Original Study

Influence of a 21-Gene Recurrence Score Assay on Chemotherapy Delivery in Breast Cancer

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Abstract

The results of the Oncotype DX assay help direct chemotherapy usage for breast cancer. However, its influence in the decision-making process is unknown relative to traditional pathologic factors. The present study determined the added influence of Oncotype DX relative to these factors using paired multivariable logistic regressions. These analyses demonstrated that Oncotype DX findings have the strongest influence on whether a patient receives adjuvant chemotherapy.

Background: We performed an analysis to determine the relative contribution of the Oncotype DX (ODX) recurrence score (RS) results in adjuvant therapy delivery compared with traditional pathologic factors. **Methods and Materials:** We performed a retrospective review of women with stage I-IIIA breast cancer treated at the Yale Comprehensive Cancer Center from 2006 to 2012 with available ODX results. We constructed separate logistic models with the clinicopathologic factors alone and also integrating RS and compared these models using the likelihood ratio test and c-statistic to determine whether integration of the RS will result in better prediction of chemotherapy (CTx) delivery. **Results:** We identified 431 women with a median age of 58 years. The RS was low (< 18), intermediate (18-30), and high (> 30) in 56%, 37%, and 7%, respectively. CTx was delivered to 30% of the patients. Age, differentiation, lymphovascular invasion, and progesterone receptor (PR) positivity < 50% were associated with CTx delivery in multivariable logistic regression of clinicopathologic factors alone ($P < .05$). In the model integrating the RS, an intermediate or a high RS was the most influential factor for CTx delivery (odds ratio, 7.87 vs. 265.35, respectively; $P < .0001$). The PR results and grade were no longer significant ($P = .74$ and $P = .06$, respectively). The integration of the RS resulted in improved model fit and precision, indicated by the likelihood ratio test ($\Delta G2$, 100.782; df = 2; $P < .0001$) and an improved c-statistic (0.720 vs. 0.856). **Conclusion:** Gene expression profiling appears to account for a substantial amount of variability in CTx delivery in current practice. Further work is needed to ensure appropriate test usage and cost-effectiveness.

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Introduction

Early-stage breast cancer (ESBC) has excellent cure rates, in large part because of the widespread adoption of systemic therapy. Nevertheless, ostensibly similar tumors differ in their distant metastatic potential, likely related to intrinsic differences in tumor biology and sensitivity to endocrine therapy. Clinicians historically have relied on their knowledge of the effect of clinical and pathologic factors when recommending adjuvant chemotherapy (CTx). More recently, gene expression profile (GEP) panels, including the Oncotype-DX (ODX) 21-gene recurrence score (RS) assay, have gained popularity owing to their ability to quantitate individual recurrence risk and identify patients who would benefit from adjuvant CTx.[1,2]

Once validated for use in ESBC, GEP use was included in the National Comprehensive Cancer Network guidelines.[3] Decreasing CTx usage has been observed in conjunction with increasing use of

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ODX.[4-6] Although ODX use might inform clinicians about the risk of distant recurrence, it is unclear how strongly the ODX RS results are weighed relative to standard clinicopathologic factors in the decision-making process of medical oncologists and to what degree the RS results supplement standard clinical decision-making. We questioned the incremental effect of ODX on the delivery of CTx relative to the clinicopathologic factors, which have historically influenced this decision-making process before the development of GEP panels such as ODX. To address this uncertainty, we assessed the patterns of CTx use in our institution and correlated these trends with the clinicopathologic factors and RS groups.

Materials and Methods

Patient Identification and Data Collection

We identified patients with a diagnosis of invasive breast cancer and accessible results of ODX testing through the Department of Pathology at the Yale Comprehensive Cancer Center. We restricted our sample to patients seen in consultation by breast medical oncologists within our institution with clear adjuvant systemic therapy (endocrine therapy or CTx) details. We reviewed the medical records of patients matching these criteria and recorded the demographic, pathologic, and treatment details. These details included age, tumor size, grade and/or degree of differentiation, presence or absence of lymphovascular invasion (LVI), number of positive and negative axillary lymph nodes, pathologic nodal stage, size of nodal metastases (if applicable), presence of nodal extracapsular extension, estrogen receptor (ER) status and percentage of positivity, progesterone receptor (PR) status and percentage of positivity, and human epidermal growth factor receptor (HER)2-neu immunohistochemistry and fluorescence in situ hybridization (FISH) results. We collected the RS results, including the numeric score and risk grouping, and defined the low-, intermediate-, and high-risk groups as RS results of < 18, 18 to 30, and > 30, respectively.[1] Finally, we recorded the details of systemic therapy for each patient, including the delivery and type of systemic therapy. Our institutional review board approved our retrospective analysis.

Analysis of Factors Associated With CTx Delivery

To determine the factors associated with CTx delivery, we compared the ODX RS, clinical data, and pathologic findings between patients who did and did not receive adjuvant CTx using Wilcoxon rank-sum tests and χ^2 analyses, as appropriate. We included factors with $P < .1$ on multivariable logistic regression to identify the independent predictors of CTx delivery. We constructed sequential multivariable logistic models with the clinicopathologic factors alone and then an additional model that also incorporated the RS results with the clinicopathologic factors. This second model was used to identify the incremental effect of RS results on CTx delivery. We assessed the influence of integrating the RS results into the decision-making process on CTx delivery by comparing the likelihood ratios of the 2 models. Finally, we used the c-statistic to determine whether the inclusion of the RS results led to more precise prediction of CTx delivery.

Results

We identified 431 patients who had undergone ODX testing from September 2006 to December 2012. The median patient age was 58 years (range, 35-84 years), and 72.6% of our sample was aged $\geq$ 50 years. The tumor characteristics are listed in Table 1. Most patients (75.2%) were strongly ER positive ($\geq$ 75% staining), and 57.5% were also strongly PR positive ($\geq$ 50% staining). A median of 1 node was positive among patients with pathologically involved axillary lymph nodes (range, 1-6). Of these, 43.9% were micrometastases and 56.1% were macrometastases. The median RS was 16.0 (mean $\pm$ SE, 17.28 $\pm$ 0.42; range, 0-61). The RS results were low risk in 240 (55.7%), intermediate risk in 162 (37.6%), and high risk in 29 (6.7%).

Adjuvant CTx was delivered to 128 patients (29.7%). The most commonly delivered CTx regimens were Taxol and cyclophosphamide (n = 84; 65.6%), and adriamycin-C plus Taxol (n = 24; 18.8%). Age, HER2-neu FISH results, LVI, tumor grade, and PR results all showed significant associations with CTx delivery in this sample (Table 2). The median age was slightly older among patients who received CTx (median, 61 years; range, 38-83 years) compared

Table 1 Pathologic Tumor Characteristics (n = 431)

Characteristic	n (%)
Size (cm)	
Median	1.6
Range	0.1-13.2
Size group	
<1 cm	80 (18.56)
≥1 cm	348 (80.74)
Differentiation and grade	
Well and low	138 (32.02)
Intermediate	259 (60.09)
Poor and high	34 (7.89)
Histologic type	
Invasive ductal	350 (81.21)
Invasive lobular	66 (15.31)
Other	15 (3.48)
ER status	
Positive	422 (97.91)
Negative	9 (2.09)
PR status	
Positive	394 (91.42)
Negative	37 (8.58)
HER2-neu status	
IHC positive (3+)	2 (0.46)
FISH positive	9 (2.09)
Nodal involvement	
Positive	57 (13.46)
Negative	374 (86.54)
ECE	
Positive	14 (3.24)
Negative	417 (96.75)
LVI	
Positive	58 (13.46)
Negative	373 (86.54)

Abbreviations: ER = estrogen receptor; ECE = extracapsular extension; FISH = fluorescence in situ hybridization; HER2-nue = human epidermal growth factor receptor-2-neu; IHC = immunohistochemistry; LVI = lymphovascular invasion; PR = progesterone receptor.