The Characteristics of Advanced Colorectal Cancer in Patients Presenting to The Academic Centers of The Witwatersrand University in Johannesburg, South Africa.

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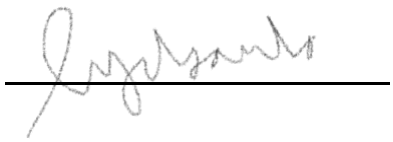
Declaration

I, Chido Nyatsambo (student no. 361752), declare that this research report is my own, unaided work. This research report is being submitted for the Degree of Master of Medicine in Surgery at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any other degree or examination at any other University.



On this 21 day of January 2021 in Johannesburg

Dedication

I would like to dedicate this MMed and associated efforts to my dear parents who have sacrificed many things in their lives for me to be at this point in my life. Thank you for believing in me, giving me the freedom to pursue my dreams and for supporting me.

Abstract

Background:

Colorectal cancer (CRC) is one of the most common cancers in South Africa. The characteristics of CRC differ in terms of anatomical location, histology and metastatic spread. The aim of this study was to assess the characteristics of the primary tumour in advanced colorectal cancer.

Objectives:

The objectives were to profile the metastatic spread in patients with T3/T4 lesions according to the characteristics of the primary lesion; to assess the percentage of synchronous metastases in patients with T3/T4 colorectal cancer; and to compare the relationship of the primary in CRC patients presenting with T3/T4 against those presenting with T1/T2 in terms of demographics, socioeconomics, risk profile, disease specific and outcome variables.

Methods:

The MRC Prospective Colorectal Cancer database (M1050446) was used. A retrospective review of 494 patients diagnosed with CRC between 2016 and October 2018 was done. Data was collected from the database and a descriptive analysis was done looking at the tumour stage, tumour site and histology.

Results:

A total of 494 patients were included 48.5% female and 51.5% male. 41.5% of the sample were older than 60 years. The rectum/anus had the highest number of tumours 231, followed by the left colon 106, and right colon 84. T3 tumours were most common in the left colon 55.7%. T4 tumours were predominantly in the right colon 46.5%. 247 out of 285 had adenocarcinoma, 38 patients had mucinous adenocarcinoma. 29.4% of the sample had synchronous metastases. There was a total of 79 liver metastases and 36 lung metastases.

Conclusion:

The rectum is the most common site for CRC. Advanced tumours are seen more in the proximal colon, compared to the distal colon. The most common histology type is adenocarcinoma. Almost 1/3 of the patients had metastases and the most common site was the liver followed by the lung.

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List of abbreviations

CRC - colorectal cancer

RC - Right colon

LC - Left colon

T – Tumour

M - Metastases

AC - Adenocarcinoma

MC - Mucinous Adenocarcinoma

SC - Signet Ring Cell Carcinoma

DM - Diabetes

HPT – Hypertension

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Chapter 1: Introduction

1.1 Background

Colorectal cancer (CRC) is the third most common cancer globally after lung and breast cancer. It ranks second amongst the leading cause of cancer death after lung cancer.(1) The WHO statistics for 2018 quote a total of 1.8 million cases of CRC and it was the second cause of cancer death at 862000 cases in 2018.(1) According to the International Agency For Research on Cancer, there were a total of 6037 new cases of CRC in South Africa in 2018 and CRC was the fifth most common cancer.(2) The reported incidence for CRC in Africa is low, the reasons for this may lie with low reporting of cases or because the actual incidence is low. However, due to changes in lifestyle towards those of western countries there may be an increase in the incidence of CRC.(3)

Mayosi's (4) demonstrated a change in the burden of diseases in South Africa in a paper he published in 2014. It was found that alcohol use, high body mass index and high blood pressure were the reason for the high proportion of disability adjusted life years lost.(4) These aforementioned risk factors happen to be some of the same risk factors for CRC. A speculation may be that this may contribute to the rising incidence of CRC in South Africa, in the sense that if these risk factors are more prevalent, it may contribute to the rise in incidence of CRC in South Africa. Arnold looked at the trends with regards to incidence and mortality of CRC in different countries and they showed that there was an increase in countries of medium and high human development index. From this study, they extrapolated that the disease burden is likely to develop in middle to low income countries in the long term.(5)

There have been a few studies done looking at CRC in South Africa researching various topics such as presentation, gender and race differences, treatment options, differences between public and private sector, and ways to detect it early. Using the MRC Prospective Colorectal Cancer database(6) characteristics of advanced colorectal cancer patients were researched.

In developed countries approximately 25% of patients present with metastatic disease and 25% develop metachronous metastases in the course of follow up.(7) The number of colorectal cancer patients presenting to the Academic institution of Witwatersrand has not been identified, nor is the year-on-year incidence and mortality clear. For these reason the findings of a hospital based sample is difficult to reference. The proportion of those presenting with stage IV disease is likely to be impacted by the fact that no screening modality for colorectal cancer is offered at a national or even regional level.

1.2 Literature Review

1.2.1 Risk Factors

Risk factors for CRC can be classified into modifiable (lifestyle, smoking, diet, diabetes, and alcohol) and non-modifiable (age, sex, genetics) risk factors. In terms of age, internationally, more than 50% of CRC patients are diagnosed after the age of 70 and less than ten percent are diagnosed before the age of 55.(3) Segal et al. described colorectal cancer in a retrospective population of mixed public and private patients presenting to hospitals in Johannesburg.(8) They found that the highest incidence for CRC in African and Caucasian patients was different. The highest incidence occurring in the sixth and eighth decade respectively. The age distribution was different with more young African patients having CRC.(8) In 2009, Cronje, Becker, and Patterson in an evaluation of pathology specimens identified a similar age distribution when histological samples were evaluated along differences in ethnicity.(9)

They suggested that there was a more aggressive type of colorectal cancer in the young African population. A larger number of African patients showed mucinous adenocarcinoma. They showed that in comparison to Caucasian patients, 15% of African patients had poorly differentiated adenocarcinomas, of which 7% were mucinous adenocarcinoma.(9)

1.2.2 Site of Metastases

The most common sites for metastases in colorectal cancer are the liver, lung, and peritoneum.(10) The location and number of metastases has been found to be of prognostic value.(11) Holch et al. showed that the most frequent site of metastases was the liver (70%) followed by pulmonary metastases (24%), lymph nodes (16%), and peritoneum (15%).(11) When comparing the site of metastases to the primary tumour location it was found that the liver was the most common metastatic site for the colon and the rectum at 71% and 60% respectively.(11–13) 70% of patients only had one anatomical site affected by metastatic disease and 19% of patients had two anatomical sites affected by metastases.(11) Literature from Asia showed that the number and pattern of metastases affected survival . A comparison of the median survival depending on metastatic site showed that patients with peritoneal metastases had a poorer survival rate compared to metastases to the liver, lung or extra-regional.(14) They also showed that median survival for a single anatomical site was better than that of patients with multiple anatomical sites.(14)

1.2.3 Site of Primary Lesion

The site of the lesion is associated with a preponderance of metastasis to specific organs as well as influencing the prognosis. Hugen et al. divided the colon into the right colon (RC) (caecum, ascending colon, transverse colon) and the left colon (LC)

(splenic flexure, descending colon, sigmoid and rectum), application of the above definition showed that the primary tumour location was associated with differences in metastatic pattern.(15) Patients who had lesions in the left colon had a higher rate of metastases in the liver and lung in comparison to patients with lesions in the right colon who had a higher rate of metastases in the peritoneum.(15) Byun et al. divided the colon into right colon (caecum, ascending colon and proximal two-thirds transverse colon), left colon (from distal third of transverse colon to sigmoid colon) and rectum.(14) They found that lesions in the rectum and the left colon more often metastasized to the liver and lung compared to lesions in the right colon. Lesions in the right colon metastasized more frequently to the peritoneum and ovary in comparison to the left colon and rectal lesions. This study also showed that there was a difference in survival in metastatic CRC with regards to the location of the primary lesion. They found that the median overall survival was 13.7, 18.0 and 19.9 months for lesions in the right colon, left colon and rectum respectively.(14)

1.2.4 Histology

It is well established that the outcomes in CRC are dependent on the specific histological subtype. Colorectal carcinoma is classified into three main histological types: adenocarcinoma (AC), mucinous adenocarcinoma (MC), and signet-ring cell carcinoma (SC). The type of histology has an impact on prognosis as well as metastatic pattern. In international figures, adenocarcinoma (approximately 89%) is the most common histological type followed by mucinous adenocarcinoma, which accounts for approximately 5-15%, and signet ring cell carcinoma, which accounts for approximately 1%.(16,17) Mekenkamp et al. investigated the prognostic significance of mucinous adenocarcinoma. He found that patients with mucinous adenocarcinoma were slightly older and had more extra-hepatic metastases compared to patients with

adenocarcinoma.(17) The tumours also had a higher T classification as well as having a higher median number of positive lymph nodes.(17,18) With regards to prognosis, Hyngstrom et al. evaluated the clinical features and survival outcome in patients with MC and SC.(16) They found that SC was found more in younger patients, MC and SC were located more often in the right colon, 60% and 62%, respectively and SC was associated with a lower five-year survival.(16) Park et al. compared the prognosis between MC and non-mucinous AC in CRC by comparing specific tumour characteristics(18). They found that patients who had MC had larger tumours, higher preoperative CEA, higher pathological T classification in staging and more of the tumours were located in the right colon.(18) Hugen et al. showed that there were differences in the pattern of metastases between histology subtypes: AC metastasized to the liver more often in comparison to MC and SC, 73%, 52.2% and 31.7% respectively and, MC and SC frequently metastasized to the peritoneal surface compared to AC.(15) SC metastasized more to distant lymph nodes compared to MC and AC.(10) Kermanshahi et al. acknowledged that patients who had peritoneal metastases had a poorer prognosis, they found that the patients who had peritoneal metastases had tumours that displayed mucinous and signet ring cell differentiation and that these lesions were predominantly found in the right colon.(19)

1.3 Justification for the study

Over the years there have been studies done looking at colorectal cancer in South Africa researching various topics. However, very few have been done using prospective data in sporadic colorectal cancer seen on the Highveld. With the available data, it is possible to characterize the epidemiology, risk profiling, presentation, management, and outcome of patients with locally advanced or metastatic CRC.

1.4 Aim

The aim of the study was to give a description of the primary lesion in colorectal cancer in relation to the metastases in patients presenting with T3/T4 tumours and assess the percentage of metastases in advanced CRC. The study also wanted to determine the demographic differences, when comparing T3/T4 (invades through muscularis propia into pericolorectal tissue/invades visceral peritoneum or adjacent structures) and T1/T2 (invades submucosa/invades muscularis propia) in this urban South African population.(20)

1.5 Objectives

Primary Objectives:

- Profile metastatic spread in patients with T3/T4 lesions according the characteristics of the primary lesion.
- Assess the percentage of synchronous metastases in patients with T3/T4 colorectal cancer (to be compared with European/American Figures)

- Compare the relationship of the primary location in colorectal cancer patients presenting with T3/T4 against those presenting with T1/T2 in terms of demographics, socioeconomics, and family history.

Chapter 2: Methods

2.1 Study Design and Data Interpretation (Collection)

This study was supported by the University of Witwatersrand/South African Medical Research Council (WITS/MRC) and Common Epithelial Cancers Research (CECRC) Grant awarded to the University of the Witwatersrand (PI: Professor Paul Ruff). It was a retrospective analysis of prospectively collected data taken from the MRC Colorectal Cancer Database. The database was commenced in January 2016 and at the time of data analysis, there were 494 study participants enrolled. The Human Research Ethics Committee of the University of Witwatersrand had approved the database (M1050446)(6).

The study participants were patients above the age of 18 with a histological diagnosis of primary adenocarcinoma of the colon or rectum with T1-T4 tumours. The participants were sampled from the Academic Teaching Hospital Complex of the University of Witwatersrand, which included Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital, Wits Donald Gordon Medical Centre, and Edenvale Hospital. Clinicians at the study site identified potential participants and referred them to the study nurse who was responsible for the enrolment process and follow up of the patients identified(6).

The data retrieved from the REDCap database was entered onto an excel sheet with the following patient demographics: age, gender, race; socioeconomic Status: employment, level of schooling; family history of cancer. Tumour variables including location (RC, LC, Rectum, Anus), Histology (AC, MC), T-staging classification and metastases (presence, site) were recorded.

The colon was divided into right colon: from caecum up to and including the splenic flexure, and left colon: distal to splenic flexure to rectosigmoid junction, rectum and anus. There were a total of 494 patients in the database at the time of sampling the data, however 86 were excluded because of missing data variables. The staging of the tumours at presentation was defined by the radiological TNM stage.(20) In those instances where surgery was carried out a pathological stage was also assigned according to the 8th Edition of TNM. These two sources were amalgamated to provide an AJCC score for each patient. It is the AJCC score that is used to define tumour stage. Where an AJCC score could not be determined, the patents were excluded. The histology was assessed by the NHLS. The pathologist reported the histology of adenocarcinoma, mucinous adenocarcinoma and signet ring cell carcinoma by using the WHO classification of Pathology.(20,21)

2.2 Ethical Approval

Ethical approval was granted by the Human Research Ethics committee of University of Witwatersrand for the database (M150446). An application for ethical approval was submitted in July 2018 to the Human Research Ethics Committee (Medical) and approval was granted in September 2018 (clearance certificate number M180828.)

2.4 Statistical analysis

SPSS was used for statistical analysis. There were categorical and numerical variables in the dataset. For the categorical variable under demographics, the frequency and percentage of the variables were assessed and the results were presented in a table. A descriptive analysis of the other variables was done and two way tables were used to cross tabulate and do a comparison between variables (e.g.

site of tumour and tumour stage). This was also represented in table format. The sample size was too small to do any statistical analysis to generate data of any significance. The multivariate analysis of the risk factors was also done however, it did not yield any statistically significant results.

Chapter 3: Results

There were a total of 494 patients in the database, 86 were excluded due to missing data variables; leaving a total of 408.

Table 1: Demographics

VARIABLE	CATEGORY	FREQ.	PERCENT
AGE GROUP (N=402 MISSING 6)	30 and below	16	4.0
	31-40 years	46	11.4
	41-50 years	60	14.9
	51-60 years	113	28.1
	>60 years	**167**	**41.5**
GENDER (N=408)	Female	198	48.5
	Male	**210**	**51.5**
RACE (N=408)	**African**	**212**	**52.0**
	Coloured/ mixed race	26	6.5
	Caucasian	139	34.0
	Other	31	7.6
EMPLOYMENT (N=408)	**No**	**231**	**56.8**
	Yes	176	43.2
FAMILY HISTORY (N=408)	Unknown	4	1
	Yes	189	46.3
	No	**215**	**52.7**

Table 1 looks at the demographics of the sample. 41.5% of the sample were older than 60 years and only 14.4% were younger than 40. There was a slight preponderance to males, with males being 51.5% and females being 48.5%. 52% of the patients were African, followed by Caucasian patients at 34%. Other ethnic groups recorded were Indian/Asian and mixed race, being at 7.6% and 6.5% of the sample respectively. 43.2% of the sample had a family history of cancer, including those patients with first- and second-degree relatives with a history of any cancer type. More than half of the patients were unemployed.

Table 2: Site of tumour in relation to stage of tumour and site of metastases

TUMOUR STAGE	RIGHT COLON	LEFT COLON	RECTUM AND ANUS
	N=84(%)	N=106(%)	N=231(%)
T0	0	1(0.9)	1(0.4)
T1	0	3(2.8)	3(1.3)
T2	7(8.3)	9(8.5)	32(13.9)
T3	38(45.2)	59(55.7)	102(44.2)
T4	39(46.5)	34(32.1)	93(40.2)
TOTAL	84(100)	106(100)	231(100)
SITE OF METASTASES			
LIVER	16(19.0)	26(24.5)	42(18.2)
LUNG	4(4.7)	10(9.4)	23(10)
INTRA-ABDO	10(11.9)	8(7.5)	15(6.5)
INTRA-PELVIC	2(2.4)	6(5.6)	7(3.0)
BONE	0	1(0.9)	9(3.9)
OTHER	2(2.4)	1(0.9)	2(0.9)
TOTAL	34(40.5)	52(49.1)	98(42.2)

84 patients had lesions in the right colon, 106 in the left colon and 231 in the rectum and anus combined. 13 patients had synchronous lesions making a total of 421 tumour sites. The majority of tumours presented with T3/T4 lesion (86%). T3 was the most common stage in the left colon (55.7%). The right colon and rectum were similar (45.2% vs 44.2%). T4 was the most common lesion in the right colon (46.5%).

With regards to site of metastases related to the location of the primary lesion, there were more liver metastases when the primary was in the left colon (24.5%) compared to when the primary was in the right colon (19.0%) or in the rectum/anus (18.2%). The rectum/anus and left colon had similar percentage of metastases to the lung; 10% and 9.4% respectively. The right colon had more metastases to the intra-abdominal cavity (11.9%) compared to the

rectum/anus (6.5%) and the left colon (7.5%). Majority of the bone metastases occurred from primary lesion in the rectum and anus. There were no brain metastases in the entire sample.

Table 3: Histology according to tumour location and tumour stage

N=285	**RIGHT COLON (%)**	**LEFT COLON (%)**	**RECTUM AND ANUS(%)**	**T0(%)**	**T1(%)**	**T2(%)**	**T3(%)**	**T4(%)**
ADENOCARCINOMA (N=247)	62(21.8)	77(27)	**108(37.9)**	1(0.3)	4(1.4)	43(15.1)	**137(48.1)**	62(21.8)
MUCINOUS ADENOCARCINOMA (N=38)	9(3.2)	6(2.1)	**20(7)**	0	0	2(0.7)	15(5.3)	**21(7.4)**

The histology was from patients who had a surgical procedure or biopsy which were 285 out of the 408. Out of all the patients with histology(285), adenocarcinoma was the most common histology type (87%), and only one patient had a neuroendocrine variant of adenocarcinoma. There were 38(13%) patients who had mucinous adenocarcinoma. Of the patients with mucinous adenocarcinoma 20(7%) of them were located in the rectum. Of the T3 tumours 90.1% of the lesions were adenocarcinoma and 9.9% were mucinous adenocarcinoma, of the T4 lesions 74.4% were adenocarcinoma and 25.3% were mucinous adenocarcinoma.

Table 4: Site of metastases

SITE OF METS	T0	T1	T2	T3	T4	TOTAL
LIVER	1(1.2%)	1(1.2%)	3(3.8)	34(43.0)	**40(50.6)**	79(100)
LUNG	0	0	0	14(38.9)	**22(61.1)**	36(100)
INTRA-ABDO	0	0	1(3.3)	6(20)	**23(76.7)**	30(100)
INTRA-PELVIC	0	0	1(7.2)	3(21.4)	**10(71.4)**	14(1000
BONE	0	0	0	5(50)	5(50)	10(100)
OTHER	0	0	0	2(40)	**3(60)**	5(100)

120 (29.4%) patients had metastases. The liver was the most common site of metastases, followed by the lung. There were a total of 159 patients with T4 tumours, 92(22%) of them did not have metastases.

Metastases were most common in patients with T3 and T4 tumours across all sites of metastases. Liver, lung, intra-abdominal (nodal, other organs like pancreas), intra-pelvic (peritoneal/krukenbrug) and other were all more common in the T4 tumours at 50.6%, 61.1%, 76.7%, 71.4% and 60% respectively. Irrespective of the tumour site, the primary lesion was frequently a T4 lesion. Bone metastases were equally derived in T3 and T4.

The numbers in the subcategories of the sample were too small to allow any statistical analyses that would produce results of significance. There were a total of 352 patients in the T3/T4 group and 56 in the T1/T2 group.

Chapter 4: Discussion

4.1: Demographics and Risk Factors

Advanced age is known to be one of the risk factor for CRC. Frequently more than 50% of CRC are diagnosed in patients over the age of 70.(3) In the sample fewer patients (41.5%) were over the age of sixty, in comparison to American Cancer statistics that showed 54% of their cases were over 65 years.(22) Less than 10% of patients are diagnosed before age 55.(3) In American colorectal cancer statistics 12% of their patients are under 50.(22) In this study 30% of the patients were younger than the age of 50 showing that a third of the patients are quite young in comparison to international figures. There was a slight preponderance to males with 51.5% being males and 48.5% being females. There were significantly more males (60%) and less females (30%) in European and Korean literature(10,11,14). A SEER base study in China showed gender predilection similar to this study, males constituted 52.4% and females 47.6%.(13)

There were more African patients (52%) in this study compared to Caucasian patients (34%), the reason for this is unknown. It is difficult to make a comparison with other areas, however in the USA the incidence of CRC is greater in African American than non-Hispanic whites. They comment that the reasons for the disparity are complex however things like risk factor prevalence, access to health care, and low socioeconomic class play a role.(22)

4.2: Characteristics of the primary tumour

The most common site of the primary tumour overall was the rectum (56%). The LC with 26% was marginally more frequent site of the primary lesion compared to the right colon with 25%. These findings show some differences when compared to international figures as

epitomised by those from Korea, where in a sample of 1115 electronic records there were 43.3% tumours found in the left colon, 34.8% in the rectum and 21.9% in the right colon.(14) Similarly, the results differed when compared to American results, as defined by the data from the American Cancer Society prepared in 2017 from North American cancer registries. An unexpected finding was that women over the age of 80 years had right sided tumours in 57% of cases where those less than 50 years of age had predominantly rectal cancer.(20) Ethnic, geographic and temporal variation in the presentation of tumour site was possibly initiated by variation in environmental and genetic risk factors. It was likely these differences that translated into the biological behaviour, of colorectal cancer, which was increasingly being seen as a heterogonous disease. This was amply demonstrated from data from the Norwegian Cancer Registry.(23) Therefore, through variation in tumour biology, site of primary as an independent variable, is conceivably going to have a significant baring on the nature of local tumour behaviour as well as the biology of metastatic spread. Because the patients eligible for evaluation of advanced disease represent a small subset of patients with colorectal cancer a meaningful understanding of the differences in the behaviour of advanced disease, as segregated by site of primary, will require much larger samples than collected in this study.

Assessing the T stage of the tumour in this sample showed that 86% of the tumours across all sites were T3 or T4 tumours. Augestad showed that T3 tumours were the most common at 49% in comparison to this study that had 47% of T3 tumours.(23) The right colon had the most T4 tumours (46.5%), a finding which was consistent with international figures there were more locally advanced cancers in the right colon compared to other sites viz 76.1% vs 67% $p > 0.01$.(24,25)

When comparing the site of the lesion with the T stage of the lesion the right and left colon both presented with advanced tumours. This could mean that patients presenting with advanced cancer are likely to have their primary lesions either in the left or right colon, however more numbers are needed to get a statistically significant result. The rectum had the most early lesion T1 and T2.

The most common histology type was adenocarcinoma (87%) and this is well recognized as the most frequent type of histology for CRC.(16,17) In this study 13% patients had mucinous adenocarcinoma. The most common sites for mucinous adenocarcinoma were the rectum and the right colon. This finding was in keeping with literature, as most times mucinous adenocarcinoma is more common in the proximal or right sided lesions. Hyngstrom et al. found that majority of tumours that had signet ring cell or mucinous histology were found in the right colon.(12,16,25) Literature from Germany found the most common histology to be adenocarcinoma and mucinous adenocarcinoma was present more in the right colon than the left.(24) The rectum was not included in this study. In this study, the patients who had mucinous adenocarcinoma were likely to have T3 or T4 lesions, correlating with the aggressive nature of this histology type as seen in previous studies.(17)

4.3: Characteristics of Metastatic spread

The prevalence of metastatic spread in the sample population was 29.4%. The most common organ for metastatic spread was the liver, followed by the lung. The lungs were the most common extra-hepatic site of metastases.(14,26)

The patterns of metastatic spread in this study was similar to other studies. When the primary was in the left colon, the metastases were more likely to be in the liver compared to the other

site.(13–15) T3/T4 lesions were more likely to spread to the liver. Engstrand et al. found a similar finding that liver metastases were associated with higher T stages.(26)

4.4: Multivariate analysis of Risk factors

Multivariate analysis did not yield any significant results. The numbers were too small, there were 352 patients in the T3/T4 group and 56 patients in the T1/T2 group. Therefore, it was not possible to identify an association of the T stage at presentation with demographic variables, smoking or diabetes in this study.

4.5: Limitations

The findings of this study should be interpreted in light of the study limitations. This was a retrospective analysis of a prospective database. The T and M stage were derived by amalgamation of clinical, pathological and radiological data (20,21) with the possibility of under or over staging of the disease.. The metastases were recorded according to findings on radiological examinations and interpretation error could play a factor. For example it is difficult to assess peritoneal metastases on a CT scan and unfortunately there was no data showing whether or not diagnostic laparoscopy was used to confirm peritoneal metastases. The was also missing histology report for 123 patients which may also affect the way in which the data was interpreted with regards to reaching a conclusion.

Chapter 5: Conclusion

Many finding in this study were similar to other studies but in the current study there was a much larger number of young patients compared to European and American series. 30% of the patients were below the age of 50 compared to American and European statistics where 12% and 10% respectively are below the age of 50. The most common site for the primary lesion was the rectum, followed by the LC then the RC. The most common histology was adenocarcinoma (87%). 13% of the tissue samples showed mucinous adenocarcinoma, which is similar to the 5-15% reported in European studies. The most common T stage was T3. The majority of the patients (86%) presented with advanced lesions(T3,T4). These late presentations may results from lack of Public health education about bowel cancer as well as a lack of resources limiting access to medical facilities. In the current series, one third of patients had metastatic disease but due to small numbers, the association of risk factors with patient demographics and tumour variables could not be made. Ongoing scrutiny of CRC cases seen in Johannesburg must continue to complete this analysis.

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Appendix:

Approved Protocol

Title:

The Characteristics Of Advanced Colorectal Cancer in Patients Presenting to The Academic Centers Of The Witwatersrand University In Johannesburg, South Africa.

Chido Nyatsambo

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MMed Surgery

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Introduction/Background:

Colorectal cancer (CRC) is one the most common cancers globally. It is the third most common cancer in the world and ranks fourth amongst the leading cause of cancer death (1). In 2012, there were approximately 1.4 million new cases and 700 000 deaths (1). The highest incidence rates in 2012 were in Australia/New Zealand and the lowest were in Western Africa (1). The reported incidence for CRC in Africa is low (1); the reasons for this may be attributed to the fact that there may be low reporting of cases or because the actual incidence is low. However, due to changes in lifestyle towards those of western countries there may be an increase in the incidence of CRC (2).

In South Africa, CRC is the fourth most common cancer in women and the second most common cancer in men (3). Mayosi et al. (4) published a paper in 2014 which points out that there has been a change in the burden of diseases in South Africa, it was found that, alcohol use, high body mass index and high blood pressure are found to be the reason for the high proportion of disability adjusted life years lost (4). These aforementioned risk factors happen to be some of the main risk factors in terms of CRC, highlighting that CRC may represent a significant health care burden in South Africa.

There have been a few studies done looking at colorectal cancer in South Africa researching various topics, however, no research has been done on prospective data of sporadic colorectal cancer in Gauteng, to characterize the epidemiology, risk profiling, presentation, management, and outcome of patients with locally advanced or metastatic CRC. This study will be a retrospective analysis using a prospective database, the MRC Prospective Colorectal Cancer Database, the first of its kind in Gauteng. “The database was created in response to the increasing burden of CRC in Sub-Saharan Africa as well as to address the paucity of Data on CRC (5).” The

database consists of patients above the age of 18 years with a diagnosis of CRC confirmed histologically. Participants are enrolled from the study sites, which are based in the Academic Teaching Hospital Complex of the University of the Witwatersrand. Clinicians at a study site identify potential participants and refer them to the study nurse who is responsible for the enrolment process (5). The study data are captured and managed using Research Electronic Data Capture (REDCap) (5). The Database started in 2016 and to date (May 2018) has 412 participants enrolled. Data captured includes: demographics, socioeconomic status, family history, previous medical or surgical history, lifestyle history, colonoscopy findings, staging at presentation, treatment modalities, biochemistry, histology, and follow-up which include disease recurrence and survival (5).

In developed countries approximately 25% of patients present with metastatic disease and 25% develop metachronous metastases along the course of follow up (6). The proportion of colorectal cancer patients presenting to the Academic institution of Witwatersrand has not been identified. The proportion of those presenting with stage IV disease is likely to be impacted by the fact that no screening modality for colorectal cancer is offered at a national or even regional level. It has been shown that the depth of invasion is an independent prognostic factor (7). We will be looking at the number of patients with T3/T4 tumours compared to those with T1/T2. These 2 groups will be differentiated by presentation with and without metastases. Apart from the demographics, we will be particularly interested in looking at the site of the colorectal cancer within the colon or rectum, histology type of the lesion, the grading, molecular features, and outcomes. The other variables used to compare the two groups can be divided into demographics, socioeconomic status, risk profiles, disease specific variables and lastly outcomes which will be defined in our data set by overall survival.

We will be using the AJCC staging system for colorectal cancer specifically looking at the Tumour staging, which describes the extent of the tumour. Some of the participants will only have clinical staging due to the fact that no surgery was done. Clinical staging comprises of physical examination, imaging studies, laboratory tests, and biopsy. This is usually done before surgery unless the participant presented needing emergent surgical management. Some participants have clinical and pathological staging, which will be taken into consideration. The limitation that arises with clinical staging is the fact that participants can be either over or under staged in terms of their T classification. We will use the M classification for metastases and this is assessed using imaging studies such as CT scans.

Risk factors for CRC will be classified into modifiable and non-modifiable risk factors. Of the non-modifiable risk factors age, sex, and lifestyle will be included. Factors such as smoking, diet, obesity, diabetes, and alcohol use will be among those factors considered modifiable. In terms of age, internationally, more than 50% of CRC patients are diagnosed after the age of 70 and less than ten percent are diagnosed before the age of 55 (2). In a paper published in 1988 Segal et al. described colorectal cancer in a retrospective population of mixed public and private patients presenting to hospitals in Johannesburg (8). He found that the highest incidence for CRC in African and Caucasian patients differed, the highest incidence occurring in the sixth and eighth decade respectively. The age distribution was also different with more young African patients having CRC (8). In 2009, Cronje, Becker, and Patterson (9) in an evaluation of pathology specimens identified a similar age difference when samples were evaluated along differences in ethnicity. They also suggested that there is a more aggressive type of colorectal cancer in the young African population. For these reasons, it will be interesting to analyze and compare the difference in the age groups

with regards to disease onset. Finally in considering non-modifiable risk factors international figures show that men may develop adenoma and CRC earlier in their lives compared to women (2).

Genetics plays an important role as a risk factor, because of the associated link when it comes to CRC. Patients who have a family history of colorectal cancer or colorectal adenoma may be at an increased risk of developing the disease. Approximately one third of CRC risk is attributable to familial factors (2). It will be interesting to look at our population and see if genetic factors play a significant role in disease appearance, progression, and prognosis.

The most common sites for metastases are the liver, lung, and peritoneum (10). The location and number of metastases has been found to be of prognostic value (11). Holch et al. (11) conducted a study in 2017 and it showed that the most frequent site of metastases was the liver at 70% followed by pulmonary metastases 24%, lymph nodes 16%, and peritoneum 15%. Comparing the site of metastases to the primary tumour location; it was found that the liver was the most common metastatic site for the colon and the rectum at 71% and 60% respectively (11,12,13). 70% of patients only had one anatomical site affected by metastatic disease and 19% of patients had two anatomical sites affected by metastases (11). A paper published in 2017 written by Byun et al. (14) showed that the number and pattern of metastases affected survival. A comparison of the median survival depending on metastatic site showed that patients with peritoneal metastases had a poorer survival rate compared to metastases to the liver, lung or extra-regional. They also showed that median survival for a single anatomical site was better than that of patients with multiple anatomical sites.

The site of the lesion plays an important role when it comes to the pattern of metastatic spread and prognosis. In this study, the colon has been divided into left and right: right colon comprising of caecum, ascending colon and transverse colon up to but not including splenic flexure, and the left colon comprising of splenic flexure, descending colon, sigmoid, and the rectum. In a study done and published in 2017 by Hugen et al. (15), application of the above definition showed that the primary tumour location was associated with differences in metastatic pattern. Patients who had lesions in the left colon had a higher rate of metastases in the liver and lung in comparison to patients with lesions in the right colon who had a higher rate of metastases in the peritoneum (15). In another study by Byun et al. (14) published in 2017, the authors divided the colon into right colon (caecum, ascending colon and proximal two-thirds transverse colon), left colon (from distal third of transverse colon to sigmoid colon) and rectum. They found that lesions in the rectum and the left colon more often metastasized to the liver and lung compared to lesions in the right colon. Lesions in the right colon metastasized more frequently to the peritoneum and ovary in comparison to the left colon and rectal lesions. This study also showed that there is a difference in survival in metastatic CRC with regards to the location of the primary lesion. They found that the median overall survival was 13.7, 18.0 and 19.9 months for lesions in the right colon, left colon and rectum respectively (14). The prospective dataset that will be used in this study will be assessed along these lines.

The histology in CRC also plays important role in the natural history of the disease. Histologically colorectal carcinoma is classified into three main histological types: adenocarcinoma (AC), mucinous adenocarcinoma (MC), and signet-ring cell carcinoma (SC). The type of histology plays a role in prognosis as well as metastatic pattern. In international figures, adenocarcinoma is the most common histological type

followed by mucinous adenocarcinoma, which accounts for approximately 5-15%, and signet ring cell carcinoma, which accounts for approximately 1% (16,17). Mekenkamp et al. (17) published a paper in 2012, investigating the prognostic value of mucinous adenocarcinoma; the findings were; patients with mucinous adenocarcinoma were slightly older and had extra-hepatic metastases compared to patients with adenocarcinoma (17). The tumours also had a higher T classification as well as having a higher median number of positive lymph nodes (17,18). In terms of prognosis, in 2012, Hyngstrom et al. (16) evaluated the clinical features and survival outcome in patients with MC and SC. They found that SC was found more in younger patients, MC and SC were located more often in the right colon, 60% and 62% respectively. In terms of survival SC was associated with a lower five-year survival (16). In another study done in 2015 by Park et al. (18), the authors compared the prognosis between MC and non-mucinous AC in CRC. They found that patients who had MC had larger tumours; higher preoperative CEA, higher pathological T classification in staging and more of the tumours were located in the right colon. There was also an observed difference in terms of five-year overall survival; the five-year overall survival for MC was 81.3% and 87.4% for the non-mucinous AC group.

The histological type is also thought to play a role in the metastatic pattern of CRC. As mentioned previously, the most common site of metastases in CRC are the liver, lungs and peritoneum, however CRC may also metastasize to the brain, bone, spleen and distant lymph nodes (10). A number of studies have been done that show that there are differences in the pattern of metastatic spread between the histological subtypes. In 2014 Hugen et al. (10) published a paper showing, that there are differences in the pattern of metastases between histology subtypes; they found that AC metastasized to the liver more often in comparison to MC and SC, 73%, 52.2% and 31.7%

respectively. MC and SC frequently metastasized to the peritoneal surface compared to AC and SC, which metastasized more to distant lymph nodes compared to MC and AC (10). Kermanshahi et al. acknowledged that patients who had peritoneal metastases had a poorer prognosis, in their study, published in 2017, they found that the patients who had peritoneal metastases had tumours that displayed mucinous and signet ring cell differentiation and that these lesions were predominantly found in the right colon (19). Once again it will be possible to use the MRC database to source these variables.

Therefore, our aim will be to:

Characterize the primary lesion in colorectal cancer in relation to the metastases in patients presenting with T3/T4 tumours and assess the percentage of metastases in advanced CRC. We also aim to characterize, against demographic, socioeconomic, risk, disease specific, and outcome variables, the relationship of the primary in CRC, when presenting as T3/T4 as apposed to T1/T2 in the urban South African population.

Study Objectives:

- Profile metastatic spread in patients with T3/T4 lesions according the characteristics of the primary lesion.
- Assess the percentage of metastases in patients with T3/T4 colorectal cancer (to be compared with European/American Figures)
- Compare the relationship of the primary in colorectal cancer patients presenting with T3/T4 against those presenting with T1/T2 in terms of demographics, socioeconomics, risk profile, disease specific, and outcome variables.

Materials and Methods:

This study is supported by the University of Witwatersrand/South African Medical Research Council (WITS/MRC) Common Epithelial Cancers Research (CECRC) Grant awarded to the University of the Witwatersrand (PI: Professor Paul Ruff). It is a retrospective analysis of data taken from the MRC Prospective Colorectal Cancer Database. The database was commenced in January 2016. To date there are 412 study participants enrolled. The Human Research Ethics Committee of the University of Witwatersrand has approved the database (M1050446) (5).

The study participants are patients above the age of 18 with a histological diagnosis of primary adenocarcinoma of the colon or rectum with T1-T4 tumours. The participants are sampled from the Academic Teaching Hospital Complex of the University of Witwatersrand, which includes Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital, Wits Donald Gordon Medical Centre, and Edenvale Hospital (5). Clinicians at the study site identify potential participants and refer them to the study nurse who is responsible for the enrolment process (5). The study data are captured and managed using REDCap (5).

The data for this study will be captured from the REDCap database into an excel spreadsheet. The following data will be captured: patient demographics, socioeconomic Status, public versus private sector, family history of colorectal cancer (FAP/HNPCC/ADENOMA), previous medical and surgical history (DM/HPT/HIV/IBD), risk factors (smoking, alcohol, diet, sedentary lifestyle), presentation (lower gastro-intestinal bleed, bowel obstruction, constitutional symptoms, change in bowel habits, referral), diagnosis (colonoscopy, CT and MRI), tumour location (right colon or left colon), histology (AC/MC/SC), staging at presentation (AJCC), T staging classification and presentation (T3/T4), metastases, and outcomes. The T staging will be done using the AJCC staging system. We will use the clinical staging mainly as well as the

pathological staging for participants that have had surgery. The limitation around clinical staging arises in the accuracy of the staging and that has to be taken into consideration when analysing the data: some participants may be over or under staged.

Data analysis:

There are categorical and numerical variables in our data set. The variables used to compare the two groups can be divided into demographics, socioeconomic status, risk profiles, disease specific variables and lastly outcomes which will be defined in our data set by overall survival. For categorical data we will represent the data using bar graphs and pie charts. For estimation of the categorical variables multivariate analyses will be performed. We will use a confidence interval of 95%. The chi-square test will be used to determine whether an association between two categorical variables is significant. If there appears to be any measures of association we will use odds ratio and/or relative risk. As there are likely only to be 100 or so patients presenting with advanced or metastatic disease a power of prediction will be assessed where significance is found.

Numerical variables, they will be graphically represented by histogram or box pot and mean and standard deviation will be used for descriptive measures. If we can estimate for the population we will use a confidence interval of 95%. When evaluating for statistical inference, we will use t-test to assess for difference between two numerical variables, and to measure the association between variable we will use the Pearson correlation coefficient.

Ethics:

Ethical approval has been granted by the Human Research Ethics committee of University of Witwatersrand for the database (M150446). However, this is a retrospective analysis of a prospective database therefore ethics approval is a requirement. Such request will be submitted in June 2018. There are no apparent ethical issues. The data is de-identified therefore all patient information is kept anonymous.

Timing:

	2018								
Process	Mar	Apr	May	Jun	Jul	Aug	Sep	Nov	Dec
Project Idea	X								
Literature Review	X	X							
Preparing Protocol		X	X						
Protocol Deadline			16/5/18						
Protocol Assessment				13/6/18					
Ethics Application				7/6/18					
Collecting Data					X	X			
Data Analysis							X	X	
Writing up – report									X
Report Submission									
Finalize//Submit-publication									

	2019								
Process	Jan	Feb	Apr	May	Jun	Jul	Aug	Sep	Oct

Project Idea									
Literature Review									
Preparing Protocol									
Protocol Deadline									
Protocol Assessment									
Ethics Application									
Collecting Data									
Data Analysis									
Writing up – report	X	X							
Report Submission			X						
Finalize//Submit-publication			X						

Funding:

No funding is required for this study.

Problems:

No problems are anticipated with regards to carrying out the study.

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Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Chido Nyatsambo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180828

NAME: (Principal Investigator)	Dr Chido Nyatsambo
DEPARTMENT:	Surgery Wits Donald Gordan Medical Centre
PROJECT TITLE:	The characteristics of advanced colorectal cancer in patients presenting to the academic centres of the University of the Witwatersrand in Johannesburg, South Africa
DATE CONSIDERED:	31/08/2018
DECISION:	Approved Unconditionally
CONDITIONS:	
SUPERVISOR:	Dr. C Jann-Kruger, Dr B Bebington and Dr Daniel Surridge
APPROVED BY:	Doctor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	25/09/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore be due in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Turn-it-in Report

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Plagiarism

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE
I __Chido Nyatsambo_____ (Student number: __361752_____) am a student registered for the degree of Master of Medicine_____ in the academic year __4th_____.

I hereby declare the following:

- - I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- - I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- - I have followed the required conventions in referencing the thoughts and ideas of others.
- - I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the

  source of the ideas or words in my writing.

- - I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection)

software indicating the level of plagiarism in my research document.

Signature: _____ Date: _____20/01/2021_____

Definitions

Right colon - Ascending colon to proximal distal transverse colon

Left colon - Distal transverse colon including splenic flexure down to rectum

Adenocarcinoma: Glandular neoplasm of the colorectum representing 98% of colonic cancers. The tumour is usually well or moderately differentiated gland forming carcinoma with marked desmoplasia (21).

Mucinous adenocarcinoma: Subtype of colorectal cancer with mucin lakes comprising at least 50% of tumour mass. There are strips of tumour cells in large extracellular mucin lakes comprising at least 50% of tumour mass. Signet ring cells may be present but should comprise less than 50% of the tumour(21).

Signet Ring Cell Carcinoma: rare subtype <1% of colorectal cancer, there is proliferation of signet ring cells with intracellular mucin that displaces nucleus to the side. No gland formation in signet ring cell component. Pools of extracellular mucin often present(21).