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Original Article

# A study of morphology and Human epidermal growth factor receptor (HER2) expression in gastroesophageal junction and gastric adenocarcinoma

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**Keywords:**

Gastric cancer; Gastroesophageal junction cancer; HER2

## ABSTRACT

**Background:** HER2 overexpression in gastric cancer varies depending on tumor histology and anatomical location. This study aimed to score and evaluate the immunohistochemical marker HER2 in gastric adenocarcinoma and also to compare the expression of HER2 between gastro-oesophageal and gastric adenocarcinoma.

**Materials and Methods:** A cross-sectional, retrospective study was conducted on 44 cases of histopathologically proven gastro-oesophageal and gastric adenocarcinoma by endoscopic Biopsy (41 cases) and gastrectomy (7 cases) specimens. Out of the 48 participants enrolled, we received both endoscopy and gastrectomy specimens from 4 cases. Hence, the analysis was based on the findings of 44 cases. HER2 immunohistochemistry was done on formalin-fixed paraffin-embedded tissues. Variables like age, gender, anatomical distribution of tumor, type of cancer, tumor grade and HER2 grade were studied.

**Results:** Out of the 44 cases, the majority of the adenocarcinoma were gastric in origin [29/44 cases (65%)], with antral adenocarcinoma accounting for the largest proportion of gastric adenocarcinoma [12/29 cases (42%)]. HER2 overexpression was seen in 6/44 cases (14%) of the total cases. Well-differentiated adenocarcinoma showed maximum HER2 expression [4/8 cases (50%)] compared to moderately differentiated and poorly differentiated adenocarcinomas.

**Conclusions:** HER2 overexpression is more frequent in well-differentiated gastric and gastro-esophageal adenocarcinomas, and in gastro-esophageal junction adenocarcinomas than in gastric adenocarcinomas.

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## INTRODUCTION

Gastric cancer ranks second in mortality and fourth in incidence among all cancers worldwide.[1] Gastric cancer is the fifth most common cancer among males and the seventh most common cancer among females in India.

HER2 is a member of the Her-family of growth factor receptors, which includes Her1, Her3, and Her4, all of which are involved in the complex regulation of cell growth, proliferation and survival.[2]

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Monitoring of the tumor HER2 status (protein over-expression and/or gene amplification) in breast cancer has turned into a routine practice, as positive HER2 status is associated with poorer prognosis, more aggressive disease, and a greater risk of disease recurrence.[2]

Since the advent and the success of adjuvant medical therapy for human epidermal growth factor receptor 2 (HER2)-positive breast cancer in the form of trastuzumab, there has been growing interest in the development of related therapies in other solid organ malignancies, including oesophageal cancer and gastric cancer.[3]

Patients with HER2-positive advanced gastric and gastroesophageal carcinoma have shown an increased overall survival rate on treatment with Trastuzumab combined with chemotherapy.

This study aimed to evaluate the expression and score the immunohistochemical marker HER2 in gastric and Gastro-esophageal junction (GEJ) adenocarcinoma and also to compare the expression of HER2 between gastro-oesophageal and gastric adenocarcinomas.

## MATERIALS AND METHODS

A cross-sectional, retrospective study was conducted on 44 histopathologically proven gastro-oesophageal and gastric adenocarcinomas diagnosed on endoscopic biopsy or gastrectomy. 41 biopsies and 7 gastrectomy specimens were received at the Department of Pathology, MES Medical College, Perintalmanna, Kerala (A tertiary care center) between December 2015 to May 2017. Inadequate biopsy, biopsies not representative of tumor, and inadequately fixed specimens were excluded from the study (4 cases).

Proper informed consent was taken from patients, and ethical clearance was obtained from the institutional review board.

The tissue were formalin-fixed and paraffin-embedded and were then stained with haematoxylin and eosin for histopathological typing and grading. The gastric adenocarcinoma and gastroesophageal junction carcinoma was both graded as per the World Health Organization Tumor Classification, 2010.[4] All the cases were further subjected to immunohistochemistry for HER2 expression. The antibody used for HER2 was Rabbit monoclonal anti HER2 antibody, clone EP3 (PathnSitu). HER2 expression and staining patterns were analyzed by the scoring system proposed by Hofmann et al.[5] that has been assimilated by CAP and FDA (Table 1). The expression pattern of HER2 and its correlation with the grade of tumor was established. For HER2, membranous staining was taken into consideration. HER2 overexpression was defined as a 3+ positivity according to Hoffman et al, while Scores 0, 1+ and 2+ were considered negative. A tumor cell cluster was described as at least five tumor cells. Equivocal HER2 IHC was considered as negative in the present study.

Data was entered in MS Excel and analysed using SPSS. Variables like age, expressed using mean, and qualitative variables like gender, anatominal distribution of tumor, type of malignancy, tumor grade, and HER2 grade were expressed in percentage. Association between HER2 expression, gender, site and tumor grade was analyzed using Chi-square test.

**Table 1: Human Epidermal Growth Factor Receptor (HER2) scoring criteria for gastric cancer[5]**

| SCORE | Surgical specimen-staining pattern | Biopsy specimen-staining pattern | HER2 interpretation |
|---|---|---|---|
| 0 | No reactivity or membranous reactivity in <10% of tumor cells | No reactivity or no membranous reactivity in any tumor cell | Negative |
| 1+ | Faintly/barely perceptible membranous reactivity in >/= 10% of tumor cells; cells are reactive only in part of their membrane | Tumor cell cluster with a faint/ barely perceptible membranous reactivity irrespective of percentage of tumor cells stained | Negative |
| 2+ | Weak to moderate, complete, basolateral or Lateral membranous reactivity in >/= 10% of tumor cells | Tumor cell cluster with a weak to moderate complete, basolateral or Lateral membranous reactivity irrespective of percentage of tumor cells stained | Equivocal |
| 3+ | Strong complete, basolateral or lateral membranous reactivity in >/= 10% of tumor cells | Tumor cell cluster with a strong complete, basolateral or Lateral membranous reactivity irrespective of percentage of tumor cells stained | Positive |

## RESULTS

Forty-four subjects meeting the inclusion criteria were enrolled in the study. For cases in which both endoscopic biopsy and gastrectomy specimens were available, the findings were regarded as concordant when HER2 immunohistochemistry was performed on both specimens. Therefore, in such patients, only the endoscopic biopsy results were considered.

Majority of the patients were males, constituting 31/44 (70%) of the total. The study group consisted of patients from the third decade to the eighth decade with a mean age of 63 years (range: 35–86 years).

Only 6 out of 44 cases showed HER2 overexpression, which formed 14% of the study. Of the 6 HER2-overexpressing cases, 4 were males and 2 were females.

Of the 44 cases, 29 were gastric and 15 were obtained from the GEJ. Of the 15 GEJ adenocarcinomas, 3 cases showed

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HER2 overexpression and this formed 20% of the GEJ tumors.

**Table 2: Number of cases showing HER2 overexpression in gastro-esophageal junction and gastric adenocarcinoma**

| | HER2 overexpressed (%) | Negative | p-value |
|---|---|---|---|
| Gastro-esophageal junction carcinoma | 3 (20%) | 12 (80%) | 0.376 |
| Gastric carcinoma | 3 (10%) | 26 (90%) | |

Of the 15 GEJ adenocarcinomas, 7(47%) were poorly differentiated, 6 (40%) were moderately differentiated and 2 (13%) were well differentiated. The gastric adenocarcinomas were predominantly poorly differentiated [19 (66%)], followed by moderately differentiated [4 (14%)] and well differentiated [6 (20%)].

Out of the 29 gastric tumors, 12 were in the antrum, 9 in the body, 6 in the fundus, and 2 in the pylorus.

Out of the 29 gastric adenocarcinomas, 3 cases showed HER2 overexpression, which constituted 10% of the total gastric tumors. Within the gastric tumors, the highest number of cases with HER2 over-expression was observed in the body (84%), followed by the fundus (16%).

**Table 3: Anatomical variation in HER2 overexpression in the stomach**

| Sublocation of stomach | Number of cases | No. of cases with HER2 overexpression (%) |
|---|---|---|
| Fundus | 6 | 1 (16) |
| Body | 9 | 2 (84) |
| Antrum | 12 | 0 |
| Pylorus | 2 | 0 |

Out of the total 6 cases (both gastric and GEJ) with HER2 overexpression, 4 cases (50%) were well-differentiated, 1 (10%) moderately-differentiated, and 1 (4%) poorly-differentiated. The difference of HER2 expression was found to be statistically significant (Table 4). (fig.1)

Signet ring cell morphology was identified in 3 out of 26 poorly-differentiated carcinomas, all of which were HER2-negative.

**Table 4: HER2 expression and tumor grade in both Gastric and Gastro-esophageal junction carcinoma**

| | Well differentiated | Moderately differentiated | Poorly Differentiated | p-value |
|---|---|---|---|---|
| Overexpressed | 4 | 1 | 1 | |
| Negative | 4 | 9 | 25 | 0.004 |
| **Total** | **8** | **10** | **26** | |

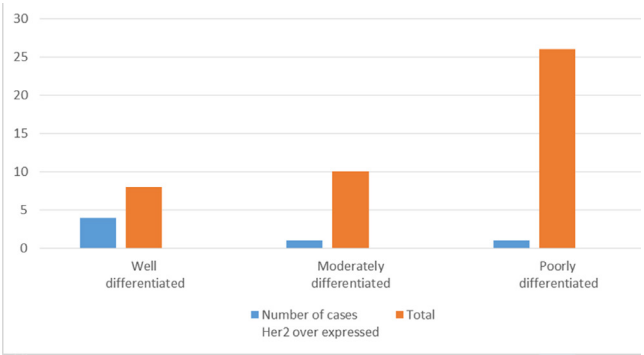


***Figure 1:*** *HER2 overexpression and tumor grade in gastric and gastroesophageal carcinomas*

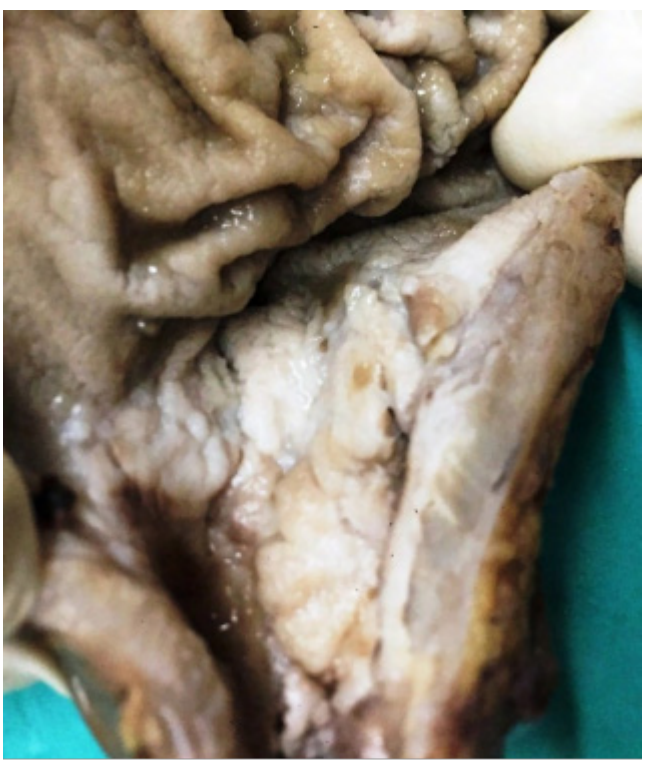

***Figure 2:*** *Gross image showing gastrectomy specimen of Adenocarcinoma - signet ring cell type.*

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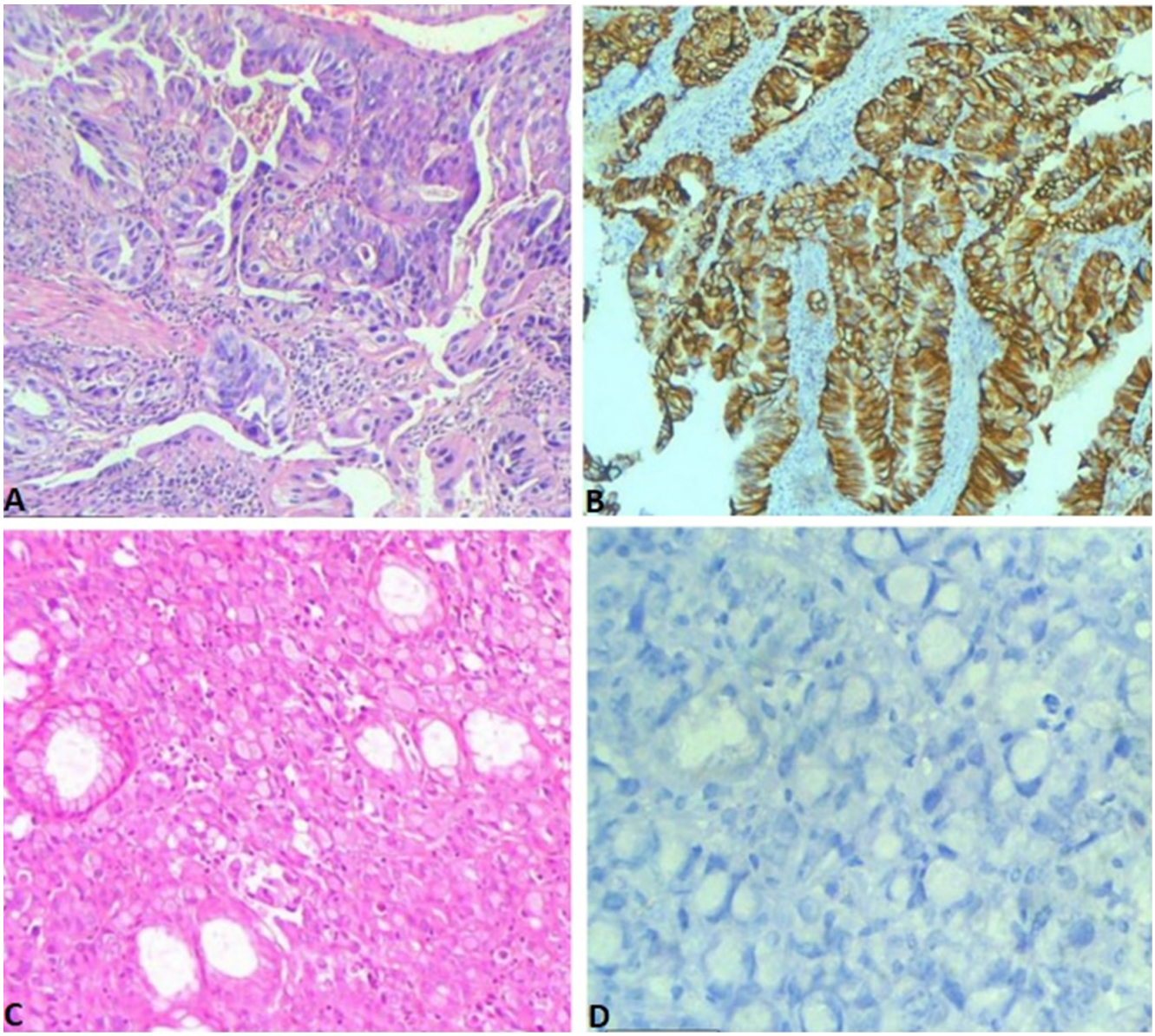


***Figure 4:*** *(A)Well-differentiated gastric adenocarcinoma. [H&E, 100x]; (B) Tumor cells exhibiting HER2overexpression. [IHC, 100x]; (C) Signet ring cell carcinoma in the body of stomach. [H&E, 100x]; (D) Negative HER2 immunostaining in signet ring cell carcinoma [IHC, 400x].*

## DISCUSSION

Gastric cancer ranks fourth in incidence and second in mortality among all cancers worldwide. Many of them are detected late, at advanced stages. HER2 overexpression in gastric and gastroesophageal junction carcinoma is associated with a poor prognosis. But the addition of targeted therapy with Trastuzumab has a survival benefit for these patients.

Our study found that HER2 overexpression occurred in 14% of gastric and gastroesophageal junction carcinoma cases. HER2 overexpression has been shown to vary widely, as per different studies (Table 5). In the TOGA trial, the HER2-positivity rate was 22.1% throughout the tumor samples (2168 patients) that were analyzed.[19]

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**Table 5: Comparison of HER2 in different studies**

| Study | No. of cases evaluated | Percentage of cases with HER2 overexpression |
|---|---|---|
| Oshima et al[6] | 82 | 45 |
| Pinto-de-sousa et al[7] | 157 | 15.3 |
| Takehana et al[8] | 352 | 8.2 |
| Ougolkov et al[13] | 40 | 13 |
| Song et al[14] | 739 | 26.2 |
| Tanner et al[9] | 131 | 12.2 |
| Yano et al[10] | 200 | 23 |
| Park et al[15] | 182 | 15.9 |
| Kim et al[16] | 248 | 22.6 |
| Gravalos et al[17] | 166 | 13 |
| Lordick et al[3] | 1527 | 22 |
| Barros-Silva et al[18] | 463 | 9.3 |
| Grabsch et al[24] | 506 | <10 |
| ToGA study[19] | 810 | 22.1 |
| Tsapralis et al[11] | 120 | 20 |
| Terashima et al[20] | 829 | 13.6 |
| Laboissiere et al[12] | 124 | 10.5 |
| **Present study** | **44** | **14** |

In the current study, HER2 overexpression was observed predominantly in well-differentiated carcinoma, whereas poorly differentiated carcinoma cases exhibited lower levels of HER2 expression. Although some studies have reported conflicting results, the majority of the literature supports the finding that HER2 overexpression is more commonly associated with well-differentiated carcinoma (Table 6). No significant association was found between HER2 overexpression and either gender or tumor topography in our study.

**Table 6: Comparison of HER2 expression with tumor grades in different studies**

| Study | Most common type of tumor grade showing HER2 over-expression |
|---|---|
| Oshima et al[6] | Well-differentiated carcinoma |
| Laboissiere et al[12] | Well and moderately differentiated carcinoma |
| Kim et al[16] | Well and moderately differentiated carcinoma |
| Halon et al[21] | Poorly differentiated carcinoma |
| Wang et al[22] | Poorly differentiated carcinoma |
| **Our study** | **Well-differentiated carcinoma** |

The present study included predominantly endoscopic biopsy specimens. In cases where HER2 expression was evaluated on both gastrectomy specimens and endoscopic biopsies, the immunohistochemistry (IHC) results were found to be concordant. According to Yano et al[10], small biopsy specimens are suitable for the evaluation of HER2 overexpression in gastric cancer. However, a study by Grabsch et al[24] reported that HER2 expression in endoscopic biopsies may be prone to false-negative results due to intratumoral heterogeneity.

## CONCLUSIONS

In present study, HER2 overexpression was observed in 14% of gastroesophageal and gastric adenocarcinomas, with higher frequency in well-differentaited tumors. GEJ adenocarcinomas showed more frequent HER2 positivity compared to gastric carcinomas. Well-differentaited tumors demonstrated the strongest association with HER2 overexpression. This study underscores the correlation of HER2 expression in gastric and GEJ adenocarcinomas with their histological grade. However, authors acknowledge the limitation of the study in its very small sample size and the unavailability of FISH to further categorize HER2-equivocal cases. Present study paves the path for future studies with a larger sample size to explore correlations between HER2 expression and other clinicopathological parameters.

**Conflicts of Interest**: Nil

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