Survival outcomes of histopathological subtypes of colorectal adenocarcinoma in Ugandan patients

ABSTRACT

Background: High grade mucinous adenocarcinomas have been found to be more common in younger patients and are associated with a poor prognosis in the West. In Uganda, survival outcomes of the different histopathologic subtypes of colorectal adenocarcinoma (CRC) and lymphovascular invasion (LVI) is unknown. We determined the survival outcome of the different histopathologic subtypes of CRC and LVI among Ugandan patients.

Methods: A retroprospective cohort study on patients diagnosed with CRC from 2008 to 2018 were identified from the Kampala Cancer Registry and hospital medical records. Retrieved data included date of diagnosis, demographics, stage, grade and location of CRC. Our outcome was survival, and the main predictor variables were the histopathologic subtype, stage, grade and LVI. We plotted Kaplan-Meier curves for survival, tested the equality of survival by log-rank tests and used multivariable Cox regression to determine factors associated with survival.

Results: 12.4% patients predominantly had mucinous adenocarcinoma/signet ring colorectal carcinoma (MAC/SRCC) and 87.6% patients had classical adenocarcinoma (AC). The median age (SD) at diagnosis of MAC/SRCC was 47.8 (16.6) years and 53.8 (15.9) years for AC. SRCC/MAC was significantly associated with more LVI than AC (p=0.002). In multivariate analysis, factors associated with increased mortality included stage III (aHR=2.56; p=0.009) and stage IV (aHR=6.64; p <0.001). After adjusting for lymph node involvement and metastasis, SRCC/MAC patients had a shorter survival than AC patients; however, this difference was not statistically significant (p=0.229).

Conclusions: In Uganda, the proportion of MAC is similar to that found in the Western world. SRCC/ MAC were associated with more LVI than AC. SRCC/MAC showed a tendency towards decreased overall survival. In Uganda, more patients present with advanced-stage CRC which was associated with poor survival hence national screening guidelines are necessary to improve survival.

Keywords: colorectal adenocarcinoma; mucinous adenocarcinoma; signet ring colorectal carcinoma; classical adenocarcinoma; lymphovascular invasion; Uganda

Introduction

One of the major leading causes of cancer mortality worldwide is colorectal carcinoma [1]. Colorectal carcinoma is the fifth most common malignancy in Sub-Saharan Africa according to the International Agency for Research on Cancer and American Cancer Society [2].

Across the world, the incidence of CRC varies with Africa and Asia having a low incidence and Western Europe, the USA, Australia/New Zealand and Japan having a high incidence of CRC. In Uganda, CRC is the fourth most common gastrointestinal malignancy [3]. The Kampala Cancer Registry has shown that colorectal carcinoma has a low incidence in Uganda; however, there are increases occurring, especially among women (4). The age standardized incidence rate has increased from 5.2 per 100,000 population for 1991-1995 to 9.0 per 100,000 population for 2006-2010 in females [4]. This gives a 4.1% annual percentage change in the incidence of CRC in females in Uganda, which is a greater increase than that in males [4].

The histopathologic subtypes of colorectal adenocarcinoma have been classified according to the WHO (World Health Organisation) classification of gastrointestinal tumours into mucinous adenocarcinomas (MACs), signet ring carcinomas (SRCCs) and classic adenocarcinomas (ACs) [5]. Apart from the TNM stage, the histopathologic subtype of colorectal adenocarcinoma may influence outcome [5]. Appropriate treatment strategies may be adopted by clinicians with knowledge of the effect of these histopathologic subtypes of colorectal adenocarcinoma on survival in Ugandan patients.

In 10%-15% of CRC, lymphovascular invasion has been identified, which is the presence of tumour cells in vascular channels or endothelium-lined channels [6,7,8]. A crucial step in the dissemination of cancer cells and lymph node metastases is lymphovascular invasion (LVI). LVI has been shown in localized carcinoma to increase the risk of micrometastases [9]. Studies in various cancers, including CRC, have shown the unfavourable prognosis associated with LVI [10-12]. Mucinous adenocarcinoma and signet ring cell carcinoma are two histopathologic subtypes of colorectal adenocarcinoma that have been associated with higher lymphovascular invasion and lymph node involvement [13-15].

A recent study in Uganda reported that younger patients commonly have mucinous adenocarcinoma and poorly differentiated histopathology [16]. Recent studies from the West have also found that MAC and SRCC present predominantly in female patients at a younger age, with a more advanced stage and with more peritoneal involvement [15-19]. Additionally, MAC and SRCC have been considered to have a poor prognosis compared to classical AC [15,19]. In Uganda, the clinicopathological features and survival of the different histopathologic subtypes and LVI status in colorectal adenocarcinoma are unknown. Hence, the aim of this study was to determine the effect of the histopathologic subtypes and lymphovascular invasion in colorectal adenocarcinoma on survival outcome in Ugandan patients.

Methodology

Study Design/Setting

This was a retroprospective cohort study that was conducted on colorectal adenocarcinoma participants with data linked to the Kampala Cancer Registry and/or data from medical records from Masaka Regional Referral Hospital, Mulago National Referral Hospital, Uganda Martyrs' Hospital Lubaga, Mengo Hospital and Hospice Africa Uganda. These CRC participants had data from the Kampala Cancer Registry and/or data from medical records that were linked to their corresponding tissue blocks situated in the archives of the Department of Pathology, Makerere University and archives of Multisystems Histology Laboratory in Kampala.

Mulago Hospital is the largest specialised hospital and the National Referral Hospital in Uganda, with a 1,500 bed capacity. Masaka Regional Referral Hospital, Mulago National Referral Hospital, Uganda Martyrs' Hospital Lubaga, Mengo Hospital and Hospice Africa Uganda are located in Central Uganda and receive patients from all regions of the country.

Study Population and Selection of Participants

Data from 201 colorectal adenocarcinoma participants, recorded from 2008 to 2018 were retrieved retrospectively from the Kampala Cancer Registry, and medical records from the hospitals mentioned in the study setting.

The retrieved data included patient demographics (age, sex), pathological factors such as CRC location, histopathological subtype (AC, MAC, SRCC), stage, grade and lymphovascular invasion of CRC tumors. The age in completed years on the incidence date was defined as the age at diagnosis. The radiological staging system was used to stage CRC. This was based on the size of the primary tumor (T), the extent of lymph node metastasis (N) and the presence of distant metastases (M) [20].

The site of colon cancer was defined as the cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon and rectosigmoid colon. Rectal cancer was defined as a cancer within 5 cm of the anal verge.

Inclusion criteria

Participants with histologically confirmed colorectal adenocarcinoma linked to data in the Kampala Cancer Registry and/or the clinical case files in the participating hospitals with the date of diagnosis were included in this study.

Exclusion criteria

We excluded participants with missing/poor tissue block samples as the outcome variable could not be determined with certainty, participants with tissue blocks obtained after having had chemotherapy or radiotherapy, participants with multiple cancers other than colorectal adenocarcinoma and duplicate cases, in situations of double entry.

Follow-up

A follow-up period of three (3) years for each study participant was imposed. A patient's follow-up began at the date of CRC diagnosis [time zero (t_0)]; and continued up to the occurrence of:- (i) death, (ii) loss to follow-up or (iii) censoring at the end of three years. 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. Figure 1 illustrates the recruitment of colorectal adenocarcinoma patients linked to CRC tissue blocks and clinical data.

Censoring

Participants who were lost before the closing period of this study or dropped out were considered consored. Random or noninformative censoring was considered when due to a factor unrelated to the study outcome. Nonrandom or informative censoring was considered when due to a factor related to the study outcome, death.

Age at diagnosis and stage of CRC were the detereminants tested for association with loss to follow-up using the Cox model.

Index date and closing date to follow up

The starting date for the calculation of survival was the index date and is actually the date of diagnosis of colorectal cancer by histological diagnosis. The inclusion dates were between 1 January 2008 and 31 December 2018 with a closing date on 31 December 2021.

Survival time

A follow up period of 3 years was imposed. Survival time was calculated at the time in months between the index date and the date of death, closing date or loss to follow-up whichever was earliest.

Data Quality

All CRC cases had histologically confirmed colon or rectum adenocarcinoma. CRC cases were not based only on death certification. Age in completed years on the incidence date defined the age at diagnosis. Birth certificates were not necessarily used to verify age, as they were not available.

Evaluation of histopathology, grade and lymphovascular invasion of colorectal adenocarcinoma

The diagnosis was confirmed to be invasive adenocarcinoma and the histopathologic subtype of colorectal adenocarcinoma (AC, SRCC and MAC) was determined by hematoxylin and eosin (H&E) staining on slides obtained from the corresponding tissue blocks. The WHO Pathologic classification of colorectal adenocarcinoma was used to classify the histopathologic subtypes of colorectal adenocarcinomas as classical adenocarcinoma (AC), mucinous adenocarcinoma (MAC), or signet ring colorectal carcinoma (SRCC) (5). Classical adenocarcinoma (AC) is defined as having classical glandular formation and glandular structures that are configured. Signet ring colorectal carcinoma (SRCC) was defined by the presence of >50% of tumour cells having signet ring cell features and having an intracytoplasmic mucin vacuole that pushes the nucleus to the periphery. Mucinous adenocarcinoma (MAC) was defined as having large glandular structures having pools of extracellular mucin with more than 50% of the tumour occupied by extracellular mucin.

The histological grade of colorectal carcinoma was determined using the WHO classification system: well differentiated (G1), moderately differentiated (G2) or poorly differentiated (G3) depending on the extent of glandular appearance (21,22). Adenocarcinomas displaying more than 95% gland formation were conisdered grade 1; Grade 2 in those between 50 and 95% gland formation; Grade 3 in those less than 50% gland formation. The presence of lymphovascular invasion was denoted by 1, and the absence of lymphovascular invasion was denoted by 0.

The confirmation of invasive adenocarcinoma, subtype of colorectal adenocarcinoma, grading and presence or absence of lymphovascular invasion were reported by two consultant pathologists who were blinded for vital status. These laboratory investigations were carried out at the Department of Pathology, School of Biomedical Sciences, College of Health Sciences, Makerere University.

Statistical Analysis

Participants' background characteristics were summarized by the mean or median (depending on the distribution) for continuous variables and percentages for categorical variables. The Kaplan-Meier method was used to estimate overall survival (OS). The log-rank test was used to compare the survival of histopathologic subtypes of adenocarcinoma. Bivariate and multivariate modelling was carried out using Cox proportional hazards regression to identify the significance of the variables associated with survival. Statistical significance was considered with a p-value of <0.05, and all statistical analyses were performed using STATA 14.0.

Results

Of the 201 colorectal cancer patients, the mean age (SD) at diagnosis for AC was 53.8 (15.9) years and 47.8 (16.6) years for SRCC or MAC. The study participants were predominantly female in the AC group (52.8%), predominantly female in the MAC group (59.1%) and predominantly male (66.7%) in the SRCC group.

The frequencies of ACs, MACs and SRCCs were 87.6%, 11.0% and 1.5%, respectively. The majority: 53.2% were females, 48.8% were in the 50-74 year age group, 53.9% were stage III, 43.5% were T3, 44.2% were N1, 57.7% were moderately differentiated adenocarcinoma, 54.2% were rectal adenocarcinoma and 79% of all colorectal adenocarcinomas had lymphovascular invasion (Table 1).

Clinicopathological characteristics

Location of CRC

SRCC and MAC were commonly found in the rectum (60%), while AC was more commonly found in the rectum (53.4%) and sigmoid colon (25.0%). The distribution of SRCC and MAC and AC across the different parts of the colon is shown in Table 1.

Grade of CRC

The percentage of SRCC and MAC and AC varied across the grade distribution. SRCC and MAC presented as high-grade tumours (poorly differentiated) in 16.0% of patients and 10.2% of high-grade tumours in AC (Table 1). SRCC and MAC presented as moderately differentiated tumours in 60% of patients, and AC presented with moderately differentiated tumours in 57.4% of patients (Table 1). ACs were well differentiated in 32.4% of patients, while 24% of SRCC and MAC were well differentiated (Table 1).

Primary Tumour invasion (T)

Table 1 shows that the majority of patients with SRCC and MAC (52.9%) at the time of presentation had diffuse invasion of tumours in the colonic wall, as demonstrated by their T3 or T4 stage. The majority of patients with AC (73.0%) also had diffuse invasion of tumours in the colonic wall (T3 or T4 stage) at the time of presentation.

Lymph node involvement

The majority of SRCC and MAC (65.7%) had lymph node involvement (N1 or N2+N3) at the time of presentation (Table 1). Among SRCC+MAC, the percentage of node-negative disease (N0) was 47 (34.3%) and 7 (41.2%) among ACs (Table 1).

AJCC Stage

The majority of SRCC+MAC and AC tended to present at an advanced stage: stage III+IV: SRCC+MAC, 64.7% and AC, 66.4% (Table 1). Early stage presentations (stage I+II: SRCC+MAC were 35.3% and 33.6% were AC (Table 1).

Lymphovascular invasion (LVI)

LVI was detected in 124 (79.0%) of all colorectal adenocarcinomas, with the presence of 100% LVI in SRCC+MAC and 75% LVI in AC. SRCC+MAC was significantly associated with more lymphovascular invasion than AC (p=0.002). The comparison between CRCs with and without LVI showed that the group more likely to be moderately and poorly differentiated was the LVI group; however, this did not reach statistical significance (p=0.711). No significant association was found for age, sex, tumour site, stage or grade between the LVI and non-LVI groups (Table 2).

Overall survival

The overall 3-year survival rate was 32.4% for all colorectal adenocarcinomas in our study (Figure 2). The 3-year survival rate for SRCC and MAC was 40.2% and was not significantly different when compared to 31.4% for AC (p=0.494) (Figure 3, Table 3).

Survival by histopathological subtypes

Table 4 shows the survival by histopathological subtype, where there was no difference in overall survival between SRCC+MAC (40.2%) and AC (31.4%) (p=0.494). For stage III, SRCC+MAC patients had better survival (67.5%) than AC patients (22.3%) (p=0.029). For lymph node involvement, SRCC + MAC patients with N2+N3 had a better survival (80.0%) than

AC patients (14.8%) (p=0.024). There was no difference in survival between SRCC+MAC and AC by grade, LVI or tumour depth.

The stage-specific overall survival rates, which included:- stage I: SRCC+MAC 40%; AC 65.3% p=0.134; and stage III SRCC+MAC, had a better survival than AC, and this difference reached statistical significance (p=0.029). The proportion of SRCC+MAC patients surviving with LVI was 40.2% higher than that of AC patients with LVI (25.9%); however, this difference did not reach statistical significance (p=0.27).

Factors associated with survival

Table 5 indicates that in the bivariate analysis, the risk of mortality was 0.82 (95% CI: 0.47-1.44) times higher in the SRCC+MAC group than in the AC group. Mortality risk was 1.09 times higher among females than males, and 0.76 and 0.79 times higher among patients aged 50-74 and >75 years at diagnosis than among those aged <49 years, respectively. Compared to patients diagnosed at stage I, patients with stage II, III and IV disease were 1.98 (95% CI: 0.87-4.48), 2.50 (95% CI: 1.24-5.05), and 6.18 (95% CI: 2.74-13.95) times more likely to die. The LVI group showed a 14% increased risk of death compared to the non-LVI group; however, this did not reach statistical significance (cHR=1.14; p=0.594). Location of CRC, and grade were not associated with mortality in the bivariate analysis.

In the multivariate model, the stage of CRC at diagnosis was the only factor independently associated with mortality. Thus, compared to stage I patients, patients who were in stages II, III and IV had a 2.00 (95% CI: 0.88-4.56), 2.56 (95% CI, 1.26-5.18) and 6.64 (95% CI, 2.85-15.44) times likelihood of mortality, respectively. Age, sex and grade of adenocarcinoma did not independently predict mortality. Although patients with SRCC+MAC showed a trend towards shorter survival than patients with AC (Figure 5), this difference in survival was not statistically significant after adjusting for lymph node involvement (p=0.229).

Association of lymphovascular invasion with overall survival

The 3-year overall survival for colorectal adenocarcinoma with lymphovascular invasion was 28.6% (95% CI: 20.7-37.0) and without lymphovascular invasion was 28.1% (95% CI: 13.4-44.9) (Figure 4).

Discussion

This cohort study analysed the relationship between clinicopathological features and survival outcomes of Ugandan patients with classic adenocarcinoma, mucinous adenocarcinoma and signet ring colorectal carcinoma. We found that compared to AC, the clinicopathological characteristics associated with SRCC and MAC involved a younger age and poorer grade of differentiation. The rectum was the most commonly involved location for SRCC, MAC and AC. SRCC and MAC were not predominantly found in the right colon. We also found that there was a tendency for the different histopathological subtypes and the presence of LVI to affect the

overall survival. Many patients in Uganda present to hospital with an advanced stage of colorectal adenocarcinoma and this was associated with poor survival.

In our study, almost nine in every ten patients had AC, approximately one in ten had MAC and approximately two in every one hundred patients had SRCC. The proportions of the different histopathologic subtypes reported in our study are similar to those reported in studies from Asian countries (AC: 93.7%, MAC: 5-15%, SRCC: approximately 1%) and Western countries (AC: 88.8%; MAC: 10.3%; SRCC: 0.9%) [1]. A study on rectal carcinoma from India showed the proportion of MAC to be 7.7%, while the proportion of SRCC was 13.6% [21-24]. This implies that the proportions of MAC and SRCC tend to vary between populations in different parts of the world [25].

We found that 12.4% of patients commonly present with MAC and SRCC and that they are more likely to have lymphovascular invasion and lymph node metastasis. Apart from MAC and SRCC being found more commonly in young patients and having poorer grades of differentiation, they were also associated with higher lymphovascular invasion. This is consistent with results from other studies [13-15, 23, 26-29]. These findings suggest that compared to AC, MAC and SRCC have a stronger tendency to metastasize and to invade the bowel wall.

A more advanced stage at presentation with MAC and SRCC has been reported compared to AC in Western and Asian studies [23, 26-29]. Before undergoing radical surgery, MAC and SRCC may already have developed subclinical metastases. However in our study, even AC tended to present with an advanced-stage CRC and this may be due to more patients in developing countries presenting with advanced-stage CRC due to a delay in coming to hospital with symptoms of CRC compared to developed countries, irrespective of the histopathological subtype of CRC.

In CRC patients, the prognostic significance of MAC and SRCC has been controversial. Our study tended to show a difference in overall survival between the SRCC+MAC group and the AC group when adjusting for lymph node status and metastasis. This is consistent with findings in small reports [30,31] and two meta-analyses [32,33] that identified MAC as an independent factor predicting poor survival. There were however no significant differences confirmed between SRCC+MAC and AC when analysed by tumour stage. However, for stage III, a better overall survival was registered for the SRCC+MAC group compared to the AC group, and this reached statistical significance. This finding is similar to findings in a study by Hogan J et al [34]. A plausible explanation may be that increased extracellular mucin from MAC due to alteration in gene expression may result in a degree of inhibition of cellular neoplastic migration into the extracellular space and subsequently into the lymphatic and systemic circulations. This results in less distant metastasis from stage III SRCC+MAC and hence a better prognosis [34].

When comparing survival outcomes, we found that the 3-year overall survival for MAC and SRCC tended to be lower than that for AC when adjusting for lymph node status. Some studies have also shown that MAC and SRCC have a negative prognostic effect on CRC patients [14,35]. MAC has been found to have a negative prognostic factor for rectal cancer but not in colon cancer on analysis of the US National Cancer data set (NCBD) [23]. Analysis of the US Surveillance, Epidemiology and End Results (SEER) dataset found that MAC had a protective effect on right-sided colon cancer but had no prognostic effect on left-sided colon cancer.

However, for rectal cancer, MAC and SRCC had a negative prognostic effect [19]. The results from these population studies inferred that MAC and SRCC in different primary locations may have different effects on CRC patients' overall survival. However, a study from Italy showed no prognostic difference in overall survival between MAC and AC irrespective of tumour location [36]. Similarly, a study from India, on rectal cancer patients showed no difference in overall survival among SRCC, MAC and AC [25, 36-38].

MAC and SRCC showed a trend towards poorer survival in our study, similar to findings from developed countries. Possible reasons are that the proportions of the different histopathological subtypes are similar in Uganda compared to developed countries. However, the stage of CRC at presentation differs in that Ugandan patients present at an advanced stage compared to patients from developed countries, hence resulting in the poor overall 3-year survival of CRC in Ugandan patients of only 32.4%.

Several studies have shown that mucinous and signet ring cell type tumours are more likely to have organ infiltration and lymph node involvement [15,39]. In our study, although the majority of SRCC and MAC presented with advanced tumour involvement of the bowel wall and lymph node involvement, so did AC present with advanced tumour involvement of the bowel wall and lymph node involvement, as many patients in Uganda present with advanced stage CRC due to a delay in diagnosis. SRCC has been shown in studies to have a poorer survival rate [40], which may be due to a higher tumour grade and stage and tendency for nodal spread and peritoneal involvement. Our study showed a tendency towards a poor survival rate with SRCC; however, there were only a few patients who presented with this histopathologic subtype. Unlike other colorectal carcinomas, which arise from the adenoma-carcinoma sequence, SRCC is considered to arise from flat colonic mucosa. Therefore few SRCC patients are diagnosed by screening colonoscopy at an early stage [41]. This issue may be overcome in the future using DNA bowel stool testing which is a noninvasive laboratory test that identifies DNA changes from colorectal cancer cells shed in a stool specimen.

MAC is a carcinoma that consists of >50% extracellular mucin, while SRCC is a carcinoma that consists of >50% signet ring cells. Mucin has been shown to demonstrate importance in the prognosis of CRC in several studies [42,43]. Studies that have enrolled CRC patients receiving chemotherapy (FOLFOX) in different stages, particularly stage III, have shown a poorer prognosis in patients with MAC [42,43]. Other recent studies have also shown that MAC is resistant to chemoradiation (33). SRCC and MAC tend to have a poor prognosis due to the higher rate of lymphovascular invasion and infiltrating tumor growth pattern [44]. An increased rate of lymph node involvement at presentation with SRCC and MAC compared to AC was found in our study, which is similar to findings in other studies. The aggressive nature of SRCC can be explained by understanding the exact molecular mechanisms underlying the pathogenesis of this subtype of colorectal adenocarcinoma. Despite SRCC having a high level of microsatellite instability, which is associated with better survival outcomes, the prognosis remains poor. SRCC has high levels of BRAF V600E mutations and low levels of K-ras mutations compared to AC. BRAF mutations are a poor prognostic factor and could explain the poor prognosis associated with SRCC [41,42, 44-48]. Overexpression of mucin regulatory genes such as MUC2, HATH1, SOX215, MUC5, claudin 18 and Reg IV in SRCC leads to excessive intracellular mucin

production, which results in disruption of cell-to-cell adhesions and the E-cadherin/β-catenin complex, and this results in metastases of CRC [34,49]. Other authors have shown that aberrant hypermethylation due to the CpG island methylator phenotype (CIMP) in SRCC leads to reduced expression of E-cadherin, facilitating the spread of the tumour [50].

This may explain the trend in poor survival in our study with SRCC and MAC histopathological subtypes. However, compelling evidence cannot be obtained from the data in our study. Late diagnosis at a more advanced stage and high risk of local recurrence with MAC has more clinical importance than the relation to survival. The low suitability of the standard approach for treating CRC may also explain the poor prognosis of patients with MAC and SRCC [51]. Special treatment targeting the genetic constitutions of SRCC and MAC may improve the treatment and prognosis of these histopathological subtypes.

In our study, a poorer survival outcome was registered with increasing stage for CRC. This finding is in agreement with many studies that showed poorer survival associated with an advanced tumour stage. For early-stage disease irrespective of histopathologic subtype, the survival rate was high despite all the limitations in health service delivery. Therefore, the findings in our study emphasize the importance of early diagnosis by having national screening programmes in place and early treatment of CRC. However, the histological subtype of colorectal adenocarcinoma may not affect survival in patients who have had resection of early-stage primary CRC with no lymphovascular invasion and no lymph node involvement [52].

The proportion of lymphovascular invasion was 79% among all colorectal adenocarcinomas in our study, with this proportion varying widely between 10% and 89.5% among populations [6,7,52]. This high proportion in our population could be explained by the presentation at an advanced stage of colorectal adenocarcinoma in Ugandan patients. Lymphovascular invasion was more commonly associated with higher CRC stage and with moderately and poorly differentiated adenocarcinomas. Therefore, lymphovascular invasion is closely related to the features of aggressive tumours. While our study showed a trend towards poorer survival with all colorectal adenocarcinomas associated with lymphovascular invasion, our findings have clinical relevance in that it suggests that the presence of lymphovascular invasion is an indication for more extensive resection of the colorectal tumour [53,54,55].

Conclusions

Despite the younger age of presentation of CRC in our population, the proportion of MAC in Uganda is similar to that found in the Western world. SRCC and MAC histopathological subtypes presented with a higher incidence of lymphovascular invasion than AC. SRCC and MAC histopathological subtypes showed a tendency for poorer survival compared to AC in Ugandan patients. More patients present with an advanced stage of CRC in our population compared to Western populations and this was associated with poor survival. This emphasizes the need for a national screening programme to detect CRC at an early stage in Uganda, which may result in a better survival outcome.

Limitations of study

There are several limitations encountered in our study. Due to the retrospective nature of the study, some data from the patients' clinical records and the Kampala Cancer Registry were missing. This could have led to a selection bias. Furthermore, many CRC tissue blocks were missing or of poor quality and could not be linked to data from the Kampala Cancer Registry and patients' clinical records. This resulted in a reduction of our sample size. When vital status was not recorded for participants outside the catchment area of the Kampala Cancer Registry, active follow-up was necessary in the community. Underreporting deaths from other causes may overestimate the cause-specific survival probability, as overall survival and not disease-free survival were used as the outcome measures. The date of onset of the symptoms of colorectal cancer in the patients would have been more appropriate for defining the start of counting the survival time; however, the date of first diagnosis was used in this study. It may be observed that the time lag between the onset of symptoms and presentation to the hospital for a diagnosis to be made, may be long, which may have led to an underestimation in measuring survival. The small number of cases of signet ring adenocarcinoma could not be analysed as a separate group; however, given the similarities with mucinous adenocarcinoma as an aggressive tumour enabled a fair comparison of classical adenocarcinomas (ACs) and signet ring cell carcinomas (SRCCs) combined with mucinous adenocarcinomas (MACs).

What is already known about this topic

- Across the world, the incidence of CRC varies with Africa and Asia having a low incidence and Western Europe, the USA, Australia/New Zealand and Japan having a high incidence of CRC.
- In Uganda similar to the rest of Sub-Saharan Africa most cases of CRC present at a later stage compared to the developed Western world.
- Studies from the West and in Uganda have found that MAC and SRCC histopathological subtypes present predominantly at a younger age in female patients, with a more advanced stage and hence a poorer prognosis.

What this study adds

- We found that 12.4% of patients in Uganda commonly present with MAC and SRCC and that they are more likely to have lymphovascular invasion and lymph node metastasis. This finding confirms that despite the younger age of presentation of CRC in Uganda, the proportion of MAC in our population is similar to that found in the Western world.
- The histopathological subtypes, SRCC and MAC showed a trend towards poor survival compared to AC in Ugandan patients.
- Similar to other Sub-Saharan African countries, the majority of patients in Uganda present with advanced stage CRC which is associated with a poor survival. This emphasizes the need for a national screening programme to detect CRC at an early stage in Uganda, which may result in a better survival outcome.

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 (HS-2574). To access and abstract data from the Kampala Cancer Registry, data from case files in the respective hospitals and conduct experiments on the corresponding tissue blocks of the participants, a waiver of consent was obtained from the Higher Degrees Research and Ethics Committee, School of Biomedical Sciences, College of Health Sciences, Makerere University.

Consent for Publication

Informed consent was obtained to actively follow up some of the participants in the community 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

The authors declare that they have no competing interests. There are no conflicts of interest between the authors.

Authors' contributions

Richard Wismayer originated the concept and proposal, designed experiments, collected data, performed the data analysis and wrote the first draft. Julius Kiwanuka performed data analysis and provided statistical support. Michael Odida and Henry Wabinga interpreted the hematoxylin and eosin slides for the histopathological subtype, grade and lymphovascular invasion status of all the participants. Michael Odida and Henry Wabinga also performed critical reviews of the manuscript. All authors approved of the final manuscript.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2018. CA Cancer J Clin. 2018; 68: 7-30.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
3. Obayo S, Lukwago L, Onem J, Faulx AL, Probert CS. Gastrointestinal malignancies at five referral hospitals in Uganda. Afr. Health Sci. 2017 Dec; 17(4): 1051-1058.
4. Wabinga HR, Nambooze S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991-2010. Int. J. Cancer. 2014; 135(2): 432-439.
5. Bosman FT, Carneiro F, Hruban RH, et al. WHO Classification of Tumours of the Digestive System, 4th edn. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer; 2010.

6. Inoue T, Mori M, Shimono R, Kuwono H, Sugimachi K. Vascular invasion of colorectal carcinoma readily visible with certain stains. Dis. Colon Rectum 1992; 35: 34-39.
7. Lim SB, Yu CS, Jang SJ, Kim TW, Kim JH, Kim JC. Prognostic significance of lymphovascular invasion in sporadic colorectal cancer. Dis. Colon Rectum 2010; 53: 377-384.
8. Ouchi K, Sugawara T, Ono H et al. Histologic features and clinical significance of venous invasion in colorectal carcinoma with hepatic metastasis. Cancer 1996; 78: 2313-2317.
9. Barresi V, Reffiani Bonetti L, Vitarelli E, DiGregorio C, Ponz de Leon M, Barresi G. Immunohistochemical assessment of lymphovascular invasion in stage I colorectal carcinoma: prognostic relevance and correlation with nodal micrometastases. 2012; Am. J. Surg. Pathol. 36: 66-72.
10. Rakha EA, Martin S, Lee AH, Morgan D, Pharoah PD, Hodi Z, McMillan D, Ellis IO. The prognostic significance of lymphovascular invasion in invasive breast carcinoma. Cancer 2012; 118: 3670-3680.
11. Dicken BJ, Graham K, Hamilton SM, Andrews S, Lai R, Listgarten J, Jhangri GS, Saunders LD, Damaraju S, Cass C. Lymphovascular invasion is associated with poor survival in gastric cancer: An application of gene-expression and tissue array techniques. Ann. Surg. 2006; 243: 64-73.
12. Cheng L, Jones TD, Lin H, Eble JN, Zeng G, Carr MD, Koch MO. Lymphovascular invasion is an independent prognostic factor in prostatic adenocarcinoma. J. Urol. 2005; 174: 2181-2185.
13. Song W, Wu SJ, Hc YL, et al. Clincopathologic features and survival of patients with colorectal mucinous, signet-ring cell or non-mucinous adenocarcinoma: experience at an institution in Southern China. Clin. Med. J. (Eng). 2009; 122(13): 1486-1491.
14. Sung CO, Seo JW, Kim K-M, Do I-G, Kim SW, Park C-K. Clinical significance of signet-ring cells in colorectal mucinous adenocarcinoma. Mod. Pathol. 2008; 21(12): 1533-1541.
15. Sasaki S, Masaki T, Umetani N, Futakawa N, Ando H, Muto T. Characteristics in primary signet-ring cell carcinoma of the colorectum, from clinicopathological observations. Jpn J. Clin. Oncol. 1998; 28(3): 202-206.
16. Dijxhoorn DN, Boutall A, Mulder CJ, Ssebuufu R, Mall A, Kalungi S, Baigrie C, Goldberg PA. Colorectal cancer in patients from Uganda: A histopathological study. East and Central African Journal of Surgery. March/April 2014 Volume 19(1).
17. Li C, Zheng H, Jia H, et al., Prognosis of three histological subtypes of colorectal adenocarcinoma: A retrospective analysis of 8005 Chinese patients. Cancer Med. 2019; 8:3411-3419.
18. Nitsche K, Zimmermann A, Spath C, et al. Mucinous and signet-ring colorectal cancers differ from classical adenocarcinoma in tumour biology and prognosis. Ann Surg. 2013; 258: 775-783.
19. Kang H, O'Connell JB, Maggard MA, Sack J, Ko CY. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis. Colon Rectum. 2005; 48(6): 1161-1168.
20. Greene FL,. TNM staging for malignancies of the digestive tract: 2003 changes and beyond. Seminars in surgical oncology. Vol.21. Issue 1. 2003 Pgs: 23-29.

21. Hamilton S, Bosman F, Baffetta P. Carcinoma of the colon and rectum. In: Bosman F, Carneiro F, Hruban R, Theise N, editors. World Health Organization classification of tumours of the Digestive System. Lyon: IARC Press; 2010. p. 131-81.
22. Turner J. Gastroinestinal Tract. In: Kumar V, Abbas A, Fausto N, Aster J, editors. Pathologic Basis of Disease. 8th ed. Philadelphia: Saunders Elsevier; 2010. P. 822-5.
23. Hyngstrom JR, Hu CY, Xing Y, You YN, Feig BW, Skibber JM, Rodriguez-Bigas MA, Cornier JN, Chang GJ. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. Ann. Surg. Oncol. 2012 Sep; 19(9): 2814-21.
24. Anthony T, George R, Rodriguez-Bigas M, Petrelli NJ. Primary signet-ring cell carcinoma of the colon and rectum. Ann. Surg. Oncol. 1996. 3:344-348.
25. Vallam KC, Desauza A, Bal M, Patil P, Engineer R, Saklami A. Adenocarcinoma of the Rectum – A composite of three different subtypes with varying outcomes. Clin. Colorectal Cancer. 2016 Jun; 15(2).
26. Yamaguchi T, Taniguchi H, Fujita S, Sekine S, Yamamoto S, Akasu T et al. Clinicopathological characteristics and prognostic factors of advanced colorectal mucinous adenocarcinoma. Histopathology. 2012;61(2): 162-9.
27. Gopalan V, Smith RA, Ho YH, Lam AKY. Signet-ring cell carcinoma of the colorectum-current perspectives and molecular biology. Int. J. Color Dis. 2011; 26(2): 127-33.
28. Gao P, Song Y-X, Xu Y-Y, et al. Does the prognosis of colorectal mucinous carcinoma depond upon the primary tumour site? Results from two independent databases. Histopathology. 2013; 63(5): 603-615.
29. Liang Z, Yan D, Li G, Cheng H. Clinical analysis of primary colorectal signet-ring carcinoma. Clin Colorectal cancer. 2018; 17(1): e39-44. http://doi.org/10.1016/j.clcc.2017.06.010 Epub 2017 Jul 8.
30. Yun SO, Cho YB, Lee WY, Kim HC, Yun SH, Park Ya et al. Clinical significance of signet-ring-cell colorectal cancer as a prognostic factor. Ann. Coloproctol. 2017; 33(6): 232-8.
31. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al. International Classification of Diseases for Oncology. 3rd ed. Geneva: World Health Organization; 2000.
32. Chen S, Song X, Chen Z, Li X, Li M, et al. (2013) CD133 Expression and the Prognosis of Colorectal Cancer: A Systematic Review and Meta-Analysis. PLoS ONE 8(2): e56380. doi:10.1371/journal.pone.0056380.
33. Verhulst J, Ferdinande L, Demetter P, Ceelen W. Mucinous subtype as prognostic factor in colorectal cancer: a systematic review and meta-analysis. J. Clin. Pathol. 2012; 65(5): 381-8.
34. Hogan, J., Burke, J.P., Samaha, G. *et al.* Overall survival is improved in mucinous adenocarcinoma of the colon. *Int J Colorectal Dis* **29,** 563–569 (2014). https://doi.org/10.1007/s00384-013-1826-2.
35. Rastogi M, Revannasiddaiah S, Thakur P et al. Signet ring cell carcinoma as a potential confounding factor in the analysis of outcomes with colorectal mucinous adenocarcinoma. Eur. J. Cancer. 2012; 48(16): 3126-3129.
36. Catalano V, Loupakis F, Graziano F et al. Prognosis of mucinous histology for patients with radicaly resected stage II and III colon cancer. Ann. Oncol. 2012; 23(1): 135-141.

37. Du W, Moh J, Lee J, Sankila R, Sankaranarayanan R, Chia K-S. Incidence and survival of mucinous adenocarcinoma of the colorectum: a population-based study from an Asian country. Dis Colon Rectum. 2004;47(1): 78-85.
38. Wu CS, Tung SY, Chen PC, Kuo YC. Clinicopathological study of colorectal mucinous carcinoma in Taiwan: A multivariate analysis. Journal of Gastroenterology and Hepatology. 1996. Jan. Vol 11(1): 77-81.
39. Lee WS, Chun HK, Lee WY, et al. Treatment outcomes in patients with signet ring carcinoma of the colorectum. Am. J. Surg. 2007; 194: 294-8.
40. Thota R, Fang X, Subbiah S. Clincopathological features and survival outcomes of primary signet ring cell and mucinous adenocarcinoma of colon: retrospective analysis of VACCR database. J. Gastrointest. Oncol. 2014; 5(1): 18-24.
41. Safaee AG, Jafarnejad SM, Tan L, Saeedi A, Li G. The prognostic value of BRAF mutation in colorectal cancer and melanoma: A systematic review and meta-analysis; 2012; PLOS ONE 7(10): e47054.
42. Kim SH, Shin SJ, Lee KY, Kim TI, Kang DR, et al. Prognostic value of mucinous histology depends on microsatellite instability status in patients with stage III colon cancer treated with adjuvant FOLFOX chemotherapy: a retrospective cohort study. Ann. Surg. Oncol. 2013; 20(11): 3407-13.
43. Maisano R, Azzarello D, Mafodda A, Bottari M, Egitto G, et al. Mucinous histology of colon cancer predicts poor outcomes with FOLFOX regimen in metastatic colon cancer. J Chemotherapy. 2012; 24(4): 212-6.
44. Inamura K, Yamauchi M, Nishihara R, Kim SA, Mima K, Sukawa Y et al. Prognostic significance and molecular features of signeting cell and mucinous components in colorectal carcinoma. Ann Surg Oncol. 2015; 22(4: 1226-35.
45. Alvi MA, Loughrey MB, Dunne P, McQuaid S, Turkington R, Fuchs MA et al. Molecular profiling of signet ring cell colorectal cancer provides a strong rationale for genomic targeted and immune checkpoint inhibitor therapies. Br J Cancer. 2017; 117(2): 203-9.
46. Kakar S, Deng G, Sahai V, Matsuzaki K et al. Clincopathologic characteristics, CpG island methylator phenotype, and BRAF mutations in microsatellite stable colorectal cancers without chromosomal instability. Arch Pathol Lab Med. 2008; 132(6): 958-64.
47. Kakar S, Smyrk TC. Signet ring cell carcinoma of the colorectum: correlations between microsatellite instability, clinicopathologic features and survival. Mod. Pathol. 2005; 18(2): 244-9.
48. Kakar S, Deng GR, Smyrk TC, Cun L, Sahai V, Kim YS. Loss of heterozygosity, aberrant methylation, BRAF mutation and KRAS mutation in colorectal signet ring cell carcinoma. Mod Pathol. 2012; 25(7): 1040-7.
49. Sentani K, Oue N, Tashiro T et al. Immunohistochemical staining of Reg IV and claudin-18 is useful in the diagnosis of gastrointestinal signet ring cell carcinoma. Am J Surg Pathol 2008; 32: 1182-9.
50. Ogino S, Sentani Odze RD, Kawasaki T, Brahmandam M, Kirkner GJ, Laird PW, Loda M, Fuchs CS. Correlation of pathologic factors with CpG island methylator phenotype (CIMP) by quantitative DNA methylation analysis in colorectal carcinoma. Am. J. Surg. Pathol. 2006 Sept; 30(9): 1175-83.
51. Fu J, Wu L, Jiang M, Tan Y, Li D, Chen F et al. Signet ring cell carcinoma of Resectable metastatic colorectal cancer has rare surgical value. J. Surg. Oncol. 2016; 114(8): 1004-8.

52. Abdulkader M, Abdulla K, Rakha E, Kaye P. Routine elastic staining assists detection of vascular invasion in colorectal cancer. Histopathology 2006; 49: 487-492.
53. Choi JY, Jung SA, Shim KN, Cho WY, Keum B, Byeon JS, Huh KC, Jang BI, Chang HY, Kong KA; Korean ESD Study Group. Meta-analysis of predictive clinicopathologic factors for lymph node metastasis in patients with early colorectal carcinoma. J. Korean Med. Sci. 2015; 30: 398-406.
54. Del Casar JM, Corte MD, Alvarez A, Garcia I, Bongera M, Gonzalez LO, Garcia-Muniz JL, Allende MT, Astudillo A, Vizaso FJ. Lymphatic and/or blood vessel invasion in gastric cancer. Relationship with clinicopathological parameters, biological factors and prognostic significance. J. Cancer Res. Clin. Oncol. 2008; 134: 153-161.
55. Fadel, M.G., Malietzis, G., Constantinides, V. *et al.* Clinicopathological factors and survival outcomes of signet-ring cell and mucinous carcinoma versus adenocarcinoma of the colon and rectum: a systematic review and meta-analysis. *Discov Onc* **12,** 5 (2021). https://doi.org/10.1007/s12672-021-00398-6.

Abbreviations

SD – standard deviation
cHR – crude hazards ratio
aHR – adjusted hazards ratio
OS – overall survival
CRC – colorectal carcinoma
MAC – mucinous carcinoma
SRCC – signet ring colorectal carcinoma
AC – classical adenocarcinoma

Table 1: Baseline characteristics of colorectal adenocarcinoma patients

Characteristic	SRCC + MAC n(%)	AC n(%)	Total n(%)
Sex			
Male	11 (44.0)	83 (47.2)	94 (46.8)
Female	14 (56.0)	93 (52.8)	107 (53.2)
Age			
Mean (SD)	47.8 (16.6)	53.8 (15.9)	53.0 (16.0)
≤49	17 (68.0)	64 (36.4)	81 (40.2)
50-74	6 (24.0)	92 (52.3)	98 (48.8)
≥75	2 (8.0)	20 (11.4)	22 (11.0)
Clinical Stage			
I	5 (29.4)	20 (14.6)	25 (16.2)
II	1 (5.9)	26 (19.0)	27 (17.5)
III	10 (58.8)	73 (53.3)	83 (53.9)
IV	1 (5.9)	18 (13.1)	19 (12.3)

Tumor size			
T1	3 (17.7)	11 (8.0)	14 (9.1)
T2	5 (29.4)	26 (19.0)	31 (20.1)
T3	4 (23.5)	63 (46.0)	67 (43.5)
T4	5 (29.4)	37 (27.0)	42 (27.3)
Lymph Node Involvement			
N0	47 (34.3)	7 (41.2)	54 (35.1)
N1	63 (46.0)	5 (29.4)	68 (44.2)
N2+N3	27 (19.7)	5 (29.4)	32 (20.7)
Grading of the CRC			
G1	6 (24.0)	57 (32.4)	63 (31.3)
G2	15 (60.0)	101 (57.4)	116 (57.7)
G3	4 (16.0)	18 (10.2)	22 (11.0)
Location			
Caecum	3 (12.0)	4 (2.3)	7 (3.5)
Ascending colon	2 (8.0)	13 (7.4)	15 (7.5)
Transverse colon	0 (0.0)	6 (3.4)	6 (3.0)
Descending colon	1 (4.0)	9 (5.1)	10 (5.0)
Sigmoid colon	4 (16.0)	44 (25.0)	48 (23.9)
Rectosigmoid	0 (0.0)	6 (3.4)	6 (3.0)
Rectum	15 (60.0)	94 (53.4)	109 (54.2)
Lymphovascular Invasion			
Yes	25 (100.0)	99 (75.0)	124 (79.0)
No	0 (0.0)	33 (25.0)	33 (21.0)

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715 **Table 2: Distribution of Lymphovascular Invasion**

Characteristic (s)	Lymphovascular Invasion		P- Value
	Present	Abscent	
Sex			
Male	58 (81.7)	13 (18.3)	0.449
Female	66 (76.7)	20 (23.3)	
Age			
≤49	54 (79.4)	14 (20.6)	0.777
50-74	57 (77.0)	17 (23.0)	
≥75	13 (86.7)	2 (13.3)	
Clinical Stage			
I	14 (73.7)	5 (26.3)	0.775
II	15 (79.0)	4 (21.0)	
III	49 (77.8)	14 (22.2)	
IV	10 (66.7)	5 (33.3)	

Tumor Size			
T1	11 (84.6)	2 (15.4)	0.119
T2	13 (61.9)	8 (38.1)	
T3	40 (85.1)	7 (14.9)	
T4	24 (68.6)	11 (31.4)	
Tumor site			
Colon	55 (74.3)	19 (25.7)	0.176
Rectum	69 (83.1)	14 (16.9)	
Histopathological sub types			
AC	99 (75.0)	33 (25.0)	0.002
SRCC + MAC	25 (100.0)	0 (0.0)	
Grading of the CRC			
G1	37 (75.5)	12 (24.5)	0.711
G2	74 (81.3)	17 (18.7)	
G3	13 (76.5)	4 (23.5)	

Table 3: Overall survival by selected characteristics at 1,2 and 3 years

Characteristic (s)	Time point	Number Beginning	Number Dead	Proportion Surviving (%)	95% Confidence Interval
Overall	1 year	123	66	65.9	58.7 - 72.2
	2 years	78	45	41.6	34.5 - 48.5
	3 years	60	17	32.4	25.8 - 39.2
SRCC+ MAC	1 year	17	7	71.5	49.3 - 85.3
	2 years	12	5	49.2	28.0 - 67.3
	3 years	9	2	40.2	20.7 - 59.1
AC	1 year	107	59	65.2	57.4 - 71.9
	2 years	67	40	40.6	33.1 - 478.0
	3 years	51	15	31.4	24.4 - 38.5
N0	1 year	40	11	79.1	65.4 - 87.9
	2 years	27	13	52.7	38.2 - 65.4
	3 years	23	3	46.7	32.5 - 59.6
N1	1 year	39	27	59.1	46.2 - 69.9
	2 years	24	15	35.8	24.4 - 47.3
	3 years	14	9	21.8	12.7 - 32.5

N2+N3	1 year	20	13	59.4	40.5 - 74.0
	2 years	12	8	34.4	18.8 - 50.6
	3 years	8	3	25	11.8 - 40.7
LVI-Present	1 year	74	44	63.4	54.0 - 71.3
	2 years	47	27	39.9	31.0 - 48.7
	3 years	33	13	28.6	20.7 - 37.0
LVI-Absent	1 year	23	7	77.3	58.1 - 88.6
	2 years	13	10	42.2	24.3 - 59.1
	3 years	8	4	28.1	13.4 - 44.9
Stage I	1 year	19	4	83.4	61.4 - 93.4
	2 years	17	2	74.1	51.0 - 87.5
	3 years	13	3	60.2	37.2 - 77.1
Stage II	1 year	21	6	77.6	56.8 - 89.3
	2 years	11	10	38.8	20.7 - 56.7
	3 years	10	0	38.8	20.7 - 56.7
Stage III	1 year	53	29	64.5	53.1 - 73.8
	2 years	34	19	40.9	30.2 -51.3
	3 years	22	11	27.3	18.1 - 37.2
Stage IV	1 year	7	12	34.2	14.2 - 55.5
	2 years	2	5	5.7	0.4 -22.9
	3 years	1	1	-	-

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724 **Table 4: Survival by histopathological sub-types of colorectal adenocarcinoma**

Study group		SRCC + MAC		AC		P-Value
	Characteristic (s)	Proportion Surviving (%)	95% Confidence Interval	Proportion Surviving (%)	95% Confidence Interval	
	Overall	40.2	20.7 - 59.1	31.4	24.4 - 38.5	0.494
Stage	I	40.0	5.2 – 75.3	65.3	38.4-82.8	0.134
	II	-	-	40.4	21.6-58.5	
	III	67.5	29.1 – 88.3	22.3	13.5-32.4	0.029
	IV	-	-	-	-	
Grade	G1	50.0	11.1 – 80.4	24.4	13.9-36.4	0.261
	G2	32.6	10.3-57.5	35.7	26.1-45.3	0.769
	G3	50.0	5.8-84.5	29.8	10.9-51.6	0.536
LVI	Present	40.2	20.7-59.1	25.9	17.5-35.0	0.27
	Absent	-	-	28.1	13.4-44.9	

Depth of tumor	T1	66.7	5.4-94.5	50.5	18.7-75.7	0.630
	T2	60.0	12.6-88.2	53.1	31.3-70.8	0.705
	T3	75.0	12.8-96.1	29.1	18.5-40.7	0.155
	T4	20.0	0.8-58.2	5.6	1.0-16.4	0.236
Lymph node	N0	28.6	4.1-61.2	49.5	34.0-63.3	0.249
	N1	53.3	6.8-86.3	19.8	10.9-30.6	0.247
	N2+N3	80.0	20.4-96.9	14.8	4.7-30.5	0.024

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734 **Table 5: Factors associated with survival of colorectal adenocarcinoma**

Characteristic (s)	crude Hazard Ratio (cHR)	95% CI	p-value	adjusted Hazard Ratio (aHR)	95% CI	p-value
Sex						
Male	1.00			1.00		
Female	1.09	0.77-1.55	0.622	1.14	0.77-1.69	0.522
Age						
≤49	1.00			1.00		
50-74	0.76	0.53-1.10	0.145	0.75	0.49-1.13	0.173
≥75	0.79	0.432-1.45	0.450	0.72	0.35-1.48	0.371
Clinical Stage						
I	1.00			1.00		
II	1.98	0.87-4.48	0.102	2.00	0.88-4.56	0.099
III	2.50	1.24-5.05	0.011	2.56	1.26-5.18	0.009
IV	6.18	2.74-13.95	<0.001	6.64	2.85-15.44	<0.001
Tumor site						

Colon	1.00					
Rectum	1.07	0.75-1.52	0.706			
Histopathological sub types						
AC	1.00					
SRCC + MAC	0.82	0.47-1.44	0.495			
Grading of the CRC						
G1	1.00			1.00		
G2	0.78	0.53-1.14	0.194	0.96	0.62-1.47	0.836
G3	0.81	0.44-1.48	0.499	1.18	0.60-2.33	0.634
LVI Absent	1.00					
LVI Present	1.14	0.71-1.84	0.594			

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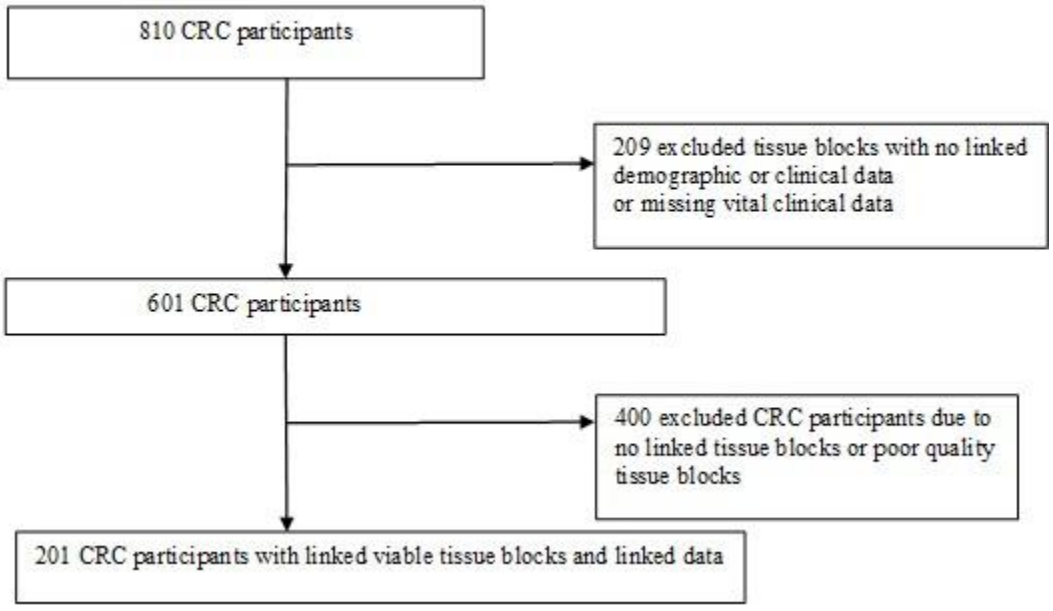

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738 **Figure 1 is a flow diagram illustrating colorectal adenocarcinoma patient recruitment for**
739 **the 2008-2018 cohort**

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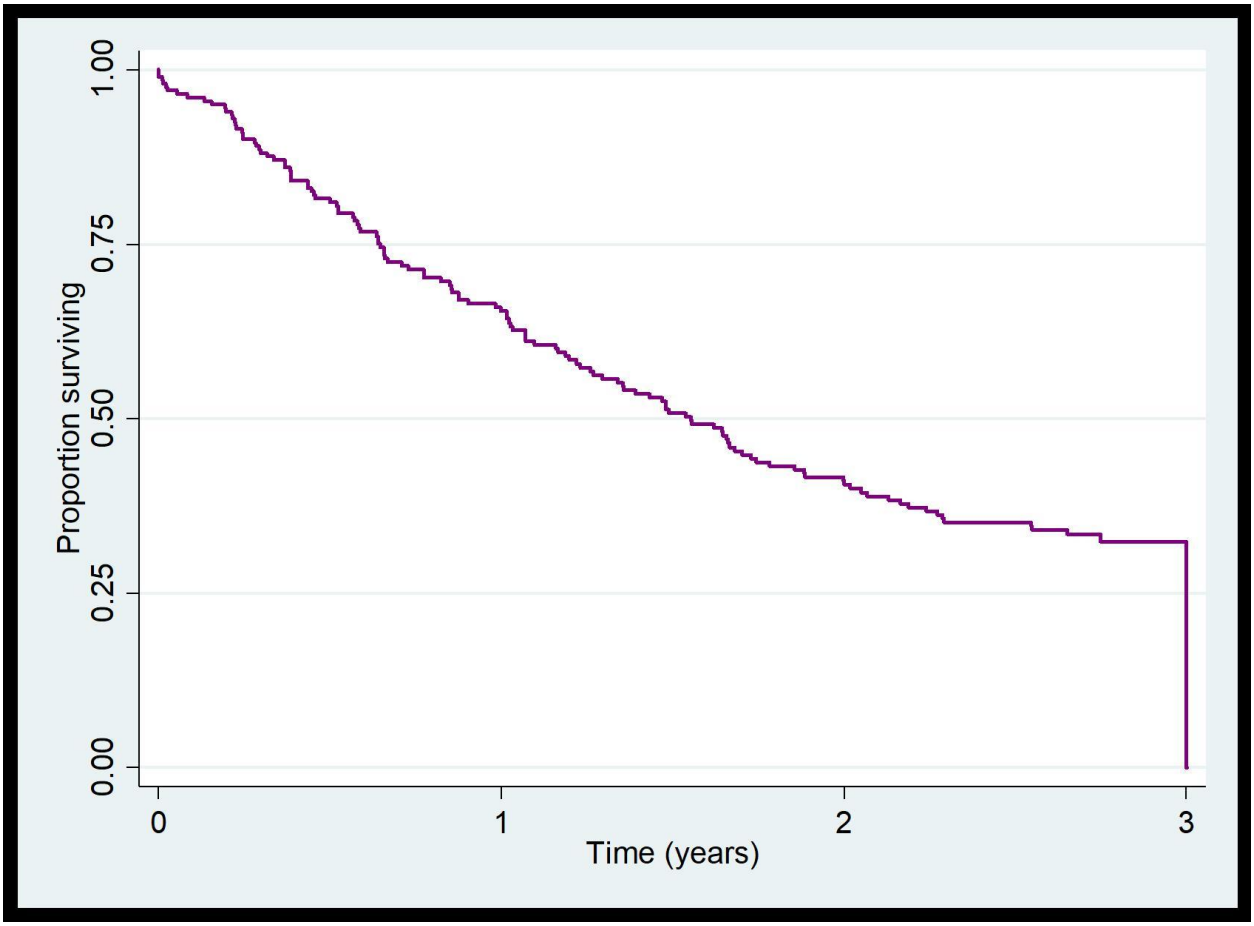

Figure 2: Overall survival of colorectal adenocarcinoma patients in Uganda

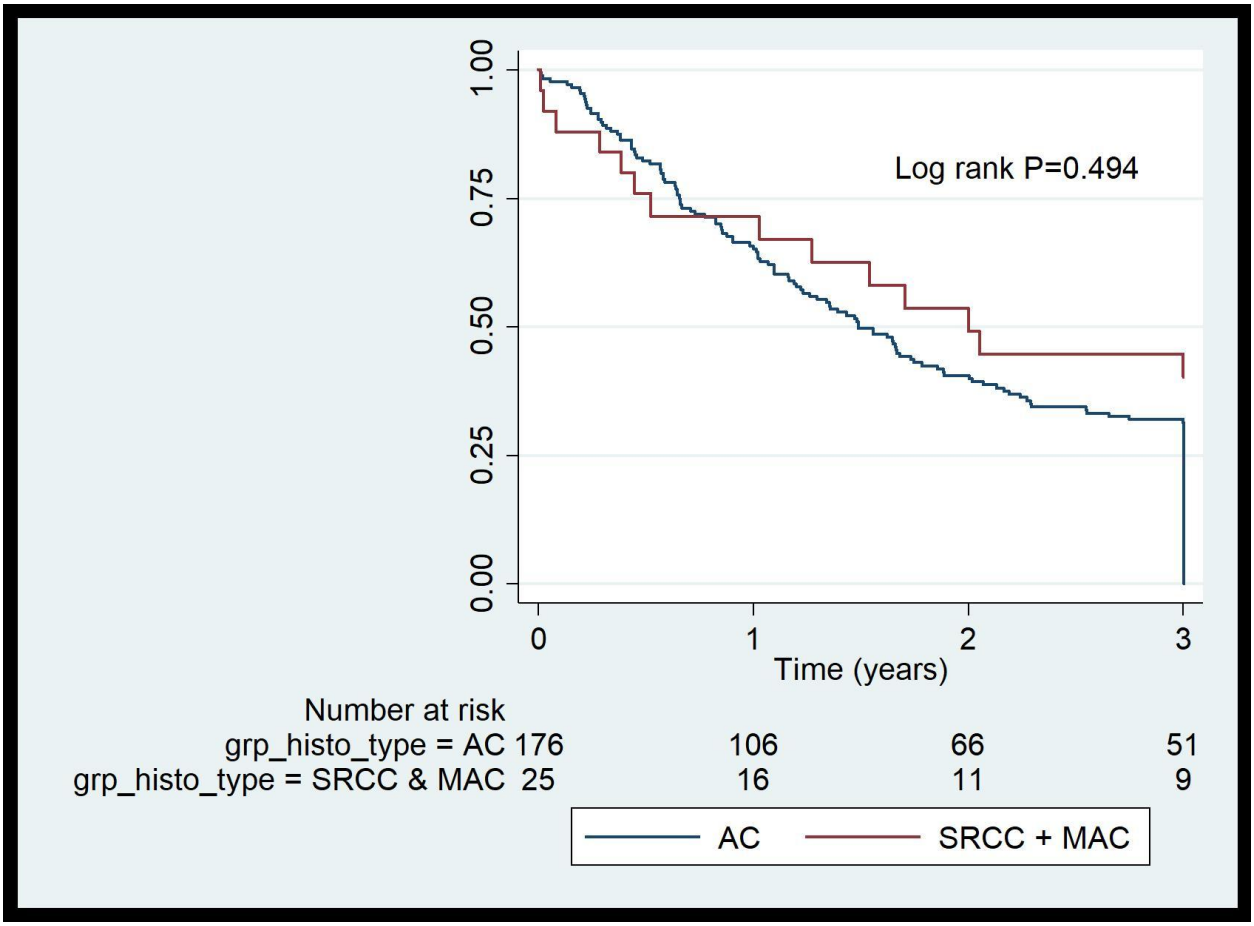

Figure 3: Overall survival of SRCC+MAC compared to AC patients in Uganda

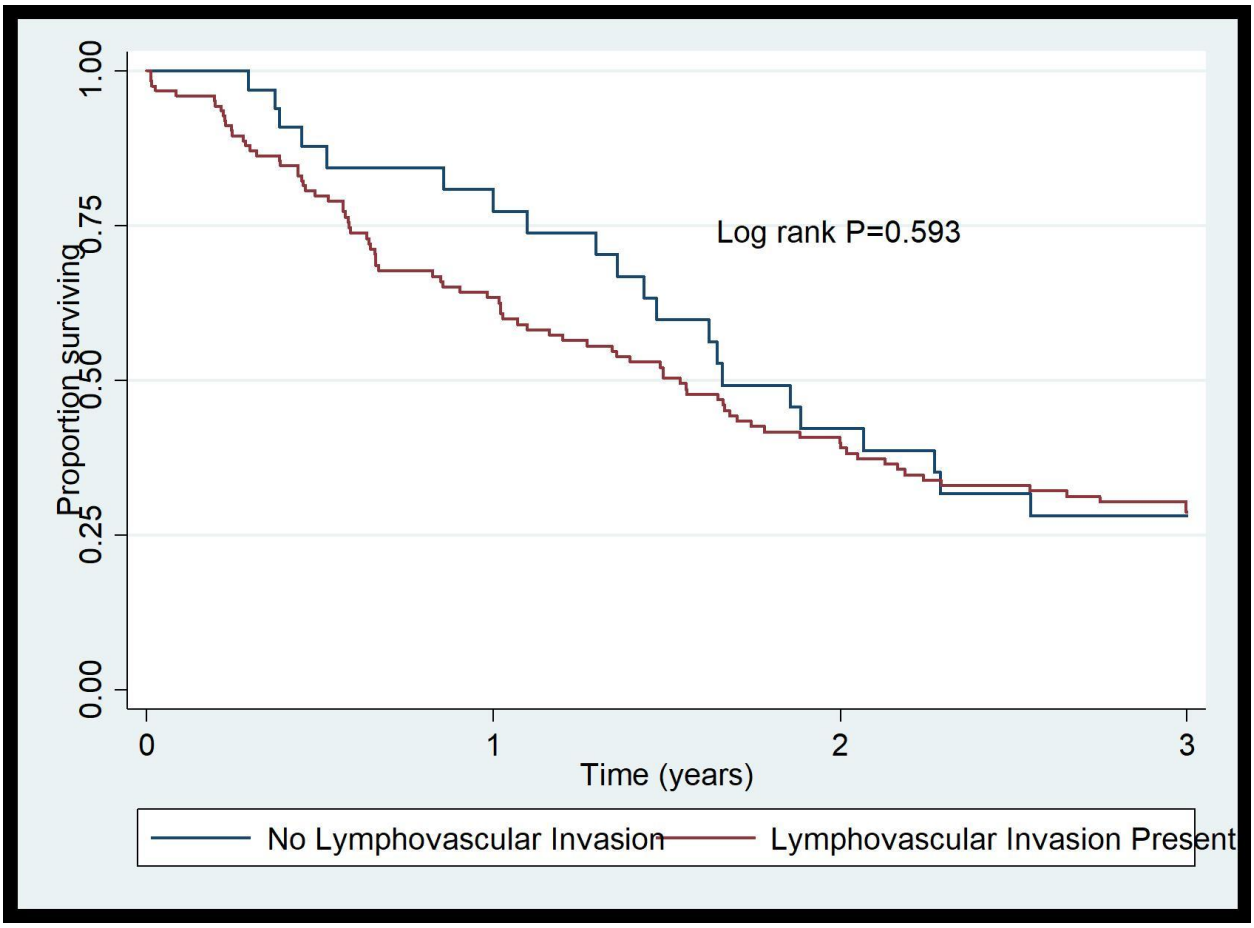

Figure 4: Kaplan-Meier curve for 3-year overall survival according to LVI status

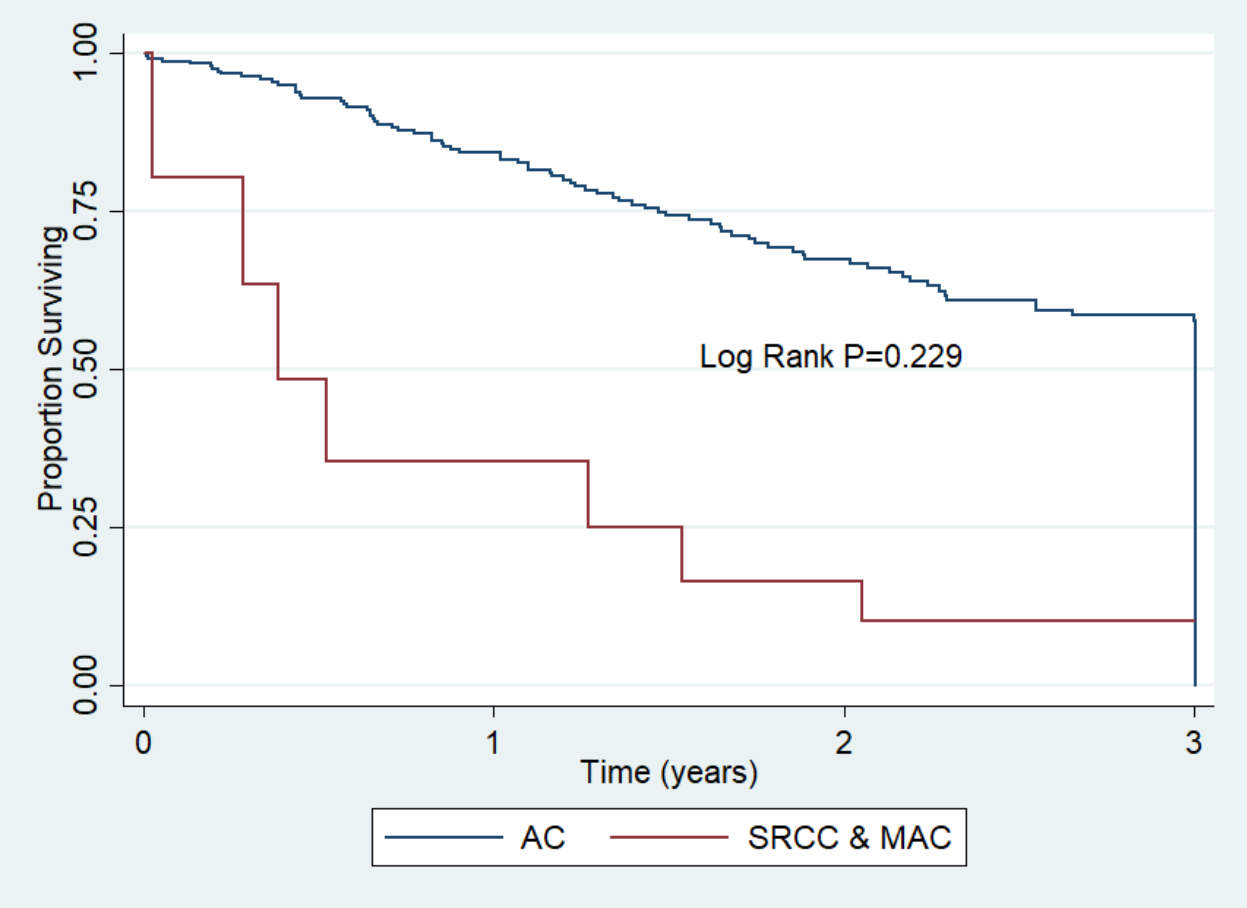

Figure 5: Survival of SRCC/MAC compared to AC adjusted for lymph node status and metastasis

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