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Original Article

Correlation of HER2 with Stages of Carcinoma Stomach

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Abstract:

Background: The variability of prognosis within a clinical & pathological stage of gastric cancer, underscores the need for speciûc biological markers to identify subgroups of patients for intensive treatment. The purpose of this study was to evaluate the correlation between HER2overexpression with different stages of carcinoma stomach. To our knowledge, this is the ûrst study from Bangladeshi population reporting on the relationship of HER-2 expression with different stages of carcinoma stomach.

Methods: This cross-sectional study included 53 patients with gastric cancer who underwent surgery at different Hospital in Dhaka city between November 2016 and October 2017. All the patients were clinically staged before surgery & tumor samples were examined for HER2 expression by immunohistochemistry (IHC). The results correlated with clinicopathological features & stages of carcinoma stomach. Percentage expression for positivity of HER2 was estimated along with 95% confidence interval. The differences in the positivity rate between different sex, stages and grades were tested through 'Chi' square test of significance and a value of p <0.05 was consider to be statistically significant.

Results: The mean age was 51.74±12.02 years, more than half (52.8%) patients were male. Almost two third (66.0%) patients had tumor location in antrum and more than three fourth (79.2%) patients had intestinal type carcinoma. Regarding the Staging it was observed that 21(39.6%) patients had T =staging 4b, 33(62.3%) N=staging 1 and 16(30.2%) M=staging 1. Nearly two third (66.0%) patients had grading 2. More than three fourth (75.5%) patients had HER2 scoring 0/1+ Negative, followed by 10(18.8%) had 3+ positive and 3(5.7%) had 2+ equivocal. Statistically no significant association (p>0.05) were found betweenHER-2 positive group with age, gender and tumor location. More than three fourth (80.0%) patients had intestinal type and 2(20.0%)had diffuse type histological pattern in HER2 positive group, which was statistically significant (p<0.05).More than three fourth (80.0%) patients had T =staging 4b in positive group and 13(30.2%) in negative group. More than two third (70.0%) had N=staging 1 in positive group and 26(60.4%) in negative group. More than three fourth (80.0%) M=staging 1 in positive group and 8(18.6%) in negative group. The difference of T =staging and M=staging were statistically significant (p<0.05) between two groups. Though there was no significant association with tumor grading.

Conclusion: The patients of gastric cancer with HER2 overexpression constitute a distinct subgroup. In this study HER2 overexpression was significantly associated with Intestinal type, T & M staging but not with N staging. Thus it evident that HER2 status is associated with advanced stages of gastric carcinoma.

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Introduction:

Gastric cancer (GC) is a significant health problem, with an estimated 989,600 new diagnoses and 738,000 deaths per annum, according to the latest global data[1]. Globally gastric cancer is the 4th most frequently diagnosed cancer and the 2nd leading cause of death from cancer[2]. The prevalence rate of carcinoma stomach in Bangladesh is about 4.7% [3]. The accurate staging of a patient's disease can have a major role in determining the final clinical outcome. The standard imaging modalities used for the pre-operative staging of gastric cancer include CT, MRI, EUS, diagnostic laparoscopy and per operative findings can be successfully used to stage gastric cancer[4]. Gastric carcinogenesis is a multistep and multi-factorial process. An accumulation of genetic and molecular abnormalities occurs during gastric carcinogenesis. Various biological (molecular) markers known to be indicators of prognosis of patients with advanced gastric cancer. HER2 protein is one of the important molecular-markers. Although various therapies for gastric carcinoma are available, the control of advance stage gastric cancer is still a challenge for physicians. In recent years, molecular targeted therapy is new treatment modality for gastric cancer and HER2 has been identified as a potential therapeutic target[1.] HER2/neu over-expression is associated with poorer survival, but its main importance is as a predictor of response to agents that target this trans-membrane protein (eg. Trastuzumab).

Materials and Methods:

This cross sectional study was carried out in the general surgery department of Sir Salimullah medical college and Mitford Hospital, Dhaka, during November 2016 and October 2017, to assess the relationship between the expression patterns of HER2 with the stages of carcinoma of stomach to establish HER2 as a routine biological marker for carcinoma stomach patient to identify subgroup needed targeted therapy. A total number of 53 consecutive admitted patients from SSMC&MH, DMCH, NICRH and BSMMU were enrolled in this study. Specimens were collected after surgery (either total or partial gastrectomy and in case of unresectable tumors endoscopic biopsy). Patients of all ages and both sex with gastric carcinoma were enrolled in this study. Patients who were not interested and patient already received treatment (radiotherapy or chemotherapy) were exclude from the study. Percentage expression for positivity of HER2 was estimated along with 95% confidence interval. The differences in the positivity rate between different sex, stages and grades were tested through 'Chi' square test of significance and a value of $p < 0.05$ was consider to be statistically significant.

Result:

The mean age was 51.74±12.02 years with ranged from 26 to 70 years. More than half (52.8%) patients were male and 25(47.2%) were female. Almost two third (66.0%) patients had tumor location in antrum and almost 80 (79.2%) patients had intestinal type according to Laurence classification. Regarding the Staging it was observed that 21(39.6%) patients had T =staging 4b, 33(62.3%) N=staging 1 and 16(30.2%) M=staging 1. Nearly two third (66.0%) patients had grading 2.

More than three fourth (75.5%) patients had HER2 scoring 0/1+ Negative, followed by 10(18.8%) had 3+ positive and 3(5.7%) had 2+ equivocal. The mean age was 56.9±10.67 years in positive group and 50.53±12.11 years in negative group. More than two third (70.0%) patients were male in positive group and 21(48.8%) in negative group. Almost two third (60.0%) patients had growth in antrum in positive group and 29(67.4%) in negative group. The difference were statistically not significant ($p>0.05$) between two groups. Almost three fourth (70.0%) patients had grading 2 in positive group and 28(65.1%) in negative group. The difference was statistically not significant ($p>0.05$) between two groups. In positive group more than three fourth (80.0%) patients had intestinal type histological pattern and in negative group 34(79.1%) patients had intestinal type histological pattern.

In positive group more than three fourth (80.0%) patients were in T =staging 4b and in negative group 13(30.2%) in staging 4b. More than two third (70.0%) had N=staging 1 in positive group and 26(60.4%) in negative group. More than three fourth (80.0%) M=staging 1 in positive group and 8(18.6%) in negative group. The association of HER2 with T staging and M staging were statistically significant ($p<0.05$) but the difference was statistically not significant ($p>0.05$) with N staging.

Table-I. *Relation of HER 2 with different variables*

Variables	HER 2 positive (n= 10)	HER 2 negative (n= 43)	P value
Mean age	56.9	50.53	0.133[ns]
Sex			
Male	7 (70%)	21 (48.8%)	0.227[ns]
Female	3 (30%)	22 (51.2%)	
Location			
Body	1 (10%)	7 (16.3%)	
Antrum	6 (60%)	29 (67%)	0.580 [ns]
Antrum & body	3 (30%)	7 (16.3%)	
Laurence classification			
Intestinal	8 (80%)	34 (79.1%)	0.948 [ns]
Diffuse	2 (20%)	9 (20.9%)	
T- Staging			
T1	0	0	
T2	0	2 (4.7%)	
T3	1 (10%)	18 (41.8%)	0.036[s]
T4a	1 (10%)	10 (23.3%)	
T4b	8 (80%)	13 (30.2%)	
N- Staging			
N0	0	4 (9.3%)	
N1	7 (70%)	26 (60.4%)	0.354[ns]
N2	3 (30%)	7 (16.3%)	
N3	0	6 (14%)	
M- Staging			
M 0	2 (20%)	35 (81.4%)	
M1	8 (80%)	8 (18.6%)	0.001 [s]
Grading			
G1	1 (10%)	3 (7%)	
G2	7 (70%)	28 (65.1%)	0.852[ns]
G3	2 (20%)	12 (27.9)	

s= significant; ns= non significant

Discussion:

This cross sectional study was carried out with an aim to assess the relationship between the expression patterns of HER2 with the different stages of carcinoma of stomach, Laurence classification and the site (location) of carcinoma of stomach. This study also assess the relationship of the expression patterns of HER2 with the degree of differentiation of carcinoma of stomach and to establish HER2 as a routine biological marker for carcinoma stomach patient to identify subgroup needed targeted therapy.

Regarding HER-2 it was observed that 52.8% patients had 0 negative, 22.6% 1+negative 5.7% 2+ equivocal and 18.9% had 3+positive. Uprak et al. also observed 0, 1+, 2+, and 3+ were 78.0%, 8.0%, 5.0% and 9.0%[5]. A total of 142 cases observed by Im et al. and that were scored for HER2 by IHC, 60.7%, 23.6%, 7.1%, and 8.6% scored IHC 0, 1+, 2+, and 3+, respectively[6], which all are similar with the current study. In the ToGA clinical trial, an overall HER2 expression (IHC 3+ and/or FISH +) was reported as 22 % in 3,665 patients and a higher rate of HER2 positivity was found in GEJ than in gastric cancer samples (34 vs. 20 %)[7].

According to this study, it was observed that 40.0% patients belonged to age 51-60 years in positive group and 39.5% in negative group. The mean age was 56.9±10.67 years in HER-2 positive group and 50.53±12.11 years in HER-2 negative group. The difference was statistically not significant (p>0.05) between HER-2 positive and negative groups. Similarly, 70.0% and 48.8% patients were male in positive and negative group respectively. The difference was also statistically not significant (p>0.05) between HER-2 positive and negative groups, which indicates that no association was found between HER2 over-expression with age and sex. Similarly, Uprak et al. showed the mean age was 60±10 years in positive group and 61±12 years in negative group[5]. More than one fourth (27.0%) were female and 73.0% were male in positive group. 35.0% female and 65.0% male in negative group. The difference were not statistically significant (p>0.05) between two groups, which is closely resembled with the current study. In an Indian study Tewari et al. reported that no association was found between HER2 over-expression with age and gender[8]. Similar association between HER2 overexpression with age was also observed by Park et al.[9], Kataoka et al.[10] and Son et al.[11]. The all the above mentioned studies are consistent with the current study.

In our study, it was observed that 60.0% patients had growth in antrum in positive group and 67.4% had antral growth in negative group. Followed by in positive group 30.0% had growth in body & antrum and 16.3% in negative group and 10.0% had growth in body in

positive group and 16.3% in negative group. The difference was statistically not significant (p>0.05) between two groups. Uprak et al. observed 36.0% cardia and 64.0% antrum in positive group and in negative group 27.0% cardia, 19.0% corpus and 51.0% antrum[5]. The difference was statistically not significant (p>0.05) between two groups, which is similar with the current study.

It was observed in the study that intestinal type was present in 80.0% patients in positive group and 79.1% in negative group. Followed by, diffuse type tumor present 20.0% in positive group and 20.9% in negative group. The difference was statistically not significant (p>0.05) between two groups. Similarly Uprak et al. found 82.0% in intestinal and 18.0% diffuse-mixed in positive group and 54.0% were intestinal and 46.0% diffuse-mixed in negative group[5], which support with the current study. Similar observations regarding the association between Lauren's classification with HER-2 also observed by Son et al. (2014) and Park et al. (2015) studies.

In this present series, it was observed that in positive group 80.0% patients had T =STAGING 4b and in negative group 30.2% had T =STAGING 4b. 70.0% had N=STAGING 1 in positive group and 60.4% in negative group. Whereas in positive group 80.0% were in M=STAGING 1 and in negative group 18.6%. T-staging 4b and M-staging 1 were significantly (p<0.05) higher in HER2 positive group. Similarly Park, et al. mentioned in their study that HER2 over-expression was more commonly observed in patients with lymph node metastasis (N0 disease, 13.2%; N1 disease, 13.3%; N2 disease, 30.3%; N3 disease, 35.1%; (p<0.05) and differences in frequency of HER2 over-expression among the T stages also were estimated to be significant (p<0.05)[9]. On TNM stage, HER2 over-expression was more commonly observed in patients with advanced stage (p<0.05). Al-Moundhri et al. found stage III and IV disease in 71.0% patient and HER-2/ neu expression correlated with histological grade and T-stage (P<0.05) and lymph node involvement in 53.7%[12] .

In this study, it was observed that 70.0% patients had grading 2 in positive group and 65.1% in negative group. The difference was statistically not significant (p>0.05) between two groups. Uprak et al. observed Grade 1 and 2 had 82.0% in positive group and 50.0% in negative group. Grade 3 had 9.0% in positive group and 27.0% in negative group[5], which is comparable with the current study.

On the basis of the relationship of HER- 2with the advanced stage of carcinoma stomach, it is now excepted that, HER-2 testing will be included in the routine diagnostic work-up of patient with advanced gastric cancer and can identify a subgroup eligible for anti HER 2 targeted therapy. Bang et al found that addition of trastuzumab to chemotherapy improved survival in patients with advanced gastric or gastro-oesophageal junction cancer compared with chemotherapy alone. Similarly Luis et al[13], Forde et al[14] found trastuzumab plays a potential role in treatment and prognosis of carcinoma stomach patient.

Conclusion:

The patients of gastric cancer with HER2 over-expression constitute a distinct subgroup, who can be recommended for trastuzumab therapy, for the treatment of patients with advanced gastric cancer. In this study most of the patients were in 6th decade and slightly male predominant. More common location was Antrum and Laurence classification was Intestinal type. There is no correlation between HER-2/neu expression with age, sex and pathological grading. Regarding TNM staging HER2 was significantly associated with T & M staging but not with N staging. Thus it evident that HER2 status is associated with advanced stages of gastric carcinoma.

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