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Is There a Role for Oncotype Dx Testing in Invasive Lobular Carcinoma?

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Abstract

Oncotype Dx Breast Cancer Assay is a 21-gene assay used in estrogen receptor (ER)-positive breast cancer to predict benefit from chemotherapy (CT). Tumors are placed into one of three risk categories based on their recurrence score (RS). This paper explores the impact of tumor histopathologic features and Oncotype Dx RS on the treatment plan for invasive lobular carcinoma (ILC). Invasive lobular carcinoma cases submitted for Oncotype Dx testing were identified from a clinical data base. The histopathologic and immunohistochemical features and RS subcategory of each tumor, and treatment regimen and medical oncologic assessments of each patient were reviewed. A total of 135 cases of ILC had RS testing, which represented 15% of all ILC diagnosed at the institution over the time period. 80% of ILC was of the classical subtype and all tumors were ER positive and human epidermal growth factor receptor 2 (HER-2) negative by immunohistochemistry. Sixty three percent of cases were low risk (LR), 35.5% were intermediate risk (IR) and 1.5% were high risk (HR). Both HR cases were pleomorphic ILC. Sixty eight percent of classical ILC had a LR score, while 70% of pleomorphic ILC had an IR score. Patients in the IR category were significantly more likely to undergo CT than patients in the LR category (54% versus 18%; $p < 0.0001$). In the LR category, those undergoing CT were significantly younger and more likely to have positive lymph nodes ($p < 0.05$). Qualitative analysis of medical oncologic assessments showed that RS played a role in decision-making on CT in 74% of cases overall. At our institution, Oncotype Dx RS currently plays a role in the management of a proportion of ILC and impacts on treatment decisions.

Keywords

invasive lobular carcinoma; Oncotype Dx; recurrence score

The advent of breast screening has wrought many changes in the incidence, natural history and management of breast carcinoma. Today, low stage, node-negative tumors constitute 50% of new breast carcinoma diagnoses in the USA every year (1). Earlier detection of smaller, localized tumors has been associated with increased rates of breast conservation

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surgery, supplemented by other modalities including radiotherapy (RT), hormonal therapy (HT), and systemic chemotherapy (CT). Survival analyses at 5 and 10 years show that the majority of early stage breast carcinoma patients will not suffer distant metastases, and thus, these patients do not acquire any survival benefit from the addition of CT to their treatment, while being exposed to the inherent risks associated with this therapy (2). Thus, the challenge for clinicians has been to develop a method to accurately identify those early stage patients who may develop disease progression, and therefore would benefit from CT.

Oncotype Dx (Genomic Health, Redwood city, CA) is one of a number of molecular platforms developed in the last decade which stratifies early stage breast carcinoma patients into separate prognostic categories, to identify the patients most likely to develop disease recurrence. It is a 21-gene reverse transcriptase polymerase chain reaction test which measures gene expression in 16 genes associated with cell proliferation, invasion, and hormone receptor expression, and inserts these data into a weighted algorithm. A recurrence score (RS) is then derived which places the patient into one of three prognostic categories—low, intermediate and high risk (HR) (2,3). Several studies have demonstrated that there is a statistically significant association between RS in these low stage breast carcinoma patients and the risk of local-regional recurrence (4), distant recurrence (5,6), and death (5,7). Oncotype Dx is now included in the NCCN guidelines for breast carcinoma management in this patient cohort.

The validation studies of this multigene assay did not include an analysis of the histologic subtypes studied. Consequently, there is a dearth of data on whether the results of these studies can be applied equally across the full range of histologic subtypes of breast carcinoma in the assessment of an individual’s risk of disease progression. Invasive lobular carcinoma (ILC) is the most common of the “rare” breast carcinoma subtypes, constituting 5–15% of total breast carcinoma cases (8,9). Classical ILC is histologically characterized by prominent cell dyshesion and is composed of small, uniform cells which infiltrate stroma in small nests or single cells. A greater proportion of classical ILC are positive for estrogen receptor (ER) and progesterone receptor (PR) than invasive ductal carcinoma (IDC), and fewer cases are HER-2 amplified (9,10).

To date, there have been no retrospective reviews or prospective studies specifically focused on the role of Oncotype Dx in the assessment and management of patients with ILC. In light of this, we undertook a retrospective review of the role of Oncotype Dx in the assessment of prognosis and treatment planning in patients with ILC at our institution.

METHODS

Following IRB approval of the study, a search of the pathology data base for the period 2008–2011 was performed to identify in-house cases of ILC that had been submitted for Oncotype Dx testing. The pathology reports of each of the ILC cases were then reviewed and tumor characteristics such as size, histologic subtype (classical versus pleomorphic), hormone receptor and HER-2 receptor status, and lymph node status were recorded. All cases had been reported by a subspecialized breast pathologist. Treatment modalities used in each case were also reviewed.

The MSKCC breast carcinoma data base was analyzed to determine what proportion of all ILC cases were tested for Oncotype Dx over the study period, and to compare the patient and tumor characteristics of those tested and not tested.

The standard protocol for submitting tissue for Oncotype Dx involved submitting 10 unstained slides, each containing a 5 μm thick section of formalin-fixed paraffin-embedded tissue, to the testing facility. Oncotype Dx results were categorized based on the manufacturer's guidelines: RS less than 18 was considered low risk (LR), RS between 18 and 30 was considered intermediate risk (IR) and RS greater than 30 was considered HR.

A qualitative review of the electronic medical record pertaining to each patient's clinical oncologic assessments was undertaken to evaluate the role played by Oncotype Dx-derived RS in CT planning. RS was defined as playing a role in treatment planning when the medical record demonstrated that it was one of the factors that played a role in decision-making, and was defined as playing no role when the medical record clearly stated that the decision on CT was made independent of the RS. In both subgroups, a small proportion of cases had inadequate documentation of the decision-making process for assessment.

Statistical analysis included Fisher's exact test, chi-squared test and Student's *t*-tests.

RESULTS

Clinicopathologic Features

Oncotype Dx testing was performed on 1489 MSKCC breast carcinoma specimens during the study period, and of these, 135 (9%) were classified as ILC. Over the 4-year study period, 878 ILC cases were diagnosed at MSKCC, therefore 15% of all ILC underwent RS testing. The mean patient age at diagnosis for the study cohort was 58 years old (range 34–79) and the overall mean tumor size was 1.6 cm (range 0.3–4.3 cm). The morphologic ILC subtype was classical in 80%, pleomorphic in 10%, and mixed classical and pleomorphic in 10%. All tumors were reported to be ER positive and Her-2 negative by immunohistochemistry. One hundred and twenty six (93%) cases were reported to be positive for PR by immunohistochemistry. Mean tumor size, tumor morphology, hormone receptor status, and nodal status in each of the three risk categories are summarized in Table 1.

Survival analysis on this patient cohort demonstrated that median length of follow-up at the time of this review was 47 months. A total of 133/135 patients (98.5%) were alive with no evidence of disease. One patient was alive with disease, following a local recurrence at 47 months of follow-up, followed by a distant recurrence at 48 months. One other patient died within 24 months of her breast cancer diagnosis, but the cause of death is unknown, and this patient has other comorbidities that may have led to her death.

In comparison with the ILC cases who did not undergo Oncotype Dx testing, our patient cohort had a smaller mean tumor size (1.6 cm versus 1.94 cm, $p = 0.0001$), and were less likely to have involved lymph nodes ($p < 0.0001$) or to be HER-2 positive ($p = 0.006$). The latter finding is unsurprising as Oncotype Dx testing is not generally performed on HER-2

positive tumors. There was no difference between the two groups in terms of mean patient age and ER status.

The overall mean Oncotype Dx RS in ILC was 16 (range 5–33). 85 (63%) of ILC cases were LR, 48 (35.5%) were IR, and 2 (1.5%) were HR. Both of the HR cases were pleomorphic ILC without lymph node metastasis (Table 1). No patients with classical or mixed-type ILC were classified as HR. Seven of the nine patients (78%) with an ER-positive, PR-negative tumor had an IR score ($p = 0.003$). Due to the very limited patient numbers in the HR category ($n = 2$), comparative analysis between this category and the LR and IR groups was not performed.

Histologic Subtype and RS

In classical ILC cases, 68% (73/108) had a low RS and 32% (35/108) had an intermediate RS. In contrast, in pleomorphic ILC only 15% (2/13) of cases had a low RS, while 70% (9/13) had an intermediate RS and 15% (2/13) had a high RS. These results were statistically significant ($p = 0.002$). In mixed classical and pleomorphic ILC, 71% (10/14) had a low RS and 29% (4/14) had an intermediate RS. There were no statistically significant differences in mean tumor size or rate of lymph node positivity between the LR and IR subgroups ($p = 0.5$).

Treatment Modalities

Table 2 documents the proportion of patients with ILC who underwent adjuvant treatment modalities (HT, RT, and CT), and the type of surgery undertaken in each RS risk group. Patients in the IR group were significantly more likely to undergo CT than those in the LR group (54% versus 18%, $p < 0.0001$). Overall, 60% of patients underwent breast conservation surgery, while 40% had mastectomy. A total of 95% of all patients had HT, while 57% had RT and 32% had CT. Of the patients who underwent RT, 97% had undergone breast conservation surgery. HT was recommended to all patients, but treatment was declined in 5% of patients. No statistically significant differences were identified between the LR and IR groups in terms of the proportions of patients who had RT or HT.

Within the LR group, those who underwent CT were significantly younger (mean 49 versus 59 years, $p = 0.003$) and significantly more likely to have positive lymph nodes (33% versus 6%, $p = 0.007$) than those who did not receive CT (Table 3). There was no statistically significant difference in the mean tumor size or the mean RS of the two groups. In the IR group, those who underwent CT had significantly larger tumors (mean size 1.6 cm versus 1.2 cm, $p = 0.02$) and had a slightly higher mean RS (22 versus 20, $p = 0.03$) than those who did not have CT. No statistically significant differences were identified in patient age or lymph node status between the two groups (Table 3).

Qualitative Assessment

Finally, qualitative analysis of the medical records pertaining to this patient cohort's clinical oncologic assessments demonstrated that the RS was recorded as playing a role in the decision whether to recommend CT in 74% of cases and had no role in decision-making in 13% of cases (Table 4). Among the 70 patients with a low RS score who did not have CT,

RS is recorded as having played a role in the decision not to recommend CT in 82% of cases. In the subgroup of patients with an IR RS who had CT, RS played a role in the decision to recommend CT in 69% of cases (Table 4).

DISCUSSION

The management of breast carcinoma has undergone remarkable evolution in recent decades. Breast screening has led to changes in tumor incidence, tumor stage at presentation and the natural history of the disease (11). Therapeutic developments such as hormonal antagonists, anti-HER-2 therapy and multidrug chemotherapeutic regimens have all contributed to the increased survival of patients with breast carcinoma. Molecular pathology has fundamentally altered the concept of “breast carcinoma” by delineating molecular-based “intrinsic subtypes” of breast cancer. As we move toward the era of “personalized” medicine, with individualized treatment regimens based on the particular patient and pathologic characteristics of each case, it becomes increasingly important to accurately identify which patients will truly benefit from each treatment modality.

Several studies have demonstrated a strong correlation between Oncotype Dx RS and the risk of both local and distant recurrences, and risk of death from breast carcinoma. Mamounas et al. (4) demonstrated that the risk of local-regional recurrence at 10 years in patients given tamoxifen only in addition to surgery, was 4.3% for LR RS, 5.2% for intermediate and 15.9% for HR RS, versus figures of 1.6%, 2.7%, and 7.8%, respectively, in patients treated with surgery, tamoxifen, and CT. Habel et al. (7) showed that in a tamoxifen-treated population, RS category was significantly associated with death at 10 years. Paik et al. (5) demonstrated that in patients with early stage, node-negative disease and a low or intermediate RS, there was no additional reduction in the rate of distant recurrence when CT was added to Tamoxifen. In the HR group, however, the outcomes were significantly different. Thus, while further studies (such as the TAILORx trial) are ongoing to better characterize the optimal management of the IR group, current evidence suggests that the LR group does not appear to benefit from additional CT, while the HR group does. Prior studies have suggested that the LR category constitutes approximately 50% of breast carcinoma cases tested (3,12). It is clear, therefore, that Oncotype Dx can have a clinically useful role in stratifying patients into accurate prognostic and predictive categories, which could be used to guide treatment decisions and prevent the over-treatment of patients in this LR category.

This review is the largest series to date on the role of Oncotype Dx RS in ILC. At our institution, 15% of all ILC treated over the study period had RS testing. Comparison between the study cohort and the total ILC population demonstrate that cases sent for Oncotype Dx testing had smaller, HER-2 negative tumors, with negative lymph nodes in the vast majority of cases. Overall, 63% of study cases were in the LR category, 35% were in the IR category, and 2% were HR. These findings are consistent with a smaller prior study (13). Both of the HR cases were pleomorphic ILC. Interestingly, only two of thirteen pleomorphic ILC were HR (15%), with the vast majority being IR. Our results suggest that a greater proportion of patients with low stage, node-negative ILC may be able to avoid systemic CT than comparable patients with IDC of a similar tumor stage (where only approximately 50% of cases were in the LR category) (3,12). In addition, our study also

shows that ILC morphology (classical or pleomorphic) cannot be used as a surrogate for RS, as both histologic subtypes demonstrate RS that span more than one risk category.

This study demonstrates that Oncotype Dx testing currently plays a significant role in treatment planning for patients with ILC at our institution. 82% of patients in the LR group did not receive adjuvant CT, compared to 46% in the IR group. Qualitative analysis of medical oncology assessments in this patient cohort demonstrated that RS played a role in the decision whether to recommend CT in 73% of all cases. These results are consistent with prior studies that assessed the impact of Oncotype Dx testing on treatment planning decisions, which demonstrated an effect on treatment recommendations in 24–51% of cases, with the majority of decisions in each study being the avoidance of CT (14–18).

It is important to note that the histologic subtype of the tumors tested in the early validation studies of Oncotype Dx was not reported. While it might be assumed that the majority of cases tested were IDC not otherwise specified (IDC NOS), there are no data available on whether the results can be generalized to other histologic subtypes, including ILC. ILC has a number of distinct features which make the application of an IDC-derived prognostic and predictive algorithm to ILC problematic. First, ILC displays a different pattern of invasion, metastasis, and recurrence to IDC NOS, with worse outcomes reported after 10 years (19,20). Furthermore, ILC is associated with higher rates of hormone receptor expression (ER and PR) and lower rates of Her-2 amplification than IDC NOS (9,10,19,20). Classical ILC is also associated with lower proliferation rates than IDC NOS, and the vast majority of ILC cases are Nottingham Grade System grade 2 (9,10,21). Finally, studies in the neo-adjuvant setting have demonstrated much lower rates of complete pathologic response in ILC compared to IDC (10,22). All of these features have the potential to impact on the utility of the Oncotype Dx RS in ILC, and further research on the use of Oncotype Dx in the setting of ILC are required to investigate this issue further.

Ultimately, the role of Oncotype Dx RS in the management of patients with ILC will only be definitively established by a study which involves patient outcome analysis in terms of RS subgroup at a minimum of 10 years of follow-up. In light of the fact that our patient cohort has a median follow-up period of only 47 months, it would be inappropriate to use this data to attempt to draw definitive conclusions on the indication for Oncotype Dx testing in ILC. Accordingly, the purpose of this study has instead been to describe current practice at our tertiary institution in the care of patients with ILC, to attempt to measure the impact of Oncotype Dx on patient management and to report on the relationship observed between ILC histologic subtypes and Oncotype Dx RS.

In conclusion, this retrospective study provides the first report on the clinical use of Oncotype Dx in ILC. We have demonstrated that the majority of classical ILC cases have a LR RS, while pleomorphic ILC cases stratify predominantly into the IR group, but neither ILC histologic subtype is confined to a single risk subgroup. Our data suggests that in current clinical practice at our institution, the Oncotype DxRS does impact on treatment decisions in patients with early stage ILC, with significantly less patients in the LR group undergoing CT than in the IR group. Further prospective analysis of longer term patient outcomes will be necessary to validate this approach in ILC.

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Table 1

Clinicopathologic Features of the Patient Population

	Overall (*n* = 135)	**LR group (*n* = 85)**	**IR group (*n* = 48)**	**HR group (*n* = 2)**
Mean patient age (range)	58 (34–79 years)	57 (34–79 years)	59 (45–77 years)	66 (61–71 years)
Mean tumor size (range)	1.6 cm (0.3–4.3 cm)	1.7 cm (0.5–4.3 cm)	1.4 cm (0.3–3.6 cm)	1.8 cm (1.2–2.4 cm)
Morphology				
Classical	108 (80%)	73 (86%)	35 (73%)	0/2 (0%)
Pleomorphic	13 (10%)	2 (2%)	9 (19%)	2/2 (100%)
Mixed	14 (10%)	10 (12%)	4 (8%)	0/2 (0%)
Hormone Receptor status				
ER positive	135 (100%)	85 (100%)	48 (100%)	2/2 (100%)
PR positive	126 (93%)	84 (99%)	41 (85%)	1/2 (50%)
HER-2 positive	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Positive lymph nodes	12 (9%)	9 (11%)	3 (6%)	0/2 (0%)

Table 2

Treatment Modalities

	Overall (*n* = 135)	LR group (*n* = 85)	IR group (*n* = 48)	HR group (*n* = 2)
Surgery				
Breast conservation	81 (60%)	42 (49%)	37 (77%)	2 (100%)
Mastectomy	54 (40%)	43 (51%)	11 (23%)	0 (0%)
Adjuvant treatment				
Hormonal therapy	128 (95%)	82 (96%)	44 (92%)	2 (100%)
Radiotherapy	77 (57%)	43 (51%)	32 (67%)	2 (100%)
Chemotherapy	43 (32%)	15 (18%)	26 (54%)	2 (100%)

Table 3

Relationship between RS Group, Clinicopathologic Features and Use of Chemotherapy

	Low risk Oncotype DX score		Intermediate risk Oncotype DX score	
	CR (*n* = 15)	**NO CR (*n* = 70)**	**CR (*n* = 26)**	**NO CR (=22)**
Patient age	49 (34–66) years	59 (43–79) years	58 (47–77) years	61 (45–77) years
Tumor size (range)	1.9 (0.9–3.0) cm	1.7 (0.5–4.3) cm	1.6 (0.7–2.6) cm	1.2 (0.3–2.3) cm
Positive lymph node	5/15 (33%)	4/70 (6%)	1/26 (4%)	2/22 (9%)
Mean Oncotype score	14	12	22	20

Table 4

Qualitative Analysis of Role of Oncotype Dx in Treatment Planning

	Low risk Oncotype DX score		Intermediate risk Oncotype DX score	
	CR (*n* = 15)	**NO CR (*n* = 70)**	**CR (*n* = 26)**	**NO CR (*n* = 22)**
Some role	7 (47%)	57 (81%)	18 (69%)	16 (73%)
No role	6 (40%)	6 (9%)	4 (14.5%)	2 (9%)
Role unclear	2 (13%)	7 (10%)	4 (14.5%)	4 (18%)