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IMMUNOHISTOCHEMICAL EXPRESSION OF HER2/neu IN GASTRIC AND GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA

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ABSTRACT

INTRODUCTION: Gastric cancer is one of the prominent reasons of cancer death worldwide and in India. The majority of individuals are diagnosed at a late stage. Various chemotherapy regimens have improved overall survival slightly. The HER2 protein, which is overexpressed in many stomach tumours, is a novel therapeutic target. Trastuzumab, a monoclonal antibody that targets HER2, has been found to enhance overall survival in advanced gastric cancer.**AIMS AND OBJECTIVES** :(1) To examine the frequency of expression of HER2 in gastric and GEJadenocarcinoma.(2) To find its correlation with clinicopathological parameters. **MATERIALS AND METHODS:** The study included 80 instances of stomach adenocarcinomas (56 biopsies and 24 gastrectomies) detected in the department of Pathology at Mallareddy Medical College for Women in Hyderabad over the previous two years (November 2019 to November 2021). A study of the slides confirmed the diagnosis, and IHC with anti-HER2 antibodies was performed using the Dako Real Envision Detection system, and scoring was done using the Hoffmann et al scoring system. **RESULTS:** The 80 cases were mostly male (60%) and averaged 65 years old.Males (34%) had HER2 positive. GEJ had 41.66% HER2 positive. Intestinal type 18 (30.5%) has HER2. The diffuse type was HER2-negative. Moderately differentiated tumours were HER2 positive (37.5% percent). Poorly differentiated tumours were HER2negative..**CONCLUSION:** HER2 positivity was found in 27.5% of cases. A significant

correlation of HER2 positivity was found with male gender, intestinal type and moderately differentiated carcinomas.

KEYWORDS: *HER2/ neu; gastric adenocarcinoma; ImmunoHisto Chemistry (IHC).*

INTRODUCTION

Gastric cancer is the fifth most prevalent type of cancer and the third leading cause of cancerrelated death worldwide. After lung and colorectal cancer, GC is the third-leading cause of cancerrelated death. It is also the fifth most common cancer diagnosed [1,2]. Oesophageal adenocarcinoma is associated with Barrett's oesophagus and dysplasia, whereas gastric adenocarcinoma is associated with Helicobacter pylori infection, atrophic gastritis, intestinal metaplasia, and dysplasia. [3].The mainstay of treatment, surgical resection, can cure individuals with early-stage cancer. Despite new treatment methods, such as preoperative chemotherapy or adjuvant chemoradiation, the survival rate of patients with advanced resectable stomach or gastroesophageal junction (GEJ) tumours remains dismal[4].Patients with advanced stomach cancer treated with palliative chemotherapy continue to have a dismal survival rate. New therapeutics are desperately required. A better understanding of cancer's molecular underpinnings has aided in the development of rationally designed molecular targeted therapeutics.The HER2 protein (HER2/neu) is a 185-kDa transmembrane tyrosine kinase (TK) receptor that belongs to the EGFR family. A gene on chromosome 17q21 codes for HER2. HER2 operates as an oncogene in carcinomas, primarily because high-level amplification of the gene causes protein overexpression in the cellular membrane and, as a result, the acquisition of beneficial qualities for a malignant cell [5].

Recent research suggests that HER2 plays a role in the development of several forms of human cancer. HER2 overexpression and/or amplification have been found in 10%–34% of invasive breast tumours and have been linked to poor response to chemotherapy and endocrine therapy[6].Overexpression and/or amplification of HER2 has also been seen in the colon,9 bladders,10 ovarian, endometrial, lung, uterine cervix, head and neck, esophageal,16 and gastric carcinomas.Trastuzumab (HerceptinTM) is a monoclonal antibody that specifically targets the HER2 protein by binding the receptor's extracellular region. Trastuzumab improves survival

rates in HER2-positive breast cancer patients with both primary and metastatic disease. 17-18 A worldwide randomised controlled study was conducted to investigate the efficacy of trastuzumab in combination with chemotherapy in HER2 positive advanced gastric cancer (TOGA trial). Following the EU approval of trastuzumab in HER2 positive advanced gastric cancer, HER2 evaluation is now required in all advanced gastric malignancies.[7]

HERs are comprised of four structurally similar components that sit on the cell surface: HER1 (also known as EGFR), HER2 (ErbB2/ neu), HER3 (ErbB3), and HER4 (ErbB4) [1]. These receptors can dimerize (form ten different homo- and heterodimers), leading to complex biological signalling pathways such as the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular-related kinase 1/2 (MAPK/ERK1/2) pathways [2,3]. Cell proliferation, survival, migration, angiogenesis (the formation of new blood vessels), and metastasis are all results of these signalling cascades. HER2 (molecular mass 185 kDa)-mediated heterodimerization is a stable and strong signal transduction mechanism among all HER dimers [4]. HER2 plays an important function in every step of cell development in healthy cells, and its mutation and/or overexpression can trigger cancer and metastasis. Mutations in neu (the rodent HER2 gene) are required for cancer in rats, but HER2 appears to have tumorigenic potential in humans through overexpression of wildtype HER2[5].

There is HER2 gene amplification and overexpression in human malignancies such as breast, gastric, ovarian, prostate, and lung, making it a promising target for cancer therapy (Fig. 1a) [6]. HER2targeted agents, such as monoclonal antibodies (mAbs; e.g., trastuzumab and pertuzumab), smallmolecule tyrosine kinase inhibitors (TKIs; e.g., lapatinib and neratinib), antibody-drug conjugates (ADCs; e.g., trastuzumab–emtansine), and biosimilars (Fig. 1b) [7]. Despite significant advancements in the discovery and application of HER2-targeted therapy, intrinsic and acquired resistance remain significant clinical problems [8,9]. Numerous factors, such as overexpression of downstream effectors, decreased binding of therapeutic drugs to HER2, modification of tyrosine kinase receptors, and/or activation of alternative pathways, have been identified in studies to understand the causes of resistance [8,10]. HER2 receptor overexpression in cancer cells, on the other hand, has prompted drug delivery researchers to target this receptor using a ligand-targeted strategy (active targeting).

Although there is no natural ligand for the HER2 receptor, different HER2-targeted delivery

systems have been developed that make use of artificial ligands such as antibodies and their fragments, affibody, peptides, and aptamers. We describe diverse HER2-targeting methods and approaches developed for HER2-targeted delivery systems in this study.

AIMS AND OBJECTIVES

1. To examine the frequency of expression of HER2 in primary gastric andgastro-esophageal junction (GEJ) adenocarcinoma.
2. To find its correlation with clinicopathological parameters like age, sex, location of the tumour, histological grade, Laurens classification, p TNM stagingand H.pylori status.

MATERIALS AND METHODS SAMPLING METHOD

Purposive sampling

INCLUSION CRITERIA

All histopathologically diagnosed adenocarcinoma of the stomach and gastroesophageal junction.

EXCLUSION CRITERIA

All biopsy specimens who are inadequate / not properly fixed

SOURCE OF DATA

A study was conducted on 24 gastrectomies and 56 biopsy specimens which were diagnosed as adenocarcinoma in the Department of Pathology, Malla Reddy Medical College forWomen , Hyderabad over 2 years (from November 2019 to November 2021).

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METHODS OF COLLECTION OF DATA

Relevant clinical details were collected wherever possible. All gastrectomy/gastric biopsy specimens were fixed in formalin. Tissue was processed, embedded in paraffin, and sections were taken and stained with routine H & E. Histopathological diagnosis was made and adenocarcinomas were classified as intestinal/diffuse according to Lauren classification. Giemsa staining was performed for H pylori status. In the case of retrospective cases, paraffin blocks were retrieved, 4 µ sections were taken,and H&E sections were made to confirm the diagnosis. Immunohistochemistry was done usingaHercep test kit, Dako, Denmark (Dako REALM En Vision Detection TM system,Peroxidase /DAB,+ K5007).

STATISTICAL METHODS

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean $\pm$SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at a 5 % level of significance.

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value:$0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

Study design: An observational comparative clinical study

RESULTS AND OBSERVATION

1. **Age:** Age of patients ranged from 31-90 years. The majority of patients belonged to theage group of 61-70 years. Mean age of the patients was 66.5 years (Table No. 1)

Table No:1 Age distribution of patients studied (n=80)

Age in years	Gastric biopsies	Gastrectomies	Total
31-40	3(5.35%)	0 (0%)	3 (3.75%)
41-50	4 (7.14%)	3 (12.5%)	7 (8.75%)
51-60	11 (19.64%)	3 (12.5%)	14 (17.5%)
61-70	15 (26.78%)	10 (41.66%)	25(31.25%)
71-80	17 (30.35%)	5 (20.83%)	22 (27.5%)
81-90	6 (10.71%)	3(12.5%)	9 (11.25%)
Total	56 (100%)	24 (100%)	80 (100%)
Mean ± SD	65.43±11.72	64.21 ±10.51	65.25±12.45

P=0.773, Not significant, Studentt test

2.Sex: The majority of patients were males (62.5%) (Table No.1).

Table No:2, Gender distribution of patients studied

Gender	Gastric biopsies	Gastrectomies	Total
Female	22 (39.28%)	8(33.33%)	30(37.5%)
Male	34(60.7%)	16(66.67%)	50 (62.5 %)
Total	56 (100%)	24 (100%)	80(100%)

P=0.153, Not significant, Chi-Square test

3.Tumor Location: The majority of tumors were located in the antrum followed by GEJ,(n=80)(Table -3)

Table No:3. Location of tumor studied (n=80)

Locations	Gastric biopsies	Gastrectomies	Total
Antrum	50 (89.2%)	14 (58.3%)	64(80%)
Body	5(8.92%)	0(0%)	5(5%)
GEJ	1(1.78%)	10(41.6%)	11(13.75%)
Total	56(100%)	24 (100%)	80(100%)

P=0.529, Not significant, Fisher Exact test

4.Lauren Classification: Majority of tumours were of the intestinal type(72.5%)and the rest were of the diffuse type(27.5%).

Table No:4, Lauren classification of patients studied (n=80)

Laurens Clasification	Gastric biopsies	Gastrectomies	Total
Diffuse	12 (21.4 %)	11 (45.8%)	23 (27.5%)
Intestinal	44 (78.5%)	13(54.1%)	57 (72.5 %)
Total	56 (100%)	24(100%)	80(100%)

P=0.053+, Significant, Chi-Square test

5. Grade of tumor: Majority of tumors were moderately differentiated (58.75%) followed by poorly differentiated (23.75%). 17.5% of tumors were of well differentiated type.(Table No.11,Graph No.5).

Table No: 5, Grade distribution of tumors studied (n=80)

Grade	Gastric biopsies	Gastrectomies	Total
Poorly	10(17.85%)	9(37.5%)	19(23.75%)
Moderately	39 (69.42%)	8(33.33%)	47(58.75%)
Well differentiated	7(12.6%)	7(29.16%)	14 (17.5%)
Total	56 (100%)	24 (100%)	80(100%)

P=0.013* Significant, Chi-Square test

6.HER2 scores of patients studied: The majority of patients were of score 0 (60.0 %), and 27.5 % of patients showed HER2 positivity (score 3+). HER2 positivity was more in gastric biopsies 20 (35.7 %) as opposed to 2(8.33%) in Gastrectomies, 5 % of cases were equivocal (score 2+) (TableNo.6)

Table No:6, HER2 scores of patients studied (n=80)

HER2	Gastric Biopsies	Gastroctomies	Total
0	28(50 %)	20 (83.3%)	48 (60 %)
1+	4(7.14 %)	2(8.33%)	6 (7.5 %)
2 +	4 (7.14 %)	0 (0 %)	4(5.0 %)
3+	20 (35.7 %)	2 (8.33%)	22(27.5 %)
Total	56(100%)	24(100%)	80(100%)

P=0.272, Not significant, Fisher Exact test

7.HER2 correlation with age of patients :HER2 positivity was found more in the age group of

31-40 years (2 out of 3 cases studied were of score 3+ and one case was equivocal). (Table No. 7).

Table No: 7, Correlation of age distribution of patients studied with HER2 (n=80)

Age in years	Number of total Patients	HER2			
		0	1+	2+	3+
31-40	3	0(0%)	0(0%)	1(25%)	2(66.6%)
41-50	7	4(66.66%)	0(0%)	2(33.34%)	1(14.2%)
51-60	14	8(57.1%)	3(21.4%)	0(0%)	3(21.4%)
61-70	25	13(52%)	2(6.89%)	3(10.34%)	7(28%)
71- 80	22	14(63.6%) 1	(5.0 %)	1(5.0 %)	6 (30%)
81-90	9	7(77.7%)	0(0%)	0(0%)	2(28.57%)
Total	80	46(57.5%)	6(7.5%)	7(8.75%)	21(26.2%)

P=0.253, Not significant , Fisher Exact test

8.HER2 correlation with gender of patients: HER2 positivity was found more in males , 32%.

Table No:8 Correlation of gender with HER2 (n=80)

Gender	Total number of patients	HER2			
		0	1+	2+	3+
Female	30	15(50%)	5(16.66%)	4(13.33%)	6(20%)
Male	50	32(64%)	0(0%)	2(4%)	16(32%)
Total	80	47(58.7%)	5(6.25%)	6(12%)	22 (27.5%)

P=0.006**, significant, Fisher Exact test

9. Correlation of HER2 with tumor location: HER2 positivity was more in GEJ at 41.66%

Table No:9, Correlation of HER2 with tumour location (n=80)

Locations	Total	HER2			
		0	1+	2+	3+
Gastric	56	34 (60.7 %)	8 (14.2%)	3(5.35%)	11 (19.6%)
GEJ	24	11(45.8%)	0(0%)	3(12.5%)	10 (41.66%)
Total	80	45 (56.25%)	8 (10%)	6(7.5%)	21 (26.25%)

P=0.265, Not significant, Fisher Exact test

10. **Correlation of HER2 with Lauren classification :** HER2 was observed in intestinal type 18 (30.5 %). None of the diffuse type showed HER2 positivity

Table No:10 Correlation of HER2 with Lauren Classification (n=80).

Lauren's Classification	Total number of patients	HER2			
		0	1+	2+	3+
Diffuse	23	16 (69.5%)	0 (0%)	7(30.4%)	0(0%)
Intestinal	57	30 (52.6 %)	6 (10.5 %)	3 (6.77 %)	18 (30.50%)
Total	80	46 (57.5%)	6 (7.5%)	10 (12.5%)	18 (22.5%)

P=0.054+, significant, Fisher Exact test

11. **HER2 correlation with tumor grade:** HER2 positivity was observed in moderately differentiated tumors (37.2percent), followed by well differentiated tumors (23.0 percent). HER2 positivity was not seen in any of the poorly differentiated tumors. (No.11 Table)

Table No:11, Correlation of grade with HER2 (n=80)

Grade	Total number of Patients	HER 2 Score			
		0	1+	2+	3+
Poorly	19	15(78.9%)	0 (0%)	4 (21.05 %)	0 (0%)
Moderately	47	21(44.6%)	5 (10.6 %)	2 (4.25%)	19 (40.4 %)
Well Differentiated	14	9 (64.2%)	0 (0%)	2 (14.2%)	3 (21.4%)
Total	80	45 (56.2%)	5 (6.25%)	10 (12.5 %)	22 (27.5%)

P=0.042*, Significant, Fisher Exact test
P=0.042*, Significant, Fisher Exact test

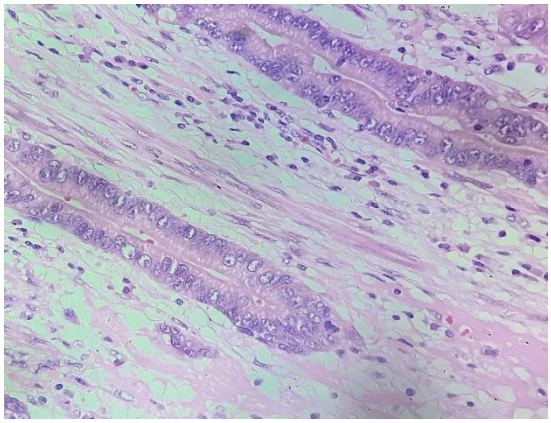

Fig.1 Well differentiated carcinoma,40x ,H&E

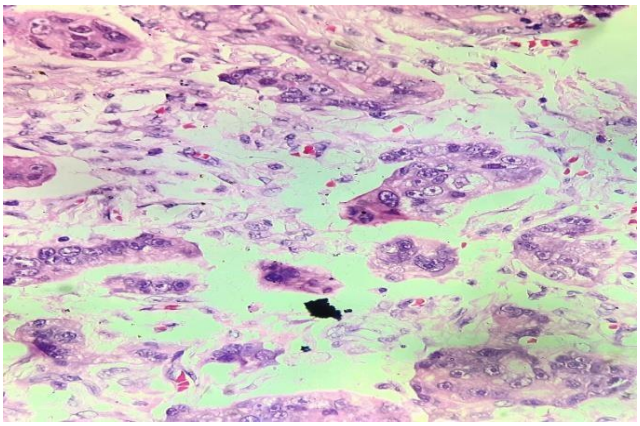

fig.2 Moderately differentiated adenocarcinoma,40x H&E

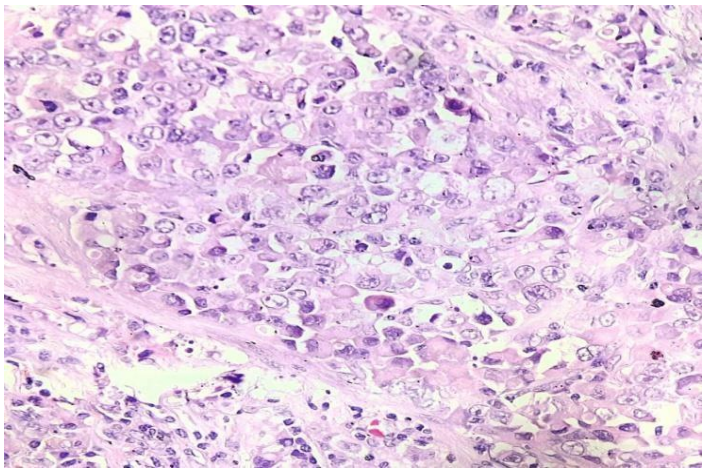

Fig.3 Poorly differentiated adenocarcinoma ,40x,H&E

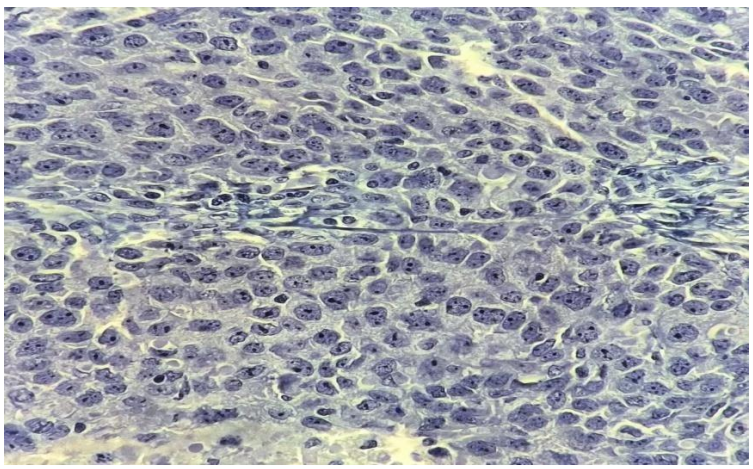

Fig.4.IHC Her2/neu Negative in poorly differentiated adenocarcinoma

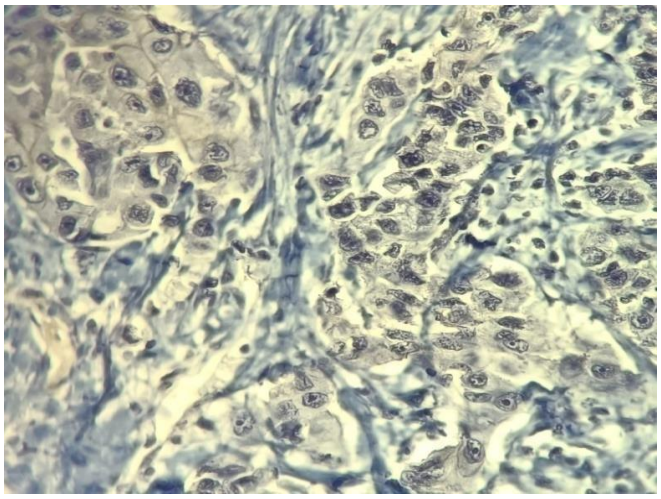

Fig.5.IHC Her2/neu +1 staining Moderately differentiated adenocarcinoma

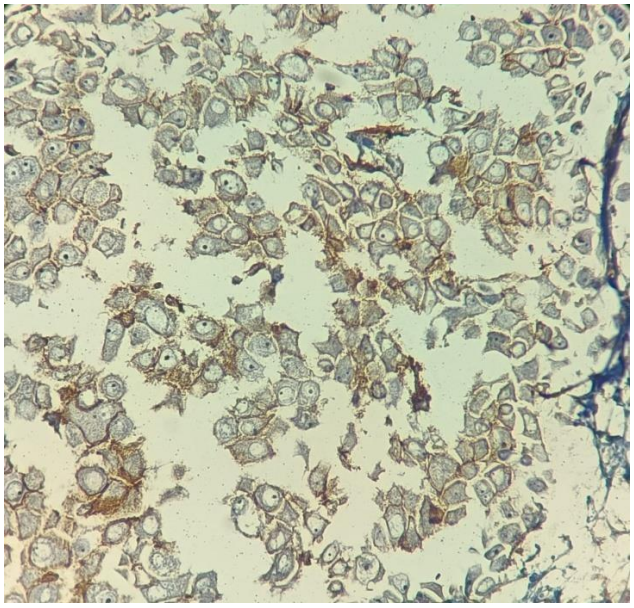

Fig.6. IHC,Her2/neu +2 Staining Moderately differentiated adenocarcinoma

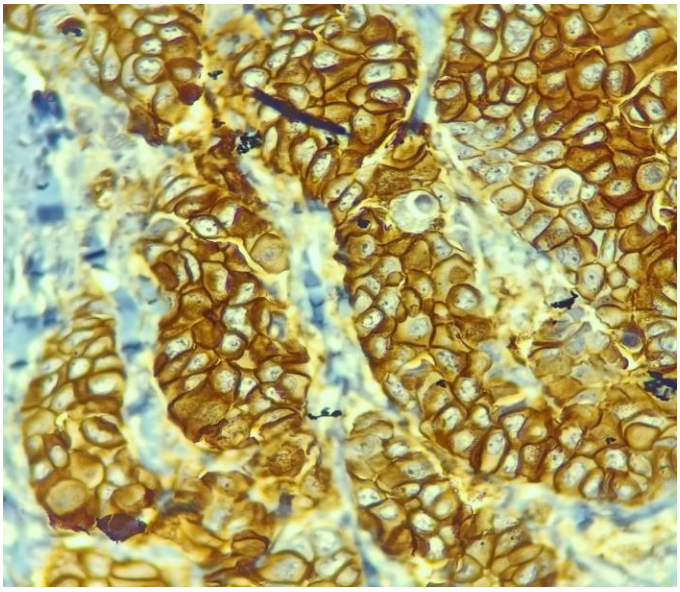

Fig.7.IHC,Her2/neu +3 staining well differentiated adenocarcinoma

DISCUSSION

The incidence of primary gastric and gastroesophageal junction (GEJ) adenocarcinomas is increasing, and these tumours are predicted to be the third and fifth leading causes of cancer deaths worldwide, respectively. Many individuals present with advanced stage disease, and the prognosis for patients with these tumours remains poor. Improvements in the treatment of stomach cancer, especially combination chemotherapy, have resulted in better overall survival compared to single-agent chemotherapy alone.Over a two-year period, we assessed HER2 positivity in 24 gastrectomies and 56 biopsy specimens reported as adenocarcinomas in the department of pathology at Mallareddy Medical College for Women (from November 2019-November 2021).

This same Khalifa et al. [11] investigation discovered 67.6 percent of the 74 patients were men. These patients' mean age at diagnosis was 62 years (range: 34 to 76 years).In the study, Shah et al., [12]discovered that the majority of instances were in the seventh decade, with the youngest patient being 29 years old and the oldest being 72 years old. There were 32 (64%) males and 18 (36% females), for a M: F ratio of 1.7:1. The most prevalent complaint was abdominal pain (76 percent).

Li et al. [13] discovered type I+II, type III, and type IV in advanced GC to be 28.1 percent, 58.9 percent, and 13.0 percent, respectively whereas Huang et al. [14]discovered 21.8 percent, 68.3 percent, and 8.32 percent. Type I+II, III, and IV advanced GC patients were 52.4 percent, 40.6 percent, and 7.0 percent in the current study, respectively. It could be attributed to differences in

GC clinicopathological features between locations and Borrmann kinds.

The majority of patients (31.25%) were between the ages of 61 and 70, confirming that stomach carcinomas are more common in older people. The average age of the patients was 65 years old. There was a male predominance (62.5 percent). This was nearly identical to a research done at Tata Memorial Hospital in Mumbai, which found a mean age of 55 years and a male predominance of 71%.

The majority of gastrectomies (62.5%) were ulcerative (Borrmann type III), 18.75% were fungating (Borrmann type II), 12.5 percent were polypoid (Borrmann type I), and 6.25 percent were infiltrative (Borrmann type IV). In our analysis, the majority of patients (87.5%) had pathological stage T2, with only one instance (6.25%) having stage T3 or T4. Only three cases (18.75 percent) had N 0 pathologic N stages, while the rest had N 1 pathologic N stages (81.25 percent). In none of the cases was distant metastases documented.

Arco et al [15] study Bormann classified lesions as polypoid (18.7 percent), fungating (39%), ulcerated (32.4 percent), and flat/infiltrative (32.4 percent) in his study (type IV, 10 percent). The majority of tumours were found in the antrum or body of the stomach (54.4 percent). (36.2%) 67.5 percent of GC patients had lymph node metastases at the time of diagnosis. (14.3 percent), stage II(35.7 percent), and stage III (50 percent). GC was intestinal (58%), diffuse (32.7%), and mixed (3 percent). (9.3%).

In our study, 70 percent of the tumours were of primary gastric origin, while 30 percent were of GEJ origin. In 89.2 percent of stomach biopsies and 58.3 percent of gastrectomies, malignancies were found in the antrum. A comparable proportion was discovered in a study undertaken by Miomir, Aleksandar, and Neboja, who discovered that 73.34 percent of tumours were situated in the antrum.

[8] This contrasts with the pattern observed in Western countries, where the incidence of distal gastric cancers has decreased while proximal gastric carcinomas has increased. This distal to proximal shift appears to correspond with the recent increase in the incidence of Barrett's oesophagus. The decline in H.pylori infection and associated atrophic gastritis may explain the decrease in incidence of mid and distal gastric cancer [16].

In our analysis, the majority of stomach tumours (72.5% percent) were of the intestinal type, with the remainder being diffuse (27.5%). Ling Shan,[17] Jiaming Ying, and Ning Lu[10] discovered intestinal type tumours 44.4 percent of the time, diffuse type 38.6 percent of the time, and mixed type 17 percent of the time in their study on HER2 expression in gastric cancer. 10 In the study conducted by Daniela Lazar et al.18, intestinal type (62.3 percent) predominated, followed by

diffuse type (27.9 percent) and mixed carcinoma (9.8 percent).

The preponderance of gastric carcinomas (58.7 %) were moderately differentiated, followed by poorly differentiated (23.7 %) and well differentiated (17.5%) . The majority of the moderately differentiated instances were from gastric biopsies, although there was an equal prevalence of poorly differentiated and moderately differentiated tumours in gastrectomies (37.5 percent each). In contrast, Daniela Lazar et al [18] found poorly differentiated carcinomas in the majority of cases in their investigation (63.9 percent).

HER2 positive was found in 27.5% of patients in our study. HER2 overexpression was more common in stomach biopsies (35.7%), whereas only 8.33 % of resected specimens were positive. The higher HER2 positivity rates in biopsies may be attributed to the larger sample size of biopsies (n=44) compared to gastrectomy (n=16). Another factor, as indicated by Ruschoff et al [19], could be improved fixation of biopsy specimens. The majority of cases (60%) had HER2 score 0, a score of 2+ was detected in 5% of cases (equivocal), and 7.5% of patients had a score of 1.

In a study by Ling Jianming et al[10], HER2 overexpression was found in 9.8 percent of 1463 patients, while 14.4 percent and 75.8 percent were ambiguous and negative, respectively. This disparity in results with our study could be related to the fact that their investigation used rabbit monoclonal primary antibodies, whereas we used polyclonal antibodies, which target more epitopes[20]. Our findings are in accordance with those ofGravalos et al,[21] and the TOGA trial, which found HER2 positive of 22.1 percent overall and 10.4 percent in resected samples.

We sought to relate HER2-neu expression to age, gender, and pTNM stage. Similarly to Ling Shan et al.10, we found no statistically significant connection between HER 2 positive and age, gender, or pTNM stage. However, in the study, we had three instances in the age category of 31-40 years, two (66.6 %) of which had a score of 3+, indicating HER 2 positive, and one case had a score of 2+. (equivocal). Both of these individuals had moderately differentiated adenocarinomas but were HER 2 positive. This is an important observation because we believe that if anti-HER 2 medication provides a survival benefit or a significant disease-free interval, it would be extremely beneficial to younger age groups who are at their most productive. Despite previous studies, we discovered a statistically significant connection between HER2 and male gender (32% percent, $p = 0.006$). This could be linked to the higher proportion of male patients in our study, as stomach adenocarcinomas are more common in men, most likely due to risk factors

such as smoking and alcohol.

In our analysis, 41.66 % of GEJ tumours had HER2 positive, compared to 19.6% of primary gastric cancers. This is consistent with the majority of reports.Gravalos et al,[21]noticed a greater rate of HER2 positive in GEJ malignancies than in stomach tumours in 231 cases investigated (24 percent Vs 12 percent). These findings were corroborated in the TOGA research,

in which HER2 positive was detected in 32% and 18% of the 3807 individuals investigated, respectively, in GEJ and gastric cancer.

In our analysis, there was a statistically significant connection between HER2 positive and colon cancer type (32.7 percent, p = 0.054). HER2 was not found in any of the diffuse instances. Despite the fact that a review of the literature suggests a lower percentage of diffuse type gastric tumours with Her2 over expression, no study has found a complete absence of HER2 expression. We relate this to our study's lesser number of diffuse type gastric cancers, 11/80, whereas others who demonstrated HER 2 expression in diffuse type gastric cancers in their respective studies had a larger number of diffuse type gastric cancers. Is regional variation a factor in diffuse HER2 expression? An exclusive investigation involving a big number of diffuse type malignancies could provide an answer to the aforementioned notion. Because the epidemiology of stomach cancer differs across India (i.e., North and South India), a regional comparison is also recommended.

Dai et al.[22] studied HER2 positivity in Asian patients with advanced GC and discovered that type III-IV tumours had higher HER2 positivity than type I–II tumours. The majority of HER2positive GC exhibited differentiated histology. Furthermore, Borrmann types with intestinal or low-grade histology were more likely to be HERCEPTEST positive.

Sakai et al.[23] were the first to describe HER2 overexpression in stomach cancer in 1986. In gastric tumours, HER2 gene expression varies but is usually between 5% and 30% [23].

In Terashima et al., [24] study, 75 cases (9%) tested positive for EGFR and 113 (13.6%) tested positive for HER2. For EGFR, HER2, and other factors, the groups were well-balanced (Table1).

The prevalence of EGFR and HER2 positive was higher in differentiated tumours than in undifferentiated malignancies (EGFR, 58.7 percent , P 0.001; HER2, 75.2 percent , P 0.001 [2test]). HER2 positivity was associated with male gender, older age, and lower tumour stage, but not with EGFR positivity (Supplementary Table S1). 18 cases (2.2 percent) tested positive for both EGFR and HER2, 57 (6.9 percent) tested positive for EGFR alone, and 95 (11.5 percent)

tested positive for HER2.

In our study, there was a significant connection between HER2 positive and tumour grade (p = 0.042). In the 80 patients analysed, 37.2 percent of the HER2 positive was found in the moderately differentiated form, with 23 percent in the well-differentiated type. HER2 was not found in any of the weakly differentiated tumours. Our findings are consistent with those of Shan et al[27], Chao,[27] who found greater frequencies of HER2 positive in well and moderately differentiated carcinomas than poorly differentiated carcinomas.Kim et al. [25] investigated HER2 expression in 595 Korean gastric cancer patients and discovered it to be an independent predictor of differentiated, resectable gastric cancer.We are also of the conclusion that 58.7% of our study group was comprised of moderately differentiated carcinomas, and thus the frequency of HER 2 positive was significantly elevated. Another reason could be that because 56/80 of the cases were biopsy specimens and the grading was done on a small tumour sample, a tendency to grade tumours to the in-between moderate grade could be a factor. In a multicenter trial, this can most likely be addressed by evaluating an approximately equal number of cases in each category (well, moderate, and poorly differentiated) for HER2 expression.AccordingtoSelcukbiriciket al ., [26] the outcomes of the Selcukbiricik et al study, metastatic lymph nodes may be HER-2 positive, and this disease may have a poor prognosis in H. pylori-positive people.There was a statistically significant difference in HER2 between the HP positive and negative groups in the Chao et al[27] trial (P0.01). HP infection was significantly linked to the HER2 index and exhibited a positive relationship (P=0.014). Previous researchbyJerroldet al [28] has found no link between HER2 positivity and H pylori status. In H. pylori-associated gastric malignancies, the course begins with H. pylori inducing intestinal metaplasia, then dysplasia, and finally malignant transformation[28]. We always sample the tumour component during malignancy diagnosis, which no longer hosts the H pylori, which may be contributing to the negative H pylori status. In the event of biopsies, we are only looking at the tumorous portion, therefore the likelihood of finding H pylori is slim. In the

case of gastrectomies, we could have been able to determine the presence or lack of H pylori association if we had analysed an area away from the tumour. We were unable to analyse the mucosa away from the tumorous location because the bulk of gastrectomies was performed retrospectively.Similar to most previous investigations, no association was detected between HER2 positive and pathological stage.

Conclusion

The most effective way to identify patients for Herceptin treatment requires an accurate assessment of HER2 expression in the patients' gastric cancer tissue. This is both an important and useful step in the process. Similar to the majority of studies conducted in India and the rest of the world, our research discovered that stomach tumours overexpress HER2 at a rate of 27.5 percent. Overexpression of HER2 was found to have a statistically significant link with male gender, intestinal-type malignancies, and moderately differentiated gastric tumours. These are the primary patient populations that would be candidates for targeted therapy with Herceptin. There is a need for additional research to investigate the role that HER2 plays as an independent prognostic factor.

It is necessary to investigate the diffuse kind of gastric cancer that does not express HER2 to verify the existence of any geographic variation (ie, North Vs South India).In the patients in our study who expressed HER2, their ages ranged from 31 to 40. Even though herceptin is licenced for advanced gastric and GEJ cancers, it still needs to be investigated whether or if it may be used in adjuvant or neoadjuvant scenarios for cancer cells that are in their early stages.

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Conflict of Interest

None

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