JNMS Journal of Nippon Medical School https://www.nms.ac.jp/sh/jnms/

Original

The Indication of Adjuvant Therapy Based on Oncotype DX Recurrence Score in Relation to Clinical and Pathological Factors, and Survival: A Retrospective Analysis of Real-World Use

Hideki Asakawa[1,2], Asuka Nakamura[2], Yuki Yanagawa[2], Takashi Shigekawa[2] and Hiroyuki Takei[1]

[1]Department of Breast Surgery and Oncology, Nippon Medical School, Tokyo, Japan
[2]Department of Breast Surgery and Oncology, Tokyo Kyosai Hospital, Tokyo, Japan

Background: Oncotype DX is an important tool for guiding perioperative treatment in estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer. Real-world retrospective studies are essential for validating its clinical utility.

Methods: We retrospectively evaluated the association of Oncotype DX Recurrence Score (ODRS) with clinical and pathological characteristics, chemotherapy regimen, and recurrence-free survival (RFS) in consecutive patients with ER-positive/HER2-negative primary breast cancer.

Results: A total of 133 patients underwent Oncotype DX testing to determine the need for adjuvant chemotherapy. Mean age was 49.2 years, 67.7% of the patients were premenopausal, and 50.4% had nodal metastases. Mean ODRS was 19.5. Patients were categorized into three risk groups: low (ODRS 0–15, 40.6%), intermediate (16–25, 36.1%), and high (≥26, 23.3%). ODRS was significantly correlated with histologic grade, ER, PgR, and Ki-67. Endocrine therapy alone was administered to all low-risk patients. Chemotherapy was administered to 20.8% of patients at intermediate risk and 67.7% of patients at high risk. Multivariate analysis confirmed that ODRS was the strongest predictor of chemotherapy administration. During a median follow-up of 30.4 months, three distant recurrences occurred (in two intermediate-risk patients and one high-risk patient). No recurrence was observed in the low-risk group. RFS was worse in higher ODRS categories.

Conclusions: Real-world data demonstrate that ODRS correlates with key pathological characteristics and can guide adjuvant therapy selection, independent of menopausal status or nodal involvement. This suggests that ODRS is useful in tailoring chemotherapy decisions in ER-positive/HER2-negative breast cancer.

(J Nippon Med Sch 2026; 93 (3): 225–235. https://doi.org/10.1272/jnms.JNMS.2026_93-307)

Keywords: adjuvant therapy, breast cancer, oncotype DX, premenopausal women, recurrence-free survival

Introduction

The Oncotype DX test (Genomic Health) uses formalin-fixed tumor specimens to analyze 16 tumor-associated genes in patients with hormone receptor-positive/human epidermal growth factor receptor 2 (HER2)-negative breast. These genes include proliferation-related factors (*Ki-67*, *STK15*, *Survivin*, *CCNB1*, and *MYBL2*), HER2-related factors (*GRB7* and *HER2*), estrogen receptor (ER)-related factors (*ER*, *PGR*, *BCL2*, and *SCUBE2*), invasion-related factors (*MMP11* and *CTSL2*), and other genes

Correspondence to Hideki Asakawa, hideki-asakawa@nms.ac.jp
https://doi.org/10.1272/jnms.JNMS.2026_93-307
Received: December 8, 2025; Accepted: December 22, 2025

(*GSTM1*, *CD68*, and *BAG1*). Five reference genes (*ACTB*, *GAPDH*, *RPLPO*, *GUS*, and *TFRC*) are also measured by reverse transcription polymerase chain reaction (RT-PCR). Oncotype DX clarifies the biological characteristics of individual tumors, particularly their sensitivity to chemotherapy[1], and yields a Recurrence Score (RS) ranging from 0 to 100. This score predicts the likelihood of distant metastasis and the additive benefit of chemotherapy in adjuvant treatment[1–6]. Furthermore, studies have shown that Oncotype DX reduces healthcare costs by preventing unnecessary chemotherapy[7]. Oncotype DX became available in Japan in 2010, and public health insurance began covering it in 2023. Consequently, the number of patients undergoing this test has recently increased.

Retrospective analyses of Oncotype DX (NSABP B-20[2] and SWOG 8814[3]) classified RS values of 0–17 as low risk, 18–30 as intermediate risk, and 31–100 as high risk. In both lymph node-negative (NSABP B-20) and lymph node-positive (SWOG 8814) groups, chemotherapy showed no additional benefit in the low-risk group but yielded a clear benefit in the high-risk group. However, the additional benefit of chemotherapy for intermediate-risk patients remains uncertain.

Subsequently, prospective trials were conducted. The criteria for recommending additional chemotherapy based on the Oncotype DX Recurrence Score (ODRS) were revised in accordance with the results of two major trials: the TAILORx trial[5], which was published in 2018 and enrolled lymph node-negative patients, and the RxPONDER trial[6], which was published in 2021 and enrolled patients with one to three positive lymph nodes. In the TAILORx trial, ODRS scores of 0–10 were classified as low-risk, 11–25 as intermediate-risk, and 26–100 as high-risk. Low-risk patients received endocrine therapy alone, whereas high-risk patients received a combination of endocrine therapy and chemotherapy. A randomized comparison of an intermediate-risk group receiving endocrine therapy alone or combined endocrine therapy and chemotherapy showed no additional benefit from chemotherapy in patients aged 50 years or older. Among patients younger than 50 years, no additional benefit from chemotherapy was observed in those with ODRS values of 11–15. However, an additional benefit from chemotherapy was observed in those with ODRS values of 16–25. In the RxPONDER trial, no additional benefit from chemotherapy was observed in postmenopausal women with ODRS values of 0–25. However, chemotherapy did yield an additional benefit in premenopausal women with ODRS values of 0–25. Thus, as research has progressed from retrospective to prospective studies, the criteria for recommending additional chemotherapy have evolved accordingly.

Despite these changes, it remains important to use real-world data to examine the value of the ODRS as a prognostic or predictive factor.

Materials and Methods

Study Design

This retrospective study evaluated the real-world use of Oncotype DX for determining whether adjuvant chemotherapy should be added to endocrine therapy. We also analyzed correlations of ODRS with clinicopathological characteristics and the effectiveness of adjuvant chemotherapy in improving recurrence-free survival (RFS) after surgery. This study was approved by the Ethics Review Board of Tokyo Kyosai Hospital (Research ID: 2505002-0).

Patients

The analysis included patients who underwent surgery at Tokyo Kyosai Hospital between May 2010 and November 2024, provided written informed consent, received Oncotype DX testing at the physician's discretion when the indication for chemotherapy was uncertain, and had ER-positive/HER2-negative breast cancer with negative lymph nodes or one to three positive lymph nodes. Patients who had received preoperative chemotherapy or had bilateral breast cancer (simultaneous or sequential) were excluded. Eligible cases meeting these criteria were retrospectively identified from the institutional database, and data from 133 patients were ultimately included in the analysis.

Clinical and Pathological Characteristics

The clinical and pathological characteristics evaluated were age at surgery, menopausal status, disease stage, pathological tumor size, pathological lymph node metastasis, histological type, histological grade, vascular invasion, ER status, PgR status, HER2 status, and Ki-67 status. Postmenopausal status was defined as absence of menstruation for at least 1 year or a history of bilateral oophorectomy. TNM staging was performed according to the Union for International Cancer Control (UICC) TNM classification[8]. Histological type was determined based on the World Health Organization (WHO) classification of Tumors, 4th edition[9]. Invasive ductal carcinoma (IDC) and invasive carcinoma of no special type were treated as equivalent. Histological grade (HG) was assessed ac-

cording to the Japanese Breast Cancer Society General Rules for Clinical and Pathological Recording of Breast Cancer[10].

Expressions of ER, PgR, HER2, and Ki-67 were evaluated by immunohistochemical staining using anti-ER (SP 1), anti-PgR (1E2), anti-HER2/neu (4B5), and anti-Ki-67 (30-9) antibodies, respectively. Immunohistochemical staining was performed according to manufacturers' instructions. ER, PgR, and Ki-67 expression was quantified as the percentage of positive cells (0–100%). HER2 was scored as 0, 1+, 2+, or 3+ by immunohistochemistry and classified as positive in cases with a score of 3+, or a score of 2+ with a HER2/CEP17 ratio ≥2.0 by in situ hybridization.

Oncotype DX Recurrence Score (ODRS)

Breast tumor tissues were fixed in formalin as quickly as possible and submitted to the pathology department. After obtaining informed consent, Oncotype DX testing was performed in accordance with the manufacturer's instructions. The pathology department prepared fifteen 5-µm-thick sections from a representative paraffin-embedded tumor block. These sections were sent via SRL (Japan) to Genomic Health, Inc. (now Exact Sciences, Inc., USA). ODRS test results were reported approximately 3 weeks later by mail or via the Internet (after public insurance approval).

In the TAILORx trial, a reduction in distant recurrence was observed in intermediate-risk patients younger than 50 years with ODRS scores of 16–25 who received adjuvant chemotherapy. On the basis of these findings, our study classified ODRS scores as follows: 0–15, low risk; 16–25, intermediate risk; and 26–100, high risk.

Adjuvant Therapy

The attending physician explained to the patient the predicted recurrence risk based on the ODRS and the expected benefit of adjuvant chemotherapy. After considering the patient's clinical and pathological characteristics, the physician determined the postoperative adjuvant therapy plan. As previously mentioned, criteria for recommending adjuvant chemotherapy have evolved over time and are based on the results of retrospective studies and two prospective trials—the TAILORx trial, published in 2018, and the RxPONDER trial, published in 2021.

Endocrine therapy included tamoxifen alone, tamoxifen combined with a gonadotropin-releasing hormone (GnRH) agonist (goserelin or leuprorelin), or aromatase inhibitors (AIs) alone (anastrozole or letrozole). Postoperative chemotherapy regimens included epirubicin and cyclophosphamide (EC) followed by paclitaxel or docetaxel, docetaxel and cyclophosphamide (TC), or tegafur/gimeracil/oteracil potassium (TS-1), which is approved in Japan as an adjuvant chemotherapy agent.

Survival

RFS was defined as the interval from surgery to breast cancer recurrence or death.

Statistical Analysis

Associations of ODRS with clinicopathological characteristics were analyzed by using correlation coefficients, the chi-square test, t-test, analysis of variance, and logistic regression. RFS was analyzed in relation to ODRS using the Kaplan-Meier method, log-rank test, and Cox proportional hazards model for multivariate analysis. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using BellCurve for Excel (SSRI Inc., Japan).

Results

Data from 133 patients were analyzed. Their clinical and pathological characteristics and ODRS scores are summarized in **Table 1**. Mean age was 49.2 ± 10.0 years. As compared with national data on Japanese patients with breast cancer, this cohort included a higher proportion of younger patients; 90 (67.7%) were premenopausal. HG1 or HG2 accounted for 128 cases (96.3%), representing most tumors, and the proportion of low-grade cases was higher than that typically reported in Japan. The mean ER-positive cell ratio was 85.6% ± 13.4%, and the mean PgR-positive cell ratio was 65.8% ± 33.0%. The degree of hormone dependence was greater than that in the general Japanese breast cancer population. In contrast, the mean Ki-67-positive cell rate was 32.1% ± 17.7%, and lymph node metastasis was observed in 67 patients (50.4%), nearly half of the cohort. Compared with national registry data, the proportion of high-risk cases was higher. The mean ODRS was 19.5 ± 10.1. When stratified into three groups—ODRS ≤15 (low risk), ODRS 16–25 (intermediate risk), and ODRS ≥26 (high risk)—the cohort included 54 (40.6%), 48 (36.1%), and 31 (23.3%) patients, respectively. High-risk cases were the least common, and low-risk and intermediate-risk cases each accounted for approximately 40% of the cohort.

Associations between clinicopathological characteristics and risk classification was evaluated using the ODRS (**Table 2**). As the HG increased from one to three, the

Table 1 Clinical and pathological characteristics of patients (N = 133)

Characteristic	Value
Age at surgery, years	22 to 77, 49.2±10.0
<50	76 (57.1)
≥50	57 (42.9)
Menopausal status	
Premenopausal	90 (67.7)
Postmenopausal	43 (32.3)
Clinical stage	
T1	76 (57.1)
T2	56 (42.1)
T3	1 (0.8)
N0	126 (94.7)
N1	7 (5.3)
Stage IA	74 (55.6)
Stage IIA	53 (39.8)
Stage IIB	6 (4.5)
Pathological tumor size (invasive size), mm	1 to 60, 20.8±9.1
>20	57 (42.9)
≤20	76 (57.1)
Pathological nodal status	
Negative	66 (49.6)
Positive	67 (50.4)
Histological type	
IDC	125 (94.0)
ILC	5 (3.8)
Special types	3 (2.3)
Histological grade	
1	71 (53.4)
2	57 (42.9)
3	5 (3.8)
Lymphovascular invasion	
Absent	59 (44.4)
Present	74 (55.6)
ER, %	20 to 100, 85.6±13.4
PgR, %	0 to 100, 65.8±33.0
Ki-67, %	1 to 70, 32.1±17.7
ODRS	0 to 54, 19.5±10.1
0–15	54 (40.6)
16–25	48 (36.1)
26–100	31 (23.3)

Values are expressed as range, mean ± SD, or n (%) unless otherwise indicated.

ER: estrogen receptor, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, ODRS: oncotype DX recurrence score, PgR: progesterone receptor.

number of low-risk cases decreased and the proportion of high-risk cases increased; this difference was statistically significant (P = 0.035). The ER- and PgR-positive cell ratios significantly progressively decreased across the low-, intermediate-, and high-risk groups (P = 0.018 and P < 0.001, respectively). Similarly, the percentage of Ki-67-positive cells significantly increased across the low-, intermediate-, and high-risk groups (P < 0.001). When categorized using cutoff values of 80% for ER, 60% for PgR, and 30% for Ki-67, the results for PgR and Ki-67 were consistent with the above analysis: each was significantly associated with ODRS-defined risk (P < 0.001). However, ODRS-defined risk was not associated with age, menopausal status, clinical stage, pathological tumor diameter, pathological nodal status, histological type, or vascular invasion. Multivariate analysis identified PgR

Table 2 Correlation of oncotype DX recurrence score with clinical and pathological characteristics of patients

		ODRS			P value	
		0–15	16–25	26–100	Univariate	Multivariate[c]
No. of patients	133	54 (40.6)	48 (36.1)	31 (23.3)		
Age at surgery, years	49.2±10.0	49.2±9.3	48.6±9.6	50.2±12.0	0.58[a]	
<50	76	34 (44.7)	28 (36.8)	14 (18.4)	0.27[b]	0.78
≥50	57	20 (35.1)	20 (35.1)	17 (29.8)		
Menopausal status						
Premenopausal	90	42 (46.7)	32 (35.6)	16 (17.8)	0.081[b]	0.45
Postmenopausal	43	12 (27.9)	16 (37.2)	15 (34.9)		
Clinical stage						
T1	76	31 (40.8)	30 (39.5)	15 (19.7)	0.90[b]	
T2	56	23 (41.1)	18 (32.1)	15 (26.8)		
T3	1	0 (0)	0 (0)	1 (100.0)		
N0	126	52 (41.3)	45 (35.7)	29 (23.0)	0.98[b]	
N1	7	2 (28.6)	3 (42.9)	2 (28.6)		
Stage IA	74	31 (41.9)	28 (37.8)	15 (20.3)	0.86[b]	0.35
Stage IIA	53	21 (39.6)	19 (35.8)	13 (24.5)		
Stage IIB	6	2 (33.3)	1 (16.7)	3 (50.0)		
Pathological tumor size (invasive size), mm	20.8±9.1	20.4±8.0	20.3±9.3	22.7±10.6	0.31[a]	
≤20	76	31 (40.8)	30 (39.5)	15 (19.7)	0.46[b]	0.58
>20	57	23 (40.4)	18 (31.6)	16 (28.1)		
Pathological nodal status						
Negative	66	22 (33.3)	25 (37.9)	19 (28.8)	0.17[b]	0.83
Positive	67	32 (47.8)	23 (34.3)	12 (17.9)		
Histological type						
IDC	125	52 (41.6)	45 (36.0)	28 (22.4)	0.85[b]	0.80
ILC	5	2 (40.0)	2 (40.0)	1 (20.0)		
Special types	3	0 (0)	1 (33.3)	2 (66.7)		
Histological grade						
1	71	31 (43.7)	27 (38.0)	13 (18.3)	0.035[b]	0.13
2	57	22 (38.6)	21 (36.8)	14 (24.6)		
3	5	1 (20.0)	0 (0)	4 (80.0)		
Lymphovascular invasion						
Present	74	34 (45.9)	26 (35.1)	14 (18.9)	0.27[b]	0.67
Absent	59	20 (33.9)	22 (37.3)	17 (28.8)		
ER, %	85.6±13.4	87.4±11.7	87.3±7.9	79.8±20.2	0.018[a]	
≤80	41	14 (34.1)	13 (31.7)	14 (34.1)	0.14[b]	0.16
>80	92	40 (43.5)	35 (38.0)	17 (18.5)		
PgR, %	65.8±33.0	78.2±25.6	64.6±30.3	45.9±38.6	<0.001[a]	
≤60	39	7 (17.9)	16 (41.0)	16 (41.0)	<0.001[b]	0.0035
>60	94	47 (50.0)	32 (34.0)	15 (16.0)		
Ki-67, %	32.1±17.7	26.3±15.7	32.4±17.6	41.9±17.4	<0.001[a]	
≤30	87	44 (50.6)	32 (36.8)	11 (12.6)	<0.001[b]	<0.001
>30	46	10 (21.7)	16 (34.8)	20 (43.5)		

[a] P value of Pearson correlation coefficient.

[b] P value of Pearson chi-square test.

[c] P value of ordinal logistic regression analysis.

Values are expressed as mean ± SD or n (%) unless otherwise indicated.

ER: estrogen receptor, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, ODRS: oncotype DX recurrence score, PgR: progesterone receptor.

(P = 0.0035) and Ki-67 (P < 0.001) as significant factors associated with the ODRS.

We evaluated associations between clinicopathological characteristics, ODRS score, and administration of additional chemotherapy. In univariate analysis, additional chemotherapy was significantly associated with PgR (P = 0.035), Ki-67 (P = 0.0068), and ODRS (P < 0.001) (**Table 3**). However, additional chemotherapy was not associated with age, menopausal status, clinical stage, pathological tumor size, pathological lymph node metastasis, histological type, HG level, or vascular invasion. In multivariate analysis, only ODRS score remained significantly associated with administration of additional chemotherapy (P < 0.001; **Table 3**). The frequency of chemotherapy increased progressively from the low- to intermediate- to high-risk categories (**Table 3**).

Of the 54 cases classified as low risk (ODRS score, 0–15), none received additional chemotherapy (**Table 3**). Premenopausal patients with positive lymph node metastasis are recommended to receive additional chemotherapy. Among the 42 patients who met these criteria, chemotherapy was administered to nine; the remaining 33 did not receive chemotherapy. The details of these 33 cases are shown in **Table 4**. Because of their low ODRS score and high ER and PgR expression, these patients were considered highly hormone-sensitive, which contributed to the decision to forgo chemotherapy in many cases. Of the 33 patients who did not receive chemotherapy, 27 (81.8%) received combination therapy with a GnRH agonist and tamoxifen.

Although chemotherapy is generally recommended when the ODRS score is 26 or higher, this study included 10 high-risk patients who did not receive chemotherapy (**Table 5**). Many of these patients were classified as high-risk on the basis of clinical and pathological characteristics. The reasons for not administering chemotherapy were as follows: five patients did not meet the initial high-risk threshold of an ODRS score of 31 or higher and five patients declined chemotherapy.

TC, the most common chemotherapy regimen, was administered to 18 patients (58.1%). EC followed by taxanes was administered to 8 patients (25.8%), and TS-1 was used in 5 cases (16.1%) (**Table 6**).

Analysis of the associations between ODRS, pathological lymph node metastasis, and chemotherapy regimen showed that TS-1 was used in 5 of 10 cases (50%) in the intermediate-risk group (ODRS 16–25) and that TC was used in 16 out of 21 cases (76.2%) in the high-risk group (ODRS ≥26). Among lymph node-positive cases, EC followed by taxanes was the most commonly administered regimen. These associations were statistically significant (**Table 6**).

Regarding RFS, metastatic recurrence occurred in three cases during a median follow-up period of 30.4 months (range, 1.0–177.4 months). Details of the three cases are summarized in **Table 7**. Two metastatic recurrences occurred in the intermediate-risk group (61 months postoperatively with bone metastasis and 97 months postoperatively with lung metastasis), and one occurred in the high-risk group (59 months postoperatively with lung metastasis). All three patients were pathologically node-negative and experienced relatively late recurrences. Cases 1 and 2 were premenopausal and had high ER and PgR but a high Ki-67 labeling index. The patients were treated with GnRH agonists and tamoxifen but did not receive TC. Case 3 was postmenopausal and had a large-diameter tumor with low ER and PgR expression levels. According to the ODRS, this case was classified as a high-risk case, and an aromatase inhibitor was administered after TC.

Among the 54 cases classified as low-risk by the ODRS, all received endocrine therapy alone and showed no recurrence or metastasis. Similarly, none of the 10 patients who were classified as high-risk by the ODRS and did not receive chemotherapy experienced recurrence or metastasis.

We evaluated the association of ODRS with clinicopathological characteristics in relation to RFS. Univariate analysis showed that RFS decreased across ODRS categories in the order of low-, intermediate-, and high-risk groups; however, the differences were not significant (**Figure 1**). The 8-year postoperative RFS rates were 100%, 85.2%, and 80.0% in the low-, intermediate-, and high-risk groups, respectively. No other clinicopathological characteristics were significantly associated with RFS.

Discussion

The present patients who were eligible for Oncotype DX testing had clinical and pathological characteristics consistent with a favorable response to endocrine therapy. They exhibited greater hormone sensitivity and lower tumor grades than the average Japanese patient with breast cancer. However, they also had high Ki-67 labeling index values and included a substantial proportion of lymph node-positive cases. These findings suggest that the cohort was at high risk and required careful evaluation of whether chemotherapy should be added to endocrine therapy. These observations indicate that the selection of

Table 3 Correlation of adjuvant therapy regimen with clinical and pathological factors of patients

		Adjuvant therapy		P value	
		Endocrine therapy alone	Endocrine therapy and Chemotherapy	Univariate[a]	Multivariate[b]
No. of patients	133	102 (76.7)	31 (23.3)		
Age at surgery, years	49.2±10.0	49.1±9.7	49.5±11.1		
<50	76	60 (78.9)	16 (21.1)	0.48	0.19
≥50	57	42 (73.7)	15 (26.3)		
Menopausal status					
Premenopausal	90	73 (81.1)	17 (18.9)	0.081	0.18
Postmenopausal	43	29 (67.4)	14 (32.6)		
Clinical stage					
T1	76	58 (76.3)	18 (23.7)	0.81	
T2	56	44 (78.6)	12 (21.4)		
T3	1	0 (0)	1 (100.0)		
N0	126	97 (77.0)	29 (23.0)	0.74	
N1	7	5 (71.4)	2 (28.6)		
StageIA	74	57 (77.0)	17 (23.0)	0.99	0.75
Stage IIA	53	41 (77.4)	12 (22.6)		
Stage IIB	6	4 (66.7)	2 (33.3)		
Pathological tumor size (invasive size), mm	20.9±9.1	20.5±8.7	22.2±10.4		
≤20	76	58 (76.3)	18 (23.7)	0.91	0.40
>20	57	44 (77.2)	13 (22.8)		
Pathological nodal status					
Negative	66	48 (72.7)	18 (27.3)	0.28	0.77
Positive	67	54 (80.6)	13 (19.4)		
Histological type					
IDC	125	97 (77.6)	28 (22.4)	0.55	0.58
ILC	5	4 (80.0)	1 (20.0)		
Special types	3	1 (33.3)	2 (66.7)		
Histological grade					
1	71	57 (80.3)	14 (19.7)	0.31	0.95
2	57	43 (75.4)	14 (24.6)		
3	5	2 (40.0)	3 (60.0)		
Lymphovascular invasion					
Absent	59	44 (74.6)	15 (25.4)	0.61	0.50
Present	74	58 (78.4)	16 (21.6)		
ER, %	85.6±13.4	86.5±12.3	82.5±16.6		
≤80	41	28 (68.3)	13 (31.7)	0.13	0.51
>80	92	74 (80.4)	18 (19.6)		
PgR, %	65.7±33.0	69.8±30.7	52.5±37.0		
≤60	39	25 (64.1)	14 (35.9)	0.027	0.61
>60	94	77 (81.9)	17 (18.1)		
Ki-67, %	32.1±17.7	29.5±16.6	40.9±18.7		
≤30	87	73 (83.9)	14 (16.1)	0.0068	0.83
>30	46	29 (63.0)	17 (37.0)		
ODRS	19.5±10.1	16.4±8.6	29.5±8.1		
0–15	54	54 (100.0)	0	<0.001	<0.001
16–25	48	38 (79.2)	10 (20.8)		
26–100	31	10 (32.3)	21 (67.7)		

[a] Pearson chi-square test.

[b] Binominal logistic regression analysis.

Values are expressed as mean ± SD or n (%) unless otherwise indicated.

ER: estrogen receptor, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, ODRS: oncotype DX recurrence score, PgR: progesterone receptor.

Table 4 Characteristics of premenopausal, node-positive patients spared chemotherapy (N = 33)

Characteristic	Value
Age at surgery, years	44.3±6.2
Pathological tumor size (Invasive size), mm	20.0±8.0
≤20 mm	20 (60.6)
>20 mm	13 (39.4)
Histological type	
IDC	33 (100.0)
ILC	0 (0)
Special types	0 (0)
Histological grade	
1	20 (60.6)
2	13 (39.4)
3	0 (0)
Lymphovascular invasion	
Present	31 (93.9)
Absent	2 (6.1)
ER, %	88.9±6.7
PgR, %	80.5±23.0
Ki-67, %	21.8±12.5
ODRS	13.5±6.3
0–15	24 (72.7)
16–25	7 (21.2)
26–100	2 (6.1)
Endocrine therapy regimen	
Tamoxifen	6 (18.2)
Tamoxifen+GnRH agonist	27 (81.8)

Values are expressed as mean ± SD or n (%) unless otherwise indicated.
ER: estrogen receptor, GnRH: gonadotropin-releasing hormone, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, ODRS: oncotype DX recurrence score, PgR: progesterone receptor.

Table 5 Characteristics of patients with high ODRS (≥26) spared chemotherapy (N = 10)

Characteristic	Value
Age at surgery, years	52.5±12.2
Menopausal status	
Premenopausal	5 (50.0)
Postmenopausal	5 (50.0)
Pathological tumor size (Invasive size), mm	20.9±10.1
≤20 mm	4 (40.0)
>20 mm	6 (60.0)
Histological type	
IDC	9 (90.0)
ILC	0 (0)
Special types	1 (10.0)
Histological grade	
1	4 (40.0)
2	5 (50.0)
3	1 (10.0)
Lymphovascular invasion	
Absent	5 (50.0)
Present	5 (50.0)
ER, %	80.5±24.2
PgR, %	40.6±44.5
Ki-67, %	38.5±16.8
Nodal status	
Positive	5 (50.0)
Negative	5 (50.0)
ODRS	34.3±9.41
Endocrine therapy regimen	
Anastrozole	1 (10.0)
Letrozole	3 (30.0)
Tamoxifen	3 (30.0)
Tamoxifen+GnRH agonist	3 (30.0)

Values are expressed as mean ± SD or n (%) unless otherwise indicated.
ER: estrogen receptor, GnRH: gonadotropin-releasing hormone, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, ODRS: oncotype DX recurrence score, PgR: progesterone receptor.

patients eligible for Oncotype DX testing was appropriate.

ODRS was significantly correlated with ER, PgR, Ki-67, and HG. Because ER, PgR, Ki-67, and HG predict prognosis and treatment sensitivity, they are important determinants of adjuvant therapy. Given the correlations between these factors and the ODRS, the ODRS is also regarded as a potential prognostic indicator. ODRS was also significantly associated with chemotherapy administration. Multivariate analysis confirmed that ODRS alone was associated with the addition of chemotherapy, which suggests that the ODRS is the primary factor guiding postoperative chemotherapy decisions in clinical practice. Indeed, because the use of conventional prognostic indicators for decisions regarding chemotherapy is challenging, it has been mostly supplanted by ODRS. In this study, none of the 42 patients in the low-risk group, including those with lymph node metastases, received additional chemotherapy, and no recurrences were observed in this group. The use of GnRH agonists in approximately 80% of the cases suggests that GnRH agonist therapy may serve as an alternative to chemotherapy. Although no significant differences were noted, disease-free survival declined across the ODRS-defined groups (low, intermediate, and high), as was the case in previous clinical trials.

Among the present endocrine therapy regimens, aromatase inhibitors were administered to postmenopausal patients when chemotherapy was not given, whereas GnRH agonists combined with tamoxifen were administered to premenopausal patients. Among the chemotherapy regimens, TC was the most frequently used,

Table 6 Correlation of chemotherapy regimen with oncotype DX recurrence score and pathological nodal status

	EC followed by taxanes	TC	TS-1	Total	P value
No. of patients	8 (25.8)	18 (58.1)	5 (16.1)	31 (100.0)	
ODRS					
0–15	0 (0)	0 (0)	0 (0)	0 (0)	
16–25	3 (30.0)	2 (20.0)	5 (50.0)	10 (100.0)	0.0055
26–100	5 (23.8)	16 (76.2)	0 (0)	21 (100.0)	
Pathological nodal status					
Negative	2 (11.1)	15 (83.3)	1 (5.6)	18 (100.0)	0.021
Positive	6 (46.2)	3 (23.1)	4 (30.8)	13 (100.0)	

Values are expressed as n (%) unless otherwise indicated.
EC: epirubicin and cyclophosphamide, ODRS: oncotype DX recurrence score, TC: docetaxel and cyclophosphamide.

Table 7 Characteristics of patients with recurrence

	Case 1	Case 2	Case 3
ODRS (risk category)	21 (intermediate)	25 (intermediate)	30 (high)
Age, years	44	42	70
Pathological tumor size, mm	35	25	60
Histological grade	1	1	2
Lymphovascular invasion	+	–	–
Pathological nodal status	–	–	–
ER, %	90	70	30
PgR, %	90	70	0
HER2	1+	2+ (FISH –)	1+
Ki-67, %	70	50	20
Menopausal status	Premenopausal	Premenopausal	Postmenopausal
Adjuvant therapy	Leuprorelin	Leuprorelin	Anastrozole
	Tamoxifen	Tamoxifen	TC
	TS-1		
RFS time (month)	61	97	59
Metastatic site	Bone	Lung	Lung

ER: estrogen receptor, FISH: fluorescent in situ hybridization, HER2: human epidermal growth factor receptor 2, ODRS: oncotype DX recurrence score, PgR: progesterone receptor, RFS: recurrence-free survival, TC: docetaxel and cyclophosphamide.

followed by EC-taxane regimens and TS-1. TC is also the most commonly used regimen in clinical trials in the United States, and the findings of this study are consistent with this observation. EC-taxane regimens are frequently administered to cases categorized as high-risk by ODRS and to pathologically node-positive cases. These results suggest that the ODRS is an important determinant in selecting chemotherapy regimens. In the POTENT clinical trial[11] of Japanese patients, TS-1 reduced the risk of recurrence by 30%, as compared with endocrine therapy alone, when added to endocrine therapy as adjuvant treatment after surgery. A 1-year oral regimen (2 weeks on, 1 week off) was approved for coverage under public health insurance for ER-positive/HER2-negative, high-risk breast cancer.

Although recurrence or metastasis occurred in only three cases, which likely influenced the results, no factor was identified as significantly affecting RFS in the univariate analysis, which prevented multivariate analysis. However, risk classification using ODRS showed a consistent trend of decreasing RFS rates across low-, intermediate-, and high-risk groups, consistent with findings from previous clinical trials. Our real-world data also suggest that the ODRS may have prognostic value.

Analysis of the three cases of recurrent metastasis showed that although all were lymph node-negative, chemotherapy was considered appropriate because of the ODRS risk classification. Some clinical and pathological

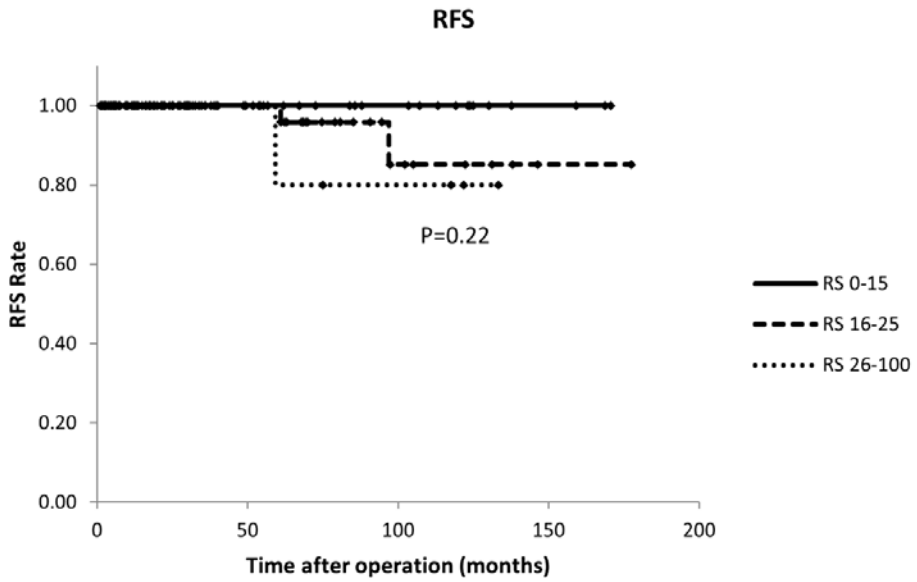

Figure 1 Recurrence-free survival (RFS) in relation to risk, as defined by Oncotype DX Recurrence Score (ODRS)
Although RFS progressively decreased as ODRS-defined risk increased, Kaplan-Meier analysis showed no association of RFS with ODRS-defined risk (P=0.22, log-rank test).

characteristics indicated a high-risk of recurrence, including high Ki-67 expression and large tumor size. Therefore, decisions regarding adjuvant drug therapy should be made cautiously, particularly when treating premenopausal and perimenopausal patients, whose social backgrounds, concerns, and preferences vary widely, making consistent judgment difficult[12–17]. For example, fertility rates are declining among adolescents and young adults[13,14], and there are concerns regarding financial burden[13,16] and patient appearance[17]. Our hospital actively uses information provided by medical social workers and has introduced scalp cooling therapy[17] to address aesthetic concerns. We strive to ensure that patients receive prompt, appropriate treatment.

This study included patients treated at community hospitals. As compared with clinical trials, this patient population exhibited greater variability in their clinical and pathological characteristics. Most patients were younger and premenopausal. Treatment selection based on ODRS risk classification, particularly for the present low-risk group (ODRS ≤15), avoided chemotherapy without recurrence. These results suggest that the addition of GnRH agonists may allow low-risk patients to avoid chemotherapy, which could help preserve fertility in premenopausal women. Therefore, treatment selection based on Oncotype DX test results may be useful even in populations with a high proportion of premenopausal patients. These findings provide context for previously reported clinical studies.

Because this study was retrospective, the results should be interpreted in conjunction with those of large-scale prospective studies.

In conclusion, perioperative treatment of young patients and those with lymph node metastases has improved long-term prognosis. Perioperative treatment guided by Oncotype DX testing enables adjuvant therapy without excess or deficiency. The Oncotype DX test is useful when considering postoperative adjuvant therapy for patients with ER-positive/HER2-negative breast cancer.

Author Contributions: All authors made substantial contributions to the study, approved the current version, and agreed to its publication.

Acknowledgments: We thank Editage (www.editage.com) for English language editing.

Funding: This study did not receive support from any funding agencies.

Conflict of Interest: Dr. Takei reports grants and personal fees from Chugai Seiyaku, Inc.; grants and personal fees from Taiho Yakuhin, Inc.; grants and personal fees from Daiichi Sankyo, Inc.; grants and personal fees from Eisai, Inc.; personal fees from AstraZeneca K.K.; and personal fees from

Pfizer outside the submitted work. Dr. Asakawa, Dr. Nakamura, Dr. Yanagawa, and Dr. Shigekawa have nothing to disclose.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: AI-assisted technologies were used exclusively for correction of English grammar. No scientific content, data analysis, or interpretations were generated by AI. The authors reviewed all AI-assisted edits and accept full responsibility for the content.

References

1. 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 [Internet]. 2004 Dec 30;351(27):2817–26. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15591335
2. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol [Internet]. 2006 Aug 10;24(23):3726–34. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16720680
3. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol [Internet]. 2010 Jan;11(1):55–65. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20005174
4. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J Clin Oncol [Internet]. 2010 Apr 10;28(11):1829–34. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20212256
5. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med [Internet]. 2018 Jul 12;379(2):111–21. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29860917
6. Kalinsky K, Barlow WE, Gralow JR, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. N Engl J Med [Internet]. 2021 Dec 16;385(25):2336–47. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34914339
7. Yamauchi H, Nakagawa C, Yamashige S, et al. Societal cost-effectiveness analysis of the 21-gene assay in estrogen-receptor-positive, lymph-node-negative early-stage breast cancer in Japan. BMC Health Serv Res [Internet]. 2014 Sep 05;14:372. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25190451
8. Brierley JD, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. 8th ed. Chichester (GB): Wiley-Blackwell; 2017.
9. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, editors. WHO classification of tumours of the breast. 4th ed. Geneva: World Health Organization; 2012.
10. Tsuda H, Akiyama F, Kurosumi M, Sakamoto G, Watanabe T. Establishment of histological criteria for high-risk node-negative breast carcinoma for a multi-institutional randomized clinical trial of adjuvant therapy. Japan National Surgical Adjuvant Study of Breast Cancer (NSAS-BC) Pathology Section. Jpn J Clin Oncol. 1998 Aug;28(8):486–91.
11. Toi M, Imoto S, Ishida T, et al. Adjuvant S-1 plus endocrine therapy for oestrogen receptor-positive, HER2-negative, primary breast cancer: a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Oncol. 2021 Jan;22(1):74–84.
12. Jacobs F, Gaudio M, Benvenuti C, De Sanctis R, Santoro A, Zambelli A. Controversies and opportunities in the clinical daily use of the 21-gene assay for prognostication and prediction of chemotherapy benefit in HR+/HER2- early breast cancer. Cancers (Basel) [Internet]. 2022 Dec 27;15(1):148. Available from: https://www.ncbi.nlm.nih.gov/pubmed/36612144
13. Benedict C, Thom B, Diefenbach M, Schapira L, Simon P, Ford JS. The impact of cancer-related financial toxicity on reproductive concerns and family-building decision-making in post-treatment survivorship. J Adolesc Young Adult Oncol [Internet]. 2023 Jun;12(3):408–15. Available from: https://www.ncbi.nlm.nih.gov/pubmed/36169520
14. Himpe J, Lammerant S, Van den Bergh L, Lapeire L, De Roo C. The impact of systemic oncological treatments on the fertility of adolescents and young adults-a systematic review. Life (Basel) [Internet]. 2023 May 18;13(5):1209. Available from: https://www.ncbi.nlm.nih.gov/pubmed/37240854
15. Ryder-Burbidge C, Diaz RL, Barr RD, et al. The burden of late effects and related risk factors in adolescent and young adult cancer survivors: a scoping review. Cancers (Basel) [Internet]. 2021 Sep 28;13(19):4870. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34638350
16. Salsman JM, Bingen K, Barr RD, Freyer DR. Understanding, measuring, and addressing the financial impact of cancer on adolescents and young adults. Pediatr Blood Cancer [Internet]. 2019 Jul;66(7):e27660. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30756484
17. Nangia J, Wang T, Osborne C, et al. Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer: the SCALP randomized clinical trial. JAMA [Internet]. 2017 Feb 14;317(6):596–605. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28196254