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ORIGINAL ARTICLE

Colorectal Cancer in India: An Audit from a Tertiary Center in a Low Prevalence Area

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Abstract Colorectal cancer (CRC) is a common cancer worldwide with a low reported incidence in India. There is significant geographical variation in the incidence rates, and the presentation may also vary. There are few studies evaluating the clinical profile of CRC in Indian patients. We analyzed a prospective database maintained at the Tata Memorial Hospital, a referral cancer center in Mumbai, of consecutive patients with CRC between August 2013 and August 2014. We captured details regarding the demography, symptoms, pathology, stage, and treatment plan. The aim was to assess the demographic and clinical details of patients with CRC in India and compare it with those of the reported literature. Eight hundred new patients with CRC were seen in the colorectal clinic in one year. The mean age was 47.2 years. Sixty-five percent were males. Patients were symptomatic for an average period of 4 months prior to presentation. The commonest symptoms were rectal bleeding (57%), pain (44%), and altered bowel habits (26%). Thirteen percent of the patients had signet ring tumors. The median CEA (carcinoembryonic antigen) level was 5.8 ng/mL. Most patients had localized or locally advanced disease. Twenty-eight percent of the patients had metastatic disease with liver being the commonest site of metastases (14%) followed by peritoneum and lung. More than half of the patients received treatment with a curative intent. Colorectal cancer in India differs from that described in the Western countries. We had more young patients, higher proportion of signet ring carcinomas, and more patients presenting with an advanced stage. Inadequate access to healthcare and socioeconomic factors may play a role in some of these differences.

Keywords Colorectal cancer · Demography · India

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Introduction and Background

Colorectal cancer (CRC) is a common cancer worldwide. It is the third most commonly diagnosed cancer in males and the second in females, with more than 1.4 million new cancer cases every year [1]. There is a geographical variation in the incidence rates with more than half of the cases of CRC occurring in developed countries. However, mortality is higher in the less developed countries who have limited resources and inadequate health infrastructure. Mortality rates have been decreasing in many Western countries due to a combination of various factors like early detection due to screening and improved treatment of CRC [2].

The age standardized rate (ASR) for CRC in India is low at 7.2 per 100,000 population in males and 5.1 per 100,000 population in women [3]. However, in a country with a population of a billion plus people, the absolute number of patients suffering from CRC is large. Five-year survival of CRC in India is one of the lowest in the world at less than 40%. In fact, the CONCORDE-2 study reveals five-year survival of rectal cancer in India is actually falling in some registries [4]. This may be a pointer to inadequacies in the diagnostic and treatment pathways for CRC. An urgent need is to

assess reasons for this poor survival. A baseline study to assess demographic and clinical profile of patients with CRC is essential for planning the strategy to tackle this disease in India, and this study aims to take a preliminary step in that direction.

There is a perception amongst oncologists in India that most cases of CRC in India present at a younger age, with more advanced-stage disease, more signet ring morphology, and more anorectal as compared to colonic site of primary as compared to that reported worldwide. There are a few published studies from India on patients with CRC. However, these involve small numbers of patients which makes it difficult to make a valid conclusion. None has evaluated the demography and clinical presentation of a large number of CRC patients. Hence, the profile of patients with CRC in India is unknown. We planned an audit of all CRC patients seen at our center over a one-year period.

Methods

We performed an audit of a prospectively maintained database in the Colorectal Clinic of Tata Memorial Hospital (TMH), a referral cancer center in western India. Institutional Ethics Committee (IEC) approval was taken for this study. The aim of this audit was to evaluate the demography and clinical presentation of CRC patients and compare it with those of the available reports in Indian as well as Western literature. All patients with diagnosed or suspected colorectal tumors presenting to the TMH were evaluated in the colorectal clinic by a multidisciplinary team including a surgical oncologist, a medical oncologist, a radiation oncologist, a gastroenterologist, and a radiologist. Treatments were planned by consensus as per prevailing standards of care. A prospective database of all patients seen in the clinic was maintained. The database included demographic features, symptoms, primary diagnosis, basic laboratory investigations, and stage information. We also noted the treatment planned. Some patients also had a nutritional assessment done.

Results

Nine hundred seventy-eight newly registered patients with known or suspected colorectal tumors were seen in a one-year period (August 2013–August 2014) in the colorectal clinic. Eight hundred patients with adenocarcinoma of the colon/rectum (colorectal cancer—CRC) on biopsy were included in this audit. We excluded 178 patients who had either received prior chemotherapy and/or radiation or did not have a malignancy or had a tumor other than adenocarcinoma. Non-adenocarcinoma tumors included 44 patients with squamous carcinoma, 13 with undifferentiated carcinomas, 10 with melanoma, 7 patients with gastrointestinal stromal tumors (GIST), and 6 with neuroendocrine tumors (NET) of the colon and rectum.

The demographic characteristics are summarized in Table 1. There were 517 (65%) males and 283 (35%) females. The mean age of the patients with CRC was 47.2 years (range 11 years–85 years). The mean age of the patients with rectal cancers was significantly lower than that with colon cancer (45.7 vs. 49.1 years, $p = 0.001$). So also, patients with left-sided tumors were significantly younger than patients with right-sided primaries (46.5 vs. 50.1 years, $p = 0.006$). Most patients (44%) were in the age group of 40–60 years, while 33% were below 40 years of age. The median duration of symptoms was 4 months (range 10 days–12 years). The commonest symptom was rectal bleeding (57%) followed by pain (44%) and altered bowel habits (26%).

Most patients (79%) had ECOG Performance Status (PS) of 1. Only 27 patients (3.4%) had PS-3, and none had PS-4. We used the subjective global assessment score (SGA) for staging malnutrition. Most of our patients were malnourished. Only 55 patients (7%) had an SGA score of A (none or minimal malnutrition). Six hundred nine (76%) were SGA-B (moderate malnutrition), and 136 (17%) were SGA-C (severe malnutrition).

The commonest primary site was rectum (333, 42%) followed by recto-sigmoid (171, 21%), anorectum (103, 13%), and colon (193 patients, 25%). One hundred forty-four (18%) had a tumor in the right colon (cecum, ascending colon, or hepatic flexure).

All 800 patients had tumor histology revealing an adenocarcinoma. Twenty-one (2.6%) had well-differentiated tumors, 381 (47.6%) had moderately differentiated tumors, and 165 (20.6%) had poorly differentiated tumors (Table 2).

Table 1 Patient demography and site of primary tumor

	N (range/frequency)
Age in years, mean (range)	47.2 (11–85 yrs)
Age group	
<20 yrs	12 (1.5%)
20–39 yrs	253 (31.6%)
40–59 yrs	352 (44%)
60–79 yrs	175 (21.9%)
>80 yrs	8 (1%)
Male gender	517 (65%)
Subsite	
Anorectum/rectum	436 (54%)
Rectosigmoid	171 (21%)
Colon	193 (25%)
Left-sided tumors	642 (80.2%)
Right-sided tumors	158 (19.8%)

Table 2 Tumor characteristics on pathology

	N = 800
Histological differentiation	
Well-differentiated	21 (2.6%)
Moderately differentiated	381 (47.6%)
Poorly differentiated	165 (20.6%)
Differentiation not reported	234 (29.2%)
Signet ring tumors	107 (13.4%)
Mucinous tumors	133 (16.6%)

Differentiation was not reported for 234 (29.2%) tumors. One hundred seven patients (13.4%) had a signet ring cell carcinoma reported, while 133 (16.6%) had mucinous carcinoma. Patients younger than 40 years of age had a higher proportion of signet ring positivity as compared to those above 40 years (22.9% vs. 8.3%, $p = 0.000$). Also, those with stage III or IV tumors had a higher proportion of signet ring positivity as compared with those with stage I/II tumors (15.1% vs. 6.7%, $p = 0.005$). Neither CEA (carcinoembryonic antigen) levels > 1000 ng/mL nor the site of the primary tumor (colon vs. rectum or left-sided vs. right-sided) was associated with more signet ring carcinomas.

The CEA level was available in 756 patients (mean 258.7 ng/mL, median 5.8 ng/mL, range 0.47–62,952 ng/mL) (Table 3). Two hundred forty-nine patients (33%) had CEA levels within the normal range (0–3 ng/mL). Seventy-three patients (9.7%) had CEA levels between 100.01 and 1000 ng/mL, and 27 (3.6%) had CEA levels above 1000 ng/mL. Higher baseline CEA level was associated with increased likelihood of stage IV disease. In patients with normal CEA, 14% had stage IV disease, as against 89% in those with CEA levels > 1000 ng/mL. The mean albumin was 3.8 g/dL, and the mean hemoglobin was 11.5 g/dL (range 4.4–17.3 g/dL).

Most patients (405, 50.7%) had stage III disease, while 230 patients (28.8%) had stage IV (metastatic) disease (Table 4). Early tumors were very rare (30 patients—3.8% had stage I disease). Most patients had oligometastatic disease. Fifty-one percent of the patients with metastatic disease had a single site of metastases, while 15% had three or more metastatic sites.

Table 3 CEA levels in patients with CRC

CEA levels (ng/mL)	*N* (range/frequency)
Mean CEA (range)	258.7 (0.47–62,952)
Median CEA	5.84
Normal CEA levels (0–3)	249 (32.9%)
CEA 3.01–10	218 (28.8%)
CEA 10.01–100	189 (25.0%)
CEA 100.01–1000	73 (9.7%)
CEA > 1000	27 (3.6%)

Table 4 Stage distribution and site of metastases

Stage	
I	30 (3.8%)
II	135 (16.7%)
III	405 (50.7%)
IV	230 (28.8%)
Site of metastasis	
Liver	115 (14.8%)
Liver only	38 (4.9%)
Lung	64 (8.2%)
Lung only	11 (1.4%)
Peritoneal	77 (9.9%)
Peritoneal only	35 (4.5%)
Ovarian[a]	15 (5.3%)
Ovarian only[a]	8 (2.8%)
Bone	11(1.4%)

[a] In women with CRC, *N* = 283

Liver metastases were seen in 115 patients (14.8%) of which 38 (4.9%) had metastases confined to the liver. Similarly, lung metastases were seen in 64 patients (8.2%) of which 11 (1.4%) had metastases confined to the lung. Peritoneal disease was present in 77 (9.9%) and was the solitary site of metastases in 35 (4.5%). Ovarian metastases were uncommon and were seen in 15 (5.3%) of women with CRC. Metastases limited to the ovary were seen in eight (2.8%) women. Bone metastases were rare and were present in 11 (1.4%) patients. Right-sided tumors had significantly higher peritoneal and ovarian metastases as compared to patients with left-sided primary tumors (Table 5). So also, patients with colonic primary had significantly higher peritoneal metastases as compared to those with rectal tumors (Table 6).

Fifteen patients (1.9%) had a significant family history and clinical features suggestive of a familial cancer syndrome (familial adenomatous polyposis—FAP or hereditary non-polyposis colon cancer—HNPCC).

The treatment plan at presentation was neoadjuvant chemoradiation in 196 patients (45% of all patients with rectal cancer, $n = 436$) who had locally advanced disease, palliative chemotherapy in 150 (18.8%), and surgery in 137 (17.1%). One hundred five patients (13%) presented to us having been operated at another hospital and were planned for adjuvant chemotherapy. Twenty-one patients (2.6%) were planned for best supportive care (BSC) only. Other patients were planned for observation or further investigations or neoadjuvant chemotherapy or palliative radiotherapy.

Table 5 Demographic and tumor profile in left- vs right-sided primary tumors

	Left-sided (splenic flexure and distal) $N = 642$	Right-sided (transverse colon and proximal) $N = 158$	p value
Age, mean (range)	46.5 yrs (15–85 yrs)	50.1 yrs (11–82 yrs)	0.006
Male gender	420 (65.4%)	97 (61.4%)	0.343
Mean CEA (ng/mL) (range)	296.1 (0.49–62,952)	106.7 (0.47–4806)	
Median CEA (ng/mL)	5.97	5.6	
Histology			
Signet ring	79 (12.3%)	28 (17.7%)	0.073
Mucinous	101 (15.7%)	32 (20.25%)	0.172
Stage IV disease	174 (27.1%)	56 (35.4%)	0.029
Site of metastasis			
Liver	91 (14.1%)	24 (15.1%)	0.252
Lung	56 (8.7%)	8 (5.0%)	0.011
Peritoneal	48 (7.5%)	29 (18.3%)	0.001
Ovarian[a]	8 (3.6%)	7 (11.5%)	0.015
Bone	10 (1.5%)	1 (<1%)	0.232

[a] In women with CRC

Table 6 Demographic and tumor profile in rectal vs colonic primary tumors

	Rectal tumors (up to 15 cm from the anal verge) $N = 436$	Colonic tumors (proximal to 15 cm from the anal verge) $N = 364$	p value
Age, mean (range)	45.7 yrs (17–85 yrs)	49.1 yrs (11–83 yrs)	0.001
Male gender	300 (68.8%)	217 (59.6%)	0.007
Mean CEA (ng/mL) (range)	388.1 (0.49–62,952)	105.4 (0.47–4806)	0.28
Median CEA (ng/mL)	5.3	6.3	
Histology			
Signet ring	63 (14.4%)	44 (12.1%)	0.328
Mucinous	70 (16.0%)	63 (17.3%)	0.636
Stage IV disease	94 (21.6%)	136 (37.4%)	0.000
Site of metastasis			
Liver	49 (11.2%)	66 (18.1%)	0.776
Lung	38 (8.7%)	26 (7.1%)	0.001
Peritoneal	16 (3.7%)	61 (16.8%)	0.000
Ovarian[a]	5 (3.7%)	10 (6.8%)	0.240
Bone	7 (1.6%)	4 (1.1%)	0.130

[a] In women with CRC

Discussion

Colorectal cancer is a common cancer worldwide with a majority of cases occurring in the developed countries. India has a low prevalence of CRC—estimated five-year prevalence is 87 per 100,000 population. Differences in dietary patterns and lifestyles are thought to be responsible for the low incidence of CRC in the developing world. Also, prevalence of obesity which is a risk factor for CRC differs in the developed and the developing world. Another possible reason for low incidence can be a younger population—CRC is more common in the elderly. It should be noted that the population registries in India cover only 7.45% of the population, while worldwide cancer registries cover 21% of the population; so, some amount of under reporting may be possible in India [5]. However, studies on Indian immigrants from countries with a high prevalence of CRC like the USA and Singapore show that CRC incidence is lower in Indians than in the native population but higher than that observed from the Indian registries [6, 7]. This shows although there are likely to be some genetic factors involved in the lower incidence of CRC, environmental factors also have a role to play.

In the United States, CRC incidence rates and disease-related death rates have declined over the last few decades in subjects above 50 years; however, the incidence rates have been increasing in the under age 50 group [8–10]. The decrease in the incidence rates has been primarily attributed to screening programs and detection and removal of adenomatous polyps. Most of these programs target the population above 50 years of age. Trends in most other Western countries have been variable. Incidence rates continue to increase in some low-resource countries of South America and Eastern Europe attributed to lifestyle factors like obesity, physical inactivity, smoking, and diet [1]. In India, some registries have shown decreasing trend/stable incidence while others have shown an increasing trend for rectal cancer [11, 12]. The six population-based registries have shown an increase in the rates of colon cancer [12]. This probably reflects changing lifestyles and urbanization leading to a change in the environmental risk factors. Also, there is no population-based screening program in India.

CRC incidence rates are higher for men in most regions of the world [1]. Sixty-five percent of our patients were male. However, there could be a referral bias here in terms of seeking treatment at a referral center. The mean age of patients in our study was 47.2 years. Thirty-five percent of the patients were below 40 years of age, and 80% were below 60 years. In a study from eastern India on 168 patients with sporadic CRC, the mean age of presentation was 47.01 years, while it was 58.4 years in a retrospective descriptive analysis of 220 cases of CRC diagnosed at colonoscopy over a five-year period [13, 14]. In another study from central India, on 233 patients over 8 years, the median age at diagnosis was 43 years with 39% of

CRC patients being diagnosed at the age of 40 or younger [15]. Other studies from India though on a small number of patients show similar results which elicits the question whether CRC occurs at a younger age in India [16, 17].

This is in contrast to Western data. In the USA, 90% of new CRC cases are above 50 years at diagnosis and 58% of all new CRC cases are above 65 years of age [10]. Similar numbers are reported from other high-incidence Western countries. Significant number of younger patients with CRC should be looked at critically. It may be a pointer to a biologically different type of disease or it could be a referral bias as younger patients are more likely to access healthcare as compared to older patients.

India has a large proportion of young population with a broad-based population pyramid. According to the data from the 2011 census, 29.5% of the population is in the age group 0–14, 62.5% of the proportion is in the age group 15–59 years, and the percentage of elderly population above 60 years is 8.0% [18]. The median age of India's population is around 25 years [19]. The average life expectancy at birth is approximately 68 years.

This is unlike Western countries which have a larger elderly population. Hence, the increased incidence of CRC in younger subjects could well be a bias due to a larger proportion of young population in India.

Studies from the US and Europe report an increasing incidence of right-sided colon cancer [20, 21]. This could be partly explained by the fact that screening sigmoidoscopies will mainly target precursor lesions in the left colon which are easily accessible. Poor preparations and incomplete evaluations during colonoscopy will also have a bigger impact on right-sided tumors. So also, fecal occult blood tests, both guaiac- and immunochemical-based, show better diagnostic performance for detecting CRC in the distal colon than in the proximal colon [22]. Thus, commonly used screening tests will be more effective in preventing left-sided than right-sided CRCs; however, there could also be a true increase in incidence of right-sided tumors with a different biology which could also contribute to a shift in distribution of CRC. In our study, most of the tumors were left-sided, the commonest primary site being rectum (41%) followed by recto-sigmoid (21%), anorectum (13%), and colon (25%). Eighteen percent had a primary tumor in the right colon. Similar findings have been reported from other single-center studies in India, especially amongst younger patients [15, 16, 23]. Left-sided tumors are more likely to present with overt bleeding per rectum and pain and therefore are more likely to become symptomatic earlier. It is uncertain whether increased proportion of left-sided tumors is a referral bias or whether rectal cancer is truly more common than colon cancer in India [24].

Most early-stage CRC are asymptomatic, and these may be diagnosed at the time of screening. Symptomatic patients can present with pain, bleeding, or obstructive symptoms, or rarely in an emergency setting with obstruction or perforation. Although screening for bowel cancer is recommended by most major societies in developed countries, the uptake rates are relatively low and most CRC would be diagnosed when symptomatic.

In our patients, the median duration of symptoms was 4 months and the commonest symptom was rectal bleeding (56.5%) followed by pain (44%) and altered bowel habits (25.6%). Most studies have reported similar common symptoms in patients with CRC [23, 25, 26].

Carcinoembryonic antigen (CEA) is a tumor marker commonly evaluated in CRC and used for prognostication, for post-treatment follow-up, and for monitoring the response of metastatic disease to systemic therapy [27]. However, it has a low diagnostic ability with a pooled sensitivity for diagnosis of CRC being 46% (95% CI 0.45–0.47) and specificity being 89% (95% CI 0.88–0.92) [28]. In our audit, 31% of the patients had CEA levels within the normal range (0–3 ng/mL). Higher baseline CEA level was associated with increased likelihood of stage IV disease especially those with CEA levels > 1000 ng/mL.

Thirteen percent of our patients had signet ring cell carcinomas which are typically associated with poorer prognosis. They were seen more frequently in younger patients (<40 years of age) or advanced stages (stage III/IV). Sixteen percent had mucinous carcinomas, and 25% of the patients had either signet ring or mucinous histology. Most Western studies report a prevalence of 5–15% for mucinous tumors and 1% for signet ring tumors [29, 30]. Higher prevalence of signet ring cell carcinomas could be due to more younger patients in our cohort, but it is interesting to note that even in patients older than 40 years, the prevalence of signet ring tumors was 8.3% which is still very high. This could point out to genetic predisposition or environmental influences that predispose to developement of signet ring tumors in Indian patients.

Approximately 20% of patients in the United States have distant metastatic disease at the time of presentation [31]. Twenty-nine percent of the patients in our study had metastatic disease. Studies from India show 10–20% prevalence of metastatic disease; however, the studies are limited by small numbers and restricted populations (young patients or rectal cancer). A higher number of advanced cancers at presentation could be attributed to the lack of population-based screening. Social and economic factors could also influence availability and timely access to healthcare. There is also the possibility of delayed diagnosis especially in younger patients where there is lesser suspicion of a malignancy and possibility of misdiagnosis as hemorrhoids/fissures.

Almost 90% of the patients were malnourished at presentation. Nutritional assessment is increasingly being recognized as an important addition to baseline assessment of all cancer patients but is frequently neglected. There are no studies evaluating the prevalence of malnutrition in patients with CRC

using validated malnutrition screening tools. Our study highlights the need for nutritional assessment to identify patients with malnutrition who can then receive adequate nutritional counseling and treatment.

Five to ten percent of CRC are thought to be hereditary. In our cohort, this group comprised less than 2%. However, the assessment of family history was done in the OPD by different clinicians with varying experiences. It is likely that the family history was not given enough importance and missed in some patients, and this underscores the need for educating the clinicians about the need for a detailed family history in all patients with CRC and the implications for patients and their families.

Our audit is the largest single-center audit of 800 consecutive patients with CRC from India, a country with a low prevalence of CRC. There is a possibility of referral bias which would be a limitation of our audit. We did not capture data related to dietary and other risk factors, and our survival data is being compiled.

This audit can help us to get an idea about the number of patients with CRC who are likely to be eligible for niche therapies like biological therapy for downstaging, lung or liver metastasectomy, hyperthermic intraperitoneal chemotherapy (HIPEC) with cytoreduction, and ovarian transposition. This can be used for strategic planning for development and budgetary allocation of resources in specialist centers. Approximately one-third of the patients at our center were younger than 40 years of age. Fertility and hormonal implications related to disease and its treatment especially in rectal cancers also need to be addressed in patients in the reproductive age group. In this population, single flexible sigmoidoscopy for screening appears to be an attractive option and can be evaluated for cost–benefit analysis. However, the large number of population to be screened may impact the economic viability of this option, and strengthening symptom-based pathways for diagnosis of CRC may be the only way forward for now in India. Training surgeons in operating locally advanced rectal cancer including major surgeries like exenteration should be made mandatory in advanced surgical oncology/surgical gastroenterology programs.

Conclusion

Though geographical variation in the incidence of CRC is known, our study also shows a wide variation in the demographic and histological features. These raise the possibility of CRC in India being a different disease as compared to the West (younger age, more signet ring tumors, more left-sided tumors, advanced stage at presentation, more malnourished patients). Younger population structure of India might contribute to the high number patients with a young age at presentation. The significantly higher number of signet ring tumors as compared to that described in the West needs to be investigated further. In light of the significant number of young patients presenting with CRC, clinicians should be trained to understand the importance of a detailed family history. Nutritional assessment and therapy should also be included in the management plan as most CRC patients are malnourished. Survival data is being compiled and will give us a better picture of the ground reality of CRC in India.

Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

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