

Evaluation of HER2 Expression and Clinico-pathological Parameters in Gastric Adenocarcinoma: An Observational Study

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Abstract:

Introduction: Gastric cancer remains the third most prevalent cancer-related death worldwide. Over expression of the human epidermal growth factor-2 (HER2) is linked to poor prognosis and therapeutic responsiveness. For patients with advanced gastric and gastroesophageal junction cancer that is HER2-positive, the combination of chemotherapy and the anti-HER2 monoclonal antibody Trastuzumab is now recommended. The present study was designed to assess the HER2 over expression in the cases with gastric adenocarcinoma.

Materials and Methods: Forty-eight cases diagnosed histopathologically as adenocarcinoma of gastroesophageal junction and stomach above 18 years of age. Specimens were undergone histopathological examination and assessed adenocarcinomas according to WHO classification and specimens were allowed for immunohistochemistry.

Results: Tumors at pyloric canal (37.5%) were frequent and tubular adenocarcinoma (58.33%) was frequently observed tumor type. Out of 18 participants undergone immune histochemistry showed grade 0 and 1+ in 3 cases (44%), grade 2+ was observed in 3 cases (17%) and grade 3+ was seen in 7 cases (39%).

Conclusion: HER2 overexpression was found in seven cases. Greater knowledge of HER2 expression in gastric cancer may influence new treatment modalities and improve staging techniques.

Keywords: Human epidermal growth factor receptor (HER2), Trastuzumab, Efficacy, Over expression.

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Introduction

In India, gastric cancer is the second leading cause of cancer-related fatalities, and it ranks fifth worldwide (1, 2). In the early stages of sickness, surgery is the basis of therapy. There is no universally recognised standard first-line regimen, despite the fact that chemotherapy increases survival in patients with advanced stomach cancer. Studies from western countries reported that the median survival was less than 1 year even with continued chemotherapy (3, 4). In this context, focusing on molecular targets can be helpful in the gastric adenocarcinoma.

HER2 over expression is essential for angiogenesis, adhesion, apoptosis, proliferation and has been demonstrated in colorectal cancer, gastric cancer, lung cancer and ovarian cancer. In gastric cancers (5). HER2 positivity in gastric cancer ranges from 4% to 53% (6, 7). Trastuzumab, a type of monoclonal antibody that blocks the action of the HER2/neu receptor, has been found to improve or prolong the survival of patients with advanced gastric cancer in the modern period. Trastuzumab is

the only targeted therapy that has shown to improve survival in gastric cancers thus far (8). According to a recent study, individuals with advanced gastric cancer who received trastuzumab in addition to regular chemotherapy lived longer (by around 2.7 months) than those who only received chemotherapy (9).

However, there are controversial statements about the prognostic value of HER2 over expression in gastric cancer. In this context, the present study was designed to assess the HER2 over expression in the cases with gastric adenocarcinoma.

Materials and Methods

The present prospective observational study was conducted in the department of Pathology at MNR Medical College and Hospital, Sangareddy from December 2021 to January 2023. A total 48 cases diagnosed histo-pathologically as adenocarcinoma of gastroesophageal junction and stomach with age group of above 18 years were included. Cases with other than adenocarcinoma to stomach, metastatic

and non-epithelial tumors, specimen with error in fixation and not willing to participate were excluded. Informed consent was obtained from all the participants and study protocol was approved by institutional ethics committee.

The detailed clinical history, demographic and lifestyle details were collected. The biopsy tissues were fixed in 10% neutral buffered formalin solution. After the tissue processing, sections were cut at 4 microns in thickness and undergone routine histological staining process as per the protocol.

The slides were examined by two experienced pathologists and adenocarcinomas were categorized according to WHO classification (10). A total of 18 cases were selected for immune-histochemistry procedure. The slides were examined by two experienced pathologists for presence of reaction, intensity of staining, localization over membranes as per the College of American pathologists (CAP).

HER2/ neu scoring for gastric cancers:

Table 1: HER2/ neu scoring for gastric cancers

Grade	HER2/neu scoring
Grade 0	No reactivity or membranous reaction in <10% of cells
Grade 1+	Faint /barely perceptible membranous reactivity in >10% of cells. Cells are reactive only in part of their membrane
Grade 2+	Weak to moderate complete or basolateral membranous reactivity in >10% of cells
Grade 3+	Moderate to strong complete or basolateral membranous reactivity in >10% of cells

The collected data was analysed by using SPSS version 23.0. Comparative analysis was performed by using chi-square test. P<0.05 was considered as statistically significant outcome.

Results

Table 2: Clinico-demographic details of the study participants.

Clinicodemographic data	Total no of participants (n=48)	
	Frequency	Percentage
Age (Mean±SD)	57.32±9.74	
Gender		
Male	30	62.5%
Female	18	37.5%
Area of living		
Rural	34	70.83%
Urban	14	29.17%
BMI (Kg/m²)	33.18±8.04	
BMI status		
Obese	32	66.66%
Overweight	12	25%
Normal	04	8.33%
Occupation		
Unemployed	14	29.16%
Skilled	08	16.67%
Unskilled	18	37.5%
Professional	03	6.25%
Daily wage employs	05	10.42%

Table 3: Distribution of cases as per pathological examination.

Pathological examination	Total no of participants (n=48)	
	Frequency	Percentage
Type of sample		
Biopsy	47	97.91%
Post-surgical specimen	01	2.08%
Tumor site		
Gastroesophageal junction	08	16.67%
Cardiac end of stomach	03	6.25%
Body of stomach	04	8.33%
Pyloric antrum	15	31.25%
Pyloric canal	18	37.5%
Histological grading of tumors		

Poor	08	16.67%
Moderate	28	58.33%
Good	12	25%
Type of gastric carcinomas		
Tubular adenocarcinoma	28	58.33%
Adeno-squamous carcinoma	01	2.08%
Papillary adenocarcinoma	01	2.08%
Mucinous adenocarcinoma	07	14.58%
Poorly cohesive carcinoma	11	22.92%
TNM staging		
IB	08	16.67%
IIA	05	10.42%
IIB	08	16.67%
IIIA	10	20.83%
IIIB	08	16.67%
IIIC	09	18.75%

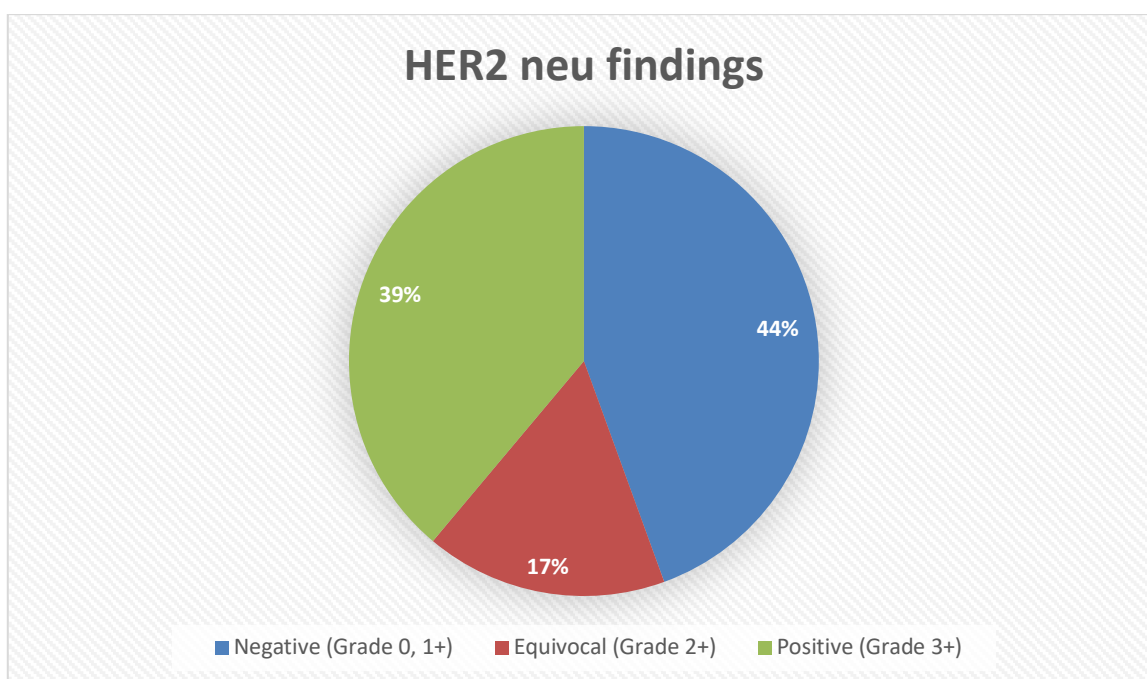


Figure 1: HER2/neu expression in study participants (n=18).

Discussion

The participants' average age was 57.32 years, with more men than women. 29.17% of participants lived in urban areas, compared to 70.83% who lived in rural areas. Participants in the study had an average BMI of 33.18 kg/m².

The majority of individuals (66.66%) were obese. According to occupation, unskilled workers made up the majority of participants (37.5%), followed by unemployed (29.16%) and skilled workers (16.67%) (Table 2). Majority samples received for pathological examination was biopsy specimen type (97.91%) and one was post-surgical specimen (2.08%). Tumors at pyloric canal (37.5%) was common, followed by pyloric antrum (31.25%), gastroesophageal junction (16.67%), body of stomach (8.33%) and cardiac end of stomach

(6.25%). According to the tumor grading, well differentiated tumors were seen in 25% of cases, moderate differentiated tumors in 58.33% and poorly differentiated tumors in 16.67% of cases. Suchitra S et al., found tumors commonly at distal stomach (n=57), followed by proximal stomach (15) and gastro-esophageal junction (06) (11). Alvarado-Cabrero I et al., found majority tumours at proximal part of stomach (86%) and 16.6% had well differentiated, 55.5% of cases had moderately differentiated, 27.7% had poorly differentiated tumours (12). Tubular adenocarcinoma (58.33%) was frequently observed tumor type, followed by poorly cohesive carcinoma (22.92%), mucinous adenocarcinoma (14.58%), adeno-squamous carcinoma (2.08%) and papillary adenocarcinoma (2.08%) (Table 3). Out of 18 participants undergone immune-histochemistry showed grade 0 and 1+ in

3 cases (44%), grade 2+ was observed in 3 cases (17%) and grade 3+ was seen in 7 cases (39%) (graph 1). A study by Suchitra S et al., on HER2 expression in gastric carcinoma by immunohistochemistry found grade 0 in 42.31%, grade 1+ in 14.10%, grade 2+ in 16.67% and grade 3+ in

26.92% (11). Alvarado-Cabrero I et al., found positive to HER2 over expression (3+) in 6 cases (6.45%), grade 2+ was seen in 16 cases (18%), grade 1+ in 10 cases (11%) and 61 cases were negative (64%) (12).

Table 3: Comparison of positive HER2/neu expression between present study and other studies.

Study/Year	Positive HER2/neu expression
Present study (2023)	39%
Suchitra S et al. (2020) ¹¹	26.92%
Alvarado-Cabrero I et al. (2017) ¹²	6.45%
De Carli et al. (2016) ²⁰	6.3%
Jung JE et al. (2013) ¹³	10.5%
Garcia-Ramirez CA et al. (2013) ¹⁵	11.2%
Beltran-Garate B et al. (2010) ¹⁴	9%

In 10%–30% of cases, HER2 overexpression seems to be linked to intestinal type gastric cancer (16, 17). Similar to this, a meta-analysis found that adenocarcinoma with good or moderate differentiation and male gender was associated with HER2 positive expression (18). According to a meta-analysis of the literature, HER2 overexpression is linked to a poor prognosis in gastric cancer. The tumour site, TNM stage, lymph node metastasis, distant metastasis, differentiation grade, and Lauren's categorization were all connected with it (19). The present study has limitations in terms of low sample size and did not assess the quality of life of participants. Further, long term follow-up studies are required with large sample size to assess the quality of life.

Conclusion

The pyloric area was the most often involved site in the current investigation, accounting for 68.75% of instances with moderately differentiated adenocarcinoma, which occurred in 58.33% of cases. In 7 (39%) of the patients, HER2/neu was over expressed. Determining the HER2/neu over expression in gastric adenocarcinoma helps to condense the qualified candidates for targeted therapy with monoclonal antibody against Her2 neu. This protein, which promotes aggressive biological behaviour and greater recurrence rates in HER2 positive tumours, can be targeted and silenced, which may improve survival and prognosis in gastric epithelial malignancies.

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