A Comprehensive Study of Colorectal Adenocarcinoma and its Correlation with COX-2 and HER-2/NEU IHC Markers

[1]Kushal Goyal, [2]Shyam Bhutra, [3]Divvy Rawat and [4]Rohit Jain
[1-4]Department of General Surgery, JLN Medical College and Hospitals, Ajmer (Raj), India

ABSTRACT

Cancer of the large bowel (colorectal cancer) includes all cancer originating from the cecum to the anus. The integration of COX-2 and HER-2/NEU markers into clinical practice could redefine diagnostic accuracy and personalize treatment strategies, leading to improved patient management and outcomes. To correlate COX-2 and HER-2/NEU IHC markers with histological grades of colorectal adenocarcinoma, to study the pattern of colorectal malignancies with respect to (a) Age, Sex, and Site (b) Clinical presentation (c) Treatment modalities. A hospital-based cross-sectional retrospective and prospective study done on 50 cases with surgery references for symptoms of colorectal malignancies or biopsy-proven colorectal adenocarcinoma, undergoing admission in general surgical wards, emergency wards and patients with surgery references for symptoms of colorectal malignancies or biopsy-proven colorectal adenocarcinoma from other departments like Medicine, Gastroenterology, Radiotherapy, in JLN Medical College and Hospitals, Ajmer in the time period between January 2019 to January 2024. All investigations relevant with pre anaesthetic check up along with X-Ray- Flat plate abdomen (erect) and Chest, USG whole abdomen and CT/ MRI, histopathology study of the resected specimen, IHC markers study for COX-2 and HER-2/ NEU was performed. Out of all the cases, the age groups 41-60 years and 60-80 years each had 19 (38%) cases. Histologically 9 cases of moderately differentiated adenocarcinoma and 4 cases with well differentiated adenocarcinoma showed HER-2 / NEU positivity. 21 cases of moderately differentiated adenocarcinoma and 12 cases with well differentiated adenocarcinoma showed COX-2 positivity. The integration of COX-2 and HER-2/NEU markers into clinical practice could redefine diagnostic accuracy and personalize treatment strategies, leading to improved patient management and outcomes.

INTRODUCTION

CRC originates as a noncancerous growth called a polyp that grows on the inner lining of the colon or rectum and propagates slowly, over a period of 10 to 20 years. Colorectal cancer (CRC) can be subdivided into colon cancer, which ranges from the cecum to the sigmoid (approximately 15cm above the anal verge), and rectal cancer, that ranges from the recto-sigmoid junction to the anus[1]. It is the second most common cancer in women and the third most common cancer in men[2]. India has very low incidence rates, between 2 and 8, per 100,000. The incidence was 4.3 per 100,000 men and 3.4 per 100,000 women[3]. Surgery still remains the primary treatment modality and pathological examination of resected specimen is a powerful tool for assessing the prognosis[4]. Colonic polyposis syndromes, Familial Adenomatous Polyposis (FAP) and its variations (Turcot, Gardener, and attenuated FAP), Lynch syndrome and non polyposis syndromes are inherited illnesses that lead to colorectal cancer[5]. Lack of physical exercise, low fiber, high-fat diet, alcohol drinking and tobacco use are all controllable risk factors. Non modifiable risk factors include age, gender and ethnicity. On the contrary consumption of omega-3 fatty acids (fish oil), vitamin D, garlic, coffee and a high-fiber diet are protective factors. Colorectal carcinoma is more common in people who have Crohn's disease or ulcerative colitis[6]. Right-sided colonic malignancy generally presents with bleeding and melena whereas, Left-sided malignancy most commonly presents with abdominal pain due to obstruction[7]. Colonoscopy is considered the primary diagnostic method to evaluate a positive less invasive screening test, whether that test is based on evaluating stool, serum (blood), or colorectal imaging. Faecal blood testing is a non- invasive test done for colorectal cancer screening. It is an alternative to colonoscopy and is most commonly preferred[8]. Faecal occult blood testing is effective in the prevention of 20% of deaths from colorectal cancer. Both sigmoidoscopy and colonoscopy are potentially effective in screening colorectal cancer[9]. The HER-2/NEU oncogene, also called c-erbB2 codes for a transmembrane tyrosine kinase receptor which is, homologous to EGFR. This receptor is involved in the growth and progression of the malignant cells[10]. Aspirin reduces the risk of developing primary colorectal cancer, especially in tumors with COX-2 (Cyclooxygenase2) over-expression[11]. Over expression of COX-2 occurs in colorectal neoplasm and plays an important role in tumorigenesis and progression of tumour in colorectal cancer[12]. COX-2 is expressed in many tissues by cytokines, oncogenes and tumour promoters[13]. High levels of expression of COX-2 in the tumor were shown to correlate with an increase in recurrence rate and poor survival[14]. Open laparotomy is the most common surgical method. With the development of better intra operative monitoring, many surgeons are performing laparoscopic hemicolectomies with resection and anastomosis. For metastasis, segmental resection with chemotherapy (FOLFOX regimen-folinic acid+5-fluorouracil+oxaliplatin) is the preferred treatment. Surgical removal of tumor and nearby lymph nodes is the mainstay of treatment for early stage of colorectal cancer. However, with a potentially curative surgery alone, up to 50% of patients will ultimately relapse and die of metastatic disease[15].

Aims and Objectives: To correlate COX-2 and HER-2/NEU IHC markers with histological grades of colorectal adenocarcinoma, To study the pattern of colorectal malignancies with respect to :
- (a) Age, Sex and Site.
- (b) Clinical presentation.
- (c) Treatment modalities.

MATERIALS AND METHODS

A hospital-based cross-sectional retrospective and prospective study done on 50 cases meeting inclusion and exclusion criteria undergoing admission in general surgical wards, emergency wards and patients with surgery references for symptoms of colorectal malignancies or biopsy-proven colorectal adenocarcinoma from other departments like Medicine, Gastroenterology, Radiotherapy, in JLN Medical College and Hospitals, Ajmer between January 2019 to January 2024. All the data collected was recorded. The Pathology department of JLN Medical College determined the status of the COX-2 and HER-2 / NEU IHC markers for the specimen. Ethical approval was taken from the institutional ethical committee. All investigations relevant with pre anaesthetic check up along with X-Ray- Flat plate abdomen (erect) and Chest, USG whole abdomen and CT/ MRI, histopathology study of the resected specimen, IHC markers study for COX-2 and HER-2/ NEU was performed.

RESULTS AND DISCUSSIONS

Table 1: Age and Sex Distribution

Age Group (years)	No. of patients (n=50)	Percent
20-40	9	18
41-60	19	38
61-80	19	38
80 and above	3	6
Sex		
Male	34	68
Female	16	32

Table 2: Treatment

Treatment	No. of patients	Percent
Laparoscopic APR	2	4
Low Anterior Resection	1	2
Open APR	5	10
Open Extended Right Hemicolectomy	4	8
Open Left Hemicolectomy	5	10
Open Right Hemicolectomy	22	44
Local resection	11	22
Total	50	100

The mean age was 56.32+15.27 years. Males showed a higher predisposition than females with a sex ratio of 2.2: 1. The chi-square value was 6.480 and the P

Table 3: Correlation Between Histologic Type and HER-2/NEU and COX-2

Histologic type	HER-2 / NEU expression		COX-2 Expression			
	Positive	Negative	Negative	Positive	Moderately Positive	Strongly Positive
Well differentiated carcinoma (n=15)	4	11	0	0	3	12
Moderately differentiated carcinoma (n=26)	9	17	0	2	3	21
Poorly differentiated carcinoma (n=6)	0	6	4	2	0	0
Mucinous carcinoma (n=3)	0	3	1	2	0	0
Total	13	37	5	6	6	33

value=0.0109 (Table 1). Among all the symptoms patients presented with lower abdomen pain (31 cases) and alteration of bowel habits (34 cases) mostly (Fig. 1). (Fig. 2) shows that the caecum was the most common site affected with 28% of cases followed by the rectum with 24% of cases. The chi-square value was 40.40 and the P value = P <0.0001.
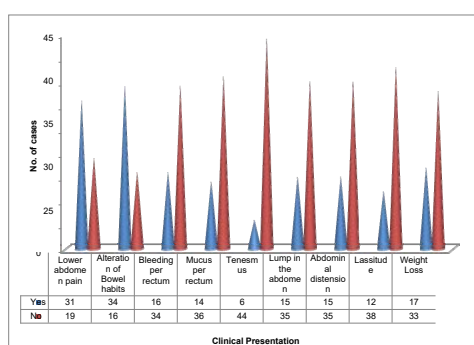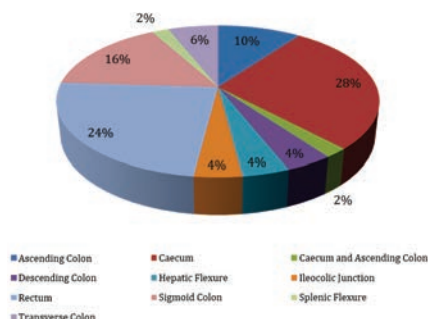

Fig. 1: Clinical Presentation

Fig. 2: Site

(Table 2) shows that, for right-sided colonic malignancy, open right hemicolectomy in 22 (44%) cases was preferred while for left-sided malignancy local resection in 11 (22%) cases was preferred. The chi-square value was 44.64 and the P value=P<0.0001. (Table 3) shows, histologically 9 cases of moderately differentiated adenocarcinoma and 4 cases with well differentiated adenocarcinoma showed HER-2/NEU positivity. The chi-square value was 16.84 and the P value=0.0008. Similarly, 21 cases of moderately differentiated adenocarcinoma and 12 cases with well differentiated adenocarcinoma showed COX-2 positivity. The chi-square value was 44.88 and the P value P<0.0001. Out of all the cases, the age groups 41-60 years and 60-80 years each had 19 (38%) cases. The mean age was 56.32+15.27 years. In the study of

Laishram[16] 60-69 years age group which is similar to our study results. In the study of Javid[17], the age specific rate for colorectal carcinoma was highest in 55-59 years (17.21/100,000), followed by 65-69 years (14.86/ 100,000). Males showed a higher predisposition than females with a sex ratio of 2.2:1. Similar findings were noted in the study of Laishram[16], they found that out of 54 patients with colorectal carcinomas, 29 (53.71%) cases were males while 25 (46.29%) cases were females with a male to female ratio of 1.16:1. Patraa[18] observed that the ratio of male and female affected in colorectal cancer was 1.6. (Table 1). In our study, out of 50 patients presented with lower abdominal pain in 31 (62%) cases, alteration of bowel habit in 34 (68%) cases majorly. Similar findings were also observed in the study of Mukherji[19], they found that the majority of the patients presented with pain (81%), altered bowel habits (72%) and bleeding per rectum (78%). (Fig. 1). In our study, caecum was the most common site affected with 14 (28%) cases followed by rectum with 12 (24%) cases. Similarly in the study of Javid[17], they found that of the 212 cases of colorectal cancers, 113 (53.3%) originated in the colon and 99 (46.7%) in the rectum. (Fig. 2). For right-sided colonic malignancy, open right hemicolectomy in 22 (44%) cases was preferred while for left-sided malignancy local resection in 11 (22%) cases was preferred. Salibasic[20] concluded that operative surgical principles must be adapted to modern trends preferably minimally invasive procedures. (Table 2). In our study, 13 (26%) cases were HER-2 receptor positive. Out of which, 9 (18%) cases were of moderately differentiated adenocarcinoma and 4 (8%) cases were of well differentiated adenocarcinoma. Similarly in the study of Kiran DK and Preethi[21] they found HER-2 expression in 47 (90.3%) cases. Out of which, 48.0% of cases of well- differentiated and 55.5% of the moderately -differentiated carcinomas exhibited HER-2 positivity. Among all the cases, COX-2 overexpression was seen in 45 (90%) cases. Out of 50 cases, 52.0% (26 cases) of the moderately differentiated adeno-carcinomas, 30.0% (15 cases) of the well differentiated adenocarcinomas, 4.0% (2 cases) of the poorly differentiated adeno -carcinomas and 4.0% (2) of the mucinous adenocarcinomas expressed COX-2. Similarly in the study of Kiran DK and Preethi[21], of the 52 colorectal adenocarcinomas, COX-2 expression was detected in 48 (92.3%) cases. Out of the 52 cases, 57.0% of the moderately-differentiated adeno-carcinomas and

50.2% of the well- differentiated adenocarcinomas expressed COX-2. (Table 3).

CONCLUSION

The disease most commonly affects individuals aged 41-80, with a notably higher incidence in males. Surgical treatment strategies should be individualized based on tumor location. The integration of COX-2 and HER-2/NEU markers into clinical practice could redefine diagnostic accuracy and personalize treatment strategies, leading to improved patient management and outcomes. Enhancing public awareness about colorectal cancer symptoms and incorporating these advanced markers into clinical practice can significantly improve early detection and personalized treatment, ultimately benefitting patient outcomes.

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