***Original Research Article***

# Surgical resection for colorectal cancer improves survival in Uganda


## Abstract

**Introduction:** In Uganda and other developing low-income countries in Sub-Saharan Africa, colorectal carcinoma (CRC) incidence and mortality rates are increasing whereas in high income developed countries, CRC rates are declining. Many patients do not have access to curative surgery and oncological treatment for CRC in Uganda. In this study, we compared the survival outcomes of patients who underwent curative surgery, and, if necessary, adjuvant chemotherapy to those who did not to assess the impact of surgery and oncology care on CRC in the resource-limited setting of a low-income developing country.
**Methods:** Participants with a diagnosis of CRC between 1 January 2008 and 31 December 2018 were included. These patients had linked data in the Kampala Cancer Registry and medical records from hospitals in Uganda. Data on whether the patients had or did not have curative surgery and adjuvant chemotherapy were obtained. Our outcome variable was survival at 3 years. We computed and compared survival using the log-rank test.
**Results:** Two hundred and forty seven patients were included in the study cohort. These were 177 (71.66%) patients that had curative surgery, while 70 (28.34%) had no curative surgery. Curative rectal cancer surgery had a better survival than no curative surgery (p=0.003). Curative colon cancer surgery tended to have a better survival than no surgery (p=0.137). Curative surgery and adjuvant chemotherapy showed better survival than no surgery with no adjuvant chemotherapy (p=0.007).
**Conclusions:** In a resource-limited environment, curative surgery and if necessary, combined with adjuvant chemotherapy improves survival. The findings in our study therefore serve to encourage the expansion of CRC care by improving the surgery and oncology infrastructure in resource-limited environments due to the increasing burden of CRC.



***Keywords:*** *Colorectal cancer; low-income developing country; curative surgery; adjuvant chemotherapy; Uganda*




## Introduction

Colorectal cancer (CRC) is ranked third in incidence and is the second leading cause of cancer mortality in both sexes worldwide [1,2]. Previously, noncommunicable diseases (NCDs) were associated with diseases of high-income developed countries; however, recent evidence has shown that they are steadily increasing in middle-income and low-income developing countries [3,4,5]. CRC incidence and mortality rates are increasing in middle- and low income developing countries, and in high-income developed countries, CRC rates have been decreasing [6,7].

In Sub-Saharan Africa and Uganda, recent data have shown that there is a steady increase in CRC rates [7-9]. Limited work has been carried out in East Africa focusing on demographics and the impact of surgical care in CRC [10]. Globally, curative surgical resection is understood to improve the prognosis of colorectal cancer patients [11,12]. However, in low-income developing countries, surgical care is often not prioritized and not available [13].

Lack of access to surgical treatment, chemotherapy and radiotherapy may be responsible for the differences reported in colorectal cancer survival between high-income developed countries and low-income developing countries. Lack of screening through faecal occult blood testing and colonoscopy and hence presentation with advanced-stage CRC may also result in the low survival rates reported in East Africa.

While it would be unethical to randomize patients to no surgery or curative surgery, this retroprospective study helps to inform the role of surgery for CRC survival in the context of a low-income developing country. To help inform the understanding of the burden of CRC and the challenges involved in the care of CRC in East Africa, we hoped to principally understand the effect of treatment on the survival of CRC patients managed in hospitals in central Uganda.

## Methodology

### Study Design & Setting

This was a retroprospective cohort study conducted on colorectal adenocarcinoma participants with data linked to the Kampala Cancer Registry and/or data from medical records in Masaka Regional Referral Hospital, Mulago National Referral Hospital, Uganda Martyrs' Hospital Lubaga, Mengo Hospital and Hospice Africa Uganda. Mulago Hospital is the National Referral Hospital and the largest hospital dealing with specialised care in the country. Hospice Africa Uganda provides palliative care for cancer patients in Uganda. All health facilities that participated in this study are located in central Uganda and receive patients from all regions of Uganda.

## Study site context

Uganda is an East African landlocked country with an area of 241,040 $km^2$ and straddling the equator [14,15] (Image 1). Currently it has a population of 42 million and by 2050 is expected to reach 100 million. The annual urban growth rate of 5.2% is the highest in the world and is expected to increase from 6.4 million in 2014 to 22 million by 2040 [15]. The Ugandan healthcare system is most free of charge and is developed by private and public providers. The majority of referrals for colorectal cancer care are sent to health facilities in central Uganda and the Uganda Cancer Institute.

The Kampala Cancer Registry was established in the Department of Pathology, School of Biomedical Sciences, College of Health Sciences, Makerere University in 1951. This registry collects data on the population of Kyadondo County, which includes the city of Kampala, the capital city of Uganda, and a peri-urban area extending some 30 km to the north. Kyadondo County lies on the equator at a longitude of approximately $34^0$E and covers an area of 1914 $km^2$.



Image 1: Map of Uganda


**Follow-up of study participants**

For each study participant, a follow-up period of three (3) years was imposed. The date of diagnosis was the time taken when the follow-up began [time zero ($t_0$)] and continued up to the occurrence of:- (i) death, (ii) censoring at the end of three years or (iii) loss to follow-up. Both passive and active follow-up methods were employed if necessary. The data regarding vital status were obtained partly from the Kampala cancer registry and partly from clinical case files. Active contact tracing was carried out in different regions of Uganda, if necessary, by research assistants for those participants who fell outside the catchment area of the Kampala cancer registry.

For participants in which information on vital status at the closing date was not available, telephone calls or home visits were carried out. For each participant, vital status was achieved at the closing date to achieve complete follow-up.

**Study Population and Selection of Participants**

Participants with histologically confirmed colorectal adenocarcinoma linked to data in the Kampala cancer registry and/or clinical case files in the participating health facilities during the period from 1 January 2008 to 31 December 2018 were included in this study. Patients were excluded if their clinical file missed demographic data, had no clinical data or had multiple cancers other than colorectal adenocarcinoma.

**Variables and measurements**

The retrieved data included patient demographics (age, sex) and pathological factors such as CRC location. On the incidence date, the age in completed years was defined as the age at diagnosis.

CRC tumors located <15 cm from the anal verge connected to the mesorectal fascia or beneath the imaginary line of the promontorium were classified as rectal tumors. Rectosigmoid tumors were located 15 cm from the anal verge at the junction of the rectum and sigmoid colon. Tumors >15 cm from the anal verge were classified as sigmoid tumors. The other colon tumor sites included the caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure and descending colon. The radiological staging system was used to stage CRC, and the TNM stage was scored on the date of diagnosis according to the American Joint Committee on Cancer (AJCC) edition 2017 [333].

Treatment factors included whether they had surgery and the type of surgery (colon cancer surgery or rectal cancer surgery). Chemotherapy was offered for selected high-risk cases of stage II and all stage III and IV colon carcinomas and chemoradiotherapy was offered for selected high-risk cases of stage II and all stage III and IV rectal carcinomas. Stage I colorectal cancers were offered curative surgery only.

Colon and rectal operations were defined according to the location of the tumour. Curative colon operations involved curative right hemicolectomy and curative extended right hemicolectomy for caecum, ascending colon, hepatic flexure and proximal transverse colon tumors. For distal transverse colon, splenic flexure, descending colon and sigmoid colon tumors the curative colon operations involved included curative left hemicolectomy and curative sigmoid colectomy. Rectosigmoid tumors were managed by curative anterior resections and were considered curative rectal operations. Rectal tumours were managed by curative anterior resections and curative abdomino-perineal resections and were considered curative rectal operations. Palliative colostomy was offered to some patients who had unresectable colon or unresectable rectal tumours.

### Sample size

Based on a study from Ghana by Agyemang-Yeboah et al, 2018, the 3-year survival rate was 21% for colorectal adenocarcinoma patients [35] Given the absence of data in Uganda, we used this study to estimate the sample size based on a hazard ratio of 1.56. A 10% loss to follow-up was adjusted for in the sample size. To achieve a hazard ratio (HR) of at least 1.56 based on a 3-year survival rate, a minimum of at least 159 events of failure (deaths) (Freeman 1982) were needed to achieve a power of 80% [36]. Therefore a total of 221 patients were included in the computed sample size [37].

### Statistical analysis

We compared continuous variables using either the Student's t-test or Pearson's chi square test depending on the distribution and compared all categorical variables using Pearson's chi square or Fisher exact chi square test. We calculated and plotted survival using Kaplan-Meier methods and compared the overall survival using the log-rank test. All the data was analysed using STATA version 14.0 [34]. In all statistical tests a p-value of less than 0.05 was considered statistically significant.

## Results

From 1 January 2008 to 31 December 2018, two hundred forty seven (247) patients were diagnosed with colorectal adenocarcinoma from the Kampala Cancer Registry and medical records from the respective hospital facilities, for those participants outside the catchment of the Kampala Cancer Registry. Data from the Kampala Cancer Registry and hospital medical records were used to ascertain any operative interventions.

The types of curative operations performed on the colon and rectal cancer patients are shown in Table 1. The overall patient characteristics stratified by treatment are shown in Table 2. There were 177 (71.66%) patients who had curative colon or rectal surgery, while 70 (28.34%) had no curative surgery. Palliative surgery was performed in only 7 (2.83%) patients for stage IV colorectal adenocarcinoma.

Among the colon cancer patients, 37 (31.1%) had curative colon surgery, while 10 (8.4%) had no curative colon surgery. Among the rectal cancer patients, 76 (63.9%) had curative rectal surgery, while 41 (34.5%) had no curative rectal surgery.

Figure 1 shows that CRC patients who underwent curative surgery had better survival than those that did not undergo curative surgery, and this difference reached statistical significance (p=0.0003).



**Table 1:** The different curative surgical resections for CRC in this study

| **Type of Operation** | **Frequency** | **Percent (%)** |
|---|---|---|
| Right Hemicolectomy | 26 | 14.69 |
| Extended Right Hemicolectomy | 6 | 3.39 |
| Left Hemicolectomy | 16 | 9.04 |
| Sigmoid colectomy | 47 | 26.55 |
| Abdomino-perineal resection | 24 | 13.56 |
| Low Anterior resection | 58 | 32.77 |

**Table 2**: Patient demographics with the comparison between patients who underwent curative resection of CRC and those who did not

| | **All** | **Curative Operation** | **No Operation** | **p-value** |
|---|---|---|---|---|
| Number of cases | 247 | 177 | 70 | |
| Mean (SD) age in years | 53.3 | 53.1 | 53.6 | 0.841 |
| Age ≤54 years(SD) | 130 | 95 | 35 | 0.602 |
| Age >54 years (SD) | 117 | 82 | 35 | |
| Colon | 125 | 101 | 24 | 0.002 |
| Rectum | 122 | 76 | 46 | |

| | | | | |
|---|---|---|---|---|
| Stage I | 27 | 21 | 6 | <0.001 |
| Stage II | 32 | 27 | 5 | |
| Stage III | 106 | 86 | 20 | |
| Stage IV | 25 | 8 | 17 | |

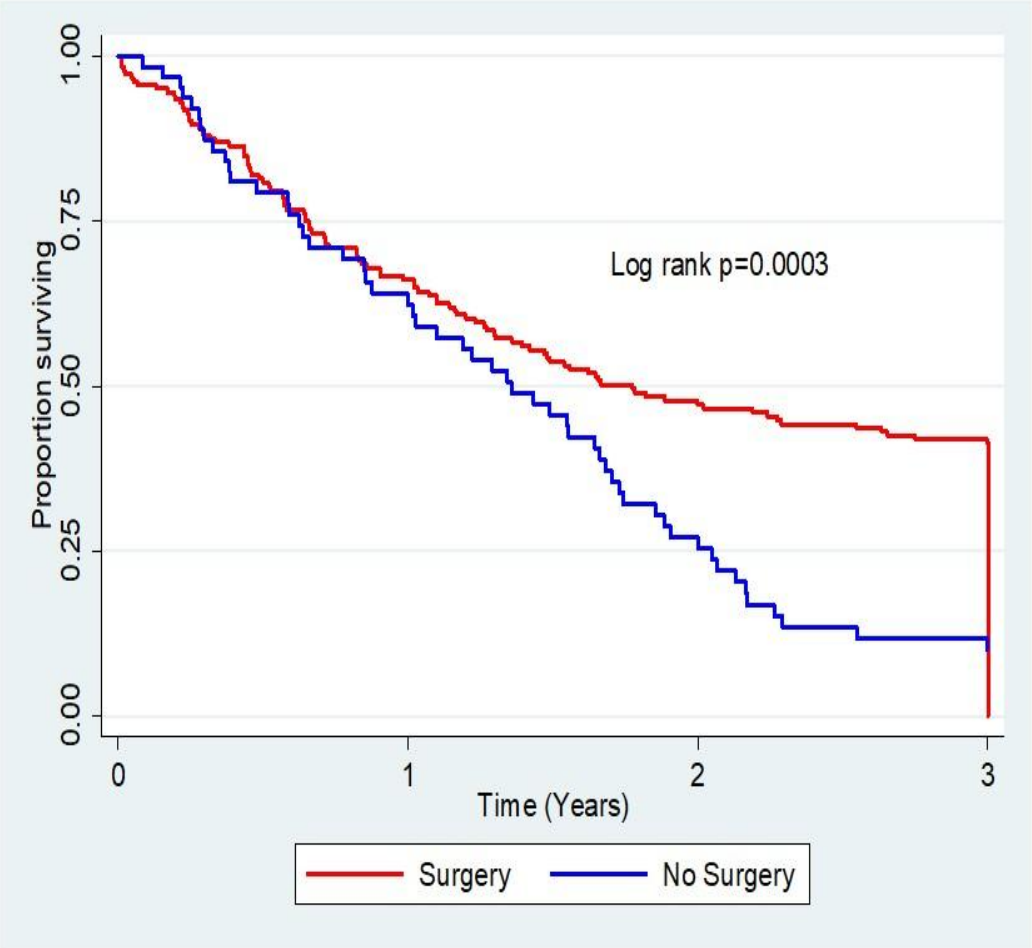


**Figure 1:** Kaplan-Meier estimates of curative surgery alone, which has better survival rates than no surgery

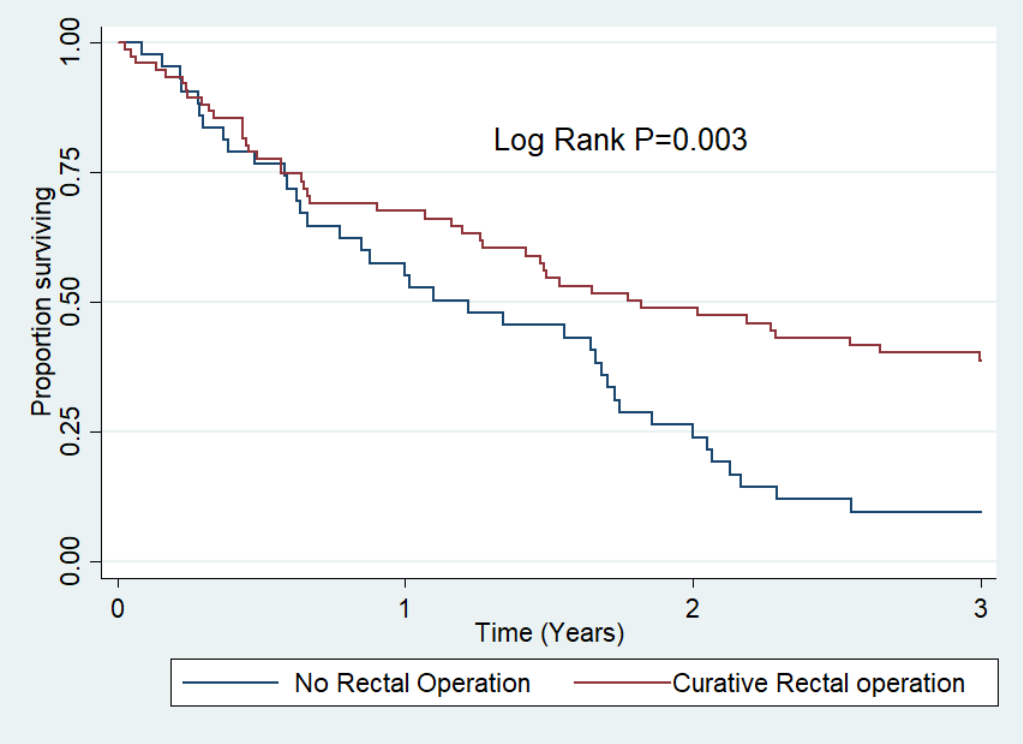


**Figure 2:** Kaplan-Meier estimates of curative rectal surgery alone, which has better survival rates than no surgery

Figure 2 shows that curative rectal cancer surgery had a better survival outcome than no curative rectal cancer surgery for rectal cancer patients, and this reached statistical significance (p=0.003). Table 3 shows the 1-, 2- and 3-year overall survival rates for curative rectal cancer surgery, which were 67.6%, 48.9% and 38.8%, respectively.

**Table 3:** 1,2 and 3-year overall survival for curative surgery versus no surgery for rectal cancer

| | **Curative Surgery** | | **No surgery** | |
|---|---|---|---|---|
| **Years** | **Survival (%)** | **95% CI** | **Survival (%)** | **95% CI** |
| 1 | 67.6 | 55.6 – 77.0 | 55.2 | 39.1 – 68.6 |
| 2 | 48.9 | 36.9 – 59.8 | 26.4 | 14.3 – 40.2 |
| 3 | 38.8 | 27.5 – 50.0 | 9.6 | 3.1 – 20.7 |

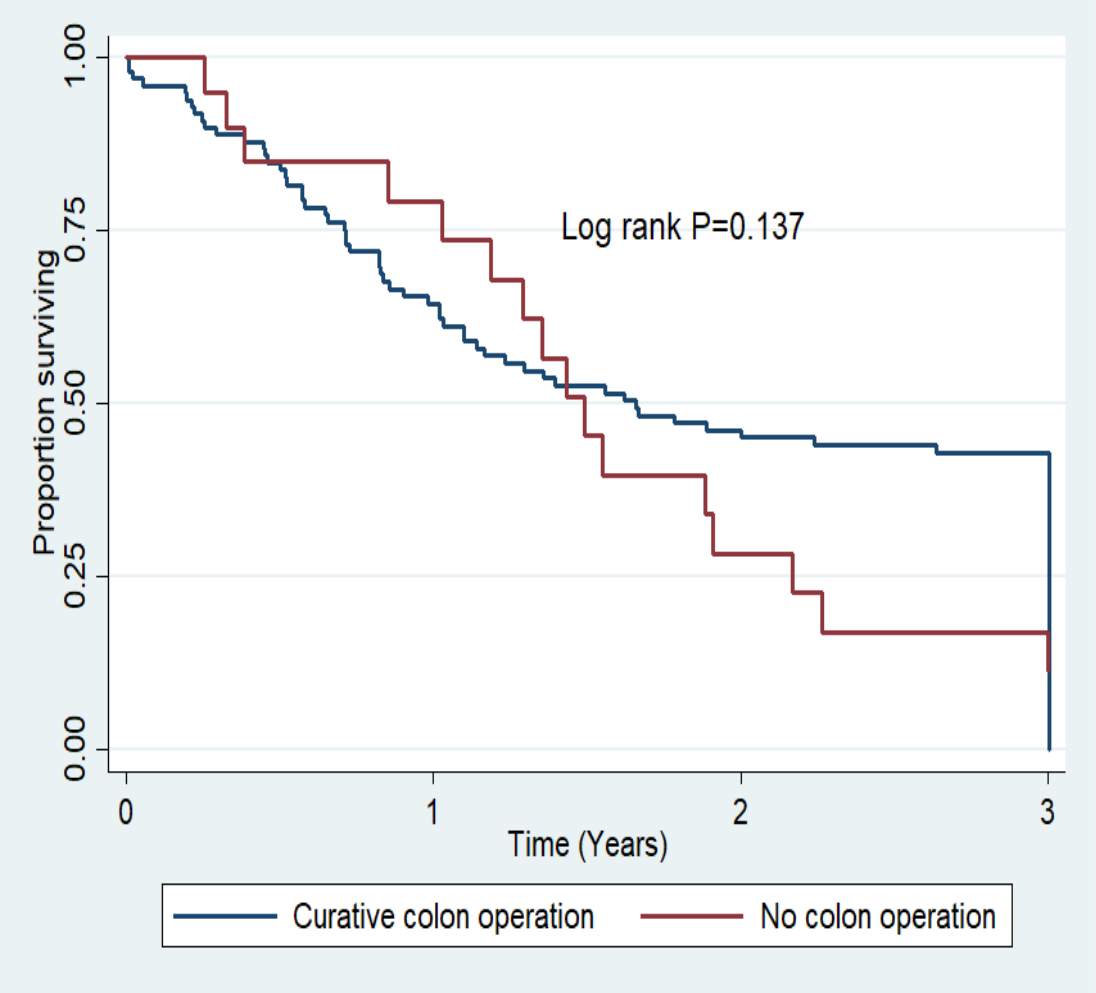


**Figure 3:** Kaplan-Meier estimates of curative colon surgery alone showing a tendency towards better survival rates than no surgery

**Table 4:** 1-,2-, and 3-year overall survival for curative surgery versus no surgery for colon cancer

| | **Curative surgery** | | **No surgery** | |
|---|---|---|---|---|
| **Year** | **Survival (%)** | **95% CI** | **Survival (%)** | **95% CI** |
| 1 | 64.4 | 53.9-73.1 | 79.3 | 53.7 – 91.7 |
| 2 | 45.1 | 34.9 – 54.8 | 28.3 | 10.4 – 49.6 |
| 3 | 43.0 | 32.9 – 52.7 | 11.3 | 1.9 – 30.2 |

Curative colon cancer surgery showed a tendency towards better survival than having no colon cancer surgery among colon cancer patients; however this did not reach statistical significance (p=0.137) (Figure 3). Table 4 shows the 1-,2-, and 3-year overall survival rates for curative colon cancer surgery, which were 64.4%, 45.1% and 43.0%, respectively.

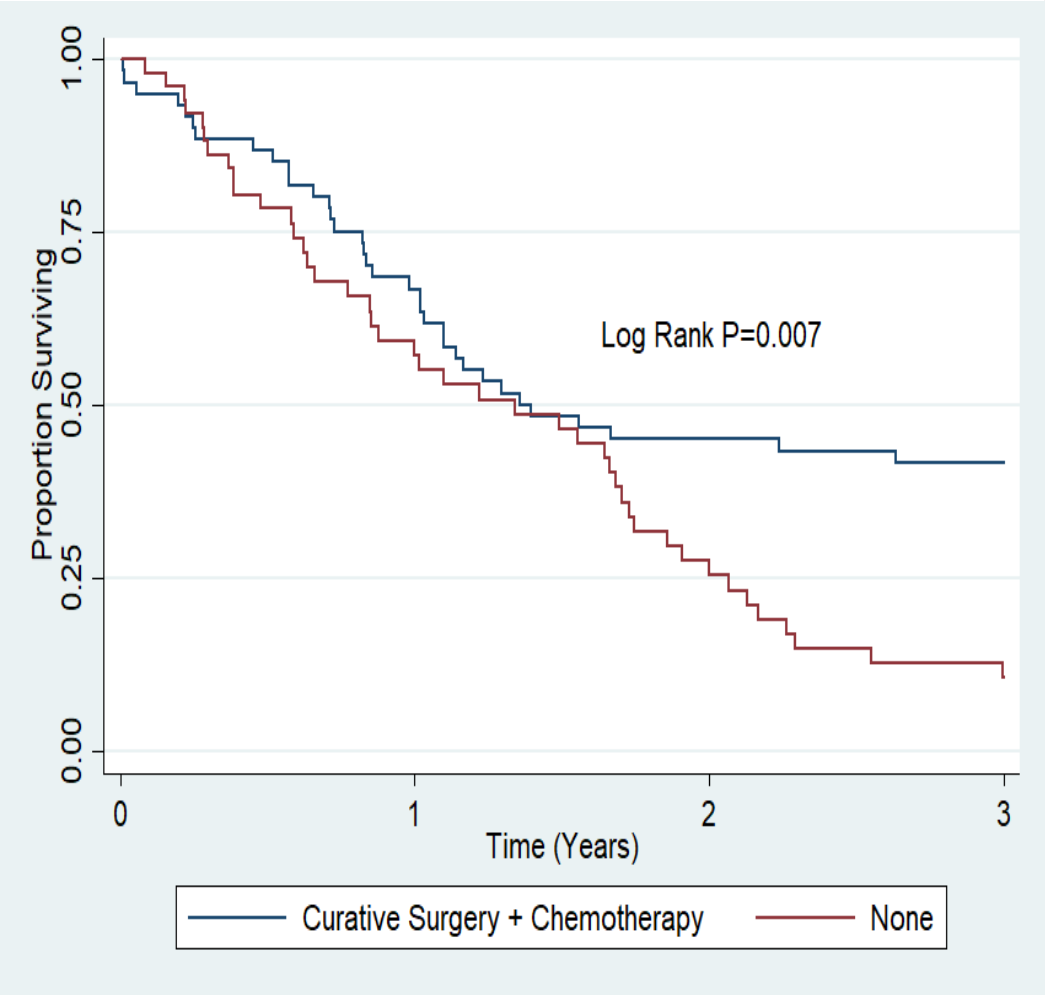


**Figure 4:** Kaplan-Meier estimates showing better survival rates with curative surgery and adjuvant chemotherapy for select cases of stage II CRC and all stage III CRC patients

Curative surgery and adjuvant chemotherapy were given to 61 (24.7%) selected stage II and all stage III colon and rectal cancer patients. Curative surgery followed by adjuvant chemotherapy for selected stage II and all stage III colon and rectal cancer patients showed a better survival than no

surgery and no adjuvant chemotherapy, and this reached statistical significance (p=0.007) (Figure 4).

**Table 5:** 1-,2-,3-year overall survival rates for curative surgery and adjuvant chemotherapy versus no treatment for selected stage II and all stage III colorectal cancer

| | **Curative Surgery** | | **No Surgery** | |
|---|---|---|---|---|
| **Years** | **Survival (%)** | **95% CI** | **Survival (%)** | **95% CI** |
| 1 | 66.8 | 53.4 – 77.2 | 57.2 | 42.2 – 69.7 |
| 2 | 45.1 | 32.3 – 57.1 | 27.6 | 15.8 – 40.6 |
| 3 | 41.8 | 29.3 – 53.8 | 10.6 | 3.9 – 21.2 |

Table 5 shows the 1-,2- and 3-year overall survival rates for curative surgery followed by adjuvant chemotherapy for selected stage II and all stage III colorectal cancer patients, which were 66.8%, 45.1% and 41.8%, respectively. Postoperative adjuvant radiotherapy following curative rectal resection was administered in only 12 (4.86%) patients and no rectal cancer patients received neoadjuvant chemoradiotherapy during this time period in this study.

## Discussion

In this study, our findings demonstrate that providing surgical and oncological care is crucially important to address the increasing burden of CRC in East Africa. The mainstay of treatment for colorectal cancer is curative surgery. Selected patients requiring adjuvant chemotherapy following curative colon or rectal resection showed improved survival. The well-established standard treatment for locally advanced rectal cancer has been neoadjuvant chemoradiotherapy, which has a survival benefit [17,18]. However, no patients had neoadjuvant chemoradiotherapy, and very few patients had adjuvant chemoradiotherapy between 2008 and 2018 in our rectal cancer patient cohort; therefore, the effect of this treatment on survival could not be assessed. During this time period, radiotherapy services were often lacking in Uganda.

The mortality risk was greater in patients who opted not to have an operation in comparison to those patients who had curative surgery in our study. The burden of disease that requires surgical care is approximately 30%; therefore, there is a considerable need for surgical care in resource-limited settings [19]. In low-income developing countries, the incidence of CRC is not as high; however, the mortality rate is high, due to differences in the early diagnosis and treatment of CRC [20].

Since low-income developing countries are experiencing a steady increase in the incidence of CRC, they are therefore experiencing a shift in the burden of cancer [21]. Therefore, an expansion in the surgical and oncological capacity is required to cope with the increasing demand for CRC patient care [22]. Millions of people in Ugandan and generally within East Africa will benefit from the expansion and decentralization of surgical and oncological care for CRC [23-25]. Survival is improved if and when curative surgical resection is an option for CRC patients.

The health facilities in our study setting are referral centres for both colonoscopy and surgery services for most of the country. However, many hospitals in the rural parts of Uganda do not have endoscopy services or specialised infrastructure for CRC surgery. The outcomes experienced in our

referral hospitals in central Uganda emphasize the need for further surgical training, oncology training and infrastructure as health priorities. Colonoscopy services are limited throughout Uganda and generally in East Africa despite flexible sigmoidoscopy screening having been shown to result in a decrease in CRC incidence and mortality [26,27]. National screening guidelines have not been developed and are still being conceptualized in Uganda, and the public through primary health care providers needs to be educated further to present early to hospital for an early diagnosis of CRC.

Even though colonoscopy services are available in our referral hospitals in central Uganda, the number of cases diagnosed with CRC by preventative screening is still very limited. Almost all of the patients in our cohort presented with symptoms and signs of CRC resulting from a long delay prior to presentation and treatment. Survival is improved with the early diagnosis and treatment of CRC [28]. In our study, a significant number of CRC patients did not opt to undergo curative resection which is a concern in this part of the world where health literacy remains a challenge even though the number of individuals seeking health care is steadily increasing. Possible reasons for avoidance of an operation include the avoidance of a colostomy, referral for preoperative radiotherapy or chemotherapy and never returning for the surgery and the cost of the operation.

The recent increase in the numbers of patients undergoing curative CRC resection may be due to increased recognition of the existence of CRC in rural Uganda and an improved referral system of CRC patients to specialised health facilities in central Uganda. However, difficulties are still encountered by patients from rural resource-limited parts of the country in accessing appropriate surgery and oncology care, which may be overcome by developing cancer patient support groups. An improvement in the early diagnosis of CRC and access to appropriate surgery and oncology treatment may help improve the CRC survival rate in Uganda.

**Comment [J1]:** The discussion requires some literature review to for comparison's sake with other studies that have been done. Unless no similar study has been conducted anywhere.

In the clinical records of our patient cohort, many patients were referred for neoadjuvant chemoradiotherapy for rectal cancer and adjuvant chemotherapy for colorectal cancer and radiotherapy for rectal cancer. However, only a small number of patients (4.85%) received radiotherapy postoperatively for rectal cancer due to the lack of these services in the country during this time period. Therefore, in our study, the impact of radiotherapy on tumour recurrence and survival could not be assessed.

Decentralization of chemotherapy and radiotherapy services in the country may increase access for CRC patients to this treatment. This is particularly important for communities in resource-limited rural areas of Uganda. In high-income developed countries, the survival of CRC patients has been shown to improve significantly with chemotherapy and radiotherapy; hence, there is a need to expand this treatment in low-income developing countries [29]. Our study unequivocally showed the benefit and improved survival of CRC patients receiving curative surgery followed, if necessary, by postoperative chemotherapy. Only seven patients received palliative surgery due to advanced presentation with large bowel perforation needing Hartman's procedure or diversion colostomy. Many of these patients had advanced rectal or colon cancers and required palliative chemotherapy postoperatively.

## Conclusions

Globally, the role of curative surgery and adjuvant therapy in the management of CRC is known; however, in resource-limited settings, the results of this study support their utilization. The findings in our study therefore serve to encourage the expansion of CRC care by improving the surgery and oncology infrastructure in resource-limited settings, due to the increasing burden from CRC in East Africa. This will lead to an improvement in the national survival rate of CRC in the Ugandan population.

## Study strengths and limitations

Our study has the largest number of patients, mainly from referral hospitals in central Uganda, who receive CRC patients from different regions of the country. Therefore, our results can be generalized for all the country. Another strength of this study is the focus on an underestimated CRC population in Uganda. Experienced research assistants from the Kampala Cancer Registry collected the data from the hospitals and had experience and a crucial role in maintaining the quality of the data. Many patients did not choose to undergo an operation for potentially curative disease, which highlights the reality of care in our setting and the need to promote surgical and oncological care.

Several limitations were encountered in our study. Compared to high-income developed countries, difficulty was encountered in obtaining complete data from the medical records retrospectively. Selection bias could have been introduced during the collection of secondary data from the Kampala Cancer Registry, as patients with no clinical data or missing demographic clinical data were excluded. This is an understood limitation when conducting research in resource-limited settings [30,31]. However, our data was complete enough to contribute to the understanding of the importance of curative surgery and oncological treatment to improve the survival rate in Uganda and other low-income developing countries in East Africa.

In our setting, loss to follow-up of CRC patients from the surgery and oncology out-patient departments is a common problem. This was overcome with active follow-up of these patients by telephone calls and home visits in the community in different regions of Uganda. The loss to follow-up in this study was 6.07%, which was less than the 10% loss to follow-up, which was taken into account when estimating the sample size. A major limitation involved data being collected from the different hospitals, and surgical treatment was not standardised. As this was a retroprospective study, staging data on 23.07% of patients were missing. Underestimating the stage was also another limitation. Staging of CRC in the years 2008 – 2018 mostly involved a plain chest-X-ray and ultrasound scanning, with some having a CT abdomen/pelvis. In low-income developing countries such as ours, CT scanning is also largely inaccessible for many patients, especially those from rural parts of the country.

Therefore, the CRC stage at diagnosis was likely to be underassessed with inadequate high precision staging capacity. Another reason for underestimating the CRC TNM stage in this study is that the stage was radiological at diagnosis and not pathological. The lymph node assessment in this study was also radiological and not pathological; hence, this could have underestimated the extent of lymph node involvement during surgery, hence influencing oncological outcome for the curative surgical operations. Another limitation is that pathological data on surgical margin resection status were not available in colon cancer patients, and in rectal cancer patients, the circumferential resection margin status was also not available.

Although the management of colon cancer differs from rectal cancer, we grouped rectal and colon cancer together to understand the impact of surgical care and adjuvant chemotherapy. We had a fairly equivalent number of colon and rectal cancer patients with no difference in outcomes.

It would seem to be more appropriate to count the start of the survival time from the date of onset of colorectal cancer in the study participants. However, the date of histopathological diagnosis was used; hence, the time lag between the time the patients presented with symptoms and signs of CRC

and a diagnosis being made may be long. This may have underestimated our overall survival rate. A significant proportion of our patients could have also died of causes unrelated to colorectal cancer, as postmortems were not carried out, resulting in an inability to estimate cancer-related deaths and hence disease-free survival. This could also have resulted in underreporting of deaths leading to an overestimated survival rate.

## Declarations

### Ethical considerations

This work was part of the PhD study, which was approved by the Higher Degrees Research and Ethics Committee, School of Biomedical Sciences, College of Health Sciences, Makerere University (reference number: SBS-HDREC-630) and Uganda National Council for Science and Technology (reference number: HS-2574). To access and abstract data from the Kampala Cancer Registry and data from case files in the respective hospitals, a waiver of consent was obtained from the Higher Degrees Research and Ethics Committee, School of Biomedical Sciences, College of Health Sciences, Makerere University. The patient data accessed from the Kampala Cancer Registry were anonymized and maintained with confidentiality. The accessed data therefore complied with relevant data and privacy regulations of the Kampala Cancer Registry.

### Consent for publication

Written informed consent was obtained to actively follow up some of the participants in the community outside the catchment area of the Kampala Cancer Registry to determine their vital status. For those participants who had their vital status recorded in the Kampala Cancer Registry, the waiver of consent obtained from the Higher Degrees Research and Ethics Committee, School of Biomedical Sciences, College of Health Sciences, Makerere University, was applied.



**COMPETING INTERESTS DISCLAIMER:**

**Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.**

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