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Original Research Article

Comparative Histopathological Analysis of HER2/neu Overexpression in Gastrointestinal Adenocarcinomas across Different Sites

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Abstract:

Background: Gastrointestinal adenocarcinomas (GIAs) constitute a major proportion of global cancer incidence and mortality. Among their diverse biological behaviours, molecular heterogeneity significantly influences prognosis and therapy. HER2/neu (human epidermal growth factor receptor-2) is a proto-oncogene encoding a tyrosine kinase receptor involved in cell growth and differentiation. Its overexpression has diagnostic and therapeutic relevance in several malignancies, notably breast and gastric cancers. This study aimed to do comparative analysis of HER2/neu overexpression in gastrointestinal adenocarcinomas across different sites.

Materials and Methods: A total of 50 cases of histopathologically proven gastric and colorectal adenocarcinomas were evaluated retrospectively and prospectively at a tertiary care teaching hospital for a extended period of two years. Immunohistochemistry (IHC) for HER2/neu was performed on formalin-fixed, paraffin-embedded sections using the Hoffmann et al. scoring system. Expression patterns were correlated with histological subtype, grade, and demographic parameters. Statistical analysis was carried out using SPSS v26 with $p < 0.05$ considered significant.

Results: HER2/neu positivity (3+) was detected in 12 (24%) of 50 cases—7 (25%) gastric and 5 (22.7%) colorectal carcinomas. Overexpression was most frequent in well-differentiated intestinal-type adenocarcinomas, while poorly differentiated tumors were uniformly negative ($p = 0.003$). No significant correlation was observed with patient age or sex.

Conclusion: HER2/neu expression correlates strongly with histological differentiation in gastrointestinal adenocarcinomas. Its assessment provides valuable adjunctive information to routine histopathology, assisting in prognostication and therapeutic stratification, especially for anti-HER2 targeted treatment.

Keywords: HER2/neu, Gastrointestinal adenocarcinoma, Histopathology, Tumor differentiation, Immunohistochemistry, Gastric carcinoma, Colorectal carcinoma.

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Introduction

Gastrointestinal tract (GIT) cancers remain among the most prevalent malignancies worldwide and represent a leading cause of cancer-related mortality. Together, gastric and colorectal adenocarcinomas account for nearly 18% of global cancer deaths [1]. Gastric carcinoma ranks fifth in incidence and third in mortality, while colorectal carcinoma ranks third in incidence and second in mortality [2,3].

Despite diagnostic and therapeutic advances, survival outcomes remain poor in advanced stages, largely due to late presentation, tumour heterogeneity, and limited responsiveness to conventional chemotherapy [4]. Pathogenesis of gastrointestinal adenocarcinoma involves a multifactorial interplay of genetic and environmental factors. Chronic Helicobacter pylori infection, dietary carcinogens such as nitrosamines, tobacco, and alcohol are important contributors to gastric carcinogenesis [5,6]. Similarly, genetic instability and chromosomal aberrations underlie the adenoma–carcinoma sequence in colorectal cancers [7]. In this complex background, the identification of reliable molecular markers has become essential for improving prognostic precision and enabling personalized therapy.

Among molecular markers, HER2/neu (Human Epidermal Growth Factor Receptor-2) has attracted immense research interest. The gene, located on chromosome 17q12, encodes a transmembrane glycoprotein of the EGFR family that activates intracellular pathways such as RAS–RAF–MAPK and PI3K–AKT–mTOR, regulating cellular growth and survival [8,9]. Overexpression of HER2/neu leads to uncontrolled receptor dimerization and continuous proliferative signaling (10). While its oncogenic role is well established in breast carcinoma, with about one-fourth of patients benefiting from trastuzumab therapy [11], subsequent evidence has demonstrated its involvement in gastric and colorectal cancers as well [12,13].

HER2 overexpression in gastric carcinoma has been variably reported in 6–35% of cases, with higher prevalence in intestinal-type and well-differentiated adenocarcinomas [14–16]. In colorectal carcinoma, positivity rates range between 5% and 25%, with inconsistent clinicopathological correlations [17,18]. The landmark ToGA trial established HER2 as a predictive biomarker for targeted therapy in gastric and gastroesophageal junction tumors, markedly improving survival outcomes [19]. This has prompted interest in evaluating HER2 expression across other gastrointestinal malignancies.

Histopathological grading remains the cornerstone of tumour assessment, providing valuable information about biological behavior and prognosis. Correlating HER2/neu expression with histological parameters can clarify whether HER2-driven oncogenesis influences differentiation patterns, tumour aggressiveness, or metastatic potential. Moreover, understanding such correlations in regional populations is vital, given geographical variations in both cancer prevalence and molecular profiles [20,21].

This study aimed to do comparative analysis of HER2/neu overexpression in gastrointestinal adenocarcinomas across different sites, with particular emphasis on tumour differentiation, grade, and anatomical site, thereby contributing to the growing body of literature on molecular pathology of gastrointestinal cancers.

Materials and Methods

This cross-sectional observational study was carried out in the Department of Pathology, in a tertiary care teaching hospital for the period of two years. Ethical approval was obtained from the Institutional Ethics Committee, and informed consent was secured from all participants.

The study comprised 50 histopathologically confirmed cases of gastric and colorectal adenocarcinomas, retrieved from both retrospective archives and prospectively collected specimens. Inclusion criteria encompassed resection or biopsy samples demonstrating adenocarcinoma morphology with adequate fixation in 10% neutral-buffered formalin. Non-adenocarcinomatous neoplasms, recurrent lesions, necrotic or scant tissue samples were excluded.

Tissue sections of 3 μm thickness were prepared from formalin-fixed paraffin-embedded blocks and mounted on poly-L-lysine-coated slides. Following deparaffinization in xylene and rehydration through graded alcohols, heat-induced epitope retrieval was performed using citrate buffer (pH 6–9.5). Endogenous peroxidase activity was blocked by treating slides with 3% hydrogen peroxide for 10 minutes. The sections were incubated with primary anti-HER2 monoclonal antibody (PathnSitu Biotechnologies, ready-to-use clone) for 60 minutes at room temperature. The bound antibody was detected using the PolyExcel HRP detection system and visualized with diaminobenzidine (DAB) chromogen. Counterstaining was done with hematoxylin, followed by dehydration and mounting with DPX.

Positive and negative controls were run concurrently. A known HER2-positive breast carcinoma served as the positive control, while omission of the primary antibody acted as the negative control.

HER2/neu expression was interpreted following the Hoffmann et al. (2008) scoring system (22):

- 0: No reactivity or membranous reactivity in < 10% of tumour cells.
- 1+: Faint/incomplete membranous staining in ≥ 10% of cells (negative).
- 2+: Weak to moderate complete/basolateral membranous staining in ≥ 10% of cells (equiv-ocal).
- 3+: Strong complete/basolateral membranous staining in ≥ 10% of cells (positive).

Equivocal (2+) cases were advised for confirmatory testing with fluorescence in situ hybridization (FISH), though not performed in the present study. Only membranous staining was considered positive; cytoplasmic reactivity was ignored. Clinical data including age, sex, tumour site, and histological grade were documented. Tumours were classified as well, moderately, or poorly differentiated according to standard WHO criteria. All results were statistically analyzed using SPSS v21 software, applying Chi-square and Fisher's exact tests; $p < 0.05$ was deemed significant.

Results

Table 1. HER2/neu Expression and Tumour Differentiation

Differentiation	HER2 Positive (3+)	HER2 Negative (0–1+)	Equivocal (2+)	Total	p-value
Well differentiated	8	6	0	14	0.003
Moderately differentiated	4	12	0	16	
Poorly differentiated	0	10	0	10	
Total	12	28	0	40	

HER2 positivity was significantly higher in well-differentiated tumours ($p = 0.003$), while none of the poorly differentiated carcinomas expressed HER2/neu.

Table 2. Distribution of HER2/neu Expression by Anatomical Site

Site	Total Cases	HER2 Positive (3+)	Percentage
Gastric	28	7	25.0%
Colorectal	22	5	22.7%
Total	50	12	24.0%

HER2/neu positivity was slightly higher in gastric carcinoma (25%) compared with colorectal carcinoma (22.7%).

Table 3. Age and Sex Correlation

Variable	HER2 Positive	HER2 Negative	p-value
Age > 50 years	9	32	0.09
Age ≤ 50 years	3	6	
Male	8	22	0.59
Female	4	16	

No statistically significant correlation was observed between HER2 expression and age or sex.

Table 4. Correlation between HER2/neu Expression and Tumour Type

Histologic Type	HER2 Positive	HER2 Negative	Total
Intestinal type	10	16	26
Diffuse type	2	14	16
Mixed type	0	8	8

HER2 positivity was predominant in intestinal-type adenocarcinomas, aligning with their glandular differentiation pattern.

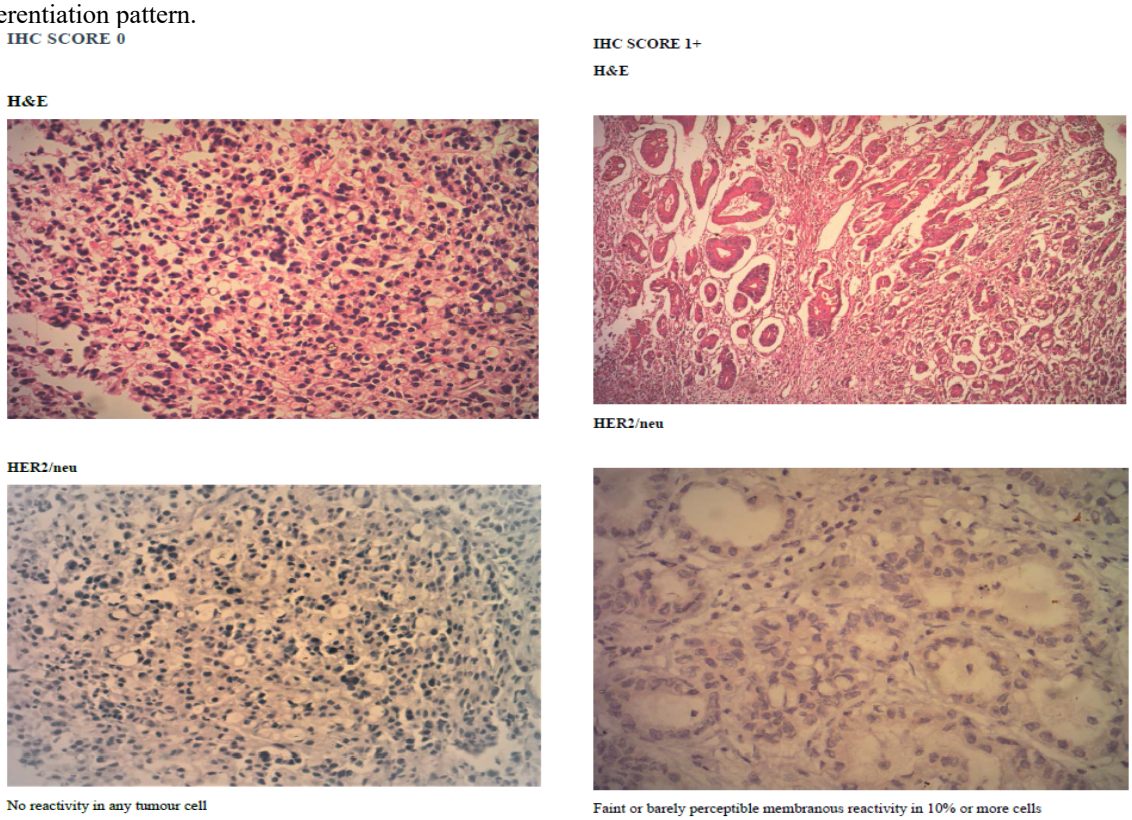

Figure 1 & 2: IHC score 0 and 1

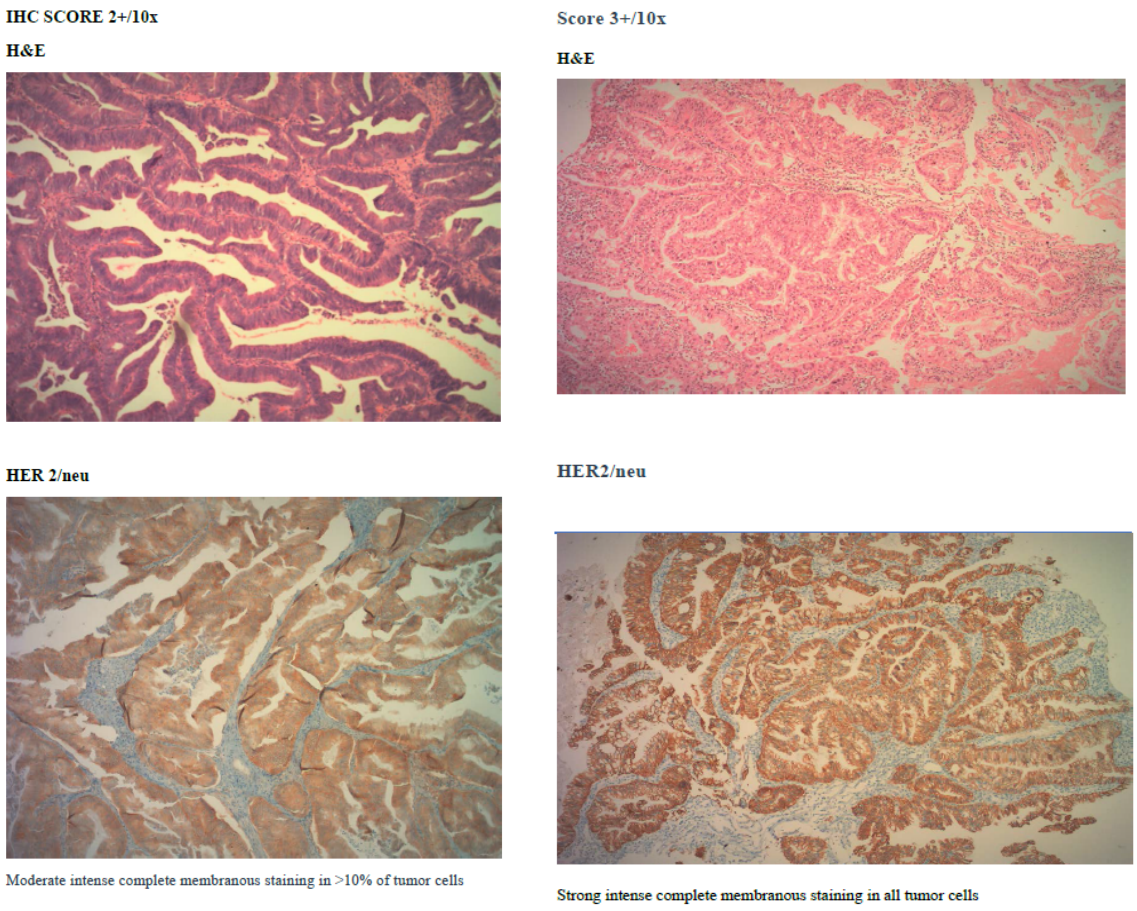

Figure 3 & 4: IHC Score 2 & 3

Discussion

This study demonstrated a significant association between HER2/neu overexpression and histological differentiation in gastrointestinal adenocarcinomas, with positivity confined primarily to well-differentiated and intestinal-type tumours. The observed positivity rate of 24% overall corroborates findings from international and Indian studies reporting frequencies between 20% and 30% [23,24].

Our data reaffirm the strong relationship between HER2/neu expression and glandular or intestinal-type morphology. Gravalos and Jimeno [25] reported HER2 positivity in 22% of gastric carcinomas, mainly intestinal type, while Gupta et al. [26] observed 24.5% positivity in Indian patients. Similar results were obtained by Halder et al. [27] and Dewan et al. (28), who also found a significant correlation with well-differentiated histology. These findings suggest that HER2 overexpression may be an early molecular event promoting differentiation rather than dedifferentiation.

In contrast, poorly differentiated and signet-ring carcinomas rarely exhibit HER2 amplification, as seen in our series where none of the poorly differentiated tumours showed overexpression. This supports the notion proposed by Raziee et al. [29] and Ling et al. [30] that loss of glandular architecture parallels loss of membrane receptor expression.

HER2/neu positivity in colorectal adenocarcinomas was 22.7% in this study, aligning with results of Ummerali and Sarojini [31] (24%) and Shabbir et al. [32] (26.6%). McKay et al. [33], however, reported only 2–3% positivity, attributing differences to stricter interpretation criteria. Rossi et al. [34] demonstrated by FISH that gene amplification corresponded closely with IHC 3+ cases, confirming the reliability of membranous staining as a surrogate for amplification.

Regarding clinicopathological correlation, HER2 expression showed no significant association with age or sex, consistent with the observations of Sayadnejad et al. [35] and Singh et al. [36]. The slightly higher rates among older males may reflect epidemiologic predominance rather than biologic influence.

The pattern of HER2 positivity in this study parallels global data: Gupta et al. [26] 24.5%, Gravalos and Jimeno [25] 22%, Halder et al. [27] 25%, Lakshmi et al. [37] 60% (southern India), and Ummerali et al. [31] 24%. Western studies such as Janjigian et al. [38] and Varga and Noske [39]

reported 17–20%, indicating comparable prevalence across populations despite methodological differences. HER2 overexpression is biologically significant because it portends aggressive clinical behavior yet provides a therapeutic target.

The ToGA trial [19] conclusively showed that addition of trastuzumab to chemotherapy improved survival in HER2-positive advanced gastric and gastroesophageal cancers. More recently, antibody–drug conjugates such as trastuzumab deruxtecan have demonstrated efficacy in HER2-expressing gastric and colorectal tumors [40]. Hence, accurate IHC assessment of HER2/neu has direct clinical implications.

Our findings thus reinforce the role of HER2/neu as a biomarker correlated with differentiation, useful both for prognostication and for identifying candidates for targeted therapy.

Limitations include limited sample size, absence of FISH confirmation for equivocal cases, and lack of long-term follow-up data. Larger multicentric studies integrating molecular assays could better delineate HER2's prognostic and predictive value in gastrointestinal adenocarcinomas.

Conclusion

HER2/neu overexpression shows a clear correlation with histopathological differentiation, being predominantly expressed in well-differentiated and coming to site, particularly intestinal-type adenocarcinomas. Its absence in poorly differentiated tumours underscores the biological diversity of these malignancies. Routine HER2/neu testing by IHC, with confirmatory molecular studies where necessary, should be adopted for comprehensive evaluation of gastrointestinal adenocarcinomas to guide prognosis and eligibility for anti-HER2 therapy.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018. CA Cancer J Clin. 2018;68(6):394–424.
2. Ferlay J, Ervik M, Lam F, et al. GLOBOCAN 2018: Cancer incidence and mortality worldwide. IARC; 2019.
3. Dikshit R, Gupta PC, Ramasundarahettige C, et al. Cancer mortality in India. Lancet. 2012; 379:1807–16.
4. Key TJ, Allen NE, Spencer EA. Diet and cancer risk. Lancet. 2002; 360:861–8.
5. Wroblewski LE, Peek RM, Wilson KT. Helicobacter pylori and gastric cancer. Clin Microbiol Rev. 2010; 23:713–39.
6. Correa P. Human gastric carcinogenesis. Cancer Res. 1992; 52:6735–40.
7. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990; 61:759–67.
8. Ross JS, McKenna BJ. The HER2/neu oncogene in GI tumors. Cancer Invest. 2001; 19:554–68.
9. Hofmann M, et al. Assessment of HER2 scoring system for gastric cancer. Histopathology. 2008; 52:797–805.
10. Le XF, Pruefer F, Bast RC. HER2-targeting antibodies modulate p27 and Akt signaling. Cell Cycle. 2005; 4:87–95.
11. Slamon DJ, et al. Human breast cancer and HE R2 amplification. Science. 1987; 235:177–82.
12. Bang YJ, Van Cutsem E, et al. Trastuzumab for HER2-positive gastric cancer (ToGA trial). Lancet. 2010; 376:687–97.
13. Gravalos C, Jimeno A. HER2 in gastric cancer. Ann Oncol. 2008; 19:1523–9.
14. Halder S, Mallick D, Mondal P, et al. HER2/neu overexpression in gastric adenocarcinoma. Indian J Med Paediatr Oncol. 2017; 38:153–7.
15. Gupta P, Rao S, Bhalla S, et al. HER2 expression in gastric carcinoma. Indian J Cancer. 2016; 53:505–11.
16. Dewan K, Madan R, Sengupta P. E-cadherin and HER2/neu in gastric carcinoma. Indian J Pathol Microbiol. 2015; 58:154–7.
17. Sayadnejad N, Firouzjahi A, Shafaee S. HER2/neu expression in colorectal cancer. Int J Cancer Manag. 2017; 10:1–8.
18. Ummerali SK, Sarojini S. Correlation of HER2 with histopathologic grade in colorectal carcinoma. J Evol Med Dent Sci. 2017; 6:4407–11.
19. Janjigian YY, Werner D, et al. Prognosis of metastatic gastric cancer by HER2 status. Ann Oncol. 2012; 23:2656–62.
20. Rossi E, Grisanti S, Villanacci V, et al. HER2 amplification by FISH and overexpression by IHC in gastric and colorectal cancers. Pathol Res Pract. 2012; 208:584–9.
21. Singh N, Kaur M, Aggarwal V, et al. HER2/neu in gastrointestinal malignancies. Indian J Cancer. 2020; 57:61–7.
22. Varga Z, Noske A. HER2 assessment in colorectal cancer. Pathobiology. 2015; 82:139–49.
23. McKay JA, Murray LJ, Curran S, et al. HER2 status in colorectal cancer and prognosis. J Clin Oncol. 2002; 20:2820–8.
24. Loupakis F, Ruzzo A, Cremolini C, et al. HER2 amplification and anti-EGFR therapy response. Ann Oncol. 2013; 24:412–9.
25. Siena S, Sartore-Bianchi A, Lonardi S, et al. Trastuzumab deruxtecan in HER2-expressing colorectal cancer. J Clin Oncol. 2021; 39:699–709.