

ORIGINAL ARTICLE

Design and methodology of a study on colorectal cancer in Johannesburg, South Africa

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Abstract

Background and Aim: Cancer is one of the foremost causes of morbidity and mortality worldwide. Globally, colorectal cancer (CRC) is the third most diagnosed and fourth most important cause of cancer death. A total of 70% of all CRC-related deaths occur in low- and middle-income countries. In Sub-Saharan Africa (SSA), estimating the burden of CRC is difficult. Only 27 of 43 SSA countries have formalized cancer registration systems; data quality is variable and national coverage rare.

Methods: This is a multidisciplinary, longitudinal cohort study started in January 2016. Patients >18 years with histologically confirmed primary adenocarcinoma of the colon and rectum, diagnosed within the previous 12 months, are eligible. Participants were assessed and were followed up for 3 years. Baseline information, including demographics, socioeconomic status, family history, medical and surgical non-cancer-related history, dietary history, colonoscopic findings, staging at presentation, treatment, and disease recurrence, is collected, as well as blood tests and histology results. Outcomes include disease recurrence (local and metastatic) and survival.

Results and Conclusion: This study aims to describe the clinical presentation, management, and outcomes of adults with CRC in a multiethnic, urban South African population. It will be the first prospective study to describe clinical presentation, demographics, risk factors, treatment, and outcomes according to population group, from both private and state health-care facilities in Johannesburg, South Africa. The results of this study will be relevant not only to South Africa but also to other SSA countries undergoing similar rates of rapid urbanization and epidemiological transition.

Introduction

Cancer is one of the foremost causes of morbidity and mortality in both low–middle- and high-income countries worldwide.¹ Lung and breast cancer are the leading causes of death, followed by colorectal, prostate, liver, stomach, and cervical cancer.¹ GLOBOCAN estimated that there were 14.1 million new cases of cancer and 8.2 million deaths from the disease in 2012.^{1,2} In addition to the increasing burden of malignant disease, there is a changing spectrum of cancers linked to levels of human development in different regions of the world.² The ongoing epidemiological cancer transition observed in low–middle-income countries (LMICs) includes a decrease in infection-related cancers, such as liver and cervical cancer, and increases in cancers linked to a Western lifestyle, such as prostate, breast, and colorectal cancer (CRC).³ Globally, CRC is the third most frequently diagnosed and fourth most important cause of cancer death, with approximately 700 000 deaths in 2012, which is expected to increase by 60% to more than 1.1 million by 2030.^{2,3} While the

incidence of CRC is greater when comparing high-income countries to LMICs, 70% of all CRC-related deaths occur in LMICs, revealing a disparate mortality burden.^{4,5} In Sub-Saharan Africa (SSA), including South Africa (SA), estimating the burden of CRC is fraught with difficulties. Only 27 of 43 SSA countries have any formalized cancer registration system; data quality is variable; and national coverage is rare, with most registries being confined to relatively small, urban regions.⁶ However, in spite of systematic underreporting, it is clear from the available data that CRC is on the rise, with a consistently higher incidence amongst males and, not surprisingly, an increase with advancing age.⁶ The International Agency for Research on Cancer (IARC) publishes global estimates on incidence and mortality through the GLOBOCAN project. The most recent data from 2012 indicate that CRC is the fifth most common cancer in SSA.^{2,7,8} Studies from SA, Kenya, and Zimbabwe suggest that CRC is on the rise in Africa, although a causal effect has not been established.^{9–11}

SA has the highest incidence of CRC in SSA, with marked ethnic disparities.¹² This is verified by the most recent data from the National Cancer Registry's pathology-based surveillance system, which confirms that CRC is among the top three cancers in South African men and women.¹³ In 2012, the NCR reported a lifetime risk (LR) of 1:81 for men and 1:135 for women, with an age-standardized incidence rate (ASR) per 100 000 of 11.67 and 6.68, respectively. The highest rates of CRC were seen in people of White, Asian, and mixed race ancestry and less commonly amongst the majority Black population.¹³ Even though there is a historically low incidence of CRC among the Black South African population, there is evidence that numbers are increasing in some areas.^{13,14} In addition, a disproportionately large number of Black patients are presenting with CRC at a young age, with a lower adenoma burden than that observed in other population groups. In isolated reports, these differences have been ascribed to genetics, changes in dietary habits and gut transit time, rural *versus* urban demography, and socioeconomic disparities, particularly with reference to access to health services.^{9,15–18}

We have established a prospective, longitudinal cohort study in response to the increasing burden of cancer in SSA in general and, in particular, to address the paucity of data on CRC. We are principally interested in addressing disparities observed in different population groups; determining associated risk factors; and describing clinical presentation, tumor histology, treatment modalities, and outcomes (morbidity and mortality). Morbidity will be assessed in relation to the complications that occur postoperatively and those arising from chemotherapy and/or radiotherapy. Outcomes will be measured as overall survival and disease-free survival. The absence of such critical information prevents the development and implementation of informed national public health policies for the screening, prevention, and appropriate cost-effective treatment of CRC in SA and the region. This paper presents the design and methodology of a study aimed at understanding the burden and nature of CRC in SA, an upper middle-income country, with an annual per capita GDP (PPP) of ~US\$13 165.¹⁹

Methods

The Colorectal Cancer in South Africa (CRCSA) study is a multidisciplinary, longitudinal cohort study, using a convenience sample. The primary purpose of this study is to describe the clinical phenotype of CRC in SA and determine the outcomes, defined as overall and disease-free survival, of those with CRC. The secondary outcome is to investigate whether the clinical phenotype and outcomes vary within different population groups in SA. The hypothesis is that those affected with CRC from the Black population group present at an earlier age, with a different spectrum of colorectal disease, and have poorer outcomes. This hypothesis is informed by previously published literature from SA and other Southern African regions.^{9–12} Recruitment commenced in January 2016 and, as of June 2017, 224 participants have been enrolled.

Setting and study sample. The study is being conducted in the city of Johannesburg, Gauteng Province, SA. Johannesburg is the largest and wealthiest city in the country, with a population of 4.4 million. The study sites are based in the Academic Teaching Hospital Complex of the University of the Witwatersrand, which includes the Charlotte Maxeke Johannesburg Academic Hospital

(CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH), Wits Donald Gordon Medical Centre (WDGMC), and Edenvale Hospital. CMJAH and CHBAH are tertiary/quaternary referral centers within the public service system, WDGMC is a private university specialist referral center, and Edenvale Hospital is a public secondary care facility. These hospitals, therefore, include both private and public health-care facilities that serve the largest urban population in the country.

Ethical approval for this study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M150446).

All patients over the age of 18 years presenting to the study sites with CRC are eligible for enrolment in the study. No case sampling is conducted. Patients with histologically confirmed primary adenocarcinoma of the colon and rectum, with or without metastatic disease, diagnosed within the previous 12 months are eligible. Patients are excluded from the study if they have histology other than adenocarcinoma; adenocarcinoma *in situ*; no histological confirmation of CRC; if they were diagnosed with CRC more than 12 months before presentation at the study site; or if they are unable to give written, informed consent.

Recruitment procedures and follow up. Potential participants are identified by attending clinicians at the study sites and referred to a study nurse. The nurse conducts the enrolment procedure, which takes 30–60 min and includes obtaining written informed consent, interviewing the patient, and data extraction from clinical records. Patients are then followed up at 6, 12, 24, and 36 months through either a clinic visit or a telephonic interview with the study nurse. The study nurse participates in weekly multidisciplinary team meetings at study sites to assist with identifying index cases for recruitment as well as to follow up with study participants regarding treatment decisions, progress, and outcomes. Loss to follow up is defined as the inability to trace a participant for ≥12 months. We anticipated a loss to follow up of 5–10%; however, so far, all enrolled participants have remained in the cohort. This has been assisted by obtaining at least one additional contact number for a close relative or friend and regular telephonic contact with participants after enrollment. Due to cost constraints, additional retention strategies, such as contact on a participant's birthday or study newsletters and updates, have not been employed.

Data collection. Initially, baseline information is collected for each participant at the study site and includes: demographics, socioeconomic status (using an asset-based score), family history of cancer, medical and surgical non-cancer-related history, dietary history, detection and diagnosis (referral, colonoscopy, imaging such as magnetic resonance imaging (MRI), and computer tomography scanning (CT)), histopathological diagnosis, anatomical location of the primary lesion (right-sided colon cancer includes lesions arising in the caecum, ascending, and transverse colon; left-sided colon cancer includes lesions arising in the descending and sigmoid colon and the rectum),²⁰ and staging at presentation (American Joint Committee on Cancer [AJCC] criteria).²¹ Therapeutic modalities include: radiotherapy (with/without a sensitizing agent), chemotherapy (standard and targeted regimens), and surgery (laparoscopic only, laparoscopic-assisted open, laparoscopic converted to open, open procedures, and the nature of the

procedure). Routine laboratory test results are collected for hemoglobin, carcinoembryonic antigen (CEA), and HIV status (no additional study-specific testing is conducted). Outstanding details are verified with treating clinicians as required.

The follow-up intervals in this study include 6, 12, 24, and 36 months after the first intervention (which may be surgery, radiation, or chemotherapy). This includes details regarding the administration of subsequent therapies (surgery, chemo-radiation, and chemotherapy) with duration and timing thereof, any associated complications, and participant outcomes. Outcomes include disease recurrence (local and metastatic) and overall survival. Follow-up routine blood test results collected include hemoglobin and CEA.

The following questionnaires and scoring systems are used at the baseline assessment:

- *Charlson Comorbidity Index*: measures comorbid disease²²;
- *Global Physical Activity Questionnaire (GPAQ)*: measures physical activity²³;
- *Eastern Cooperative Oncology Group (ECOG)*: measures patient performance status (PS).²⁴

Preoperatively, the American Society of Anesthesiologists (ASA) physical status classification is used as a predictor of post-operative outcome.²⁵ Postoperatively, the Clavien–Dindo Classification of Surgical Complications is used.²⁶

Study data are collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the Faculty of Health Sciences, University of the Witwatersrand. REDCap is a secure, web-based application designed to support data capture for research studies. REDCap allows for data quality checks by identifying missing values, incorrect data type, and outliers. In addition, data rules allow for specifying the limits/ranges of values and alerting the data capture at the point of entry.²⁷

Limitations. This study is limited by the convenience sampling study design and urban location, which precludes rural population representation and comparison. The observational nature of the study and differences in clinical practice across sites creates challenges for data integrity. Furthermore, the study is restricted to characterizing the clinical phenotype with no exploration of genetic risk profiling.

Statistical analysis. Descriptive analysis of the data will be carried out as follows: categorical variables will be summarized by frequency and percentage tabulation and illustrated by means of bar charts. Continuous variables will be summarized by the mean, standard deviation, median, and interquartile range and their distribution illustrated by means of histograms. The χ^2 test will be used to assess the relationships between categorical variables. Fisher's exact test will be used for 2×2 tables or where the requirements for the χ^2 test could not be met. The strength of the associations will be measured by Cramer's *V* and the phi coefficient. The following scale of interpretation will be used: ≥ 0.50 = strong association, 0.30 – 0.49 = moderate association, 0.10 – 0.29 = weak association, and < 0.10 = little/if any association. The relationship between risk variables will be assessed by one-way Analysis of Variance (ANOVA) for three groups and the unpaired *t*-test for two groups. Post-hoc tests for ANOVA will be conducted using the Tukey–Kramer adjustment for multiple

comparisons. Where the data do not meet the assumptions of the test, a nonparametric alternative, the Kruskal–Wallis test, will be used for three groups and the Wilcoxon rank sum test for two groups. The strength of the associations will be measured by Cohen's *d* for parametric tests and the *r*-value for the nonparametric tests. The following scale of interpretation will be used: ≥ 0.80 = large effect, 0.50 – 0.79 = moderate effect, 0.20 – 0.49 = small effect, and < 0.20 = near zero effect. Overall survival estimates will be determined by the Kaplan–Meier (KM) method, and between-group comparisons will be made using Cox Proportional Hazards (PH) regression. Data analysis will be carried out using SAS version 9.4 for Windows. The 5% significance level will be used.

Discussion

This longitudinal, observational cohort study aims to describe the clinical presentation, management, and outcomes of adults with CRC in a multiethnic, urban South African population. It will also be the first prospective study to describe clinical presentation, demographics, risk factors, treatment, and outcomes according to the population group from both privately funded and state health-care facilities in Johannesburg, SA. The observational nature of the study was chosen bearing in mind the critical paucity of clinical information on CRC within a milieu of limited human and financial resources for research. Thus, the investigators designed a study that would address the critical clinical information deficit but, at the same time, be replicable and affordable to implement across multiple sites. Since inception, this study has indeed been extended to an additional site in a large metropolitan area, Tshwane (Gauteng Province), in collaboration with the University of Pretoria.

By locating this study (and future sites) within an Academic Complex of Hospitals, a well-described cancer-specific cohort will seed multiple research hypotheses for further studies and allow research capacity building through Masters and PhD training. The results of this study, and future substudies, will have relevance, not only to SA but also to other SSA countries undergoing similar rates of rapid urbanization and epidemiological transition.

Apart from occasional retrospective publications, pathological and clinical South African CRC data were last systematically described in the 1950s and 1960s.²⁸ With population-based registration in its infancy in SA, studies such as CRCSA will assist with the clarification of the burden of cancers of public health priority in various populations. In the presence of a constrained service delivery system for cancer in SA, it is more than likely that numerous barriers to care exist. These include the absence of a national CRC screening program, poor referral mechanisms, and limited access to specialized care to diagnose and treat CRC. The specialized care includes human resources (trained staff), access to diagnostic procedures (colonoscopy), pathology laboratory services, appropriate surgery, chemo-radiation, and chemotherapy within a multidisciplinary team approach. This study will assist with identifying such barriers and hopefully facilitate policy changes to urgently address these challenges. Furthermore, there are differences in clinical management between public and private health-care centers. With the diversity of hospitals included in this study, the heterogeneity of service delivery and clinical practices can be described along with their impact on disease outcomes.

It is well known that research on cancer outcomes in SA is limited. While studies on mortality are possible and have been conducted using vital national registration data, these are biased by the poor quality of cause of death data provided on death certificates.²⁹ Retrospective medical record reviews have also been used to determine survival, but prospective follow up remains the gold standard for overall survival and quality-of-life indices.

Researchers undertaking prospective cohort studies face unique challenges in the local setting. Patients may not have a fixed abode, and changes in address are common through dynamic job-seeking behavior; the majority of residents do not have a telephonic landline, and mobile phone numbers change regularly. Furthermore, poverty and lack of money for transport costs result in patients defaulting on follow up and treatment continuation. To date, loss to follow up in this study has been minimal; however, further strategies to maximize retention in care will be considered as the study numbers grow.

Future goals of this study include the collection of biological specimens for biomarker and genetic investigations. Broader awareness of the study and training of clinicians in patient referral to the study will improve the recruitment rate. Importantly, the researchers are currently discussing the sharing of data collection tools with other South African sites beyond those already mentioned. By linking various regional CRC studies, the researchers aim to portray the national picture of CRC in order to achieve the ultimate goal of this study, which is to inform a national CRC screening, prevention, and management policy for the country.

Conclusion

Other than fixed clinical audits, there has been no systematic collection of clinical data from patients with CRC in SA. The most thorough longitudinal data have been derived from accumulated pathology records,³⁰ but these studies were conducted more than 30 years ago, and there have been enormous political, socioeconomic, and demographic changes in the country since then. The long-term maintenance of this prospective clinical database will improve the quality of local statistics and the clinical management of patients. To improve the value of research to clinicians, it will benefit researchers involved in the evaluation of CRC elsewhere in SA to collaborate and so increase the size and geographical spread of the cohorts examined.

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