Original Article

Clinicopathologic and Prognostic Significance of Her2 Neu and p53 Overexpression in Gastric Adenocarcinoma

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Abstract

Background: Gastric cancer is one of the major causes of mortality worldwide. Human epidermal growth factor receptor 2 is a protooncogene present on chromosome 17. Genetic alternations play a pivotal role in the pathogenesis of cancers involving carcinoma of stomach. The most frequent change is observed in p53 gene. The objective of this study is to determine the percentage of expression of Her2 Neu and p53 nuclear protein in gastric adenocarcinoma and compare the expression with other clinicopathological variables.

Methods: In this cross-sectional observational study, 90 cases of gastric adenocarcinoma in the time period of 3 years were taken. Scoring for Her2 Neu and p53 expression was done using specific scoring systems for all the cases. Data were entered in Microsoft Excel and analysed using SPSS software.

Results: In our analysis, majority of patients were distributed in the 61-70 age group (37.8%). Male to Female ratio was 2.56. Out of 90 cases, 71.7% was intestinal type of adenocarcinoma. p53 expression was seen in 44.4% of gastric adenocarcinomas and intestinal type cases showed increased expression, while Her2 Neu expression was seen in 11 cases and all the cases were of intestinal type. In this study, statistically significant association was found between p53 expression and lymph node involvement in the tumour and also between p53 expression and serosal invasion of the tumour. No statistically significant association was found between Her2 Neu overexpression and other variables.

Conclusion: p53 expression correlates with poor prognosis of the patients as it is more frequently associated with cases showing lymph node metastasis and increased depth of invasion of tumour. p53 expression was also frequent among higher grade tumours which also indicate the poor prognostic value of this marker. Targeted therapy with anti-Her2 Neu antibody can be implemented in the cases with Her2 Neu overexpression.

Keywords: Gastric adenocarcinoma; p53; Her2 Neu

Introduction

One of the most common and deadly diseases in the world today is gastric cancer. However, very little is known about the antiquity, epidemiology, and development of cancer in earlier human populations. Gastric cancer is currently one of the major causes of mortality worldwide [1]. The incidence is currently declining due to early detection, decreased Helicobacter pylori infection rates, and the spread of healthy lifestyles (including quitting smoking and healthy food habits), but certain geographical variances in its incidence and mortality rate still exist. In India, the number of new gastric cancer patients is approximately 34,000 each year with a male to female ratio of 2:1. Gastric carcinoma is the second most common cause of cancer related death in both men and women in India [2].

Human epidermal growth factor receptor 2 is a protooncogene present on chromosome 17. The Her2 Neu has transmembrane tyrosine kinase activity that promotes cell proliferation and supresses apoptosis, thereby leads to tumorigenesis. Her2 Neu is involved in the pathogenesis and poor outcomes of a subset of breast and advanced gastric cancers [3].

After the recent approval of Transtuzumab (anti-Her2 Neu antibody) for the treatment of Her2 Neu overexpressed gastric adenocarcinoma, importance of Her2 Neu testing is increasingly recognized. There are fair numbers of studies available worldwide on Her2 Neu status in gastric cancer patients. However, data regarding Her2 Neu expression in the Indian gastric cancer patients is available in only a limited number of studies.

Genetic alterations are known to play a pivotal role in pathogenesis of cancers, including carcinoma of the stomach. Among these, the most frequent change is observed in the p53 gene. Normally, p53 gene encodes wild-type p53 protein, which has a very short half-life, and controls the cell cycle (G1 phase arrest) and apoptosis of cells with damaged DNA. Point mutation, deletion, or rearrangement of p53 gene causes formation of mutant p53 protein [4]. Mutant form of p53 protein is very stable and can accumulate in the nuclei of tumour cells. IHC staining with specific antibody can be used to detect mutant p53 protein.

In this study, we are evaluating the IHC expression of Her2 Neu and p53 in gastric adenocarcinoma and their association with other clinicopathological parameters. Studies have reported that p53 overexpression was associated with more aggressive tumor behaviour and was an independent prognostic factor [5, 6]. Hence, immunohistochemical evaluation of p53 protein in our study allows in selection of a group of patients with an aggressive therapeutic indication such as extensive lymphadenectomy and adjuvant chemotherapy.

Her2 Neu expression has become an important biomarker for identifying patients who could respond to Her2 Neu targeting therapy using the fully humanized monoclonal antibody transtuzumab [7]. Thus, this study will help in identifying a subgroup of patients who could receive effective targeted therapy by assessing Her2 Neu overexpression by immunohistochemistry.

Materials and Methods

This was a cross sectional observational study carried out at a tertiary care centre in Kerala, collecting data of patients that have come to the centre over a period of 3 years.

Sample size was calculated using the formula, $n = \frac{4pq}{d^2}$. n=required sample size; p=prevalence (40%) [8]; q=100-p=60; d=precision (10%). Therefore, $n = \frac{4\times40\times60}{100} \approx 90$.

Inclusion criteria: All histopathologically diagnosed cases of gastric adenocarcinoma during the study period were included in the study.

Exclusion criteria: Endoscopic biopsy cases which proceed to resection, in which case the resected specimen will be used. Biopsies from gastro-oesophageal junction. Patients who have received chemotherapy prior to resection.

Clinical details were collected from IP records and from patients according to proforma. Samples received were fixed in 10% formalin for 24 hours and grossed as per standard guidelines, tissue paraffin blocks were made and sections of 4-5 μm were cut and stained with H&E stains. IHC study for Her2 Neu and p53 were performed on tissue blocks. Mouse monoclonal antibody p53-BP-53-12 from PathnSitu was used for p53 while rabbit monoclonal antibody NGLP from PathnSitu was used for Her2 Neu. Scoring of Her2 Neu was done by ASCO/CAP guidelines using Hoffman's criteria. Data was entered in Microsoft Excel and analysed using SPSS software.

Results

Ages in our studied population ranged from 35 to 85 years. The majority of patients were in the age group of 61-70 years (37.8%), followed by 51-60 years (30%), as depicted in Figure 1. Out of 90 cases, 64 cases were male, constituting to 71.1% of the study population.

On examination, majority of cases presented with a tumor of size less than 5 cm and in the range of 5-10 cm (44.2% each), while only 11.5% of cases presented with a tumor size exceeding 10 cm. Histopathological examination showed that 64 cases received were of intestinal type (71.1%) of gastric adenocarcinoma, while 26 cases were of diffuse type (28.9%). Histological subtyping of the tumors were done and the results showed that majority cases were tubular type adenocarcinoma (81.1%), followed by non signet ring type adenocarcinoma, signet ring type and mucinous type (Table 1).

Out of the 90 cases, 34 cases showed lymph node involvement and 15 cases were uninvolved.

Histopathological grading of tumors showed that 39 cases were moderately differentiated (54.2%), 26 cases were well differentiated (36.1%) and 7 cases were poorly differentiated (9.7%).

p53 Score: p53 scoring was done using Streptavidin Biotin Immunoperoxidase method (Table 2). Out of the 90 cases,

26 cases showed weak positivity (28.9%), 21 cases showed moderate positivity (23.3%) and 19 cases showed strong positivity (21.1%). For the purpose of this study, all the cases that showed p53 positivity were grouped as p53 positive cases, irrespective of the intensity of staining. Figure 2 shows intestinal type gastric adenocarcinoma (A) and p53 IHC staining done showing 3+ (strong) nuclear positivity (B).

Correlation of p53 expression with other variables: The P value on correlating p53 expression with age of the patient was 0.717 which is statistically insignificant. Among the cases showing p53 positivity, 72.7% were males and 27.3% were females and in the cases showing p53 negativity, 66.7% were males and 33.3% were females. This association was statistically insignificant.

On correlating the size of the tumour with p53 expression, among the 38 cases showing p53 positivity, 42% were less than 5 cm and 42% were between 5 to 10 cm in size. This association was statistically insignificant. On correlating with Lauren's classification, 65.2% of cases with p53 positivity were intestinal type and only 34.8% of cases were of diffuse type, and this association is statistically significant. p53 negative tumors showed that 87.5% was of intestinal type while the rest was of diffuse type (Table 3 and Figure 3).

On correlating the lymph node status with p53 expression, 80% cases showed lymph node involvement and only 20% cases were showing no lymph node involvement. This association is having a P value 0.011 and is statistically significant (Table 4). On correlating Histological type of tumor with p53 expression, 72.6% of tubular adenocarcinoma cases showed p53 positivity, while 77.7% of cases with non signet ring type and 83.3% of cases with signet ring type showed p53 positivity. Mucinous type of adenocarcinoma showed 50% cases with p53 expression. But this association is statistically insignificant (Table 5). On correlating histological grade with p53 expression, 53.8% of cases with p53 positivity were of moderately differentiated type, followed by 36.5% of well differentiated tumors and 9.6% of poorly differentiated tumors. But this association was found to be statistically insignificant.

On correlating the Depth of infiltration of tumour with p53 expression, 65.7% of cases with p53 positivity showed serosal involvement while only 28.6% of p53 negative tumors showed serosal involvement (Figure 4). This association has a P value of 0.018 and therefore it is statistically significant.

Her2 Neu Score: Her2 Neu scoring was done by ASCO/CAP guidelines as given in Table 6.

Out of the 90 cases, Her2 Neu overexpression was seen in 4 cases (4.4%) and equivocal expression was seen in 5 cases (5.6%), while the rest showed Her2 Neu scoring of 0 or 1. Figure 5 shows H&E-stained section of gastric adenocarcinoma-intestinal type (A) and IHC done showing 3+ (strong membranous) positivity for Her2 Neu (B).

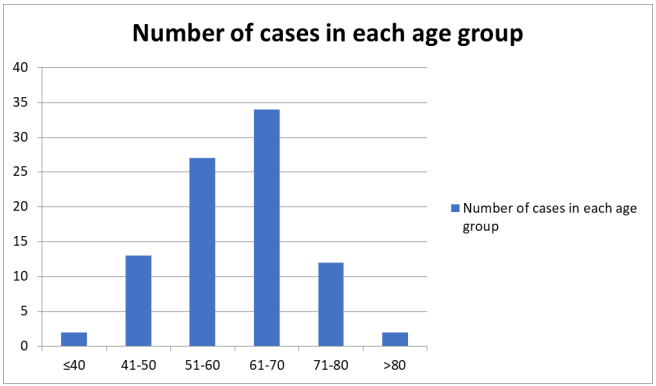

Figure 1: Distribution of cases according to age.

Table 1: Histological Type of gastric tumors in the study population.

Histological Type	Frequency	Percent (%)
Mucinous	2	2.2
Non signet ring type	9	10.0
Signet ring type	6	6.7
Tubular adenocarcinoma	73	81.1
Total	**90**	**100.0**

Correlation of Her2 Neu expression with other variables: On correlating age of patient with IHC expression, all cases which showed Her2 Neu over expression belonged to 61-70 age group. On correlating Gender of patient with IHC expression, all cases that showed Her2 Neu overexpression were males. But this association is statistically insignificant. Correlation of Her2 Neu expression with histological type of tumour showed that all cases with Her2 Neu overexpression is of Tubular

Table 2: Scoring of p53 by Streptavidin-Biotin Immunoperoxidase method by DAKO.

p53 Score	Intensity of Stain	Interpretation
1	<5% of tumor cells showing nuclear stain	Negative
2	5-20% of tumor cells showing nuclear stain	Weakly positive
3	20-50% of tumor cells showing nuclear stain	Moderately positive
4	>50% of tumor cells showing nuclear stain	Strongly positive

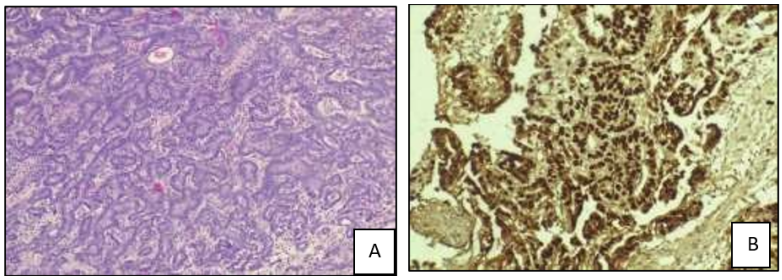

Figure 2: (A) shows intestinal type gastric adenocarcinoma. (B) shows 3+ (strong) nuclear positivity of p53.

Table 3: Association of Laurens type with p53 expression (χ^2=4.279, df=1, p=0.039).

	p53 Positive		p53 Negative		Total	
Laurens Type	**N**	**%**	**N**	**%**	**N**	**%**
Diffuse Type	23	34.8	3	12.5	26	28.9
Intestinal Type	43	65.2	21	87.5	64	71.1
Total	**66**	**100.0**	**24**	**100.0**	**90**	**100.0**

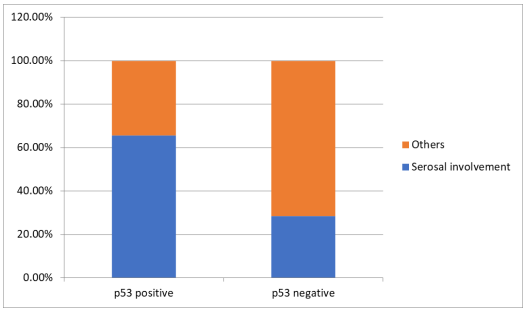

Figure 3: Correlation of Laurens type with p53 expression.

Table 4: Association of Lymph node status with p53 expression (χ^2=6.495, df=1, p=0.011).

	p53 Positive		p53 Negative		Total	
Lymph Node Status	**N**	**%**	**N**	**%**	**N**	**%**
Involved	28	80.0	6	42.9	34	69.4
Uninvolved	7	20.0	8	57.1	15	30.6
Total	**35**	**100.0**	**14**	**100.0**	**49**	**100.0**

Type. But this association is statistically insignificant. On correlating the Histological Grade with Her2 Neu expression, 75% of cases with Her2 Neu overexpression were moderately differentiated grade. This association is statistically insignificant.

Discussion

Testing for Her2 Neu has now become routine practice in guiding treatment and prognosis in breast cancer. The recommended methods for assessing the Her2 Neu status are gene amplification using Fluorescence In-situ Hybridization (FISH) and protein over expression by Immunohistochemistry (IHC). Out of the two methods, IHC is the method of choice for Her2 Neu status in breast and gastric cancers. This is due to cost-effective set up of IHC and ease of performing the test. In India, Her2 Neu testing in gastric cancers has been done only in few studies.

Table 5: Association of histological Type with p53 expression (χ^2=0.974, df=3, p=0.807).

	p53 Positive		p53 Negative		Total	
Histological Type	**N**	**%**	**N**	**%**	**N**	**%**
Mucinous	1	1.5	1	4.2	2	2.2
Non signet ring	7	10.6	2	8.3	9	10.0
Signet ring type	5	7.6	1	4.2	6	6.7
Tubular	53	80.3	20	83.3	73	81.1
Total	**66**	**100.0**	**24**	**100.0**	**90**	**100.0**

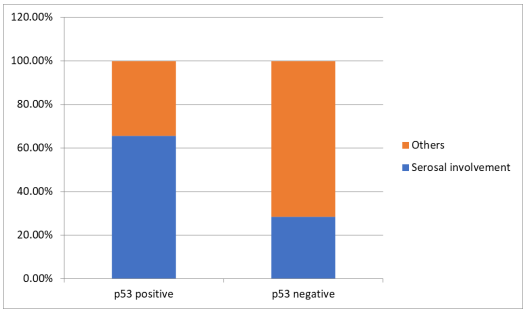

Figure 4: Correlation of Depth of infiltration with p53 expression.

Table 6: Scoring of Her2 Neu by ASCO/CAP guidelines using Hoffman's criteria.

Her2 Neu Score	Staining Pattern	Interpretation
0	No reactivity/ no membranous reactivity in any tumour cell	Negative
1	Tumor cell cluster with a faint / barely perceptible membranous reactivity	Negative
2	Tumor cell cluster with a weak to moderate complete basolateral or lateral membranous reactivity	Equivocal
3	Tumor cell cluster with a strong complete basolateral or lateral membranous reactivity	Over expression

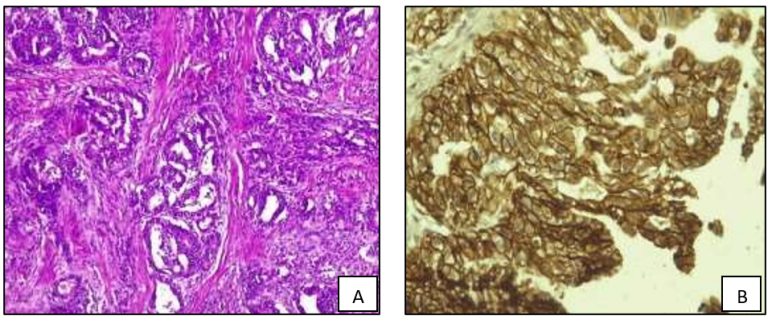

Figure 5: (A) shows intestinal type gastric adenocarcinoma. (B) shows 3+ (strong) membranous positivity of Her2 Neu.

In this study, our aim is to determine the expression of p53 and Her2 Neu in gastric adenocarcinoma and compare the expression with other clinicopathological variables including age, gender, histological type, histological Grade, lymph node status, and depth of infiltration of the tumor.

In our analysis, patients were primarily distributed in the 61-70 years age group (37.8%), followed by 51-60 age group (30%), 41-50 age (14.4%), and 71-80 age (13.3%). This age distribution was similar to earlier studies conducted both in India and outside. The male to female ratio obtained is 2.46:1.

In the present study, statistically significant correlation was found between p53 expression and lymph node involvement, and also between p53 expression and serosal involvement, with P value < 0.05. Similar to our study, Al-Moundhri et al. noticed that expression of p53 was associated with more aggressive tumor behavior and was an independent prognostic factor [9]. A study by Tzanakis et al. also suggested that more pronounced expression of p53 as a prognostic factor [10]. However, there have been studies showing no significant association between p53 expression and sex, age, disease stage, and pathological type of tumor [11, 12]. Goncalves et al. noted that p53 expression was more frequent among gastric-intestinal type of adenocarcinoma, which is similar to our results [13].

In the present study, higher rate of Her2 Neu over expression was seen in intestinal type rather than diffuse type. But no statistically significant association was observed between Her2 Neu expression and other clinicopathological variables like age, gender, depth of invasion, histological type or grade. Similarly, a study by Daniela Lazar et al. showed p53 expression in 41% of the studied samples and significantly increased immunoreactions of p53 was found in intestinal type carcinomas. Among histological types, tubular adenocarcinomas showed increased percentage of p53 positivity and p53 positivity was more in moderate/poor differentiated carcinomas and those associated with lymph node involvement [14]. These findings are all comparable to our present study.

Tanner et al. observed Her2 Neu amplification in 12% out of 131 gastric adenocarcinomas and 24% out of 100 GEJ tumors [15]. In his study, Her2 Neu amplifications was strongly associated with the intestinal type according to Lauren's classification, but it was not associated with gender, age at diagnosis, or clinical stage.

The study by C. Gravalos et al. also observed high rate of Her2 Neu over expression in intestinal rather than diffuse type (16% vs 7%) [16].

In the Finnish study, amplification of Her2 Neu was strongly associated with poor carcinoma specific survival, particularly evident in the subgroup of intestinal type of cancers (P=0.0019), which is considered to associate with more favorable prognosis than the diffuse type of gastric adenocarcinoma [17]. Intestinal type cancers also exhibited higher rates of Her2 Neu amplifications than diffuse type of adenocarcinoma.

Although many studies have thus reported significant association between Her2 Neu and the clinicopathological variable, the present study shows no such significant correlation. This warrants the need for an extensive, population based study to truly establish the association between Her2 Neu and the clinical prognosis. P53, as evidenced in other studies, has shown significant association with clinical prognosis in this study too.

Conclusion

Higher rate of p53 expression was seen in intestinal type of adenocarcinoma and significant association was found between p53 expression and lymph node involvement. Also, p53 expression was higher among cases with serosal involvement. This shows that p53 overexpression is linked with worse prognosis in gastric Adenocarcinoma patients.

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