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Influence of gross tumor morphology on clinicopathological profile of colorectal cancers

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ABSTRACT

Background: Clinical presentation of colorectal cancers (CRCs) also depends on the gross tumor morphology. This has also been found to be an important prognostic variable.
Objectives: The objective of this study was to evaluate the influence of gross tumor morphology on clinicopathological profile of CRCs in Kashmiri population.
Methods: This 5-year study is a prospective (2 yrs) and retrospective (3 yrs) study conducted from 2011 to 2016 in the Colorectal Surgery Division at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Kashmir, India. Parameters studied were age, sex, site of lesion, clinical presentations, gross tumor morphology, and histopathology of the lesion.
Results: A total of 930 patients with CRC were included. Infiltrative variety was the most common morphology in patients aged 15–25 years and patients older than 75 years (*P*-value <0.0001). Gross tumor morphology of CRC had no relation with the sex of the patient, patient demographics, dietary habit, and smoking history. There was statistically significant correlation between the gross tumor morphology and bleeding per rectum (P/R). The most common type of tumor leading to pallor was proliferative (51.7%). All the 20 patients with ulceroinfiltrative growth in our study had poorly differentiated histology, and a majority of patients (58.2%) with proliferative lesions had well-differentiated adenocarcinoma. Among 149 patients in our study with poorly differentiated histology, 76 (51%) had infiltrative lesion (*P*-value<0.0001).
Conclusion: Different morphological types of CRC vary with respect to clinical presentation. Microscopically, degree of differentiation also varies in different gross morphological types. We concluded that clinical presentation of CRCs also depends on the gross tumor morphology and, in turn, the gross tumor morphology is an important prognostic variable.

1. Introduction

The lifetime risk of colorectal cancers (CRCs) is about 6% in Western population, that is, 1 in 17 individuals of the general population will be affected by CRC, making it an important public health issue.[1] CRC is one of the major causes of patient sufferings in both developed and underdeveloped countries of the world. In addition, the cost of treatment of CRCs in terms of surgery and adjuvant and neoadjuvant therapies and for maintenance of stomas is very high for the patient and for the institutions. Globally, CRC is the 2nd most common cancer among women and the 3rd most common one among men.[2] The incidence of rectal cancer is higher in men, and that of colonic cancer is higher in women. In high-incidence countries, approximately 25% of CRCs are located in the rectum, 21% among women and 30% among men.[3] CRCs clinically present with bleeding per rectum, altered bowel habits, anemia, generalized weakness, obstruction, perforation, and peritonitis. The patients may present with a single symptom or group of these symptoms. However, occasionally, CRC can be diagnosed in asymptomatic patients on screening colonoscopy. About 15–30% of CRCs present as a surgical emergency such as obstruction (78%), perforation (10%), or bleeding (4%).[4,5] Besides other disease- and

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patient-related factors, the clinical presentation also depends on the gross tumor morphology of the CRCs. Early small cancers may be asymptomatic, while ulcerative growths usually present with bleeding per rectum and proliferative growths usually present with constipation and altered bowel habits. Therefore, by proper evaluation of the patient's history, one can predict the tumor morphology and indirectly the treatment response and prognosis. Although there is a close correlation between the stage of the colorectal cancer and its prognosis, it has been shown that the outcome of a patient with CRC depends not only on the anatomic extent of disease but also on other patient- and tumor-related factors such as gross tumor morphology.[6] Macroscopically, the tumor can display a number of forms such as polypoidal, infiltrative, ulcerative, or ulceroinfiltrative.[7] In addition to the degree of differentiation, gross tumor morphology has been found to be an important prognostic variable.[8] In addition, in a multivariate analysis conducted on the clinicopathologic factors, the gross appearance of the tumor was identified as an independent factor affecting recurrence (*P*-value = 0.020).[9]

2. Objectives

The purpose of this study was to evaluate the influence of gross tumor morphology on clinicopathological profile of CRCs in the Kashmiri population.

3. Materials and methods

This study is prospective and retrospective study conducted in the Colorectal Division of Department of General and Minimal Invasive Surgery of Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Kashmir, India. It is a study conducted for almost 5 years. Prospectively, all the patients presenting with CRC from August 2014 to June 2016 were included in the study. Retrospectively, the data of 3 years of all the patients with CRC were reviewed from the records obtained from the Department of Medical Records, SKIMS. All patients were evaluated with respect to detailed history and physical examination and were investigated to confirm the diagnosis and stage of disease. Study tools were study questionnaire, investigations (routine blood tests, carcinoembryonic antigen (CEA), colonoscopy, ultrasonography (USG), contrast-enhanced computed tomography, and magnetic resonance imaging], and histopathological reports. Intraoperative findings were recorded from operative notes. Parameters studied were age, sex, site of lesion, clinical presentations, gross tumor morphology, and histopathology of the lesion. To draw inferences, the collected data were analyzed statistically using the SPSS, version 20, software.

4. Results

A total of 930 patients were included in this prospective (2 years) and retrospective (3 years) study, carried out from 2011 to 2016. We included patients of all age groups, with a male-to-female ratio of 3:2. Of 930 patients, 558 (60%) were male and 372 (40%) were female. Overall, the most common gross morphological tumor type was proliferative type (n = 386; 41.5%), with a *P*-value of <0.0001, followed by infiltrative (n = 321; 34.5%), ulcerative (n = 203; 21.8%), and ulceroinfiltrative (n = 20; 2.2%). Regarding the relation of tumor morphology with the gender, there was no significant difference. The most common type in men was proliferative (n = 233; 41.7%), followed by infiltrative (n = 195; 34.9%), ulcerative (n = 120; 21.5%) and ulceroinfiltrative (n = 10; 1.8%). Similarly in women, the proliferative morphology was most common (n = 153; 41.1%), followed by infiltrative (n = 126; 33.9%), ulcerative (n = 83; 22.3%) and ulceroinfiltrative (n = 10; 2.7%). Statistically, there was no relation of gross tumor morphology of CRC with the sex of the patient.

Regarding the age distribution, CRC was most common in the age group of 56–65 years, accounting for 24.2% (n = 225) of patients, followed by the age group of 66–75 years (n = 186; 20%) and 46–55 years (n = 160; 17.2%). About 19.25% (n = 179) of patients were younger than 35 years while, only 6.76% (63) of patients presented after 75 years of age (Table 1). This study included 47 patients younger than 25 years, and all of them (100%) had infiltrative morphology. In addition, in the age group of 25–35 years, of 132 patients, 86 (65.1%) had proliferative, 36 (27.3%) had infiltrative, and 10 (7.6%) had ulceroinfiltrative lesions. Infiltrative variety was the most common morphology in patients in the age group of 15–25 years (100%) and patients older than 75 years (44.4%), whereas proliferative type was the most common one in the rest of the age groups. Overall, there was statistically significant (*P*-value <0.0001) relation between the gross tumor morphology and the age of the patient.

Most of our patients belonged to rural areas (n = 585; 63%) as compared with urban areas (n = 345; 37%). Regarding the patient demographics, there was no statistically significant difference in the type of tumor morphology between rural and urban patients. The most common morphology in both rural and urban patients was proliferative followed by infiltrative and ulcerative types.

Most (n = 894; 96%) patients were nonvegetarian. Again, the most common morphology in both nonvegetarian and vegetarian patients was proliferative followed by infiltrative and ulcerative types. Of 930 patients, 438 (47%) were smokers (*P*-value 0.552). There was no significant difference with respect to smoking history in the tumor morphology of patients with CRC. The most common gross tumor morphology in both smokers and nonsmokers was proliferative followed by infiltrative, ulcerative, and ulceroinfiltrative types.

Clinically, of 930 patients, 633 (68%) presented with bleeding per rectum (PR). Most of the patients with bleeding PR had infiltrative tumors (n = 220; 34.7%), closely followed by proliferative (n = 208; 32.8%) and ulcerative tumors (n = 185; 29.2%). All patients (n = 20; 100%) with ulceroinfiltrative lesions and 91.13% of patients with ulcerative tumors had bleeding PR, which was

Table 1
Morphological characteristics of colorectal carcinoma in different age groups.

Age group (yrs)	No. of cases (%)				Total no. of cases (%)
	Proliferative	Ulcerative	Infiltrative	Ulceroinfiltrative	
15–25	0 (0.00)	0 (0.00)	47 (100.00)	0 (0.00)	47 (5.05)
26–35	86 (65.15)	0 (0.00)	36 (27.27)	10 (7.58)	132 (14.20)
36–45	53 (45.30)	35 (29.91)	29 (24.79)	0 (0.00)	117 (12.59)
46–55	68 (42.5)	47 (29.38)	45 (28.13)	0 (0.00)	160 (17.20)
56–65	100 (44.44)	45 (20.00)	70 (31.12)	10 (4.44)	225 (24.20)
66–75	70 (37.63)	50 (26.88)	66 (35.48)	0 (0.00)	186 (20.00)
Above 75	9 (14.29)	26 (41.27)	28 (44.44)	0 (0.00)	63 (6.76)
Total	386 (41.51)	203 (21.82)	321 (34.52)	20 (2.15)	930 (100)
P-value	<0.0001	<0.0001	<0.0001	–	<0.0001

statistically significant (*P*-value = 0.017). Among patients with proliferative lesions, 53.8% presented with bleeding PR, and among those with infiltrative lesions, 68.5% had bleeding PR. Regarding the clinical presentation of various tumor morphologies, from these statistical data, we inferred that incidence of bleeding PR is most common in the ulceroinfiltrative (100%) type followed by ulcerative (91.13%), infiltrative (68.5%), and proliferative (53.8%) lesions. Therefore, there was a statistically significant correlation between the gross tumor morphology and bleeding PR.

Clinically, 485 (52%) patients had pallor and anemia. Overall, the most common type of tumor leading to pallor was proliferative (n = 251; 51.7%) followed by infiltrative (n = 125; 25.7), ulcerative (n = 89; 18.35%), and ulceroinfiltrative (n = 20; 4.1%) types. Pallor was seen in all patients (100%) with ulceroinfiltrative lesions. In addition, pallor was present in 65% of patients with proliferative lesions, in 43.8% of patients with ulcerative lesions, and in 38.9% of patients with infiltrative lesions.

The most common site of involvement by CRC was the rectum (n = 410; 44%), followed by the right colon (ascending colon and cecum) (n = 270; 29%), descending colon (n = 110; 12%), sigmoid colon (n = 93; 10%), and transverse colon (n = 47; 5%). The most common morphology of rectal carcinoma was ulcerative (n = 155; 37.8%) followed by infiltrative (n = 140; 33.7%) and proliferative (n = 97; 23.7%). However, the most common morphology of right-sided carcinoma (cecum and ascending colon) was proliferative (n = 221; 81.9%). The relation between gross tumor morphology and location of tumor in CRC is shown in Table 2.

Histologically, most of the patients (n = 925; 99.4%) had adenocarcinoma, while non-Hodgkin lymphoma was seen in 3 patients and small-cell carcinoma in 2 patients. Among 925 adenocarcinomas, 49.7% (n = 460) were well differentiated, 34.2% (n = 316) moderately differentiated, and 16.1% (n = 149) poorly differentiated. Degree of differentiation varied with the tumor morphology. All the 20 patients with ulceroinfiltrative growth in our study had poorly differentiated histology, whereas a majority of patients (n = 219; 58.2%) with proliferative lesions had well-differentiated adenocarcinoma. Among 149 patients with poorly differentiated histology, 76 (51%) had infiltrative lesion, 40 (26.8%) had ulcerative lesion, and 20 (13.4%) had ulceroinfiltrative lesion, whereas only 13 (8.7%) had proliferative tumor morphology. This difference is statistically significant (*P*-value<0.0001).

5. Discussion

CRC is one of the major causes of patient sufferings in both developed and underdeveloped countries in the world. In addition, the cost of treatment of CRCs in terms of surgery and adjuvant and neoadjuvant therapies and for maintenance of stomas is very high for the patient and for the institutions. Besides other disease- and patient-related factors, the clinical presentation also depends on the gross tumor morphology of the CRC. In addition to degree of differentiation, gross tumor morphology has been found to be an important prognostic variable.[8]

Keum et al.[9] who retrospectively studied 434 patients in their study suggested that the location of the tumor (*P*-value = 0.009), T stage (*P*-value = 0.010), and gross findings (*P*-value = 0.017) are significant in the univariate analysis of the clinicopathologic factors affecting recurrence. In addition, on multivariate analysis, gross finding of the tumor (*P*-value = 0.020) was identified as an independent factor affecting recurrence. They also showed that colon cancers have 1.4% incidence of recurrence, while it was 6.6% in rectal cancers. Gross morphologically fungating/ulcerofungating lesions had 3.9% recurrence, and ulceroinfiltrative/infiltrative lesions had 10.9% recurrence rate.[9] In addition, in our study, the ulceroinfiltrative/infiltrative lesions are more common in the rectum than in the colon and ulceroinfiltrative/infiltrative lesions are known to have poor prognosis and more recurrence than the proliferative or fungative lesions.

Park et al.[6] in their study to define the prognostic factors in Korean patients with CRC performed univariate and multivariate analyses on data from 2230 consecutive patients who underwent resection for colorectal cancer at the Seoul National University Hospital. They concluded that among the prognostic variables entered into the univariate analysis, Dukes' stage, extent of bowel wall invasion, lymph node metastasis and the number of involved lymph nodes, preoperative CEA level, histological grade, and gross morphology of the tumor strongly correlated with the long-term outcome of patients ($P = 0.001$). Location of the tumor, bowel obstruction, bleeding symptoms, age, and leukocyte count also showed significant correlation ($P < 0.05$). Sex, symptom duration, and tumor size did not show any statistically significant correlation with prognosis. On multivariate analysis for colon cancer, Dukes' stage, CEA level, gross morphology of the tumor, lymph node metastasis, and depth of bowel wall invasion showed significant difference.[6] Regarding the clinical presentation of various tumor morphologies of CRC, from our statistical data, we inferred that incidence of bleeding PR is most common in the ulceroinfiltrative (100%) variety, followed by ulcerative (91.13%), infiltrative (68.5%), and proliferative (53.8%) lesions.

The most common morphology of rectal carcinoma in our study was ulcerative (n = 155; 37.8%), followed by infiltrative (n = 140; 33.7%) and proliferative (n = 97; 23.7%), while the most common morphology of right-sided carcinoma (cecum and ascending colon) was proliferative (n = 221; 81.9%). Nawa et al.[10] also showed that polypoid-type early cancer was dominant in the left colon (left 59%; right 40%) ($P < 0.01$), while the proportion of flat-type early cancer in the right colon was significantly higher than that in the left colon (left 25%; right 44%) (*P-value* <0.01).

This study included 47 patients younger than 25 years, and all of them (100%) had infiltrative morphology. Therefore, the infiltrative variety was the most common morphology in patients in the age group of 15–25 years (100%) and in patients older than 75 years (44.4%), while the proliferative type was most common one in the rest of the age groups. Ghazi et al.[11] also showed that young patients with CRC more often had perineural invasion, an infiltrative

Table 2
Distribution of tumors with different morphology as per site of lesion.

Location of tumor	Total no. of cases (%)	No. of cases (%)				*P*-value
		Proliferative	Ulcerative	Infiltrative	Ulceroinfiltrative	
Rectum	410 (44.1)	97 (23.7)	155 (37.8)	138 (33.7)	20 (4.9)	<0.0001
Sigmoid	93 (10.0)	37 (39.8)	28 (30.1)	28 (30.1)	0 (0.0)	0.363
Descending colon	110 (11.8)	18 (16.4)	20 (18.2)	72 (65.5)	0 (0.0)	<0.0001
Transverse colon	47 (5.1)	13 (27.7)	0 (0.0)	34 (72.3)	0 (0.0)	<0.0001
Ascending colon/cecum	270 (29.0)	221 (81.9)	0 (0.0)	49 (18.1)	0 (0.0)	<0.0001
Total	930 (100)	386 (41.5)	203 (21.8)	321 (34.5)	20 (2.2)	–

tumor margin, and high-stage tumors.

Histologically, most of our patients (99.4%) had adenocarcinoma. All the 20 young patients with ulceroinfiltrative growth in our study had poorly differentiated histology. In a study by Stewart et al.,[12] of 522,630 patients, about 96% of CRCs were adenocarcinomas. They also found that with respect to age, higher percentages of mucin-producing adenocarcinomas, signet ring cell tumors, and carcinoid tumors were found in individuals younger than 40 years.

A study by Mogoanta et al.[13] showed higher incidence of cancer of the rectum (119 cases, representing 37.53%) than that of individual segments of the colon. Regarding the degree of cell differentiation, of the total 245 adenocarcinomas, 87 (35.52%) were well-differentiated adenocarcinomas, 127 (51.83%) were moderately differentiated, and 31 (12.65%) were poorly differentiated. However, in our study, of 925 adenocarcinomas, 49.7% (n = 460) were well differentiated, 34.2% (n = 316) moderately differentiated, and 16.1% (n = 149) poorly differentiated.

6. Conclusion

The most common gross morphological tumor type of CRC was proliferative type. The different morphological types of CRC vary with respect to clinical presentation such as age at presentation, bleeding PR, and anemia. Incidence of different gross tumor morphological types also varies with respect to the site of tumor. Microscopically, the degree of differentiation of CRC also varies in different gross morphological types. This variability in tumor differentiation in turn has an influence in the prognosis of CRC. Thus, from this study, we concluded that clinical presentation of CRCs also depends on the gross tumor morphology and, in turn, the gross tumor morphology is an important prognostic variable.

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Conflict of interest

No conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmrp.2019.09.007.

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