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Uncovering missed opportunities — A root-cause analysis of post-colonoscopy colorectal cancer in a tertiary care setting

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DOI: 10.17235/reed.2025.11320/2025
Link: PubMed (Epub ahead of print)

Please cite this article as:
Ruiz-Rodríguez Jorge, Román de la Fuente Carolina, Torres Nieto María Ángeles, Bayo Juanas Paula, Ruiz Núñez Isabel, Martínez Cuevas Cristina, Sanjosé Crespo Alicia, Díez Redondo Pilar, García-Alonso Francisco Javier. Uncovering missed opportunities — A root-cause analysis of post-colonoscopy colorectal cancer in a tertiary care setting. Rev Esp Enferm Dig 2025. doi: 10.17235/reed.2025.11320/2025.

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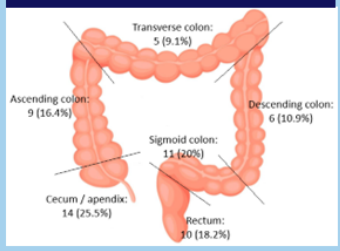
Population:

Retrospective single-center study (May 2018 - April 2022).

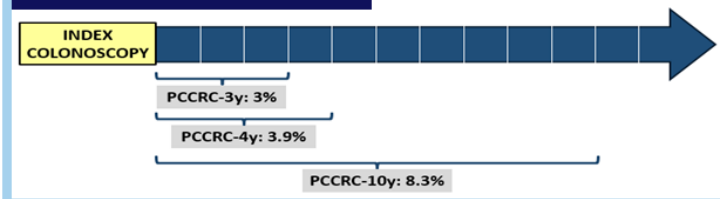
660 colorectal cancer cases

55 (8.3%) post-colonoscopy colorectal cancers

PCCRC location:



PCCRC rates:



Most plausible explanation of PCCRC:		All PCCRCs	Likely new CRCs excluded*
Total number of cases		55 (100%)	26 (100%)
Possible missed lesion with a prior adequate examination		38 (69.1%)	14 (53.8%)
Possible missed lesion with a prior inadequate examination		10 (18.1%)	6 (23.1%)
	Poor bowel preparation	7 (12.7%)	5 (19.2%)
	Incomplete colonoscopy	3 (5.4%)	1 (3.8%)
Likely incomplete resection of a previously identified lesion		7 (12.7%)	6 (23.1%)
Detected lesion, not resected		0 (0%)	0 (0%)

*'Likekely new colorectal cancers excluded' (analysis considering only PCCRC-4y cases), in accordance with WEO recommendations.

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Uncovering missed opportunities — A root-cause analysis of post-colonoscopy colorectal cancer in a tertiary care setting

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Keywords: Post-colonoscopy colorectal cancer. Interval cancer. Root-cause analysis.

Abbreviations list: Colorectal cancer (CRC), post-colonoscopy colorectal cancer (PCCRC), World Endoscopy Organization (WEO), standard deviation (SD), interquartile range (IQR).

Lay summary

Colorectal cancer is a common and serious disease, but it can often be prevented through colonoscopy by identifying and removing precancerous lesions. However, in some cases, cancer still develops after a colonoscopy that fails to detect abnormalities. These cases are known as post-colonoscopy colorectal cancers (PCCRCs). Understanding why this happens can help improve colonoscopy quality.

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In this study, we reviewed the medical records of patients diagnosed with colorectal cancer at our hospital between 2018 and 2022. We looked at how many colonoscopies they had before their cancer diagnosis and analyzed those cases to understand why the cancers might have been missed.

Out of 660 colorectal cancer cases, 55 occurred in patients who had previously undergone a colonoscopy in which no cancer was detected. Most of these cases were due to unidentified lesions or inadequate bowel preparation. In some cases, cancers developed due to the incomplete removal of a previously detected lesion. These missed cancers were more common in the right colon and rectum.

Most patients received treatment with curative intent, however, many were diagnosed at an advanced stage. This study highlights the importance of improving colonoscopy practices, particularly by ensuring better bowel preparation and enhancing the detection and complete removal of lesions.

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Abstract

Introduction: Colorectal cancer is a leading cause of cancer-related mortality. Colorectal cancers diagnosed after a colonoscopy with no cancer detected—post-colonoscopy colorectal cancers (PCCRCs)—remain a quality concern.

Objectives: To estimate the proportion of PCCRC, identify their most plausible causes, and describe tumor characteristics and patient outcomes.

Material and Methods: We conducted a retrospective single-center study including all colorectal cancer cases diagnosed between May 2018 and April 2022. These were cross-referenced with all colonoscopies performed between May 2009 and April 2022. PCCRCs were defined using World Endoscopy Organization criteria. Clinical data, colonoscopy quality indicators, and outcomes were retrieved from medical records and analyzed descriptively.

Results: Among 660 colorectal cancer cases, 55 (8.3%) were classified as PCCRC. Most were males (61.8%) with a median age of 72 (IQR 65-81). The 3- and 4-year PCCRC rates were 3.0% and 3.9%, respectively. High-risk factors were present in 14.5% of patients. Tumors were mostly located in the right colon and rectum. Advanced-stage cancer (stage III/IV) was diagnosed in 43.1% of cases. The most frequent etiology (69.1%) was a missed lesion during a prior adequate colonoscopy. Incomplete resection accounted for 12.7% of cases. Stage IV CRC (HR: 6.93 (95% CI: 2.24-21.4), p=0.001) and age at diagnosis (HR: 1.08 (1.02-1.14), p=0.01) were associated with a higher risk of death on multivariable analysis.

Conclusions: The majority of PCCRCs resulted from missed lesions, especially in the right colon and rectum. Enhancing mucosal visualization, improving bowel preparation, and optimizing polypectomy may reduce these rates.

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related deaths (1). In Spain, CRC ranks first in incidence, second in prevalence, and second in mortality (2).

CRC typically originates from adenomatous polyps that undergo a sequence of mutations that accumulate over time (3). CRC screening involves conducting tests on asymptomatic individuals to detect CRC early and remove adenomatous lesions (4).

Unfortunately, the diagnostic accuracy of colonoscopy is not perfect. Cancers appearing after a colonoscopy in which no cancer is diagnosed are known as post-colonoscopy colorectal cancer (PCCRC) (5). The proportion of PCCRC among the CRC diagnosed has been reported as a quality metric since 2011 (6). However, until the World Endoscopy Organization (WEO) proposed a common framework and definitions, interpreting earlier studies in PCCRC was cumbersome (5). Although a significant progress, follow-up recommendations issued by scientific societies show wide variations, significantly influencing estimates (3).

The primary objective of colonoscopy quality improvement initiatives should be to reduce the occurrence of PCCRC. However, the PCCRC rate is inherently limited as a quality metric, as detecting significant differences requires extremely large sample sizes due to the 0.2-1% CRC incidence in screening cohorts (7). Furthermore, there is a year-long delay before the outcomes are obtained. Thus, easily obtained, rapidly evaluable surrogates such as the adenoma detection rate are employed (8).

Despite all these drawbacks, the proportion of PCCRC remains a relevant quality measure. While not all PCCRC can be attributed to errors or oversights, understanding their incidence, type and possible causes is a relevant source of information. Thus, we aimed to estimate the proportion of PCCRC in our institution, identify the most plausible explanation of the PCCRC and describe the CRC characteristics and outcomes of these patients.

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Methods

We conducted a single-center retrospective observational study to estimate the PCCRC rate in our institution. The study was performed according to the Declaration of Helsinki and approved by the institutional review board (Identification number: 23-PI062).

Patients

All CRC diagnoses in our institution between May 2018 and April 2022 were retrieved from the prospective database kept by the Pathology department. This database includes all malignant colorectal tumors.

The endoscopic procedures were retrieved from the prospective database kept in the Endoscopy unit, which includes all procedures performed. A dataset with all colonoscopies performed between May 2009 and April 2022 was generated. This dataset included the patient identification number and the date of the procedure.

Both databases were matched to determine the number of colonoscopies performed before the CRC diagnosis. Electronic medical records from all patients with 1 or more colonoscopies performed before the CRC diagnosis (colonoscopies undertaken more than 10 years prior to diagnosis with no indication of follow-up were not included in this number) were reviewed manually.

Aims

The primary aim of this study was to estimate the proportion of PCCRC (PCCRC among the CRC diagnoses) considering the previous examinations during a 3-, 4- and 10-year period (PCCRC-3y, PCCRC-4y and PCCRC-10y, respectively). Secondary aims included identifying the most plausible explanation of the PCCRC and describing the CRC characteristics and outcomes of these patients.

Definitions

Definitions were based on the WEO consensus statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer (5).

CRCs identified in subsequent colonoscopies included in the same diagnostic process, were not considered PCCRC. Procedures within a single diagnostic process included those performed within a 3-month interval, those performed as suggested by the previous colonoscopy report (e.g. patients with a poor bowel cleansing who undergo a second colonoscopy) or required by the attending physician due to the previous colonoscopy findings (e.g. lesions with a malignant appearance on endoscopy without conclusive histologic findings).

Neoplasms located proximally to impassable strictures and those found in patients whose last colonoscopy was performed >10 years prior and had no findings requiring endoscopic follow-up to the diagnosis were not considered PCCRC.

Depending on the interval between the last colonoscopy and the diagnosis of CRC, PCCRC were classified into:

- Interval cancers: the cancer was identified before the next recommended screening or surveillance examination, as per valid guidelines at the time of the procedure (9).
- Type A non-interval cancers: the cancer was identified at the recommended screening surveillance.
- Type B non-interval cancers: the cancer was identified after the recommended screening surveillance.
- Type C non-interval cancers: the cancer was identified in patients without any scheduled follow-up examination within 10 years post-colonoscopy.

The causes of PCCRC were assumed as per the WEO recommendations(5), including:

- “Possible missed lesion, prior examination adequate”.

- "Possible missed lesion, prior examination inadequate". Either due to inadequate bowel preparation or because the area was not reached (except in cases where the cause was an impassable stricture).
- "Detected lesion, not resected".
- "Likely incomplete resection of previously identified lesion". Cases in which a polyp larger than 10 mm, a smaller advanced lesion (e.g., intramucosal carcinoma, tubulovillous adenoma), or serrated lesions in the right or transverse colon had been removed in the area where the neoplasm subsequently developed.

Bowel cleansing was considered inadequate following the recommendations of the classifications employed (10,11) or if specifically stated. If not stated, it was considered adequate. Cecal intubation was accepted if stated or photographically documented.

Data retrieval

Baseline characteristics were retrieved from electronic medical records and included demographics and CRC risk factors (inflammatory bowel disease, hereditary syndromes). A detailed description of the CRC was also retrieved, including CRC grade, stage, location and treatment received. Follow-up after CRC diagnosis was also retrieved.

All endoscopic procedures prior to the CRC diagnosis were reviewed. Data retrieved included bowel preparation, landmarks reached, operator, findings and a detailed description of the polypectomies performed.

Data extraction was performed by JRR and CRdlF. A third investigator (FJGA) arbitrated disagreements.

Statistical analysis

Categorical variables are described with percentages. Continuous variables with a normal distribution are presented as means and standard deviation (SD) and those

without are summarized as medians and interquartile range (IQR). Kaplan-Meier curves were used to assess the PCCRC survival. Multivariable Cox proportional hazards regression was used to assess possible risk factors of death during follow-up; results were reported using hazard ratios (HRs) with 95% confidence intervals (CIs). The following items were initially assessed using univariable regression analysis: age at PCCRC diagnosis, sex, high risk of CRC, previous diagnosis of advanced adenomas, PCCRC location (right vs left colon), presence of symptoms at diagnosis, incomplete resection as cause of PCCRC, CRC stage (0-I, II-III, IV). Those with a significance level ≤0.10 were included in a multivariable model using bidirectional elimination. A P value <0.05 was considered statistically significant. Analyses were performed with Stata 18 (StataCorp., College Station, Texas, USA).

Results

During the study period, 660 CRC cases were diagnosed. The annual number of CRC ranged from 137 to 177. Overall, 87 cases (13.2%) fulfilled the inclusion criteria and were manually reviewed, ultimately identifying 55 cases of PCCRC (8.3%). The remaining 32 patients included 19 patients with no previous colonoscopies (procedures had been scheduled but not undertaken), 5 patients had a colonoscopy over 10 years before diagnosis with no findings requiring follow-up and 8 subjects had a previous colonoscopy in the same diagnostic process.

Patients' and CRC characteristics

Among the 55 cases of PCCRC, 34 (61.8%) were men, with a median age of 72 years (IQR 65-81). High-risk factors were identified in 8 patients (14.5%). Most colonoscopies (60%) were performed due to symptoms, followed by surveillance of previous lesions in 17 cases (30.9%), and screening procedures in 5 cases (9.1%).

Tumor location is shown in Figure 1. Nearly 40% were identified in the right colon. Notably, 10 lesions (18.2%) were in the rectum. Over 40% of patients presented TNM stage III (29.4%) and IV (13.7%) at diagnosis. These findings are shown in Table 1.

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Clinical outcomes

Most patients, 38 (69.1%), underwent surgery with or without chemotherapy. In 6 cases (10.9%), endoscopic treatment was performed, and 11 patients (20%) received chemotherapy and/or supporting care. After a median follow-up of 20 months (IQR 12-33), 12 patients (21.8%) died due to the PCCRC and 4 (7.3%) died from other causes. Only one case (1.8%) was lost to follow-up. Overall survival is shown in Figure 2. Univariable Cox regression analysis identified stage IV CRC (Hazard Ratio (HR): 6.90 (95% CI: 2.24-21.26), p=0.001), age at diagnosis (HR: 1.08 (1.02-1.14), p=0.01), stage 0/I CRC (HR: 0.16 (0.02-1.20), p=0.08) and incomplete advanced adenoma resection (HR: 2.60 (0.83-8.10), p=0.10) as factors conditioning overall survival. However, on multivariable analysis only stage IV CRC (HR: 6.93 (95% CI: 2.24-21.4), p=0.001) and age at diagnosis (HR: 1.08 (1.02-1.14), p=0.01) attained statistical significance.

Previous endoscopic examinations

Thirty-eight subjects (69.1%) had only one previous colonoscopy. Ten patients (18.2%) had undergone 2, and four (7.3%) had undergone 3 colonoscopies. The remaining three patients had 4, 5 and 6 previous colonoscopies respectively. Overall, 12 procedures (21.8%) presented poor bowel cleansing. The cecum was reached in 50 patients (90.9%). In three patients (5.5%), it was not reached due to poor bowel preparation (although in one of them loop formation was also noted). In the remaining two patients (3.6%), the cause was loop formation and adverse respiratory events.

Overall, 26 subjects (47.3%) had at least one adenoma resected in the last colonoscopy before the diagnosis of PCCRC. Advanced adenomas were identified in 11 patients (20%) with a median size of 20 mm (IQR 12-30). Six (54.5%) presented one advanced adenoma, four (36.4%) presented 2 and one (9.1%) presented 4 advanced adenomas.

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PCCRC rates and types

The PCCRC-3y was 3%. The PCCRC-4y was 3.9% and the PCCRC-10y was 8.3%.

The most frequent type of PCCRC were interval cancers (Table 2), accounting for 31 (56.4%) patients. We observed 11 (20%) type A non-interval cancers, 12 (21.8%) type B non-interval cancers and only one (1.8%) was diagnosed in a patient who, after undertaking a colonoscopy with 78 years, declined further endoscopic surveillance.

Etiology of PCCRCs

The most common cause of PCCRC was a "possible missed lesion with a prior adequate examination", accounting for 38 cases (69.1%). "Possible missed lesion with a prior inadequate examination" was identified in 10 cases (18.1%), including 7 related to poor bowel preparation and 3 due to incomplete colonoscopies, caused by loop formation, a combination of loop formation and inadequate preparation, or adverse events. Lastly, "likely incomplete resection of a previously identified lesion" was observed in 7 cases (12.7%), with a median lesion size of 20 mm (range: 12–30 mm). In this group, four cases (7.3%) also had inadequate bowel preparation.

Categorization of PCCRCs according to their most plausible explanation, based on the WEO root-cause algorithm (5), is shown in Table 3.

We specifically compared the 7 incompletely resected advanced adenomas leading to PCCRC with the remaining 11 advanced adenomas resected. The polyp size (incomplete resection: 20 mm (range: 12–30 mm); remaining adenomas: 18 mm (range 10-30)) and resection techniques employed were similar (28.6% vs 27.3% piecemeal mucosal resection). However, incompletely resected adenomas were more frequently flat (0-IIa/0-IIb) (71.4% vs 36.4%).

Discussion

We conducted a single-center retrospective study to estimate PCCRC rates between 2018 and 2022 and performed a root-cause analysis to determine the etiology as per WEO recommendations (5).

We identified a 3% PCCRC-3y-rate, which lies within the range of previously published data. A single-center Belgian cohort reported a 2.5% rate (12), while a multicenter Spanish cohort presented even better results, a 2.2% PCCRC-3y rate (13), although this second study excluded high-risk patients (IBD, hereditary CRC syndromes). Conversely, a single center English cohort reported a higher 4.7% PCCRC-3y rate (14), but including 43% high-risk patients (14.5% in our cohort). Higher PCCCR 3y-rates have also been reported; in a multicenter U.S. cohort, Cooper et al. attained a 7.2% rate after excluding patients with IBD (15), while Forsberg et al. and Cheung et al. (16,17) , identified 7.9% PCCCR 3y-rates in population-based cohorts from Sweden and Hong Kong. Interestingly, few studies report the WEO-recommended 4y-rate. A multicenter study in the Central Denmark Region, identified a 2.9% PCCRC 4y-rate, however, 20% potential PCCRCs were excluded due to missing information.

The primary cause of PCCRC in our study was unidentified lesions (69.1%), aligning with most studies, which attribute up to 70% of PCCRC cases to this factor (12,13,18–21). Only one study reported inadequate examination as the leading cause of PCCRC, accounting for 58% of cases (14). Incomplete polypectomies represented 12.7% of cases in our study, with a median size of 20 mm (range 12-30), underscoring the role of incomplete resection as a significant contributor to PCCRC, particularly for larger polyps (22). Another potential cause of PCCRC not considered in our study is the rapid progression of precancerous polyps; however, this is estimated to represent only a small proportion of cases (23).

In agreement with previous studies (12,13,15,18,24,25). This tendency might be related to poorer bowel preparation in proximal segments or to a higher frequency of serrated or flat lesions on the right side (26). Interestingly, Cheung et al. reported that 82.8% of PCCRC were distal in a multicenter Hong Kong cohort, consistent with the higher prevalence of distal cancers among Chinese patients (17). Rectal adenocarcinomas accounted for a significant 18.2% of our PCCRC cohort, aligning with

the prevalence reported in other studies (13,15,18). Over 40% of PCCRC cases were diagnosed at advanced stage III or IV, comparable to the 38.3% and 36.4% reported in previous studies, respectively (12,13).

These results should be a call to action, namely implementing measures to decrease the PCCRC rate. However, changes are time- and resource-consuming. Various interventions are currently available with promising results. Intraprocedural techniques such as dual observation, water exchange; narrow-band imaging and computer-aided detection (CADe) systems among endoscopic technologies, distal attachment devices, and oral methylene blue administration have been proposed (27). However, their real impact is still debatable. CADe systems reduce the adenoma miss rate but do not improve the detection of advanced adenomas or lesions measuring 6–9 mm or ≥10 mm (28), and only narrow-band imaging improves the detection of serrated lesions (OR 2.94; 95% credible interval, 1.46–6.25) (27), highlighting the importance of continuous quality assessment.

This study presents a series of strengths. Records from all possible cases were manually reviewed. Beyond following the WEO framework, it also estimates the 3- and 10-year PCCRC, simplifying comparisons. However, it also presents a significant drawback stemming from its design, namely a probable underestimation of the PCCRR rate due to several factors. Firstly, we only attained data from procedures performed in our center; some patients might have had colonoscopies elsewhere before their diagnosis. Secondly, CRC developing in patients undergoing a previous colonoscopy in our center might have been diagnosed and treated in other institutions. Furthermore, single center studies present a high risk of selection bias, affecting the generalizability of these results. Additionally, we depended on endoscopy reports and electronic medical records for labelling procedures as belonging to the same diagnostic process. If verbal recommendations were made to undergo another colonoscopy due to inadequate bowel preparation, such examinations would still be part of the same diagnostic process, with delays potentially caused by external factors.

In conclusion, we estimated a 3.9% PCCRC-4y rate. Most of these tumors were in the right colon and rectum, with missed lesions during prior colonoscopy being the

primary contributing factor. Implementing successful strategies to enhance the examination of these regions, improve bowel preparation quality, and refine polypectomy techniques may lead to lower PCCRC rates.

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Table 1. PCCRC characteristics.

		N (%)
Gender	Male	34 (61.8%)
High risk factors	Lynch syndrome	6 (10.9%)
	Familial adenomatous polyposis	1 (1.8%)
	Ulcerative colitis	1 (1.8%)
	No	47 (85.5%)
Diagnostic colonoscopy indication	Screening	5 (9.1%)
	Follow-up of previous lesions	17 (30.9%)
	Symptoms	33 (60%)
Location	Cecum / apendix	14 (25.5%)
	Ascending colon	9 (16.4%)
	Transverse colon	5 (9.1%)
	Descending colon	6 (10.9%)
	Sigmoid colon	11 (20%)
	Rectum	10 (18.2%)
Staging	0	3 (5.9%)
	I	14 (27.5%)
	II	12 (23.5%)

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	III	15 (29.4%)
	IV	7 (13.7%)
Treatment	Endoscopic resection	6 (10.9%)
	Surgery	38 (69.1%)
	Chemotherapy and/or supporting care	11 (20%)

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Table 2. Types of PCCRC according to the different time thresholds employed.

	PCCRC-3y (n=20)	PCCRC-4y (n=26)	PCCRC-10y (n=55)
Interval Cancer	12 (60%)	17 (65.4%)	31 (56.4%)
Type A	6 (30%)	7 (26.9%)	11 (20%)
Type B	2 (10%)	2 (7.7%)	12 (21.8%)
Type C	0	0	1 (1.8%)

PCCRC: Post-Colonoscopy Colorectal Cancer

Interval cancer: lesions identified before the next recommended screening. Type A non-interval cancers are diagnosed at the recommended screening surveillance. Type B are identified after the recommended screening surveillance. Type C are diagnosed in patients with no subsequent examination scheduled

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Table 3. Most plausible explanation of all post-colonoscopy colorectal cancers and those considering the previous examinations during a 4-year period (PCCRC-4y).

Most plausible explanation		**All PCCRCs**	**PCCRC-4y**
Total number of cases		55 (100%)	26 (100%)
Possible missed lesion with a prior adequate examination		38 (69.1%)	14 (53.8%)
Possible missed lesion with a prior inadequate examination		10 (18.1%)	6 (23.1%)
	Poor bowel preparation	7 (12.7%)	5 (19.2%)
	Incomplete colonoscopy	3 (5.4%)	1 (3.8%)
Likely incomplete resection of a previously identified lesion		7 (12.7%)	6 (23.1%)
Detected lesion, not resected		0 (0%)	0 (0%)

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Figure 1. Tumor location: number of PCCRC (%).

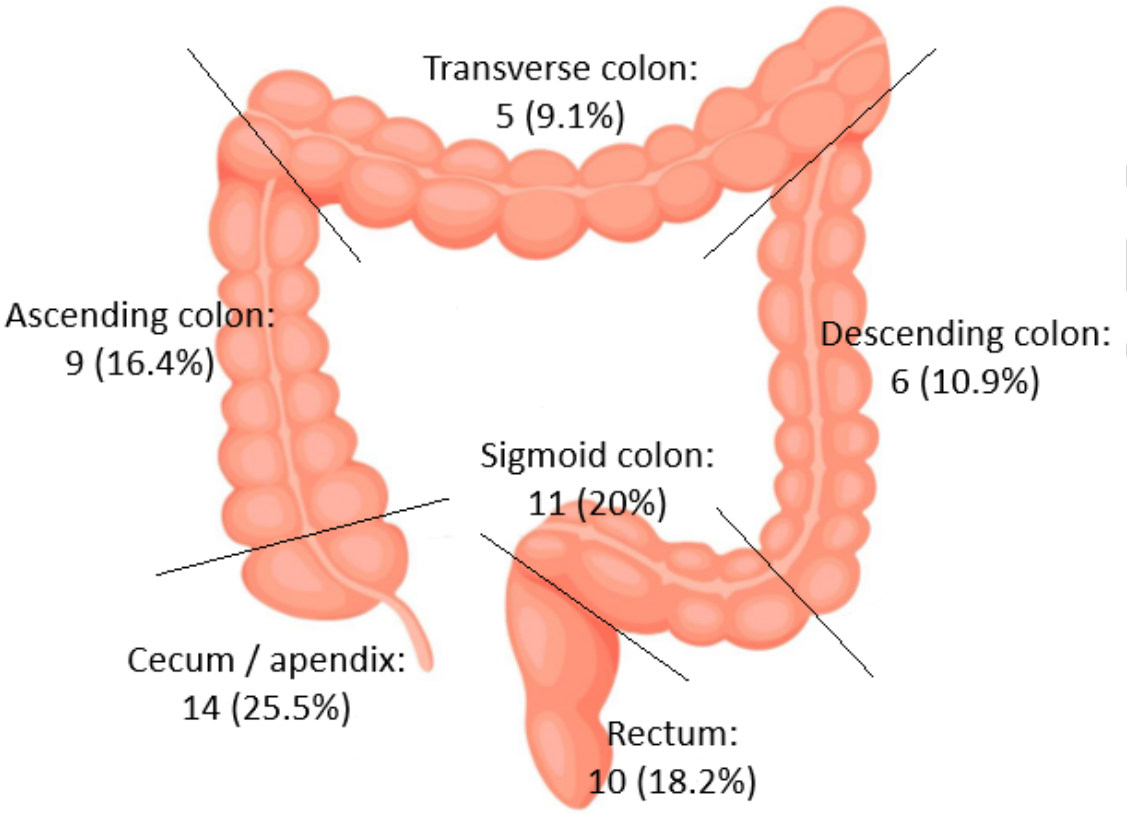

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Figure 2. Survival curve (all-cause mortality) built using the Kaplan–Meier method