



## Original Article

# HER2 Expression in Gastric Cancer and Gastroesophageal Junction Cancer

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### ABSTRACT

**Background:** Carcinoma of the stomach is a major cause of cancer mortality worldwide. Due to social impact of gastric carcinoma (GC), there is a need to stratify patients into appropriate screening, surveillance and treatment programs. Although histopathology remains the most reliable and less expensive method, numerous efforts have been made to identify and validate novel biomarkers to accomplish the goals. In recent years, several molecules have been identified and tested for their clinical relevance in GC management. Among the biomarkers with the exception of HER2, none of the biomarkers is currently used in clinical practice, and some of them were described in single studies.

**Materials and Methods:** This prospective type of observational study was performed in the Department of Surgery, Dhaka Medical College Hospital, Dhaka, 6 months from approval of protocol. Total 45 consecutive patients aged 18 years and above without consideration of gender were selected purposefully. Every patient was evaluated by clinical examination, appropriate investigations and after a confirm diagnosis of the tissue from the cancer. All patients have undergone operative intervention and Gastrectomy specimens were subtotal (including cardiac and pylorus), subtotal (including the pylorus), total radical gastrectomy and oesophago-gastrectomy sample.

All specimens obtained were immersed in 10% formalin. Samples of whom were sent to the department of pathology, DMCH for histopathology examination. Portion of representative tissue/block was sent to AFIP (Armed Forces Institute of Pathology, Dhaka) for immunohistochemistry to find out the HER2 expression in gastric cancer and gastro-oesophageal cancer. Data was collected in a pre-designed questionnaire by face to face interview.

**Result and observation:** In this study when 45 cases were categorized according to WHO grading system it was observed that majority (30) patients were found in grade II, among them 3(10%) were HER2 positive. But with grade III tumour the HER2 positivity were found more i.e; 37.5% (3/8). Grade-I tumor show HER2 neu expression 28.57% (2/7) and according to location most of the cases with HER2 positive expression was located in the gastro-oesophageal junction which is 27.27% (3/11) than gastric carcinoma which is 14.70% (5/34).

**Conclusion:** Most of the patients of gastric and gastroesophageal junction adenocarcinoma are diagnosed at a very late stage, so they require special attention in treatment protocol, including chemotherapy and immunotherapy for increasing their survivability. The study showed with poorly differentiated (high grade) tumour, the HER2 positivity were found more.

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### Introduction

Carcinoma of the stomach is a major cause of cancer mortality worldwide. Its prognosis tends to be poor, with cure rates little better than 5-10 percent<sup>1</sup>. Gastric cancer (GC) still represent a major health problem, despite a decrease in its incidence in the last years<sup>2</sup>. It is the fourth most commonly diagnosed cancer and second common cause of cancer related death world wide<sup>3</sup>. According to the most recent estimates, GC

accounts for 8% of the total cancer cases and for 10% of the death for all cancers<sup>4</sup>. GC is characterized by a clear geographical distribution, with over 70% of the cases occurring in developing countries. This is partly due to dietary habits as well as Helicobacter Pylori infection prevalence. Indeed, the reasons accounting for the decreased GC incidence in most countries are related to changes in dietary habits, amelioration of food preservation, reduction in H. Pylori chronic infection<sup>5</sup> as well as reduction in smoking<sup>6</sup>. In this study, we will only address the adenocarcinomas as “GCs”.

Although histopathology remains the most reliable and less expensive method, in recent years, several molecules have been identified and tested for their clinical relevance in GC management. There are some biomarkers reported to use in GC. With the exception of HER2, none of the biomarkers is currently used in clinical practice, and some of them were described in single studies<sup>7</sup>. The HER2(ERBB2) is a transmembrane protein of 185 KD weight having a tyrosin kinase activity. These receptors cooperate the regulation of different processes, such as cell proliferation, differentiation, and survival<sup>8</sup>. Activation of HER2 receptors leads to the activation of cellular transduction system, resulting in the cellular transformation and cell proliferation events associated with cancer. Rate of HER2 expression in gastric cancer shows a wide variety in literature. By immunohistochemical (IHC) method expression rate was found as 6.8%-34% and 7.1%-42% by fluorescence in situ hybridization (FISH) method<sup>11</sup>. Due to the recent approval of trastuzumab for HER2-positive GC in Europe, HER2 diagnostics is now mandatory. Immunohistochemistry is used as primary test, and it is followed by fluorescence in situ hybridization(FISH) in IHC2+ cases<sup>14</sup>.

### Material and Methods

This is a prospective type of observational study which was carried out at the Department of Surgery, Dhaka Medical College Hospital, during the period from July 2015 to Jan 2016. This study was carried on patients who were diagnosed as Gastric and Gastro-oesophageal junction adenocarcinoma on endoscopic biopsy examination and underwent gastrectomy and oesophagogastric operation. A total of 45 cases were selected.

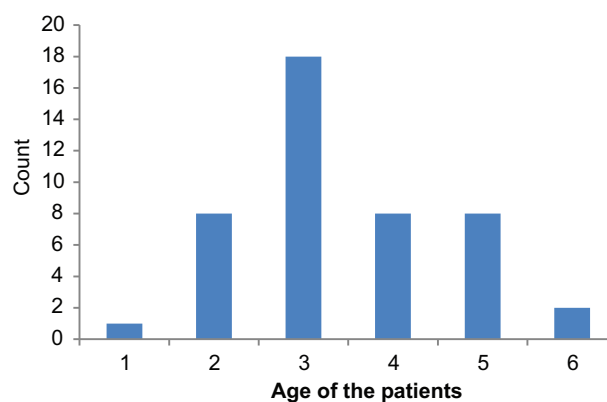
Gastric and gastro-oesophageal cancer patients in surgery department of Dhaka Medical College hospital irrespective of sex aged 18 years and above, admitted in hospital.

To do this study ethical clearance was taken from institutional ethical committee of Dhaka Medical College, Dhaka. Total 45 patients aged 18 years and

above without consideration of gender with a clinical diagnoses of gastric and gastroesophageal cancer and confirmed by endoscopic and histopathological examination were selected purposefully. All specimens obtained were immersed in 10% formalin. Samples of whom were sent to the department of pathology, DMCH for histopathology examination. Portion of representative tissue/block was sent to AFIP (Armed Forces Institute of Pathology, Dhaka) for immunohistochemistry to find out the HER2 expression in gastric cancer and gastro-oesophageal cancer. Data was collected in a pre-designed questionnaire by face to face interview.

### Age distribution of the patients

The bar diagram shows the maximum number of patient of this study in 41-50 years of age.

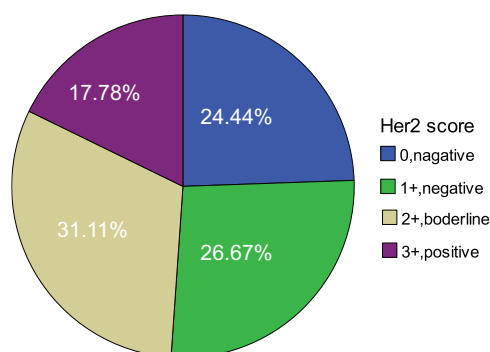


1:18-30, 2:31-40, 3:41-50, 4:51-60, 5:61-70, 6:71-80

**Figure 1.** Bar diagram showing age distribution of the study patients

### HER2 expression rate among the study patients

Pie chart showing that positive HER2 expression was seen in 17.78% cases, borderline in 31.11% cases, 0 negative in 24.44% and 1+ Negative were 26.67%.



**Figure 2.** Pie diagram showing rate among the study patients

**Table 1.** Distribution of the study patients according to site of tumor with HER2 expression (n=45).

Site of tumor	HER2 expression				Total (n=45)	P value
	0 Negative (n=11)	1+ Negative (n=12)	Borderline (n=14)	Positive (n=8)		
Gastric Carcinoma	9	1	10	5	34	.684 <sup>ns</sup>
Proximal	1	0	3	1	6	
Distal	8	1	7	4	28	
Gastro-oesophageal junction	2	2	4	3	11	

NS : Not significant

### Location of HER2 positive cases in the stomach

Most of the cases with HER2 positive expression was located in the gastro-oesophageal junction which is 27% (3/11) than gastric carcinoma which is 14.70% (5/34). The difference was not statistically significant ( $p > 0.05$ ).

### Discussion

Gastric cancer (GC) is the fourth most common diagnosed cancer and the second most common cause of cancer-related deaths world wide (Ferlay J et al, 2010). Although the incidence of gastric cancer has gradually decreased over the last half century but cancer at proximal stomach is on the rise. According to the most recent estimates, GC accounts for 8% of the total cancer cases and 10% of the deaths for all cancer<sup>4</sup>.

This study included 45 patients with curative resection of primary gastric and gastro-oesophageal junction cancer. HER2 expression was assessed by IHC (immunohistochemistry) and using the scoring scheme that was employed in the ToGA study<sup>6</sup>.

In this study highest number of cases (18) were in the 41-50 yrs of age. According to Islam SMJ et al (2009) and Alim MA et al (2007) the mean age was 43.14 year and  $47.1 \pm 12.7$  year.

In the present study it was observed that majority 30(66.7%) patients came from lower, 1(2.2%) from lower middle and 14(31.1%) from middle economic condition. No one came from higher socioeconomic condition. Similar observation was made by Guggenheim DE and Shah MA (2013).

The most common macroscopic type of the tumor according to Bormann classification was ulcerated mass 37, next in order of frequency were polypoid 7 and diffuse infiltrative 1. These findings were consistent

with the observations of Rudi et al (1995); Komoto et al (1998) and Plummer et al (2005).

In this present study 30 tumors were moderately differentiated, 8 were poorly differentiated and 7 were well differentiated. Fei Z. et al (2012) reported an association between HER2/neu over expression/ amplification and WHO histologic grade in their study done on 227 patients. They found HER2 positivity 27.3% in well differentiated tumor, 13.9% in moderately differentiated and 2.5% in poorly differentiated tumor.

In this study HER2 expression was evaluated by immunohistochemistry in 45 cases. HER2 expression was found positive (score 3+) in 17.78% cases, borderline (score 2+) in 31.11% cases and (0 Negative) in 24.44% cases, (1+Negative) in 26.67%. The result was almost similar to the ToGA trial which was 10.4% by IHC only and 15%-25% when it was supplemented by FISH.

In the present study of the total 37 gastric carcinoma with ulcerated growth HER2 overexpression was found in 7 cases (18.91%), while of the 7 polypoid growth HER2 positivity observed in 1 cases (14%). The highest positivity of HER2 was observed in ulcerated growth. The HER2 expression in the different types of gastric carcinoma according to Bormann classification is statistically not significant ( $P > .05$ ). These findings were consistent with the observations of Rudi et al (1995); Komoto et al (1998) and Plummer et al (2005).

When the histological types were individually analysed according to location, most of the cases with HER2 positive expression was located in the gastro-oesophageal junction which is 27% (3/11) than gastric carcinoma which is 14.70% (5/45).

These HER2 positive tumors are aggressive but they can be treated with monoclonal antibody (trastuzumab) against HER2/neu protein. The tumor of GEJ and

poorly differentiated carcinoma is expected to give better response with trastuzumab as their expression to HER2/neu protein is more.

### Conclusion

Gastric carcinoma could be regarded as one of the common malignant tumors in our population. Most of the patients of gastric and gastro-oesophageal junction adenocarcinoma are diagnosed at a very late stage, so they require special attention in treatment protocol, including chemotherapy and immunotherapy for increasing their survivability. The study showed GEJ carcinoma shows HER2 positivity more than gastric cancer and poorly differentiated carcinoma shows more positivity than other grade.

Further large scale study is needed to establish the need of doing HER2 in gastric and gastro-oesophageal junction cancer specially; -A. Poorly differentiated B. Cancinoma in GEJ C. Ulcerated carcinoma

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