



## Clinical and Pathological Presentation of Colorectal Cancer Among Young Sudanese Adults in Khartoum State Hospitals (2019-2021)

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### Abstract

**Background:** 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 a western lifestyle.

**Objectives:** The study aimed to identify the clinical and pathological presentation of colorectal cancer among Sudanese adults aged 50 years and below versus those above 50 years of age.

**Methods:** A prospective and retrospective comparative study of histological confirmed cases of colorectal cancer. Retrospective from June/2019 to Nov/2020 and prospective from Dec/2020-Dec/2021. The study was multicenter conducted within the main three colorectal services units in Khartoum state; Ibrahim Malik teaching hospital, Ibn Sina hospital and Soba university hospital. Data had been collected by the researcher using administered questionnaire which included all the variables. Either by direct interview or through phone call with the colorectal cancer confirmed patients. Consents were obtained from all patients included in the study. It was cross-sectional collection and age independent. Prospective follow up has been conducted for the new cases that presented during 2020-2021. The cases presented during 2019 had been contacted by the researcher and their data and history of presentation were documented retrospectively. The total numbers of cases were 120 cases. They had been divided into two groups, group A (50 years and below) and group B (>50 years).

**Results:** A total of 120 colorectal cancer patients were enrolled in the study. The mean age of patients at presentation was 51.2 years with standard deviation of 15. (50.8%) 61 cases were belong to age group B (>50 years) and (49.2%) 59 cases were belong to group A (50 and below). Male: female ratio in group A was (1.5:1) and in group B was (1.3:1). A significant number 65 (54.3%) presented with rectal cancer, 35 (60%) of younger adult and 30 (54.2%) of elderly. CRC was most frequently misdiagnosed with dysentery which counted about 25 (42.4%) cases among younger and 17 (27.9%) among elderly. The most dominating presenting symptom among young adults were bleeding per rectum which counted 48 (81.4%), while weight loss was the most common presenting symptom in elderly with a percentage of 48 (78.8%).

The adenocarcinoma was the most common histopathological type 115 (95.8%). Both groups at presentation had advanced radiological stage III B (29.5%) 13, (32.6%) 14 in A and B respectively. The commonest Postoperative histopathological TNM stage in group A was IIA (15 cases, 34.9%). In group B Stage III B and IIA (26.5%, 13 cases) were dominating. One hundred and six (88.3%) patients underwent surgical procedures for colorectal cancer, (84%) 89 was curative, (4.7%) 5 intention curative and (11.3%) 12 palliative. Postoperative complications and morbidity rates were 64.6% and 58.2% for group A and B respectively. One hundred and five out of 120 are alive (96.6%) and available for follow-up at the end of 2 years. Cancer recurrence was reported in 3 cases from group B (2.9%) and metachronous tumor also was detected in two cases from group B.

**Conclusion:** In this study we identified that young Sudanese adult has different remarkable presentations. They presented mainly with lower GIT symptoms. Rectal followed by left side CRC was the most common site among young adults, in contrast to older where rectal followed by RT side were dominating. Molecular genetic studies are increasing the understanding of the pathobiology of colorectal cancer and may ultimately allow at-risk patients to be identified at an earlier stage.

**Keywords:** Colorectal Cancer; Colonic Cancer; Rectal Cancer; Early-Onset Colorectal Cancer; Lower GIT Symptoms

## Abbreviation

AJCC: American Joint Committee on Cancer; CCa: Colon Cancer; CEA: Carcino Embryonic Antigen; CRC: ColoRectal Cancer; CT: Computed Tomography; ER: Endoscopic Resection; GIT: Gastro Intestinal Tract; HNPCC: Hereditary Nonpolyposis Colorectal Cancer; M/F: Male/Female; MDT: Multi-Disciplinary Team; PCQ: Patient Consultation Questionnaire; PET: Positron Emission Tomography; SEER: Surveillance Epidemiology and End Results; SLE: Systemic Lupus Erythematosus; SMSB: Sudan Medical Specialization Board; SPSS: Statistical Package for Social Sciences; UK: United Kingdom; USPSTF: United States Preventive Services Task Force

## Introduction

As the third most common malignancy and the second most deadly cancer, colorectal cancer (CRC) estimated 1.9 million cases per year and 0.9 million deaths worldwide in 2020. The global new CRC cases is predicted to reach 3.2 million in 2040 [1].

Of interest, while we have witnessed a declining incidence trend over the past few decades in the older population, young-onset CRC has been increasing steadily [2]. According to recent statistic has been done in US, the incidence rate increased by approximately 2% annually among those aged less than 50 [3]. Furthermore, an over view of 8695 articles with applying of their inclusion criteria, they identified 40 studies from 12 countries across five continents. The systematic review highlights increasing young onset-CRC risk in North America and Australia driven by rising rectal cancers in younger adults over the past two decades [4].

In Africa a prospective analysis in South Africa including demographics, clinical presentation, site, staging and grading over 2232 during 18-year period with a different races [5]. The proportion of young patients (< 40 years old) was 28%, 7%, 9% and 3% among Africans, Indian, Colored and White patients respectively. In conclusion of that study African patients were the youngest compared to the other race groups. Mucinous differentiation predominated in Africans and young adults.

In Sudan two descriptive studies were conducted in Ibn Sina Hospital. Firstly, Seventy-three (73) patients of colorectal cancer who presented in the period from January 2010 to December 2012 were included. More than 17% of the study populations were below the age of 40 years, and 43.84% was below 50 years [6]. The second study was carried between 2010 -2012; the sample size was 63 only where the median age appeared 50 and their presentation rang was 10 months [7].

Moreover, a retrospective study was conducted in Khartoum Teaching Hospital (Sudan). Two hundred and seventy-seven (277)

patients who presented in the period 1st January 2000 to 31st December 2006 were occurred. Results: More than 100 (34.5%) of the study population (n = 277) were below the age of 40 years, and 17.3% were below 30 years. The male to female ratio was 1.5:1. Intestinal obstruction was the most common cause of emergency presentation of colorectal cancer (94%) [8].

These studies were the only done in Khartoum state hospital and they were descriptive analytical studies mainly highlight the percentage of colorectal cancer and presentation in all age groups. In Sudan there was no previous studies handle and assess the clinical and pathological presentation of CRC among young adults. Furthermore, the treatment of colorectal cancer currently carried in the same manner, where identification of the clinical and pathological presentation will significantly tailored the screening and management strategies.

## Back ground

### Risk Factors

Increasing age is the most important risk factor for most cancers. Other risk factors for colorectal cancer include the following:

- Family history of colorectal cancer in a first-degree relative.
- Personal history of colorectal adenomas, colorectal cancer, or ovarian cancer.
- Hereditary conditions, including familial adenomatous polyposis (FAP) and Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]). (The clinical criteria (**Amsterdam's**) needed to diagnose hereditary nonpolyposis colorectal cancer (HNPCC—Lynch syndrome) in a family:
  - There are at least three relatives with an HNPCC-associated cancer (large bowel, endometrium, small bowel, ureter or renal pelvis, but not stomach, ovary, brain, bladder or skin).
  - One affected person is a first-degree relative of the other two.
  - At least two successive generations are affected. At least one person was diagnosed before the age of 50 years.
  - Familial adenomatous polyposis has been excluded.
  - Tumors have been verified by pathologic examination.
- Personal history of long-standing chronic ulcerative colitis or Crohn colitis.
- Excessive alcohol use.
- Cigarette smoking.
- Race/ethnicity: African American.
- Obesity [9].

Colon cancer (Cca) could present as sporadic (70%), familial clustering (20%) and inherited syndromes (10%) [10].

The prognosis of patients with colon cancer is clearly related to the following:

- The degree of penetration of the tumor through the bowel wall.
- The presence or absence of nodal involvement.
- The presence or absence of distant metastases [9].

These three characteristics form the basis for all staging systems developed for this disease.

Other prognostic factors include the following:

- Bowel obstruction and bowel perforation are indicators of poor prognosis.
- Elevated pretreatment serum levels of carcinoembryonic antigen (CEA) have a negative prognostic significance [9].

Symptoms and sign

- The colorectal cancer may present with symptoms related to the tumor site

Right side

- Abdominal mass
- Anemia
- Maleana
- Diarrhea
- Change in bowel habits

Left side

- Constipation
- Bleeding per rectum
- Abdominal distention
- Abdominal mass
- Sense of incomplete evacuation
- Anal mass

Systematic symptoms which include

- Weight loss
- Fatigability
- Loss of appetite.etc

The tumor, node, metastasis (TNM) staging 8<sup>th</sup> edition system of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) 2017 is the preferred staging system for CRC. This was adopted in this study table 1.

## Diagnosis and treatment [11].

- American cancer society recommendation for colorectal cancer diagnosis and treatment as follows:
- An assessment of disease-specific symptoms, past medical and family history, physical examination, and serum CEA level should typically be evaluated in patients with colon cancer
- When possible, patients with presumed or proven colon cancer should undergo a full colonic evaluation with histological assessment of the colonic lesion before treatment.
- Preoperative radiologic staging with a chest/abdomen/pelvis CT should typically be performed.
- Positron emission tomography/CT (PET/CT) is generally not recommended for routine colon cancer staging.
- Colon cancer staging should be performed according to the American Joint Committee on Cancer (AJCC)/TNM system and include an assessment of the completeness of surgical resection designated by the residual tumor code "R".
- A thorough surgical exploration should be performed and the findings documented in the operative report.
- The extent of resection of the colon should correspond to the lymphovascular drainage of the site of the colon cancer.
- Routine performance of extended lymphadenectomy is not recommended.
- Resection of adherent or grossly involved adjacent organs should be en bloc.
- Synchronous colon cancers may be treated by 2 separate resections or subtotal colectomy.
- Sentinel lymph node mapping for colon cancer does not replace standard lymphadenectomy.
- When expertise is available, a minimally invasive approach to elective colectomy for colon cancer is preferred.
- Hand-assisted laparoscopic and robotic surgical techniques for right colon cancer result in oncologic outcomes that are equivalent to open or straight laparoscopic techniques.
- Treatment of the malignant polyp is determined by the morphology and histology of the polyp.
- Management of Stage IV Disease The treatment of patients presenting with synchronous or metachronous stage IV colon cancer should be individualized and guided by a multidisciplinary team [11].

## Literature Review

### Incidence of early stage CRC

Davis, *et al.* [12]. evaluated the rates of change in CRC incidence within the Surveillance Epidemiology and End Results (SEER) database (1987-2006). They reported that people older than 50 had decreasing incidences, where colonic and rectal cancer increased in 56% and 94% of the study participant, respectively. They also noted a

higher incidence across age groups 20-49 years in 2006 than in 1987. Most significantly, the highest increase (67%) occurred in age 40-44 (from a low of 10.7 per 100,000 in 1988 to 17.9 per 100,000 in 2006).

In a retrospective study using data from the Surveillance Epidemiology and End Results (SEER) Cancer Registry, Meyer, *et al.* [13], identified 7,661 colon and rectal cancer patients under age 40 years between 1973 and 2005. After calculating the change in incidence over time for colon and rectal cancers, the researches described that while colon cancer rates remained flat, rectal cancer rates have been increasing. Between 1984 and 2005, rectal cancer rate rose by 3.8% per year. This finding led the authors' state that "in young people presenting with rectal bleeding or other common signs of rectal cancer, endoscopic evaluation should be considered in order to rule out a malignancy". They also suggested that more frequent endoscopic evaluation could decrease the documented delay in diagnosis among young people. But, as the overall incidence of rectal cancer is relatively low, the authors did not advocate for a change in screening guidelines.

An another study in Tunis aim to provide an updated overview on clinicopathological features, treatment and outcome of colorectal cancer in young adults under the age of 40. It was a retrospective study, they covered 32 cases of colorectal cancer in young adults aged less than 40 years that were diagnosed at the pathology department of Mongi Slim hospital over a fifteen-year period (April 2000 - November 2014). Where included 13 male and 19 female patients (sex-ratio M/F = 0,68) between 17 and 39 years of age (mean = 31,25 years). The presenting clinical symptoms were dominated by altered bowel habits (n = 17), followed by bleeding per rectum (n=16). Histopathological examination of the surgical and biopsy specimens established the diagnosis of mucinous adenocarcinoma in nine cases, well-differentiated adenocarcinoma in 11 cases, moderately differentiated adenocarcinoma in six cases, poorly differentiated adenocarcinoma in four cases and signet ring cell carcinoma in two cases. The tumors were classified after surgery as stage I (n = 2) (6%), stage IIA (n = 7) (22%), stage IIB (n = 4) (13%), stage IIC (n = 1) (3%), stage IIIB (n = 8) (25%), stage IIIC (n = 4) (12%), stage IVA (n = 4) (13%) and stage IVB (n = 2) (6%). During the follow-up period which ranged between one month and 9 years, local recurrence of the tumor occurred in six cases, seven patients had hepatic metastases and seven patients died after a mean follow-up period of seven months [14].

### International recommendations

In an effort to detect the disease at early stages, the United State Preventive Services Task Force (USPSTF) recommended CRC screening in adults aged 45-49 years with a grade "B" recommendation. While the recommendation recognizes the aggressive nature of early-onset CRC [15], it also reflects the implications of early-onset CRC in terms of the choice of therapies and prognosis. Accordingly, it is

imperative to characterize age groups with the highlighting the risk of early-onset CRC and to investigate it is trends in this young population [15].

In an interesting retrospective study, O'Connell, *et al.* [16] collected data on 6425 patients from 55 manuscripts in the literature. While the majority of articles (n = 37) defined "young" those patients under 40 years of age, four articles (7%) focused attention on patients younger than 35 years, 14 articles (25%) looked at patients before 30 years and only one article looked at patients before 25.

According to the literature, a non-worthless fraction of CRC patients were diagnosed before 40 years in approximately 0.8 to 14.6% [17].

Furthermore, recent publications have documented a disproportional increase in CRC incidence among young people [18]. Especially within this young group, one recognizes the need to investigate if the malignancy represents an apparent sporadic CRC or if it is associated with some form of hereditary CRC (mainly Familial Adenomatous Polyposis or Lynch Syndrome) or inflammatory bowel disease.

Attempts to describe clinical, pathological and molecular features in young patients have reached controversial conclusions regarding tumor grade and disease stage at diagnosis. So far, there is no consensus if age should be considered an adverse independent prognostic factor if other features such as topography and staging are considered together. However, it is commonly accepted that diagnosis in young patients is always difficult, because both patient and the doctor usually don't give credit to the presenting symptoms, leading to a frequent unfavorable outcome of the disease [19].

Tumor tissues were prospectively collected from patients from two tertiary hospitals in the Philippines. Patients of age  $\leq$  45 years with resected adenocarcinoma of the colon or rectum were recruited. Seventy-seven out of 124 patients had tumor samples sent for immunohistochemistry. Of these, 61 samples (79%) were found to have proficient status while 16 samples (21%) had deficient status. Mismatch repair protein deficiencies, when present, more commonly involved MSH2 and MSH6 (9%) rather than MLH1 and PMS2 (5%). The deficient group had a mean age of 37.1 years and a female preponderance (56.25%), presenting as locally advanced ascending or descending colon tumors with mucinous histology in half of the population. The mismatch repair proficient group presented as locally advanced rectal and sigmoid tumors but with fewer mucinous adenocarcinomas (26.2%) compared to the deficient group. In both the mismatch repair proficient and deficient patients with family history reports, most did not have any known relative with cancer (75.4% and 68.75%, respectively) [20].

### Clinicopathological presentation among young adults

By reviewing the recent studies, In UK they conducted study over 105 patients below 50 where revealed the steadily increase in early-onset (CRC) mainly left sided and particularly rectal (3.9%) per year [21]. Sixty-eight percent of the cases were symptomatic on presentation and this is associated with more advanced stage at diagnosis and poorer outcomes. on the other hand, few cases of bowel cancer in the UK are detected in the early stages and almost one-third of patients have a delay in diagnosis of more than 6 months, with little evidence of improvement over the past 60 years [21]. so even in well developed countries early detection of CRC among young remain controversial.

In order to improve early detection rate in UK another study was done in 2286 patient with low colorectal symptoms. Patient consultation questionnaire (PCQ) linked to a computerized record were used. They detected only 95 cases with early stage CRC. In conclusion, patient consultation questionnaire depends on history alone in conjunction with the weighted numerical score can be used as an accurate system for prediction of symptomatic colorectal cancer [22,23].

However, in 2021, given the rising incidence in younger adults, the United States Preventive Services Task Force (USPSTF), has aligned with the American Cancer Society and issued an updated recommendation to initiate screening at age 45 in all adults [15].

### Investigation tools

The appropriateness and diagnostic yield of colonoscopy referrals in an African setting using the American Society of Gastrointestinal Endoscopy guidelines was investigated by a prospective, descriptive, cross-sectional hospital-based study. In under developed countries where the screening program is not implementing colonoscopy is mandatory among patient elder than 50 whom presenting with lower GIT symptoms [24].

In almost all patients, a diagnostic or screening colonoscopy is required for tissue biopsy pathological confirmation of colon carcinoma. Baseline computed tomography (CT) of the chest, abdomen, and pelvis with contrast and carcinoembryonic antigen (CEA) are the preferred cost-effective, colon-cancer staging studies done before surgical resection.

Initial evaluation and diagnosis may involve barium enema or CT colonography if available, but ultimately a colonoscopy is required for tissue biopsy. Colonoscopy sensitivity is about 94.7% (95% CI 90% to 97%) and may miss from 2% to 6% of cases, mostly right-sided, depending on preparation quality and hands experience [25].

The stage at presentations is mandatory to map the management approach for all cases. Currently all cases are managed in the same manner independent to age.

### Colon cancer management

Surgical resection is the main treatment modality for localized non-metastatic stage Cca at any age with acceptable performance status and optimized co morbidities. Endoscopic resection (ER) is reserved for selected favorable-risk and early-stage colon carcinomas found in a polyp (cT0-1 [25]. Neoadjuvant therapy is not standard of care for Cca and reserved for advanced disease surgical conversion intend. Adjuvant therapy is recommended for all Cca stage III (node-positive) and individualized by stage II with high-risk features<sup>(25)</sup> Surgery in conjunction with peri-chemotherapy may provide a curative option on oligo-metastatic lung and liver disease. Palliative systemic chemotherapy is offered to non-surgical candidates with unrespectable locally advanced disease or high metastatic burden to improved quality of life and prolongs life expectancy. Individualized local-recurrent disease patients may achieve cure with further multimodality therapy [25].

From literatures there was study reflect a decreased mortality from advanced colorectal cancer in the era of modern combination chemotherapy in younger and older patients. Younger age, non-right-sided tumors, and absence of signet ring histology significantly associate with better survival. Younger patients had a greater proportion of negative clinicopathologic features (male sex, African American ethnicity, and signet ring or mucinous histology). In multivariate analysis, older age, male sex, African American ethnicity, right-sided tumors, and signet ring histology were associated with higher mortality risk. Younger patients had improved survival (hazard ratio 0.72; 95% confidence interval: 0.70-0.75) compared with older patients, whereas all patients experienced increased 2-year survival by join point analysis beginning in 1999-2000 [26].

### Problems statement

Colorectal cancer incidence has been rapidly rising in those under the age of 50years over the last 20 years. They tend to have a different spectrum of clinical and pathologic presentation compared to CRC diagnosed in older individuals.

### Justifications

- Although there were pervious descriptive studies that showed rising in CRC among young Sudanese, but still no study had covered CRC presentations among young Sudanese adults.

- The burden of young adults’ colorectal cancer in Sudan is unknown.
- Assessment of the disease behavior in different groups will lead to remap the treatment strategies.

**Objectives**

**General objectives**

To identify the clinical and pathological presentation of colorectal cancer among Sudanese adults aged below 50yrs (group A) versus those above 50yrs (group B)of age.

**Specific objectives**

- To identify the early and more common symptoms and signs in both groups.
- To identify the most common histological types of colorectal cancer among both groups.
- To identify the most common colorectal cancer sites among both groups.
- To assess the most common misdiagnosis before confirmation.
- To study the management practice of colorectal cancer among both groups in Sudan.

**Patients and Methods**

**Data collections**

Data has been collected by the researcher using administered questionnaire which included all the variables. Either by direct interview or through phone call with the colorectal cancer confirmed patients. Consents were obtained from all patients included in the study or their relatives. The data was collected Crosse -sectional and age independent.

A prospective follow up has been conducted for the new cases that presented during 2020-2021. The patients who presented during 2019 had been contacted by the researcher and their data were collected directly from them as they were still on regular follow up. The total number of cases was120 cases. The familial history was taken for all cases. lynch syndrome had been assessed according to Amsterdam criteria’s I (see background). The FAP cases which were included had malignant changes on histopathology.

The radiological staging and TNM staging were taken according to AJCC 8<sup>TH</sup> Edition. Clavien Dindo classification had been applied to assess the post operative complications in patients underwent curative surgeries.

**Clavien-Dindo classification of surgical complications [6].**

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
IVa	Single organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
Grade V	Death of a patient

**Table a**

**Study design**

A prospective and retrospective comparative study of histological confirmed cases of colorectal cancer. Retrospective from June/2019 to Nov/2020. And prospective from Dec/2020- Dec/2021.The cases had been divided in to two groups according to age, group A (50 years and below) and group B (>50years).

**Study area**

It was multicenter that conducted in colorectal cancer services units in Khartoum state hospital:

- Ibrahim malik teaching hospital.
- Ibn sina hospital
- Soba university hospital

**Study populations**

**Inclusion criteria**

- All patients who had histological confirmed colorectal cancer during the study period and were managed within the study’ centers
- Patient’s contacts availability.

**Exclusion criteria**

- Patient’s contacts and follow up were lost.
- Patient who refused to be enrolled in the study.

AJCC stage <sup>[2]</sup>	TNM stage <sup>[2]</sup>	TNM stage criteria <sup>[2]</sup>
Stage 0	Tis N0 M0	Tis: Tumor confined to mucosa; cancer- <i>in-situ</i>
Stage I	T1 N0 M0	T1: Tumor invades submucosa
	T2 N0 M0	T2: Tumor invades muscularispropria
Stage II-A	T3 N0 M0	T3: Tumor invades subserosa or beyond (without other organs involved)
Stage II-B	T4a N0 M0	T4a: Tumor perforates the visceral peritoneum
Stage II-C	T4b N0 M0	T4b: Tumor invades adjacent organs
Stage III-A	T1-2 N1 M0 or T1, N2a, M0	N1: Tumor cells in 1 to 3 regional lymph nodes. T1 or T2. N2a: Tumor cells in 4 to 6 regional lymph nodes. T1
	T3-4a, N1 M0 or T2-3, N2a, M0 or T1-2 N2b M0	N1: Tumor cells in 1 to 3 regional lymph nodes. T3 or T4 N2a: Tumor cells in 4 to 6 regional lymph nodes. T2 or T3 N2b: Tumor cells in 7 or more regional lymph nodes. T1 or 2
Stage III-B	T4a N2a M0 or T3-4a N2b M0 or T4b N1-2, M0	N2a: Tumor cells in 4 to 6 regional lymph nodes. T4a N2b: Tumor cells in 7 or more regional lymph nodes. T3-4a N1-2: Tumor cells in at least one regional lymph node. T4b
	any T, any N, M1a	M1a: Metastasis to 1 other part of the body beyond the colon, rectum or regional lymph nodes. Any T, any N.
[Stage IV b	any T, any N, M1b	M1b: Metastasis to more than 1 other part of the body beyond the colon, rectum or regional lymph nodes. Any T, any N.
Stage IV c	any T, any N, M1c	M1c: Metastasis to the peritoneal surface. Any T, any N.

Table b

**Sampling**

The sample size is total coverage bound to study duration.

**Study variables**

A-Background variables

- Personal data
- Family background.

FAP

Lynch syndrome

Family history with similar condition.

- Misdiagnosed diseases
- Co morbid diseases

B-Independent variables

- Diagnostic tools
- Management
- Outcome of treatment

C-Dependent variables

- Age
- Clinical Presentation
- Radiological and histopathology TNM staging.

**Data management:**

Data has been processed and sorted in relevant master sheet. Analysis was done by SPSS version 25. Chi-square test was used with the p-value< (0.05) considered significant and standard deviation of 95%.

**Ethical considerations**

- All patients were consented verbally and by written consent.
- Ethical clearance was obtained from the ethical committee in Sudan medical specialization board.
- Hospital permissions were obtained.
- The data confidentiality was maintained and well secured.

**Results**

**Socio-demographic characteristics of patients**

A total of 120 patients were included. They were divided in two groups according to age, group A (50 and less than 50years) and group B (more than 50years). They presented with percentage of (49.2%)59 and (50.8%)61 for A and B respectively.

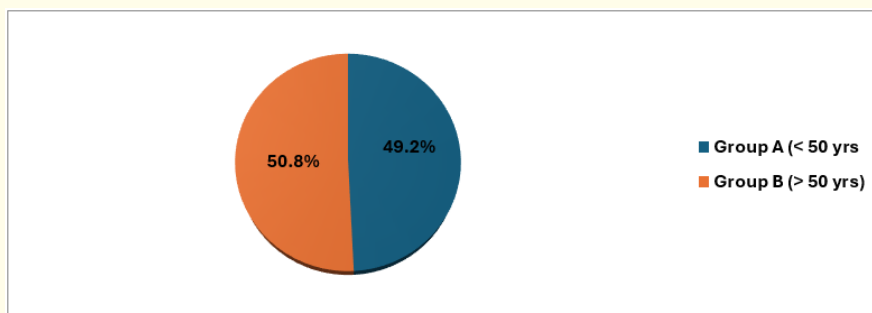


Figure 1: Age distribution among the 120 CRC cases. Who were presented during 2019-2021 in Khartoum state GIT units.

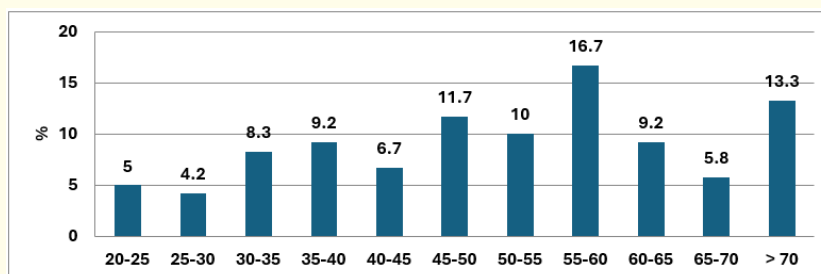


Figure 2: Show age categories distributions among the 120 CRC cases who were presented during 2019-2021 in Khartoum state GIT units.

The mean age was 51.2 with standard deviation of 15.2. There were no significant differences in male to female ratio in both groups. In group A male: female ratio was 1.5:1, male=35 (59.2%), female=24 (40.8%). In group B it was 1.3:1, male=35 (57.3%), female=26 (42.6%).

**Presentation**

Rectal cancer was reported as the commonest CRC in both age groups. In group A rectal cancer percentage was (60%) 35, followed by left side CRC (20.3%) 12. In group B rectal cancer percentage was (49.2%) 30 followed by right side CRC 15 (24.6%). However, synchronous tumor detected in three cases in group A one of them is FAP and two cases from group B. There were 3 (4.9%) metachronous tumors among elderly while one (1.8%) case among younger figure 3.

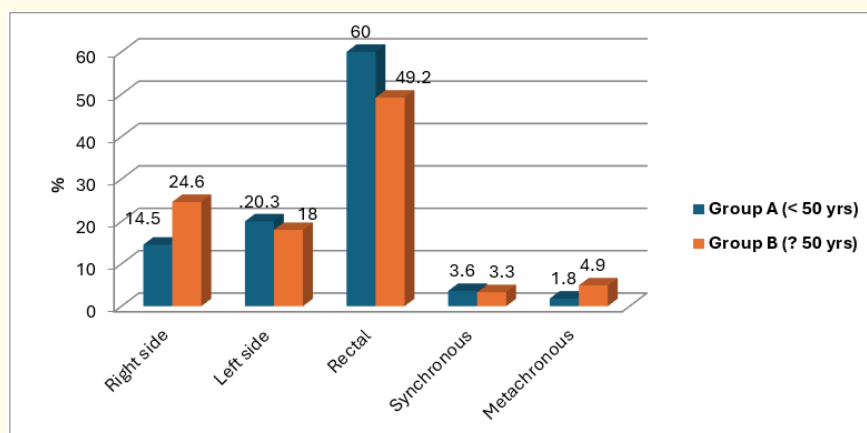


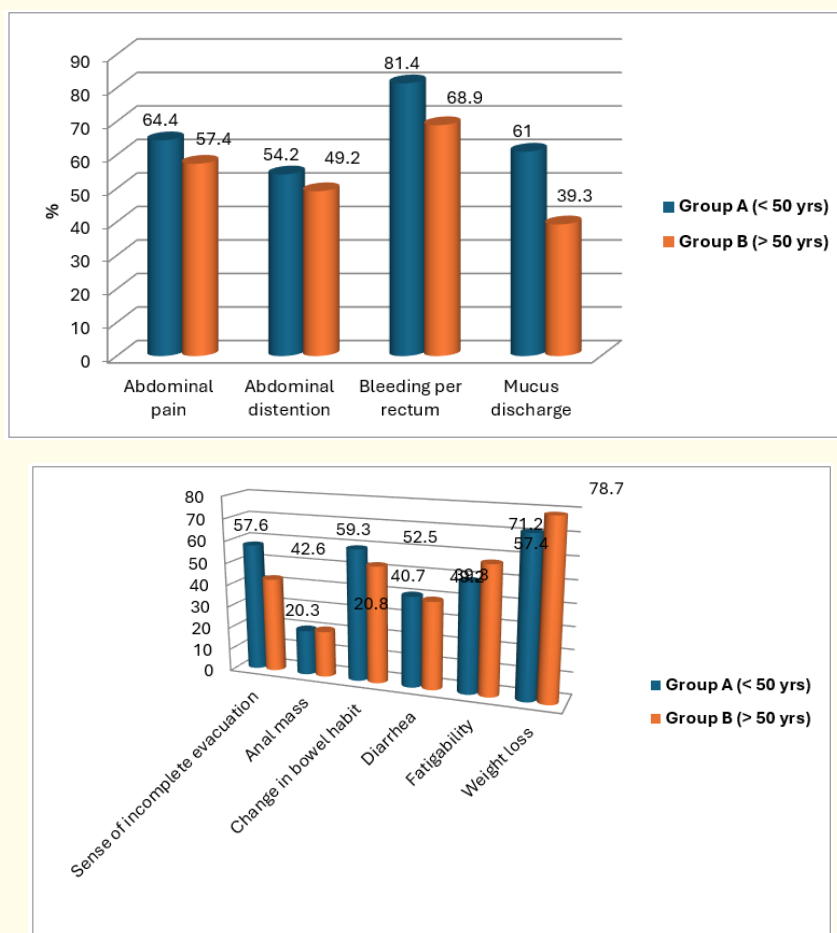
Figure 3: Show the tumor site distribution among the 120 CRC cases who were presented during 2019-2021 in Khartoum state GIT units.



**The most dominating presenting symptoms**

The most dominating symptoms among young adults was bleeding per rectum which counted 48 (81.4%) followed by weight loss 42 (71.2%) then abdominal pain with a proportion of 38 (64.4%). On the

other hand, weight loss was the most common presenting symptoms in group B with a percentage of 48 (78.8%) followed by bleeding per rectum 42 (68.9%) then constipation which counted 26 (42.6%) of the patients figure 4,5.



**Figure 4 and 5:** Distribution of presenting symptoms by age among the 120 CRC cases who were presented during 2019-2021 in Khartoum state GIT units.

**Familial backgrounds**

The highest incidence was for the Sporadic CRC without any familial background. Among group A was 46 cases (78%) and 50 (85%) in group B.

In group A there were 13 (22%) cases with a positive family history. There were 2 cases with FAP and one case with lynch I syndrome who met the Amsterdam I criteria's. In group B 11 (18%) had familial background, seven cases with first degree relatives and four with second degree table 1.

**The most frequent misdiagnosed diseases**

CRC most frequently was misdiagnosed with dysentery. Which counted about 25 (42.4%) cases among younger and 17 (27.9%)

among elderly. On the other hands ano-rectal conditions reported high percentage in elderly 20 (32.8%) as a misdiagnosed disease. However, fifteen cases (25.4%) from both groups were mistakenly diagnosed with IBS. There was no reported case with IBD in the study.

**The most frequent co morbid diseases**

Only ten cases from group A and six cases from group B recalled a history with GIT belharziases. However diabetes mellitus was reported among 13 cases (21.3%) from group B and seven cases (11.9%) from group A.

**Ways of diagnoses**

The CRC cases always were investigated according to presentation suggested CRC in both groups (78% and 68.9%) for group A and B respectively. No one in group A had been enrolled with in a screen-

Similar condition in family		Age group		Total
		Group A (< 50 yrs)	Group B (> 50 yrs)	
Yes	n	13	11	24
	%	22.0%	18.0%	20.0%
No	n	46	50	96
	%	78.0%	82.0%	80.0%
Total	n	59	61	120
	%	100.0%	100.0%	100.0%

**Table 1:** Distribution of age group by similar condition in family among the 120 CRC cases during 2019-2021 in the Khartoum state GIT units.

$\chi^2 = .300$ ;  $DF = 1$ ;  $P\text{-value} = .375$  (Not significant).

ing program. Only two cases from group B diagnosed with CRC during self-screening. There were documented number of the study populations had CRC discovered incidentally during investigations for other mistaken diseases 9 (7.5%) cases from group A and 12 (10%) cases from group B. Those who came with emergency presentations among group A were three cases, one case with appendicitis and two cases with intestinal obstruction. Six (5%) cases from group B had emergency presentations, one case with right side iliac fossa abscess and 5cases with intestinal obstructions.

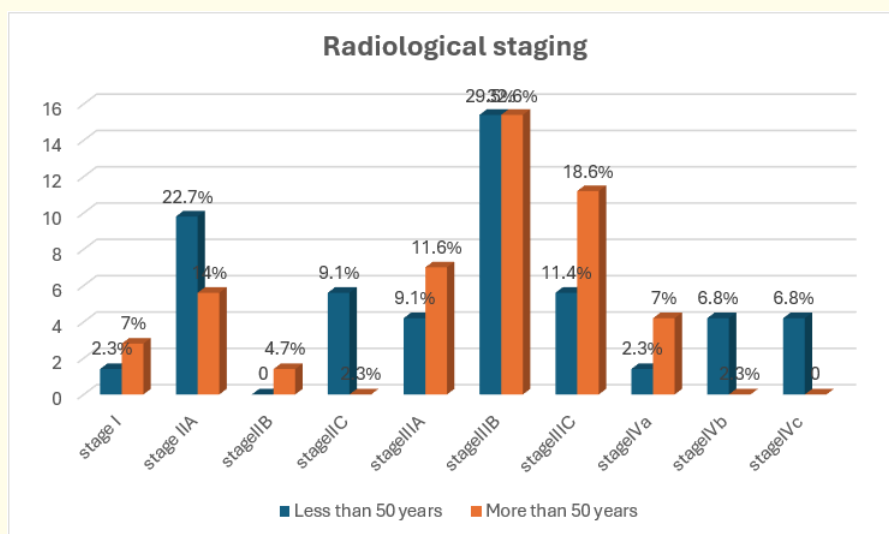
**The radiological staging**

The preoperative radiological staging was examined in 44 (36.6%) cases from group A and 43 (35%) cases from group B. CT abdomen

were not done in two cases from group A and four cases from group B. The radiological staging were deficient in 20 (16%) cases from group A and 26 (21%) from group B. In group A there were 13 (29.5%) cases with stage IIIB, 10 (22.7%) stageIIA and 5 (11.4%) stage IIIC. In group B 14 (32.6%) cases presented with stage IIIB, 8 (18.6%) stage IIIC and 6 (14%) stage IIA. There were no significant differences (p value = 0.235) figure 6.

**Histological TNM Stage**

Moreover, in the patients who were operated the histopathological TNM stage revealed that the most reported stage in group A was stage IIA (34.9%,15 cases) followed by stage IIIB (20.9%,9 cases) in contrast to group B where stage IIIB and IIA were the most counted one (26.5%,13 cases). There were no significant differences (p value = 0.157) table 2.



**Figure 6:** Radiological staging by age groups according to AJCC 8th edition among the 120 CRC cases from 2019-2021 in khartoum state GIT units.

		Age group		Total	P-value
		Group A (< 50 yrs)	Group B (> 50 yrs)		
Stage 0	n	3	2	5	.157
	%	7.0%	4.1%	5.4%	
Stage I	n	2	13	15	
	%	4.7%	26.5%	16.3%	
Stage IIA	n	15	13	28	
	%	34.9%	26.5%	30.4%	
Stage IIB	n	2	1	3	
	%	4.7%	2.0%	3.3%	
Stage IIC	n	0	1	1	
	%	.0%	2.0%	1.1%	
Stage IIIA	n	3	1	4	
	%	7.0%	2.0%	4.3%	
Stage IIIB	n	9	13	22	
	%	20.9%	26.5%	23.9%	
Stage IIIC	n	6	3	9	
	%	14.0%	6.1%	9.8%	
Stage IVa	n	2	2	4	
	%	4.7%	4.1%	4.3%	
Stage IVC	n	1	0	1	
	%	2.3%	.0%	1.1%	
Total	n	43	49	92	
	%	100.0%	100.0%	100.0%	

**Table 2:** Histological TNM stage by age groups among the 120 CRC cases from 2019-2021 in Khartoum state GIT units.

\*P-value considered significant at less than 0.05 levels.

**Histological finding**

Adinocarcinoma was the most encountered histological type of colorectal cancer among both groups which included 96.9% and 95.1% for group A and B respectively. Furthermore, grade II adenocarcinoma was the commonest one in both groups 27cases,36 cases for A and B respectively. There was one case reported with ano-rectal squamous cell cancer in each group table 3.

In group A, five (4.1%) cases mucinous and two (1.6%) cases signet ring cells were detected. In group B, there were three case (2.5%) mucinous and one case signet ring cell.

**Surgical treatment and outcome**

The total number of patients who underwent surgery were 49 (83%) from group A and 57 (93.4%) cases from group B. About44 (89.7%) of group A and 50 (86%) cases from group B were considered curative procedure. Palliative surgeries were done in 12 cases,7and 5 from A and B respectively table 4.

According to Clavien Dindo classifications which was applied for curative surgeries only, almost most of the cases experience grade1 complications (29 out of 48from (A), 30 out of 55 from (B), only 2cases died from group A and no deaths had been reported from group B post operation (grade V), p = .706 table 5.

One hundred and five cases are still alive and well. In group A55 (93.2%), in groupB50 (81.9%). Two cases from group A died before surgery and two died after. In group B deaths were reported in five cases, five after surgeries and one death before surgery. No recurrences or metachronous tumor had been reported among group A. There were three cases with recurrent CRC and two metachronous tumor had been documented among group B.

**Discussion**

Colorectal cancer among young adults or early onset- CRC still being considered as international challenging issue. The cut age definition still not known. In this study 50 is used, as the age recommended

Histological type	Age group			Total	P-value
		GroupA (< 50 yrs)	Group B (> 50 yrs)		
Adenocarcinoma	n	57	58	115	.807
	%	96.6%	95.1%	95.8%	
Neuroendocrine tumor	n	1	1	2	
	%	1.7%	1.6%	1.7%	
lymphoma	n	0	1	1	
	%	.0%	1.6%	.8%	
Squamous cell cancer	n	1	1	2	
	%	1.7%	1.6%	1.7%	
Total	n	59	61	120	
	%	100.0%	100.0%	100.0%	

**Table 3:** Distribution of age group by histological type among the 120 CRC cases from 2019-2021 in Khartoum state GIT units.

\*P-value considered significant at less than 0.05 levels

Surgical procedure	Age group			Total
		Group A (< 50 yrs)	Group B (> 50 yrs)	
Curative	n	44	50	94
	%	89.7%	86.0%	88.0%
Palliative	n	5	7	12
	%	10.2%	12.3%	11.3%
Total	n	49	57	106
	%	100.0%	100.0%	100.0%

**Table 4:** Show the surgical procedure aim among both groups of the 120 CRC cases during 2019-2021 in Khartoum state GIT units.

Complication after surgery	Age group			Total	P-value
		Group A (< 50 yrs)	Group B (> 50 yrs)		
Grad 1	n	29	30	59	.514
	%	65.9%	60.0%	62.8%	
Grade ii	n	5	7	12	
	%	11.4%	14.0%	12.8%	
Grade iii-a	n	0	2	2	
	%	.0%	4.0%	2.1%	
Grade iii-b	n	1	1	2	
	%	2.3%	2.0%	2.1%	
Grade IV-a	n	0	1	1	
	%	.0%	2.0%	1.1%	
Grade V	n	2	0	2	
	%	4.5%	.0%	2.1%	
No complications	n	7	9	16	
	%	15.9%	18.0%	17.0%	
Total	n	44	50	94	
	%	100.0%	100.0%	100.0%	

**Table 5:** Show Calvien Dindo classifications grades among postoperatively in both groups of the 120 CRC cases during 2019-2021 in Khartoum state GIT units.

\*P-value considered significant at less than 0.05 levels

Short term outcome		Age group		Total	P-value
		Group A (< 50 yrs)	Group B (> 50 yrs)		
Alive	n	55	50	105	222
	%	93.2%	81.9%	87.5%	
Death before surgery	n	2	1	3	
	%	3.3%	1.6%	2.5%	
Death after surgery	n	2	5	7	
	%	3.3%	8.1%	5.8%	
Metachronous tumour.	n	0	2	2	
	%	.0%	3.3%	1.7%	
Recurrence	n	0	3	3	
	%	.0%	4.9%	2.5%	
Total	n	59	61	120	
	%	100.0%	100.0%	100.0%	

**Table 6:** Distribution of age groups by short term outcome among the 120 CRC cases during 2019-2021 in Khartoum state GIT units.

\*P-value considered significant at less than 0.05 levels.

by most of the international screening programs, despite the recent recommendation by US Preventive Services Task to reduce the age to 45 for low-risk patients [15]. In Sudan the colorectal cancer screening is not well established with deficiency in information background and adoption of other countries guideline.

The data had been collected retrospectively from June/2019 to November/2020 and prospectively from November/2020 to December/2021. Direct interview were done with patients using administered questionnaire.

One hundred and twenty patients were enrolled in the study from the three main GIT surgical units in Khartoum state which are providing colorectal cancer services. The patients had been collected randomly to identify the pattern of the early onset-CRC among Sudanese populations. Patients aged 50 were added to group A as they have long interval between complains and hospital presentations which ranged between 4-10months.

The young adults CRC incidence in the study was 59 (49.2%) and most of them were between 45-50 (23.7%). This may supports the US preventive task recommendation [15] to reduce the screening age to 45. In group B the most rated cases lied in age category 55-60 (31%) which goes with the 2020 colorectal cancer statistics (CRC increase among 50-64age population annually by (1%) [27-29].

According to statistic in US Sporadic CRC among young adult incidence about 50% [29,30]. However it reached (78%) in our study. That goes with study was carried in US that revealed African Americans have higher CRC incidence and mortality than Whites [31]. The included cases of FAP in the study had malignant changes back-

ground where those with benign histological finding were excluded. It is noticeable that IBD weren't reported in the study [32].

Significant proportions of group A experienced rectal cancer (57%). These results had been detected by several previous international studies and figures [33,34] that revealed rectal cancer is the most predominating site among all ages. Left side CRC in younger group was the second most detected tumor which resembles a finding in a study done in South Africa [35]. Also in UK by reviewing 17 international papers an overall young adult with CRC has arising prevalence of distal colon and rectal cancers. Early -onset CRC tend to have poorly differentiated tumors and were managed more aggressively<sup>(30)</sup>. Bleeding per rectum was the most reported symptoms among young because rectal and left side CRC are common. On the other hand, rectal cancer followed by right side colon cancer among elderly was commonly detected in our study with the dominating symptoms of weight loss. That was supported with a study was done to 1059 elderly patient with colon cancer that showed the proximal shift of cancer has direct proportion with age [35].

Four cases below 50 had synchronous tumor on presentations, need MDT approach and one of them presented with liver metastasis. He is receiving palliative neoadjuvant chemotherapy which is advocated by several panels [36]. Despite surgeries for the primary tumors are applied in certain practice.

Dysentery in Sudan is always diagnosed clinically by a history of abdominal pain and bleeding per rectum that is why most of CRC were misdiagnosed with it. In this study dysentery was found to be the most frequent misdiagnosed disease. However, chronic gastro-

intestinal parasitic infections in Africa may be associated with the increasing incidence of CRC, this hypothesis was supported by study had been done in Uganda. It investigated the CRC patients with schistosomiasis and amebiasis infections background. Out of 350 patients with chronic disease, 42 patients (12%) developed cancers (18 male and 24 female patients); 20 in the sigmoid colon-rectum, 14 in the colon. But still remain an area for more investigations and researches [37]. In our study also 10 (8.3%) cases had schistosomiasis chronic infections among young group and 6 (5%) from group B. There was one case reported in Soba University Hospital. That showed association between schistosomiasis and colon cancer in young adult aged 35 yrs with the tumor site loaded with schistosoma ova which was documented during histopathology [38].

The ways of diagnosing patients also had been investigated in the study. Incidental means diagnosis during investigations for another disease where emergency for patients need emergency interventions. Intestinal obstruction was the most common emergency presentations.

Accurate preoperative radiological staging was done in 87 cases. It wasn't done in the rest, either because they present in an emergency situation or the CT was unremarkable. Stage IIIB was counted as the most detected radiological stage among both groups. In contrast to post-operative histopathological staging (TNM AJCC 8<sup>th</sup> edition), where stage IIA occurred more frequently than stage IIIB in group A. Among older group stage IIIB was the commonest post-operative histopathological stage. That might be explained by the remarkable response to neoadjuvant therapy with good down staging, as most of the cases were rectal cancer. Second reason that the radiological stage overestimated their condition or the lymph nodes which were detected by radiological imaging appeared negative in histopathology. On the other side, for those who presented with early radiological stage and appeared more advanced postoperatively this may be related to the long interval between the presentations and surgeries.

Adenocarcinoma was the dominating histological type during the study which is a reliable finding goes with the international statistic [39] mucinous and signet ring type more detected among group A which has poorer prognosis [40]. Pure squamous cell cancer was detected in two cases one from each group who presented with anorectal CRC. The grade is moderately differentiated among most of the cases 63 (30%) and no significant differences between both groups 27 (42%) in group A and 29 (46%) in group B.

The neoadjuvant therapy was noticed to be given more in group A (29) 24.1%. because rectal cancer had high incidence among young group. In general, 84% of the cases who received neoadjuvant therapy are still alive with good treatment response. Adjuvant therapy was harbored in almost equal cases (33 cases vs. 31 cases) from both

groups and 89.1% still experience good response. Metachronous tumors were reported in 2 cases above 50. According to literature, the occurrence of metachronous advanced neoplasia in young adults is similar to older adults [41].

The type of surgeries in the study divided into curative, intention curative and palliatives. Intention curative related to procedures that adopted to resect the primary tumor without need for accurate oncological resection which occurred in an emergency setting. Palliative surgeries for those who presented with unrespectable tumor and need diversion colostomy. In the study curative procedures had been undertaken more frequent in 49 (40.8%) of group B and only 40 (33.3) from group A. The rest of the patient in the study whom not operated either they are taking neoadjuvant therapy about 10 (8.3%) in group A and 4 cases from group B (3.3%) or died before surgery. Two cases from group A refused the surgery and preferred traditional treatments.

The short term outcome of surgeries had been assessed during the study. By applying Calvien Dindo classifications which was tested during the first post-operative month. Grade I complication was the dominating grade among both groups who they experience favorable post-operative sequences where two deaths were recorded among group A with massive PE had been reported as the cause of death. Only one death in group B.

The short term outcome that had been assessed during the study were applied for 4-6 months following their presentations. One hundred and five cases by the end of the study are still alive and well. The cases who developed recurrence or metachronous tumors were not included with in the 105 cases.

## Conclusion and Recommendations

### Conclusion

#### Based on the study objectives it can be concluded that

- In this study we identify that bleeding per rectum was the most frequent symptoms of CRC among young Sudanese adults aged 50 years and below followed by weight loss.
- In patients aged above 50 years weight loss was the commonest presenting symptoms that followed by bleeding per rectum then constipations.
- Rectal cancer was the most dominating CRC site among both age groups. It followed by left site colonic cancer among young population where right site colonic cancer was the second dominating site among elderly which explained their presenting symptoms.
- The delaying in diagnosis of colorectal cancer in young Sudanese adults appeared clearly due to misdiagnosis with dysentery. Which was used to be diagnosed clinically by a history of abdominal pain and bleeding per rectum.

- There are no significant differences in the histological types among both groups.
- There are no significant differences in the radiological and post operative pathological staging of CRC among both groups.
- Preoperative radiological staging was not available in some cases because of reports deficiency that need more focus from radiologist and need to increase their level of practice.

### Recommendations

- This retro-prospective study from Sudan provides an overview on clinical symptoms, radiological features, treatment and outcome in young adult and elderly patients' <50 years of age and > 50 year with CRC.
- Molecular genetic studies are increasing the understanding of the path biology of colorectal cancer and may ultimately allow risk patients to be identified at an earlier stage.
- Future interventions tailored to this young population may help achieve improvements in their overall prognosis.
- In terms of the management practice of colorectal cancer among both groups in Sudan, the early detection of CRC followed by a sufficient oncologic treatment is crucial regardless of age.
- Outcome of younger patients could be improved if screening colonoscopy would start early as young patients could be diagnosed at an earlier tumor stage.
- We recommend to do colonoscopy or at least sigmoidoscopy for each patients aged 50 or below who are presenting with lower GIT symptoms especially per rectal bleeding.

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