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Original Article

Real-world Utilization of the 21-gene Assay in Taiwanese Female Patients with Early-stage Breast Cancer: Experience from a Single Institute

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Abstract

Background: Clinical trials have demonstrated that the 21-gene assay (Oncotype DX) can predict the benefits of adjuvant chemotherapy in patients with hormone receptor-positive (HR+) and human epidermal growth factor 2-negative (HER2−) breast cancer. This study investigated the real-world utilization of this genomic test in Taiwanese patients. **Materials and Methods:** We compiled data on the recurrence score (RS) and clinicopathological characteristics of patients who received the 21-gene assay between August 2016 and August 2021. Survival outcomes were analyzed using the Kaplan–Meier method and log-rank test. Correlations between clinicopathological characteristics and RSs were analyzed using the Chi-square test or Fisher's exact test. **Results:** Of the 106 recruited patients, 34 and 72 were classified into different risk groups using conventional and Trial Assigning Individualized Options for Treatment (TAILORx)-based cutoff points, respectively. In the conventional stratification group, 61.8%, 29.4%, and 8.8% of the patients were classified into the low-risk (RS: 0–17), intermediate-risk (RS: 18–30), and high-risk (RS: 31–100) categories, respectively. In the TAILORx stratification group, 18.1%, 72.2%, and 9.7% of the patients were classified into the low-risk (RS: 0–10), intermediate-risk (RS: 11–25), and high-risk (RS: 26–100) categories, respectively. In survival analysis, recurrence-free survival did not significantly differ among discrete risk categories. The high-risk category determined using TAILORx-based cutoff points was associated with the presence of >14% Ki-67-positive cells (P = 0.004) and tumor histology Grade III (P = 0.001). **Conclusion:** Using the Oncotype DX assay, we classified a small proportion of our Taiwanese patients into the high-risk category; no survival difference was observed among the

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patients in distinct risk categories. These results suggest the clinical utility of the 21-gene assay in Taiwanese patients with early HR+/HER2−breast cancer.

Keywords: Adjuvant chemotherapy, breast cancer, Oncotype DX, recurrence score

Introduction

Breast cancer is the most prevalent malignancy in women worldwide, accounting for 11.7% of newly diagnosed cancer cases in 2020.[1] In Taiwan, breast cancer is the most common type of cancer, and its incidence has been steadily increasing among women.[2] According to the Cancer Registry Annual Report, the incidence rate of breast cancer reached 73/100,000 women, with approximately 14,000 newly diagnosed cases being reported in Taiwan in 2019. Therefore, breast cancer has become an emerging public concern over the past decade in Taiwan. Breast cancer is a group of heterogeneous diseases characterized by discrete pathological features and survival outcomes.[3,4] Hormone receptor (HR)-positive (HR+) and human epidermal growth factor 2 (HER2)-negative (HER2−) breast cancer is the most common pathological subtype. In patients with early HR+/HER2− breast cancer, the 5-year survival rate after surgical excision and adjuvant treatment is approximately 90%.[4-8] Furthermore, 15% of patients receiving adjuvant endocrine therapy alone may develop tumor recurrence 10 years after surgery.[5-8] The addition of adjuvant chemotherapy can reduce the rate of tumor recurrence by approximately 5% in patients with early HR+/HER2− breast cancer. However, if every patient is treated with adjuvant chemotherapy, the majority would be overtreated resulting in unnecessary toxicity related to chemotherapy. Therefore, the stratification method used to identify patients who may benefit from adjuvant chemotherapy is crucial to the management of early HR+/HER2− breast cancer.

The 21-gene reverse-transcriptase polymerase chain reaction (RT-PCR) assay (Genomic Health, Inc., Redwood City, CA, USA), which integrates the expression levels of 16 cancer-related genes and five reference genes, is a commercially available assay used to guide treatment decisions for patients with early HR+/HER2− breast cancer.[5-8] On the basis of the expression levels of these genes, a recurrence score (RS), ranging from 0 to 100, is calculated to predict the recurrence risk and chemotherapy benefit for patients with HR+/HER2−breast cancer after surgery. Clinical studies have reported that patients can be divided into three risk categories: low risk (RS <18), intermediate risk (RS: 18–30), and high risk (RS >30). A high RS is correlated with an increased rate of tumor recurrence and more benefits from adjuvant chemotherapy.[5-7] A large prospective clinical trial recruiting over 10,000 patients, namely the Trial Assigning Individualized Options for Treatment (Rx) (TAILORx), validated these findings.[8,9] The cutoff values of the RS for risk group classification in the TAILORx trial were different from those reported in earlier studies. To establish more effective treatment guidelines, the recurrence risk of patients in the TAILORx trial was divided into three categories: low risk (RS <11), intermediate risk (RS: 11–25), and high risk (RS ≥26). Although chemotherapy may be beneficial for some patients aged ≤50 years with a RS of 16–25, on the basis of prospective evidence, the TAILORx trial recommended avoiding chemotherapy for most patients with early HR+/HER2− breast cancer with low- or intermediate-risk RSs.[8,9]

To date, most studies using the 21-gene RT-PCR assay have been conducted in Western countries, and the clinical utility of this assay has seldom been examined in an Asian population.[10-14] A Westernized lifestyle might be the cause of the rapidly increasing incidence of breast cancer in East Asia. However, several studies have demonstrated considerable differences in clinicopathological features, molecular characterizations, and survival outcomes between East Asian and Western patients with breast cancer.[15-19] East Asian patients tend to be younger (aged <50 years), and their breast tumors are more commonly characterized as the HR + subtype (or the so-called luminal subtype). Therefore, the clinical utility of these gene expression assays in guiding treatment decisions for patients with breast cancer in East Asia should be examined. This study investigated the clinical utility of the 21-gene RT-PCR assay in patients with early HR+/HER2− breast cancer at a tertiary medical center. We analyzed clinicopathological characteristics and survival outcomes with RS results to evaluate the clinical significance of the Oncotype DX assay in Taiwanese patients.

Materials and Methods

Data sources and study population

We collected information on RSs, clinicopathological characteristics, and treatment outcomes of female patients with early HR+/HER2− breast cancer who received the Oncotype DX assay at National Cheng Kung University Hospital (NCKUH) between August 2016 and August 2021. By reviewing electronic medical records, we collected information on the patients' age, menopause status, tumor-node-metastasis stage, operation dates, and adjuvant therapies. From the pathology report of each patient's tumor tissue, we obtained data regarding the percentage of HR (i.e. estrogen and progesterone receptors), presence of Ki-67-positive cells, HER2 status, histology grade, presence of lymphatic tumor emboli, and pathological staging. When the Ki-67 percentage was presented as a range, the average value was calculated. Patients were classified into low-, intermediate-, and high-risk categories according to their RSs at diagnosis. For a RS calculated before December 2018, conventional published risk stratification was applied to assist clinical treatment decision-making; the low-, intermediate-, and high-risk

categories were defined as an RS of <18, 18–30, and >30, respectively. For RSs calculated after January 2019, the risk categories were based on the results of the TAILORx clinical trial: RS <11, 11–25, and >25 for low-, intermediate-, and high-risk categories, respectively.[8,9] The clinical risk was determined using a modified version of Adjuvant! Online adopted in the MINDACT trial.[20] All patients enrolled into this study underwent surgery with curative intent. Patients at NCKUH are advised to receive chemotherapy if they have a conventional RS ≥31 or a TAILORx RS ≥26. Chemotherapy is not suggested for patients in the conventional and TAILORx groups who have a RS of <18 and <11, respectively. Chemotherapy is also not recommended for patients >50 years of age with an RS between 11 and 25. For other categories, the decision of whether or not to administer chemotherapy is left to the physician after considering the patient's willingness, their underlying condition, menopausal status, and the score itself. This study was approved by the Institutional Review Board of NCKUH, which waived the requirement of informed consent of the patients (IRB No. B-ER-111-026).

Statistical analyses

All data and statistical analyses in this study were conducted using Microsoft Excel (Microsoft Corporation, Redmond, WA) or SPSS 22.0 software (IBM Corp, Armonk, NY, USA). Cases with missing data were excluded from the analysis and noted in the results. Survival outcomes were estimated and analyzed using the Kaplan–Meier method and the log-rank test, respectively. Recurrence-free survival (RFS) was determined from the date of the initial diagnosis to the onset of an event. The Chi-squared test and Fisher's exact test were performed to determine the significance of correlations between clinicopathological characteristics and RSs depending on the group size. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics of patients

A total of 106 Taiwanese patients with early HR+/HER2− breast cancer in whom the Oncotype DX assay was used to guide postoperative treatment decisions at NCKUH were included in this study. The median age of the patients was 54 years (range, 32–80 years), and 37.7% were premenopausal. Most of the tumor specimens were characterized as pT1 (82.1%), pN0 (97.1%), and histological Grade II (61%); the luminal B subtype (Ki-67-positive tumor cells >14%) was identified in approximately 50% of the specimens. Table 1 and Figure 1 summarize the basic clinicopathological characteristics of the study patients.

Clinical effect of RS classification on the patients

The median RS of all patients was 16, ranging from 0 to 39. Figure 2 presents the distribution of each recurrence category based on the conventional or TAILORx stratification criteria. In the conventional stratification group (n = 34), the demographic distribution of risk categories was defined as follows: 21 (61.8%) had a low risk, 10 (29.4%) had an intermediate risk, and 3 (8.8%) had a high risk. No patient in the low-risk category received chemotherapy; 20% (2/10) of the patients in the intermediate-risk category and all of the patients in the high-risk category received chemotherapy. In the TAILORx stratification group (n = 72), 72.2% of the patients were classified into the intermediate-risk category, followed by 18.1% into the low-risk category and 9.7% into the high-risk category. One (6.2%) and six (85.7%) patients in the intermediate-risk and high-risk categories, respectively, received adjuvant chemotherapy. The distribution of patients receiving chemotherapy according to each risk stratification category and menopausal status is summarized in Table 2.

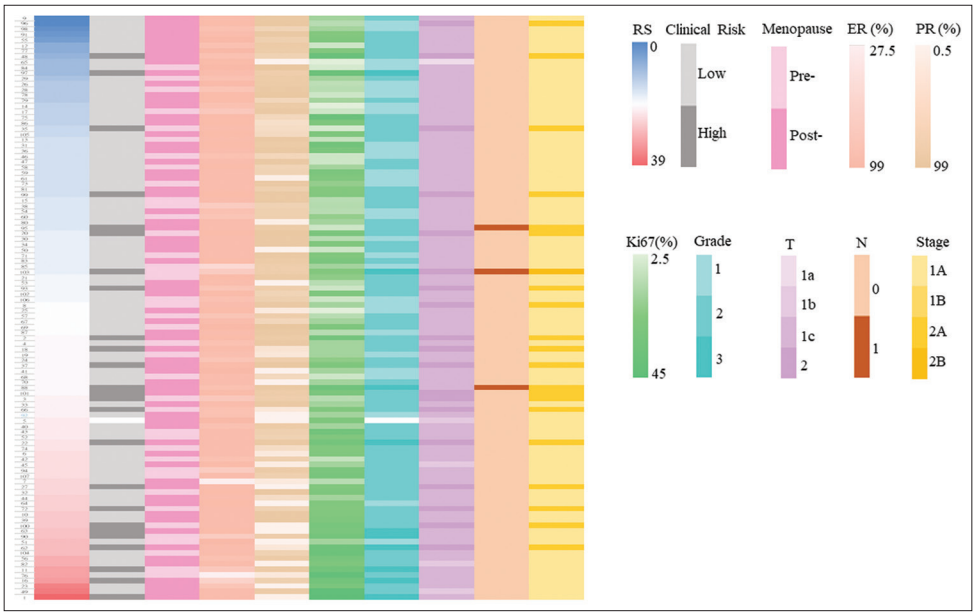

Figure 1: A heatmap illustrating the distribution of major clinicopathological characteristics of the 106 patients. The white column indicates missing data. RS: recurrence score; ER: estrogen receptor; PR: progesterone receptor

Table 1: Characteristics of the 106 patients at baseline

Characteristics	Total, *n* (%)	Conventional stratification Group, *n* (%)	TAILORx stratification Group, *n* (%)
Age (years)			
<50	36 (34)	12 (35.3)	24 (33.3)
≥50	70 (66)	22 (64.7)	48 (66.7)
Menopausal status			
Premenopausal	40 (37.7)	13 (38.2)	27 (37.5)
Postmenopausal	66 (62.3)	21 (61.8)	45 (62.5)
Pathological stage			
Stage I	85 (80.2)	27 (79.4)	58 (80.6)
Stage II	21 (19.8)	7 (20.6)	14 (19.4)
Pathological T stage			
T1	87 (82.1)	27 (79.4)	60 (83.3)
T2	19 (17.9)	7 (20.6)	12 (16.7)
Pathological N stage			
N0	102 (97.1)	34 (100)	68 (95.8)
N1	3 (2.9)	0	3 (4.2)
Estrogen receptor-positive cell percentage			
>10%	104 (98.1)	33 (97.1)	71 (98.6)
≤10%	2 (1.9)	1 (2.9)	1 (1.4)
Progesterone receptor-positive cell percentage			
>10%	71 (74)	26 (76.5)	55 (76.4)
≤10%	25 (26)	8 (23.5)	17 (23.6)
Ki-67 positive cell percentage			
>14%	54 (50.9)	15 (44.1)	39 (54.2)
≤14%	52 (49.1)	19 (55.9)	33 (45.8)
Histology grade			
I	31 (29.5)	9 (27.3)	22 (30.6)
II	64 (61)	20 (60.6)	44 (61.1)
III	10 (9.5)	4 (12.1)	6 (8.3)
Lymphatic tumor emboli			
Present	12 (11.7)	6 (18.2)	6 (8.6)
Absent	91 (88.3)	27 (81.8)	64 (91.4)
Clinical risk			
Low risk	80 (76.2)	24 (72.7)	56 (77.8)
High risk	25 (23.8)	9 (27.3)	16 (22.2)

TAILORx: Trial Assigning Individualized Options for Treatment

During a median follow-up period of 659 days, one patient experienced tumor recurrence. This 57-year-old female had a history of stage IIIA gastric adenocarcinoma and underwent subtotal gastrectomy with complete adjuvant chemotherapy in 2014. She was diagnosed with right breast cancer and underwent total mastectomy in September 2018. The pathology report of the resected tumor tissue revealed the presence of invasive lobular carcinoma with histological grade II and pathological stage IIA (pT2N0M0). Because the RS was 22, she was classified into the intermediate-risk category in accordance with the conventional stratification criteria. She received adjuvant endocrine therapy with letrozole from November 2018 until the disease relapsed with right axillary lymph node involvement in July 2020. She subsequently received axillary lymph node dissection in July 2020, followed by adjuvant chemotherapy and radiotherapy. She has been receiving tamoxifen for tumor control since January 2021, and no evidence of disease recurrence has been noted.

To investigate the prognostic effect of RSs on Taiwanese patients, we analyzed correlations between RFS and clinicopathological variables in the overall patient cohort. The results of the Kaplan–Meier method and log-rank test indicated that a shorter RFS was significantly correlated with patients with pathological stage II and T2 disease [both $P = 0.032$; Table 3 and Figure 3]. No significant difference in RFS was found among the different RS risk categories ($P = 0.607$). Although statistical significance was not reached, the RFS of the patients with high clinical risk was lower than those with low clinical risk [$P = 0.056$; Figure 3d]. Moreover, among 34 patients in the conventional group, a shorter RFS was associated with cancer specimens containing ≤10% progesterone receptor–positive cells ($P = 0.02$; Table 4 and Figure 4). Similarly, no significant difference in RFS was observed among different RS risk categories [$P = 0.279$; Table 4 and Figure 4].

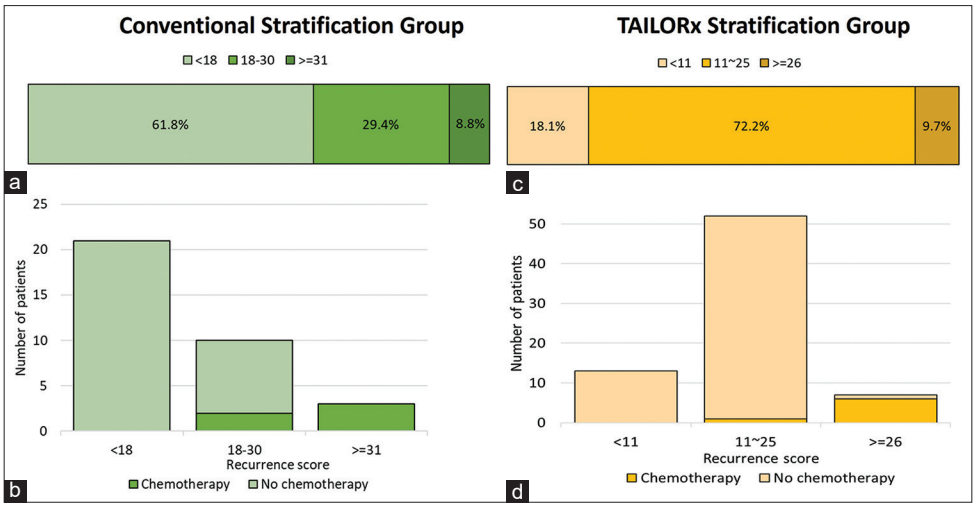

Figure 2: (a) Category distribution of patients and (b) chemotherapy use according to the conventional definition of the RS category. (c) Category distribution of patients and (d) chemotherapy use according to the TAILORx definitions of low-, intermediate-and high-risk RSs. TAILORx: Trial Assigning Individualized Options for Treatment, RSs: Recurrence score

Table 2: Distribution of patients receiving chemotherapy according to risk stratification and menopausal status

	Total number	Chemotherapy + Endocrine therapy number, *n* (%)	Endocrine therapy only number, *n* (%)
Conventional Group (*n*=34)			
Low risk	21		
Premenopause		0	9 (100)
Postmenopause		0	12 (100)
Intermediate risk	10		
Premenopause		1 (33.3)	2 (66.7)
Postmenopause		1 (14.3)	6 (85.7)
High risk	3		
Premenopause		0	0
Postmenopause		3 (100)	0
TAILORx Group (*n*=72)			
Low risk	13		
Premenopause		0	1 (100)
Postmenopause		0	12 (100)
Intermediate risk	52		
Premenopause		1 (4.3)	22 (95.7)
Postmenopause		0	29 (100)
High risk	7		
Premenopause		3 (100)	0
Postmenopause		3 (75)	1 (25)

TAILORx: Trial Assigning Individualized Options for Treatment

Associations between clinicopathological characteristics and RSs

To identify the clinicopathological characteristics associated with the RSs of our patients, we examined correlations between clinicopathological variables and RSs. When the RSs of all patients were classified based on TAILORx-based cutoff points, the high-risk category (RS ≥26) was correlated with the presence of >14% Ki-67-positive cells ($P = 0.004$) and tumor histology Grade III ($P = 0.001$). No significant correlation was noted among the high-risk category, advanced pathological stages, and the presence of lymphatic tumor emboli [Table 5].

Discussion

Breast cancer is a complex group of heterogeneous diseases arising from breast tissue. The integration of different types of treatments including surgery, radiotherapy, endocrine therapy, and chemotherapy is essential for the management of breast cancer.[21,22] Adjuvant chemotherapy can reduce tumor recurrence in a certain proportion of patients with early HR+/HER2− breast cancer. Several genomic tests have been developed to identify patients who may benefit from adjuvant chemotherapy and to avoid chemotherapy-associated toxicity in the remaining patients.[23,24] Several studies have reported that

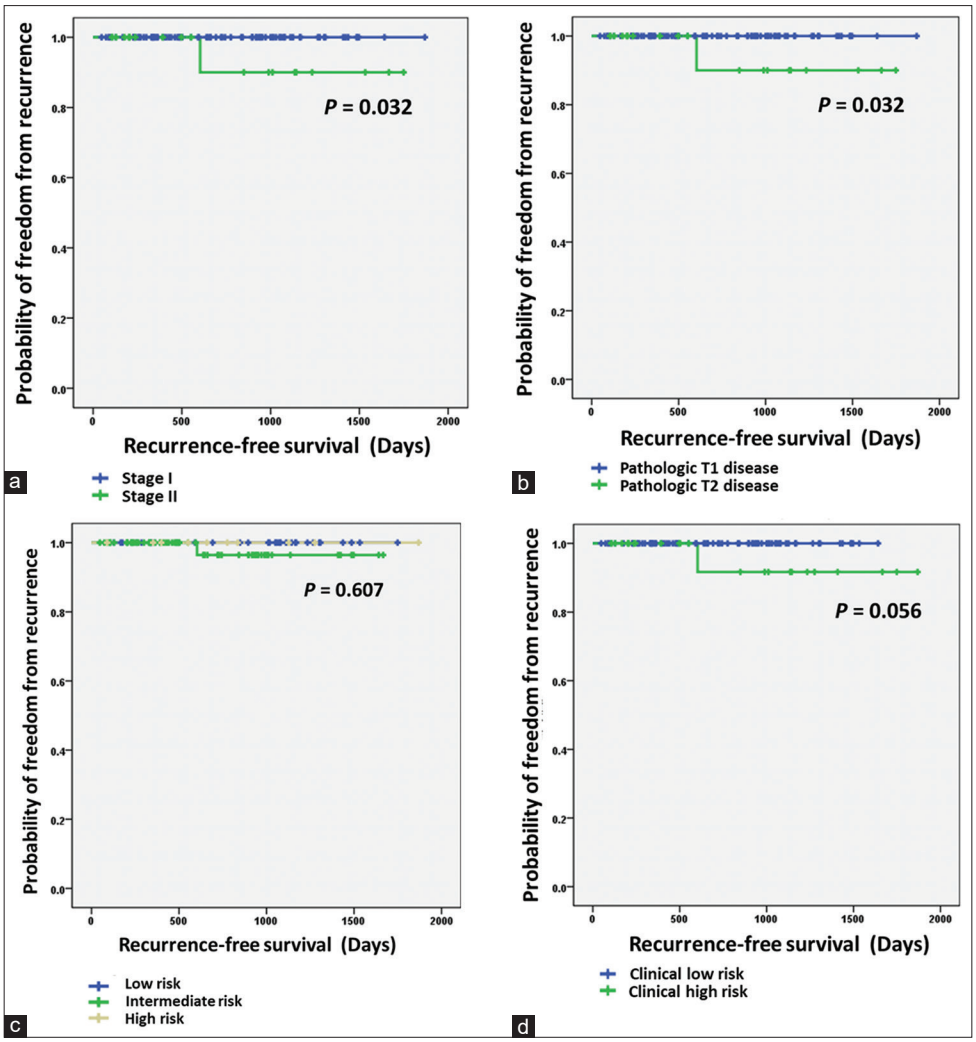

Figure 3: Survival analyses of all 106 patients demonstrating significant recurrence-free survival differences between different pathological stage groups (a) and T disease (b), but nonsignificant recurrence-free survival differences among different RS (c) and clinical risk (d) groups. RS: Recurrence score

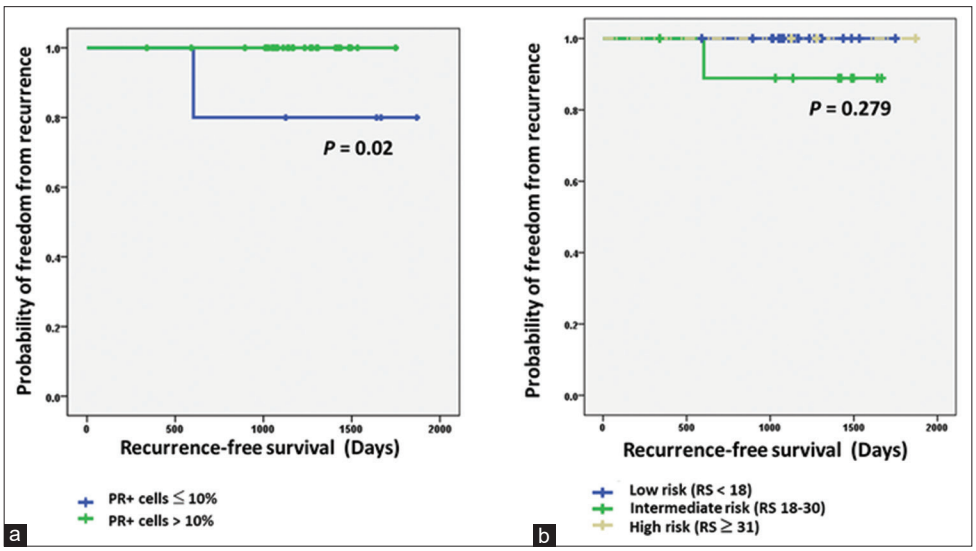

Figure 4: Survival analyses of 34 patients based on the conventional stratification definition demonstrating significant recurrence-free survival differences between different progesterone receptor expression groups (a) but nonsignificant recurrence-free survival differences among different RS risk groups (b). PR: progesterone receptor; RS: Recurrence score

Table 3: Univariable log-rank analysis of the clinical characteristics of the 106 patients

Characteristics	Recurrence-free survival	
	Event number	*P*
Age (years)		
<50	0	0.456
≥50	1	
Menopausal status		
Premenopausal	0	0.456
Postmenopausal	1	
Pathological stage		
Stage I	0	0.032*
Stage II	1	
Pathological T stage		
T1	0	0.032*
T2	1	
Progesterone receptor-positive cell percentage		
>10%	0	0.069
≤10%	1	
Ki-67 positive cell percentage		
>14%	1	0.214
≤14%	0	
Histologic grade		
I–II	1	0.779
III	0	
Lymphatic tumor emboli		
Present	0	0.703
Absent	1	
Recurrence score		
Low	0	0.607
Intermediate	1	
High	0	
Adjuvant treatment		
Only endocrine therapy	1	0.683
Chemo-endocrine therapy	0	
Clinical risk		
Low	0	0.056
High	1	

*Statistical significance

Table 4: Univariable log-rank analysis of the clinical characteristics of 34 patients in the conventional stratification group

Characteristics	Recurrence-free survival	
	Event number	*P*
Age (years)		
<50	0	0.500
≥50	1	
Menopausal status		
Premenopausal	0	0.469
Postmenopausal	1	
Pathological stage		
Stage I	0	0.059
Stage II	1	
Pathological T stage		
T1	0	0.059
T2	1	
Progesterone receptor-positive cell percentage		
>10%	0	0.02*
≤10%	1	
Ki-67 positive cell percentage		
>14%	1	0.197
≤14%	0	
Histologic grade		
I–II	1	0.700
III	0	
Lymphatic tumor emboli		
Present	0	0.624
Absent	1	
Recurrence score		
Low (<18)	0	0.279
Intermediate (18–30)	1	
High (≥31)	0	
Adjuvant treatment		
Only endocrine therapy	1	0.667
Chemo-endocrine therapy	0	

*Statistical significance

the use of the 21-gene RT-PCR assay (Oncotype DX) enabled more effective classification of patients into different risk categories and prediction of the potential benefits of adjuvant chemotherapy.[5-8] Currently, the National Comprehensive Cancer Network guidelines suggest this genomic assay to guide postoperative treatment decisions for female patients with pN0-1 HR+/HER2− breast cancer.[25] In the present study, only a small proportion of the patients were classified into the high-risk category, as determined by the Oncotype DX assay. Among the patients whose RS risk categories were determined using the conventional stratification criteria, no difference in RFS was noted between the patients receiving adjuvant chemoendocrine therapy and those receiving endocrine therapy alone. Among the patients whose RS risk categories were determined using the TAILORx stratification criteria, the high-risk category was correlated with a high percentage of Ki-67-positive cells and advanced tumor histology grade. To the best of our knowledge, this is the first study to investigate the clinical utility of the Oncotype DX assay in guiding treatment decisions for Asian patients with early HR+/HER2−breast cancer.

In this study, 8.8% and 9.7% of the patients were classified into the high-risk category based on the conventional and TAILORx stratification criteria, respectively. These results are comparable to those of studies conducted in the United Kingdom, the United States, and Italy,[10-13] suggesting that only a small proportion of Taiwanese patients with early HR+/HER2−breast cancer can benefit from adjuvant chemotherapy. Most of the patients in this study were diagnosed with pT1c (n = 83; 78.3%) and pT2 (n = 19; 17.9%) disease, for whom adjuvant chemotherapy was recommended before the availability of the Oncotype DX assay. Among the patients with pT1c and pT2 disease, seven (three in the conventional and four

Table 5: Comparisons between the recurrence score and clinical characteristics of patients receiving the Oncotype DX assay

Characteristics	Recurrence score <26 (*n*=95), *n* (%)	Recurrence score ≥26 (*n*=11), *n* (%)	*P*
Age (years)			
<50	31 (32.6)	5 (45.5)	0.395
≥50	64 (67.4)	6 (54.5)	
Menopausal status			
Premenopausal	36 (37.9)	4 (36.4)	0.921
Postmenopausal	59 (62.1)	7 (63.6)	
Pathological stage			
Stage I	75 (78.9)	10 (90.9)	0.689
Stage II	20 (21.1)	1 (9.1)	
Pathological T stage			
T1	77 (81.1)	10 (90.9)	0.684
T2	18 (18.9)	1 (9.1)	
Pathological N stage			
N0	92 (96.8)	10 (100)	1.000
N1	3 (3.2)	0	
Progesterone receptor-positive cell percentage			
>10%	75 (78.9)	5 (45.5)	0.089
≤10%	20 (21.1)	6 (54.5)	
Ki-67 positive cell percentage			
>14%	42 (44.2)	10 (90.9)	0.004*
≤14%	53 (55.8)	1 (9.1)	
Histology grade			
I–II	88 (93.6)	7 (63.6)	0.001*
III	6 (6.4)	4 (36.4)	
Lymphatic tumor emboli			
Present	11 (11.8)	1 (10)	1.000
Absent	82 (88.2)	9 (90)	

*Statistical significance

in the TAILORx stratification groups) and one patient (in the TAILORx stratification group) were classified into the high-risk category, respectively. Moreover, patients with pN1 disease (presence of one to three metastatic lymph nodes) may develop tumor recurrence, and adjuvant chemotherapy is always administered to such patients in Taiwan. A recent clinical trial, the RxPONDER study, reported that postmenopausal patients with pN1 HR+/HER2− breast cancer and a RS of <26 did not benefit from adjuvant chemotherapy.[26] In this randomized trial, the invasive disease-free survival rates at 5 years for the postmenopausal patients were 91.9% and 91.3% in the endocrine-only and chemoendocrine groups, respectively (95% confidence interval: 0.82–1.26; $P = 0.89$). In our study, three postmenopausal patients with pN1 disease were included and classified into the intermediate-risk category on the basis of the TAILORx stratification criteria. All the three patients received only an adjuvant aromatase inhibitor for anticancer treatment; no evidence of tumor recurrence was noted in these patients. These findings support the clinical utility of the 21-gene RT-PCR assay in Taiwanese patients with early HR+/HER2− breast cancer, especially in postmenopausal patients.

Unlike the uniformity of clinical practice in patients classified into the low- and high-risk categories, the use of chemotherapy is less well defined in patients classified into the intermediate-risk category. In the landmark TAILORx trial, approximately 6700 patients with intermediate RSs (11–25) were randomly assigned to receive either adjuvant chemoendocrine therapy or endocrine therapy alone.[9] The results of the TAILORx trial revealed no difference in survival outcomes between these treatment groups. The authors concluded that the efficacy of adjuvant endocrine therapy and chemoendocrine therapy was similar in the patients with pN0 HR+/HER2− breast cancer who were classified into the intermediate-risk category, although the clinical benefits of chemotherapy were observed in some patients aged <50 years. However, clinical data and a clear consensus for the use of chemotherapy in patients in the intermediate-risk category prior to the TAILORx trial are lacking. In the present study, one postmenopausal patient with pathological stage IIA (pT2N0M0) breast cancer developed tumor recurrence with local lymph node metastasis 23 months after tumor resection. The pathological features of the initially resected tumor tissue were as follows: estrogen receptor-positive cells = 90%, progesterone receptor-positive cells = 1%, Ki-67-positive cells = 20%, and tumor grade II. Because her RS was 22, she did not receive adjuvant chemotherapy according to the conventional cutoff points. If the risk

category of this patient was reclassified on the basis of the TAILORx stratification criteria, chemotherapy would still not be recommended according to the intermediate-risk category.

To evaluate the prognosis of patients with treatment decisions guided by RS-based risk categories, we examined correlations between the crucial clinicopathological variables and the RFS of patients in this study. Because of the relatively longer follow-up period in the conventional group, we analyzed survival outcomes of the patients in this group. The 34 patients in the conventional group were followed for a median of 1169 days, and tumors with ≤10% progesterone receptor-positive cells were correlated with a shorter RFS [Table 4 and Figure 4a]. Consistent with the findings of previous studies, our results suggest that the expression of the progesterone receptor is a significant prognostic factor for patients with estrogen receptor-positive breast cancer.[27-29] Because of the limited number of patients in this study, no difference in survival outcomes was observed between different RS risk categories. However, the RFS rates at 3 years were 88.9% and 96.9% in the intermediate-risk category and the entire conventional group, respectively. These survival results are in agreement with those of previous studies.[5,14] Moreover, no recurrence was observed in the high-risk patients who received chemotherapy in this study. Taken together, these findings indicate the practical performance of this genomic test in Taiwanese patients.

Some studies have examined the correlations between RSs and clinicopathological characteristics;[8,30-32] however, these correlations have not been evaluated in Taiwanese patients. When all RSs were classified using the TAILORx stratification criteria, we observed that the Ki-67-positive cell percentage and tumor histology grade were significantly correlated with the high-risk category. These two well-known prognostic biomarkers of breast cancer are associated with RS because of their involvement in 16 genes included in the RS algorithm of the Oncotype DX assay.[5] These findings can help identify patients requiring careful prognostic evaluation and potentially requiring genomic tests. Through the careful assessment of these crucial biomarkers, the 21-gene RT-PCR assay can be utilized in a cost-effective manner for the management of breast cancer. In addition, the RS algorithm of the Oncotype DX assay includes progesterone receptor expression.[5] Although statistical significance was not reached, the percentage of tumor tissues with ≤10% progesterone receptor-positive cells was higher than that of tumor tissues with >10% progesterone receptor-positive cells in the high-risk category (P = 0.089; Table 4). Moreover, the percentage of progesterone receptor-positive cells of tumor tissue from the patient with disease recurrence was 1%. Our survival analysis indicated that progesterone receptor expression was a prognostic factor for RFS. These findings provide insights into incorporating the RS and conventional biomarkers, especially progesterone receptor expression, to guide treatment decisions for patients with early HR+/HER2− breast cancer. Additional studies integrating the RS and novel biomarkers into clinical applications are warranted.

In addition to a short follow-up period and a small sample size, this study has some limitations. The retrospective study design and selected study population (considering the cost of the Oncotype DX assay) can be potential biases. Because the clinicopathological features of this study population were mostly classified as indicating intermediate risk, such as tumor grade II, high percentage of progesterone receptor-positive cells, and borderline Ki-67-positive cell percentage, this may restrict our findings to a limited population in clinical practice. In addition, the high cost of this genomic test may be a significant limitation of this study. Only patients with high socioeconomic status in Taiwan would be able to receive it. Moreover, the relevance of this test for postmenopausal Taiwanese patients with pN1 disease remains unclear, because only three such patients were recruited in this study. Notably, most of the patients had pathological T1cN0 disease (n = 81; 76.4%). As mentioned above, the results of the TAILORx trial demonstrated that some survival benefits were found in premenopausal or perimenopausal patients with pN0 HR+/HER2− breast cancer and midrange RSs. In patients aged <50 years, adjuvant chemotherapy was correlated with a lower distant recurrence rate than endocrine therapy if the RS was 16–25.[9] In the present study, most of the premenopausal patients with a midrange RS received adjuvant endocrine therapy alone [Table 2]. Regular and long-term follow-up for tumor recurrence is advised for these patients; however, the survival outcomes are notable.

Conclusion

Approximately 10% of our Taiwanese patients with early HR+/HER2− breast cancer were classified into the high-risk category using the Oncotype DX assay. Adjuvant chemotherapy was spared in most patients classified into the intermediate- and low-risk categories. On the basis of RS-guided treatment decisions, survival outcomes were similar between the patients with different RS risk categories. These real-world data suggest that the Oncotype DX assay is practical to guide treatment decisions for Taiwanese patients. In addition, the high-risk category was associated with a high percentage of Ki-67-positive cells and advanced tumor histology grade. Careful assessment of these conventional biomarkers can enable the utilization of this genomic test in a cost-effective manner. Precise prediction models should be developed to examine the benefits of adjuvant chemotherapy based on genomic tests and relevant clinicopathological factors for Taiwanese patients.

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Conflicts of interest

There are no conflicts of interest.

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