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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Role of Oncotype DX® Recurrence Score in Predicting Axillary Response After Neoadjuvant Chemotherapy in Breast Cancer

Jaime A. Pardo, MD, Betty Fan, DO, Alessandra Mele, MD, Stephanie Serres, MD PHD, Monica G. Valero, MD, Isha Emhoff, MD MPH, Amulya Alapati, MD, and Ted A. James, MD MHCM

Department of Surgery, BreastCare Center, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA

ABSTRACT

Introduction. Oncotype DX® recurrence score (RS) is well-recognized for guiding decision making in adjuvant chemotherapy; however, the predictive capability of this genomic assay in determining axillary response to neoadjuvant chemotherapy (NCT) has not been established.

Methods. Using the National Cancer Data Base (NCDB), we identified patients diagnosed with T1-T2, clinically N1/N2, estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER +/HER2 −) invasive ductal carcinoma of the breast between 2010 and 2015. Patients with an Oncotype DX® RS who received NCT were included. RS was defined as low (< 18), intermediate (18–30), or high (> 30). Unadjusted and adjusted analyses were performed to determine the association between axillary pathologic complete response (pCR) and RS.

Results. This study included a total of 158 women. RS was low in 56 (35.4%) patients, intermediate in 62 (39.2%) patients, and high in 40 (25.3%) patients. The majority of patients presented with clinical N1 disease (89.2%). Axillary pCR was achieved in 23 (14.6%) patients. When stratifying patients with axillary pCR by RS, 11 (47.8%) patients had a high RS, 6 (26.1%) patients had an intermediate RS, and 6 (26.1%) patients had a low RS. Comparing cohorts by RS, 27.5% of patients with high RS tumors had an axillary pCR, compared with only 9.7% in the intermediate RS group, and 10.7% in the low RS group ($p = 0.0268$).

Conclusion. Our findings demonstrate that Oncotype DX® RS is an independent predictor of axillary pCR in patients with ER +/HER2 − breast cancers receiving NCT. A greater proportion of patients with a high RS achieved axillary pCR. These results support Oncotype DX® as a tool to improve clinical decision making in axillary management.

Historically, axillary lymph node dissection (ALND) was the mainstay for staging and regional disease control.[1,2] However, improved screening methods leading to more patients presenting without nodal involvement, together with advances in surgical technique, resulted in practices shifting to the use of sentinel lymph node biopsy (SLNB) in the 1990s. SLNB has since become a standard for staging early-stage, clinically node-negative patients with breast cancer, reducing the morbidity associated with ALND (i.e. lymphedema, limited shoulder motion, and neuropathic pain).[3–5] The role of SLNB has expanded beyond clinically node-negative patients, and the feasibility of SLNB in patients with clinically positive nodes undergoing neoadjuvant chemotherapy (NCT) has been evaluated and validated in recent clinical trials.[6–8]Patients who become clinically node-negative following NCT may be candidates for SLNB as opposed to the more invasive ALND.

One of the most widely used genomic tools is the Oncotype DX® recurrence score (RS), which consists of a 21-gene reverse transcriptase–polymerase chain reaction (RT-PCR) assay for patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative

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T. A. James, MD MHCM
e-mail: ted.james@bidmc.harvard.edu

(ER +/HER2 −) breast tumors.[9] The Oncotype DX® RS has proven useful in predicting recurrence in patients with breast cancer, and informs decisions for adjuvant systemic therapy.[10], [11] Initially implemented for node-negative patients, the multigene assay was validated to predict the likelihood of chemotherapy benefit in selected node-positive patients.[12] Studies are emerging exploring the role of Oncotype DX® in predicting response to NCT. A recent study by Pease et al. [13] identified that a high Oncotype DX® RS was associated with an increased likelihood of pathologic complete response (pCR) after NCT. The study suggested that while pCR is less frequent in ER +/HER2 − breast cancers, there may be a subgroup of ER +/HER2 − cancers based on high Oncotype DX® RS who have a greater likelihood of pCR; [13] however, the study comprised few patients with clinically positive nodes. Research to date remains scarce regarding the role of the Oncotype DX® RS in predicting axillary response following NCT in clinically node-positive patients. Identifying which patients are likely to achieve axillary pCR; therefore, avoiding ALND will help improve decision making for axillary management and decrease surgical morbidity. This study aimed to determine the predictive capability of Oncotype DX® RS with axillary response to NCT. Specifically, we sought to assess whether Oncotype DX® RS corresponds to rates of achieving axillary pCR in patients with ER +/HER2 − , clinically node-positive breast cancer receiving NCT.

METHODS

Data Source

The National Cancer Data Base (NCDB), a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, contains information on approximately 70% of all new invasive cancer diagnoses in the US. This national registry was used as our data source. Our Institutional Review Board deemed this study as exempt.

Cohort Selection and Characteristics

The study cohort consisted of 158 patients with T1-T2, clinically N1/N2, ER +/HER2 − invasive ductal carcinoma of the breast, diagnosed between 2010 and 2015. All patients underwent NCT and had an Oncotype DX® RS performed. RS results were defined as low (numerical score < 18), intermediate (score 18–30), or high (score > 30). From this cohort, we excluded patients who received neoadjuvant hormonal therapy, had distant metastases, or who had missing information for tumor grade or staging. Characteristics collected included age, ethnicity, pathologic stage, clinical T and N stage, tumor grade, and Oncotype RS.

Definition of Pathologic Complete Response

The primary outcome was complete pathologic response in the axilla, defined as no remaining disease in the axillary lymph nodes on pathologic review, corresponding to NCDB codes for ypN0. Patients were stratified based on the presence or absence of complete axillary response.

Statistical Analysis

Descriptive statistics were used to summarize the study cohort according to demographic data, tumor characteristics, and Oncotype DX® RS. Chi square tests were employed to compare these characteristics between the axillary pCR subgroups. Statistical analyses were completed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The patient cohort selection process is described in Fig. 1. Of the 158 patients who had an Oncotype DX® RS and received NCT, RS was low in 56 (35.4%) patients, intermediate in 62 (39.2%) patients, and high in 40 (25.3%) patients. Additionally, 49 (31%) patients had a clinical T1 tumor and 109 (69%) patients had a clinical T2 tumor. Within our cohort, 141 (89.2%) patients had cN1 disease and 17 (10.8%) had cN2 or higher disease. The cohort included 105 (66.5%) low- to intermediate-grade tumors and 53 (33.5%) high-grade tumors. After receiving NCT, 10 (6.3%) patients had a pCR in the breast (i.e. ypT0) and 148 (93.7%) patients had residual breast cancer on final pathology. Twenty-three (14.6%) patients achieved axillary pCR. The patient and tumor characteristics of the cohort are shown in Table 1.

When stratifying patients with axillary pCR by the Oncotype DX® RS, we found that of the 23 patients who had a pCR in the axilla, 11 (47.8%) had a high RS, 6 (26.1%) had an intermediate RS, and 6 (26.1%) had a low RS. When comparing the cohorts by Oncotype DX® RS categories, among patients who had tumors with high RS, 27.5% had an axillary pCR, compared with only 9.7% in the intermediate RS group and 10.7% in the low RS group ($p = 0.0268$). Characteristics of the cohort stratified by axillary pCR status are displayed in Table 2.

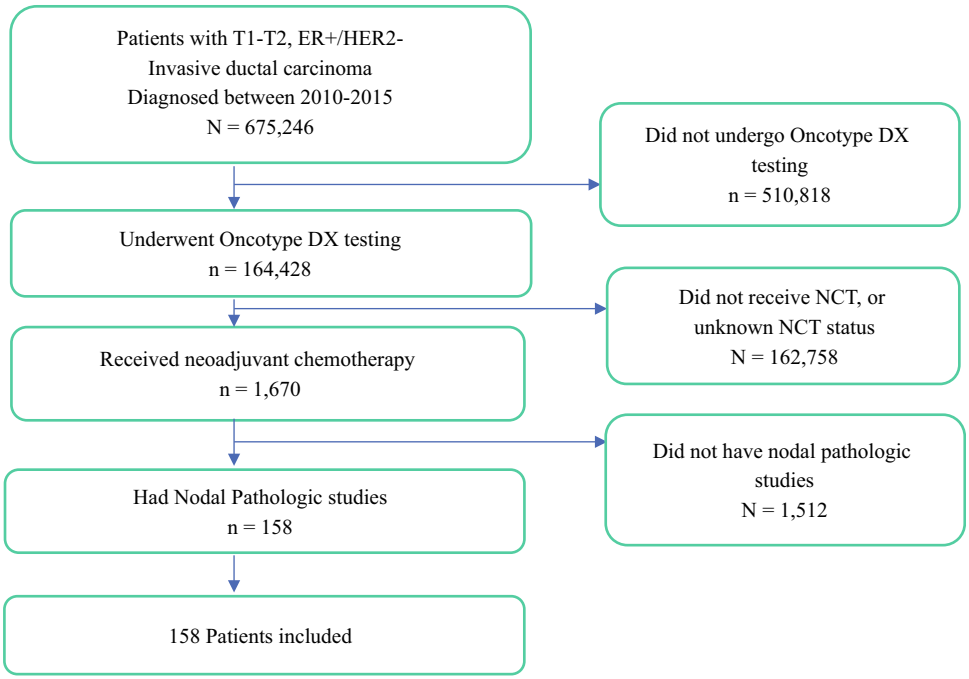

FIG. 1 Patient cohort selection. *ER* +estrogen receptor-positive, *HER2* −human epidermal growth factor receptor 2-negative, *NCT* neoadjuvant chemotherapy

DISCUSSION

Our study demonstrated that a high Oncotype DX® RS is associated with an increased axillary pCR (47.8%), compared with intermediate and low Oncotype DX® RS in patients with T1-T2, clinically N1/N2, ER +/HER2 − invasive ductal carcinoma of the breast. For patients with a high RS, an axillary pCR of 27.5% can be expected, as opposed to only 9.7% or 10.7% in intermediate and low RS tumors, respectively.

The practice of omitting ALND in clinically node-positive patients who achieve axillary pCR following neoadjuvant therapy is well established.[6,14,15] The results of our study suggest that Oncotype Dx® RS may further help identify patients who are optimal candidates for using NCT to downstage the axilla in an attempt to avoid ALND. These results may therefore also play an important role in determining the sequencing of care.

Several models and nomograms have been previously developed to predict which patients with breast cancer have a higher response rate to neoadjuvant therapies.[16–19] Recent studies have demonstrated that much of the predictive capability of these nomograms, based primarily on traditional tumor characteristics, correlate closely with genomic assessment results.[20–24] Future studies may determine if the addition of genomic data to established nomograms can improve their performance. Furthermore, we may ultimately discover that complicated decision algorithms can be reliably replaced by genomic assessment with equal, if not superior, predictive accuracy.

Preoperative Oncotype DX® testing in patients with clinically involved nodes is a promising approach to improving clinical decision making in breast cancer; however, barriers to routinely incorporating this approach into clinical workflows may include difficulty with insurance approval and the lack of evidence from prospective clinical trials.[25]

One interesting finding noted in our results was that we had a greater proportion of axillary pCR in larger breast tumors (T2 compared with T1), as well as in higher nodal status (≥ N2 compared with N1), which may seem counterintuitive at first. However, the results are consistent with our previous study utilizing the NCDB to evaluate overall pCR rates using Oncotype DX® RS.[13] Others have found the same counterintuitive result that tumor size may not be a clinical determinant of pCR. Perhaps in certain cases, factors other than tumor size play a larger role in determining NCT response.[26] Additionally, a higher incidence of axillary pCR compared with breast pCR was noted in our study cohort. This finding is consistent with prior results using large clinical databases demonstrating higher axillary pCR rates than breast pCR.[27]

In our study, the authors chose to focus only on clinically node-positive invasive ductal ER +/HER2 − breast cancers. Several studies have shown that invasive ductal carcinomas tend to have a higher rate of pCR after NCT compared with invasive lobular carcinomas.[28–31] Therefore, we wanted to focus on those ER +/HER2 − breast cancers, which would be expected to have the highest rate of nodal pCR to guide future studies.

TABLE 1 Patient and tumor characteristics

Characteristic	*N*	%
Age group, years		
< 40	13	8.2
40–54	63	39.9
55–69	63	39.9
≥ 70	19	12
Ethnicity		
Non-Hispanic White	114	72.2
Other	44	27.9
Pathological T		
Negative pathology (PCR)	10	6.3
Positive pathology (no PCR)	148	93.7
Pathological N		
No (PCR)	23	14.6
N1Mi	4	2.5
N1	94	59.5
n2	30	19.0
n3	7	4.4
Clinical T		
T1	49	31
T2	109	69
Clinical N		
N1	141	89.2
≥ N2	17	10.8
Grade		
Low/intermediate	105	66.5
High	53	33.5
Oncotype		
Low RS	56	35.4
Intermediate RS	62	39.2
High RS	40	25.3

PCR pathologic complete response, *RS* recurrence score

Traditionally, the categories of low, intermediate, and high Oncotype scores were divided into < 18, 18–30, and > 30. TAILORx results shifted these categories to RS ≤ 25 and > 25 for low–intermediate and high scores, respectively, in node-negative ER +/HER2 − breast cancers.[32] However, the authors chose to continue to use the cut-offs of < 18, 18–30, and > 30 because our study focused on clinically node-positive ER +/HER2 − breast cancers for which prospective data is still pending with the RXPonder trial.[25] It is currently recommended, based on the National Comprehensive Cancer Network, to use the numeric cut-offs of < 18, 18–30, and > 30 in node-positive ER +/HER2 − breast cancers to determine the risk category.[33]

TABLE 2 Axillary response after neoadjuvant chemotherapy among clinical variables

Characteristic	pCR		No pCR		*p* Value
	N = 23	%	*N* = 135	%	
Clinical T					0.0028
T1	1	2	48	98	
T2	22	20.2	87	79.8	
Clinical N					0.7021
N1	20	14.2	121	85.8	
≥ N2	3	17.7	14	82.3	
Grade					0.0116
Low/intermediate	10	9.5	95	90.5	
High	13	24.5	40	75.5	
Oncotype					0.0268
Low RS	6	10.7	50	89.3	
Intermediate RS	6	9.7	56	90.3	
High RS	11	27.5	29	72.5	

PCR pathologic complete response, *RS* recurrence score

Our study has the inherited limitations of a retrospective database review, as well as specific limitations of the NCDB. Although we identified patients receiving NCT, the NCDB does not contain information about the particular type of chemotherapy regimen used. Therefore, the findings cannot address differences in treatment protocols and their relation to the study outcomes. Additionally, within the NCDB, the numerical values for Oncotype DX® RS are limited to categorical designations of low, intermediate, and high in a subset of patients. Numerical values were also converted to categorical values (i.e. low, intermediate, high) to standardize the reporting. Although categorical assignments remain practical for clinical applications, given this limitation, we were not able to determine if there is a numerical threshold at which point the axillary pCR becomes most likely to occur. Furthermore, because of the retrospective nature and limitations of the NCDB, we could not confirm that all patients included had an Oncotype DX® prior to initiation of their NCT. However, we suspect that many medical oncologists may have obtained Oncotype DX® RS as part of their workflow prior to determining their neoadjuvant treatment plans. Nevertheless, regardless of the timing of their Oncotype DX®, the results of the nodal response to NCT determine whether the Oncotype DX® RS correlates with, and can therefore be predictive of, NCT effectiveness. Our hope is that the results of our study will further encourage routine early Oncotype testing to optimize therapy decisions in the future.

CONCLUSION

Our findings suggest that Oncotype DX® RS is an independent predictor of axillary pCR in patients with ER +/HER2 − breast cancer receiving NCT. In the high RS group, a greater proportion of patients achieved axillary pCR. These results show promise in utilizing the Oncotype DX® RS as a tool to improve clinical decision making in axillary management, and potentially avoid unnecessary ALNDs.

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