Original Article

Study of Expression of COX-2 and HER2/neu in Colorectal Cancer and Their Correlation with Histological Grades

Vandana Yadav[1], Vandana Porwal[1], Nidhi Yadav[1], Shyam Bhutra[2]

[1]Department of Pathology, J.L.N Medical College, Ajmer, Rajasthan, India
[2]Department of General Surgery, J.L.N Medical College and Associated Group of Hospitals, Ajmer, Rajasthan, India

DOI: 10.21276/APALM.3554

***Corresponding Author**:
Dr Vandana Yadav
vandnayadav.vy466@gmail.com

Submitted: 06-Apr-2025
Final Revision: 05-Jun-2025
Acceptance: 19-Jun-2025
Publication: 30-Jun-2025

Abstract

Background: Colorectal cancer (CRC) is a significant global health concern with increasing incidence and poor prognosis in advanced stages. This study evaluates HER2/neu and COX2 expression, key biomarkers in CRC, using immunohistochemistry. Their correlation with age, sex, tumor location, and histological grade is analyzed to refine diagnosis and guide personalized treatment.

Materials and Methods: Fifty resected colorectal carcinoma specimens diagnosed between January 2019 and December 2023 at J.L.N. Medical College, Ajmer, were analyzed. Immunohistochemical staining was performed using a rabbit monoclonal antibody for HER2/neu and a rabbit polyclonal antibody for COX2. Expression levels were correlated with clinicopathological parameters.

Results: Patients ranged from 20 to 82 years (mean: 55.6), with a male predominance. The rectum and caecum were the most common tumor sites. Adenocarcinoma accounted for 76% of cases, with grade II being most frequent (63.16%). HER2/neu overexpression was observed in 26% of cases, significantly correlating with serosal invasion, lymph node involvement, histological grade, and stage. COX2 overexpression occurred in 70% of cases, also showing significant associations with these factors. A strong positive correlation was noted between HER2/neu and COX2 expression.

Conclusion: HER2/neu and COX2 overexpression contribute to CRC progression, aiding in tumor invasion and metastasis. Targeting these markers, alone or with standard therapies, offers a promising strategy for personalized CRC treatment. COX2 inhibition may also play a role in prevention and therapy.

Keywords:

Colorectal carcinoma, HER2/neu, COX2, immunohistochemistry

Introduction

Cancer remains a significant global health challenge, with colorectal cancer (CRC) representing the third most common cancer in men and the second in women [1]. Its incidence has risen globally, influenced by aging, lifestyle changes, and Westernization, particularly in developing countries. While CRC rates are higher in industrialized nations, countries like the USA have seen declines due to effective screening and early detection [2,3].

CRC develops through a multistep process involving genetic and epigenetic changes, often progressing from adenoma to

carcinoma [4,5]. Advanced CRC presents treatment challenges, with metastases significantly reducing survival rates. Early detection and localized treatments offer favorable outcomes, while advancements in combinational therapies, including targeted treatments like monoclonal antibodies, have improved management for metastatic CRC [6,7].

Emerging research focuses on understanding tumor invasion, metastasis, and resistance mechanisms, emphasizing the need for personalized therapeutic strategies [8]. Immunohistochemistry plays a pivotal role in CRC diagnostics, with markers like CEA, CDX2, MLH1, and HER2/neu aiding diagnosis, prognosis, and treatment planning. HER2/neu, a target in breast cancer, shows potential in CRC for therapeutic intervention, while COX2, associated with inflammation and tumor progression, correlates with poor prognosis and recurrence [9,10,11].

This study utilized immunohistochemical methods to examine HER2/neu and COX2 expression in CRC, analyzing their associations with histological grading. Findings aim to enhance diagnostic accuracy, prognostic evaluation, and therapeutic approaches for CRC.

Materials and Methods

This record-based cross-sectional study was conducted in the Department of Pathology, Jawaharlal Nehru Medical College, Ajmer, from January 2019 to December 2023. The study included all colorectal carcinoma resected specimens meeting inclusion criteria while excluding small biopsies, secondary metastatic disease, and poorly fixed samples.

Inclusion Criteria: Resected specimens of colorectal carcinoma (all cases diagnosed as colorectal cancer from resected specimens from right hemicolectomy, left hemicolectomy, transverse colectomy, descending colectomy, sigmoid colectomy, anterior resection, and abdomino-perineal resection were included in the study).

Exclusion Criteria: Small biopsies, Secondary metastatic disease of the colon, Specimens not well fixed in formalin.

Patient demographic and clinical details were recorded. Paraffin-embedded blocks of eligible cases were sectioned, stained with Hematoxylin and Eosin, and mounted for microscopic evaluation. Sections were further prepared for immunohistochemical (IHC) staining of HER2/neu and COX2 using specific antibodies. A semi-quantitative scoring system assessed staining results for diagnostic accuracy, with histological diagnosis as the gold standard.

Tissue processing involved fixation, dehydration, clearing, embedding, and sectioning. IHC protocols included dewaxing, rehydration, antigen retrieval, and staining with primary and secondary antibodies, followed by DAB visualization and counterstaining. HER2/neu and COX2 expression levels were scored based on proportional and intensity criteria.

HER2/neu was scored as follows: 0 = no staining of all or membrane staining in <10% of tumor cells; 1 = faint or barely perceptible membranous staining in >10% of tumor cells; 2 = weak to moderate staining of entire membrane in >10% of tumor cells; 3 = strong staining of entire membrane in >10% of tumor cells. Scores 0 and 1 = negative; 2 = equivocal; and 3 = positive [12].

The proportion of cells stained for COX2 was scored as follows: 0 = 0%-5%; 1 = 6%-25%; 2 = 26%-50%; 3 = 51%-75%; 4 = 75%-100%. Staining intensity was scored as follows: 1 = faintly yellow; 2 = brownish yellow; 3 = brown. A combined score was categorized as negative (−; combined score = 0-1), positive (+; combined score = 2-3), moderately positive (++; combined score = 4-5), or strongly positive (+++; combined score = 6-7) [8].

Statistical analysis was performed using IBM SPSS version 21. Qualitative data were expressed as numbers and percentages, and quantitative data as mean ± standard deviation. Associations were analyzed using the chi-square test, with significance set at P <

0.05.

Results

In this study, a total of 50 specimens from patients with colorectal carcinoma were thoroughly examined across a range of demographic, histological, and molecular parameters.

Of the 50 cases studied, 66% were male and 34% were female. The most affected age group was 61–70 years (28%), followed by 41–50 years (24%). In younger age groups (20–30 and 31–40 years), the prevalence was significantly lower, accounting for 10% and 6% of cases, respectively (Figure 1).

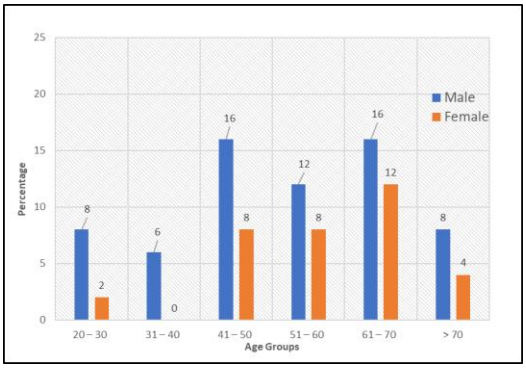

Figure 1: Age and gender wise distribution of study subjects in colorectal carcinoma

The rectum and caecum were the most common tumor sites, each comprising 24% of cases, followed by the sigmoid colon (14%). The rectum was more frequently affected in males, while the caecum was the most common site in females (Table 1).

Table 1: Site distribution of colorectal carcinoma in study subjects

Site	Number of cases			Percentage (%)
	Male	Female	Total	
Ascending colon	6	0	6	12
Caecum	4	8	12	24
Descending Colon	2	1	3	6
Hepatic flexure	1	0	1	2
Ileocaecal junction	3	1	4	8
Transverse colon	3	0	3	6
Splenic flexure	0	1	1	2
Sigmoid colon	3	4	7	14
Rectum	10	2	12	24
Rectosigmoid	1	0	1	2
Total	33	17	50	100

Tumor size was evenly distributed, with 50% of cases having tumors <5 cm and the remaining 50% ≥5 cm. There was no significant correlation between tumor size and HER2/neu or COX2 overexpression. Adenocarcinoma was the most prevalent histological type, constituting 76% of cases (26 males and 12 females). Mucinous carcinoma accounted for 22%, while signet ring cell carcinoma was rare (2%).

Moderately differentiated adenocarcinomas (Grade II) were the most common (63.16%), followed by well-differentiated (Grade I) at 28.95% (Figure 2), and poorly differentiated carcinomas (Grade III) at 7.89%. Grade III tumors were exclusively associated

with advanced disease stages and HER2/neu and COX2 overexpression. Stage I was the most frequent (38%), followed closely by Stage III (36%). Stage IV accounted for 8% of cases, predominantly associated with poorly differentiated tumors and significant biomarker overexpression.

Molecular Marker Analysis

HER2/neu Expression: HER2/neu overexpression (scores 2–3) [Figure 3] was detected in 13 cases (26%). Among these, adenocarcinomas had the highest overexpression (9 cases), followed by mucinous carcinomas (3 cases) and signet ring cell carcinoma (1 case) [Table 2].

Table 2: HER2/neu and COX2 scoring in colorectal carcinoma

Histological type	Total	HER2/neu Overexpression (score 2 – 3)	COX2 Overexpression (score 2 – 7)
Adenocarcinoma	**38**	9	26
Mucinous carcinoma	**11**	3	8
Signet ring cell carcinoma	**1**	1	1
Total	**50**	**13**	**35**

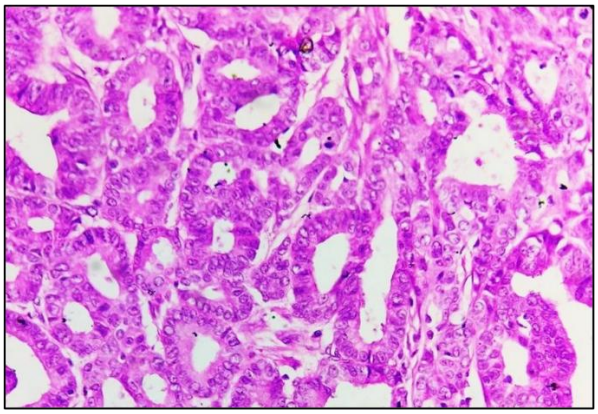

Figure 2: Well differentiated adenocarcinoma showing well-formed glands with basally oriented nuclei and without significant stratification H&E, (400X)

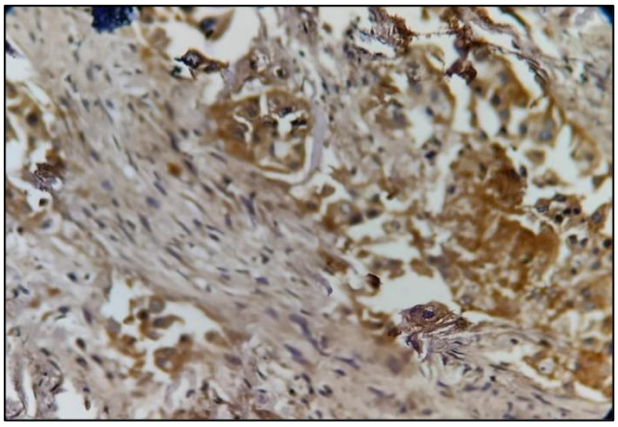

Figure 3: HER2/neu immunohistochemistry-HER2/neu score-3+(400X)

A total of 50 cases were examined; among these, only 13 cases showed overexpression for HER2/neu, while the remaining 37 cases did not. Conversely, 35 cases showed overexpression for COX2, with the remaining 15 cases not showing overexpression. Histological Grades: 100% of Grade III tumors, 16.67% of Grade II, and 18.18% of Grade I [$p < 0.00004$] [Table 3].

Table 3: Correlation of HER2/neu immunoreactivity to the histological grade of the studied cases

Histological Grade	HER2/ neu score		% of HER2/ neu over expression
	HER2/neu Negative (score 0 – 1)	HER2/neu Overexpression (score 2 – 3)	
Well Differentiated (I)	9	2	18.18
Moderately Differentiated (II)	20	4	16.67
Poorly Differentiated (III)	0	3	100
Total	**29**	**9**	**23.68**
P value	**0.00004**		

In this table, only conventional adenocarcinoma was included; mucinous and signet ring subtype adenocarcinomas were not included. Overexpression was significantly correlated with: Advanced Stages: 7 cases in Stage III, 4 in Stage IV, and 2 in Stage II [$p < 0.0001$]. Lymph Node Involvement: 11 of 13 HER2/neu-overexpressing cases had lymph node involvement [$p < 0.0001$]. Serosal Invasion: Present in 8 of 13 cases [$p = 0.025$].

COX2 Expression

COX2 overexpression (scores 2–7) [Figure 4] was observed in 35 cases (70%) [Table 2], with significant findings in: Tumor Types: 26 adenocarcinomas, 8 mucinous carcinomas, and 1 signet ring cell carcinoma. Histological Grades: 100% of Grade III tumors, 70.83% of Grade II, and 54.54% of Grade I [$p = 0.013$] [Table 4].

Table 4: Correlation of COX2 immunoreactivity to the histological grade of the studied cases

Histological Grade	COX2 score		% of overexpression
	COX2 Negative (score 0 – 1)	COX2 Overexpression (score 2 – 7)	
Well Differentiated (I)	5	6	54.54
Moderately Differentiated (II)	7	17	70.83
Poorly Differentiated (III)	0	3	100
Total	**12**	**26**	**68.42**
P value	**0.013**		

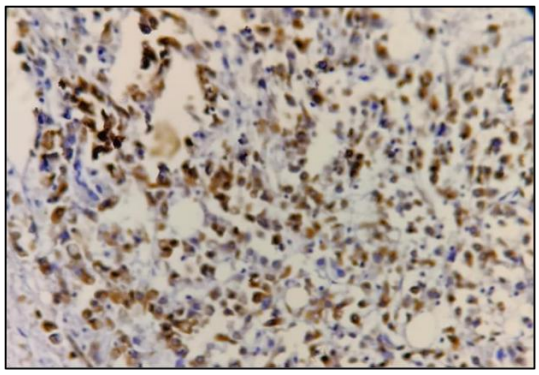

Figure 4: COX2 Immunohistochemistry-COX2 score-7+(400X)

In this table, only conventional adenocarcinoma was included; mucinous and signet ring subtype adenocarcinomas were not included.

Overexpression was significantly correlated with: Advanced Stages: Predominantly in Stage III (15 cases) and Stage IV (4 cases), with a lesser prevalence in Stage I (9 cases) and Stage II (7 cases) [p = 0.004]. Lymph Node Involvement: 17 cases with lymph node positivity [p = 0.018]. Serosal Invasion: Significant association seen in 17 cases with positive invasion [p = 0.004].

Correlation Between HER2/neu and COX2

A significant positive correlation was established between HER2/neu and COX2 overexpression [p = 0.041]. Among 35 COX2-overexpressing tumors, 12 also overexpressed HER2/neu, suggesting a potential cooperative role of these biomarkers in tumor progression.

These detailed findings highlight the multifaceted nature of colorectal carcinoma, with specific demographic patterns, histological distinctions, and molecular marker expressions. The significant correlations between HER2/neu and COX2 overexpression and advanced stages, high histological grades, serosal invasion, and lymph node involvement underscore their potential as prognostic markers and therapeutic targets. This integrated analysis provides a robust framework for improving colorectal carcinoma diagnosis, prognosis, and treatment strategies.

Discussion

Colon cancer is the third most prevalent cancer globally among men and women, accounting for approximately 10% of cancer-related deaths. The annual worldwide incidence of colon cancer is increasing at an alarming rate of nearly 2% [13]. Since the early 1990s, substantial research efforts have advanced our understanding of the tumor biology and pathogenesis of colorectal carcinoma. Current evidence highlights the role of complex interactions between genetic predispositions and environmental factors in cancer development [14].

The present study analyzed 50 colorectal carcinoma cases from J.L.N. Medical College, Ajmer, collected between January 2019 and December 2023. The histological examination revealed that 76% of cases were adenocarcinomas, 22% were mucinous carcinomas, and 2% were signet ring cell carcinomas. This distribution aligns with global findings, emphasizing adenocarcinoma as the predominant type.

Age and Gender Distribution: The age of patients ranged from 20 to 82 years, with a mean age of 53.6 years. These findings are consistent with studies like Gill MK et al. (2011) [15] and Tu J et al. (2015) [16], though some studies reported a higher mean age, likely due to demographic and lifestyle differences. A male preponderance was observed (66%), with a male-to-female ratio of 1.94:1, similar to findings from Lee WS et al. (2014) [17] and Negi RR et al. (2019) [18].

Tumor Location and Size: The most commonly affected sites were the proximal colon and rectum (24% each), followed by the sigmoid colon (14%). This pattern contrasts with studies like Kiran DK et al. (2023) [19] and Mohsenifar Z et al. (2023) [20], where the distal colorectal region was more frequently involved. Tumor size distribution was equal, with 50% of tumors <5 cm and 50% ≥5 cm, paralleling findings from Tu J et al. (2015) [16].

Histological Grades and Stages: Moderately differentiated adenocarcinomas (Grade II) were the most common (48%), followed by well-differentiated (Grade I) and poorly differentiated (Grade III) tumors. Stage I was the most frequent (38%), followed by Stage III (36%), indicating that early detection plays a critical role in managing colorectal cancer. These findings align with Nandi

S et al. (2024) [21], though other studies, such as Fazeli MS et al. (2007) [22], reported Stage II as the most common.

HER2/neu and COX2 Overexpression: HER2/neu is a protein with tyrosine kinase activity encoded by cellular oncogenes. Under normal circumstances, oncogenes are inactive and participate in growth. Its overexpression is associated with pathologic morphology and biological behavior in a wide variety of tumor specimens, including breast, gastric, ovarian, and colorectal carcinoma.

In our study, HER2/neu overexpression was seen in 26% of colorectal carcinoma cases. This was in concordance with the study done by Mohsenifar Z et al. (2023) [20] and Park et al. (2007) [23].

Cases with HER2/neu overexpression did not show any correlation with age, sex, tumor location, or tumor size.

HER2/neu overexpression showed a significant correlation with both serosal invasion and lymph node involvement, which aligns with research by Wu QB et al. (2015) [8]. This suggests that HER2/neu could serve as an important marker for assessing the invasiveness and metastatic potential of colorectal cancer.

Statistical analysis of our study showed a strong correlation between tumor grade and HER2/neu overexpression, as all cases of poorly differentiated adenocarcinoma (Grade III) showed HER2/neu overexpression. These findings were in accordance with the studies done by Tavangar et al. (2005) [24] and Kiran DK et al. (2023) [19].

A strong correlation was also observed between tumor stage and HER2/neu overexpression in the present study. All cases of Stage IV showed HER2/neu overexpression (100%). These findings were in accordance with the study done by Seo AN et al. (2014) [25].

Cyclooxygenase is a rate-limiting enzyme in prostaglandin metabolism. The carcinogenic effects of COX2 have been studied in cancers of various organs, such as breast, lung, esophagus, head and neck, bladder, and liver. Cyclooxygenase-2 has also been found to be overexpressed in colorectal cancer.

COX2 expression in tumor tissue is correlated with prognosis in colon cancer cells. With high COX2 expression, the adhesion of cells to the matrix and the potential of cancer cells to metastasize increase, both of which are conducive to the development, progression, and metastasis of cancer. Nonsteroidal anti-inflammatory drugs are known to reduce the risk and mortality of colorectal cancer by inhibiting cyclooxygenase.

Similarly, COX2 overexpression was found in 70% of our cases, which is consistent with findings from Nagi RR et al. (2019) [18] and Joo YE et al. (2002) [26].

All colorectal carcinoma cases with COX2 overexpression did not show any correlation with age, sex, tumor location, or tumor size.

We observed a strong correlation between COX2 overexpression and both serosal invasion and lymph node involvement, supporting the role of COX2 in cancer progression and metastasis, as described by Wu QB et al. (2015) [8]. This highlights COX2 as a potential target for therapeutic strategies aimed at reducing cancer spread.

Statistical analysis of our study showed a strong correlation between COX2 overexpression and tumor grade, as all cases of poorly differentiated adenocarcinoma (Grade III) showed COX2 overexpression. The results of our study were in accordance with studies done by Sheehan KM et al. (1999) [27] and Al-Maghrabi J et al. (2012) [28].

As shown in our study, all cases of Stage IV showed COX2 overexpression, followed by Stage III. The results of our study were in concordance with the results of Albasri et al. (2018) [29].

As COX2 expression is significantly associated with tumor stage, it is considered a prognostic factor for colorectal cancer.

A notable finding from our study was the significant co-expression of HER2/neu and COX2 in 34.28% of cases. This dual overexpression was associated with more aggressive tumor characteristics, such as advanced stages and increased metastatic potential. These results are in line with Wu QB et al. (2015) [8], who also found a strong correlation between HER2/neu and COX2 positivity in colorectal cancer. The simultaneous overexpression of these markers could serve as a potential prognostic indicator, suggesting a poorer outcome and highlighting the need for combined therapeutic approaches targeting both pathways.

Our study's findings suggest that HER2/neu and COX2 could be valuable biomarkers for evaluating tumor aggressiveness in colorectal cancer. While the immunohistochemical methods used in our study are relatively simple and widely accessible, they are subject to variability based on reagent quality and operator skill. Future research could focus on refining detection methods, such as fluorescence in situ hybridization or quantitative PCR, to ensure more consistent and reliable results.

Conclusion

The findings underscore the importance of integrating demographic, histological, and molecular markers for a comprehensive understanding of colorectal carcinoma. HER2/neu and COX2 overexpression serve as potential prognostic indicators and therapeutic targets. Future research should focus on standardized detection methods and explore targeted therapies to improve outcomes for colorectal cancer patients.

Acknowledgements: The authors are thankful to the Principal, JLN Medical College, and the Multi-Disciplinary Research Unit, Ajmer, Rajasthan, India, for providing facilities and their support.

Funding: Marker provided by the Multi-Disciplinary Research Unit, JLN Medical College, Ajmer.

Competing Interests: None

References

1. López PJ, Albero JS, Rodríguez-Montes JA. Primary and secondary prevention of colorectal cancer. Clin Med Insights Gastroenterol. 2014 Jul;7:CGast-S14039.
2. Soltani G, Poursheikhani A, Yassi M, Hayatbakhsh A, Kerachian M, Kerachian MA. Obesity, diabetes and the risk of colorectal adenoma and cancer. BMC Endocr Disord. 2019 Dec;19(1):1-10.
3. Cho YA, Lee J, Oh JH, Chang HJ, Sohn DK, Shin A, et al. Genetic risk score, combined lifestyle factors and risk of colorectal cancer. Cancer Res Treat. 2019 Jul;51(3):1033-40.
4. Xiong B, Sun TJ, Hu WD, Cheng FL, Mao M, Zhou YF. Expression of cyclooxygenase-2 in colorectal cancer and its clinical significance. World J Gastroenterol. 2005 Feb 28;11(8):1105-9.
5. Lin PC, Lin YJ, Lee CT, Liu HS, Lee JC. Cyclooxygenase-2 expression in the tumor environment is associated with poor prognosis in colorectal cancer patients. Oncol Lett. 2013 Sep;6(3):733-9.
6. Lichtenstern CR, Ngu RK, Shalapour S, Karin M. Immunotherapy, inflammation and colorectal cancer. Cells. 2020 Mar 4;9(3):618.
7. 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 Nov;111(10):1977-84.
8. Wu QB, Sun GP. Expression of COX-2 and HER-2 in colorectal cancer and their correlation. World J Gastroenterol. 2015 May 28;21(20):6206-14.
9. Dabbs DJ. Diagnostic immunohistochemistry: theranostic and genomic applications. 5th ed. China: Elsevier; 2019. p.509-41.

10. Achalla LS, Shinde RK, Jogdand S, Vodithala S. Review of the role of HER2/neu in colorectal carcinomas. Cureus. 2022 May 27;14(5):e25322.
11. Tomozawa S, Tsuno NH, Sunami E, Hatano K, Kitayama J, Osada T, et al. Cyclooxygenase-2 overexpression correlates with tumour recurrence, especially haematogenous metastasis, of colorectal cancer. Br J Cancer. 2000 Aug;83(3):324-8.
12. Perez EA, Cortés J, Gonzalez-Angulo AM, Bartlett JM. HER2 testing: current status and future directions. Cancer Treat Rev. 2014 Mar;40(2):276-84.
13. Bandhate K, Diwan AK, Mahobia V, Khan S. Changing trend in colorectal carcinomas in Central India. Asian J Med Res. 2021;10(1):5-10.
14. Li Q, Yu M, Lv H, Zhang L, Deng Y, Yu H. Burden of early-onset colorectal cancer along with attributable risk factors from 1990 to 2019: a comparative study between China and other G20 countries. BMC Public Health. 2023 Jul 31;23(1):1463.
15. Gill MK, Manjari M, Jain K, Kaur TA. Expression of Her-2/neu in colon carcinoma and its correlation with the histological grades and the lymph nodes status. J Clin Diagn Res. 2011 Dec;5(8):1564-8.
16. Tu J, Yu Y, Liu W, Chen S. Significance of human epidermal growth factor receptor 2 expression in colorectal cancer. Exp Ther Med. 2015 Jan;9(1):17-24.
17. Lee WS, Park YH, Lee JN, Baek JH, Lee TH, Ha SY. Comparison of HER2 expression between primary colorectal cancer and their corresponding metastases. Cancer Med. 2014 Jun;3(3):674-80.
18. Negi RR, Rana SV, Gupta V, Gupta R, Chadha VD, Prasad KK, et al. Over-expression of cyclooxygenase-2 in colorectal cancer patients. Asian Pac J Cancer Prev. 2019;20(6):1675-80.
19. Kiran DK, Preethi NS. COX2 and HER2 expression in colorectal cancer and their histopathological correlation. J Cardiovasc Dis Res. 2023;14(7):1-6.
20. Mohsenifar Z. Evaluation of HER2 in colorectal cancer with aggressiveness of the tumor and follow-up patients. J Gastro Hepato. 2023;10(4):1-8.
21. Nandi S, Das C, Kundu A, Mukhopadhyay M, Basu A. Role of HER2/neu in colorectal carcinoma: a cross-sectional study from a tertiary care centre in West Bengal, India. Natl J Lab Med. 2024;18(1):336-40.
22. Fazeli MS, Adel MG, Lebaschi AH. Colorectal carcinoma: a retrospective, descriptive study of age, gender, subsite, stage, and differentiation in Iran from 1995 to 2001 as observed in Tehran University. Dis Colon Rectum. 2007 Jul;50(7):990-5.
23. 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 May;22(5):491-7.
24. Tavangar A, Shariftabrizi E, Soroush B. HER2/neu over-expression correlates with more advanced disease in Iranian colorectal cancer patients. Med Sci Monit. 2005;11(3):CR126-9.
25. 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 May 30;9(5):e98528.
26. Joo YE, Kim HS, Min SW, Lee WS, Park CH, Park CS, et al. Expression of cyclooxygenase-2 protein in colorectal carcinomas. Int J Gastrointest Cancer. 2002 May;31(2-3):147-54.
27. Sheehan KM, Sheahan K, O'Donoghue DP, MacSweeney F, Conroy RM, Fitzgerald DJ, et al. The relationship between cyclooxygenase-2 expression and colorectal cancer. JAMA. 1999 Oct 6;282(13):1254-7.
28. Al-Maghrabi J, Buhmeida A, Emam E, Syrjänen K, Sibiany A, Al-Qahtani M, et al. Cyclooxygenase-2 expression as a predictor of outcome in colorectal carcinoma. World J Gastroenterol. 2012 Apr 4;18(15):1793-9.
29. Albasri AM, Elkablawy MA, Hussainy AS, Yousif HM, Alhujaily AS. Impact of cyclooxygenase-2 over-expression on the prognosis of colorectal cancer patients: an experience from Western Saudi Arabia. Saudi Med J. 2018 Aug;39(8):773-9.