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Histomorphological Study of Gastric Carcinoma and Correlation with P53 Immunohistochemistry

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Abstract

Aim: To evaluate the association and prognostic significance of P53 in gastric neoplasms with tumor site and its macroscopic appearance.

Methods: A total of 48 cases of endoscopic gastric biopsies and surgically resected specimens that include both pre-malignant and malignant neoplasms were collected. The following inclusion and exclusion criteria were adopted:

Inclusion criteria: All gastric adenocarcinoma cases reported in both endoscopic biopsies as well as resected specimens, irrespective of age and sex were included for the study. Exclusion Criteria: Non-neoplastic lesions and benign tumors of stomach, Malignancies other than adenocarcinoma and gastrostomies performed for reasons other than gastric tumors were excluded from the study.

Results: GCs had a peak incidence in the age group of 51-60 years. The youngest age of presentation of gastric cancer was at 37 years in this study. 30 (62%) cases were reported in males and 18 (38%) cases were reported in females with male: female ratio accounting to 1.6:1. 25(52.08%) cases involved the pyloro-antrum, 12 (25%) involved body, 5 (10.42%) involved eso-cardia, 3 (6.25%) cases involved fundus and 3(6.25%) cases involved pan-gastric region. Ulcero-proliferative type(35%) was the most common gross appearance followed by ulcerative type(29%). P53 positivity was observed in 84% of tumors in pyloro-antrum, 83.2% of tumors in body, 40% of tumors in eso – cardia. 33.1% of tumors in fundus and 66.7% in pan – gastric tumors. The association with respect to site was found to be statistically significant with increased expression seen in tumors of pyloro-antrum. Among various gross types, P53 positivity was noted in 8 cases (57.8%) of ulcerative type, 9 cases (75%) of nodular type, 15 cases (88.2%) of ulcero-proliferative type and 3 cases (60%) of proliferative type. P53 expression showed statistically significant association with tumor location but not with macroscopic appearance.

Conclusion: Identifying expression of P53 in GC could be helpful in categorizing patients eligible for targeted therapy. Patients at high risk of recurrence and poor survival can also be identified. A larger sample size and follow-up of these patients for 5 more years could throw more light on role of P53 mutation as long-term prognostic indicator.

Keywords: Gastric carcinoma • P53 • Schizophrenia • Prognostic indicator

Introduction

Cancer being a major contributor of mortality rate worldwide, its incidence is progressively increasing [1]. Among the cancers, Gastric carcinoma (GC) remains the fifth most common neoplasm globally following the cancers of Breast, oral cavity, cervix and lung according to GLOBOCAN 2018 and ranks as third most common in males and fifth most common in females in India on report of 2018 cancer statistics by ICMR (Charts 1,2).

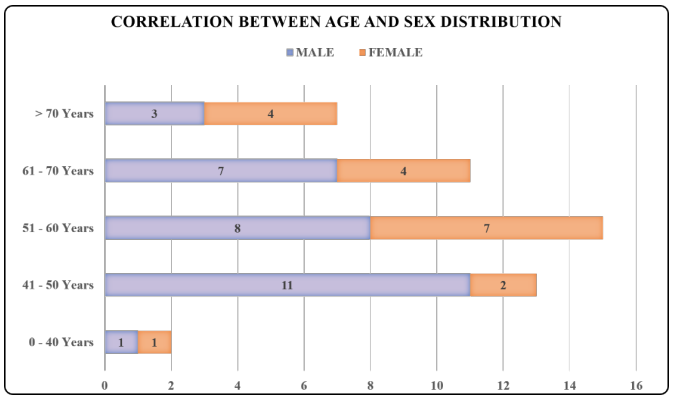

Chart 1. Correlation between age and sex distribution of gastric cancer.

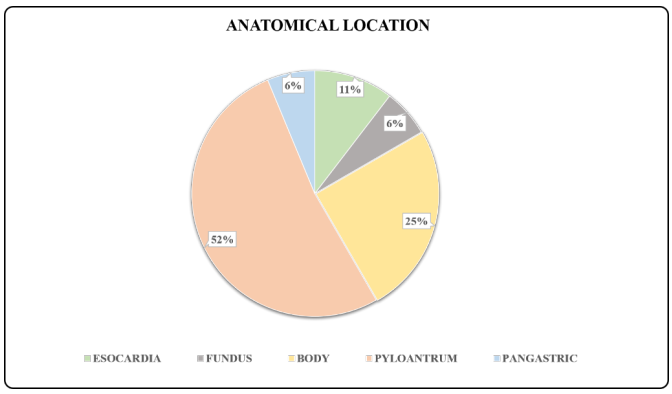

Chart 2. Distribution of gastric carcinoma based on anatomical location.

GLOBOCON 2018 says, Asia ranks one among other countries in incidence as well as mortality rate followed by Europe and South America in GC [2]. About 7, 69,728 new cases of GC were reported in 2018 in Asia, among which 57,394 cases were from India. Mortality rate is also high in Asia accounting for about 5, 84,375 deaths, among which 51,429 is from India [3].

The element of danger for gastric cancer include non-genetic factors like Pylori infection, consuming Alcohol, high salt intake in diet, Smoking cigarettes, Pernicious anemia and Genetic predisposition such as BRCA1 and BRCA2 mutations [4].

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The high mortality rate is because late presentation of cases with higher stages, sometimes even with lymph node metastasis and bad prognosis [5]. This marks the significance of evaluating prognostic markers to diagnose the cases at an early stage to overcome the awkwardness in cure and treatment. This helps in treatment plan and patient survival, as the survival rate and prognosis rely on the presenting stage of GC.

Several studies and so much of effort put in to identify specific biological markers that would help in diagnosing GC at an early stage. These markers would also help in diagnosing malignant and pre-malignant lesions and would also aid in the treatment of target therapy (Chart 3).

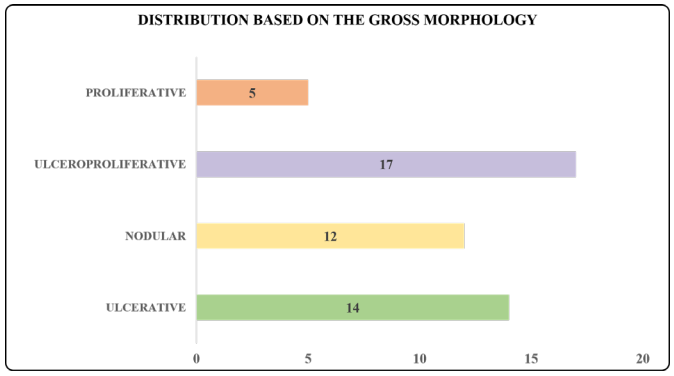

Chart 3. Distribution of gastric cancer based on gross morphology.

Currently, markers like P53, Her2/neu, Her3, E-cadherin, EGFR and FGFR are being used in neoplasms of stomach to evaluate its prognosis [6]. P53, a nuclear protein functions as a transcription factor with a purpose to maintain genomic stability. When there is DNA damage, the mechanism of this nuclear protein is to bind to the DNA which activates the transcription of genes responsible for cell-cycle arrest leading to apoptosis of the cell.

P53 is encoded by Tumor Suppressor Gene (TSG) TP53 which is located on the chromosome 17q13. TP53 is inactivated in gastric neoplasms and in other malignancies as well. TP53 mutation causes nuclear staining owing to accumulation of mutant P53 nuclear protein, which is resistant to degradation. Therefore, when there is no TP53 mutation, there is no accumulation of P53 protein and the staining will be negative.

In this study, expression of P53 in malignant and pre-malignant neoplasms of stomach is studied with Immunohistochemistry. Prognostic significance of P53 and its association with other important factors are also being analyzed.

Materials and Methods

All the endoscopic gastric biopsies as well as surgically resected specimens sent for histopathological evaluation from the Department of Medical Gastroenterology, Sree Balaji Medical College and Hospital, Chromepet, Chennai during the study period (November 2018-September 2020) were included in the study.

A total of 48 cases of endoscopic gastric biopsies and surgically resected specimens that include both pre-malignant and malignant neoplasms were collected.

The following inclusion and exclusion criteria were adopted:

Inclusion criteria

All gastric adenocarcinoma cases reported in both endoscopic biopsies as well as resected specimens, irrespective of age and sex were included for the study (Table 1).

Exclusion criteria

1) Non-neoplastic lesions and benign tumours of stomach,

2) Malignancies other than adenocarcinoma,

3) Gastrectomies performed for reasons other than gastric tumors were excluded from the study.

Detailed history of cases regarding age, sex, clinical presentation, investigations done along with the findings, type of procedure done were obtained for all the gastric specimens received during the study period. Hematoxylin and Eosin stained 4-micron thick sections of the paraffin tissue blocks of all cases were prepared and cases reported as gastric adenocarcinoma were selected (Table 2). Among 48 adenocarcinoma cases reported, 37 cases were endoscopic biopsies and 11 cases were resected specimens (Figure 1). Further, formalin-fixed, paraffin-embedded tissue samples were subjected to H & E stain and immunohistochemical analysis with P53 marker (Figure 2) (Chart 4).

Interpretation for P53: Tumour cells were scored positive when there was golden-brown nuclear staining in the neoplastic cells.

1) P53-negative (-): immunostaining in <10% of the tumour nuclei.

2) P53-positive (+): immunostaining in >10% of the tumour nuclei.

S. No.	Age group	No. of cases	Total No.(%)	Surgery
		Males	Females	
1	0-40 Years	1	1	2(4%)
2	41-50 Years	11	2	13(27%)
3	51-60 Years	8	7	15(31%)
4	61-70 Years	7	4	11(23%)
5	>70 Years	3	4	7(15%)
Total		30 (62%)	18(18%)	48 (100%)

Table 1. Age and sex wise distribution of gastric cancer.

S. No	Site of gastric cancer	Total No. (%)
1	Eso-cardia	5 (10.42%)
2	Fundus	3 (6.25%)
3	Body	12 (25%)
4	Pylo-antrum	25 (52.08%)
5	Pan-gastric	3 (6.25%)
Total		48 (100%)

Table 2. Distribution of gastric cancer based on its anatomical location.

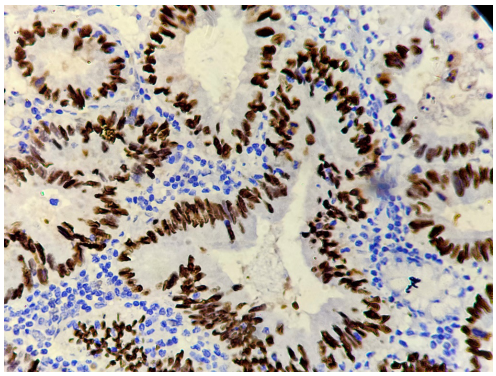

Figure 1. Strong nuclear positivity of p53 in gastric adenocarcinoma.

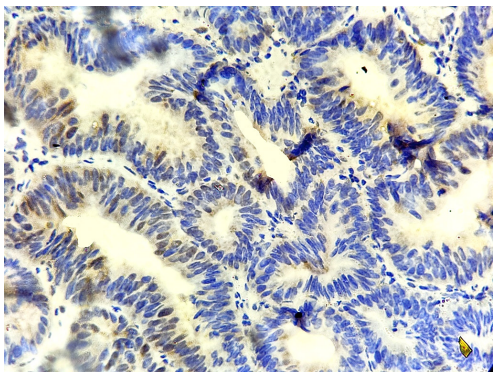

Figure 2. Negative expression of p53 in gastric adenocarcinoma.

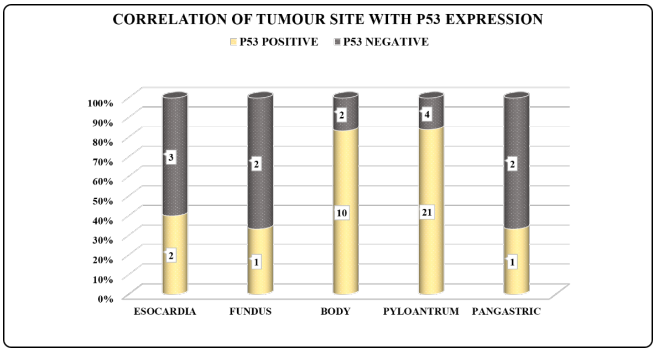

Chart 4. Correlation of tumour site with P53 expression.

Statistical analysis

Statistical analyses were performed using SPSS for window 21.0 software (IBM Corp.). The clinical properties of patients were calculated using mean ± SD and percentage values. Parametric parameters were investigated with students T-test. Results were evaluated within 95% CI and a P<0.005 is considered as significant (Chart 5).

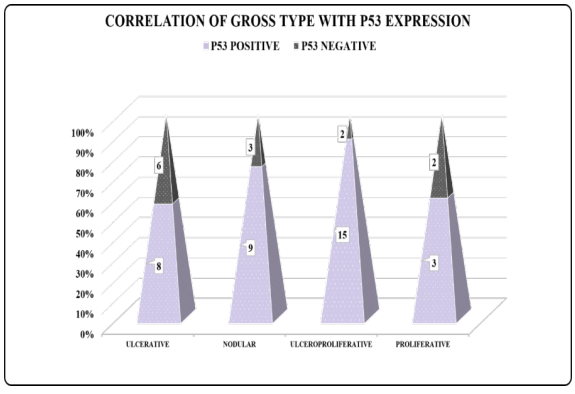

Chart 5. Correlation of gross type with P53 expression.

Results

Among the selected cases, 81.2% were Adenocarcinoma of stomach, 6.2% were EGC, 4.2% were High grade Dysplasia and 8.4% were Low grade Dysplasia cases. GCs had a peak incidence in the age group of 51-60 years. The youngest age of presentation of gastric cancer was at 37 years in this study. Among the 48 cases, 30 (62%) cases were reported in males and 18 (38%) cases were reported in females with male:female ratio accounting to 1.6:1 (Table 3).

S. No.	Gross morphology	Total No.(%)
1	Ulcerative	14 (29%)
2	Nodular	12 (25%)
3	Ulcero-proliferative	17 (35%)
4	Proliferative	5 (11%)
	Total	48 (100%)

Table 3. Distribution of gastric cancer based on gross morphology.

Discussion

GC is common in elderly age group but, is also reported in younger individuals. Literature says, the distal part of stomach is the common site of adenocarcinoma, but recently incidence of tumor emerging from gastro-esophageal junction appears to increase.

In 1996, based on location of tumor in GEJ, Siewert et al. [7] proposed a classification of GEJ adenocarcinomas, which was internationally recognized. He said that the tumor that lies between 5 cm proximal and 5 cm distal to the GEJ was considered as esophagogastric junction tumors and classified them as:

1) Type I-The tumor lies 1-5 cm proximal to the gastro-esophageal junction,

2) Type II-The tumor lies between 1 cm proximal and 1 cm distal to the junction

3) Type III-The tumor lies 1-5 cm distal to the junction.

Early gastric cancer

EGC is otherwise called as superficial spreading carcinoma or surface carcinoma [8]. It usually occurs in younger age group and with long duration and present mainly in the corpus and antrum of stomach. It is defined as carcinoma which is limited to the mucosa or the mucosa and submucosa only, irrespective of the lymph node status. Subdivided into:

1) Intramucosal

2) Submucosal carcinoma.

Japanese Gastro-enterological Endoscopic Society has made another classification based on gross appearance of EGC both in endoscopy and in gastrectomy specimen [9].

Advanced gastric cancer

Defined as carcinoma which has spread beyond submucosa into muscularis propria and beyond, irrespective of lymph node status? The survival rate is much less when compared to EGC. A German surgeon and pathologist, Dr. R. Borrmann, in 1926, proposed 'macroscopic classification of advanced gastric cancer'.

1) Type I: Polypoid/Nodular

2) Type II: Ulcerative, localized/Fungating

3) Type III: Ulcerative, infiltrative

4) Type IV: Diffusely infiltrative.

Ulcerated tumors occur frequently in antrum and on lesser curvature of stomach. Whereas polypoid, fungating and nodular tumors occur in body of stomach, greater curvature, posterior wall or fundus (Figure 3). Infiltrative cancers spread superficially in mucosa and submucosa producing plaque-like lesions. Commonly accompanied by thickness of entire stomach wall producing the so-called linitis plastica or "leather bottle" stomach [10].

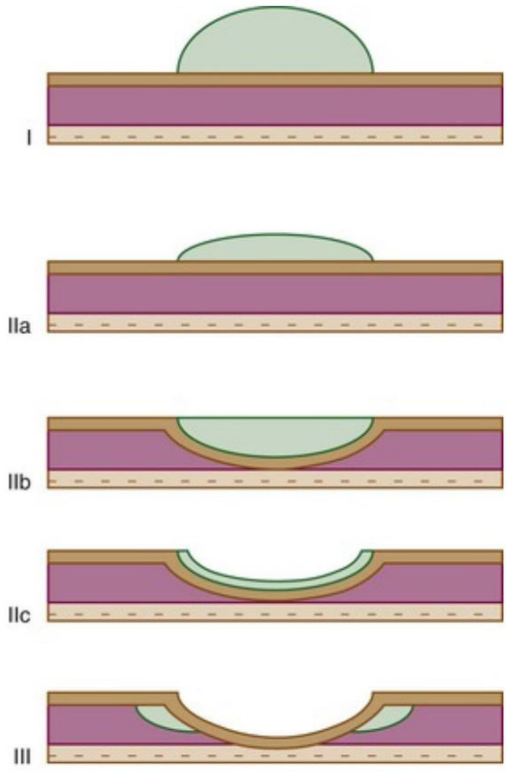

Figure 3. Correlation of gross type with P53 expression.

Most common site of GC in this study was pyloro-antrum (52%). This is almost similar to study of Tzanakis et al. and Lazar et al. In their study, Tzanakis et al observed 51.6% tumors in antrum and Daniela Lazar et al observed 50.8% tumors in antrum. Czyzewska et al. also observed 60% of tumours occurred in antrum (Figure 4) [11-13].

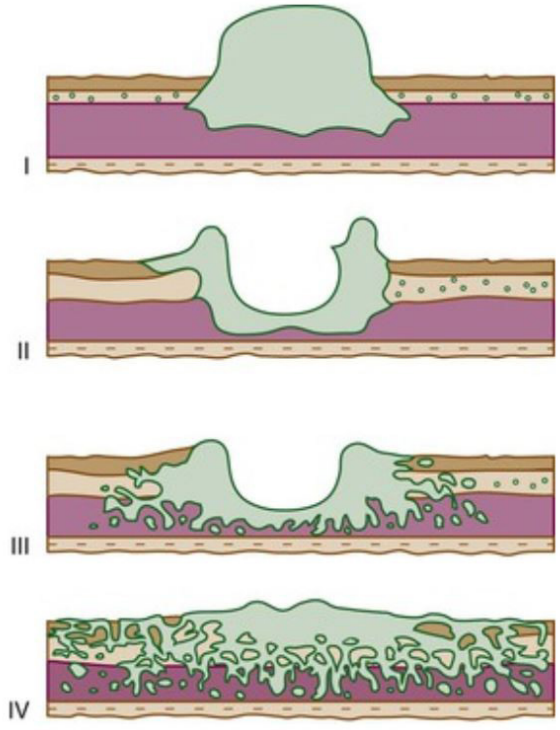

Figure 4. Macroscopic classification of advanced gastric cancer.

Daniela Lazar et al. and Jurgen et al. observed 8.2% of Ulcerative type, 32.7% of Nodular type, 36% of Ulcero-proliferative and 14.7% of proliferative type of tumors. Similar results were observed in present study with 29% of Ulcerative type, 25% of Nodular type, 35% of Ulcero-proliferative and 11% of Proliferative type (Chart 1).

P53 protein

Normal P53 protein is rapidly removed from nucleus. Whereas, mutant forms of P53 have a prolonged half-life, which favours intranuclear accumulation, becoming detectable immuno-histochemically. Mutations of P53 gene was observed in a wide variety of human carcinomas, such as colorectal carcinoma, breast carcinoma, gallbladder carcinoma, oesophageal carcinoma and GC. Numerous studies reported correlation between overexpression of P53 and poor prognosis of patients with these tumors (Tables 4-6) [14].

S. No.	Site	IHC (P53) results		Total No. (%)	Pearson's chi-square test
		Positive	Negative		
1	Eso-cardia	2 (40%)	3 (60%)	5 (100%)	P=0.045
2	Fundus	1 (33.1%)	2 (66.9%)	3 (100%)	
3	Body	10 (83.2%)	2 (16.8%)	12 (100%)	
4	Pylo-antrum	21 (84%)	4(16%)	25 (100%)	
5	Pan-gastric	1 (66.7%)	2 (33.3%)	2 (100%)	
	Total	35	13	**48 (100%)**	

Table 4. Correlation of tumour site with P53 expression.

S. N.	Gross oappearance	IHC (P53) results		Total No.(%)	Pearson's chi-square test
		Positive	Negative		
1	Ulcerative	8 (57.1%)	6 (42.9%)	14 (100%)	P=0.246
2	Nodular	9 (75%)	3 (25%)	12 (100%)	
3	Ulcero-proliferative	15 (88.2%)	2 (11.8%)	17 (100%)	
4	Proliferative	3 (60%)	2 (40%)	5 (100%)	
	Total	35	13	**48 (100%)**	

Table 5. Correlation of gross type with P53 expression.

S. No.	Tumour location	Tzanakis et al (12)	Lazar et al.(13)	Czyzewska et al (14)	Current study
1	Eso-cardia	14%	13.1%	15.6%	13%
2	Fundus	-	-	-	6%
3	Body	34.4%	24.5%	20%	23%
4	Pylo-antrum	51.6%	50.8%	60%	52%
5	Pan-gastric	-	11.4%	4.4%	6%

Table 6. Comparison of distribution of gastric tumour location.

Conclusion

In comparison with western population, incidence of GC was higher in this study group. Many patients presented in older age with predominance in males. P53 was overexpressed in 72.9% of cases which is similar to western population.

P53 expression was significantly associated with tumor location but not with its macroscopic feature. To conclude, role played by cell proliferation in growth and aggressiveness of gastric tumors is complex and not clarified. However, identifying expression of P53 in GC could be helpful in categorizing patients eligible for targeted therapy. Patients at high risk of recurrence and poor survival can also be identified. A larger sample size and follow-up of these patients for 5 more years could throw more light on role of P53 mutation as long-term prognostic indicator.

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