ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2025.108.4.219
Annals of Surgical Treatment and Research

Characteristics of premenopausal breast cancer patients with a midrange 21-gene recurrence score

Jung Min Park[1,2,*], Suk Jun Lee[3,*], Jee Hyun Ahn[4], Chan Seok Yoon[1], Seho Park[4]

[1]Department of Surgery, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Korea
[2]Yonsei University Graduate School of Medicine, Seoul, Korea
[3]Division of Breast Surgery, Department of Surgery, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Korea
[4]Division of Breast Surgery, Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

Purpose: The results of the TAILORx trial have shown that premenopausal patients with intermediate Oncotype Dx (ODx) recurrence score of 16–25 may benefit from adjuvant chemotherapy. In addition, the clinicopathological features showed the information complementary to ODx results. However, the characteristics may vary depending on menopausal status even in the same score. This study aimed to analyze the differences in the clinical characteristics by menopausal status.
Methods: This study conducted a retrospective analysis of 756 patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative, and node-negative breast cancer who underwent the ODx test from July 2013 to December 2020 at the Severance Hospital.
Results: Of the 756 patients, 261 patients were postmenopausal, and 495 were premenopausal. The premenopausal patients with a midrange ODx had similar clinicopathological features as compared to those with a high ODx. Conversely, the postmenopausal patients with a midrange ODx did not show significantly different clinicopathological features from those with a low ODx, whereas a difference was seen as compared to those with a high ODx.
Conclusion: In this study, unlike the postmenopausal patients, some of the clinicopathological characteristics of the premenopausal patients with a midrange ODx were closer to those with a high ODx than those with a low ODx. In the premenopausal patients with a midrange ODx, considering the baseline characteristic itself, there was a significant difference between those with a low ODx when compared with postmenopausal patients. Therefore, more aggressive treatment decisions may be helpful in premenopausal patients with a midrange ODx.
[Ann Surg Treat Res 2025;108(4):219-230]

Key Words: Breast neoplasms, Clinical features, Gene expression profiling, Postmenopause, Premenopause

INTRODUCTION

Since breast cancer is recognized as a heterogeneous disease rather than a single disease entity, the characteristics of breast cancer could be classified using histopathological and immunohistochemical methods [1,2]. This heterogeneity

Received December 4, 2024, **Revised** December 25, 2024, **Accepted** January 13, 2025

Corresponding Author: Seho Park
Division of Breast Surgery, Department of Surgery, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-2134, **Fax:** +82-2-313-8289, **E-mail:** psh1025@yuhs.ac, **ORCID:** https://orcid.org/0000-0001-8089-2755
Co-Corresponding Author: Chan Seok Yoon
Department of Surgery, CHA Gangnam Medical Center, CHA University School of Medicine, 566 Nonhyon-ro, Gangnam-gu, Seoul 06135, Korea
Tel: +82-2-3468-3369, **Fax:** +82-2-3468-3507, **E-mail:** yoondoc@gmail.com, **ORCID:** https://orcid.org/0000-0001-6971-5926

*Jung Min Park and Suk Jun Lee contributed equally to this work as co-first authors.

enables the discrimination of patient survival. Therefore, the decision of appropriate treatment can be affected by the presence of distinctive molecular subtypes, such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2) status [3-5]. However, even among the same subtype of breast cancer, the prognosis and treatment effect may vary depending on the individual's genetic information [6,7].

Oncotype Dx (ODx, Genomic Health), a 21-gene recurrence score (RS) for breast cancer, is a multigene assay, which can predict the risk of recurrence and help to decide on whether to add chemotherapy or not in ER-positive, HER2-negative early breast cancer patients [8,9]. However, it is still unclear whether adding chemotherapy is beneficial for patients with an intermediate RS. Several studies have suggested aids to clinical decisions in the intermediate RS group and have incorporated menopausal status [10,11]. The Trial Assigning IndividuaLized Options for Treatment (TAILORx) trial showed that premenopausal young patients with an intermediate RS of 16–25 could benefit from adjuvant chemotherapy and in cases with an RS of 21–25, benefits were more prominent [12]. On the other hand, endocrine therapy was found to be noninferior to chemoendocrine therapy in postmenopausal patients with an RS of 16–25. Although the ambiguous benefit of adjuvant chemotherapy according to menopausal status in women with intermediate risk scores could make clinical decision-making difficult, there is no doubt that menopausal status or age cutoff of 50 years should be considered when interpreting the ODx results nowadays.

In a secondary analysis of the TAILORx trial, clinicopathological features provided information complementary to the ODx results [13,14]. Adjuvant chemotherapy or ovarian function suppression with endocrine therapy could be considered as treatment options for premenopausal patients with an RS of 21–25, irrespective of the clinical risk [15]. In addition, the same treatment could be also optional for premenopausal patients with an RS of 16–20 and high clinical risk factors [12]. In a subsequent analysis, RSClin (Recurrence Score-Clinical risk assessment tool) was introduced, which is an index that accurately suggests distant recurrence rates and absolute chemotherapy benefits by integrating an RS with tumor size, grade, and age. It suggests that the risk of recurrence is closely associated with not only genetic determinants of primary tumors but also traditional anatomical risk factors [13].

However, the clinical dilemma still exists owing to the different levels of therapeutic efficacy according to menopausal status in patients with an intermediate RS. Moreover, anatomical risk factors do not always correlate with genetically determined prognostic risk parameters, including the ODx. Menopausal status cannot be accurately determined based on the age cutoff of 50 years. Therefore, the association of the ODx results with clinicopathological risk factors stratified by menopausal status should be explored. In this study, we focused on the indeterminate, midrange RS score of 21–25 considering menopausal status. This study aimed to analyze whether a midrange RS of 21–25 indicates different clinicopathological features and survival outcomes by menopausal status compared to scores of ≤20 and ≥26.

METHODS

Ethics statement

The project was reviewed and approved by the Institutional Review Board (IRB) of the Severance Hospital (No. 4-2023-0436) and Gangnam CHA Hospital (No. 2023-06-014-003). The patient's consent to participate was waived by the IRB due to its retrospective nature with no or minimal risk of harm to the patients.

Study population

We retrospectively reviewed 995 patients with ER-positive, HER2-negative, and node-negative breast cancer, who underwent the ODx test at the Severance Hospital and Gangnam CHA Hospital in Seoul, Korea between January 2013 and December 2021. In our study, the low, midrange, and high ODx groups were defined as an RS of 0–20, 21–25, and ≥26, respectively, according to subclassifications of the TAILORx trial [12].

The clinical and pathologic data including ODx reports were obtained from medical records. ER status was determined according to the Allred scoring methods from 3 to 8 points. The Allred scores of PR were divided into 3 groups: negative (0), low (1–5), and high (6–8 points) expression. Immunohistochemical staining was applied to determine HER2 status, and in the case of 2+, additional *in-situ* hybridization assays were performed. Immunohistochemical Ki-67 level was calculated either manually or automatically after scanning using the Roche Ventana iScan HT slide scanner (Ventana Medical Systems, Inc.). Ki-67 status was divided into 2 groups: ≤15% and >15%. In addition, the binary clinical risk group was categorized by the combination of histologic grade with tumor size according to the Adjuvant! algorithm and the Microarray In Node-negative Disease may Avoid ChemoTherapy (MINDACT) trial [16-18].

Menopausal status was defined according to the Health Insurance Review and Assessment Service chemotherapy guidelines: (a) 50 years or older women who have experienced no menstrual periods for 1 year or more since their last menstrual period. (b) Women under 50 years of age who meet at least one of the following criteria: (1) Amenorrhea for 1 year or more prior to cancer treatment. (2) Women with a history of hysterectomy and less than 1 year of amenorrhea, whose serum follicle-stimulating hormone (FSH) levels are 30–40 mIU/mL

or higher on tests performed 3–6 months apart before cancer treatment. (3) Women with pretreatment serum FSH levels below 30–40 mIU/mL, whose serum FSH levels are consistently 30–40 mIU/mL.

Women who have undergone bilateral oophorectomy, resulting in artificial menopause. The ODx RS report also presented the quantitative single gene scores of *ESR1*, *PGR*, and *ERBB2* expression. When analyzing gene scores, *ER* scores of <3.7 were considered as 3.6, and values of ≥12.5 were considered as 12.5. For *PR* scores, cases reported as <3.2 were considered as 3.1 and those reported as ≥10.0 were considered as 10.0. In cases of *HER2* scores, patients reported as <7.6 were considered as 7.5 and those reported as ≥13.0 were considered as 13.0.

Statistical analysis

Clinicopathological characteristics of patients were compared using the chi-square test and if appropriate, Fisher exact test for categorical variables. Continuous parameters were calculated using an independent t-test for 2 groups and a one-way analysis of variance (ANOVA) for 3 groups. Multinominal logistic regression models were calculated to explore significant parameters of the low and high ODx subgroups compared to the midrange RS group in premenopausal and postmenopausal patients, respectively. The tests were 2-sided and a P-value of <0.05 was considered to be statistically significant. When multiple comparisons were implemented in premenopausal and postmenopausal women, a corrected α ($P < 0.05/3 \fallingdotseq 0.017$) was applied. Multiple comparisons of ANOVA were corrected by the Bonferroni method.

Disease-free survival (DFS) and overall survival (OS) curves were plotted using the Kaplan-Meier method and the groups were compared using the log-rank test. DFS was measured from the date of surgery to the date of first locoregional or distant recurrence or date of death, whichever came first, and OS was calculated from the date of surgery to the date of last follow-up or death from any cause. The Cox proportional hazard model was used to identify factors associated with survival. All statistical analyses were conducted using the IBM SPSS Statistics ver. 26 (IBM Corp.).

RESULTS

Clinicopathologic characteristics of a total study population

Of a total of 995 patients, 64.5% were premenopausal and 35.5% were postmenopausal women. Approximately 2/3 of patients received breast-conserving surgery. Radiation therapy was done in 65.3% of patients and chemotherapy was administered in 21% of patients. Endocrine therapy was administered with selective ER modulators (SERMs) alone in 48.5% and with aromatase inhibitors or SERMs ± gonadotropin-releasing hormone agonists in 51.5% of the population. The low, midrange, and high ODx groups consisted of 692 (69.5%), 142 (14.3%), and 161 patients (16.2%), respectively. The median age was 48 years (range, 23–78 years) in all patients.

Table 1 shows the clinicopathological characteristics and the ODx results according to menopausal status. Postmenopausal patients showed a higher proportion of high RS and high body mass index (BMI) compared to the premenopausal group. The proportion of high ER Allred score, negative/low PR expression,

Table 1. Baseline characteristics of the whole study population

Characteristic	Premenopausal group (n = 642)	Postmenopausal group (n = 353)	P-value
ODx RS	17.0 ± 7.8	18.8 ± 9.6	0.003[a]
Low (0–20)	473 (73.7)	219 (62.0)	<0.001
Midrange (21–25)	86 (13.4)	56 (15.9)	
High (26–100)	83 (12.9)	78 (22.1)	
Age (yr)	43.5 ± 5.7	59.1 ± 5.8	<0.001[a]
≤40	184 (28.7)	0 (0)	<0.001
41–50	407 (63.4)	17 (4.8)	
51–60	51 (7.9)	192 (54.4)	
>60	0 (0)	144 (40.8)	
BMI (kg/m^2)	22.3 ± 3.0	24.2 ± 3.3	<0.001[a]
<18.5	43 (6.7)	2 (0.6)	<0.001
≥18.5, <23	342 (53.3)	128 (36.3)	
≥23, <25	162 (25.2)	110 (31.2)	
≥25	95 (14.8)	113 (32.0)	
Histologic type			
IDC	535 (83.3)	303 (85.8)	0.132
ILC	59 (9.2)	35 (9.9)	
Others	48 (7.5)	15 (4.2)	
T-stage			
pT1a	8 (1.2)	2 (0.6)	0.129
pT1b	128 (19.9)	52 (14.7)	
pT1c	380 (59.2)	220 (62.3)	
pT2–3	126 (19.6)	79 (22.4)	
Histologic grade			
I	172 (26.8)	86 (24.4)	0.442
II	413 (64.3)	228 (64.6)	
III	57 (8.9)	39 (11.0)	
Clinical risk group			
Low risk	493 (76.8)	254 (72.0)	0.092
High risk	149 (23.2)	99 (28.0)	
ER Allred score			
Low (3–5)	50 (7.8)	13 (3.7)	0.011
High (6–8)	592 (92.2)	340 (96.3)	
PR Allred score			
Negative (0)	32 (5.0)	87 (24.6)	<0.001
Low (1–5)	122 (19.0)	118 (33.4)	
High (6–8)	488 (76.0)	148 (41.9)	
HER2 score			
0	169 (26.3)	74 (21.0)	0.008
1+	289 (45.0)	145 (41.1)	
2+ & ISH(–)	184 (28.7)	134 (38.0)	

Table 1. Continued

Characteristic	Premenopausal group (n = 642)	Postmenopausal group (n = 353)	P-value
Ki-67 level (%)			
≤15	332 (51.7)	184 (52.1)	0.901
>15	310 (48.3)	169 (47.9)	
Single gene score			
ESR1	9.5 ± 0.9	10.7 ± 1.2	<0.001[a]
PGR	7.9 ± 1.2	6.6 ± 1.7	<0.001[a]
ERBB2	9.1 ± 0.7	9.2 ± 0.7	0.022[a]
Type of surgery			
Breast-conserving surgery	375 (58.4)	259 (73.4)	<0.001
Total mastectomy	267 (41.6)	94 (26.6)	
Radiation therapy			
Not done	252 (39.3)	93 (26.3)	<0.001
Done	390 (60.7)	260 (73.7)	
Chemotherapy			
Not done	505 (78.7)	281 (79.6)	0.727
Done	137 (21.3)	72 (20.4)	

Values are presented as mean ± standard deviation or number (%). ODx RS, Oncotype Dx recurrence score; BMI, body mass index; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor type 2; ISH, *in-situ* hybridization assay.
[a]Independent t-test was used to compare means between premenopausal and postmenopausal patients.

and HER2 2+ result was significantly higher in postmenopausal patients. These trends were significantly maintained in quantitative single gene scores of an RS assay. Tumor stage, histologic type and grade, clinical risk group, and Ki-67 index were not significantly different between the 2 groups.

Clinicopathologic characteristics according to the ODx groups in premenopausal and postmenopausal patients

Table 2 presents clinicopathological features according to the ODx results in premenopausal ER(+)/HER2(–) women with node-negative breast cancer. Histologic grade, clinical risk, PR expression, and Ki-67 levels were statistically different between the 3 groups. Multiple comparison analyses showed that while the difference between the midrange RS group and the high-risk group was statistically nonsignificant, there existed a significant difference between the midrange RS group and the low-risk group. These results suggested that premenopausal patients with a midrange RS demonstrated similar characteristics to those in the high RS group. The low ODx group showed unique favorable characteristics compared to those with a midrange or high RS; lower histologic grade, higher low clinical risk, higher proportion of high PR expression, and more than half of patients with a low Ki-67 proliferative index. The age distribution, BMI, histologic type, and pathological tumor stage were not significantly different among the ODx risk groups.

However, postmenopausal patients with a midrange RS demonstrated contradictory results compared to their premenopausal counterparts. The midrange RS group demonstrated similar characteristics to those observed in the low RS group, except for the PR score (Table 3). As expected, higher grade, negative/low PR expression, and high proliferation index were more frequently observed in patients with a high RS as compared to those in the midrange or low RS group. Similar to the results of the premenopausal group, age at diagnosis, BMI, histologic type, tumor stage, and HER2 score were not statistically different among the ODx subgroups.

Regarding systemic treatments, premenopausal low, midrange, and high RS groups received chemotherapy in 1.7%, 55.8%, and 97.6% of patients. However, postmenopausal low, midrange, and high RS groups received chemotherapy in 0.0%, 5.4%, and 88.5% of patients. Endocrine therapy initiation was done with SERM alone in 68.7% of premenopausal women and with aromatase inhibitors in 88.1% of postmenopausal patients.

Multinominal logistic regression analysis

We performed multinomial logistic regression analyses to calculate which parameters were significant in the low or high ODx group compared to the midrange RS group. Age, tumor stage, histologic grade, PR status, and Ki-67 level were entered into models in premenopausal (Table 4) and postmenopausal (Table 5) patients. In premenopausal women, odds ratios of smaller pT1 stage, lower histologic grade, higher PR score, and lower Ki-67 were significantly higher in the low RS group. However, in the high ODx group, a higher PR score alone showed a significantly negative association and most variables were not different from those of the midrange ODx group.

Opposite results were found in postmenopausal patients. Most variables except for PR expression in the low ODx group were statistically similar to those of the midrange group. However, histologic grade, PR score, and Ki-67 level were significantly different between the high and midrange RS groups.

The ODx single gene score

We analyzed *ER*, *PR*, *HER2* gene scores according to the ODx groups stratified by menopausal status (Fig. 1). In premenopausal patients, the average score of *ESR1* was 9.7 in the low, 9.1 in the midrange, and 9.0 in the high ODx group; the low-risk group showed significantly higher *ESR1* scores than the other groups. The mean score of *PGR* in the low, midrange, and high groups was 8.4, 7.2, and 6.3, respectively; *PGR* score gradually decreased as ODx RS increased with statistical significance. The average score of *ERBB2* was 9.2, 9.0,

Table 2. Clinicopathological characteristics of premenopausal patients

Characteristic	Low ODx RS (0–20) (n = 473)	Midrange ODx RS (21–25) (n = 86)	High ODx RS (26–100) (n = 83)	P-value		
				Overall (3 groups)	Low *vs.* midrange	High *vs.* midrange
Age (yr)						
≤30	13 (2.7)	4 (4.7)	5 (6.0)	0.097	0.075	0.277[a]
31–40	110 (23.3)	29 (33.7)	23 (27.7)			
41–50	311 (65.8)	50 (58.1)	46 (55.4)			
51–60	39 (8.2)	3 (3.5)	9 (10.8)			
BMI (kg/m^2)						
<23	274 (57.9)	56 (65.1)	55 (66.3)	0.490	0.457	0.925
≥23, <25	124 (26.2)	19 (22.1)	19 (22.9)			
≥25	75 (15.9)	11 (12.8)	9 (10.8)			
Histologic type						
IDC	390 (82.5)	72 (83.7)	73 (88.0)	0.763	0.868	0.733
ILC	47 (9.9)	7 (8.1)	5 (6.0)			
Others	36 (7.6)	7 (8.1)	5 (6.0)			
T-stage						
pT1a/b	111 (23.5)	14 (16.3)	11 (13.3)	0.090	0.133	0.802
pT1c	278 (58.8)	50 (58.1)	52 (62.7)			
pT2–3	84 (17.8)	22 (25.6)	20 (24.1)			
Histologic grade						
I & II	457 (96.6)	70 (81.4)	58 (69.9)	<0.001	<0.001[a]	0.081
III	16 (3.4)	16 (18.6)	25 (30.1)			
Clinical risk group						
Low	390 (82.5)	57 (66.3)	46 (55.4)	<0.001	0.001	0.148
High	83 (17.5)	29 (33.7)	37 (44.6)			
ER Allred score						
Low (3–5)	31 (6.6)	8 (9.3)	11 (13.3)	0.094	0.357	0.416
High (6–8)	442 (93.4)	78 (90.7)	72 (86.7)			
PR Allred score						
Negative (0)	8 (1.7)	9 (10.5)	15 (18.1)	<0.001	<0.001	0.017
Low (1–5)	65 (13.7)	23 (26.7)	34 (41.0)			
High (6–8)	400 (84.6)	54 (62.8)	34 (41.0)			
HER2 score						
0	132 (27.9)	17 (19.8)	20 (24.1)	0.255	0.116	0.496
1+/2+ & ISH(–)	341 (72.1)	69 (80.2)	63 (75.9)			
Ki-67 level (%)						
≤15	271 (57.3)	36 (41.9)	25 (30.1)	<0.001	0.008	0.112
>15	202 (42.7)	50 (58.1)	58 (69.9)			

Values are presented as number (%).
ODx RS, Oncotype Dx recurrence score; BMI, body mass index; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; *HER2*, human epidermal growth factor receptor type 2; ISH, *in-situ* hybridization assay.
[a]Fisher exact test was used to compare groups.

and 8.8 in the low, midrange, and high groups, respectively; however, statistical significance was noted between the low and midrange groups but not in between the midrange and high groups.

Similar patterns were noted in postmenopausal women. The mean score of *ESR1* was 10.9 in the low, 10.4 in the midrange, and 10.3 in the high RS group; the low RS group showed significantly higher *ESR1* scores than the other groups. The average score of *PGR* in the low, midrange, and high groups was 7.3, 6.0, and 5.0, respectively; similar to premenopausal patients, *PGR* gradually decreased as RS increased. Lastly, the mean score of *ERBB2* was 9.3, 9.1, and 9.2 in low, midrange, and high RS groups; however, no statistical significance was demonstrated among groups.

Survival analysis

The mean follow-up duration was 46.0 months (standard deviation, 25 months) in all patients. A low recurrence rate of 2.7% and a rare death rate of 0.6% were detected. Survival curves are presented in Fig. 2 according to the ODx

Table 3. Clinicopathological characteristics of postmenopausal patients

Characteristic	Low ODx RS (0–20) (n = 219)	Midrange ODx RS (21–25) (n = 56)	High ODx RS (26–100) (n = 78)	P-value		
				Overall (3 groups)	Low *vs.* midrange	High *vs.* midrange
Age (yr)						
41–50	13 (5.9)	1 (1.8)	3 (3.8)	0.630[a]	0.531[a]	0.749[a]
51–60	115 (52.5)	30 (53.6)	47 (60.3)			
61–70	81 (37.0)	24 (42.9)	27 (34.6)			
>70	10 (4.6)	1 (1.8)	1 (1.3)			
BMI (kg/m^2)						
<23	77 (35.2)	20 (35.7)	33 (42.3)	0.228	0.664	0.513
≥23, <25	63 (28.8)	19 (33.9)	28 (35.9)			
≥25	79 (36.1)	17 (30.4)	17 (21.8)			
Histologic type						
IDC	183 (83.6)	48 (85.7)	72 (92.3)	0.390	0.866	0.360[a]
ILC	25 (11.4)	5 (8.9)	5 (6.4)			
Others	11 (5.0)	3 (5.4)	1 (1.3)			
T-stage						
pT1a/b	38 (17.4)	7 (12.5)	9 (11.5)	0.725	0.679	0.959
pT1c	132 (60.3)	36 (64.3)	52 (66.7)			
pT2–3	49 (22.4)	13 (23.2)	17 (21.8)			
Histologic grade						
I & II	205 (93.6)	54 (96.4)	55 (70.5)	<0.001	0.539[a]	<0.001
III	14 (6.4)	2 (3.6)	23 (29.5)			
Clinical risk group						
Low risk	168 (76.7)	41 (73.2)	45 (57.7)	0.006	0.584	0.065
High risk	51 (23.3)	15 (26.8)	33 (42.3)			
ER Allred score						
Low (3–5)	8 (3.7)	1 (1.8)	4 (5.1)	0.610[a]	0.691[a]	0.400[a]
High (6–8)	211 (96.3)	55 (98.2)	74 (94.9)			
PR Allred score						
Negative (0)	31 (14.2)	19 (33.9)	37 (47.4)	<0.001	<0.001	0.012
Low (1–5)	65 (29.7)	20 (35.7)	33 (42.3)			
High (6–8)	123 (56.2)	17 (30.4)	8 (10.3)			
HER2 score						
0	43 (19.6)	14 (25.0)	17 (21.8)	0.665	0.377	0.664
1+/2+ & ISH(–)	176 (80.4)	42 (75.0)	61 (78.2)			
Ki-67 level (%)						
≤15	127 (58.0)	32 (57.1)	25 (32.1)	<0.001	0.909	0.004
>15	92 (42.0)	24 (42.9)	53 (67.9)			

Values are presented as number (%).
ODx RS, Oncotype Dx recurrence score; BMI, body mass index, IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor type 2; ISH, *in-situ* hybridization assay.
[a]Fisher exact test was used to compare groups.

RS. In premenopausal patients, the high RS group showed significantly worse DFS but no difference in OS was observed according to ODx RS. In postmenopausal women, 21-gene RS was not statistically associated with DFS, and excellent survival was observed regarding OS. Multivariable Cox's hazard model showed that high RS and no use of chemotherapy increased the risk of recurrence in premenopausal women, but no variable was associated with DFS in postmenopausal patients (Table 6). Among patients with midrange RS of 21–25, premenopausal women receiving chemotherapy showed better DFS, but no statistical significance was noted (Fig. 3).

DISCUSSION

In the TAILORx trial, an RS of <11 was reclassified as low risk, an RS of 11–25 as intermediate risk, and an RS of ≥26 as high-risk groups. According to the results of the TAILORx trial in 2018, endocrine therapy alone was noninferior to chemoendocrine therapy in patients with an RS of 11–25, except for patients aged 50 years or less with an RS of 16–25.

Table 4. Multinominal logistic regression in premenopausal patients

Variable	β	Odds ratio (95% CI)	P-value
Low vs. midrange ODx RS			
Intercept	–1.620		0.001
Age (yr), 41–60 *vs*. ≤40	0.430	1.538 (0.923–2.562)	0.098
T-stage, pT1 *vs*. pT2–3	0.585	1.795 (1.018–3.165)	0.043
Histologic grade, I & II *vs*. III	1.563	4.773 (2.191–10.398)	<0.001
PR Allred score, 6–8 *vs*. 0–5	1.185	3.271 (1.932–5.537)	<0.001
Ki-67 level (%), ≤15 *vs*. >15	0.525	1.691 (1.028–2.781)	0.038
High *vs*. midrange ODx RS			0.168
Intercept	0.688		
Age (yr), 41–60 *vs*. ≤40	0.404	1.498 (0.775–2.898)	0.230
T-stage, pT1 *vs*. pT2–3	0.077	1.080 (0.525–2.220)	0.835
Histologic grade, I & II *vs*. III	–0.489	0.613 (0.285–1.320)	0.211
PR Allred score, 6–8 *vs*. 0–5	–0.941	0.390 (0.207–0.736)	0.004
Ki-67 level (%), ≤15 *vs*. >15	–0.503	0.604 (0.309–1.181)	0.141

CI, confidence interval; ODx RS, Oncotype Dx recurrence score; PR, progesterone receptor.

Table 5. Multinominal logistic regression in postmenopausal patients

Variable	β	Odds ratio (95% CI)	P-value
Low vs. midrange ODx RS			
Intercept	1.445		0.092
Age (yr), >60 *vs*. 41–60	–0.147	0.863 (0.468–1.589)	0.636
T-stage, pT1 *vs*. pT2–3	–0.013	0.987 (0.481–2.027)	0.972
Histologic grade, I & II *vs*. III	–0.599	0.549 (0.115–2.624)	0.453
PR Allred score, 6–8 *vs*. 0–5	1.081	2.948 (1.566–5.548)	0.001
Ki-67 level (%),≤15 *vs*. >15	0.172	1.187 (0.638–2.209)	0.588
High *vs*. midrange ODx RS			<0.001
Intercept	3.210		
Age (yr), >60 *vs*. 41–60	–0.554	0.575 (0.269–1.228)	0.153
T-stage, pT1 *vs*. pT2–3	–0.094	0.910 (0.380–2.177)	0.833
Histologic grade, I & II *vs*. III	–2.293	0.101 (0.021–0.481)	0.004
PR Allred score, 6–8 *vs*. 0–5	–1.491	0.225 (0.085–0.597)	0.003
Ki-67 level (%), ≤15 *vs*. >15	–0.680	0.507 (0.236–1.086)	0.081

CI, confidence interval; ODx RS, Oncotype Dx recurrence score; PR, progesterone receptor.

Moreover, further analysis of the TAILORx trial applying the clinical risk group classification according to the Adjuvant! algorithm used in the MINDACT trial was conducted to clarify the absolute benefit of chemotherapy in the intermediate-risk group with an RS of 16–25, in patients aged 50 years or less, or in premenopausal patients [13].

In this study, we analyzed the clinicopathologic factors of the midrange RS group compared with the low and high RS groups in both premenopausal and postmenopausal patients. As described above, regarding histologic grade, Ki-67, and clinical risk, unfavorable features of the midrange RS in premenopausal patients were similar to those of the high RS group, unlike in the postmenopausal patients. Since prior studies have already suggested that the clinicopathological features could provide prognostic information that is complementary to genomic assays, more aggressive therapy may be considered in the clinical setting for a specific subset of patients [19-21].

As mentioned earlier, we showed that the PR scores significantly differed in all subgroups, irrespective of the RS groups or menopausal status. As previous studies have already shown, lower PR expression was highly correlated with a higher RS [22-24]. A recently updated nomogram using the National Cancer Database showed a higher probability of a high-risk ODx in grade III with the highest score and subsequently in PR-negative case with the second highest score [25]. Previous large, sampled studies categorized simply PR into positive versus negative. However, the current study used the PR Allred score, which has more detailed information. Taken together, not only ODx gene scores but also PR gene expression could show significant differences according to ODx groups in both

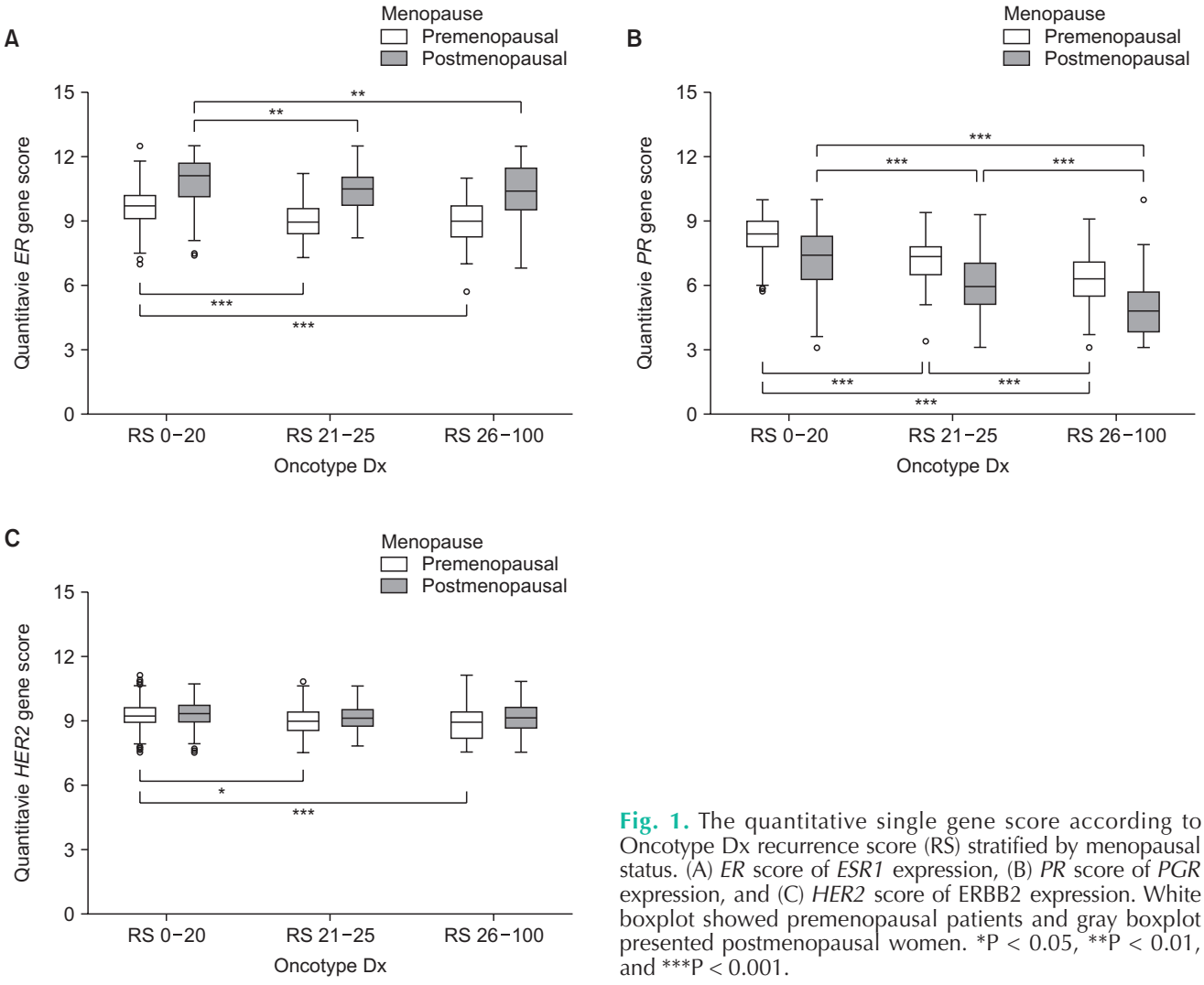

Fig. 1. The quantitative single gene score according to Oncotype Dx recurrence score (RS) stratified by menopausal status. (A) *ER* score of *ESR1* expression, (B) *PR* score of *PGR* expression, and (C) *HER2* score of ERBB2 expression. White boxplot showed premenopausal patients and gray boxplot presented postmenopausal women. *P < 0.05, **P < 0.01, and ***P < 0.001.

premenopausal and postmenopausal patients.

It is difficult to make treatment decisions for patients with discordant risk results, such as in patients with high clinical risk and low genomic risk or vice versa. In this study, 122 premenopausal patients (19.0%) had clinical-high/RS of 16–20 or clinical-any/RS of 21–25 risk categories. When making treatment decisions of administering chemotherapy or not for high clinical risk patients in real-world practice, physicians tend to follow the genomic risk guidelines [26,27]. Recently updated results of the MINDACT trial reported beneficial effects of chemotherapy for patients with high clinical risk, while different effects were observed according to age for low genomic risk patients [28]. Furthermore, in the high clinical risk premenopausal patients with an RS of 16–20, more aggressive treatment decisions are recommended rather than 5-year tamoxifen only [13]. In our premenopausal cohort with RS 21–25, only 24.4% received SERM alone without chemotherapy which were lower than the proportion of patients in arm B of the TAILORx trial [12].

In clinical practice, physicians choose chemotherapy in midrange RS with high clinical risk because of the beneficial effects of chemotherapy in young or premenopausal patients; one is a direct cytotoxic effect to eradicate any possible micrometastases and the other is an antiestrogenic effect from chemotherapy-induced ovarian suppression [29-31]. Although our study results would not suggest new treatment options, we focus on the relationship between premenopausal midrange RS and postmenopausal high RS. Based on the similarities in clinicopathological factors and PR Allred scores, further molecular biological research could potentially identify new factors that address the diagnostic limitations of ODx.

There were several limitations to this study. First, a relatively small number of patients were enrolled. In addition, this was a retrospective study and it was hard to compare the actual therapeutic effect due to the short follow-up duration and small number of events. More importantly, the patient who underwent the ODx assay was possibly selected according to the judgment of clinicians. The proportion of patients with high-risk RS (16.2%) was higher than that of the TAILORx trial

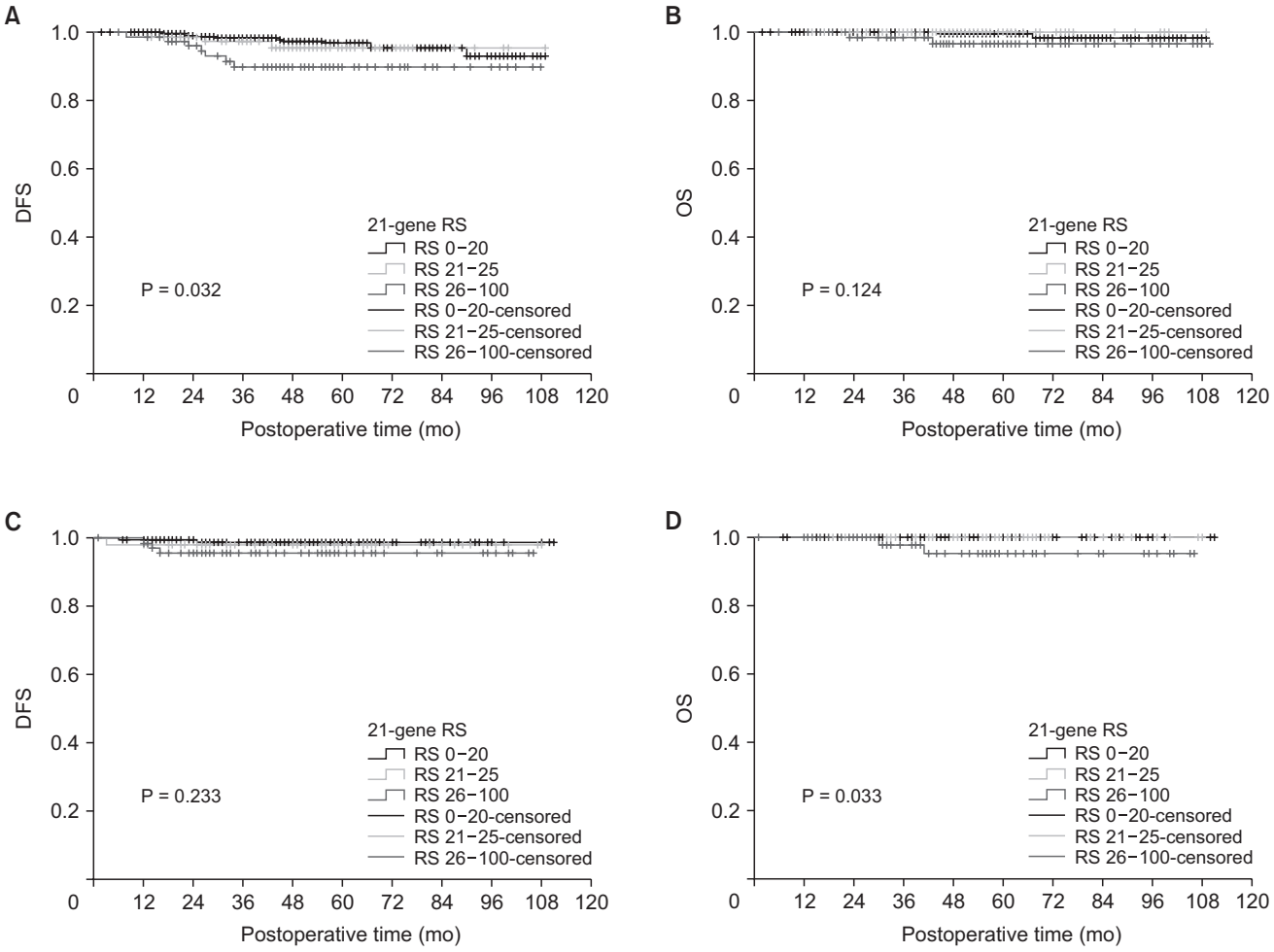

Fig. 2. Kaplan-Meier survival curve according to Oncotype Dx recurrence score (RS) stratified by menopausal status. (A) Disease-free survival (DFS) and (B) overall survival (OS) in premenopausal patients. (C) DFS and (D) OS in postmenopausal patients.

Table 6. Multivariable Cox's regression model for disease-free survival stratified by menopausal status

Variable	Hazard ratio (95% CI)	P-value
Premenopausal patients		
ODx RS		
0–20	Reference	
21–25	2.417 (0.629–9.281)	0.199
26–100	15.108 (2.191–104.150)	0.006
Clinical risk group, low vs. high	1.697 (0.671–4.293)	0.264
Chemotherapy, done vs. not done	5.697 (0.922–35.188)	0.061
Postmenopausal patients		
ODx RS		
0–20	Reference	
21–25	1.733 (0.147–20.386)	0.662
26–100	1.675 (0.027–103.190)	0.806
Clinical risk group, low vs. high	0.998 (0.175–5.695)	0.998
Chemotherapy, done vs. not done	0.368 (0.008–17.283)	0.611

CI, confidence interval; ODx RS, Oncotype Dx recurrence score.

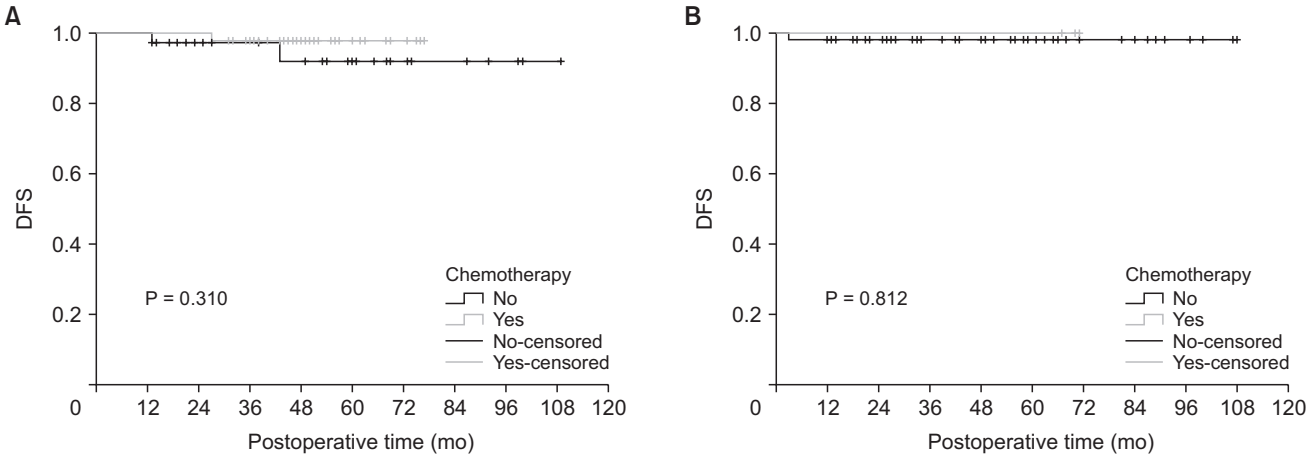

Fig. 3. Disease-free survival (DFS) curve according to use of adjuvant chemotherapy in patients with Oncotype Dx recurrence score (RS) 21–25. (A) Premenopausal patients and (B) premenopausal women. Black line showed no use of chemotherapy and gray line presented use of chemotherapy.

(14.3%) [12], and this bias may have influenced the results of this study. Additionally, we could only obtain the gene scores of *ER*, *PR*, and *HER2* from the ODx reports. Other gene scores including proliferation-related gene group could also affect the RS and may reflect differences in the clinicopathological features. Since the scores of other genes were not available for analysis, the question remains unanswered.

In conclusion, this study highlighted the unique clinicopathological characteristics of premenopausal patients with midrange RS, which were similar to those of the high RS group. Nonetheless, these findings should not be directly connected to the therapeutic decision-making for premenopausal ER+/HER2-, node-negative breast cancer patients with the 21-gene RS of 21–25. Additional supporting studies should be performed to confirm these relationships in a larger patient cohort. We also recommend that in real-world practice, considering current evidence, the benefits and harms of adjuvant systemic treatment should be discussed and explored with patients until we find definite answers.

Conflict of Interest

Seho Park, serving as an member of the Editorial Board of *Annals of Surgical Treatment and Research*, did not participate in the review process of this article. No other potential conflicts of interest pertinent to this article were reported.

ORCID iD

Jung Min Park: https://orcid.org/0000-0002-6190-5781
Suk Jun Lee: https://orcid.org/0000-0003-3839-5071
Jee Hyun Ahn: https://orcid.org/0000-0003-4176-3277
Chan Seok Yoon: https://orcid.org/0000-0001-6971-5926
Seho Park: https://orcid.org/0000-0001-8089-2755

Author Contribution

Conceptualization, Project Administration: CSY, SP
Formal Analysis: JMP, SJL
Investigation: JMP, SJL, JHA
Methodology: JHA
Writing – Original Draft: JMP, SJL
Writing – Review & Editing: All authors

ACKNOWLEDGEMENTS

Fund/Grant Support

None.

REFERENCES

1. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000;406:747-52.
2. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: how special are they? Mol Oncol 2010;4:192-208.
3. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl

Cancer Inst 2004;96:218-28.
4. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869-74.
5. Untch M, Thomssen C, Bauerfeind I, Braun M, Brucker SY, Felberbaum R, et al. Primary therapy of early breast cancer: evidence, controversies, consensus: spectrum of opinion of German specialists on the 16th St. Gallen International Breast Cancer Conference (Vienna 2019). Geburtshilfe Frauenheilkd 2019;79:591-604.
6. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, 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.
7. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ, et al. Strategies for subtypes: dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011;22:1736-47.
8. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-26.
9. Carlson JJ, Roth JA. The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis. Breast Cancer Res Treat 2013;141:13-22.
10. Tsai M, Lo S, Audeh W, Qamar R, Budway R, Levine E, et al. Association of 70-gene signature assay findings with physicians' treatment guidance for patients with early breast cancer classified as intermediate risk by the 21-gene assay. JAMA Oncol 2018;4:e173470.
11. D'Alfonso TM, van Laar RK, Vahdat LT, Hussain W, Flinchum R, Brown N, et al. BreastPRS is a gene expression assay that stratifies intermediate-risk Oncotype DX patients into high- or low-risk for disease recurrence. Breast Cancer Res Treat 2013;139:705-15.
12. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018;379:111-21.
13. Sparano JA, Gray RJ, Ravdin PM, Makower DF, Pritchard KI, Albain KS, et al. Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. N Engl J Med 2019;380:2395-405.
14. Sparano JA, Crager MR, Tang G, Gray RJ, Stemmer SM, Shak S. Development and validation of a tool integrating the 21-gene recurrence score and clinical-pathological features to individualize prognosis and prediction of chemotherapy benefit in early breast cancer. J Clin Oncol 2021;39:557-64.
15. Regan MM, Fleming GF, Walley B, Francis PA, Pagani O. Adjuvant systemic treatment of premenopausal women with hormone receptor-positive early breast cancer: lights and shadows. J Clin Oncol 2019;37:862-6.
16. Olivotto IA, Bajdik CD, Ravdin PM, Speers CH, Coldman AJ, Norris BD, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. J Clin Oncol 2005;23:2716-25.
17. Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 2016;375:717-29.
18. Yoon KH, Lee SJ, Kim Y, Ahn JH, Kim JY, Park HS, et al. A simplified risk scoring system for predicting high-risk groups in gene expression tests for patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative, and node-positive breast cancer. Ann Surg Treat Res 2023;105:360-8.
19. Goldstein LJ, Gray R, Badve S, Childs BH, Yoshizawa C, Rowley S, et al. Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features. J Clin Oncol 2008;26:4063-71.
20. Tang G, Cuzick J, Costantino JP, Dowsett M, Forbes JF, Crager M, et al. Risk of recurrence and chemotherapy benefit for patients with node-negative, estrogen receptor-positive breast cancer: recurrence score alone and integrated with pathologic and clinical factors. J Clin Oncol 2011;29:4365-72.
21. Rakha EA, Reis-Filho JS, Baehner F, Dabbs DJ, Decker T, Eusebi V, et al. Breast cancer prognostic classification in the molecular era: the role of histological grade. Breast Cancer Res 2010;12:207.
22. Chaudhary LN, Jawa Z, Szabo A, Visotcky A, Chitambar CR. Relevance of progesterone receptor immunohistochemical staining to Oncotype DX recurrence score. Hematol Oncol Stem Cell Ther 2016;9:48-54.
23. Mattes MD, Mann JM, Ashamalla H, Tejwani A. Routine histopathologic characteristics can predict oncotype DX(TM) recurrence score in subsets of breast cancer patients. Cancer Invest 2013;31:604-6.
24. Huang JL, Kizy S, Marmor S, Altman A, Blaes A, Beckwith H, et al. Tumor grade and progesterone receptor status predict 21-gene recurrence score in early stage invasive breast carcinoma. Breast Cancer Res Treat 2018;172:671-7.
25. Orucevic A, Bell JL, King M, McNabb AP, Heidel RE. Nomogram update based on TAILORx clinical trial results: oncotype DX breast cancer recurrence score can be predicted using clinicopathologic data. Breast 2019;46:116-25.
26. Gao W, Lin L, Fei X, Chen X, Shen K. Decision-making of adjuvant chemotherapy for breast cancer patients with discordant risk classifications between clinical-pathological factors and 21-gene recurrence score. J Cancer 2020;11:2509-17.
27. Dieci MV, Guarneri V, Zustovich F, Mion M, Morandi P, Bria E, et al. Impact of 21-gene breast cancer assay on treatment decision for patients with T1-T3, N0-N1, estrogen receptor-positive/human epidermal growth receptor 2-negative

breast cancer: final results of the prospective multicenter ROXANE study. Oncologist 2019;24:1424-31.
28. Piccart M, van 't Veer LJ, Poncet C, Lopes Cardozo JM, Delaloge S, Pierga JY, et al. 70-Gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol 2021;22:476-88.
29. Swain SM, Jeong JH, Geyer CE Jr, Costantino JP, Pajon ER, Fehrenbacher L, et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. N Engl J Med 2010;362:2053-65.
30. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol 2006;24:5769-79.
31. Francis PA, Regan MM, Fleming GF. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 2015;372:1673.