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Research Article

Comparison of the Effects of C-Erbb-2 (HER-2) Expression on Prognosis and Treatment in Gastric Cancer

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Abstract

Objective: The importance of positivity of human epidermal growth factor-2 (HER-2)/neu in gastric cancer is controversial. We investigated the positivity rate of HER-2 in gastric cancer, its correlation with clinicopathological findings and its effect on prognosis.

Methods: The records of patients who underwent subtotal and total gastrectomy for gastric tumor in the general surgery clinic of Ataturk Training and Research Hospital between 2007-2017 were evaluated retrospectively. Tissue samples were stained by immunohistochemical (IHC) method.

Results: 121 patients diagnosed with adenocarcinoma were included in the study out of 147 patients who underwent subtotal and total gastrectomy. (42), 34.7% of the patients were women and (79) 65.3% were men. The mean age of the patients was 69.40 ± 13.14 years. While 88.43% of the patients (107) were HER-2 negative, (14) 11.57% were positive. When HER-2/neu positive patients were compared with negative patients, HER-2/neu positivity was significantly higher in the intestinal type according to Lauren classification (p = 0.041). There was no significant difference between the other clinicopathological parameters. There was also no significant difference in overall survival.

Conclusion: There was no significant correlation between HER-2/neu positivity and clinicopathological parameters, stage of disease and overall survival in gastric cancer.

Keywords: Gastric Cancer; Human Epidermal Growth Factor Receptor 2; Prognosis; Clinicopathological Characteristics

Introduction

Despite the decrease of gastric cancer incidence day by day, it is still the fifth most common malignancy and remains one of the leading causes of cancer-related deaths [1,2]. In Turkey, gastric cancer ranks fifth among the most common malignancies [3]. In 2012, it was reported that 951,000 cases of gastric cancer were diagnosed and 723,000 people died of gastric cancer [4]. Gastric cancer is 2 to 3 times more common in men than in women [3,4]. Due to studies for early detection and prevention of gastric cancer, its incidence has decreased annually by 1.7% for men and by 0.8% for women [5]. In addition to radical gastrectomy and despite extended lymphadenopathy and combined chemotherapy the 5 -year survival is around 30% [6]. Both environmental and genetic factors play a role in the etiology of gastric cancer. Activation of oncogenes in the stomach, inactivation of tumor suppressor genes, cell cycle regulators, cell adhesion molecules, DNA repair genes, and genetic instability, as well as multiple genetic and epigenetic changes in telomerase activation, are involved in the multistage process of human gastric carcinogenesis. Therefore, it is important to know the molecular biology of gastric cancer [7,8]. Human epidermal growth factor receptor-2 (HER-2) neu positivity in breast cancer is a poor prognostic factor [9,10]. HER-2 gene amplification and overexpression are involved in the pathogenesis and progression of many human cancers and are therefore often considered a poor prognostic factor [11]. However, although HER-2/neu positivity in gastric cancer has been found to be correlated with negative prognosis, its prognostic significance is controversial [12-16]. Anti-HER2 therapy (Trastuzumab) in combination with chemotherapy may be considered as an alternative to standard therapy in gastroesophageal junction cancers [17,18]. HER-2 positivity/amplification is detected in more than 30% of tumors originating from the gastroesophageal junction, whereas less than 20% of gastric tumors are HER2-positive [19]. In this study, we aimed to determine the incidence of HER-2/neu positivity in patients operated for gastric cancer in our clinic and to investigate its effect on prognosis as well as clinicopathological parameters.

Materials and Methods

The records of 147 patients who underwent subtotal and total gastrectomy for the gastric tumor in the general surgery clinic of Atatürk Training and Research Hospital between 2007 - 2017 were evaluated retrospectively. Preoperative diagnosis was done using

endoscopic biopsy. Ultrasonography (USG), oral / IV abdominal tomography and positron emission tomography / computed tomography (PET / CT) were used for staging on need. Patients' age, sex, type of surgery, tumor localization and diameter, histopathological diagnosis, depth of invasion, lymph vascular invasion, perineural invasion, and lymph node metastasis availability were recorded. Immunohistochemistry (IHC) HER-2 staining was performed on the samples obtained from Ankara Atatürk Training and Research Hospital Pathology Laboratory archives. HER-2 expression levels were evaluated according to their immunoreactivity by giving 0, +1, +2 and +3 points. HER-2/neu ratio 0 and +1 scores were accepted as negative, and samples with ≥2 were considered positive.

Results

Of the patients in our study, 121 had adenocarcinoma, 20 had a gastrointestinal stromal tumor (GIST) and 6 had a neuroendocrine tumor (NET). (42) 34.7% of the patients with adenocarcinoma were female (79) and 65.3% were male. The mean age of the patients was 69.40 ± 13.14 years (Table 1). Tumor diameter ranged between 0.3 - 13 cm and the mean tumor diameter was 5.51 ± 3.01. According to Lauren classification, 74.38% of the patients (90) were intestinal type and (31) 25.62% were diffuse type. According to the World Health Organization (WHO) classification out of the 121 patients; (73) 60.34% had tubular type, (7) 5.78% had papillary type, (25) 20.66% had mucinous type, (11) 9.09% had signet ring cell carcinoma and (5) 4.13% had other tumors. In the localization of the tumors (27) 22.31% were detected in the cardia, (24) 19.83% in the corpus and (68) 56.19% in the antrum. Lienitis Plastica was detected in two patients. When classified according to tumor stage, 11% of patients (16) were on Stage IA, (28) 19.3% were on Stage IB, (33) 22.8% were on Stage IIA, (13) 9% were on Stage IIB (10) 6.9% were on Stage IIIA, (22) 15.2% were on IIIB, (22) 15.2% were on IIIC and (1) 0.7% were on Stage IV. In all patients (53), 43.8% completed 5 years of life. While the mean survival was 31.30 months in patients with adenocarcinoma it was 23.48 months in patients with signet ring cell carcinoma.

84.3% (102) of the patients had 0+ staining, (5) 4.12% had 1+ (5) 4.12% had 2 + and (9) 7.43% had 3 + HER-2 expression detected. Patients with HER-2/neu ratio greater than 1 were considered positive. The number of HER-2/neu positive patients was 14 (11.57%) and the number of HER-2/neu negative patients was 107 (88.43%). When a comparison was made according to Lauren classification, HER-2 positivity was found to be significantly higher in intestinal-type (p = 0.041). When HER-2/neu positive and negative patients were compared, there was no statistically significant difference in terms of patient age, sex, localization and diameter of the tumor, histopathological diagnosis, depth of invasion, lymph vascular invasion, perineural invasion, lymph node metastasis, stage, and five-year survival. There was no statistically significant difference between the elderly (> 65 years) and other (< 65 years) patients in terms of HER-2 expression and survival (p = 0.499, p = 0.263 respectively) (Table 2-3). There was no statistically significant difference between tumor grade and HER-2 expression and survival (p = 0.739, p = 0.099).

		HER2 Negative		HER2 Positive		P Value
		n	%	n	%	
Number of patients		107	88.4	14	11.6	
Gender	Female	38	35.5	4	28.6	0.769
	Male	69	64.5	10	71.4	
Age Mean	±SD	69.84 ± 12.46		66.0 ± 17.66		0.540
	±SD					
Tumor Diameter	≤5	43	40.2	7	50.0	0.680
	>5	64	59.8	7	50.0	
Differentiation Degree	Poorly	43	40.2	7	50.0	0.739
	Moderately	41	38.3	4	28.6	
	Well	23	21.5	3	21.4	
Tumor Location	SM+M	30	28	2	14.3	0.350
	S+SA	77	72	12	85.7	
Lauren Classification	İntestinal	58	54.21	12	85.71	0.041
	Diffuse	49	45.79	2	14.29	
WHO Classification	P	6	5.61	1	7.14	0.755
	T	60	56.08	13	92.86	
	M	25	23.36	0	0	
	TY	11	10.28	0	0	
	Other	5	4.67	0	0	
TNM T Classification	T1	13	12.1	0	0	0.525
	T2	17	15.9	2	14.3	
	T3	40	37.4	7	50.0	
	T4	37	34.6	5	35.7	
TNM N Classification	N1	48	44.9	4	28.6	0.304
	N2	14	13.1	1	7.1	
	N3	13	12.1	4	28.6	
	N4	32	29.9	5	35.7	
Stage	I	24	22.4	2	14.3	0.431
	II	38	35.5	3	21.4	
	III	44	41.1	9	64.3	
	IV	1	1	0	0	
5 Year Survival	<5	58	54.2	10	71.4	0.263
	>5	49	45.8	4	28.6	

Table 1: Distribution of HER2 / neu positive and negative cases.

Disease Stage	Over All Survival	Number of Cases	Percent (%)	*P* Value
Stage I	< 5 Yıl	6	23.1	<0.001
	≥ 5 Yıl	20	76.9	
Stage II	< 5 Yıl	21	51.2	
	≥ 5 Yıl	20	48.8	
Stage III	< 5 Yıl	40	75.5	
	≥ 5 Yıl	13	24.5	
Stage IV	< 5 Yıl	1	100	
	≥ 5 Yıl	0	0	

Table 2: 5 years of survival in gastric tumors by stage.

Stage	Number of Cases	Mean (Month)	Std. Deviation	*P* Value
I	26	45,77	26,352	0.002
II	41	32,76	26,101	
III	53	23,02	22,431	
IV	1	8,00		

Table 3: The life span of patients with gastric adenocarcinoma by stage.

Discussion

The prognosis of patients with gastric cancer is correlated with the age of the patient, the size of the tumor, the depth of invasion, the type of histopathology, the extent of lymph node dissection, and the stage of the disease [20-22]. Some pathological features suggest that there are biological factors that lead to the aggressive course of the tumor [13,14]. Although there are many studies on HER-2 among these factors in gastric cancer, the results are inconsistent [12-16]. HER-2/neu ratio was detected as positive in 8 -15% of patients with gastric cancer. In addition, there was no difference between HER-2 positive and negative patients in terms of overall and relapse-free survival [23-25]. In our study, the rate of HER-2 positive patients was detected as 11.57% and was consistent with the literature. No difference was detected between the groups in terms of survival. HER-2 positivity has been reported to be higher in male patients than in females [26]. The rate of HER-2 positive male patients (71.43%) was significantly higher in our study. According to the Lauren classification, HER-2 positivity was higher in the intestinal type while in some studies it was reported that there was only HER-2 positivity in the intestinal type [23,26]. It was detected that the HER-2 positivity was significantly higher in the intestinal type in our study. HER-2 positivity has been reported to be higher in elderly patients [26]. However, in our study, similar to some other studies, no statistically significant difference was detected between HER-2 expression and advanced age [23,27].

Although there are studies reporting higher HER-2 positivity in low-grade gastric cancer, no significant correlation has been reported between tumor grade and HER-2 positivity [27,28]. In our study, no significant difference was detected between tumor grade and HER-2 positivity and survival.

Conclusion

HER-2 positivity was detected to be low in patients undergoing total or subtotal gastrectomy. There was no significant correlation between HER-2 positivity and patient age, sex, localization and diameter of the tumor, histopathological diagnosis, and degree of differentiation, depth of invasion, lymphovascular invasion, perineural invasion, lymph node metastasis, stage, and 5-year survival. According to Lauren classification, there was a significant association between intestinal-type and HER-2 positivity. There was no effect of HER-2 positivity on overall survival. There was no effect of HER-2 expression on the prognosis of gastric cancer.

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