How Does Invasive Breast Cancer Oncotype Dx Recurrence Score on Core Needle Biopsies Influence Neoadjuvant Treatment Decision? A Descriptive Study

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Abstract

Background: Oncotype Dx (ODx) is a genomic assay which estimates the risk of distant recurrence and predicts adjuvant chemotherapy benefit in early stage breast cancer patients. Most ODx data is derived from excisional specimens. **Aim:** We assess the utility of ODx on core needle biopsies (CNB) and measure its impact on neoadjuvant treatment decisions, particularly in patients with clinically complicated situations. **Methods:** Consecutive ODx results on breast CNBs with invasive carcinoma from 2012-2020 at 3 tertiary care hospitals with dedicated Breast Health Centers were reviewed. Clinical indications to perform ODx on CNB were recorded through a review of patients' electronic medical records. Clinicopathologic features, surgical or oncologic modalities and follow-up data were recorded. **Results:** Three distinct clinical indications for performing ODx on CNB in 85 ER+ invasive breast carcinomas were identified: 1) Excisions with insufficient tissue to perform ODx, 2) adjudicate neoadjuvant therapy versus primary surgical resection, and 3) select neoadjuvant chemotherapy (NAC) versus neoadjuvant endocrine therapy (NET). Primary surgery was selected in patients with low score RS (<18), and NET was preferred in patients with intermediate or high RS (>18). NET was preferred over NAC in patients with low RS (<18). **Conclusion:** This study shows that CNB ODx RS helps guide treatment decisions in a neoadjuvant setting along with other contributing factors such as the presence of pathogenic mutations, node positivity, patient age, and comorbidities. The use of ODx on CNB is furthermore valuable in the midst of the COVID-19 pandemic for early breast cancer patients to administer effective therapy in a timely manner.

Keywords

Oncotype Dx, recurrence score, core needle biopsy, neoadjuvant, neoadjuvant hormonal therapy, neoadjuvant chemotherapy

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Introduction

Oncotype Dx (ODx) is a 21 gene RT-PCR-based multigene assay developed by Genomic Health which estimates the risk of distant recurrence and helps predict adjuvant chemotherapy benefit in estrogen receptor (ER) positive node-negative or positive (N1-3) breast cancer patients.[1-5] The ODx has been widely incorporated in various guidelines and is recommended by the National Institute for Health and Care Excellence (NICE) for use in clinical practice to guide adjuvant chemotherapy treatment decisions for patients with early-stage breast cancer. The vast majority of ODx data and research are derived from excisional specimens, some from core needle biopsies (CNB).[1-6] Eleven percent of ODx tests between

2005 and 2009 were performed on CNB.[7] Benefits of neoadjuvant chemotherapy include survival benefit, downstaging patients desiring breast-conserving surgery (BCT), achieving an axillary response in clinically node-positive patients, and ensuring timely administration of chemotherapy prior to complex mastectomy and reconstructions. On the other hand, chemotherapy inadvertently comes with high costs, potential side effects, and toxicity. Several studies have shown that the use of neoadjuvant endocrine therapy (NET) was equally as effective for selected hormone receptor-positive breast cancers as NAC with less toxicity.[8,9] This descriptive study emphasizes the current oncologic use of ODx testing on CNB to facilitate the neoadjuvant treatment decision-making process.

Materials and Methods

This retrospective, HIPAA-compliant study was reviewed and approved by the institutional review board. Consecutive ODx results on breast CNBs from 2012-2020 performed at 3 tertiary care hospitals with dedicated Breast Health Centers (Rhode Island, Miriam, and Women and Infants Hospitals) were reviewed. The study included patients with clinical T1-T4, ER-positive primary invasive breast cancer. Clinicopathologic features and clinical indications to perform ODx on CNB were recorded from electronic medical records. All patients in our study were considered clinically complicated, whereby the patient's age, tumor histologic grade, hormone receptor status, lymph node status, and patient preferences, among other factors, did not provide the clinicians with definitive neoadjuvant treatment plan without ODx RS. HER2 receptor status was assessed using immunohistochemistry and in situ hybridization according to American Society of Clinical Oncology and College of American Pathologists guidelines.[10] The ODx RS was categorized based on the original criteria from the NSABP B-14 study; low RS <18, intermediate RS of 18-30, and high ≥31 and TAILORx trial; low <10, intermediate 11-25, and high ≥26. The surgical or oncologic modalities and follow-up data such as final pathologic stage and recurrence were recorded. Statistical analysis was performed using JMP 14.1.0 (SAS). Associations between ODx RS and clinicopathologic features were analyzed using Pearson's correlation coefficient analysis (for categorical variables) and analysis of variance (for numerical variables). Two-sided $P < 0.05$ was considered statistically significant.

Results

Overall Clinicopathologic Features

Eighty-five breast cases with ODx testing on CNB were identified. One CNB with insufficient material was excluded. The mean age was 58 years (range 33-83). Our study population consisted of 83 females and 1 male. The most common tumor subtype was invasive ductal carcinoma (55/83; 66%), followed by invasive lobular carcinoma (18/83; 22%) (Table 1). There was no breast cancer of specific types in the study

Table 1. Clinicopathologic Features According to ODx on CNB Indication Groups.

Characteristic	Group 1 (Limited tissue on excision)	Group 2 (Primary surgery vs neoadjuvant therapy)	Group 3 (Neoadjuvant chemoendocrine vs endocrine)	P value
Age (years)				0.38
Mean (SD)	52.5 (8.7)	58.9 (11.9)	58.5 (9.3)	
Histologic type				0.20
Ductal	3	29	19	
Lobular	2	6	10	
Mixed ductal and **lobular features**	1	1	6	
Clinical T stage				0.01
T1	6	14	6	
T2	0	19	22	
T3	0	1	5	
T4	0	1	1	
Clinical node status				0.08
Negative	6	29	22	
Positive	0	5	12	
Clinical prognostic stage				0.06
IA	6	11	6	
IB	0	21	20	
IIA	0	2	6	
IIIA/B	0	2	2	
IV	0	1	0	
Nottingham grade				0.83
1	1	6	7	
2	4	27	22	
3	1	3	6	
Oncotype RS (original criteria)				0.05
Low	3	15	23	
Intermediate	3	18	6	
High	0	4	6	
Oncotype RS (TRAILORx criteria)				
Low	1	6	7	
Intermediate	5	22	20	
High	0	9	8	

set. Most tumors were Nottingham grade 2 (57, 69%). All tumors were ER-positive. The tumors were predominantly progesterone receptor (PR) positive and HER2 negative by IHC and/or in situ hybridization (ISH). Most patients (67/82; 82%) were clinical prognostic stage I (AJCC, 8th ed) at presentation. The mean ODx RS was 20 (range 0-73). Applying the original NASBP B-14 study criteria, 52% of the cases had low RS and with TAILORx criteria, 57% had intermediate RS.

Indications for ODx Testing on CNB

Three main clinical indications were identified for performing ODx on CNB, and patients were divided into these 3 groups. Group 1 consisted of 6 patients in which the final excision specimen did not provide adequate tissue for ODx testing. All tumors in group 1 were T1 stage and node-negative (Table 1).

Table 2. Treatment Management and Follow up.

Characteristic	Group 1 (Limited tissue on excision)	Group 2 (Primary surgery vs neoadjuvant therapy)			Group 3 (Neoadjuvant chemoendocrine vs endocrine)			P value
Oncotype RS group on CNB		L	I	H	L	I	H	
Neoadjuvant therapy								0.33
Yes								
• Endocrine	1	1	11	1	16	3	2	
• Chemo-endocrine	0	0	0	0	5	3	4	
No (primary surgery only)	5	14	6	3	0	0	0	
Surgery type								0.80
Breast conserving surgery	4	11	7	1	5	5	3	
Total mastectomy	2	3	9	3	13	0	2	
Pathologic stage on resection								>0.05
pT1	6	10	4	2	6	1	3	
pT2	0	3	7	2	7	2	2	
pT3	0	0	3	0	5	2	0	
pT4	0	1	0	0	0	0	0	
Pathologic nodal status								
N0	6	8	7	2	6	2	4	
N1-2	0	6	7	2	12	3	1	
Adjuvant therapy								>0.05
Endocrine	5	11	8	0	13	1	4	
Chemotherapy	1	3	6	4	4	4	1	
Recurrence	0	0	0	1	1	1	0	0.38
Mean follow up (months)	36	33			28			

Group 2 consisted of 37 patients in which ODx testing was performed to adjudicate neoadjuvant therapy versus primary surgical resection. Group 2 consisted of low clinical prognostic stage tumors: mostly T1cN1 and T2 tumors and histological grade ≤2. Twelve patients with tumor RS of ≥18 (11 cases of intermediate RS and 1 high RS) received neoadjuvant therapy before undergoing surgery (Table 2). Three patients with high RS received primary surgery without neoadjuvant therapy due to the detection of genetic mutations such as *BRCA1/2*. The majority of patients with low RS (14/15) and 6/17 intermediate RS cases received primary surgery.

Group 3 comprised 35 patients in which neoadjuvant treatment was indicated, and ODx RS was used to select NAC versus NET. The NET was selected over NAC in 16/21 cases with low RS and 3/6 cases with intermediate RS (highest RS being 21). Despite low RS, 5 patients received NAC due to

node positivity with fine-needle aspiration. Four of 6 patients with high RS and 3 of 6 patients with intermediate RS (RS ≥ 23) received NAC. One patient with high RS did not receive NAC after a comprehensive evaluation of significant comorbidities (hepatic encephalopathy, cardiac pathology, and thrombocytopenia), and primary surgery was performed.

Follow Up Pathologic Response and Recurrence

Overall, 34/77 patients received NET, 12/77 received NAC, and 31/77 received primary surgery. The most common chemotherapy regimen was docetaxel+ cyclophosphamide (n = 6) followed by adriamycin+ cyclophosphamide (n = 3) and paclitaxel (n = 1). Of those patients who received neoadjuvant therapy, no patient in our study achieved pathologic complete response (pCR), defined as ypT0 or ypTis, along with N0, on final excision.

In group 2, the preferred surgery with RS ≥18 was a total mastectomy, whereas BCS was preferred in patients with RS <18 (Table 2). The BCS rate for patients who received NET was 64% and did not statistically differ from those who received upfront surgery (52%, P = 0.54). One patient with an RS of 34 developed a locoregional recurrence 24 months after the surgery despite the adjuvant chemotherapy. This patient was a 55-year-old patient with a *BRCA2* variant of uncertain significance and underwent primary surgery.

In group 3, NET and total mastectomy was the preferred therapeutic modality in RS <18. The BCS rates for patients who received NAC vs. NET were 55% and 43% (P = 0.75). Two patients had recurrences, including 1 patient who was a 55-year-old female with an invasive lobular carcinoma with a low RS of 11. Due to low RS, she received NET and underwent a unilateral mastectomy with a sentinel lymph node dissection. The final pathologic stage was ypT3N1a; she received adjuvant chemotherapy and radiation therapy, and she was lost to follow up. She presented again with widely metastatic disease to the brain, spine, lungs, lymph nodes, and eye and died of the disease. The second patient was a 52-year-old with an RS of 27 who received NAC with a minimal response on excision ypT1cN0. She underwent adjuvant chemo- and endocrine therapy with radiation. Unfortunately, she developed a locoregional recurrence and metastases to the lungs, bones, and mediastinal lymph nodes after 48 months.

Discussion

We confirm that CNB material is sufficient for ODx testing, which has been reported in previous studies.[7,11-15] Our study primarily focused on highlighting the current practical uses for ODx testing on CNB. The most common indication for CNB ODx testing was to determine neoadjuvant therapy versus primary surgical resection (47%). Primary surgery without neoadjuvant treatment was selected in patients with low RS (<18), and NET was preferred in patients with intermediate or high RS (>18). Almost half of the ODx testing (45%) on CNB was performed to assess potential NAC benefit, provided that the

neoadjuvant treatment was clinically chosen based on other factors such as tumor size and nodal status. The NET was selected in patients with low RS (<18). A RS ≥25 was the perceived cut-off by the treating physician to decide on NAC, although the sample size of this study is a limiting factor. A less common but highly useful indication to perform ODx on CNB was on small T1 tumors did not yield enough tumor for testing on excision. In excisions, the residual tumor is often mixed with the biopsy-related reactive granulation tissue, which may falsely elevate the RS.[16]

Our study observed 3 patients who underwent primary surgery without neoadjuvant treatment even with high ODx RS after the knowledge of *BRCA1/2* mutations. Despite low RS, 5 patients in our study received NAC due to node positivity. Significant comorbidities and patient age are also considerations since they may not be good chemotherapy candidates despite high RS. It is also prudent to reiterate the current recommendation to incorporate patient's age in neoadjuvant decision-making due to exploratory subgroup analysis results by TAILORx and NASBP B-20 studies.[6] The subgroup analysis for RS <25 showed that patients ≤50 years old (younger group) might benefit from NAC; patients >50 years old (older group) have little chemotherapy benefit. CNB ODx RS is used in conjunction with contributing factors, such as patient's age, presence of pathogenic mutations, nodal status, and patient comorbidities to determine neoadjuvant management.

As early as 2005, multiple small studies have focused on correlating ODx RS and various endpoints such as clinical and pathologic complete response rates and BCS rate.[11-15,17-20] The pCR rate, defined as the absence of invasive disease in breast on excision, was 12% by Gianni *et al* 2005[19] and 17% by Yardley *et al* 2015.[14] Pease *et al* 2019[11] involved the largest sample size of 989 patients compared to other studies and adopted more stringent criteria for pCR. The pCR was defined as no remaining invasive disease in the breast or axillary nodes corresponding to NCDB codes for pathologic stages of T0 or Tis with N0. Pease *et al* 2019[11] reported pCR of 4.3%. Chang *et al* 2008[13] used a clinical complete response defined by RECIST criteria and found the CR rate was 17%. Gianni *et al* 2005,[19] Yardley *et al* 2015,[14] Pease *et al* 2019,[11] and Chang *et al* 2008[13] have all observed that a high ODx RS correlated with an increased CR. In our study, we had not observed any cases of pCR even when less strict criteria of the absence of invasive disease in breast on excision was applied. This may be due to the fact that our study consisted of only 13% (n = 10) of grade 3 tumors versus 88% (n = 150) in Gianni *et al* 2005[19] study as we know from previous studies[20] and experience that high-grade tumors respond better to neoadjuvant therapy. Iwata *et al* 2019[20] and Bear *et al* 2017[12] showed a higher BCS rate in low RS with NET (note the low RS cut-off was <18 in Iwata *et al*, <11 in Bear *et al*). However, our study did not show a statistically significant difference between BCS rate with RS, although limited by a small sample size.

The main purpose of this study was to confirm the feasibility of ODx on CNB in the neoadjuvant setting as proposed by Pease *et al* 2019 and Bear *et al* 2017. Also, we identified the discrete indication groups currently adopted by clinicians in utilizing ODx RS on CNB to provide additional tumor biology information in guiding treatment decisions in the neoadjuvant setting. In the midst of the COVID-19 pandemic, many elective surgeries, including patients with early-stage ER+, HER2− breast cancer, are being deferred, prioritizing patients by treatment urgency to minimize COVID-19 exposure risk without compromising long term outcomes. The use of ODx on CNB in these patients is furthermore valuable in management to deliver effective treatment in a timely fashion as recommended by COVID-19 Pandemic Breast Cancer Consortium by the American College of Surgeons.[11-23]

Authors' Note

Declaration of Conflicting Interests

Funding

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