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Original Research Article

CLINICOPATHOLOGICAL STUDY OF COLORECTAL CARCINOMAS AND EVALUATION OF HER2/NEU OVEREXPRESSION

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ABSTRACT

Background: Colorectal carcinoma exhibits substantial clinicopathological and molecular heterogeneity. HER2/neu overexpression defines a small but potentially clinically actionable subgroup; however, its frequency and relationship with conventional pathological characteristics remain inadequately characterised in many Indian populations.

Materials and Methods: This hospital-based descriptive cross-sectional study included 74 histopathologically confirmed primary colorectal carcinomas comprising 61 surgical resections and 13 endoscopic biopsies. Clinical information and tumour location were recorded, and histological typing, grading and pathological staging were performed using standard criteria. HER2/neu expression was assessed immunohistochemically using colorectal cancer-specific HERACLES criteria. IHC scores of 0/1+, 2+ and 3+ were interpreted as negative, equivocal and overexpressed, respectively. Clinicopathological associations were analysed using Fisher's exact test, with $p<0.05$ considered significant.

Results: The mean patient age was 56.7±13.2 years, and 59.5% were male. Bleeding per rectum was the most frequent presentation (52.7%). Left-sided tumours constituted 71.6% of cases, with the rectum being the most common site (41.9%). Conventional adenocarcinoma accounted for 82.4%, and 64.9% of tumours were moderately differentiated. Among resection specimens, 82.0% were pT3–pT4, 55.7% showed nodal involvement, and 55.7% were stage III–IV. Lymphovascular invasion, perineural invasion and high tumour budding were observed in 41.0%, 27.9% and 23.0%, respectively. HER2/neu IHC scores of 0/1+, 2+ and 3+ were identified in 82.4%, 9.5% and 8.1% of cases. Overexpression was significantly more frequent in poorly differentiated carcinomas than in well or moderately differentiated tumours (25.0% versus 3.4%; $p=0.018$). No significant associations were observed with age, sex, sidedness, tumour size, stage, lymphovascular invasion or perineural invasion.

Conclusion: Colorectal carcinomas predominantly showed left-sided location and advanced pathological characteristics. HER2/neu overexpression occurred in 8.1% and was significantly associated with poor differentiation. HER2 testing, supplemented by confirmatory in-situ hybridisation and molecular profiling, may help identify patients potentially eligible for HER2-directed treatment.

Keywords: Colorectal carcinoma; HER2/neu; ERBB2; immunohistochemistry; clinicopathological characteristics.

INTRODUCTION

Colorectal carcinoma (CRC) is a major global health problem and exhibits substantial geographical, biological, and clinicopathological heterogeneity. In 2022, approximately 1.9 million new CRC cases and 904,000 related deaths occurred worldwide, making it the third most commonly diagnosed malignancy and the second leading cause of cancer mortality.[1] In India, an estimated 64,863 new cases and 38,367 deaths were reported in 2022, with an increasing burden attributed to population ageing, urbanisation, lifestyle transition, and inadequate population-based screening.[2]

Adenocarcinoma constitutes the predominant histological type of CRC; however, tumours vary considerably with respect to anatomical location, differentiation, mucinous or signet-ring-cell morphology, depth of invasion, lymph-node involvement, tumour budding, lymphovascular invasion, and perineural invasion.[3,4] These parameters influence pathological staging, metastatic potential, recurrence, and survival. Their systematic assessment is therefore essential for prognostication and treatment planning.

Human epidermal growth factor receptor 2 (HER2/neu), encoded by the ERBB2 gene on chromosome 17q12, is a transmembrane receptor tyrosine kinase belonging to the epidermal growth factor receptor family. Gene amplification or protein overexpression promotes receptor dimerisation and activates downstream RAS–RAF–MAPK and PI3K–AKT signalling, thereby enhancing tumour-cell proliferation, survival, invasion, and treatment resistance.[5,6] Although HER2 positivity is less frequent in CRC than in breast or gastric carcinoma, a recent meta-analysis estimated a prevalence of 4.1% overall and 6.1% among RAS wild-type tumours; positivity is enriched in left-sided and microsatellite-stable cancers.[7]

HER2 status can be assessed initially by immunohistochemistry, with equivocal cases confirmed by in-situ hybridisation. Nevertheless, variations in staining patterns, scoring criteria, tumour heterogeneity, and study populations have produced inconsistent prevalence estimates.[8] The demonstrated activity of HER2-directed treatment in refractory metastatic CRC further supports its clinical relevance.[9,10] Therefore, evaluating HER2/neu overexpression alongside conventional clinicopathological variables may identify distinct tumour subsets and provide locally relevant prognostic and therapeutic information.

MATERIALS AND METHODS

Study design and setting: This hospital-based descriptive cross-sectional study was conducted in the Department of Pathology in collaboration with the Department of General Surgery at a tertiary-care teaching hospital in North India, for a period of 2 years from November 2023 to October 2025. Consecutive histopathologically confirmed cases of primary colorectal carcinoma diagnosed during the study period were included. The study aimed to describe the clinicopathological spectrum of colorectal carcinomas, determine HER-2/neu protein expression by immunohistochemistry, and examine its association with established clinicopathological variables.

Study population and eligibility criteria

All colorectal resection specimens and endoscopic biopsy specimens showing primary colorectal carcinoma and containing adequate viable tumour tissue for immunohistochemical evaluation were eligible. Resection specimens were used for comprehensive pathological staging, whereas biopsy specimens were included only for variables that could be reliably assessed, including histological type, differentiation and HER-2/neu expression. Cases with inadequate clinical information, extensive tumour necrosis, insufficient paraffin-embedded tissue, poorly fixed specimens, recurrent tumours, non-epithelial malignancies, metastatic tumours involving the colorectum, and carcinomas treated with neoadjuvant chemotherapy or radiotherapy were excluded. If multiple tissue blocks were available, the block containing the maximum proportion of viable invasive tumour with minimal necrosis was selected.

Clinical and specimen-related data

Clinical information was obtained from requisition forms, case records and hospital electronic databases using a structured proforma. Variables recorded included age, sex, presenting symptoms, tumour location, radiological findings, operative procedure and presence of distant metastasis. Tumours arising from the caecum to the transverse colon were categorised as right-sided, while those involving the splenic flexure, descending colon, sigmoid colon and rectum were categorised as left-sided. Rectal carcinomas were additionally documented separately because of their distinct clinical behaviour and treatment considerations.

Histopathological examination

Resection specimens were received in 10% neutral-buffered formalin and grossed according to standard oncological pathology protocols. Tumour location, maximum dimension, circumferential extent, serosal involvement, distance from resection margins, perforation and relationship to adjacent structures were documented. Representative sections were obtained from the tumour, tumour–normal interface, deepest invasive front, suspicious vascular or perineural foci, proximal and distal margins, circumferential resection margin, adjacent mucosa and all retrieved lymph nodes. Sections of 3–4 µm thickness were prepared from formalin-fixed, paraffin-embedded tissue and stained with haematoxylin and eosin.

Tumours were classified according to the World Health Organization classification of digestive-system tumours. Histological type, grade, depth of invasion, lymph-node status, tumour deposits, lymphovascular invasion, perineural invasion,

tumour budding, necrosis and margin involvement were evaluated. Conventional adenocarcinomas were graded as well/moderately differentiated or poorly differentiated according to gland formation. Mucinous adenocarcinoma was diagnosed when extracellular mucin constituted more than 50% of the tumour, while signet-ring-cell carcinoma required more than 50% signet-ring cells. Pathological staging was performed using the eighth edition of the American Joint Committee on Cancer TNM classification.

HER-2/neu immunohistochemistry

Immunohistochemistry was performed on 3–4 µm sections mounted on poly-L-lysine-coated slides using a validated monoclonal anti-HER-2/neu antibody. Following deparaffinisation and rehydration, heat-induced epitope retrieval was performed using the buffer recommended by the manufacturer. Endogenous peroxidase activity was blocked, sections were incubated with the primary antibody, and antigen–antibody binding was visualised using a polymer-based detection system with 3,3′-diaminobenzidine as the chromogen. Slides were counterstained with haematoxylin. A known HER2-positive carcinoma was used as an external positive control, while a section processed without the primary antibody served as the negative control.

Membranous staining was assessed using colorectal cancer-specific HERACLES criteria. A score of 0 indicated no appreciable membranous staining; 1+ represented faint, incomplete membranous staining; 2+ indicated moderate circumferential, basolateral or lateral membranous staining; and 3+ denoted intense membranous staining in at least 50% of tumour cells. Cases scoring 0 or 1+ were considered negative, 2+ cases were regarded as equivocal, and 3+ cases were classified as showing HER-2/neu overexpression. Equivocal cases were not categorised as positive without confirmatory in-situ hybridisation. Two pathologists independently evaluated the slides while blinded to the clinical outcomes, and discrepancies were resolved by joint review.

Statistical analysis: Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics, version 20.0. Continuous variables were presented as mean ± standard deviation or median with interquartile range, as appropriate, while categorical variables were expressed as frequencies and percentages. Associations between HER-2/neu expression and categorical clinicopathological variables were assessed using the chi-square test or Fisher's exact test. Continuous variables were compared using the independent-samples t test or Mann–Whitney U test. A two-sided p value <0.05 was considered statistically significant.

Ethical considerations: The study protocol was approved by the Institutional Ethics Committee. Patient identifiers were removed before analysis, and confidentiality was maintained throughout the study. Written informed consent was obtained for prospectively enrolled participants; for retrospective archival material, a consent waiver was obtained wherever permitted by the ethics committee.

RESULTS

The mean age of the participants was 56.7 ± 13.2 years, with an age range of 25–82 years. Most patients were aged ≥60 years (45.9%), followed by 40–59 years (43.2%), while 10.8% were younger than 40 years. Males constituted 59.5% of the cohort, giving a male-to-female ratio of 1.47:1. The mean duration of symptoms was 5.8 ± 3.7 months, and the mean haemoglobin level was 10.8 ± 2.1 g/dL. Bleeding per rectum was the most frequent presentation (52.7%), followed by abdominal pain (45.9%), altered bowel habits (43.2%), weight loss or loss of appetite (36.5%), anaemia-related symptoms (28.4%), and intestinal obstruction (13.5%) [Table 1].

Table 1: Demographic and clinical characteristics of patients with colorectal carcinoma (N=74).

Characteristic	Frequency (%)/mean ± SD
Age, years	56.7 ± 13.2
Age range, years	25–82
Age group	
<40 years	8 (10.8)
40–59 years	32 (43.2)
≥60 years	34 (45.9)
Gender	
Male	44 (59.5)
Female	30 (40.5)
Male-to-female ratio	1.47:1
Duration of symptoms, months	5.8 ± 3.7
Haemoglobin, g/dL	10.8 ± 2.1
Presenting manifestations*	
Bleeding per rectum	39 (52.7)
Abdominal pain	34 (45.9)
Altered bowel habits	32 (43.2)
Weight loss or loss of appetite	27 (36.5)
Fatigue or clinically documented anaemia	21 (28.4)
Intestinal obstruction	10 (13.5)

*Patients could have multiple presenting manifestations; therefore, symptom percentages do not total 100%.

The rectum was the most common tumour location, accounting for 31 (41.9%) cases, followed by the sigmoid colon in 13 (17.6%) and ascending colon in 10 (13.5%) cases. Overall, 53 (71.6%) tumours were left-sided, including rectal carcinomas, whereas 21 (28.4%) were right-sided. Surgical resection specimens comprised 61 (82.4%) cases, while 13 (17.6%) were endoscopic biopsies. Among resection specimens, the predominant gross morphology was ulceroinfiltrative growth (49.2%), followed by annular or constricting growth (27.9%). The mean maximum tumour size was 5.1 ± 1.9 cm, and 34 (55.7%) resected tumours measured ≥5 cm [Table 2].

Table 2: Anatomical distribution and specimen characteristics of colorectal carcinomas (N=74).

Characteristic	Frequency (%)/mean ± SD
Primary tumour location	
Caecum	6 (8.1)
Ascending colon	10 (13.5)
Transverse colon	5 (6.8)
Descending colon	5 (6.8)
Sigmoid colon	13 (17.6)
Rectosigmoid junction	4 (5.4)
Rectum	31 (41.9)
Tumour sidedness	
Right-sided	21 (28.4)
Left-sided, including rectum	53 (71.6)
Type of specimen	
Surgical resection	61 (82.4)
Endoscopic biopsy	13 (17.6)
Gross characteristics of resection specimens (n=61)	
Ulceroinfiltrative growth	30 (49.2)
Annular/constricting growth	17 (27.9)
Polypoidal growth	10 (16.4)
Diffuse infiltrative growth	4 (6.6)
Maximum tumour size, cm	5.1 ± 1.9
Tumour size <5 cm	27 (44.3)
Tumour size ≥5 cm	34 (55.7)

Right-sided tumours included carcinomas arising from the caecum to transverse colon; left-sided tumours included those arising from the descending colon to rectum. Gross morphology and tumour size were assessed only in surgical resection specimens (n=61).

Conventional adenocarcinoma was the predominant histological type, observed in 61 (82.4%) cases. Mucinous adenocarcinoma accounted for 8 (10.8%) cases, while signet-ring-cell carcinoma was identified in 3 (4.1%); medullary and adenosquamous carcinomas constituted one case each. Most tumours were moderately differentiated (64.9%), followed by poorly differentiated (21.6%) and well-differentiated carcinomas (13.5%). Tumour necrosis and Crohn-like peritumoural lymphoid reaction were present in 29.7% and 21.6% of cases, respectively. Among the 61 resection specimens, low, intermediate and high tumour budding were identified in 52.5%, 24.6% and 23.0%, respectively [Table 3].

Table 3: Histopathological characteristics of colorectal carcinomas (N=74).

Histopathological characteristic	Frequency (%)
Histological type	
Conventional adenocarcinoma	61 (82.4)
Mucinous adenocarcinoma	8 (10.8)
Signet-ring-cell carcinoma	3 (4.1)
Medullary carcinoma	1 (1.4)
Adenosquamous carcinoma	1 (1.4)
Histological grade	
Well differentiated	10 (13.5)
Moderately differentiated	48 (64.9)
Poorly differentiated	16 (21.6)
Tumour necrosis present	22 (29.7)
Crohn-like peritumoural lymphoid reaction present	16 (21.6)
Tumour budding in resection specimens (n=61)	
Low, 0–4 buds	32 (52.5)
Intermediate, 5–9 buds	15 (24.6)
High, ≥10 buds	14 (23.0)

Histological typing and grading were performed according to the World Health Organization classification. Tumour budding was evaluated at the invasive front in a 0.785-mm² hotspot and categorised as low (0–4 buds), intermediate (5–9 buds), or high (≥10 buds).

Among the resection specimens, pT3 was the most frequent pathological tumour category, observed in 36 (59.0%) cases, while 14 (23.0%) tumours showed pT4 invasion. Regional lymph-node metastasis was

present in 34 (55.7%) cases, including 20 pN1a/pN1b, 3 pN1c and 11 pN2 tumours. Stage III disease was the most common stage (47.5%), followed by stage II (31.1%), stage I (13.1%) and stage IV (8.2%). Lymphovascular invasion was identified in 25 (41.0%) cases, perineural invasion in 17 (27.9%), tumour deposits in 9 (14.8%), and resection-margin involvement in 5 (8.2%). The median lymph-node yield was 15, and an adequate yield of ≥12 nodes was achieved in 78.7% of resections [Table 4].

Table 4: Pathological staging and adverse prognostic features in colorectal carcinoma resection specimens (n=61).

Pathological characteristic	Frequency (%)/median (IQR)
Pathological tumour category	
pT1	3 (4.9)
pT2	8 (13.1)
pT3	36 (59.0)
pT4a	10 (16.4)
pT4b	4 (6.6)
Pathological nodal category	
pN0	27 (44.3)
pN1a/pN1b	20 (32.8)
pN1c	3 (4.9)
pN2a/pN2b	11 (18.0)
AJCC pathological stage	
Stage I	8 (13.1)
Stage II	19 (31.1)
Stage III	29 (47.5)
Stage IV	5 (8.2)
Lymphovascular invasion present	25 (41.0)
Perineural invasion present	17 (27.9)
Tumour deposits present	9 (14.8)
Involved resection margin	5 (8.2)
Distant metastasis at diagnosis	5 (8.2)
Lymph nodes retrieved	15 (12–19)
≥12 lymph nodes retrieved	48 (78.7)
<12 lymph nodes retrieved	13 (21.3)

Pathological staging was performed according to the eighth edition of the American Joint Committee on Cancer TNM classification. Stage IV incorporated documented synchronous distant metastasis. AJCC: American Joint Committee on Cancer; TNM: tumour–node–metastasis; IQR: interquartile range.

HER-2/neu immunohistochemistry demonstrated a score of 0 in 43 (58.1%) tumours and a score of 1+ in 18 (24.3%). Equivocal 2+ membranous staining was identified in 7 (9.5%) cases, whereas intense 3+ staining consistent with HER-2/neu overexpression was observed in 6 (8.1%). Accordingly, 61 (82.4%) tumours were classified as immunohistochemically negative, 7 (9.5%) as equivocal, and 6 (8.1%) as HER-2/neu overexpressed. The equivocal cases were not categorised as HER2-positive in the absence of confirmatory in-situ hybridisation [Table 5].

Table 5: Immunohistochemical expression and scoring of HER-2/neu in colorectal carcinomas (N=74).

HER-2/neu IHC result	Frequency (%)
Score 0: no appreciable membranous staining	43 (58.1)
Score 1+: faint/incomplete membranous staining	18 (24.3)
Score 2+: moderate membranous staining	7 (9.5)
Score 3+: intense membranous staining in ≥50% of tumour cells	6 (8.1)
Final IHC interpretation	
Negative, scores 0 and 1+	61 (82.4)
Equivocal, score 2+	7 (9.5)
HER-2/neu overexpressed, score 3+	6 (8.1)

HER-2/neu expression was assessed using colorectal cancer-specific HERACLES criteria. Scores 0 and 1+ were considered negative, 2+ was considered equivocal, and 3+—defined as intense circumferential, basolateral or lateral membranous staining in ≥50% of tumour cells—was considered overexpression. IHC: immunohistochemistry; ISH: in-situ hybridisation; HER2: human epidermal growth factor receptor 2.

HER-2/neu overexpression was significantly more frequent in poorly differentiated carcinomas than in well or moderately differentiated tumours (25.0% versus 3.4%; p=0.018). Overexpression was observed exclusively in left-sided tumours, although the association with tumour sidedness was not statistically significant (11.3% versus 0%; p=0.175). HER-2/neu overexpression was numerically more frequent in special histological types (15.4%), tumours measuring ≥5 cm (11.8%), stage III–IV disease (11.8%), lymphovascular-invasion-positive tumours (16.0%), and perineural-invasion-positive tumours (17.6%); however, these associations did not reach statistical significance. No significant association was found with age or sex [Table 6].

Table 6: Association of HER-2/neu overexpression with clinicopathological characteristics of colorectal carcinomas.

Characteristic	HER-2/neu overexpressed	Not overexpressed	p value
	Frequency (%)		
Age group			
<60 years (n=40)	4 (10.0)	36 (90.0)	0.681
≥60 years (n=34)	2 (5.9)	32 (94.1)	
Gender			
Male (n=44)	4 (9.1)	40 (90.9)	1.000
Female (n=30)	2 (6.7)	28 (93.3)	
Tumour sidedness			
Right-sided (n=21)	0 (0.0)	21 (100.0)	0.175
Left-sided, including rectum (n=53)	6 (11.3)	47 (88.7)	
Histological type			
Conventional adenocarcinoma (n=61)	4 (6.6)	57 (93.4)	0.283
Special histological types (n=13)	2 (15.4)	11 (84.6)	
Histological grade			
Well/moderately differentiated (n=58)	2 (3.4)	56 (96.6)	0.018
Poorly differentiated (n=16)	4 (25.0)	12 (75.0)	
Tumour size in resections (n=61)			
<5 cm (n=27)	1 (3.7)	26 (96.3)	0.371
≥5 cm (n=34)	4 (11.8)	30 (88.2)	
Pathological stage (n=61)			
Stage I–II (n=27)	1 (3.7)	26 (96.3)	0.371
Stage III–IV (n=34)	4 (11.8)	30 (88.2)	
Lymphovascular invasion (n=61)			
Absent (n=36)	1 (2.8)	35 (97.2)	0.149
Present (n=25)	4 (16.0)	21 (84.0)	
Perineural invasion (n=61)			
Absent (n=44)	2 (4.5)	42 (95.5)	0.127
Present (n=17)	3 (17.6)	14 (82.4)	

HER-2/neu overexpression was defined as an IHC score of 3+. The non-overexpressed category included scores 0, 1+ and 2+, because equivocal 2+ cases were not regarded as positive without confirmatory ISH. Special histological types included mucinous, signet-ring-cell, medullary and adenosquamous carcinomas. Two-sided Fisher's exact test was used because of the small number of overexpressing tumours. IHC: immunohistochemistry; ISH: in-situ hybridisation; HER2: human epidermal growth factor receptor 2.

DISCUSSION

The present study characterised the clinicopathological profile and HER-2/neu expression of 74 colorectal carcinomas. The mean age was 56.7±13.2 years, 59.5% were male, and 10.8% were younger than 40 years. These findings closely resemble the Indian series by Peedikayil et al., which reported a mean age of 58.4 years, 67.7% male predominance and 12.7% of cases below 40 years.[11] In contrast, the Tata Memorial Hospital audit reported a younger mean age of 47.2 years and 33% of patients below 40 years, possibly reflecting referral of younger and more advanced cases to a specialised cancer centre.[12] Male predominance may partly reflect sex-related differences in dietary exposures, tobacco and alcohol consumption, visceral adiposity, and healthcare utilisation.

Bleeding per rectum was the most frequent presentation (52.7%), followed by abdominal pain (45.9%) and altered bowel habits (43.2%). Left-sided tumours constituted 71.6%, with the rectum being the most common site (41.9%). Peedikayil et al., similarly found 74% of cancers distal to the splenic flexure, while Patil et al. reported 80.2% left-sided tumours and rectal involvement in approximately 42%.[11,12] Deo et al., in an Indian cohort of 970 patients, also documented rectal cancer in 58.7%.[13] Distal tumours commonly produce visible rectal bleeding and altered bowel habits because of luminal narrowing, whereas proximal cancers may remain clinically silent until anaemia, pain or advanced disease develops.

Conventional adenocarcinoma predominated (82.4%), while mucinous and signet-ring-cell carcinomas accounted for 10.8% and 4.1%, respectively. Most tumours were moderately differentiated (64.9%). Nitsche et al., reported conventional, mucinous and signet-ring-cell histology in 88%, 11% and 0.9%, respectively, and observed that special histological subtypes frequently presented with higher grade and stage.[14] The greater biological aggressiveness of signet-ring-cell carcinoma has been attributed to reduced cell adhesion, diffuse mural infiltration and early lymphatic or peritoneal dissemination. Among resected tumours, 82.0% were pT3–pT4, 55.7% showed nodal involvement and 55.7% belonged to stages III–IV. This predominance of locally advanced disease may reflect symptom neglect, diagnostic delay and the absence of organised population-based screening.

High tumour budding was present in 23.0% of resections. Tumour buds represent isolated cells or small clusters undergoing epithelial–mesenchymal transition, with loss of epithelial cohesion and acquisition of migratory capability; consequently, budding is associated with nodal metastasis and

recurrence.[15] Lymphovascular and perineural invasion occurred in 41.0% and 27.9%, respectively. Knijn et al., reported a pooled perineural-invasion prevalence of 18.2% and established it as an independent adverse prognostic factor.[16] Similarly, Yuan et al., found lymphovascular invasion to be associated with poorer overall survival in stage I–II CRC (pooled hazard ratio 2.15).[17] These features indicate access to vascular, lymphatic and neural planes, thereby facilitating regional and distant tumour dissemination.

HER-2/neu scores of 0, 1+, 2+ and 3+ were found in 58.1%, 24.3%, 9.5% and 8.1% of cases, respectively. The observed 8.1% overexpression rate was comparable to the 11% protein-overexpression rate reported by Kavanagh et al,[18] but higher than the 1.6% reported by Ingold Heppner et al., in 1,645 primary CRCs.[19] Seo et al., found approximately 6% IHC 2+/3+ expression and 5.8% gene amplification,[20] whereas Richman et al., demonstrated overexpression in 1.3% of stage II–III and 2.2% of stage IV tumours.[21] Differences in antibodies, fixation, whole-section versus tissue-microarray assessment, scoring thresholds, tumour heterogeneity and molecular case mix can explain this variability. Importantly, the seven equivocal 2+ cases in the present study were not classified as positive without in-situ hybridisation, preventing inflation of the positivity rate.

HER-2/neu overexpression was significantly associated with poor differentiation (25.0% versus 3.4%; p=0.018). HER2-mediated activation of RAS–RAF–MAPK and PI3K–AKT pathways may enhance proliferation, inhibit apoptosis and promote loss of glandular differentiation. Park et al., similarly associated HER2 overexpression with recurrence and poorer survival,[22] while Sun et al., reported higher HER2 expression in advanced-stage and node-positive cancers.[23] Nevertheless, Seo et al., and Wu et al., found no consistent relationship with aggressive clinicopathological features or prognosis.[20,24] In the present study, overexpression was confined to left-sided tumours and was numerically higher with larger size, advanced stage, lymphovascular invasion and perineural invasion, but these associations were nonsignificant, probably because only six tumours were overexpressed. Thus, HER-2/neu identifies a small but potentially biologically aggressive and therapeutically relevant CRC subset, warranting confirmatory molecular testing and correlation with RAS/BRAF status.

Limitations: This study was limited by its single-centre design and relatively small sample, particularly the low number of HER2-overexpressing tumours, which reduced the power to detect clinicopathological associations. Follow-up and survival outcomes were unavailable. Equivocal IHC 2+ cases were not evaluated by in-situ hybridisation, and RAS, BRAF and MSI/MMR status was not assessed. Inclusion of biopsy specimens also prevented complete pathological staging in all participants.

CONCLUSION

This study demonstrates that colorectal carcinoma predominantly affected older adults and males, with a marked left-sided and rectal distribution. Most resected tumours were locally advanced and frequently exhibited nodal metastasis, lymphovascular invasion, perineural invasion or tumour budding, emphasising the importance of comprehensive histopathological assessment. HER2/neu overexpression was identified in 8.1% of carcinomas and was significantly associated with poor differentiation. Although its associations with left-sided location, advanced stage and invasive characteristics were not statistically significant, the observed trends suggest a potentially aggressive tumour phenotype. HER2 evaluation may therefore identify a small, clinically relevant subgroup requiring confirmatory molecular testing and consideration for targeted treatment.

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–263.
2. Shivshankar S, Patil PS, Deodhar K, Budukh AM. Epidemiology of colorectal cancer: a review with special emphasis on India. Indian J Gastroenterol. 2025;44(2):142–153.
3. WHO Classification of Tumours Editorial Board. Digestive system tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2019.
4. Chen K, Collins G, Wang H, Toh JWT. Pathological features and prognostication in colorectal cancer. Curr Oncol. 2021;28(6):5356–5383.
5. Iqbal N, Iqbal N. Human epidermal growth factor receptor 2 (HER2) in cancers: overexpression and therapeutic implications. Mol Biol Int. 2014;2014:852748.
6. Siena S, Sartore-Bianchi A, Marsoni S, Hurwitz HI, McCall SJ, Penault-Llorca F, et al. Targeting the human epidermal growth factor receptor 2 (HER2) oncogene in colorectal cancer. Ann Oncol. 2018;29(5):1108–1119.
7. Singh H, Kang A, Bloudek L, Hsu LI, Palanca-Wessels MC, Stecher M, et al. Systematic literature review and meta-analysis of HER2 amplification, overexpression, and positivity in colorectal cancer. JNCI Cancer Spectr. 2024;8(1):pkad082.
8. Valtorta E, Martino C, Sartore-Bianchi A, Penault-Llorca F, Viale G, Risio M, et al. Assessment of a HER2 scoring system for colorectal cancer: results from a validation study. Mod Pathol. 2015;28(11):1481–1491.
9. Sartore-Bianchi A, Trusolino L, Martino C, Bencardino K, Lonardi S, Bergamo F, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016;17(6):738–746.
10. Cervantes A, Adam R, Roselló S, Arnold D, Normanno N, Taïeb J, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34(1):10–32.
11. Peedikayil MC, Nair P, Seena SM, Radhakrishnan L, Sadasivan S, Naryanan VA, et al. Colorectal cancer distribution in 220 Indian patients undergoing colonoscopy. Indian J Gastroenterol. 2009;28(6):212–215.
12. Patil PS, Saklani A, Gambhire P, Mehta S, Engineer R, De'Souza A, et al. Colorectal cancer in India: an audit from a

tertiary center in a low prevalence area. Indian J Surg Oncol. 2017;8(4):484–490.
13. Deo SVS, Kumar S, Bhoriwal S, Shukla NK, Sharma A, Thulkar S, et al. Colorectal cancers in low- and middle-income countries—demographic pattern and clinical profile of 970 patients treated at a tertiary care cancer center in India. JCO Glob Oncol. 2021;7:1110–1115.
14. Nitsche U, Zimmermann A, Späth C, Müller T, Maak M, Schuster T, et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Ann Surg. 2013;258(5):775–782.
15. Lugli A, Kirsch R, Ajioka Y, Bosman F, Cathomas G, Dawson H, et al. Recommendations for reporting tumour budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol. 2017;30(9):1299–1311.
16. Knijn N, Mogk SC, Teerenstra S, Simmer F, Nagtegaal ID. Perineural invasion is a strong prognostic factor in colorectal cancer: a systematic review. Am J Surg Pathol. 2016;40(1):103–112.
17. Yuan H, Dong Q, Zheng B, Hu X, Xu JB, Tu S. Lymphovascular invasion is a high-risk factor for stage I/II colorectal cancer: a systematic review and meta-analysis. Oncotarget. 2017;8(28):46565–46579.
18. Kavanagh DO, Chambers G, O'Grady L, Barry KM, Waldron RP, Bennani F, et al. Is overexpression of HER-2 a predictor of prognosis in colorectal cancer? BMC Cancer. 2009;9:1.
19. Ingold Heppner B, Behrens HM, Balschun K, Haag J, Krüger S, Becker T, et al. HER2/neu testing in primary colorectal carcinoma. Br J Cancer. 2014;111(10):1977–1984.
20. Seo AN, Kwak Y, Kim DW, Kang SB, Choe G, Kim WH, et al. HER2 status in colorectal cancer: its clinical significance and the relationship between HER2 gene amplification and expression. PLoS One. 2014;9(5):e98528.
21. Richman SD, Southward K, Chambers P, Cross D, Barrett J, Hemmings G, et al. HER2 overexpression and amplification as a potential therapeutic target in colorectal cancer: analysis of 3256 patients enrolled in the QUASAR, FOCUS and PICCOLO colorectal cancer trials. J Pathol. 2016;238(4):562–570.
22. Park DI, Kang MS, Oh SJ, Kim HJ, Cho YK, Sohn CI, et al. HER-2/neu overexpression is an independent prognostic factor in colorectal cancer. Int J Colorectal Dis. 2007;22(5):491–497.
23. Sun SJ, Lin Q, Sun Q, Li J, Zhang XY, Tan ZG, et al. High HER-2 protein levels correlate with clinicopathological features in colorectal cancer. J Cancer Res Ther. 2016;12(1):323–333.
24. Wu SW, Ma CC, Li WH. Does overexpression of HER-2 correlate with clinicopathological characteristics and prognosis in colorectal cancer? Evidence from a meta-analysis. Diagn Pathol. 2015;10:144.