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Original Article

Pathology Section

Clinicopathological and Histomorphological Evaluation of Colorectal Cancers for Features of Microsatellite Instability

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ABSTRACT

Introduction: Colorectal Cancer (CRC) is the fourth most common cancer in men and third most common cancer in women. Microsatellite Instability-High (MSI-H) is a distinctive feature of Hereditary non-polyposis CRC syndrome (HNPCC) and it accounts for 15% of sporadic CRC. Identification of MSI-H colorectal tumours serves as a prognostic marker of patient outcome, as a predictive marker of response to chemotherapy and as a screening tool for HNPCC.

Aim: The purpose of this study was to describe the clinical presentation and the histomorphological features of MSI.

Materials and Methods: An ambispective type of validation study was carried out in Father Muller Medical College Hospital, Mangalore, Karnataka, India. The total duration of the study was 2.5 years. Whereas case collection was done from October 2017 to April 2019 for a period of 17 months. Surgical resection specimens of all the age groups for CRC were included in the study. Relevant patient history and clinical details were noted. Histomorphological features for MSI in CRC were noted using Revised Bethesda Guidelines. The results were analysed using Chi-square test.

Results: A total of 104 cases were analysed during the study period. Majority of the patients with CRCs were in the age group of 51-60 years (30 cases, 28.84%), followed by 61-70 years age group (25 cases, 24.03%). Out of 104 cases, 72 (69.23%) of them were located in distal colon and among the various histomorphological types, adenocarcinoma accounted for 93 (89.42%) cases. Forty-nine (47.11%) of them were found to be in stage III disease. Crohn like lymphocytic reaction was a frequent histomorphological feature of MSI in about 50 (48.07%) cases of CRCs.

Conclusion: The IHC test is the gold standard for MSI testing and most literature on Hospital-based study recommend IHC as the first line of testing. Identification of MSI-H by conventional histopathology by following Revised Bethesda Guidelines can be used as a screening tool for rapid selection of sporadic CRC for molecular testing, with the potential to recover a majority of MSI-H cases. MSI-H have better prognosis than stable cancers. MSI, particularly in stage II CRCs have better prognosis and do not benefit from 5FU- based adjuvant chemotherapy. Therefore, it is the most important prognostic marker in CRC and especially in stage II CRC.

Keywords: Crohn's like lymphocytic reaction, Revised Bethesda guidelines, Tumour infiltrating lymphocytes

INTRODUCTION

The Colorectal Cancer (CRC) is the 4th most common malignancy in male and 3rd most common malignancy in female worldwide, accounting for 9.4% of all the cancers [1]. MSI is present in approximately 15% of the sporadic CRCs and in almost all HNPCC/Lynch syndrome associated CRC patients [2]. MSI is characterised by widespread alterations in the length of repetitive DNA sequences [3,4]. MSI in Lynch syndrome occurs due to the germ line mutation in one of the DNA Mismatch Repair genes (MMR). The DNA MMR genes which undergo mutations are MutL homolog 1(MLH1) (32%), MutS homolog 2(MSH2) (39%), post meiotic segregation increased 2 (PMS2) (15%) and MutS homolog 6 (MSH6) (14%). Where as in sporadic CRCs MMR deficiency occurs due to the silencing of mostly MLH1 in more than 80% of the cases [5]. Several studies have proven that CRCs that have MSI have better prognosis than Microsatellite Stable (MSS) cancers [6-8]. Previous studies have shown that MSI cancers do not benefit from 5-flurouracil (5FU) based chemotherapeutic regimens [6,9,10]. Recent studies show that MSI particularly in Stage II CRC have better prognosis and do not benefit from 5FU- based adjuvant chemotherapy. Therefore, it is the most important prognostic marker in stage II CRC [11]. Histomorphological features of MSI-H defined by the Revised Bethesda Guidelines are Tumour-Infiltrating Lymphocytes (TILs), Crohn-like Lymphocytic Reaction (CLR), mucinous/signet-ring cell differentiation, medullary growth pattern, Right-sided location, intratumoural heterogeneity, high grade histology and lack of dirty necrosis. It does not provide predictive value of these features, but it recommends further analysis by MSI testing and Immunohistochemistry (IHC) analysis [12]. Thus, it is essential to identify MSI-H colorectal tumours, as MMR deficiency serves as a prognostic marker, predictive marker of response to chemotherapy and screening tool to identify the patients with Lynch syndrome [13]. Histological assessment for MSI features is the most underused guideline [12]. Hence, aim of this study was to identify features of MSI by a histomorphological study.

Objectives of the study were:

- To study the clinical presentation with regards to age, gender, location of the tumour and stage of the disease.
- To study histomorphological features of MSI in all resected specimens of CRC.

MATERIALS AND METHODS

An ambispective type of validation study was carried out in Father Muller Medical College Hospital, Mangalore. The total duration of the study was 2.5 years. Whereas case collection was done from October 2017 to April 2019 for a period of 17 months. Surgical resection specimens of all the age groups for CRCs received in the histopathology department were included in the study. Relevant patient history, clinical details, radiological investigations was noted. Institutional Ethics Committee approval was obtained prior to performing the study (FMMC/FMIEC/4418/2017).

Inclusion criteria: All resection specimens for CRCs received in the Histopathology Department of Father Muller Medical College from October 2017 to April 2019 were included in the study.

Exclusion criteria: Individuals with preoperative radiotherapy or chemotherapy adenomas with intramucosal carcinoma or carcinoma in-situ and colonoscopic biopsies were excluded from the study.

Documentation of MSI features in the histopathology report was recommended by CAP (College of American Pathologists) guidelines in June 2017 [14]. The histomorphological MSI features were enumerated by Revised Bethesda Guidelines [13,15,16]. However, definite criteria for individual feature was not clearly defined [13]. Immunohistochemical testing for MSI would be expensive and time-consuming procedure. Identification of MSI-H by conventional histopathology using Revised Bethesda Guidelines can be used as a screening tool for rapid selection of sporadic CRC for molecular testing, with the potential to recover a majority of MSI-H cases [15].

Criteria for the Individual Feature Followed in the Present Study is Mentioned Below

Tumour Infiltrating Lymphocytes (TILs): Area with most TILs was scanned under the low power. TILs were identified on haematoxylin and eosin stained sections as small mononuclear cells that typically have a halo around them. Stromal lymphocytes were excluded and only the lymphocytes that were within the tumour epithelium were counted. TILs were considered significant if there were three or more in a high-power field. The criteria was based on CAP guidelines [14].

Crohn-like Lymphocytic Reaction (CLR): The advancing edge of the tumour containing lymphoid aggregates at the interface of the muscularis propria and pericolic fibroadipose tissue was considered as a CLR. A minimum of three lymphoid aggregates per section was considered to be prominent. The criteria was taken from a study done by Greenson JK et al., [17].

Mucinous differentiation: Tumours exhibiting more than 50% of extracellular mucin were considered as having mucinous differentiation. Whereas, tumours showing less than 50% extracellular mucin were classified as having focal mucinous differentiation [17].

Focal Signet Ring Cell Differention (FSRCD): Signet ring cells are the tumour cells containing intracytoplasmic vacuoles of mucin. More than 50% of the tumour having this morphology was considered to have signet-ring cell differentiation. If less than 50% of signet ring cells were present in a tumour, it was considered to have focal signet-ring cell differentiation [17].

Medullary growth pattern: Solid masses of tumour cells having a well circumscribed margin with a marked lymphocytic infiltrate that is both peritumoural and intratumoural was considered having medullary growth pattern [12].

Right-sided location: Tumours located in caecum, ascending colon, hepatic flexure and proximal two thirds of transverse colon were considered as right-sided tumours [18].

Intratumoural heterogeneity: Tumours having two divergent growth patterns were classified as intratumoural heterogeneity. Mucinous differentiation was not considered to be a heterogeneity component. If not, all the tumours having focal mucinous component would be classified as having this feature [17].

High-grade histology: All conventional adenocarcinomas, having poorly differentiated morphology/grade III with 0-40% gland formation were considered as having a high-grade tumour [2].

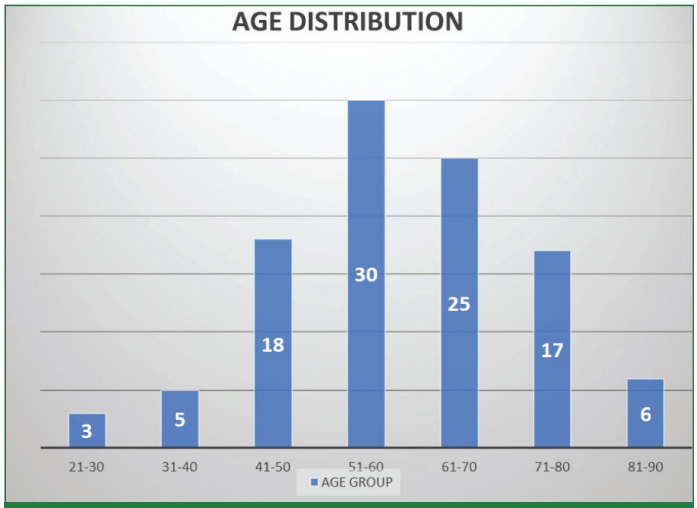
Lack of Dirty Necrosis (LDN): Tumour with absence or presence of necrosis in less than 10% of the tumour was considered as negative [17].

STATISTICAL ANALYSIS

The data was entered into Microsoft Excel spread sheet and subjected to statistical analysis using Chi-square test.

RESULTS

Majority of the patients with CRCs were in the age group of 51-60 years (30 cases, 28.84%), followed by in 61-70 years age group (25 cases, 24.03%) [Table/Fig-1]. The ratio of male to female is 1:1. Both male and female accounted for 50% of the cases (52 cases each) [Table/Fig-2]. Percentage of Right Colonic Cancers (RCC) were slightly higher in females (17 cases, 54.83%) with a male to female ratio of 0.8:1 [Table/Fig-3].



[Table/Fig-1]: Age distribution of Colorectal Cancer (CRC) cases.

Gender	Total	Percentage (%)
Female	52	50
Male	52	50
Total	104	100

[Table/Fig-2]: Gender distribution of Colorectal Cancer (CRC) cases.

Gender distribution	Right colonic cancers		Left colorectal cancers	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Males	14	45.16	37	51.39
Females	17	54.83	35	48.61
Total	31	100	72	100
Male: female ratio	0.8:1		1.05:1	

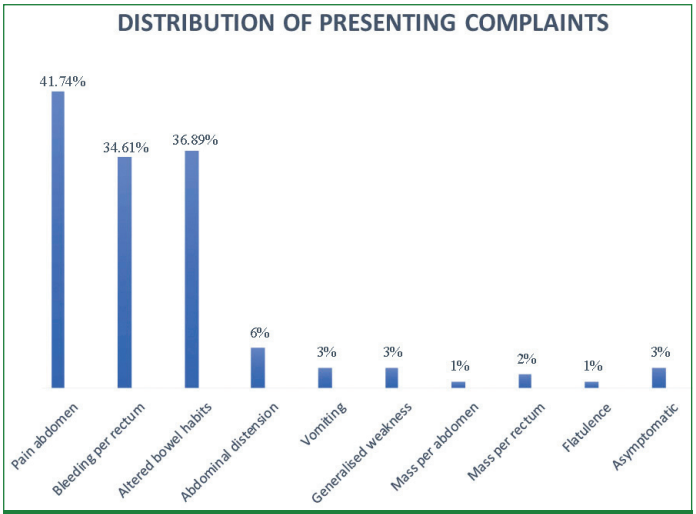
[Table/Fig-3]: Gender distribution in Right Colonic Cancers (RCC) and Left CRC.

Most of the cases were located in distal colon (72 cases, 69.2%) and the rest of the were proximal in location cases (31 cases, 29.80%). One case was could not be categorised based on location of the tumour, as it was a case of synchronous malignancy having tumour on either side of the colon (0.96%).

Predominantly the patients presented with complaints of pain abdomen (42 cases, 41.74%) followed by altered bowel habits (37 cases, 36.89%) and bleeding per rectum (36 cases, 34.61%) [Table/Fig-4]. RCCs presented mostly with pain abdomen (19 cases, 61.29%) whereas left CRCs presented with altered bowel habits (32 cases, 44.44%) [Table/Fig-5].

With respect to anatomical site, rectum (28/104, 26.92%) was the commonest site, followed by sigmoid colon (16/104, 15.38%) [Table/Fig-6]. Ascending colon (11/31, 35.5%) was the most involved site in the RCCs, followed by caecum (8/31, 25.80%) [Table/Fig-7]. In left CRCs, rectum (28/72, 38.9%) was the most common site for occurrence of the tumour, followed by sigmoid colon (16/72, 22.22%) and recto-sigmoid (13/72, 18.05%) [Table/Fig-8].

Adenocarcinoma was the dominant histological type of CRC (93 cases, 89.42%) [Table/Fig-9]. Similarly, adenocarcinoma was the most common histological type in RCC (24 cases, 77.4%) and left CRCs (68 cases, 94.4%) [Table/Fig-10].



[Table/Fig-4]: Distribution of clinical presentation of Colorectal Cancer (CRC) case.

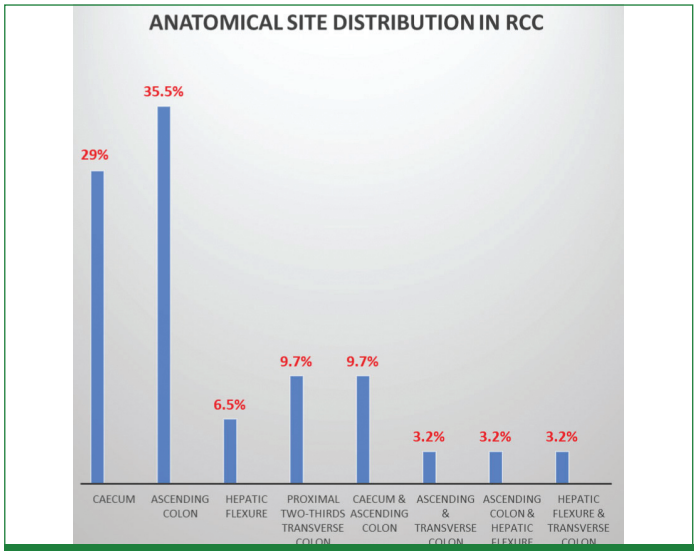
Presenting complaints	Right colonic cancers		Left colorectal cancers	
	Frequency (N=31)	Percentage (%)	Frequency (N=72)	Percentage (%)
Pain abdomen	19	61.29	23	31.94
Bleeding per rectum	8	25.80	28	38.88
Abdominal distension	2	6.45	4	5.55
Altered bowel habits	5	16.12	32	44.44
Vomiting	2	6.45	1	1.38
Flatulence	1	3.22	-	-
Generalised weakness	1	3.22	2	2.77
Asymptomatic	1	3.22	2	2.77
Mass per rectum	-	-	2	2.77
Mass per abdomen	-	-	1	1.38

[Table/Fig-5]: Distribution of presenting complaints in Right Colonic Cancers (RCC) and Left Colorectal Cancers.

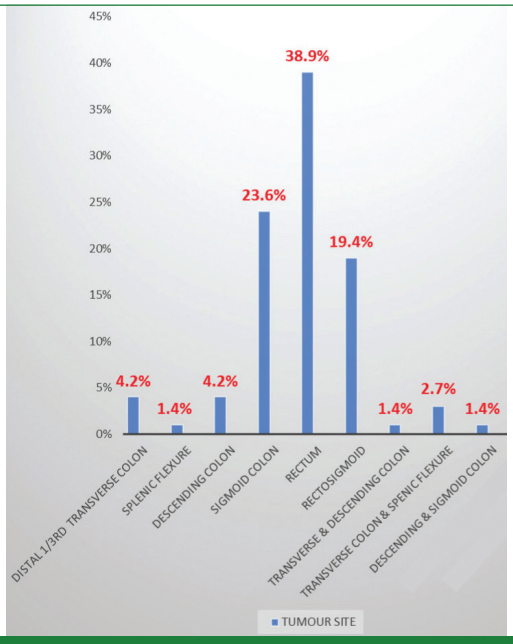
Anatomical site	Grand total	Percentage (%)
Rectum	28	26.92
Sigmoid colon	16	15.38
Rectosigmoid	15	14.4
Ascending colon	11	10.57
Caecum	8	7.69
Transverse colon	6	5.76
Descending colon	3	2.88
Caecum and ascending colon	3	2.88
Hepatic flexure	2	1.92
Transverse colon and splenic flexure	2	1.92
Splenic flexure	1	0.96
Ileo-caecum	1	0.96
Ascending colon and hepatic flexure	1	0.96
Transverse colon and hepatic flexure	1	0.96
Ascending and transverse colon	1	0.96
Transverse and descending colon	1	0.96
Descending and sigmoid colon	1	0.96
Synchronous Colorectal Cancer (CRC)	3	2.88
Total	104	100

[Table/Fig-6]: Anatomical site distribution of Colorectal Cancers (CRC).

Based on three-tiered stratification, 87.09% (81 cases) of the adenocarcinomas were of grade I, followed by 10.75% (9 cases)



[Table/Fig-7]: Anatomical site wise distribution in Right Colonic Cancers (RCC).



[Table/Fig-8]: Anatomical site wise distribution of Left Colorectal Cancers (Left CRC).

Histological types of colorectal cancers	No. of cases (N=104)	Percentage (%)
Adenocarcinoma	93	89.42
Mucinous adenocarcinoma	7	6.73
Medullary carcinoma	1	0.96
Mixed Adenoneuroendocrine Carcinoma (MANEC)	1	0.96
Adenosquamous carcinoma	1	0.96
Adencarcinoma with neuroendocrine differentiation	1	0.96

[Table/Fig-9]: Histological types of Colorectal Cancers (CRC).

Histological type of colorectal cancers	Right Colonic Cancers (RCC)		Left Colorectal Cancers (CRC)	
	Total	Percentage (%)	Total	Percentage (%)
Adenocarcinoma	24	77.4	68	94.4
Mucinous adenocarcinoma	4	12.9	3	4.1
Medullary carcinoma	1	3.2	-	-
Mixed Adenoneuroendocrine Carcinoma (MANEC)	1	3.2	-	-
Adenocarcinoma with neuroendocrine differentiation	1	3.2	-	-
Adenosquamous carcinoma	-	-	1	1.3
Total	31	100	72	100

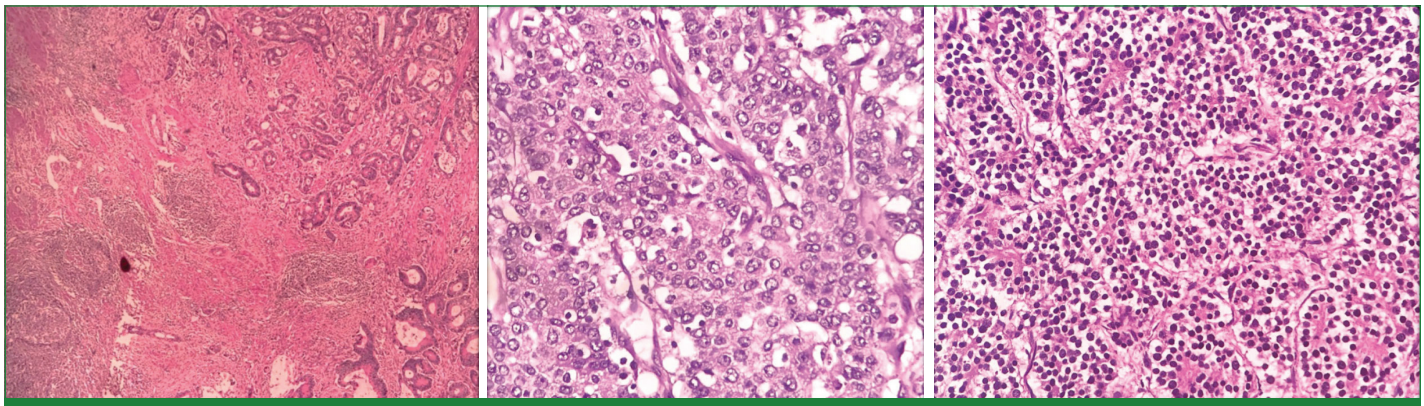
[Table/Fig-10]: Comparison of histological types in Right Colonic Cancers (RCC) and left Colorectal Cancers (CRC).

of grade II tumours and 3.22% (3 cases) of grade III tumours. On the basis of two-tiered stratification, Low grade tumours (90 cases, 96.77%) constituted majority of the adenocarcinomas. Grade I adenocarcinomas dominated in both RCC and left CRC.

Majority of the cases belonged to stage III (49 cases, 47.11%), followed by stage II (37 cases, 35.57%), stage I (14 cases, 13.46%) and stage IV (4 cases, 3.84%). Majority of the RCC were found to be in stage II disease and in left CRCs most of them were in stage III disease.

Number of CLR ranged from 3-16 per section with an average of 5.64 per section [Table/Fig-11]. Whereas number of TILs ranged from 3-50 per HPF with an average of 10.7 per HPF [Table/Fig-12]. Maximum number of TILs was 50 that was found in two of the cases of which one was grade I adenocarcinoma and the other was Mixed Adenoneuroendocrine Carcinoma (MANEC) [Table/Fig-13]. CLR was the most common histomorphological feature of MSI accounting to 48.07% (50 cases), followed by TILs in 38.46% (40 cases), focal mucinous differentiation in 32.69% (34 cases), lack of dirty necrosis in 25.96% (27 cases) of the cases [Table/Fig-14].

In RCC, TILs were the most common MSI feature noted in about 64.51% (20 cases) of the cases, followed by CLR in 61.29% (19 cases). In left sided CRCs, CLR was the predominant MSI feature accounting to 41.66% (30 cases), followed by TILs in 27.77% (20 cases) of the cases [Table/Fig-14]. In stage I CRC, TILs were the frequently observed MSI feature in about 57.14% (8/14) of the cases. Whereas, CLR was the commonest MSI feature noted in the stage 2 and stage 3 CRC accounting to 54.05% (20/37) and 42.85% (21/49), respectively. There was no dominant MSI feature observed in stage IV CRC.



[Table/Fig-11]: Grade 1 adenocarcinoma- Crohn like lymphocytic reaction. H&E stain (40X); **[Table/Fig-12]:** Grade III adenocarcinoma with Tumour infiltrating lymphocytes. H&E Stain (100X); **[Table/Fig-13]:** Mixed adeno-neuroendocrine carcinoma (MANEC) showing neuroendocrine elements and Tumour infiltrating lymphocytes. H&E (100x). (Image from left to right)

MSI features	Right colonic cancers		Left colorectal cancers	
	Frequency (n=31)	Percentage (%)	Frequency (n=72)	Percentage (%)
TILs	20	64.51	20	27.77
CLR	19	61.29	30	41.66
Mucinous differentiation	4	12.90	3	4.16
Focal mucinous differentiation	16	51.61	17	23.61
Focal signet ring cell differentiation	5	16.12	2	2.71
Medullary growth pattern	1	3.22	-	-
Lack of dirty necrosis	11	35.48	15	20.88
Tumour heterogeneity	7	22.58	6	8.33

[Table/Fig-14]: Comparison of histomorphological features of Microsatellite Instability (MSI) in Right Colonic Cancers (RCC) and left Colorectal Cancers (CRC).

When comparing histomorphological features of MSI with clinical symptoms it was found that, most of the cases with TILs and CLR had abdominal pain as a predominant presenting complaint in most of the cases (50%). However, bleeding per rectum was the most common symptom seen in those cases which had lack of dirty necrosis as the MSI feature in about 55.5% of the cases [Table/Fig-15].

DISCUSSION

During the study course, a total of 104 cases of CRCs were evaluated for clinicopathological findings and histomorphological features for MSI. The age of patients ranged from 26-88 years. Overall, majority of the cases of colorectal malignancies belonged to 6th decade (28.84%) and 7th decade (24.03%) of life. In our study, distribution of CRCs was seen mostly in the elderly population. The mean age at presentation was 59 years which was similar with the several other studies [Table/Fig-16] [4,17,19-22].

Equal distribution was noted in both the genders with a male to female ratio of 1:1. In contrast, a male predominance was seen in

S. No.	Clinical features	Histomorphlogical features of Microsatellite Instability (MSI) (N=104)							
		TILs	CLR	MUC	FMD	FSRCD	MED	LDN	HTG
1	Pain abdomen	50%	50%	42.8%	52.9%	28.5%	0	33.3%	38.4%
2	Bleeding per rectum	25%	34%	42.8%	32.3%	57.1%	100%	55.5%	38.4%
3	Altered bowel habits	27.5%	30%	42.8%	26.4%	28.5%	0	25.9%	46.1%
4	Abdominal distension	2.5%	2%	0	5.8%	0	0	0	0
5	Vomiting	5%	2%	14.2%	2.9%	14.2%	0	3.7%	0
6	Generalised weakness	5%	2%	0	2.9%	0	0	3.7%	46.1%
7	Mass per abdomen	0	0	0	0	0	0	0	0
8	Mass per rectum	5%	2%	0	0	0	0	0	0
9	Flatulence	2.5%	2%	0	2.9%	0	0	0	0
10	Asymptomatic	7.5%	2%	0	2.9%	14.2%	0	3.7%	46.1%

[Table/Fig-15]: Comparision of histomorphological features of Microsatellite Instability (MSI) with clinical symptoms.
TILs: Tumour infiltrating lymphocytes; CLR: Crohn-like lymphocytic reaction; MUC: Mucinous differentiation; FMD: Focal mucinous differentiation; FSRCD: Focal signet ring cell differentiation; MED: Medullary growth pattern; LDN: Lack of dirty necrosis; HTG: Tumour heterogeneity

Studies	Year of publication	Sample size	Mean age (years)
Current study	2021	104	59.5
Agy FE et al., [4]	2019	330	54.6
Greenson JK et al., [17]	2009	238	71
Halvarsson B et al., [19]	2008	1649	70
Pinol V et al., [20]	2005	1222	70
Khiari H and Hsairi M [21]	2017	1755	60
Cienfuegos JA et al., [22]	2017	950	75

[Table/Fig-16]: Mean age at presentation of Colorectal Cancer (CRC) in various studies [4,17,19-22].

a study done by Khiari H and Hsairi M, and Yusuf I et al., with male to female ratio of 1.2:1 and 2.3:1, respectively [21,23]. In our study, the mean age of presentation was 59 years in males and 60 years in females.

Most of the patients presented with the complaints of pain abdomen (41.34%) followed by altered bowel habits (36.53%) and bleeding per rectum (34.61%). The remaining 3% of the cases were incidentally detected on routine radiological scan without having any clinical symptoms. Family history of malignancy in first-degree relatives was noted in three of the cases.

Rectum (26.92%) was the most common site for CRC, followed by sigmoid colon (15.38%). Similar results were found in the study conducted by Yusuf I et al., [23]. In another study done by Benedix F et al., on-colon cancers, found sigmoid colon to be the most common site (42.5%) followed by ascending colon (16.5%) and caecum (15.7%) [24]. However, rectal cancers were excluded in their study [Table/Fig-17] [24].

Studies	Year of publication	Most common location of the tumour	Percentage
Current study	2021	Rectum	27%
Yusuf I et al., [23]	2017	Rectum	62.3%
Benedix F et al., [24] (Rectal cancers were excluded)	2010	Sigmoid colon	42.5%

[Table/Fig-17]: Most common site for Colorectal Cancer (CRC) in various studies [23,24].

Incidence of synchronous CRC was 2.88%, whereas in a study done by Hsu Y et al., and Gomez D et al., incidence was 2% and 1%, respectively [25,26]. Synchronous malignancy occurred in the patients less than 60 years of age with one case of Familial Adenomatous Polyposis (FAP) and positive family history of CRC in two of the cases in their first-degree relatives.

Histopathologically, adenocarcinoma (89.42%) was the most frequent type of CRC followed by mucinous adenocarcinoma (6.73%) which was similar to the results of other studies [Table/Fig-18] [4,23,27].

Studies	Year of publication	Sample size	Adenocarcinoma	Mucinous adenocarcinoma
Current study	2021	104	93 (89.42%)	7 (6.73%)
Agy FE et al, [4]	2019	330	278 (84.2%)	29 (8.8%)
Yusuf I et al., [23]	2017	53	45 (84.9%)	5 (9.4%)
Benatti P et al., [27]	2005	1263	1052 (83.2%)	211 (16.7%)

[Table/Fig-18]: Commonest histopathological type of tumour in various studies of Colorectal Cancer (CRC) [4,23,27].

Out of 104 cases that were evaluated, grading was applicable only for 93 cases of adenocarcinomas since the grading system is not applicable to the other histological types. Most them were of well differentiated type (87.09%) in contrast to another study done by Pinol V et al., which showed predominance of moderately differentiated adenocarcinomas (68.3%) [20].

This study found a slightly higher percentage of patients with stage III disease (47.11%), followed by stage II disease (35.57%). This was in contrast with the other studies wherein majority of the patients were in stage II disease [Table/Fig-19] [20,27,28].

Studies	Year of publication	Sample size	Stage I	Stage II	Stage III	Stage IV
Current study	2021	104	14 (14.5%)	37 (38.4%)	49 (50.9%)	4 (4.1%)
Pinol V et al., [20]	2005	1222	161 (13%)	510 (41.7%)	337 (27.6%)	214 (17.5%)
Benatti P et al., [27]	2005	1263	126 (9.9%)	491 (38.8%)	461 (36.5%)	184 (14.5%)
Ward R et al., [28]	2001	310	51 (16.4%)	113 (36.4%)	97 (31.2%)	49 (15.8%)

[Table/Fig-19]: Stage of the Colorectal Cancer (CRC) in various studies [20,27,28].

The dominant histomorphological feature of MSI in this study was CLR (48%). Our findings in this regard are similar to a study done by Jenkins M et al., and Halvarsson B et al., [12,19]. The second most common MSI feature was TILs (38.46%) which was similar to a study done by Jenkins M et al., and Halvarsson B et al., [Table/Fig-20] [12,19].

Studies	Year of publication	Crohn like lymphocytic reaction (%)	Tumour infiltrating lymphocytes (%)
Current study	2017	48%	38%
Jenkins M et al., [12]	2007	28%	20.3%
Halvarsson B et al., [19]	2008	44.7%	16.6%

[Table/Fig-20]: Histomorphological features of Microsatellite Instability (MSI) in various studies [12,19].

In our study, number of CLR ranged from 3-16 per section with an average of 5.64 per section. Whereas, number of TILs ranged from 3-50 per HPF with an average of 10.7 per HPF. TILs were identified on haematoxylin and eosin stained sections as small mononuclear cells that typically have a halo around them. Apoptotic cells may falsely be counted as lymphocytes. Hence, it was evaluated cautiously.

These were the lymphocyte aggregates or follicles at the tumour edge, not associated with pre-existing lymph node.

Comparison between RCC and left CRC: Comparison was done between 31 cases of RCC and 72 cases of left sided CRCs. Remaining one case of synchronous CRC was excluded, as this case had tumour on either side of the colon. The mean age of diagnosis in RCCs was 59.9 years and 59.36 years in left CRCs. However, incidence of RCCs was found slightly more in advancing or elderly age which was documented in the literature [22,24-26,29].

Females were found to have slightly higher percentage of developing RCCs. This was comparable with the other studies of which showed increased percentage of RCC in females and left CRCs in males [25,22,24,29]. In RCC, pain abdomen (61.29%) was the commonest clinical presentation whereas left sided CRCs presented more often with altered bowel habits (44.44%). Studies done by Cienfuegos J et al., and Benedix F et al., found anaemia and bleeding per rectum as the predominant manifestation in the RCC and left CRCs, respectively [22,24].

Majority of the CRC cases were located distally (69.23%) than in proximal location (29.80%) which was in agreement with the several other studies [4,12,20,23,26,29]. In contrast, Halvarsson B et al., in their study had preponderance of proximally located tumours in their study [19]. Ascending colon was the most involved anatomical site in RCC, while rectum in left sided CRCs.

Adenocarcinomas constituted majority of the left CRC (94.4% vs 77.4%), while mucinous adenocarcinomas in the RCC (12.9% vs 4.1%). Results of this study was similar with a study done by Hsu Y et al., [25]. Most of the left sided adenocarcinomas were found to be of well differentiated type, whereas moderate and poorly differentiated adenocarcinomas were located more in the right colon. In the study

done by Hsu Y et al., poorly differentiated tumours were located in the right colon [25].

Maximum number of stage I and II disease were located in right colon, while stage III and IV in the left colon. This finding is comparable with a study done by Natsume S et al., [29]. Our study showed dominance of all the histopathological features of MSI in RCC when compared with left sided CRCs.

Limitation(s)

In this institution, all the cases were not subjected to IHC or molecular testing for MSI. Hence, in the present study, histomorphological features of MSI could not be confirmed by standard tests.

CONCLUSION(S)

The CRC is mostly the malignancy of elderly population and occurs predominantly in the distal colon. Molecular genetic studies have shown that 10-15% of CRCs have high level MSI-H. MSI-H have better prognosis than stable cancers. MSI, particularly in stage II CRCs have better prognosis and do not benefit from 5FU- based adjuvant chemotherapy. Therefore, it is the most important prognostic marker in CRC and especially in stage II CRC. MSI features were predominantly seen in RCCs based on histomorphological evaluation in the present study and individual histomorphological feature of MSI is not a good marker to predict MSI status. Thus, MSI status should be confirmed by IHC or molecular testing.

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