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Trastuzumab significantly improves survival in resectable HER-2 positive gastric cancer: A retrospective study

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ABSTRACT

Objective: Gastric cancer (GC), with a five-year survival rate of approximately 20%, frequently displays aggressive behavior when HER-2 is overexpressed. While trastuzumab, a monoclonal antibody against human epidermal growth factor receptor-2 (HER-2), has improved outcomes in advanced GC, its effect in resectable disease is less studied.

Material and Methods: This retrospective study included patients who underwent total gastrectomy with D2 lymph node dissection between 2016 and 2021. Among 180 patients, HER-2 status was determined for 97 cases. Of these, 20 HER-2 positive patients received trastuzumab-containing therapies. A control group of 40 HER-2 negative patients was randomly selected. Overall survival (OS) was compared between groups. Univariate and multivariate analyses were used to identify prognostic factors.

Results: Sixty patients with a median follow-up of 29.5 months were analyzed. HER-2 positivity was associated with significantly improved OS (p=0.038). Univariate analyses revealed that HER-2 positivity (p=0.047), younger age (p=0.001), advanced tumor stage (p<0.001), and larger tumor size (p=0.010) were significantly related to OS. In the multivariate model, advanced tumor stage [hazard ratio (HR)=3.634, p=0.001] and younger age (HR=0.213, p<0.001) remained independent predictors of worse survival, while HER-2 positivity and tumor size lost their significance. Tumor subtype and location did not significantly influence OS.

Conclusion: The findings suggest that trastuzumab-containing treatment strategies can markedly improve survival in resectable HER-2 positive GC. Routine assessment of HER-2 status and integration of targeted therapies may enhance patient outcomes. In addition, advanced stage and younger age emerged as key prognostic factors.

Keywords: Trastuzumab, resectable gastric cancer, HER-2, survival, prognostic factors

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide, with a 5-year survival rate of 20% (1,2). Over the years, advancements have been made in the treatment of GC; however, surgery remains the key component of curative treatment.

Overall survival (OS) in GC is influenced by factors such as age, stage of the disease, and immunohistochemical (IHC) subtypes. One of these IHC subtypes involves the c-ErbB-2 protein, also known as human epidermal growth factor receptor-2 (HER-2), which is a 185 kDa transmembrane tyrosine kinase protein (3). Activation of HER-2 promotes cell proliferation, adhesion, and migration (4). Excessive proliferation of cells results in uncontrollable tissue growth, and enhances aggressiveness of the tumor. Overexpression of HER-2 has been linked to poorer outcomes in many cancers, most notably in breast and GC (5). Trastuzumab, a recombinant humanized monoclonal antibody targeting HER-2, has been shown to significantly improve OS in HER-2 positive GC (6).

Tumor stage is the most crucial prognostic factor in GC, with a 5-year survival rate exceeding 90% for patients diagnosed at an early stage (7). Tumor stage not only affects outcomes but also influences treatment strategies. Tumor size, lymphovascular invasion and nodal status are other important ffactors, but all of

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these factors also contribute to overall staging (8). Tumors ≥4 cm in largest-diameter have worse outcomes (3).

According to the latest European Society for Medical Oncology (ESMO) guidelines, trastuzumab is recommended in combination with chemotherapy for HER-2 positive metastatic GC but is not yet a standard of care for non-metastatic resectable cases. However, recent studies published suggest a potential benefit of trastuzumab in the perioperative setting for HER-2 positive GC, emphasizing the need for further investigation into its role in non-metastatic disease (9,10).

Current guidelines do not endorse the use of immune checkpoint inhibitors in the perioperative treatment of locally advanced resectable GC. Our rationale for incorporating trastuzumab into our treatment strategy was based on emerging evidence and biological plausibility, as HER-2 overexpression is associated with aggressive tumor behavior.

In this study, we aimed to investigate the effect of trastuzumab on OS of the HER-2 positive resectable GC. As secondary objectives, we also investigated the prognostic significance of age, tumor size, tumor location, tumor subtype, and stage of the disease.

MATERIAL and METHODS

Ethical Approval and Study Design

• Ethical approval for this study was granted by our Institute's Local Ethics Committee of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital on January 26, 2023 (approval no: B.10.1.TKH.4.34.H.GP.0.01/23).

• This is a retrospective, propensity-score matched cohort study analyzing patients who underwent total gastrectomy with D2 lymph node dissection (TG-D2) between 2016 and 2021.

• Propensity-score matching (PSM) was performed based on age, sex, tumor stage, and tumor size to balance baseline characteristics between HER-2 positive and HER-2 negative groups.

• Demographical, histopathological, follow-up, and adjuvant chemotherapy data were extracted from hospital records.

Patient Selection

● Patients included in this study:

• Patients who underwent open TG-D2 and had confirmed HER-2 status through IHC and fluorescence *in situ* hybridization (FISH).

• Those who had HER-2 testing on endoscopic biopsy and had a positive result were included in the study, regardless of whether the surgical specimen was tested for HER-2.

● Exclusion criteria:

• Patients with unknown HER-2 status.

• Patients with a negative HER-2 assessment on endoscopic biopsy and no HER-2 testing on the surgical specimen.

• Patients who underwent prior gastric resections, subtotal gastrectomy, or had inadequate lymphatic dissection.

• Patients with unresectable tumors.

Surgical Technique

• All patients underwent open total gastrectomy with D2 lymph node dissection.

• Lymph node dissection was performed according to established guidelines (11,12):

• Perigastric lymph node stations (1-6) and distant lymph node stations (7-11) were dissected.

• Although most tumors were located in the antrum, total gastrectomy was preferred due to institutional surgical strategy.

HER-2 Status Determination

Tumor cells were evaluated for their immunoreactivity patterns and scored according to the criteria recommended by Hofmann et al. (13).

• HER-2 status was determined by IHC (HercepTest, Dako, Denmark).

• Tumors with IHC scores of 2+ underwent confirmatory FISH testing (Dako, Denmark).

• HER-2 positivity was defined as IHC 3+ or IHC 2+ with FISH positivity.

• HER-2 negative patients were matched using PSM, eliminating the need for random selection.

Treatment Protocols

• Neoadjuvant chemotherapy was not routinely administered due to institutional practice during the study period.

• All HER-2 positive patients received trastuzumab in combination with adjuvant chemotherapy.

• Adjuvant chemotherapy regimens included:

• CAPOX (capecitabine + oxaliplatin)

• FOLFOX (5-fluorouracil + oxaliplatin + leucovorin)

• HER-2 positive patients received CAPOX or FOLFOX + trastuzumab.

• Docetaxel-based perioperative FLOT (fluorouracil + leucovorin + oxaliplatin + docetaxel) was not routinely used due to institutional treatment protocols during the study period.

Follow-up

• Patients were followed until death or the study cut-off date (June 1, 2023).

• Follow-up intervals:

• Every 3 months for the first 2 years.

• Every 6 months for the next 2 years.

• Annually thereafter.

• Follow-up imaging included CT or PET-CT scans.

• Disease-free survival was not analyzed.

Outcome Measures

• Primary outcome: OS, defined as time from surgery to death.

• Secondary outcomes:

• Association of HER-2 status with clinicopathologic variables.

• Prognostic factors affecting OS.

Statistical Analysis

SPSS version 26 (Windows) was used for statistical analysis. PSM was performed using a 1:1 ratio, balancing groups for age, sex, tumor stage, and tumor size. Comparisons were made using the chi-square test for categorical data, Student's t-test for parametric data, and the Mann-Whitney U test for non-parametric data. Survival analysis was performed using the Kaplan-Meier method with the log-rank test. A Cox proportional hazards regression model identified independent prognostic factors associated with OS. P-values <0.05 were considered statistically significant.

RESULTS

A total of 180 patients underwent surgery for resectable GC in our clinic. However, only 97 patients were evaluated for HER-2 status immunohistochemically, and the remaining 83 patients were excluded due to the absence of HER-2 testing. Among the 97 tested patients, 20 (20.6%) were HER-2 positive (IHC 2+ or 3+), with 12 patients (12.3%) scoring 2+ and 8 patients (8.3%) scoring 3+. To ensure comparability between groups, 40 HER-2 negative patients were selected using PSM, resulting in a final study cohort of 60 patients (Figure 1).

Of the 60 patients included in the study, 36 (60%) were male, and 24 (40%) were female, with an age range of 31 to 86 years (median: 63 years). The median follow-up duration was 29.5 months, and no patients were lost to follow-up. Demographic and histopathological characteristics were compared between HER-2 positive and HER-2 negative groups. There were no statistically significant differences in age (p=0.642), gender (p=0.721), tumor location (p=0.543), tumor subtype (p=0.911), or TNM tumor stage (p=0.367), as detailed in Table 1.

HER-2 positivity was associated with a significantly better OS (p=0.038, log-rank test). The mean OS was 55.52±6.35 months [95% confidence interval (CI): 43.07-68.98] in the HER-2 positive group and 34.98±4.48 months (95% CI: 26.19-43.77) in the HER-2 negative group. Median survival could not be computed for the HER-2 positive group since more than 50% of the patients remained alive at the end of the follow-up period, whereas it was 28.0 months in the HER-2 negative group. The mean survival for the entire cohort was 41.72±4.05 months (95% CI: 33.77-49.66). The Kaplan-Meier survival curve (Figure 2) illustrates the survival difference between the groups.

Univariate analysis identified HER-2 status (p=0.047), age (p=0.001), tumor stage (p<0.001), and tumor size (p=0.01) as factors significantly associated with OS. Tumor subtype (p=0.911) and tumor localization (p=0.321) were not significant prognostic factors. Statistically significant variables from the univariate analysis were included in the multivariate model.

In multivariate analysis, tumor stage was the most significant predictor of OS, with higher tumor stages correlating with over a threefold increased risk of death [hazard ratio (HR)=3.634, 95% CI: 1.735-7.613, p=0.001]. Kaplan-Meier analysis by stage, confirmed these findings, demonstrating that while stage 1 patients had no mortality throughout the follow-up period, stage 4 patients exhibited a rapid decline in survival (Figure 3).

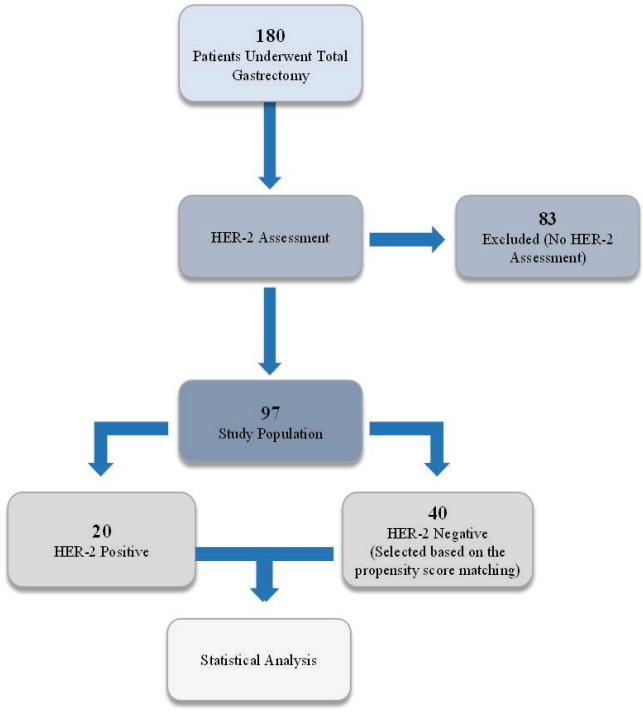

Figure 1. Study flowchart.
HER-2: Human epidermal growth factor receptor-2

Younger age emerged as a protective factor for OS (HR=0.213, 95% CI: 0.092-0.493, p=0.0001). Tumor size >4 cm was associated with a shorter OS (20.7 months vs. 39.6 months in tumors ≤4 cm), but this did not reach statistical significance in multivariate analysis (HR=2.195, 95% CI: 0.785-6.135, p=0.134). Tumor type and tumor localization were excluded from multivariate analysis due to their lack of significance in univariate testing. Detailed information on prognostic factors is provided in Table 2.

Table 1. Demographic and tumor specific data

	HER-2 positive	HER-2 negative	p (signicance)
Age			
<65 years	10 (50%)	22 (55%)	0.787
≥65 years	10 (50%)	18 (45%)	
Gender			
Female	7 (35%)	17 (42%)	0.576
Male	13 (65%)	23 (58%)	
Tumor size			
<4 cm	13 (65%)	13 (32%)	0.017*
≥4 cm	7 (35%)	27 (68%)	
Tumor location			
Cardia	4 (20%)	8 (20%)	0.889
Corpus	3 (15%)	8 (20%)	
Antrum	13 (65%)	24 (60%)	
Tumor type			
Intestinal	17 (85%)	29 (72%)	0.364
Diffuse	2 (10%)	10 (25%)	
Mixt	1 (5%)	1 (0.025)	
TNM stage			
Stage I	6 (30%)	6 (15%)	0.593
Stage II	4 (20%)	10 (25%)	
Stage III	9 (45%)	22 (55%)	
Stage IV	1 (5%)	2 (5%)	

HER-2: Human epidermal growth factor receptor-2.

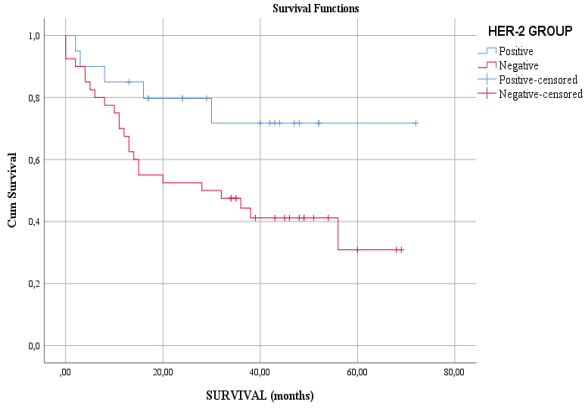

Figure 2. Kaplan-Meier survival curves showing the impact of HER-2 status on OS.

HER-2: Human epidermal growth factor receptor-2, OS: Overall survival

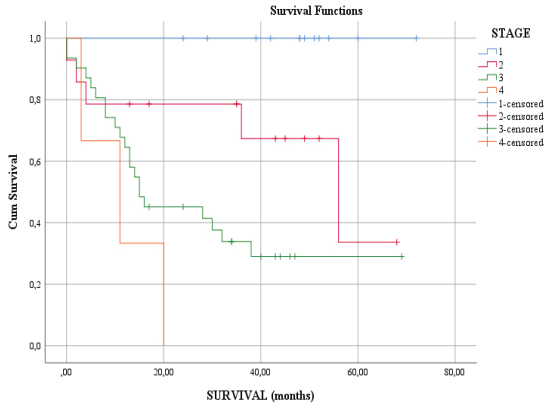

Figure 3. Kaplan-Meier survival curves showing the impact of stage on OS.

OS: Overall survival

Table 2. Associated risk for prognostic factors

	Univariate			Multivariate		
	HR	**CI 95%**	**p**	**HR**	**CI 95%**	**p**
HER-2 status (negative vs. positive)	2.656	1.012-6.973	0.047	1.837	0.681-4.958	0.230
Age (<65 vs. ≥65 years)	0.267	0.125-0.569	**0.001**	0.213	0.092-0.493	**0.000**
Stage	3.346	1.885-5.938	**0.000**	3.634	1.735-7.613	**0.001**
Tumor type	1.040	0.520-2.081	0.911			
Tumor localization	1.280	0.786-2.085	0.321			
Tumor size	5.201	1.963-13.777	**0.01**	2.195	0.785-6.135	0.134

HR: Hazard ratio, CI: Confidence interval, HER-2: Human epidermal growth factor receptor-2. Cox Regression Analysis, statistical significance at p<0.05.

DISCUSSION

HER-2 overexpression in GC can be observed in up to 30% of cases (4,14-16). In our study, 20 of 97 patients (20%) demonstrated HER-2 overexpression. Since HER-2 was first introduced in the literature, the role of HER-2 overexpression on GC prognosis has been studied widely. Previous studies have reported a fivefold increase in mortality risk among HER-2 positive GC patients (5,17,18). Before the advent of trastuzumab, HER-2 overexpression in resectable GC was a negative prognostic factor, decreasing 5-year OS from 63% to 21% (19). Following the ToGA trial and introduction of trastuzumab for HER-2 positive GC, trastuzumab became an indispensable part of standard treatment leading to improvement in patient outcomes (20).

In our cohort, all HER-2 positive patients were treated with trastuzumab containing regimens, thus we cannot compare the effect of trastuzumab directly. Although we could not directly isolate the effect of trastuzumab, the HER-2, positive group exhibited remarkably better OS than the HER-2, negative group. Considering that the OS of the HER-2 positive patients was significantly lower in former studies, the substantial improvement observed in our study (mean OS=55.5±6.4 vs. 35.0±4.5 months) strongly suggests that the addition of trastuzumab has a profound impact on survival. The 2021 Japanese Gastric Cancer Association Treatment Guidelines recommend trastuzumab-containing regimens to patients with IHC 3+ or IHC 2+/FISH-positive tumors (21). Similarly, 2024 National Comprehensive Cancer Network (NCCN) GC guidelines suggest that trastuzumab should be added to first-line chemotherapy for advanced HER-2 overexpression-positive adenocarcinoma. However, it is important to note that the current ESMO and NCCN guidelines primarily recommend trastuzumab for metastatic GC, with limited evidence supporting its routine use in non-metastatic resectable GC. While our study suggests a potential benefit of trastuzumab in this setting, further prospective studies are needed to validate these findings (22,23). Despite these recommendations for advanced disease, the role of trastuzumab in perioperative settings remains unclear, and randomized controlled trials are warranted to clarify its effectiveness in resectable GC.

This study also aimed to assess the prognostic value of TNM stage, patient age, tumor size, tumor location, and subtype. Considerable debate exists regarding the prognostic significance of patient age at diagnosis and the appropriate age cut-off for defining subgroups. Although some studies reported that age does not affect prognosis (24,25), most data contradict these findings (26,27). In a recent study, patients' age greater than 80 was found to be associated with worse disease-free survival (28). However, some reports indicate worse OS in younger patients, potentially due to more aggressive tumor biology (29,30). Lai et al. (31) found that younger patients had more undifferentiated tumors compared to older patients, yet, they showed better OS. In our study, we found that younger patients had significantly better survival. This could be attributed to factors such as the presence of comorbidities, which may impact treatment tolerance and overall health status, as well as a naturally lower life expectancy in this age group. Future studies should explore how comorbidities, treatment tolerance, and competing risks impact OS in older patients to guide personalized treatment approaches.

The prognostic value of TNM stage is well established (32,33). Consistent with literature, we observed a strong negative correlation between increasing TNM stage and OS, with TNM stage emerging as the most important prognostic factor in our cohort.

Tumor size has been included in staging systems for several tumors. Although it does not directly alter TNM stage in GC, larger tumors generally exhibit more invasive behavior, which correlates with worse OS. Debate on the cut-off point for tumor size is ongoing (34). Giuliani et al. (35) divided the patients into three groups according to the largest diameter of the tumor, <25 mm, 25 mm -5 cm, and >5 cm, and reported significantly better OS for patients with smaller tumors. Adachi et al. (36) grouped patients as <4 cm, 4 cm -10 cm, and >10 cm, and reported similar results, where patients with tumors <4 cm showed 92%

OS in ten years. Another study set the cut-off at 6 cm and also reported similar results to prior findings (34). Lastly, in a recent study, Chiu et al. (37) found that patients with early recurrence following surgery had larger tumors. We chose 4 cm as the cut-off and found tumor size to be a significant factor in univariate analysis, though it did not retain significance in the multivariate model.

A large meta-analysis by Petrelli et al. (38) reported 128,000 cases of GC and found a 25% increased risk of disease-related mortality in patients with proximal gastric tumors. Another study showed proximal cancer is not a prognostic factor (39). Yilmaz et al. (40) recently reported that tumor location serves as an independent risk factor for OS. In our study, we could not demonstrate a risk associated with tumor location.

In conclusion, our results, similar to former studies, show that trastuzumab substantially improves patient survival in HER-2 positive GC. Assessing HER-2 status and other molecular factors in tumor tissue is essential for better understanding tumor biology and tailoring patient-specific treatment. However, given the current guidelines and the limited evidence supporting trastuzumab use in resectable disease, its routine application in this setting should be approached cautiously. Prospective trials are needed to establish its role in non-metastatic GC. For the secondary results, TNM stage, younger age, and larger tumors were found to be significant negative prognostic risk factors.

Study Limitations

Our study has several limitations. First, the retrospective, single-center design may limit the generalizability of our results. The small sample size necessitated random selection of HER-2 negative patients as controls, introducing potential bias and affecting the robustness of some statistical findings. Additionally, not all patients were assessed for HER-2 positivity, further limiting the representativeness of our sample.

CONCLUSION

Finally, we did not account for patient performance status or comorbidities, factors that could influence OS and diminish the credibility of our conclusions. Furthermore, the absence of a control group treated without trastuzumab prevents a definitive conclusion regarding its benefit in resectable GC. Future prospective studies are required to confirm these findings and determine optimal patient selection criteria.

Ethics

Ethics Committee Approval: Ethical approval for this study was granted by our Institute's Local Ethics Committee of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital on January 26, 2023 (approval no: B.10.1.TKH.4.34.H.GP.0.01/23).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Concept - T.C.; Design - O.E.; Supervision - K.T.; Materials - M.E.B.; Data Collection or Processing - O.E.; Analysis or Interpretation - O.E.; Literature Search - S.A.; Critical Review - K.T., T.C.; Writing - O.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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