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ORIGINAL ARTICLE – BREAST ONCOLOGY

Are we Overtreating Hormone Receptor Positive Breast Cancer with Neoadjuvant Chemotherapy? Role of OncotypeDx® for Hormone Receptor Positive Patients Undergoing Neoadjuvant Chemotherapy

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ABSTRACT

Background. The utilization of OncotypeDx in the setting of neoadjuvant chemotherapy (NCT) is not well defined. The objective of this study was to determine what proportion of hormone receptor (HR)-positive patients undergoing NCT would not benefit from chemotherapy based on OncotypeDx recurrence scores (RS) and predictors of a high RS as defined by the TAILORx trial.

Methods. The National Cancer Data Base was used to identify patients with unilateral clinical stage I–III HR+/Her2− breast cancer who had an OncotypeDx score and who had undergone NCT. Patients undergoing adjuvant chemotherapy were used as a comparison group.

Results. Of 307,666 patients, 41.8% had testing with OncotypeDx. Of these, 76.6% had no chemotherapy, 22.3% adjuvant chemotherapy, and 1.1% NCT. OncotypeDx testing in NCT patients increased from 4.9% in 2010 to 8.2% in 2015. Of NCT patients with OncotypeDx testing, 11.6% had RS < 11, 44.4% RS 11–25, and 43.9% RS > 25. In patients age ≤ 50 years, 14.5% had RS < 11, 12.4% RS 11–15, 31.4% RS 16–25, and 41.7% RS > 25. Predictors of RS > 25 on multivariable analysis included grade 3 tumors (odds ratio [OR] 3.83) and PR-negative tumors (OR 5.26) but not clinical T or N stage ($p > 0.05$).

Conclusions. More than half of patients with OncotypeDx testing are being overtreated with NCT, and a third of younger patients are being overtreated. Predictors of a high RS are reliably available at core biopsy, suggesting an application of OncotypeDx in determining the need for NCT for some HR-positive breast cancers.

OncotypeDx is a 21-gene assay designed and validated for use in early-stage, estrogen receptor (ER)-positive, Her2neu (Her2)-negative breast cancer to determine the need for adjuvant systemic chemotherapy in addition to endocrine therapy. OncotypeDx has been validated to predict the distant recurrence risk for both node-negative and node-positive disease.[1–4] In initial studies, a low recurrence score (RS) < 18 was shown to correlate with a low distant recurrence risk and RS > 30 correlated with a high distant recurrence risk. It was not clear whether intermediate RS (18–30) would benefit from adjuvant chemotherapy. The TAILORx trial was a prospective, randomized trial of hormone receptor (HR)-positive, Her2-negative, node-negative breast cancer that randomized patients with a RS of 11–25 to adjuvant endocrine therapy or combined chemotherapy and endocrine therapy. At 9 years, the trial showed no significant differences in disease-free or overall survival between the two arms, suggesting that patients with RS < 25 can be treated with endocrine therapy alone.[5]

OncotypeDx has been incorporated into clinical guidelines and updated breast cancer staging, and is used in approximately one-third of breast cancer patients

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nationwide.[6–8] There has been increasing interest in the utilization of OncotypeDx in the neoadjuvant setting. One study showed that 11% of all OncotypeDx assays were performed on core biopsy tissue samples from 2005 to 2009.[9] A few single-institutional studies have suggested that higher RS (> 30) is associated with clinical response and pathologic complete response (pCR), whereas others show no differences in tumor response among recurrence scores.[10–13] Additionally, two neoadjuvant hormonal trials have shown that low RS are associated with higher tumor response to neoadjuvant hormonal therapy than high RS.[14,15]

Another application of OncotypeDx in the neoadjuvant setting is to determine whether a HR-positive, Her2-negative cancer would benefit from chemotherapy at all. Earlier trials utilizing OncotypeDx have demonstrated that many HR-positive tumors, even with tumor-involved nodes, do not require chemotherapy.[1–4] An OncotypeDx performed in the neoadjuvant setting could potentially select those patients who would not benefit from chemotherapy and would benefit from hormonal therapy alone. Additionally, this test would be helpful if clinical features of the tumor could reliably predict for a high RS, enabling physicians to select certain HR positive patients for OncotypeDx. The objective of our study was to determine trends and characteristics associated with utilization of OncotypeDx in NCT patients and to determine which proportion of NCT patients wound benefit from chemotherapy using TAILORx criteria.

METHODS

Data Source

The National Cancer Data Base (NCDB) is a joint project of the American Cancer Society and the American College of Surgeons Commission on Cancer (CoC), which collects data on 70% of new cancer diagnoses nationwide.[16] Data are compliant with the privacy requirements of the Health Insurance Portability and Accountability Act (HIPPA). This project is IRB-exempt by the NorthShore University Health System Institutional Review Board. The American College of Surgeons and CoC have not verified and have no responsibility for the analytical or statistical methodology employed, nor the conclusions drawn by the investigators.

Data Variables

The following variables were analyzed in our dataset: patient demographics (age, race, insurance), facility information (type and location of cancer center), tumor characteristics (histology, grade, clinical and pathologic stage), and treatment course (type and timing of systemic therapy, radiation, and surgery). Site-specific factors for the breast cancer participant user file include ER, progesterone receptor (PR), and Her2 status, as well as data on OncotypeDx utilization and RS results (listed as an absolute number 0–100). Data on chemotherapy are limited to timing and whether single or multi-agent therapy was used. No details on completion of therapies are available.

Study Population

The 2015 breast cancer participant user file was used for analysis. Inclusion criteria are shown in Fig. 1. We included only patients with HR-positive, Her2-negative breast cancer from 2010 to 2015 that underwent OncotypeDx testing. These years were included, because both Her2 and multigene panel data began reporting in 2010 in the NCDB. HR-positive was defined as either ER- or PR-positive. NCT was defined as a start date of chemotherapy occurring before the surgery date. Adjuvant chemotherapy was defined as a start date of chemotherapy occurring after the surgery date. Recurrence scores were classified as < 11, 11–25, and > 25 based the TAILORx trial criteria.[5] AJCC 7th edition anatomic clinical staging was used, because this was the standard staging system during the timeframe of study.[17] Complete pathologic response was defined as ypT0N0. Partial pathologic response was defined as a pathologic stage group less than the clinical stage group. As such, not all partial responses could be captured, because they may not result in a change in clinical T or N staging.

Statistical Analysis

All analyses were performed by SPSS statistical software version 19.0 (IBM Corp., Armonk, NY). Statistical tests were two-sided, and p value < 0.05 was considered statistically significant. Chi square tests were used to compare neoadjuvant chemotherapy patients that had OncotypeDx and those that did not, trends over time, and characteristics across recurrence scores. Multivariable regression was used to examine predictors of OncotypeDx utilization in patients that had neoadjuvant chemotherapy and was adjusted for patient age, race, insurance, cancer center type and location, histology, grade, clinical stage, and year of diagnosis. Odds ratio (OR) > 1 suggests increased odds of undergoing OncotypeDx testing. Multivariable regression also was used to examine predictors of RS > 25 in patients that underwent neoadjuvant chemotherapy, adjusting for age, race, insurance, recurrence score category, histology, grade, PR status, clinical T and N stage, cancer center type and location, and year of diagnosis. ER status was not adjusted for, because most

Study Criteria	N
Unilateral cancer	2,444,349
Female	2,422,369
1st cancer	1,753,527
Treated at reporting facility	963,400
Diagnostic needle biopsy	832,492
HR+, Her2; 2010-2015	402,027
Exclude other gene panel testing	317,965
Exclude unknown chemotherapy	312,228
Exclude unknown recurrence score	307,666

OncotypeDx testing
N=128,506 (41.8%)

No chemotherapy N=98,535 (7.6%)			Adjuvant chemotherapy N=28,594 (22.3%)			Neoadjuvant chemotherapy N=1,377(1.1%)		
RS <11	RS 11-25	RS >25	RS <11	RS 11-25	RS >25	RS <11	RS 11-25	RS >25
34.4% (33,867)	61.3% (60,406)	4.3% (4,262)	5.8% (1,669)	47.7% (13,641)	46.5% (13,284)	11.6% (160)	44.4% (612)	43.9% (605)

FIG. 1 Selection criteria and breakdown of OncotypeDx by recurrence score, stratified by chemotherapy status

patients were ER-positive (96.0%). OR > 1 suggests increased odds of RS > 25. All confidence intervals (CI) are reported at the 95% level.

RESULTS

Cohort Characteristics

A total of 307,666 women with unilateral clinical stage I-III HR+, Her2− breast cancer were included, of which 128,506 (41.8%) underwent OncotypeDx testing. Of these 128,506 women, 98,535 (76.6%) did not undergo chemotherapy, 28,594 (22.3%) underwent adjuvant chemotherapy, and 1377 (1.1%) underwent NCT. Of the 1377 NCT patients with OncotypeDx testing, 772 (56.0%) had a RS < 25 compared with 15,310 (53.5%) of patients in the adjuvant chemotherapy cohort (Fig. 1).

Trends in OncotypeDx Utilization

The use of OncotypeDx increased from 33.0% in 2010 to 47.1% in 2015 ($p < 0.01$) amongst all patients and across all cohorts (Fig. 2). OncotypeDx in patients who underwent NCT increased from 4.9% in 2010 to 8.2% in 2015 ($p < 0.01$).

OncotypeDx in Neoadjuvant Chemotherapy Patients

Among patients undergoing NCT, OncotypeDx was significantly more common in patients older than age

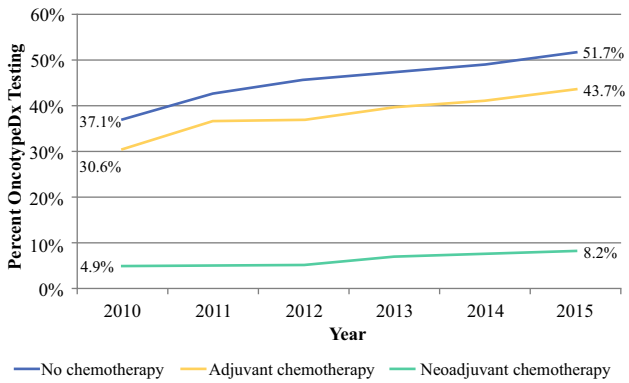

FIG. 2 Trends in OncotypeDx Utilization from 2010 to 2015 in patients with hormone receptor-positive, HER2-negative breast cancer, n = 307,666

50 years (61.2% vs. 54.9%, $p < 0.01$), Caucasian patients (78.1% vs. 70.5%, $p < 0.01$), and those with private insurance (71.2% vs. 64.0%). Less aggressive tumor characteristics were associated with OncotypeDx testing compared with no OncotypeDx among NCT patients, including clinical T1 stage, clinical node negativity, and grade 1 tumors (Table 1).

On multivariate analysis adjusting for patient, facility, and tumor factors, independent predictors of OncotypeDx in patients undergoing NCT included age > 50 (OR 1.36, CI 1.19–1.55), more recent year of diagnosis (OR 1.54–1.74, CI 1.23–2.16 for 2013–2015), lower grade (OR 1.55, CI 1.20–2.00 for grade 1/2), lower clinical stage (OR

TABLE 1 Patient and tumor characteristics stratified by OncotypeDx status in patients undergoing NCT, n = 21,102

Characteristic	OncotypeDx		No OncotypeDx		p value
	N = 1377	% (col)	N = 19,725	% (col)	
Age, yr					< 0.01
≤50	534	38.8	8902	45.1	
>50	843	61.2	10,823	54.9	
Race					< 0.01
Caucasian	1076	78.1	13,901	70.5	
African American	160	11.6	3066	15.5	
Hispanic	84	6.1	1828	9.3	
API	50	3.6	803	4.1	
Other	7	0.5	127	0.6	
Insurance					< 0.01
Private	980	71.2	12,631	64.0	
Medicare	238	17.3	3520	17.8	
Medicaid	110	8.0	2540	12.9	
Uninsured	33	2.4	825	4.2	
Other	16	1.2		1.1	
Cancer center type					0.01
Community	97	7.0	1426	7.2	
Comprehensive	513	37.3	7450	37.8	
Academic	439	31.9	5828	29.5	
Integrated network	193	14.0	2288	11.6	
Unknown	135	9.8	2733	13.9	
Cancer center location					< 0.01
Northeast	240	17.4	3190	16.2	
Midwest	297	21.6	4501	22.8	
South	464	33.7	6357	32.2	
West	241	17.5	2944	14.9	
Unknown	135	9.8	2733	13.9	
Clinical stage					< 0.01
I	352	25.6	1036	5.3	
II	854	62.0	11,218	56.9	
III	171	12.4	7471	37.9	
Clinical T stage					< 0.01
cT1	419	30.4	2606	13.2	
cT2	720	52.3	9471	48.0	
cT3	193	14.0	4789	24.3	
cT4	40	2.9	2736	13.9	
cTx	5	0.3	123	0.7	
Clinical N stage					< 0.01
cN0	957	69.5	6611	33.5	
cN+	406	29.5	12,896	65.4	
cNx	14	1.0	218	1.1	
Grade					< 0.01
Grade 1	187	13.6	1673	8.5	
Grade 2	712	51.7	8406	42.6	
Grade 3	406	29.5	8208	41.6	
Unknown	72	5.2	1438	7.3	

TABLE 1 continued

Characteristic	OncotypeDx		No OncotypeDx		*p* value
	N = 1377	% (col)	*N* = 19,725	% (col)	
Histology					< 0.01
Ductal	1034	75.1	15,251	77.3	
Lobular	181	13.1	2026	10.3	
Mixed	155	11.3	2076	10.5	
ER status					< 0.01
ER positive	1371	99.6	18,845	95.5	
ER negative	6	0.7	876	4.5	
PR status					0.07
PR positive	1143	83.0	15,801	80.1	
PR negative	234	17.0	3919	19.9	

3.54, CI 2.94–4.26 for stage I; OR 1.74, CI 1.47–2.06 for stage II), and node negativity (OR 4.31, CI 3.8–4.87).

Recurrence Score in Neoadjuvant Chemotherapy Patients

Of the 1377 patients that had OncotypeDx testing that underwent NCT, 160 (11.6%) had RS < 11, 612 (44.4%) had RS 11–25, and 605 (43.9%) had RS > 25. When further stratifying patients age ≤ 50 years, 75 (14.5%) had RS < 11; 64 (12.4%) had RS 11–15; 162 (31.4%) had RS 16–25; and 215 (41.7%) had RS > 25. Additional patient and tumor characteristics stratified by recurrence score are shown in Table 2.

Multivariable analysis adjusting for patient, facility, and tumor factors was used to identify predictors of having a RS > 25. Grade 3 tumors (OR 3.83) and PR-negative tumors (OR 5.26) were associated with significantly increased odds of RS > 25. Nonductal histology was associated with lower odds of RS > 25. Overall, clinical T stage ($p = 0.52$) and clinical N stage ($p = 0.09$) were not significantly associated with RS > 25 (Table 3).

A subgroup analysis of patients age ≤ 50 years was done to identify predictors of RS > 16 ($n = 534$). Grade 3 tumors (OR 1.58, CI 0.93–2.70) were the only significant predictor of RS > 16 in this analysis. Lobular tumors were associated with decreased odds of a RS > 16 (OR 0.32, CI 0.16–0.62).

DISCUSSION

In this study of 307,666 HR+, Her2− patients from the NCDB, we found that the use of OncotypeDx has increased 13.0% between 2010 and 2015 and increased 3.3% in patients undergoing NCT. When applying TAILORx categorization of RS, more than 50% of patients had RS < 25, which would not benefit from chemotherapy regardless of whether they received chemotherapy in the adjuvant or neoadjuvant setting. Our findings suggest that OncotypeDx use before surgery could potentially spare 50% of patients NCT.

It is important to mention several caveats to our study. First, it is not clear whether OncotypeDx results on a core biopsy correlate well with OncotypeDx results on a resected specimen, because the biopsy often is only a small sampling of the tumor and may not be fully reflective of the true tumor heterogeneity. Second, OncotypeDx patients in the NCDB represent a selected cohort of patients who were selected for OncotypeDx testing by their physicians, because universal OncotypeDx testing of all newly diagnosed breast cancer patients is not endorsed by any national guideline. Indeed, our data show that NCT patients who had OncotypeDx performed had a higher proportion of smaller tumors that had not metastasized to the nodes, which suggests that physicians may be changing their criteria for NCT in HR-positive patients. Perhaps the number of patients that OncotypeDx could spare chemotherapy would be even higher if all patients underwent testing. Third, we do not have access to any physician intention or decision-making data. We do not know how many of the 128,506 patients who underwent OncotypeDx testing were actually considered for NCT, only how many actually underwent NCT. The NCDB does not contain data on whether OncotypeDx was ordered before or after surgery. It is possible that many more patients were considered for NCT but did not actually undergo NCT possibly based on their OncotypeDx score. Lastly, our findings provide insufficient data to support the use of OncotypeDx in the neoadjuvant setting but do demonstrate a potential interesting role for OncotypeDx in the neoadjuvant setting. Further studies on the use of OncotypeDx in the NCT setting are needed to validate its use.

TABLE 2 Tumor characteristics of patients with OncotypeDx undergoing neoadjuvant chemotherapy, stratified by recurrence score, $n = 1377$

	Overall ($n = 1377$)		RS < 11 ($n = 160$)		RS 11–25 ($n = 612$)		RS > 25 ($n = 605$)		p value
	N	%(col)	*N*	%(col)	*N*	%(col)	*N*	%(col)	
Age, yr									0.03
≤50	534	38.8	75	46.9	244	39.9	215	35.5	
>50	843	61.2	85	53.1	368	60.1	390	64.5	
Grade									< 0.01
Grade 1/2	899	65.3	110	68.8	485	79.2	304	50.2	
Grade 3	406	29.5	37	23.1	90	14.7	279	46.1	
Unknown	72	5.2	13	8.1	37	6.0	22	3.6	
Histology									< 0.01
Ductal	1034	75.1	107	66.9	407	20.9	520	86.0	
Lobular	181	13.1	26	16.3	128	66.5	27	4.5	
Mixed	155	11.3	26	16.3	76	12.4	23	8.8	
PR status									< 0.01
PR positive	1143	83.0	148	92.5	565	92.3	430	71.1	
PR negative	234	17.0	12	7.5	47	7.7	175	28.9	
Tumor size									0.01
cT1	419	30.4	42	26.3	182	29.7	195	32.2	
cT2	720	52.3	80	50.0	305	49.8	335	55.4	
cT3	193	14.0	34	21.3	100	16.3	59	9.8	
cT4	40	2.9	4	2.5	22	3.6	14	2.3	
cTx	5	0.3	0	0.0	3	0.3	2	0.3	
Nodal status									0.04
cN0	957	69.5	99	61.9	414	67.6	444	73.4	
cN+	406	29.5	58	36.3	192	31.4	156	25.8	
cNx	14	1.0	3	1.9	6	1.0	5	0.8	
Clinical stage									< 0.01
I	352	25.6	32	20.0	152	24.8	168	27.8	
II	854	62.0	103	64.4	370	60.5	381	63.0	
III	171	12.4	25	15.6	90	14.7	56	9.3	
Pathologic response									< 0.01
Complete	62	4.5	7	4.4	8	1.3	47	7.8	
Partial	451	32.8	53	33.1	180	29.4	218	36.0	
None	836	60.7	95	59.4	419	68.4	322	53.2	
Unknown	28	2.0	5	3.1	5	0.8	18	3.0	

An interesting finding from our study were the independent predictors of a RS > 25. Our study found that in patients undergoing NCT, a high RS of > 25 was not associated with tumor size or nodal status but rather other tumor characteristics, such as high-grade, tumor histology, and PR-negative tumors. We attempted to further define predictors of RS > 16 for young women aged ≤ 50 years due to the TAILORx trial suggestion that RS 16–25 may benefit from chemotherapy; however, the small number of patients in this cohort limited the power of the analysis. This finding is interesting, because clinical staging of tumor size and node status can sometimes be unreliable; however, tumor grade, PR status, and histology tend to be more reliable tumor characteristics on core biopsy. Perhaps these factors could be used to determine the likelihood of a high RS that requires chemotherapy. More studies with larger volumes of patients are needed to validate these findings.

Several studies have examined whether OncotypeDx RS can predict tumor response to treatment. Gianni et al.[10] examined 171 pretreatment tumor specimens treated with neoadjuvant doxorubicin and paclitaxel ± fluorouracil and cyclophosphamide. A positive association was seen between higher RS and likelihood of pCR . Chang et al.[11]

TABLE 3 Multivariable logistic regression analysis of independent predictors of a high recurrence score > 25 in patients undergoing NCT, $n = 1377$

	Predictors of RS > 25	
	OR (95% CI)	p value
Age (yr)		
≤50	Reference	
>50	1.26 (0.94–1.68)	0.13
Grade		
1/2	Reference	
3	3.83 (2.90–5.06)	< 0.01
PR status		
PR positive	Reference	
PR negative	5.26 (3.63–7.63)	< 0.01
Histology		
Ductal	Reference	
Lobular	0.21 (0.13–0.33)	< 0.01
Mixed	0.59 (0.40–0.87)	0.01
Clinical T stage		
cT1	Reference	
cT2	0.96 (0.73–1.28)	0.79
cT3	0.69 (0.45–1.05)	0.08
cT4	0.64 (0.30–1.40)	0.26
Clinical N stage		
cN0	Reference	
cN+	0.79 (0.60–1.04)	0.09
Cancer center type		
Community	Reference	
Comprehensive	1.23 (0.74–2.02)	0.42
Academic	1.11 (0.67–1.85)	0.68
Integrated network	1.19 (0.68–2.11)	0.54
Cancer center location		
Midwest	Reference	
Northeast	0.53 (0.36–0.79)	0.01
South	0.99 (0.71–1.40)	0.97
West	0.01 (0.60–1.34)	0.61

examined core biopsies from 72 patients treated with neoadjuvant docetaxel and also found a positive association between higher RS and rate of clinical response and pCR. Yardley et al.[12] examined 72 breast biopsy samples in patients who underwent neoadjuvant ixabepilone and cyclophosphamide for Her2-negative breast cancer and found pCR only in patients with high RS > 31. However, all of these studies included ER-negative patients. Soran et al. examined 60 pretreatment core needle biopsies in ER+, Her2− patients who received NCT with no significant correlation between treatment response and RS.[13] A recent study by Pease et al. using the NCDB from 2010 to 2015 found pCR to be associated with high RS > 30 (OR 4.87); however, only 4.3% of the ER+, Her2− cohort had pCR.[18] Our study similarly found pCR was associated with a higher RS > 25, but overall rate of pCR was only 4.5%. Because pCR is a rare occurrence after NCT for HR+ tumors, it does not appear that OncotypeDx would have a particularly useful application for predicting complete pathologic response.

Limitations of our study include the retrospective nature of the data set and thus the propensity for selection bias. Our study covers the years 2010–2015, while the TAILORx trial was published in 2018. Thus, our assessment of overtreatment is retrospectively applying the TAILORx criteria and not reflective of the state of knowledge during that time frame. Prospective analyses of RS with chemotherapy in the future will better inform trends in overtreatment. We do not have details on the type of chemotherapy given or its completion. Additionally, we cannot correlate RS with recurrence, as NCDB has only overall survival outcome data.

In conclusion, TAILORx RS criteria suggest that 50% of patients with HR+, Her2− tumors are being overtreated with chemotherapy, both in the adjuvant and neoadjuvant settings. Use of OncotypeDx is increasing in the neoadjuvant setting, and even in patients who were selected for OncotypeDx by their physicians, approximately half could have been spared chemotherapy. Further studies are needed on the validity and clinical utility of genomic testing in the neoadjuvant setting.

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