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Histopathological Study of Gastric Adenocarcinoma with Special Reference to Expression of HER2/neu and Ki-67 Assessed by Immunohistochemistry

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Abstract

Introduction Gastric cancer has become the third leading cause of cancer deaths globally. It accounts for 5.7% of cancer around the world, with a rate of mortality around 8.2%. Evaluation of human epidermal growth factor receptor 2 (HER2)/neu overexpression for targeted therapies is presently the mainstay of treatment in gastric cancer. High Ki-67 index expression in gastric cancer is an indicator of poor prognosis.

Objectives To study the prevalence of HER2/neu expression and Ki-67 index in various types, sites, grade, and stage of gastric adenocarcinoma and to determine the correlation between HER2/neu expression and Ki-67 index.

Materials and Methods This is a prospective study in a tertiary care hospital, Kolkata from January 2019 to June 2020. Gastrectomy and endoscopic biopsy of gastric adenocarcinoma were studied for histopathology and immunohistochemistry (HER2/neu and Ki-67 index). Statistical analysis used: SPSS (version 21.0, IBM, Chicago, Illinois, United States) for windows software.

Results Among 54 cases, most of them were intestinal type, antral, moderately differentiated, stage III cases. HER2 expression and high Ki-67 index were observed in 28.0 and 40.75% cases, respectively. Statistically significant correlation was found in both HER2 expression and high Ki-67 index with location of the tumor and pathological nodal (pN) stage. A positive correlation was found between HER2/neu score and Ki-67 index ($p = 0.007$) (correlation coefficient = 0.4).

Conclusion A positive correlation was found between HER2/neu positivity and high Ki-67 index, both were associated with higher pathological tumor stage and pN stage. So, advanced cases may be considered for targeted therapy using trastuzumab.

Keywords
- gastric adenocarcinoma
- HER2/neu
- Ki-67 index
- trastuzumab

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Introduction

Gastric cancer ranks third globally in terms of overall cancer mortality, trailing only colorectal and lung cancer, according to GLOBOCAN[a] 2018 data. Among all cancers, gastric cancer has the fifth highest incidence, accounting for 5.7% of newly diagnosed cases.[1,2] Ten percent of deaths caused by cancer globally are attributable to gastric carcinoma (GC), which has a 70% case fatality rate.[3]

Males are more likely to develop gastric cancer. In developed countries, men have 2.2 times greater likelihood than women to get diagnosed with stomach cancer. The ratio in developing countries is 1.83.[1] Although most patients are older than 50 years, rare cases arise in younger individuals and even children.[4]

Early-stage cancers are typically treated with surgical resection; however, the majority of patients get diagnosed when the disease has advanced and is frequently incurable. Despite chemotherapy, the outcome for patients with advanced resectable stomach cancer is still pathetic. Therefore, early tumor detection and the use of molecular targeted therapy can increase patient survival by reducing the risk of recurrence and metastasis.[2,3]

In gastric cancer, overexpression of human epidermal growth factor receptor 2 (HER2)/neu plays a pathogenetic, therapeutic, and predictive role. One of the mainstays of treatment is presently to assess HER2/neu overexpression along with other biomarkers for targeted treatments.[5] HER2/neu oncogene overexpression and amplification has emerged as a critical indicator for determining patient's response to HER2/neu targeted therapy.

There has been some evidence that Ki-67 can be correlated with outcome in stomach cancer.[6]

This study aimed to investigate the clinicopathological spectrum of gastric cancer, and to assess HER2/neu and the Ki-67 index using immunohistochemistry (IHC) techniques on diagnosed cases of adenocarcinoma. This study tried to find correlation of HER2/neu expression and the Ki-67 index with various histomorphological variations and grade of gastric adenocarcinoma.

This study was undertaken to diagnose the cases of gastric adenocarcinoma by histopathology, determine its incidence, and study the prevalence of HER2/neu expression and Ki-67 index according to location, histopathological types, grading, and staging. The correlation between HER2/neu and Ki-67 was also determined.

Objectives

The objectives were to study the prevalence of HER2/neu expression and Ki-67 index in various types, sites, grade, and stage of gastric adenocarcinoma and to determine the correlation between HER2/neu expression and Ki-67 index.

[a] An online database providing global cancer statistics and estimates of incidence and mortality in 185 countries for 36 types of cancer, and for all cancer sites combined.

Materials and Methods

Study Design

This is a prospective study done in a tertiary care hospital, Kolkata, West Bengal from January 2019 to June 2020.

Primary Outcome

To study the prevalence of HER2/neu expression and Ki-67 index in various types, sites, grade, and stage of gastric adenocarcinoma.

Secondary Outcome

To study the correlation between HER2/neu expression and Ki-67 index.

Inclusion Criteria

Patients clinically diagnosed with gastric adenocarcinoma and who underwent gastric endoscopic biopsy or gastrectomy for the same.

Exclusion Criteria

Patients with a history of gastric adenocarcinoma, treated with chemotherapy and gastric cancer cases diagnosed other than gastric adenocarcinoma were excluded. Detailed history, clinical features, and radiological investigation were evaluated.

The specimens were processed for histopathological and immunohistochemical study. Hematoxylin and eosin stain was used to stain the sections for histopathological study and cases diagnosed as gastric adenocarcinoma were evaluated for immunohistochemical study with HER2/neu and Ki-67.

The three authors independently scored HER2/neu IHC using the Gastric Cancer Scoring System for surgical specimens.[7] The cases were examined with standard HER2/neu positive criteria. Brown staining of malignant cell membrane was used to assess positivity. A score of 3+ was considered positive for HER2/neu.

HER2 IHC Pattern in Surgical Specimen

Score 0 negative: No reactivity or membranous reactivity in $<$10% of cancer cells.
Score 1+ negative: Faint or barely perceptible membranous reactivity in $\geq$10% of cancer cells; cells are reactive only in part of their membrane.
Score 2+ equivocal: Weak to moderate complete, basolateral or lateral membranous reactivity in $\geq$10% of tumor cells.
Score 3+ positive: Strong complete, basolateral or lateral membranous reactivity in $\geq$10% of cancer cells.

HER2 IHC Pattern in Biopsy Specimen

Score 0 negative: No reactivity or no membranous reactivity in any cancer cell.
Score 1+ negative: Cancer cell cluster[b] with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive.
Score 2+ equivocal: Cancer cell cluster[b] with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive.

[b] Cancer cell cluster consisting of $\geq$5 neoplastic cells

Score 3+ positive: Cancer cell cluster[b] with a strong complete basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive.

Ki-67 IHC scoring was performed in accordance with the International Ki-67 in Breast Cancer Working Group[8] criteria, with Ki-67 positive staining defined as positive nuclear staining only, irrespective of intensity of staining. At least 1,000 nuclei counted at high power (×40 objective) was required for scoring.

The Ki-67 score/index or proliferation index was calculated as percentage of positively stained nuclei in the area scored out of total number of nuclei.

Cases were then divided into two groups for suitable grouping of results: GCs having high Ki-67 score (>20%) and GCs having low Ki-67 score (≤20%).

Statistical Analysis

Available data were statistically evaluated with SPSS (version 21.0, IBM, Chicago, Illinois, United States) for windows software.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. We began our research only after receiving approval from the ethical committee. This work has been approved by our institution's proper ethical committee. Ethical approval number is EC-CNMC/2019/220, date January 11, 2019, Institutional Ethics Committee, Calcutta National Medical College.

Results

In our study, the patient's mean age was 59.1 ± 10.9 years, having a range from 32 to 83 years, with male preponderance (3:1). We studied 38 (70%) specimens of gastrectomy, whereas gastric biopsies account 16 (30%) cases. Antrum (48.15%) was the most frequent location followed by pylorus (24.07%).

Intestinal variant was higher (87.04%) than the diffuse variant and majority of gastric adenocarcinoma cases were moderately differentiated (grade 2) (62.96%) (►**Fig. 1**), followed by poorly differentiated (grade 3) (27.78%) and few cases were well differentiated (grade 1) (9.26%).

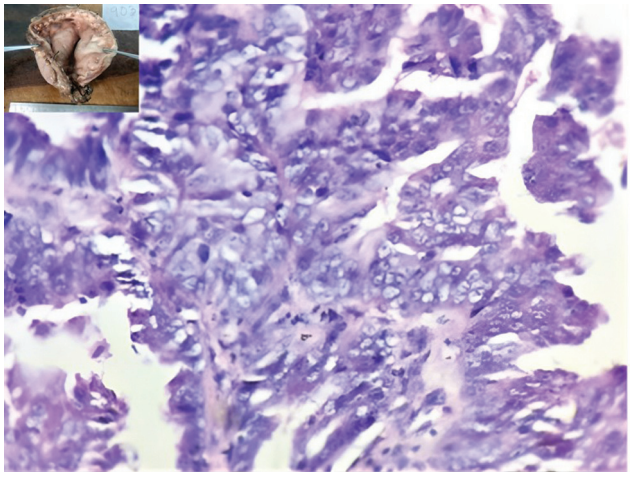

Fig. 1 Moderately differentiated gastric adenocarcinoma; hematoxylin and eosin stain ×40 and inset showing gross specimen of radical gastrectomy showing diffuse infiltrative growth involving whole of the specimen.

Table 1 Clinicopathological characteristics of patients

Characteristics	Number of patients ($n = 54$) (%)
Age	
Range	32–83
Mean	59.1 ± 10.9
Sex	
Male	40 (74.07)
Female	14 (25.93)
Type of specimen	
Gastrectomy	38 (70.37)
Gastric biopsy	16 (29.63)
Location of tumor	
GE junction	2 (3.7)
Fundus	1 (1.85)
Body	9 (16.67)
Incisura	3 (5.56)
Antrum	26 (48.15)
Pylorus	13 (24.07)
Lauren's classification	
Intestinal	47 (87.04)
Diffuse	7 (12.96)
Grade of tumor	
Well differentiated	5 (9.26)
Moderately differentiated	34 (62.96)
Poorly differentiated	15 (27.78)
Pathological tumor stage	
T1	16 (29.63)
T2	5 (9.26)
T3	25 (46.30)
T4	8 (14.81)
Pathological nodal stage	
Nx	16 (29.63)
N0	6 (11.11)
N1	6 (11.11)
N2	16 (29.63)
N3	10 (18.52)

Table 1 (*Continued*)

Characteristics	Number of patients ($n = 54$) (%)
TNM stage	
I	3 (7.90)
II	10 (26.32)
III	25 (65.78)
IV	0 (0)
HER2/neu score	
0	19 (35)
1+	6 (11)
2+	14 (26)
3+	15 (28)
Ki-67 proliferation index	
High	22 (40.75)
Low	32 (59.25)

Abbreviations: GE, gastroesophageal; HER2, human epidermal growth factor receptor 2.

The majority of gastrectomy patients (65.78%) had stage III disease according to TNM staging (►**Table 1**).

In this study, including 54 cases of gastric adenocarcinoma, 15 cases (28%) were positive for HER2/neu (►**Fig. 2**). HER2/neu expression was more prevalent in adenocarcinoma of distal part of stomach, antrum (38%), pylorus (30%) which is statistically significant ($p = 0.02$). Out of the 15 HER2/neu positive cases, there were 14 intestinal variant cases and only 1 was diffuse variant case.

Adenocarcinoma with moderate differentiation (grade 2) displayed highest HER2/neu positivity (score 3+) (►**Fig. 3**) followed by poor differentiation (grade 3).

No significant association ($p = 0.06$) was noted among positive expression of HER2/neu and pathological tumor (pT) stage, but a statistically significant association ($p = 0.009$) noted among positive expression of HER2/neu and pathological nodal (pN) stage (►**Table 2**).

In our study of 54 cases, 40.75% cases had high Ki-67 proliferation index (►**Fig. 4**), out of which 62% had T4 stage gastric adenocarcinoma cases showing high Ki-67 score.

A significant correlation was noted between Ki-67 index and site of gastric adenocarcinoma ($p = 0.05$).

The diffuse type (57%) had high Ki-67 score and poorly differentiated adenocarcinoma (53%) had high Ki-67 score (►**Fig. 5**).

A statistically significant correlation was noted between Ki-67 score and pN stage ($p = 0.002$). pN3 gastric adenocarcinoma (90%) cases showed high Ki-67 score (►**Table 3**).

Thirteen out of total 15 HER2/neu positive cases had high Ki-67 score. A positive correlation was noted HER2/neu score and Ki-67 score ($p = 0.007$) (correlation coefficient = 0.4) (►**Table 4**).

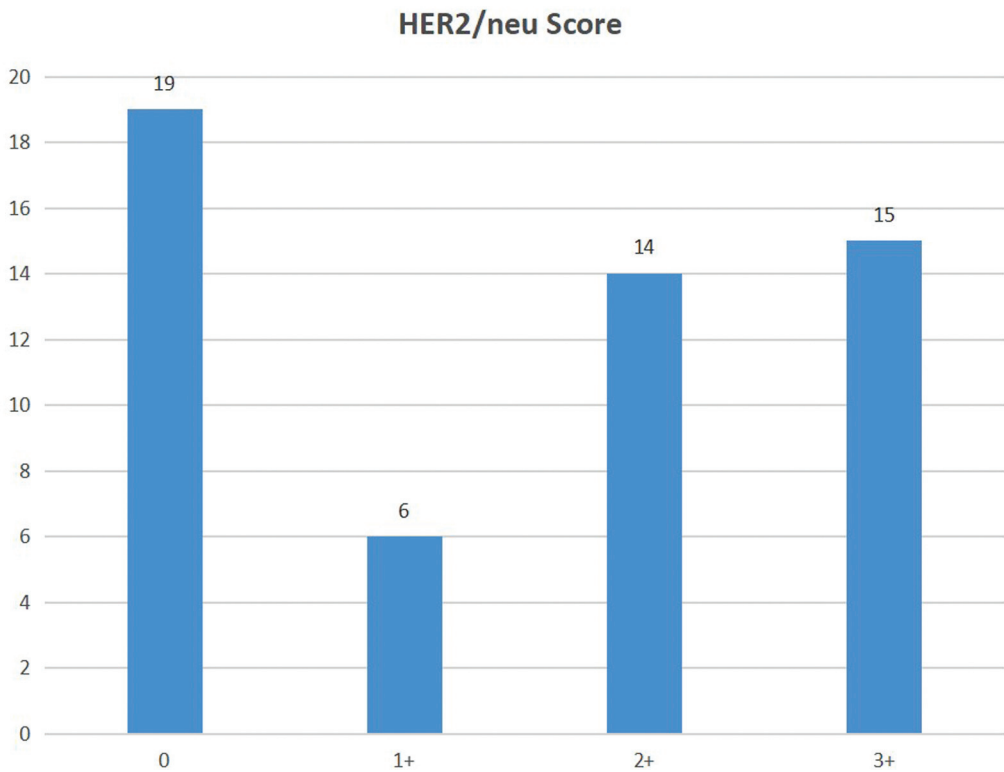

Fig. 2 Bar diagram showing distribution of gastric adenocarcinoma cases according to HER2/neu score. HER2, human epidermal growth factor receptor 2.

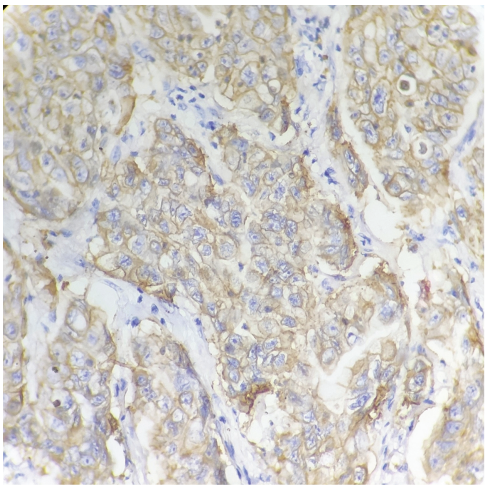

Fig. 3 Moderately differentiated gastric adenocarcinoma showing positive membranous staining for HER2/neu; immunohistochemistry ×40. HER2, human epidermal growth factor receptor 2.

Discussion

A study conducted by Amrani et al[9] and Ahadi et al[10] which was similar to our study also showed that patient's mean age was 59.1 ± 10.9 years, with male preponderance (3:1).

In our study, antrum (48.15%) was the most frequent location followed by pylorus (24.07%) similar to Aditi et al[11] and Mohapatra et al's study.[12]

Intestinal subtype was more common (87.04%) than the diffuse subtype in our study, similar to the study of Shah et al (2019)[13] and Shabbir et al (2018).[14]

Raj et al's[15] study also similarly showed that majority of gastric adenocarcinoma cases were moderately

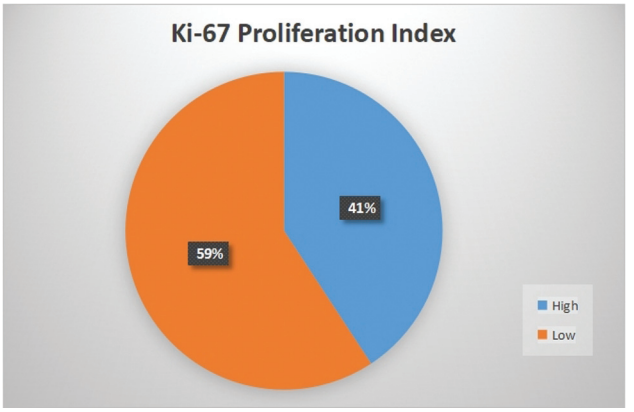

Fig. 4 Pie chart showing distribution of gastric adenocarcinoma cases according to Ki-67 proliferation index.

Table 2 Association between HER2/neu of the patients with different clinicopathological parameters

Clinicopathological parameters	HER2/neu score				p-Value
	0	1+	2+	3+	
Site					
Proximal (GE junction, incisura, fundus, body) ($n = 15$)	7	0	7	1	0.02
Distal (antrum, pylorus) ($n = 39$)	12	6	7	14	
Type					
Intestinal ($n = 47$)	18	5	10	14	0.23
Diffuse ($n = 7$)	1	1	4	1	
Grade					
Well differentiated (grade 1) ($n = 5$)	3	2	0	0	0.09
Moderately differentiated (grade 2) ($n = 34$)	12	2	8	12	
Poorly differentiated (grade 3) ($n = 15$)	4	2	6	3	
Pathological tumor stage					
T1 ($n = 16$)	9	2	5	0	0.06
T2 ($n = 5$)	3	2	0	0	
T3 ($n = 25$)	7	1	7	10	
T4 ($n = 8$)	0	1	2	5	
Pathological nodal stage					
Nx ($n = 16$)	9	2	5	0	0.009
N0 ($n = 6$)	5	1	0	0	
N1 ($n = 6$)	2	1	3	0	
N2 ($n = 16$)	3	1	4	8	
N3 ($n = 10$)	0	1	2	7	

Abbreviations: GE, gastroesophageal; HER2, human epidermal growth factor receptor 2.

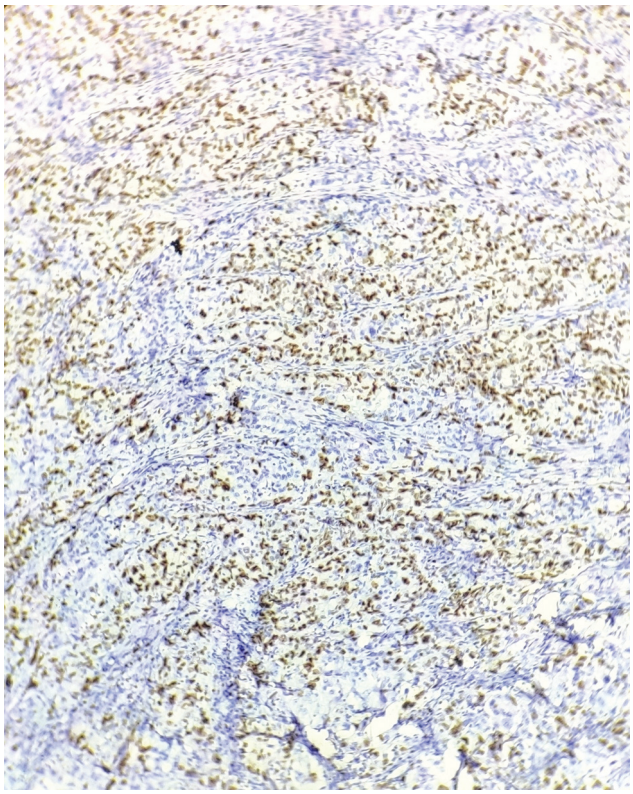

Fig. 5 Poorly differentiated gastric adenocarcinoma showing score 3+ positive nuclear staining for Ki-67 marker; immunohistochemistry ×10.

differentiated (grade 2) (62.96%), followed by poorly differentiated (grade 3) cases (27.78%) and least cases were well differentiated (grade 1) (9.26%).

In our study, most of the gastrectomy patients (65.78%) had stage III disease which was comparable to the research conducted by Aditi et al (2016)[11] and Pramanik et al[16] where out of 17 resection specimens, 10 had (58.8%) stage III disease and majority (71.1%) had stages III and IV disease, respectively.

Among 54 cases, HER2/neu positivity was expressed by 15 (28%) cases which was comparable to the research done by Aditi et al (2016),[11] Ghosh et al (2016),[17] and Pramanik et al (2020).[16]

HER2/neu expression was more prevalent in adenocarcinoma of distal part of stomach, antrum (38%), pylorus (30%) which was found to be statistically significant ($p = 0.02$) and concordant with the findings of the study by Mohapatra et al (2020).[12]

Among 15 HER2/neu positive cases, there were 14 intestinal cases and only one diffuse case which is consistent with the research of Dawa and Zedan (2018),[18] Ghosh et al (2016),[17] and Aditi et al (2016).[11]

Adenocarcinoma with moderate differentiation (grade 2) displayed highest HER2/neu positivity (score 3 +) followed by poor differentiation (grade 3).

Similar findings also were seen in the study by Raj et al (2018)[15] and Shah et al (2019)[13].

Our study showed no significant correlation between positive HER2/neu score and pT stage ($p = 0.06$) as also shown in the research by Ahadi et al (2020)[10] and Pramanik et al (2020).[16]

But a statistically significant correlation was seen between HER2/neu positivity and pathologic T-stage ($p = 0.026$) in the study by El-Gendi et al (2015).[19]

A statistically significant association was noted among HER2/neu positivity and pN stage ($p = 0.009$) similarly as in the research by Mohapatra et al (2020).[12]

In our study, 40.75% of the 54 patients had Ki-67 proliferation index comparable to the research by Ahadi et al (2020) [10] where 33.75% patients had high Ki-67 proliferation index.

Low Ki-67 index tumors were more proximally located, similar to the study findings by Fradique et al.[20].

The Ki-67 index showed significant association with gastric adenocarcinoma site in our study ($p = 0.05$).

The diffuse gastric adenocarcinoma (57% cases) showed high Ki-67 score which was similar with the study by Pramanik et al (2020).[16]

In our study, 53% of poorly differentiated adenocarcinoma (grade 3) showed high Ki-67 proliferative index which was consistent with the study by Lazăr et al (2010).[21]

In our study, 62% of T4 stage gastric adenocarcinoma cases showed high Ki-67 index which was in concordance with the findings done by El-Gendi et al (2015).[19]

In our study, 90% of pN3 gastric adenocarcinoma cases showed high Ki-67 index which had statistical significance ($p = 0.002$), whereas for pN2 and pN3 carcinomas, Lazăr et al's study (2010)[21] noted "high Ki-67 scores in only 39.1 and 25% of cases."

Our study showed 13 out of 15 HER2/neu positive cases with high Ki-67 score, and positive correlation was noted between HER2/neu score and Ki-67 index ($p = 0.007$) (correlation coefficient = 0.4) which is consistent with the study of Ahmed and Al-Tamimi (2018)[22] where "high Ki-67 index was significantly significant, p-value <0.01 in HER2/neu positive cases."

Conclusion

To conclude, our study showed out of 54 cases of gastric adenocarcinoma, there were predominantly males of age 59.1 ± 10.9 years. Most of the gastric adenocarcinoma cases present on antrum and were moderately differentiated, stage III intestinal type.

HER2/neu overexpression was found in 28.0% cases which was statistically significant and correlated with location ($p = 0.02$), pN stage ($p = 0.009$) of the tumor.

High Ki-67 index expression were shown in 40.75% cases of gastric adenocarcinoma. Out of which majority were poorly differentiated, stage III diffuse type. There was a significant correlation between Ki-67 index with location of tumor ($p = 0.05$) and pN stage ($p = 0.002$).

Positive HER2/neu and high Ki-67 index had association with higher pT stage and pN stage evidencing an aggressive behavior.

Our study supports the view that patients with HER2/neu positivity and high Ki-67 index have poorer prognosis.

Positive HER2/neu cases (87%) showed high Ki-67 score and a positive correlation noted between HER2/neu score and Ki-67 score ($p = 0.007$) (correlation coefficient = 0.4).

Table 3 Association between Ki-67 index of the patients with different clinicopathological parameters

Clinicopathological parameters	Ki-67 index		*p*-Value
	Low	High	
Site			
Proximal (GE junction, incisura, fundus, body) ($n=15$)	12	3	0.05
Distal (antrum, pylorus) ($n=39$)	20	19	
Type			
Intestinal ($n=47$)	29	18	0.34
Diffuse ($n=7$)	3	4	
Grade			
Well differentiated (grade 1) ($n=5$)	4	1	0.37
Moderately differentiated (grade 2) ($n=34$)	21	13	
Poorly differentiated (grade 3) ($n=15$)	7	8	
Pathological tumor stage			
T1 ($n=16$)	12	4	0.19
T2 ($n=5$)	4	1	
T3 ($n=25$)	13	12	
T4 ($n=8$)	3	5	
Pathological nodal stage			
Nx ($n=16$)	12	4	0.002
N0 ($n=6$)	6	0	
N1 ($n=6$)	5	1	
N2 ($n=16$)	8	8	
N3 ($n=10$)	1	9	

Abbreviation: GE, gastroesophageal.

Table 4 Correlation between HER2/neu scoring and Ki-67 index in gastric adenocarcinoma

HER2/neu score	Ki-67 +ve	Ki-67 −ve
HER2/neu +ve ($n=15$)	13 (87%)	2 (13%)
HER2/neu −ve ($n=39$)	9 (23%)	30 (27%)
Total ($n=54$)	22 (41%)	32 (59%)

Abbreviation: HER2, human epidermal growth factor receptor 2.

Though unavailability of fluorescence in situ hybridization for equivocal HER2/neu cases and follow-up of all the patients could not be assessed; however, immunohistochemical assessment of the HER2/neu score and Ki-67 score in our study appeared to be useful in detecting prognostic correlation in patients with advanced adenocarcinomas.

Our study can help clinicians to optimize the management of gastric adenocarcinoma patients by choosing candidates for trastuzumab-based therapy and may help improve understanding of the therapy's efficacy in HER2/neu positive gastric cancers.

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Conflict of Interest
None declared.

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