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

Results: GCs had a peak incidence in the age group of 51 to 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 tumour 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; Prognostic indicator

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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 [1].

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 769,728 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 584,375 deaths, among which 51,429 is from India [2,3].

The element of danger for gastric cancer include non-genetic factors like *H. pylori* infection, consuming Alcohol, high salt intake in diet, smoking cigarettes, pernicious anemia and genetic predisposition such as *BRCA1* and *BRCA2* mutations [3,4].

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.

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 a 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 [6]. 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 to 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.

Exclusion criteria

- Non-neoplastic lesions and benign tumors of stomach,
- Malignancies other than adenocarcinoma,
- 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. Among 48 adenocarcinoma cases reported, 37 cases were endoscopic biopsies and 11 cases were resected specimens. Further, formalin-fixed, paraffin-embedded tissue samples were subjected to H&E stain and immunohistochemical analysis with P53 marker.

Interpretation for P53

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

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

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.

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 to 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 (Tables 1-3).

Among the 48 cases, 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.

Based on gross morphology, the GC were divided into 4 groups. Ulcero-proliferative type (35%) was the most common gross appearance followed by ulcerative type (29%) (Charts 1-3).

Table 1: Age and Sex wise distribution of Gastric cancer.

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

Table 2: Distribution of gastric cancer based onits anatomical location.

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 3: Distribution of gastric cancer based on gross morphology.

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%)

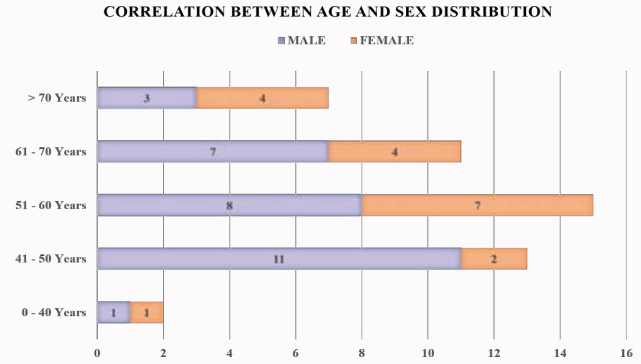

Chart 1: Correlation between Age and Sex distribution of Gastric cancer.

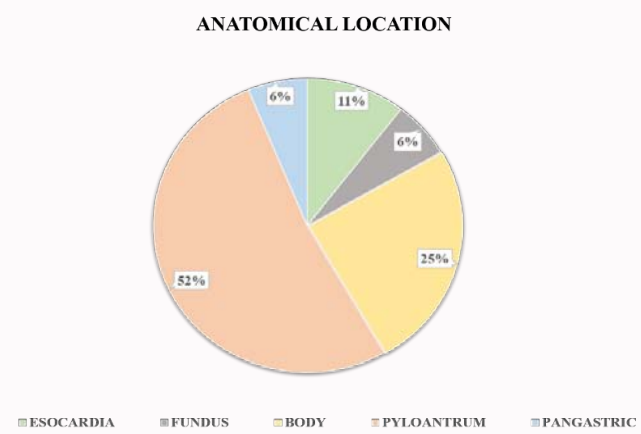

Chart 2: Distribution of Gastric carcinoma based on anatomical location.

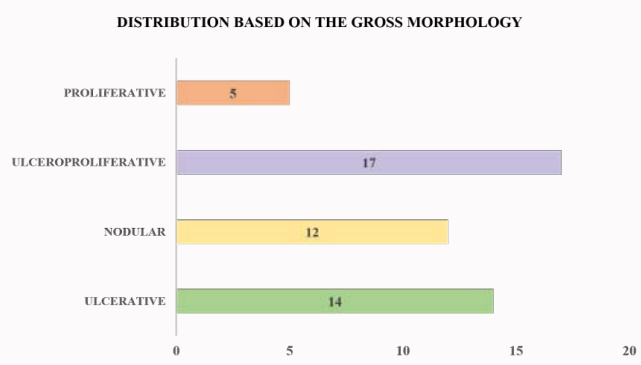

Chart 3: Distribution of Gastric cancer based on gross morphology.

Staining Pattern

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

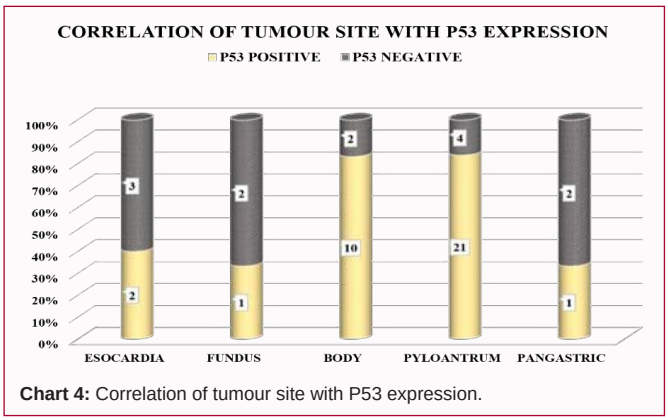

Chart 4: Correlation of tumour site with P53 expression.

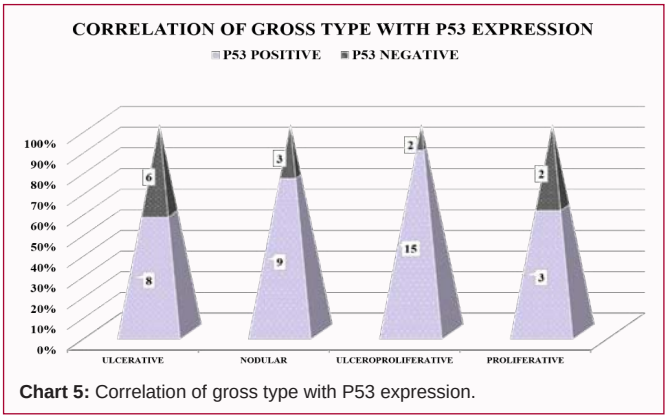

Chart 5: Correlation of gross type with P53 expression.

increased expression seen in tumors of pyloro-antrum (Figure 1, 2).

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 (Table 4, 5) (Chart 4, 5).

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 tumour emerging from gastro-esophageal junction appears to increase.

In 1996, based on location of tumour 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 were considered as esophagogastric junction tumors. And classified them as:

- Type I- The tumor lies 1 cm to 5 cm proximal to the gastro-esophageal junction,
- Type II- The tumor lies between 1 cm proximal and 1 cm distal to the junction
- Type III- The tumor lies 1 cm to 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 (Figure 3). Subdivided into:

Table 4: Correlation of tumour site with P53 expression.

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 5: Correlation of gross type with P53 expression.

S. No.	Gross appearance	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 6: Comparison of distribution of gastric tumour location.

S. No.	Tumour location	NE. Tzanakis et al. [11]	Daniela Lazar et al. [12]	Czyzewska J et al. [14]	Current study
1	Eso-cardia	14%	13.10%	15.60%	13%
2	Fundus	-	-	-	6%
3	Body	34.40%	24.50%	20%	23%
4	Pylo-antrum	51.60%	50.80%	60%	52%
5	Pan-gastric	-	11.40%	4.40%	6%

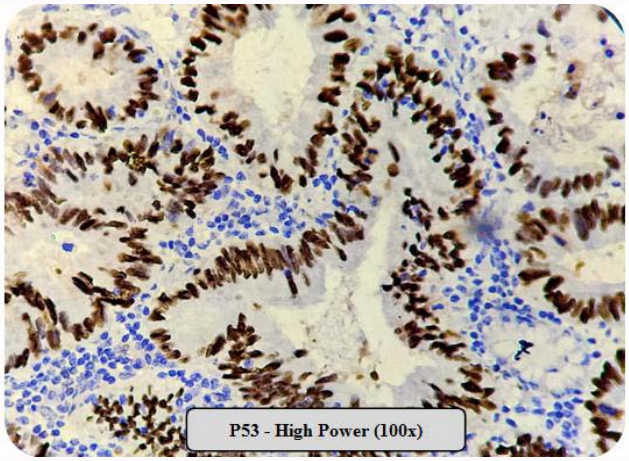

Figure 1: Strong nuclear positivity of p53 in gastric adenocarcinoma.

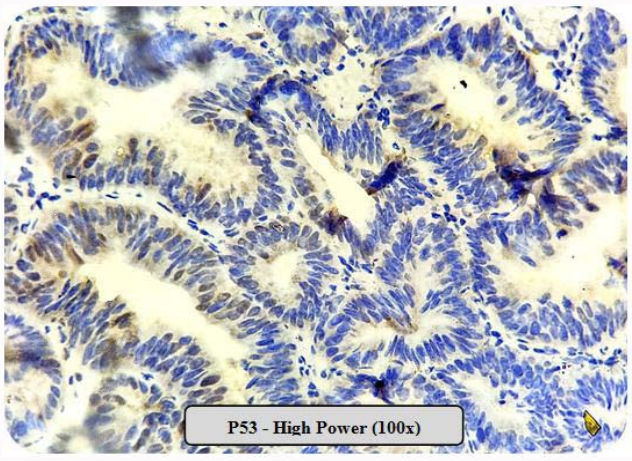

Figure 2: Negative expression of p53 in gastric adenocarcinoma.

- Intramucosal and
- 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].

Type I- Protruded - The tumor projects clearly into lumen and includes all polypoid, nodular and villous tumors.

Type II- Superficial

II a- Elevated above surrounding mucosa by few millimeters. This is seen as a well-circumscribed flat plaque.

II b- Flat. No abnormality is macroscopically visible.

II c- Depressed. The surface is slightly depressed below adjacent mucosa.

Type III- Excavated Ulceration of variable depth into the gastric wall.

Advanced Gastric Cancer

Defined as carcinoma which has spread beyond submucosa into muscularis propria and beyond, irrespective of lymph node status. The

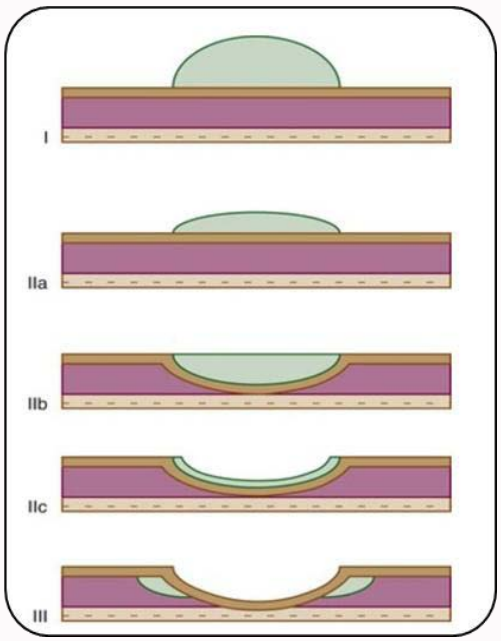

Figure 3: Macroscopic classification of early gastric cancer [9].

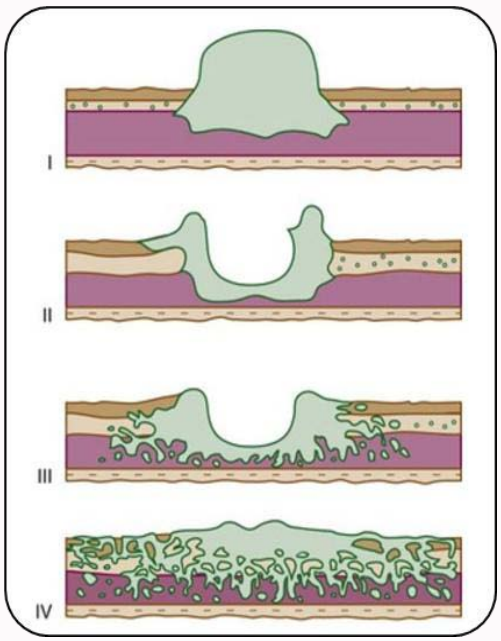

Figure 4: Macroscopic classification of advanced gastric cancer [9].

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' (Figure 4).

- Type I- Polypoid/Nodular
- Type II- Ulcerative, localized/Fungating
- Type III- Ulcerative, infiltrative
- 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. 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 [10,11].

Most common site of GC in this study was pyloro-antrum (52%). This is almost similar to study of Tzanakis NE et al. [12] in their study; Tzanakis et al. [12] observed 51.6% tumors in antrum and Daniela Lazar et al. [13] observed 50.8% tumors in antrum. Czyzewska et al. [14] (75) also observed 60% of tumors occurred in antrum (Table 6).

Daniela Lazar et al. [13] and Czyzewska et al. [14] (76) 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.

P53

Normal P53 protein is rapidly removed from nucleus. Whereas, mutant forms of P53 have a prolonged half-life, which favors intranuclear accumulation, becoming detectable immunohistochemically. Mutations of P53 gene was observed in a wide variety of human carcinomas, such as colorectal carcinoma, breast carcinoma, gallbladder carcinoma, esophageal carcinoma and GC. Numerous studies reported correlation between overexpression of P53 and poor prognosis of patients with these tumors.

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 tumour 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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