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LOWER GIT SURGERY

Epidemiological and histopathological features of colorectal adenocarcinoma in the Western Cape public health sector between 2018 and 2020

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Background: There is a paucity of epidemiological colorectal adenocarcinoma data in sub-Saharan Africa. This deficiency coupled with the rising trends of colorectal cancer (CRC) incidence and mortality necessitated the need for an epidemiological colorectal adenocarcinoma study to be conducted in the South African setting.
Methods: A retrospective analysis of demographic and histopathological data of colorectal adenocarcinoma patients diagnosed in the Western Cape public health sector was performed through the utilisation of the National Health Laboratory Services (NHLS) Academic Affairs and Research Management System (AARMS) database.
Results: A total of 612 patients were diagnosed with colorectal carcinoma in the Western Cape during the study period. 595/612 (97.2%) were diagnosed with adenocarcinoma, of these 284 (48%) of patients with primary rectal adenocarcinoma, 304 (51%) with primary colon adenocarcinoma and 7 (1%) with synchronous colorectal adenocarcinoma or a lesion involving both the colon and the rectum. Rectal adenocarcinoma most commonly occurred in 99/284 (34.9%), in the > 60–70 age group, while colon adenocarcinoma occurred most commonly in the > 50–60 age group, 78/304 (25.7%). The commonest stage of rectal adenocarcinoma patients was IIA 35/119 (29.4%), whereas stage IIIB was the commonest colon adenocarcinoma stage comprising 66/212 (31.3%) patients. Forty patients had mutations of mismatch repair genes, 7 of which had a positive BRAF mutation.
Conclusion: The study showed an even distribution of colorectal adenocarcinoma incidence between males and females, with the highest rates of diagnosis in patients aged more than 50 years. Patients with stage III and IV disease had a higher rate of serum CEA elevation as compared to stage I and II.
Keywords: colorectal adenocarcinoma, epidemiology, oncology

Introduction

Colorectal adenocarcinoma is the third most commonly diagnosed and the second deadliest cancer worldwide.[1] There is a variable distribution of the disease across geographical regions, with Europe, Australasia and North America experiencing the highest incidence rates, while South Asia and sub-Saharan Africa report the lowest.[1,2] However, this distribution pattern is steadily changing. Over the last decade, South Africa, like other developing countries, has witnessed a rise in the incidence and mortality of colorectal adenocarcinoma.[2]

According to the International Agency for Research on Cancer, in 2020, colorectal cancer (CRC) was the fifth most commonly diagnosed and the fifth deadliest cancer in South Africa.[3] The steady rise in incidence and mortality is thought to be multifactorial; these factors include the adoption of a western diet, obesity, lack of physical activity, smoking, lack of CRC screening programmes and an overburdened public healthcare system.[4]

The increase in incidence and mortality experienced in South Africa, especially among black South Africans, mirrors the trend observed in the African American population.[4] Researchers hypothesise a link between these two population groups, involving both genetic and epigenetic similarities. African Americans are being diagnosed at an earlier age, with aggressive subtypes involving the proximal colon.[4,5]

McCabe et al.[6] conducted an epidemiological CRC study at Charlotte Maxeke Johannesburg Academic Hospital which confirmed that black South Africans were diagnosed at a younger age group compared to other race groups (median age of diagnosis 56 vs 62 years, respectively), $p < 0.0001$. Another study conducted in KwaZulu-Natal Province by Madiba and colleagues indicated that 28% of black patients were diagnosed before the age of 40, considerably higher than other race groups.[7] Cronje et al.[8] conducted a trial in Gauteng province which also demonstrated earlier age of diagnosis among black patients as well as a higher proportion of black patients being diagnosed with proximal

tumours and significantly more poorly differentiated cancers ($p = 0.006$).[6-8]

The rising trends in CRC have significant psychological, social and economic implications. Further research is required to obtain a better understanding of the disease. There is limited published epidemiological research of CRC in the South African setting. This study aims to address this gap by identifying the demographic and histopathological features of patients diagnosed with CRC in the Western Cape public health sector between 2018 and 2020. This information may provide insights into the development of the disease in our setting and guide decisions on formulating CRC screening policies.

Methods

A retrospective, descriptive study was performed to evaluate the demographic and histopathological features of adult patients diagnosed with CRC in the Western Cape between 1 January 2018 and 31 December 2020. The setting for the study was the department of Medical Imaging and Clinical Oncology of Tygerberg Hospital, Tygerberg Hospital National Health Laboratory Services (NHLS) histopathology laboratory and Groote Schuur NHLS histopathology laboratory. This drainage area is inhabited by an estimated 6.2 million people, of whom fewer than 25% are covered by medical insurance.[9-10] The study included all patients with histologically proven CRC extracted from the NHLS Academic Affairs and Research Management System (AARMS) database.

Inclusion criteria were histological diagnosis of CRC and adult population defined as persons 18 years of age and older.

Exclusion criteria were patients with CRC recurrence.

To enhance the accuracy of the data collected, all patients diagnosed with CRC, including those with incomplete information were included in the study. Data were obtained with the assistance of the NHLS utilising their AARMS portal. An application to conduct research, research protocol, Stellenbosch University Human Research Ethics Committee approval letter (S21/11/228), rationale of study, supervisor details, principal investigator details and request for information were uploaded onto their platform. AARMS was not provided with any patient names/identifiers. NHLS provided information based on their records. The AARMS application was performed by the principal investigator under the guidance of the research supervisor. Unfortunately, ethnicity data was not provided by the NHLS AARMS as their policy precludes them from sharing this beneficial data.

Data analysis was performed by Stellenbosch University, Department of Epidemiology and Biostatistics using R v4.1.1. Patients with synchronous colorectal adenocarcinomas or adenocarcinomas involving both the colon and rectum (total 7/595) were excluded from the analysis, given that their small number was not expected to meaningfully affect the observed trends and associations. Frequencies and percentages were calculated to summarise categorical data. Inferential statistics were performed using chi-square or Fisher's exact tests for categorical data. Median, quartiles and ranges were calculated to summarise numerical data. The aim of the statistics was to identify and describe demographic and histopathological trends pertaining to rectal and colon adenocarcinomas. The level of significance was defined as p-values less than 0.05.

Results

A total of 595 patients were diagnosed with colorectal adenocarcinoma in the Western Cape public health sector between 2018 and 2020. Among these patients, 284 (48%) had primary rectal adenocarcinoma, 304 (51%) had primary colon adenocarcinoma and 7 (1%) had synchronous colorectal adenocarcinoma or a lesion involving both the colon and the rectum.

Table I demonstrates the demographic data findings of colon and rectal cancer patients during the study period. Rectal adenocarcinoma occurred most commonly, 99/284 (34.9%), in the > 60–70 age group while colon adenocarcinoma occurred most commonly in the > 50–60 age group. The bar graph, Figure 1 illustrates that the majority of both colon and

Table I: Demographic data

Demographic variable	Number of cases (%)	Rectal adenocarcinoma cases	Colon adenocarcinoma cases	Statistical analysis (chi-square)
Gender				***p* = 0.160**
Male	299 (50.8)	156	143	
Female	289 (49.2)	128	161	
Age group ()				***p* = 0.017**
18-30 (A)	13 (2.2)	9	4	
> 30–40 (B)	44 (7.5)	17	27	
> 40–50 (C)	84 (14.3)	33	51	
> 50–60 (D)	150 (25.5)	72	78	
> 60–70 (E)	171 (29.1)	99	72	
> 70 (F)	126 (21.4)	54	72	
District of residence				***p* = 0.997**
Cape Winelands	98 (16.7)	46	52	
City of Cape Town	433 (73.6)	207	226	
Garden Route	44 (7.5)	24	20	
Overberg	8 (1.4)	4	4	
West Coast	5 (0.8)	3	2	

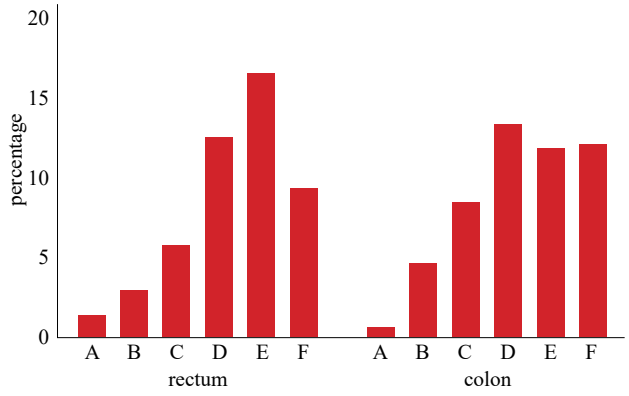

Figure 1: Bar graph depicting percentage of patients vs rectal and colon cancer age groups

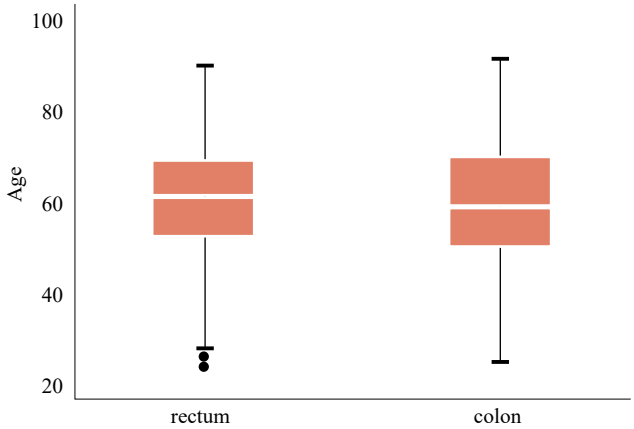

Figure 2: Box plot illustrating age distribution of rectal, combined rectal and colon, and colon cancer patients

rectal adenocarcinoma patients are being diagnosed during the fifth, sixth and seventh decade of life. Figure 2 clearly depicts the similarities in median age and age distribution between rectal and colon adenocarcinoma patients. The mean age of diagnosis for rectal cancer was 59.9, median age 61, minimum age 24 and maximum age was 90. While the mean age of diagnosis for colon cancer was 59.2, median age 59, minimum age 25 and maximum age 92.

Table II contains the pathological data findings of colon and rectal cancer patients during the study period. It is important to note that not all pathological variables were available for every patient diagnosed, and therefore all totals do not necessarily tally to 587. Interestingly, on investigation of the 74 patients for whom the sub-type was specified, mucinous adenocarcinoma was the most frequently diagnosed subtype, constituting 20/27 (74.1%) in the rectal adenocarcinoma group and 36/47 (76.5%) in the colon adenocarcinoma group. The majority of pathological specimens demonstrated a grade II differentiation – 177/228 (77.6%) for rectal adenocarcinoma and 196/256 (76.5%) for colon adenocarcinoma.

The majority of pathological specimens did not demonstrate lymphovascular or perineural invasion. The commonest stage of rectal cancer patients was IIA 35/119 (29.4%), closely followed by stage I 29/119 (24.4%). Stage IIIB was the commonest colon cancer stage comprising 66/212 (31.1%) patients.

Table II: Pathological data

Pathological and biochemical variables	Number of cases (%)	Rectal adenocarcinoma cases	Colon adenocarcinoma cases	Statistical analysis
Histological adenocarcinoma subtype				$p = 0.805$
Mucinous	56 (75.7)	20	36	
Signet ring cell	15 (20.3)	7	8	
Medullary	1 (1.4)	0	1	
Hepatoid	1 (1.4)	0	1	
Spindle cell	1	0	1	
Total specimens reviewed	74			
Differentiation				$p = 0.970$
Grade 1	77 (15.9)	37	40	
Grade 2	373 (77.1)	177	196	
Grade 3	34 (7)	14	20	
Total specimens reviewed	484			
Lymphovascular invasion				$p = 0.0$
Present	114 (25.7)	34	80	
Absent	330 (74.3)	169	161	
Total specimens reviewed	444			
Perineural invasion				$p = 0.992$
Present	73 (20.2)	30	43	
Absent	289 (79.8)	121	168	
Total specimens reviewed	362			
Polyp/s				$p = 0.768$
Present	55 (27.5)	22	33	
Absent	145 (72.5)	50	95	
Total specimens reviewed	200			
Pathological final stage AJCC 8th edition[11]				$p = 0.0$
I	43 (13)	29	14	
IIA	87 (26.2)	35	52	
IIB	20 (6)	6	14	
IIC	6 (1.8)	1	5	
IIIA	12 (3.6)	6	6	
IIIB	92 (28)	26	66	
IIIC	34 (10.3)	8	26	
IVA	12 (3.6)	3	9	
IVB	4 (1.2)	0	4	
IVC	21 (6.3)	5	16	
Resection and biopsy data				
Resection	331	119	212	
Biopsy	257	175	82	
Neoadjuvant treatment				
Received	68 (11)	67	1	
CEA				$p = 0.336$
< 5	196 (47)	94	102	
5 or more	221 (53)	122	99	
Total specimens reviewed	417			

Table III: Mismatch repair protein deficiency (dMMR) data

	*h*MLH1	*h*MSH2	*h*MSH6	*h*PMS2	Number of patients with dMMR	BRAF
Male	8	5	5	10	15	1
Female	21	9	7	20	25	6
Total	29	14	12	30	40	7

Locally advanced, primary inoperable rectal cancer is treated with neoadjuvant therapy. Sixty-eight rectal adenocarcinoma patients were treated with a neoadjuvant treatment approach. A total of 417 colon and rectal adenocarcinoma patients had a serum carcinoembryonic antigen (CEA) assessment and 221/417 (53%) had an elevated CEA level (defined as a level 5 or more), while 196/417 (47%) of patients had a normal serum CEA level.

Two-hundred and thirty-four of the pathological specimens were evaluated by immunochemistry for mismatch repair protein deficiency (dMMR). Positive dMMR data is presented in Table III. A total of 40 patients had a dMMR. Of these 40 patients, 7 had BRAF positivity and are therefore unlikely to harbour a genetic condition predisposing them to CRC. The most frequent dMMR was of hPMS 2 (30 patients) closely followed by *h*MLH1 (29 patients).

Discussion

This median age of diagnosis for both rectal (59 years old) and colon adenocarcinoma (59 years old) are comparable to other studies conducted in South Africa.[6,7] Statistically significant age distribution data showed that older individuals are at an increased risk of developing CRC compared to younger population groups ($p = 0.017$). Younger individuals, aged 18–30, had the lowest incidence of CRC in this study, 13 (2.2%). It is worth noting that high Human Development Index (HDI) countries are experiencing an increasing incidence of CRC in younger populations, but this study was not specifically designed to investigate this phenomenon. Nevertheless, information from this study, in collaboration with other epidemiological studies in sub-Saharan Africa conducted over a longer time interval, could provide insight into this new phenomenon.

The gender distribution among the diagnosed patients was approximately equal, with 289 females and 299 males. However, when analysing the site of cancer, differences were noted. A higher incidence of rectal cancers was observed in males (55% males vs. 45% females), which aligns with global trends. Conversely, a larger cohort of females were diagnosed with colon cancer (53% females vs. 47% males). These gender differences were not statistically significant, emphasising that gender cannot be considered a risk factor for the development of CRC, in line with global data findings.

Analysis of age groups in relation to lymphovascular invasion, perineural invasion and differentiation did not lead to any statistically significant findings. The majority of pathological specimens across all age groups did not demonstrate lymphovascular invasion or perineural invasion and Grade 2 differentiation was commonly identified. The commonest pathological stage in the > 30–40 age group was IIIC (25%); this is in contrast to the commonest pathological stage (IIIB) seen in the > 40–50 (28.9%), > 50–60 (28.6%), > 60–70 (29.2%) age groups. Interestingly elderly patients aged > 70, commonly presented with stage IIA CRC (36.2%).

In terms of geographical distribution, the two most populous districts accounted for the most CRC cases in the Western Cape Province.[9] South African community survey data from 2016 confirmed that the Western Cape is the fourth most populous province of South Africa with a total population of 6 279 731.[9] The City of Cape Town accounts for 4 005 016 (63.8%) of the population, while the second most populous district is the Cape Winelands with a population of 866 001 (21.6%).[9] As expected, the City of Cape Town had the most cases of CRC in this study 433 (73.6%), followed by the Cape Winelands district with 98 (16.7%). Notably, the City of Cape Town has 63.8% of the province's population but is responsible for 73.6% of all CRC cases in this study.[9] There could be several reasons for this discrepancy, such as the use of population data from 2016 while the study was conducted between 2018 and 2020, without considering potential population changes during that period. Additionally, domestic medical migration is common in the South African context, where patients temporarily leave their primary residence to seek healthcare expertise in cities and towns. Therefore, caution should be exercised when interpreting these geographical data results.

In this study population, the commonest pathological stage was stage IIIB, accounting for 92 out of 331 patients (27.8%). It was closely followed by stage IIA, which represented 26.2% (87 out of 331) of patients. The combined pathological stage data showed that 43 out of 331 patients (12.9%) presented with stage I disease, 113 out of 331 patients (34.1%) with stage II disease, 138 out of 331 patients (41.7%) with stage III disease and 37 of 331 patients (11.2%) with stage IV disease. These findings differ from global epidemiological databases where 20–25% of CRC patients typically present with stage IV disease.[1,2] The discrepancy in this study's findings can be attributed to several factors. Firstly, the findings were based solely on pathological specimens, and only 331 out of 588 patients had complete pathological staging data. Patients without pathological staging data had biopsy-confirmed CRC, but they might have been lost to follow-up, defaulted on follow-up, continued their treatment in the private sector, or not been candidates for further oncological management. Therefore, their pathological staging information could not be obtained. A larger percentage of the population could have actually presented with stage IV disease. In the sub-Saharan African context, with delayed index presentation, the rates of de novo metastatic disease may exceed the 20–25% seen in the rest of the world.

Neoadjuvant treatment approaches undertaken in the rectal adenocarcinoma population likely affect the pathological stage. Neoadjuvant treatment information was received from the pathology specimen forms and populated on the NHLS AARMS. As a result of the pathological staging, locally advanced rectal adenocarcinomas were likely downstaged with neoadjuvant treatment, resulting in a higher number of rectal cancer patients falling into the stage I and II categories in this study.

The biochemistry findings attempted to establish a relationship between an elevated CEA and stage of CRC presentation. Of the 417 patients with recorded CEA measurements 221 (52.9%) had an elevated result. The data capturing of CEA measurement made use of the index CEA serum level performed as certain patients had CEA measurements performed pre, during and post their treatment. Interestingly, data showed that stage I and II patients had a lower rate of CEA elevation, while stage III had a higher and stage IV the highest rate of CEA elevation. 38 patients with stage I disease had a CEA measurement of which 13 (34.2%) were raised, 82 patients with stage II disease had a CEA measurement of which 22 (26.8%) were raised. In contrast, 100 patients with stage III disease had a CEA measurement of which 47 (47%) were raised and 16 patients with stage IV disease had a CEA measurement of which 15 (93.8%) were raised. This is a small dataset, with statistically insignificant findings, but does attempt to establish a relationship between CEA level and stage of presentation.

The hereditary component of CRC accounts for 7–10% of all cases, with Lynch syndrome being the commonest specific hereditary syndrome accounting for 2–4%.[2] This study demonstrated that 40 (6.8%) patients had an established deficiency in at least one mismatch repair gene. Results of germline mutational analysis were not available in this subset of patients. Of the 40 patients, seven had BRAF mutations and therefore most likely represent sporadic tumours.

This study had several limitations. The study was conducted in the public sector of the Western Cape Province of South Africa. Sixteen per cent of the South African population seek private health care services and were thus not represented in this study cohort.[10] Domestic and international medical migration results in patients residing in other provinces of South Africa or other Southern African countries seeking healthcare services in the Western Cape public healthcare sector and subsequently being included in this study cohort.

A further study including the evaluation of clinical records, such as clinical examination and special investigation information, would provide more accurate data on stages at presentation. This study also does not consider the undiagnosed population. These are the individuals that have CRC but are yet to be diagnosed. Lastly, germline mutational analysis is recommended for the 40 patients with established deficiency in mismatch repair genes.

Conclusion

In conclusion, this study is one of the few provincial epidemiological studies performed in sub-Saharan Africa. The study showed an even distribution of CRC incidence between males and females, the middle-aged to elderly (> 50-year-old) population had the highest rates of cancer diagnosis, most pathological specimens did not demonstrate perineural or lymphovascular invasion, commonest histological type being adenocarcinoma and commonest histological adenocarcinoma subtype being mucinous. Stage III was the most frequent pathological stage and patients with stage III and IV disease had a higher rate of CEA positivity as compared to stage I and II. 40 patients had mutations of mismatch repair genes, 7 of which had a positive BRAF mutation. As a result, 33 (5.6%) patients have a high likelihood of having Lynch syndrome and would require germline mutational analysis.

The limitations of this study highlight the need for further investigation into the ethnic distribution of CRC in South Africa, use of radiological data for clinical staging, evaluating risk factors of patients diagnosed with CRC and assessing survival outcomes in our CRC population. Nevertheless, studies such as these are imperative for the establishment of South African based cancer registries, which will result in improved quality CRC data being used to assist with prevention, screening, intervention and monitoring policies in the South African setting.

Conflict of interest

The authors declare no conflict of interest.

Funding source

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Ethical approval

Prior to commencement of the study, ethical approval was obtained from the Stellenbosch University Health Research Ethics Committee (Ref: S21/11/228).

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AJCC Colorectal cancer TNM staging, 8th edition

Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or intramucosal carcinoma
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into the peri-colorectal tissues
T4a	Tumour invades through visceral peritoneum
T4b	Tumour directly invades or is adherent to other organs or structures
Regional lymph node involvement (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumour deposit(s) in the subserosa, mesentery, or non-peritonealised, pericolic, or perirectal/mesorectal tissues without regional nodal metastasis
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1a	Metastasis confirmed to one site or organ without peritoneal metastasis
M1b	Metastasis to two or more sites or organs without peritoneal metastasis
M1c	Metastasis to peritoneal site alone or with other sites or organ metastasis

Metastatic staging comprises of either a (c) or (p) suffix.
(c) – preoperative clinical assessment of metastatic disease by imaging and other investigations
(p) – pathological evaluation of metastatic disease

AJCC Colorectal cancer TNM stage grouping, 8th edition

0	Tis	N0	M0
1	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1/T2	N1a/N1b/N1c	M0
	T1	N2a	M0
IIIB	T3/T4a	N1a/N1b/N1c	M0
	T2/T3	N2a	M0
	T1/T2	N2b	M0
IIIC	T4a	N2a	M0
	T3/T4a	N2b	M0
	T4b	N1/N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c