Impact of 21-Gene Expression Assay on Staging Estrogen Receptor–Positive HER2-Negative Breast Cancer

Andrea Breaux,[1] Bradley Turner,[3] Xiaoyong Wu,[4] Shesh N. Rai,[4,5] Elizabeth C. Riley,[2] Mounika Mandadi,[2] Mary Ann Sanders[1]

Abstract

This retrospective study investigated the impact of Oncotype DX (ODX) on the newly updated breast cancer staging system. Of the 816 cases reviewed, ODX rarely affected stage, thus supporting the American Joint Committee on Cancer 8th edition expert panel's statement that ODX is not required for staging.

Purpose: The 8th edition of the American Joint Committee on Cancer (AJCC) breast cancer staging system requires histologic grade (GR), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and stage (assessed by the tumor, node, metastasis classification system). For T1-2 N0, ER^+/HER2− tumors, if the 21-gene expression assay is ordered and Oncotype DX (ODX) recurrence score (RS) is 0 to 10, the stage is IA. The purpose of this study was to determine the impact of the ODXRS on staging ER^+/HER2− tumors. **Materials and Methods:** This is a retrospective review of ER^+/HER2− invasive breast cancer (BC) with ODXRS results from 2 institutions (n = 816) between 2006 and 2018. Stage based on the AJCC 7th and 8th editions, and stage using the 8th edition with and without ODXRS were compared. Significant associations among pathologic parameters and ODX risk groups were determined. Clinical histories were reviewed. **Results:** Nearly half of the patients (43%) had a change in BC stage using the new staging system. Only 4 patients changed stage as a direct result of ODXRS. Influence of ODXRS on staging is limited to T2N0 tumors that are either GR 3 and strongly ER^+ and PR^+ or GR 1-2 and ER^+/PR−. Sixty-one percent of cases of recurrence (11/18) were downstaged using the new staging system. **Conclusion:** ODXRS has little influence on staging, thus supporting the view of the AJCC 8th edition expert panel that ODX is not required for staging. Downstaging of more than half of cases of recurrence suggests that continued refinement of the staging system, as proposed by the expert panel, could be beneficial in this subgroup of patients.

Clinical Breast Cancer, Vol. 19, No. 1, e261-9
Keywords: AJCC, Oncotype DX, Prognostic stage, Recurrence score, Staging guidelines

Presented in part as a poster at the annual USCAP conference in Vancouver, BC, Canada, March 20, 2018.

[1]Department of Pathology and Laboratory Medicine
[2]Department of Medicine, University of Louisville School of Medicine, University of Louisville Hospital, Louisville, KY
[3]Department of Pathology, University of Rochester Medical Center, Rochester, NY
[4]Biostatistics Shared Facility, James Graham Brown Cancer Center, University of Louisville, Kosair Charities Clinical and Translational Research Building, Louisville, KY
[5]Department of Bioinformatics and Biostatistics, University of Louisville School of Medicine, Louisville, KY

Submitted: Aug 10, 2018; Revised: Oct 22, 2018; Accepted: Oct 22, 2018; Epub: Oct 29, 2018

Address for correspondence: Mary Ann Sanders, MD, PhD, Department of Pathology and Laboratory Medicine, University of Louisville Hospital, 530 S Jackson St, Louisville, KY 40202
E-mail contact: maryann.sanders@louisville.edu

Introduction

The 8th edition of the American Joint Committee on Cancer (AJCC) breast cancer staging system, published in October 2016 and updated in November 2017, established a new staging system that combines histologic grade (GR) and biological markers with traditional anatomic stage (tumor, node, metastasis classification system, TNM), resulting in better discrimination among stage group assignment than TNM alone.[1] Anatomic stage is now used only in areas of the world where biologic markers are not available.

The prognostic stage was devised using survival data from the National Cancer Data Base for women diagnosed with invasive mammary carcinoma (IMC) from 2010 to 2012.[1,2] Using different combinations of the AJCC 7th edition TNM, GR, estrogen receptor (ER), progesterone receptor (PR), and human epidermal

1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2018.10.005

growth factor receptor 2 (HER2) resulted in 120 categories of patients. Survival was determined for each category, and a prognostic stage group (PSG) was assigned. Triple negative and GR3 IMC showed decreased survival, while ER^+/PR^+ IMC, regardless of HER2 status, showed better survival compared to tumors in the same 7th edition stage group. These results were consistent with published data by Mittendorf et al[3] utilizing Bioscore, a proposed staging system combining TNM, GR, ER, and HER2 that was subsequently validated using Surveillance, Epidemiology, and End Results data and the California Cancer Registry.[4] The new staging system consists of a clinical prognostic stage and a pathologic prognostic stage (PPS), with the latter used for patients who receive surgical resection as the initial treatment and the former for all other patients. The expert panel notes that the new staging system is only relevant in the context of appropriate therapy.[1]

In addition to GR and receptor status, the PPS table includes an Oncotype DX (ODX) recurrence score (RS) of < 11. ODX is a 21-gene reverse transcriptase PCR assay that predicts chemotherapy benefit in patients with ER^+/HER2−, lymph node (LN)-negative IMC. Although ODX is available for 1 to 3 LN-positive IMC, the American Society of Clinical Oncology (ASCO) recommendations for testing are restricted to IMC node-negative, isolated tumor cell, or micrometastatic nodal disease.[5,6] In the TAILORx trial, a subgroup of patients with T1-2 N0, hormone receptor positive, and HER2− IMC who had an ODXRS < 11 (arm A of the trial) were treated systemically with adjuvant endocrine therapy alone and were found to have a 5-year distant recurrence-free survival of 99.3%.[7] On the basis of these findings (recognized as AJCC level I evidence), breast cancer (BC) can be staged as pathologic PSG (pPSG) IA[1] if the patient meets the eligibility criteria for arm A of the TAILORx study.

ODX is one of many multigene panels. However, as of the November 2017 version of the AJCC 8th edition, ODX is the only multigene panel included to assign pPSG, as stated in note 3 of the pPSG table.[1] Although the 8th edition's expert panel emphasizes that use of ODX is not required for staging and that they do not endorse its use over other panels for treatment purposes,[1] it remains to be determined if the PPS will influence any changes in practice when ordering these tests.

The National Comprehensive Cancer Network guidelines recommend ODX for hormone receptor positive HER2− IMC, > pT1a and pN0, pN0(i+) or pN1mi.[8] However, this assay is not necessarily ordered on all IMC that meet the criteria. Many studies have demonstrated that routine pathologic parameters can predict ODXRS without the high cost or delays in treatment while awaiting ODX results. Most notable is the IHC4 score, which is a prognostic algorithm based on immunohistochemistry (IHC) results of ER, PR, HER2, and Ki-67, and which has been shown to have similar prognostic value as the ODXRS.[9] Because the PPS incorporates many of these same routine histologic parameters, the ODXRS may have a limited impact on staging.

To achieve a better understanding of how ODXRS influences staging, we reviewed cases of IMC that were ER^+/HER2− with available ODX results and determined the proportion of cases that would be downstaged as a direct result of the ODXRS using the PPS. We also sought to identify routine pathologic parameters that could predict whether the ODXRS would change the stage.

Materials and Methods

This was a retrospective study with institutional review board approval. The pathology archives at the University of Louisville and University of Rochester Medical Center were searched for consecutive cases of IMC diagnosed between January 2006 and January 2018 where an ODX result, tumor size, GR, LN status, and ER, PR, and HER2 results were known. Patients with disease found to be triple negative or $HER2^+$ according to the most recent ASCO/College of American Pathologists guidelines were excluded.[10,11] Clinicopathologic data were recorded, including age, GR, histologic type, ER and PR results, HER2 IHC, and/or HER2 fluorescence in-situ hybridization results, pathologic tumor classification (pT), pathologic LN classification (pN), Ki-67, ODXRS, and clinical follow-up.

ODXRS risk groups were categorized on the basis of commercial (standard) cutoffs as low risk (LR) (RS = 0-17), intermediate risk (IR) (RS = 18-30), and high risk (HR) (RS = 31-100), and were categorized on the basis of TAILORx cutoffs[7] as RS = 0-10, RS = 11-25, and RS = 26-100. ODXRS was further subcategorized using both standard and TAILORx cutoffs into very LR (vLR) (RS = 0-10), remainder of LR (rLR) (RS = 11-17), low-intermediate risk (LIR) (RS = 18-25), high-intermediate risk (HIR) (RS = 26-30), and HR (RS = 31-100).

ER/PR intensity score (weak, intermediate, strong) was not provided in all cases, and therefore ER/PR percentage staining was used for analysis. An ER/PR cutoff of 33% was used to distinguish low ($\leq$ 33% staining) versus high (> 33% staining) ER/PR status and is based on the Allred proportion scores of 0 through 3 (0%-33% staining) and scores of 4 and 5 (> 33% staining), respectively, for percentage staining of tumor nuclei.[12] Mattes et al[13] showed routine histopathologic characteristics can predict ODXRS; they used the Allred score, the sum of the proportion score plus intensity score, for ER/PR analysis. Mattes et al used an Allred score cutoff of 4, where scores of 0 to 4 indicated negative/weak staining and scores of 5 to 8 strong staining. For an Allred score of 4, the proportion score can be no greater than a score of 3 (nuclear staining 10%-33%). A Ki-67 cutoff of 20% was used and is based on the cutoff value favored by the St Gallen 2013 expert panel.[14] A low Ki-67 refers to $< 20\%$ staining, and a high Ki-67 refers to $\geq 20\%$ staining.

The anatomic stage group (ASG) and pPSG were determined for each case using the most recent version of the AJCC 8th edition staging system.[1] The number of cases with a change in stage when comparing ASG to pPSG was calculated. To determine the effect that ODXRS has on staging, pPSG without ODXRS and pPSG with ODXRS were recorded for each case, and the number of cases with a change in stage was calculated. Per the 8th edition, assignment of pPSG IA with ODXRS < 11 only applies to a subgroup of tumors that are T1-2, N0, M0, ER^+/HER2−. Therefore, T1-2 N0 cases were analyzed separately.

Associations between continuous factors with ODX risk were tested by t test or ANOVA, and associations between categorical factors with ODX risk were tested by the chi-square or Fisher exact test for the expected frequency, within any cell < 5 in a 2×2 table.[15,16]

The descriptive statistics of tumor characteristics for 816 patients are summarized in Table 1. Table 2 shows treatment by subgroup.

Table 1 Patient and Tumor Characteristics (N = 816)

Characteristic	N (%)
Age, y	
<50	176 (22)
≥50	640 (78)
Histologic Type	
Ductal	674 (83)
Lobular	123 (15)
Other	19 (2)
Histologic Grade	
1	282 (35)
2	391 (48)
3	143 (17)
ER	
Positive (≥1%)	100 (100)
Negative (<1%)	0 (0)
PR	
Positive (≥1%)	755 (92.5)
Negative (<1%)	61 (7.5)
Tumor Classification	
pT1a	11 (1)
pT1b	103 (13)
pT1c	389 (48)
pT2	277 (34)
pT3	36 (4)
Lymph Node Classification	
pN0	688 (84)
pN1	128 (16)
ODXRS	
LR (0-17)	461 (57)
vLR (0-10)	166 (20)
rLR (11-17)	295 (37)
IR (18-30)	287 (35)
LIR (18-25)	223 (27)
HIR (26-30)	64 (8)
HR (31-100)	68 (8)
ASG	
IA	437 (54)
IB	18 (2)
IIA	271 (33)
IIB	79 (10)
IIIA	11 (1)
PSG Without ODXRS	
IA	691 (84.8)
IB	86 (10.5)
IIA	28 (3.4)
IIB	10 (1.2)
IIIA	1 (0.1)
PSG With ODXRS	
IA	695 (85.2)
IB	83 (10.2)
IIA	27 (3.3)
IIB	10 (1.2)
IIIA	1 (0.1)

Abbreviations: ASG = anatomic stage group; ER = estrogen receptor; HIR = high-intermediate risk; HR = high risk; IR = intermediate risk; LIR = low-intermediate risk; LR = low risk; ODXRS = Oncotype DX recurrence score; PR = progesterone receptor; PSG = prognostic stage group; rLR = remainder of low risk; vLR = very low risk.

The results from comparing ODX risk among factor groups for 663 patients with T1-2N0 cases using TAILORx categories are presented in Table 3. Associations were considered significant at $P < .05$. All calculations were performed by SAS 9 statistical software (SAS Institute, Cary, NC).

Results

A total of 816 ER^+/HER2− cases were identified that met our criteria. Clinicopathologic characteristics are summarized in Table 1. When comparing ASG to pPSG, 351 (43%) of 816 cases changed stage using pPSG (Table 1). Of the cases that changed stage, all (100%) were downstaged, with 74% (258/351) downstaged to pPSG IA. Only 4 (0.5%) of the 816 cases changed stage as a direct result of the ODXRS, and all were T2N0 that were either GR3 and strongly ER^+ and PR^+ or GR2 and PR− (Table 4). Of note, all 4 cases had high Ki-67.

All ODX risk categories and subcategories using standard and TAILORx cutoffs were significantly associated with GR, PR, and Ki-67 (Figure 1A-C). These associations maintained significance when analyzing only T1-2N0 tumors (Table 3). Although a Ki-67 cutoff of 20% was significantly associated with all ODX risk categories, a high Ki-67 was seen in 20% (31/153) of all vLR cases (Figure 1B) and 22% (25/116) of T1-2 N0 vLR cases (Table 3).

Analysis of all 166 vLR cases showed that 95% (158 cases) were either GR1 or GR2 (Figure 1A). Of the 166 cases, 81 (49%) were T1N0, 19 (11%) were T1N1, 47 (28%) were T2N0, 14 (8%) were T2N1, 4 (3%) were T3N0, and 1 (1%) was T3N1. When using PPS, 158 (95%) were group IA and 8 (5%) were IB. Percentage ER and PR were available in 165 (99%) of the 166 vLR cases. Two cases (1%) were low ER, and 15 (9%) were low PR, with 4 cases (2%) that were PR− (Figure 1C). All low ER and low PR cases were GR1 or GR2. All 4 PR− cases had high ER, with 2 (50%) that were GR1 with low Ki-67, and 2 (50%) that were GR2 with high Ki-67. One PR− case was T2N0 and was downstaged from pPSG IIA to IA on the basis of ODXRS (Table 4, case 1). Two PR− cases were T1N0 and thus were already pPSG IA, and one was T1N1a not meeting criteria for downstaging with ODXRS. Ki-67 was available in 153 (92%) of the 166 vLR cases (median, 10%; range, 0%-40%), and 80% (122/153) had low Ki-67 (Figure 1B). Eight (5%) of 166 vLR cases were GR3, and all (100%) were high ER and PR (Figure 1D), with percentage staining ranging from 84% to 100%. For these 8 cases, Ki-67 ranged from 15% to 30% (median, 20%; mean, 22%). Three (38%) of the 8 GR3 cases were T2N0 and were downstaged from pPSG IB to IA

Table 2 Treatment by Subgroup

Subgroup	Adjuvant Therapy, N (%)			
	H	C	H + C	None
ODXRS				
vLR (n = 65)	58 (89)	0 (0)	3 (5)	4 (6)
rLR (n = 147)	122 (83)	1 (1)	18 (12)	6 (4)
LIR (n = 114)	74 (65)	1 (1)	36 (31)	3 (3)
HIR (n = 25)	12 (48)	1 (4)	12 (48)	0 (0)
HR (n = 25)	3 (12)	2 (8)	20 (80)	0 (0)
PSG With ODXRS				
IA (n = 324)	243 (75)	4 (1)	64 (20)	13 (4)
IB (n = 38)	19 (50)	1 (3)	18 (47)	0 (0)
IIA (n = 8)	5 (63)	0 (0)	3 (37)	0 (0)
IIB (n = 5)	2 (40)	0 (0)	3 (60)	0 (0)
IIIA (n = 1)	0 (0)	0 (0)	1 (100)	0 (0)

Abbreviations: C = chemotherapy; H = hormone therapy; HIR = high-intermediate risk; HR = high risk; LIR = low-intermediate risk; ODXRS = Oncotype DX recurrence score; PR = progesterone receptor; PSG = prognostic stage group; rLR = remainder of low risk; vLR = very low risk.

on the basis of ODXRS (Table 4, cases 2, 3, and 4). The other 5 cases were T1N0 and thus were already pPSG IA.

In contrast, analysis of all HR cases showed that 76% were GR3 (52/68) (Figure 1A). Of these 68 HR cases, 40 (59%) were T1N0, 20 (29%) were T2N0, 6 (9%) were T2N1, 1 (1%) was T3N0, and 1 (1%) was T3N1. Forty-three HR cases (63%) were pPSG IA, 10 (15%) were IB, 10 (15%) were IIA, and 5 (7%) were IIB. Twelve HR cases (18%) were low ER, and all were associated with low PR. Fifty-three HR cases (78%) were low PR, and of these, 18 (34%) were PR− (Figure 1C). Thirteen PR− cases (72%) were GR3. Ki-67 was available in 63 (93%) of the 68 HR cases and ranged from 5% to 90% (median, 40%; mean, 38%), with 13 low Ki-67 cases (19%) (Figure 1B). Of the 52 GR3 tumors in the HR category, only 12 (23%) had high ER and PR (Figure 1D). Ki-67 results were available in 10 (83%) of these 12 cases, with indices ranging from 5% to 90% (median, 35%; mean, 42%). Of note, the 2 cases that were GR1 in the HR category were both invasive lobular carcinoma and pN0. One was a 0.8 cm tumor with 80% ER, 0% PR, and 5% Ki-67; the second was a 3.4 cm tumor with 20% ER, 5% PR, and 7.5% Ki-67.

Follow-up was available in 409 (50%) of 816 cases and ranged from 2 to 129 months (median, 60 months; mean, 56.28 months). Data regarding adjuvant systemic therapy were available in 376 (92%) of 409 cases (Table 2), and 303 of the 376 cases (81%) were T1-2N0 (Table 3). Cases with follow-up included 70 (42%) of 166 vLR cases, 162 (55%) of 295 rLR cases, 121 (54%) of 223 LIR cases, 29 (45%) of 64 HIR cases, and 27 (40%) of 68 HR cases. Eighteen (4%) of 409 patients with follow-up experienced recurrence (Table 5). Sixty-one percent of patients (11/18) who experienced recurrence were downstaged on the basis of the new staging system, with 44% (8/18) downstaged from either stage II or III to stage I. None of the cases were downstaged on the basis of ODXRS. Of these 18 cases, 1 (6%) was in the vLR category, 11 (61%) were rLR/LIR, and 6 (33%) were HIR/HR. The single patient in the vLR group had disease staged as IA by ASG and pPSG (Table 5, case 1). Of the 11 rLR/LIR cases, 5 (45%) were downstaged to stage I, and 6 (55%) had no change in stage when comparing ASG to pPSG. Two rLR/LIR cases were GR3, ASG IIA, and pPSG IB (Table 5, cases 4 and 12). These 2 patients experienced distant recurrence and died of their disease. Of note, in one rLR/LIR case that was stage IA by ASG and pPSG, the patient declined systemic therapy (Table 5, case 8). Of the 6 HIR/HR cases, 3 (50%) were downstaged to stage I, 1 (17%) was downstaged from stage III to stage II, and 2 (33%) remained stage I when comparing ASG to pPSG. For the HIR/HR cases that were downstaged, all patients were treated systemically with hormone therapy only (Table 5, cases 14, 15, 16, and 18).

Discussion

The most significant change introduced in the 8th edition of the AJCC breast cancer staging system is the prognostic stage. In our review of ER$^+$/HER2− IMC, the disease of close to half of our patients changed stage using required biologic markers alone, and all were downstaged with the majority to IA. Only rare cases were downstaged on the basis of the ODXRS. This is the result of several factors. First, the ability of ODXRS to change stage is limited to tumors that meet the criteria for arm A of the TAILORx trial.[7] Our findings show that the majority of these tumors are both ER$^+$ and PR$^+$ and GR1 or GR2. Sparano et al[7] had similar findings for this subgroup, with > 99% ER$^+$, 98% PR$^+$, and 93% GR1 or GR2. Thus, the required biologic markers that downstage ER$^+$/HER2− tumors to pPSG IA overlap with the biologic characteristics of tumors that tend to have an ODXRS < 11. Second, the number of cases eligible for downstaging on the basis of ODXRS is further limited to T2N0 tumors that are either PR− or GR3, because all other tumors fitting the criteria for arm A of TAILORx are already pPSG IA. Sparano et al reported that 31% (505/1626) of tumors measured 2.0 to 5.0 cm, 7% (111/1578) were GR3, and 2% (28/1590) were PR− in arm A. Our study shows similar findings (Table 3), with only 10% (67/663) of T1-2N0 cases that were T2N0 and either GR3 or PR−. Therefore, the probability is low that ODXRS will change stage based on the current PPS table.

Although the 8th edition does not require an ODXRS result for pPSG, our analysis identified pathologic parameters that are associated with potential for downstaging based on an ODXRS < 11. These parameters include classification as T2N0 and tumors that are either GR3 with high ER and high PR, or GR1-2 and ER$^+$/PR− (Figure 2). In contrast, GR3 tumors that are either low ER or low PR, or both ER and PR low predict an ODXRS > 10, and these tumors would not be downstaged on the basis of ODXRS. In the same respect, although T1-2N0, GR1-2 tumors that are ER$^+$/PR$^+$ are better candidates to have an ODXRS < 11, these tumors are already pPSG IA, and therefore ODXRS cannot downstage these cases. Similar findings on pathologic parameters predicting LR and HR categories have been published.[17,18]

In our analysis of Ki-67 and ODX risk categories, we found that approximately 20% of vLR cases were high Ki-67, including all 4 cases that changed stage according to ODXRS. Although Ki-67 can assist in understanding tumor biology when combined with other pathologic parameters, additional studies using standardized methods of testing and interpretation of Ki-67 are needed. Not surprisingly, Ki-67 is recognized as AJCC level III evidence because

Table 3 Characteristics of T1-2N0 Cases Using TAILORx Categories (N = 663)

Characteristic	RS 0-10 (n = 128)	RS 11-25 (n = 422)	RS 26-100 (n = 113)	*P*
Age (y), median (min-max)	59.5 (33-83)	57 (32-82)	57 (21-83)	.175
T size (cm), median (min—max)	1.8 (0.4-5.0)	1.7 (0.3-5.0)	1.7 (0.5-5.0)	.286
pT				.545
T1	80 (62.5)	281 (67)	78 (69)	
T2	48 (37.5)	141 (33)	35 (31)	
pPSG No RS				<.001
Stage IA	124 (97)	388 (92)	90 (80)	
Stage IB	3 (2)	27 (6)	15 (13)	
Stage IIA	1 (1)	7 (2)	8 (7)	
GR				<.001
1	62 (48.4)	140 (33)	12 (11)	
2	58 (45.3)	223 (53)	43 (38)	
3	8 (6.3)	59 (14)	58 (51)	
ER, n/N (%)				<.001
≤33%	2/127 (2)	0/421 (0)	12/113 (11)	
>33%	125/127 (98)	421/421 (100)	101/113 (89)	
PR				<.001
Negative	3 (2)	24 (6)	21 (19)	
Positive	125 (98)	398 (94)	92 (81)	
PR, n/N (%)				<.001
≤33%	10/127 (8)	108/421 (26)	77/113 (68)	
>33%	117/127 (92)	313/421 (74)	36/113 (32)	
Ki-67 (%), median (min-max)	10 (0-35)	10 (1-65)	25 (5-90)	<.001
Ki-67, n/N (%)				<.001
<20%	91/116 (78)	255/366 (70)	38/102 (37)	
≥20%	25/116 (22)	111/366 (30)	64/102 (63)	
Treatment				
Hormone therapy alone	48/53 (91)	164/210 (78)	10/40 (25)	
Chemotherapy alone	0/53 (0)	1/210 (0.4)	2/40 (5)	
Hormone + chemotherapy	1/53 (2)	37/210 (17.6)	28/40 (70)	
Neither	4/53 (7)	8/210 (4)	0/40 (0)	

Data are presented as n (%) unless otherwise indicated.
Abbreviations: ER = estrogen receptor; GR = histologic grade; PR = progesterone receptor; pPSG = pathologic prognostic stage group; RS = Oncotype DX recurrence score.

of a lack of standardized testing and interpretation, as well as a lack of consensus on an optimal cutoff value.[1]

As of the November 2017 update, ODX is the only multigene panel included to classify PPS.[1] Therefore, a possible inadvertent effect that the PPS could have on practice is influencing which panel is ordered. Per the expert panel, substantial data from the MINDACT trial could support incorporating MammaPrint for assigning pPSG.[19] However, incorporation has not yet occurred.

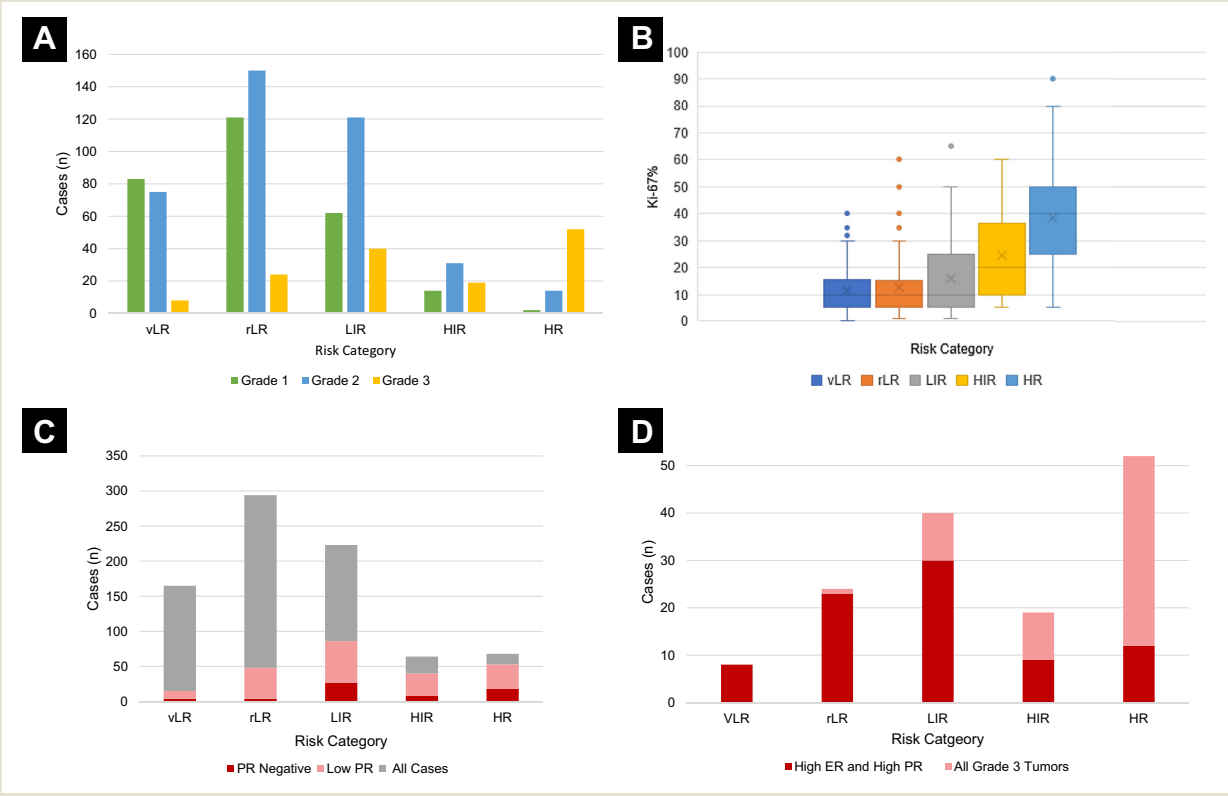
Going forward, the expert panel anticipates updates to the staging system at shorter intervals to permit continued refinement of staging criteria.[1] In our study, only rare cases had known recurrence, but in more than half of these cases, the patients' BC was downstaged using the PPS. Of note, 6 cases of recurrence that were downstaged from either stage II or III to stage I had high Ki-67. Five of these 6 cases were grade 3 and/or ODXRS HIR/HR, and 4 of these cases occurred in patients who experienced recurrence within 5 years.

Table 4 Cases Downstaged to pPSG IA Based on ODXRS

No.	Histologic Type	GR	ER (%)	PR (%)	Ki-67 (%)	pTpN	ODXRS	Initial pPSG
1	ILC	2	80	0	25	T2N0	7	IIA
2	Other	3	100	90	25	T2N0	0	IB
3	IDC	3	90	90	20	T2N0	10	IB
4	IDC	3	95	95	20	T2N0	0	IB

Abbreviations: ER = estrogen receptor; GR = histologic grade; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; ODXRS = Oncotype DX recurrence score; pPSG = pathologic prognostic stage group; PR = progesterone receptor.

Figure 1 Pathologic Parameters Significantly Associated With ODXRS Subcategories in All Cases (N = 816). (A) GR Is Significantly Associated With ODXRS Subcategories. Total of 166 vLR Tumors With 50% (83 Cases) GR1, 45% (75 Cases) GR2, and 5% (8 Cases) GR3; 295 rLR Tumors With 41% (121 Cases) GR1, 51% (150 Cases) GR2, and 8% (24 Cases) GR3; 223 LIR Tumors With 28% (62 Cases) GR1, 54% (121 Cases) GR2, and 18% (40 Cases) GR3; 64 HIR Tumors With 22% (14 Cases) GR1, 48% (31 Cases) GR2, and 30% (19 Cases) GR3; 68 HR Tumors With 3% (2 Cases) GR1, 21% (14 Cases) GR2 and 76% (52 Cases) GR3. (B) Box-and-Whisker Plots Showing Ki-67 Index and 20% Cutoff (n = 733) Are Significantly Associated With ODXRS Subcategories, With vLR, rLR and LIR Median Ki-67 Index at < 20% and HIR and HR Median Ki-67 Index at > 20%. Percentage Ki-67 Mean and Median (Range) for Each ODXRS Subcategory: vLR Tumors (n = 153), 11.3% and 10% (0%-40%); rLR Tumors (n = 264), 13% and 10% (1%-60%); LIR Tumors (n = 195), 16.2% and 10% (1%-65%); HIR Tumors (n = 58), 22.5% and 19% (5%-60%); HR Tumors (n = 63), 38.4% and 40% (5%-90%). (C) PR Is Significantly Associated With ODXRS Subcategories. Of 166 vLR Tumors, 9% (15 Cases) Are Low PR and 2% (4 Cases) Are PR−. Of 295 rLR Tumors, 16% (48 Cases) Are Low PR and 1% (4 Cases) Are PR−. Of 223 LIR Tumors, 39% (86 Cases) Are Low PR and 12% (27 Cases) are PR−. Of 64 HIR Tumors, 63% (40 Cases) Are Low PR and 13% (8 Cases) Are PR−. Of 68 HR Tumors, 78% (53 Cases) Are Low PR and 27% (18 Cases) Are PR−. (D) GR3 (n = 143) With High ER and High PR Is Significantly Associated With ODXRS Subcategories. One Hundred Percent of GR3 vLR Tumors (8/8), 96% of GR3 rLR Tumors (23/24), 75% of GR3 LIR Tumors (30/40), 47% of GR3 HIR Tumors (9/19), and 23% of GR3 HR Tumors (12/52) Are GR3 With High ER and High PR



Abbreviations: ER = estrogen receptor; GR = histologic grade; high ER = > 33% staining; high PR = > 33% staining; HIR = high-intermediate risk (RS = 26-30); HR = high risk (RS = 31-100); LIR = low-intermediate risk (RS = 18-25); low PR = 0%-33% staining; ODXRS = Oncotype DX recurrence score; PR = progesterone receptor; rLR = remainder of low risk (RS = 11-17); RS = risk score; vLR = very low risk (RS = 0-10).

Although this is a small number of cases, it highlights possible opportunities for further investigation into additional biomarkers that could contribute to improved discrimination among stage group assignment. Given that the new staging system is only relevant in the context of appropriate therapy, one could make the argument that some of these patients with recurrence may have not received optimal therapy. Of the patients with recurrence whose disease was downstaged to stage I using PPS, only one received systemic chemotherapy.

Recently published results from the TAILORx trial showed that patients with an ODXRS of 11 to 25 do equally as well as patients with an ODXRS of < 11, reporting a 9-year distant recurrence-free survival of 94.5% with adjuvant endocrine therapy alone.[20] It remains to be seen if the PPS table will expand the criteria for pPSG IA to incorporate an ODXRS of 11 to 25. Our data could caution against such a move because the majority of our cases of recurrence had an ODXRS of 11 to 25, with the majority treated systemically with hormone therapy alone, and the majority with distant recurrence. In contrast, only one of our cases of recurrence had an RS < 11, but the recurrence was local, not distant.

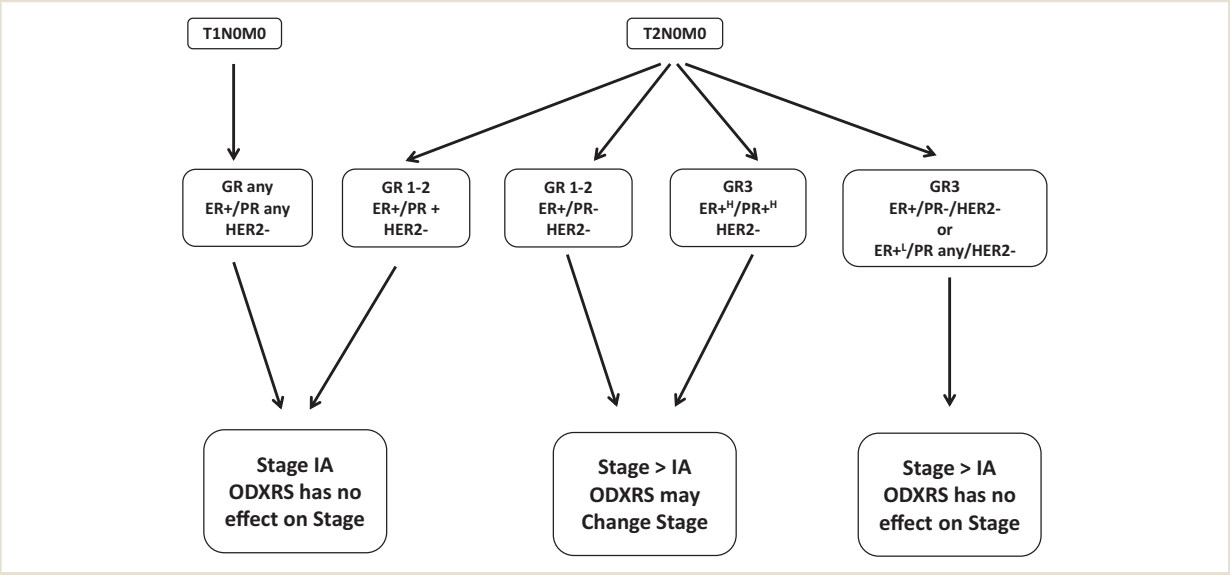
In summary, our analysis shows that ODXRS rarely affects staging, and our data are therefore in line with the statements issued

Table 5 Follow-up for Cases of Recurrence

No.	Age (y)	Diagnosis	GR	ER (%)	PR (%)	Ki-67 (%)	T Size (cm)	pTpN	ASG	pPSG	ODXRS	Time to Recurrence (mo)	Site of Recurrence	DOD	Treatment at Diagnosis
1	57	IDC	2	95	95	NP	1.8	T1cN0 (sn)	IA	IA	5, vLR	30	Ipsilateral chest wall	N	H, Mast, No XRT
2	60	IDC	2	80	60	27	3.0	T2N0	IIA	IA	11, rLR	84	Pleural effusion	N	H, Mast, No XRT
3	54	IDC	1	100	5	20	0.7	T1bN0 (sn)	IA	IA	13, rLR	72	Ipsilateral breast	N	H, Mast, XRT
4	61	IDC	3	100	100	55	2.7'	T2N0 (sn)	IIA	IB	14, rLR	25	Liver	Y	H
5	46	IDC	2	100	100	NP	1.1	T1cN0 (sn)	IA	IA	15, rLR	129	Ipsilateral breast	N	H, Mast, No XRT
6	63	IDC	1	90	70	NP	1.1	T1cN0	IA	IA	15, rLR	72	Contralateral breast, MSBM	Y	H, Lump, XRT
7	59	ILC	1	40	30	5	4.0	T2N1a	IIB	IIA	15, rLR	36	MSBM	Y	H, Mast, XRT
8	64	IDC	1	95	95	NP	1.1	T1cN0 (sn)	IA	IA	16, rLR	101	Spine		None
9	70	IDC	1	90	90	5	4.0	T2N0	IIA	IA	16, rLR	12	L1 vertebra	N	H, Mast, No XRT
10	72	IDC	2	90	1	60	3.5	T2N1mi	IIB	IIA	17, rLR	36	Liver	N	H, Mast, No XRT
11	43	IDC	1	95	15	NP	4.0	T2N0	IIA	IA	19, LIR	72	MSBM	N	H, Lump, XRT
12	51	IDC	3	80	35	35	2.4	T2N0 (sn)	IIA	IB	24, LIR	12	Liver, lymph nodes, bone and lung	Y	C,H, Mast, No XRT
13	21	IDC	2	70	50	35	1.4	T1cN0	IA	IA	27, HIR	24	Bilateral lungs and hilar lymph nodes	N	C,H, Lump, XRT
14	68	IDC	1	90	7	25	1.0	T1bN1a	IIA	IB	28, HIR	84	Pleural effusion	N	H, Mast, No XRT
15	71	ILC	1	95	15	35	8.5	T3N1c	IIIA	IB	28, HIR	24	Ipsilateral chest wall, MSBM	Y	H, Lump, XRT
16	81	IDC	3	90	1	45	5.5	T3N1a	IIIA	IIB	31, HR	<12	Chest wall, lung, brain, MSBM	Y	H, Mast, XRT
17	28	IDC	2	100	70	35	1.7	T1cN0 (sn)	IA	IA	34, HR	47	Femur	N	C,H, Mast, No XRT
18	83	IDC	3	70	30	70	5.0	T2N0	IIA	IB	44, HR	24	Ipsilateral breast, lung	Y	H, Lump, No XRT

Abbreviations: ASG = anatomic stage group; C = chemotherapy; DOD = died of disease; ER = estrogen receptor; GR = histologic grade; H = hormone therapy; HIR = high-intermediate risk; HR = high risk; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; IR = intermediate risk; LIR = low-intermediate risk; LR = low risk; Lump = lumpectomy; Mast = mastectomy; MSBM = multiple-site bony metastases; NP = not performed; ODXRS = Oncotype DX recurrence score; pPSG = pathologic prognostic stage group; PR = progesterone receptor; sn = 1 to 5 axillary lymph nodes sampled; rLR = relative low risk; vLR = very low risk; XRT = radiotherapy.

Figure 2 Pathologic Prognostic Stage Group and Effect of ODXRS. Only Tumors That Are T2N0 and Either GR1-2, ER$^+$/PR−/HER2−, Staged as pPSG IB and IIA, Respectively, or GR3 Tumors That Are High ER/High PR/HER2−, Staged as pPSG IB, Have the Possibility of Having ODXRS < 11 and Thus Are Eligible for Downstaging to pPSG IA if Oncotype DX Is Ordered and ODXRS Is < 11



Abbreviations: ER = estrogen receptor; ER$^+$H = > 33% staining; ER$^+$L = 1%-33% staining; GR = histologic grade; HER2 = human epidermal growth factor receptor type 2; high ER = > 33% staining; high PR = > 33% staining; ODXRS = Oncotype DX recurrence score; pPSG = pathologic prognostic stage group; PR = progesterone receptor; PR$^+$H = > 33% staining.

in the AJCC 8th edition on ordering multigene panels for IMC. In addition, ordering ODX is most beneficial when pathologic parameters result in uncertainty about whether a patient can be spared chemotherapy. These uncertain cases happen to encompass cases with potential for downstaging on the basis of ODXRS. Therefore, as long as physicians and patients are attuned to the role of ODX in PPS, an increase in ODX testing should not occur in response to the new staging system, particularly for practices where ODX has always been the favored multigene panel. Finally, emphasis should be placed on the fact that the new staging system is only relevant in the context of appropriate therapy, and therefore downstaging of tumors using the PPS should not be used as evidence to withhold therapy.

Clinical Practice Points

- Tumors that are T2N0 and either GR3 with high ER and high PR or GR1-2 and ER$^+$/PR− are the most likely to change stage if associated with an ODXRS of < 11.
- This represents a small subset of cases, and although ODX is included to help classify tumors in the PPS, it rarely results in a change of stage.
- The PPS assumes that patients will be receiving optimal therapy for their disease, and thus is only relevant in this context.

Disclosure

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

References

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
2. Sanders MA, Wong SM, Iorgulescu JB, Lester SC. Changes and clarifications in the eighth edition of the AJCC cancer staging system for breast cancer. *AJSP Rev Rep* 2018; 23:113-7.
3. Mittendorf EA, Chavez-MacGregor M, Vila J, et al. Bioscore: a staging system for breast cancer patients that reflects the prognostic significance of underlying tumor biology. *Ann Surg Oncol* 2017; 24:3502-9.
4. Chavez-MacGregor M, Mittendorf EA, Clarke CA, Lichtensztajn DY, Hunt KK, Giordano SH. Incorporating tumor characteristics to the American Joint Committee on Cancer breast cancer staging system. *Oncologist* 2017; 22:1292-300.
5. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; 351:2817-26.
6. Henry NL, Somerfield MR, Abramson VG, et al. Role of patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer: American Society of Clinical Oncology endorsement of Cancer Care Ontario guideline recommendations. *J Clin Oncol* 2016; 34:2303-11.
7. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med* 2015; 373:2005-14.
8. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer. 2018. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed: May 26, 2018.
9. Cuzick J, Dowsett M, Pineda S, et al. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. *J Clin Oncol* 2011; 29:4273-8.
10. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). *Arch Pathol Lab Med* 2010; 134:e48-72.
11. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *J Clin Oncol* 2018; 36:2105-22.
12. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol* 1999; 17:1474-81.

13. Mattes MD, Mann JM, Ashamalla H, Tejwani A. Routine histopathologic characteristics can predict Oncotype DX™ recurrence score in subsets of breast cancer patients. *Cancer Invest* 2013; 31:604-6.
14. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer, 2013. *Ann Oncol* 2013; 24: 2206-23.
15. Agresti A. *Categorical Data Analysis*. 2nd ed. New York, NY: Wiley; 2002.
16. Fleiss JL, Levin BA, Paik MC. *Statistical Methods for Rates and Proportions*. 3rd ed. Hoboken, NJ: Wiley-Interscience; 2003.
17. Orucevic A, Bell JL, McNabb AP, Heidel RE. Oncotype DX breast cancer recurrence score can be predicted with a novel nomogram using clinicopathologic data. *Breast Cancer Res Treat* 2017; 163:51-61.
18. Gage MM, Rosman M, Mylander WC, et al. A validated model for identifying patients unlikely to benefit from the 21-gene recurrence score assay. *Clin Breast Cancer* 2015; 15:467-72.
19. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med* 2016; 375:717-29.
20. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med* 2018; 379:111-21.