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Post-colonoscopy colorectal cancers in privately insured patients in South Africa

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Background. Post-colonoscopy colorectal cancers (PCCRCs) are colorectal cancers (CRCs) that are diagnosed within 3 - 5 years of a colonoscopy where a cancer was not detected. Colonoscopy is the current gold standard for the diagnosis of colorectal cancer. The rate of PCCRC is an indicator of the quality of colonoscopy, because the aim of a high-quality colonoscopy is to detect CRCs and advanced adenomas.

Objective. To calculate the rate of PCCRC in a privately insured population in South Africa (SA).

Methods. Data were retrospectively obtained from the largest private health insurance company in SA. Patients diagnosed with CRC from the period of 1 January 2013 to 31 December 2019 were included. Patients who were members of the fund for <5 years prior to diagnosis were excluded. Patients with conditions predisposing to CRC were excluded from the study. Patients with CRC who had undergone colonoscopy 6 - 60 months prior to the diagnosis of CRC were defined as PCCRC. Patients diagnosed with CRC were identified by ICD-10 codes and from the oncology registry. Colonoscopies were identified by procedure codes.

Results. A diagnosis of CRC was made in 19 538 patients in the 7-year period. Following exclusions, 4 765 patients were included in this study for analysis. PCCRC was identified in 415 patients (8.72%) between 6 and 60 months, of whom 315 were identified between 6 and 36 months (6.61%). The median (interquartile range (IQR)) age in the overall study group presenting with CRC was 64 (53 - 73) years, with that of the PCCRC group (n=415) being higher at a median (IQR) age of 67(53 - 72) years when compared with the non-PCCRC group (n=4 350) of 64 (53 - 72) years (p=0.0002). Overall, 21.3% of CRC patients were aged ≤50 years, and 51.3% were male. The percentages of patients aged ≤50 years in the PCCRC v. non-PCCRC groups were 17.1% (n=71/415) and 21.7% (n=945/4 350), respectively (p=0.03). The gender ratio did not differ in the PCCRC group v. the non-PCCRC group. Rectal cancers were more likely to be present in the PCCRC group at 32.8% (n=136/415) v. the non-PCCRC group at 24% (n=1 043/4 350) (p<0.001). In the PCCRC subset, 73.8% of colonoscopies were performed by surgeons, 13.4% by gastroenterologists and 12.8% by physicians and general practioners/others. The PCCRC rate was 14.4% for gastroenterologists and 7.9% for surgeons.

Conclusion. This study is the first study from SA to analyse PCCRC. The overall PCCRC rate was 6.61%, in line with published series.

Keywords: post-colonoscopy colorectal cancer, colorectal cancer, colonoscopy

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Colorectal cancer (CRC) is one of the most frequently occurring cancers globally, and is the leading cause of cancer-related death worldwide.[1] CRC is one of the fourth most common cancers in South Africa (SA), according to our national cancer registry.[2,3] Early diagnosis significantly impacts cancer survival.[4] Screening programmes have been shown to reduce mortality.[5,6] Colorectal cancers are typically adenocarcinomas arising in the colon and rectum. These cancers mainly develop via the adenoma-carcinoma sequence. Colorectal cancer has a neoplastic precursor lesion called an adenoma, which is a neoplastic polyp with varying degrees of dysplasia that occurs in the colon and rectum. Adenomatous polyps are known for their ability to become malignant over time if left untreated.[7,8] Adenoma detection and removal during colonoscopy form the basis of colorectal cancer prevention and CRC mortality reduction.[5,9,10]

The UK Bowel Cancer Screening Programme showed that the CRCs diagnosed in a screened population of patients were more likely to be early cancers.[11] A large retrospective study found that the incidence of CRC was 31% lower in people who had a colonoscopy than the average population risk.[12] The National Polyp Study in the USA reported the results of a 23-year follow-up. They found that removing polyps by colonoscopy reduced CRC mortality by 53%.[13]

The following criteria are used to assess the quality of colonoscopy: caecal intubation rate, adenoma detection rate, withdraw time and good bowel preparation.[14-16] The post-colonoscopy CRC (PCCRC) rate is an additional important marker of the quality of the endoscopy.[15]

Inappropriately long screening intervals may increase the risk of PCCRC. The screening intervals recommended by gastrointestinal societies are premised on patient risk and the findings at colonoscopy.[17]

The World Endoscopy Organization provides a definition for PCCRC through an expert consensus agreement. PCCRC is divided into two groups. The first is made up of post-colonoscopy interval colorectal cancers (PCICRC), where CRC is diagnosed before the next scheduled colonoscopy. The second group is comprised of PCCRC where CRC is diagnosed at (type A), or after (type B), the next scheduled examination. Type C is where no subsequent colonoscopy was scheduled.[18] The organisation also recommends the following method for calculation of PCCRC rate: PCCRC/(PCCRC + non-PCCRC) × 100.[18]

Tumour biology-related risk factors are associated with increased risk of PCCRC. Tumours with microsatellite instability were found to be higher in patients with interval CRC.[19] An association was also established between Cpg island methylator phenotype (CIMP) and interval cancers.[20] It was also discovered that patients with mutations

in their mismatch repair (MMR) genes in Lynch syndrome have a higher risk of interval cancers.[20,21]

Patients with an inflammatory bowel disease such as Crohn's disease and ulcerative colitis have a higher risk of developing CRC than the average population, and are also at higher risk for PCCRC.[22]

Procedure-related risk factors that significantly contribute to the risk of PCCRChave been identified as poor bowel preparation, incomplete colonoscopy, incomplete polypectomy and colonic polyp >10 mm in size. Polyps >10 mm in size were more likely to be incompletely excised. Adenomas with high-grade dysplasia were also found to increase the risk of developing a post-colonoscopy cancer.[23]

A meta-analysis identified certain patient-related risk factors for PCCRC, which included advanced age and poorer physiological status.[24] Endoscopist-related factors, such as colonoscopies performed by non-gastroenterologists (surgeons and other healthcare workers), have also been identified.[25]

A recent meta-analysis[26] published in 2021 analysed 15 studies that reported on 25 872 cases of PCCRC. The overall PCCRC rate was 8.2% (confidence interval 6.9 - 9.4).

PCCRC poses a significant problem. It may mean that an endoscopist missed a significant lesion, or a lesion was inadequately treated during colonoscopy.[26] The PCCRC is regarded as a marker and an indicator of the quality and effectiveness of colonoscopy.[15] The risk of PCCRC is increased in patients with tumours that have an accelerated adenoma-carcinoma sequence.[20,27]

A large population-based retrospective study from the Netherlands determined that 86.4% of PCCRCs were potentially preventable, and that improvements should be made in the quality of colonoscopies.[29] There are no published series that have investigated the PCCRC rate in SA.

This study defines the PCCRC rate as CRC diagnosed in patients who had a colonoscopy in the preceding 6 - 60 months and 6 - 36 months. These parameters were decided upon to allow for an easy comparison with other studies. Most studies report 6 - 36 months' data, but 5 years can be understood as the mean sojourn time for CRC.[24,30] Six months was chosen as this can be considered a reasonable time frame to schedule follow-up examinations. This is also consistent with the definitions used by other authors.[26]

Objectives

The primary objective of this study was to determine the proportion of PCCRC in a cohort of privately insured patients who had a colonoscopy in the preceding 6 - 60 months in SA.

The secondary objectives were to assess whether patient demographics, the anatomical location of the cancer or the specialty of the doctor performing the colonoscopy were associated with the PCCRC rate.

Methods

Data were collected retrospectively from the largest private health insurer in SA, Discovery Health. Patients diagnosed with CRC were identified from the Discovery Health Oncology Registry and their ICD-10 codes. Data were anonymised by Discovery Health by assigning a number to each case instead of a name or insurance number. Procedure codes were used to ascertain whether these patients had had a colonoscopy in the preceding 6 - 60 months. We identified the specialty of the endoscopist by their practice registration with Discovery Health, and their Board of Healthcare Funders' registration number. Patient demographics were obtained from the Discovery Health database. Ethics approval was obtained from the Wits University Human Research Ethics Committee (ref. no. M190824 Med19-01-062).

Inclusion criteria: All patients insured by Discovery Health who were diagnosed with CRC in a 10-year period between 1 January 2009 and 31 December 2018.

Exclusion criteria: Using ICD-10 codes at the time of colonoscopy, patients were excluded from the study population if they had a shorter adenoma-carcinoma sequence or a high risk for CRC, including polyposis syndromes, hereditary non-polyposis CRC, previous CRC, previous adenomas and inflammatory bowel disease. In addition, patients who were not continuous members of Discovery Health for at least 5 years prior to their diagnosis of CRC were excluded.

The proportion or rate of PCCRC was determined as follows: number of persons with CRC who had a previous colonoscopy 6 - 36 or 6 - 60 months prior to CRC diagnosis divided by the total number of persons with CRC identified.

Raw data exported into an Excel (Microsoft, USA) spreadsheet were subsequently imported into STATA version 16 (StataCorp, USA) for statistical analysis. The Shapiro-Wilks test was applied to determine the normality of continuous data, such as age. Descriptive statistics for continuous variables were reported as medians and interquartile ranges (IQR), and for continuous variables, frequencies and proportions were reported. The Mann-Whitney *U* test was applied when comparing continuous data according to PCCRC status and endoscopist specialty, whereas associations with categorical variables were determined by means of the Pearson χ^2 test and/or Fisher's exact test, as appropriate. $P<0.05$ was considered statistically significant.

The statistical data of this study were retrieved by the University of the Witwatersrand Surgical Statistics hub.

Results

Study population

The initial study population diagnosed with CRC consisted of 19 538 patients, of whom 14 773 were excluded, either based on membership criteria or their underlying risk factors, as per the exclusion criteria. In total, 4 765 patients fulfilled the criteria for analysis (Fig. 1).

PCCRC rate

A total 4 350 patients did not have a diagnosis of PCCRC. The 415 patients who did have PCCRC were categorised into two groups: 415 were identified in the 6 - 60 months period, a PCCRC rate of 8.7%, and 315 of these patients were identified within the 6 - 36-month period at a PCCRC rate of 6.6 (Fig. 1).

Study demographics

The demographic and clinical characteristics of the 4 765 study patients are shown according to PCCRC status in Table 1. The median age of the PCCRC group was older than the non-PCCRC group at 67 v. 64 years, respectively ($p=0.0002$). Also, there were more non-PCCRC patients <50 years old than PCCRC patients (21.7% v. 17.1%, respectively; $p=0.03$). There was no significant difference in gender according to PCCRC status. Overall and in the PCCRC subset analysis, the median age for males was older than females. at 65 v. 63 ($p<0.001$) and 69 v. 65 ($p=0.03$), respectively.

CRC anatomical location

Overall, 63.5% of CRCs occurred in the colon, 24.7% occurred in the rectum and the remainder were classified as disseminated (11.8%). When only considering the colon and rectal locations, 65.5% colon and 34.5% rectal cancers were found in the PCCRC subset, showing a higher rectal location in PCCRC patients (Bonferroni corrected $p=0.01$) (Table 1).

Stage of disease

Table 2 refers to the PCCRC subset of patients. The stage of disease at presentation is shown, with the majority of PCCRC patients (44.3%) presenting with stage 1 disease.

Endoscopist

In the PCCRC subset of patients, 73.8% of colonoscopies were performed by surgeons,13.4% by gastroenterologists and 12.8% by other endoscopists. Table 3 shows the PCCRC rate per specialty. The PCCRC rate for surgeons was the lowest, at 7.9%, with that of physicians and general practitioners, and gastroenterologists, at 8.5% and 14.4%, respectively. Evidently the gastroenterologist specialty had a higher PCCRC rate (p=0.001), and this is further investigated below.

Univariate analysis of age, gender, stage at presentation and anatomical location of the cancer

A univariate analysis of age, gender, stage at presentation and anatomical location of the cancer according to endoscopist specialty in the PCCRC cohort is shown in Table 4. PCCRC patients in the gastroenterologist group were younger (p=0.009), with more disseminated cancers (p=0.045) when compared with those scoped by other endoscopists. There was no difference in gender or stage at presentation between these two specialist groups.

Discussion

This study found PCCRC rates of 6.6% (6 - 36 months) and 8.7% (6 - 60 months). This is similar to those described in the UK and Europe (Table 5).[26,31-32] However, we recognise that various methods have been used to calculate PCCRC by different investigators, and this may affect the reported rate. Methods that allow for a bigger denominator will result in a lower reported PCCRC rate.[31] In the present study we used the following method to calculate PCCRC rate: PCCRC/(PCCRC + non-PCCRC) × 100. This method was chosen to avoid underestimating the PCCRC rate. It is also the method recommended by the World Endoscopy Organization consensus paper, so it may facilitate easier comparison with future studies.[18] The patients in our study population all had a colonoscopy prior to diagnosis, but the diagnosis of CRC was not restricted to those diagnosed by colonoscopy. This gave us a larger denominator than some investigators, who only included CRC diagnosed by colonoscopy in the denominator. In the event where an individual underwent multiple colonoscopies in the designated timeframe, only the most recent colonoscopy that failed to diagnose the cancer was considered.

A Danish study showed that in a PCCRC subgroup, MMR was found in 24% of cases, and B-rapidly accelerated fibrosarcoma gene (BRAF) in 23% of cases.[21] In our study we decided to exclude all conditions that may be associated with an accelerated adenoma-carcinoma rate, so that our data is more reflective of the quality of the endoscopy as opposed to the tumour biology. Patients with polyposis and non-polyposis syndromes, patients with inflammatory bowel disease and patients with history of polyps and CRC were excluded from the study population.

In this study we found that the PCCRC group was older than the non-PCCRC subset (p=0.0002). Similarly, we found that the non-PCCRC group had more patients aged <50 years (p=0.03). It has been shown in other studies that older people have a higher rate of PCCRC.[24]

In this study, we established that 34.5% of the PCCRC was situated in the rectum, which was a higher proportion than the 27.4% rectal cancers seen in the non-PCCRC group (p=0.01). We were unable to subanalyse the colonic CRC for site because most colon cancers were loaded on the health insurer's database with the C18.9 code (CRC site unspecified). It was, however, interesting to discover more rectal cancers in

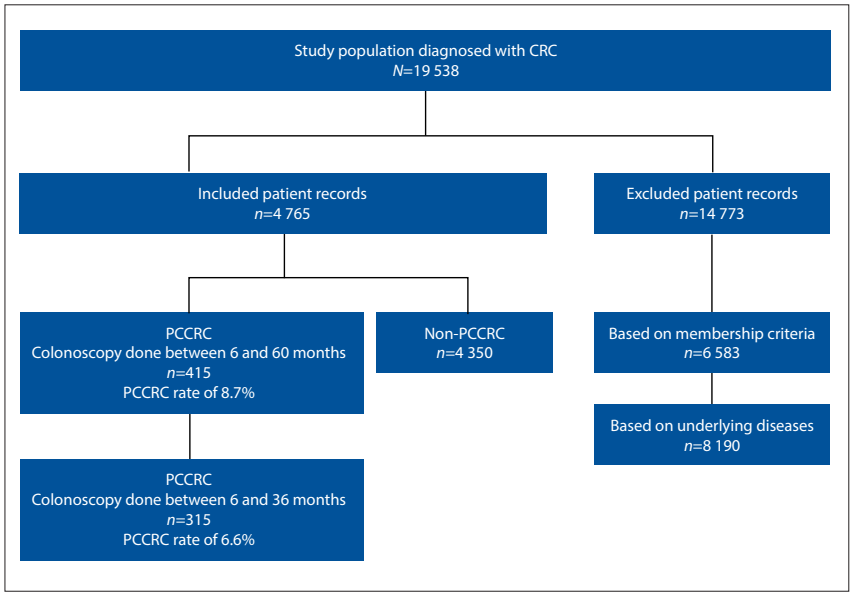


Fig. 1. Consort diagram of patient records included in the study. (CRC = colorectal cancer; PCCRC = post-colonoscopy colorectal cancer.)

Table 1. Demographic and clinical characteristics according to post-colonoscopy colorectal cancer

Parameter	All (N=4 765)	PCCRC (n=415)	Non-PCCRC (n=4 350)	p-value
Age (years), median (IQR)	64 (53 - 73)	67 (55 - 75)	64 (53 - 72)	0.0002
Gender, *n* (%)				
Male	2 445 (51.3)	219 (52.8)	2 226 (51.2)	0.54
Female	2 317 (48.7)	196 (47.2)	2 121 (48.8)	
Anatomical location, *n* (%)				
Colon	3 025 (63.5)	258 (62.2)	2 767 (63.6)	<0.001
Rectum	1 179 (24.7)	136 (32.8)	1 043 (24.0)	
Disseminated	561 (11.8)	21 (5.1)	540 (12.4)	

PCCRC = post-colonoscopy colorectal cancer; IQR = interquartile range.

the PCCRC group when compared with the non-PCCRC group. This differs from what is broadly described in the literature. A systematic review of 12 studies evaluated the risk factors for interval colorectal cancer, and found that interval CRC occurred more frequently in the right colon.[24,33] A reason for this difference could be the lack of routine retroflexion in the rectum, poor bowel preparation and inadequate treatment of rectal polyps.

Most of the PCCRC in this study presented as stage 1 disease. This is consistent with other studies that similarly found that patients with PCCRC were more likely to be diagnosed at an early stage.[24] There is also evidence to suggest that patients with PCCRC do not have a worse outcome than that found in sporadic CRC.[27]

Gastroenterologists in this study had a higher rate of PCCRC (p=0.001) and did fewer colonoscopies than the surgeon group. In the PCCRC subset, 73.8% of colonoscopies were done by surgeons, with a PCCRC rate of 7.9%, whereas gastroenterologists performed 7.9% of colonoscopies and had a PCCRC rate of 14.4% (Table 3).

This finding was further investigated by univariate analysis according to endoscopist specialty (Table 4), and revealed that gastroenterologists had a significantly younger patient population than the other groups, with a median age of 62 years v. 68 years. Young patients are more likely to have more aggressive tumour biology. Mueller *et al.*[34] found that patients <50 years had a higher risk of having poorly differentiated tumours, locally advanced disease and metastatic disease at presentation. Similarly, a study from the Czech Republic including 192 241 patients found more advanced presentation in younger patients. This may be the reason that the gastroenterologists in this study had significantly more patients with disseminated cancer.[35]

Table 2. Cancer stage in PCCRC disease

Stage	*n* (%)
1	135 (44.3)
2	65 (21.3)
3	34 (11.2)
4	71 (23.3)

PCCRC = post-colonoscopy colorectal cancer.

Study limitations

We were unable to exclude undiagnosed risk factors.

Additionally, it must be noted that limitations were present in our method of identifying specialists. We relied on practice numbers and the recorded practice type as per the health insurer. We also note

Table 3. PCCRC rate per specialty (6 - 60 months)

		Colonoscopies performed, *n* (%)	
Specialty	PCCRC rate, %	PCCRC subset (*n*=382)	All patients (*N*=4 487)
Surgeons	7.9	282 (73.8)	3553 (79.2)
Gastroenterologist	14.4	51 (13.4)	355 (7.9)
Physicians and general practitioners	8.5	49 (12.8)	579 (12.9)

PCCRC = post-colonoscopy colorectal cancer.

Table 4. Univariate analysis of age, gender, stage at presentation and anatomical location of cancer according to endoscopist specialty in the PCCRC cohort

Parameter	Other endoscopists (*n*=341)	Gastroenterologists (*n*=51)	*p*-value
Age (years), median (IQR)	68 (57 - 76)	62 (51 - 71)	0.009
Gender, *n* (%)			
Male	182 (53.4)	24 (47.1)	0.40
Female	159 (46.6)	27 (52.9)	
Stage, *n* (%)			
1	119 (46.3)	11 (35.5)	1.08
2	58 (22.6)	4 (12.9)	
3	27 (10.5)	4 (12.9)	
4	53 (20.6)	12 (38.7)	
Total	257 (89.2)	31 (10.8)	
Anatomical location, *n* (%)			
Colon	209 (61.3)	33 (64.7)	0.045
Rectal	117 (34.3)	12 (23.5)	
Disseminated	15 (4.4)	6 (11.8)	

PCCRC = post-colonoscopy colorectal cancer; IQR = interquartile range.

Table 5. PCCRC rates reported in the literature

Source	Country/region	Patients in study, *n*	PCCRC rate reported (%)	Interval period investigated post colonoscopy
Stoffel EM, *et al.*, 2016[21]	Denmark	10 365	7.0	6 - 10 years
Morris EJ, *et al.*, 2015[31]	UK	297 956	7.7	6 - 36 months
Forsberg A, *et al.*, 2020[32]	Sweden	19 184	7.2	6 - 36 months
Kang JH-E, *et al.*, 2021[26]	European countries	25 872	8.2	6 - 36 months

PCCRC = post-colonoscopy colorectal cancer.

that some practices that are registered as physicians are practising gastroenterologists because the subspecialist training is relatively new in SA.

This study was not designed to report on the case volume of the individual endoscopist, nor the quality metrics of the individual endoscopist. These are, however, important factors that endoscopy units should audit.

Conclusion

This study demonstrated that the PCCRC rate in our study population compares favourably with that of other regions such as the UK, Europe and the USA according to published data. The PCCRC rate has not previously been published for any SA study population. Further research evaluating the ability of colonoscopy to reduce the CRC incidence and mortality in SA should be conducted.

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

Declaration. None.

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Author contributions. LF: first author; DB and DK: co-authors.

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