e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(3); 78-84

Original Research Article

Role of HER2/neu Overexpression in Gastrointestinal Adenocarcinoma: Potential for Targeted Therapy

R. Kalpana[1], J. Sujatha[2], Madhumita K.[3]

[1]Assistant Professor, Department of Pathology, Government Mohan Kumaramangalam Medical College, Salem, Tamilnadu, Inda

[2]Professor and HOD, Department of Pathology, Government Mohan Kumaramangalam Medical College, Salem, Tamilnadu, Inda

[3]Department of Computer Science and Engineering, Amrita School of Computing, Amrita Vishwa Vidyapeetham, Chennai, Tamilnadu, Inda

Received: 01-12-2025 / Revised: 15-01-2026 / Accepted: 21-02-2026

Corresponding author: Dr. R. Kalpana

Conflict of interest: Nil

Abstract

Background: Gastrointestinal adenocarcinomas (GIAs), particularly gastric and colorectal cancers, remain major global health burdens. HER2/neu (human epidermal growth factor receptor-2) is a proto-oncogene encoding a transmembrane tyrosine kinase receptor that plays a critical role in cell proliferation and differentiation. Overexpression of HER2/neu has been associated with poor prognosis and aggressive tumor behavior in several malignancies. The present study aimed to determine the prevalence and pattern of HER2/neu overexpression in gastrointestinal adenocarcinomas and to correlate these findings with demographic and histopathological parameters.

Materials and Methods: This was a retrospective and prospective cross-sectional study of 50 histologically confirmed cases of gastric and colorectal adenocarcinomas obtained for two years in the Department of Pathology in a tertiary care teaching hospital. Immunohistochemical (IHC) evaluation of HER2/neu was performed using standard protocols and scored according to Hoffmann et al. (2008) criteria. A score of 3+ was taken as positive, 2+ equivocal, and 0–1+ as negative.

Results: HER2/neu positivity (3+) was observed in 12 (24%) of 50 gastrointestinal adenocarcinomas, with 7/28 (25%) gastric and 5/22 (22.7%) colorectal cases showing overexpression. HER2/neu overexpression was significantly associated with well-differentiated histology ($p = 0.003$), but not with age, sex, or tumor site.

Conclusion: HER2/neu overexpression was found in nearly one-fourth of gastrointestinal adenocarcinomas. Given its significant association with tumor differentiation, HER2/neu assessment by IHC should be included in the routine evaluation of gastrointestinal adenocarcinomas to identify patients who may benefit from targeted anti-HER2 therapy.

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

DOI: 10.25258/ijcpr.18.3.14

Introduction

Gastrointestinal malignancies are among the leading causes of cancer-related morbidity and mortality worldwide. Gastric adenocarcinoma is the fifth most common malignancy and second leading cause of cancer death globally, accounting for nearly one million deaths annually [1]. Its incidence is particularly high in East Asia, Eastern Europe, and parts of South America. In India, the incidence rate of gastric cancer is estimated at 10.6 per 100,000 population [2]. Colorectal cancer (CRC), on the other hand, ranks third in incidence and second in mortality, with 1.8 million new cases and 881,000 deaths reported in 2018 [3]. The pathogenesis of gastrointestinal adenocarcinoma is complex and multifactorial, involving both environmental and genetic factors. Dietary habits such as high salt intake, consumption of smoked foods, and low intake of fruits and vegetables have been implicated as risk factors [4]. Chronic Helicobacter pylori infection is an established etiological factor for gastric carcinogenesis and is classified as a Class I carcinogen by the World Health Organization [5]. The progression of gastric cancer follows a "precancerous cascade" as described by Correa, in which normal mucosa undergoes sequential transformation through

atrophic gastritis, intestinal metaplasia, dysplasia, and finally invasive carcinoma [6,7]. Despite advances in diagnostic techniques and multimodal therapy, the prognosis for advanced gastrointestinal cancers remains dismal. The 5-year survival rate for advanced gastric cancer ranges between 4–13%, and while surgery remains the cornerstone of treatment, outcomes are significantly improved only in early-stage disease [8]. Consequently, there has been a growing interest in identifying molecular biomarkers that may serve as diagnostic, prognostic, or therapeutic targets.

Among these biomarkers, HER2/neu (human epidermal growth factor receptor 2)—encoded by the ERBB2 gene on chromosome 17q12—has received particular attention [9]. It belongs to the epidermal growth factor receptor (EGFR) family, which includes HER1 (EGFR), HER2, HER3, and HER4 [10]. These receptors have extracellular ligand-binding domains, transmembrane regions, and intracellular tyrosine kinase domains [11]. HER2/neu activation triggers intracellular signalling cascades, notably the MAPK, PI3K/AKT, and PKC pathways, which promote cellular proliferation, differentiation, and survival [12]. HER2/neu overexpression or amplification results in constitutive activation of these pathways, contributing to uncontrolled tumor cell growth, invasion, and metastasis [13]. In breast carcinoma, HER2/neu overexpression occurs in approximately 25–35% of cases and serves as both a prognostic marker and a predictive factor for response to targeted therapy with trastuzumab, a monoclonal antibody that inhibits HER2 signalling [14,15]. The landmark ToGA trial (2010) demonstrated a significant survival benefit in patients with HER2-positive advanced gastric or gastroesophageal junction cancers treated with trastuzumab in combination with chemotherapy [16].

Given these results, there is increasing interest in exploring HER2/neu expression in non-breast malignancies, including gastric and colorectal adenocarcinomas [17,18].

However, studies have shown variable rates of HER2/neu positivity ranging from 6–35% in gastric and 0–83% in colorectal cancers, depending on the population studied and the criteria used [19–21]. This variability underscores the need for region-specific data and standardization of HER2/neu testing protocols. Therefore, the present study was undertaken to determine the frequency and pattern of HER2/neu overexpression in gastrointestinal adenocarcinomas and to correlate HER2/neu status with clinicopathological parameters, thereby assessing its potential diagnostic and therapeutic significance.

Materials and Methods

This research was conducted as a retrospective and prospective cross-sectional observational study in the Department of Pathology of a tertiary care teaching hospital for a period of two years. The study comprised 50 histopathologically confirmed cases of gastric and colorectal adenocarcinomas. Ethical clearance was obtained from the Institutional Ethics Committee prior to initiation of the study, and informed consent was secured from patients or their relatives as applicable.

The study included all biopsy and resection specimens that were diagnosed histologically as adenocarcinoma arising from the stomach or large intestine. Both retrospective cases, identified through archival paraffin blocks, and prospective cases, obtained during the study period, were included. Cases were selected based on adequate fixation in 10% neutral buffered formalin, sufficient tissue for analysis, and intact morphology suitable for immunohistochemical (IHC) evaluation. Non-adenocarcinomatous malignancies, recurrent tumors, and samples with insufficient or necrotic tissue were excluded.

For each selected case, representative paraffin-embedded tissue blocks were sectioned at 3 µm thickness using a rotary microtome. Sections were mounted on poly-L-lysine coated slides and incubated at 60°C for one hour to promote adhesion. Following deparaffinization in xylene and rehydration through graded alcohols, heat-induced antigen retrieval was carried out using citrate buffer (pH 6.0–9.5) in a pressure cooker. Endogenous peroxidase activity was quenched using 3% hydrogen peroxide for 10 minutes. The slides were then incubated with a primary monoclonal antibody against HER2/neu (ready-to-use clone, supplied by PathnSitu Biotechnologies) for 60 minutes at room temperature.

After thorough washing, a Polyexcel HRP (horseradish peroxidase) secondary antibody system was applied, followed by visualization with diaminobenzidine (DAB) chromogen. Finally, counterstaining was performed with Harris hematoxylin, and the slides were dehydrated, cleared, and mounted using DPX.

A case of breast carcinoma known to be HER2/neu positive served as the positive control, while the negative control was prepared by omitting the primary antibody. All slides were independently reviewed by two senior pathologists to minimize observer bias.

HER2/neu immunoreactivity was evaluated based on Hoffmann et al. (2008) criteria [22]. A case was scored as 0 if there was no membranous staining or staining in <10% of tumor cells; 1+ for faint, incomplete membranous staining in ≥10% of cells; 2+ (equivocal) for weak to moderate complete or

basolateral membranous staining in ≥10% of cells; and 3+ (positive) for strong complete or basolateral membranous staining in ≥10% of cells. Only membranous staining was considered; cytoplasmic reactivity was disregarded.

Cases with a 2+ score were considered equivocal and recommended for confirmatory testing by fluorescence in situ hybridization (FISH), although this was not performed in the present study. All clinical data including age, sex, site, and histological grade were recorded and correlated with HER2/neu expression. Statistical analysis was performed using SPSS software version 21. Descriptive statistics were expressed in frequencies and percentages. Associations between HER2/neu expression and various parameters were analyzed using the Chi-square test and Fisher's exact test, with a p-value < 0.05 considered statistically significant.

Results

Table 1: Distribution of HER2/neu Expression among 50 Gastrointestinal Adenocarcinomas

HER2/neu Expression	Number	Percentage
Negative (0–1+)	30	60.0%
Equivocal (2+)	8	16.0%
Positive (3+)	12	24.0%
Total	**50**	**100.0%**

HER2/neu overexpression (3+) was observed in **12 cases (24%)**, equivocal in 8 (16%), and negative in 30 (60%).

Table 2: Site-wise HER2/neu Positivity

Site	Total Cases	HER2/neu Positive	Percentage
Gastric	28	7	25.0%
Colorectal	22	5	22.7%
Total	**50**	**12**	**24.0%**

HER2/neu positivity was slightly higher in gastric carcinomas (25%) compared to colorectal adenocarcinomas (22.7%).

Table 3: Correlation with Histologic Grade

Grade	HER2 Negative	HER2 Positive	Total	p-value
Well Differentiated	6	8	14	
Moderately Differentiated	12	4	16	
Poorly Differentiated	10	0	10	**0.003**

HER2 positivity was significantly higher in well-differentiated tumors (p = 0.003), suggesting an association between differentiation and HER2/neu overexpression.

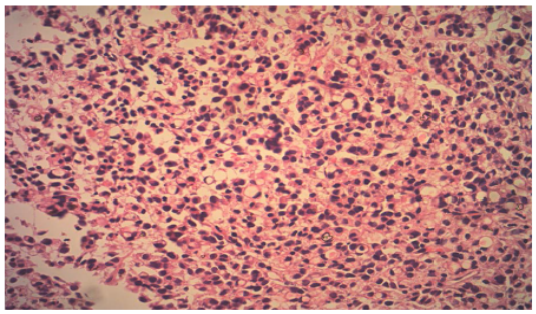
Table 4: Age and Sex Distribution

Variable	HER2 Negative	HER2 Positive	p-value
Age >50 years	29	12	0.092
Male	22	8	0.598
Female	16	4	

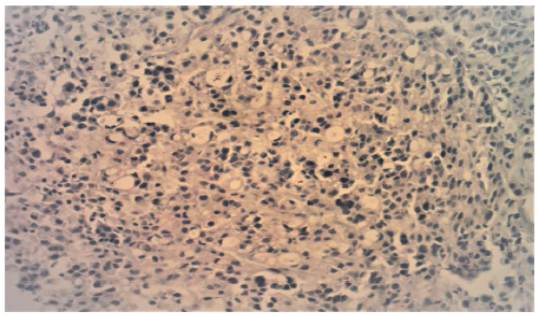
HER2 positivity was more frequent in patients aged >50 years and males, though the associations were not statistically significant.

IHC SCORE 0

H&E



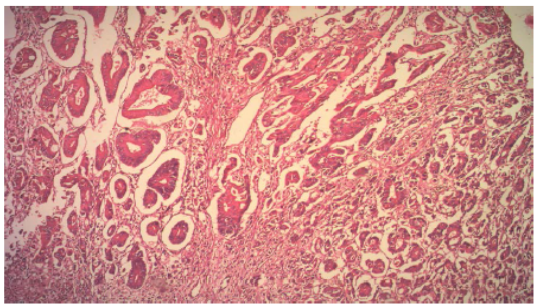
HER2/neu



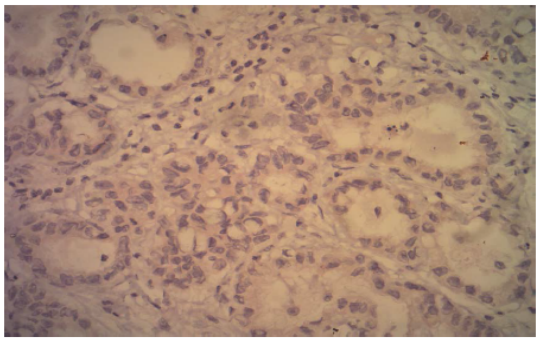
No reactivity in any tumour cell

IHC SCORE 1+

H&E



HER2/neu

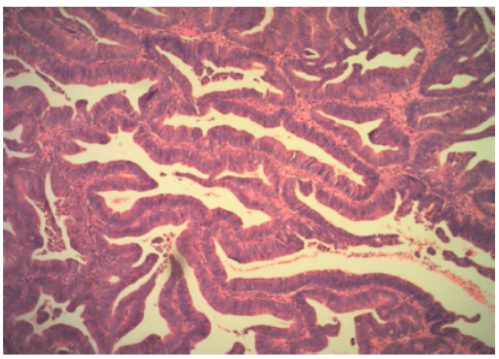


Faint or barely perceptible membranous reactivity in 10% or more cells

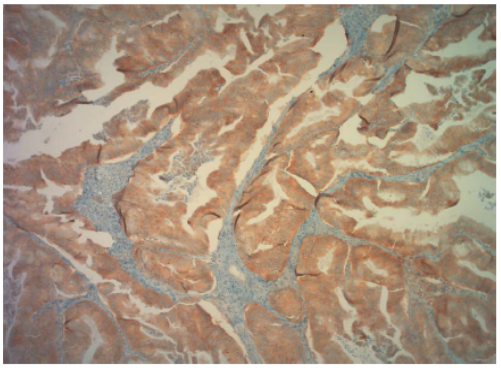
Figure 1 & 2: IHC score 0 and 1

IHC SCORE 2+/10x

H&E



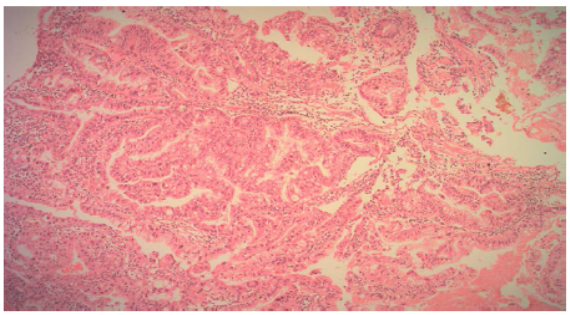
HER 2/neu



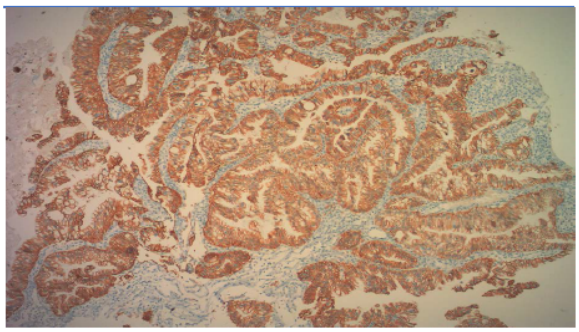
Moderate intense complete membranous staining in >10% of tumor cells

Score 3+/10x

H&E



HER2/neu



Strong intense complete membranous staining in all tumor cells

Figure 3 & 4: IHC Score 2 & 3

Discussion

The present study revealed HER2/neu overexpression (3+ IHC score) in 24% of gastrointestinal adenocarcinomas, consistent with reported global data of 6–35% for gastric and 0–30% for colorectal carcinomas [23–25].

HER2/neu in gastric adenocarcinoma: Among the 28 gastric adenocarcinoma cases, 25% showed HER2 positivity. Gupta et al. [26] reported 24.5% HER2 positivity in Indian gastric carcinoma patients, which aligns closely with our findings. Similarly, Gravalos and Jimeno [27] and Halder et al. [28] reported rates of 22% and 25%, respectively. However, studies by Sekaran et al. [29] and Lakshmi et al. [30] observed higher rates (44% and 60%), possibly due to population heterogeneity and differences in scoring criteria.

HER2/neu overexpression in gastric carcinoma has been associated with intestinal-type histology and well-differentiated tumors, as per the Lauren classification [31]. The current study supports this association, showing a statistically significant correlation ($p = 0.003$) between HER2 positivity and well-differentiated histology. This suggests that HER2-driven oncogenic signaling might be an early event in carcinogenesis, promoting differentiation and proliferation in gland-forming adenocarcinomas.

HER2/neu in colorectal adenocarcinoma: HER2 positivity was observed in 22.7% of colorectal adenocarcinomas, consistent with findings from Ummerali et al. [32] who reported 24%, and Shabbir et al. [33] who found membranous expression in 26.6% of positive cases. McKay et al. [34], however, reported minimal HER2 involvement, suggesting geographic and methodological variability.

Notably, our study used Hoffmann's strict membranous positivity criteria, excluding cytoplasmic staining, which enhances specificity for therapeutic relevance.

Correlation with clinicopathological features: In the present study, HER2/neu overexpression showed a significant association with tumor differentiation ($p = 0.003$) but not with age, gender, or tumor site. Similar correlations were noted by Dewan et al. [35], Raziee et al. [36], and Ling et al. (37]. HER2 positivity was higher among older patients (>50 years) and males, though not statistically significant, possibly reflecting the general epidemisology of gastrointestinal malignancies.

Therapeutic implications: The therapeutic importance of HER2/neu testing lies in identifying candidates for trastuzumab therapy. The ToGA trial [38] demonstrated that adding trastuzumab to chemotherapy improved median overall survival in HER2-positive advanced gastric or gastroesophageal junction cancers. Moreover, ongoing trials are evaluating dual HER2 blockade and antibody-drug conjugates for HER2-positive colorectal cancers, highlighting the translational potential of accurate HER2 testing.

When reviewing the literature collectively, our results correlate well with global and Indian data. Studies conducted by Gupta et al. [19], Gravalos et al. [20], Lakshmi et al. (23), Halder et al. [21], and Ummerali et al. [27] report HER2 positivity ranging between 20% and 30%, similar to our findings. This reinforces the reliability of HER2/neu as a marker of clinical significance in gastrointestinal adenocarcinomas. The variability observed across studies emphasizes the influence of geographic, genetic, and methodological factors on HER2 expression and underscores the importance of standardized assessment criteria.

Limitations: This study's limitations include a relatively small sample size and lack of confirmatory FISH or PCR analysis for equivocal (2+) cases. Furthermore, patient follow-up and survival analysis could not be conducted, precluding assessment of prognostic significance.

Conclusion

HER2/neu overexpression was identified in 24% of gastrointestinal adenocarcinomas, predominantly in gastric cancers. A strong correlation was noted between HER2 positivity and well-differentiated histology. Routine assessment of HER2/neu status using standardized IHC protocols is recommended for gastrointestinal adenocarcinomas, both for prognostic evaluation and potential eligibility for anti-HER2 targeted therapy. Confirmation of equivocal cases by FISH/PCR and inclusion in molecular oncology panels could further refine therapeutic decision-making.

References

1. Bray F, Ferla J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Dikshit R, Gupta PC, Ramasundarahettige C, Gajalakshmi V, Aleksandrowicz L, Badwe R, et al. Cancer mortality in India: a nationally representative survey. Lancet. 2012;379 (9828):1807–16.
3. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. GLOBOCAN 2018: Cancer incidence and mortality worldwide. Lyon: International Agency for Research on Cancer; 2019.

4. Key TJ, Allen NE, Spencer EA, Travis RC. The effect of diet on risk of cancer. Lancet. 2002;360(9336):861–8.
5. Wroblewski LE, Peek RM, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev. 2010;23(4):713–39.
6. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res. 1992;52(24):6735–40.
7. Correa P, Piazuelo MB. The gastric precancerous cascade. J Dig Dis. 2012;13(1):2–9.
8. Yamazaki H, Oshima A, Kikuchi S, Nashimoto A, Naruke T. Long-term follow-up of gastric cancer detected by mass screening. Cancer. 1989;63(3):613–7.
9. Ross JS, McKenna BJ. The HER2/neu oncogene in tumors of the gastrointestinal tract. Cancer Invest. 2001;19(5):554–68.
10. Hofmann M, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008;52(7):797–805.
11. Le XF, Pruefer F, Bast RC Jr. HER2-targeting antibodies modulate p27Kip1 and Akt signaling through different mechanisms in human breast cancer cells. Cell Cycle. 2005;4(1):87–95.
12. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235(4785):177–82.
13. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA trial): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
14. Gravalos C, Jimeno A. HER2 in gastric cancer: a novel prognostic factor and a target for therapy. Ann Oncol. 2008;19(9):1523–9.
15. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist. 2009;14(4):320–68.
16. Hofmann M, et al. Assessment of HER2 expression in gastric carcinoma and correlation with clinicopathological parameters. Histopathology. 2008;52:797–805.
17. Janjigian YY, Werner D, Pauligk C, Steinmetz K, Kelsen DP, Jäger E, et al. Prognosis of metastatic gastric cancer by HER2 status: a European multicentre analysis. Ann Oncol. 2012;23(10):2656–62.
18. Halder S, Mallick D, Mondal P, Mandal S, Das S, Datta C. HER2/neu overexpression in gastric adenocarcinoma: a study from eastern India. Indian J Med Paediatr Oncol. 2017;38(2):153–7.
19. Gupta P, Rao S, Bhalla S, Khanna S, Sharma V. HER2 expression in gastric carcinoma and its association with histopathological parameters. Indian J Cancer. 2016;53(4):505–11.
20. Lakshmi V, Valluru VR, Madhavi J. HER2/neu expression in gastric carcinoma: a 3-year study in South Indian population. Indian J Appl Res. 2014;4(4):1–4.
21. Sekaran A, Balakrishnan M, Duraipandian N, Balamurugan P. Study of HER2/neu expression in gastric adenocarcinoma and its association with clinicopathological parameters. J Clin Diagn Res. 2016;10(9):EC01–4.
22. Dewan K, Madan R, Sengupta P. Correlation of E-cadherin and HER2/neu expression with histological parameters in gastric carcinoma. Indian J Pathol Microbiol. 2015;58(2):154–7.
23. Raziee HR, Kermani T, Ghavamnasiri R. Expression of HER2/neu in resectable gastric cancer and its relationship with clinicopathological factors. Iran J Basic Med Sci. 2007;10(3):139–45.
24. Ling S, Jianming Y, Ning L, Zhiyong L, Wenhui Z, Jian L. Expression and clinical significance of HER2/neu in gastroesophageal junction adenocarcinoma. Diagn Pathol. 2013;8:76.
25. Sayadnejad N, Firouzjahi A, Shafaee S. HER2/neu expression in colorectal cancer and its correlation with clinicopathological features. Int J Cancer Manag. 2017;10(5):1–8.
26. Ummerali SK, Sarojini S. Correlation of HER2/neu expression with histopathologic grading in colorectal carcinoma. J Evol Med Dent Sci. 2017;6(57):4407–11.
27. Shabbir A, Mirza T, Khalid AB, Mustufa MA. Frequency of HER2/neu expression in colorectal adenocarcinoma: association with clinicopathological parameters. BMC Cancer. 2016;16(1):855.
28. McKay JA, Murray LJ, Curran S, Ross VG, Agarwal M, Morris RG, et al. Evaluation of HER2 status in colorectal cancer: relationship with prognosis and other molecular markers. J Clin Oncol. 2002;20(10):2820–8.
29. Rossi E, Grisanti S, Villanacci V, Cengia G, Marcheselli L, Rizzi S, et al. HER2/neu amplification by FISH and overexpression by IHC in gastric and colorectal cancers:

correlation and clinical significance. Pathol Res Pract. 2012;208(10):584–9.
30. Gupta R, Sharma S, Mehndiratta M, et al. HER2/neu expression in colorectal cancer and its correlation with histopathologic parameters. Indian J Pathol Microbiol. 2019;62(3):444–50.
31. Lauren P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. Acta Pathol Microbiol Scand. 1965;64(1):31–49.
32. Varga Z, Noske A. HER2 assessment in colorectal cancer: Is it ready for daily practice? Pathobiology. 2015;82(3–4):139–49.
33. Loupakis F, Ruzzo A, Cremolini C, et al. HER2 amplification and response to anti-EGFR therapy in metastatic colorectal cancer. Ann Oncol. 2013;24(2):412–9.
34. Siena S, Sartore-Bianchi A, Lonardi S, et al. Trastuzumab deruxtecan (DS-8201a) in HER2-expressing metastatic colorectal cancer: phase II DESTINY-CRC01 trial. J Clin Oncol. 2021;39(7):699–709.
35. Gomez-Martin C, Garralda E, Echarri MJ, et al. HER2 in gastric cancer: a new prognostic factor and potential target for therapy. Int J Mol Sci. 2014;15(4):6552–65.
36. Singh N, Kaur M, Aggarwal V, et al. HER2/neu expression and its correlation with clinicopathologic parameters in gastrointestinal malignancies. Indian J Cancer. 2020;57(1):61–7.
37. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610–21.
38. Van Cutsem E, Bang YJ, Feng-Yi F, et al. HER2 screening data and clinical outcome of ToGA: a phase 3 trial of trastuzumab for HER2-positive advanced gastric cancer. Eur J Cancer. 2011;47(14):2159–68.