Original Article

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The Oncotype Dx Assay in ER-Positive, HER2-Negative Breast Cancer Patients: A Real Life Experience from a Single Cancer Center

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ABSTRACT

Objective: To determine the influence of the Oncotype Dx assay on the treatment of patients with Estrogen Receptor (ER)-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative, axillary lymph node-negative or micrometastatic carcinoma of the breast in a single cancer center. In addition, patients with intermediate Oncotype Dx recurrence scores were analyzed to assess the factors influencing therapeutic decisions for adjuvant chemotherapy.

Materials and Methods: Data from medical records of women diagnosed with carcinoma of the breast and qualified for the Oncotype Dx assay were extracted (OncoDx cohort). Patient demographic and cancer characteristics, genomic report, and course of treatment data, including survival outcomes and treatment decision-making, were analyzed. A matched cohort of patients with similar tumor stage and biology (ER-positive, HER2-negative) from the era before the introduction of the Oncotype Dx assay was analyzed for comparison (pre-OncoDx cohort).

Results: Two hundred and one patients were included in the OncoDx cohort and one hundred and sixty patients were included in the pre-OncoDx cohort. Oncotype Dx recurrence score (RS) was low (<11) in fifty-six patients (28%), intermediate (11-25) in one hundred and twenty-three patients (61.5%) and high (>25) in twenty one patients (10.5%). Demographic and cancer clinicopathologic characteristics between OncoDx and pre-OncoDx cohorts were similar. Overall, 10.9% of the patients in the OncoDx cohort received adjuvant chemotherapy, versus 23.8% of the patients in the pre-OncoDx cohort (Fisher exact p=0.003). Fewer patients were recommended adjuvant chemotherapy in the OncoDx era compared to the pre-OncoDx era (17.9% vs 30.6%, respectively, Fisher exact p=0.006). The decision to recommend chemotherapy within the intermediate-risk cohort was influenced by the patient's RS. The mean RS of patients in the intermediate-risk cohort who did not receive chemotherapy was 21.5 while the score of those that received chemotherapy was 24.6 (p=0.000). The series confirmed excellent PFS and OS for both OncoDx and pre-OncoDx cohorts.

Conclusion: This single cancer center analysis confirms the avoidance of chemotherapy in the great majority of patients with early ER-positive, HER2-negative, lymph node-negative or micrometastatic carcinoma of the breast since the introduction of the Oncotype Dx assay. A higher recurrence risk score within the intermediate group may influence the decision for chemotherapy inclusion in the adjuvant treatment plan. A lower PR percentage by IHC and higher grade may predict higher Oncotype Dx scores.

Keywords: Oncotype Dx, breast cancer, recurrence risk, prediction, retrospective

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Introduction

Carcinomas of the breast with the estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative phenotype represent the most common subtype of breast cancer, accounting for 75% of the total breast cancer patient population (1, 2). Many of these patients present with localized and axillary lymph node-negative disease, which would usually suggest a good prognosis (3). Yet, some patients possess a significant risk of disease recurrence. Indeed the ER-positive, HER2-negative subset of breast cancers contains two genomically distinct groups, termed luminal A and luminal B, with the latter having a decreased response to hormonal therapies and a worse prognosis (4). Thus, the underlying genetics of the tumor may be more important in predicting its behavior than a patient's individual characteristics or the overall stage and grade of the malignancy at the time of presentation.

Several new genomic tests, which examine the genetic content of the tumor cells and incorporate the results into a prognostic recurrence risk, have been created and validated (5-9). One of these tests is the Oncotype Dx by Genomic Health Inc. (Redwood City, CA), a twenty-

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one-gene assay which examines the simultaneous expression of sixteen genes, together with five control genes, by Polymerase Chain Reaction (PCR), in an individual patient's breast cancer tissue, and returns a recurrence risk score (RS) and a percentage risk of distant disease recurrence at ten years if hormonal therapy (tamoxifen) alone is used as systemic therapy in the adjuvant setting (10-12). The test has been validated in ER-positive, HER2-negative, lymph node-negative or micrometastatic patients and allows for predicting which patients would derive minimal or no benefit from adjuvant chemotherapy and may be safely spared from it, thus avoiding toxicity and cost, without compromising outcomes (13).

Our study examined the influence of Oncotype Dx testing in the adjuvant therapy of patients with early ER-positive, HER2-negative breast carcinomas treated at a community cancer program and compares treatment decisions and outcomes of these patients with a cohort of similar patients treated in the same center in the era before the introduction of Oncotype Dx testing. Factors that may affect therapeutic decisions and may predict Oncotype Dx stratification are also discussed.

Materials and Methods

Two hundred and one breast cancer patients who had the Oncotype Dx assay were identified in the database at our cancer center, and their records were retrieved and reviewed. Four hundred and fifty-one patients who were diagnosed at our center with carcinoma of the breast in the period prior to the introduction of the Oncotype Dx assay were also identified. After exclusion of two hundred and ninety-one patients that would not qualify for the Oncotype assay because of more advanced stage or other receptor phenotypes, one hundred and sixty patients with ER-positive, HER2-negative carcinoma of the breast were retained in the pre-OncoDx cohort.

The patients' demographic and tumor characteristics were extracted from medical records. The course of treatment, including decision-making regarding the adjuvant treatment plan, as well as disease recurrence and survival outcomes were recorded. The details of the Oncotype Dx report were also recorded, including distant recurrence risk at ten years and RS, as well as ER, Progesterone Receptor (PR) and HER2 scores.

Group comparisons were performed using the cut-off points according to the TAILORx study (low-risk group RS <11, intermediate group RS 11-25, high-risk group RS >25) (10).

Statistical analysis was performed with the Fisher exact test or the x^2 test for comparison of ratios, the t-test for comparison of mean differences of continuous variables, and the Log-Rank test for comparison of Kaplan-Meier plots. All p values were considered significant at the level <0.05. Calculations were carried out using online statistical calculators (www.socialstatistics.com and https://merser.shinyapps.io/survival) and using STATA software. The protocol for this research was approved by the Ethics Committee of the institution. As this was a retrospective study, no informed consent was obtained from individual patients.

Results

Comparisons according to TAILORx cut-offs in the OncoDx Cohort

We assessed the OncoDx cohort using the TAILORx study cutoffs. Table 1 shows the characteristics of the three groups of patients classified as per these cut-offs (low-risk group: RS <11, intermediate-risk group: RS=11-25, high-risk group: RS >25) and compares the high-risk group with the two others combined. According to the TAILORx cutoffs, fifty-six patients (28%) belonged to the low-risk group, 123 patients (61.5%) belonged to the intermediate-risk group, and 21 patients (10.5%) belonged to the high-risk group. The comparison of the high-risk group per the TAILORx cutoff versus the two other groups showed statistically significant differences in grade, and ER and PR staining intensity (Table 1). The difference in PR staining with a cutoff of >20% by immunohistochemistry (IHC) between the low-risk and intermediate-risk cohorts based on the TAILORx cutoffs were statistically significant. 3.6% of patients in the low-risk cohort had ≤20% of PR positivity, while this ratio was 35% in the intermediate-risk cohort (Fisher exact test p=0.000). However, there were no statistically significant associations between the low and intermediate-risk cohorts in mean age at presentation, the percentage of patients above age 65, the percentage of post-menopausal patients, or in the size, histology and node status of the tumors, and in the percentage of patients with ER ≥90% scores or whether HER2 negativity was confirmed by either IHC or Fluorescence in itu hybridization (FISH) (Table 1).

Using the TAILORx cut-offs, eighteen of twenty-one patients (85.7%) in the high-risk cohort were recommended chemotherapy. Three patients were not recommended chemotherapy due to co-morbidities or advanced age, in the context of a RS at the lower margin of high-risk. Twelve of twenty-one patients (57.1%) accepted the recommendation and received adjuvant chemotherapy (Table 2).

The most important function of the Oncotype Dx assay is to help with the chemotherapy decision, and virtually all patients in our study were recommended chemotherapy if they were in the TAILORx high-risk group and their general status allowed. Therefore, an analysis was performed among factors that were statistically significant in the high-risk group comparison with the two other groups to identify an optimal combination of factors predicting membership in the high-risk group. Among the factors with the most significant difference in the comparison between the high-risk group and the two other groups, the combination of grade III and PR staining percentage of ≤20% when both present predicted membership in the high-risk group in eleven of nineteen patients (57.9%). Conversely, presence of none or one of these factors predicted membership in the low or intermediate TAILORx groups in one hundred and seventy-one of one hundred and eighty-one patients (94.5%). The addition of ER positivity data did not add to the sensitivity or specificity of the PR/grade index, as a significant majority (96%) of the high-risk cohort had high ER positivity (≥90% of tumor cells).

Therapeutic recommendations and outcomes in the OncoDx Cohort

In our series, no patients with a RS of less than 18 were recommended adjuvant chemotherapy, consistent with the intent of the Oncotype Dx assay. We examined, next, therapeutic recommendations in patients with RS between 18 and 31. In this group, twenty-seven of the sixty patients (45.0%) were recommended adjuvant chemotherapy (Table 3). The decision to recommend chemotherapy within this cohort with intermediate-risk was heavily influenced by the patient's RS (Table 3). Specifically, twenty-three (69.7%) patients were not recommended adjuvant chemotherapy because their RS was considered to confer a recurrence risk similar to the low-risk cohort. In eight patients (24.2%), no specific rationale was noted for not recommending adjuvant chemotherapy. In two patients (6.1%), adjuvant chemotherapy was not recommended due to their significant comorbidities.

Table 1. Demographic and clinicopathologic characteristics of patients in the Oncotype cohort, with low (RS <11), intermediate (RS 11-25), or high (RS >25) risks according to the TAILORx risk category. The two last columns provide comparisons between the low and intermediate risk groups and between low + intermediate risk and high risk groups. The Fisher exact test in grade refers to comparison between combined grades I and II versus grade III. Bolded is statistically significant (p<0.05)

Parameter	Category	Total (n=201)	Low Risk (<11) (n=56)	Intermediate Risk (11-25) (n=123)	High Risk (>25) (n=21)	p (Low+Intermediate vs. High)
AGE	Mean	65.1	66.7	64.5	64.4	0.08 (t)
	≤65	93 (46.3)	24 (42.9)	59 (48.0)	9 (42.9)	0.81 (Fisher)
	>65	108 (53.7)	32 (57.1)	63 (52.0)	12 (57.1)	
MENOPAUSE STATUS	Pre-/peri-	22 (10.9)	4 (7.1)	14 (11.4)	4 (19.0)	0.25 (Fisher)
	Post-	179 (89.1)	52 (92.9)	109 (88.6)	17 (81)	
PRIMARY SIZE	<1 cm	37 (18.4)	12 (21.4)	23 (18.7)	2 (9.5)	0.08 (χ^2)
	1-2 cm	116 (57.7)	35 (62.5)	70 (56.9)	10 (47.6)	
	>2 cm	48 (23.9)	9 (16.1)	30 (24.4)	9 (42.9)	
HISTOLOGY	Ductal	139 (69.1)	40 (71.4)	83 (67.5)	16 (76.2)	0.89 (χ^2)
	Lobular	26 (12.9)	4 (7.1)	20 (16.3)	2 (9.5)	
	Mixed	20 (10.0)	6 (10.7)	12 (9.8)	2 (9.5)	
	Other	16 (8.0)	6 (10.7)	8 (6.4)	1 (4.8)	
GRADE	I	57 (28.3)	21 (37.5)	35 (28.5)	1 (4.8)	0.000 (χ^2)
	II	101 (50.3)	30 (53.6)	66 (53.7)	4 (19.0)	
	III	43 (21.4)	5 (8.9)	22 (17.8)	16 (76.2)	
ER STAINING	<90%	8 (4.0)	1 (1.8)	2 (1.6)	5 (25.0)	0.000 (Fisher)
	≥90%	191 (96.0)	54 (98.2)	121 (98.4)	15 (75.0)	
PR STAINING	≤20%	59 (30.0)	2 (3.6)	43 (35.0)	13 (61.9)	0.001 (Fisher)
	>20%	141 (70.0)	53 (96.4)	80 (65.0)	8 (38.1)	
HER2 STATUS	IHC 0-1+	115 (58.1)	35 (63.6)	67 (55.4)	12 (57.1)	1.0 (Fisher)
	FISH-	83 (41.9)	20 (36.4)	54 (44.6)	9 (42.9)	
LYMPH NODE STATUS	Negative	184 (94.4)	51 (96.2)	112 (93.3)	20 (95.2)	1.0 (Fisher)
	Micrometastatic	11 (5.6)	2 (3.8)	8 (6.7)	1 (4.8)	
SURGERY TYPE	Lumpectomy	157 (78.9)	40 (71.4)	98 (81.0)	18 (85.7)	0.57 (Fisher)
	Mastectomy	42 (21.1)	16 (28.6)	23 (19.0)	3 (14.3)	

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; FISH: fluorescent in situ hybridization; Fisher: Fisher's exact test

Table 2. Patients' decisions on accepting adjuvant chemotherapy recommendation in the high-risk cohort (RS >25) as per TAILORx cutoffs, and mean recurrence score (RS)

Therapeutic Decision	Number of Patients (n=21) (%)	Mean RS
Chemotherapy not recommended	3 (14.3)	27
Chemotherapy recommended—Accepted recommendation	12 (57.1)	35
Chemotherapy recommended—Rejected recommendation	6 (28.6)	

For those patients who were recommended chemotherapy (Table 3), twenty-six (96.3%) recommendations were influenced primarily by the recurrence risk being on the upper margin of the intermediate range. Only one of the twenty-seven patients was recommended adjuvant chemotherapy on the explicit basis of both her Oncotype Dx RS and the characteristics of her malignancy (i.e. grade III, 2.2 cm tumour with a PR staining positivity at 15%). However, these characteristics may have influenced decision-making in other patients, even without being explicitly stated in the patient's chart.

Table 3. Recommendations and rationale for or against adjuvant chemotherapy in patients with a recurrence score (RS) of 18-31

Therapeutic Recommendation	Rationale	Number of Patients (n=60) (%)
Adjuvant chemotherapy		27 (45.0)
	Recurrence score confers sufficient risk	26 (96.3)
	Totality of tumour risk factors	1 (3.7)
No adjuvant chemotherapy		33 (55.0)
	Recurrence score marginally above low risk	23 (69.7)
	No specific rationale noted	8 (24.2)
	Significant patient comorbidities	2 (6.1)

Table 4. Patients' ultimate decision on accepting or rejecting the adjuvant chemotherapy recommendation in the group of patients with recurrence score (RS) of 18 to 31, and comparison of mean RS between those for whom chemotherapy was recommended and those for whom it was not recommended

Therapeutic Decision	Number of Patients (n=60) (%)	RS	p
Chemotherapy not recommended	33 (55.0)	21.5	0.000 (t)
Chemotherapy recommended—Accepted recommendation	16 (26.67)	24.6	
Chemotherapy recommended—Rejected recommendation	11 (18.33)		

Sixteen patients (26.7%) ultimately accepted the chemotherapy recommendation (Table 4). Five patients (45.5%) rejected the recommendation for adjuvant chemotherapy due to concern for the toxicity the chemotherapy regimen would entail. The remaining six patients did not have data on the reason for their rejecting the recommendation. Patients within the cohort with a RS of 18 to 31 who received adjuvant chemotherapy had a statistically significant higher mean RS than the patients within the cohort who did not receive chemotherapy (Table 4).

Overall, twenty-two (10.9%) patients in the entire OncoDx cohort received chemotherapy. The most commonly used regimens were the FEC-D (3 cycles of 5-Fluorourcacil-Epirubicin-Cyclophosphamide, followed by 3 cycles of Docetaxel) regimen and the DC (4 cycles of Docetaxel-Cyclophosphamide) regimen.

With a mean follow-up for the whole OncoDx cohort of 33.9 months, progression-free survival (PFS) and overall survival (OS) were favorable in both the low and intermediate-risk cohorts (Figure 1). The low-risk cohort had a mean follow-up of 34.65 months compared to 32.09 months in the intermediate-risk cohort. This was not a statistically significantly difference (p=0.22). There were no statistically significantly differences between the low-risk and intermediate-risk cohorts in PFS or OS either (LogRank test p=0.41 and 0.44, respectively). Three patients (1.5%) had a disease recurrence, one of whom was in the low-risk cohort and two in the intermediate-risk cohort. Seven patients (3.5%) died, four of whom were in the low-risk cohort and three in the intermediate-risk cohort. Only one (14.3%) of these patients died due to progression of her breast cancer, while the remaining six patients died from other diseases.

Comparisons, OncoDx and Pre-OncoDx Cohorts

The pre-OncoDx cohort consisted of one hundred and sixty patients (Table 5). The mean age was 64.9 years (SD 12.75). This was not statistically significantly different from the OncoDx cohort. Most patients had carcinoma of the breast that was stage I, tumor size between 11 and 22 mm, ductal histologic type, and histologic grade II. None of these parameters were statistically significantly different from the OncoDx cohort. Most patients were also post-menopausal and had no evidence of axillary lymph node micrometastases. However, a greater ratio of patients in the OncoDx cohort had breast-conserving therapy with lumpectomy than in the pre-OncoDx cohort (Fisher exact test p<0.000). As a result, a greater ratio of patients in the OncoDx cohort received adjuvant radiation compared to the pre-OncoDx cohort (Fisher exact test p<0.000). Additionally, ER staining percentage of ≥90% of tumor cells was statistically significantly higher in the OncoDx cohort compared to the pre-OncoDx cohort (Fisher exact test p=0.001). Finally, 10.9% of patients in the OncoDx cohort received adjuvant chemotherapy, while this percentage was 23.8% of patients in the pre-OncoDx cohort (Fisher exact test p=0.001).

With a mean follow-up of 87.3 months in the pre-OncoDx cohort, twenty-eight patients died (17.5%), ten of whom (58.8%) died due to progression of their breast cancer. Eleven patients (6.9%) had a recurrence of breast cancer. There was no statistically significant difference in overall survival and progression-free survival between the OncoDx and pre-OncoDx cohorts (Log-Rank p=0.35 for PFS (Figure 2a) and p=0.83 for OS (Figure 2b)).

The rationale used to recommend chemotherapy in the pre-OncoDx era was documented in the patients' records in only 46.4% of cases (Table 6). The single-most influential element of the recommendation was that the Adjuvant! online prediction tool (currently not available) favored the addition of adjuvant chemotherapy (26.5% of cases). Similarly, in recommending against chemotherapy, the rationale was documented in only 43.9% of cases (Table 6). The most influential

Table 5. Demographic and clinicopathologic characteristics patients in the pre-OncoDx cohort. Last column provides comparisons between the pre-OncoDx and OncoDx patients. Bolded is statistically significant (p<0.05)

Parameter	Category	Pre-OncoDx Cohort (n=160) (%)	OncoDx Cohort (n=201) (%)	p
AGE	Mean	64.9	65.1	0.43 (t)
	≤65	75 (46.9)	93 (46.3)	
	>65	85 (53.1)	108 (53.7)	
MENOPAUSE STATUS	Pre-/peri-	33 (21.3)	22 (10.9)	
	Post-	122 (78.7)	179 (89.1)	
PRIMARY SIZE	<1 cm	35 (26.5)	37 (18.4)	0.11 (x^2)
	1-2 cm	62 (47.0)	116 (57.7)	
	>2 cm	35 (26.5)	48 (23.9)	
HISTOLOGY	Ductal	113 (72.9)	139 (69.1)	0.68 (x^2)
	Lobular	19 (12.3)	26 (12.9)	
	Mixed	10 (6.5)	20 (10.0)	
	Other	13 (8.4)	16 (8.0)	
GRADE	I	34 (23.1)	57 (28.3)	0.44 (x^2)
	II	75 (51.0)	101 (50.3)	
	III	38 (25.9)	43 (21.4)	
ER STAINING	<90%	19 (14.2)	8 (4.0)	0.0016 (Fisher)
	≥90%	115 (85.8)	191 (96.0)	
PR STAINING	≤20%	44 (32.8)	59 (30.0)	0.55 (Fisher)
	>20%	90 (67.2)	141 (70.0)	
HER STATUS	IHC 0-1+	95 (67.4)	115 (58.1)	0.09 (Fisher)
	FISH-	46 (32.6)	83 (41.9)	
LYMPH NODE STATUS	Negative	135 (95.1)	184 (94.4)	0.81 (Fisher)
	Micrometastatic	7 (4.9)	11 (5.6)	
SURGERY TYPE	Lumpectomy	84 (53.2)	157 (78.9)	<0.000 (Fisher)
	Mastectomy	74 (46.8)	42 (21.1)	

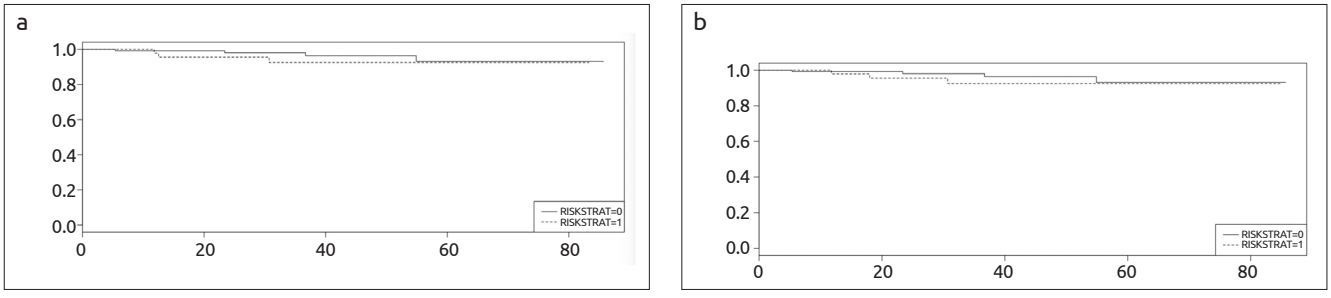

Figure 1. a, b. Kaplan-Meier progression-free survival (PFS) curves (a) and overall survival curves (b) in months, of patients in the low recurrence risk (riskstrat=0) cohort versus patients in the intermediate recurrence risk cohort (riskstrat=1). LogRank test p=0.41 and 0.44 respectively

reason for not recommending chemotherapy was either that the specific characteristics of the tumor were considered to confer a low risk of recurrence (13.1% of cases) or because the Adjuvant! online prediction tool showed a minimal benefit from the addition of adjuvant chemotherapy (11.2% of cases).

Overall, adjuvant chemotherapy was recommended to forty-nine of one hundred and sixty (30.6%) patients (Table 6). 77.6% of the patients who were recommended chemotherapy accepted the recommendation. The reason for patient's rejecting the recommendation was not mentioned in the records in any of the cases.

Our analysis demonstrates that the addition of the Oncotype Dx assay at our cancer center resulted in decreased use of adjuvant chemotherapy while maintaining very good survival outcomes.

Table 6. Recommendations to receive or not receive adjuvant chemotherapy, the rationale, and the patients' ultimate decision in the pre-OncoDx cohort, percentage of total number of patients in the pre-OncoDx cohort

Therapeutic Recommendation and Decision	Rationale	Number of Patients (n=160) (%)
Adjuvant Chemotherapy		49 (30.6)
	No specific rationale noted	26 (53.6)
	Online prediction tools supported benefit	13 (26.5)
	Totality of tumour characteristics	9 (18.4)
Accepted Recommendation		38 (77.6)
Rejected Recommendation		11 (22.4)
No Adjuvant Chemotherapy		111 (69.4)
	No specific rationale noted	60 (56.1)
	Totality of tumour characteristics	14 (13.1)
	Online prediction tools did not support benefit	12 (11.2)

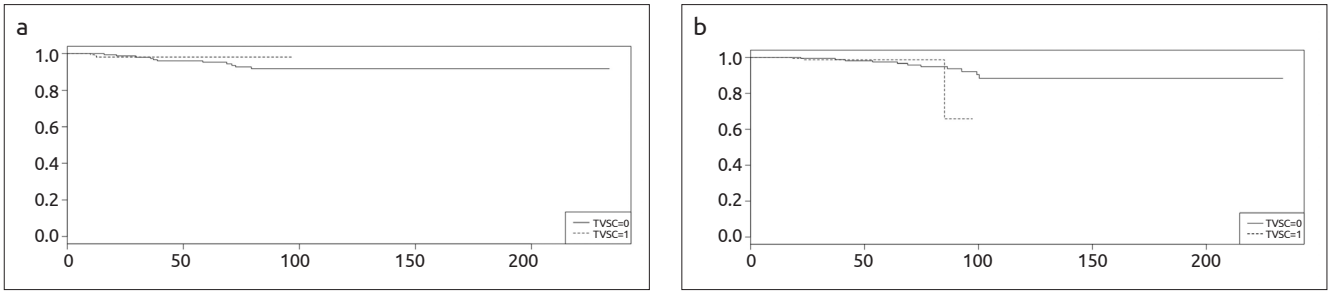

Figure 2. a, b. Kaplan-Meier progression-free survival (PFS) curves (a) and overall survival curves (b) in months, of patients in the pre-OncoDx cohort (TvsC=0) versus patents in the OncoDx cohort (TvsC=1). LogRank test p=0.35 and 0.83 respectively

Discussion and Conclusion

Before the advent of genomic assays, clinical and pathologic parameters, such as the patient's age and general state of health, menopause status, and size and grade of the tumor at the time of presentation had been used to determine risk of disease recurrence in patients with early ER-positive, HER2-negative carcinoma of the breast. Estimated higher risk suggested the need for the addition of adjuvant chemotherapy to adjuvant hormonal therapy in the treatment plan. However, the underlying genetic lesions of the tumor may be more important in predicting its behavior than a patient's individual characteristics or the overall stage and grade of the malignancy at the time of presentation. This new knowledge was corroborated by the introduction of genomic profiling, which categorized breast cancers in distinct approximated but not completely overlapping groups, with the groups defined by IHC for ER, PR, and HER2 receptors (14). Two ER-positivity and HER2-negativity breast cancer sub-types with overlapping IHC profiles have been defined by genomic profiling, termed luminal A and luminal B. Both have distinct prognosis and response to hormonal therapy but are difficult to predict clinically given the overlapping clinicopathologic profile (15). Several genomic tests have been introduced and validated in the clinical setting attempting to predict outcomes of cancers in the ER-positive, HER2-negative spectrum, based on expressions of a subset of genes, ranging from a few to several dozen in the tumor genome. Genomic tests include the 70-gene signature, the PAM50 test, the BCI, and the Oncotype Dx assay, the latter of which has been used in our cancer center and is the subject of this report.

The Oncotype Dx assay is a proprietary RT-PCR-based test that examines expression of sixteen genes along with five controls. The genes included in the assay are involved in tumor proliferation and invasion as well as hormone and growth factor signaling (13). In addition to providing a RS and a numeric estimation of ten-year distant recurrence risk if only hormonal therapy (tamoxifen) is used in the adjuvant setting, the Oncotype Dx assay provides an estimation of the benefit of adding adjuvant chemotherapy to adjuvant hormonal therapy. Excellent results have been reported in low RS patients treated only with adjuvant hormonal therapy (16). Moreover, a decrease in the use of chemotherapy in the ER-positive, HER2-negative, lymph node-negative population has also been reported (11). These results confirm that the assay succeeds in decreasing the use of chemotherapy without compromising survival outcomes.

Patients with a high RS from the Oncotype Dx assay derive benefit from adjuvant chemotherapy due to their higher risk of disease recurrence, and the patients in the low RS category conversely do not accrue further benefits with the addition of adjuvant chemotherapy. However, the optimal approach for patients with intermediate RS has been uncertain, given the higher risk of recurrence but only minimal benefit of adjuvant chemotherapy (10, 11). 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. This practice has been recently validated by the results from the intermediate group of the TAILORx study that confirmed minimal, if any, benefit from chemotherapy in the intermediate group with a RS of 11 to 25 (17). An exemption may

be for patients below age 50 and a RS of 20 to 25 who may derive some benefit from adjuvant chemotherapy.

In our retrospective analysis of women diagnosed with carcinoma of the breast at our cancer center, we observed the avoidance of adjuvant chemotherapy in low and low-intermediate recurrence risk patients with early ER-positive, HER2-negative, lymph node-negative or micrometastatic disease. The decision to offer adjuvant chemotherapy in most intermediate-risk patients seemed to be influenced by the patient's RS from the Oncotype Dx assay. This result is similar to the conclusion of another study in Ontario (11). Additionally, our analysis demonstrated that a higher RS in the intermediate-risk cohort predicted use of adjuvant chemotherapy. The PR staining intensity was also statistically different for the low and intermediate-risk cohorts, which is consistent with the degree to which a lower PR staining by IHC correlates with recurrence risk. This is consistent with the results reported by other series (18-20). Finally, we found that survival outcomes were favorable in both low and intermediate-risk cohorts.

Prediction of a RS above 25 may be of special clinical interest in settings where the Oncotype Dx assay is not available, given that patients in this range could actually be among the subgroup who would benefit from the addition of adjuvant chemotherapy. In our analysis, the three pathological factors most significantly associated with a RS >25 were high grade and a low positivity for ER (<90%) and for PR (≤20%). These results concord with another investigation that proposed a combination of ER, PR, and Ki67 immunohistochemical score as a valid predictor of the Oncotype Dx RS (18). The two component (PR/grade) predictor we propose is simpler and avoids the inclusion of Ki67, which may not be universally available, and has a similar discriminatory value (21).

Compared with the pre-OncoDx cohort, our analysis demonstrated a decrease in the use of adjuvant chemotherapy in the Oncotype era (89.1% versus 76.3%, respectively, Fisher exact test p=0.0016). In addition, fewer patients were recommended adjuvant chemotherapy in the Oncotype era compared to the pre-Oncotype era (17.9% versus 30.6%, respectively, Fisher exact test p=0.0059). Both cohorts were largely similar from a demographic and clinicopathologic characteristics perspective. Our study also demonstrated that both cohorts had favorable survival rates, with no statistically significant differences in the comparisons of Kaplan-Meier plots, though there was an absolute higher number of death and progression in the pre-Oncotype cohort. This is likely partially related to a longer follow-up in this cohort. From limited available data, the most significant influence on recommending adjuvant chemotherapy in the pre-OncoDx cohort was the use of Adjuvant! online prediction tool. Thus, in both the Oncotype and pre-Oncotype era, recommendations on the addition of adjuvant chemotherapy relied on predictive tools to complement clinical judgment.

Besides the general disadvantages of retrospective and non-randomized comparisons, our analysis is limited by the fact that the rationale for the chemotherapy recommendation in the pre-Oncotype era was not well documented, making a comparison of decision-making changes between pre-OncoDx and OncoDx cohorts incomplete.

In conclusion, the addition of the Oncotype Dx assay at our cancer center resulted in decreased use of adjuvant chemotherapy while maintaining excellent survival outcomes. This, together with the fact that genomic tests seem to be cost effective, suggests continued utility in clinical practice [22]. Future investigations will aim at providing even better prognostic and therapy predictive tools to further advance personalized oncology.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Sault Area Hospital.

Informed Consent: Informed consent was not taken due to retrospective design of the study.

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