

Overexpression of HER2/Neu in Gastric Adenocarcinoma and Its Correlation with Clinicopathological Parameters

Abstract

Background: Gastric cancer is the fifth most common cancer in the world. HER2/neu is a proto-oncogene that has a key role in the pathogenesis of several human cancers including gastric cancer. The introduction of trastuzumab has increased overall survival in HER2/neu-positive, locally advanced, and metastatic gastric cancer. **Aim:** To study the HER2/neu expression in different histopathological types of gastric carcinomas and to correlate its expression with clinicopathological parameters. **Materials and Methods:** A total of 80 cases of gastric adenocarcinoma that had undergone curative resection from July 2016 to June 2019 were selected for the study. All tumor samples were tested for HER2/neu overexpression and it was correlated with various clinicopathological parameters. **Results:** In our study, the mean age of patients was 59 years. Majority of the tumors (60%) were located in the pyloric antrum region. Sixty-six percent were intestinal type followed by diffuse (29%) and mixed type (5%). HER2/neu overexpression was seen in 9% of cases. There was no significant correlation between HER2/neu overexpression and age, gender, site, histological type, or grade of the tumor. **Conclusion:** There was no statistically significant correlation between HER2/neu expression and age, gender, site of tumor, histological type, or differentiation of the tumor. Thus, HER2/neu can be considered as having no prognostic significance in gastric carcinoma.

Keywords: Gastric cancer; HER2/neu; immunohistochemistry

Introduction

Gastric cancer is the fifth most common cancer in the world.^[1] In India, it is the third most common cancer in men and the fifth most common cancer in women. Overall, it is the fourth most common cancer in India.^[2]

Curative resection is the key therapy for gastric carcinomas. However, most patients present in an advanced stage where the tumor cannot be resected and surgery as an option is unavailable. For such patients, chemotherapy remains an option. Nevertheless, prognosis remains poor in spite of it. Hence, there is a call for new therapeutic targets which can improve the prognosis and overall survival in patients with advanced gastric cancer.

The human epidermal growth factor receptor (HER) family has a key role in the pathogenesis of several human cancers. Numerous studies have been done on them and the role of HER2/neu in breast

cancers as a predictive and prognostic marker with its therapeutic implications has been well established. The overexpression of HER2/neu has also been studied in cancers of ovary, endometrium, bladder, lung, colon, head and neck, gastric, and gastroesophageal cancers.^[3]

Numerous studies have been done on prognostic significance of HER2/neu in gastric cancer with varied results. The studies done by Hilton and West,^[4] Ross and McKenna,^[5] and Gomez-Martin *et al.*^[6] showed that HER2/neu had a favorable prognosis, while studies done by Nakajima *et al.*,^[7] Yonemura *et al.*,^[8] and Cheng *et al.*^[9] showed that patients with HER2/neu-positive gastric cancer had a poor prognosis. Furthermore, the studies done by Tateishi *et al.*,^[10] Sakai *et al.*,^[11] and Son *et al.*^[12] revealed that HER2/neu had no prognostic significance in gastric cancer.

In 2010, the results of an international, Phase III randomized controlled trial (trastuzumab for gastric cancer) showed

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that the anti-HER2/neu monoclonal antibody trastuzumab had a significantly increased overall survival, as compared to chemotherapy alone, in patients with HER2/neu-positive advanced gastric cancer. Based on this study, trastuzumab was approved by the Food and Drug Administration (FDA) for patients with immunohistochemistry (IHC) 3+ or IHC 2+/fluorescence *in situ* hybridization + advanced gastric cancer.^[13]

In HER2/neu-positive breast cancer and gastric cancer patients, trastuzumab-based therapy is being used effectively. Trastuzumab acts by inducing passive immunity against malignant cells. It also induces antibody-based cytotoxicity which forms the basis of antigen-specific immunotherapy against tumor cells. These studies have led to generation of vaccines against tumor cells expressing HER2/neu.^[14,15]

This further strengthens the importance of biological markers in cancer treatment. As the prognosis of gastric cancer is poor and the role of HER2/neu as a prognostic marker in gastric cancer stands controversial, further studies are required to establish its role in it.

This study was done to know the pattern of the HER2/neu expression in different histopathological types of gastric adenocarcinoma and its correlation with clinicopathological parameters and to evaluate its utility as a prognostic marker.

Materials and Methods

The biopsy-proven gastric adenocarcinoma cases that were diagnosed and resected from July 2016 to June 2019 were selected for our study. The secondary data of these patients including age, sex, symptoms, histological type, and grading of tumor were obtained. The specimens were grossed and the sections were fixed in 10% formalin and paraffin embedded. Consecutive 4 µm sections were cut from the paraffin blocks. These sections were evaluated microscopically to select blocks without necrotic and hemorrhagic areas. Histopathological diagnosis was established on routine hematoxylin and eosin staining of the sections. IHC for HER2/neu was performed on BioGenex Xmatrix Fully Automated Front-end Processing System using monoclonal antibody against HER2/neu protein (EP3 Monoclonal Antibody; BioGenex).

Immunoreactivity for HER2/neu was evaluated semiquantitatively by two observers under ×40 and scoring was done by the Ruschoff/Hofmann method.

- No reactivity or membranous reactivity in <10% of tumor cells – score 0 (negative)
- Faint/barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane – score 1+ (negative)
- Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells – score 2+ (equivocal)
- Strong complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells – score 3+ (positive).

The observers were kept blind about the report of each other. After initial evaluation of the results, cases with major discordance in reports were rechecked by both the observers, and after reaching an agreement, the report was submitted. The HER2/neu scoring was correlated with clinicopathological parameters. The frequency of HER2/neu-positive tumors with each variable was analyzed using Chi-square; $P < 0.05$ was considered statistically significant.

Since FISH was not available in our setup, all equivocal cases were considered negative for the purpose of this study.

Results

Out of total of 80 cases of gastric cancer, 60 (75%) patients were male and 20 (25%) were female. The mean age of patients was 59 years (range: 38–82 years). The tumor was located in the pyloric antrum region in 48 (60%) cases, body in 27 (34%) cases, at the gastroesophageal junction in 3 (4%) cases, and 1 (1%) case each in the cardia and involving the whole stomach. Among 80 cases, 15 (19%) tumors were well-differentiated adenocarcinomas, 40 (50%) cases were moderately differentiated, and 25 (31%) cases were poorly differentiated adenocarcinomas. Based on the Lauren's classification, 23 (29%) cases were of diffuse type, 53 (66%) cases of intestinal type, and 4 (5%) cases of mixed type. 61 (76%) cases showed infiltration into serosa, 12 (15%) cases showed perigastric extension, 3 (4%) cases each infiltrating into submucosa and muscularis propria, and 1 (1%) case with only intramucosal spread. Lymphovascular invasion was detected in 26 (32%) cases and lymph nodes were involved in 57 (71%) cases [Table 1].

Out of a total of 80 cases, 7 (9%) cases showed positivity for HER2/neu [Figures 1-3] and 5 cases (6%) were equivocal for HER2/neu. Sixty-eight cases (85%) were negative for HER2/neu. Localization of staining was predominantly membranous. The relationship between HER2/neu overexpression and several clinicopathological variables is summarized in Table 1. In our study, 6% of patients below 60 years of age and 12% of patients above 60 years of age showed HER2/neu overexpression. HER2/neu positivity was 8% in males and 10% in females. Pylorus and antrum tumors showed HER2/neu overexpression in 10% of cases and tumors in the body showed it in 7% of cases. However those tumors located in the gastro esophageal junction(GEJ), cardia and those involving the entire stomach did not show positivity for HER2/neu. Well-differentiated adenocarcinoma showed HER2/neu positivity in 20% of cases, moderately differentiated adenocarcinoma in 10% of cases, whereas poorly differentiated adenocarcinoma did not show any positivity. In Lauren's histological type, 13% of intestinal type showed HER2/neu overexpression. None of the cases of diffuse type or mixed type showed any positivity.

Discussion

In the present study, HER2/neu overexpression in gastric

Table 1: Clinicopathological correlation with human epidermal growth factor receptor 2/neu expression (n=80)

Clinicopathological parameters	n (%)	HER2/neu positive, n (%)	P
Age			
≤60	47 (59)	3 (6)	0.439
>60	33 (41)	4 (12)	
Gender			
Male	60 (75)	5 (8)	1.000
Females	20 (25)	2 (10)	
Tumor location			
GEJ	3 (4)	0	0.950
Cardia	1 (1)	0	
Body	27 (34)	2 (7)	
Pylorus and antrum	48 (60)	5 (10)	
Linitis plastica	1 (1)	0	
Pathologic grade			
Well differentiated	15 (19)	3 (20)	0.088
Moderately differentiated	40 (50)	4 (10)	
Poorly differentiated	25 (31)	0	
Lauren's histological type			
Diffuse	23 (29)	0	0.142
Intestinal	53 (66)	7 (13)	
Mixed	4 (5)	0	

HER: Human epidermal growth factor receptor,
GEJ: Gastroesophageal Junction

cancer was studied using IHC and was correlated with clinicopathological parameters to assess the utility of HER2/neu overexpression in the prognosis of gastric cancer.

Our study was a prospective, cross-sectional study conducted in 80 patients with gastric adenocarcinoma. Among the 80 cases in our study, 7 (9%) cases were HER2/neu positive which was comparable with HER2/neu positivity in the studies done by Takehana *et al.*^[16] (8.2%), Devi *et al.*^[17] (10%), and Kumarasinghe *et al.*^[18] (10.4%).

It is primarily a disease of old age and most patients are over 50 years of age. The incidence of cancer rises sharply after 50 years. In our study, age of patients ranged between 38 and 82 years which was comparable to the study done by Lazăr *et al.*,^[19] Park *et al.*,^[20] and Lee *et al.*^[21] Maximum patients were found to be older than 50 years ($n = 68, 85\%$). In this study, 6% of the patients who were below 60 years of age and 12% of patients above 60 years of age showed overexpression of HER2/neu, which was comparable to the study done by Son *et al.*^[12] However, no significant correlation was found between age and HER2/neu overexpression ($P = .439$). Comparable results were found by Lee *et al.*^[21] ($P = 0.07$), Son *et al.*^[12] ($P = 0.102$), and Devi *et al.*^[17] ($P = 0.432$).

Gastric cancer is more commonly seen in males with the male-to-female ratio varying from 1 in young adults to 2 or more at the age of 60 years. Reasons for the gender disparity are not fully understood. In our study, the

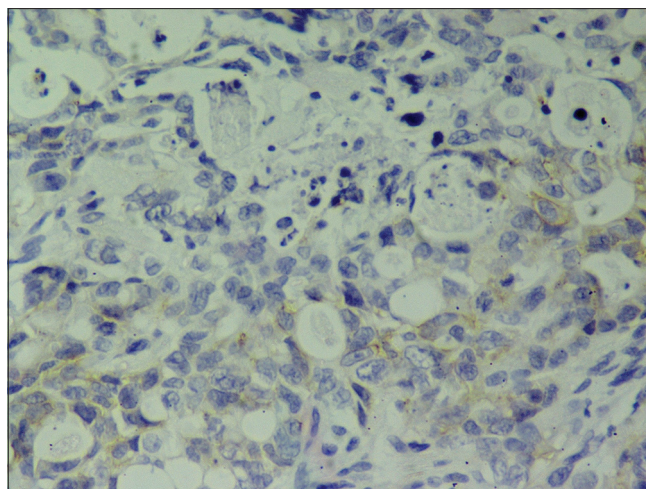


Figure 1: Score 1+, Faint Membranous positivity of HER2/neu expression in gastric carcinoma (IHC, ×400)

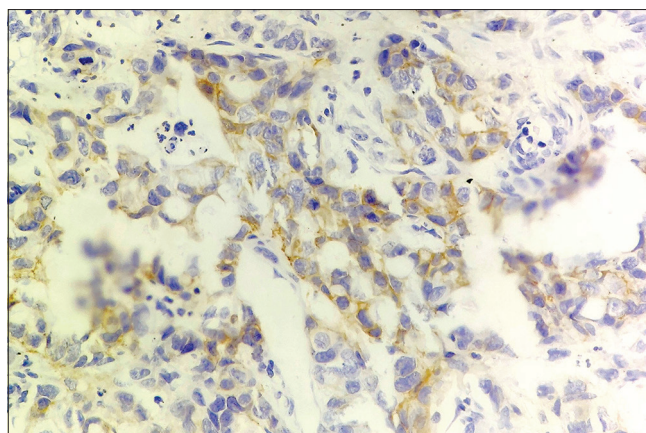


Figure 2: Score 2+, Weak to moderate Membranous positivity. HER2/neu expression in gastric carcinoma (IHC, ×400)

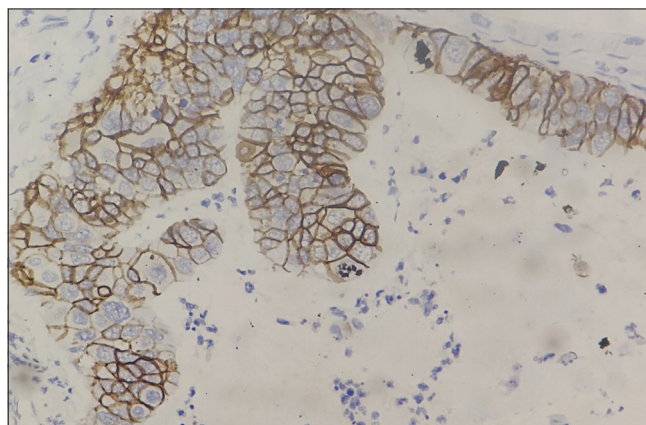


Figure 3: Score 3+, Strong Membranous positivity of HER2/neu expression in gastric carcinoma (IHC, ×400)

male-to-female ratio was 3:1, which was comparable to the study done by Raziee *et al.*^[22] and Zu *et al.*^[23] Our study revealed HER2/neu positivity in 8% of all male patients and 10% of all female patients. The results were comparable for males in a study done by Son *et al.*^[12] and were comparable

for females in the studies done by Lee *et al.*^[21] However, no significant correlation was observed between HER2/neu and gender of patients in our study ($P = 1.000$). These observations are in concordance with other studies like Son *et al.*^[12] ($P = 0.111$) and Park *et al.*^[20] ($P = 0.546$), which found no significant correlation between HER2/neu and gender.

Majority of cases of gastric adenocarcinoma in the present study were located in the pyloric antrum region (60%), followed by body, gastroesophageal junction, cardia, and involving the whole stomach. These observations are concordant with studies done by Son *et al.*^[12] and Park *et al.*^[20] Discordance was seen with Niu *et al.*^[24] who found body and fundus as the most commonly involved site comprising 66% of cases. Only 10% of cases located in the pyloric antrum and 7% of cases located in the body showed overexpression of HER2/neu. HER2/neu positivity was not found in tumors of gastro esophageal junction, cardia and those involving the whole of the stomach. This was in contrast to the study done by Panda and Panda,^[25] in which 66.7% of the tumors of the body were positive for HER2/neu and only 19.6%–15.4% tumors of pylorus and gastroesophageal junction overexpressed HER2/neu, respectively. There was no statistically significant correlation between HER2/neu positivity and site of tumor ($P = 0.950$) in our study similar to Ghaderi *et al.*,^[26] Raziee *et al.*,^[22] and Devi *et al.*^[17]

There are several histological classifications of gastric adenocarcinoma, among which Lauren's classification is the most commonly used in routine practice with intestinal type having a higher survival rate and hence a better prognosis. In our study, 66% of cases were of intestinal type, 29% of diffuse type, and 5% of mixed type. Similar findings were reported by Akl *et al.*^[27] and Halder *et al.*,^[28] where the percentage of intestinal tumors was 59.3% and 63.8%, respectively. In contrast, a study done by Panda and Panda^[25] reported diffuse-type adenocarcinoma as more common than intestinal type.

In the present study, 13% of the intestinal cases were positive for HER2/neu and none of the diffuse-type cases or mixed-type cases showed any positivity for HER2/neu. This was comparable to the study done by Devi *et al.*,^[17] in which none of the diffuse-type cases were positive for HER2/neu although the percentage of intestinal-type (23%) positive for HER2/neu was higher. In the study done by Ghaderi *et al.*,^[26] 18% of the intestinal-type adenocarcinoma were positive for HER2/neu which was comparable to our study, but 13% of the diffuse type were HER2/neu positive which was higher than the present study. There was no statistically significant relationship between the Lauren's histological type and overexpression of HER2/neu.

Gastric adenocarcinomas are graded as well-differentiated, moderately differentiated, and poorly differentiated. In the present study, most of the cases (50%) were of moderately

differentiated type, followed by poorly differentiated (31%) and well differentiated type (19%). Setala *et al.*,^[29] Rajagopal *et al.*,^[30] and Aditi *et al.*^[31] also reported moderately differentiated adenocarcinoma as the most common variant. Other authors like Panda and Panda^[25] and Devi *et al.*^[17] found more cases of poorly differentiated adenocarcinoma. Out of 15 (19%) of well-differentiated carcinoma, 3 (20%) revealed HER2/neu positivity. Similar findings were noted by Son *et al.*^[12] and Sunitha *et al.*^[32] in 20.3% and 20% of well-differentiated carcinoma, respectively. Four cases (10%) of moderately differentiated adenocarcinomas showed HER2/neu positivity, which was comparable to the study done by Sunitha *et al.*^[32] and Devi *et al.*^[17] None of the poorly differentiated cases showed HER2/neu positivity. This was comparable to the study done by Halder *et al.*^[28]

Overall, in our study, no significant correlation was found between HER2/neu overexpression and age, gender, site of tumor, histological type, and differentiation. Similar conclusions were drawn in the studies done by Ghaderi *et al.*^[26] and Sunitha *et al.*^[32]

Still, HER2/neu testing in gastric carcinoma stands vital due to availability of targeted therapy against it which has shown promising results and has been approved by the FDA.

Conclusion

There was no statistically significant correlation between HER2/neu expression and age, gender, site of tumor, histological type, or differentiation of the tumor. Thus, HER2/neu can be considered as having no prognostic significance in gastric carcinoma. Since HER2/neu is an important marker in planning targeted therapy in gastric carcinomas, more studies are required to evaluate the utility of HER2/neu as a prognostic marker in gastric carcinomas.

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Conflicts of interest

There are no conflicts of interest.

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