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Clinical Usefulness of a Multigene Testing in Patients with Special Histologic Type Breast Cancer

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Purpose: Rare special histologic types of breast cancer usually show a favorable prognosis but often has atypical features. Multigene tests (MGTs) in patients with special types of breast cancer have not been well studied. Therefore, we aimed to examine the association between MGTs and histopathology and to evaluate the prognosis of MGTs in patients with special types of breast cancer.

Materials and Methods: A total of 133 patients with special histologic types of breast cancer who underwent MGTs were selected from two institutions from 2013 to 2022. Special types were divided into favorable and unfavorable groups. The patients' clinicopathological characteristics and MGT results were compared, and disease-free survival (DFS) was analyzed.

Results: The unfavorable group consisted of 76 (57.1%) patients and included more older patients, multiple tumors, grade II/III tumors, high-risk MGT results, and chemotherapy administration. High-risk MGTs were found in 16.5% of the total cohort. The unfavorable type tended to have high-risk MGTs, but multivariate analysis demonstrated that grade II/III tumors, low progesterone receptor expression, and high Ki-67 levels were associated with high-risk MGTs in special type breast carcinomas. MGTs were significantly associated with DFS, particularly in the unfavorable subgroup, in which no recurrence occurred among patients with low-risk MGTs.

Conclusion: Unfavorable special types of breast cancer were more likely to have high-risk MGTs. The MGT result was a significant prognostic factor and could support decision-making for adjuvant therapies in patients with special histologic types of breast cancer.

Key Words: Breast neoplasms, histologic type, multigene test, prognosis, special subtype

INTRODUCTION

The microscopic appearance of breast cancer has a broad spectrum, and most are not specialized. Rare histologic types comprise approximately 5% of breast cancers and have distinct pathological and clinical features, with good, poor, or even unclear prognosis.[1,2] When a special morphological pattern is present in ≥90% of tumors, a pure special histologic type, such as lobular, mucinous, tubular, and papillary carcinomas, is designated.[3] Mixed invasive ductal carcinoma of no special type (IDC-NST) and special subtype carcinoma are defined when the special type comprises 10%–90% of tumors with IDC-NST.[4] The National Comprehensive Cancer Network clinical guidelines recommend that pure mucinous, pure tubular, pure cribriform, and encapsulated or solid papillary carci-

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nomas be considered favorable histologies, which are often combined with estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative status and thus do not usually require adjuvant chemotherapy.[5] However, if atypical pathologic or clinical features are detected, the tumor should be considered IDC-NST.

The multigene test (MGT) can be used to determine the risk of recurrence and to guide decisions regarding adjuvant endocrine and chemotherapy in patients with ER-positive and HER2-negative breast cancer with node-negative or 1–3 positive lymph nodes.[6] Morphological histological types can provide prognostic information. However, due to their rarity and heterogeneity, well-designed studies are limited, and classifications of special histology have changed over time.[7-9] Research on MGTs in patients with special histology has been limited. Since multifocal or multicentric breast tumors and mixed types of carcinomas are often encountered in daily practice, detailed, personalized information on patients with special histologic types of breast carcinoma needs to be clarified.

Earlier studies examined the Oncotype Dx 21-gene recurrence score (RS) according to histologic types, with the results from small number of cases showing that most patients with mucinous, tubular, and papillary types had a 21-gene RS of ≤25.[10,11] The Central Genomic Health clinical laboratory reported RS distribution by tumor subtype using various cutoffs. The proportion of patients with a high-risk RS >25 was 9.4% for mucinous carcinoma, 12.1% for papillary carcinoma, 3.2% for tubular carcinoma, and 7.0% for cribriform carcinoma.[12] However, follow-up information was not available. The surveillance, epidemiology, and end results (SEER) database showed that breast cancer survival curves were not clearly stratified according to the 21-gene RS in patients with mucinous, tubular, and cribriform carcinomas.[13] In the SEER study, the 5-year breast cancer-specific survival was nearly 100% in patients with tubular and cribriform carcinomas, regardless of whether the RS was in the low-risk or high-risk groups. This was attributed to the short follow-up time and the very low number of deaths in those special histologic subtypes.

The association between special types and MGTs was investigated to determine the clinical implications of MGTs in patients with special histologic types of breast carcinoma. We also examined survival outcomes according to histological type and MGT results, considering the use of adjuvant chemotherapy.

MATERIALS AND METHODS

Patient selection and clinicopathological characteristics

We retrospectively selected 133 patients with special histological types of breast carcinoma who underwent MGTs at Severance Hospital and Gangnam CHA Hospital, Seoul, Republic of Korea between November 2013 and December 2022. The patients' clinicopathological features and survival data were obtained from medical records. The MGTs included Oncotype Dx, MammaPrint, and EndoPredict. A high risk in each MGT was defined as a 21-gene RS of ≥26, irrespective of menopausal status in Oncotype Dx, a MammaPrint index of ≤0.000 in MammaPrint, and an EPclin score of ≥3.4 in EndoPredict.

In this study, we evaluated nine special histologic types of breast cancer: mucinous carcinoma, mucinous carcinoma with neuroendocrine differentiation, tubular carcinoma, invasive solid papillary carcinoma,[14] encapsulated papillary carcinoma with invasion, invasive cribriform carcinoma,[15] secretory carcinoma, invasive apocrine carcinoma, and micropapillary carcinoma. These types, excluding invasive lobular carcinoma (ILC), were categorized as favorable[5] and unfavorable[8,16] and are summarized in Supplementary Table 1 (only online). Most patients had mucinous, papillary, and tubular histologic types, in order of frequency. TNM stage was determined according to the anatomic staging system in the American Joint Committee on Cancer Staging Manual. Clinical risk groups were categorized as low or high risk based on grade, nodal status, and tumor size, as suggested by the MammaPrint report. ER and progesterone receptor (PR) were evaluated using the Allred scoring method. HER2 expression was determined by immunohistochemistry, from 0 to 3+, and in cases with 2+ results, in situ hybridization tests were performed. The Ki-67 labeling index was categorized as <20% or ≥20%.

Statistical analysis

The clinicopathological characteristics of categorical variables were compared using chi-square tests and Fisher's exact test. Continuous parameters were calculated using an independent t-test. Univariable and multivariable logistic regression models were applied to calculate significant parameters associated with the high-risk category of MGTs. Disease-free survival (DFS) was measured from the operation date to the first recurrence, death without relapse, or the last follow-up date. Only one patient died of a non-disease-related cause, and overall survival was not investigated. DFS curves were drawn using Kaplan–Meier methods, and groups were compared using the log-rank test. Cox proportional hazards model was used to identify factors associated with DFS. The test was two-sided, and a p-value<0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 26 (IBM Corp., Armonk, NY, USA).

Ethics approval and consent to participate

This study was reviewed and approved by the Institutional Review Board (IRB) of Severance Hospital (IRB No. 4-2023-0436) and Gangnam CHA Hospital (IRB No. 2023-06-014-003). The requirement for patient consent was waived by the IRB due to the retrospective nature of the current study. This study was conducted in accordance with the Declaration of Helsinki.

Table 1. Clinicopathological Characteristics of Patients

Characteristics	Favorable group (n=57)	Unfavorable group (n=76)	*p*
Age (yr)			0.064
≤40	14 (24.6)	12 (15.8)	
41–50	30 (52.6)	31 (40.8)	
51–60	4 (7.0)	16 (21.1)	
>60	9 (15.8)	17 (22.4)	
BMI (kg/m^2)			0.627
<23	29 (50.9)	41 (53.9)	
23–24	17 (29.8)	25 (32.9)	
≥25	11 (19.3)	10 (13.2)	
Multifocality/multicentricity			0.002
Single	49 (86.0)	47 (61.8)	
Multiple	8 (14.0)	29 (38.2)	
Histology			<0.001
Mucinous	27 (47.4)	34 (44.7)	
Tubular	12 (21.1)	12 (15.8)	
Papillary	7 (12.3)	29 (38.2)	
Others	11 (19.3)	1 (1.3)	
Tumor stage			0.554
pT1a-b	11 (19.3)	18 (23.7)	
pT1c	27 (47.4)	39 (51.3)	
pT2-3	19 (33.3)	19 (25.0)	
Node stage			0.636*
pN0	50 (87.7)	63 (82.9)	
pN1mi	3 (5.3)	3 (3.9)	
pN1	4 (7.0)	10 (13.2)	
Grade			<0.001*
I	42 (73.7)	28 (36.8)	
II	15 (26.3)	42 (55.3)	
III	0 (0.0)	6 (7.9)	
Clinical risk group			0.302
Low risk	31 (83.8)	35 (74.5)	
High risk	6 (16.2)	12 (25.5)	
ER Allred score			0.253
4–6	8 (14.0)	6 (7.9)	
7–8	49 (86.0)	70 (92.1)	
PR Allred score			0.837
0	7 (12.3)	12 (15.8)	
1–4	8 (14.0)	11 (14.5)	
5–8	42 (73.7)	53 (69.7)	
HER2			0.112
0	23 (40.4)	20 (26.3)	
1+	20 (35.1)	40 (52.6)	
2+/ISH no amplification	14 (24.6)	16 (21.1)	
Ki-67 labeling index (%)			0.907
<20	43 (75.4)	58 (76.3)	
≥20	14 (24.6)	18 (23.7)	
Multigene test			0.211
Oncotype Dx	42 (73.7)	53 (69.7)	
MammaPrint	2 (3.5)	9 (11.8)	
EndoPredict	13 (22.8)	14 (18.4)	
Result of multigene test			0.010
Low risk	53 (93.0)	58 (76.3)	
High risk	4 (7.0)	18 (23.7)	
Type of surgery			0.801
Breast conservation surgery	31 (54.4)	43 (56.6)	
Total mastectomy	26 (45.6)	33 (43.4)	
Radiation therapy			0.440
No	24 (42.1)	27 (35.5)	
Yes	33 (57.9)	49 (64.5)	
Chemotherapy			0.015
No	51 (89.5)	55 (72.4)	
Yes	6 (10.5)	21 (27.6)	

BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; ISH, in-situ hybridization.
Data are presented as n (%).
*Fisher's exact test was applied.

RESULTS

Descriptive features of the study population

The mean age at diagnosis was 49.2 years [standard deviation (SD) 10.7], and the mean follow-up duration was 42.3 months (SD 28.9) in 133 patients. Favorable and unfavorable special histologic types were identified in 57 (42.9%) and 76 (57.1%) patients, respectively. The mean tumor size was 1.8 cm, and 20 (15%) patients had nodal micro-/macrometastases. The TNM stage was IA in 80 (60.2%), IB in 5 (3.8%), IIA in 42 (31.6%), and IIB in 6 (4.5%) patients. MGTs were performed using Oncotype Dx in 95 (71.4%), MammaPrint in 11 (8.3%), and EndoPredict in 27 (20.3%) patients. Except for one postmenopausal patient who declined treatment, endocrine treatments were initiated using selective ER modulators (SERMs) alone in 65 (48.9%), SERMs plus gonadotropin-releasing hormone (GnRH) agonists in 24 (18.0%), upfront or switched aromatase inhibitors (AIs) in 39 (29.3%), AIs plus GnRH agonists in 3 (2.3%), and a GnRH agonist alone in 1 (0.8%) patient.

Clinicopathological characteristics associated with high-risk MGTs

A comparison of clinicopathological characteristics is presented in Table 1 according to special histology grouping. Unfavorable types were more frequent in older women, multifocal or multicentric tumors, papillary types with or without IDC, grade II/III diseases, high-risk MGTs, and chemotherapy administration. The TNM stage, clinical risk group, ER and PR

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Allred scores, HER2 status, Ki-67 levels, and local therapies were not significantly different between the groups. High-risk MGTs were noted in 26.2% of the mucinous and 16.7% of the papillary categories, while tubular and other types of carcinomas showed no high-risk results.

Univariable logistic models showed that unfavorable histologic type, larger tumor, grade II/III, lower PR Allred score, and higher Ki-67 labeling index were highly associated with high-risk MGTs. In multivariable analysis, histological grade, PR expression, and Ki-67 level maintained statistical significance for being associated with high-risk MGTs (Table 2).

Survival analysis

During follow-up, six DFS events occurred, including one death without recurrence. The 5-year DFS rate was 94.0% in all patients. The DFS curves are presented in Fig. 1 according to special type grouping and MGT result. Traditional special histology was not related to DFS, but patients with high-risk MGTs showed significantly worse DFS. In the subgroup of 57 patients with favorable histologic type, the results of MGTs were not associated with DFS. However, in patients with unfavorable histologic type, high-risk MGTs demonstrated significantly worse DFS (p<0.001), while no DFS events were noted in patients with low-risk MGTs (Supplementary Fig. 1, only online).

Multivariable Cox regression model showed that high-risk MGT was significantly associated with DFS when special histological type, age at diagnosis, clinical risk group, and Ki-67 level were entered as covariates (Table 3). However, if the use of chemotherapy was additionally entered into the model, no significant factors were found. Fig. 2 presents the Kaplan–Meier plot for DFS according to the combined result of MGT and use of chemotherapy. Patients with high-risk MGTs showed

Table 2. Logistic Regression Analysis of Factors Associated with High Risk in Multigene Tests

Variables	Univariable analysis			Multivariable analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Histologic type						
Unfavorable vs. Favorable	4.112	1.308–12.930	0.016	2.885	0.733–11.347	0.129
Age (yr)						
>50 vs. ≤50	1.736	0.686–4.394	0.244	-	-	-
BMI (kg/m^2)						
≥23 vs. <23	0.912	0.364–2.284	0.844	-	-	-
Multifocal/multicentric						
Multiple vs. Single	0.525	0.165–1.671	0.276	-	-	-
Tumor stage						
pT2-3 vs. pT1	2.470	0.963–6.338	0.060	2.770	0.860–8.915	0.088
Node stage						
Node positive vs. Negative	1.882	0.604–5.862	0.275	-	-	-
Grade						
II/III vs. I	6.600	2.094–20.797	0.001	4.042	1.083–15.093	0.038
PR Allred score						
0–4 vs. 5–8	4.969	1.903–12.971	0.001	8.099	2.287–28.679	0.001
HER2						
Low-positive (1+/2+) vs. Negative	1.770	0.606–5.167	0.296	-	-	-
Ki-67 labeling index (%)						
≥20 vs. <20	3.371	1.291–8.807	0.013	5.889	1.560–22.240	0.009

OR, odds ratio; CI, confidence interval; BMI, body mass index; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

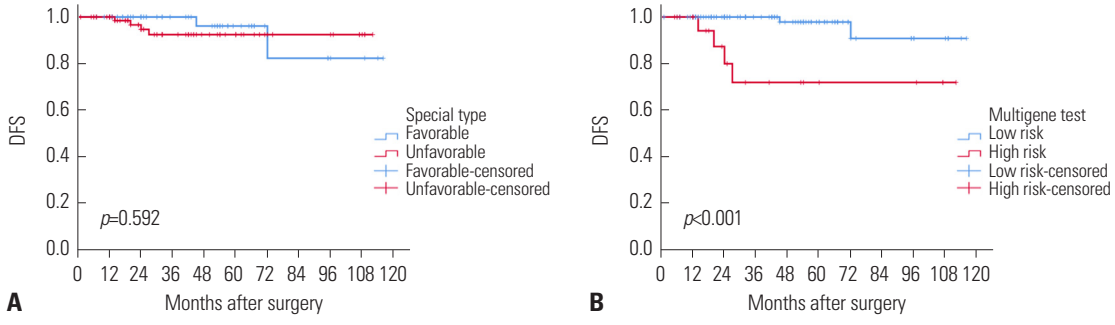

Fig. 1. Kaplan–Meier plots for disease-free survival (DFS) according to special histologic type (A) and result of multigene test (B).

the worst DFS, even when most patients in this group received adjuvant chemotherapy. Only three cases with high-risk MGTs and no use of chemotherapy demonstrated no DFS events; however, as the follow-up duration was <2 years, no reliable conclusion could be made in this regard.

DISCUSSION

In the current study, special histology was divided into favorable and unfavorable types based on traditional histopathologic features, and the relationship between MGT results and survival outcomes was examined. Overall, 16.5% of patients with special histology had high-risk MGTs. This is comparable to the TAILORx trial, in which 1389 of the 9719 node-negative patients (14.3%) had an RS ≥26, and to the RxPONDER trial, in which 1035 of the 6118 node-positive patients (16.9%) had an RS ≥26, although the details of histologic types were not presented in these two prospective large clinical trials.[17,18]

Patients with an unfavorable special type had a higher probability of high-risk MGT results, although the statistical significance disappeared in the multivariable analysis. Even among patients with favorable types, 7% demonstrated high-risk MGTs. Thus, if a tumor shows suspicious clinicopathological features, including unfavorable histologic type, it would be helpful to examine MGTs to calculate the risk of recurrence. PR-negativity, high Ki-67, and high histologic grade are also closely associated with high-risk RS in breast cancer.[19] Therefore, patients with such features should also be considered for MGT examination.

Table 3. Multivariable Cox Regression Analysis for Disease-Free Survival

Factors	HR	95% CI	*p*
Multigene test			
High risk vs. Low risk	8.348	1.232–56.541	0.030
Histologic type			
Unfavorable vs. Favorable	0.822	0.130–5.220	0.836
Age (yr)			
≤50 vs. >50	0.396	0.058–2.690	0.344
Clinical risk group			
High risk vs. Low risk	1.045	0.141–7.768	0.965
Ki-67 level (%)			
≥20 vs. <20	3.912	0.637–24.019	0.141

HR, hazard ratio; CI, confidence interval.

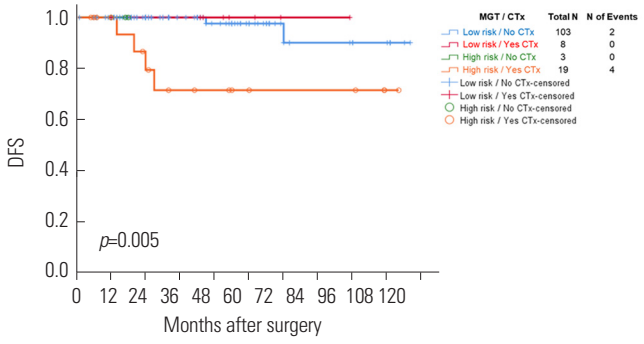

Fig. 2. DFS curve according to the result of MGT and use of chemotherapy. DFS, disease-free survival; MGT, multigene test; CTx, chemotherapy.

Breast cancers often have multifocal or multicentric features. When clinicians consider performing MGTs, selecting which tumor blocks to test can be problematic, given the discordance reported among tumor foci.[20,21] Clinically, three options are possible: 1) test only the largest or most microscopically aggressive tumor; 2) test the first focus followed by the second one when the first is low risk; and 3) test both lesions simultaneously.[20] However, delays in risk confirmation, consecutive treatment, or company regulation sometimes make option 2) or 3) difficult to implement in practice. Most of our cases with multiple lesions followed option 1). Even though we cannot perform MGTs on all the multicentric lesions, according to a previous study,[21] the discordant RS score between multicentric lesions was very low and not significantly associated with high-risk RS. However, since the possibility of differing RS scores in multicentric lesions cannot be excluded, further studies should consider performing MGTs on each lesion in patients with multiple or mixed tumors and compare the results.

Most trials and research on MGTs have been conducted for patients with IDC-NST or ILC, with only limited or retrospective research on those with special types of breast carcinomas.[22,23] Furthermore, the cutoffs of the 21-gene RS to determine the high-risk category have recently been changed from the original 31 to 26.[12,13] During the last decades, the regimen and duration of adjuvant chemotherapy and endocrine therapy have progressed for the management of patients with breast cancer.[24] A review of retrospective literature suggests that these factors have caused difficulties in developing optimal management algorithms for patients with special histologic types.

Although the follow-up duration was short and disease-related events rarely occurred in the current study, prognosis by MGT categories was more important than histopathological special subtypes. Our subgroup analysis suggests that the survival difference is more prominent according to MGT results when an unfavorable histologic type is diagnosed. However, statistical significance was not maintained when the use of chemotherapy was incorporated into multivariable analysis. Since the recently published 12-year follow-up result of the TAILORx trial demonstrated that late recurrences beyond 5 years exceeded earlier and non-recurrent events substantially contributed to event rates, long-term follow-up is required to confirm the prognostic implications of MGTs in patients with ER+/HER2- special histologic types.[25]

A previous retrospective study showed that special types were closely associated with a lower probability of high-risk RS >30 than IDC-NST or ILC, although the majority had mucinous

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carcinoma.[26] Patients with special types had lower expression of proliferation-related genes, including CCNB1, Ki-67, MYBL2, and STK15, than those with IDC-NST, and the 21-gene RS was not significantly associated with disease outcomes, even though 12.3% of patients with special types received chemotherapy.[26] In our cohort, 20.3% were treated with chemotherapy, which was more frequently administered in patients with unfavorable characteristics, and patients with high-risk MGTs who received chemotherapy showed the worst DFS. The recent SEER data using a cutoff of ≥26 for determining high risk showed that mucinous, tubular, and micropapillary types had lower odds of high-risk MGTs than IDC-NST. Additionally, in the subgroup with a high-risk RS >25, breast cancer-specific mortality according to histologic types was not statistically different, although other types showed low mortality (p=0.07).[27] Our results showed no significant difference in DFS between favorable and unfavorable subgroups, not only in the whole study population but also in the low- or high-risk MGT subpopulations (data not shown).

Our study has several limitations that warrant discussion. First, the number of enrolled patients was small and the patients were retrospectively selected, meaning that only cases that underwent MGTs at clinicians' or patients' discretion could be analyzed. The small patient cohort arises from the fact that we excluded patients with ILC in this study, since we wanted to focus on rare special type histology. Second, categorization into favorable and unfavorable special types was arbitrary and arguable. Risk grouping was based on the three MGT methods available at our institutions, and premenopausal intermediate 21-gene RS was not differentiated. Since discordance among MGTs has been reported, the results should be interpreted prudently.[28] Third, the relatively short follow-up duration and low event rates precluded calculation of the clinical benefits from adjuvant systemic treatments. Nevertheless, we believe that our study highlights the clinical role of MGTs in patients with special histologic types, which clinicians occasionally encounter in daily practice.

In conclusion, the current study highlighted that unfavorable special types by traditional histopathology were more likely to have high-risk MGTs based on tumoral biology. These results were directly connected with decision-making regarding adjuvant therapies, in line with clinical practice guidelines. In patients with special histologic types, the results of MGTs were significantly associated with prognosis. As cost restraints remain a significant issue when MGTs are performed, it is also necessary to establish clear indications for their use to determine whether they are warranted in patients with special types of breast cancer. Continuous attention should be focused on rare special types of breast cancer to improve management algorithms.

AVAILABILITY OF DATA AND MATERIAL

The datasets generated and/or analyzed during the current study are not publicly available due to the inclusion of sensitive personal data, but may be available from the corresponding authors upon reasonable request and with appropriate IRB approval.

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AUTHOR CONTRIBUTIONS

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