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# PROGNOSTIC SIGNIFICANCE OF HER2NEU IN GASTRIC & GASTROESOPHAGEAL JUNCTION CARCINOMAS

Oncology

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## ABSTRACT

**Background** Human epidermal growth factor receptor 2 (HER2) has a predictive role in metastatic gastric and Gastroesophageal (GE) junction tumours. The role of HER2 in Early and locally advanced gastric and GE junction tumours is not yet clear. This study aimed to evaluate the HER2 overexpression and its prognostic role in Gastric & GE junction carcinomas. **Materials and methods:** A total of 72 patients with Gastric and GE junction tumours (Stage I to IV) were retrospectively analysed. Patient's Demographic data, tumour histopathological characteristics, survival rates were assessed. The association between HER2 expression and patients clinicopathological features and survival rates were analysed by chi-square test and anova test. **Results:** Median age was 56years (Range:30-85). Majority of the patients in this study were males (M: F-2.7:1). Most common site of involvement was antropylorus i.e., distal stomach (n=35;48.6%). Most cases presented in advanced stage- Stage IV (n=37;51.4%). Her2neu overexpression was detected by IHC in 9 out of 72 (12.5%) patients. There was no significant correlation between HER2 overexpression and age, gender, performance status, tumour site, grade and stage. Out of 9 (12.5%) HER2 +ve patients,6(66.7%) patients were dead and 3(33.3%) patients were alive. On median follow up duration of 6.8 months, Overall Survival rate was 41.7%(n=30) in this study **Conclusion:** HER2 is important prognostic marker in gastric and GE junction Tumours. This study not demonstrated that HER2 as an independent prognostic marker in gastric and GE junction Tumours.

## KEYWORDS

### INTRODUCTION AND BACKGROUND:

Gastric and GE junction tumours are more aggressive form of tumours and common risk factors include dietary habits, sedentary life style and Helicobacter pylori infection prevalence.[1] Gastric cancer is the fifth most common neoplasm worldwide and the fourth leading cause of cancer-related deaths (7.7%).[2] Continuous efforts are kept to identify certain specific biological markers that could help in diagnosing the disease early and also help in improving the targeted therapy. Markers like HER2, E - cadherin, PD L1, Microsatellite instability etc. are currently used to evaluate prognosis of disease.[3,4]HER2 (Human epidermal growth factor receptor 2) is a proto-oncogene encoded by ERBB2 on chromosome 17. It is a transmembrane protein having tyrosine receptor. It regulates signal transduction pathway causing cell growth and differentiation.[5] There is evidence suggested that HER2 is an important biomarker in gastric and gastroesophageal junction tumors.[6] Analysis of HER2 status by immunohistochemistry and in situ hybridization techniques, using different scoring methods or assays, suggested that HER2 is overexpressed in 34% of Gastric tumors.[6,7] The trastuzumab along with chemotherapy for metastatic Gastric cancer & GE junction tumours showed survival benefit in TOGA trial and based on this trial, trastuzumab combined with chemotherapy has been officially approved for first-line treatment of HER2 positive advanced Gastric and GE junction tumour.[8] The role of HER2 expression and its targets in early and locally advanced Gastric and GE junction tumours not yet clearly demonstrated.

This study was conducted to evaluate the HER2 expression in Gastric and GE junction tumours not only in metastatic setting but also in localised disease.

### PATIENTS AND METHODS

### AIMS AND OBJECTIVES:

- To evaluate the HER2 overexpression and its prognostic role in Gastric & Gastroesophageal (GE) junction carcinomas
- To correlate the relationship between HER2µ status and clinicopathological features in Gastric and Gastroesophageal (GE) junction tumor patients.

### METHODOLOGY:

This study is a retrospective observational study conducted in the department of medical oncology, in Government Stanley Hospital, Chennai, for a period of one and half year (from Jan 2021 to June 2022). Approval from the Institutional Ethics Committee was taken for the study. Histologically diagnosed cases of adenocarcinoma by routine H&E of Gastrectomy specimens and endoscopic biopsy from gastric & gastroesophageal junction were included. This study was performed on 72 cases of Gastric and Gastroesophageal (GE) junction carcinomas with stage I to IV (according to TNM staging). Patient's demographic data, tumor histopathological characteristics, survival rates were assessed. The association between HER2/neu and patient's clinicopathological features & survival rates were analysed by using chi-square test and anova test.

### HER2neu Immunohistochemistry

Her2/neu expression was determined by immunohistochemistry (IHC) on formalin fixed paraffin embedded tissue samples (both biopsy and gastrectomy specimen included). IHC results were analyzed by experienced pathologist and score of 0 to 3+ was assigned as per criteria recommended by Hoffman et al as per the membrane staining

in at least 10% of the tumor cells in the HER2neu slides.[7] The slides with score of 0 and 1+ considered as HER2neu negative, score of 2+ as HER2 equivocal while scores of 3+ defined as HER2neu positive. **(Figure.1)**

**Statistical analysis**

Data were analysed by Statistical package for the social sciences (SPSS) 20.0 version. The association between HER2 expression and patients clinicopathological features and survival rates were analysed by chi-square test and anova test.

**RESULTS**:

This study included 72 cases of Gastric and Gastroesophageal (GE) junction carcinomas with stage I to IV (according to TNM staging). Out of 72 samples, 59.7% (n= 43) were biopsy samples obtained through OGD scopy and 40.3% (n=29) samples were gastrectomy specimens. Patient demographic data depicted in **Table.1**. Pathological features depicted in **Table.2**. Median age was 56 years (Range;30-85). Two third (n=53;73.6%) of patients were males in this study and 19 (26.4%) patients were females. Male: female ratio is 2.7:1. Most common symptom was pain abdomen (53%), followed by weight loss (46%) and vomiting (40%). Majority of the patients were smokers and alcoholics (63.9%, n=46). Most common site of involvement was antropylorus i.e., distal stomach (48.6%, n=35). Other sites of involvement were body of stomach (22.2%, n=16,2nd MC), proximal part (15.3%, n=11), GE junction (8.3% (n=6) and GJ stump (5.6%, n=4). The stage wise presentation as follows: stage I - 4.2% (n=3), stage II - 11.8% (n=8), stage III - 33.3%(n=24), stage IV - (51.4% (n=37). Most of the patients presented with metastatic disease and metastatic sites were liver (34.7%), omental &peritoneal (23.6%), nonregional lymph nodes (15.3%). Majority of the patients were treated with chemotherapy in this study. According to scoring system of HER2neu expression by immunohistochemistry in gastric cancer, it was positive (3+) in 9 cases (12.5%), equivocal (2+) in 4 cases (5.6%) and negative (0,1+) in 59 cases (81.9%). Her2 status depicted in **Figure.2** There was no significant correlation between HER2 overexpression and age of patient, Gender, performance status of individual, tumour site, tumour grade and tumour stage **(Table.3).** Out of HER2 +ve patients, 66.7% (n=6) patients were dead and 33.3% (n=3) patients were alive. No statistically significant correlation was seen between HER2neu expression and treatment outcome or overall survival (**Figure.3**). on median follow up of 6.8 months, overall survival rate was 41.7% (n=30) in this study.

**Table.1(Demographic data)**

| Clinical parameters | Frequency |
|---|---|
| Age | |
| Median age (range) | 56 years (36-85) |
| >60 years | 28(38.9%) |
| <60 years | 44(61.1%) |
| Gender, n (%) | |
| Men | 53(73.6%) |
| Women | 19(26.4%) |
| Smokers/alcoholics | |
| Present | 46(63.9%) |
| Absent | 26(36.1%) |
| Primary tumour location | |
| Antropylorus | 35(48.6%) |
| Body | 16(22.2%) |
| Proximal stomach | 11(15.3%) |
| GE Junction tumors | 6(8.3%) |
| GJ site | 4(5.6%) |
| Initial cancer staging according to AJCC 8th edition, n (%) | |
| Stage I | 3(4.2%) |
| Stage II | 8(11.1%) |
| Stage III | 24(33.3%) |
| Stage IV | 37(51.4%) |
| Metastatic site | |
| Omental+peritoneal | 17(23.6%) |
| Liver mets | 25(34.7%) |
| Non regional nodal mets | 11(15.3%) |
| Survival | |
| Alive | 30(41.7%) |
| Dead | 42(58.3%) |

**Table.2(pathological features)**

| Pathological features | Frequency (n,%) |
|---|---|
| Grade | |
| Moderate | 35(48.6%) |
| Poor,signet ring cell &mucinous | 37(51.4%) |
| Lauren classification | |
| Intestinal | 37(51.4%) |
| Diffuse | 35(48.6%) |
| HER2neu Status | |
| 0,1+ | 59(81.9%) |
| 2+ | 4(5.6%) |
| 3+ | 9(12.5%) |
| Gastrectomy(n=29) | |
| Total | 12(41.37%) |
| Subtotal | 12(41.37%) |
| Distal | 4(13.7%) |
| Esophagogastrectomy | 1(3.4%) |

**Table.3 (Correlation of her2neu in study population)**

| Patient characteristics | Total No.of patients(n=72) | HER2neu status | | | P value |
|---|---|---|---|---|---|
| | | 0,1+ | 2+ | 3+ | |
| **Age (years)** | | | | | |
| Median (range) | 56(30-85) | | | | |
| > 60 years | 28(38.9%) | 21(35.6%) | 2(50%) | 5(55.6%) | |
| <60 years | 44(61.1%) | 38(64.4%) | 2(50%) | 4(44.4%) | 0.465 |
| **Gender, n (%)** | | | | | |
| Men | 53(73.6%) | 43(69.5%) | 4(100%) | 8(88.9%) | |
| Women | 19(26.4%) | 18(30.5%) | 0 | 1(11.1%) | 0.22 |
| **Primary tumour location** | | | | | |
| Antropylorus | 35(48.6%) | 30(50.8%) | 2(50%) | 3(33.3%) | |
| Body | 16(22.2%) | 13(22%) | 0 | 3(33.3%) | |
| Proximal stomach | 11(15.3%) | 9(15.3%) | 1(25%) | 1(11.1%) | 0.803 |
| GJ site | 4(5.6%) | 3(5.1%) | 0 | 1(11.1%) | |
| GE Junction tumors | 6(8.3%) | 4(6.8%) | 1(25%) | 1(11%) | |
| **Grade** | | | | | |
| Moderate | 35(48.6%) | 28(47.5%) | 2(50%) | 5(55.6%) | 0.901 |
| Poor, Signet ring cell & Mucinous | 37(51.4%) | 31(52.5%) | 2(50%) | 4(44.4%) | |
| **Lauren Classification** | | | | | |
| Intestinal | 37(51.6%) | 31(52.5%) | 2(50%) | 5(55.6%) | 0.901 |
| Diffuse | 35(48.4%) | 28(47.5%) | 2(50%) | 4(44.4%) | |
| No gastrectomy(n=43) | 43(59.7%) | 36(61.0%) | 2(50%) | 5(55.6%) | 0.342 |
| Gastrectomy(n=29) | 29(40.3%) | 23(39.0%) | 2(50%) | 4(44.7%) | |
| **Initial cancer staging according to AJCC 8th edition, n (%)** | | | | | |
| Stage I | 3(4.2%) | 3(5.1%) | 0 | 0 | |
| Stage II | 8(11.1%) | 7(11.9%) | 0 | 1(11.1%) | 0.916 |
| Stage III | 24(33.3%) | 18(30.5%) | 2(50%) | 4(44.4%) | |
| Stage IV | 37(51.4%) | 31(52.5%) | 2(50%) | 4(44.4%) | |
| **Gastrectomy(n=29)** | | | | | |
| Total | 12(41.3%) | 10(83.3%) | 1(8.3%) | 1(8.3%) | |
| Subtotal | 12(41.3% | 9(75%) | 1(8.3%) | 2(16.3%) | |
| Distal | 4(13.7%) | 4(100%) | 0 | 0 | 0.823 |
| Oesophago gastrectomy | 1(3.4%) | 0 | 0 | 1(100%) | |

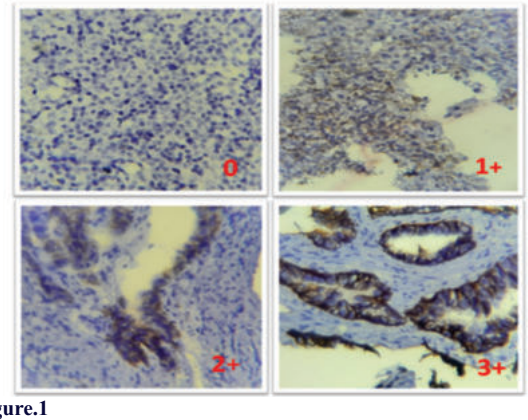


**Figure.1**

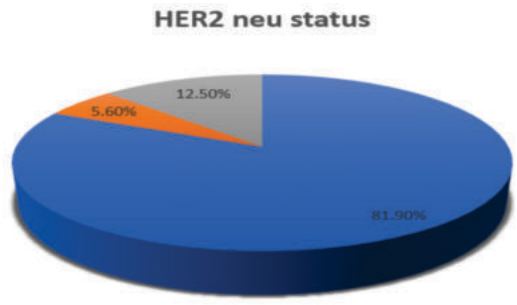


**Figure.2**

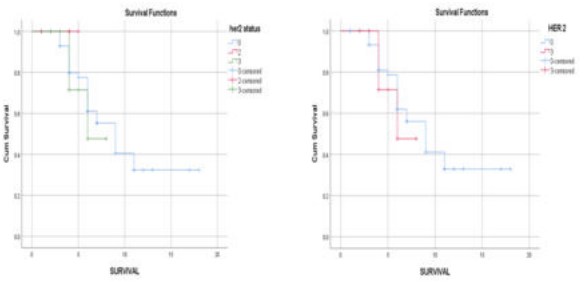


**Figure.3**

## DISCUSSION:

Gastric cancer is prevalent all over the world, with over 70% of the cases occurring in developing countries.[1] Majority of these tumours may present as advanced disease with distant metastasis, warranting identification of novel biomarkers to understand the behavior of the disease. HER2neu overexpression results in receptors transmitting excessive cell proliferative signals to the nucleus; thereby directly leading to tumorigenesis and clinical aggressiveness of the tumour as well as associated with poor prognosis.[9] Trastuzumab is monoclonal antibody targeting HER2 protein and approved for advanced Gastric cancer and GE junction tumours based on TOGA trial.[8] out of 72 samples, 9 (12.5%) had HER2neu 3+ positivity in this study which was comparable with one study which showed a similar percentage.[10]There was wide variation in HER2neu overexpression ranging from 4 – 53% as mentioned in systematic review of 49 studies comprising of 11337 patients.[11]This variability of HER2 neu positivity attributable to intratumoral heterogeneity of HER2neu, different selection of primary antibodies ,either monoclonal or polyclonal, different scoring systems employed and the skills of pathologist.Men are affected two times more than the females in both western and eastern world, the results were almost in similar with our study of M:F ratio of 2.7:1.Our study found that the highest number of gastric cancer were in the antropylorus (48.6%) followed by body (22.3%), proximal stomach (15.3%) and GE junction(8.3%) which is similar to the findings of our study conducted by Cherian et al.[12]

In the current study, there was no significant correlation between HER2 overexpression and age (p =0.465) which is concordance with previous study done by two studies Marx et al[13] and Park et al.[14]There was also no significant relationship between overexpression of HER2 and gender (p=0. which is similar with previous studies done by Ali Basi et al.[15] distal (33.8%) and body (33.8%) of gastric tumours showed similar HER2 overexpression, which showed discordance with a study done by Gravalos et al[6] who found higher HER2 positivity in Gastro oesophageal junction compared to the stomach. Although there was no statistical correlation between the anatomical site and HER2 overexpression (p>0.05), similar observations were also found by Sekaran et al.[9]There was also no significant relationship between HER2 overexpression and grading of the tumour in this study.

The limitations of the present study were small sample size, various analytical variables such as intratumor heterogeneity, variation in scoring methods may also have contributed to a statistically non-significant relationship and the HER2 equivocal cases (score 2+) were not subjected to fluorescent in situ hybridization (FISH) because of financial constraints.

## CONCLUSION:

In this study, increased frequency of HER-2/Neu overexpressed cases was belonged to male preponderance, moderately differentiated grade, and T3 level of infiltration, with stage III being the most common, but no statistically significant association present. Identifying the expression of HER-2/Neu in gastric carcinoma can help to identify patients with reduced survival and to identify eligible candidates for targeted therapy. Although HER2 has emerged as an important therapeutic target in gastric cancer, its role as a prognostic marker in this tumor is still controversial. Indeed, some studies demonstrated that HER2 overexpression is a poor prognostic factor, while others showed that it may be favorable or irrelevant for prognosis but our study could not demonstrate the role of HER2neu as an independent prognostic marker in Gastric & Gastroesophageal (GE) junction carcinomas. A larger sample size and follow-up for a longer period might shed more light on the role of the above markers in Gastric and GE junction tumors.

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## Conflict of interest

No conflict of interest

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