



## Role of Her 2 Neu in Gastric Carcinoma-3 Year Study in a Medical College Hospital

### KEYWORDS

Her 2/neu, EGFR 2, Trastuzumab, Gastric cancer

### Varra Lakshmi

Asst.prof.,Dept.of pathology,Kurnool medical college,Kurnool

### Venkata rangareddy valluru\*

Asso.prof.of gastroenterology,Kurnool medical college,Kurnool \*Corresponding Author

### Madhavi J

MD,Sr.resident,Dept.of pathology,Gandhi medical college,Hederabad

### Neelima valluru

prognostic significance, Kurnool medical college,Kurnool

### Introduction:

Gastric cancer is the 5<sup>th</sup> most common cancer world wide as per incidence and 3<sup>rd</sup> most common cause of mortality of all cancers in both sexes. It constitutes 8.5% of all cancers with 73.5% of all gastric cancers occurring in Asian countries. The crude and age standardised rate are 12.2 and 11.4/1,00,000 population world wide and in India it is 5.0 and 6.1/ 1,00,000 population respectively.<sup>1</sup> Gastric adenocarcinoma has a dismal prognosis with a median survival of few months in advanced cases.<sup>2</sup> There is a constant search for newer modalities of treatment in gastric cancer to improve the survival. A recent phase III trial (ToGA trial) in which trastuzumab with chemotherapy was given in Her 2 positive cancers, there was improvement in overall survival in locally advanced, recurrent and metastatic gastric cancer when compared to chemotherapy alone.<sup>2</sup> Her 2 /neu is a transmembranetyrosinekinase receptor which is a member of the growth factor receptor family and targeted therapy by monoclonal antibody was found effective in neoadjuvant, adjuvant and palliative setting in breast cancer in various randomized controlled trials. As in breast cancer wherein 30% of cases have Her 2/neu positivity the incidence of Her2 positivity in gastric cancer varied in different studies based on stage of cancer, location of tumor and geographic area where it was studied.<sup>3</sup> The techniques used are fluorescence in situ hybridization(FISH), silver in situ hybridization (SISH), Chemogenin situ hybridization(CISH) and immunohistochemistry(IHC). Her 2 overexpression and or amplification was 7-34 % in advanced cases (most of the studies 15-25%)<sup>3</sup> and 10.4%-13.6% in early stage malignancies.

Here in this study we had prospectively tested for Her 2 receptor positivity in biopsies and gastrectomy specimens in a medical college to know the rate of positivity in our population. This study may lead to further studies to evaluate the benefit of testing in our region so that targeted therapy can be added to treat these patients.

### Materials and methods:

We performed a prospective study for a period of three years from July 2010 to July 2013 in the Department of Pathology in kurnool medical college hospital. During the study period an analysis of gastric biopsies and gastrectomy specimens diagnosed as gastric carcinoma was done. All the sections from gastric biopsies and gastrectomy specimens were submitted for routine processing, cutting and staining with haematoxylin and eosin stain.

All biopsies were reviewed with regard to histological sub-type, grade and stage and classified according to WHO classification of gastric cancer. Those patients with gastric adenocarcinoma were included in the study and other pathologies like GIST, lymphoma and metastases were excluded in the study. These specimens were subjected to IHC by using A0485 (DAKO, Carpinteria, CA, in the HercepTest), a rabbit polyclonal antihuman antibody directed at an epitope on the cytoplasmic portion of the receptor or CB11 mouse monoclonal antibody (MAb) (Novocastra, Newcastle upon Tyne, England), which also detects an epitope on the internal portion of the receptor. Patients with staining of 2+ or 3+ were considered as positive and 0 or 1+ considered as negative for Her2. Results were studied and compared with the results of other studies.

### Results:

During the study period we had received 98 specimens of which 62 were biopsies and 24 were gastrectomy specimens. Of these 98 specimens received 12 patients had benign conditions which were excluded from the study and 86 had gastric malignancies. In the 86 cases of gastric malignancies 78 had gastric adenocarcinoma, 3 had GIST, 2 cases of lymphoma and 3 cases of metastatic cancers. Hence the study was performed in 78 patients with proven gastric adenocarcinoma. The general clinicopathological characteristics were described in Table.1. The number of male patients were more than female. The type of specimens were gastric biopsy in 57 patients and gastrectomy specimens in 21 patients. On endoscopic examination the ulcerative lesion was the most common lesion found followed by fungating type as per Bormanns classification (Fig.1).

Most of the tumors were located at pylorus- antrum (40 patients) and the number of patients involving fundus, cardia and GEJ were 6. Eleven patients had diffuse involvement of entire stomach like linitis plastica. The histopathological examination revealed Lauren's intestinal variant as most common pathology in 66 patients. Routine-histopathological examination by haematoxylin and eosin staining showed tubular adenocarcinomas as the most common type (57 patients) and the signet ring cell adenocarcinoma was found in 12 patients. Most of them had poorly differentiated adenocarcinoma (29 patients) (Fig. 2). In patients who had underwent gastrectomy, 7 were stage I, 7 were stage II, 6 were stage III and one patient had stage IV dis-

ease.

Immunohistochemistry for Her2/neu was performed and we had 28 patients who had a score of 3+ (Fig.3). Of these 25 patients had intestinal variant and 3 had diffuse adenocarcinoma. Her2 was 0 in 20 patients, 1+ in 22 patients and 2+ in 8 patients (Table .2). Intestinal variant of gastric cancer had more Her2 positivity (37.8%) compared to diffuse variant (2.5%). Well differentiated adenocarcinomas had more Her2 positivity compared to patients with poorly differentiated carcinoma (60% vs 20.6%) (Table.3). In relation to site of location of tumor .....

#### Discussion:

Her2 is human epidermal growth factor receptor which plays an important role cell proliferation and suppression of apoptosis. Its detected in many tissues like breast<sup>4</sup>, gastrointestinal tract, kidney and heart]. Amplification and overexpression of Her 2 is proven to be a poor prognostic factor in breast cancer and it plays an important role in tumorigenesis and spread of tumor. Recent National Comprehensive Cancer Network (NCCN) guidelines recommend trastuzumab in recurrent, advanced and metastatic gastric cancer based on the evidence of ToGA study which has shown overall survival benefit in these group of patients<sup>5</sup>.

In our series of 78 cases of gastric carcinoma-66 cases (84.6%) were of Intestinal type of Adenocarcinoma and 12 cases (15.3%) are Diffuse type. According to Gulia et al (2013) it is 68% in intestinal type and 10% in diffuse type, Afzal et al (2006) it is 60% in intestinal type and 8% in diffuse type, Dickens et al it is 75% in intestinal type and 10% in diffuse type. In our study Ulcerative growth was the most common endoscopic presentation comprising of 67.44% (43.5%) of cases, followed by polypoid and infiltrative variants. According to Antoniolli et al and Dickens et al ulcerative growth is more common 67% and 82% respectively.

HER2 positivity in well differentiated adenocarcinoma is 60%- 15 cases out of 25 cases of Intestinal Adenocarcinoma in our study as compared to 41% and 18.4% according to Raziee et al and Deng et al respectively. HER2 positivity is more in well differentiated Adenocarcinoma which is statistically significant, compared to 29.1%, in moderately differentiated Adenocarcinoma and 20.6% in poorly differentiated Adenocarcinoma. In our present study according to Lauren classification, HER2 positivity in Intestinal type of Adenocarcinoma is 37.8% and Diffuse type is 2.5%, p Value is 0.001 which is statistically significant. According to Tanner it is 21.5% in intestinal and 2% in diffuse, according to Gravalos it is 16% in intestinal and 7% in diffuse, according to Lordick, 34% positivity in intestinal and 6% positivity in diffuse and Matsubara et al 32.5% in intestinal and 6% in diffuse type. Depending on the location of tumor, studies have shown higher Her2+ in patients with Gastroesophageal junction tumors compared to tumors of body and distal growths. Our study is a small study with 6 patients with proximal cancers. As etiology and pathology of the GEJ tumors are different from distal tumors they tend to have higher Her2+ positivity. Similarly there are studies which have shown difference in Her2 positivity rate depending on the specimen used for testing and the technique used for testing. The difference in Her 2 positivity on the specimen used may be due to the difference in criteria used to classify tumors as Her 2+ in gastrectomy and biopsy specimens. There was also difference in the positivity rate based on type of testing- insitu

hybridization (ISH) vs IHC.

Unlike Breast cancer where Her 2+ is associated with poor prognosis, the evidence in gastric cancer is associated with controversy. There are few studies which have shown poor survival in patients with Her 2+ in gastric cancer and there are similarly studies which have shown good prognosis in Her 2+ patients and studies which had shown no association<sup>6</sup>. Her 2+ have been used as guidance for treatment in patients with advanced gastric cancer as personalized treatment and has shown survival benefit. Recently newer drugs like Laptinib and Pertuxumab have been attempted for treatment which act through the same pathway. Further studies required to know the role of Her 2+ as a prognostic marker and as guide for adjuvant treatment.

#### Conclusion:

This is one of the first studies from the sub-continent where Her 2 was tested for gastric cancer. The Her 2+ was found more common than in other studies. We had Her 2+ more common in intestinal variant, well differentiated tumors and ulcerative variant. Further studies to determine its role for planning treatment in our country are required.

**Table 1: Clinicopathological characteristics of Patients:**

Characteristics	Number of patients (Total N = 78)
Age	
Mean	54.02 years
Range	27-85 years
Sex	
Male	54
Female	24
Type of specimen	
Gastric biopsy	57
Gastrectomy	21
Endoscopic appearance of tumor (Borman's classification)	
Polypoidal	18
Fungating	20
Ulcerative	34
Infiltrative	06
Location of tumor	
Pyloro-antrum	40
Body	13
Lesser curvature	08
Fundus and cardia	06
Entire stomach	11
Lauren's classification of tumor	
Intestinal	66
Diffuse	12

Histopathological Examination (WHO classification)	
Papillary adenocarcinoma	03
Tubular adenocarcinoma	57
Mucinous adenocarcinoma	06
Signet-ring cell carcinoma	12
Grade of tumor	
Well differentiated (I)	25
Moderately differentiated(II)	24
Poorly differentiated (III)	29
Stage of tumor (Post Gastrectomy specimens)	
Stage I	7
Stage II	7
Stage III	6
Stage IV	1

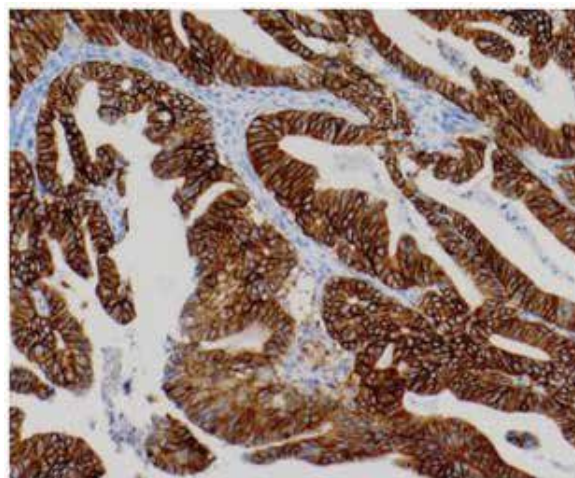


Figure 2. IHC showing HER2 expression

Table : 2: Her2 positivity according to Lauren classification

Lauren Classification	Her 2 Score	No. of Cases(78)	% Positive
Intestinal	3+	25(66)	37.87%
Diffuse	3+	03(12)	2.50%
Total	3+	28(78)	35.89%

Table 3: Correlation of Her2 positivity with conventional grading

Conventional grading	No of Her2 positive cases	% Positive
Well differentiated carcinoma	15(25)	60.0%
Moderately differentiated carcinoma	07(24)	29.1%
Poorly differentiated carcinoma	06(29)	20.6%

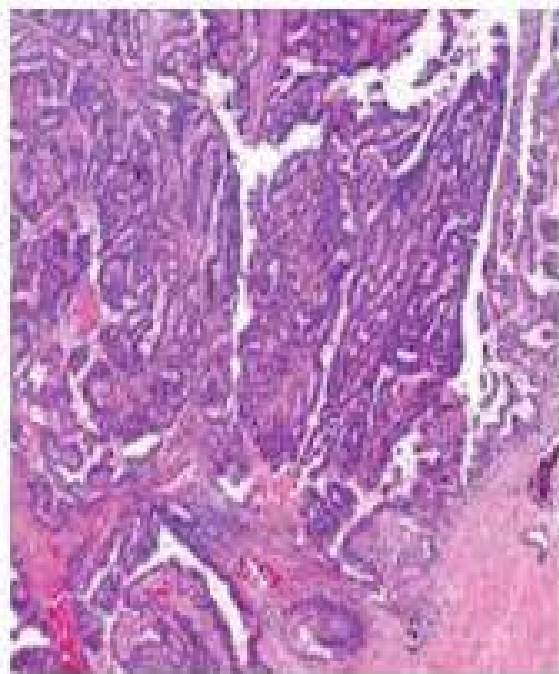


Figure 1: Poorly differentiated carcinoma

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