Original Article

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A Study of Epidermal Growth Factor Receptor 2 (HER2/neu) Expression in Endoscopic Biopsies and Gastrectomy Specimens of Gastric Adenocarcinomas

Pathology Section

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ABSTRACT

Introduction: Gastric carcinoma (GC) is the fourth most commonly diagnosed cancer and has poor prognosis, since most of the patients present with advanced disease and the therapeutic options available are very few. The rate of HER2/neu gene amplification and protein overexpression by Fluorescent in situ Hybridization (FISH) and Immunohistochemistry (IHC) respectively range from 5%-53%. Treatment with HER2 inhibitor, trastuzumab, has been reported to increase overall survival in HER2-positive, inoperable, locally advanced and metastatic gastric carcinoma.

Aim: To study the expression of HER2 in Gastric/Gastro-Esophageal Junction (GEJ) adenocarcinomas and to assess the relationship of HER2 expression with clinico-pathological parameters.

Materials and Methods: Sixty cases of gastric/ gastro esophageal junction adenocarcinomas were evaluated for HER2/neu expression by immunohistochemistry (IHC) using anti-c-erbB-2. Thirty cases each of endoscopic gastric biopsies and gastrectomy specimens were randomly selected for evaluation. The results including various histopathological features and IHC expression of HER2 were compared.

Results: Out of 30 gastrectomy cases, primary gastric cancers were 29 (96.6%) and one (3.3%) was primary GEJ adenocarcinoma. Thirteen (43.3%) were intestinal type and seventeen (56.6%) were diffuse type. HER2 overexpression (3+) was seen in three (10%) cases, one(3.33%) was equivocal (2+) and the rest were negative (score 0). HER2 positivity was associated with intestinal type adenocarcinoma ($p<0.049$). Three (10%) of 30 gastric biopsies were HER2/neu positive.

Conclusion: Overexpression of HER2 may play a crucial role in the management of gastric adenocarcinoma, and therefore testing for HER2 by IHC has clear advantages, as it is easy, cost effective and feasible.

Keywords: Fluorescent in situ hybridization (FISH), Gastric cancers, Immunohistochemistry (IHC)

INTRODUCTION

Gastric carcinoma (GC) is common with 70% of the cases occurring in developing countries. It is the second most common cause of cancer-related deaths [1]. Adenocarcinomas are the commonest type accounting to 95% of GCs.The biological and etiological characteristics are different in intestinal Gastric Carcinoma (IGC) and Diffuse Gastric Carcinoma (DGC) type [2]. Gastric resection is generally curative for early stage GC. However, for patients with advanced resectable disease, the clinical benefit with perioperative adjuvant therapy varies [3].

Human epidermal growth factor receptor 2 (HER2), a membrane receptor which can be therapeutically targeted is over-expressed in several cancers, which include cancer of breast, lung, salivary gland, ovary, colon, prostate and pancreas [3-5]. In gastric cancers, the rate of HER2 gene amplification by fluorescent in-situ hybridization (FISH) and protein overexpression by immunohistochemistry (IHC) vary widely from 5% - 53% [3]. Therefore, trastuzumab which targets HER2 could be considered as a new option for patients with HER2-positive advanced gastric and Gastro-esophageal junction cancers [6].

The objective of this study was to know the prevalence of HER2 expression in gastric/gastroesophageal junction adenocarcinomas and to evaluate the relationship between HER2 expression with various clinico-pathological parameters in a tertiary care centre in Southern India.

MATERIALS AND METHODS

This was an observational study undertaken at a tertiary hospital in Mysore District of South India. A total of 60 patients with primary gastric or gastroesophageal adenocarcinomas, with 30 cases each of endoscopic gastric biopsies and gastrectomies were studied prospectively for a period of five years between 2010 and 2014. Ethical clearance was obtained from the institutional ethical committee.

All endoscopic gastric biopsies and gastrectomy specimens histologically diagnosed as gastric adenocarcinoma were included in the study. Histological types other than adenocarcinoma were excluded from the study. The following patient data were reviewed: age, gender, type of surgery, tumor location, tumor size, macroscopic appearance, histological type, tumor grade, depth of invasion, number of lymph nodes resected and the number of lymph nodes with metastasis.

Tissue specimens were fixed in 10% of neutral buffered formalin for 24-48 hours and embedded in paraffin. Deparaffinized sections were stained with hematoxylin and eosin. Tumors were classified according to Lauren's histological classification into intestinal and diffuse type [7]. Tumor(T), Node(N) and Metastasis(M) (TNM) cancer staging system of the American Joint Committee of Cancer (AJCC), seventh edition, was followed for staging of the gastrectomy specimens [8].

Immunohistochemical Staining- Paraffin blocks best representing the tumor in each patient were selected after reviewing the hematoxylin and eosin (H&E) slides. IHC for HER2 was done on 4 µm thick paraffin embedded wax sections on poly-l lysine coated slides. Antigen retrieval was done in tri sodium citrate buffer at pH-6. Monoclonal antibody HER2 (Biogenex, mouse monoclonal antibody: CB11, AM134-5ME) was used for HER2 antigen detection by one step Horseradish peroxidase (HRP) polymer method. A section from HER2 positive breast carcinoma was used as positive control, whereas sections treated with tris-buffer solution instead of the primary antibody was used as negative control.

The scoring was done using the scoring scheme proposed by Hofmann et al.,[9] [Table/Fig-1].

Score	Surgical Specimen-Staining Pattern	Biopsy Specimen-Staining Pattern	HER2 Over-expression Assessment
0	No reactivity or membranous reactivity in <10% of tumor cells	No reactivity or no membranous reactivity in any tumor cell	Negative
1+	Faint/barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane	Tumor cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained	Negative
2+	Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell cluster with a strong complete, basolateral,or lateral membranous reactivity irrespective of percentage of tumor cells stained	Positive

[Table/Fig-1]: Human epidermal growth factor receptor 2 (HER2) scoring criteria for gastric cancer.

STATISTICAL ANALYSIS

Descriptive statistics was applied and the chi-square test was used to analyze association between HER2 status, clinico-pathological parameters, endoscopic biopsies and gastrectomy specimens. The p-value of <0.05 was considered significant. The SSPS software, version 20.0 was used for data analysis.

RESULTS

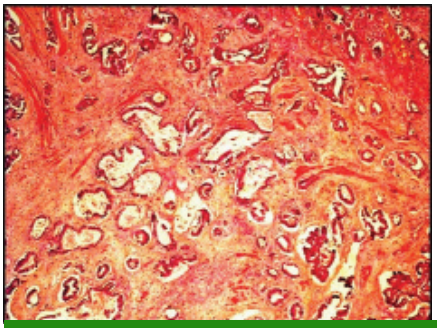
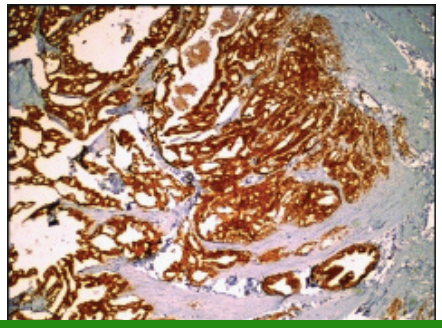
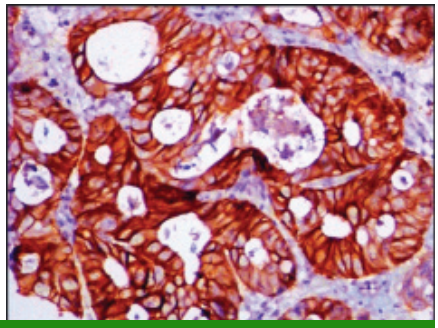
Out of the 60 cases, majority were in the age group of 41 to 50 and 61 to 70 years. The youngest patient in this study was 19-year-old and the oldest was 80 years, with a mean age of 55.95 ±13.62 years. Thirty nine (65%) were males and 21(35%) were females with a male to female ratio of 1.8:1. In terms of tumor location, 56 (93.3%) tumors were gastric and four (6.6%) were located in the gastroesophageal junction.

Out of 30 gastrectomy specimens, grossly 12 (40%) were ulcerative, 11 (36.6%) were ulceroproliferative, six (20%) were diffusely infiltrative and one (3.3%) was polypoidal. Based on the tumor size, the tumors were divided into three categories. Only one case (3.3%) was <2cm in the greatest dimension, 16 cases (53.3%) were 2-5 cm in size and 13 (43.3%) cases were >5cm in size. Histologically, 17 cases (56.7%) were of diffuse type and 13 cases (43.3%) were intestinal type by Lauren's classification. Twenty cases (66.7%) were poorly differentiated, seven cases (23.3%) were moderately differentiated and the rest three cases (10%) were well differentiated.

Out of 60 cases of gastric adenocarcinomas, HER2 overexpression was seen in seven (11.6%) cases. Among the 30 gastric biopsies, 4 cases displayed HER2 positivity. Of the 30 gastrectomy specimens, three cases (10%) showed overexpression of HER2 (score 3+), one (3.3%) was equivocal (score 2+) and the rest 26 cases (86.6%) were negative (score 0). Three of thirteen (23%) of the intestinal type showed HER2 overexpression. The positive staining cases were gastric in location [Tables/Fig-2-4].

HER2 Expression and Clinicopathological Correlation

The frequency of HER2 expression and association of HER2 expression with clinicopathological features were studied and the following results were obtained. HER2 positivity was seen in three (23%) out of 13 cases of intestinal type of gastric adenocarcinoma. There was significant association between HER2 expression and intestinal histological type (p-value=0.049). None of the diffuse type of gastric

[Table/Fig-2]: Moderately differentiated adenocarcinoma with tumor infiltrating the muscularis propria (H&E, ×40). **[Table/Fig-3]:** IHC of HER2 score 3+ showing strong membranous staining involving >10% of the tumor (HER2, ×100). **[Table/Fig-4]:** IHC of HER2 showing strong complete, basolateral membranous staining of neoplastic glands in gastric biopsy (HER2, ×400). (Images from left to right)

adenocarcinomas showed HER2 expression. There was no significant association of HER2 expression with age, gender, tumor location, tumor size, gross appearance, tumor grade, depth of invasion and nodal status [Table/Fig-5].

DISCUSSION

Gastric carcinoma represents a major health problem and the geographic distribution is quite characteristic with highest incidence documented in Eastern Asia, South America and Eastern Europe. In India, gastric cancer is the fifth most common cancer among males and seventh most common cancer among females [10].

The understanding of molecular biology leading to gastric cancer has identified prognostic factors and predictive markers of response [11]. Efforts have been made towards identifying and validating novel biomarkers, although histopathology is reliable and less expensive [2]. Trastuzumab has been approved for HER2 positive GC in Europe and study of HER2 expression is now mandatory. IHC is used as primary test for overexpression of HER2 and IHC 2+ cases are followed by Fluorescence in-situ Hybridization (FISH) for gene amplification [12].

Studies have found an association between HER2 overexpression and advanced age, which support the hypothesis that gastric cancer of early onset has a different profile of molecular expression than disease of late onset [13-15]. However, no such association was seen in the present study and in various other studies [16,17]. Kataoke et al., have recorded frequent expression of HER2 in males [13]. Most of the patients were men but we did not find any positive correlation between gender and HER2 expression similar to other studies [12,15,18].

Majority of the cancers (93.3%) were located in the gastric region and there was no positive association with HER2 positivity in relation to the site of tumor which was in accordance with other studies [15,16,19]. One South Indian study has shown 45.5% HER2 positivity in GEJ tumours versus 22.4% in primary gastric tumours [10]. In one of the largest Chinese studies of 1463 cases and in the ToGA trial, high HER2 positivity was noted in GEJ adenocarcinoma.This finding was regardless of sample size and has been explained by the occurrence of different ratio of intestinal:diffuse cancer [17,20,21]. In the present study, this finding could be attributed to the limited sample size and tumor location in GE Junction being only 3.3% and the high ratio of diffuse:intestinal cancer. There was no significant association of HER2 expression with the tumor size, though it is one of the established clinical prognostic factors [16].

A high correlation between HER2 expression and intestinal histologic type has been reported in many studies. In the ToGA trial, the reported HER2 positivity was 34% in intestinal type, 6% in diffuse type and 20% in mixed type [22]. In the present study, 23% of intestinal type expressed HER2 revealing a significant association between HER2 expression and intestinal type histology which supports the concept that there are substantial molecular differences between different histologic tumor types, and also likely develop through different pathways [12,18,23]. The association of HER2 oncogene with a specific histologic tumor type indicates the preferential expression of certain characteristics. However, not all tumors of the intestinal type overexpress HER2, and therefore this cannot be the only factor involved. The reasons for this association appear more complex [18].

A positive association between HER2 positivity and intestinal-type cancers was identified in many studies including the present study [10,23]. In the ToGA trial, where 3280 patients were tested for HER2 expression, 810 patients (22.1%) were found to be positive for HER2/neu expression and countries with higher ratios of intestinal: diffuse/ mixed cancer had increased HER2-positivity rates [22].

There was no statistical association with grading of the tumors, majority of them being poorly differentiated as reported in other studies [15,16,19]. But some authors have found a statistically significant association between well/moderately differentiated tumors and HER2 positivity [10,17].

Pathologic Feature	Overall	HER2 Over expression	HER2 Equivocal	HER2 Negative	p value
	N=30	03 (10.0%)	01 (3.3%)	26 (86.6%)	
Age at Diagnosis					
<60 years	22 (73.3%)	03 (13.6%)	01 (4.5%)	18 (81.8%)	0.432
≥60 years	08 (26.7%)	0	0	08 (100%)	
Sex					
Male	19 (63.3%)	0	01 (5.2%)	18 (94.7%)	0.056
Female	11 (36.7%)	03 (27.7%)	0	08(72.7%)	
Tumor Location					
GC	29 (96.7%)	03 (10.3%)	01 (3.4%)	25 (86.2%)	0.924
GEJ	01 (3.3%)	0	0	01 (100%)	
Tumor Size					
<2cm	01 (3.3%)	0	0	01 (100%)	0.867
2-5cm	16 (53.3%)	02 (12.5%)	01 (6.2%)	13 (81.2%)	
>5cm	13 (43.3%)	01 (7.6%)	0	12 (92.3%)	
Tumor Gross					
Ulcerative	12 (40.0%)	01 (8.3%)	01 (8.33%)	10 (83.3%)	0.789
Ulcero-proliferative	11 (36.7%)	02 (18.1%)	0	09 (81.8%)	
Diffusely infiltrative	06 (20.0%)	0	0	06 (100%)	
Polypoidal	01(3.3%)	0	0	01(100%)	
Tumor Type					
Intestinal	13 (43.3%)	03 (23.0%)	01 (7.6%)	9 (69.2%)	0.049
Diffuse	17 (56.7%)	0	0	17 (100%)	
Tumor Differentiation					
Well	03 (10.0%)	01 (33.3%)	0	02 (66.6%)	0.570
Moderately	07 (23.3%)	01 (14.2%)	0	06 (85.7%)	
Poorly	20 (66.7%)	01 (5.0%)	01 (5%)	18 (90.0%)	
pT Status					
pT2	07 (23.3%)	0	0	07 (100%)	0.512
pT3	10 (33.3%)	01 (10.0%)	01 (10.0%)	08 (80%)	
pT4	13 (43.3%)	02 (15.3%)	0	11 (84.6%)	
pN Status					
pN0	06 (20.0%)	0	0	06 (100%)	0.693
pN1	14 (46.6%)	01 (7.1%)	01 (7.1%)	12 (85.7%)	
pN2	03 (10.0%)	01 (33.3%)	0	02 (66.6%)	
pN3	07 (23.3%)	01 (14.2%)	0	06 (85.7%)	

[Table/Fig-5]: Correlation between HER2 expression status and clinicopathological parameters in gastrectomy.

TNM stage is the most important prognostic parameter for GC in clinical practice. No correlation was found between HER2 expression and tumor and nodal factors in the present study and is in accordance with many studies [3,10,14,24,]. Allgayer et al., have shown a positive association with tumor stage [19]. A statistically significant correlation between HER2 positivity and TNM stage was observed by some [2]. A larger proportion of patients with stage III –IV lesions were HER2 positive compared to stage I-II lesions (95% vs 26%) and nodal metastasis [25,26]. These findings suggest that HER2 overexpression occurs in any stage of the disease, though positivity is high in higher stages. However, in the present study, there were less number of patients in the early stage and further studies are needed to determine the association between HER2 expression and pathological stage.

Aggressive biological behavior such as lymphovascular invasion and lymph node metastases, usually lead to poor prognosis. While most of the studies did not find any significant association between nodal involvement and HER2 expression similar to this study, a few studies have found frequent expression in cases with nodal metastasis [2,13,14,16,17].

Overall, HER2 overexpression was found in 11.6% (7/60) of the cases [13,21]. It was noted in 13% (4/30) of the gastric biopsies and 10% (3/30) of gastrectomy specimens [Table/Fig-6]. The p-value was 0.6876 and was not statistically significant when they were compared. Therefore, study of HER2 expression in small biopsy samples may be equally relevant as in resection specimens and hence, may be used as an initial screening procedure on small endoscopic biopsies. In the ToGA study, the HER2 positivity rate was higher in biopsies than in surgically-resected specimens (23.1% vs. 19.9%; p=0.03). The biopsy samples were also more likely to be HER2 amplified than surgical samples when analysed by FISH (p=0.01) than by IHC [22]. A large variation in the HER2 positivity rate has also been noted in individual studies varying from 6% to 90%. The reason for this large variation has been attributed to many factors such as the differences in the population studied, heterogeneity of HER2/neu expression in GC, availability of only biopsy samples in advanced unresectable GC, non-standardized assays using different antibodies, monoclonal versus polyclonal antibodies wherein monoclonal antibodies are highly sensitive, application of different scoring criteria which have taken varying percentage cut-offs for tumor cells staining positive for HER2 without taking intensity of staining into consideration [15].

A less variation has been noted in many studies where scoring criteria proposed by Hofmann et al., [9] was used (9.4% - 15.7 %) and the same method was used in the present study [16,21,25,26].

Despite the high level of concordance between IHC and ISH methods to evaluate HER2 expression in GC, the current recommendations suggest that samples with IHC2+ should be referred to ISH techniques [14]. There was a single equivocal case with IHC 2+ in the present study, which however was not subjected for ISH.

Authors	No of Cases Studied	Geographic Zone	Histologic Type		Localisation		HER2 Expression by IHC (%)
			Intestinal	Diffuse	GEJ	Gastric	
Gravalos et al.,[27] (2008)	n= 166	Europe	16	07	25	9.5	13
Lordick et al.,[28] (2007)	n= 1527	Europe, Asia, Latin America	34	06	32	18	22
Tewari M et al.,[29] (2013)	n= 70	North India (Varanasi)	45 (n=11)	12 (n=44)	—	—	21.4
Rajagopal I et al., [10] (2014)	n= 60	South India	32.7(n=49)	0 (n=11)	45.5	22.4	26.7
Present study (2016)	n=60 (30 each of biopsies and gastrectomy)	South India	23 (n=13)	0 (n=17)	6.6	93.3	11.6

[Table/Fig-6]: Comparison of overall Her 2 expression in gastric cancers and based on tumor location and histological type by various authors with our study.

LIMITATIONS

The limitations of this study are the small sample size, IHC positive cases not being confirmed by ISH, though there was only a single case with IHC2+ and lack of follow-up after treatment.

CONCLUSION

Gastric cancer is one of the common cancers reported in South Indians with substantial morbidity and mortality. Histopathology is still the most important tool for the management of gastric adenocarcinomas. The different responses to seemingly identical tumors have prompted for the detection of novel biomarkers. One such marker is HER2, which was used in this study; it was credibly overexpressed in intestinal type of gastric adenocarcinoma. Since, overexpression of HER2 may play a crucial role in the management of gastric adenocarcinomas, testing for HER2 by IHC has clear advantages, as it is easy, cost effective and feasible in a developing country. However, the sample size was small and may have undermined statistical significance between HER2 and other clinicopathological parameters. Further, studies with large samples and clinical trials in this part of the world are necessary to assess other clinical dimensions of HER2/neu involvement which may provide an in depth impact evaluation of gastric cancers.

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