

Large Bowel Perforation in Patients with Colorectal Cancer: A South African Perspective

Jocelynn Norman¹, Yoshan Moodley^{1,2*}

¹Gastrointestinal Cancer Research Group, Department of Surgery, University of KwaZulu-Natal, Durban, South Africa, ²Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

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Correspondence:

Yoshan Moodley, Faculty of Medicine and Health Sciences at Stellenbosch University, Francie van Zijl Drive, Parow Cape Town, South Africa 7505. E-mail: yoshanm@sun.ac.za

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Abstract

Introduction: Large bowel perforation (LBP) occurs in up to 10% of colorectal cancer (CRC) patients and is a potential surgical emergency. Data on LBP in CRC patients from resource-limited countries are required to improve the management of this condition in these settings. Our study aimed to describe LBP amongst CRC patients in KwaZulu-Natal, South Africa. **Materials and Methods:** This was a descriptive sub-analysis of LBP data from an ongoing CRC registry. This study explores free and contained perforations and describes LBP characteristics, surgical management, histological findings, overall survival, and CRC recurrence. **Results:** Ninety-four out of 2523 CRC patients had LBP (3.7%). The median age was 53.0 years (interquartile range: 43.0-64.0). The male-to-female ratio was 1.4:1. Thirty-three patients (35.1%) had a coexisting bowel obstruction. Tumor site perforations occurred in 87 patients (92.6%) and were mostly in the sigmoid colon (36.2%). Perforations were contained in 77 patients (81.9%). Eighty-nine patients (94.7%) underwent resection (elective resection: 76/89 patients, 85.4%). The post-operative inpatient mortality rate was 2.2%. Most patients had Stage III CRC (46 patients, 48.9%) and moderately differentiated tumors (77 patients, 81.9%). Overall survival at 12 months following CRC diagnosis was 55.4%. The early recurrence rate for CRC disease was 5.4%. **Conclusion:** Tumor site perforations predominated, and most were contained. Patients were younger when compared with the international literature. We reaffirm that diastatic-free and contained perforations are two distinct clinical entities.

Keywords: Colorectal neoplasms; intestinal perforation; large intestine; South Africa

Introduction

In South Africa, classified as a middle-income country, colorectal cancer (CRC) is the fourth most common cancer in both men and women.^[1] Large bowel perforation (LBP) is among the most

important complications observed in CRC patients, with a prevalence of 2-10%.^[2,3]

LBP can either result in free spillage of bowel contents into the general peritoneal cavity, leading to generalized or localized peritonitis, or can

remain contained by surrounding tissues, where spillage is avoided.^[4,5] Patients with free perforation generally require emergent surgical intervention.^[6] In a contained perforation, a full-thickness hole is created by the perforation. While free spillage is possible, it is usually prevented because contiguous organs and inflammation create a barrier around the area.^[4,5,7] Bowel perforation in CRC can occur at the tumor or distant sites.^[8] Distant site (diastatic) perforations are usually a proximal colon rupture or blow-out from an obstructed tumor and a competent ileocecal valve, producing a closed-loop obstruction.^[4,5] Diastatic perforations are almost always free perforations, leading to spillage of the bowel contents.^[4] Perforations occurring at the tumor site are much more common.^[7]

Compared to malignant obstruction, the literature on LBP is sparse. Of the limited studies on malignant perforation, the majority are from high-income countries.^[3] The few available studies on LBP in CRC patients are mostly heterogeneous.^[8] The major limitation of these studies is that they regard LBP as a uniform entity and do not differentiate between distant and tumor-site perforation nor between free- and contained perforation.^[9] The current study sought to describe LBP amongst CRC patients in our local setting. To achieve this, we analyzed data from an ongoing CRC patient registry from KwaZulu-Natal (KZN), South Africa.

Materials and Methods

Study design and setting

This was a descriptive study that was conducted on a CRC patient registry. The patient registry was established at the Durban Colorectal Unit, situated at Inkosi Albert Luthuli Central Hospital (IALCH). IALCH is a tertiary referral hospital in the City of Durban, South Africa. It provides medical and surgical services to the population residing on the Eastern Seaboard of the KZN Province, South Africa. IALCH houses both a Colorectal and an Oncology unit which participate in Gastrointestinal Cancer multidisciplinary team (MDT) activities. Additional Colorectal and Oncology units are situated at Addington Hospital (ADH) in

Durban and Grey's Hospital (GH) in Pietermaritzburg, both of which are subsidiaries of the Main Units at IALCH. All patients with CRC cancer are discussed at the Multidisciplinary Clinics consisting of an MDT of surgeons, oncologists, and radiologists. Members of the Colorectal Unit are also members of the MDT. The proposed treatment plan is thus collectively decided by the MDT.

CRC patient registry

The CRC patient registry was initiated in 2000, and patient enrolment is ongoing. The patient registry is curated by members of the Gastrointestinal Cancer Research Group and the Department of Surgery at the University of KZN (UKZN). New patients are identified at the initial presentation at the three hospitals (IALCH, ADH, and GH) with Colorectal and Oncology services. Follow-up data are collected from the Colorectal and Oncology records (i.e., patient medical charts) for each patient and entered onto an electronic spreadsheet. The data collected for each patient includes demographics, clinical presentation, staging, surgical management, histopathological findings, survival outcome, and CRC disease recurrence. All patients were followed up to 12 months after CRC diagnosis for survival outcomes and recurrent disease.

Study population

Patients that were enrolled in the registry from 2000 to 2019 and were found to have had LBP were included in the analysis. A separate variable in the registry indicates whether the patient had a perforated bowel or not. The diagnosis of bowel perforation was based either on gross operative findings confirmed by histology or entirely on histopathologic review. Ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KZN (Reference number: E198/04). This research was guided by the Declaration of Helsinki.

Data management and statistical analysis

Data were kept in an *AppSheet* database file. The statistical analyses were performed using the

Statistical Package for the Social Sciences (SPSS) Version 26.0 (IBM Corp, USA). Descriptive statistics were used to analyze the study data. Continuous variables were summarized as medians with interquartile range (IQR). Categorical variables were summarized as frequencies with percentages. Overall survival up to 12 months following CRC diagnosis was estimated using Kaplan-Meier analysis. Data from the Kaplan-Meier analysis are presented as mean survival time along with the corresponding 95% confidence intervals (95% CI).

Results

At the end of 2019, the registry consisted of 2523 patients with CRC. Of these 2523 CRC patients, 94 patients (3.7%) also had LBP. The median age at presentation was 53.0 (IQR 43.0-64.0) years. Twenty patients (21.3%) were younger than 40 years of age, and the remainder were 40 years old or older (74 patients, 78.7%). There were 51 males (54.3%), giving a male-to-female ratio of 1.4:1. Tumors were primarily located in the sigmoid colon (34 patients; 36.2%), caecum and ascending colon (24 patients; 25.5%), and rectum (12 patients; 12.8%). The proximal colonic disease was seen in 36 patients (38.3%), and distal colonic disease in 45 patients (47.9%). Thirty-three patients (35.1%) had a coexisting bowel obstruction.

As per Figure 1, tumor site perforation was seen in 87 patients (92.6%), and there were seven diastatic

perforations (7.4%). Seventy-seven patients had contained perforation (81.9%), all occurring at the tumor site. The remaining 17 patients had free perforation (18.1%).

The management of CRC patients with LBP is also outlined in Figure 1. In total, 89 patients (94.7%) underwent surgical resection. Most of these patients had elective resection (76 patients, 85.4%). However, a small number of patients also underwent emergency resection (13 patients, 14.6%). The 89 patients who underwent surgical resection included 13 patients with free perforation (9 tumor site perforations and 4 distant perforations) and 76 patients with contained perforation (all 76 were tumor site perforations). The post-operative inpatient mortality rate was 2.2%. Of the patients who did not undergo surgical resection, one patient with free perforation at the tumor site was managed conservatively, and four patients underwent colostomy (one patient with contained perforation at the tumor site and three patients with free perforation at a distant site).

Table 1 shows tumor staging and differentiation in the study population. Most patients had Stage III disease (46 patients, 48.9%), and moderately differentiated tumors (77 patients, 81.9%).

Follow-up data were available for 92 patients (two patients had missing survival and disease

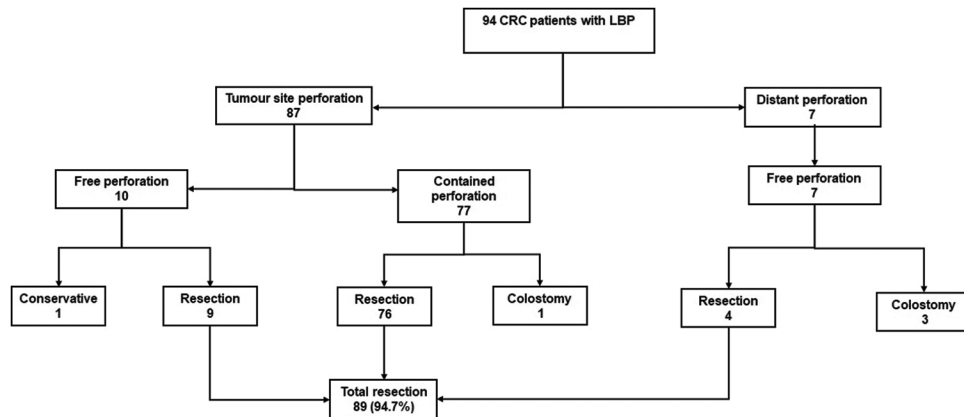


Figure 1: Location of large bowel perforation (LBP) in relation to colorectal cancer (CRC) (tumor site vs. diastatic) and subsequent management

recurrence data). A summary of overall survival in the study population up to 12 months following CRC diagnosis is presented in Figure 2. Only 51/92 patients (55.4%) were still alive in the 12 months following their CRC diagnosis. The mean overall survival time was 8.3 (95% CI: 7.4-9.3) months. There were 5/92 patients (5.4%) who had recurrent CRC and all 5 of these patients had local disease recurrence.

Table 1: Tumor staging and differentiation in 94 colorectal cancer patients with large bowel perforation

Staging	
Stage	n (%)
Stage I	0
Stage II	32 (34.1)
Stage III	46 (48.9)
Stage IV	10 (10.6)
No staged	6 (6.4)
Differentiation	
Differentiation	n (%)
Moderate	77 (81.9)
Mucinous	4 (4.3)
Poor	3 (3.2)
Undifferentiated	1 (1.1)
Well	1 (1.1)
Not stated	8 (8.4)

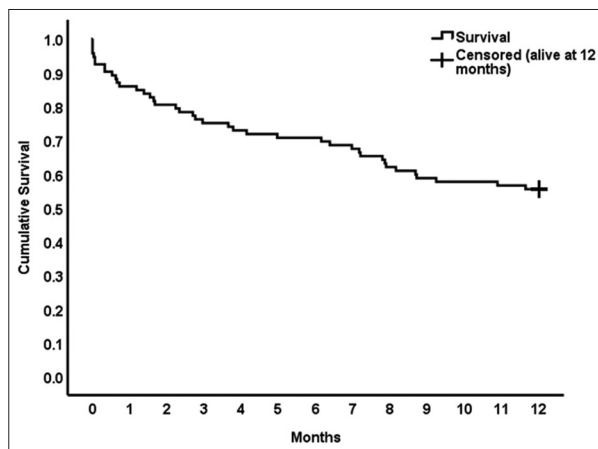


Figure 2: Overall survival at 12 months following CRC diagnosis in the study population

Discussion

LBP was observed in 3.7% of patients with CRC. This figure falls within the 2-10% reported in the world literature for malignant colorectal perforation.^[4,10] According to reports on the frequency of different morphological patterns of perforation, tumor site perforation accounts for 70-80% of cases as opposed to diastatic perforation, which is seen in 20-30% of cases.^[4,11] In this study, most of the perforations were at the tumor site, and most were contained.

The age at presentation was 53 years, which is much lower than the 63-72 years reported in the literature.^[4,12] Epidemiological studies on CRC in sub-Saharan Africa reveal that the disease presents at a young age of 41-59 years with CRC.^[13,14] A prior analysis of patients in the KZN CRC patient registry showed a young age at presentation, which agrees with what is observed for CRC in sub-Saharan Africa.^[15] In addition, the frequency of LBP was comparable between both sexes in this study, which is an observation that other investigators have also made.^[3,15]

The site that was most affected by LBP was the sigmoid colon, followed by the caecum and rectum. This site distribution differs from the general population of patients with CRC. It has previously been documented in a local study^[3] and international series.^[2,9,12] The literature is unclear about the reason for the deviation in disease distribution for tumor site perforations from CRC. Other authors have made similar observations. For example, Banaszkiwicz and colleagues noted more colon cancers than rectal cancers (8% vs. 3%) and left colonic cancer was more common than right colonic cancer.^[16] Cheynel *et al.* reported similar disease distribution between perforated and uncomplicated CRC. However, perforated CRC was seldom located in the rectum.^[17] The relatively higher proportion of patients with right-sided colonic perforation may be explained by the fact that diastatic perforations tend to occur at sites proximal to an obstructing tumor.

The resection rate was very high, at almost 95%. Various authors report emergency operations for patients with perforated CRC, which is not surprising since these authors report on free diastatic perforations.^[4] Our observation differed from these findings in that the vast majority of the perforations were contained perforations and did not have spillage of contents into the general peritoneal cavity; these contained perforations were picked up at elective or semi-elective surgery or at histopathological analysis. Therefore, contained perforations do not always necessitate emergency surgery as they are discovered after the fact. Studies have shown that diastatic perforation is associated with high post-operative mortality of 25-60% due to peritonitis and other septic complications.^[4,11,17] In stark contrast, the mortality rate for tumor site perforations is slightly lower at 8-37% because their development is associated with the development of an inflammatory mass, thereby reducing the risk of generalized peritonitis and sepsis with for tumor site perforations.^[4,17] This study reports a postoperative inpatient mortality rate of 2.2%. While indicative of the higher number of tumor site perforations in the study population (vs. diastatic perforations), it is still much lower than the post-operative mortality rate reported in the published literature. Further research is required to establish why the post-operative mortality rate in this study is lower than that reported in other studies of LBP in CRC patients.

In this study, 34% and 48% of patients presented with Stage II and Stage III CRC, respectively. This observation is supported by the international literature, which reveals that perforated CRC is directly associated with locally advanced staging.^[4,17,18] The limitation of these published reports remains that they do not differentiate between diastatic or tumor site perforations. However, one study emphasized that free perforation generally shows a more aggressive histopathologic profile and a more advanced stage than elective cases.^[19]

We report a worse overall survival rate at 12 months when compared with another South African study of CRC patients (55.4% in our study vs. 89% in the

other South African study).^[20] This difference in overall survival might be due to our population being in much poorer health than that reported in the other South African CRC study (given that our patients were selected from the patient registry because they were already complicated with LBP), and this would have made our study population at higher risk of more severe complications such as mortality. The early CRC recurrence rate in our study (5.4%) was within the range of early recurrence rates reported in the published literature (3.5-9.9%).^[21]

The study does have some limitations. This was a retrospective analysis. The patient population was sourced from the KZN province and did not represent the whole of South Africa. The registry represents patients seen in the public health sector in South Africa, and 16-18% of patients seen in the Private Health sector were not included because they follow a different referral pattern.^[22,23] There was a high attrition rate in our population during the 2nd year following CRC diagnosis. Therefore, we were only able to reliably investigate overall survival and disease recurrence data up to 12 months following an initial CRC diagnosis in this study. Nonetheless, a major strength of this study was that the data were from one of the largest and longest-running CRC patient registries on the African continent. Likewise, data were retrieved from a single CRC patient registry incorporating almost all CRC patients from the KZN Province (from three major CRC management centers in KZN), and thus our findings are much more generalizable than had the data been obtained from a single hospital-based audit.

In conclusion, tumor site perforations predominated but tended to be contained in patients with CRC. All patients were younger than reported in the international literature, but the age at presentation was similar to that reported for CRC patients in sub-Saharan Africa. Contained perforations do not always necessitate emergency surgery, as they are discovered after the fact. Surgery for contained perforation is not associated with the recognized short-term morbidity and mortality of emergency surgery for peritonitis. Finally, we reaffirm that

diastatic free and contained perforations are two distinct clinical entities with unique outcomes.

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Author Contributions

Conceived and designed the analysis: JN and YM; Collected the data: JN; Contributed analysis tools: Performed the analysis: YM; Wrote the paper: JN and YM.