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Clinicopathological Impact of HER2/Neu Overexpression in Gastric Cancer Patients

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ABSTRACT

Globally, gastric cancer ranks seventh in terms of incidence. A proto-oncogene that plays an important role in the pathophysiology of several human malignancies, such as gastric cancer, is HER2/neu. The introduction of trastuzumab has improved overall survival for gastric cancer that is HER2/neu-positive, locally advanced, and metastatic. To investigate the expression of HER2/neu in various histological types of stomach cancers and to establish the relationship between it and clinicopathological characteristics. 80 cases of gastric adenocarcinoma that were surgically removed between July 2016 and June 2019 were selected for the study. HER2/neu overexpression was detected in all tumor samples and was associated with several clinicopathological characteristics. In our study, the mean age of the patients was 59 years. The majority of the tumors (60%) were located in the pyloric antrum area. Intestinal type accounted for 66% of cases, followed by diffuse (29%) and mixed (5%). HER2/neu overexpression was detected in 9% of patients. There was no significant association between HER2/neu overexpression and age, gender, location, histological type, or tumor grade. No statistically significant association was found between HER2/neu expression and tumor differentiation, age, gender, tumor location, or histological type. Therefore, it may be said that HER2/neu has no bearing on prognosis in gastric cancer.

Keywords: Gastric cancer, HER2/Neu, Immunohistochemistry, Clinicopathological

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Introduction

The fifth most frequent type of cancer worldwide is gastric cancer [1]. In India, it is the third most frequent cancer in males and the fifth most common cancer in women. In India, it ranks as the fourth most prevalent kind of cancer overall [2].

The main treatment for gastric cancers is curative resection; however, the majority of patients arrive at an advanced stage, where surgery is not an option and the tumor cannot be removed; in these cases, chemotherapy is still an option, but the prognosis is still poor. For this reason, there is a need for new therapeutic targets that can improve the prognosis and overall survival of patients with advanced gastric cancer.

Numerous human malignancies have a pathogenesis that is significantly influenced by the human epidermal growth factor receptor (HER) family. The importance of HER2/neu in breast tumors as a prognostic and predictive marker with therapeutic implications has been well established by the numerous research studies conducted on them. Cancers of the ovary, endometrial, bladder, lung, colon, head and neck, stomach, and gastroesophageal regions have also been shown to overexpress HER2/neu [3].

HER2/neu has been the subject of several research studies on the prognostic relevance of gastric cancer, with varying degrees of success. Research by Hilton and West [4], Ross and McKenna [5], Gomez-Martin *et al*. [6], Nakajima *et al*. [7], and Yonemura *et al*. [8], and Cheng *et al*. [9] demonstrated that patients with HER2/neu-positive gastric cancer had a bad prognosis. Moreover, research by Tateishi *et al*. [10], Sakai *et al*. [11], and Son *et al*. [12] showed that HER2/neu had no predictive value for gastric cancer.

According to the findings of a global Phase III randomized controlled trial conducted in 2010 on trastuzumab for gastric cancer, patients with HER2/neu-positive advanced gastric cancer who received the anti-HER2/neu monoclonal antibody had a noticeably higher overall survival rate than those who received chemotherapy alone. Trastuzumab was authorized by the Food and Drug Administration (FDA) for patients with advanced gastric cancer who had immunohistochemistry (IHC) 3+ or IHC 2+/fluorescence in situ hybridization based on this discovery [13].

Patients with HER2/neu-positive breast cancer and gastric cancer are successfully treated with trastuzumab-based treatment. Inducing passive immunity against cancerous cells is how trastuzumab works. Antigen-specific immunotherapy against tumor cells is based on the cytotoxicity induced by antibodies. As a result of these investigations, vaccinations that target tumor cells that express HER2/neu have been developed [14, 15].

This emphasizes even more how crucial biological indicators are to the therapy of cancer. Given the poor prognosis of gastric cancer and the contentious significance of HER2/neu as a prognostic marker in the disease, more research is necessary to determine its relevance.

This work was done to determine the pattern of HER2/neu expression in distinct histological kinds of gastric adenocarcinoma, its association with clinicopathological features, and to evaluate its value 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 □m 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 a 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 an initial evaluation of the results, cases with major discordance in reports were rechecked by both 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 this study.

Results and Discussion

Of the 80 instances of stomach cancer, 20 patients (25%) were female and 60 patients (75%) were male. Patients were between the ages of 38 and 82 years, with a mean age of 59.48 years. 60% of the patients had a tumor in the pyloric antrum area, 27 cases (34%) had a tumor in the body, 3 cases (4%) had a tumor at the gastroesophageal junction, and 1 case (1%) included the whole stomach and the cardia. Of the 80 patients, 15 (19%) had well-differentiated adenocarcinomas, 40 (50%) had moderately-differentiated adenocarcinomas, and 25 (31%) had poorly-differentiated adenocarcinomas. Lauren's categorization showed that 4 (5%) instances were of mixed type, 53 (66%) were of intestinal type, and 23 (29%) were of diffuse type. 61 patients (76%) had infiltration into the serosa, 12 patients (15%) had perigastric extension, 3 patients (4%) had infiltration into the submucosa and muscularis propria, and 1 patient (1%) had solely intramucosal spread. In 26 instances (32%), lymphovascular invasion was found, while in 57 cases (71%), lymph nodes were implicated **(Table 1)**.

7 of the 80 individuals (9%) had HER2/neu positive **(Figures 1–3)**, while 5 (6%) had ambiguous HER2/neu. 68 instances (85%) were negative for HER2/neu. Staining was mostly found in membranes. **Table 1** summarizes how HER2/neu overexpression is related to several clinicopathological factors. In our research, HER2/neu overexpression was found in 6% of patients under 60 years and 12% of patients over 60 years. The percentage of males and females with HER2/neu positive was 8% and 10%, respectively. HER2/neu overexpression was seen in 10% of pylorus and antrum tumors and 7% of body cancers. HER2/neu was not detected in cancers affecting the whole stomach, the cardia, or the gastroesophageal junction (GEJ). 10% of instances of moderately differentiated adenocarcinoma and 20% of cases of well-differentiated adenocarcinoma displayed HER2/neu positive, whereas poorly differentiated adenocarcinoma exhibited no positivity. In Lauren's histological type, HER2/neu overexpression was seen in 13% of intestinal types. There was no positive evidence in any of the diffuse or mixed-type instances.

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

Clinicopathological parameters	**n (%)**	**HER2/neu positive, *n* (%)**	**P-value**
Age (years)			
≤ 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%)	0.950
Cardia	1 (1%)	0 (0%)	
Body	27 (34%)	2 (7%)	
Pylorus and antrum	48 (60%)	5 (10%)	
Linitis plastica	1 (1%)	0 (0%)	
Pathologic grade			
Well-differentiated	15 (19%)	3 (20%)	0.088
Moderately differentiated	40 (50%)	4 (10%)	
Poorly differentiated	25 (31%)	0 (0%)	
Lauren’s histological type			
Diffuse	23 (29%)	0 (0%)	0.142
Intestinal	53 (66%)	7 (13%)	
Mixed	4 (5%)	0 (0%)	

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

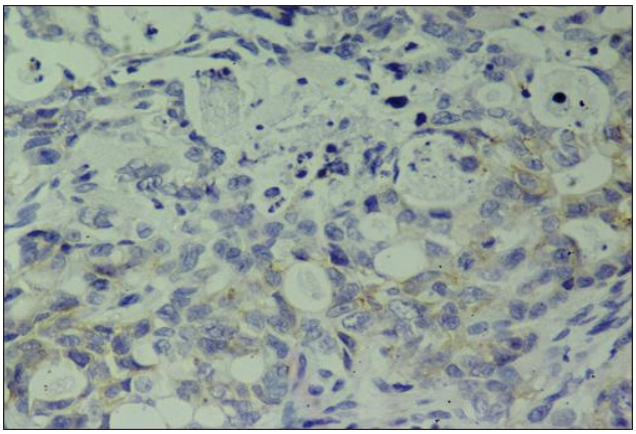

Figure 1. Score 1+, faint membranous positivity of HER2/neu expression in gastric carcinoma (IHC, ×400).

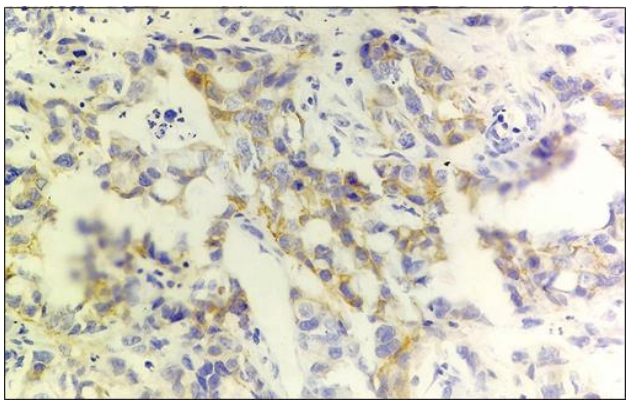

Figure 2. Score 2+, weak to moderate membranous positivity; HER2/neu expression in gastric carcinoma (IHC, ×400).

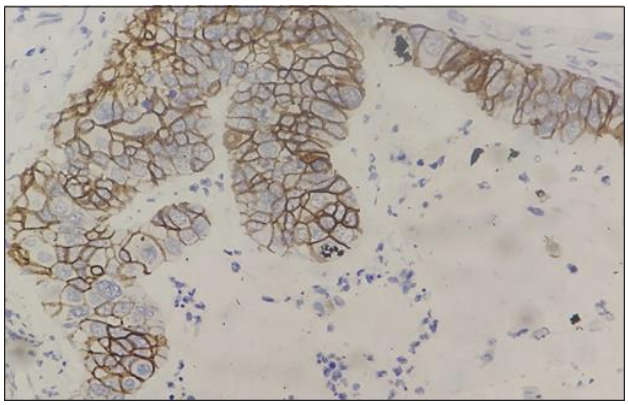

Figure 3. Score 3+, strong membranous positivity of HER2/neu expression in gastric carcinoma (IHC, ×400).

To evaluate the usefulness of HER2/neu overexpression in the prognosis of gastric cancer, the current study used IHC to investigate HER2/neu overexpression in gastric cancer and connected it with clinicopathological features. Eighty individuals with stomach cancer participated in our prospective, cross-sectional research. The HER2/neu positivity of 7 of the 80 patients (9%) in our investigation was equivalent to that of the studies conducted by Takehana *et al*. [16] (8.2%), Devi *et al*. [17] (10%), and Kumarasinghe *et al*. [18] (10.4%).

The majority of patients are above 50 years, and it is predominantly an age-related illness. After fifty years, the incidence of cancer increases significantly. The patients in our research varied in age from 38 to 82 years, which was similar to the findings of studies conducted by Lazăr *et al*. [19], Park *et al*. [20], and Lee *et al*. [21]. The majority of patients (n = 68, 85%) were found to be above 50.6% of patients under 60 years, and 12% of patients over 60 years in this research had overexpression of HER2/neu, which was similar to the findings of Son *et al*. study [12]. HER2/neu overexpression and age did not, yet, significantly correlate (P = .439). Similar findings were made by Son *et al*. [12] (P = 0.102), Devi *et al*. [17] (P = 0.432), and Lee *et al*. [21] (P = 0.07).

Males are more likely than females to get gastric cancer, with the male-to-female ratio ranging from 1 in young adults to 2 or more around age 60. The causes of the gender gap are not entirely known. The male-to-female ratio in our study was 3:1, which was similar to the findings of studies by Raziee *et al*. [22] and Zu *et al*. [23]. In our study, 10% of all female patients and 8% of all male patients tested positive for HER2/neu. In research by Son *et al*. [12], the findings were similar for men, and in investigations by Lee *et al*. [21], they were similar for females. HER2/neu and patient gender, however, did not significantly correlate in our research (P = 1.000). These findings are consistent with earlier research that demonstrated no significant association between HER2/neu and gender, such as Son *et al*. [12] (P = 0.111) and Park *et al*. [20] (P = 0.546).

The pyloric antrum area accounted for 60% of the gastric cancer cases in this research, with the body, gastroesophageal junction, cardia, and whole stomach following in order of incidence. These findings align with research conducted by Son *et al*. [12] and Park *et al*. [20]. In contrast, Niu *et al*. [24] discovered that the body and fundus were the most frequently affected sites, accounting for 66% of cases. Only 7% of cases found in the body and 10% of those found in the pyloric antrum had overexpression of HER2/neu. HER2/neu positive was not observed in malignancies of the gastroesophageal junction, cardia, or the whole stomach. The research by Panda

and Panda, however, found that only 19.6% to 15.4% of the pylorus and gastroesophageal junction cancers overexpressed HER2/neu, while 66.7% of all tumors tested positive for HER2/neu [25]. Our study, like those of Devi *et al*. [17], Raziee *et al*. [22], and Ghaderi *et al*. [26] found no statistically significant link between HER2/neu positive and tumor location (P = 0.950).

Lauren's classification is the most often utilized in ordinary practice among the several histological classifications of gastric cancer, with the intestinal type having a greater survival rate and, thus, a better prognosis. Intestinal type accounted for 66% of the cases in our study, followed by diffuse type (29%) and mixed type (5%). Akl *et al*. [27] and Halder *et al*. [28] showed similar results, with 59.3% and 63.8% of intestinal cancers, respectively. However, research by Panda and Panda [25] found that intestinal-type adenocarcinoma is less prevalent than diffuse-type adenocarcinoma.

All diffuse-type and mixed-type patients in the current investigation did not exhibit any HER2/neu positivity, but 13% of intestinal cases tested positive. The research conducted by Devi *et al*. [17] was similar in that none of the diffuse-type patients tested positive for HER2/neu, whereas a greater number of intestinal-type cases (23%) tested positive for HER2/neu. 18% of intestinal-type adenocarcinomas were HER2/neu positive in the research of Ghaderi *et al*. [26], which was similar to our analysis. However, 13% of diffuse-type adenocarcinomas were HER2/neu positive, which was higher than in the current study. The overexpression of HER2/neu and Lauren's histological type did not correlate in a statistically meaningful way.

Well-differentiated, moderately differentiated, and poorly differentiated gastric adenocarcinomas are the three classifications. The majority of the instances in this research (50%) were of the moderately differentiated kind, with the next most common types being poorly differentiated (31%) and highly differentiated (19%). Setala *et al*. [29], Rajagopal *et al*. [30], and Aditi *et al*. [31] all indicated moderately differentiated adenocarcinoma as the most prevalent type. Other authors, including Panda and Panda [25] and Devi *et al*. [17], discovered further examples of poorly differentiated adenocarcinoma. 3 (20%) of the 15 well-differentiated carcinomas (19%) tested positive for HER2/neu. Son *et al*. [12] and Sunitha *et al*. [32] reported similar results in 20.3% and 20% of well-differentiated carcinomas, respectively. 4 instances (10%) of moderately differentiated adenocarcinomas had HER2/neu positive, which was equivalent to the studies done by Devi *et al*. [17] and Sunitha *et al*. [32]. None of the poorly differentiated patients tested positive for HER2/neu. This was equivalent to the study conducted by Halder *et al*. [28].

Overall, our analysis revealed no discernible relationship between HER2/neu overexpression and differentiation, histological type, age, gender, or tumor location. The research conducted by Ghaderi *et al*. [26] and Sunitha *et al*. [32] came to similar findings.

HER2/neu testing is still essential for gastric cancer since there is a targeted therapy that has been licensed by the FDA and has shown encouraging outcomes.

Conclusion

No statistically significant association was found between HER2/neu expression and tumor differentiation, age, gender, tumor location, or histological type. In gastric cancer, HER2/neu can thus be regarded as having little predictive relevance. To assess the usefulness of HER2/neu as a prognostic marker in gastric carcinomas, additional research is necessary since it is a crucial marker in the design of targeted therapy.

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Conflict of Interest: None

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Ethics Statement: None

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