patients were grouped to a low-risk, an intermediate-risk, or a high-risk for recurrence group according to cutoffs used in the commercial test report (low-risk group RS < 18, intermediate group RS 18—30, high-risk group RS > 30) and those used in the TAILORx study (low-risk group RS < 11, intermediate-risk group RS 11—25, high-risk group RS > 25).

PREDICT (available at www.predict.nhs.uk) is an online tool used to predict 5- and 10-year overall survival in breast cancer patients. It uses several parameters that include the patient's age, mode of cancer detection, tumor size and grade, number of positive lymph nodes, ER, HER2 receptor, and Ki67 status, and chemotherapy regimen administered. Using these parameters, it then calculates survival at 5 and 10 years if no adjuvant treatment is given, as well as the predicted survival benefit from adjuvant hormonal therapy, chemotherapy, and trastuzumab treatment. In our report, the PREDICT tool (version 2.0) was used to calculate 10-year survival in every patient of the cohort and results were correlated with the 10-year distant relapse-free survival as predicted by the Oncotype Dx test.

An Oncotype Dx RS predictive tool proposed by Eaton et al. [7] (the simplified risk score) calculates a score ranging from 0 to 21 by assigning points depending on ER, PR, tumor size, nuclear grade, and histologic grade. This score is used for the prediction of the corresponding Oncotype Dx RS. In our report, the simplified risk score was calculated for each patient in our cohort, and the predictive value of the score for predicting the actual Oncotype Dx category was calculated.

Another tool for prediction of the Oncotype Dx RS was proposed by investigators at the University of Tennessee Medical Center (Knoxville, TN, USA) [8]. This predictor takes into consideration several factors that include the patient's age, tumor size and grade, PR status, presence of lymphovascular invasion, and histologic type. It then assigns points that predict the probability that the patient will have an RS either above or below the limit for the low or high risk categories according to the commercial or the TAILORx cutoffs. Thus, the Tennessee prognosticator calculates four probabilities for each patient: (a) a probability of being in the high-risk group according to the commercial cutoff (RS > 30); (b) a probability of being in the low-risk group according to the commercial cutoff (RS < 18); (c) a probability of being in the high-risk group according to the TAILORx cutoff (RS > 25); and (d) a probability of being in the low-risk group according to the TAILORx cutoff (RS < 11). In our report, each of the four probabilities were calculated for each patient in our cohort, and the sensitivity, specificity and accuracy values for each prediction were estimated by comparison with the actual Oncotype Dx category to which the patient was assigned.

Both tools (i.e., the simplified risk score and Tennessee prognosticator) included PR status and elements of tumor grade in their evaluations, and these parameters were also included in a third published tool that suggested six combinations of grade and PR (with a cutoff of Allred score of 5) to predict Oncotype Dx RS [9]. In our cohort, tumor grade and PR (with a cutoff of 20% tumor cell positivity) were the strongest discriminatory factors in multivariate analysis between the three RS groups. Thus, we devised a predictor based on these parameters and compared its predictive performance of the RS score with the simplified risk score and Tennessee prognosticator. This predictor, termed GR-PR, attributes one point each for Grade 3 and PR staining of any intensity in $\leq$20% of tumor cells count. As a result, GR-PR will output a value of 0, 1, or 2 in each patient depending on whether none, one, or both of these conditions are met. Finally, the sensitivity and specificity, positive predictive value (PPV) and negative predictive value (NPV), and accuracy of each tool were calculated and compared between the various RS cutoff points.

The Pearson correlation coefficient was used to evaluate the concordance of the PREDICT 10-year survival estimate with the Oncotype Dx 10-year distant recurrence-free survival estimate from the genomic reports for each patient.

The research protocol was approved by the Institutional Ethics Committee of the Sault Area Hospital (Sault Ste. Marie, ON, Canada).

Table 1 Demographic and clinicopathologic characteristics of patients in the entire cohort and as categorized according to the Oncotype Dx risk groups (commercial cutoffs): low (RS < 18), intermediate (RS 18—30), or high (RS > 30) risks.

Parameter	Category	Total (n = 201) (%)	Low risk, <18 (n = 132) (%)	Intermediate risk, 18—30 (n = 60) (%)	High risk, >30 (n = 9) (%)	p
Age	Mean	65.1	65.4	65.0	61.8	0.39 (t)
Menopause status	Pre-/peri-	22 (10.9)	13 (9.9)	6 (10.0)	3 (33.3)	1.0 (Fisher)
	Post-	179 (89.1)	119 (90.1)	54 (90.0)	6 (66.7)	
Mode of detection	Screening	131 (68.2)	91 (72.8)	38 (65.5)	2 (22.2)	0.38 (Fisher)
	Palpable/Symptoms	61 (31.8)	34 (27.2)	20 (34.5)	7 (77.8)	
Clinical stage	I	153 (76.1)	108 (81.8)	40 (66.7)	5 (55.6)	**0.03 (Fisher)**
	II	48 (23.9)	24 (18.2)	20 (33.3)	4 (44.4)	
Primary size	<1 cm	37 (18.4)	26 (19.7)	10 (16.7)	1 (11.2)	0.07 (χ^2)
	1—2 cm	116 (57.7)	82 (62.1)	30 (50.0)	4 (44.4)	
	>2 cm	48 (23.9)	24 (18.2)	20 (33.3)	4 (44.4)	
Histology	Ductal	139 (69.1)	87 (65.9)	44 (73.3)	8 (88.9)	0.46 (χ^2)
	Lobular	26 (12.9)	18 (13.6)	8 (13.3)	0	
	Mixed	20 (10.0)	14 (10.6)	6 (10.0)	0	
	Other	16 (8.0)	13 (9.9)	2 (3.4)	1 (11.1)	
Grade	I	57 (28.3)	45 (34.1)	12 (20.0)	0	**<0.00001** (χ^2)
	II	101 (50.3)	76 (57.6)	25 (41.7)	0	
	III	43 (21.4)	11 (8.3)	23 (38.3)	9 (100)	
ER staining	<90%	8 (4.0)	3 (2.3)	2 (3.3)	3 (37.5)	0.65 (Fisher)
	$\geq$90%	191 (96.0)	128 (97.7)	58 (96.7)	5 (62.5)	
PR staining	$\leq$20%	59 (30.0)	24 (18.3)	28 (46.7)	7 (77.8)	**0.000009 (Fisher)**
	>20%	141 (70.0)	107 (81.7)	32 (53.3)	2 (22.2)	
Her status	IHC 0—1+	115 (58.1)	80 (61.5)	31 (52.5)	4 (44.4)	0.27 (Fisher)
	FISH—	83 (41.9)	50 (38.5)	28 (47.5)	5 (55.6)	
Surgery type	Lumpectomy	157 (78.9)	98 (74.8)	53 (89.8)	6 (66.7)	**0.02 (Fisher)**
	Mastectomy	42 (21.1)	33 (25.2)	6 (10.2)	3 (33.3)	

Note. Last column provides comparisons between the low- and intermediate-risk groups. Data in bold are statistically significant (p < .05). ER = estrogen receptor; FISH = Fluorescent In Situ Hybridization; IHC = Immunohistochemistry; PR = progesterone receptor; RS = recurrence score.

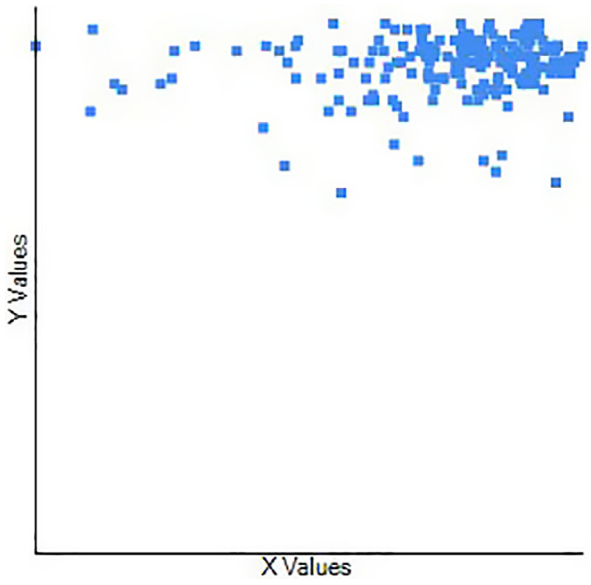

Fig. 1 Correlation of PREDICT 10-year overall survival prediction (X axis) with the Oncotype Dx 10-year distant RFS prediction (Y axis). Pearson $R = 0.1292$, $p = .068$. *Note*. RFS = recurrence-free survival.

Results

Baseline clinicopathologic characteristics of the patients in the cohort are given in Table 1. Percentages of baseline characteristics in each RS risk group according to the commercial cutoffs are also presented. Table 1 compares various baseline characteristics between the low, intermediate, and high RS groups. The most significant differences are observed in tumor grade, and PR staining intensity. In tumor grade, 90% of patients in the low-risk RS group had a Grade 1 or 2 tumor, whereas only about 60% of patients in the intermediate RS group had Grade 1 or 2 tumors, and 100% of patients in the high-risk RS group had Grade 3 tumors. In PR staining intensity, the high PR category (expression of any intensity in >20% of tumor cells) was observed in 81%, 53%, and 22% of patients in the low-, intermediate-, and high-risk groups, respectively. Statistically significant but smaller differences between risk groups were observed in tumor stage and type of surgery (i.e., lumpectomy vs. mastectomy). Similar results were observed when patients were categorized according to the TAILORx study cutoffs (not shown).

Prediction of 10-year overall survival was calculated for each patient in the cohort with the PREDICT online tool, and results were correlated with the 10-year distant disease-free survival provided by the Oncotype Dx assay, using the Pearson correlation test (Fig. 1). There was no correlation of the two predictions (Pearson $R = 0.1292$, $p = .068$).

The predictive ability of the simplified risk score in predicting the actual Oncotype Dx RS according to commercial cutoffs and TAILORx cutoffs in our cohort of patients is shown in Tables 2 and 3. A low simplified risk score of less than 7 could correctly classify 100% of patients in the intermediate- or low-risk RS commercial categories. In contrast, a high simplified risk score of above 12 could correctly classify only 19% of patients in the high RS categories, whereas the rest of patients having a high simplified risk score had a low (21%) or intermediate (59.5%) Oncotype Dx RS (Table 2). Similarly, a low simplified risk score of less than 7 could correctly classify 100% of patients in the intermediate or low RS risk TAILORx categories, but about two-thirds of the patients with a high simplified risk score of above 12 had a low or intermediate Oncotype Dx RS according to TAILORx cutoffs (Table 3).

The Tennessee prognosticator calculates separate probabilities that a given patient will have an Oncotype Dx RS of

Table 2 Simplified risk score versus actual Oncotype Dx RS (commercial cutoffs).

		OncoDx recurrence score: commercial cutoffs, *n* (%)			
		<18	18–30	>30	Total
Simplified risk score	<7	27 (79.4)	7 (20.6)	0	34
	7–12	93 (76.9)	28 (23.1)	0	121
	>12	9 (21.4)	25 (59.5)	8 (19.1)	42
	Total	129	60	8	197

Table 3 Simplified risk score versus actual Oncotype Dx RS (TailoRx Cutoffs).

		OncoDx recurrence score: TAILORx cutoffs, *n* (%)			
		<11	11–25	>25	Total
Simplified risk score	<7	12 (35.3)	22 (64.7)	0	34
	7–12	41 (33.9)	76 (62.8)	4 (3.3)	121
	>12	2 (4.8)	24 (57.1)	16 (38.1)	42
	Total	55	122	20	197

Table 4 Mean scores of Tennessee prognosticator [with 95% confidence intervals (CI), $n = 160$] in patients that actually did or did not have the predicted Oncotype Dx Recurrence Score (RS).

Prediction of tennessee predictor	Actual OncoDx RS	Mean %	95% CI
>25	>25	75.16	43—100
	≤25	28.35	2.1—54.6
<11	<11	78.75	60.0—97.5
	≥11	61.25	28.4—94.2
>30	>30	69.57	44.3—94.8
	≤30	13.96	0—35.8
<18	<18	93.02	82.5—100
	≥18	65.05	33.4—96.6

above 25 or 30 or below 18 or 11. Table 4 shows the mean probabilities obtained by the Tennessee prognosticator of the group of patients classified according to each of the four cutoffs. The discrimination at the 30 cutoff level was the only probability that was acceptably robust in classifying patients with an actual RS of >30, where the mean probability of being predicted to be >30 by the Tennessee prognosticator was 69.5%. Patients with an actual RS below 30 had a mean probability of being predicted to be >30 by the Tennessee prognosticator of 14%. Meanwhile, 95% confidence intervals were not overlapping for the 30 cutoff, as opposed to all other three cutoffs (Table 4). To further explore the usefulness of the Tennessee prognosticator, we calculated the percentage of patients in each RS cutoff point that were correctly classified and their probability of being so classified was >80%. Inversely, we also calculated the percentage of patients who were actually outside the predicted Oncotype Dx RS interval of interest and were estimated to have a probability of being classified as being inside the Oncotype Dx RS interval of interest of <20%. Table 5 illustrates that the percentage of patients correctly classified to be in a certain interval (probability >80% by the Tennessee prognosticator) and correctly classified not to be in a certain interval (probability <20% by the Tennessee prognosticator) was mostly low and in some occasions very low. A notable exemption was the prediction of RS below 18 in which case the Tennessee prognosticator was correct (i.e., producing a probability of 80% and above) in 91.2% of patients actually having an Oncotype Dx RS below 18. Overall, this analysis suggests that the Tennessee prognosticator offered limited confidence in forecasting the actual RS in our cohort.

Table 6 Grade and PR expression characteristics of patients according to their Oncotype Dx category (TAILORx Cutoffs).

Grade	PR	*n*	OncoDx Score TAILORx			Total grade
			<11	11—25	>25	
1	>20	43	20	22	1	56
	≤20	13	0	13	0	
2	>20	74	29	43	2	100
	≤20	26	1	23	2	
3	>20	24	4	15	5	43
	≤20	19	1	7	11	
			55	123	21	199

Note. PR = progesterone receptor.

Table 7 GR-PR tool prediction score versus Oncotype Dx category (TAILORx cutoffs).

		OncoDx Score TAILORx			
		<11	11—25	>25	Total
GR-PR score	0	50	65	3	118
	1	5	51	7	63
	2	1	7	11	19
		56	123	21	200

Note. GR-PR assigns one point each for Grade 3 and PR positivity in ≤20% of tumor cells.

Categorization of patients in our cohort according to our proposed GR-PR (i.e., grade of their tumor and PR positivity with any staining intensity in ≥20% of tumor cells) in relation to their membership in the TAILORx RS risk groups is shown in Table 6. Tables 7 and 8 display the relationships of GR-PR scores according to a patients' Oncotype Dx risk group (TAILORx cutoffs in Table 7 and commercial cutoffs in Table 8). A GR-PR score of 0 successfully predicted membership in the low RS commercial category in about five out

Table 5 Tennessee prognosticator ($n = 160$) correctness (i.e., % of predictions that were >80% in the calculated Tennessee prognosticator probability and were correct in the actual Oncotype Dx, and percentage of predictions that were <20% in the calculated Tennessee prognosticator probability and were incorrect for the actual Oncotype Dx).

Prediction of Tennessee tool	Prediction > 80%/actual OncoDx above or below limit, *n*/*N* (%)	Prediction ≤ 20%/actual OncoDx not above or below limit, *n*/*N* (%)
>25	11/18 (61.1)	87/142 (61.3)
<11	26/44 (59.1)	23/116 (19.8)
>30	3/7 (42.9)	118/153 (77.1)
<18	93/102 (91.2)	7/58 (12.1)

Table 8 GR-PR tool prediction score versus Oncotype Dx category (commercial cutoffs).

		OncoDx Score commercial			
		<18	18—30	>30	Total
GR-PR score	0	98	20	0	118
	1	33	29	2	64
	2	1	11	7	19
	Total	132	60	9	201

Note. GR-PR assigns one point each for Grade 3 and PR positivity in ≤20% of tumor cells.

of six patients, and a GR-PR score of 2 correctly categorized most patients of the high RS commercial category. GR-PR was relatively less successful in predicting membership in the TAILORx categories.

The sensitivity, specificity, PPV, NPV, and accuracy of all three tools are presented in Table 9. The accuracy of GR-PR is shown to be comparable to the best performing of the two other prediction tools for all four cutoff points.

Discussion

The Oncotype Dx assay is a valuable prognostic tool for predicting recurrence in patients with ER-positive, HER2-negative, axillary lymph node-negative, or micrometastatic carcinomas of the breast. The introduction of the Oncotype Dx test in clinical practice has led to decreased use in adjuvant chemotherapy in these patients without compromising survival results [10]. Decreased use of chemotherapy in early ER-positive, HER2-negative, lymph node-negative, or micrometastatic breast cancers from about 25—10% in the pre- and post-Oncotype Dx eras was recently demonstrated in our center (manuscript submitted). Decreased utilization of chemotherapy, besides the obvious benefits for patients' quality of life and well-being, provides financial benefit for public health systems by reducing costs associated with chemotherapy administration and adverse effects management. However, the Oncotype Dx test is itself costly, and this expenditure could be avoided if its results are reliably predicted by other available clinicopathologic parameters. Several tests based on such parameters have been published [11—14]. In this paper, using a cohort of patients from a single cancer center, two previously published prediction tools for the Oncotype Dx RS, as well as a novel simple tool we proposed based on just two parameters, overall tumor grade and PR staining status, are examined for their accuracy in prediction of the RS. Results show that a low simplified risk score as proposed by Eaton et al. [7] may reliably predict when a patient does not have a high Oncotype Dx RS (by either the commercial or the TAILORx study cutoffs), but cannot reliably categorize these patients in either intermediate or low RS risk groups. This is important because

Table 9 Sensitivity and specificity, PPV, NPV, and accuracy comparisons.[a]

Prediction cutoff		Simplified risk score (>12 or <7), %	Tennessee prognosticator, %	PR-GR (2 or 0), %
>25	Sensitivity	80	61.1	52.4
	Specificity	85.3	93.7	95.5
	PPV	38.1	55	57.9
	NPV	97.4	95	94.5
	Accuracy	84.8	90	91
<11	Sensitivity	21.8	59.1	89.3
	Specificity	84.5	47.4	52.8
	PPV	35.3	29.9	42.4
	NPV	73.6	75.3	92.7
	Accuracy	67	50.6	63
>30	Sensitivity	100	42.9	77.8
	Specificity	82	97.4	93.8
	PPV	19	42.9	36.8
	NPV	100	97.4	98.9
	Accuracy	82.7	95	93
<18	Sensitivity	20.9	91.2	74.2
	Specificity	89.7	56.9	71
	PPV	79.4	78.8	83.1
	NPV	37.4	78.6	59
	Accuracy	44.7	78.8	73.1

Note. NPV = negative predictive value; PPV = positive predictive value.

[a] For the high prediction point cutoffs (>25 or > 30) the cutoff for the simplified risk score tool was >12 (vs. ≤ 12) and for the GR-PR was 2 (vs. 0 and 1). For the low prediction point cutoffs (<11 or <18) the cutoff for the simplified risk score tool was <7 (vs. ≥7) and for the GR-PR index was 0 (vs. 1 and 2). For the Tennessee prognosticator tool, a prediction was considered correct if the predicted probability was >80%.

prognosis and role for adjuvant chemotherapy may differ. A high simplified risk score predicted that most patients would not have a low TAILORx RS (<11), but is not capable of reliably categorizing patients above this cutoff. The Tennessee prognosticator performs best where it predicts that the Oncotype Dx RS will be less than 18, wherein 91% of patients that were actually in this range had a Tennessee predicted probability of being in that range of RS of more than 80% (Table 5). The tool performs poorer for the other cutoffs. Our proposed GR-PR score, when 0, may reliably categorize patients as not belonging to the high commercial Oncotype Dx RS (>30). A high GR-PR score of 2 may correctly predict that patients do not belong to the low Oncotype Dx RS risk categories. A comparison between the three tools shows that the GR-PR test performs about as well as or better than the best performing of each of the two other tests for each cutoff. The accuracy of GR-PR is 91% and 93% for the high categories but lower (63% and 73%) for the low categories. Given the simplicity of the GR-PR tool for clinicians, it may be the preferable option for prediction of Oncotype Dx RS in situations where the assay is not available.

Our cohort seems to be slightly skewed toward lower Oncotype Dx scores compared with the extensive TAILORx population. An Oncotype Dx score of above 25 was observed in 10.5% of patients in our cohort versus 16.9% of patients in TAILORx [10]. This may relate to a higher mean age of our cohort compared to the mean age of patients included in TAILORx. Although sensitivity and specificity of a given test depend on the specific population studied, variation of this degree can be expected between populations and could affect sensitivity and specificity of the tool results.

The main benefit of Oncotype Dx test is to determine who among patients with ER-positive, HER2-negative, axillary lymph node-negative, or micrometastatic carcinoma of the breast will benefit from the addition of adjuvant chemotherapy in their treatment plan and who can be safely spared this treatment without compromising their primary oncologic outcome. In practice, most treating physicians would consider all patients with a high Oncotype Dx RS (above 30) and most patients above 25 to be candidates for chemotherapy, and this practice has been recently validated by the results from the intermediate group of the TAILORx study that confirmed minimal benefit from chemotherapy in the intermediate group, at least for patients older than 50 years [15]. Thus, the ideal predictive tool of the Oncotype Dx RS would be the one that reliably categorizes patients above or below these cutoffs. To this end, none of the 118 patients (59% of the whole cohort) with a score of 0 in our newly proposed GR-PR score had an Oncotype Dx RS above 30 and only three of those patients (2.5%) had an Oncotype Dx RS above 25. Thus, patients with tumor Grades 1 or 2 and PR positivity in >20% of their tumor cells could be safely spared chemotherapy, without the need for performing the Oncotype Dx, especially in the clinical context where the decision to add chemotherapy is predicated on an RS >30. For premenopausal women, the TAILORx study could not exclude a small but significant benefit of chemotherapy addition in patients with RS above 20. Given that the GR-PR score of 0 has a lower discriminatory power in the intermediate Oncotype Dx RS group, it should be used with more caution in patients of this age group.

The Oncotype Dx assay, besides reporting an RS, provides an estimation of 10-year distant recurrence-free survival if only hormonal therapy is administered. We sought to determine whether the 10-year recurrence-free survival prediction by the Oncotype Dx test correlates with the 10-year overall survival prediction of a commonly used tool, the PREDICT online tool. The demonstrated lack of such correlation in our study cannot be attributed to patient age, as the mean age of the cohort was about 65 years, implying a remaining life expectancy beyond 10 years. The alternative explanation for the lack of correlation would be that either of the tools over- or underestimate the predicted survivals, or that there may be prolonged overall survival of patients even after development of distant metastases. The latter could certainly be the case, especially in luminal A breast cancers with bone-only metastatic disease [16]. These data may suggest limitations in predicting long-term outcomes. Whether the proposed GR-PR tool could predict long-term outcomes is not addressed in the current study as no long-term follow-up is available.

Overall, our current investigation provides a novel simple and useful tool, based on grade and PR staining percentage, for avoiding the need for the costly Oncotype Dx test (or any of the other available and equally costly genomic tests) in some patients with ER-positive, HER2-negative, axillary lymph node-negative, or micrometastatic breast cancer, especially in health system environments where financial resources are limited. Comparatively, more complicated previously proposed tools are of limited additional predictive value.

Conflict of interest

The authors have no conflicts of interest to disclose.

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