

Expression of HER2 in Gastric Carcinoma According to Tumor Location

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Abstract: *Introduction:* HER2/neu (c-erbB-2) is an oncogene that encodes a transmembrane glycoprotein with tyrosine kinase activity known as 185 kDa. This 185 kDa belongs to the epidermal growth factor receptor. Though HER-2 expression has been extensively found in advanced gastric cancer, few recent studies have evaluated the same in early gastric cancers. HER-2 overexpression is considered one of the poorest prognostic variables after nodal status in early gastric cancers too. *Aim of the study:* To find out the expression of HER2 in gastric carcinoma according to tumor location. *Material & Methods:* This cross-sectional study was conducted in the Department of Surgical Oncology of National Institute of Cancer, Research and Hospital, Mohakhali, Dhaka. The study period was from March 2014 to April 2015. A total of 80 patients were included in the study. After receiving the gastrectomy specimen, it was fixed in 10% formaldehyde. Statistical analysis was carried out using a computer-based software package for social science (SPSS 16.1). Ethical clearance was taken from the ethical committee of NICRH. *Results:* The highest patients were from the 61-70 years age group and the lowest were from 71-80 years. The mean age of the patients was 59.71 (± 10.19) years. The female to male ratio in this study was 1: 2.48. The leading number of patients presented with abdominal pain where the vague abdominal discomfort was also included. They were 75%. This clinical condition was followed by vomiting which coined 58.75% of respondents. Out of 80 patients, 27 (33.75%) patients bore A +ve blood group whereas 23 (28.75%) patients had B+ve blood group. Most of the tumors were located in the distal (Noncardiac) part of the stomach (75%). Regarding staging 79 (98.75%) patients were in the advanced stage of the disease. Most of the tumors were located in the distal part of the stomach (11.67%). *Conclusion:* We reported a 12.5% of positive HER2 expression (IHC=3+ & 2+) in a series of 80 surgical specimens of gastric cancer patients. We also observed that positive HER2 expression varied depending on the histology and the primary tumor localization.

Keywords: Expression, HER2/neu, Gastric Carcinoma, Tumor, Growth Factor

1. Introduction

HER2/neu (c-erbB-2) is an oncogene that encodes a transmembrane glycoprotein with tyrosine kinase activity known as p185. This p185 hormone belongs to the family of epidermal growth factor receptor (Hormone receptors /HER2, val-2). The binding of different ligands to the extracellular domain initiates a signal transduction cascade that can influence many aspects of tumor cell biology including proliferation, differentiation, and apoptosis [1]. HER2 does not bind to any known ligand but is the preferred

heterodimerization partner of other members of the HER family. Though HER-2 expression has been extensively found in advanced gastric cancer, few recent studies have evaluated the same in early gastric cancers. HER-2 overexpression is considered one of the poorest prognostic variables after nodal status in early gastric cancers too [2] HER2 protein (p185, HER2/neu, ErbB-2) is a 185-kDa transmembrane amino acid enzyme (TK) receptor and a member of the epidermal protein receptors (EGFRs) family. This family is mainly composed of 4 members, such as HER1 (also known as the EGFR), HER2, HER3 (also termed ErbB-3), and HER4 (also termed ErbB-4). These receptors

share a similar microscopic structure with an extracellular ligand-binding domain, a short transmembrane domain, and an intracellular domain with TK activity (excepting the HER3). The binding of different ligands to the extracellular domain can initiate a signal transduction cascade which can influence many aspects of tumor cell biology, as well as cell proliferation, apoptosis, adhesion, migration, and differentiation. The etiology of gastric cancer is comprised of multiple factors and can include both dietary and nondietary factors. The development of esophageal adenocarcinoma often leads to dysplasia, which is a pre-cancerous stage in Barrett's esophagus, where the cell develops abnormal features. [3] Ailments such as helicobacter pylori infection, atrophic gastritis, intestinal metaplasia, and dysplasia are mostly related to gastric adenocarcinoma [4]. The development of gastric cancer is a difficult, multipart process that involves several genetic and epigenetic changes of oncogenes, tumor suppressor genes, DNA repair genes, cell cycle regulators, and signaling molecules. Recent advancements in molecular medicine have shed some light on the carcinogenesis of gastric cancer, while also offering novel approaches in the fields of prevention, diagnosis & therapeutic intervention. A common pattern seen in our country is that most gastric cancer patients are diagnosed in the advanced stage. For some of these patients, systemic chemotherapy is the primary treatment option, as it can persist in survival without compromising the quality of life. Many singular agents and even some combinations of multiple agents are effective in the treatment of metastatic disease. Objective response rates can range from 10% to 30% for singular-agent therapy and 30% to 60% for the combination of multiple regimens [5]. Investigations of HER2 overexpression in gastric and gastroesophageal junction adenocarcinoma first began during the late 1980s. Various studies conducted worldwide demonstrated varied HER2 expression in gastric and GEJ adenocarcinomas. Tanner et al [6] demonstrated 12% and 24% HER2 expression in gastric and GEJ carcinomas respectively.

2. Methodology and Materials

This cross-sectional study was conducted in the Department of Surgical Oncology of National Institute of Cancer, Research and Hospital, Mohakhali, Dhaka. The study period was from March 2014 to April 2015. A total of 80 patients were included in the study according to the following inclusion and exclusion criteria. The aim of the study was to find out the expression of HER2 in gastric carcinoma according to tumor location. After receiving the gastrectomy specimen, it was fixed in 10% formaldehyde. After fixation, a systemic gross examination was performed and adequate tissue sections were submitted and embedded in paraffin. Then histologic sections with 3–5-micron thickness was obtained from paraffin blocks and were initially stained with hematoxylin-eosin for histological assessment. H & E-stained slides were evaluated for histological examination (tumor classification, grading, and depth of tumor, nodal

stage, and lymphovascular invasion). Gastric cancer was classified histopathologically according to Lauren's system (Intestinal, diffuse and mixed) and on the grading (well-differentiated, moderately differentiated, and poorly differentiated). Only the gastric adenocarcinomas, diagnosed in hematoxylin and eosin sections were selected for immunohistochemical examination. Endogenous peroxidase activity was removed by being kept in 3% hydrogen peroxide. Finally, the sections were counterstained with Mayers hematoxylin. Data were compiled and necessary statistical analysis was carried out using a computer-based software package for social science (SPSS 16.1). Ethical clearance was taken from the ethical committee of NICRH.

1) Inclusion Criteria

Patients of any age, sex, stage having histopathologically confirmed carcinoma stomach.

2) Exclusion Criteria

- a) Previous history of gastric surgery.
- b) Patients with a history of radiotherapy.

3. Results

The highest number of patients were from the 61-70 years age group and the lowest were from 71-80 years. The mean age of the patients was 59.71 (± 10.19) years. The age followed an almost gradual increase with increasing of age that was dropped suddenly in the last age group (Figure 1). Out of 80 patients with carcinoma stomach, 57 were male (71.25%) and 23 were female (28.75%). The female-to-male ratio in this study was 1: 2.48 (Figure 2). The leading number of patients presented with abdominal pain where the vague abdominal discomfort was also included. They were 75%. This clinical condition was followed by vomiting which coined 58.75% of respondents (Table 1). Out of 80 patients, 66 (82.5%) patients were presented with anemia which was followed by 39 (48.75%) cases with dehydration (Figure 3). Out of 80 patients, 27 (33.75%) patients bore A +ve blood group whereas 23 (28.75%) patients bore B+ve blood group. A considerable number of patients bore O+ve blood group which was 19 (23.75%) in number. No patients with AB –ve blood group was found. So, the number of patients with a positive blood group was maximum among the carcinoma stomach patients (Figure 4). A significant number of patients showed a lower level of serum albumin with carcinoma stomach. The percentage of the hypoalbuminemia patient was 51.25% (Figure 5). Most of the tumors were located in the distal (Noncardiac) part of the stomach (75%). Regarding staging 79 (98.75%) patients were in the advanced stage of the disease. More than half of cases were intestinal type (Table 2). Out of 80 patients 38 (47.5%) respondents showed ulcerative type of lesion whereas 36 (45%) showed ulcer proliferative lesions. The minimum patients showed linitus plastica and polypoid growth (Figure 6). Total 12.5% patients showed HER2 positivity out of 80 respondents of carcinoma stomach (Table 3). Most of the tumors were located in the distal part of the stomach (11.67%). Regarding staging 79 (12.65%) patients were in the advanced stage of the disease. More than half of

cases were intestinal type (Table 4).

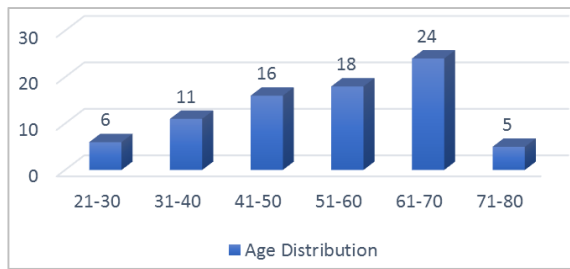


Figure 1. Shows the age distribution of the patients.

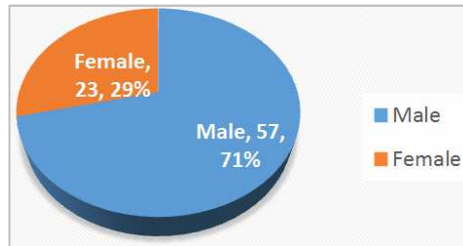


Figure 2. Shows the sex distribution of the patients.

Table 1. Distribution often causes by symptoms (n=80).

Symptoms	Frequencies (%)	Percentage (%)
Weight loss	19	(23.75%)
Anorexia	34	(42.5%)
Abdominal pain	60	(75%)
Weakness.	29	(36.25%)
Vomiting	47	(58.75%)
Dyspepsia	13	(16.25%)
Dysphagia	14	(17.5%)
Melaena	9	(11.25%)
Lump	8	(10%)
Painless	1	(0.8%)
Haematemesis	2	(2.5%)

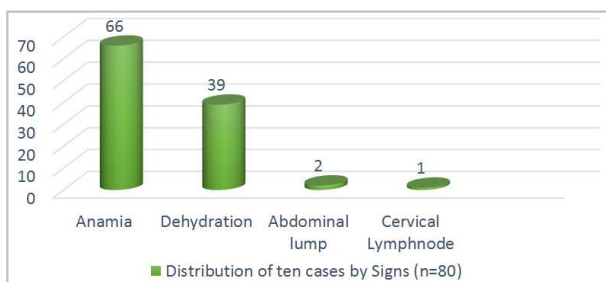


Figure 3. Shows distribution of cases by sign (n=80).

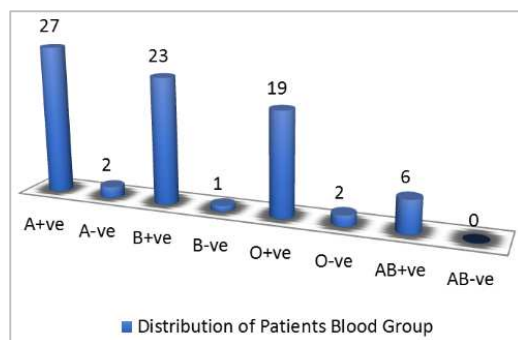


Figure 4. Shows distribution of patients with blood group (n=80).

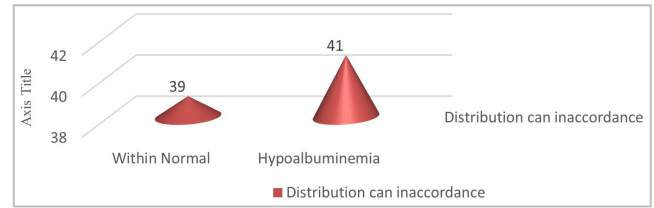


Figure 5. Shows distribution of patients following serum albumin level (n=80).

Table 2. Distribution of the cases by tumor morphology (n=80).

Tumor morphology	Frequency	Percentage
Location		
Proximal	20	(25%)
Distal	60	(75%)
Staging		
Early	1	(1.25%)
Advanced	79	(98.75%)
Grading		
Well to Moderately differentiated	44	(55%)
Poorly differentiated	36	(45%)
Laurence type		
Intestinal	45	56.25%
Diffuse	35	43.75%

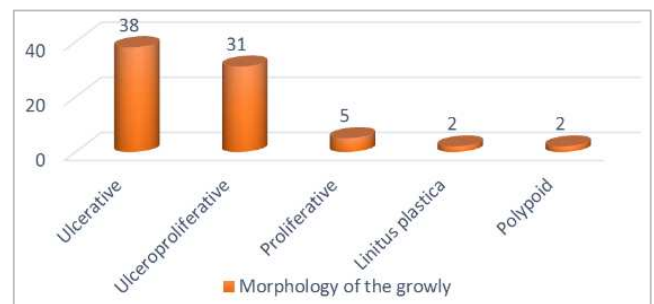


Figure 6. Shows distribution of morphology of the patients (n=80).

Table 3. Distribution of the cases by HER-2 positivity (n=80).

Scoring	No of patients	Percentage (%)
3+	9	11.25%
2+	1	1.25%
1+	10	12.50%
0	60	75%
Total	80	100%

Table 4. Distribution of correlation of patients with tumor morphology, frequency and HER2 positivity (n=80).

Tumor morphology	Frequency	HER 2 Positive	Percentage
Location			
Proximal	20	3	(15%)
Distal	60	7	(11.67%)
Staging			
Early	1	0	(0%)
Advanced	79	10	(12.65%)
Grading			
Well to Moderately differentiated	44	7	(15.91%)
Poorly differentiated	36	3	(8.33%)
Laurence type			
Intestinal	45	8	(17.78%)
Diffuse	35	2	(5.71%)

4. Discussion

This study was designed to investigate the frequency of HER2 overexpression in gastric cancer patients. Mean age 59.71 with male predominance (male:female = 2.48:1). HER2/neu overexpression was present in 12.5% of gastric adenocarcinoma and was positively associated with only age and lymph node metastasis but not with other important clinicopathological variables. Overexpression of HER2 protein in gastric cancer, using Immunohistochemistry (IHC), was first described in Sakai et al [7]. In our study, the HER2 overexpression was found only 12.5% which is similar to that of Yonemura et al.[1] According to the Japanese series by Yonemura et al [1], it was assumed that with immunohistochemical stains the rate of HER2 overexpression in gastric adenocarcinoma is 12%. In our study, 27 (33.75%) patients bore A +ve blood group whereas 23 (28.75%) patients bore B+ve blood group. A considerable number of patients bore O+ve blood group which was 19 (23.75%) in number. No patients with AB –ve blood group was found. The association of the blood group A with males, with diffuse-type gastric cancer is stronger than with females, or intestinal-type gastric cancer Kramer and Johnson [8]. Some reports from the 1990s showed a 9%-38% of HER2 positive tumors using polyclonal antibodies which were directed against different domains of HRE2 proteins and restricted the evaluation to the staining of the cell membrane [1, 9]. Some recent studies where HERCEP Test is used to determine HER2 overexpression by IHC have observed similar rates [2, 10]. A Japanese research study found HER2 overexpression by IHC in 23% of the cases, and gene amplification by FISH in 27% of the cases [11]. The present study reported a 12.5% of positive HER2 expression among 80 cases of gastric cancer patients. Positive HER2 expression varying depending on the histology (intestinal type 17.78%. diffuse-type 5.71%) and primary tumor localization (15% proximal vs 11.67% distal) was also observed in this study. A study by Lordick et al followed a modified HER2 scoring system and centrally tested tumor samples using both IHC and FISH to identify eligible patients for enrollment in the ToGA clinical trial [12]. In the abstract of their study, which was presented at the European Cancer Organization in 2007, 22% of the tumors were HER2 positive. HER2 positivity differed greatly based on histological subtypes (intestinal 34%, diffuse 6%) and the site of the tumors (32% proximal, 18% distal). In 2008, an update of the study was presented at Gastrointestinal Cancers Symposium, where they presented an overall HER2 overexpression of 22% in patients who were tested and confirmed a higher rate of positivity in proximal tumors than distal cancer samples (14% increase) [12, 13]. A study by Tanner observed HER2 amplification by CISH in 12% of gastric cancers and in 24% of GEJ tumors [6]. Multiple studies have been conducted to study and analyze the relationship between HER2/neu and clinicopathological characteristics in gastric cancer patients. The frequency of gene expression was reported as 14.2% in one study where a correlation with the depth of tumor invasion, histological subtype, growth pattern, and liver metastasis was observed [14]. Yonemura et al found a positive correlation between the intensity of HER2/neu staining and

tumor size, invasion to serosal layer, and lymph node metastasis [1]. A correlation with the depth of tumor invasion, histological subtype, growth pattern, and liver metastasis was found. It was a cross-sectional single-centered study with small sample size. Immunohistochemistry for gastric carcinoma is at its initial stage in our country. Also FISH procedure was not available.

5. Conclusion and Recommendations

In our study, we reported a 12.5% of positive HER2 expression (IHC = 3+ & 2+) in a series of 80 surgical specimens of gastric cancer patients. We also observed that positive HER2 expression varied depending on the histology (intestinal type 17.78%. diffuse-type 5.71%) and the primary tumor localization (15% cardiac vs 11.67% noncardiac). These variables were sex, tumor size, distant metastasis, Laurence histological classification. But their association with the HER2 overexpression was not found statistically significant. More research with larger sample size and long-term follow-up needs to be conducted to draw a clear image regarding the role of HER2/neu overexpression as an independent prognostic factor. The study should be on a multi-center basis. A multi-disciplinary approach should be mandatory to get a good outcome where the surgical oncologists, Thoracic surgeons, Gastroenterologists, Histopathologists, Geneticists are included. FISH procedures should be available for equivocal cases in every center. The experts involved in immunohistochemistry should go through continuous training.

Ethical Approval

The study was approved by the Institutional Ethics Committee.

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