

Clinical-Pathological Characteristics of Colorectal Carcinoma and Factors Influence 2-Years Survival among Patients Attending Ocean Road Cancer Institute Dar es Salaam Tanzania

Nebert Lulabuka^{1*} , Nazima Dharsee², Crispin Kahesa², Oscar Kivike³

¹Department of Clinical Oncology, Muhimbili University of Health and Allied Science, Dar es Salaam, Tanzania

²Ocean Road Cancer Institute, Dar es Salaam, Tanzania

³Department of Surgery, College of Health Sciences, The University of Dodoma, Dodoma, Tanzania

Email: *lulabuka34@gmail.com, njdharsee@gmail.com, crispinkahesa@yahoo.co.uk, oscarkivike@yahoo.com

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Abstract

Background: Colorectal carcinoma usually arises from an adenomatous polyp and observational studies suggest that the adenoma-to-carcinoma sequence takes approximately 10 to 15 years. Risk factors are adoption of westernized diets, obesity, cigarette smoking, and alcohol and reduced physical activity. Clinical Presentations are blood per rectum, abdominal pain, Anemia, change in bowel habits and bowel obstructive symptoms. The treatment of colorectal cancer is a dependent stage which includes chemotherapy, radiotherapy, surgery or both. **Objective:** This study aims at describing the clinical pathological characteristics of colorectal carcinoma and factors influencing survival among patients treated at Ocean Road Cancer Institute. **Methods:** This was a cross sectional study that involved histological confirmed colorectal carcinoma treated at Ocean Road Cancer Institute from 2010-2015. **Results:** Among 100 files extracted, 63% were males and 37% females. 21% were below 40 years of age. Left-sided tumor accounted for 46%. Abdominal pain, rectal bleeding and constipation were 72%, 68% and 55% respectively. Moderately differentiated adenocarcinoma accounted for 80%. Patients presented at stage III and IV were 37% and 56% respectively. Colostomy was the most surgical procedures performed. Folinic acid, Fluorouracil and Oxaliplatin were the most common chemotherapies used. Median overall survival was estimated to be 9.4 months. **Conclusion:** A significant proportion of patients in this study population are young. Survival from colorectal cancer is poor owing largely to the late presentation seen in this study group.

Keywords

Colorectal Cancer Tanzania, Ocean Road Cancer Institute

1. Introduction

Colorectal cancer is one of the most common cancers worldwide and its incidence is reported to be increasing in resource-limited countries, probably due to the acquisition of western lifestyle [1].

The prevalence of colorectal cancer is estimated to be 1.23 million (9.7%). There was a 1.5% decrease in incidences levels of rectal cancer and 2% increase for colon cancer every year from 2005 to 2015 [2]. Although estimates seem to suggest that the incidence is low, there is significant under-diagnosis and under-reporting.

Colorectal carcinoma usually arises from an adenomatous polyp and observational studies suggest that the adenoma-to-carcinoma sequence takes approximately 10 to 15 years. Early detection of precancerous lesions will have a major impact on colorectal cancer incidence in the population [3].

There are significant differences in the pathology of colorectal cancers according to its location within colon and rectum and therefore it is of interest to correlate symptoms of patient with tumor histology, location and TNM staging.

The risk factors of colorectal cancer are often related to adoption of westernized diets, obesity, and reduced physical activity [4].

Dietary factors account for between 30% and 50% [5]. Diet variably acts as a pro- and antitumor risk modifier across the colorectal cancer tumorigenesis process.

In Tanzania, the nutrition transitions in recent years have contributed to low fiber, high sugar, and saturated fat-laden diets often related to processed and packaged foods. The exponential growth in availability of inexpensive calorie-laden foods has led to gradients in energy intake between rural and urban populations [6].

Studies with diverse populations showed that physically active individuals are at a lower risk for colorectal cancer, an effect that was independent of other risk factors (*i.e.* diet and body weight) [7].

Cigarette smoke contains over 60 known carcinogens and free radicals, which could affect the colorectal mucosa, thereby potentiating the alteration of cancer-related genes [8].

An association between alcohol consumption and colorectal cancer was reported in more than 50 prospective and case-control studies, with no difference in the risk for colon and rectal cancers [9].

The most frequent symptoms and findings that prompted diagnostic colonoscopy in a series of 388 consecutive patients diagnosed with colorectal cancer between 2011 and 2014 included Blood per rectum 37%, Abdominal pain 34%,

Anemia 23%.

Six patients (1.9%) had incidental colonic hyper-metabolic activity detected by PET/CT. Only four individuals (1.3%) underwent diagnostic colonoscopy because of change in bowel habits (diarrhea). Obstructive symptoms are more common with cancers that encircle the bowel the so-called “apple-core” description seen on radiologic imaging [10]. Rectal cancer can cause tenesmus, rectal pain, and diminished caliber of stool [11].

At Ocean Road Cancer Institute the treatment of colon cancer is adjuvant chemotherapy consisting of 5-FLUOROURACIL + LEUCOVORIN. Alternatively the Capecitabine can be used.

For stage IV metastatic or recurrent cancer Folinic acid, Fluorouracil and Oxaliplatin 4, and Capecitabine and Oxaliplatin are used for rectal cancer the treatment is Neoadjuvant-Chemoradiation consist of 5-FLUOROURACIL + LEUCOVORIN + Radiotherapy (45 Gy) followed by Adjuvant chemotherapy.

1.1. Problem Statement

Colorectal ranks fourth amongst all types of cancers in East, Central South and West Africa. Also it's commonly seen at Ocean Road Cancer Institute according to the data (2006-2014) [12]. Until now the colorectal cancer survival has not been well studied in our setting, and association of clinical presentation with pathological characteristics as well as prognostic factors is not well documented.

1.2. Broad Objective

To describe clinical pathological characteristics of colorectal cancer and factors influence survival among patients treated at Ocean Road Cancer Institute Dar es Salaam Tanzania.

1.3. Specific Objectives

- 1) To describe social demographic characteristics of patients presenting with colorectal cancer at Ocean Road Cancer Institute Dar es Salaam Tanzania.
- 2) To describe clinical-pathological characteristics of patient with colorectal cancer seen at Ocean Road Cancer Institute Dar es Salaam Tanzania.
- 3) To describe treatment protocols received by colorectal cancer patients seen at Ocean Road Cancer Institute Dar es Salaam Tanzania.
- 4) To determine 2 years overall survival of colorectal cancer patients seen at Ocean Road Cancer Institute Dar es Salaam Tanzania.
- 5) To determine relationship between histopathological characteristics and treatment outcome of colorectal cancer patients seen at Ocean Road Cancer Institute Dar es Salaam Tanzania.

1.4. Rationale of the Study

This study aim was to evaluate association of clinical presentation with histological characteristics and treatment outcome of colorectal cancer patients treated

at Ocean Road Cancer Institute. The study will help to evaluate colorectal cancer management program and address survival of patient with colorectal cancer.

2. Methodology

2.1. Study Design

This is a cross-sectional study based on secondary hospital data from 2010-2015 with 2 years follow-up.

2.2. Study Site

The study site is Ocean Road Cancer Institute located at Dar es Salaam Tanzania. Ocean Road Cancer Institute is the only specialized facility for cancer treatment in Tanzania. The facility was established in 1895 by the German colonial government. In 1996, it was made an independent autonomous institute by an Act of Parliament. It offers patient services including laboratory services, chemotherapy, radiotherapy, palliative care and cervical cancer screening.

2.3. Study Sample

All files of patients who presented to Ocean Road Cancer Institute from 2010 to 2015 with histologically confirmed colorectal cancer was taken to constitute the sample.

3. Study Variables

3.1. Independent Variables

Social demographic characteristics and clinical presentation Right-sided, left-sided tumor TNM staging, histopathology, and treatment protocols.

3.2. Dependent Variables

Treatment outcome, HIV status and Performance status before treatment.

3.3. Inclusion Criteria

All patients with the histologically confirmed colon, recto-sigmoid junction and rectal cancer.

3.4. Exclusion Criteria

Tumors of the appendix and anal canal, carcinoid tumors, Kaposi sarcoma, lymphomas and gastrointestinal stromal tumors.

All patients with missing variables of interest.

4. Data Collection

Researcher assistants under the supervision of Principal investigator used data extraction forms to retrieve data from patient's records stored in patients' medical files and/or files available on the electronic medical records.

Data extraction forms were used to collect patient's demographic data, clinical symptoms at presentation, disease stage, treatment given and laboratory and imaging report.

4.1. Data Analysis

All data was anonymized and analyzed using SPSS Version 23.

Data were summarized in the form of proportions and frequency tables for categorical variables. Continuous variables were summarized using mean, median mode and standard deviation. Chi-square test was used to test for significance associations between the predictor and outcome variables in the categorical variables.

4.2. Ethical Consideration

Ethical clearance was obtained from the Muhimbili University of Health and Allied Services Institutional Review Board and from Ocean Road Cancer Institute (ORCI) to use data from patient's records. Waiver of informed consent was obtained from the ethical committee due to the fact that the records of patients that were analyzed are available in the hospital records.

5. Results

5.1. Study Population and Demographic Data

During the study period, a total of 122 files were extracted. Of these, 22 files were excluded due to the missing information. **Table 1** shows the mean age was 49.79 years with standard deviation 16.589 years. Males were 63 (63%) and the number of females was 37 (37%) with males to female ratio 1.7:1. Majority of patients (61.0%) came from the coastal region.

Table 1. Social demographic data of the study population.

Variable	n (%)
Gender	
Male	63 (63.0)
Female	37 (37.0)
Mean (SD)	49.8 (16.5)
Age	
Less than 20 yrs	4 (4.0)
21 - 30	8 (8.0)
31 - 40	21 (21.0)
41 - 50	18 (18.0)
Above 50	49 (49.0)
Residence	
I	61 (61.0)
II	16 (16.0)
III	13 (13.0)
IV	10 (10.0)

Key: I: Coastal zone; II: Northern Highland zone; III: Lake and central zone; IV: Southern zone: the table summaries the social demographic data of patients with colorectal carcinoma seen at ORCI.

5.2. Anatomical Site, Gender and Stage

Forty-one (41.0%) patients presented with rectal carcinoma and thirty-six (36.0%) patients diagnosed with colon carcinoma as shown in **Table 2**. There were twenty (20.0%) patients diagnosed with recto-sigmoid carcinoma.

Table 3 shows that age at diagnosis was not determined the location of tumor. Males and females were both affected equally. And both patient with colon and rectal carcinoma presented at late stage (stage IV). No patients were seen during the study presented at stage I.

5.3. Clinical Presentations and Frequency of Occurrence

In this study, 72% of patients with CRC presented with abdominal pain, 68% presented with rectal bleeding and 55% presented with constipation. Other symptoms were infrequently seen (**Figure 1**).

5.4. Histological Patterns

Microscopically, adenocarcinoma was the most common histological tumor (80.0%) patients. (16.0%) presented with mucinous adenocarcinoma. Squamous

Table 2. Site distribution of CRC patients.

Site	Number (n)	Percent %	Standard deviation (SD)
Colon	36	36.0	0.482
Caecum	3	3.0	0.141
Recto-sigmoid	20	20.0	0.394
Rectal	41	41.0	0.494

The table summarizes the distribution of CRC among different anatomical sites. Most patients presented with colon and rectal cancers.

Table 3. Number of patients according to tumor location, gender and stages.

Age groups	Colon	Rectal
<20	0	1
21 - 30	3	3
31 - 40	7	10
41 - 50	6	6
Above 50	20	21
Gender		
Male	24	27
Female	12	14
Stages (TNM)		
I	0 (0.0%)	0 (0.0%)
II	2 (5.6%)	2 (4.8%)
III	12 (33.3%)	14 (33.3%)
IV	22 (61.1%)	26 (61.9%)

The table summarizes the number of patients diagnosed with CRC based on the age groups, gender and stage at diagnosis.

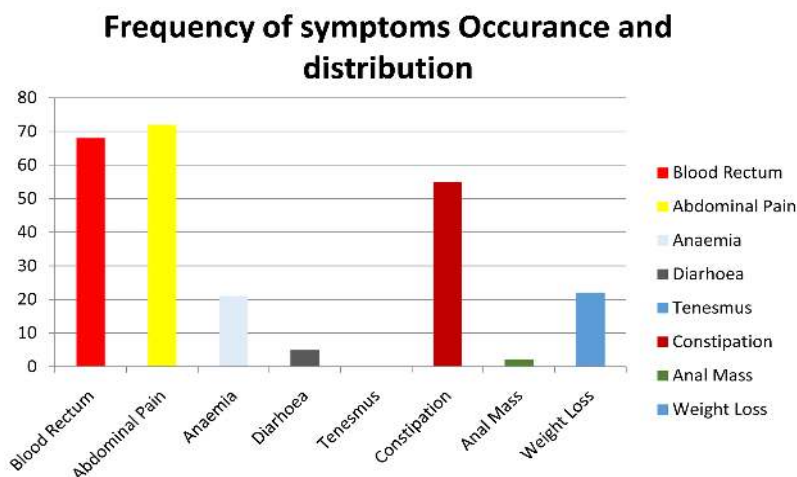


Figure 1. Distribution of patients according to clinical presentation. Abdominal pain, rectal bleeding and constipation were commonly presenting symptoms observed accounting for 72%, 68% and 55% respectively.

cell carcinoma was rarely seen in study (**Figure 2**).

The majority of the adenocarcinomas were moderately differentiated 42.0%, 37.0% were well differentiated and 21.0% were poorly differentiated carcinoma (**Figure 3**).

According to TNM staging, most patients in this study presented at stage IV (56%). Only 36% presented with stage III (**Figure 4**).

5.5. Treatment Modalities/Regimes

Out of 100 patients involved in this study, 43 (43.0%) received FOLFOX4 for the treatment of colorectal carcinoma. Patients with diagnosed with rectal carcinoma were treated with RT alone as per ORCI protocols. Others were given alternative chemotherapy based on the availability.

No patients received target therapy.

Table 4 summarized the treatment received by patient with CRC treated at ORCI. Most patients received FOLFOX4.

5.6. Response to Treatment

Most patients with rectal cancer had no response to treatment compared to colon cancer patients but the association was not statistically significant (**Table 5**).

5.7. Survival

The patients were followed up for 2-years to assess survival of the patients with colorectal cancer, survival tends to decrease, and median overall survival was estimated to be 9.4 months (**Figure 5**).

Median survival time was estimated to be 9.4 months.

5.8. Survival Rectal and Colon Carcinoma

Survival of the patients diagnosed with colon and rectal carcinoma was performed

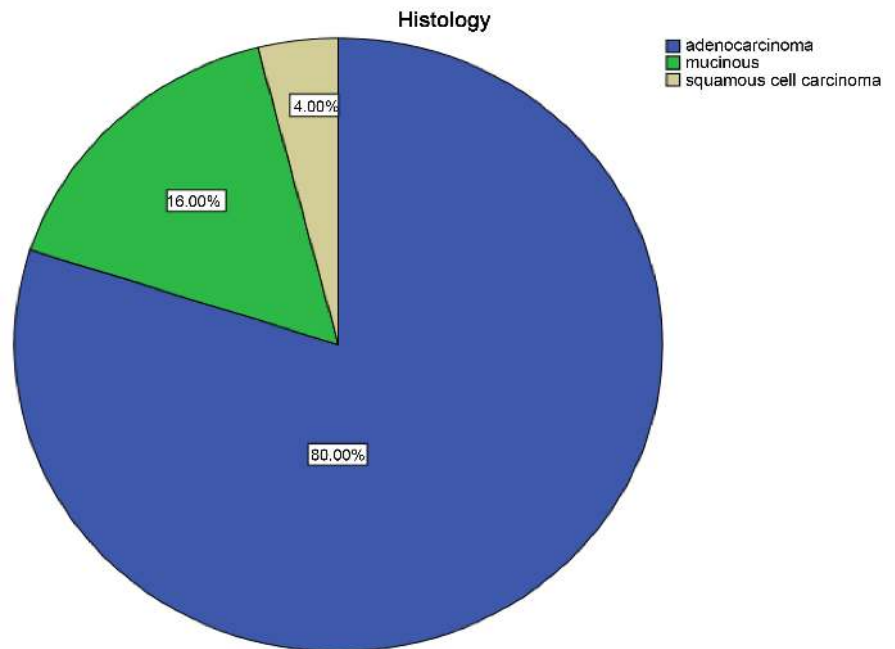


Figure 2. Represent histological pattern of colorectal carcinoma. Microscopically, adenocarcinoma was the most common histological pattern in 80% of patients. Followed by mucinous type seen in 16% of patients with colorectal carcinoma.

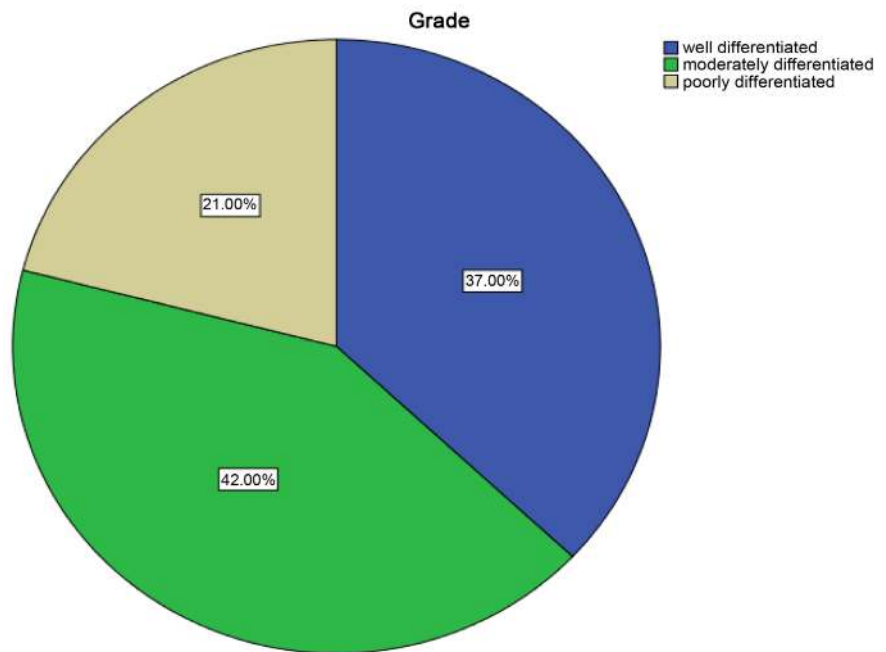


Figure 3. Degree of tumor differentiation (tumor grade) among patients with CRC. The majority of tumors were moderately differentiated which accounts for 42%; well-differentiated tumor was 37%, while poorly differentiated was 21%.

separately (**Figure 6**). Colon cancer patients had slight improved survival compared to rectal cancer patients but were not statistically significant ($P = 0.122$).

According to the figure there was a trend of increased OS of patients with

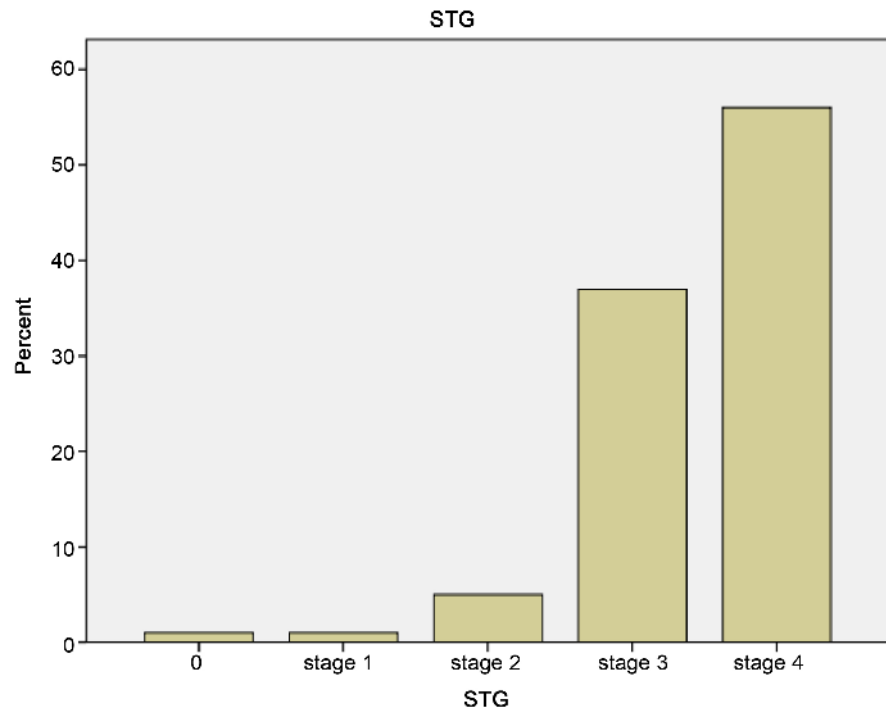


Figure 4. Tumor stage distribution.

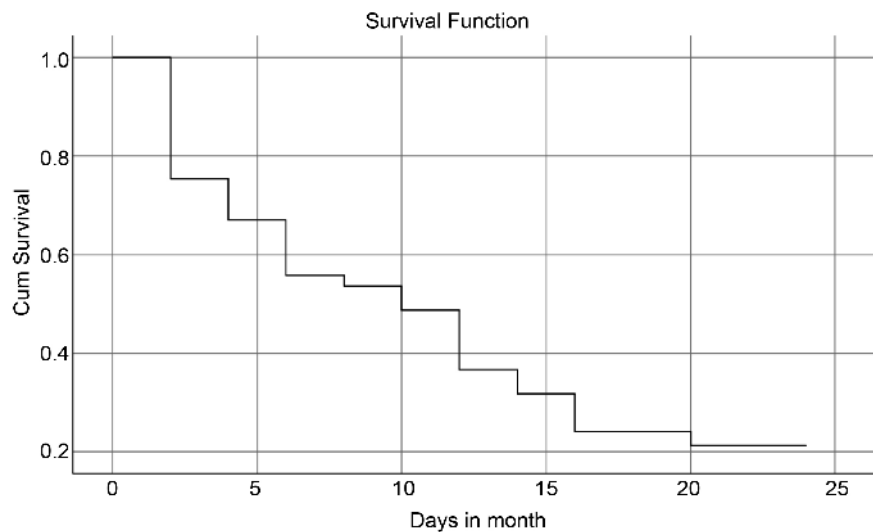


Figure 5. Overall survival of colorectal cancer patients seen at ORCI.

colon cancer compared to rectal cancer but the association was not statistically significant by log rank test.

5.9. Predictors of Survival

Analysis of factors associated with overall survival (OS) in colorectal carcinoma was analyzed (**Table 6**). The group stage (TNM) was statistically significant predictor of survival in colorectal carcinoma ($P = 0.003$). Other factors were not statistically significant.

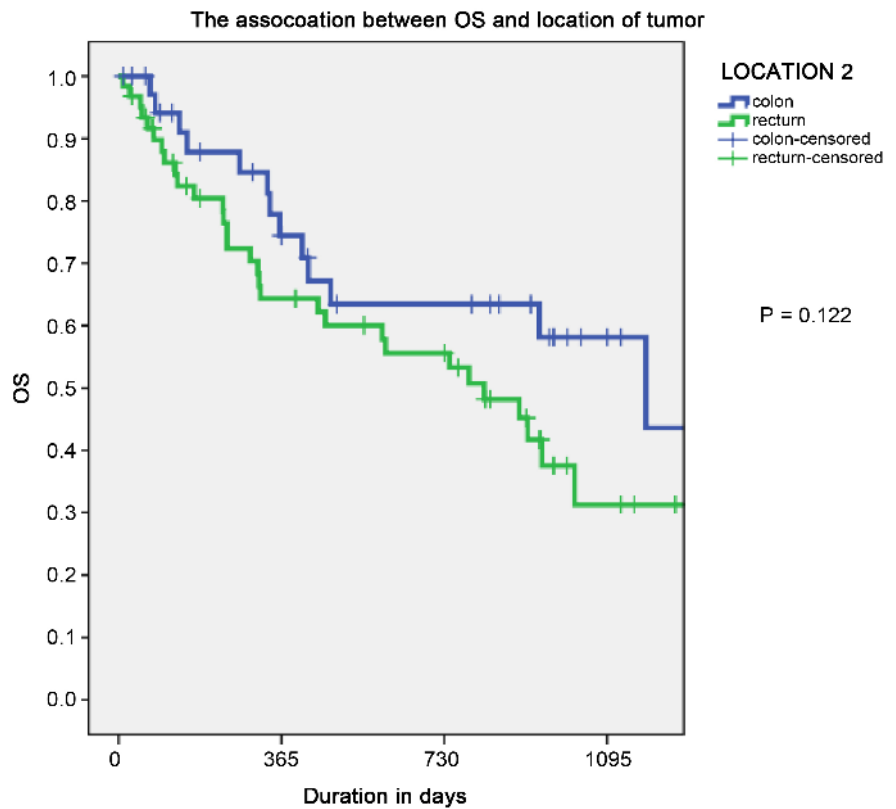


Figure 6. Overall survival of colon and rectal cancer patients.

Table 4. Treatment regimen received by patients with CRC treated at ORCI.

Type of treatment	No. of patients	Percentage (%)
Chemotherapy		
FOLFOX4	43	43.0
CAPOX	09	9.0
XELOX	1	1.0
OTHER	12	12.0
RT (Rectal alone)	35	35.0

KEY: FOLFOX4; Oxaliplatin, Leucovorin, 5-FU. CAPOX; Capecitabine, Oxaliplatin. XELOX; Oxaliplatin, Capecitabine. RT; Radiotherapy.

Table 5. Association between tumor location and treatment response.

		Location of the tumor	
		Colon	Rectum
Treatment response	CR	8 (21.1%)	12 (19.2%)
	PR	17 (44.7%)	15 (27.3%)
	No response	13 (34.2%)	35 (56.5%)
		38 (100%)	62 (100%)

Fisher's exact test 0.62. According to the table most patients with rectal cancer had no response treatment compared to colon cancer but the association was not statistically significant.

Table 6. The predictors of survival in study population.

Variables	N (%)	P-value
Age		
Below 20	4 (4.0)	0.341
21 - 30	8 (8.0)	
31 - 40	21 (21.0)	
41 - 50	18 (18.0)	
Above 50	49 (49.0)	
Histology		
Adenocarcinoma	80 (80.0)	0.942
Mucinous	16 (16.0)	
SCC	4 (4.0)	
Residence		
Coastal zone	61 (61.0)	0.574
Northern highlands	16 (16.0)	
Lake & central	13 (13.0)	
Southern zone	10 (10.0)	
Group Stage (TNM)		
I	1 (1.0)	0.003
II	5 (5.0)	
III	37 (37.0)	
IV	56 (56.0)	
Grade		
I	36 (36.0)	0.112
II	43 (43.0)	
III	21 (21.0)	
Anatomical location		
Left	46 (46.0)	0.249
Right	21 (21.0)	
Rectal	33 (33.0)	

In multiple cox regression analysis only group stage was found to be significant predictor of colorectal cancer survival with P-value of 0.003.

6. Discussion

Early age onset of colorectal carcinoma was also seen in some studies [3] and the median age of onset of colorectal carcinoma was found to be 49.50 years which is three years older compared to other studies which reported median age of 46 years. In this study 21% were between age group 31 - 40, the figure that is alarming. Colorectal cancer shows increase trend towards young age population, that necessitate the importance of cancer screening program and this report should be considered in future studies to evaluate predisposing and genetics factors.

Furthermore, other studies reporting age standardize incidence of 1.9 per

100,000 in males and 1.4 per 100,000 in females [13] which is consistent to our finding which shows male predominance. Male gender have poor prognosis compared to female during analysis of this study with $P = 0.032$, and also males gender presented with distant metastasis $P = 0.031$.

The majority of patients diagnosed with CRC are males, In general, a four-to ten-year age difference by gender has been reported, with female incidence higher in the age range of 70 - 74 and male incidence higher in the age range of 60 - 64 [2].

Majority of patients in this study came from urban areas whereby coastal zone contributed to 60%, this is different from other studies done in developing countries in which majority came from rural areas [14] [15].

The most common presenting symptoms in this study were abdominal pain. Other studies reported rectal bleeding to be the most common symptoms in these patients that prompt to seek medical advice. This may explain late presentation of CRC because these patients may be treated as other medical condition before diagnosis made.

From the study 46% of cancer occurred on the left sided while 22% were right sided tumor and 33% presented as rectal tumors. This was also reported in PROVETTA study, whereby during population study left-sided tumor was reported in 72.0% of patients [16].

Histopathologically, adenocarcinoma was the most common presentation accounting for 80.0%. Similar findings were also reported in study by Chalya *et al.* [1].

In terms of differentiation category or tumor grade moderately differentiation (GRADE II) was reported in this study, this is contrary to WHO classification of tumor 2010 which shows 95% are well-differentiated tumors [17].

Majority of patients presented at late stage, this was also seen in some studies conducted in Africa, most of the reasons given out are lack of screening program and lack of awareness [1].

Overall survival was assessed using Kaplan-Meier and the results showed median survival was 9.4 months. This was much lower compared with other studies conducted in developed countries, which shows trends towards survival improvement in CRC patients [18].

Group stage was statistically significant factor for survival ($P = 0.003$). Study by Eetu Heerva *et al.* reported increase survival of colorectal carcinoma patients as compared with patients diagnosed in mid 90s. Potential factors contributing to the improvement were introduction of multidisciplinary meetings, centralization of rectal cancer surgery, and use of adjuvant chemotherapy and systemic preoperative radiotherapy of rectal cancer. In this study left-sided primary tumors had longer OS, specifically stage III disease the median OS was 7.6 years compared to 3.5 years for patient with right-sided tumor [18].

In Africa most studies reported three-year overall survival was 40%, in contrast to better rates at even longer follow-up, 65% for whites and 55% for Africa Americans at five years [19].

7. Conclusions

- The results of this study showed that colorectal carcinoma tends to occur at the age below 40 years and had low median survival of less than 1 year.
- Late stage presentation was also observed in this study; many patients diagnosed with CRC at stage III and IV.
- The stage of disease was the main predictor of survivorship.
- From the study the common presenting symptoms were abdominal pain, rectal bleeding and constipation.
- Radiotherapy seems to improve survival in colorectal cancer patient but in our study only 35% received radiotherapy; most patients received palliative dose due to resource-limited country.

Recommendations

- Patients with colorectal cancer should have intensive follow-up care, if a complete colonoscopy was not possible prior to surgical resection, colonoscopy should be offered within 3 - 6 months to detect synchronous lesions.
- We have identified common presenting symptoms which are key for developing tool of high index of suspicious which can be used for educating lower cadre of health professional as well as to refer early the cases.

Limitations of Study

- The retrospective study design is a basic limit of the present study.
- Preoperative imaging was not performed to all patients and most patients lost to follow-up.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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