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Prognostic Significance of HER2 Expression for Gastric Cancer With Clinically Para-aortic Lymph Node Metastasis

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Abstract. *Background/Aim: To determine the prognostic utility of trastuzumab-based chemotherapy based on human epidermal growth factor receptor 2 (HER2) expression in patients with para-aortic lymph node (PAN) metastasis from gastric cancer. Patients and Methods: A total of 41 patients with clinical PAN metastasis from gastric cancer who underwent chemotherapy were retrospectively enrolled. Results: Eighteen (43.9%) patients had HER2-positive tumors and consequently, received trastuzumab-based chemotherapy. A total of 11 patients underwent surgery. HER2 status was significantly correlated with the number of distant metastatic sites, the presence or absence of trastuzumab-based chemotherapy, and the presence or absence of gastrectomy. HER2-positive patients had significantly better prognosis than HER2-negative patients. Multivariate analysis identified age and trastuzumab-based chemotherapy based on HER2 status as an independent prognostic factor. Conclusion: Assessing HER2 expression and subsequent trastuzumab-based chemotherapy can be an effective method for determining the prognosis of patients with PAN metastasis from gastric cancer.*

Gastric cancer has remained one of most common gastrointestinal malignancies and the third leading cause of cancer-related death worldwide (1). Nonetheless, the rapid advancements in chemotherapy have dramatically improved the prognosis of patients with advanced gastric cancer. Recently, Yoshida *et al*. proposed a new biological classification that would guide the therapeutic management of patients with stage IV gastric cancer (2). According to this classification, patients with para-aortic lymph node (PAN) nos. 16a2 and/or 16b1 and no peritoneal dissemination would belong under category 1 (2), which indicates stage IV status with technically resectable metastasis. Notably, studies have suggested that neoadjuvant chemotherapy (NAC) could be a promising therapeutic strategy in category 1 patients, such as those with PAN nos. 16a2 and 16b1 metastasis (2). Similar, the Japan Clinical Oncology Group 0405 study demonstrated that NAC using S-1 plus cisplatin had potential for improving prognosis in patients with extensive lymph node metastasis, including PAN metastasis (3). On the other hand, patients with another distant metastasis, such as peritoneal dissemination, aside from PAN metastasis, are classified into category 3 or 4 (2). Among patients with PAN metastasis, those belonging to categories 3 and 4 have exceedingly worse prognosis compared to those belonging to category 1. Consequently, the 2018 Japanese Gastric Cancer Treatment Guidelines recommend systemic chemotherapy as the initial treatment for gastric cancer with distant metastasis, including category 3 or 4 patients (4).

The ToGA trial demonstrated the clinical utility of trastuzumab as a first-line regimen in patients with human epidermal growth factor receptor 2 (HER2)-positive unresectable advanced or recurrent gastric cancer (5). Similarly, the 2018 Japanese Gastric Cancer Treatment Guidelines strongly recommended trastuzumab-containing regimens for patients with HER2-positive advanced gastric cancer (4). However, studies have shown only 11.7% to 23.0% of patients with HER2-positive gastric cancer (6-13), indicating low HER2 positivity rates among patients with advanced gastric cancer. As such, the clinical indication of trastuzumab for patients with HER2-positive gastric cancer

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has remained limited. Moreover, the clinical significance of HER2 expression has remained controversial in patients with gastric cancer despite the numerous studies regarding the matter (9-13). Unfortunately, only a few studies have evaluated the prognostic impact of HER2 expression in patients with PAN metastasis.

The current study sought to determine the prognostic utility of trastuzumab-based chemotherapy based on HER2 expression in patients with PAN metastasis by investigating HER2 expression, tumor response to chemotherapy, the presence or absence of surgery among patients with PAN metastasis, and the relationship between HER2 status and clinicopathological factors or prognosis.

Patients and Methods

Patients. A total of 41 patients with clinical PAN metastasis from gastric cancer who underwent chemotherapy at Kagoshima University Hospital (Kagoshima, Japan) between June 2011 and November 2019 were retrospectively reviewed. Patients with synchronous or metachronous cancer in other organs were excluded from this study. All patients underwent blood examinations, esophagogastroduodenoscopy, endoscopic ultrasonography, and computed tomography (CT) before chemotherapy. Patients were classified and staged based on the TNM classification for gastric carcinoma (14). This retrospective study was approved by the Ethics Committee of Kagoshima University and conducted in accordance with the Declaration of Helsinki (approval number: 200191).

Assessment of para-aortic lymph node metastasis and tumor response. Metastatic PAN was clinically defined as that of 1 cm or more in diameter, confirmed via CT (15, 16). Tumor response was determined every three chemotherapy cycles and evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST) (17). The present study classified tumor response into the following four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Immunohistochemistry and fluorescence in situ hybridization for HER2 expression. Pretherapeutically, biopsied specimens were used for immunohistochemistry (IHC). All paraffin-embedded specimens were cut into 4-μm thick slices using a conventional histological technique and transferred to a slide. IHC was then performed using the Hercept test kit (Dako, Carpinteria, CA, USA) according to the protocol recommended by the manufacturer, using an automatic immunostainer (Dako). Thereafter, staining intensity was classified into the following four categories according to the Hercept test scoring criteria: 0, 1+, 2+, and 3+ (5).

Fluorescence *in situ* hybridization (FISH) was performed using the Abbott PathVysion HER2 DNA Probe Kit protocol (Abbott Laboratories, Abbott Park, Des Plaines, IL, USA) according to the manufacturer's instructions. *HER2* gene amplification status was evaluated by counting the number of HER2 and CEP 17 signals in 20 adjacent interphase tumor cell nuclei examined under a fluorescent microscope with the appropriate filters. Positive HER2 amplification was subsequently defined as an HER2:CEP17 ratio of ≥2.0 (5).

The criteria for HER2 positivity were an IHC score of 3+ or an IHC score of 2+ plus FISH positivity (5).

Statistical analysis. The relationship between HER2 status and categorical clinicopathological factors was assessed using the chi-squared test, Fisher's exact test, or Wilcoxon rank-sum test. Survival time was defined as the duration from chemotherapy initiation until death or last follow-up. Survival curves were generated using the Kaplan–Meier method, while the prognostic difference was determined using the log-rank test. Prognostic factors were determined using univariate and multivariate analyses (Cox proportional hazards regression modeling). All data were analyzed using JMP14 (SAS Institute Inc., Cary, NC, USA) with a p-value of <0.05 indicating statistical significance.

Results

Clinicopathological features. Table I summarizes the clinicopathological factors of all 41 patients (31 men and 10 women; mean age, 66.2 years, ranging from 43 to 87 years). Among the 41 patients, 1, 6, and 34 had clinical T2, T3, and T4 tumors, respectively. Moreover, 4, 8, and 29 patients had clinical nodal status of N1, N2, and N3, respectively. Among the 27 patients with ≥2 distant metastatic sites besides PAN, 12, 9, 3, and 9 had peritoneal dissemination, liver metastasis, bone metastasis, and distant lymph node metastasis except PAN metastasis, respectively.

HER2 expression and chemotherapy regimens. Among the 41 patients enrolled herein, 9, 4, 10, 7, and 11 had an IHC score of 0, 1+, 2+ plus negative FISH, 2+ plus positive FISH, and 3+, respectively (Figure 1). Collectively, 18 of the 41 patients (43.9%) had HER2-positive tumors.

Platinum- and taxane-based chemotherapy was provided as the first-line regimen to 33 and 8 patients, respectively (Table I). Furthermore, 18 patients with HER2-positive status received trastuzumab combined with chemotherapy.

Tumor response to chemotherapy and surgery. The RECIST revealed that 1, 17, 17, and 6 patients had CR, PR, SD, and PD, respectively. Accordingly, the current study found a response and disease control rate of 43.9% (18/41) and 85.4% (35/41), respectively.

Among the 41 patients, 11 (26.8%) underwent gastrectomy with lymphadenectomy after chemotherapy.

Relationship between HER2 status and clinicopathological factors. Among the 23 HER2-negative patients, 19 (82.6%) had ≥2 distant metastatic sites. In contrast, among the 18 HER2-positive patients, only 8 (44.4%) had ≥2 distant metastatic sites. Therefore, HER2 status was significantly correlated with the number of distant metastatic sites (1 *vs.* ≥2) (p=0.0192) (Table II). Moreover, all HER2-positive patients (n=18) received trastuzumab combined with chemotherapy, whereas none of the HER2-negative patients (n=23) received trastuzumab-based chemotherapy. Accordingly, HER2 status was significantly associated with the presence or absence of trastuzumab-based

Table I. *Clinicopathological factors (n=41).*

Factor	n (%)
Gender	
Male	31 (75.6)
Female	10 (24.4)
Mean age (range), years	66.2 (43-87)
Tumor location	
Whole	5 (12.2
Upper	18 (43.9)
Middle	9 (22.0)
Lower	9 (22.0)
Macroscopic type	
Type 2	4 (9.8)
Type 3	34 (83.0)
Type 4	3 (7.3)
Depth of tumor invasion	
cT2	1 (2.4)
cT3	6 (14.6)
cT4	34 (82.9)
Lymph node metastasis	
cN1	4 (9.8)
cN2	8 (19.5)
cN3	29 (70.7)
Number of distant metastatic sites	
1	14 (34.1)
2	17 (41.5)
3	9 (22.0)
4	1 (2.4)
Peritoneal dissemination	
Absence	29 (70.7)
Presence	12 (29.3)
Liver metastasis	
Absence	32 (78.0)
Presence	9 (22.0)
Bone metastasis	
Absence	38 (92.7)
Presence	3 (7.3)
Distant lymph node metastasis except para-aortic lymph node metastasis	
Absence	32 (78.0)
Presence	9 (22.0)
Histological type	
Differentiated	15 (36.6)
Undifferentiated	26 (63.4)
HER2 status	
IHC 0	9 (22.0)
IHC 1+	4 (9.8)
IHC 2+ and FISH –	10 (24.4)
IHC 2+ and FISH +	7 (17.1)
IHC 3+	11 (26.8)
First-line chemotherapy regimen	
Platinum-based chemotherapy	33 (80.5)
Taxane-based chemotherapy	8 (19.5)
Combination of trastuzumab	
Absence	23 (56.1)
Presence	18 (43.9)

FISH: Fluorescence *in situ* hybridization; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry.

chemotherapy ($p<0.0001$) (Table II). Among the 41 patients included herein, 2 HER2-negative (8.7%) and 9 HER2-positive (50.0%) patients underwent gastrectomy. Consequently, our results showed a close relationship between HER2 status and the presence or absence of gastrectomy ($p=0.0046$) (Table II).

Relationship between trastuzumab-based chemotherapy based on HER2 status and prognosis. HER2-negative and -positive patients had a median survival time (MST) of 324 and 896 days, respectively (Figure 2). Accordingly, HER2-positive patients who received trastuzumab combined with chemotherapy had a significantly better prognosis compared to HER2-negative patients ($p=0.0003$) (Figure 2).

Univariate analysis of pretherapeutic factors identified age (<70 *vs*. ≥70 years), peritoneal dissemination, trastuzumab-based chemotherapy based on HER2 status, and gastrectomy as factors significantly correlated with survival ($p=0.0256$, $p=0.0350$, $p=0.0006$, and $p=0.0063$, respectively) (Table III). Multivariate analysis identified age and trastuzumab-based chemotherapy based on HER2 status as independent prognostic factors correlated with survival ($p=0.0153$ and $p=0.0385$, respectively) (Table III).

Discussion

Currently, trastuzumab-containing regimens have been used as first-line chemotherapy in patients with HER2-positive unresectable advanced or recurrent gastric cancer (4). Accordingly, patients with clinical PAN metastasis from HER2-positive gastric cancer generally receive trastuzumab-based chemotherapy as their initial treatment. Moreover, conversion surgery has been highlighted as a potential therapeutic strategy for improving prognosis in responders to chemotherapy (2, 18, 19). However, impact of HER2 expression on prognosis or surgical outcomes in patients with clinical PAN metastasis from gastric cancer has remained poorly understood. To the best of our knowledge, the current study has been the first to examine the association between trastuzumab-based chemotherapy based on HER2 expression and surgical or prognostic outcomes among patients with clinically PAN metastasis from gastric cancer.

Recently, an experimental study suggests that microRNAs may be related with HER2 expression in patients with gastric cancer (20). Evidence has shown that gastric cancer exhibits low HER2 positivity rates due to its heterogeneous expression in tumor cells (6-13). Surprisingly, however, 43.9% of the patients included in the present study were HER2-positive. Matsumoto *et al*. reported an HER2 positivity rate of 27.0% (24/89) in patients with bulky N2 or PAN metastasis from locally advanced gastric cancer (21). Furthermore, our study showed that HER2 status was significantly associated with the number of distant metastatic sites (1 *vs*. ≥2) ($p=0.0192$). PAN metastasis alone without other distant metastasis occurred in

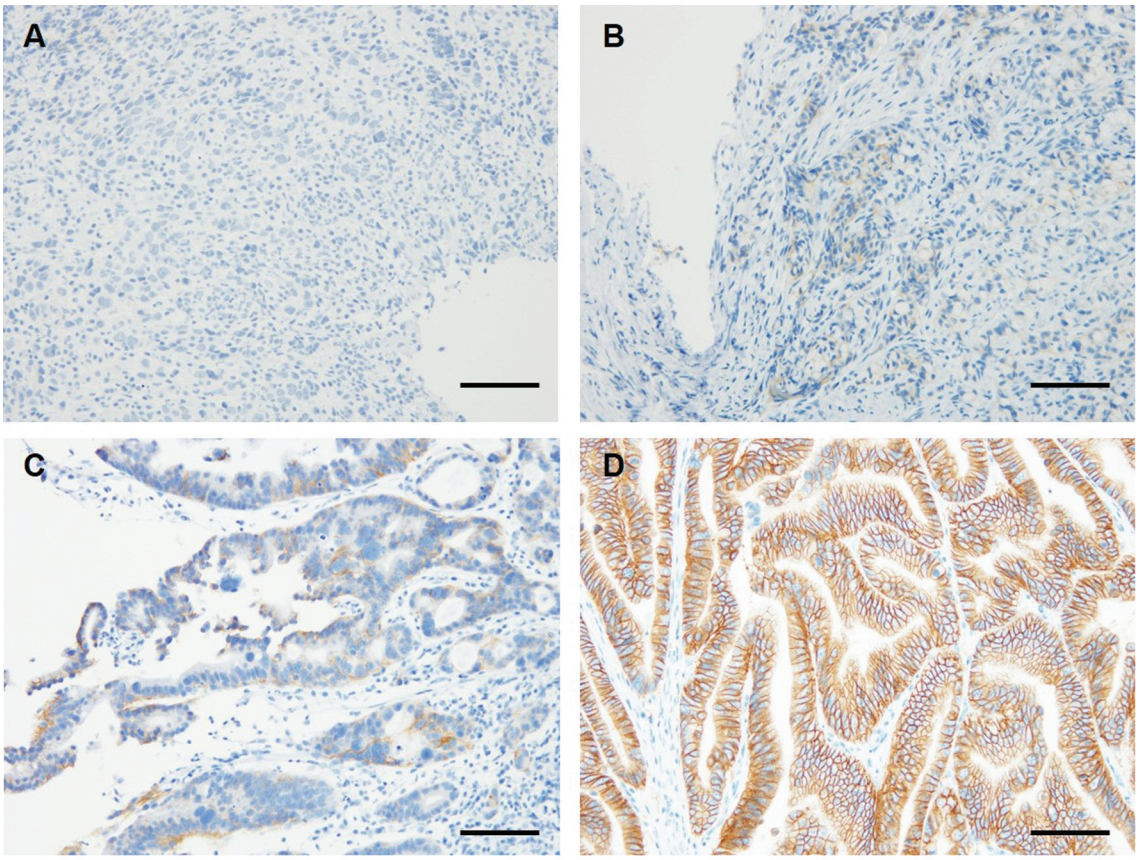

Figure 1. *Representative immunohistochemical staining images of HER2 expression. A) Immunohistochemistry (IHC) score of 0. B) IHC score of 1+. C) IHC score of 2+. D) IHC score of 3+. Scale bars indicate 100 μm. Original magnification ×200.*

17.4% and 55.6% of HER2-negative and -positive patients, respectively, suggesting that patients with extensive lymph node metastasis, including PAN metastasis, had higher HER2 positivity rates compared to those with other cancer types. Collectively, our results suggest that patients with PAN metastasis can receive trastuzumab-containing regimens at high frequencies as their first-line chemotherapy. This chemotherapeutic strategy may be clinically advantageous for patients with PAN metastasis from gastric cancer. However, a recent study demonstrated that trastuzumab plus chemotherapy or chemotherapy alone produced loss of HER2 expression (22). Accordingly, it is clinically important to reassess HER2 expression during chemotherapy in HER2-positive patients with PAN metastasis.

Unsurprisingly, all HER2-positive patients included herein had received trastuzumab-containing regimens. Accordingly, our results showed that HER2-negative and -positive patients had a chemotherapy response rate of 30.4% and 61.1%, respectively. Although no significant difference in response rate had been observed between both groups (p=0.0640), HER2-positive patients tended to have greater response rates compared to HER2-negative patients. According to the ToGA trial, patients with HER2-positive gastric cancer who underwent trastuzumab-containing chemotherapy had an overall tumor response rate of 47% (5). These findings indicate that trastuzumab-based chemotherapy was considerably effective in patients with HER2-positive advanced gastric cancer. Furthermore, HER2-negative and -positive patients included herein had a surgical resection rate of 8.7% and 50.0%, respectively. Although limited evidence is available regarding the clinical significance of surgery after trastuzumab-containing chemotherapy, the aforementioned findings demonstrate that HER2 positivity may be correlated with high surgical resection rates due to the favorable response rates. Taken together, the current study showed that assessing HER2 expression can help guide the planning of gastrectomy, including conversion surgery, after chemotherapy in patients with clinically PAN metastasis from gastric cancer. Interestingly, Namikawa *et al*. showed a high status of neutrophil-lymphocyte ratio was associated with a poor prognosis in HER2-positive gastric cancer who underwent

Table II. *Relationship between HER2 status and clinicopathological factors.*

Factor	HER2 status, n (%)		*p*-Value
	HER2 negative (n=23)	HER2 positive (n=18)	
Gender			0.7379
Male	17 (73.9)	14 (77.8)	
Female	6 (26.1)	4 (22.2)	
Mean age, years	68.2±11.4	63.6±12.5	0.2262
Tumor location			1.0000
Whole/upper	13 (56.5)	10 (55.6)	
Middle/lower	10 (43.5)	8 (44.4)	
Macroscopic type			1.0000
Type non–4	21 (91.3)	17 (94.4)	
Type 4	2 (8.7)	1 (5.6)	
Depth of tumor invasion			0.2086
cT2–3	2 (8.7)	5 (27.8)	
cT4	21 (91.3)	13 (72.2)	
Lymph node metastasis			1.0000
cN1–2	7 (30.4)	5 (27.8)	
cN3	16 (69.6)	13 (72.2)	
Number of distant metastatic sites			0.0192
1	4 (17.4)	10 (55.6)	
≥2	19 (82.6)	8 (44.4)	
Peritoneal dissemination			0.1713
Absence	14 (60.9)	15 (83.3)	
Presence	9 (39.1)	3 (16.7)	
Liver metastasis			1.0000
Absence	18 (78.3)	14 (77.8)	
Presence	5 (21.7)	4 (22.2)	
Bone metastasis			0.2427
Absence	20 (87.0)	18 (100.0)	
Presence	3 (13.0)	0 (0.0)	
Distant lymph node metastasis except para-aortic lymph node metastasis			0.0535
Absence	15 (65.2)	17 (94.4)	
Presence	8 (34.8)	1 (5.6)	
Histological type			0.5149
Differentiated	7 (30.4)	8 (44.4)	
Undifferentiated	16 (69.6)	10 (55.6)	
First-line chemotherapy regimen			1.0000
Platinum-based chemotherapy	18 (78.3)	15 (83.3)	
Taxane-based chemotherapy	5 (21.7)	3 (16.7)	
Combination of trastuzumab			<0.0001
Absence	23 (100.0)	0 (0.0)	
Presence	0 (0.0)	18 (100.0)	
Tumor response			0.0640
PD–SD	16 (69.6)	7 (38.9)	
CR–PR	7 (30.4)	11 (61.1)	
Gastrectomy			0.0046
Absence	21 (91.3)	9 (50.0)	
Presence	2 (8.7)	9 (50.0)	

CR: Complete response; HER2: human epidermal growth factor receptor 2; PD: progressive disease; PR: partial response; SD: stable disease.

HER2-targeted chemotherapy (23). Accordingly, pretherapeutic systemic inflammatory response may be a promising blood marker for predicting prognosis in the clinical management of HER2-positive advanced gastric cancer.

The ToGA trial showed that patients with HER2-positive gastric cancer who underwent trastuzumab plus chemotherapy and chemotherapy alone without trastuzumab had an MST of 13.8 and 11.1 months, respectively (5). Moreover, even patients

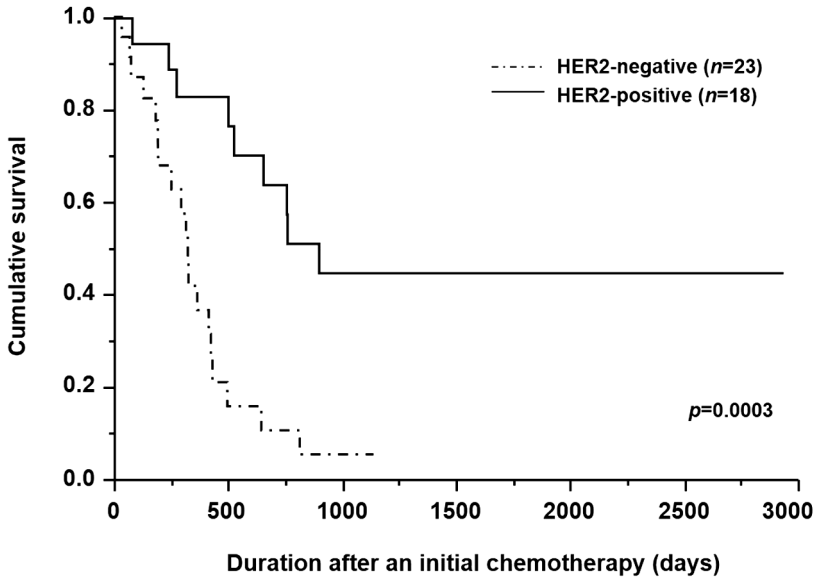

Figure 2. *Kaplan–Meier survival curves according to HER2 expression.*

with HER2-positive gastric cancer without measurable lesions who underwent trastuzumab with S-1 plus cisplatin had an MST of 14.4 months (24). In the present study, however, HER2-positive patients who underwent trastuzumab-containing chemotherapy had an MST of 29.9 months (896 days), with a 3-year overall survival (OS) rate of 44.7% (data not shown). Nonetheless, it should be noted that the patients included in the ToGA trial had different clinicopathological factors compared to those included herein, and the presence or absence of conversion surgery remained obscure in the ToGA trial. Furthermore, although univariate analysis identified the presence or absence of gastrectomy as an independent prognostic factor (p=0.0063), multivariate analysis did not (p=0.0683). This could have been attributed to our sample size, which may have been too small to indicate evidence of statistical differences during multivariate analysis. Nonetheless, the present study proposed that surgery after trastuzumab-containing chemotherapy may be a promising therapeutic strategy for improving the prognosis of patients with clinical PAN metastasis from HER2-positive gastric cancer. Similarly, Takahashi *et al*., who retrospectively compared the prognosis of patients with stage IV HER2-positive gastric or gastroesophageal junction cancer according to whether they received chemotherapy followed by surgery or chemotherapy alone, reported that patients who underwent surgery following trastuzumab-based chemotherapy had 1- and 3-year OS rates of 100% and 89.5% and 1- and 3-year relapse-free survival rates of 80.0% and 58.9%, respectively (25). The aforementioned findings, including those presented herein, suggest that conversion surgery has a favorable prognostic impact in patients with stage IV HER2-positive gastric cancer who responded to trastuzumab-based chemotherapy.

Several limitations of the present study are worth noting. First, this was a single-center retrospective study based on a small population (n=41). Second, trastuzumab-containing chemotherapy was clinically selected as the first-line regimen in patients with HER2-positive status, whereas patients with HER2-negative status underwent chemotherapy using varying regimens based on clinical trial registration, the patient's condition, or physician's discretion. Third, surgery after chemotherapy was clinically indicated for patients with a performance status of 0-2, non-PD, and tumors predicted to achieve curative resection based on the patient's general condition and physician's decision. Fourth, PAN metastasis was assessed by size alone based on CT. However, the diagnostic accuracy of lymph node metastasis by CT has been reported to display a wide range (26). These limitations might have induced bias that could have affected several results. Therefore, further larger-scale studies are needed to validate our findings.

In conclusion, the current retrospective study demonstrated that assessing HER2 expression can help physicians establish a therapeutic strategy, including chemotherapy regimens and subsequent surgery, and consequently improve prognosis in patients with clinical PAN metastasis from gastric cancer.

Conflicts of Interest

All Authors have no conflicts of interest to disclose in relation to this study.

Table III. *Univariate and multivariate analyses of survival*.

	Univariate analysis			Multivariate analysis		
Independent factor	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Gender			0.4490			
Female	1.000	Reference				
Male	0.728	0.320-1.657				
Age (years)			0.0256			0.0153
<70	1.000	Reference		1.000	Reference	
≥70	2.386	1.112-5.120		2.707	1.210-6.052	
Tumor location			0.5458			
Middle/lower	1.000	Reference				
Whole/upper	1.264	0.591-2.700				
Macroscopic type			0.4717			
Type non–4	1.000	Reference				
Type 4	1.570	0.460-5.364				
Depth of tumor invasion			0.4395			
cT2–3	1.000	Reference				
cT4	1.521	0.525-4.404				
Lymph node metastasis			0.3253			
cN1–2	1.000	Reference				
cN3	1.512	0.664-3.443				
Number of distant metastatic sites			0.1625			
1	1.000	Reference				
≥2	1.768	0.795-3.932				
Peritoneal dissemination			0.0350			0.4597
Absence	1.000	Reference		1.000	Reference	
Presence	2.376	1.063-5.314		1.392	0.579-3.345	
Liver metastasis			0.8550			
Absence	1.000	Reference				
Presence	1.083	0.460-2.554				
Bone metastasis			0.0818			
Absence	1.000	Reference				
Presence	3.914	0.842-18.199				
Distant lymph node metastasis except para-aortic lymph node metastasis			0.1255			
Absence	1.000	Reference				
Presence	2.057	0.818-5.175				
Histological type			0.0639			
Differentiated	1.000	Reference				
Undifferentiated	2.276	0.954-5.432				
Trastuzumab-based chemotherapy based on HER2 status			0.0006			0.0385
Absence	1.000	Reference		1.000	Reference	
Presence	0.232	0.101-0.535		0.366	0.141-0.948	
First-line chemotherapy regimen			0.9775			
Platinum-based chemotherapy	1.000	Reference				
Taxane-based chemotherapy	0.987	0.399-2.440				
Gastrectomy			0.0063			0.0683
Absence	1.000	Reference		1.000	Reference	
Presence	0.187	0.056-0.623		0.306	0.086-1.093	

CI: Confidence interval; HER2: human epidermal growth factor receptor 2.

Authors' Contributions

T.A., D.M., K.O., K.S., Y.T., Y.K., S.M., S.Y., Y.U., H.K., and T.O. contributed to the study design. T.A., D.M., K.O., K.S., and Y.T. were involved in data collection and data interpretation. T.A., Y.K., S.M., S.Y., Y.U., H.K., and T.O. contributed to the statistical analyses. T.A. wrote the manuscript. All Authors have read and approved the final manuscript.

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