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Clinicopathological Evaluation of Colorectal Carcinoma: A Unicenter Study

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Abstract

Introduction: Colorectal cancer (CRC) is a significant cause of morbidity and mortality and population based time trend studies have shown a rising trend in incidence of CRC in India. As the literature on the issue in India is limited, we undertook the study with the objective of evaluating the histopathological features of CRC and correlating these with certain clinicopathological variables. *Material and Method:* All the cases of colectomy and abdominoperineal resection specimen, received in the Pathology Department, over a period of three years (between July 2012 and July 2015) were evaluated. *Statistical Analysis*: Continuous data and qualitative variables were summarised using descriptive statistics and frequency respectively. Fisher's exact test was used to compare the tumour grade with other clinicopathological variables. *Results:* The study included 51 cases of CRC with male: female ratio of 2.2:1. The mean patient age was 52.3± 13.2 years, with most of the cases occurring in the 5th decade (33.3%). Majority of the cases were located in the rectum (39.2%) and the commonest gross tumour morphology was ulceroinfiltrative (45.1%). Conventional adenocarcinoma (ACa- NOS) was the commonest histologic type (74.5%) followed by mucinous adenocarcinoma (MACa) (19.6%) and signet ring cell carcinoma (SCa) (5.9%). The most frequent grade observed was G2 (45.1%). Majority of the patients were in stage III (52.9%). *Conclusions:* Our age and sex distribution is comparable, to a larger extent, with other related nationwide studies. As many previous studies worldwide have consistently demonstrated, we found positive correlation between tumour grade and nodal metastasis, extent of local tumour spread and TNM stage.

Keywords: Adenocarcinoma; Colorectal Carcinoma; Mucinous Adenocarcinoma; Tumour Grade; TNM Stage.

Introduction

Colorectal cancer (CRC) is the fourth leading cause of cancer death worldwide and second frequent cause of cancer mortality in industrialised world [1]. It is the second most common cancer in women (6,63,904 new cases/ year, 9.4% of all cancers) and third common cancer in men (5,71,204 new cases/ year, 10.0% of all cancers) [2-4]. In India, population based time trend studies have shown a rising trend in incidence of CRC and the results of surgical resection for advanced CRC are still poor [2]. The most powerful predictors and guide to treatment in CRC are the pathologic aspects of the resected specimen like stage and stage-independent factors including histologic grade, microscopic tumour type, lymphovascular invasion, and surgical margins [4]. Thus meticulous histopathological examination of the CRC specimen is indispensable. The aim of the present study was to evaluate the various histopathological features of CRC and to correlate these features with certain clinicopathologic variables.

Key Messages

There is a rising trend in incidence of CRC in India. As majority of our patients present at advanced stage, screening of high-risk populations, public awareness and early diagnosis is necessary to reduce the mortality and morbidity.

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Material and Methods

This was a single centre prospective study of all the cases of colectomy and abdominoperineal resection specimen, received in the Pathology Department, M.S Ramaiah Medical College and Hospitals, Bangalore over a period of three years (between July 2012 and July 2015). In every case the standard protocol for surgical grossing of resected specimens was followed. After a detailed gross specimen examination (including tumour size, site and appearance), multiple representative tissue bits were taken from the tumour, surgical margins, mesocolon and all the lymph nodes. The latter were processed as per standard protocol and paraffin embedded tissue blocks were cut and stained by haematoxylin and eosin (H & E). The H & E stained slides were studied for the tumour histology, grade, lymphovascular invasion and lymph node metastasis and other features. The WHO classification of colorectal carcinomas was followed for histological tumour typing and AJCC cancer staging system was used for tumour staging [5,6]. Adenocarcinomas were divided into three grades based on the arrangement of cells with regard to degree of tumour differentiation into well differentiated/ G1, moderately differentiated/ G2 and poorly differentiated/ G3 [5,7-9]. Cases where only a biopsy, endoscopic mucosal resection or polypectomy had been performed were excluded from the study, as in such cases all the pathologic prognostic parameters were not available for assessment. Cases which had received neoadjuvant chemotherapy prior to surgery were also excluded.

Statistical Analysis

Continuous data was summarised using descriptive statistics. Qualitative variables were summarized using frequency and percentage. Fisher's exact test was used to compare the tumour grade with TNM stage, extent of local tumour spread/depth of colonic wall invasion and lymph node metastasis. P-value <0.05 was considered as statistically significant.

Results

A total of 51 cases of CRC were obtained during the three year study period. The mean patient age was 52.3± 13.2 years (age range: 26 to 93 years), with most of the cases occurring in the 5th decade (33.3%) followed by 4th decade (23.5%) [Table 1]. 10% of the cases occurred in individuals below 40 years of age. 68.6% of the cases occurred in males and 31.4% cases occurred in females with a male: female ratio of 2.2:1. The mean age in males was 52.5± 11.9 (age range: 26 to 72) and the mean age in females was 51.6± 15.9 (age range: 28 to 93). Majority of the cases were located in the rectum (39.2%) followed by sigmoid colon (17.6%) [Table 2]. Tumour appearance: ulceroinfiltrative/ endophytic gross morphology was present in 45.1% (23/51) followed by ulceroproliferative/ exophytic in 35.3% (18/51), annular with circumferential involvement of colonic wall in 13.7% (7/51) and diffuse infiltrative/ linitis plastic-like 5.9% (3/51). Microscopic examination identified conventional adenocarcinoma (ACa- NOS) as the commonest histologic type (74.5%) followed by mucinous adenocarcinoma (MACa) (19.6%) and signet ring cell carcinoma (SCa) (5.9%) [Table 2] [Figures 1, 2 and 3]. The most frequent grade observed was G2 (45.1%) [Tables 3 and 4]. Majority of the patients were in stage III (52.9%) [Tables 3 and 4]. There was a statistically significant difference in the distribution of histologic grade with respect to TNM stage (p=0.007). G3 tumours were associated with advanced TNM stage in comparison with G1 and G2 tumours (80% and 13.3% of G3 tumours presented respectively at stages III and IV whereas only 30.8% and 0% of G1 tumours presented at stages III and IV and 47.8% and 0% of G2 tumours at stages III and IV) [Table 4].

Significant association was observed between histologic grade and extent of local tumour spread/ depth of colonic wall invasion by tumour (p=0.002). G3 tumours showed deep invasion of colonic wall in contrast to G1 and G2 tumours [86.7% and 13.3% of G3 tumours respectively showed invasion through the muscularis propria into the pericolorectal tissues (T3) and penetration of the visceral peritoneum (T4)] [Table 4].

Positive lymph nodes were present in 29 cases [Table 3 and 4]. G3 tumours showed higher percentage of nodal metastasis in comparison with G1 and G2 tumours (93.3% of G3 vs. 47.8% of G2 and 30.8% of G1) and this association was statistically significant (p=0.006).

In all the cases, the circumferential radial margin and proximal and distal surgical resected margins were free of tumour involvement.

Three (5.8%) cases occurred in the setting of familial adenomatous polyposis coli. Sporadic tubular adenomas and villous adenoma were present in four (7.8%) cases and one (1.9%) case respectively. Distant metastasis to the lungs and liver was present in two cases.

Table 1: Age and sex distribution of CRC

Age group	No. of cases (%)	Sex distribution	
		Male	Female
21- 30	3 (5.9%)	2	1
31- 40	7 (13.7%)	4	3
41- 50	12(23.5%)	8	4
51- 60	17(33.3%)	14	3
61- 70	8(15.7%)	5	3
71- 80	3 (5.9%)	2	1
81- 100	1(1.9%)	0	1
Total	51	35	16

Table 2: Anatomical site and histologic subtype of CRC

Anatomical site	No. of cases (%)	Histologic type		
		ACa-NOS	MACa	SCa
Cecum	7	3	2	2
Ascending colon	4	4	0	0
Hepatic flexure	6	3	3	0
Transverse colon	1	1	0	0
Splenic flexure	1	1	0	0
Descending colon	3	2	1	0
Sigmoid colon	9	7	2	0
Rectum	20	17	2	1
Total	51	38	10	2

ACa-NOS- adenocarcinoma, MACa- mucinous adenocarcinoma, SCa- signet ring cell carcinoma.

Table 3: Distribution of cases by histologic subtype, histologic grade, TNM stage and lymph node metastasis

Histologic type	Mean age ±SD	Histologic grade			TNM stage				LN mets (%)
		G1	G2	G3	I	II	III	IV	
ACa-NOS (n=38)	54.4± 13.2	9	17	12	5	11	21	1	22(43.1%)
MACa (n=10)	46.7± 12.5	4	6	0	2	3	5	0	5(50%)
SCa (n=3)	44 ± 5.6	0	0	3	0	1	1	1	2 (66.7%)
Total	-	13	23	15	7	15	27	2	29

ACa-NOS- adenocarcinoma, MACa- mucinous adenocarcinoma, SCa- signet ring cell adenocarcinoma, LN mets- No. of cases with lymph node metastasis

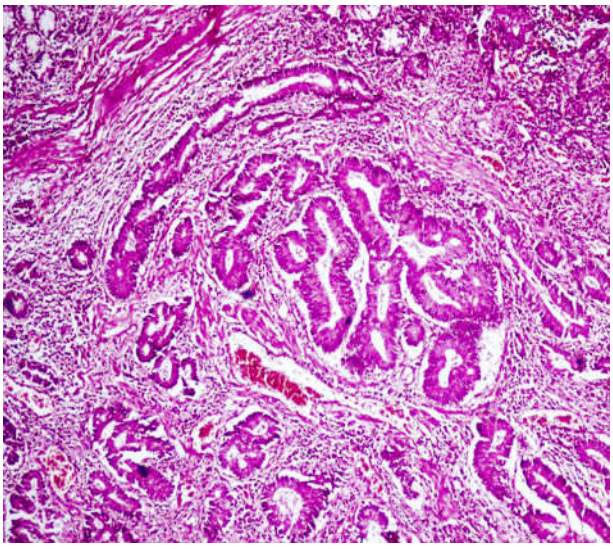

Fig. 1: Well differentiated adenocarcinoma composed of well formed glandular structures lined by focally pseudostratified columnar epithelium (H&E x100)

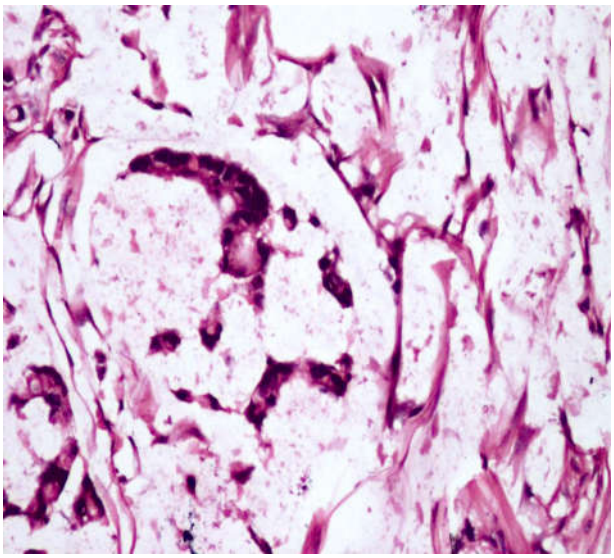

Fig. 2: Mucinous adenocarcinoma with strips and acinar formations of tumour cells in lakes of mucin. (H&E x200)

Table 4: Distribution of cases by histologic grade, TNM stage, depth of invasion and lymph node metastasis.

Histologic grade	Depth of invasion				TNM stage				LN mets(%)	Mean no. of LN
	T1	T2	T3	T4	I	II	III	IV		
G1 (n=13)	1	6	5	1	4	5	4	0	4 (30.8%)	2.8±0.9
G2 (n= 23)	1	12	9	1	3	9	11	0	11 (47.8%)	2.1±1.6
G3 (n=15)	0	0	13	2	0	1	12	2	14(93.3%)	5.4±4
Total	2	18	27	4	7	15	27	2	29	-

LN mets- No. of cases with lymph node metastasis
Mean number of LN- average number of lymph nodes with metastasis, in each subgroup of histologic grade.

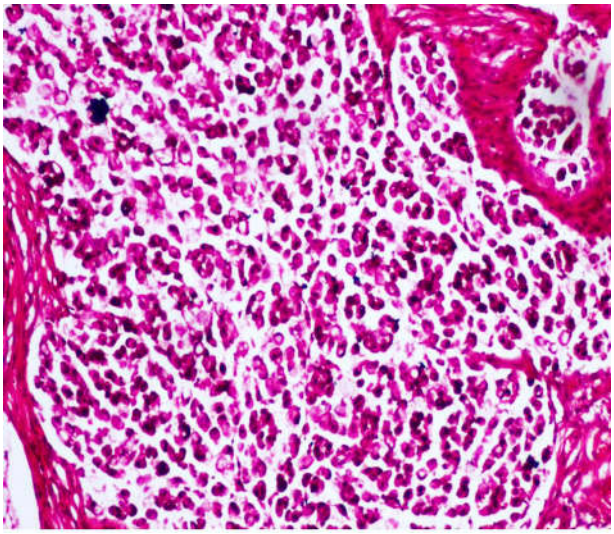

Fig. 3: Signet ring cell carcinoma with discohesive tumour cells exhibiting intracytoplasmic mucin vacuole and peripherally disposed hyperchromatic nucleus. (H&E x100)

Discussion

Age and Sex

Various studies showed age at presentation of colorectal carcinoma ranging from 18 - 90 years [3,10,11]. Mean age in this study was slightly higher than other Indian studies conducted by Laskar et al (43.4 years), Sarvesh et al (49.5 years) and Moshin-ul-rasool et al (50.5 years) and lower than some Asian studies (Hajmanoochehri et al, Safee et al) [3,10-12]. In synchrony with our findings, studies by Moshin-ul-rasool et al and Sarvesh et al showed that maximum number of patients presented in 4th to 6th decade [3,11]. Similar to our study, a male predominance was seen in many Asian studies [10,11,13]. However, a south Indian study by Sarvesh et al showed equal sex incidence [3]. These variations in age and sex distribution are acceptable and could be due to differing material and methods and patient selection criteria, dietary habits, lifestyle, social and cultural characteristics and race.

Several Indian studies have documented increasing frequency of CRC in the younger age group [2,11,12]. A north east Indian study found that 48.1% of patients were <40 years of age [12]. The frequency in our study (10%) was slightly lower than another south Indian study (Sarvesh et al) where 13.2 % of patients were aged <40 years [3]. Studies have attributed the increasing incidence of CRC in young adults to lifestyle factors like physical inactivity, westernisation of diet, obesity and environmental pollution [2,12,14].

Tumour Location

Majority of the CRC are located in the rectum and sigmoid colon, however in the recent years there is evidence of changing distribution with an increase in the incidence of more proximal CRC [3,5]. An Italian cancer registry showed an increase of 33.7% in all colonic segments with a decrease in frequency of rectal tumours [4]. This increasing trend of right colic tumours necessitates total colonoscopy for screening and surveillance [4]. Similar to some of the other Indian studies, we did not find any increase in frequency of proximal CRC [3,11]. Moshin-ul-rasool et al quoted rectum (40.1%) followed by ascending (24%) and sigmoid colon (11.9%) as the commonest sites [11]. In the study conducted by Sarvesh et al most of the CRC occurred in rectum (79.4%) followed by descending colon (5.9%), ascending colon (4.4%) and sigmoid colon (4.4%) [3]. In our study rectum was the commonest site (79.4%) followed by sigmoid colon (17.6%) and cecum (13.7%).

Tumour Type, Grade and Stage

Different tumour types vary with respect to local behaviour, response to therapy and propensity for metastasis rendering determination of tumor type mandatory [13]. Consistent with other Indian studies and world's literature, conventional adenocarcinoma (ACa-NOS) was the most frequent histologic type of CRC in our study [3,4,10,11,13,15]. These tumours were characterised by glandular formations that varied in size and configuration with intervening stromal desmoplastic and inflammatory response. At foci, some of the glands contained "dirty necrosis". Well differentiated/ G1 ACa showed >95% gland

formation. These glands were well formed and lined by simple to focally pseudostratified columnar epithelium reminiscent of adenomatous epithelium. Moderately differentiated/ G2 ACa showed 50- 95% gland formation. These glands were simple, irregular and architecturally complex, lined by predominantly stratified epithelium with prominent nuclear atypia. Poorly differentiated/ G3 ACa showed <50% gland formation with predominance of solid areas.

Mucinous adenocarcinoma (MACa) comprised the second common histologic type, a finding in synchrony with Indian studies and other studies world wide [4,10,13,15]. These tumours were characterised by abundant extracellular mucin that comprised >50% of the tumour volume. Large glandular structures, acinar formations, strips of cells and individual cells were seen floating in pools of mucin. When columnar mucus secreting epithelium was present these tumours were graded as G1. When the epithelium was in irregular chains or irregular clusters they were graded as G2 [16]. The prognosis of MACa in comparision with ACa-NOS is controversial among different studies [9]. MACa occurring in the setting of hereditary nonpolyposis colorectal cancer (HNPCC) behave in low grade fashion where as MACa that are microsatellite stable behave in an more aggressive fashion [9]. In the present study the frequency of MACa with advanced stage and lymph node metastasis at presentation (50%) was slightly more than that of ACa-NOS (43.1%).

Signet ring cell carcinoma (SCa) comprised 0.9% to 11% of CRC in various studies [10,13,15]. These tumours are composed of >50% signet ring cells that exhibited prominent intracytoplasmic mucin vacuole and peripherally disposed hyperchromatic nucleus. These tumours were graded as poorly differentiated G3. In synchrony with world's literature, majority of our cases of SCa (66.7%) presented at advanced stage with lymph node metastasis [13,15].

Similar to many of the other related studies, we did not encounter the rarer histologic variants of CRC listed in the World Health organisation classification like medullary, micropapillary, serrated, adenosquamous and spindle cell [3,10,11,13].

In spite of the inherent variability in reporting it, histologic grade has consistently been demonstrated by multivariate analysis as a stage-independent prognostic factor [14,17]. A study involving 302 cases showed that patients with G1 tumours had the best survival (81.3 months) followed by G2 (55.6±3 months), G3 (36.1±7.3 months) and G4 (4.9±0.8 months) [4]. Specifically, it has been shown that high grade tumours (G3) are associated with deeper invasion of colonic wall, lymph node metastasis, high stage [4,13]. Our findings are also similar, G3 tumours were associated with deeper colonic wall invasion, higher frequency of nodal metastasis and advanced TNM stage in comparison with G1 and G2 tumours.

In the current study, the majority of patients presented with advanced stage which is in synchrony with other related studies in developing countries [18].This late presentation could be due to unavailability of screening programs, low socioeconomic status with limited resources, low education standard, poor access to tertiary health care centres, and lack of public awareness of the disease risk factors and symptoms. Early diagnosis is indispensable to mitigate the high mortality and morbidity associated with advanced stage.

Conclusion

This report provides comprehensive information about the clinicopathological features of CRC, at a south Indian tertiary health care centre over a period of 3 years. The age and sex distribution is comparable, to a large extent, with other nationwide studies. Majority of the tumours are located in rectum and ulceroinfiltrative morphology is the most frequent gross appearance. ACa-NOS is the commonest histologic type and majority of the tumours are moderately differentiated. Most of our patients presented at Stage III. As many previous studies worldwide have consistently demonstrated, we found positive correlation between tumour grade and nodal metastasis, extent of local tumour spread and TNM stage. As majority of our patients presented at stage III, screening of high-risk populations, public awareness and early diagnosis is necessary to reduce the mortality and morbidity.

References

1. Hegazy A, Daoud SA, Ibrahim WS, El-Atrebi K, Saker M, Abdel-Wahab N.Role of Ki-67, P53 and Bcl-2 in Advanced colorectal carcinoma (Histopathological and Immunohistochemical study). Academic J. Cancer Res. 2014; 7: 168-72.
2. Mohandas KM. Colorectal cancer in India: controversies, enigmas and primary prevention. Indian J Gastroenterol. 2011; 30: 3–6.
3. Sarvesh BM, Abhishek MG. Histomorphological Study of Colorectal Malignancies. J of Evidence Based Med & Hlthcare. 2015; 2: 4402-12.
4. Vasile L, Olaru A, Munteanu M, Plesea IE, Surlin V,

Tudorascu C. Prognosis of colorectal cancer: clinical, pathological and therapeutic correlation. Rom J Morphol Embryol. 2012; 53: 383-91.

5. Hamilton SR, Rubio CA, Vogelstein B, Sobin L.H, Kudo S, Fogt F, et al. Carcinoma of the colon and rectum. In: Hamilton SR, Aaltonen LA, editors. World Health Organization classification of tumours. Tumours of the digestive system. Lyon, France: IARC Press. 2000; 103–19.
6. Edge SB, Byrd DR, Compton CC, Fritz AC, Greene FL, Trotti A. AJCC Cancer Staging Manual. Seventh Edition. Springer. 2009: 143–59.
7. Jass JR, O'Brien J, Riddell RH, et al. Recommendations for the reporting of surgically resected specimens of colorectal carcinoma: Association of Directors of Anatomic and Surgical Pathology. Am J Clin Pathol. 2008; 129: 13–23.
8. Cooper HS. Intestinal neoplasm. In: Stacey EM, editor. Sternberg's Diagnostic surgical Pathology. Philadelphia: Lippincott Willams & Wilkins. 2010: 1368-431.
9. Fleming M, Ravula S, Tatishchev SF, Wang LH. Colorectal carcinoma : Pathologic aspects. J Gastrointest Oncol. 2012; 3: 153-73.
10. Hajmanoochehri F, Asefzadeh S, Kazemifar AM, Ebtehaj M Clinicopathological Features of Colon Adenocarcinoma in Qazvin, Iran: A 16 Year Study. Asian Pac J Cancer Prev. 2014; 15; 951-55.
11. Mohsin-ul-Rasool, Mubeen B, Andrabi RS, Hamid S, Rasool Z , Shah P, et al. Histopathological Study of Neoplastic lesions of large Intestine in Kashmir, Valley, India. Int. Res. J. Medical Sci. 2015; 3: 1-5.
12. Laskar RS, Talukdar FR, Mondal R, Kannan R, Gosh SK. High frequency of young age rectal cancer in a tertiary care centre of southern Assam, North East India.
13. Nabi U, Nagi AH, Riaz S, Sami W. Morphological Evaluation of Colorectal Carcinoma with, Grading Staging and Histological types. JPMA. 2010; 60: 998- 1001.
14. Rebecca L. Siegel, Ahmedin Jemal, and Elizabeth M. Ward. Increase in Incidence of Colorectal Cancer Among Young Men and Women in the United States. Cancer Epidemiol Biomarkers Prev. 2009; 18: 1695-98.
15. Marzouk O, Schofield J. Review of Histopathological and Molecular Prognostic features in Colorectal Cancer. Cancers. 2011; 3: 2767-810.
16. Jass JR. Tumors of the small and large intestines (including the anal region). In: Fletcher CDM, editor. Diagnostic Histopathology of tumours. Philadelpia: Elseviver Limited. 2007: 379-416.
17. Washington MK, Berlin J, Branton P, Burgart LJ, Carter DK, Patrick L. Fitzgibbons PL, et al. Protocol for the Examination of Specimens From Patients WithPrimary Carcinoma of the Colon and Rectum. Arch Pathol Lab Med. 2009; 133: 1539–51.
18. Chalya PL, Mchembe MD, Mabula JB, Rambau PF, Jaka H, Koy M, et al. Clinicopathological patterns and challenges of management of colorectal cancer in a resource-limited setting: a Tanzanian experience. World Journal of Surgical Oncology. 2013; 11: 88-97.