

Original Research Article

Study of HER-2/neu status in adenocarcinoma of stomach and gastroesophageal junction

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Received: 25 September 2020

Accepted: 30 October 2020

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ABSTRACT

Background: To study the expression of Human epidermal growth factor receptor 2 (HER-2/neu) in adenocarcinoma of stomach and gastroesophageal junction and to study and describe the association of HER-2/neu expression with various clinicopathological parameters in Indian population.

Methods: Immunohistochemical testing was done on 91 cases diagnosed as adenocarcinoma of gastric and gastroesophageal junction by histological examination to determine HER2 status. HER2 amplification was confirmed by fluorescence in situ hybridization (FISH) on cases that had equivocal (immunohistochemistry-IHC score 2+) HER2 expression. The association between HER-2 positivity and clinicopathological parameters was assessed by Chi-square test.

Results: The HER-2 IHC results are as follows: score 3+ (positive): 8.79%; score 2+ (equivocal): 10.99%; score 0 and 1+ (negative): 80.22%. Of the 10 cases of equivocal IHC results, 2 cases (20%) showed amplification of HER-2 gene demonstrated by dual probe FISH analysis. The overall prevalence of HER-2 positivity detected using immunohistochemistry and FISH was 10.99% (10/91 cases). HER-2 positivity correlated with the tumor grade (well and moderately differentiated tumor, $p=0.013$) and intestinal type ($p=0.025$) but not with age, gender, pathological stage and lymph node metastasis.

Conclusions: HER-2 positivity in our study was 10.99%. HER-2 positivity significantly correlated with intestinal type of adenocarcinoma and the grade of the tumor. Two cases with strong HER-2 staining but in less than 10% of the tumor showed gene amplification by FISH.

Keywords: Gastric carcinoma, Gastroesophageal junction, Gene amplification, HER-2/neu, Trastuzumab

INTRODUCTION

Gastric cancer is the fifth most commonly diagnosed cancer in the world and the third leading cause of cancer death in men and women.¹ Surgical resection is the main modality of therapy for both gastric and esophageal carcinoma; however, most patients are diagnosed at an unresectable stage. Therefore, new therapeutic strategies, treatment options and novel therapeutic targets are desperately needed.

The 2009 Trastuzumab for gastric cancer (ToGA) trial reported that approximately 33% of gastro-esophageal junction and 22.1% of gastric adenocarcinomas were Human epidermal growth factor receptor 2 (HER2) positive by either immunohistochemical (IHC) study or fluorescence in-situ hybridization (FISH) analysis. The data of the ToGA trial showed that patients with HER2 protein over-expression benefit from anti-HER2 therapy. Since the approval of trastuzumab- a humanized monoclonal antibody directed against the HER2 receptor, as the first targeted therapy in advanced gastric cancer in

February 2010, the analysis of HER2 status in gastric cancer has evolved to be a very important task.²

HER2, a proto oncogene, is a member of the HER-family of growth factor receptors. Genomic alterations involving the HER2 gene locus leads to amplification of the gene on chromosome 17. HER2 gene amplification is an early event in tumor development and drives protein expression, resulting in a marked increase in the number of HER2 receptor protein molecules on the surface of each tumor cell. The ensuing signaling cascade and signal transduction drives cellular proliferation, migration, enhances cell survival pathways and promotes angiogenesis, contributing to an aggressive biology and clinical behavior for tumors with this molecular alteration.³

Patient-individualized treatment aims to avoid unnecessary medication in patients who are unlikely to respond to therapy. Also, targeted therapy should reach every patient eligible for the treatment; hence it is now recommended that, the HER-2/neu status be assessed on gastrectomy or GE junction specimens routinely by either immunohistochemistry or FISH. Though FISH has a high sensitivity and specificity for detecting HER-2 gene amplification, in the non-availability of FISH or cost constraints, immunohistochemistry serves as a valuable alternative. Owing to the sensitivity of HER-2 positive tumors to Trastuzumab, a strategy of treating these cases with the monoclonal antibody is proposed.

In India, only a limited number of studies have been conducted evaluating HER-2 expression in adenocarcinoma of stomach and gastroesophageal junction. Moreover, correlation of HER-2 IHC equivocal cases by FISH has been evaluated only in a handful of cases. Thus, studies showing HER2 expression in these tumors, availability of monoclonal antibodies against HER2 like trastuzumab and its proven efficacy has encouraged this study.

METHODS

Resected specimens of stomach and gastroesophageal junction submitted to the department of Histopathology during a 9 years period (January 2008 to December 2016) were included in this cross-sectional study. 91 cases diagnosed as adenocarcinoma of gastric and gastroesophageal junction by histological examination were further studied.

Biopsy samples, diagnoses other than adenocarcinomas (lymphoma, squamous cell carcinoma, gastrointestinal stromal tumor, neuroendocrine tumor etc.), inadequately processed tissue or otherwise unsatisfactory tissues were excluded from the study. Resection specimens are few in number with an average of about 10 cases per year at our institute. Moreover, the exclusion of endoscopic biopsies from the study resulted in a significant drop in the sample size.

Several studies in the world literature also have included a similar sample size example: Halon et al (78 cases), Tewari et al (70 cases) etc.^{4,5}

Both the primary investigator and the supervisor were blinded regarding the diagnosis of the cases. Staining using hematoxylin and eosin (HE) was done on all selected cases. Histological typing, grading and staging in all cases was analyzed. Immunohistochemical testing was done to determine HER2 status using an automated slide stainer, Ventana Benchmark® XT. Rabbit monoclonal primary antibody (4B5) was used. HER2 amplification was confirmed by FISH on cases that had equivocal (IHC 2+) HER2 expression.

The tumors were graded in accordance with CAP protocol, 2014 as grade 1, grade 2 and grade 3. Typing of the cancer was done based on the Lauren classification (intestinal, diffuse, mixed).⁶ The TNM staging system for gastric carcinoma of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) was followed. Only T (primary tumor) and N (regional lymph node) stage were correlated as the details of M (metastasis) stage were not available in all cases. Based on the extent of infiltration, cases were divided into 2 groups (Group 1- T1 and T2, Group 2- T3 and T4). Based on the nodal status, the cases were divided into 2 groups (Group 1- with no nodal metastasis, group 2- with no nodal metastasis).

HER2 immunoscore was done as per the criteria followed by Ruschoff et al as summarized in table 1.⁷ Nonspecific staining within non-neoplastic lesions like intestinal metaplasia and edge/crushing artifacts affecting tumor cells were excluded from scoring. Cytoplasmic or nuclear staining or only basal/ luminal /granular staining were also excluded from scoring. Only distinct membranous staining either complete (chicken-wire type), basolateral or only lateral between cell-cell contacts were considered.

The FISH scoring was done according to the scoring criteria defined by ASCO/CAP guidelines followed by Wolff et al⁸ as summarized in figure 1. The entire FISH slide was scanned prior to counting and IHC was used to define the areas of potential HER2 amplification.

After staining, the cases were examined and reported by both the primary investigator and the co-investigator separately. A HE diagnosis was formed; detailed histomorphology including tumour grade, histopathological subtype and pathological T and N stage, and HER-2 expression was scored as per the adopted scoring system. The cases were then reviewed by both the investigators together on a multi-headed microscope; and thus any discrepancies in the diagnoses were discussed and a final consensus diagnosis was reached. The same procedure was repeated for HER-2 scores of each case. FISH was performed on the cases with equivocal IHC results. The treatment plans were dealt with by another

department, hence the results of follow-up regarding hormonal manipulation were not available. The data thus accumulated was recorded in a Microsoft excel spreadsheet and was analyzed using IBM® Statistical package for social sciences (SPSS) statistics software, version 23.0. Demographic data and clinicopathological data was recorded. The association between HER-2 positivity and clinicopathological parameters was assessed by Chi-square test and $p < 0.05$ was considered statistically significant.

RESULTS

Age

The age at diagnosis of the cases ranged between 22 and 90 years with a mean of 60.4 years and median of 61 years. The age of patients positive for HER-2 ranged between 43 years and 90 years with an arithmetic mean and median age of 60.9 years and 57 years respectively. No correlation was found between HER-2 status and age of the patients in our study ($p = 0.079$).

Gender

Majority of patients in the study were males (male: female ratio=3.8:1). Almost equal percentage- 11.11% of the males and 10.53% of the females were HER-2 positive. There was no significant correlation between HER-2 positivity and the gender ($p = 0.942$).

Tumor histological type

All the HER-2 positive cases showed intestinal type of morphology (10/55; 18.18%). HER-2 positivity significantly correlated with the intestinal type of adenocarcinoma ($p = 0.025$).

Tumor grade, stage and nodal status

Twenty five percent of the well-differentiated tumors, 14.29% of the moderately differentiated tumors and 2.17% of the cases with poorly differentiated morphology were HER-2 positive. HER-2 positivity was seen to significantly correlate with the tumor grade ($p = 0.013$). There was no significant correlation of HER-2 status with the tumor stage and nodal status.

HER-2 IHC AND FISH results

HER-2 overexpression by IHC (3+) was seen in 8 cases (8/91; 8.79%), equivocal (2+) IHC results were obtained in 10 other cases (10/91; 10.99%) and HER-2 was negative (scores 0 and 1+) in 73 cases (73/91; 80.22%). Of the 10 cases of equivocal IHC results, 2 cases (20%) showed amplification of HER-2 gene demonstrated by dual probe FISH analysis. Two out of 12 tumors at the GE junction were positive (16.66%) and 8 out of 79 gastric adenocarcinomas were positive for HER-2 (10.1%).

Table 1: Scoring criteria for HER-2/neu immunohistochemistry and FISH in adenocarcinoma of stomach and gastroesophageal junction.

IHC results		
IHC Score 0	Negative	no reactivity at 40x
IHC Score 1+	Negative	barely visible at 40x in $\geq 10\%$ of tumor cells
IHC Score 2+	Equivocal	weak to moderate intensity at 10-20x in $\geq 10\%$ of tumor cells
IHC Score 3+	Positive	visible to the naked eye, displays unequivocal staining of strong intensity at low magnification (2.5x/5x) in $\geq 10\%$ of tumor cells
FISH results		
Negative	HER2/CEP17 ratio < 2.0 and average HER2 copy number < 4 signals/cell	
Equivocal	HER2/CEP17 ratio < 2.0 with average HER2 copy number ≥ 4 and < 6 signals/cell	
Positive	HER2/CEP17 ratio ≥ 2.0 with average HER2 copy number ≥ 4 signals/cell	
	HER2/CEP17 ratio ≥ 2.0 with average HER2 copy number < 4 signals/cell	
	HER2/CEP17 ratio < 2.0 with average HER2 copy number ≥ 6 signals/cell	

Table 2: Results of HER-2 status in relation to clinicopathological parameters.

	Total	HER2 positive	HER2 negative	P value
Age				
<60 years	40 (43.96%)	7 (17.5%)	33 (82.5%)	0.079
≥ 60 years	51 (56.04%)	3 (5.88%)	48 (94.12%)	
Gender				
Male	72 (79.12%)	8 (11.11%)	64 (88.89%)	0.942
Female	19 (20.88%)	2 (10.53%)	17 (89.47%)	
Type of adenocarcinoma				
Diffuse	33 (36.26%)	0 (0%)	33 (100%)	0.025*

Continued.

	Total	HER2 positive	HER2 negative	P value
Intestinal	55 (60.44%)	10 (18.18%)	45 (81.82%)	
Mixed	3 (3.30%)	0 (0%)	3 (100%)	
Grade				
Grade I	24 (26.37%)	6 (25%)	18 (75%)	
Grade II	21 (23.08%)	3 (14.29%)	18 (85.71%)	0.013*
Grade III	46 (50.55%)	1 (2.17%)	45 (97.83%)	
Tumor stage				
T1 + T2	27 (29.67%)	2 (7.41%)	25 (92.59%)	0.478
T3 + T4	64 (70.33%)	8 (12.5%)	56 (87.5%)	
Nodal status				
Positive	67 (73.63%)	8 (11.94%)	59 (88.06%)	0.628
Negative	24 (26.37%)	2 (8.33%)	22 (91.67%)	
Total	91	10	81	

*p<0.05, statistically significant

Table 3: Comparison of the present study with reported literature with reference to correlation with various histopathological features.

	Present study	Laboissiere et al ¹¹	Mizutani et al ¹²	Yoon et al ¹³	Figueroa-Barojas et al ¹⁴	Sekaran et al ¹⁵	Cidon et al ¹⁶	Rajagopal et al ¹⁷
Prevalence of HER2 positivity	10.99%	10.5%	14%	17%	35%	44.2%	7.5%	26.7%
Correlation with clinicopathological parameters								
Age (≥60 years)	- ^a	-	-	-	+ ^b	-	-	-
Gender								
Male	-	-	-	-	+	-	-	+
Female	-	-	-	-	-	-	+	-
Grade								
I/II	+	+	+	+	-	-	-	+
III	-	-	-	-	-	-	+	-
Type (intestinal)	+	+	-	-	-	-	+	+
Pathologic stage								
Advanced stage	-	-	+	-	-	-	+	-
Early stage	-	-	-	+	-	-	-	-
Lymph node status								
	-	-	-	-	+	-	+	-

'a' denotes no statistically significant association, 'b' denotes presence of statistically significant association

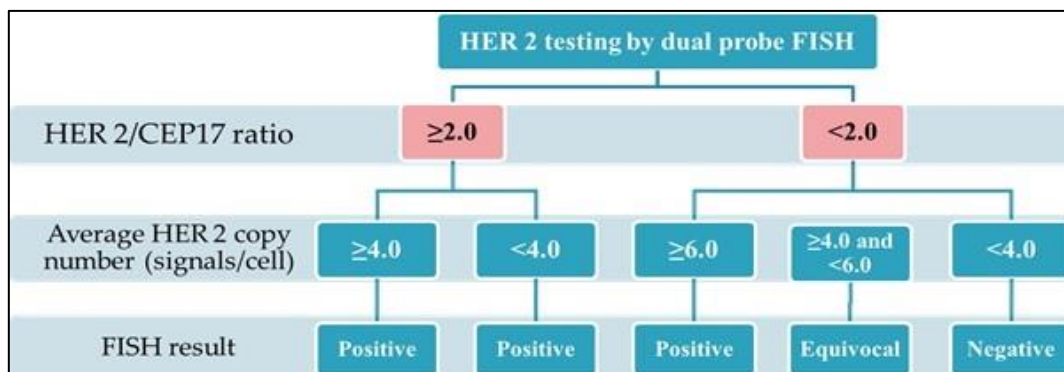


Figure 1: FISH scoring criteria defined by ASCO/CAP guidelines.

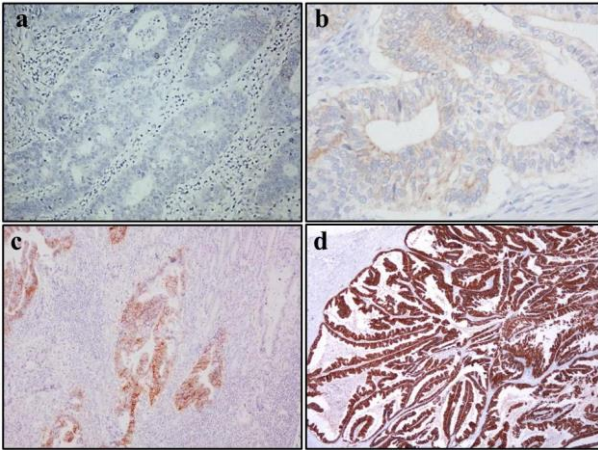


Figure 2: IHC scoring of HER-2/neu (a) 0: no reactivity at 40x (b) 1+: barely visible at 40x (c) 2+: weak to moderate intensity at 10 -20x (d)3+: strong intensity at 2.5x/5x.

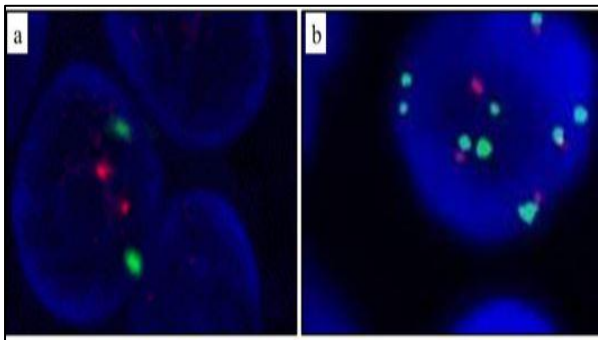


Figure 3: FISH-Red probes target chromosome 17centromere, green probes target HER2 gene, nuclei stained blue with DAPI:(a) No HER-2 amplification (b)HER-2 amplification.

The concordance rate between cases with equivocal HER-2 results and their corresponding FISH results was found to be 20%. The overall prevalence of HER-2 positivity detected using immunohistochemistry and FISH was 10.99% (10/91 cases).

The results of HER-2 status in relation to clinicopathological parameters are presented in table 2.

Our noteworthy findings include

Two cases with HER-2 staining of strong intensity in less than 10% of the tumor showed gene amplification by FISH. Also, cases showing staining of moderate intensity on IHC failed to show gene amplification by FISH.

DISCUSSION

Gastric cancer is the third leading cause of death due to cancer in the world.¹ Determination of HER-2 status is important because, it can represent an additional parameter

that can affect morbidity of patients with gastric cancer. The role of HER-2/neu in predicting the prognosis of patients with gastric cancer is controversial.

Certain studies like those conducted by Xie et al showed that HER-2/neu has a powerful adverse prognostic effect.⁹ Similarly, Motojima et al reported that the survival rate of patients with HER-2 positive tumors was significantly lower than patients with HER-2 negative tumors.¹⁰ However, a study by Kim et al. reported that there was no significant difference in terms of overall survival.¹¹

Before the ToGA trial, cases with IHC score 2+ and 3+ were regarded as HER-2 over-expressing. Such studies gave false positive results and thereby reported a higher positivity rate. The standard for interpretation of HER-2 over-expression later changed to IHC 3+ or IHC 2+ with gene amplification. The ToGA trial also showed that HER-2 status is an important predictive factor of response to trastuzumab.

Several factors are known to affect HER-2 staining results in immunohistochemical studies, like type of fixative used, duration of fixation, pH of fixative, type of specimen, time before fixation and the antibody used.¹²

In our study, we used rabbit monoclonal antibody 4B5 for IHC studies. The 4B5 antibody was reported to yield the highest positivity rate in the study conducted by Laboissiere et al that compared the performance of various antibodies like Hercep test, SP3 and 4B5 on tissue microarrays and whole-tumor sections.¹³

Table 3 summarizes the comparison of the present study with reported Indian literature with reference to correlation with various clinicopathological features.

Studies conducted in the Indian population are very few in number and most of these studies have incorporated only immunohistochemistry as a tool to determine HER-2 status. Only 3+ score on IHC were considered positive in studies conducted by Halder et al, Gupta et al, Rajagopal et al and Ghosh et al.¹⁸⁻²¹ In another study conducted by Tewari et al⁵, both 2+ and 3+ scores on IHC were considered positive resulting in a HER-2 positive rate of 21.4%. Among the Indian studies, FISH was performed on equivocal (IHC 2+) cases only in limited studies- Patil et al, Sunitha et al, Aditi et al and Sekaran et al.¹⁴⁻¹⁷

The overall HER-2 positivity described by various studies in English literature ranged between 7% and 44.2%.^{14,17} The variation in prevalence rates in several studies could be attributed to the varying protocols followed for designating HER-2/neu status and the antibody used in IHC technique.

The HER-2 positivity rate in our study is 10.99% which was comparable to several other studies like those conducted by Laboissiere et al.¹³ The methodology adopted by Sekaran et al was similar to that of our study.¹⁷

However, they reported positive results in 44.2%. Rajagopal et al reported 26.7% positivity considering only cases with score 3+ as positive.²⁰ This high value could be attributed to the use of polyclonal antibody which was known to target more epitopes.

In our study, no correlation was found between HER-2 status and age of the patients in our study ($p=0.079$). Most of the studies reviewed did not show statistically significant correlation between the HER-2 positive and negative cases in terms of age except for the study conducted by Figueroa-Barojas et al.²²

Majority of the patients in our study were males (79.12%) and females comprised a smaller proportion (20.88%). Our study showed that almost equal percentage of males (11.11%) and females (10.53%) were HER-2 positive and statistically significant correlation between HER-2 status and gender was not found ($p=0.942$) similar to studies conducted by Sekaran et al, and Tewari et al.^{5,17} Studies by Figueroa-Barojas et al and Cidon et al, reported a positive correlation between HER-2 positivity with male ($p=0.0396$) and female gender ($p=0.019$) respectively.^{22,23}

A large proportion of the cases included in our study showed intestinal type of histology. All the HER-2 positive cases in our study showed intestinal type of histology with significant correlation ($p=0.025$) similar to the studies conducted by Rajagopal et al.²⁰ Few studies, like those conducted by Laboisserie et al showed that in addition to the intestinal type, few cases with mixed type of histology also showed HER-2 positivity.¹³ Studies by Figueroa-Barojas et al, Sekaran et al revealed no correlation between the two ($p>0.05$).^{17,22}

In our study, 25% of the grade-I tumors and 14.29% of the grade-II tumors were HER-2 positive. Only a small percentage of the grade-III tumors (2.17%) were HER-2 positive. Significant correlation was observed between HER-2 positive cases and well to moderately-differentiated tumors ($p=0.013$). Shan et al and Laboisserie et al found a significant correlation similar to our study.^{13,24} However, in contrast, Ghosh et al.²¹ identified a statistically significant association between HER-2 positivity and undifferentiated tumors (grade-III) with a $p=0.0159$. Certain studies conducted by Xie et al, Figueroa-Barojas et al found no association between HER-2 status and grade of the tumor ($p>0.05$).^{9,22}

In our study, 12.5% of the advanced stage tumors and 7.41% of the early stage tumors were HER-2 positive. No correlation was found between HER-2 status and pathological stage of the tumor in our study ($p=0.478$). Similarly, studies conducted by Laboisserie et al, Rajagopal et al and Shan et al reported nil association between the two.^{13,20,24} However, study conducted by reported an association between HER-2 positivity and tumors with advanced pathological stage ($p<0.05$).

In our study, among the cases with nodal metastases, 11.94% were HER-2 positive. This was comparable to the study conducted by Barros-Silva et al (16.95%).²⁵ A statistically significant correlation was not seen between HER-2 status and nodal status in our study ($p=0.628$). This was similar to the studies performed by Laboisserie et al, Shan et al, Barros-Silva et al, etc. with a $p>0.05$.^{13,24,25} In contrast, few studies showed that there was significant association between HER-2 status and nodal positivity example- studies by Figueroa-Barojas et al, Cidon et al.^{22,23}

Limitations of our study

In our study, cases with IHC score 1+ were not tested for gene amplification by FISH as recommended by Barros-Silva et al.²⁵ Therefore, it is possible that a small proportion of cases were falsely reported as negative. Our sample size was limited, which moreover originated from a localized area. A larger sample size; possibly in the form of a multi-centric study; would introduce demographic heterogeneity in the analysis, thus better simulating the diverse population of the country. Pre-analytical variables like type, concentration and pH of the fixative used, duration of fixation etc. that can significantly affect the IHC staining were not analysed in our study. Possible relationship with *H. pylori* infection or the histological profiles of non-cancerous gastric mucosa with HER-2 expression was not assessed in the study.

CONCLUSION

We conclude that HER-2 over-expression/ amplification was seen in 10.99% of the cases in our study. Significantly higher rates of HER-2 positivity were seen in well- to moderately- differentiated tumors and intestinal type of tumors. No association with other clinicopathological parameters like age, gender, pathological stage and nodal status was seen.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Fathima N, de Padua M, Gowrishanka S, Goud I. Study of HER-2/neu status in adenocarcinoma of stomach and gastroesophageal junction. *Int J Res Med Sci* 2020;8:4388-94.