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ORIGINAL ARTICLE – BREAST ONCOLOGY

Clinical Implication of HER2 Status in Hormone Receptor-Positive Mucinous Breast Cancer

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ABSTRACT

Purpose. Mucinous carcinoma (MC) is a rare breast cancer with favorable outcome. Unlike typical breast cancer, the current guidelines do not recommend chemotherapy or anti-human epidermal growth factor receptor 2 (HER2) therapy for hormone receptor (HR)-positive MC, regardless of HER2 status. We evaluated the prognostic implication of HER2 status in HR-positive MC.

Methods. We retrospectively reviewed the data of 471 patients with pure MC (stages I–III) who underwent curative surgery. We analyzed 5-year disease-free survival (DFS) and distant metastasis-free survival (DMFS), according to clinicopathological characteristics.

Results. The median follow-up duration was 79.0 months. Overall, the 5-year DFS rate was 95.7% and the 5-year DMFS rate was 96.2%. Nodal status was the only significant factor for DFS (relative risk [RR], 3.40; 95% confidence interval [CI] 3.40–9.67, $p = 0.021$). Among HR-positive/node-negative patients with tumor size ≥ 3 cm, HER2-positive patients showed significantly worse DFS (RR, 8.76; 95% CI 1.45–52.76, $p = 0.018$) and DMFS (RR, 11.37; 95% CI 1.37–74.70, $p = 0.011$). This finding was consistently significant, when combining both "HR-positive/node-negative/tumor size ≥ 3 cm" and "HR-positive/node-positive" MC (n = 125) for DFS (RR, 4.30; 95% CI 1.43–12.97, $p = 0.009$) and DMFS (RR, 4.93; 95% CI 1.63–14.90, $p = 0.005$). Intriguingly, within this subgroup, among HER2-positive tumors, whereas 5-year DFS was 60.2% in patients who did not receive trastuzumab, 100% of those who received trastuzumab were disease free ($p = 0.053$).

Conclusions. In HR-positive, node-negative MC with tumor size ≥ 3 cm, patients with HER2-positive MC showed worse survival, suggesting a potential role of an anti-HER2 strategy in this subgroup.

Mucinous carcinoma (MC) is an uncommon type of breast cancer and comprises approximately 4% of all cases of invasive breast cancer. MC is characterized by abundant extracellular mucin production.[1,2] MC has a more favorable prognosis and often presents higher estrogen receptor (ER) and progesterone receptor (PR) expression and lower probability of nodal metastasis than typical breast cancer. Such clinicopathological characteristics lead to a more favorable prognosis than for invasive ductal carcinoma (IDC).[3–6]

Based on its relatively better prognosis in comparison with IDC, the current recommendation for adjuvant treatment in patients with MC differs from that of patients with usual breast cancer histology.[7] For patients with hormone receptor (HR)-positive and lymph node-negative (or micrometastasis) MC, adjuvant chemotherapy is not recommended, regardless of tumor size or human epidermal growth factor receptor 2 (HER2) status.[7] Additionally, even for patients with HR-positive and lymph node-positive MC, HER2 status is not stated as a considerable factor

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in establishing an adjuvant treatment plan; however, in HR-negative patients, the recommendation is the same as that for patients with usual breast cancer histology.[7]

Unlike IDC, due to its relatively low probability of overexpression or amplification, the prognostic implication of HER2 status in HR-positive MC is yet to be investigated.[4,8,9] Recently, the incidence of breast cancer in Korea has been increasing considerably and proper analysis of clinicopathological characteristics and prognosis of MC based on a large group of patients is necessary, to understand more about this rare type of disease.[10,11] In the present study, we evaluated the clinicopathological characteristics of MC and the prognostic implication of HER2 status, particularly in HR-positive MC.

MATERIALS AND METHODS

Patients and Treatments

We retrospectively reviewed the 25-year cumulative data of patients with pure mucinous breast cancer from the database of the breast cancer center at Asan Medical Center, Korea, between 1990 and 2014. We reviewed the data for a total of 471 patients with pure MC (stages I–III) who underwent curative surgery. Pure MC was defined as a tumor with a more than 90% mucinous component, diagnosed by a specialized pathologist. We analyzed 5-year, disease-free survival (DFS) and distant metastasis-free survival (DMFS), according to tumor size, lymph node metastasis, HR/HER2 status, and therapy received. We also performed subgroup analyses of HR-positive/node-negative/tumor size $\geq$ 3 cm (group 1) and HR-positive/node-positive (group 2) MC.

The initial diagnostic and subsequent workup included mammography, breast ultrasound imaging, magnetic resonance imaging, chest radiography, blood sampling, and clinical examination. ER and PR expression were evaluated according to the Allred scoring system.[12] All patients with HR-positive tumors received tamoxifen or aromatase inhibitors as adjuvant treatment. Positive HER2 status was confirmed with an immunohistochemistry score of 3 + or a score of 2 + or 1 + with positive detection of fluorescence or silver on in situ hybridization *for HER2* amplification.[13] All clinical and histopathological staging assessments were based on the 7th edition of the American Joint Committee on Cancer Manual.[14]

Statistical Analysis

Disease-free survival (DFS) was defined as the time from the date of surgery to the first date of disease recurrence, and distant metastasis-free survival (DMFS) was defined as the time until the first distant metastatic recurrence or death from any cause. The probability of survival was estimated using the Kaplan–Meier method followed by the log-rank test, and multivariate analysis was performed using the Cox proportional hazards model with the following clinical parameters: age at diagnosis, clinical tumor stage, lymph node status, HR status, and HER2 status. Sixteen patients who received trastuzumab were included in the analysis to assess the survival rate of the entire cohort and the benefit of trastuzumab in HER2-positive MC. All statistical tests were conducted using IBM SPSS version 23.0 for Windows (IBM Corp., Armonk, NY). A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

A total of 471 patients with pure mucinous breast cancer were included in the analysis. During a median follow-up of 79 months, 34 relapses (7.2%, including 24 systemic metastases) and 29 deaths (6.2%) were observed among the included patients. The mean age at diagnosis was 46.99 (range 20–88) years. Among participants, 438 (92.9%) were HR-positive (either ER or PR or both) and 405 (86.0%) were node-negative. A total of 55 (11.8%) patients were HER2-positive, and 16 of the 55 (29.1%) HER2-positive patients received trastuzumab (2 patients received trastuzumab only, and 14 patients received trastuzumab with either anthracycline or taxane-based chemotherapy or both). Among the 375 patients who were HR-positive and node-negative, the tumor size was < 1 cm in 46 patients, 1–2.9 cm in 260 patients, and $\geq$ 3 cm in 69 patients; 31 patients tested HER2-positive (9/31, 29.0% received trastuzumab). Among patients with HR-positive and node-positive MC, 17 were HER2-positive (6/17, 35.3%, received trastuzumab) and 59 of 63 (93.7%) patients received chemotherapy (Table 1).

Overall, the 5-year DFS rate was 95.7%, and the 5-year DMFS rate was 96.2%. In the univariate analysis using a Kaplan–Meier plot, multiple variables (nodal status/ER status/HER2 status/chemotherapy/radiotherapy) showed a correlation with both DFS and DMFS. However, in the Cox regression analysis, lymph node metastasis was the only significant prognostic factor for DFS (relative risk (RR), 3.40; 95% confidence interval (CI) 1.119–9.67, $p = 0.021$), and HER2 status was the only significant prognostic factor for DMFS (RR, 3.78; 95% CI 1.39–10.27, $p = 0.009$; Table 2). In group 1 (HR positive/node negative with tumor size $\geq$ 3 cm), HER2 positivity was the only variable significantly associated with both DFS (RR, 14.49; 95% CI 2.20–95.39, $p = 0.001$) and DMFS (RR, 11.37; 95% CI 1.37–74.70, $p = 0.011$; Table 2; Fig. 1). In group 2 (HR

TABLE 1 Clinicopathological characteristics of the entire cohort of patients with MC and HR(+) subgroups

Variables	No. of patients (%)					
	Entire cohort: N = 471		HR(+), node(−): N = 375		HR(+), node(+): N = 63	
Age, yr	Mean 46.99 (20–88)		Mean 46.98 (20–88)		Mean 45.70 (27–75)	
≤ 34	52	11.0%	40	10.7%	8	12.7%
35–50	282	59.9%	226	60.3%	41	65.1%
≥ 51	137	29.1%	109	29.1%	14	22.2%
pT stage						
T1	250	53.1%	216	57.6%	15	23.8%
T2	197	41.9%	149	39.7%	35	55.6%
T3	20	4.2%	10	2.7%	9	14.3%
T4	4	0.8%	0	0%	4	6.3%
Lymph node status						
Negative	405	86.0%	375	100.0%	0	0%
Positive	66	14.0%	0	0%	64	100.0%
Histologic grade						
G1	99	21.0%	87	23.2%	8	12.7%
G2	263	55.9%	216	57.6%	40	63.5%
G3	11	2.3%	5	1.3%	3	4.8%
Unknown	98	20.8%	67	17.9%	12	19.0%
ER status						
Positive	430	91.3%	368	98.1%	61	96.8%
Negative	28	5.9%	7	1.9%	2	3.2%
Unknown	13	2.8%	0	0%	0	0%
PR status						
Positive	351	74.5%	305	81.3%	46	73.0%
Negative	106	22.5%	70	18.7%	17	27.0%
Unknown	14	3.0%	0	0%	0	0%
HER2 status						
Positive	55	11.8%	31	8.3%	17	27.0%
Trastuzumab Tx.	*16*	*(29.1%)*	*9*	*(29.0%)*	*4*	*(23.5%)*
Negative	354	75.2%	309	82.4%	39	61.9%
Unknown	62	13.2%	35	9.3%	7	11.1%
Chemotherapy						
Yes	160	66.0%	87	23.2%	4	6.3%
No	311	34.0%	288	76.8%	59	93.7%
Radiotherapy						
Yes	309	65.6%	255	68.0%	37	58.7%
No	162	34.4%	120	32.0%	26	41.3%
Hormone therapy						
Yes	434	92.1%	359	95.7%	62	98.4%
No	37	7.9%	16	4.3%	1	1.6%

MC mucinous carcinoma, *HR* hormone receptor, *pT stage* pathologic tumor stage, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *Tx* treatment

positive/node positive), HER2 status and radiotherapy were correlated with DMFS in univariate analysis; however, no factors were significantly correlated with survival in multivariate Cox analysis (Table 2; Fig. 2). When combining both group 1 and group 2 (n = 125), HER2 positivity was the only factor that was significantly correlated with DFS (RR, 4.30; 95% CI: 1.43–12.97, $p = 0.009$) and DMFS (RR, 4.93; 95% CI 1.63–14.90, $p = 0.005$; Table 2; Fig. 3). Intriguingly, within this subgroup of "HR-positive/node-negative/tumor size ≥ 3 cm" and "HR-positive/node-positive" MC, among HER2-positive tumors, whereas the 5-year DFS was 60.2% in patients who did not receive

TABLE 2 Univariate and multivariate analyses of DFS and DMFS in the entire patient cohort and subgroups

[a]Entire patient cohort $N = 455$		DFS			DMFS		
		Univariate p[e]	Multivariate RR (95% CI)[f]	p	Univariate p[e]	Multivariate RR (95% CI)[f]	p
Age (year) ≤ 50 versus > 50		0.896	–	–	0.253	–	–
Tumor size (cm)[a]	< 1.0	No event with tumor size < 1.0 cm[a]			No event with tumor size < 1.0 cm[a]		
	1.0–2.9	0.509	–	–	0.077	–	–
	≥ 3.0	0.897	–	–	0.002	1.49 (0.57–3.90)	0.409
Node		< 0.001	3.40 (1.19–9.67)	0.021	< 0.001	2.58 (0.99–6.75)	0.052
ER		0.007	1.86 (0.46–7.43)	0.377	0.023	1.04 (0.25–4.23)	0.950
PR		0.046	2.28 (0.94–5.52)	0.067	0.101	–	–
HER2		< 0.001	2.07 (0.74–5.80)	0.162	< 0.001	3.78 (1.39–10.27)	0.009
Chemotherapy		0.002	1.61 (0.46–5.55)	0.449	0.009	1.51 (0.51–4.49)	0.453
Radiotherapy		< 0.001	1.20 (0.46–3.16)	0.702	< 0.001	1.75 (0.67–4.56)	0.249

[b]Group 1 HR(+), node(−) Tumor size ≥ 3.0 cm $N = 68$	DFS			DMFS		
	Univariate p[e]	Multivariate RR (95% CI)[f]	p	Univariate p[b]	Multivariate RR (95% CI)[f]	p
Age (year) ≤ 50 versus > 50	0.398	–	–	0.507	–	–
HER2	0.001	14.49 (2.20–95.39)	0.005	0.001	11.37 (1.37–74.70)	0.011
Chemotherapy	0.174	–	–	0.828	–	–
Radiotherapy	0.896	–	–	0.744	–	–

[c]Group 2 HR(+), node(+) $N = 57$	DFS			DMFS		
	Univariate p[e]	Multivariate RR (95% CI)[f]	p	Univariate p[e]	Multivariate RR (95% CI)[f]	p
Age (year) ≤ 50 versus > 50	0.609	–	–	0.637	–	–
HER2	0.150	–	–	0.027	2.44 (0.58–10.27)	0.222
Chemotherapy	0.794	–	–	0.816	–	–
Radiotherapy	0.403	–	–	0.040	2.44 (0.54–10.99)	0.244

[d]Group 1 + *Group 2* $N = 125$	DFS			DMFS		
	Univariate p[e]	Multivariate RR (95% CI)[f]	p	Univariate p[e]	Multivariate RR (95% CI)[f]	p
Age (year) ≤ 50 versus > 50	0.282	–	–	0.940	–	–
Node	0.076	–	–	0.098	–	–
HER2	0.001	4.30 (1.43–12.97)	0.009	< 0.001	4.93 (1.63–14.90)	0.005
Chemotherapy	0.096	–	–	0.402	–	–
Radiotherapy	0.685	–	–	0.131	–	–

[a]Sixteen patients given trastuzumab were excluded, out of 55 HER2-positive patients in the group

[b]One patient given trastuzumab was excluded, out of eight HER2-positive patients in the group

[c]Six patients given trastuzumab were excluded, out of 17 HER2-positive patients in the group

[d]Seven patients given trastuzumab were excluded, out of 25 HER2-positive patients in the group

[e]Log-rank test

[f]Cox model

Group 1: HR(+), node(−) and tumor size ≥ 3.0 cm. Group 2: HR(+), node(+)

DFS disease-free survival, *DMFS* distant metastasis-free survival, *RR* relative risk, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor

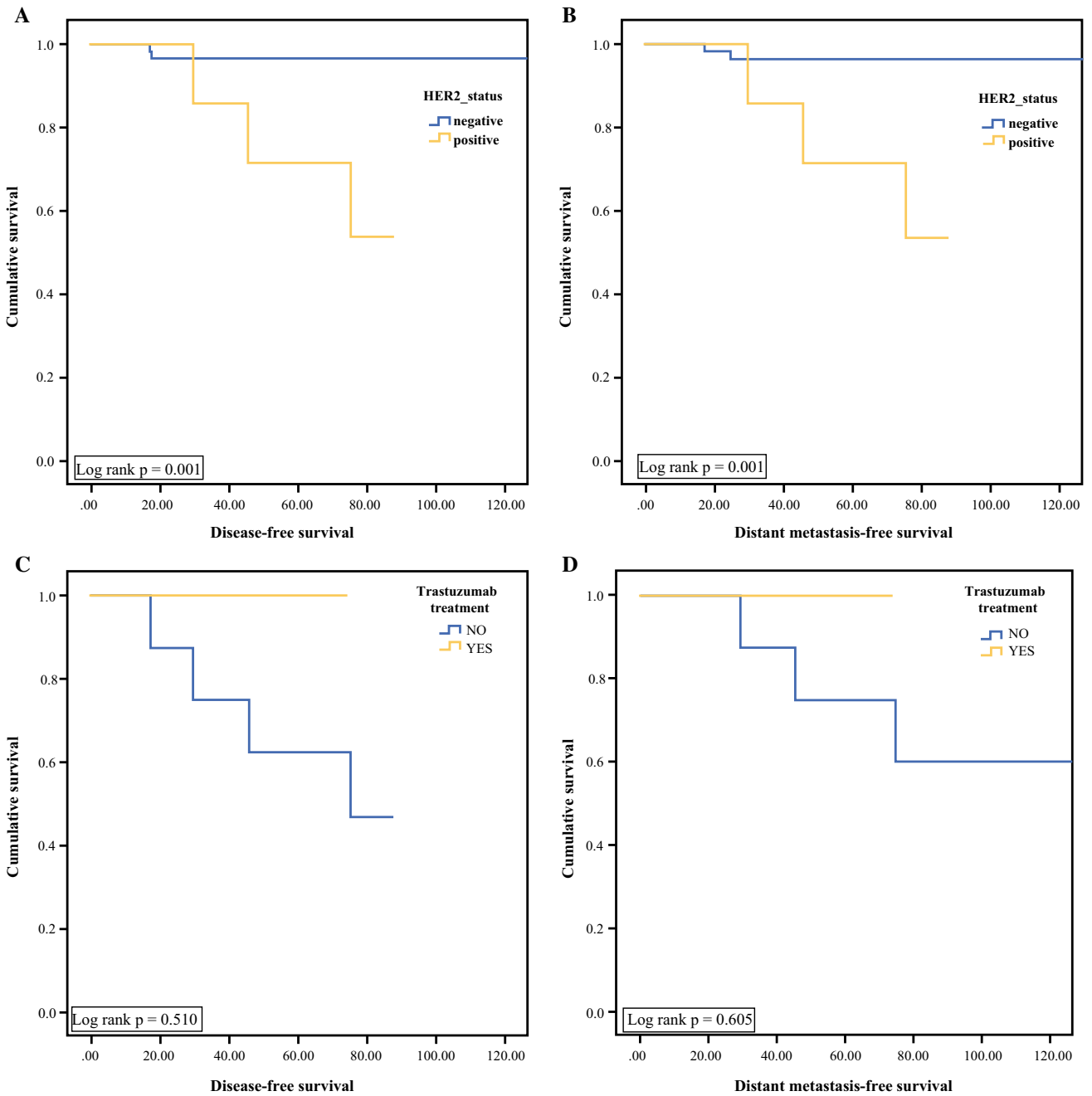

FIG. 1 Univariate Kaplan–Meier plots for DFS and DMFS according to HER2 status (**a**, **b**) and trastuzumab treatment (**c**, **d**) in HR(+), node(−) and tumor size ≥ 3.0 cm mucinous carcinoma. *DFS* disease-free survival, *DMFS* distant metastasis-free survival, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor

trastuzumab, 100% of patients who received trastuzumab were disease-free, with a considerable trend toward significance ($p = 0.053$; Fig. 3).

DISCUSSION

Many studies have shown that MC presents better prognosis with favorable clinicopathological characteristics, such as fewer axillary lymph node metastases and more frequent HR expression than IDC.[6,8,15–22] We observed a similar prognosis (95.7% of 5-year DFS and 96.2% of 5-year DMFS), higher rate of HR positivity (91.3% and 74.5% positivity for ER and PR, respectively), low incidence (14.0%) of lymph node metastasis (range, 2-14% in other reports) [23–27] and low HER2-positive rate (11.8%) (range, 2.9–22.0% in other reports).[8,28–31] However, the mean age at diagnosis of MC in this study was 46.99 years, which was lower than other reported in studies

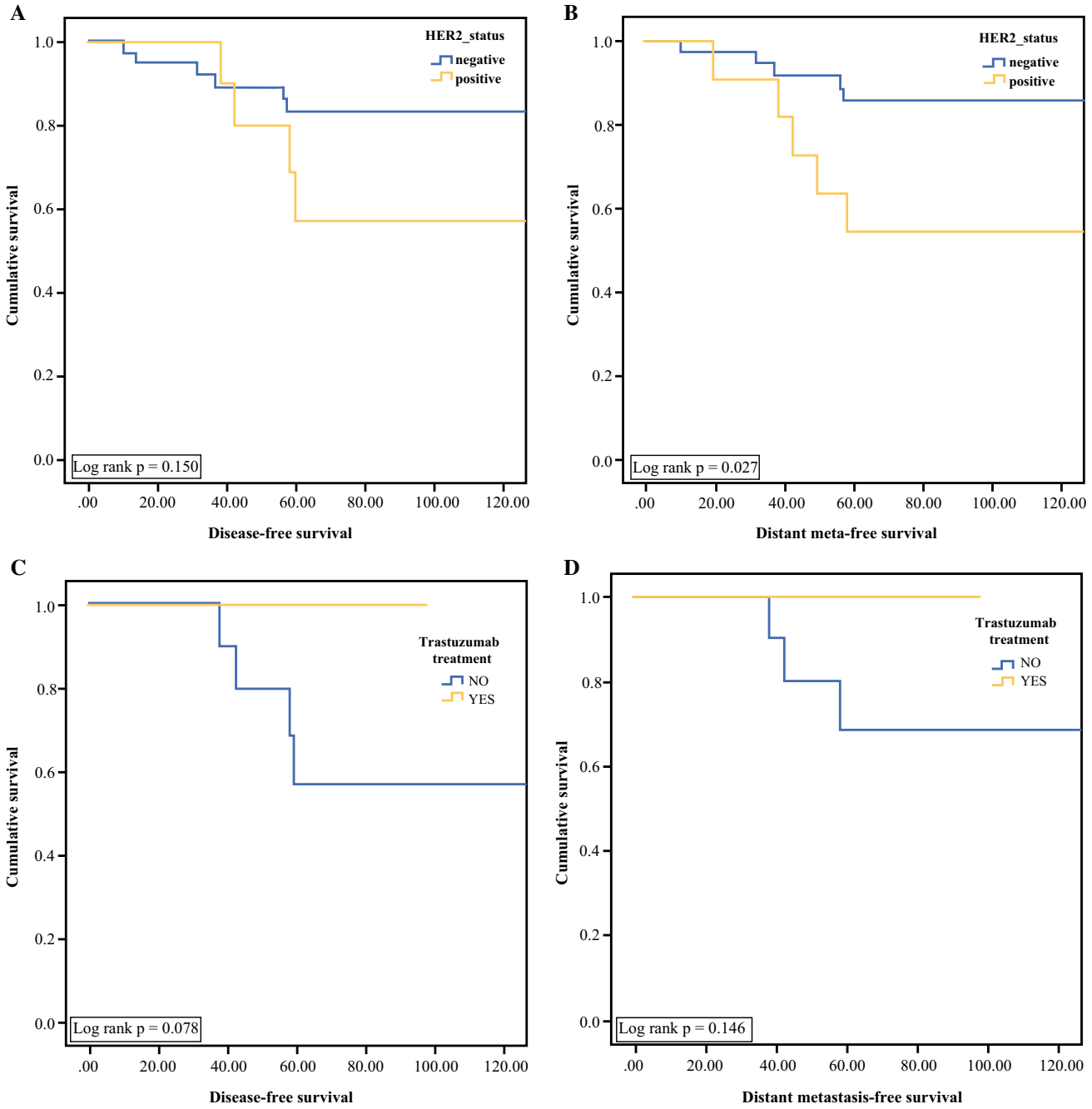

FIG. 2 Univariate Kaplan–Meier plots for DFS and DMFS according to HER2 status (**a**, **b**) and trastuzumab treatment (**c**, **d**) in HR(+), node(+) mucinous carcinoma. *DFS* disease-free survival, *DMFS* distant metastasis-free survival, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor

among western patients.[6,32] In the entire patient cohort, although multiple variables showed correlation with prognosis in the univariate analysis, nodal status was the most significant predictor of DFS in the multivariate analysis, which has been supported in other studies.[2,6,33]

Unlike typical cases of breast cancer, the *National Comprehensive Cancer Network* suggests a somewhat different tumor size classification in the treatment guideline for HR-positive, node-negative MC (tumor size < 1.0 cm/1.0–2.9 cm/≥ 3 cm). This may be due to the fact that most of the mucin component of the tumor volume in MC may have less impact on survival.[16] Additionally, in HR-positive, node-negative, and node-positive MC, HER2 status is not stated as a considerable factor in establishing an adjuvant treatment plan.[7] These differences between MC and usual breast cancer may be based on the relatively low

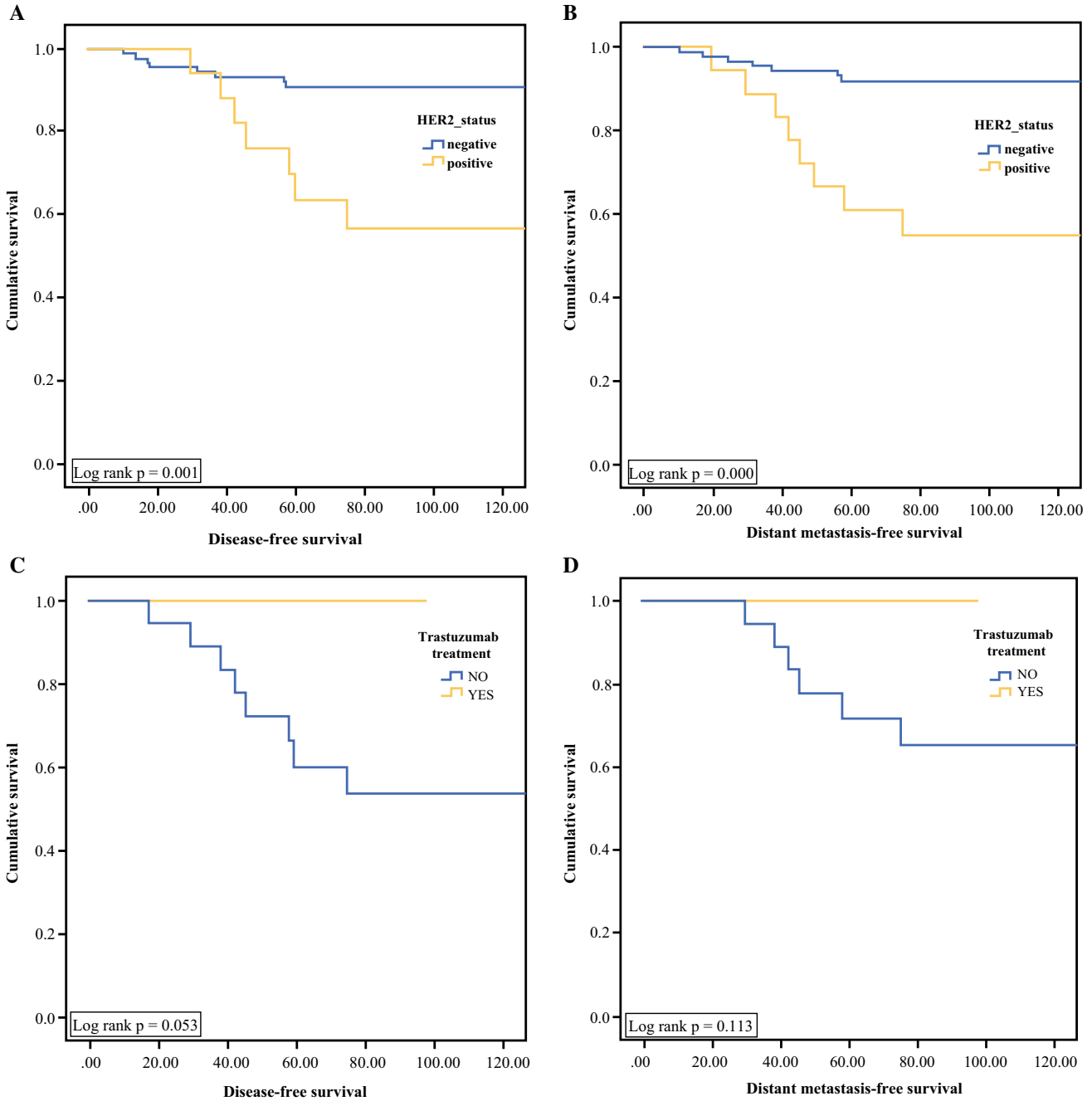

FIG. 3 Univariate Kaplan–Meier plots for DFS and DMFS according to HER2 status (**a**, **b**) and trastuzumab treatment (**c**, **d**) in combined group 1: HR(+), node(−) and tumor size ≥ 3.0 cm, and group 2: HR(+), node(+) mucinous carcinoma. *DFS* disease-free survival, *DMFS* distant metastasis-free survival, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor

incidence of HER2 positivity and its lesser impact on prognosis compared with other features in MC.[1,2,8,15,16,19–21,23–,34]

Although t*here are few case reports regarding HER2 status and trastuzumab treatment in MC,*[35,36] *to the best of our knowledge, this is the first* study on the clinical implications of HER2 status and trastuzumab treatment in MC among a considerable number of patients. We showed the prognostic impact of HER2 status in a certain group of MCs (HR-positive/node-negative/tumor size ≥ 3 cm MC), demonstrating significant survival (DFS and DMFS) among HER2-positive patients in this study. Although we could not identify a statistically significant influence of HER2 on prognosis (DFS and DMFS) within the subgroup "HR-positive/node-positive" MC, which may due to a small number of cases (further studies are warranted to

determine the prognostic importance of HER2 in this group with a larger number of patients), among HR-positive and HER2-positive MC, patients who received trastuzumab treatment showed better prognosis (100% survival rate within the follow-up period), with borderline significance.

The methodological limitation in this study was the retrospective use of medical records for data collection. Another limitation is the relatively short follow-up period to assess survival for prognosis, as most patients with ER-positive mucinous breast cancer would be expected to have delayed recurrence, even beyond 10 years after surgery. Further prospective study with longer follow-up data should be performed to validate the potential role of an anti-HER2 strategy, for guiding treatment options.

CONCLUSIONS

Nodal status was the most significant prognostic factor for DFS in pure mucinous breast cancer. However, in HR-positive and lymph node-negative mucinous breast cancer with tumor size $\geq$ 3 cm, HER2-positive MC showed worse survival (DFS and DMFS), suggesting a potential role of an anti-HER2 strategy in this patient subgroup.

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COMPLIANCE WITH ETHICAL STANDARDS

DISCLOSURE None.

CONFLICT OF INTEREST The authors declare no conflict of interest.

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