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Evaluation of Prognosis in Hormone Receptor—Positive/*HER2*-Negative and Lymph Node—Negative Breast Cancer With Low Oncotype DX Recurrence Score

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Abstract

Patients in both the 1–10 group and the 11–18 group had good prognoses. Those who experienced recurrence were more likely to be premenopausal and to have failed to comply with the recommended endocrine therapy regimen. Endocrine therapy remains important in these patients.

Introduction: Hormone receptor–positive/human epidermal growth factor receptor 2 (*HER2*)-negative breast cancers without lymph node metastasis have good prognosis. We compared the prognosis of hormone receptor–positive, *HER2*-negative, lymph node–negative cancers with Oncotype DX score ranges of 1 to 10 (1–10 group) and 11 to < 18 (11–18 group).

Patients and Methods: A total of 107 cases in the 1–10 group and 225 cases in the 11–18 group were reviewed. All patients received surgery. The use of chemotherapy, radiotherapy, and endocrine therapy, and overall survival (OS), disease-free survival (DFS), and distant metastasis were compared between groups.

Results: There were no statistical differences in the use of chemotherapy (5.05% vs. 6.05%, $P = .724$) or radiotherapy (52.53% vs. 59.07%, $P = .276$) between the 1–10 group and the 11–18 group, respectively. The median OS and DFS were 47 and 45 months, respectively, in the 1 −10 group, and 49 and 48 months in the 11–18 group. No significant difference was seen in OS ($P = .995$), DFS ($P = .148$), or rates of metastasis ($P = .998$). The 11–18 group had more death events and distant metastasis (death, 5 events; recurrence, 2 events; metastasis, 2 events) than the 1–10 group (death, 0 events; recurrence, 4 events; metastasis, 0 events). The majority of recurrences seen in both groups were in young patients who failed to comply with their endocrine therapy regimen.

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Disclosure

The authors have stated that they have no conflict of interest.

Conclusion: Patients in both the 1–10 group and the 11–18 group had good prognoses. Those who experienced recurrence were more likely to be premenopausal and to have failed to comply with the recommended endocrine therapy regimen. Endocrine therapy remains important in these patients.

Keywords

Disease-free survival; ER positive; Metastasis; Overall survival

Introduction

Breast cancer is the most common cancer in women worldwide and in the United States; approximately 1 (12%) in 8 US women will develop invasive breast cancer over the course of a lifetime. In 2017, an estimated 252,710 new cases of invasive breast cancer are expected to be diagnosed in women in the United States.[1] Breast cancer mortality rates, however, have been decreasing since the 1970s, partially as a result of improved breast cancer screening and improvements in systemic therapy.[2–4] Breast cancer is no longer regarded as a single disease.[5] Clinically, breast cancers are subclassified by estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (*HER2*) gene amplification. Different subtypes have different tumor biology that affects prognosis and response to therapies.[6–12] Hormone receptor (HR)-positive (ER^+ and/or PR^+) and *HER2*-negative breast cancers generally have a good prognosis.[13–20]

Approximately 70% to 80% of breast cancers are ER and/or PR positive, and almost all of these patients will receive endocrine therapy for at least 5 years as part of the standard of care. Not all of these patients need chemotherapy, however, particularly when diagnosed at an early disease stage, and overtreatment with chemotherapy is important to avoid because chemotherapy can have significant short-term and long-term toxicities. For patients with HR-positive/*HER2*-negative, lymph node (LN)-negative cancers, a 21-gene expression assay (Oncotype DX; ODX) can provide additional prognostic information and can be predictive of benefit from adjuvant chemotherapy independent of clinicopathologic features such as tumor grade, Ki-67 index, and lymphovascular invasion.[21] Before the development and validation of this assay, treatment guidelines in the United States and Europe recommended consideration of chemotherapy for most patients.[22,23] The analysis of ODX scores in tamoxifen-treated versus tamoxifen plus chemotherapy–treated patients in the NSABP B20 trial showed that patients with an ODX score of 18 or less derived minimal, if any, benefit from chemotherapy. Since the publication of this trial and other subsequent studies, guidelines and national practice patterns have started to change.[24]

Several prospective studies were conducted after the initial validation of the ODX assay. In 2015, a study of 1626 women with node-negative, < 5 cm ER^+ and/or PR^+ breast cancers with a recurrence score of 0 to 10 who were assigned to receive endocrine therapy with no chemotherapy showed rate of invasive disease-free survival of 93.8%, rate of freedom from distant recurrence of 99.3%, and rate of overall survival (OS) of98.0%.[25]This gave further support to the notion that for the lowest-risk patients with ER^+ breast cancer, chemotherapy would likely do more harm than good.

We were interested in learning more about how the other half of the low-risk ODX group, those with scores of 11 to 18, performed compared to those with scores of 0 to 10. We conducted a retrospective single-institution study evaluating patients with HR^+/*HER2*–/LN– breast cancer who had ODX scores of 0 to 18. We compared rates of local and distant disease-free survival and OS between patients with scores 0 to 10 and those with scores 11 to 18.

Patients and Methods

Data from a total of 332 patients with ER^+/*HER2*–/LN– breast cancer diagnosed from 2006 to 2014 were retrieved from our institution. Among the 332 patients, 107 had an ODX score of 1 to 10 (1–10 group), and 225 had an ODX score between 11 to < 18 (11–18 group). The median follow-up of the 1–10 group was 47 months and that of the 11–18 group was 49 months. All patients received surgery. Age at diagnosis, race, ER and PR expression, *HER2* immunohistochemistry evaluation (negative vs. equivocal), Ki-67 score, Nottingham tumor grade, lymphovascular invasion, tumor size and stage, receipt of chemotherapy, receipt of radiotherapy, OS, disease-free survival (DFS), and distant metastasis (metastasis other than axillary LN metastasis) were evaluated and compared between these 2 groups. Levels of ER, PR, and Ki-67 expression were evaluated using positive percentage and H score. The H score was calculated as positive percentage (0–100%) times staining intensity (intensity 1–3). This study was approved by the Emory University institutional review board.

Statistical Analysis

Statistical analysis was conducted by SAS 9.4 (SAS Institute, Cary, NC). For numeric covariates, means and SDs were calculated and are presented. Frequency and their percentages are shown for categoric variables. One-way ANOVA and Kruskal-Wallis tests were performed for numerical covariates and for univariate analysis if appropriate. Chi-square test or Fisher's exact test was used for categorical covariates when appropriate. The univariate association of each covariate on OS, DFS, or distant metastasis was assessed by the Cox proportional hazards model with Firth's penalization. A multivariable Cox model was fitted by a backward variable selection method with an alpha = .20 removal criterion. The significance level was set at .05.

Results

The 2 group of patients had similar age at diagnosis, race distribution, tumor size and grade, Ki-67 score, ER expression, presence of lymphovascular invasion, and tumor stage distribution (all $P > .05$; Table 1). All patients received surgery. Similar proportions of patients in each group received chemotherapy (5.05% in the 1–10 group, 6.05% in the 11–18 group; $P = .724$) and radiotherapy (52.53% in the 1–10 group, 59.07% in the 11–18 group; $P = .276$). The only significant difference between these 2 groups of patients was that the 11–18 group had lower PR H scores and higher numbers of equivocal *HER2* cases by immunohistochemistry (both $P < .05$; Table 1). All of the cases for which *HER2* was equivocal by immunohistochemistry had negative fluorescence in-situ hybridization results.

Patients in the 1–10 group had similar DFS to patients in the 11–18 group. The median DFS was 45 months in the 1–10 group and 48 months in the 11–18 group. In univariate analysis, no significant difference was seen in DFS between patients in the 1–10 group and the 11–18 group (hazard ratio = 1.82; 95% confidence interval, 0.44–7.50; $P = .406$; Table 2). Nottingham histologic grade 3 and receipt of chemotherapy were significantly associated with worse DFS in univariate analysis (all $P < .05$; Table 2). In multivariate analysis, only the use of adjuvant chemotherapy (hazard ratio = 6.85; 95% confidence interval, 1.55–30.29; $P = .011$) was significantly associated with worse DFS (Table 3) after adjusting for other covariates.

There were 4 recurrences (3.7%) in the 1–10 group and 4 (1.8%) in the 11–18 group. Five of these 8 total local recurrences were in patients who either declined the adjuvant endocrine therapy that was recommended, or who only briefly received endocrine therapy. Six of the 8 local recurrences were in patients under the age of 50 at diagnosis (4 of 8 were under the age of 40), representing a younger demographic than the overall population studied (mean age at diagnosis in the overall cohort was 57–58 years).

Patients in the 11–18 group had more distant metastases and death events. There were 2 distant metastases in the 11–18 group of patients and 0 in the 1–10 group. There were 5 deaths in the 11–18 group and 0 in the 1–10 group. Two of the 5 deceased patients died of complications of distant metastasis. The other 3 deaths were not related to breast cancer. Because of the small number of events, significant univariate or multivariate analysis could not be performed (Table 4).

Discussion

In this study, patients with an ODX score of 1 to 18 had very good prognosis. There was a trend toward more distant metastatic events and worse OS in patients with higher ODX scores. However, the small numbers of recurrences seen in this cohort makes it hard to draw definitive conclusions about differential risks between the 2 groups.

One interesting trend was that of the 8 patients who experienced recurrence (local or distant), 5 (62.5%) had either declined endocrine therapy altogether or did not complete the recommended 5 years of treatment. In addition, 75% of the recurrences were in women under the age of 50 at diagnosis, and 50% were under the age of 40. This suggests that even though an ODX score may be low enough to withhold chemotherapy, compliance with standard endocrine therapy is important for these patients with low-grade, HR^+ cancers. This may be particularly true in younger patients—an important finding to highlight, given that younger patients are generally less compliant with tamoxifen use.[26,27] The SOFT and TEXT trials found that for patients younger than 35 at the time of diagnosis with ER^+ breast cancer, more intensive endocrine therapy with ovarian suppression plus either tamoxifen or an aromatase inhibitor led to significantly higher rates of breast cancer DFS at 5 years than tamoxifen alone.[28] It would stand to reason that omitting endocrine therapy for this population of patients would put them at the highest risk of recurrence.

Interestingly, the administration of chemotherapy was also associated with poorer prognosis in this study. Those who received chemotherapy were likely those with more concerning features at the time of diagnosis—larger tumor size, higher grade disease, or lymphovascular invasion—which almost certainly confounds these results. It is also possible that HR^+ tumors that have clinically high risk features but a low ODX score may not benefit from the addition of chemotherapy.

Some important limitations of our study include our small numbers (107 patients in the 1–10 group and 225 in the 11–18 group) and the fact that all cases reviewed were from a single institution. Our conclusions will need to be confirmed in additional studies that include larger numbers of women. However, it is encouraging that the low recurrence rates seen in our cohort are similar to those seen in larger studies, such the recently published prospective TAILORx data for Oncotype scores < 11,[25] and in the retrospective—prospective evaluation of patients receiving tamoxifen in NSABP 14, where patients with recurrence scores of < 18 had a 6.8% risk of recurrence at 10 years.[29] Of interest, the patient population in our study was 30% African American and 67% white, and race did not significantly affect prognosis. For comparison, the NSABP 14 cohort that was used to validate the Oncotype assay was 5% African American and 91% white.[29] Small studies like ours that include larger numbers of African American patients may play an important role in confirming that genomic tests can be predictive of outcomes without regard to race.

With the widespread use of ODX and other assays such as MammaPrint to determine genomic risk before administering systemic therapy for breast cancer, we may be moving into an era where the importance of endocrine therapy in strongly HR^+ breast cancers becomes more recognized. Just as there are different intensities of chemotherapy regimens that we use for patients with different risk profiles (anthracycline-based vs. non—anthracycline-based therapies), there may be different levels of intensity of endocrine therapy that are most appropriate. Many physician are already using ovarian suppression plus tamoxifen or an aromatase inhibitor in our young ER^+ cancer patients based on the SOFT and TEXT data.[28] An analysis of recurrence risk in these data incorporated age, nodal status, tumor size and grade, and ER, PR, and Ki-67 levels. For the highest-risk patients, a 10% to 15% improvement in the 5-year breast cancer–free interval was seen in exemestane plus ovarian suppression versus tamoxifen alone.[30] This improvement was seen in high-risk patients who received chemotherapy as well as in high-risk patients who did not receive chemotherapy.

There may be a group of patients with HR^+ breast cancers that actually benefit more from enhanced endocrine therapy than from chemotherapy. Other ongoing studies, such as PALLAS (NCT02513394), which is evaluating the addition of palbociclib to standard endocrine therapy in patients with stage II and III ER^+ breast cancers, and S1207 (NCT01674140), which is examining the use of everolimus in addition to standard endocrine therapy in this same population, will undoubtedly provide additional information on this topic once results become available.

In conclusion, patients with early-stage *HR^+/HER2–* breast cancer at our institution with ODX scores 1 to 18 had an excellent prognosis. Local and distant recurrences were closely

associated with failure to comply with endocrine therapy, highlighting the importance of endocrine therapy in this population. Recurrences were also seen mostly in younger patients, indicating the importance of monitoring compliance in these patients, who may be more likely than their older counterparts to stop or refuse therapy. Although patients in the 11–18 group had a similar prognosis statistically to patients in the 1–10 group, there were 5 death events in this group and several cases of distant metastatic disease. Further analysis in a larger patient population is needed to better understand the differences between these 2 groups of patients and to determine how these differences might affect treatment recommendations.

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Clinical Practice Points

- Patients with low Oncotype DX score have good prognosis.
- Patients with recurrence are likely to be premenopausal and not to comply with endocrine therapy.
- Endocrine therapy is important in these patients.

Table 1

Association of Clinical Parameters With ODX Score by Univariate Analysis

Covariate	Statistics	Level	ODX Score		P^a
			1 to 10 (N = 107)	11 to < 18 (N = 225)	
Race	N (%)	African American	38 (38.78)	55 (25.7)	.064
	N (%)	White	58 (59.18)	152 (71.03)	
	N (%)	Other	2 (2.04)	7 (3.27)	
ER (%)	N (%)	Weakly positive (1–10)	1 (0.93)	0 (0)	.322
	N (%)	Strongly positive (>10)	106 (99.07)	225 (100)	
PR (%)	N (%)	Negative	1 (0.93)	15 (6.67)	.056
	N (%)	Weakly positive (1–10)	5 (4.67)	12 (5.33)	
	N (%)	Strongly positive (>10)	101 (94.39)	198 (88)	
Ki-67 (%)	N (%)	Weakly positive (<10)	36 (37.11)	66 (35.48)	.235
	N (%)	Intermediate positive (10–20)	34 (35.05)	51 (27.42)	
	N (%)	Strongly positive (>20)	27 (27.84)	69 (37.1)	
Stage	N (%)	IA	84 (79.25)	175 (78.13)	.690
	N (%)	IIA	21 (19.81)	43 (19.2)	
	N (%)	IIB	1 (0.94)	6 (2.68)	
HER2 IHC	N (%)	Negative	96 (89.72)	182 (80.89)	.042 *
	N (%)	Equivocal	11 (10.28)	43 (19.11)	
Nottingham tumor grade	N (%)	I	54 (50.94)	99 (44)	.240
	N (%)	II	50 (47.17)	114 (50.67)	
	N (%)	III	2 (1.89)	12 (5.33)	
LVI	N (%)	Absent	97 (91.51)	204 (90.67)	.803
	N (%)	Present	9 (8.49)	21 (9.33)	
Radiotherapy	N (%)	No	47 (47.47)	88 (40.93)	.276
	N (%)	Yes	52 (52.53)	127 (59.07)	
Chemotherapy	N (%)	No	94 (94.95)	202 (93.95)	.724
	N (%)	Yes	5 (5.05)	13 (6.05)	
Age at diagnosis (years)	N		107	225	.145
	Mean		58.96	57.06	

Covariate	Statistics	Level	ODX Score		P^a
			1 to 10 (N = 107)	11 to < 18 (N = 225)	
	SD		10.37	11.42	
Tumor size (cm)	N		106	224	.093
	Mean		1.48	1.71	
	SD		0.97	1.25	
Ki-67 H score	N		97	182	.217
	Mean		54.96	64.08	
	SD		53.27	61.3	
ER H score	N		107	225	.983
	Mean		265	264.86	
	SD		58.54	55.25	
PR H score	N		107	225	.005 *
	Mean		225.23	193.52	
	SD		87.94	102.54	

Abbreviations: ER = estrogen receptor; *HER2* = human epidermal growth factor receptor 2; IHC = immunohistochemistry; LVI = lymphovascular invasion; ODX = Oncotype DX; PR = progesterone receptor.

[a]Parametric *P* was calculated by ANOVA for numerical covariates and chi-square test for categorical covariates; nonparametric *P* was calculated by Kruskal-Wallis test for numerical covariates and Fisher's exact test for categorical covariates.

*Statistically significant.

Table 2

Association of Clinical Parameters With DFS by Univariate Analysis

			DFS (Months)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**Hazard Ratio *P***	**Log-Rank *P***
Oncotype DX score	1 to 10	107	1.82 (0.44–7.50)	.406	.403
	11 to < 18	225	—	—	
Chemotherapy	Yes	18	8.77 (2.06–37.30)	.003*	<.001*
	No	296	—	—	
Radiotherapy	Yes	179	1.49 (0.32–7.07)	.614	.503
	No	135	—	—	
Race	African American	93	0.51 (0.07–3.62)	.502	.588
	Other	9	2.80 (0.11–74.09)	.538	
	White	210	—	—	
ER (%)	Weakly positive (1–10)	1	20.59 (0.85–500.13)	.063	.882
	Strongly positive (>10)	331	—	—	
PR (%)	No intensity	16	3.61 (0.52–25.12)	.194	.474
	Weakly positive (1–10)	17	0.84 (0.04–19.67)	.912	
	Strongly positive (>10)	299	—	—	
Ki-67 (%)	Weakly positive (<10)	102	1.31 (0.22–7.70)	.768	.805
	Intermediate positive (10–20)	85	1.69 (0.29–9.96)	.560	
	Strongly positive (>20)	96	—	—	
Stage	IIB	7	3.88 (0.16–95.33)	.406	.301
	IIA	64	3.01 (0.69–13.08)	.142	
	IA	259	—	—	
HER2 IHC	Equivocal positive	54	1.79 (0.38–8.52)	.464	.588
	Negative	278	—	—	
Nottingham tumor grade	III	14	5.38 (0.88–32.74)	.068	.038*
	II	164	0.68 (0.13–3.48)	.645	
	I	153	—	—	
LVI	Present	30	2.20 (0.33–14.72)	.416	.665

Covariate	Level	N	DFS (Months)		
			Hazard Ratio (95% CI)	Hazard Ratio *P*	Log-Rank *P*
	Absent	301	—	—	
Age at diagnosis (years)		332	0.94 (0.88–1.01)	.070	—
Tumor size (cm)		330	1.34 (0.92–1.96)	.126	—
Product Ki-67		279	1.00 (0.98–1.01)	.690	—
Product ER		332	1.00 (0.99–1.01)	.772	—
Product PR		332	1.00 (0.99–1.01)	.995	—

Firth's penalized maximum-likelihood estimation was used.

Abbreviations: CI = confidence interval; DFS = disease-free survival; ER = estrogen receptor; *HER2* = human epidermal growth factor receptor 2; IHC = immunohistochemistry; LVI = lymphovascular invasion; PR = progesterone receptor.

*Statistically significant.

Table 3

Association of Clinical Parameters With DFS by Multivariable Analysis

		DFS (Months)		
Covariate	**Level**	**Hazard Ratio**	**Hazard Ratio *P***	**Type 3 *P***
Oncotype DX score	1 to 10	3.07 (0.65–14.52)	.156	.156
	11 to < 18	—	—	
Chemotherapy	Yes	6.85 (1.55–30.29)	.011*	.011*
	No	—	—	
Radiotherapy	Yes	1.86 (0.37–9.38)	.451	.451
	No	—	—	
Age at diagnosis (years)		0.95 (0.89–1.02)	.137	.137

Numbder of observations in original data set, 332; number of observations used, 314. Backward selection with alpha level of removal of .20 was used. The following variable was removed from the model: Nottingham tumor grade.

Abbredviation: DFS = disease-free survival.

*Statistically significant.

Table 4

Frequency of Events by Oncotype DX Score

Event	ODX Score	Total Number	No. of Events
Death	1 to 10	107	0
	11 to < 18	220	5
Recurrence	1 to 10	103	4
	11 to < 18	221	4
Local recurrence	1 to 10	103	4
	11 to < 18	223	2
Distant metastasis	1 to 10	107	0
	11 to < 18	223	2