

Colorectal cancer in South Africa: An assessment of disease presentation, treatment pathways and 5-year survival

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Background. Colorectal cancer (CRC) is the fourth most common cancer in South Africa (SA), and the sixth most lethal. Approximately 25% of patients will have synchronous metastatic disease at the time of their primary CRC diagnosis. Although chemotherapy is used in most stages of the disease, surgical resection of the primary tumour and metastases remains the most successful treatment modality to achieve cure or prolong survival. To date, no data on CRC presentation and management have been published in SA.

Objectives. To determine CRC presentation, general management patterns and overall survival in the SA private healthcare sector.

Methods. A retrospective review of a private healthcare funder's database from 1 January 2008 to 31 December 2015. *International Statistical Classification of Diseases and Related Health Problems* (10th revision) (ICD-10) diagnosis codes were used to identify colorectal cancer and liver and/or pulmonary metastatic disease. Procedure codes assigned to hospital admissions were used to identify type of surgical treatment. Chemotherapy was identified by the World Health Organization Anatomical Therapeutic Chemical Classification System of medicines. Treatment patterns were determined and 5-year survival rates for these were calculated. Survival was estimated using the Kaplan-Meier method, and Cox proportional hazards regression was used for between-group comparisons of survival. Data analysis was carried out using SAS version 9.4 for Windows.

Results. A total of 3 412 patients were included in the study, 2 267 with CRC only and 1 145 with liver (LM) or pulmonary metastases (PM). The mean age was 64.1 years (range 21 - 97), and 54.6% were male; these did not differ statistically between the study groups. Twenty percent of patients with LM or PM underwent surgical resection of their metastases. Five-year survival rates following surgical resection of all disease for CRC only, CRCLM, CRCPM and CRCLMPM were 71.7%, 57.3%, 31.5% and 26.0%, respectively.

Conclusions. SA CRC patients treated in the private healthcare sector have similar disease presentation to that in published international series, with similar outcomes following various treatment pathways; however, it seems that fewer resections of metastases are undertaken compared with international trends.

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In South Africa (SA), colorectal cancer (CRC) is the fourth most common cancer among both men and women. The crude incidence is 7.17/100 000/year for men and 5.80/100 000/year for women,^[1] and CRC ranks sixth in cancer-related mortality.^[2]

The cumulative lifetime risk of developing CRC in SA is 1.24 for males and 0.74 for females.^[1] At the time of CRC diagnosis, 20 - 25% of patients will have metastatic disease,^[3] the liver being the most common site.^[4] More than half of the patients who undergo curative resection may expect to have tumour recurrence, either locally or as metastatic disease.^[5] CRC therefore represents a significant healthcare burden.

Five-year overall survival rates for CRC are 93.2% for stage I, 72.2 - 84.7% for stage II, 52.3 - 83.4% for stage III and 8.1% for stage IV.^[6] Stage IV disease treated with chemotherapy alone has a median overall survival of 12 months.^[7] Various treatment algorithms have been incorporated into international guidelines, but common to most is that, when possible, surgical resection of the primary lesion and its metastases offers the best survival benefit for patients.^[8] So far, a specific treatment algorithm tailored to SA patients has not been published.

Objectives

To describe the presentation of CRC patients in a privately insured population in SA, general clinical management trends, and 5-year overall survival for various disease stages.

Methods

Study design and data collection

A retrospective review of a private healthcare funder's database from 1 January 2008 to 31 December 2015 was undertaken. Ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (ref. no. M141027), and consent to obtain deidentified data was given by the principal officer of the private healthcare funder. The initial dataset was based on claims by and clinical information on active members of the medical scheme. Data were extracted from tables developed by the medical scheme for analysis where the table development included data validation. Unique entities were identified from these data tables of members with a validated CRC diagnosis.

Patients included in this study were enrolled on the scheme's oncology benefit for the treatment of CRC. *International Statistical*

Classification of Diseases and Related Health Problems (10th revision) (ICD-10) diagnosis codes were used to identify CRC only, with or without liver and/or pulmonary metastatic disease. Once identified, secondary or unspecified malignant neoplasms of the digestive organs or respiratory tract were sought for in this patient population. The authors examined each identified record to determine whether or not the additional diagnosis was relevant to the initial CRC diagnosis. Sites of metastases other than the liver and lungs were excluded.

All procedure codes assigned to hospital admissions were captured, and each code was examined by the authors to identify surgical treatments relevant to resections of CRC and CRC metastases. All other procedures were excluded. Chemotherapy was identified by the World Health Organization Anatomical Therapeutic Chemical Classification System of medicines. The number of days from diagnosis of CRC and/or CRC metastases and from surgical resection were collected. Death was based on date of withdrawal from the medical scheme, and survival on ongoing contribution to the scheme. Patients were excluded if they were aged <18 years or were diagnosed before 1 January 2008, and if they were diagnosed on or after 1 January 2014 to ensure that we did not miss any treatment modalities and that patients had at least 1 year of follow-up.

Each patient's treatment was assessed as surgical resection of the cancer with or without chemotherapy, chemotherapy without surgical resection, or no treatment (no surgical resection or chemotherapy). Four patient groups were used for analysis: (i) CRC only; (ii) CRC and liver metastases (CRCLM); (iii) CRC and pulmonary metastases (CRCPM); and (iv) CRC, liver and pulmonary metastases (CRCLMPM).

Statistical analysis

Crude incidence was calculated and represented as 100 000/year. Categorical variables were summarised as percentages, and continuous variables were summarised as means, standard deviations (SDs), medians and interquartile ranges. Survival was estimated using the Kaplan-Meier method and Cox proportional hazards regression was used for between-group comparisons of survival. The 5% significance level was used. Data analysis was carried out using SAS version 9.4 for Windows (SAS Institute, USA).

Results

A total of 3 412 patients were included in the study (Fig. 1). Their demographic features are set out in Table 1. The total number of members on 1 January 2015 was 2 658 100, with 5 093 diagnosed with CRC. The crude incidence of CRC in this insured population increased from 18.9/100 000 in 2008 to 21.3/100 000 in 2015. The gender composition for each patient group was similar, apart from the proportion of males being significantly higher in the CRCLM group compared with the CRC-only group ($p=0.037$) (Table 1). The mean age of the CRC-only group (64.1 years, SD 12.8) was significantly higher than that of the CRCLMPM group (61.5 years, SD 11.7) ($p<0.0001$). There was no statistically significant difference between the CRCLM, CRCPM and CRCLMPM groups (Table 1).

Disease presentation, proportions of cancer with or without metastases, and management pathways of the study group are presented in Fig. 2. One-third of patients either presented with or developed LM and/or PM, the most common being LM. Two-thirds of these patients underwent surgical resection, but only 7.2% (83/1 145) of patients with metastatic disease underwent metastatectomy. The most common was resection of LM, but only 10.0% (60/601) of patients with LM underwent liver resection; of these, 6.7% (4/60) underwent more than one liver resection. Of patients with CRC only, the majority underwent resection of their primary lesion. No treatment was recorded by the medical aid scheme for 16.5% of patients.

Fig. 3 depicts overall survival regardless of therapy. Using the CRC-only group as reference, the risk of death was higher for all the other three cancer groups, and highest for CRCLMPM. Five-year overall survival (5YOS) for CRCPM was better than for CRCLM.

Table 2 describes treatment-related 5-year survival. The best 5YOS was for CRC without metastatic disease treated by surgical resection and chemotherapy. For patients with metastatic disease, CRCLM resection preceded by chemotherapy provided the best 5YOS of 40.7%. CRCPM resection with chemotherapy had 5YOS of 31.7%. There were 5-year overall survivors who did not have surgical

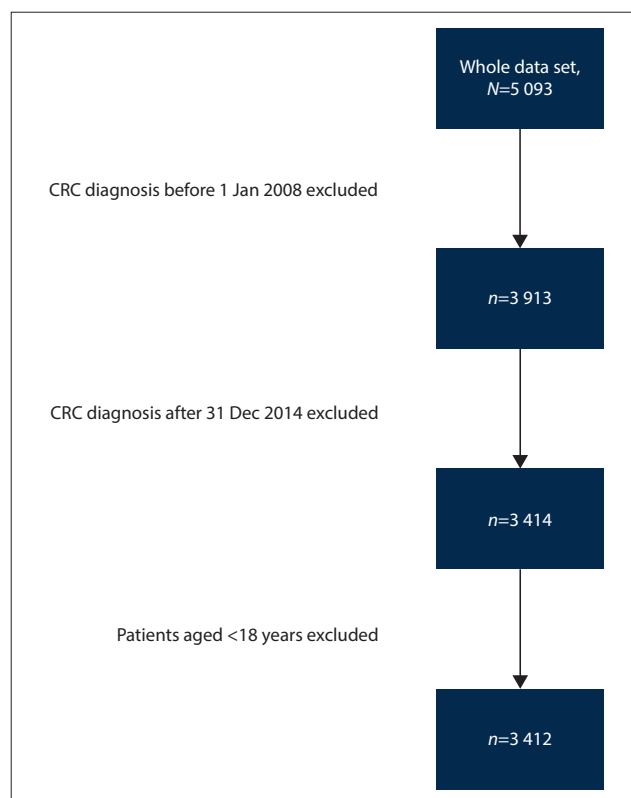


Fig. 1. Data selection, 1 January 2008 - 31 December 2015. (CRC = colorectal cancer.)

Table 1. Overview of CRC patients

	All cases	CRC only	CRCLM	CRCPM	CRCLMPM
Survival, <i>n</i> (%)	3 412	2 267 (66.4)	601 (17.6)	182 (5.3)	362 (10.6)
Age (yr), mean (range)	64.1 (21 - 97)	64.7 (21 - 97)	63.6 (25 - 93)	62.6 (23 - 85)	61.5 (23 - 87)
Gender, <i>n</i> (%)					
Males	1 862 (54.6)	1 203 (53.1)	357 (59.4)	97 (53.3)	205 (56.6)
Females	1 550 (45.4)	1 064 (46.9)	244 (40.6)	85 (46.7)	157 (43.4)

CRC = colorectal cancer; LM = liver metastases; PM = pulmonary metastases.

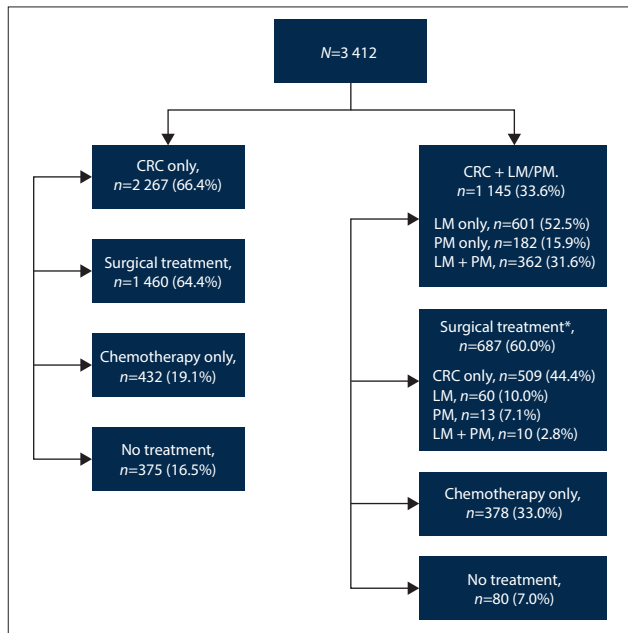


Fig. 2. Disease presentation and management. (CRC = colorectal cancer; LM = liver metastases; PM = pulmonary metastases. *Patients may or may not have received chemotherapy.)

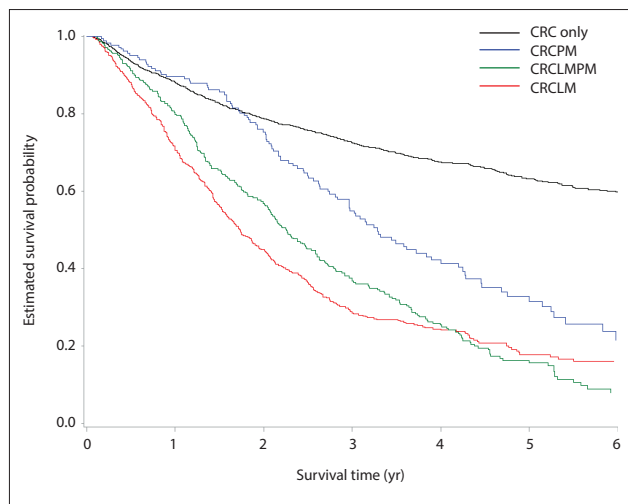


Fig. 3. Overall survival of disease groups, regardless of treatment. (CRC = colorectal cancer; LM = liver metastases; PM = pulmonary metastases.)

resection of metastases, but the figure was significantly lower than if they had had all their disease resected.

Discussion

This is the first study to determine survival outcomes of CRC with or without LM and/or PM in a selected, privately insured SA population. We have demonstrated that one-third of patients with CRC present with or develop LM and/or PM, of whom 7% undergo surgical metastatectomy. 5YOS is best for patients with disease isolated to the colon or rectum that is resected and treated with chemotherapy. Furthermore, there is improved survival with surgical resection in combination with chemotherapy of LM and/or PM.

Incidence and presentation of CRC

The global incidence rates of CRC, overall and in males and females, are 17.2/100 000, 20.6/100 000 and 14.3/100 000, respectively. The

incidence rates of CRC in Europe, overall and in males and females, are 29.5/100 000, 37.3/100 000 and 23.6/100 000, respectively.^[1] The corresponding figures for sub-Saharan Africa are 5.8/100 000, 6.4/100 000 and 5.4/100 000, respectively.^[1] The incidence in this study falls in between that for developed countries and African statistics, possibly indicating that screening and surveillance of CRC are better than in developing countries but may not be as stringent as in developed countries.

Management and overall survival of CRC groups

CRC only

In our study, patients who received chemotherapy either before or after resection of the primary CRC appeared to have improved survival compared with those who underwent surgical resection only (Table 2). CRC treatment has been shown to be more effective when surgery is combined with chemotherapy.^[9] The long survival of the chemotherapy-only group in this study is not in keeping with international series, and cannot be explained owing to the limited available clinical information such as accurate tumour staging.

CRCLM

Complete resection of CRCLM is the only treatment associated with long-term survival, with 37 - 54% 5YOS following surgical resection as opposed to 4 - 9% without surgical resection,^[10] and potential cure in up to 16% of patients.^[11]

In this series, 5YOS following resection of all disease was 57.3% if chemotherapy was administered before tumour resection, and 40.7% if surgery preceded chemotherapy (Table 2). Synchronous resection of the primary lesion as well as the liver metastases has been reported to have 40 - 47% 5YOS.^[12] We were not able to determine 5YOS for synchronous resection in this study.

CRCLM resection is safe, with a mortality rate of <2% and a major morbidity rate of ~12.5%,^[13,14] including patients aged >75 years, who can achieve 5YOS of 58%.^[15] Patients may undergo repeated liver resections for recurrent CRCLM with similar survival figures to patients who only have one liver resection and no recurrence. One case series reported 47% 5YOS for repeat liver resection.^[10] We were not able to perform survival analyses for repeated resections owing to the low numbers of these procedures.

CRCPM

Since the more widespread use of chemotherapy for pulmonary CRC metastases, overall survival has improved.^[16] PM are typically single or multiple nodules, as opposed to a miliary type of spread or lymphangitis carcinomatosa, and hence more amenable to surgical resection.^[17] 5YOS following pulmonary metastectomy has been reported as 24 - 61.4%,^[18] and in this study was 31.5% (Table 2). The CRCPM resection mortality rate is <1% and the morbidity rate is ~14%.^[19]

CRCLMPM

5YOS for patients with pulmonary metastectomy following hepatic metastectomy is 31.6%.^[17] In this study, 5YOS was 26.0% (Table 2). Our figures also highlight the fact that relatively few patients undergo surgical resection of their metastatic disease. Median overall survival has been shown to be significantly improved with complete or macroscopically clear resection margins of CRCLMPM compared with palliative chemotherapy,^[20] as well as resection of the primary CRC only in stage IV disease.^[21]

Study limitations

There are limitations to this study. Data were retrieved from a single private healthcare funder's database which represents 53% of the

Table 2. Five-year overall survival according to treatment pattern

Group	Survival, n (%)	95% CI
CRC only		
Surgery only	489 (60.1)	54.2 - 66.5
Surgery and chemotherapy	886 (71.7)	67.6 - 75.3
Chemotherapy upfront followed by surgery	85 (69.9)	56.1 - 80.1
Chemotherapy only, no surgical resection	432 (56.3)	50.5 - 61.6
CRCLM		
Chemotherapy upfront followed by surgical resection of all cancer	19 (57.3)	30.5 - 77.0
CRC surgery followed by chemotherapy and further resections	41 (40.7)	20.0 - 60.5
CRC surgery only and chemotherapy, no metastases resected	23 (15.6)	9.9 - 22.4
Chemotherapy only, no surgical resection	180 (9.8)	5.6 - 15.5
CRCPM		
Chemotherapy and resection of all cancer	13 (31.5)	23.4 - 40.0
CRC surgery only and chemotherapy, no metastases resected	62 (25.4)	12.2 - 40.9
Chemotherapy only, no surgical resection	65 (22.4)	11.8 - 35.2
CRCLMPM		
Chemotherapy and resection of all cancer	10 (26.0)	8.5 - 47.9
CRC surgery only and chemotherapy, no metastases resected	101 (13.1)	6.8 - 21.6
Chemotherapy only, no surgical resection	133 (5.3)	1.6 - 12.4

CI = confidence interval; CRC = colorectal cancer; LM = liver metastases; PM = pulmonary metastases.

open market. This database is primarily designed for health economic data capture with limited clinical information. These results are based on treatments claimed from the medical scheme. Members may not necessarily submit all treatment claims to the scheme; for example, they may receive treatment as part of a clinical trial, use self-funded medication, or receive treatment from state facilities. Because of the paucity of clinical information, only general treatment patterns are reported. The survival estimates and Kaplan-Meier plot are limited by the fact that the analysed data do not originate from primary clinical data, but from secondary medical aid administrative and claims data. There may therefore be loss of accuracy and missing information. Furthermore, we could not adjust for covariates. However, we believe that the Kaplan-Meier plot remains the best way to display survival data, and we capped the estimates to 5 years, beyond which there are too few patients at risk for reliable estimates. We have provided 95% confidence intervals for these estimates.

Whether CRC in SA differs from internationally published series or whether patients are being managed appropriately cannot be determined from this study. Furthermore, our results cannot be extrapolated to the public healthcare sector, as the treatment of this disease appears to differ significantly with regard to disease presentation as well as access to chemotherapy and biological agents.

Future research

Appropriate clinical information should be collected by private healthcare funders to facilitate audit as well as to understand clinical decision-making and outcomes. The importance of multidisciplinary teams (MDTs) cannot be over-emphasised in the assessment of CRC with metastases to determine optimal patient management. A prospective study of an MDT showed that despite 84% of clinicians being certain of their management plan, following the MDT discussion 36% changed their management plan; 72% of these changes were major ones.^[22] Furthermore, studies have shown lower survival rates following non-adherence to MDT decisions.^[23] Finally, a national CRC registry should be established so that understanding of disease epidemiology, presentation, outcomes and therapeutic resources can be improved.

Conclusions

CRC patients treated in the SA private healthcare sector have improved survival following resection of the primary tumour and metastatic disease, which is further enhanced by the use of chemotherapy as opposed to chemotherapy alone or no treatment.

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Conflicts of interest. None.

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