Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

COX2 and HER2 Expression in colorectal cancer and their Histopathological correlation

Dr. Devarakonda Kranti Kiran[1], Dr. Nuka Sai Preethi[2*]

[1]Senior Resident, Department of Pathology, Government Medical College, Jangaon, Telangana, India.

[2]Senior Resident, Department of Pathology, Government Medical College, Jangaon, Telangana, India

***Corresponding author: Dr. Nuka Sai Preethi,** Senior Resident, Department of Pathology, Government Medical College, Jangaon, Telangana, India

ABSTRACT

Aim and Objectives: In order to determine the prognostic value of COX2 and HER2 expression in colorectal adenocarcinomas, it is necessary to assess the expression of COX2, HER2, and immunostaining in all diagnosed cases of colorectal carcinoma. This evaluation includes determining the score of positivity and negativity of COX2 and HER2 expression in the colorectal lesions.

Methods: The current study was conducted at the Department of Pathology, MGM Hospital in Warangal, India, for two and a half years (2 years prospectively and 6 months retrospectively), from 2019 to 2021.

Results: In the current study, the most prevalent age range was 50 to 59 years, and the majority of the lesions were identified as adenocarcinomas. The majority of cases (31) involved females, and the rectum was the most frequently affected region in our study. The majority of patients (57.6%) in this study are colorectal adenocarcinomas that are highly differentiated. Of the 52 colorectal adenocarcinomas, cox2 expression was detected in 48 (92.3%) cases and her2 expression in 47 (90.3%). Out of the 52 cases, 48.0% of the well-differentiated and 55.5% of the moderately-differentiated carcinomas exhibited Her2 positive, while 57.0% of the moderately-differentiated adenocarcinomas and 50.2% of the well-differentiated adenocarcinomas expressed Cox2. The expression of Cox2 and Her2 is significantly correlated with grade. Poorly differentiated carcinomas typically have higher scores than well- and moderately-differentiated carcinomas. Cox2 and Her2 expression are significantly correlated (P 0.02) with the grade of colorectal adenocarcinoma, although age, gender, and tumour site are not significantly correlated.

Conclusion: The results point to a positive association between COX2 and HER2 expression, show that simultaneous Cox2 and HER2 expression can boost colorectal cancer's potential to metastasize and invade, and suggest a poor prognosis for individuals with colorectal cancer.

Keywords: Immunostaining, Colorectal cancer, COX2, HER2.

INTRODUCTION

The leading cause of death and morbidity worldwide is colorectal cancer. A malignant epithelial tumour of the colon or rectum is colorectal cancer. Only tumours that have entered the submucosa through the muscularis mucosae are deemed malignant at this location [1]. It is the second most prevalent cancer in developed nations, right after lung cancer. From 25.3 per 100,000 in Eastern Europe to 45.8 per 100,000 in Australia, the incidence rate ranges [2]. India has very low incidence rates, between 2 and 8, per 100,0003. The incidence was 4.3 per

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

100,000 men and 3.4 per 100,000 women [3].

The majority of the GI tract's length is made up of the small intestine and colon, which are also the sites of a wide range of illnesses such diarrhoea and malabsorption as well as several infectious and inflammatory disorders [4]. In the western population, the colon is where GI neoplasia most frequently occurs. With mortality following incidence, colon and rectum cancer is the third most frequent cancer in women and the fourth most common cancer in men worldwide [4].

Strong risk factors for IBD include male gender, ageing, the existence of long-standing IBD, and familial susceptibility. The average incidence age is 62 years old. Cancer is primarily age-related, with incidence rising steadily with age. 8% of patients in high-risk regions are under 50 years old. The prognosis for young patients is different from that for older people [4]. Approximately 60% of patients with colorectal cancer will have locally advanced illness when they are first diagnosed [5]. Males are slightly more likely than females to experience this. Right colon cancer is more common in females of all ages.

Males above the age of 70 are more likely to get left colon cancer than females under the age of 50. Both men and women can develop right colon cancer depending on their age. 30% each in the left and right colons, and 40% in the male rectum. 40% of female cases occur in the right colon, 30% in the left colon, and rectum [6].

Colorectal cancer has a complicated aetiology that involves the interaction of hereditary and environmental factors. According to histological precursor lesions and molecular genetic changes such adenomatous polyposis coli (APC), KRAS, and p53, colorectal cancer develops in a multistep process [7]. APC and K-RAS gene mutations happen early in the development of cancer, but p53 alterations happen later. Nearly half of CRC8 had TP53 tumour suppressor gene mutations. Therefore, there has been a lot of interest in finding new tumor-based indicators that can better anticipate how this cancer will progress as well as figuring out the best adjuvant therapy regimens.

MATERIALS & METHODS

The current study was conducted at the Department of Pathology, MGM Hospital in Warangal, India, for two and a half years (2 years prospectively and 6 months retrospectively), from 2019 to 2021.

INCLUSION CRITERIA:

- Only samples with definite histopathological diagnosis of carcinoma were considered.
- Representative areas in the biopsies are only included.

EXCLUSION CRITERIA:

- Non neoplastic lesions.
- Congenital lesions like Hirschsprungs disease are excluded.
- Inadequate samples are excluded.

SPECIMEN HANDLING

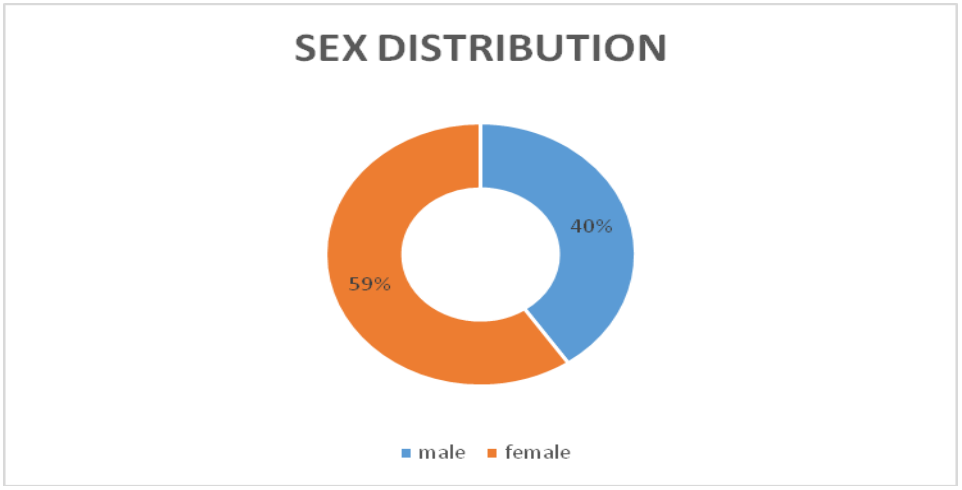
The specimens from colorectal biopsies and resections were fixed in 10% formalin before being sent for standard histopathological analysis. The paraffin blocks of the samples that had met the criteria for inclusion are collected once a histological diagnosis of the lesion has been determined. Basic information about each case, such as the biopsy number, age and sex,

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

clinical specifics, and histological diagnosis, is kept on file.

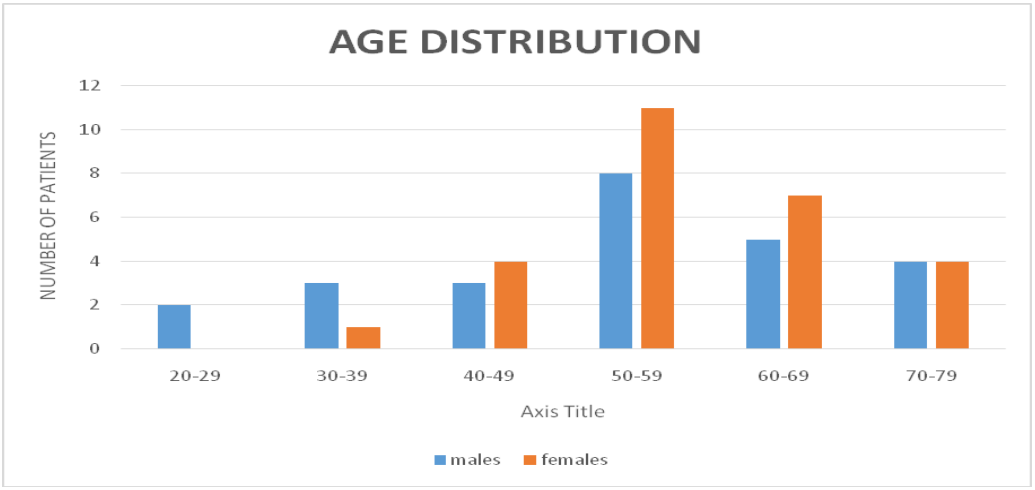
RESULTS

In the current study, 52 patients between the ages of 20 and 70 were examined for colorectal resections and a small number of biopsies from 2019 to 2021 (2 years prospectively and 6 months retrospectively) at MGM Hospital, Warangal.



GRAPH 1: SEX DISTRIBUTION

Out of 52 patients of colorectal carcinoma cases male patients were 21(40%) and female patients were 31 (59%).



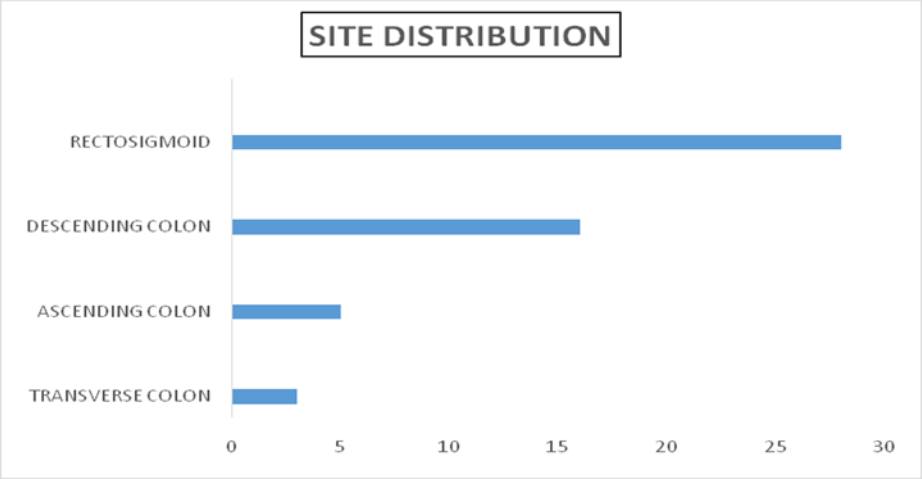
GRAPH 2: AGE DISTRIBUTION

The sixth decade of the research has the highest incidence of colorectal cancer (37%), with the majority of patients being female. Only 2 cases—all involving male patients—are observed in the 20–29 year age range. Most of the individuals in our study are between the ages of 50 and 59.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

TABLE NO 1: COX2 AND HER2 EXPRESSION IN COLORECTAL CARCINOMAS

TYPE	TOTAL	COX2	HER2
CONVENTIONAL	46	45	43
MUCINOUS	06	03	03
TOTAL	52	48	46



GRAPH 3: SITE DISTRIBUTION

The rectosigmoid is the most common place in the current study, accounting for 28 instances (53.8%), with approximately 16 cases (30.7%) in the descending colon. The transverse colon had the fewest occurrences, or about 5.7%, with only three, while the ascending colon had five cases, or about 9.6%.

TABLE NO 2: GRADING OF COLORECTAL CARCINOMA

GRADE	NO OF CASES	MALES	FEMALES	TOTAL
WELL DIFFERENTIATED	30	13	17	57.6%
MODERATELY DIFFERENTIATED	16	06	10	30.7%
POORLY DIFFERENTIATED	04	01	03	7.6%
UNDIFFERENTIATED	02	01	01	3.8%

In the current investigation, there were 52 total cases, of which 30 were classified as having good differentiation, 16 as having moderate differentiation, 4 as having poor differentiation, and only 2 as having undifferentiated tumours.

COX2 AND HER2 IMMUNOSTAINING RESULTS ON COLORECTAL CARCINOMA

Out of the 52 cases 48 were positive for COX2 and 47 were positive for HER24 cases were negative for COX2 and 5 cases were negative for HER2.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

TABLE NO 3: COX2 SCORE IN RELATION TO HISTOLOGICAL GRADE

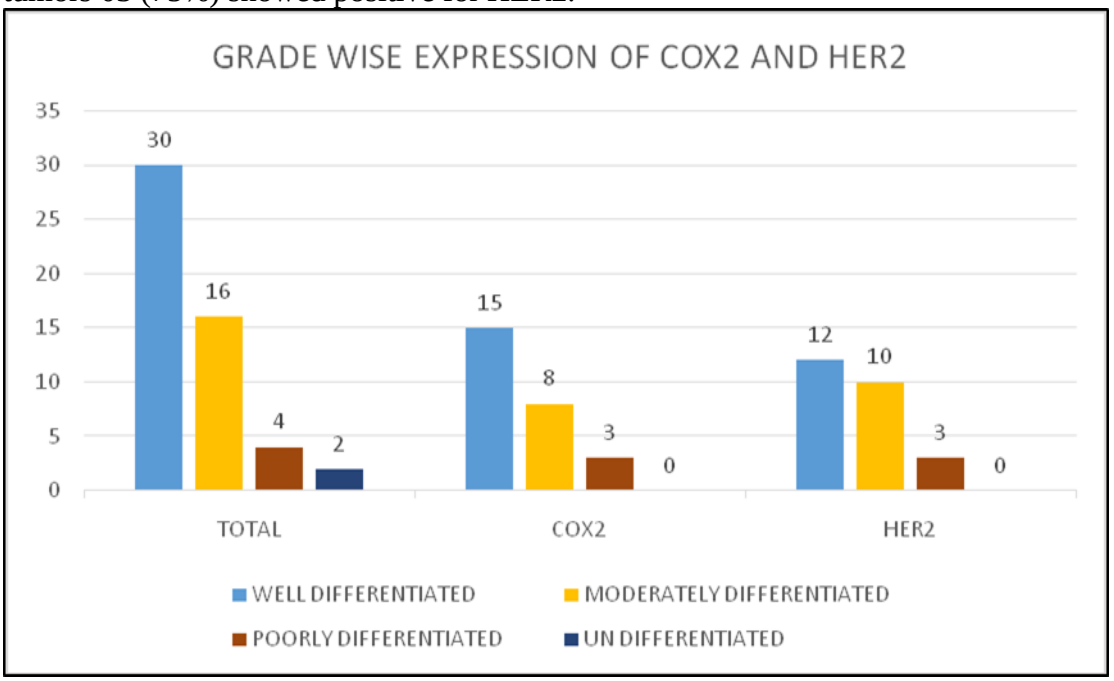
HISTOLOGICALGRADE	COX2 SCORE				TOTAL	TOTAL POSITIVE AND PERCENTAGE
	1+	2+	3+	4+		
WELL DIFFERENTIATED	15	13	2	0	30	50%(15)
MODERATELY DIFFERENTIATED	6	2	2	4	14	57%(08)
POORLY DIFFERENTIATED	1	2	1	0	04	75%(03)

Out of 30 cases of well differentiated tumors 15 showed positivity (50%) for cox2, out of 14 moderately differentiated cases 8 cases showed positive, and out of 4 cases of poorly differentiated cases 03 cases (75%) showed positive for cox2.

TABLE NO 4: HER2 SCORE IN RELATION TO HISTOLOGICAL GRADE

HISTOLOGICAL GRADE	HER2 SCORE				TOTAL	TOTAL POSITIVE &PERCENTAGE
	0	1+	2+	3+		
WELL DIFFERENTIATED	13	2	1	9	25	48%(12)
MODERATELY DIFFERENTIATED	8	8	1	1	18	55.5%(10)
POORLY DIFFERENTIATED	1	2	1	0	04	75.2%(03)

Out of 25 cases of well differentiated tumors 12 showed positive for her2 out of18 cases of moderately differentiated tumors 10 showed positive, out of 4 cases of poorly differentiated tumors 03 (75%) showed positive for HER2.



ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

GRAPH 4: GRADE WISE EXPRESSION OF COX2 AND HER2.

Figure no. 1: GROSS – DESCENDING COLON GROWTH.

Figure no. 2: GROSS – ASCENDING COLON GROWTH.

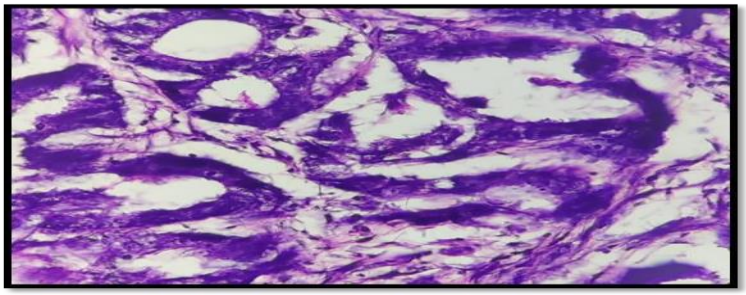


Figure no. 3: WELL DIFFERENTIATED ADENOCARCINOMA H&E(40X)

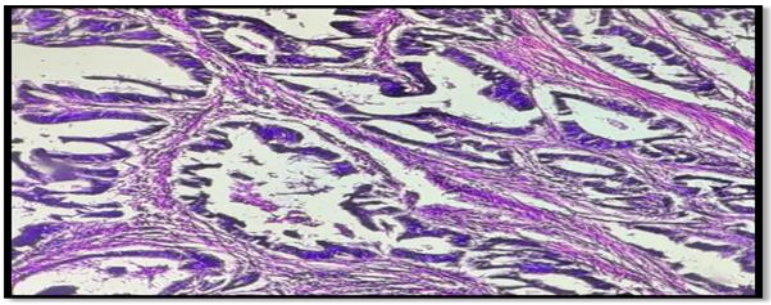


Figure no. 4: MODERATELY DIFFERENTIATED ADENOCARCINOMAH&E(20X)

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

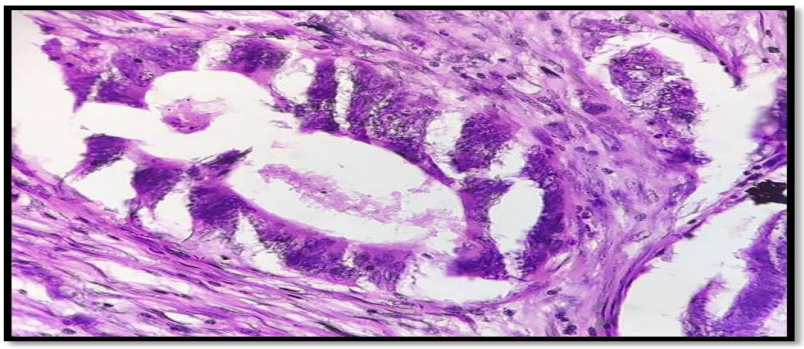


Figure no. 5: MODERATLY DIFFERENTIATED ADENOCARCINOMAH&E(40X)

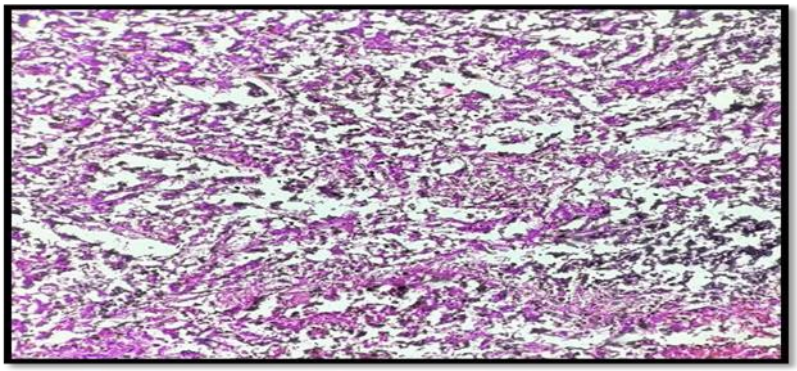


Figure no. 6: POORLY DIFFERENTIATED ADENOCARCINOMAH&E(40X)

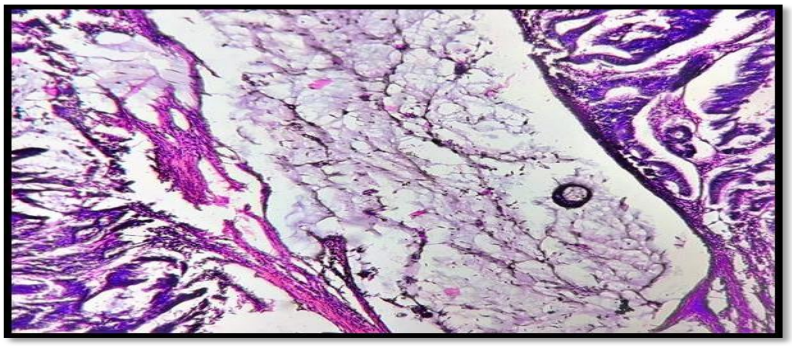


Figure no. 7: MUCINOUS ADENOCARCINOMA H&E(40X)

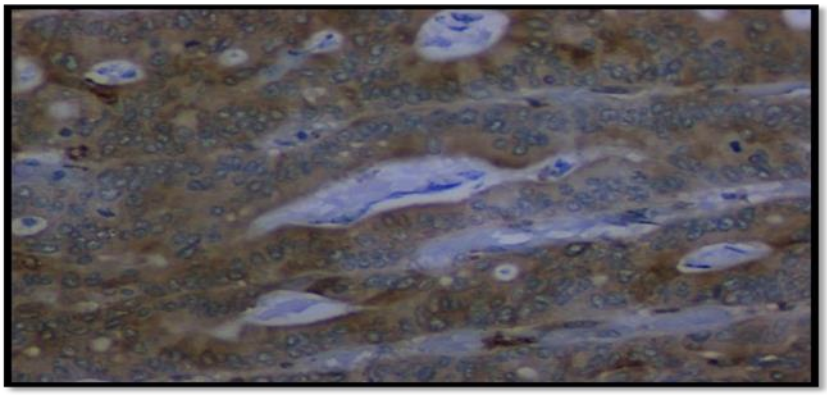


Figure no. 8: ADENOCARCINOMA COX2 POSITIVE SCORE 4 IHC (40X)

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

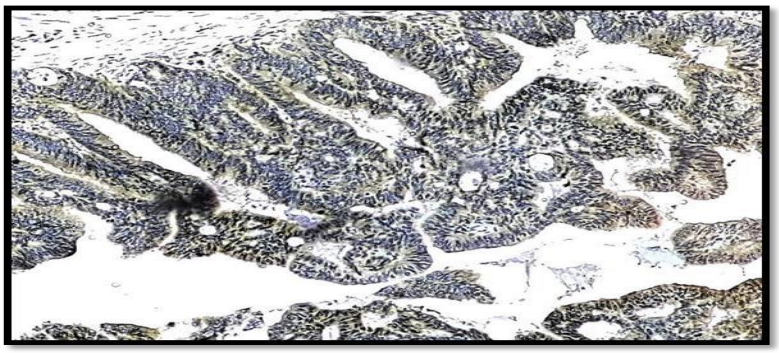


Figure no. 9: ADENOCARCINOMA COX2 POSITIVE SCORE 3 IHC 40X

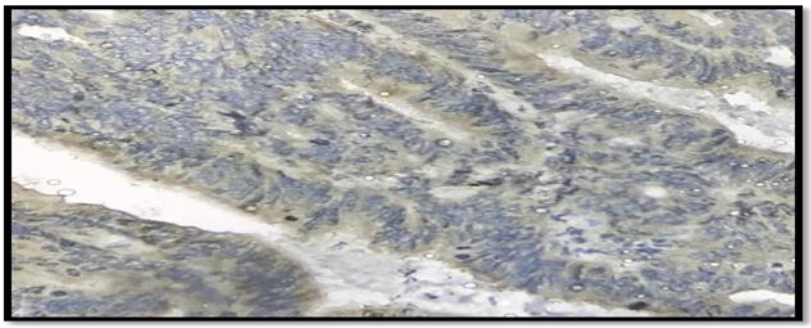


Figure no.10: ADENOCARCINOMA MODERATELY DIFFERENTIATED COX2 POSITIVEIHC SCORE2 (40X)

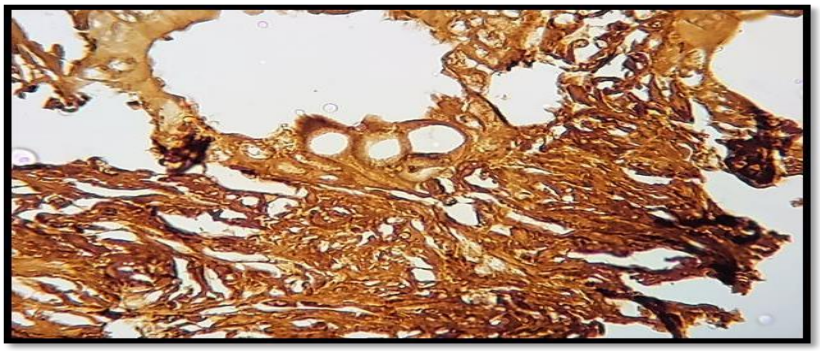


Figure no.11: ADENOCARCINOMA WELLDIFFERENTIATED HER2 IHC POSITIVE SCORE3 (40X)

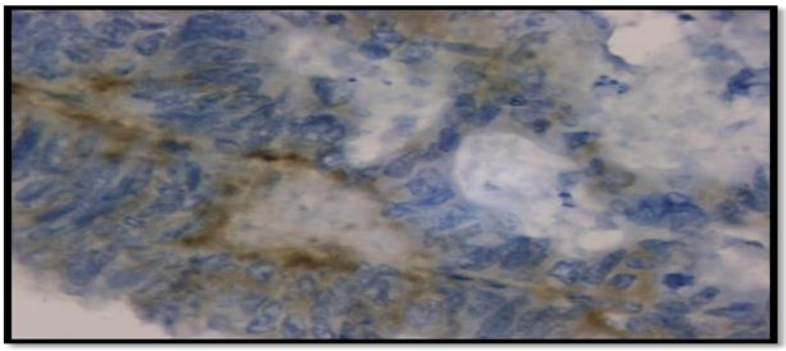


Figure no.12: ADENOCARCINOMA HER2 POSITIVE SCORE 2 IHC (40X)

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

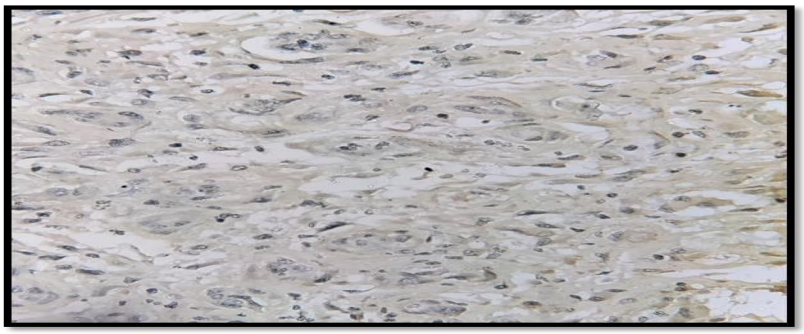


Figure no . 13: ADENOCARCINOMA HER2 POSITIVE SCORE1IHC (40X)

DISCUSSION

Colorectal carcinoma is by far most common and most curable cancer of GIT. More 90% of cancers in this region areadenocarcinomas. In this study group ranges from 20-80 years and highest incidence found between 50-59 years. most of colorectal carcinomas exhibited ulceroproliferative growth grossly.

TABLE NO 5: COMPARISION TABLE OF AGE PRESENTATION WITH OTHER STUDIES.

STUDY	AGE GROUP	ASSOCIATION
Dara O Kavanagh et al., [8]	60-69	NO ASSOCIATION
B Ingold Heppner et al [9]	60-69	NO ASSOCIATION
Neha Ratan B et al [10]	70-79	NO ASSOCIATION

TABLE NO 6: COMPARISION TABLE OF GENDER PRESENTATION WITH OTHER STUDIES

STUDY	GENDER	ASSOCIATION
Richard Fux et al [11]	MALE	NO ASSOCIATION
ADAM ELZAGHEID et al [12]	FEMALE	ASSOCIATION
Payman MS Salim et al [13]	FEMALE	ASSOCIATION

In this study most carcinomas are present in female patients, a similar finding in consistent with study done by Payman MS. Salim [13]. Rectum was the most common site in both sex and in all age groups, followedby descending colon. This is consistent with study done by Xin-Yu WANG et al [14].

TABLE NO 7: COMPARISION TABLE OF SITE DISTRIBUTION WITH OTHER STUDIES

STUDY	SITE	ASSOCIATION
Ai-Wen et al [15]	RECTUM	ASSOCIATION
Xin-Yu Wang et al [14]	RECTUM	ASSOCIATION
B Schuell et al [16]	COLON	NO ASSOCIATION

In line with Mia-ouyang's [17] findings, there was no correlation between Cox2 expression and age, sex, or the location of colorectal cancer in the current investigation.

Adenocarcinoma made up 95.2% of the cases in the current study, undifferentiated carcinoma made up 3.8%, and both of these instances were of the mucinous type. This is in line with the findings of the study by Nicholas FS Watson et al. [18].

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

TABLE NO 8: COMPARISION OF HER2 EXPREESION IN COLORECTAL ADENOCARCINOMAS IN PRESENT STUDY WITH QI-BING WU et al [19] STUDY

VARIBLES	QI-BING STUDY			PRESENT STUDY		
	CASES	HER2 POSITIVE	HER2 NEGATIVE	CASES	HER2 POSITIVE	HER2 NEGATIVE
Well-differentiated	155	67(43.2%)	88(56.8%)	25	12(48%)	13(52%)
Moderately differentiated	582	258(43.8%)	331(56.2%)	18	10(55%)	08(44.4%)
Poorly differentiated	282	149(52.8%)	133(47%)	04	03(75.2%)	01(33%)

TABLE NO 9: COMPARISION OF COX2 EXPRESSION IN COLORECTAL ADENOCARCINOMA IN PRESENT STUDY WITH Jaudah Al-MAGHRABI et al [20] STUDY

VARABLES	Al-Maghrabi STUDY			PRESENT STUDY		
	CASES	COX2 POSITIVE	COX2 NEGATIVE	CASES	COX2 POSITIVE	COX2 NEGATIVE
Well differentiated	25	14(56%)	11(44%)	30	15(50%)	15(50%)
Moderately differentiated	56	30(53.7%)	26(46.4%)	14	08(57%)	06(42%)
Poorly differentiated	11	08(72.7%)	O3(27.2%)	04	03(75%)	01(33.3%)

Qi-Bing Wu [19] et al studied HER2 expression by immunostaining in 800 cases of colorectal cancers and correlated the Her2 expression with grade, location, size of tumors. 52.8% percent of the poorly differentiated and 43.6% of moderate and well differentiated tumors were positive for HER2.

In present study 75% of poorly differentiated and 57% of moderately differentiated, 53% of well differentiated tumors showed positivity for HER2, results are comparable to QI-Bing [21] et al study.

Similarly AI-Maghrabi [20] studied COX2 immunostaining expression in 72 cases of colorectal carcinomas. 56% percent of well differentiated, 53% of moderately differentiated, 72% of poorly differentiated tumors were positive expression of cox2.In present study 50% of well differentiated, 53% of moderately differentiated, 75% of poorly differentiated tumors showed positiveexpression of cox2, results are comparable to AI-Maghrabi study.

TABLE NO 10: COMPARISION OF HER2 EXPRESSION AND THE ASSOCIATION WITH GRADE OF ADENOCARCINOMA AMONG VARIOUSSTUDIES

PREVIOUS STUDIES ON HER2 EXPRESSION	RESULTS	HER2 EXPRESSION ASSOCITION WITH GRADE
QI-BING et al STUDY [19]	Showed 52.3% over expression in poorly differentiated and 46% in moderately differentiated colorectal carcinomas.	Showed significant association with grade of adenocarcinoma.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

Lilav Adel et al [22]	Showed 57% expression in well andmoderately differentiated carcinomas, 77.8% in poorly differentiated carcinoma.	Showed significant association with grade of tumor.
Suma et al study [23]	Showed higher expression in poorly differentiated tumor when compared to welland moderately differentiated.	Showed association with grade of tumor.
Suma Shameem et al Study [24]	Showed higher expression in well differentiated tumors.	Showed No significant association.
Present study	Showed high Her2 positivity in grade 3 tumors and low positivity in grade 1 tumors.	(P=0.02) showed significant associationwith grade of tumor.

TABLE NO 11: COMPARISION OF COX2 EXPRESSION AND ASSOCIATION WITH GRADE OF ADENOCARCINOMA AMONG VARIOUSSTUDIES

PREVIOUS STUDIES ON COX2 EXPRESSION	RESULTS	COX2 EXPRESSION ASSOCIATION WITH GRADE
AI-Maghrabi et al [20]	Showed 56% of well differentiated tumors cox2 positivity,72.7% of poorly differentiated tumors with cox2 positivity.	Showed Significant association with gradingof tumor.
Katherine et al study [25]	Showed higher expressionin poorly differentiated tumors when compared to well differentiated tumors.	Showed significant association with grade of tumor.
Qi-Wu Bing et al Study [19]	Showed 63% of well differentiated tumors cox2 positivity, 74.5% of poorly differentiated tumors cox2 positivity.	Showed significant association with gradingof tumors.
Behrang et al study [26]	Showed 65%of well differentiated tumors cox2 positivity,5.7% of poorly differentiated tumors cox2 positivity.	No significant association with grading.
Present study	Showed higher positivity(75%) in poorly differentiated tumors compared to well differentiated tumors (50%)	(p=0.02) showed significant associationwith grade of tumor.

In present study higher expression of HER2 immunopositivity showed in poorlydifferentiated carcinomas which is consistant with Qi-Bing [19] et al, Lilay [22] et al, Suma [23] et al studies.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

In present study expression of COX2 immunopositivity higher in poorly differentiated carcinoma which is consistant with Al-Magharabi [20] et al,Katherine [25] et al study,Qi-Wu Bing [19] et al study.

Inhibition of the enzyme cyclooxygenase-2 (COX-2) is thought to enhance epithelial proliferation, especially in response to damage. COX-2 is highly expressed in 90% of colorectal carcinomas and 40% to 90% of adenomas.

Angiogenesis, inflammation, and carcinogenesis are all significantly regulated by COXs. The endoplasmic reticulum's luminal side is home to COXs, which are connected to the nuclear envelope [12].

Sub-epithelial tissue, not epithelial, is the location of COX-2 overexpression in the early intestinal cancer tissue. Early murine intestine adenomas' sub-epithelial location for inducible COX-2 expression contradicts with other data suggesting that colorectal epithelial cells are where this enzyme is upregulated.

Cox2 was found in the cytoplasm of tumour epithelial cells as well as in the endothelial cells of tumour vasculature.

Although there was no correlation between the tumour sites within the colon, COX2 immunoreactivity was more common in poorly differentiated adenocarcinomas compared to well and moderately differentiated adenocarcinomas.

In colorectal cancer, higher COX-2 expression was substantially linked to disease progression and histological markers of a poor prognosis [19].

The majority of HER2 was found on the membrane of cancer cells, and the membrane of Her2 positive cells displayed brownish granules.

A significant degree of malignancy and a poor prognosis are suggested by HER2's malignant transforming activity and overexpression. HER2/neu expression is regarded as a sign for a bad prognosis in colon cancer. It is used to forecast how colorectal cancer patients will respond to adjuvant treatment.

In the current study, poorly differentiated tumours with greater Her2 expression have a poorer clinical prognosis.

COX2 AND HER2 EXPRESSION IN RELATION TO SEX

In the study, there was no connection between cox2 and her2 positive and sex. In their respective research, Al Temini [27] et al. and reyhanbayrak [28] et al. likewise discovered no

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

statistically significant correlation between Cox2 and Her2 positive.

COX2 AND HER2 EXPRESSION IN RELATION TO TUMOR LOCATION

In this study, Cox2 and Her2 positive cases were more frequently found on the left side of the colon, with the rectosigmoid region (53.2%) accounting for the majority of cases, followed by the descending colon (32.2%) and the ascending colon (9.6%). However, no correlation between Cox2 and Her2 expression and tumour site was discovered.

Similar findings were reported in the Lilav Adel et al investigation, where the rectum was the most frequent site (66%) of cases. followed by a descending colon, albeit no statistically significant association between the tumor's position and the expression of Cox2 and Her2 was discovered.

CONCLUSION

In the current study, I looked at 52 colorectal cancer patients, of which 48 had Cox2 positivity and 4 had Cox2 negativity, and 47 had Her2 positivity and 5 had Her2 negativity. The majority of patients with inadequate differentiation express Cox2 and Her2. When compared to well and moderately differentiated colorectal adenocarcinomas, poorly differentiated adenocarcinomas significantly express Cox2 and Her2. Therefore, Cox2 and Her2 indicators play a crucial part in the differentiating of colorectal cancer. Since grade is a known prognostic marker, Cox2 and Her2 expression and scoring will also serve as a prognosis marker in colorectal carcinomas. As a result, there is a significant link between Cox2 and Her2 expression and cancer grade (Pvalue0.05). However, there is no correlation between the expression of Cox2 and Her2 and other factors including age, gender, or tumour site. Conclusion: The results point to a positive association between COX2 and HER2 expression, show that simultaneous Cox2 and HER2 expression can boost colorectal cancer's potential to metastasize and invade, and suggest a poor prognosis for individuals with colorectal cancer.

FUNDING

Nil

CONFLICT OF INTEREST

None

REFERENCES

1. Hamilton SR, Aaltonen LA, editors: WHO classification of tumors. Pathology and genetics of tumours of the digestive system. IARC press Lyon; 2000: p103–142.
2. Peter Boyle, J S Langman. ABC of colorectal cancer Epidemiology, Clinical review : BMJ volume 321, 30 September 2000 bmj.com.
3. Ahmedin Jemal, DVM, PhD; Freddie Bray, PhD; Melissa M. Centre, MPH; Jacques Ferlay, ME; Elizabeth Ward, PhD; David Forman, PhD. Global Cancer Statistics; CA CANCER J CLIN 2011;61:69–90.
4. Parkin DM Global cancer statistics in the year 2000; Lancet Oncol.2000:2; 533-543.
5. Cecilia M. Fenoglio-preiser. Gastrointestinal pathology-An atlas and text.3rd

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

ed.Philadelphia:Lippincott Williams and Wilkins;2008.p.988-92.

6. BD Chaurasia's - Human Anatomy, regional and applied dissection and clinical, 4th edition vol 2; p 205-255.
7. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. genetic alterations during colorectal-tumor development. N Engl J Med. 1988; 319: 525 - 532.
8. Dara O Kavanagh, Gillian Chambers1, Liam O' Grady2, Kevin M Barry1, Ronan P Waldron1, Fadel Bennani2, Paul W Eustace1 and IqdamTobbia Is overexpression of HER-2 a predictor of prognosis in colorectal cancer.
9. B Ingold Heppner,, H-M Behrens, K Balschun, J Haag, S Kru¨ ger, T Beckerand C Ro¨ cken HER2/neu testing in primary colorectal carcinoma.
10. Neha Ratan B, Vijayalaxmi V Suranagi Original Research Article Frequency of overexpression of Her2/neu in colorectal adenocarcinomas– A hospital based cross-sectional study.
11. Richard Fux, Matthias Schwab, Klaus-Peter Thon, Christoph H.Gleiter,1 and Peter Fritz4 Cyclooxygenase-2 Expression in Human Colorectal Cancer Is Unrelated to Overall Patient Survival.
12. Adam Elzagheid, Fatma Emaetig, Lamia Alkikhia, Abdelbaset Buhmeida, Kari Syrjänen, High Cyclooxygenase-2 Expression Is Associated with Advanced Stages in Colorectal Cancer.
13. MS.Salim, "The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis," Oncogene, vol. 26, no. 45, pp. 6469–6487, 2007.
14. Xin-Yu Wang, Zhi-Xue Zheng, Yu Sun, Yan-Hua Bai, Yun-Fei Shi, Li-Xin Zhou, Yun-Feng Yao, Ai-Wen Wu, Deng-Feng Cao Retrospective Study Significance of HER2 protein expression and HER2gene amplification in colorectal adenocarcinomas.
15. Ai-Wen Wu, Jin Gu, Jia-Fu Ji, Zhen-Fu Li, Guang-Wei Xu Role of COX-2 in carcinogenesis of colorectal cancer and its relationship with tumor biological characteristics and patients' prognosis.
16. B Schuell, T Gruenberger, W Scheithauer, Ch Zielinski1 and F WrbaResearch articleHER 2/neu protein expression in colorectal cancer.
17. Mia Ouyang Marx AH, Burandt EC, Choschzick M, Simon R, Yekebas E, Kaifi JT, Mirlacher M, Atanackovic D, Bokemeyer C, Fiedler W, Terracciano L, Sauter G, Izbicki JR (2010) Heterogenous high-level HER-2 amplification in a small subset of colorectal cancers. Hum Pathol 41(11): 1577–1585.
18. Nicholas FS WatsonAntonacopoulou AG, Tsamandas AC, Petsas T, Liava A, Scopa CD, Papavassiliou AG, et al. EGFR, HER-2 and COX-2 levels in colorectal cancer. Histopathology 2008;53(6):698-706.
19. Qi-Bing Wu, Guo-Ping Sun Expression of COX-2 and HER-2 in colorectal cancer and their correlation.
20. Jaudah Al-Maghrabi, Abdelbaset Buhmeida, EmanEmam, Kari Syrjänen, Abdulrahman Sibiany, Mohmmad Al-Qahtani, Mahmoud Al-Ahwal Cyclooxygenase-2 expression as a predictor of outcome in colorectal carcinoma.
21. M Ilyas, X-P Hao, K Wilkinson, IPMTomlinson, A M Abbasi, A Forbes, 73 W F

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

Bodmer, Loss of Bcl-2 expression correlates with tumour recurrence in colorectal cancer,I C Talbot 1998;43:383-387.

22. Lilav Adel Kamal1 * Jalal Ali Jalal2 Immunohistochemical expression of HER2/neu in colorectal carcinoma in Erbil city, Kurdistan Region.
23. Suma, Langman JS: ABC of colorectal cancer: Epidemiology. BMJ 2000; 321:805-808.
24. Suma S, Shameem K Ummerali HER2/neu Expression in Colorectal Cancers.
25. Katherine M. Sheehan,MB Kieran Sheehan, MRCPathDiamuid P. ODonoghue,FRCP. The relationship between Cycloxygenase-2 Expreesionand Colorectal Cancer.
26. Behrang Kazeminegad, Abbas Mirafsharieh, FreidoonSolhjoo Evaluation of Expression of EGFR, HER-2 and COX-2 in Colorectal Cancer ranian Journal of Pathology (2012) 7 (3), 139- 144.
27. Al-Temimi SM. HER-2/neu expression in colorectal carcinoma andits correlation with pathological parameters by immunohistochemistery. Med J Babylon. 2011;8(2):253–262.
28. Nida Iqbal1 and Naveed Iqbal Review Article Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications.