# The Incidence, Distribution and Clinicopathology of Missed Colorectal Cancer After Diagnostic Colonoscopy

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***Cite this article as:*** Laurent E, Hussain H, Poon T, Ayantunde A. The incidence, distribution and clinicopathology of missed colorectal cancer after diagnostic colonoscopy. *Turk J Gastroenterol.* 2021;32(11):988-994.

## ABSTRACT

***Background:*** *Colonoscopy does miss some lesions that may be later diagnosed as post-colonoscopy colorectal cancers (PCCRCs). We evaluated the rate of PCCRCs in a cohort of our patients.*

***Methods:*** *The data of patients diagnosed with first primary colorectal cancers (CRCs) between July 2014 and June 2017 were analyzed. Colorectal cancers were considered to be missed if they occurred among patients who have had an index colonoscopy between 7 and 36 months prior to their diagnosis. The incidence of missed lesions and the distribution of such lesions in the large bowel are presented.*

***Results:*** *In the study, 399 of the total 541 patients whose CRCs were diagnosed by colonoscopy were included. The median age of the patients (213 males and 186 females) was 75.3 (32.4-82.1) years. Seven patients with diagnosis of primary CRCs had undergone index colonoscopy between 7 and 36 months prior to their diagnostic colonoscopy. Therefore, the PCCRC rate in this cohort was 1.8% (7/399 × 100). The mean time interval between the false negative colonoscopy (index colonoscopy) and diagnostic colonoscopy was 18.7 (9.1-34.9) months. Missed CRCs were located in the ascending (2), transverse (1), descending (1), and sigmoid colon (2) and in the rectum (1).*

***Conclusion:*** *Our PCCRC rate was 1.8%, which is lower than the usually reported rate.*

***Keywords:*** *Colonoscopy, colorectal cancer, post-colonoscopy colorectal cancer rate, colorectal adenomatous polyps, interval cancer*

## INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent cancers worldwide and the fourth leading cause of cancer death.[1,2] The pathogenesis of CRC from adenomas is well documented in what is described as adenoma–carcinoma sequence.[3] The only currently available diagnostic gold standard for CRCs and adenomatous lesions is colonoscopy. In addition, interventional colonoscopic techniques are also increasingly used to remove colorectal adenomas, polyp cancers, and other early colorectal lesions, thereby halting their progression.

The basis of either screening and/or diagnostic colonoscopy is to pick up colorectal lesions in their earliest pathological stage and thereby avoid delayed diagnosis in nonsymptomatic and symptomatic patients. The best and optimal survival rates of CRC are achieved in patients whose cancers are diagnosed and treated at the early stage.[4] The National Polyp Study (NPS) was the first to report that colonoscopic polypectomy is associated with a significant reduction in the overall incidence of CRC.[5]

Colonoscopy is a key diagnostic test for the detection of CRC and other adenomatous lesions. However, it is now well established by various reports that colonoscopy does miss some adenomatous polyps and early CRCs, which are then later diagnosed as postcolonoscopy colorectal cancers (PCCRCs) or otherwise known as interval CRCs. Therefore, PCCRC as an entity may then represent a missed cancer, a cancer arising in missed or incompletely removed adenomas or a CRC that had started to develop very rapidly after index colonoscopy.[6,7] Postcolonoscopy colorectal cancer rates are potentially the most important markers of the quality of colonoscopy services. However, PCCRC rates are difficult to measure and interpret.[8] The reported rates of PCCRCs vary significantly between 2.1% and 7.5% depending on the methods and the datasets used in their calculation.[9,10] The overall proportion of the cases of PCCRC within 3 years of a colonoscopy undertaken between 2001 and 2007 in the English National Health Service (NHS) was 8.6%, but the rates fell from 10.6% in 2001 to 7.3% in 2007.[10] The rates of PCCRCs have been shown to have further fallen from 10.6% to 6.8%.[10,11]

The quality of colonoscopy service has been clearly implicated in PCCRC rates.[12-19] The risks of PCCRC have been variously identified and reported in the literature. These risk factors may be contributing significantly to the

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*Received:* ***September 21, 2020*** *Accepted:* ***June 23, 2021*** *Available Online Date:* ***November 25, 2021***

*DOI:* ***10.5152/tjg.2021.20500***

various rates of missed lesions in index colonoscopy. The factors such as older age group, gender of the patients, quality of bowel preparation, experience of the endoscopist, location of the missed lesion, and the presence of colonic diverticular disease have been implicated in the varying rates of missed lesions.[9,10,12-19]

We evaluated the rate of PCCRCs in a cohort of patients diagnosed with first primary CRCs by colonoscopy. We also demonstrated the distribution and the clinicopathological characteristics of such cancers.

### *PATIENTS AND METHODS*

We retrospectively evaluated our prospectively collected data of all patients diagnosed with first primary CRC between July 2014 and June 2017. We collected patients' demographic data, Charlson comorbidity index, and clinical data that included indications, findings, and the total number of colonoscopies prior to diagnosis (detailed in Figure 1). Of these patients, we then identified a subgroup of patients who had undergone an earlier index colonoscopy between 7 and 36 months before the diagnosis of colorectal cancer. In that period, the cancers were considered to be new or missed. Colorectal cancers picked up among patients by diagnostic colonoscopy within 6 months of diagnosis were considered as detected based on the criteria laid out by Stoffel et al.[20] Other exclusion criteria applied to the cohort in this study are detailed in Table 1.

The index diagnostic colonoscopic procedures were performed by consultant gastroenterologists or consultant surgeons of varying years of experience, but all

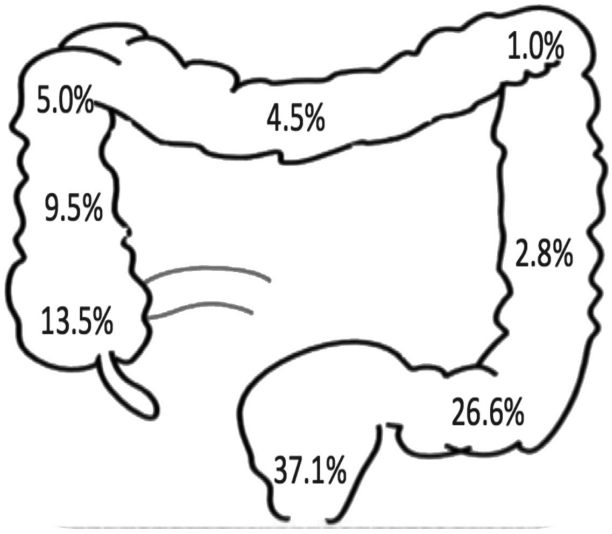


**Figure 1.** Distribution of all colorectal cancers (CRCs) diagnosed by colonoscopy.

### *MAIN POINTS*

- *Colonoscopy is considered as a gold standard investigation in the diagnosis of colorectal adenomatous polyps and malignancy. A polyp takes approximately more than 3 years to develop into colorectal cancer (CRC); therefore, a patient cannot have a normal result (i.e., no polyps or lesions) on a colonoscopy that was done 3 years or less prior to the diagnosis of CRC. These CRCs are classified as the post-colonoscopy colorectal cancer (PCCRC). Between July 2014 and June 2017, we had 541 patients diagnosed with CRC. Of these, 399 were diagnosed by colonoscopy and met our inclusion criteria and were therefore included in our study.*
- *Significant association between the quality of endoscopic services and postcolonoscopy colorectal cancer (PCCRC) rates is well recognized. In spite of the advances in endoscopic services, PCCRCs seem inevitable for various reasons that may interplay in a complex fashion. We reported a PCCRC rate of 1.8%, which is below the national average.*
- *These PCCRCs are fairly evenly distributed throughout the colorectum, with slightly increased rates noted in the right and sigmoid colon. Regional predominance patterns have been previously reported and are due to the failure of the endoscopist reaching the site of the tumor on the right colon, inadequate bowel preparation, and the presence of multiple sigmoid folds with the presence of diverticular disease, thereby distorting the anatomy. Therefore, it is advisable that endoscopists pay very close attention to adequate mucosal visualization, especially around the folds and in the diverticular segment as these areas may be harboring sinister small polyps and cancers.*
- *In this study, the clinicopathological data from 7 of our patients with PCCRCs revealed 5 locally advanced lesions, and those patients had treatment with curative intent. Fortunately, all patients were alive and have had no recurrent or metastatic disease on follow-up. The remaining 2 had significant medical comorbidities and were palliated for reasons other than CRC.*

**Table 1.** Exclusion Criteria Applied to the Study Population

| | |
|---|---|
| 1 | Incomplete colonoscopy due to technical problem and/or poor bowel preparation |
| 2 | Previous bowel cancer |
| 3 | Previous colorectal resection for either malignant and/or benign pathology |
| 4 | Patients whose primary colorectal cancers (CRCs) were diagnosed by imaging |
| 5 | History of inflammatory bowel disease (IBD) |
| 6 | History of familial adenomatous polyposis syndrome, hereditary non-polyposis syndrome and/or familial colorectal cancers (CRCs) |

of them had at least 3 years of experience as independent endoscopists. The endoscopists were all certified by the UK Joint Advisory Group (JAG) on gastrointestinal (GI) endoscopy and had performed a minimum of 100 colonoscopies per year with successful cecal intubation rate of at least 95% and adenoma detection rate of at least 20%.[11]

Post-colonoscopy colorectal cancer rate is defined as the number of false negative colonoscopies divided by the total number of colonoscopies undertaken. We calculated the PCCRC rate by dividing the number of patients with primary CRC diagnosis who had undergone index colonoscopy between 7 and 36 months preceding their diagnostic colonoscopy by the total number of patients diagnosed by colonoscopy (Bressler's method).[6,9,10]

The data was collected and analyzed using SPSS version 23.0 to present descriptive statistics. We calculated the incidence of missed lesions (PCCRC rate) by index colonoscopy and demonstrated the regional distribution of such lesions in the large bowel. We also presented the clinicopathological data of the cancers and the outcomes of the patients with PCCRC in this cohort.

## RESULTS

A total of 541 patients were diagnosed with CRCs between July 2014 and June 2017. Of these, 399 patients had their cancers diagnosed by colonoscopy and were included in the study. In the study, 142 of 399 patients who failed to meet our inclusion criteria were excluded from the final data analysis. The exclusion criteria applied to the cohort in this study is shown in Table 1. The anatomical distributions of the primary CRCs and the PCCRCs are shown in Figures 2 and 3, respectively.

Of the 399 patients in the study, the median age at CRC diagnosis was 75 (32-88) years. There were 213 males and 186 females. The median Charlson comorbidity index score was 1 (0-6). The predominant symptoms of patients that are in various combinations and/or the indications for diagnostic colonoscopy leading to the diagnosis of the primary CRCs are detailed in Table 2.

Seven of the 399 patients with diagnosis of primary CRCs had undergone index colonoscopy between 7 and 36 months prior to their diagnostic colonoscopy. These 7 patients were considered to have developed PCCRCs based on the set criteria. Therefore, the PCCRC rate in this cohort is 1.8% (7/399 × 100). The mean time interval between the false negative colonoscopy (index

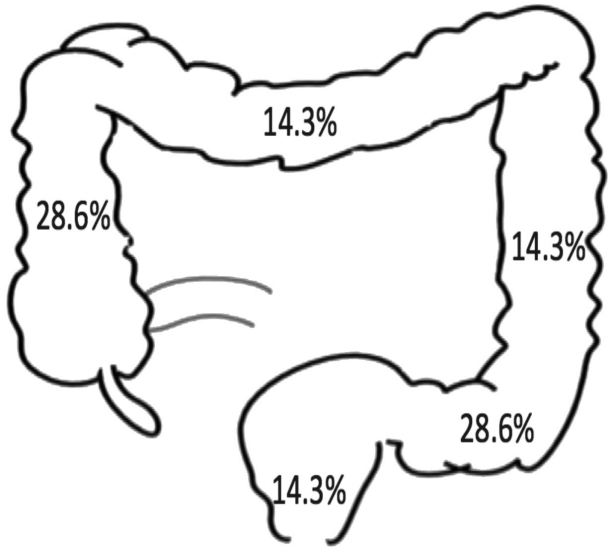


**Figure 2.** Distribution of all post colonoscopy colorectal cancer (PCCRCs).

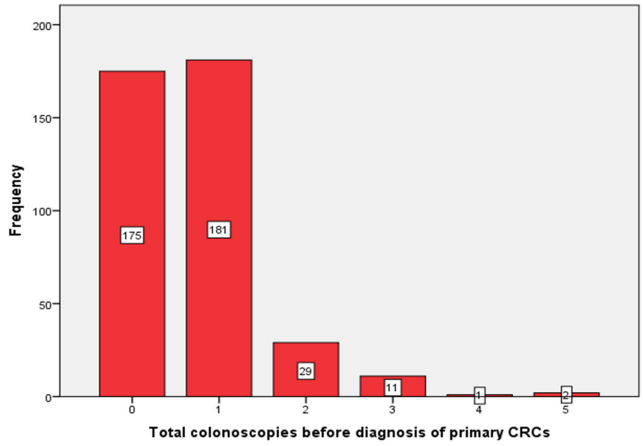


**Figure 3.** Distribution of post-colonoscopy colorectal cancers (PCCRCs). A bar chart showing the total number of colonoscopies each patient had before a diagnosis of colorectal cancer (CRC) was made. Those who zero colonoscopies were diagnosed with CRC by other investigations.

**Table 2.** Presenting Symptoms by Patients and/or Indications for Diagnostic Colonoscopy

| Symptoms | Present (%) | Absent (%) |
|---|---|---|
| Change in bowel habit | 170 (42.6) | 229 (57.4) |
| Rectal bleeding | 180 (45.1) | 219 (54.9) |
| Anemia | 110 (27.6) | 289 (72.4) |
| Abdominal pain | 84 (21.1) | 315 (78.9) |
| Weight loss | 87 (21.8) | 312 (78.2) |

**Table 3.** Clinicopathological Data of 7 Patients with Post-colonoscopy Colorectal Cancers (PCCRCs)

| No. | Age | Sex | Interval[a] (Months) | No. of Colonoscopy[b] | Location | Tumor Stage (TNM) | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | 68 | F | 9 | 2 | Rectum | T3N1M0 | Curative | Alive |
| 2 | 64 | M | 10 | 3 | Rectosigmoid | T3N0M0 | Curative | Alive |
| 3 | 78 | M | 14 | 3 | Sigmoid colon | T3N0M0 | Palliative | Dead |
| 4 | 59 | M | 16 | 3 | Ascending colon | T4N2M0 | Curative | Alive |
| 5 | 68 | F | 34 | 2 | Descending colon | T4N1M0 | Curative | Alive |
| 6 | 88 | M | 19 | 3 | Ascending colon | T2N0M0 | Palliative | Dead |
| 7 | 77 | F | 24 | 2 | Transverse colon | T3N0M0 | Curative | Alive |

[a]Interval between index and diagnostic colonoscopy in months; [b]Number of colonoscopies before diagnostic colonoscopy.
TNM, tumor node and metastasis.

colonoscopy) and the diagnostic colonoscopy identifying colorectal cancer was 18.7 (9-34.9) months.

The clinicopathological data of the patients with PCCRCs are shown in Table 3. There were 4 males and 3 females with the median age at diagnosis of CRCs of 68 (59-88) years. All 7 patients with PCCRCs have had 2-3 diagnostic colonoscopic procedures before the eventual diagnosis of the primary CRCs (Table 3). The majority of the PCCRCs was locally advanced, with 5 of the 7 patients undergoing treatment with curative intent. Five patients with PCCRCs who had curative treatment were alive, with no evidence of recurrent or metastatic disease at follow-up. Two patients were subjected to palliative care pathway because of the presence of significant comorbidities precluding the offer of radical curative treatment. These 2 patients died by the end of this study period. They died of their associated significant medical comorbidities and not of colorectal cancer.

## *DISCUSSION*

This cohort single-center study has demonstrated a low PCCRC rate of 1.8%, which is at the lower end of what has been generally reported in the published literature using the standard-definition colonoscopy equipment.[9-11,17-19] We also showed the distribution of the primary CRCs and PCCRCs within the colorectum. The clinicopathological characteristics of the 7 patients with PCCRCs were demonstrated.

Colonoscopy is considered as a gold standard investigation in the diagnosis of colorectal adenomatous polyps and malignancy. The use of colonoscopy and/or the excision of colonic adenomatous lesions where possible is considered as a gold standard of care for the prevention of the progression of such lesions to invasive colorectal cancer. It has been variously reported that colorectal polypectomy is associated with a significant reduction in the overall incidence of colorectal cancer worldwide.[5,8,12] Several authors have demonstrated significant associations between the quality of endoscopic services and PCCRC.[14,15] However, in spite of the advances in endoscopic services, PCCRCs seem inevitable for various reasons that may interplay in a complex fashion.[16] Morris et al.[10] in their article on the post-colonoscopy colorectal cancer rates in the English NHS stressed this inevitability, no matter how well the endoscopic services are organized and/or the colonoscopic procedures are performed.

There have been large variations in the prevalence of PCCRCs or the previously so-called "interval" CRCs reported in the published literature. The reported rates depend on the datasets used and the methodology applied in the calculation of PCCRC rates.[7-10] We employed Bressler's[6,9,10] method in the calculation of PCCRC rate and found the rate of 1.8% in this cohort study to be lower than the various rates reported previously in many published works using the standard-definition colonoscopy. There are reports of the use of high-definition and/or high-resolution colonoscopy with better images and better detection of adenomas than by the standard-definition equipment.[17,18] Iwatate et al using high-definition colonoscopy reported an overall PCCRC rate of 1.2% among 892 colorectal cancer patients from 2 centers.[18] The lower PCCRC rate observed in this study may be due to many reasons. This study was based on a symptomatic cohort of patients who were subjected to diagnostic colonoscopy. We had applied very strict exclusion criteria among other things, including the exclusion of patients with failed cecal intubation due to technical

problem and/or poor bowel preparation. We had also excluded patients with a higher-than-average risk of developing CRC such as inflammatory bowel disease, family history of CRCs, familial adenomatous polyposis syndrome, and hereditary non-polyposis syndrome and/or familial CRCs. Samadder et al[16] previously reported that a family history of colorectal cancer is more common among patients with an interval CRC compared with those with detected cancer. Our results may also be explained by the fact that we actually evaluated raw clinical and pathological data in a secondary healthcare setting rather than a population-based data, the reports of which have been variously published with potential data heterogeneity, coding errors, selection bias, and overall potential data errors because of inaccuracy.

Many authors have attributed the great variations in the reported PCCRC rates to various factors including differences in the study design (retrospective versus prospective), the different definitions and the methods used to calculate PCCRC rate, the different datasets used (administrative versus clinical data), differences in the studied population (screening versus diagnostic indications), and differences in the experience and the specialties of the endoscopists.[6,10,21] Therefore, it means that the interpretation of the PCCRC rates will have to be carefully considered in the light of the study setting, the selection criteria, and the study methodology employed in each case. Many authors have actually submitted that the published data on PCCRC rates may after all not be suitable for use in comparing the quality of colonoscopy services because of the many aforementioned factors discussed.[10,13,14] Morris et al.[10] particularly emphasized the need to an agreed single methodology in the calculation of PCCRC rates in order to make reasonable comparisons of data and colonoscopy services possible.

Post-colonoscopy colorectal cancers have been shown to occur due to complex interplay of several factors. Bressler et al[9] offered possible reasons for the occurrence of PCCRCs such as failure of index colonoscopy to reach the site of the cancer, poor bowel preparation leading to inadequate mucosal visualization, and small-sized lesions located behind the folds at the time of index colonoscopy, or there may have been rapidly progressing cancers that were not present at the time of index colonoscopy. These factors have been further stressed and demonstrated in many studies including systematic reviews and large population-based studies.[6,8,10,12-16,21-23] In this study, we have excluded incomplete colonoscopy due to failure of cecal intubation and poor mucosal visualization due to poor bowel preparation, and this, in a way, has excluded some of the reasons reportedly responsible for PCCRCs.

In our study, post-colonoscopy colorectal cancers were almost evenly distributed in the colorectum, with slightly increased rates noted in the right and sigmoid colon. The slightly increased prevalence in these 2 areas has been previously reported usually due to the failure of the endoscopist reaching the site of the tumor on the right colon, inadequate bowel preparation, and the presence of multiple sigmoid folds with the presence of diverticular disease, thereby distorting the anatomy.[6,8,9,12-16] It is advisable that endoscopists pay very close attention to adequate mucosal visualization especially around the folds and in the diverticular segment as these areas may be harboring sinister small polyps and cancers.

There are also various studies that have evaluated the unique characteristic biological behavior of PCCRCs to explain the reasons for their occurrence. These studies further stressed the risk factors for their occurrence and their differential outcomes including the overall survival of the patients with PCCRCs than with other primary CRCs.[6,8,9,12,13,15,16,20,21,22] In this study, we were unfortunately not able to make such assertion and a comparison between PCCRCs and other primary CRCs because of the small sample size. We also excluded from our cohort the patients with a history of familial adenomatous polyposis syndrome, hereditary non-polyposis syndrome and/or familial CRCs with known unique biological behavior and characteristics. This background history may pose potential risk factors for the occurrence of PCCRCs.[13,15,16,21-23] Samadder et al.[16] however, noted that colorectal cancer predisposition syndromes do not particularly seem to be an explanation for the majority of interval cancers. Seven patients with PCCRCs in this cohort study had locally advanced lesions but were amenable to radical treatment with curative intent. However, 2 of the patients were unfit for this treatment because of the presence of significant medical comorbidities and were therefore subjected to palliative care only.

We accept that there are few limitations to this study. First, this is a single secondary healthcare institution-based study with a small sample size. Second, although we had used our prospectively collected colorectal cancer database, this study is more or less a retrospective cohort study with the assumption of a reliable and accurate data

entry source throughout the study period. There is always the possibility of potential bias and data entry errors with such assumption. Although we had not taken into account the specific individual endoscopist's experience and adenoma detection rate figures, but all of the endoscopists have had at least 3 years of experience as independent colonoscopists and had been accredited by the UK Joint Advisory Group in GI endoscopy to have fulfilled the minimum certification criteria.[11] The endoscopists are required to continue maintaining this level of skills and be able to demonstrate this through regular appraisal.

## CONCLUSION

Post-colonoscopy colorectal cancer rate in our cohort was 1.8%, which is lower than the widely reported rates in the published literature. The lower PCCRC rate in this study may be multifactorial, including our strictly applied exclusion criteria and the small sample size. Post-colonoscopy colorectal cancers in our study were almost evenly distributed in the colorectum, with slightly increased rates in the right colon and the sigmoid colon. It is advisable that endoscopists pay very close attention to key colonoscopic landmarks and adequate mucosal visualization especially around the folds and in the diverticular segment.

**Ethics Committee Approval:** This study followed the guidance from the Declaration of Helsinki and approved by Southend University Hospital National Health Service Trust; Approval number: 18040.

**Informed Consent:** Informed consent is not necessary due to retrospective nature of this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – E.L., A.A.A., T.K.C.P., H.H.; Design – E.L., A.A.A., T.K.C.P., H.H.; Supervision – A.A.A., E.L.; Resource – E.L., A.A.A., T.K.C.P., H.H.; Materials – E.L., A.A.A., T.K.C.P., H.H.; Data Collection and/or Processing – E.D., A.A.A., T.K.C.P., H.H.; Analysis and/or Interpretation – E.L., A.A.A., T.K.C.P., H.H.; Literature Search – E.L., A.A.A., T.K.C.P., H.H.; Writing - E.L., A.A.A., T.K.C.P., H.H.; Critical Reviews – E.L., A.A.A., T.K.C.P., H.H.

**Acknowledgments:** This work was presented at the Association of Surgeons in Great Britain and Ireland (ASGBI) international conference in 2019 and at the Association of Surgeons in Training (ASiT) in 2019, and the study was awarded with the Dukes Prize for the best abstract.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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