

# HER-2 incidence in gastric cancer, its association with prognosis and clinicopathological parameters

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## ABSTRACT

**Objective:** Human epidermal growth factor-2 (HER-2) overexpression has prognostic value in breast cancer. However, the significance of HER-2 positivity in gastric cancer is controversial. In this study, we investigated the frequency of overexpression of HER-2 and its relationship with clinicopathological findings and impact on survival in gastric cancer.

**Material and Methods:** Gastric cancer patients, operated in Marmara University Faculty of Medicine, Pendik Training and Research Hospital, General Surgery Department, between January 2012-December 2013 were enrolled in this study. Medical records were retrospectively evaluated. Tissue samples were stained by immunohistochemistry (IHC) method, and were followed by fluorescence in situ hybridization (FISH) in those with positive results. HER-2 expression rates and its association with other histopathological features and survival have been analyzed.

**Results:** 135 patients were enrolled in the study, with 88 (65%) male and 47 (35%) female patients. The median age was 61 (29-84) years. Only 11 patients (8%) were positive for HER-2. HER-2 positive patients were similar to negative patients in terms of age, gender, tumor size, tumor location, tumor T stage, lymph node metastasis, histological type, differentiation, lymphovascular invasion, perinodal, perineural invasion and stage. No significant difference was detected on 1 and 2-year overall and disease-free survival rates between receptor positive and negative groups.

**Conclusion:** Consistent with the literature data, HER-2 positivity rate in this study was approximately 8%, but this positivity has not been found to be associated with either clinical and pathological parameters or overall and disease-free survival.

**Keywords:** HER-2, gastric cancer, prognosis

## INTRODUCTION

Gastric cancer is one of the most common cancer types, as well as being one of the main causes of cancer-related mortality throughout the world (1). Many patients present with advanced stage and/or metastatic disease at the time of diagnosis (2). Combined chemotherapeutic agents have been shown to increase overall survival as compared to single-agents (3). However, development of new and more effective treatment methods is required due to the reported survival rate of approximately 20% (4).

Human epidermal growth factor receptor-2 (HER-2)/neu positivity is regarded as a poor prognostic criterion in breast cancer (5). However, the prognostic significance of HER-2/neu positivity in gastric cancer remains to be controversial. Trastuzumab is known to improve survival in primary and metastatic HER-2 positive breast cancer patients. Likewise, the addition of trastuzumab to chemotherapy in advanced gastric and gastroesophageal junction cancers has been shown to improve survival (6).

Increased HER-2 gene amplification or protein expression is detected in 7-34% of primary gastric tumors (7, 8). We aimed to determine the frequency of Her-2/neu positivity in gastric cancer patients who have been operated in our clinic, and to demonstrate the correlation of increased HER-2 expression with clinical and pathological parameters as well as its impact on prognosis.

## MATERIAL AND METHODS

Patients who were operated on for a diagnosis of gastric cancer in Marmara University Faculty of Medicine Pendik Training and Research Hospital General Surgery Clinics between January 2012-December 2013 were enrolled in the study. The preoperative diagnosis was established by endoscopic biopsy, and oral/IV abdominal tomography and positron emission tomography-computed tomography (PET/CT), when required, were obtained for staging purposes. The data obtained from patient files were retrospectively analyzed. Our university ethics committee on non-invasive clinical research studies approved the study.

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Data regarding age, sex, date of diagnosis, tumor localization, and treatment modalities (surgery, chemotherapy, radiotherapy) were extracted from patient files. In addition, histologic type, degree of differentiation, tumor invasion depth, presence of lymphovascular, perineural and perinodal invasion, lymph node metastasis status, Lauren and Ming types were extracted from pathology reports. The presence of HER-2 expression was evaluated by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) methods in surgical specimens obtained from the archives of Marmara University School of Medicine Pathology Laboratory. The correlation of HER-2 expression levels with tumor histopathology, grade, serosal invasion, lymphovascular, perineural and perinodal invasion, Lauren type, tumor localization, TNM stage, presence of recurrence or metastasis during follow-up was evaluated, as well as its impact on survival.

#### Exclusion Criteria

Patients with emergency operations, with gastric adenocarcinoma showing neuroendocrine differentiation, with presence of preoperative metastatic disease and neoadjuvant therapy were excluded from the study.

#### HER-2 Evaluation Methods

HER-2 evaluation in gastric carcinoma samples was carried out according to the data available in the literature (6, 9). Accordingly, they were assigned scores of 0, +1, +2 and +3 according to their immune-reactivity. HER-2 signals and chromosome 17 signals were counted in at least twenty cells for FISH evaluation. FISH was applied only to samples with IHC scores of +2 and +3. Samples with a HER-2/CEP17 ratio  $\geq 2$  by FISH were accepted as positive. IHC scores of 0 and +1 were accepted as negative, and FISH was not performed on these samples.

#### Statistical Analysis

Statistical analysis was performed by using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 17.0 package program. Student t test or Mann-Whitney U test was used for continuous variables. Fisher's exact test or chi-square test was used for categorical assessments. The median value was stated for non-parametric values. The correlation between HER-2 expression and other parameters was evaluated with the chi-square test. Survival analysis was assessed by the Kaplan-Meier method. The effect of HER-2 expression on survival was assessed by the log-rank test. A "p" value less than 0.05 was considered as significant.

#### RESULTS

One hundred and thirty-five patients were enrolled in the study. Eighty-eight (65%) patients were male and 47 (35%) were female, with a median age of 61 (29-84) years. Twenty-seven patients had a family history of gastric cancer in their first-degree relatives. Sixty-four patients underwent total gastrectomy, 61 subtotal gastrectomy, and 10 had proximal gastrectomy. Multi-organ resection was performed in seven patients including five patients with invasion. Seven patients were detected to have liver metastases and seven had carcinomatosis, in the perioperative period. The median tumor diameter was determined as 6 cm (1-25 cm).

The tumors were localized in the cardia in 37 (27%), the corpus in 25 (19%), and in the gastric antrum in 70 patients (52%). Three (2%) patients had linitis plastica. Evaluation according to the WHO classification revealed that 66 patients (49%) had tubular type, 12 (9%) had signet-ring cell, 12 patients (1.5%) had papillary type, 12 (9%) had mucinous, 24 (18%) had mixed-type, and 17 patients (13%) had poorly cohesive tumors.

The median number of lymph nodes removed was determined as 17 (4-55), and the median number of metastatic lymph nodes was 4 (0-37). According to Lauren classification; 41 (31%) patients had diffuse type carcinoma, 76 (56%) intestinal type carcinoma, 15 (11%) mixed type carcinoma, and three (2%) patients were not classified. According to the Ming classification; 118 patients (87%) had infiltrative, 12 patients (9%) expanding, and 2 patients (1.5%) had mixed tumors, and 3 patients (2%) were not classified. 57 patients (42%) had vascular invasion, and 101 (75%) had lymphatic invasion. There was perineural invasion in 66 patients (49%), while perinodal spread was observed in 83 patients (62%). The surgical margins were positive in 35 patients (26%).

Seventy-three patients (54%) had stage 3 disease based on pathologic results. According to the TNM staging, 57 patients (42%) had T4 tumors, while 35 patients (26%) were pN0 and 100 patients (64%) were pN positive. Fifty-two patients (38%) received postoperative chemoradiotherapy.

HER-2 expression analysis showed that 115 (85%) patients were negative (IHC 0, +1), 7 (5%) patients were IHC +2 suspicious, and 12 (9%) patients were positive (IHC +3). All patients with an immunohistochemistry score of +2 were detected to be negative by FISH, while 11 of the 12 patients (92%) with a IHC score of +3 expressed HER-2 amplification as detected by the FISH method.

In conclusion, only 11 of the 135 patients (8%) were HER-2 positive (Table 1). Evaluation of clinical and histo-pathologic features of these 11 HER-2 positive patients revealed that they were mostly male (73%) with a median age of 60 years. One patient had grade 3, and 9 patients had grade 2 tumors, while the tumor grade of one patient was unknown. According to the WHO classification; tubular type was observed in 8

Table 1. HER-2 immunohistochemistry results and FISH rates

HER-2	n (%)
<b>Immunohistochemistry</b>	
0+	105 (78)
1+	11 (8)
2+	7 (5)
3+	12 (9)
<b>FISH</b>	
Positive	11 (8)
Negative	8 (6)
FISH: fluorescence in situ hybridization; HER-2: human epidermal growth factor receptor 2	

Table 2. Clinic and pathologic characteristics of HER-2 positive patients	
	n (%)
Age	60 years (47-77)
Gender	
Male	8 (73)
Female	3 (27)
Family history	
Yes	3 (27)
No	8 (73)
Operative procedure	
Total gastrectomy	8 (73)
Subtotal gastrectomy	2 (18)
Proximal gastrectomy	1 (9)
Peroperative liver metastasis	2 (18)
Peroperative carcinomatosis	0
Multiorgan resection	1 (9)
Tumor location	
Cardia	4 (36)
Antrum	7 (64)
<i>H. pylori</i>	
Positive	4 (36)
Negative	7 (64)
Number of dissected lymph nodes (median)	22 (5-40)
Number of metastatic lymph nodes (median)	6 (0-21)
Grade	
G1	1 (9)
G2	8 (72)
G3	1 (9)
Other	1 (9)
Lauren	
Intestinal	9 (82)
Diffuse	2 (18)
Ming	
Infiltrative	10 (91)
Expansive	1 (9)
Tumor diameter (median, cm)	5 (3-11)
Angioinvasion	7 (63)
Lymphatic invasion	10 (91)
Perinodal invasion	8 (82)
Perineural invasion	6 (55)
Surgical margin positivity	3 (27)
HER-2: human epidermal growth factor receptor 2	

patients (73%), papillary type in 1 (9%), and mixed type in 2 patients (18%).

Eight patients out of 11 HER-2 positive patients underwent total gastrectomy. Perioperative liver metastases were detected in two of these patients and carcinomatosis was not observed in any. In seven HER-2 positive patients (64%) the tumors were found to be localized in the antrum. Nine patients were classified as intestinal type by Lauren classification, and 10 patients as infiltrative type according to Ming classification. The median tumor diameter was 5 cm (3-11). Seven patients (64%) had vascular, 10 patients (91%) had lymphatic, 8 patients (82%) had perinodal and 6 patients (55%) had perineural invasion. Three patients (27%) were identified to have positive surgical margins (Table 2). Nine (82%) patients had differentiated grade 1 and 2 tumors. Ten out of 11 HER-2 positive patients were staged as T3 and T4 tumors (91%). Lymph node involvement was detected in 10 patients (91%), grade 1 and 2 tumors in two patients (18%), and grade 3 and 4 tumors were observed in 9 patients (82%).

There was no significant difference between HER-2 positive and negative patients in terms of age, sex, tumor size, tumor location, tumor T stage, and lymph node metastasis. There was also no significant difference between the two groups according to histologic type and degree of differentiation. There were no significant differences between HER-2 positive and negative groups in terms of vascular, lymphatic, perinodal and perineural invasion. Within HER-2 positive patients, 18% had stage I-II and 82% had stage III-IV tumors, and this showed no significant difference when compared with HER-2 negative patients (Table 3, 4).

Three of the 135 patients were lost to follow-up. The remaining 132 patients were followed-up for a median of 12 months (1-28 months). Twenty-seven patients died within one year, yielding a 1-year overall survival rate of 80% (Figure 1). The mean overall survival of these patients after one year was found to be  $11 \pm 0.3$  months. The overall survival for the two-year follow-up period was calculated as 71% (Figure 2). The mean survival was found to be  $18 \pm 0.7$  months.

On analysis of one-year survival data, there was no significant difference in overall survival between HER-2 negative (70%) and HER-2-positive (64%) patients ( $11 \pm 0.9$  months and  $9 \pm 1.3$  months, respectively;  $p=0.52$ ) (Figure 3). There was also no significant difference between HER-2-negative and HER-2 positive patients on two-year survival analysis ( $18 \pm 3$  months and  $16 \pm 3$  months, respectively;  $p=0.5$ ) (Figure 4).

Disease-free survival was found to be 85% at one-year follow-up of 132 patients. No significant difference was detected in comparison of the two groups ( $p=0.9$ ). Two-year disease-free survival rate was 78% (Figure 5). The disease-free survival at two years was 60% in HER-2-negative patients and 82% in HER-2 positive patients, with no significant difference ( $p=0.4$ ) (Figure 6).

There was no statistically significant difference between the two groups in terms of one-year and two-year disease-free survival, on the survival analysis performed after exclusion of

**Table 3. Comparison of clinic and pathologic parameters in HER-2 positive/negative patients**

	All patients n=135	HER-2 (+) n=11 (%)	HER-2 (-) n=124 (%)	P*
Age (mean)	61	60±10	61±12	0.5
Gender				
Female	47	3 (27)	44 (35)	0.7
Male	88	8 (73)	80 (65)	
Family history	27	3 (27)	24 (19)	0.5
Operative procedure				
Total gastrectomy	64	8 (73)	56 (45)	
Subtotal gastrectomy	61	2 (18)	59 (48)	0.08
Proximal gastrectomy	10	1 (9)	9 (7)	
Peroperative liver metastasis	7	2 (18)	5 (4)	0.1
Peroperative carcinomatosis	7	0	7 (5)	1
Multiorgan resection	7	1 (9)	6 (4)	1
Tumor location				0.5
Cardia	37	4 (36)	33 (27)	
Corpus	24	0	24 (19)	
Antrum	70	7 (64)	63 (51)	
Entire stomach	4	0	4 (3)	
<i>H. pylori</i>				
Positive	41	4 (36)	37 (30)	
Negative	94	7 (64)	87 (70)	0.75
Grade				
G1, G2	71	9 (82)	62 (50)	
G3	34	1 (9)	33 (27)	0.13
Other	30	1 (9)	29 (23)	
Number of dissected lymph nodes (mean)	17	18±10	22±10	0.18
Metastatic lymph node (median)	4	6 (0-21)	4 (0-37)	0.3
Lauren classification				
Intestinal	76	9 (82)	67 (54)	
Diffuse-mixed	59	2 (18)	57 (46)	0.11
Tumor diameter (cm) (mean)	6	6±2	7±4	0.24
Angio-invasion				
Yes	57	7 (64)	50 (40)	
No	78	4 (36)	74 (60)	0.2
Lymphatic invasion				
Yes	101	10 (91)	91 (73)	
No	34	1 (9)	33 (37)	0.3
Perinodal invasion				
Yes	83	9 (82)	74 (60)	
No	52	2 (18)	50 (40)	0.2
Perineural invasion				
Yes	66	6 (55)	60 (48)	
No	69	5 (45)	64 (52)	0.7

Chemotherapy				
Yes	84	8 (73)	76 (61)	
No	48	3 (27)	45 (36)	0.8
Unknown	3	0	3 (3)	
Radiotherapy				
Yes	52	6 (55)	46 (37)	
No	80	5 (45)	75 (60)	0.5
Unknown	3	0	3 (3)	

P value: refers to comparison of HER-2 positive and negative groups. HER-2: human epidermal growth factor receptor 2

**Table 4. Comparison of HER-2 positive/negative patients according to TNM stage**

	All patients n=135 (%)	HER-2 (+) n=11 (%)	HER-2 (-) n=124 (%)	P
T stage				
T1/T2	33 (24)	1 (9)	32 (26)	
T3/T4	102 (76)	10 (91)	92 (74)	0.3
N stage				
N 0	34 (25)	1 (9)	33 (27)	
N positivity	101 (75)	10 (91)	91 (73)	0.29
Stage				
Stage I-II	48 (36)	2 (18)	46 (37)	
Stage III-IV	87 (64)	9 (82)	78 (63)	0.33

P value: refers to comparison of HER-2 positive and negative groups. HER-2: human epidermal growth factor receptor 2

patients with positive surgical margins (n=35) (p=0.8). There was also no statistically significant difference between the two groups when those with perioperative liver metastases and carcinomatosis (n=8) were excluded (p=0.9). In subgroup analysis of patients with antrum tumor (n=69) according to HER-2 status, no significant difference was detected in 1-year overall and disease-free survival (with p=0.2 and p=0.7). Likewise, intergroup analysis of patients with grade 1-2 and grade 3-4 tumors revealed no significant difference in disease-free survival (p=0.6 and p=0.7).

## DISCUSSION

The prognosis of gastric and gastroesophageal junction cancers is still poor despite recent advances in treatment. Although the number of patients diagnosed at early stages is increasing, the majority of patients are still being diagnosed in advanced stages or with metastatic disease. The 5-year survival rate in advanced disease despite treatment is less than 15% (10). The role of new molecular targeted agents is being investigated in an effort to improve the survival rate. Within these agents, HER-2 constitutes the most recent research topic (11). In studies on gastric cancer, the HER-2 expression rate has been reported in a wide range of 4-44% with immunohistochemical methods. This wide range is thought to result from differences in sample sizes, patient population, and scoring methods used in these studies (9).

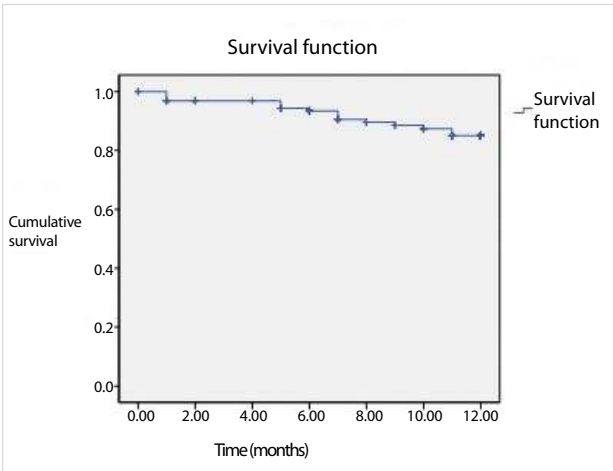


Figure 1. One year overall survival

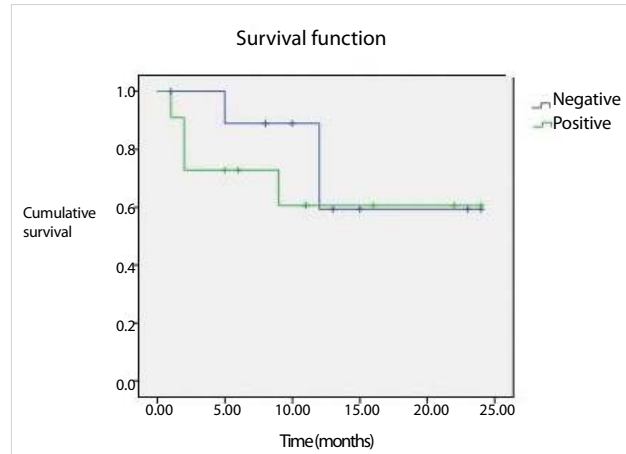


Figure 4. Two year overall survival according to HER-2 negativity/positivity status

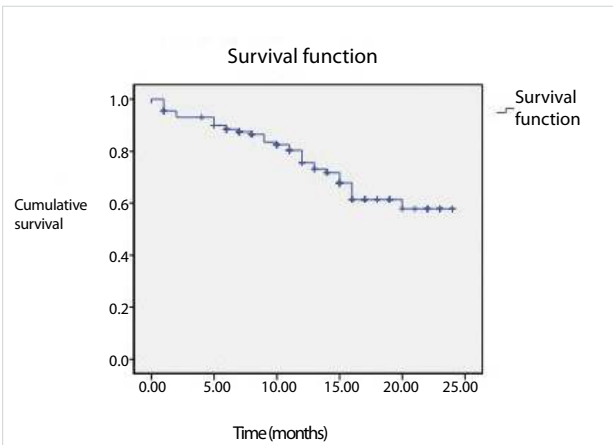


Figure 2. Two year overall survival

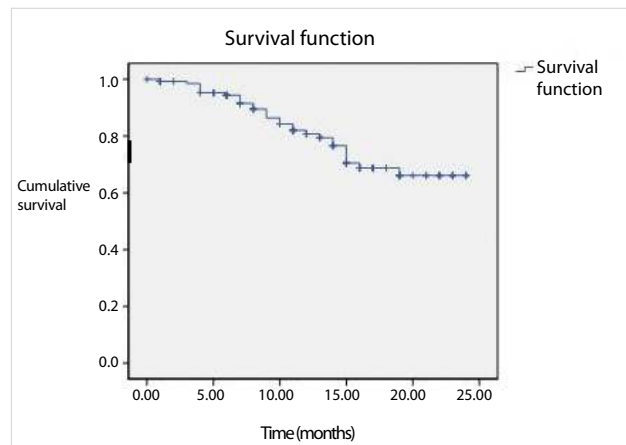


Figure 5. Two year disease free survival

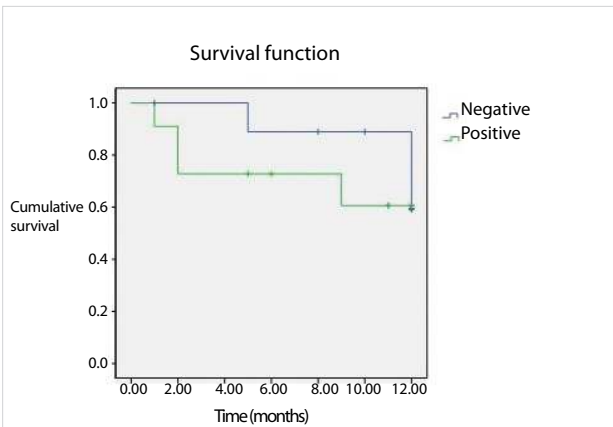


Figure 3. One year overall survival according to HER-2 negativity/positivity status

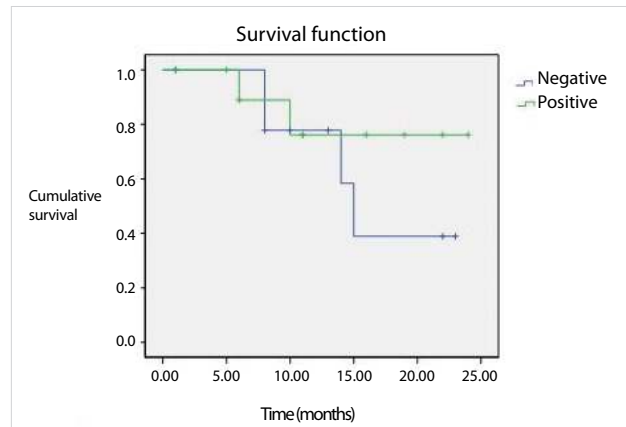


Figure 6. Two year disease free survival according to HER-2 negativity/positivity status

In a study by Yu et al. (12) that included 1143 patients, the HER-2 expression rate was determined as 28% by using immunohistochemistry and Western blot methods. They also identified that HER-2 positivity was more common in well/moderate differentiated, proximal located gastric cancers. In another study that examined 829 tissue samples by IHC and DISH, HER-2 expression rate was found as 9% (13). The HER-2 positivity rate

in our study was 8%, which was consistent with the literature. Geographical differences, tumor heterogeneity, differences in scoring systems and pathologist expertise may have caused the variations in HER-2 positivity rates between studies.

It has been reported that intestinal type gastric cancer has a higher rate of HER-2 positivity than diffuse type gastric cancer. HER-2 positivity rate is reported to be between 16-34% in

the intestinal type gastric cancer, 2-7% in diffuse-type gastric cancer, and 5-20% in the mixed type (6, 8). In this study, HER-2 positivity was found in 9 patients (12%) with intestinal type gastric cancer (n=67). However, there was no significant difference between HER-2-positive and negative patients in terms of histologic subtype ( $p=0.11$ ). It was observed in the ToGA study that HER-2 expression rate changed according to tumor localization. The rate of HER-2 positivity was reported as 34% in proximal, and 20% in distal gastric cancer ( $p=0.001$ ) (6). In our study, 11% of tumors located in the cardia and 7% of those located in the distal region were HER-2 positive tumors. There was no significant difference between proximal and distal cancers in terms of HER-2 positivity.

Kim et al. (14) found that HER-2 protein expression was increased in advanced age (>60 years), male gender, well-moderately differentiated and intestinal type tumors. However, other studies found no association between HER-2 and age and gender in the literature. In our study, there was no correlation between HER-2 and age and gender. Studies investigating the correlation of increased HER-2 expression with tumor stage, lymph node metastasis, distant metastasis, lymphovascular invasion, tumor size, histopathologic type reported various results. In their study of 226 patients, Mizutani et al. (15) reported a correlation between increased HER-2 expression and depth of invasion, histological type, growth pattern, and liver metastases. HER-2 expression was significantly higher in advanced stages, in non-scirrhous papillary carcinoma, in well-differentiated carcinoma and in patients with lymph node and liver metastases. However, in another study on 231 patients, there was no correlation between HER-2 and clinical stage (7). Yonemura et al. (16) detected a correlation between HER-2 and tumor size, serosa invasion, lymphatic invasion, and lymph node metastasis. Motojima (17) reported that increased HER-2 expression was related to tumor stage and depth of invasion.

In our study, there was no correlation between tumor size, depth of invasion, lymph node metastasis, distant organ metastasis, lymphovascular invasion, perineural invasion, and tumor stage with HER-2 positivity. Several studies have found HER-2 expression at a higher rate in well-differentiated tumors (18, 19). In our study, HER-2 was positive in nine patients (12%) with well and moderately differentiated tumors and in 1 patient with poorly differentiated tumor (2%). However, this difference was not statistically significant ( $p=0.13$ ).

There are many studies on the effect of HER-2 positivity on prognosis. In a study conducted in Korea on 182 patients, the median overall survival was reported to be shorter (31 months and 108 months) in HER-2 positive tumors, and the 5-year survival rate was 21% in HER-2 positive patients while this rate was 63% in HER-2 negative patients (20).

In the study by Kim et al. (14), there was no significant difference between the two groups in terms of overall survival while a significant difference was detected in disease-free survival. In multivariate analysis, HER-2 positivity was found as an independent risk factor for disease-free survival. Motojima et al. (17) reported the HER-2 positivity rate as 27.5% in 120 gastric

cancer patients with curative resection, and determined that the survival rate in these patients were significantly shorter as compared to HER-2 negative patients. It was also found that the survival rate of patients with HER-2-positive well-differentiated tumors was significantly lower than patients with HER-2 negative well-differentiated tumors, while HER-2 status did not affect survival in poorly differentiated tumors. In the same study, HER expression was identified as an independent prognostic factor affecting survival. In a study on 260 gastric cancer patients, it has been reported that the relative risk of death increased 5-fold in HER-2 positive patients as compared to HER-2-negative tumors, and HER-2 expression was identified as an independent prognostic factor (16). In their study on 231 patients with gastric and gastro-esophageal junction cancer, Tanner et al. (7) reported that the presence of HER-2 amplification was associated with short overall survival. In a retrospective study of 364 patients, Shitara et al. (21) reported that within HER-2-positive patients, the trastuzumab group had a higher overall survival rate as compared to patients not receiving this medication.

On the other hand, many studies stated that HER-2 positivity does not have a significant prognostic value. Tateishi et al. (18) did not detect significant difference in the 5-year survival rates of HER-2 positive and negative patients. Lee et al. (22) determined that 27.4% of 225 patients who underwent locally advanced curative gastric resection showed increased HER-2 expression and that there was no significant difference in overall survival between HER-2 positive and negative groups. Sasano et al. (23) reported the HER-2 expression rate as 27%, but there was no correlation with prognosis. Oghuri et al. (24) detected HER-2 expression in 25.7% of primary gastric carcinoma samples, and 44% of metastatic lymph nodes; however, there was no survival difference between HER-2-positive and negative patients in the comparison of 5-year survival rates. In three retrospective studies including 120 to 1036 patients, HER-2 positivity was not detected to be an independent prognostic factor (25-27).

In our study, there was no significant difference on survival rates between HER-2-positive and negative patients over a median 12-month follow-up period. The two-year overall survival rate was calculated as 71%. The mean survival was  $18\pm 0.7$  months. There was no correlation between overall survival and HER-2 positivity. Similarly, there was no significant difference between HER-2 positive and negative groups in our study in terms of disease-free survival.

#### Study Limitations

The low number of patients, short follow-up period, and heterogeneity of patient groups are factors that make it difficult to evaluate the prognostic significance of HER-2 positivity. Prospective randomized trials with more patients are required to be able to comment on this.

#### CONCLUSION

1. The rate of HER-2-positivity in patients with surgically treated gastric cancer was low (8%) in our study, which was consistent with the rates reported in the literature.

2. There was no association between HER-2-positivity and clinical and pathological parameters.
3. HER-2 positivity did not have an impact on overall and disease-free survival.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Marmara University Faculty of Medicine.

**Informed Consent:** We did not receive informed consent because the study was performed retrospectively.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - T.K.U.; Design - T.K.U., C.Y.; Supervision - C.Y., W.A.; Funding - C.Y.; Materials - G.A.; Data Collection and/or Processing - T.K.U., G.A.; Analysis and/or Interpretation - Ç.A.Ç., T.K.U., W.A.; Literature Review - T.K.U., G.A.; Writer - T.K.U., W.A.; Critical Review - C.Y., W.A., Ç.A.Ç.; Other - T.K.U., W.A., Ç.A.Ç.

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