Ann Surg Oncol (2019) 26:366–371
https://doi.org/10.1245/s10434-018-07107-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Oncotype DX® Recurrence Score as a Predictor of Response to Neoadjuvant Chemotherapy

Alison M. Pease, MD[1], Luis A. Riba, MD[2], Ryan A. Gruner, MD[2], Nadine M. Tung, MD[3], and Ted A. James, MD, MHCM[2]

[1]Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [2]Department of Surgery/Linsey BreastCare Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [3]Department of Medicine/Division of Hematology – Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

ABSTRACT

Background. The Oncotype DX® assay has been validated in predicting response to adjuvant chemotherapy in breast cancer. Its role in neoadjuvant chemotherapy (NCT) has not been established.

Methods. The National Cancer Database was used to identify all patients with T1–T3, ER-positive, HER2-negative primary invasive breast cancer diagnosed from 2010 to 2015 who had Oncotype DX recurrence scores (RS) and received NCT. RS were classified as low, intermediate, or high. Unadjusted and adjusted regression analyses were performed to determine the association between pathologic complete response (pCR) and RS.

Results. A total of 989 patients (mean age, 54.6 years) with available RS who underwent NCT were identified. RS were low in 227 (23.0%) patients, intermediate in 450 (45.5%) patients, and high in 312 (31.5%) patients. Most patients had a T1 (431 [43.6%]) or T2 tumor (451 [45.6%]). Most had N0 disease (757 [76.5%]). Tumor grades were 1 (123 [12.4%]), 2 (517 [52.3%]), or 3 (349 [35.3%]). pCR was achieved by 42 (4.3%) patients. Adjusted multivariable analysis showed a significant association between pCR and high RS (odds ratio 4.87; 95% confidence interval 2.01–11.82).

Conclusions. High Oncotype DX RS was associated with pCR after NCT in this national cohort of ER-positive, HER2-negative patients. Oncotype DX testing could help to identify patients most suited for NCT and should be considered for incorporation into the multidisciplinary decision-making process.

First Received: 15 July 2018;
Published Online: 12 December 2018

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

Systemic treatment decisions for early breast cancer have historically hinged on factors, such as tumor size, presence of axillary metastases, and pathologic characteristics.[1] The role of biomarkers, such as the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), subsequently ushered in an era of biological subtype-based treatment assessment and targeted therapy for selected patients. More recently, multigene molecular tests have become available and provide additional information about both prognosis and suitability for potential systemic treatments.[2] The most widely known of these tests is Oncotype DX, a 21-gene RT-PCR assay for patients with ER-positive, HER2-negative tumors, which was introduced commercially in 2004.[3] The test provides patients and physicians with a "Recurrence Score" (RS) that has been validated to predict distant cancer recurrence and benefit of adjuvant chemotherapy.[4–6]

In contrast to adjuvant treatment, neoadjuvant chemotherapy was once relegated to patients with initially inoperable disease. However, NCT has now been shown to be beneficial in several clinical strategies, including downstaging patients desiring breast conserving surgery, achieving axillary response in clinically node-positive patients, and ensuring the timely administration of chemotherapy prior to complex mastectomy/reconstruction procedures.[7–9] Neoadjuvant chemotherapy is also known to have equivalence in survival compared to adjuvant therapy.[10] Moreover, one study found that 11% of Oncotype DX tests between 2005 and 2009 were already being

performed on core needle biopsy specimens, illustrating the potential for Oncotype DX-guided neoadjuvant therapy.[11] Despite this, the use of Oncotype DX for predicting chemosensitivity in the neoadjuvant setting is not well-established. Several small studies have investigated the neoadjuvant setting, with some suggesting a correlation between RS and outcomes.[12,13] However, no studies have examined the use of Oncotype DX RS to guide neoadjuvant chemotherapy on a national level. We conducted a retrospective study using the National Cancer Database to characterize the use of Oncotype DX in the neoadjuvant setting and to determine whether the Oncotype DX assay predicts NCT response as measured by pathologic complete response.

METHODS

Data Source

This study was a retrospective review of data derived from de-identified National Cancer Database (NCDB) participant user files. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society and contains information from more than 70% of the cancer cases in the United States.[14] Please note that in accordance with the NCDB Data Use Agreement, we have suppressed the reporting of absolute numbers of small groups of patients (i.e., when the number of patients in a given category or cell within a table was < 10). The Beth Israel Deaconess Medical Center Institutional Review Board determined this study does not constitute human subjects research.

Cohort Selection

The study cohort consisted of patients with clinical T1–T3, ER-positive, HER2-negative primary invasive breast cancer who were diagnosed between 2010 and 2015 and received NCT (Fig. 1). Only patients with a recorded Oncotype DX RS were included. RS results were defined as low (coded in the NCDB as "low" or numerical score < 18), intermediate (coded "intermediate" or score 18–30), or high (coded "high" or score > 30). From this cohort, we also excluded patients who received any neoadjuvant hormonal therapy, who were coded as having distant metastases, whose tumor grade was not available, or whose pathology results for T or N staging were not available or recorded as Tx or Nx.

Definition of Pathologic Complete Response

For the primary outcome, patients were stratified by whether or not they achieved pCR following NCT. In this study, pCR was defined as the patient having no remaining invasive disease in breast or axillary nodes on pathologic review, corresponding to NCDB codes for pathologic stages of T0 or Tis along with N0.

Statistical Analysis

Statistical analysis was performed with SAS Version 9.4 (SAS Institute Inc., Cary, NC). Descriptive statistics were

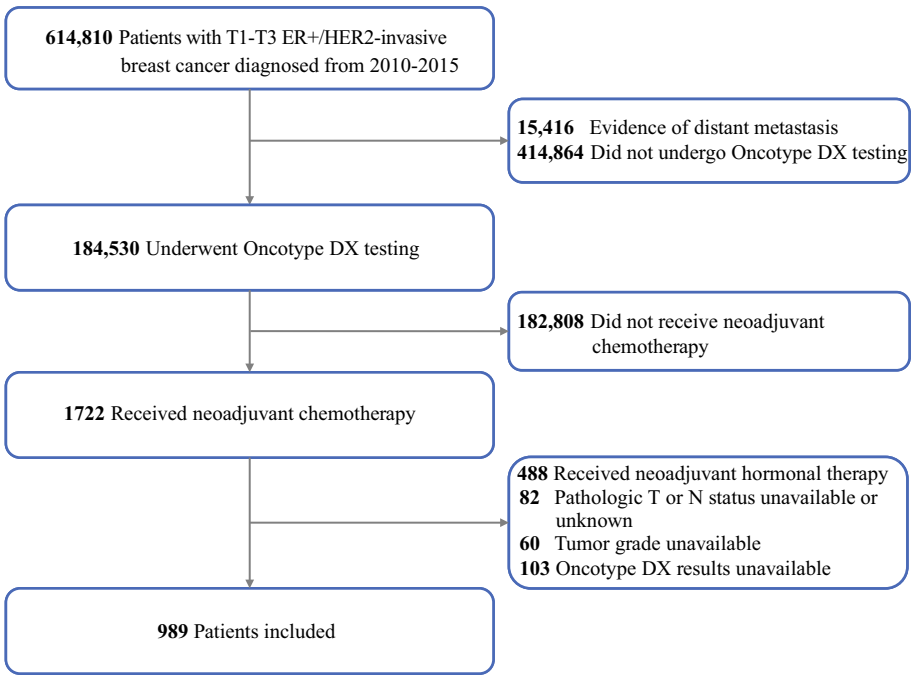

FIG. 1 Sample construction of patients with T1–T3 ER-positive/HER2-negative primary invasive breast cancer diagnosed from 2010 to 2015 receiving neoadjuvant chemotherapy after oncotype DX testing

used to summarize the study cohort according to demographic data and tumor characteristics. Chi square tests were employed to compare these characteristics between the pCR subgroups. Both unadjusted and adjusted multinomial logistic regression analyses were performed to determine the association between the achievement of pCR and RS. The multivariable adjusted analysis controlled for regional lymph node involvement, tumor grade, and tumor size as measured by clinical T stage.

RESULTS

Our study cohort consisted of 989 patients who had an Oncotype DX recurrence score and received NCT. The mean age was 54.6 (range 23–83) years. RS was low in 227 (23.0%) patients, intermediate in 450 (45.5%), and high in 312 (31.5%). In this cohort, 431 (43.6%) patients had a T1 tumor, 451 (45.6%) had a T2 tumor, and 107 (10.8%) had a T3 tumor. In addition, 757 (76.5%) had N0 disease; the remaining 232 (23.5%) had node-positive disease. The cohort included 123 (12.4%) patients with a grade 1 tumor, 517 (52.3%) with a grade 2 tumor, and 349 (35.3%) with a grade 3 tumor. Pathologic complete response was achieved by 42 (4.3%) patients. General characteristics of the cohort, stratified by pCR status, are shown in Table 1.

TABLE 1 Study cohort characteristics according to pCR subgroup

Characteristic	No pCR n = 947 (95.8%) %	PCR n = 42 (4.3%) %	p value
Age (years)			
Mean (SD)	54.6 (11.0)	51.4 (12.3)	
Ethnicity			
Non-hispanic white	97.0	3.0	< 0.001
Other	91.6	8.4	
Clinical T stage			
T1	98.6	1.4	< 0.001
T2/T3	93.6	6.5	
Node status			
Negative	95.2	4.8	0.152
Positive	97.4	2.6	
Tumor grade			
1	99.2	0.8	< 0.001
2	97.3	2.7	
3	92.3	7.7	
Oncotype score			
Low	97.8	2.2	< 0.001
Intermediate	98.4	1.6	
High	90.4	9.6	

N.b., reporting of absolute numbers is suppressed in this table as NCDB data use rules prohibit reporting cells with < 10 cases

We found varying rates of pCR stratified by Oncotype DX Recurrence Score. A pCR was achieved by 2.2% of low RS patients, 1.6% of intermediate RS patients, and 9.6% of high RS patients ($p < 0.001$). Unadjusted modeling for the occurrence of pCR showed a significant association with Oncotype DX RS. Tumors with high RS were found to have a positive association with pCR compared with the reference intermediate RS group (odds ratio [OR], 6.73; 95% confidence interval [CI], 2.92–15.54). Low RS was not associated with a difference in pCR achievement compared with the reference group (OR 1.43; 95% CI 0.45–4.54). Multivariable logistic regression analysis confirmed the significant relationship between increased rates of pCR and high RS (OR 4.87; 95% CI 2.01–11.82) while controlling for other clinical variables. A low RS was again not associated with pCR in the multivariable analysis (OR 1.48; 95% CI 0.46–4.79).

DISCUSSION

We found that a high Oncotype DX recurrence score was associated with an increased pathologic complete response rate in 989 patients with ER-positive, HER2-negative invasive breast cancer. This association was noted in both unadjusted and adjusted analyses, with odds ratios of 6.73 and 4.87, respectively, compared with a reference group of patients with intermediate RS. This finding is in concordance with some but not all of the smaller studies which have investigated similar research questions. As early as 2005, Gianni et al.[12] studied 89 patients with locally advanced cancer receiving neoadjuvant paclitaxel and doxorubicin and found that higher RS was significantly associated with pCR. A 2008 study of 72 evaluable patients also found that clinical complete response after neoadjuvant docetaxel was more likely in patients with higher RS.[13] More recently, a 2015 study examining neoadjuvant ixabepilone and cyclophosphamide in 168 HER2-negative patients found that high RS was correlated with pCR, suggesting that its predictive utility may extend beyond taxane-focused regimens.[15]

However, two other published studies have failed to find similar results regarding the association between RS and disease response. The first was a 2007 study of 45 patients receiving neoadjuvant doxorubicin and docetaxel, which did not find an association between RS and pCR.[16] In addition, though its endpoint was not pCR itself, a 2016 study of 60 patients with ER-positive, HER2-negative tumors receiving neoadjuvant therapy found that RS did not predict the percentage of tumor response.[17] Notably, the first study featured the smallest sample size of any of the above studies and had a high percentage of patients (20%) with inflammatory breast cancer; it also did not find

associations between pCR and age, tumor size, tumor grade, or ER status. The second study employed an endpoint—percentage tumor response—which is distinct from pCR. It remains plausible that RS could significantly predict the binary outcome of pCR while not showing a significant association with percentage of tumor response. When interpreting these varying results, it is important to note that our study possesses several advantages compared with the previously published literature on this topic. Namely, we undertook a much larger investigation of 989 patients, employed a broad national database, and included patients regardless of specific NCT regimen.

Overall, pCR in our sample was 4.3%. Breast cancer investigations have reported a wide range of pCR rates based on disease subtype, specific definitions of pCR, and other variables. A 2014 meta-analysis by Cortazar et al.[18] found that hormone-receptor positive, HER2-negative tumors exhibited a pCR of 7.5% for grades 1 or 2 and 16.2% for grade 3. Unlike some published literature, including some trials examined in the above meta-analysis, our definition of pCR was moderately strict in that it required an NCDB code of N0 disease, as opposed to simply no invasive disease within the breast. Moreover, the NCDB provides a "real-world" sample, which included patients with diagnoses extending back to 2010. Our sample could reasonably be expected to produce a lower pCR rate than a sample produced in the highly selective environments of clinical trials with novel therapeutic regimens that were then selected for publication.

Our study included both node-negative (757/989 [77%]) and node-positive (232/989 [23%]) patients in an effort to study real-world practice and capture as many patients as possible. Importantly, our multivariable analysis controlled for nodal status. However, the utility of Oncotype DX in the node-positive setting remains an area of active inquiry. One prominent 2010 analysis of the SWOG-8814 trial suggested that node-positive patients with low RS may not benefit from chemotherapy.[19] The forthcoming RxPONDER trial is expected to add valuable prospective information on this topic.[20] On a practical level, recent research has shown that Oncotype testing was being used in 16.5% of patients with node-positive, early-stage breast cancer and that RS was significantly associated with chemotherapy recommendation.[21] Clearly, further studies are needed to evaluate the predictive capacity of Oncotype DX on nodal response to chemotherapy in patients predominantly with cN1 disease. Until then, if there are concerns about the risk of persistent nodal disease mandating axillary lymph node dissection following NCT, one approach may be to perform a sentinel lymph node biopsy before initiating NCT. This would allow patients to have the axilla managed according to the ACOSOG Z0011 protocol, while still receiving NCT for the breast.[22] This too represents an area of potential investigation that could benefit from a prospective clinical protocol. Finally, it should be noted that patients undergoing mastectomy do not meet criteria for ACOSOG Z0011 and currently would require definitive axillary management regardless of chemotherapy.[23]

Our results also raise the related but broader question of which patients with ER-positive/HER2-negative core biopsies should undergo Oncotype DX testing. Our view is that this could hold value for all such patients. First, those with tumors of any size found to have a low RS and therefore likely no benefit of chemotherapy could make a better-informed choice to pursue either neoadjuvant hormonal therapy or initial surgery. Patients with intermediate RS also might be able to forego chemotherapy. Our finding that intermediate RS patients see less benefit from NCT than high RS patients is compatible with the recent TAILORx trial's finding that intermediate RS patients derived no additional benefit from chemotherapy when combined with endocrine therapy (although an alternate definition of "midrange" RS was used). Second, for patients with clinically large tumors in which significant neoadjuvant cytoreduction might facilitate breast conservation, obtaining an RS has particular value in potentially informing both treatment sequence and the type of surgery that is performed. Third, patients found to have a high RS can make initial treatment sequencing decisions while knowing that chemotherapy will likely be a part of their treatment regimen. This may, for example, have bearing on decisions regarding the type and timing of breast reconstruction: patients with a high RS who are undergoing mastectomy and autologous reconstruction may opt for neoadjuvant therapy or delayed reconstruction to avoid potential treatment delays with systemic therapy.[24] Overall, this study provides greater confidence that patients with a high RS will likely benefit from chemotherapy regardless of when it is delivered.[5] More broadly, together with the TAILORx trial and other recent research, our results point toward a future in which breast cancer chemotherapy delivered at any point in the treatment sequence is increasingly targeted toward patients with the highest-risk tumor biology.

Finally, our study has some recognized limitations. First, as a retrospective study, despite controlling for relevant clinical variables in our multivariable regression, there remains the possibility of unmeasured confounders. Second, although this work represents the largest-ever study that has attempted to answer our research question, results may still have been underpowered to detect additional pCR associations or provide highly precise odds ratios. Third, while some RS were reported to the National Cancer Database by exact numerical score, some were reported by score category (low, intermediate, or high). In an effort to capture all possible patients, we converted numerically

reported RS to the relevant score category. However, this precluded analysis of RS as a continuous variable, and it remains possible that there is a specific threshold numerical value over which pCR is higher. In addition, although quantitative gene-by-gene analysis is not recorded in the NCDB, it remains possible that a different assortment of tumor genetic characteristics could predict neoadjuvant pCR as well or better than the Oncotype DX assay. However, Oncotype DX remains a widely used and accepted assay with proven value in the adjuvant setting. Fourth, we excluded all patients who received neoadjuvant endocrine therapy, as this remains an investigational area. Finally, the primary outcome of this study was the surrogate endpoint of pathologic complete response rather than overall survival or quality of life. However, pCR remains a widely used endpoint and provides important information in decisions about the extent of surgical resection or radiation therapy.[25]

CONCLUSIONS

Our findings demonstrate a positive association between high Oncotype DX recurrence score and pathologic complete response to neoadjuvant chemotherapy in a national sample of patients. These results help to inform patients and physicians as they determine sequencing of treatment and systemic regimen selection among patients with ER-positive, HER2-negative breast cancer. Oncotype DX testing could be helpful in identifying patients most suited for NCT and should be considered for incorporation into the multidisciplinary decision-making process.

ACKNOWLEDGEMENT The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed or the conclusions drawn from these data by the investigator.

DISCLOSURES None.

REFERENCES

1. Nicolini A, Ferrari P, Duffy MJ. Prognostic and predictive biomarkers in breast cancer: past, present and future. *Semin Cancer Biol* 2017;52:56–73.
2. Győrffy B, Hatzis C, Sanft T, Hofstatter E, Aktas B, Pusztai L. Multigene prognostic tests in breast cancer: past, present, future. *Breast Cancer Res BCR* 2015;17(1):11.
3. Genomic Health, Inc. Announces Publication of Comprehensive Economic Analysis Confirming Cost-Effectiveness of Oncotype DX™ in the *American Journal of Managed Care* [press release]. Redwood City, CA, May 13, 2005.
4. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;351(27):2817–26.
5. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor–positive breast cancer. *J Clin Oncol* 2006;24(23):3726–34.
6. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol* 2010;28(11):1829–34.
7. Riba LA, Gruner RA, Fleishman A, James TA. Surgical risk factors for the delayed initiation of adjuvant chemotherapy in breast cancer. *Ann Surg Oncol* 2018;25:1904–11.
8. Kantor O, Sipsy LM, Yao K, James TA. A Predictive model for axillary node pathologic complete response after neoadjuvant chemotherapy for breast cancer. *Ann Surg Oncol.* 2018;25:1304–11.
9. Ajmani GS, James TA, Kantor O, Wang CH, Yao KA. The impact of facility volume on rates of pathologic complete response to neoadjuvant chemotherapy used in breast cancer. *Ann Surg Oncol* 2017;24(11):3157–66.
10. Haddad TC, Goetz MP. Landscape of neoadjuvant therapy for breast cancer. *Ann Surg Oncol* 2015;22(5):1408–15.
11. Anderson J, Shak S, Millward C, et al. Molecular characterization of breast cancer core biopsy specimens by gene expression analysis using standardized quantitative RT-PCR. *Cancer Res* 2009;69(24 Suppl):6021–1.
12. Gianni L, Zambetti M, Clark K, et al. Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer. *J Clin Oncol* 2005;23(29):7265–77.
13. Chang JC, Makris A, Gutierrez MC, et al. Gene expression patterns in formalin-fixed, paraffin-embedded core biopsies predict docetaxel chemosensitivity in breast cancer patients. *Breast Cancer Res Treat* 2008;108(2):233–40.
14. American College of Surgeons. National Cancer Database. https://www.facs.org/quality-programs/cancer/ncdb. Accessed 20 Dec 2017.
15. Yardley DA, Peacock NW, Shastry M, et al. A phase II trial of ixabepilone and cyclophosphamide as neoadjuvant therapy for patients with HER2-negative breast cancer: correlation of pathologic complete response with the 21-gene recurrence score. *Breast Cancer Res Treat* 2015;154(2):299–308.
16. Mina L, Soule SE, Badve S, et al. Predicting response to primary chemotherapy: gene expression profiling of paraffin-embedded core biopsy tissue. *Breast Cancer Res Treat* 2007;103(2):197–208.
17. Soran A, Bhargava R, Johnson R, et al. The impact of Oncotype DX(R) recurrence score of paraffin-embedded core biopsy tissues in predicting response to neoadjuvant chemotherapy in women with breast cancer. *Breast Dis* 2016;36(2–3):65–71.
18. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet (London, England)* 2014;384(9938):164–72.
19. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* 2010;11(1):55–65.
20. Brufsky AM. Predictive and prognostic value of the 21-gene recurrence score in hormone receptor–positive, node-positive breast cancer. *Am J Clin Oncol* 2014;37(4):404–10.
21. Jasem J, Fisher CM, Amini A, et al. The 21-gene recurrence score assay for node-positive, early-stage breast cancer and impact of RxPONDER Trial on chemotherapy decision-making: have clinicians already decided? *J Natl Compr Cancer Netw JNCCN* 2017;15(4):494–503.
22. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and

sentinel node metastasis: a randomized clinical trial. *JAMA* 2011;305(6):569–75.
23. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014;15(12):1303–10.
24. Riba LA, Gruner RA, Fleishman A, James TA. Surgical risk factors for the delayed initiation of adjuvant chemotherapy in breast cancer. *Ann Surg Oncol* 2018;25(7):1904–11.
25. US Food and Drug Administration. Guidance for Industry: pathological complete response in neoadjuvant treatment of high-risk early-stage breast cancer: use as an endpoint to support accelerated approval. October 2014.