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HER 2 Overexpression in Gastric Cancer: Current Insights and Future Horizons

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Abstract

Background: Several risk factors like family history of gastric cancer, dietary habits and infections such as H-pylori and Epstein-Barr virus play significant role in developing gastric cancer. **Aims:** To determine the prevalence of HER2 overexpression in gastric cancers and to offer an updated, practical overview of HER2 testing and scoring methods essential for identifying patients eligible for trastuzumab therapy. **Methods**: Present study was carried out in the Chughtai Institute of Pathology from September 2024 to February 2025. This Study enrolled 58 confirmed cases of primary gastric adenocarcinoma that were evaluated for HER2 overexpression in Biopsy and resection specimens at our clinical setup. All clinical data was analyzed through spss v26. Chi-square test or Fisher's exact test was applied on categorical variables for comparison with P-value ≤0.05 was take as significant. **Results:** Among the 58 cases, the most common tumor site was the antrum (63.8%). The majority of adenocarcinomas based on histology were moderately differentiated (50.0%), followed by poorly differentiated (48.3%) and well-differentiated tumors (1.7%). HER2 overexpression (score +3) was observed in 7 cases (12.1%) by using CAP (2017) scoring protocol. Correlation between histological differentiation and HER2 expression was statistically insignificant. **Conclusion**: It was concluded that HER2/neu over-expression was an independent prognostic factor for gastric cancer. However, it may assist in therapeutic decisions and improve survival rates among patients.

Introduction

According to previous literature, fifth most common malignancy worldwide is Gastric carcinoma (GC).[1] According to the Global Cancer Statistics 2020, it accounts for over 1 million new cases and almost 700,000 deaths/year.[2] Several risk factors like family history of gastric cancer, dietary habits and infections such as H-pylori and Epstein-Barr virus play significant role in developing gastric cancer.[2]

According to the Lauren classification, it is broadly categorized into two main subtypes based on histology i.e intestinal and the diffuse type. Tubular or glandular structures are present in intestinal type but it is linked with several environmental risk factors like alcohol drinking and diet. In contrast, the other one is composed of poorly cohesive cells, including signet ring cells, and lacks glandular formation.[3] Gastric carcinoma of diffuse type is more prevalent in females and younger individuals, and it is frequently associated with hereditary genetic syndromes.[2]

Most patients diagnosed with gastric cancer present at an advanced stage followed by low survival duration (≤ 12 months) from the time of diagnosis as per previous literature.[3,4] For unresectable gastric cancers, cytotoxic chemotherapy remains the most effective systemic treatment compared to best supportive care, offering improvements in both quality of life and overall survival. However, despite therapeutic advancements in recent years, advanced gastric carcinoma still has poor prognosis and high mortality rate.[4] Compared to the wide range of therapeutic options available for breast cancer, targeted therapies for HER2-positive gastric cancer remain relatively limited.[5] As documented by previous studies, most common molecular pathology of gastric carcinoma is HER2/neu over-expression.[3,4] Trastuzumab is an established treatment option for HER2-positive gastric cancers. It exerts its therapeutic effect by directly binding to HER2 receptor thus inhibits downstream signaling pathways. Additionally, trastuzumab promotes receptor internalization and degradation thus contributing to tumor cell death.[5]

HER2 is located on chromosome 17 that encodes a transmembrane receptor tyrosine kinase that activates downstream signaling pathways. HER2 expression is most notable in tissues such as the breast, gastrointestinal tract, kidneys, and heart. Dysregulation or overexpression of HER2 can contribute to oncogenesis in various malignancies.[6] Overexpression of this gene is commonly seen in intestinal-type gastric cancers that constitutes 17-20% of gastric cancer cases.[7] Immunohistochemistry (IHC) is a standard method for assessing its overexpression in GC tissue and determining HER2/neu status.[3] Immunohistochemical scoring for HER2 in GC varies from breast carcinoma due to the heterogeneous expression of HER2 and the presence of incomplete, basolateral, or lateral membranous staining patterns.[8]

Local data in this regard is limited. To the best of our knowledge, no studies have been done in Pakistan to evaluate prevalence of HER2 overexpression in gastric cancers and to offer an updated, practical overview of HER2 testing and scoring methods essential for identifying patients eligible for trastuzumab therapy.

Methods:

Present descriptive study was held at Chughtai Institute of Pathology from September 2024 to February 2025. This Study enrolled 58 confirmed cases of primary gastric adenocarcinoma that were evaluated for HER2 overexpression in Biopsy and resection specimens at our clinical setup. Patients with metastatic carcinomas who received neoadjuvant chemotherapy or had malignant non epithelial tumors were excluded from this study. IHC techniques with the Auto Stainer Link 48 (DAKO) were used to determine HER2 protein expression in current project. The procedure was carried out according to the manufacturer's instructions. The evaluation was carried out by two consultant pathologists independently, according to the College of

American Pathologists (CAP) reporting protocols 2017 for gastric and Gastroesophageal junction adenocarcinomas as used in past study.[9]

Statistical analysis:
All clinical data was analyzed through spss v26. Chi-square test or Fisher's exact test was applied on categorical variables for comparison with P-value ≤0.05 was take as significant.

Results:
Most patients were males (n = 46, 79.3%), while females accounted for 12 cases (20.7%). The patient's with a mean age of 56.86 ± 13.77 years were enrolled. Baseline parameters like age, location of tumours and histological distribution of gastric carcinomas were presented as frequency (n) and percentage (%) in Table-1. Among the 58 cases, the most common tumor site was the antrum (n = 37, 63.8%). The majority of adenocarcinomas based on histology were moderately differentiated (50.0%), followed by poorly differentiated (48.3%) and well-differentiated tumors (1.7%) as shown in table-1 and figure 1-3.

Table-1. Baseline Parameters of Patients with Gastric Carcinoma (n = 58)	
Age Group (years)	**Frequency (%)**
21-40	9(15.5%)
41-60	28 (48.3%)
61-80	17 (29.3%)
81-100	4 (6.9%)
Age (mean ± SD)	56.86 ± 13.77 years
Location of tumor	
Site	**Frequency (%)**
Cardia	1 (1.7%)
Fundus	11 (19.0%)
Antrum	37(63.8%)
Pylorus	9 (15.5%)
Distribution of adenocarcinoma cases	
Tumor Differentiation	**Frequency (%)**
Well differentiated	1 (1.7 %)
Moderately differentiated	29 (50.0%)
Poorly differentiated	28 (48.3%)

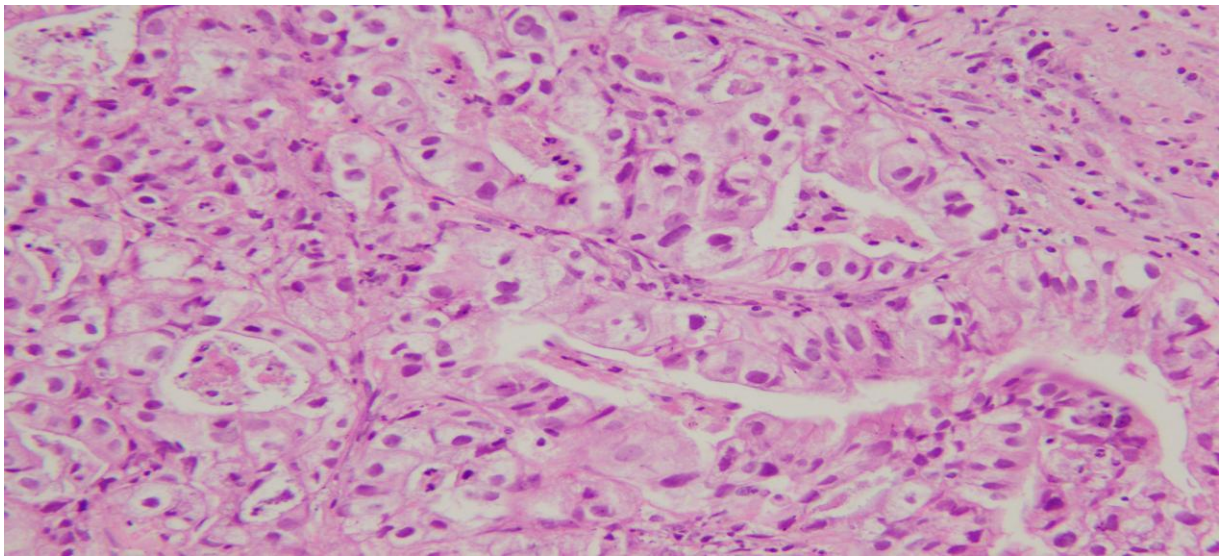


Figure-1: Moderately differentiated Adenocarcinoma (H&E)

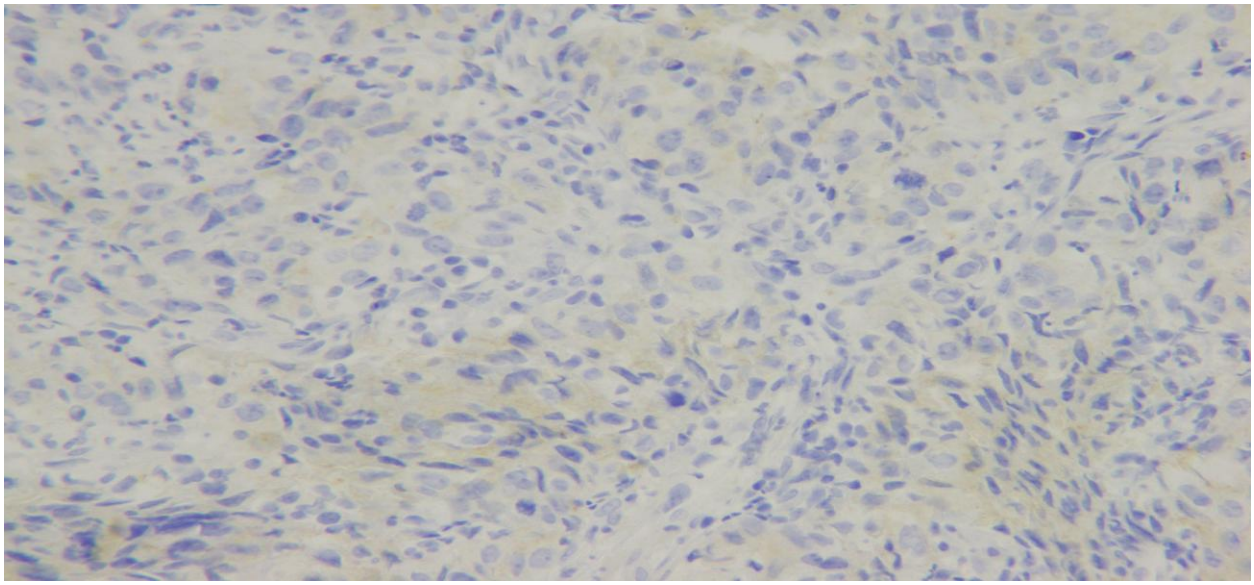


Figure-2: HER2 immunohistochemistry showing absence of membranous staining in GC

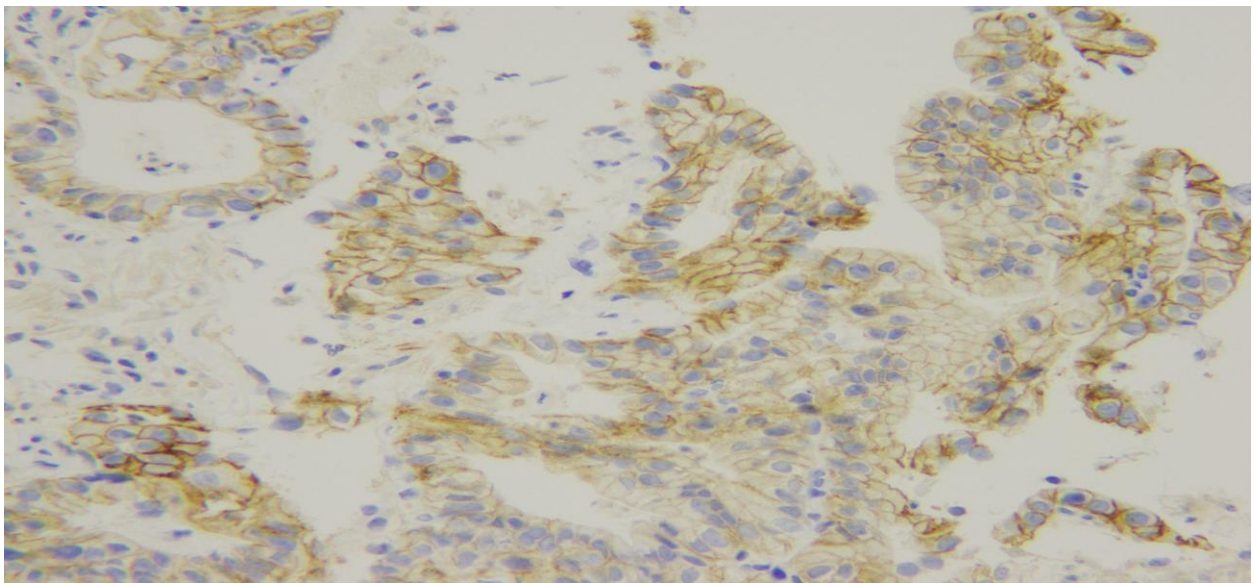


Figure-3: HER2 IHC in gastric adenocarcinoma showing HER2 overexpression

Of the 58 cases, 57 (98.3%) specimens were biopsies, and only one (1.7%) was a gastrectomy sample. HER2 overexpression (score +3) was observed in 7 cases (12.1%) by using CAP (2017) scoring protocol as shown in Table-2.

Table-2: Frequency of HER2 expression among Enrolled Cases (n = 58)	
HER2 Expression Score	**Frequency (%)**
0	16 (27.6%)
+1	25 (43.1%)
+2	10 (17.2%)
+3	7 (12.1%)

Correlation between histological differentiation and HER2 expression was statistically insignificant with p-value of 0.99 as shown in table-3.

Correlation between the tumor's location and HER2 expression was analyzed using

Table-3:Correlation between histological differentiation and HER2 expression score					
Histological Differentiation	**HER2 Expression Score**				**Total (%)**
	Score 0	**Score +1**	**Score +2**	**Score +3**	
Well	0	0	0	1	1
Moderately	6	12	7	4	29
Poorly	10	13	3	2	28
Total	16	25	10	7	58

the Chi-square test, which yielded a value of 0.43 (statistically insignificant) as shown

Table-4:Correlation between location of tumor and HER2 expression score					
Location of the tumor	**HER2 Expression Score**				**Total (%)**
	Score 0	**Score +1**	**Score +2**	**Score +3**	
Cardia	1	0	0	0	1
Fundus	2	4	2	3	11
Antrum	11	15	8	3	37
Pylorus	2	6	0	1	9
Total	16	25	10	7	58

in table-4.

Discussion:

It is difficult to predict the therapeutic benefit from HER2-targeted therapy among patients with gastric/GEJ carcinomas by interpreting HER2 status. Evolutionary role of trastuzumab in treatment of HER2 positive breast cancer patients has elicited great interest in its application for HER2-positive GC cases as reported by previous study.[10] Almost 12-23% GC patients account for HER2 positivity as per documented by NCCN.[11] According to various societies and guidelines, it has been documented that frequency of HER2 upregulation in GEJ was 7-38%.[9,10]

This study revealed a male predominance in GC consistent with prior studies.[10,11] The distal portion (antrum) of the stomach is the most prevalent location of GC in this study, consistent with previous studies.[10-12] Although HER2-overexpression was more frequent in the antrum (37%), the difference was not clinically significant. A study by one researcher reported that 21% cases of gastric carcinoma involved GEJ whereas 38% cases involved only proximally located gastric tumors.[12]

In our study, 12.1% of patients with strong expression (3+) were considered to have HER2 overexpression, and 27.6% of patients with absent/weak expression (0-1+) were considered to have HER2 under expression. IHC techniques are the first option for all patients in these groups, with hybridization techniques reserved for patients with moderate or equivocal expression. This distinction minimizes the cost and time required for HER2 determination.[11] Thus HER2 overexpression in present project was

low compared to a study by one researcher[11] and close to the positivity rate reported by one previous study.[10]

The present study showed HER2 overexpression more frequently in moderately differentiated tumors (29%), followed by poorly differentiated tumors (28%). In a study[10], HER2 overexpression was more commonly seen in poorly differentiated carcinomas. Other researchers documented that well-differentiated histology GC cases had higher rate of HER2 overexpression, however, this was insignificant and was in line with findings of present study.[13-15] Variations in HER2-positivity rates between countries and different populations may be due to the proportion of carcinomas with certain characteristics that have been correlated with HER2-positivity.

LIMITATIONS:

This study has certain limitations that should be noted. A lack of patient data, particularly tumor stage, lymph node or distant metastasis or subtype (intestinal or diffuse) has precluded examination of these characteristics. Our study's main limitation was the lack of FISH/ISH investigation for determining HER2 amplification in HER2 equivocal (score 2+) cases. This could have altered variations and associations between clinic-pathological characteristics. Non-availability of further genetic testing is the main limitation of our study followed by financial and limited human resources.

CONCLUSION:

It was concluded that HER2/neu over-expression was an independent prognostic factor for gastric cancer. However, it may assist in therapeutic decisions and improve survival rates among patients. Hence, testing for HER2 overexpression should be recommended as routine to provide a therapeutic advantage among GC cases at our setups.

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