THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2021.23356
Med Bull Sisli Etfal Hosp 2021;55(2):224–231

Original Research

Evaluation of Human Epidermal Growth Factor Receptor 2 Overexpression, Clinicopathological Characteristics, and Factors Affecting Survival in Gastric Cancer

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Abstract

Objectives: The objective of the study was to evaluate the human epidermal growth factor receptor 2 (HER2) overexpression, clinicopathological features, and factors affecting survival in patients with gastric cancer.

Methods: The study is a retrospective study conducted with 128 cases of gastric cancer who were admitted to Şişli Hamidiye Etfal Training and Research Hospital between 2005 and 2012. Patients' demographic characteristics, performance score, tumor localization, information about surgery, HER2 measurements, histopathological characteristics, stage, treatment features, metastasis sites, and overall survival time were obtained from medical records. Immunohistochemical analysis was performed for HER2 scoring.

Results: There were 89 (69.5%) men and 39 (30.5%) women in the study group, and the median age of the patients was 64 years. The median survival time of the patients was 24.43 months. The survival rate of the patients was calculated as 35.4±5.9%. Overall survival time was found to be shorter in the group with higher HER2 levels and also those with advanced-stage cancer. The survival rate was found to be significantly lower in patients with perineural invasion and advanced stage. However, the survival rate was not associated with lymphovascular invasion, surgical margin involvement, and HER2 levels. In the multivariate Cox Regression analysis performed to assess the effects of gender, histological subtype, stage, and surgical margin on overall survival, disease stage was found to be the only factor effective on survival. Gender, histological subtype, and the surgical margin did not affect prognosis.

Conclusion: The survival rate in gastric cancers was found to be lower in those with advanced-stage disease. Higher HER2 level and the disease stage were associated with shorter overall survival time.

Keywords: Gastric cancer, neoplasm, oncogene, survival rate, survival time.

Please cite this article as "Celayir OM, Selcukbiricik F, Tanik C, Altuntas Y. Evaluation of Human Epidermal Growth Factor Receptor 2 Overexpression, Clinicopathological Characteristics, and Factors Affecting Survival in Gastric Cancer. Med Bull Sisli Etfal Hosp 2021;55(2):224–231".

Gastric cancer is one of the leading causes of cancer-related death worldwide. Around 1 million people are diagnosed with gastric cancer each year, making gastric cancer the seventh most common cancer worldwide. The cumulative risk of developing stomach cancer from birth to the age of 74 is estimated to be 1.87% in men and 0.79% in women. According to GLOBOCAN 2018 statistics, gastric cancer is the sixth most common cancer in Turkey with an incidence of 12.5/100.000 individuals (17.6 for men and 4.8 for women).[1]

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Submitted Date: December 01, 2020 **Accepted Date:** March 23, 2021 **Available Online Date:** July 02, 2021

Gastric cancers are caused by various environmental factors in association with the predisposing effects of specific genetic characteristics. Some of the factors can be listed as Helicobacter pylori infection, Ebstein Barr Virus infection, alcohol use, smoking, unbalanced diet, obesity, family history of stomach cancer, and genetic predisposition.[2] Ninety-five percent of stomach cancers are adenocarcinomas. Gastric adenocarcinomas are divided into cardia and non-cardia cancers according to localization and into two main types according to histology: diffuse and intestinal.[2]

Human epidermal growth factor receptor 2 (HER2), also known as CerbB-2, is located on chromosome 17q21, which encodes a transmembrane protein with tyrosine kinase activity. HER2 plays a role in signal transduction and it is a protooncogene that activates transduction pathways by causing cell growth and differentiation.[3] HER2-positive tumors have more aggressive properties than HER2-negative tumors.[4] The frequency of HER2 overexpression in gastric cancer ranges from 4.4% to 53.4%.[4] Following the favorable survival results of Trastuzumab-based chemotherapy for HER2-positive gastric cancers in the ToGA trial, Trastuzumab was proposed as a standard approach in HER2-positive gastric cancers.[5]

The average 5-year survival rate for stomach cancer is 26% in Europe, 19% in the UK, and 31% in the USA. Iceland has the highest 5-year survival rate in Europe, with 42% for women.[1] Although the standard treatment method for resectable gastric cancers is radical surgical resection and lymphadenectomy, survival time varies greatly depending not only on the treatment but also on the clinicopathological characteristics of the patients.[6] HER2 overexpression and evaluation of clinicopathological features in gastric cancers are important in predicting and improving survival outcomes.

The study aimed to evaluate HER2 overexpression, clinicopathological features, and factors affecting survival in gastric cancer cases.

Methods

This is a retrospective study conducted with gastric cancer cases who applied to Şişli Hamidiye Etfal Training and Research Hospital, Medical Oncology clinic between 2005 and 2012.

All histological subtypes of gastric cancer were included in the study except for gastric lymphoma. From the medical records of the patients, information such as demographic characteristics, performance score at the time of diagnosis, location of the tumor, information about surgery, HER2 level, histopathological features, tumor, node, metastasis (TNM) stage, treatment decisions, metastasis regions, and overall survival time were recorded.

The overall survival time was defined as the time from diagnosis to the last outpatient control or death. Patients without up-to-date records were reached and their latest status was recorded. The study group consisted of 128 gastric cancer cases. Patients with missing follow-up information in their files were not included in the study group.

The surgical methods applied to gastric cancer patients who were followed routinely in our clinic consisted of total gastrectomy, subtotal gastrectomy, or palliative surgery depending on the clinical condition of the patients.

In the study group, the Eastern Cooperative Oncology Group (ECOG) performance score was used to evaluate the well-being of the patients. The score ranges from 0 to 5, with 0 denoting very good health and five denoting death.[7]

The TNM staging used in the study was performed according to the classification published by the World Health Organization.[8]

Histopathological Method

Immunohistochemical (Clone SP3, Rabbit Monoclonal Antibody, Lab Vision Corp.) analysis was performed for HER2 scoring as the histopathological method. HER2 oncoprotein in malignant cells obtained from gastric tissue using antibodies developed against HER2 oncoprotein was evaluated by calculating the percentage of fluorescence through the immunoperoxidase method. No staining in invasive tumor cells or <10% membrane staining was evaluated as IHC 0, barely perceptible partial membrane staining of more than 10% was evaluated as IHC1 +, complete or basolateral membrane staining was evaluated as IHC2 +, and the presence of full or basolateral membrane staining of tumor cells with mild to strong staining was evaluated as IHC3 +.

Statistical Methods

Statistical analysis of the data was done using IBM SPSS (Version 15.0) statistics package program. Kaplan-Meier analysis was used for survival analysis. Group comparisons were analyzed using the Log-Rank test. The survival effect of variables thought to be associated with mortality was evaluated by Cox-Regression analysis. Statistical significance level was accepted as $p<0.05$.

Results

The study group consisted of 128 patients, 89 (69.5%) males and 39 (30.5%) females. The median age of the patients was 64 years. The median follow-up time of the patients was 10.53 months, and the median survival time was 24.43 months. The survival rate of the patients was calculated as 35.4±5.9%. Performance scores of 63.8% of the pa-

tients were ECOG 0-1-2, surgery type was total gastrectomy in 46.1%, dissection type was D2-D3 in 52.3%, and adenocarcinoma was identified in 28.9%. It was found that 51.0% of those who underwent HER2 screening had a HER2 level of IHC0. Multiple recurrences were recorded in 20% of patients (Table 1 and Fig. 1).

The most common HER2 level was identified as IHC0. The most frequently detected HER2 level in those receiving DCF treatment was IHC 2 (Table 2).

Survival percentages according to the stages are given in Table 3.1, according to the nodal status of the patients are in Table 3.2, and according to the T stage are given in Table 3.3.

It was found that the survival time of gastric cancer patients was associated with disease stage (Log Rank p<0.01). The median survival time of Stage II patients was significantly higher than Stages III and IV (p=0.002) patients. No significant difference was found between the survival times of the patients in Stages III and IV. It was found that, as the HER2 level increased in the study group, the overall survival time decreased. IHC 2 group has the shortest overall survival and IHC 0 group has the longest survival time (p=0.08) (Table 4).

Here are some images of cell concentrations showing HER2 expression with a score of 3 at HER2×400 and a score 3 case with FISH method mutations (Fig. 2, 3).

The survival rates were not associated with lymphovascular invasion (p=0.065), and the survival rate was significantly lower in gastric cancer patients with perineural invasion (p<0.001). It was found that the survival rate did not differ significantly according to surgical margin involvement or HER2 level (Table 5 and Fig. 4) (Figs. 5, 6).

In the multivariate Cox Regression analysis performed to evaluate the effects of gender, histological subtype, stage, and surgical margin on overall survival, disease stage was found to be the only factor effective on survival (p<0.01). The risk of death was 71.8% lower (hazard ratio=0.282) in Stage I patients compared to Stage IV patients (p=0.024). Similarly, the risk of death in Stage II patients was 78.2% lower (hazard ratio=0.218) than in Stage IV patients (p=0.004). Gender (p=0.632), histological subtype (p=0.120) and surgical margin (p=0.465) had no effect on prognosis.

Table 1. Demographic characteristics of the study group

	n	(%)
Age (Median, year)	64.00	
Follow-up time (month)	10.53	(0.17-80.30)
Survival time (month)	24.43	(19.66-29.20)
Gender		
Female	89	(69.5)
Male	39	(30.5)
Baseline performance score		
PS 0-1-2	82	(64.1)
PS 3-4	46	(35.9)
Type of surgery		
Total gastrectomy	59	(46.1)
Subtotal gastrectomy	57	(44.5)
Inoperable/palliative	12	(9.4)
Dissection types		
D0 dissection	13	(10.2)
D1 dissection	48	(37.5)
D2-D3 dissection	67	(52.3)
Histopathological type		
Intestinal	19	(14.8)
Signet ring cell carcinoma	38	(29.7)
Tubular carcinoma	12	(9.4)
Mucinous carcinoma	7	(5.5)
Adenocarcinoma	39	(30.5)
Diffuse carcinoma	1	(0.8)
Mixed neuroendocrine non-neuroendocrine neoplasia (Mucinous+well-differentiated neuroendocrine neoplasm)	3	(2.3)
Others (more than one type)	9	(7.0)
HER2 level (n=53)		
IHC0	27	(51.0)
IHC1+	4	(7.5)
IHC2+	15	(28.3)
IHC3+	7	(13.2)
Zone of relapse (n=40)		
Stomach	5	(12.5)
Liver	6	(15.0)
Colorectal area	1	(2.5)
Lung	6	(15.0)
Esophagus	2	(5.0)
Peritoneum	4	(10.0)
Adrenal gland	2	(5.0)
Pancreas	2	(5.0)
Multiple	12	(30.0)

PS: Performance Score; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry.

Discussion

Prognostic factors for gastric cancer are routinely limited by clinicopathological features. Classically, histopathological type, tumor size, tumor stage, invasion of the gastric wall, vascular invasion, and lymph node involvement, Ebstein Barr Virus, Helicobacter pylori infection, and HER2 overexpression are reported as some of the important prognostic factors.[9] In the current study, we investigated clinicopathological features, HER2 overexpression, and factors affecting survival in gastric cancer patients.

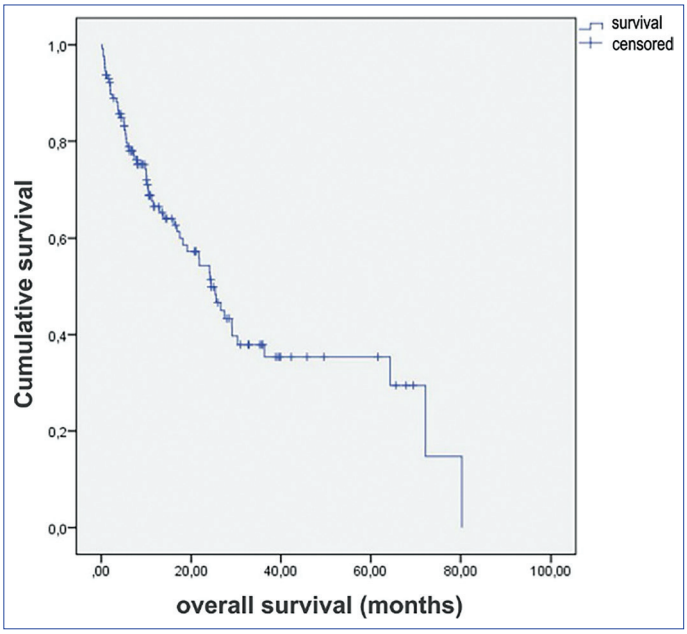

Figure 1. Overall survival in gastric cancers.

The lymphatic system plays an important role in the spread and recurrence of tumors. Lymphatic vessel invasion is considered a prognostic factor in various types of cancer. One of these cancers is gastric cancer, and lymphatic invasion has been reported to be an independent prognostic factor in this disease.[10] Survival rates have also been demonstrated to be lower in those with lymphovascular invasion in the previous studies.[11-14] However, Berkeşoğlu et al.[15] reported that there was no relationship between lymphovascular invasion and survival. In our study, similarly, there was no difference between patients with and without lymphovascular invasion in terms of survival rate.

Perineural invasion is the infiltration of the perineurium or neural fascicles by cancer cells around a tumor.[16] Various studies on gastric cancer cases have reported that having perineural invasion negatively affects the survival rate in gastric cancer.[12,14,16] There are also studies reporting that there is no relationship between perineural invasion and survival.[13,15] In this study, we found that the survival rate was lower in gastric cancer patients with perineural invasion as a result of univariate analysis.

Gastric cancer patients with moderately differentiated adenocarcinoma have a better prognosis than those with poorly differentiated adenocarcinoma. Patients with signet ring cell cancer and mucinous adenocarcinoma have a worse prognosis than those with well- or moderately-differentiated adenocarcinoma.[11] In this study, we found that the histological subtype was not one of the factors affecting survival. In a study by Wang et al.,[11] it was reported that the survival rate was higher in well-differentiated gastric cancers. In the study of Katai et al.,[17] it was reported that the survival rate was lower in patients with undifferentiated gastric cancer compared to those who were differentiated. However, countering arguments to these results also exist, with various studies failing to find any significant relationship between histological type and survival rate-similar to findings.[10,18,19]

Table 2. Comparison of HER2 level and clinicopathological features

	IHC 0 (%)	IHC 1 (%)	IHC 2 (%)	IHC 3 (%)
Gender				
Female	6 (46.2)	1 (7.7)	3 (23.1)	3 (23.1)
Male	21 (52.5)	3 (7.5)	12 (30.0)	4 (10.0)
Tumor site				
Proximal	10 (55.6)	2 (11.1)	5 (27.8)	1 (5.6)
Distal	16 (50.0)	2 (6.2)	10 (31.2)	4 (12.5)
Histopathological type				
Intestinal	6 (54.5)	2 (18.2)	2 (18.2)	1 (9.1)
Signet ring cell carcinoma	9 (52.9)	2 (11.8)	5 (29.4)	1 (5.4)
Tubular carcinoma	2 (40)	0 (0.0)	3 (60)	0 (0.0)
Mucinous carcinoma	1 (50)	0 (0.0)	0 (0.0)	1 (50)
Adenocarcinoma	6 (46.2)	0 (0.0)	5 (41.6)	1 (7.7)
Vascular invasion	20 (58.8)	1 (2.9)	11 (32.4)	2 (5.9)
Lymphatic invasion	18 (51.4)	2 (5.7)	12 (34.3)	3 (8.6)
Perineural invasion	19 (51.4)	2 (5.4)	14 (37.8)	2 (5.4)
Adjuvant therapy	20 (50)	1 (2.5)	13 (32.5)	6 (15)
Type of adjuvant therapy				
FUFA	10 (55.6)	1 (5.6)	5 (27.8)	2 (11.1)
DCX	5 (62.5)	0 (0)	2 (25)	1 (12.5)
DCF	0 (0)	0 (0)	2 (66.7)	1 (33.3)

IHC: Immunohistochemistry; FUFA: 5-Fluorouracil+Calcium folinate; DCX: Docetaxel+Cisplatin+Capecitabine; DCF: Docetaxel+Cisplatin+5-Fluorouracil

Gastric cancers become symptomatic at an advanced stage. For this reason, the majority of patients diagnosed with gastric cancer present at the advanced stage of the disease.[20] The survival rate is highly associated with the disease stage at the time of surgery.[1] The prognosis of gastric cancer is poor in more advanced stages.[20] In the current study, the 5-year survival rate was found to be significantly lower in those with advanced gastric cancer. This is consistent with the results reported by the previous studies.[11-13,14,17,21-24] There are also studies reporting that the stage could not be found as an independent prognostic factor affecting survival rate.[15,19] The poor prognosis in the advanced stage shows the importance of diagnosis and treatment at earlier stages.

In this study, there was no significant relationship between survival rate and HER2 level, but it was found that overall

Table 3.1. Survival rates in patients with gastric cancer according to their stages

Stages	1 year %	3 year %	5 year %
Stage I	84.2 (±8.4 SE)	52.6 (±18.7 SE)	52.6 (±18.7 SE)
Stage II	81.2 (±7.1 SE)	57.9 (±10.2 SE)	57.9 (±10.2 SE)
Stage III	49.9 (±8.5 SE)	19.3 (±8.1 SE)	19.3 (±8.1 SE)
Stage IV	60.1 (±9.9 SE)	8.6 (±8.1 SE)	8.6 (±8.1 SE)

SE: Standart Error.

Table 3.2. Survival rates in patients with gastric cancer according to their nodal status

Node	1 year %	3 year %	5 year %
Node 0	81.1 (±6.4 SE)	50.1 (±12.1 SE)	50.1 (±12.1 SE)
Node 1	77.5 (±10.1 SE)	38.1 (±13.7 SE)	38.1 (±13.7 SE)
Node 2	59.9 (±10.0 SE)	40.3 (±11.7 SE)	40.3 (±11.7 SE)
Node 3	42.1 (±10.0 SE)	59.9 (±10.0 SE)	59.9 (±10.0 SE)

SE: Standart Error.

Table 3.3. Survival rates in patients with gastric cancer according to the T stage

T stage	1 year %	3 year %	5 year %
T1	81.3 (±9.8 SE)	60.9 (±19.1 SE)	60.9 (±19.1 SE)
T2	88.2 (±7.1 SE)	56.1 (±16.4 SE)	56.1 (±16.4 SE)
T3	66.5 (±8.1 SE)	46.1 (±9.5 SE)	46.1 (±9.5 SE)
T4	45.1 (±8.4 SE)	4.5 (±4.3 SE)	4.5 (±4.3 SE)

SE: Standart Error.

Table 4. Evaluation of the relationship between HER2 level and overall survival

	n	Estimated mean (month)	Standardized error	95% Confidence interval	p
IHC 0	27	48.9	6.5	36.3-61.6	0.08
IHC 1	4	30.9	5.5	20.2-41.6	
IHC 2	15	15.3	1.4	12.6-18.0	
IHC 3	7	26.2	5.5	15.5-36.9	

HER2: Human epidermal growth factor receptor 2;
IHC: Immunohistochemistry.

survival time decreased with increasing HER2 level. The main role of HER2 in tissues is to promote cell proliferation and suppress apoptosis, a role that may facilitate uncontrolled cell growth and tumor formation or progression. However, the prognostic role of HER2 in gastric cancer remains unclear.[25] Studies to date on gastric cancer have revealed inconsistent findings regarding the prognostic relevance of HER2. While some previous studies reported that

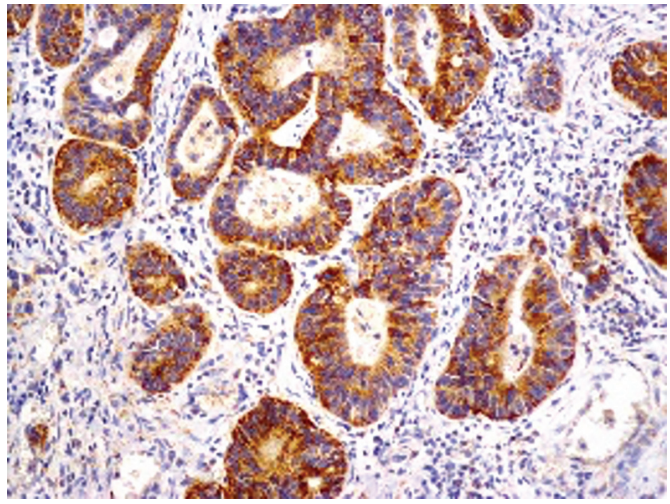

Figure 2. The concentration of cells showing human epidermal growth factor receptor 2 (HER2) expression with score 1 at HER2×200.
HER2: Human epidermal growth factor receptor 2.

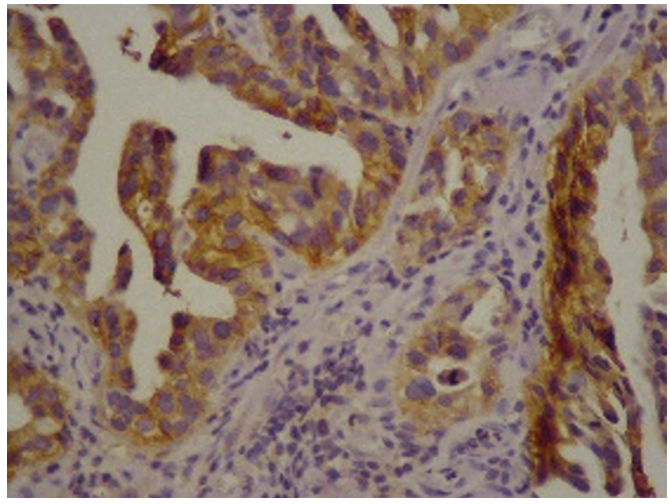

Figure 3. The concentration of cells showing human epidermal growth factor receptor 2 (HER2) expression with score 2 at HER2×200.
HER2: Human epidermal growth factor receptor 2.

there was no relationship between HER2 positivity and survival,[14,26,27] similar to our results with survival duration, other researchers reported that HER2 positivity was associated with poor prognosis in gastric cancer, increased aggression of the disease, and shorter survival time.[28,29] Interestingly, a study by Janjigian et al.[30] found that survival time was significantly longer in HER2-positive patients. Nevertheless, a meta-analysis including numerous studies concluded that HER2 expression was associated with poor prognosis in patients with gastric cancer.[31] Trastuzumab has made great progress in the treatment of HER2 overexpressing gastric cancers, and TOGA research has been a cornerstone in this regard. Two-Phase II and one retrospective study

Table 5. Distribution of survival rates in gastric cancer patients between groups

	Survival rate± Standardized error	p
Lymphatic invasion		
Present	28.1±6.1	0.065
Absent	46.9±14.3	
Perineural invasion		
Present	23.1±6.1	<0.001
Absent	58.1±12.1	
Surgical border involvement		
Present	13.9±12.7	0.360
Absent	37.6±6.3	
HER2 level		
IHC0	66.0±14.0	0.068
IHC1*	0	
IHC2	15.1±13.8	
IHC3	47.6±22.5	

IHC: Immunohistochemistry; *: No cases were followed up after the 3rd year.

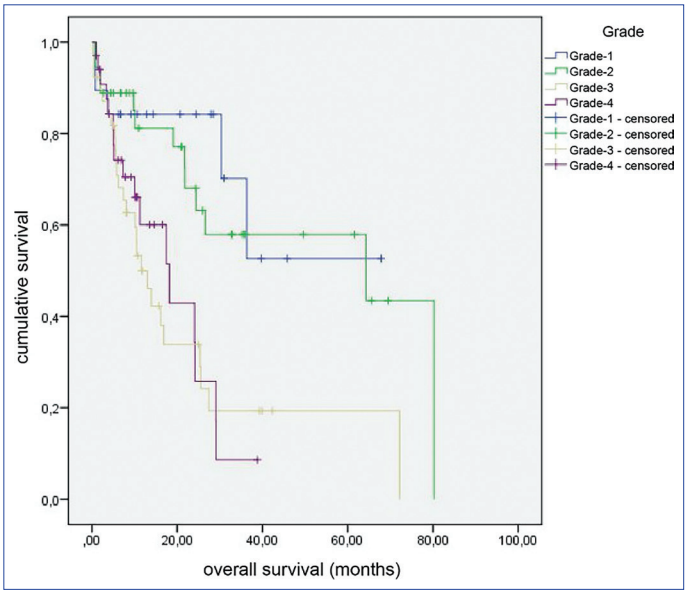

Figure 4. Survival by stage in patients with gastric cancer.

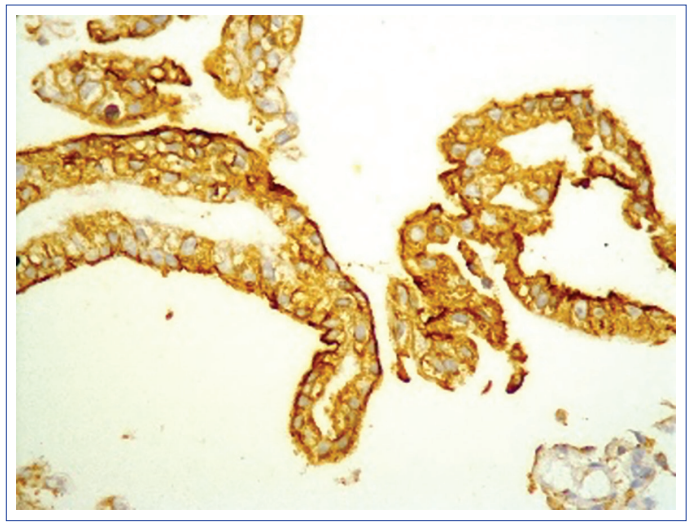

Figure 5. The concentration of cells showing human epidermal growth factor receptor 2 (HER2) expression with score 3 at HER2×400.
HER2: Human epidermal growth factor receptor 2.

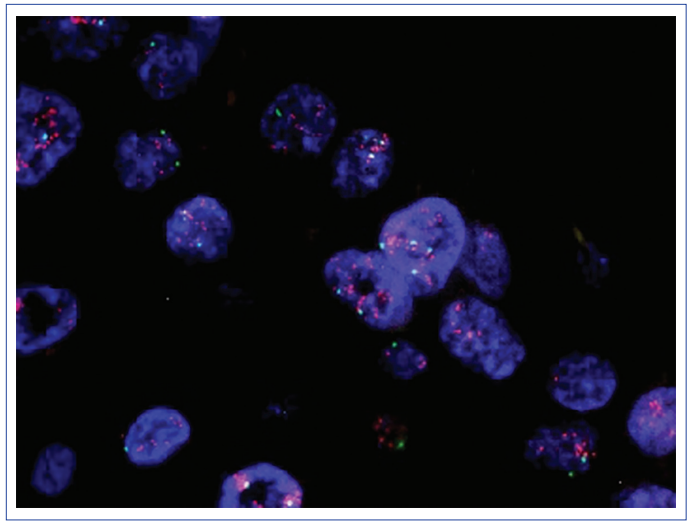

Figure 6. Evaluation of "HER2 score 3" case by FISH method; a score 3 case with a mutation with the red marked Human epidermal growth factor receptor 2 centromere and the green marked chromosome 17 centromere.
HER2: Human epidermal growth factor receptor 2.

evaluating the results of Trastuzumab treatment in different chemotherapy regimens in HER2-positive advanced gastric cancer reported similar results to TOGA.[5,32-34] It was thought that early diagnosis and treatment would be beneficial in patients with HER2 overexpression to improve the lower survival rates obtained in the case of increased HER2 expression.

Limitations

The fact that the study was conducted retrospectively with a relatively limited number of patients in a single-center and the lack of HER2 confirmation through FISH are among the limitations of the study. Due to the retrospective nature of the study, selection bias may have occurred in the diagnosis, treatment, and follow-up of patients. Nevertheless, the study is valuable due to the simultaneous evaluation of the clinicopathological features, HER2 overexpression, and survival characteristics of gastric cancer cases.

Conclusion

The median survival time in the study group was 24.43 months and the survival rate was calculated as 35.4±5.9%. The survival rate in gastric cancer patients was found to be

associated with the disease stage. Gender, histological subtype, surgical margin, HER2 level, and surgical margin positivity were not associated with survival rate. Besides, it was found that overall survival time decreased with increasing HER2 level. It was thought that prospective studies with larger patient groups would be useful to elucidate the clinicopathological characteristics of gastric cancer cases and their relationship with survival.

Disclosures

Ethics Committee Approval: This is a retrospective study conducted with gastric cancer cases who applied to Şişli Hamidiye Etfal Training and Research Hospital, Medical Oncology clinic between 2005 and 2012.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Financial Disclosure: The authors declare that this study received no financial support.

Authorship Contributions: Concept – O.M.C.; Design – O.M.C.; Supervision – F.S., Y.A.; Materials – O.M.C., C.T.; Data collection &/or processing – O.M.C.; Analysis and/or interpretation – O.M.C., F.S.; Writing – O.M.C.; Critical review – F.S., Y.A.

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