Comparing tumour site and overall survival in colon v. rectal cancer in a longitudinal cohort study in Johannesburg, South Africa

A Pincus,[1*] final-year medical student; **Y Moodley,**[1*] final-year medical student; **L Campbell,**[2] PhD; **D Kruger,**[3] PhD; **V Soldati,**[2] MMed (Surg), Cert Gastroenterology (SA) Surg; **J Fabian,**[2] Cert Nephro (SA), PhD; **P Gaylard,**[2] PhD; **T K Marumo,**[1,4] FCS (SA), Cert Gastroenterology (SA); **L Prodehl,**[1,4] FCS (SA), Cert Gastroenterology (SA); **N Harran,**[2] MMed (Surg), Cert Gastroenterology (SA) Surg; **B Bebington,**[2,3] FCS (SA); **P Ruff,**[1] FCP (SA), MMed (Int Med)
**Joint first authors*

[1] *School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Wits Donald Gordon Medical Research Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[3] *Department of Surgery, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[4] *Department of Surgery, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa*

Corresponding author: *A Pincus (ariel.pincus1@gmail.com)*

Background. Colorectal cancer (CRC) incidence is increasing globally, with disproportionately high mortality in low- and middle-income countries. Although colon and rectal cancers are often grouped together, anatomical, molecular and clinical differences suggest they may be distinct entities, warranting unique work-up, management and diagnosis. Data from sub-Saharan Africa comparing clinical presentation and mortality outcomes among those with colon and rectal cancer remain limited. This study aimed to address this knowledge gap.
Objectives. To compare the clinicopathological features, associated risk factors and overall survival (OS) of patients with colon and rectal cancers in the cohort from the Colorectal Cancer in South Africa Study in Johannesburg, South Africa (SA).
Methods. The cohort eligible for inclusion in this study comprised 325 patients, recruited from 2016 to 2019, with follow-up to January 2023. Sociodemographic, clinical, treatment and OS data were analysed. Comparison by tumour location was made using *t*-tests and ANOVA. Cox proportional hazards regression models assessed associations with OS. Kaplan-Meier analysis was used for survival estimation.
Results. Rectal cancers accounted for 52.3% of cases, right-sided colon cancers 26.2% and left-sided colon cancers 21.5%. When comparing those who presented with colon v. rectal cancers, no significant differences were observed in self-reported ethnicity, socioeconomic status (SES), family history of cancer, tobacco use, body mass index, or presence of comorbidities. Alcohol use was more common among those with colon cancer (p=0.035), and treatment differed significantly by tumour site (p<0.0001). Male sex (hazard ratio (HR) 1.81, 95% confidence interval (CI) 1.25 - 2.61, p=0.0017), low SES (HR 3.24, CI 1.86 - 5.65, p<0.0001) and distant disease at presentation (HR 3.85, CI 2.26 - 6.57, p<0.0001) were most strongly associated with poorer OS. The tumour site had no impact on OS.
Conclusion. In this SA cohort of patients with CRC, tumour site did not affect overall survival. However, male sex, advanced stage at diagnosis and low socioeconomic status were associated with poorer OS.

Keywords: colon, rectum, colorectal cancer, overall survival, South Africa

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Globally, the incidence of colorectal cancer (CRC) continues to rise, particularly among those aged ≤50 years. Along with increasing incidence, disproportionate mortality has been reported in low- and middle-income countries (LMICs), including sub-Saharan Africa and South Africa (SA).[1-3] Colon and rectal cancers are often considered a single entity, and reported as such in most clinical and epidemiological studies. However, differences in embryological origin, function, histological features and associated risk factors have prompted many to support the distinction between colon cancers, specifically left- and right-sided, and rectal cancers, with some suggesting these should be considered separate malignant entities.[4-7] Rectal cancers are less influenced by family history and lifestyle factors such as physical activity, smoking and diet, which are more relevant to colon cancers.[8-12] From a molecular perspective, rectal tumours more frequently exhibit chromosomal instability, whereas right-sided colon cancers are often microsatellite instability-high.[13-14] Additionally, there appear to be distinct (and sometimes conflicting) differences in responses to treatment and survival outcomes, with some studies showing poorer survival with rectal cancers,[15-17] while others report worse survival with colon cancers, particularly at advanced stages of disease.[18-20]

Among continental Africans, isolated studies from west and southern Africa describe heterogeneous patterns of tumour distribution, with rectal cancers occurring more frequently, but few studies report whether tumour site influences mortality risk.[21-25] In this study, we aimed to compare clinicopathological features, associated risk factors and survival outcomes of left- and right-sided colon and rectal cancers in a multi-ancestry cohort in Johannesburg, South Africa (SA).

Methods

Study sample selection and clinical characteristics

This retrospective sub-study accessed available data from the Colorectal Cancer in South Africa (CRCSA) Study. Details of the CRCSA study design and methodology have previously been

published.[26] In summary, the study recruited adults presenting with CRC to four urban referral hospitals in the University of the Witwatersrand (Wits) Academic Teaching Hospital Complex: Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital, the Wits Donald Gordon Medical Centre (WDGMC) and Edenvale Hospital. Eligible participants who provided consent were recruited from 1 November 2016 to 31 December 2019, with overall survival follow-up to 31 January 2023. Baseline clinical and follow-up data for each participant were collected using Research Electronic Data Capture (REDCap), a secure, web-based platform hosted by the Faculty of Health Sciences at Wits.[27,28]

For this sub-study, patients were excluded if they had anal carcinoma or carcinoma-*in-situ*, synchronous lesions, or CRC diagnosed >12 months previously, or if treatment intent was not curative, or treatment was refused. Patients presenting with metastatic disease at the time of diagnosis were reviewed at oncology multidisciplinary team meetings to determine eligibility for curative treatment. The following clinical data were accessed: age at diagnosis; sex; self-reported ethnicity; socioeconomic status (SES); first-degree family history of CRC; comorbidities; current smoking status; current or previous alcohol use; body mass index (BMI); location of malignancy (left colon, right colon, rectum); staging of malignancy at presentation; treatment information; histology post surgery; and survival data (date of death (all-cause mortality) or date last seen). The assessment of SES used employment status, number of people in the household, assets score and highest level of education, from which an overall composite score was derived using principal component analysis. The first component was used as the SES score, which was then categorised as follows: the lowest 40% of households as 'poor'; the highest 20% as 'wealthy'; and the remaining as the 'intermediate' group.[29] Comorbidity was assessed using a modified Charlson comorbidity index (CCI), the details of which have been published for this cohort.[30] In summary, the CCI was calculated based on whether participants had any history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, connective tissue disorders, dementia, peptic ulcer disease, diabetes mellitus, moderate to severe renal disease, hemiplegia, leukaemia, malignant lymphoma, solid malignancies (non-CRC), or hepatic disease. For staging of malignancy, the American Joint Committee on Cancer (AJCC) system[31] was used preferentially, followed by Duke's[32] staging if AJCC data were unavailable. If neither of these systems was available, post-surgical histological tumour, node, metastasis (TNM) staging was used to infer AJCC staging, followed by radiological TNM staging.[33] Staging was then classified as local, regional, or distant (Table 1). Time delays between diagnosis and staging were not considered for this analysis.

Statistical analysis

For sample size estimation, equally sized malignancy groups (colon v. rectal cancer) were assumed, with accrual and final follow-up periods of 2.5 years and 3.5 years, respectively, and a 40% survival rate at 6 years.[34] Detecting a hazard ratio of at least 1.6 with 80% power at $p<0.05$ significance level required a minimum sample size of 284 patients.[29] Comparison between location of the malignancies for continuous variables was done using the independent samples *t*-test (for two groups) or the Wilcoxon rank sum test if the assumptions of this test were not met; one-way analysis of variance (ANOVA) was used for comparing three groups, or the Kruskal-Wallis test if the assumptions of this test were not met. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death from any cause, or the date the participant was last seen. OS was then illustrated by the Kaplan-Meier method. The effect of each of the selected study variables on OS was determined univariately using Cox proportional hazards (PH) regression. Significant variables, plus location of malignancy and variable interactions with location of malignancy, were combined into a multivariable Cox PH model. Prior to this, confounding between significant variables was explored: variables with Cramer's V >0.50 were not included together in the multivariable model. In the multivariable model, non-significant interactions and main effects were removed sequentially for model parsimony. The PH assumption was checked by examination of the Schoenfeld residuals. Data analysis was carried out using SAS version 9.4 for Windows (SAS Institute, USA). A significance level of $p<0.05$ was used.

Ethical approval

The CRCSA study was approved by the Wits Medical Human Research Ethics Committee (ref. no. M141027).

Results

The cohort for this sub-study comprised 325 participants. Derivation of this sub-study cohort is summarised in Fig. 1.

The sociodemographic and clinical characteristics of the study cohort are summarised in Table 2. More than half (170/325; 52.3%) of the cancers occurred in the rectum. Of the cancers occurring in the colon (155/325), 45.2% (70/155) were in the left and 54.8% (85/155) in the right colon. When comparing features between those with colon or rectal cancer, there were no statistically significant differences in self-reported ethnicity, SES status, family history of cancer, tobacco use, BMI, or presence of comorbidities. The only significant difference identified was that current or previous use of alcohol was associated with colonic malignancies ($p=0.035$), in particular, right-sided colonic malignancies ($p=0.024$).

The treatment approach differed significantly between participants with colon and rectal malignancies ($p<0.0001$; Table 3). Those with colon cancer were more likely to be treated with surgery alone, contrasting with rectal cancer, where treatment was more likely to include chemotherapy, radiotherapy, or combination chemo- and radiotherapy, with or without surgery (Table 3). Among those who had surgical resections (234/325, 72.0%), histologically confirmed serosal involvement was significantly lower in those with rectal

Table 1. Staging of colorectal cancer

Staging	Local	Regional	Distant
AJCC[31]	0, I, IIA, IIB, IIC	IIIA, IIIB, IIIC	IV
Duke's[32] staging	A, B	C	D
Post-surgery histological TNM	Only T, no N or M	T and N, no M	T, N and M
Radiological pre-treatment TNM	Only T, no N or M	T and N, no M	T, N and M
No staging/unable to stage			Recorded as distant

AJCC = American Joint Committee on Cancer; TNM = tumour, node, metastasis.

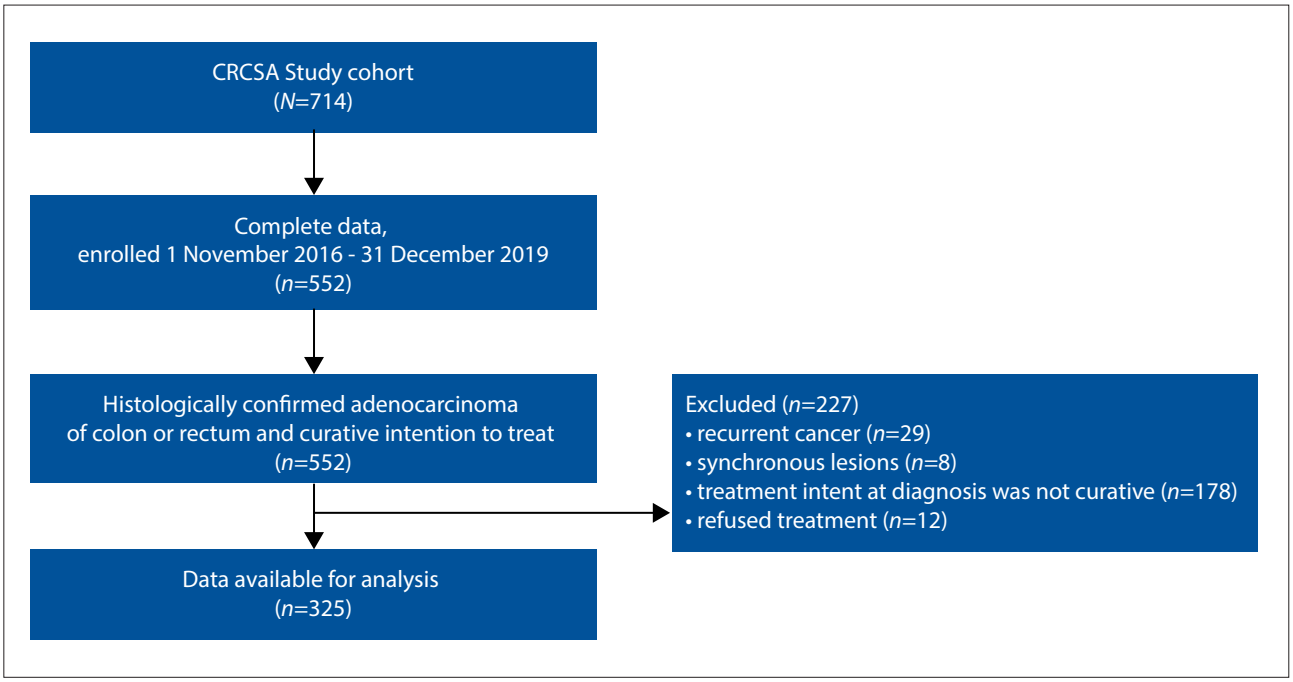

Fig. 1. Flow diagram of sample selection from the Colorectal Cancer in South Africa (CRCSA) Study.

Table 2. Sociodemographic and clinical characteristics of the study cohort by location of the malignancy (*N*=325)

Characteristic, *n* (%)*	Overall	Left colon, *n*=70	Right colon, *n*=85	Rectum, *n*=170	*p*-value
Age at diagnosis, years, mean (SD)	57 (13)	59 (15)	56 (13)	57 (12)	0.52
Sex (male)	162 (49.8)	31 (44.3)	44 (51.8)	87 (51.2)	0.57
Self-reported ethnicity					0.13
White	144 (44.3)	30 (42.9)	39 (45.9)	75 (44.1)	
Black	135 (41.5)	36 (51.4)	34 (40.0)	65 (38.2)	
Other†	46 (14.2)	4 (5.7)	12 (14.1)	30 (17.6)	
SES status‡					0.98
Poor	127 (39.8)	28 (41.8)	32 (38.1)	67 (39.9)	
Intermediate	127 (39.8)	26 (38.8)	33 (39.3)	68 (40.5)	
Wealthy	65 (20.4)	13 (19.4)	19 (22.6)	33 (19.6)	
First-degree relative with CRC§	25 (7.7)	5 (7.1)	9 (10.7)	11 (6.5)	0.49
Current smoker	52 (16.0)	11 (15.7)	13 (15.3)	28 (16.5)	0.98
Current/previous alcohol use	212 (65.2)	42 (60.0)	68 (81.0)	102 (60.0)	0.0024
BMI, kg/m^2¶					0.095
<25	132 (41.6)	27 (39.7)	36 (43.4)	69 (41.6)	
25 - <35	158 (49.8)	39 (57.4)	35 (42.2)	84 (50.6)	
≥35	27 (8.5)	2 (2.9)	12 (14.5)	13 (7.8)	
CCI score‖					0.50
0	257 (79.8)	51 (73.9)	72 (85.7)	134 (79.3)	
1	48 (14.9)	13 (18.8)	9 (10.7)	26 (15.4)	
≥2	17 (5.3)	5 (7.2)	3 (3.6)	9 (5.3)	
Overall survival, % (95% CI)					-
1 year	85 (81 - 88)	85 (81 - 99)	84 (77 - 88)	86 (80 - 91)	
3 year	64 (59 - 70)	64 (59 - 70)	67 (58 - 74)	63 (55 - 69)	
5 year	56 (50 - 61)	56 (50 - 61)	59 (50 - 66)	53 (45 - 61)	

SD = standard deviation; BMI = body mass index; SES = socioeconomic status; CRC = colorectal cancer; CCI = Charlson comorbidity index; CI = confidence interval.
*Unless otherwise indicated.
†Other: self-reported ethnicity defined as mixed race (South African coloured), Indian, East Asian, or Asian.
‡Data available on 319/325 participants.
§Data available on 323/325 participants.
¶Data available on 317/325 participants.
‖Data available on 322/325 participants.

cancer compared with those with left or right colonic malignancies (p=0.0027).

The median follow-up time for the study cohort was 3.5 years. We presented the OS as hazard ratios (HRs) and 95% confidence intervals (CIs). Univariate analysis to determine the effect of clinical characteristics on OS showed that the following variables significantly contributed to poorer survival: age <50 years v. 50 - 59 years (HR (95% CI) 1.80 (1.13 - 2.87)), male sex (1.71 (1.21 - 2.42)), black v. white ethnicity (2.05 (1.43 - 2.94)), intermediate (1.84 (1.05 - 3.24)) and poor SES (2.98 (1.73 - 5.15)), current smoking (1.64 (1.08 - 2.48)), BMI category of 25 - 35 (v. <25) kg/m^2 (0.65 (0.45 - 0.92)), regional (2.49 (1.50 - 4.12)) or distant tumour (v. local) at presentation (4.76 (2.84 - 7.97)), and non-surgical treatment (v. surgical only treatment) (3.48 (2.30 - 5.28)) (Fig. 2A - D; Appendix Fig. S1 A - D; Appendix Table S1). Treatment type and tumour site were confounded, and thus treatment type was excluded from the multivariable model. In the final multivariable model, male sex, intermediate and poor SES, and regional and distant tumour status were significantly associated with poorer OS. The effect of tumour site on OS was not significant, whether assessed by colon v. rectum; or right-sided colon v. left-sided colon v. rectum (Table 4, Fig. 2A - D; Appendix Fig. S1A - D). Of note, 24.6% of patients with distant disease were treated with curative intent.

Discussion

In our longitudinal cohort of CRC patients recruited in Johannesburg, SA, rectal cancers represented more than half of all tumours, consistent with prevalence rates reported by the SA National Cancer Registry, and those of other African countries, namely Nigeria, Ghana, Zambia and Zimbabwe.[21-23,35,36] This relatively high regional prevalence of rectal cancer contradicts that reported from high-income, predominantly European-ancestry populations in the USA and UK, where colon cancers occur more frequently.[37,38] While the tumour site did not significantly affect overall survival, male sex, lower SES, and more advanced disease at the time of presentation were risk factors associated with a higher mortality risk, consistent with published studies.[45,46] These findings were somewhat unexpected by the clinical team, who hypothesised that variables such as tumour biology and location, African ancestry and BMI would play a significant role in overall survival. In the SA context, the impact of self-identified ancestry and SES were confounded, making the interpretation of risk difficult.

The impact of age at diagnosis on tumour location has been debated in local and international literature, with some studies reporting an association between younger age at diagnosis and rectal cancers.[17,18,39] However, as seen in our cohort, there was no significant association between age of diagnosis and tumour location.[16] In our study, the lack of male predominance in rectal cancer, as well as the absence of expected links between colon cancer and smoking or obesity, challenge prevailing assumptions, and highlight the need for population-specific studies.[9,11,12,17,18,39] The only characteristic significantly associated with tumour site was alcohol consumption, with a greater prevalence among right-sided colon cancers. Still, the literature remains inconclusive regarding the differential effect of alcohol by anatomical site, with conflicting conclusions in several meta-analyses.[40,41] It is noteworthy that most in this cohort presented with advanced-stage disease (regional and/or distant tumours), a finding likely reflective of delayed symptom recognition and diagnosis (particularly in younger people), the absence of national CRC awareness and screening programmes, as well as possible difficulties in accessing appropriate specialist healthcare services.

Histopathological features, including margin status, grade of differentiation and lymphovascular invasion, showed no significant differences between colon and rectal tumours in our cohort, also

Table 3. Tumour morphology of the study cohort by location of the malignancy (N=325)

Characteristic, n (%)	Overall	Left colon, n=70 (26.2)	Right colon, n=85 (21.5)	Rectum, n=170 (52.3)	p-value
Tumour stage					
Local	96 (29.5)	28 (40.0)	22 (25.9)	46 (27.1)	0.17
Regional	149 (45.8)	29 (41.4)	37 (43.5)	83 (48.8)	
Distant	80 (24.6)	13 (18.6)	26 (30.6)	41 (24.1)	
Treatment/s					
Surgery only	123 (37.8)	44 (62.9)	46 (54.1)	33 (19.4)	<0.0001
Surgery and chemotherapy	52 (16.0)	18 (25.7)	22 (25.9)	12 (7.1)	
Chemotherapy and/or radiation therapy	91 (28.0)	4 (5.7)	13 (15.3)	74 (43.5)	
Chemotherapy and/or radiation therapy and surgery	59 (18.2)	4 (5.7)	4 (4.7)	51 (30.0)	
Underwent surgical resection (n=234)					
Excision margin*	19 (8.7)	4 (6.5)	9 (13.0)	6 (6.8)	0.30
Grade differentiation†					
Grade 1 (G1): well differentiated	13 (7.1)	3 (5.6)	5 (8.1)	5 (7.4)	0.14
Grade 2 (G2): moderately differentiated	154 (83.7)	42 (77.8)	51 (82.3)	61 (89.7)	
Grade 3 (G3): poorly differentiated	17 (9.2)	9 (16.7)	6 (9.7)	2 (2.9)	
Vascular invasion‡	46 (23.4)	13 (22.0)	16 (26.2)	17 (22.1)	0.81
Lymphatic invasion§	98 (45.0)	30 (47.6)	33 (50.0)	35 (39.3)	0.37
Serosal involvement¶	26 (12.6)	13 (22.0)	10 (16.1)	3 (3.5)	0.0027

*Data available on 219/234 participants. Histopathology indicates that the tissue margin is clear of malignancy (R0 resection – negative microscopic margin).
†Data available on 184/234 participants.
‡Data available on 197/234 participants;
§Data available on 218/234 participants.
¶Data available on 206/234 participants.

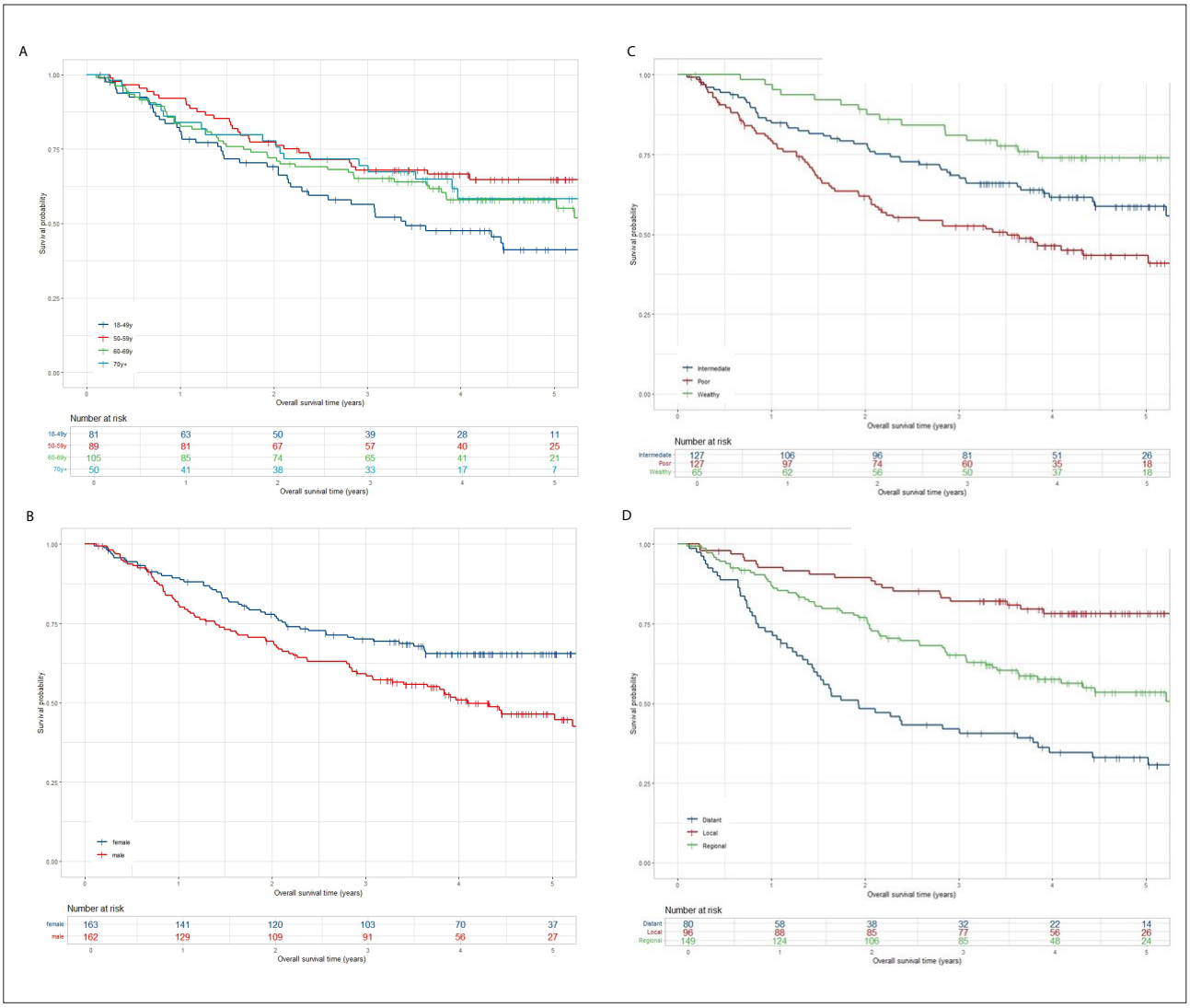

Fig. 2. Kaplan-Meier plots of overall survival by A: age; B: sex; C: socioeconomic status; and D: tumour stage.

Table 4. Results of the multivariable model assessing factors associated with overall survival

Characteristic	HR for death	95% CI for HR	*p*-value
Location of malignancy			
Rectum	1.00	reference	
Right colon	1.04	0.65 - 1.65	0.87
Left colon	0.96	0.63 - 1.46	0.84
Sex			
Female	1.00	reference	
Male	1.81	1.25 - 2.61	0.0017
SES class (from PCA)			
Wealthy	1.00	reference	
Intermediate	2.00	1.13 - 3.54	0.017
Poor	3.24	1.86 - 5.65	<0.0001
Tumour stage			
Local	1.00	reference	
Regional	2.30	1.38 - 3.84	0.0014
Distant	3.85	2.26 - 6.57	<0.0001

HR = hazard ratio; CI = confidence interval; SES = socioeconomic status; PCA = principal component analysis.
Overall model statistics: likelihood ratio test: $p<0.0001$; area under curve 0.744.

consistent with previous comparative analyses.[16] Studies in other populations have reported rectal cancers to be smaller and less invasive, suggesting possible population-level variability.[17] While serosal involvement was significantly lower in rectal cancers in our cohort, this was an expected finding considering the anatomical differences between these sites, and potential reductions in tumour size and staging following neoadjuvant therapy.[42-44]

Study strengths and limitations

This study has both strengths and limitations. The strengths lie in the sample size, the multicentre design, the depth and scope of the multi-ancestry cohort, and the 3-year follow-up period to ascertain overall survival. Regarding the limitations, all participants were recruited from tertiary academic referral centres where the spectrum of CRC pathology may reflect inherent referral biases. For example, those with rectal cancer are more likely to be referred due to the complexity of their treatment regimens, compared with resectable colon cancers that can be managed by general surgeons in more peripheral hospital settings. Because all recruitment occurred in the large urban metropolis of Johannesburg, our findings may not be generalisable to other urban centres, nor to rural SA sites, given the unique demographic, environmental and health system factors known to impact CRC. Although longitudinal follow-up

for evaluation of OS provided valuable insights, we were unable to determine more nuanced outcomes based on treatment regimens (including chemotherapy and radiotherapy), the site of metastatic disease and the cause of death.

Conclusion

This study provides a comparative analysis of colon and rectal cancers within a longitudinal cohort recruited in Johannesburg, SA, contributing to the limited literature on CRC in LMIC settings. Despite known differences in epidemiology, risk factors and tumour biology, most clinicopathological and survival outcomes did not significantly differ between colon and rectal cancers in this study. Serosal involvement and alcohol consumption were the only site-specific variables with significant associations. These findings underscore the influence of anatomical features on tumour behaviour, and highlight the evolving landscape of CRC prognosis in the context of improved treatment strategies. Future research should focus on larger, prospective and multi-centre cohorts to better characterise site-specific CRC patterns in sub-Saharan Africa, and inform tailored screening and treatment protocols.

Data availability. The data used for this study are available on request.

Declaration. None.

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Author contributions: AP and YM: primary authors, conceptualised the study, wrote the first draft of the article, incorporated edits and redrafted the article to its final format, and submitted the article; BB, JF, LC and NH: conceptualised the study and revised the final draft of the article; PG: performed statistical analysis of the study data and revised the final draft of the article; DK, VS, TKM and LP: all contributed to patient recruitment and management and data collection, and revised the final draft of the article; PR: principal investigator on the study and the grant holder.

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Conflicts of interest. None.

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