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Her2/Neu Overexpression in Gastric Cancer and its Correlation with Histopathological Grade and Subtype

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Abstract- Gastric cancer is one of the leading causes of cancer mortality in the world. At advanced stage majority of cases are diagnosed. The survival rate of patients with advanced unresectable gastric cancers remains poor despite new treatment strategies, such as perioperative chemotherapy or adjuvant chemoradiation [1]. In certain gastric tumors added therapy gives superior survival benefits. One such targeted protein of interest is HER2 /neu. We have undertaken this study to evaluate the overexpression of HER-2/Neu gene in gastric cancer and its correlation with several pathological features.

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Her2/Neu Overexpression in Gastric Cancer and its Correlation with Histopathological Grade and Subtype

Dr. Kuldeep Kaur [α], Dr. Molly Joseph [σ], Dr. Jagriti Yadav [ρ], Dr. Hema Goyal [ω] & Dr. Richa Jindal [¥]

Abstract- **Gastric cancer is one of the leading causes of cancer mortality in the world. At advanced stage majority of cases are diagnosed. The survival rate of patients with advanced unresectable gastric cancers remains poor despite new treatment strategies, such as perioperative chemotherapy or adjuvant chemoradiation [1]. In certain gastric tumors added therapy gives superior survival benefits. One such targeted protein of interest is HER2 /neu. We have undertaken this study to evaluate the overexpression of HER-2/Neu gene in gastric cancer and its correlation with several pathological features.**

Keywords: gastric adenocarcinoma, grade and subtype, her2/neu overexpression, immunohistochemistry, her 2 scoring in gastric cancer, trastuzumab.

I. Introduction

Gastric cancer is one of the leading causes of cancer mortality in the world, with the majority of cases presenting at an advanced stage. Gastric cancer is the fifth most common cancer overall and it is the third most common cause tumor-related deaths globally [1].The incidence of gastric cancer in India is 10.6 per 100000 population [2].

The mainstay of treatment is surgical resection and can cure patients with early-stage cancer. The survival rate of patients with advanced resectable gastric or gastroesophageal junction (GEJ) tumors, however, remains poor despite new treatment strategies, such as perioperative chemotherapy or adjuvant chemoradiation [3]. Improvements in the treatment modality of gastric cancer, including combination chemotherapy, have resulted in improved overall survival. In certain gastric tumors added therapy gives superior survival benefits.

Human epidermal growth factor receptor 2 (HER2/neu) protein is a cellular target for the added therapy. It is a growth factor of EGFR family with intrinsic protein tyrosine kinase activity and is associated with tumor proliferation, migration and differentiation. The production of HER2/neu protein, is regulated by the HER2/neu gene. Amplification of HER2/neu gene is seen at different sites like breast, stomach, colon, etc. and its overexpression is associated with poor prognosis.

Recently published data, from the randomised, prospective phase III clinical trial TOGA provided first documentation of the clinical benefit of Trastuzumab, anti-HER2/neu an antibody, when used in combination with chemotherapy in the setting of advanced gastric carcinoma [4]. The Stage is the most important prognostic factor for gastric carcinoma followed by the histological subtype and since there is limited data available on HER2/neu overexpression in gastric cancer and its correlation to histopathological stage, grade and subtype, we propose to conduct this study to evaluate the same since an accurate assessment of HER2/neu overexpression in gastric cancer patients is of great utility in the optimal selection of patients for Trastuzumab therapy.

II. Material and Methods

A total of 49 patients, with gastric carcinoma, were included in this study period of seven years (Jan 2011 to May 2018) in the Department of Pathology, St. Stephen's Hospital, New Delhi, India. The detailed clinical history and results of relevant investigations were obtained from the patient's case files. The method of study was immunohistochemistry, using the HER-2/Neu antibody.

III. Statistical Analysis

Qualitative variables are expressed as frequencies/percentages and compared between groups using Chi-square Test. Quantitative variables are expressed as mean±sd and compared across groups using ANOVA and unpaired t-test. A p-value < 0.05 is considered statistically significant. The data is analysed using Statistical Package for Social Sciences (SPSS) version 16.0 software.

Study Design: Cross-sectional study

Sample size determination:

The formula used for sample size estimation is:

$$n = z2\ P(1 - P)/d2$$

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IV. Result and discussion

During January 2011 to May 2018, a total of 50 samples (from 49 patients) reported as gastric adenocarcinoma on histopathological examination at St.Stephen's hospital, Delhi were included in the study.

Among 49 patients, gastric carcinoma had a peak incidence in the age group of 50 to 60 years. The oldest age of presentation was 85 years and the youngest was 24 years.

a) Demographic data in our study

Our study included 50 cases. The age of the patients varied from 24 years to 85 years, with a mean age of 57.69 years. In our study, the incidence of gastric carcinoma in males and females were 77.1% and 22.9% respectively (male: female ratio =3:1)

b) Clinical manifestations

In our study, chief complaints of patients were dysphagia (43.7%) followed by loss of appetite (35.4%), pain abdomen (33.3%), vomiting (29.2%), weight loss (22.9%), hematemesis (6.2%) and melena (4.2%). Gastric carcinoma often produces no specific symptoms when it is superficial and can be removed surgically, although up to 50% of patients may have nonspecific gastrointestinal complaints such as dysphagia, anorexia, nausea, vomiting, weight loss as well as abdominal pain that is vague and insidious.

Site

The most common site of gastric carcinoma in our study was the antral region.

Table 1: Comparison of Location of Gastric Carcinoma:

Location	H R Raziee et al. [5]	C Fondevile et al. [6]	Czyzwski J et al. [7]	Our study
Cardia	37%	7%	15.6%	6%
Body	33%	40%	20%	22%
Antrum	30%	51%	60%	52%

c) Histopathological subtype

In our study, poorly cohesive carcinoma (66%) was the most common subtype followed by tubular carcinoma (26%). However, intestinal-type was the most common subtype (Lauren's classification) according to studies done by Raziee et al.(5) and ToGA trial (4). This difference could be explained by the low sample size in our study and heterogeneity of pathological classifications. The increase in the proportion of poorly cohesive carcinoma can be explained by changes in the pathological classification systems used to characterise these cancers. Since the publication of the WHO classification of gastric cancers in 1990, signet ring cell adenocarcinoma constitutes one specific histotype and therefore can be better identified among gastric cancers. WHO 2010 further classified Signet ring cell and diffuse variety into a single group of poorly cohesive carcinoma. Previously, signet-ring cell adenocarcinoma was classified as "diffuse-type" according to Lauren's classification[8] and "infiltrative type" by Ming[9].

d) Histopathological grade

Table 2: Comparison of Histopathological Grades of Gastric Carcinoma

Grade	H R Raziee et al. [5]	Lazar et al. [10]	Fondevila et al. [6]	Our study
Well	54	3.2	4	0
Moderately	17	32.8	47	46
Poorly	29	64	49	54

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In our study, poorly differentiated grade tumors were more common than other grades accounting for 54% of cases, which is similar to observations made by Lazar et al.(64%) and Fondevila et al. (49%) in their studies.

e) *Depth of Infiltration*

In our study, a higher proportion of tumours belonged to T4 subtype 63.6% which is similar to the observation made by Lazar et al [8] (approximately 50%).This is explained by later presentation of gastric carcinoma due to nonspecific symptoms and hence delayed diagnosis.

HER2 Overexpression

In our study, HER2 overexpression is noted in 20% of cases, which is similar to observations made worldwide by Marx et al.(19%), Xie et al.(18.8%), Lee et al.(17.4%), and Yoshida et al.(17%) in their studies.

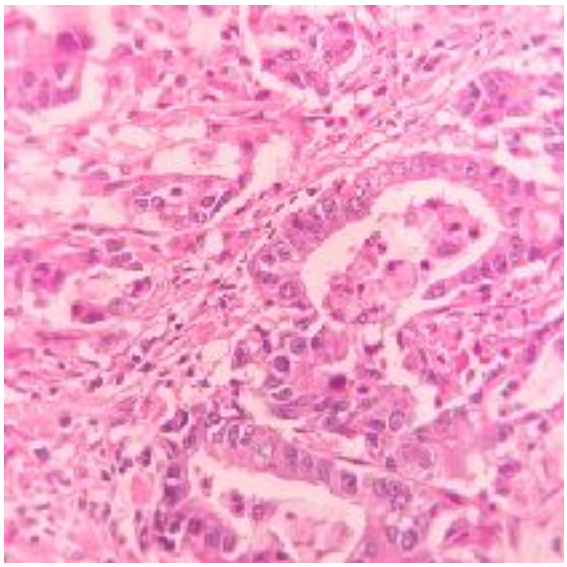
Table 3: Comparison of the rate of HER2/neu positivity in various studies

Authors	Year	Population studied	No of patients	HER2 positivity
Hofmann et al. [11]	2007	Germans	178	10.7 %
Raziee et al. [5]	2007	Iranians	100	26 %
Marx et al. [12]	2009	Germans	166	19 %
Xie et al. [13]	2009	Chinese	218	18.8 %
Lee et al. [14]	2010	Australians	178	17.4 %
Sekaran et al. [2]	2011	Indians	52	44.2 %
Lakshmi V et al. [15]	2014	Indians	78	35.9 %
Yoshida et al. [16]	2014	Japanese	207	17 %
Our study	2018	Indians	48	20%

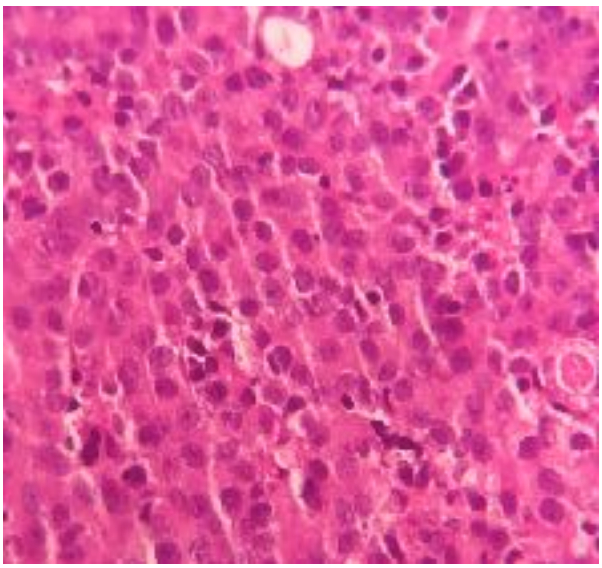
Correlation of HER-2/Neu OverExpression with Various clinico-pathological factors.

In our study, there is no correlation between HER-2/neu overexpression and various clinicopathological factors such as age, gender, complaints, site or gross appearance in gastrectomy specimens. Increased frequency of HER-2/neu overexpression was associated with elderly age, male gender, poorly cohesive carcinoma (according to WHO subtype), moderately differentiated grade and T4 level of infiltration, but statistically insignificant.

IMAGES

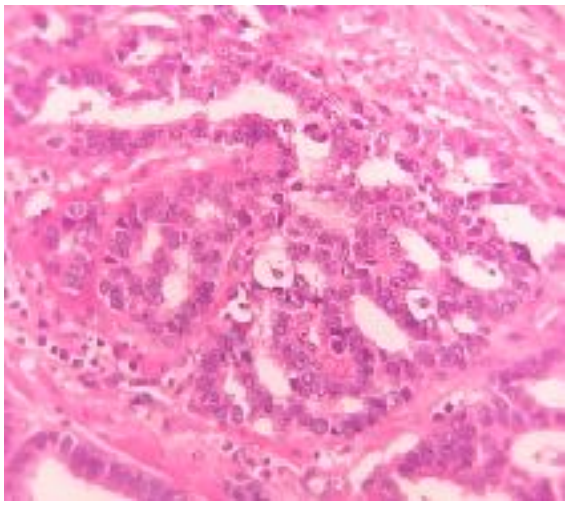


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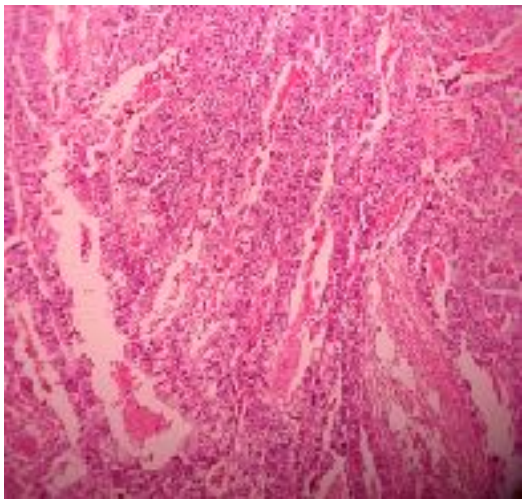


[POORLY DIFFERENTIATED ADENOCARCINOMA]

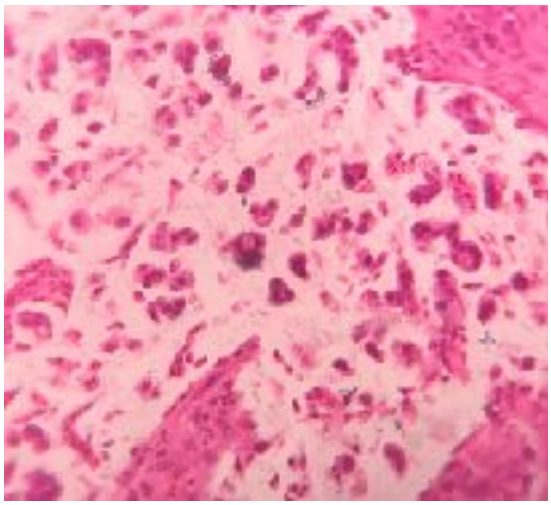
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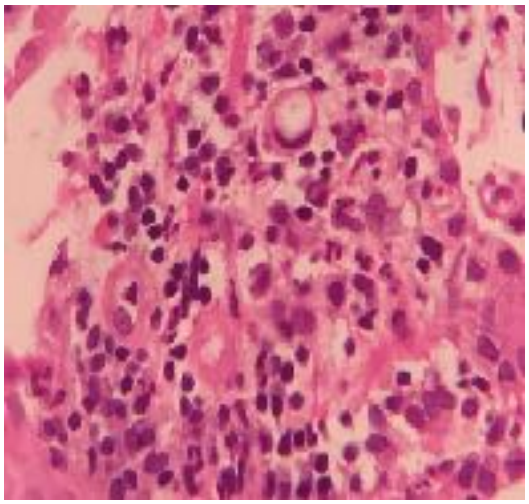
[TUBULAR ADENOCARCINOMA]



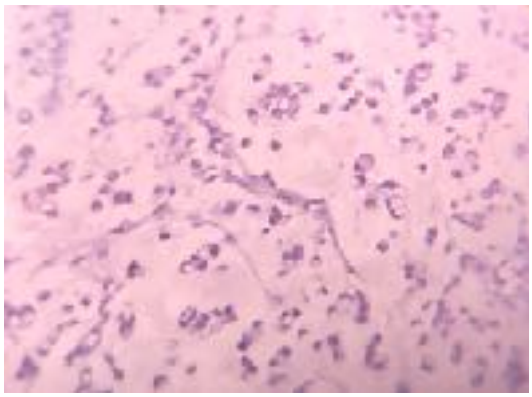
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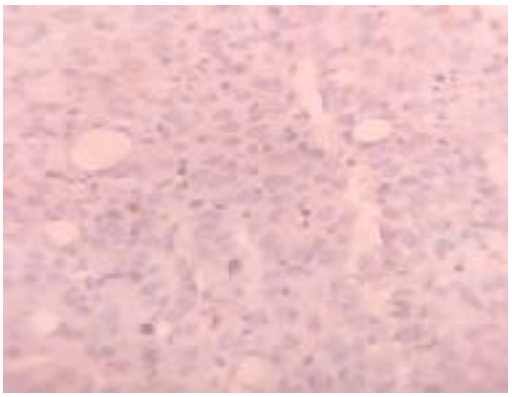
[MUCIN SECRETING ADENOCARCINOMA]



[ADENOCARCINOMA WITH SIGNET RING]

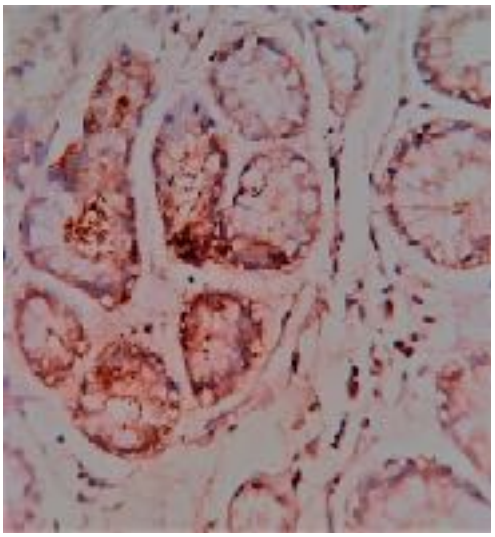


[HER 2 SCORE 0]

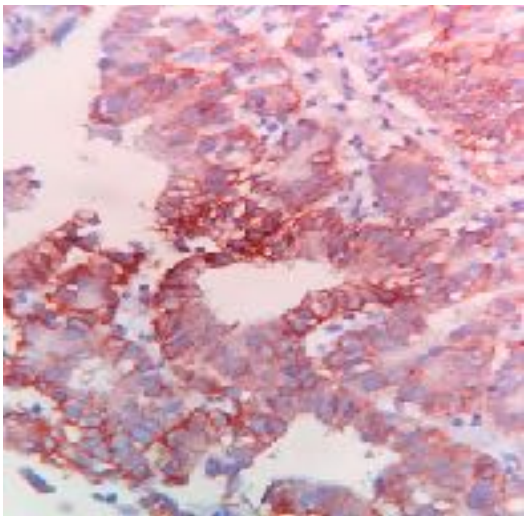


[HER2 SCORE 1 +]

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[HER2 SCORE 2 +]



[HER2 SCORE 3+]

V. Conclusion

1. The present work reported that advanced age, especially in male patients is a risk factor for gastric carcinoma.
2. The percentage of HER2/neu overexpression in gastric adenocarcinoma is correlating with other studies.
3. Correlation between HER2/neu overexpression and clinico-pathological variables like age, gender, site, gross, subtype, grade and depth of tumor infiltration is statistically insignificant.
4. Majority of cases overexpressing HER 2/neu were of poorly cohesive subtype (according to WHO classification, 2010), but results were statistically insignificant.

VI. Recommendation

1. Larger sample size and follow up might shed more light on the role of HER 2/neu in gastric carcinoma. Increasing the sample size in future studies, and designing prospective studies with close observation of survival, the utility of HER2/neu overexpression as an important prognostic marker can be enhanced.
2. Geographical differences, tumor heterogeneity, differences in scoring systems, and pathologist expertise may have caused the variations in HER-2/neu positivity rates between the studies.
3. The precise role of Her2/neu in cancer development and progression need to be detected to modulate the current therapeutic approaches targeting those proteins. It is mandatory to standardize Her2/neu staining and scoring methods for accurate assessment of its role in gastric carcinogenesis and tumor progression besides avoiding the failure of molecular target therapy.

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