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OncotypeDX Recurrence Score Does Not Predict Nodal Burden in Clinically Node Negative Breast Cancer Patients

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ABSTRACT

Background. OncotypeDX recurrence score (RS)® has been found to predict recurrence and disease-free survival in patients with node negative breast cancer. Whether RS is useful in guiding locoregional therapy decisions is unclear. We sought to evaluate the relationship between RS and lymph node burden.

Methods. Patients with invasive breast cancer who underwent sentinel lymph node dissection from 2010 to 2015 were identified from a prospectively maintained database. Patients were excluded if they were clinically node positive or if they received neoadjuvant chemotherapy. RS was classified as low (< 18), intermediate (18–30), or high (> 30). The association between RS, lymph node burden, and disease recurrence was evaluated. Statistical analyses were performed in R version 3.4.0; $p < 0.05$ was considered significant.

Results. A positive SLN was found in 168 (15%) of 1121 patients. Completion axillary lymph node dissection was performed in 84 (50%) of SLN-positive patients. The remaining 84 (50%) patients had one to two positive SLNs and did not undergo further axillary surgery. RS was low in 58.5%, intermediate in 32.6%, and high in 8.9%. RS was not associated with a positive SLN, number of positive nodes, maximum node metastasis size, or extranodal extension. The median follow-up was 23 months. High RS was not associated with locoregional recurrence ($p = 0.07$) but was significantly associated with distant recurrence ($p = 0.0015$).

Conclusions. OncotypeDX RS is not associated with nodal burden in women with clinically node-negative breast cancer, suggesting that RS is not useful to guide decisions regarding extent of axillary surgery for these patients.

The OncotypeDX recurrence score (RS)® is a genomic assay that incorporates 16 cancer-related genes and 5 reference genes. It has been validated in quantifying the risk of distant recurrence in patients with early stage estrogen receptor (ER)-positive breast cancer postoperatively. Paik and colleagues demonstrated a 10-year distant recurrence rate of 6.8% in patients with low RS, 14.3% in patients with intermediate RS, and 30.5% in patients with a high RS.[1] An association between RS and disease-free and overall survival also has been described. Therefore, RS is frequently utilized to guide adjuvant systemic therapy treatment decisions.[2–5] Recently, Sparano and colleagues reported that patients with ER-positive, node-negative breast cancer with intermediate-risk RS did not benefit from the addition of chemotherapy in terms of survival

TABLE 1 Demographics and clinicopathologic characteristics

	N = 1121 n (%)
Age (mean, range)	56 (27–86)
Ethnicity	
African American	69 (6.2)
Asian	58 (5.2)
Caucasian	803 (71.6)
Hispanic	163 (14.5)
Native American	4 (0.4)
Unknown	24 (2.1)
Clinical T stage	
T1	756 (67.4)
T2	345 (30.8)
T3	18 (1.6)
T4	2 (0.2)
Pathologic stage	
I	704 (62.8)
II	399 (35.6)
III	18 (1.6)
Breast procedure	
Segmental mastectomy	666 (59.4)
Total mastectomy	455 (40.6)
Final axillary procedure	
Sentinel lymph node dissection	1032 (92.1)
Axillary lymph node dissection	89 (7.9)
Hormone receptor status	
Negative	5 (0.4)
Positive	1116 (99.6)
Her2 status	
Negative	1104 (98.5)
Positive	5 (0.4)
Unknown	12 (1.1)
Nuclear grade	
1	198 (17.7)
2	688 (61.4)
3	223 (19.9)
Unknown	12 (1.1)
Oncotype RS	
Low (< 18)	656 (58.5)
Intermediate (18–30)	365 (32.6)
High (> 30)	100 (8.9)
Chemotherapy	
No	809 (72.2)
Yes	302 (26.9)
Unknown	10 (0.9)
Endocrine therapy	
No	83 (7.4)
Yes	979 (87.3)
Unknown	59 (5.3)

outcomes compared with endocrine therapy alone.[6] Mamounas and colleagues have shown that RS correlates with locoregional recurrence (LRR) with 10-year LRR estimates of 4.3%, 7.2%, and 15.8% in low, intermediate, and high RS groups respectively.[7]

While initially developed for use in patients with node negative disease, the application of RS has been expanded to patients with node-positive disease. In patients with node-positive breast cancer, RS has been found to correlate with recurrence, disease-free survival, and overall survival.[8–11] In the West German Study Group Plan B trial, patients who were clinically high risk with low RS were found to have 99% overall survival at 5 years with endocrine therapy alone.[12] OncotypeDX RS has increasingly been applied to patients with positive nodes and is used to guide systemic therapy treatment decisions.[6,11] However, no published studies have evaluated long-term outcomes when RS was used to guide locoregional treatment decisions.

We sought to evaluate RS in relation to presence of nodal disease and nodal burden in clinically node-negative patients with invasive breast cancer. Our aims were: (1) to evaluate the relationship between RS and positive sentinel lymph nodes (SLN); (2) to assess if RS correlated with lymph node burden; and (3) to analyze the association between RS and locoregional and distant recurrence. The goal of our study was to determine if RS is a useful tool to help guide surgeons in decision making with respect to axillary management.

METHODS

Data Source and Patients

The research protocol was approved by the institutional review board. Patients were identified from a retrospective review of a prospectively maintained comprehensive database from 2010 to 2015. Patients with invasive breast cancer who underwent sentinel lymph node dissection (SLND) and who had Oncotype DX RS performed on the primary tumor were included for analysis. At our institution Oncotype DX RS is ordered by the patient's medical oncologist postoperatively. Exclusion criteria included clinically or biopsy proven node-positive patients and patients who received neoadjuvant chemotherapy. For patients with synchronous bilateral breast cancers, each cancer was analyzed separately.

Explanatory Variables

Demographic and patient characteristic variables, as well as tumor characteristics, including clinical and

FIG. 1 Study patient population
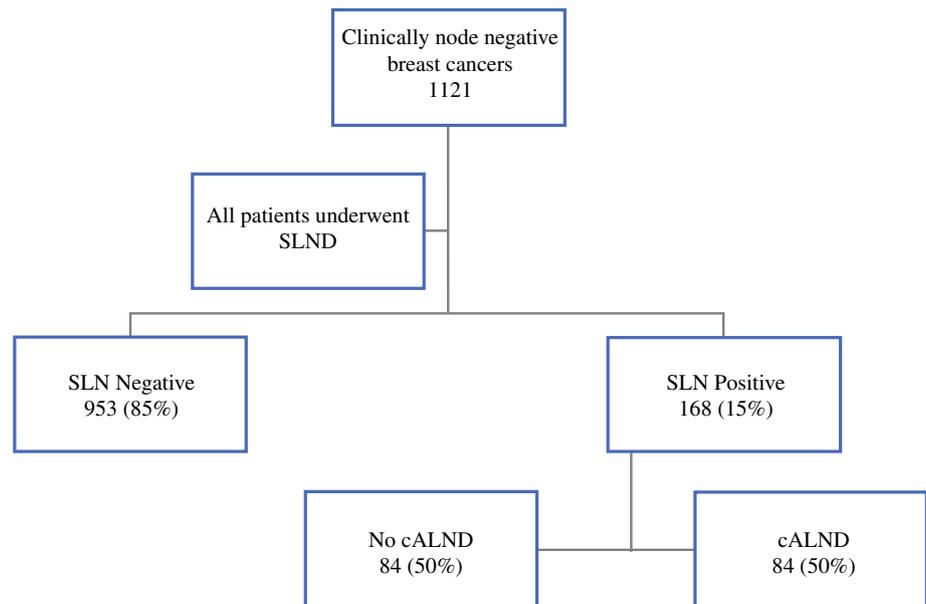
pathologic stage, hormone receptor status, and nuclear grade, were evaluated. The use of adjuvant radiation, chemotherapy, and endocrine therapy was assessed. The type of axillary and breast procedures were evaluated as operative variables. OncotypeDX 21-Gene RS was evaluated in the following groups: low (< 18), intermediate (18–30), and high (> 30).[1,3] We also evaluated the data using the classification in the Trial Assigning Individualized Options for Treatment (TAILORx). Cutoffs used in the TAILORx study were: low (< 11), intermediate (11–25), and high (> 25).[4]

Outcome Measures

The primary outcome of interest was nodal burden. All nodal variables were obtained from the final pathology report. We evaluated SLN status (positive versus negative) and number of positive SLNs and number of positive nodes in patients who underwent completion axillary lymph node dissection (cALND). We also assessed maximum lymph node metastasis size and presence of extranodal extension. Secondary outcomes of interest included locoregional recurrence (LRR) and distant recurrence.

Statistical Analysis

Descriptive statistics were used to characterize the study population in relation to demographics, tumor characteristics, treatment, and RS. The association between RS and lymph node status, number of positive lymph nodes, maximum lymph node metastasis size, and presence of extranodal extension were evaluated with Fisher's exact test (categorical variables) and Kruskal–Wallis test

(continuous variables). The time to locoregional and distant recurrence were estimated using the Kaplan–Meier method, and distributions were compared using the log-rank test. All statistical analyses were performed in R version 3.4.0. p Values < 0.05 were considered significant.

RESULTS

A total of 1095 women with 1121 breast cancers who had OncotypeDX testing performed were identified. All patients underwent SLND (Fig. 1). Of these, 168 patients (15%) were found to have positive SLNs with one positive node in 145 (86%) patients, two positive nodes in 19 (11%) patients, three positive nodes in 2 (1%) patients, and four positive nodes in 2 (1%) patients. Of the 168 patients with positive SLNs, 84 (50%) underwent cALND. The remaining 84 (50%) patients had 1–2 positive lymph nodes and did not undergo further axillary surgery. All of these patients had breast conserving surgery and met ACOSOG Z11 criteria. An additional 5 patients were found to have negative SLNs with positive non-SLNs and also underwent cALND. Therefore, a total of 173 patients had a positive SLN or non-SLN at the initial surgery, and 89 (51%) underwent cALND. On average, 1.5 (range 1–7) positive lymph nodes were identified in patients who underwent cALND.

Table 1 demonstrates patient demographics, clinical and pathologic characteristics, and adjuvant treatment modalities. The mean age of the patient population was 56 years, and the majority (71.6%) were Caucasian. Segmental mastectomy was performed in 59.4% of patients and total mastectomy in 40.6%. The vast majority of tumors were

TABLE 2 OncotypeDX recurrence score and nodal burden

	All patients N = 1121 n (%)	RS < 18 N = 656 n (%)	RS 18–30 N = 365 n (%)	RS > 30 N = 100 n (%)	p value
SLN status					
Positive	168 (15.0)	98 (14.9)	61 (16.7)	9 (9.0)	0.12
Negative	953 (85.0)	558 (85.1)	304 (83.3)	91 (91.0)	
No. of positive LN (mean, range)	1.3 (1–7)	1.3 (1–7)	1.3 (1–3)	1.4 (1–3)	0.36

RS OncotypeDX recurrence score, *SLN* sentinel lymph node, *LN* lymph node

TABLE 3 Positive lymph node characteristics by OncotypeDX recurrence score

	All patients N = 174 n (%)	RS < 18 N = 102 n (%)	RS 18–30 N = 63 n (%)	RS > 30 N = 9 n (%)	p value
Maximum LN Metastasis size (mean)	3.7 mm	3.6 mm	3.5 mm	4.9 mm	0.98
Presence of ENE	26 (14.9)	18 (17.6)	7 (11.1)	1 (11.1)	0.53

RS OncotypeDX recurrence score, *LN* lymph node, *ENE* extranodal extension

TABLE 4 OncotypeDX recurrence score and recurrence

	All Patients N = 1121 n (%)	RS < 18 N = 656 n (%)	RS 18–30 N = 365 n (%)	RS > 30 N = 100 n (%)	p value
Locoregional recurrence	5 (0.4)	2 (0.3)	1 (0.3)	2 (2.0)	0.07
Distant recurrence	9 (0.8)	3 (0.5)	1 (0.3)	5 (5.0)	0.0015

ER-positive (99.5%), progesterone receptor (PR)-positive (89.8%), and HER2-negative (98.5%). Most patients (62.8%) had pathologic stage I disease.

Of note, five tumors were HER2-positive. Upon review of these patients, OncotypeDX RS was requested by the medical oncologist. Eighteen patients had pathologic stage III disease where OncotypeDX RS was evaluated to determine eligibility for the SWOG S1007 Rx for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) trial.[13]

OncotypeDX RS was low in 58.5%, intermediate in 32.6%, and high in 8.9% of patients (Table 1). The study population was treated with adjuvant radiation therapy in 55.8%, and 577 (87%) patients received radiation therapy after segmental mastectomy and 48 (11%) received radiation therapy after total mastectomy. Adjuvant chemotherapy was administered in 26.9% and endocrine therapy in 87.3%. The median follow-up time was 23.3 months.

The association between OncotypeDX RS and nodal burden is outlined in Table 2. There was no significant association between higher-risk RS and SLN status (p = 0.12) or number of positive lymph nodes (p = 0.36). Similarly, as demonstrated in Table 3, there was no

association between RS and maximum lymph node metastasis size (p = 0.98) or presence of extranodal extension (p = 0.53).

Table 4 lists locoregional and distant recurrence by OncotypeDX RS. Distant recurrence was significantly associated with RS with a 5% distant recurrence rate in the high RS group compared with 0.5% in the low RS group (p = 0.0015). While there was a trend toward higher LRR in the high RS group (2%) compared with the low and intermediate groups (0.3%), the difference did not reach statistical significance (p = 0.07). Of the five patients with LRR, the initial operation for three patients was total mastectomy and two patients underwent segmental mastectomy with adjuvant radiation therapy. All five of the patients with LRR recurred in the breast/chest wall, whereas two of the five also had axillary recurrence.

We also evaluated the association between OncotypeDX RS and nodal burden, locoregional recurrence, and distant recurrence using the RS groupings from the TAILORx study (low < 11, intermediate 11–25, and high > 25). We did not find any differences in the results using these alternate RS cutoffs (Supplementary Tables 1 and 2).

DISCUSSION

In a large cohort of clinically node negative breast cancer patients, identified in a prospectively maintained database, we found that the OncotypeDX RS was not associated with nodal burden. The RS did not predict for a positive sentinel lymph node, the number of positive nodes, size of lymph node metastases, or the presence of extranodal extension. A trend towards an association between RS and LRR was noted; however, this analysis was likely limited by the very low number of LRR events. There was a significant association between RS and distant recurrence; those in the high RS group were most likely to develop distant metastasis.

Others have studied the use of genomic assays in conjunction with clinical risk to determine the benefit of systemic therapy in breast cancer patients. Cardoso et al. evaluated patients found to have high clinical risk (based on a modified version of Adjuvant! Online) and low genomic risk as predicted by a 70-gene signature test (Mammaprint).[14] The authors found a 1.5% difference in survival without distant metastasis in patients who did not receive chemotherapy compared with patients who did receive chemotherapy. The relationship between OncotypeDX 21-Gene RS and prognosis in breast cancer patients has been well described.[8,12,15] Paik and colleagues evaluated breast cancer patients from the NSABP B-14 trial who were randomized to receive tamoxifen versus placebo and found that patients with low RS had a 6.8% risk of distant recurrence at 10 years, whereas the 10-year distant recurrence rate was 30.5% in patients with high RS ($p < 0.001$).[1] We found a comparable pattern for distant recurrence rates in our patient population: patients with low scores had a distant recurrence rate of 0.5% compared with 5% in patients with high RS. We noted a trend towards increasing LRR rates in patients with high RS (2% vs. 0.3%); however, the difference did not reach statistical significance reflecting low event rates.

While the use of multigene assays in understanding prognosis and guiding systemic treatment decision making has been established, the use of multigene assays in locoregional treatment decisions has not been as well developed.[5,16] Mamounas et al. analyzed LRR in relation to RS in patients from two NSABP trials (NSABP B-14 and B-20).[7] Those with a low RS were found to have a 10-year LRR risk of 4.3% compared with 7.2% in patients with intermediate RS and 15.8% in patients with high RS. In addition to age and initial treatment, RS remained an independent predictor of LRR in these trials. In 2300 patients from their institutional database, Turashvili and colleagues found that RS was an independent predictor of LRR after controlling for lymphovascular invasion and T category.[17] Patients with intermediate RS were found to

have a threefold increase in LRR, and patients with high RS were found to have greater than fourfold increased risk of LRR. A subsequent study of more than 1000 patients at their institution demonstrated a very low rate (0.9%, median follow-up 52 months) of LRR in patients with RS < 18.[18] Of the 13 patients with LRR, 8 recurred in the ipsilateral breast, 3 in the chest wall, 1 in axillary nodes, and 1 in internal mammary nodes.

In contrast to these previously published studies, we did not find a significant association between RS and LRR. The results of this study may differ due to timing of data collection. Our study evaluated patients from 2010 to 2015 with short follow-up time, whereas the NSABP trials were performed in the 1980–1990s. Much has changed in the workup and treatment of breast cancer since the 1980s, including more frequent screen detected cancers, imaging of the axilla for nodal disease, the development and generalized acceptance of SLND, and advances in systemic treatment with endocrine therapy. Perhaps at some point in the future, a genomic assay will be used at the time of diagnosis to guide both locoregional and systemic treatment.

To our knowledge, the relationship between OncotypeDX RS and nodal burden in patients with invasive breast cancer has not been previously evaluated. We did not identify a significant association between RS and lymph node positivity, nodal burden, metastasis size, or extranodal extension. Our study population was lower risk based on clinical findings with negative SLNs in 85%, and in those patients with positive SLNs, the mean number of positive nodes was only 1.3. Furthermore, patients at our institution routinely undergo ultrasound of regional nodal basins at the time of diagnosis, which identifies patients with a larger burden of disease preoperatively.

This study has limitations inherent to a single institutional study. There may be selection bias in this study, because OncotypeDX RS testing is not ordered routinely for all patients. At our institution, testing is performed at the discretion of the treating medical oncologist in conjunction with the patient. We were unable to assess RS in association with mortality given a low event rate in this clinically low-risk patient population. Our ability to assess locoregional recurrence and association with RS was similarly hampered due to low rates of locoregional recurrence in our patient population and relatively short patient follow-up. As reported in a meta-analysis of > 62,000 patients by Pan and colleagues, the risk of breast cancer recurrence steadily increases up to 20 years after diagnosis in patients with ER-positive tumors.[19] To more rigorously study this question, a prospective trial where OncotypeDX testing is ordered at the time of diagnosis in all patients could be performed. Patients could then be followed to assess nodal burden and LRR.

In conclusion, our study did not demonstrate an association between OncotypeDX RS and nodal burden in clinically node-negative women with invasive breast cancer. Therefore, other factors, such as number of positive lymph nodes and plan for radiation therapy, will be important to consider when determining the extent of nodal surgery.

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