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Clinicopathologic Features and Prognosis of HER2-Positive Gastric Cancer

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Background: The role of human epidermal growth factor receptor 2 (HER2) overexpression has been well established in breast cancer, with corresponding targeted therapies. In contrast, the clinicopathologic features and prognosis of HER2 overexpression in gastric cancer remain inconclusive.

Methods: In this study, 334 patients with gastric cancer who received surgical resection between May 2017 and June 2021 were enrolled at a single medical center in Taiwan. HER2 status was determined by immunohistochemistry (IHC) staining or fluorescence in situ hybridization (FISH). The clinicopathologic features and survival curves of the HER2-positive and HER2-negative gastric cancer patients were analyzed.

Results: The HER2-positive ratio was 7.2%. HER2-positive gastric cancer was associated with more differentiated tumors ($P = 0.016$), more Lauren intestinal type ($P = 0.010$), and

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a higher portion of Ming expanding type ($P = 0.033$) in the univariate analysis, but only Lauren intestinal type was an independent factor in the logistic regression model ($P = 0.015$). The overall survival and disease-free survival between the HER2-positive and HER2-negative groups were not significantly different. Patients with HER2-positive gastric cancer were more likely to have distant lymphatic recurrence than those with HER2-negative gastric cancer ($P = 0.026$).

Conclusions: HER2-positive gastric cancer is associated with intestinal histologic type and distant lymphatic recurrence, but HER2 is not an independent prognostic factor.

Key words: Gastric cancer – HER2 – Prognosis – Trastuzumab – Distant lymphatic recurrence

Gastric cancer is the fifth most common cancer and the fourth most common cause of cancer death worldwide.[1] The treatment for gastric cancer is surgical resection with curative intention for patients without distant metastasis. For advanced or metastatic disease, survival is generally poor. However, improvements in chemotherapy with add-on targeted therapy or immunotherapy have led to survival benefits, which means that tumor biology is more important than ever.[2]

Overexpression of human epidermal growth factor receptor 2 (HER2) is well known to promote oncogenesis in several cancers. The HER2 protein is a 185-kDa transmembrane tyrosine kinase (TK) receptor and a member of the epidermal growth factor receptor (EGFR) family. It is encoded by the Her2/neu oncogene located on chromosome 17q21 and is associated with tumor cell proliferation by activating downstream signals, such as PI3K/Akt/mTOR and MAPK.[3,4] In breast cancer, the role of HER2 has been well established. Numerous targeted agents have been approved for the treatment of HER2-positive breast cancer. In contrast, the role of HER2 overexpression in gastric cancer is still inconclusive. The HER2-positive rate in gastric cancer has been reported to range widely from 3.8% to 50% by 2 meta-analyses. The 2 meta-analyses have demonstrated that HER2 overexpression is associated with male sex, intestinal type, and well/moderate cell differentiation.[5,6] However, the prognostic value of HER2 in gastric cancer is still controversial.[7–10]

This study aims to investigate the clinicopathologic features and prognosis of HER2-positive gastric cancer in the Taiwanese population.

Materials and Methods

Patient collection

A total of 334 gastric cancer patients with adenocarcinoma who underwent surgical resection between May 2017 and June 2021 at the Department of Surgery in Taipei Veterans General Hospital were enrolled in this study. Patients with pathology other than adenocarcinoma were excluded from this study.

Prior to surgery, all patients underwent upper gastrointestinal endoscopy, chest radiography, and computerized tomography scans of the abdomen. Radical total gastrectomy was performed for proximal-third lesions, and radical subtotal gastrectomy was performed for middle- or distal-third lesions. For early gastric cancer, at least D1+ lymph node dissection was performed. For advanced gastric cancer, D2 lymph node dissection was performed.[11]

The gross features of the pathologic specimens were evaluated according to the tumor location, tumor size, and Borrmann classification. The microscopic features of histology, pathology, and cell differentiation were analyzed according to the cell grade of tumor differentiation, Lauren histology (intestinal or diffuse type), Ming histology (expanding or infiltrating type), and lymphovascular invasion patterns. The pathologic staging was defined according to the 8th American Joint Committee on Cancer/Union for International Cancer Control Tumor-Node-Metastasis (TNM) classification of malignant tumors.[12]

After the surgery, oral fluoropyrimidine S-1 or adjuvant systemic therapy as per the physician's choice was given for stage II or stage III gastric cancer patients after curative surgery. For patients with palliative resection, salvage concurrent chemoradiotherapy or systemic therapy was given by an oncologist.

Postoperative follow-up assessments were performed as per local practice guidelines: every 3 months for the first 3 years and every 6 months thereafter until the patient's death. The follow-up procedures included physical examinations, blood tests including tumor markers (*e.g.*, carcinoembryonic antigen and carbohydrate antigen 19-9), liver function tests, chest films, abdominal sonography,

and computerized tomography scans. Tumor recurrence was diagnosed by biopsies or by imaging studies when biopsies were not obtained. Tumor recurrence in the remnant stomach, hepatoduodenal ligament, celiac axis, or peripancreatic region is considered locoregional recurrence. We defined remote lymphatic metastasis (in the para-aortic, Virchow, and inguinal nodes) and pulmonary lymphangitic spread as distant lymphatic recurrence. Tumor recurrence is classified as locoregional, peritoneal, hematogenous, and distant lymphatic. Overall survival (OS) was defined as the period from the date of surgery to the date of death or the latest follow-up. Disease-free survival (DFS) was defined as the period from the date of surgery during which the patient survived without tumor recurrence. Patients with palliative resection were excluded from the DFS analysis.

Immunohistochemical staining and fluorescence in situ *hybridization*

For HER2 immunohistochemistry (IHC) staining, the antihuman c-erbB-2 A0485 polyclonal antibody (dilution 1:500; Dako, Denmark) was used, and IHC staining was performed using a BenchMark Ultra Platform (Ventana Medical Systems, Tucson, AZ) with the Optiview DAB Detection Kit (Ventana Medical Systems). According to the ToGA scoring systems, HER2 immunoreactivity was scored as 0, 1+, 2+, or 3+, with the following definition: 0, no reactivity or membranous reactivity in less than 10% of tumor cells; 1+, faint or barely perceptible membranous reactivity in at least 10% of tumor cells; 2+, weak to moderate complete, basolateral or lateral membranous reactivity in at least 10% of tumor cells; and 3+, strong complete, basolateral or lateral membranous reactivity in at least 10% of tumor cells.[13] For specimens with an IHC score of 2+, fluorescence *in situ* hybridization (FISH) analysis of HER2 status was performed with the PathVysion HER2 DNA Probe Kit (Abbott, Abbott Park, IL). Positive HER2 gene amplification was defined as a HER2/CEP17 ratio ≥ 2.[14] HER2 positivity was defined as an IHC score of 3+ or an IHC score of 2+ with a positive FISH result.

Ethical approval

Written informed consent for tissue collection was obtained from all patients before surgery. All samples used in this study had been previously collected from the biobank of Taipei Veterans General Hospital and were anonymized. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB-TPEVGH no. 2022-10-003CC).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 19.0 (Armonk, NY). All the results in the text and tables are presented as the means ± SD. The clinicopathologic differences were compared using Pearson χ^2 test or Fisher exact test. Corrections of data were performed using multiple testing in a logistic regression model. The distributions of OS and DFS were evaluated using the Kaplan-Meier method. Univariate analysis of the covariates (prognostic factors) of OS was performed first. The covariates with a P value <0.05 were selected for multivariate analysis using a Cox regression model with the forward stepwise method. A P value of less than 0.05 was considered statistically significant.

Results

Among the 334 included gastric cancer patients, the HER2 status of the tumor samples were determined by IHC staining as follows: score 0, 233 (69.8%); score 1+, 72 (21.6%); score 2+, 11 (3.3%); and score 3+, 18 (5.4%) (Fig. 1). Of the 11 tumor samples with an IHC score of 2+, 6 (54.5%) were HER2-positive by FISH (Fig. 2). In total, 24 tumor samples (7.2%) were categorized as HER2-positive.

The patients' clinicopathologic features according to HER2 status were analyzed (Table 1). The univariate analysis showed that the HER2-positive gastric cancer group was associated with more differentiated tumors (66.7% versus 41.3%; $P = 0.016$), more Lauren intestinal type (75% versus 44.7%; $P = 0.010$), and more Ming expanding type (37.5% versus 18.4%; $P = 0.033$) compared with the HER2-negative gastric cancer group. After multiple testing in a logistic regression model, only Lauren classification was an independent factor associated with HER2-positive gastric cancer (odds ratio, 3.264; $P = 0.015$).

The OS and DFS were compared between the HER2-positive and HER2-negative groups, and there was no significant difference found in either OS ($P = 0.190$) or DFS ($P = 0.236$; Fig. 3). Univariate analysis of prognostic factors with OS as an end point showed that tumor size, gross appearance, lymphovascular invasion, and TNM stage were associated with prognosis. After multivariate adjustment, only TNM stage was an independent prognostic

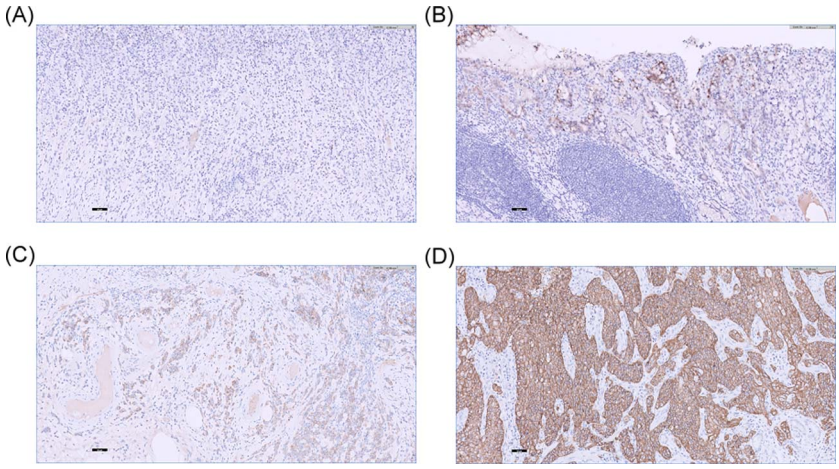

Fig. 1 Immunohistochemical staining of HER2. (A) HER2: 0, (B) HER2: 1+, (C) HER2: 2+ and (D) HER2: 3+.

factor. HER2 status failed to be a prognostic factor (Table 2).

Among the 299 patients with curative resection, 57 patients (19%) had tumor recurrence. The initial recurrence pattern was compared according to the HER2 status (Table 3). The patients with HER2-positive gastric cancer were more likely to have distant lymphatic recurrence than those with HER2-negative gastric cancer (15.8% versus 2.9%, $P = 0.026$).

A subgroup analysis of 12 patients with stage III/IV HER2-positive gastric cancer was performed. Among those 12 patients, 5 patients (41.7%) received anti-HER2 targeted therapy. For stage III/IV HER2-positive gastric cancer, the OS was significantly better for the patients with anti-HER2 therapy than for those without anti-HER2 therapy ($P = 0.019$).

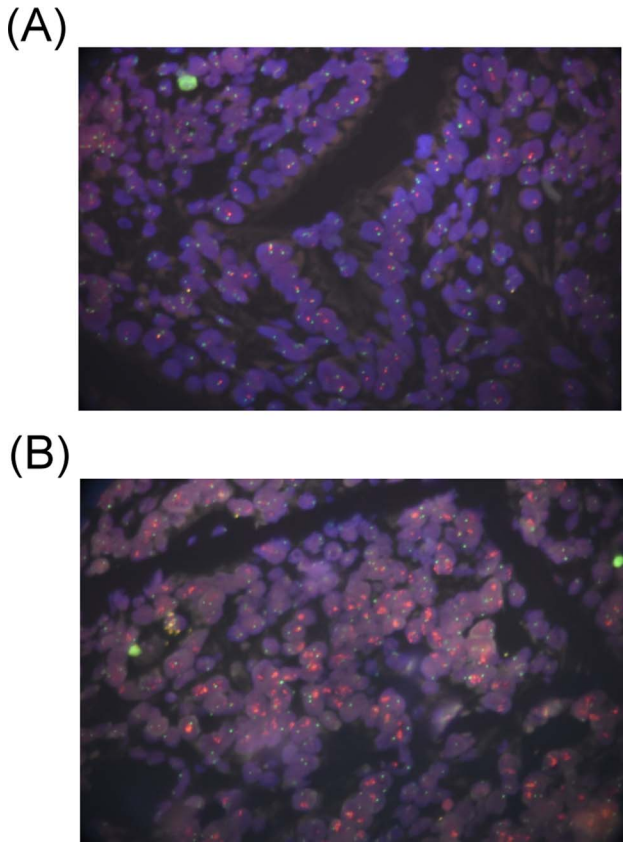

Fig. 2 Fluorescence in situ hybridization detecting HER2 signals (red) and CEP17 signals (green). (A) Negative HER2 gene amplification and (B) positive HER2 gene amplification.

Discussion

The HER2-positive ratio was 7.2% in our study using standardized testing methods according to the ToGA trial. The range of the HER2-positive ratio has been reported widely from 3.1% to 50%.[5,6] The reported wide range could be a result of ethnic variation and differences in methodology. For studies using the HER2-positive definition of IHC scores of 2+ and 3+ without FISH, the positive ratio could be overestimated. When studying the same population using the same criteria, Hsu *et al*[9] demonstrated a similar positive ratio of 6.1%.

The association between HER2-positive gastric cancer and intestinal type as well as differentiated histology has been widely reported in most published literature, including two meta-analyses.[5–9,15–17] Our study demonstrated consistent findings that HER2-positive gastric cancer was associated with more differentiated tumors, more Lauren intestinal type, and a higher portion of Ming expanding type in the univariate analysis. After further logistic regression, only Lauren classification was an independent

Table 1 Clinicopathologic features of gastric cancer patients according to HER2 status

Variables	HER2 negative (n = 310)	HER2 positive (n = 24)	*P* value	OR	95% CI	*P* value
Mean age, y	66.63 ± 12.51	65.79 ± 12.95	0.752			
Sex, n (%)			0.971			
Male	182 (58.7)	14 (58.3)				
Female	128 (41.3)	10 (41.7)				
Tumor size	4.89 ± 3.32	6.10 ± 3.48	0.086			
Tumor location, n (%)			0.356			
Upper third	46 (14.8)	6 (25.0)				
Middle third	138 (44.5)	10 (41.7)				
Lower third	119 (38.4)	7 (29.2)				
Whole stomach	7 (2.3)	1 (4.2)				
Gastrectomy			0.363			
Subtotal	267 (86.1)	19 (97.2)				
Total	43 (13.9)	5 (20.8)				
Curative resection			0.092			
Yes	280 (90.3)	19 (79.2)				
No	30 (9.7)	5 (20.8)				
Gross appearance, n (%)			0.159			
Superficial type	77 (24.8)	2 (8.3)				
Borrmann type 1 & 2	57 (18.4)	6 (25.0)				
Borrmann type 3 & 4	176 (56.8)	16 (66.7)				
Differentiation, n (%)			0.016			0.653
Yes (well/moderate)	128 (41.3)	16 (66.7)				
No (poor)	182 (58.7)	8 (33.3)				
Lauren classification, n (%)			0.010			0.015
Intestinal type	148 (47.7)	18 (75.0)		3.264	1.261–8.443	
Diffuse type	162 (52.3)	6 (25.0)		1.000		
Ming classification, n (%)[a]			0.033			0.182
Expanding type	57 (18.4)	9 (37.5)				
Infiltrating type	252 (81.6)	15 (62.5)				
Lymphovascular invasion, n (%)			0.304			
No	150 (48.4)	9 (37.5)				
Yes	160 (51.6)	15 (62.5)				
Pathologic T stage, n (%)			0.180			
T1	100 (32.3)	9 (37.5)				
T2	52 (16.8)	1 (4.2)				
T3	71 (22.9)	9 (37.5)				
T4	87 (28.1)	5 (20.8)				
Pathologic N stage, n (%)			0.713			
N0	142 (45.8)	9 (37.5)				
N1	38 (12.3)	3 (12.5)				
N2	57 (18.4)	4 (16.7)				
N3	73 (23.5)	8 (33.3)				
TNM stage, n (%)[b]			0.423			
I	123 (39.7)	9 (37.5)				
II	63 (20.3)	3 (12.5)				
III	107 (34.5)	9 (37.5)				
IV	17 (5.5)	3 (12.5)				

[a]One datum unavailable in HER2-negative group.
[b]According to the American Joint Committee on Cancer staging manual, 8th edition.

factor associated with HER2-positive gastric cancer. Lauren classification categorized gastric cancer into the intestinal type and diffuse type, and the two different types have distinct tumor behaviors.[18] The intestinal type is associated with atrophic gastritis, intestinal metaplasia, preserved glandular appearance, and better differentiation. In contrast, the diffuse type lacks glandular architecture and is poorly differentiated. Because Lauren classification already plays a role in terms of differentiation, the significance

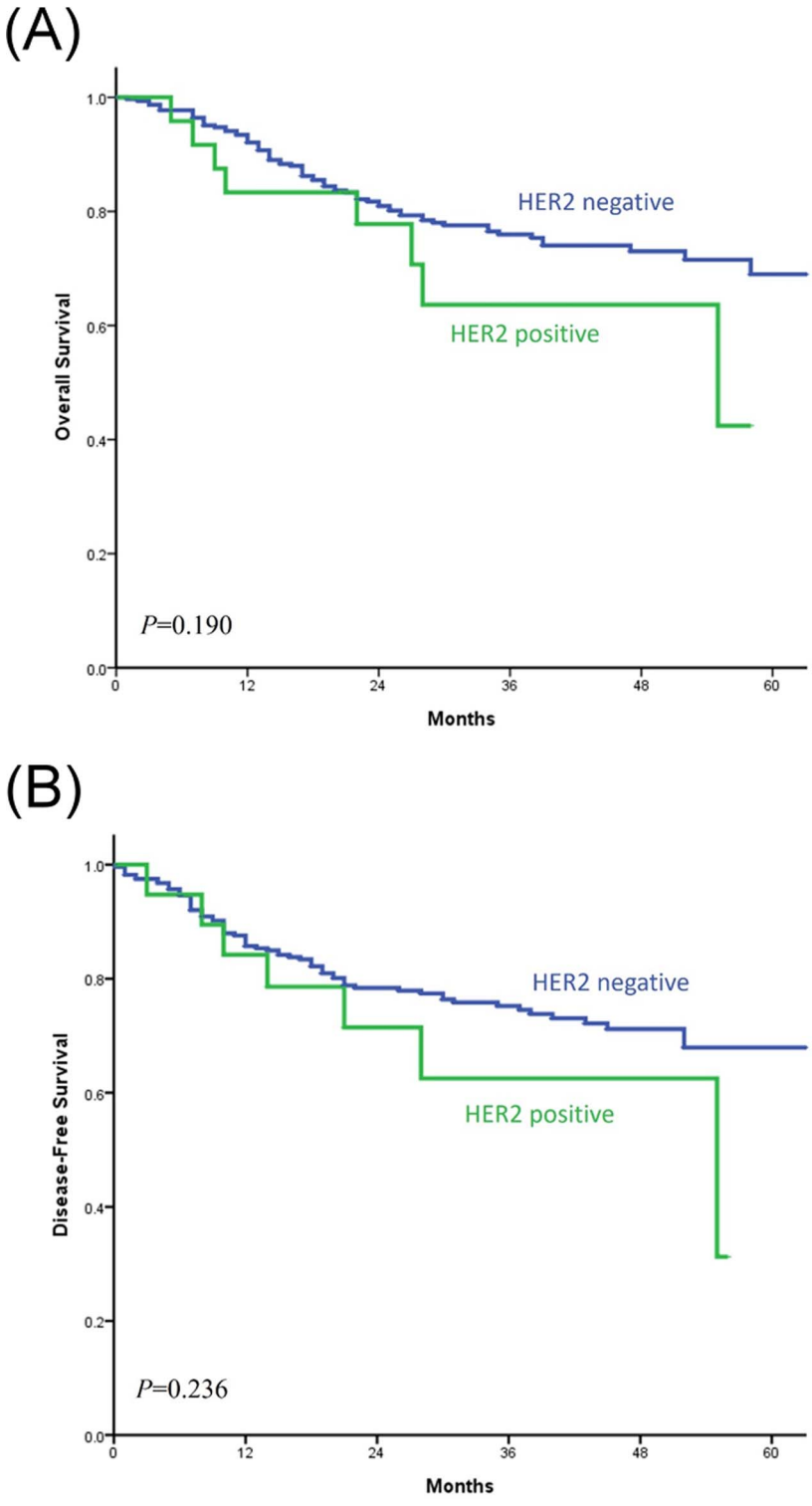

Fig. 3 (A) The OS (months) for patients with HER2-positive and HER2-negative gastric cancer (log-rank $P = 0.190$). (B) The DFS (months) for patients with HER2-positive and HER2-negative gastric cancer (log-rank $P = 0.236$).

of differentiation is likely to be adjusted in logistic regression, as is shown in our statistical results.

We found that HER2-positive gastric cancer patients were more likely to have distant lymphatic recurrence than those with HER2-negative gastric cancer. In addition, among the 5 patients with HER2-positive gastric cancer who received palliative resection, 3 patients had para-aortic lymph

Table 2 Univariate and multivariate analyses of prognostic factors with OS as an end point

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age			0.728			
<65 y	1					
≥65 y	1.082	0.695–1.683				
Sex			0.573			
Male	1					
Female	1.135	0.731–1.764				
Tumor size			<0.001			0.766
<5 cm	1					
≥5 cm	2.261	1.438–3.555				
Tumor location			0.456			
Upper third	1					
Middle third	1.066	0.555–2.049				
Lower third	0.938	0.477–1.845				
Whole stomach	2.215	0.713–6.877				
Gross appearance			0.005			0.312
Superficial type	1					
Borrmann type 1 & 2	3.584	1.496–8.584				
Borrmann type 3 & 4	3.681	1.676–8.088				
Differentiation			0.095			
Yes (well/moderate)	1					
No (poor)	1.485	0.934–2.361				
Lauren's classification			0.417			
Intestinal type	1					
Diffuse type	1.201	0.772–1.868				
Ming classification			0.097			
Expanding type	1					
Infiltrating type	1.801	0.899–3.067				
Lymphovascular invasion			<0.001			0.175
No	1					
Yes	2.992	1.803–4.966				
TNM stage			<0.001			<0.001
I	1			1.000		
II	2.667	1.104–6.440		2.667	1.104–6.440	
III	6.657	3.249–13.637		6.657	3.249–13.637	
IV	20.438	8.900–46.932		20.438	8.900–46.932	
HER2 status			0.196			
Negative	1					
Positive	1.621	0.780–3.367				

CI, confidence interval; HR, hazard ratio.

node metastasis. Both results imply that HER2 positivity is associated with distant lymphatic spreading. A similar finding of a higher HER2-positive rate in gastric cancer patients with extensive lymph node metastasis was reported by Matsumoto *et al*.[19]

Our results showed that for stage III/IV HER2-positive gastric cancer, the OS was significantly better for patients with anti-HER2 therapy than for those without anti-HER2 therapy. Among the 5 patients treated with anti-HER2 therapy, 2 patients were Lauren intestinal type (2 of 5; 40%), and 3 patients were Lauren diffuse type (3 of 5; 60%). Among the 7 patients without anti-HER2 therapy, 5 patients were Lauren intestinal type (5 of 7; 71.4%), and 2 patients were Lauren diffuse type (2 of 7; 28.6%). Lauren diffuse type is associated with poorer survival compared to intestinal type.[20] Despite the differences in Lauren classification, patients receiving anti-HER2 therapy showed significantly improved survival. For the 3 patients with distant lymph node metastasis who received anti-HER2 therapy and palliative resection, the outcome was even more encouraging. All 3 patients were disease-free with survival up to 58 months. Arigami

Table 3 The initial recurrence pattern in gastric cancer patients after curative surgery according to HER2 status[a]

	HER2 negative n = 280, n (%)	HER2 positive n = 19, n (%)	*P* value
Total patients with recurrence	52 (18.6)	5 (26.3)	0.376
Locoregional recurrence	18 (6.4)	0 (0.0)	0.615
Peritoneal dissemination	20 (7.1)	2 (10.5)	0.640
Hematogenous metastasis	13 (4.6)	1 (5.3)	0.610
Distant lymphatic recurrence	8 (2.9)	3 (15.8)	0.026

[a]Some patients had more than 1 recurrence pattern.

et al[21] demonstrated similar findings that HER2 overexpression could be used to determine the prognosis of patients with para-aortic lymph node metastasis from gastric cancer.[21] From their study, a higher HER2-positive ratio (43.9%) was noted, and HER2-positive patients who received trastuzumab-based chemotherapy had a significantly better prognosis than HER2-negative patients in gastric cancer with para-aortic lymph node metastasis. It seems that patients with HER2-positive gastric cancer and distant lymph node metastasis can benefit the most from anti-HER2 therapy. However, this hypothesis needs further larger-scale prospective studies for validation.

HER2 overexpression was thought to be associated with a poorer prognosis in node-positive and node-negative breast cancer.[22] With the development of anti-HER2 therapy, the role of HER2 has changed. For patients treated with anti-HER2 agents appropriately, HER2-positive breast cancers are associated with favorable outcomes compared with HER2-negative breast cancers in the 8th American Joint Committee on Cancer staging system.[23] A similar result is anticipated but not yet established in the era of gastric cancer. The ToGA trial, a phase 3 randomized study by Bang *et al*,[14] demonstrated a survival benefit of trastuzumab for HER2-positive metastatic gastric or gastroesophageal junction cancer.[14] In contrast, in the NRG Oncology/RTOG 1010 randomized phase 3 trial, the addition of trastuzumab to neoadjuvant chemoradiotherapy was not effective.[24]

The JACOB trial, a phase 3 randomized controlled study conducted by Tabernero *et al*[25] showed that adding pertuzumab to trastuzumab and chemotherapy did not improve OS for HER2-positive metastatic gastric or gastroesophageal junction cancer. Despite the negative result of the JACOB trial, the efficacy of dual blockade in the perioperative setting is still being investigated. The PETRARCA phase 2 trial, even though it was closed prematurely, demonstrated that the addition of trastuzumab and pertuzumab to perioperative FLOT significantly improved pathologic complete remission (35% versus 12%; $P = 0.019$) and preliminary survival benefit in patients with HER2-positive resectable esophagogastric adenocarcinoma.[26] The INNOVATION trial has been conducted to evaluate the effect of chemotherapy alone versus chemotherapy plus trastuzumab versus chemotherapy plus trastuzumab plus pertuzumab in the neoadjuvant setting.[27] The pending results are essential to determine the role of neoadjuvant trastuzumab and pertuzumab.

The efficacy of trastuzumab-based antibody–drug conjugates is also controversial. The GATSBY trial concluded that trastuzumab emtansine (T-DM1) was not superior to taxane in patients with previously treated HER2-positive advanced gastric cancer.[28] In the DESTINY-Gastric01 trial, the result of trastuzumab deruxtecan (T-DXd) was totally different. Trastuzumab deruxtecan significantly improved the response and OS compared with standard therapies among patients with treated HER2-positive gastric cancer.[29] Although the results of anti-HER2 agents for HER2-positive gastric cancer are inconsistent, numerous trials with various settings are still ongoing to determine the potential benefit for HER2-positive gastric cancer.

According to our study, TNM stage remains the most crucial prognostic factor. None of the remaining studied factors can be predictive of prognosis. This result again emphasizes the importance of early detection and early management for gastric cancer.

There are limitations in our study. First, it is a single-center retrospective study with only Taiwanese individuals included. Therefore, potential selection bias exists. Second, the number of HER2-positive cases is limited because of the low positive ratio of 7.2%. Therefore, it is difficult to perform further analysis in terms of prognostic value. Nevertheless, we found that HER2-positive gastric cancer is highly correlated with distant lymphatic spreading and its

potential role as a favorable prognostic factor if treated with anti-HER2 therapy.

Conclusion

HER2-positive gastric cancer was associated with intestinal histologic type. Patients with HER2-positive gastric cancer were more likely to have distant lymphatic recurrence, but HER2 was not an independent prognostic factor.

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