

Attempt to Substitute the Oncotype DX Breast Recurrence Score[®] Test by Histopathological Factors and MUC1 Protein Expression

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Abstract. Background/Aim: Oncotype DX Breast Recurrence Score[®] test (ODx) is a gene profiling assay predicting the benefit of adjuvant chemotherapy for early-stage hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer. Meanwhile, to avoid unnecessary financial burden on the patient, many studies have attempted to establish alternatives to ODx using conventional clinicopathological factors, but these have not yet been successful. Thus, we retrospectively investigated clinicopathological factors to establish alternatives to ODx. Patients and Methods: Data from 114 Japanese women who underwent ODx were retrospectively examined to investigate the relationship between ODx recurrence score (RS) and clinicopathological features, including MUC1 staining patterns on immunohistochemical assessment. An RS of 0-25 was defined as low, and 26-100 as high. Results: Ninety patients (79%) had low RS and 24 patients (21%) had high RS. Univariate analysis revealed that low tumor grade, high progesterone receptor (PgR) expression, and low Ki67

labeling index (LI) were significantly associated with low RS ($p=0.025$, $p<0.001$, and $p<0.001$, respectively). Tumors with an apical pattern of MUC1 staining also frequently had a low RS ($p=0.024$). In multivariate analysis, PgR expression and Ki67 LI were independent factors associated with RS ($p<0.001$, for both). When the ODx results were categorized with a combination of these two factors, only 2% of the PgR-high and Ki67-low group (one in 51 cases) had a high RS. Conclusion: PgR expression and Ki67 LI were independent factors correlated with RS. MUC1 staining pattern also has the potential to be a useful marker. We believe that it is crucial to continue attempts to identify patients who are unlikely to benefit from ODx.

After curative surgery for early-stage breast cancer, cytotoxic agents are administered when the risk of future recurrence is clinically judged to be high. However, the benefits obtained from chemotherapy depend on the biological characteristics of individual tumors. In addition, although chemotherapy reduces the risk of recurrence, treatment-related toxicity can cause hair loss, amenorrhea, drug-induced cardiomyopathy, or secondary leukemia; thus, the balance of advantages and disadvantages must be considered. Therefore, it is often difficult to determine the indication for adjuvant chemotherapy based solely on the usual pathological factors.

To assess the risk of recurrence in early-stage breast cancer, there are various multi-gene assays, such as MammaPrint[®] and Curebest[™] 95GC Breast (1, 2). Oncotype DX Breast Recurrence Score[®] test (ODx, Genomic Health, Redwood City, CA, USA) is a gene profiling assay that was developed to predict the benefit of adjuvant chemotherapy for HR-positive and HER2-negative early-stage breast cancer (3). ODx calculates the recurrence score (RS) from 0 to 100 by quantifying the expression of specific mRNAs for 21

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Key Words: Breast neoplasms, gene profiling assay, oncotype DX, recurrence score, MUC1, luminal type, intrinsic subtype, adjuvant chemotherapy.

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genes by utilizing reverse transcription polymerase chain reaction (RT-PCR). The TAILORx trial focusing on patients with T1b-T2 tumors without lymph node involvement revealed that, in patients with an RS of 11-25, the 9-year disease-free survival rate did not differ significantly between a group treated with the combination of chemotherapy and endocrine therapy, and the control group treated with endocrine therapy alone (4). Additionally, the RxPONDER trial focusing on patients with lymph node metastasis, demonstrated that the benefit of adjuvant chemotherapy differed according to menstrual status, and there was no improvement in disease-free survival and distant recurrence-free survival by additional chemotherapy for postmenopausal patients with an RS 0-25 (5). This study suggested that ODX was also useful in determining the eligibility for adjuvant chemotherapy in patients who had a relatively high risk for recurrence.

In contrast, due to the economic burden on patients, and the bias that may arise when using such genetic analysis tools, investigational attempts have been made to use conventional clinicopathological factors as substitutes for genetic tests (6-8). For example, Lashen *et al.* revealed a correlation of ODX RS with histological type, grade, estrogen receptor (ER)/progesterone receptor (PgR) and Ki-67 expression levels (6). However, alternative tools to ODX RS have not yet been established.

We have recently demonstrated that the subcellular localization of MUC1 protein may be a prognostic factor in hormone receptor-positive HER2-negative breast cancer (9). Patients with MUC1 staining only on the cell membrane had the best outcomes, suggesting a luminal-A nature. Therefore, in the current study, we retrospectively examined the relationships between clinicopathological factors, including MUC1 staining patterns, and ODX RS to establish alternatives to ODX.

Patients and Methods

Patients. A total of 114 patients, all Japanese women, with HR-positive/human epidermal growth factor receptor (HER) 2-negative invasive breast cancer who underwent ODX after curative surgery from 2017 to 2023 at our Institute, were included in the study. None of them received systemic treatment before surgery. From their data, we retrospectively investigated the relationships between the results of Odx and clinicopathological features, including anti-MUC1 mAb staining patterns. In the current study, the results of RS, ranging from 0 to 100, where higher scores correspond to a worse prognosis and a likely benefit from adjuvant chemotherapy according to some clinical trials (4, 5), were defined as low for RS 0-25 (low RS) and high for RS 26-100 (high RS).

This study was performed with approval from the Ethics Committee of Juntendo University Hospital (E23-0168). Patients could see the research plan on the hospital website and were offered the choice to opt out of the study at any time. All data were anonymized before use.

Pathological assessment. Pathological examinations were carried out at the Juntendo University Hospital by two experienced pathologists. Tumor grade was judged based on the modified Bloom-Richardson histological grading system. Estrogen receptor (ER) and progesterone receptor (PgR) statuses were assessed semi-quantitatively with immunohistochemistry, and reported as positive when >1% of cancer cell nuclei were stained. HER2 was judged as positive when more than 10% of tumor cells showed strong staining of the entire cell membrane, or *HER2/neu* gene amplification was observed by fluorescence *in situ* hybridization. HER2-positive cases were excluded from the current study. The Ki67 labeling index (LI) was semi-quantitatively evaluated by the percentage of cells positive for nuclear Ki67 within a microscopically selected hotspot under high magnification.

For the immunohistochemical assessment of MUC1 staining, anti-MUC1 mAb Ma695 (Leica Biosystems, Tokyo, Japan) was used. The same surgical specimens from 101 cases, for which sample were available, were used as those in which ODX was performed. The staining patterns in cancer tissues were assessed and classified into four groups according to the methods employed in previous reports (9) as; apical (Ap), apical + cytoplasmic (Ap + Cy), cytoplasmic (Cy), or negative. The classifications, Ap and Ap + Cy, were made when more than 10% of cancer cells examined had these patterns.

Statistical assessment. Statistical analyses were performed using the JMP 14.2.0 software (SAS Institute Inc., Cary, NC, USA). For comparisons of mean values between the two groups, the two-sided *t*-test was employed. As a test of independence, the Pearson's Chi-squared test was used. A logistic regression model was constructed to identify factors relating to RS. For full-model analysis, considering sample size and clinical significance of variables examined, menstrual status, histological type, presence of macro-metastasis of lymph node, tumor grade, lymphovascular invasion, ER status, PgR status, Ki67 LI and MUC1 staining pattern (Ap alone vs. others) were selected. To identify cutoff values of some factors to differentiate low and high RS, the receiver operating characteristic (ROC) curve was drawn. A *p*-value <0.05 was considered to indicate a significant difference.

Results

Clinicopathological features and MUC1 staining patterns on the 114 patients. The clinicopathological features and MUC1 staining patterns are shown in Table I. The mean patient age was 51.9 years (range=30-77), and 61 patients (54%) were premenopausal. The distributions of pathological stage were; Stage IA: 29%, IB: 9%, IIA: 39%, IIB: 21%, and IIIA: 2%. Thirteen patients (11%) had high-grade tumors, and the mean Ki-67 labeling index was 39.4%. MUC1 staining patterns were Ap in 10 (9%), Ap + Cy in 43 (38%), Cy in 54 (48%) and negative in five (4%) tumors.

Relationship between clinicopathological features and RS. The mean RS of the 114 patients was 18.0 (range=0-53). Ninety patients (79%) had a low RS (0-25) and 24 patients (21%) had a high RS (26-100). The relationship between RS and each clinicopathological factor was then analyzed with

Table I. Clinicopathological features of the 114 patients included in the study.

Variables		(%)/[range]
Age (mean)		51.9 [30-77]
Menstrual status	Premenopausal	61 (54%)
	Postmenopausal	53 (46%)
Histology	NST	96 (84%)
	Others	18 (16%)
Tumor size (mm, mean)		24.2 [5-80]
Lymph node metastasis	Yes	
	Macro	33 (29%)
	Micro	20 (18%)
	No	60 (53%)
	Not evaluated	1 (1%)
pStage	IA	33 (29%)
	IB	10 (9%)
	IIA	45 (39%)
	IIB	24 (21%)
	IIIA	2 (2%)
Tumor grade	High	13 (11%)
	Low/intermediate	101 (89%)
Ly	Yes	80 (70%)
	No	34 (30%)
ER (mean)		89% [20-100]
PgR (mean)		66% [0-100]
HER2	Null	30 (26%)
	Low	84 (74%)
Ki67 labeling index (mean)		39.4% [5-80]
MUC1 staining	Ap	10 (9%)
	Ap+Cy	43 (38%)
	Cy	54 (48%)
	Negative	5 (4%)

NST: No special type; Ly: lymphatic vessel invasion; ER: estrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2. Ap: apical; Ap+Cy: apical + cytoplasmic; Cy: cytoplasmic.

logistic regression models (Table II). Univariate analysis revealed that tumor grade, PgR status, and Ki67 LI were significantly associated with RS ($p=0.025$, <0.001 , and <0.001 , respectively). In other words, tumors with low/intermediate tumor grade, higher PgR values, and lower Ki67 LI frequently had a low RS. In addition, tumors with MUC1 staining showing Ap also frequently had a low RS ($p=0.024$). Meanwhile, no association was observed with other factors, including lymph node metastasis, expression levels of ER and HER2 (null vs. low). In multivariate analysis, PgR status and Ki67 LI were independent factors associated with RS (both $p<0.001$).

Cut-off values of PgR status and Ki67 LI for distinguishing low and high RS. Since PgR status and Ki67 LI were factors independently associated with RS, we next attempted to calculate the cutoff values of these factors for separating low/high RS by ROC curves. The results are shown in Figure 1A, where the cutoff values of PgR status and Ki67

LI were 60% (AUC=0.80) and 50% (AUC=0.72), respectively. Furthermore, using these cutoff values, we divided all patients into four groups according to the combination of PgR status and Ki67 LI (Figure 1B). As expected, ODx results were neatly delineated according to the combination of these two factors, as only 2% of the PgR-high and Ki67-low group (one in 51 cases) had a high RS, while 70% of the PgR-low and Ki67-high group had a high RS (seven in 10 cases).

Relationships between MUC1 staining patterns and RS. In the logistic regression analysis described above, patients were divided into two groups, Ap type and others, but we further analyzed the distribution of RS for each MUC1 staining pattern. Figure 2 shows that RS tends to increase with a change in MUC1 staining pattern in the order: Ap, Ap+Cy, and Cy; *i.e.*, as staining shifts from the cell membrane to the cytoplasm. Notably, all 10 Ap-type tumors were classified as low RS, with an RS below 25 in all cases.

Discussion

We examined the relationship between clinicopathological factors and the ODx RS. PgR status and Ki67 LI were correlated with RS. This result is in line with several other studies reporting that PgR status and Ki67 LI were associated with RS (6, 10-12). The genes encoding these two proteins are, indeed, among the 16 genes analyzed by ODx (13). ODx is a tool to analyze mRNA expression, and it is not always necessary to evaluate all 16 proteins to proxy the results. The fact that the expression of these two proteins parallels the RS results is understandable. Zarella *et al.* added examination of BCL2, also included in the ODx panel as an ER signaling-related factor, and reported that the combination of expression of these three proteins predicted RS more accurately (11).

An approach similar to the current study has been conducted in a number of previous studies. Employing classical clinicopathological factors, the establishment of nomograms that predict ODx results has also been attempted (14, 15). The conflicting results are presumably due to differences in patient background and analysis methods (7). Nevertheless, there exist limitations in predicting a prognosis solely based on patient-intrinsic factors, such as age and tumor size, and it may be important to focus more on tumor factors. Globally, biomarkers have been integrated into staging, as in the American Joint Committee on Cancer (AJCC) TNM staging system, which incorporates tumor grade, HR, and HER2 status into classical anatomic staging and proposes the clinical prognostic stage (16). Wilson *et al.* pointed out that histological findings were also important, as invasive micropapillary carcinoma and pleomorphic lobular carcinoma had a high RS (17). Tumor budding was

Table II. The relationship between clinicopathological features and ODx recurrence score.

Variables		Low RS (n=90)	High RS (n=24)	Univariate			Multivariate		
				OR	95% CI	p-Value	OR	95% CI	p-Value
Age, mean, y		52.3	50.4	0.4*	0.04-3.5	0.379			
Menstrual status	Postmenopausal	43	10	0.8	0.3-1.9	0.594	0.5	0.1-1.6	0.222
	Premenopausal	47	14						
Histology	NST	74	22	2.4	0.5-11.2	0.272	4.1	0.5-32.5	0.158
	Others	16	2						
		25.1	20.8	0.2*	0.01-2.6	0.158			
Tumor size, mean, mm	Yes	28	5	0.6	0.5-4.8	0.381	0.6	0.1-2.6	0.487
	No	62	18						
Lymph node metastasis**	Yes	7	6	4.0	1.2-13.2	0.025	1.6	0.3-9.6	0.621
	Low/intermediate	83	18						
Tumor grade	Yes	62	18	0.7	0.3-2.1	0.556	0.4	0.1-2.1	0.290
	No	28	6						
ER, mean, %		89.7	84.8	0.1*	0.01-1.6	0.113	0.1	0.9-1.01	0.134
PgR, mean, %		72.6	41.7	0.1*	0.01-0.2	<0.001	0.02	0.90-0.98	<0.001
HER2	Low	67	17	0.8	0.3-2.3	0.721			
	Null	23	7						
Ki67 L.I., mean, %		36.1	51.5	19.3*	3.0-124.3	<0.001	144.7	6.8-3067.5	<0.001
MUC1 staining	Apical	10	0	1.1E-07	n.e.	0.024	3.2E-09	n.e.	0.069
	Others	78	24						

RS: Recurrence score; OR: odds ratio; CI: confidence interval; NST: no special type; Ly: lymphatic vessel invasion; ER: estrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2; L.I.: labelling index; Cy: cytoplasmic; n.e.: not evaluated; *Range odds ratio. **Macro-metastasis.

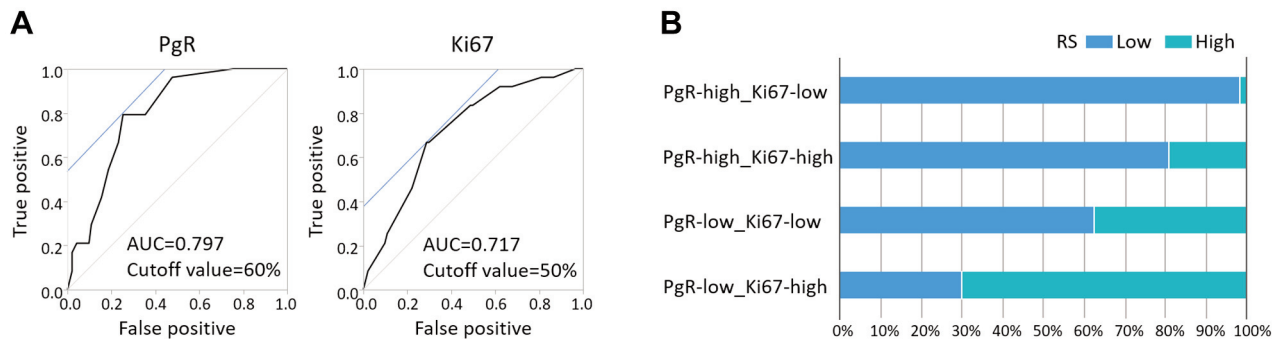


Figure 1. Cutoff values for distinguishing low and high RS. (A) ROC curve analysis of PgR status and Ki67 labeling index for distinguishing low and high RS. (B) Bar charts show the distributions of RS according to PgR status and Ki67 labeling index. Blue bars indicate a low RS, while green bars indicate a high RS. RS: Recurrence score; ROC: receiver operating characteristic.

reportedly correlated with high RS in a recent study (18). In a recent report by Lashen *et al.*, a strong relationship between pleomorphism and mitotic scores and RS were observed (6), suggesting that careful evaluation of histological findings is also important.

Nevertheless, no combination of clinicopathological factors can completely replace ODx. However, some patients may not be able to afford the ODx. In countries where ODx is available through insurance coverage, it is assumed that to

some extent ODx puts pressure on health economies, although specific figures are not known. Therefore, in clinical practice, it is necessary to continue to try and identify patients unlikely to benefit from ODx. The fact that only one of 51 patients in the PR-high and Ki67-low group in the current study had a high RS may indicate that ODx may be omitted in such a population.

In the present study, we also analyzed MUC1 staining. Although not an independently relevant factor in multivariate

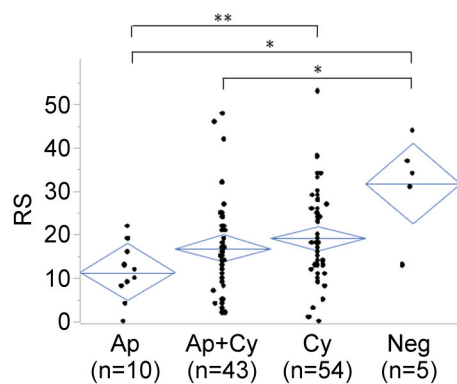


Figure 2. The relationship between MUC1 staining patterns and RS. RS according to the MUC1 staining pattern. Horizontal lines indicate the mean values of each group. RS: Recurrence score; Ap: apical; Ap + Cy: Apical + cytoplasmic; Cy: cytoplasmic; Neg: negative. ** $p < 0.010$, * $p < 0.05$.

analysis, all Ap-type tumors had a low RS, with a significant association with RS in univariate analysis. The fact that MUC1 stains only the cell membrane in these tumors may imply preserved cell polarity, which may reflect a luminal A nature (9, 19). Immunostaining for MUC1 is an inexpensive and simple evaluation method used in routine pathological diagnosis. We believe that the evaluation of MUC1 staining patterns has the potential to add useful information to existing pathological factors, although its validity should be confirmed in future studies.

The main limitation of the current study was that it included a small number of cases from a single institution. Furthermore, this study was a retrospective study which only included patients that had ODX done due to clinical need, thus there could be a strong bias in patient selection. More data clearly needs to be accumulated for practical clinical application.

We confirmed that PgR status and Ki67 LI were independent factors, among routinely examined clinicopathological factors, that were correlated with the ODX RS. Our data also revealed that assessment of MUC1 staining patterns may provide useful information to establish alternatives to ODX.

Conflicts of Interest

The Authors have no potential conflicts of interest to disclose.

Authors' Contributions

Yuka Nozaki and Yoshiya Horimoto designed this study. Yuka Nozaki, Ryoko Semba, Yuko Ueki and Yumiko Ishizuka collected clinical data. Yoshiya Horimoto, Hiroko Onagi, and Takuo Hayashi conducted pathological assessment. Yuka Nozaki, Ryoko Semba, and Yoshiya Horimoto conducted data analysis and statistics. Yuka Nozaki and Yoshiya Horimoto drafted the original manuscript and

Takahiko Kawate, Takashi Ishikawa, and Junichiro Watanabe substantively revised it. All Authors have read and approved the manuscript.

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