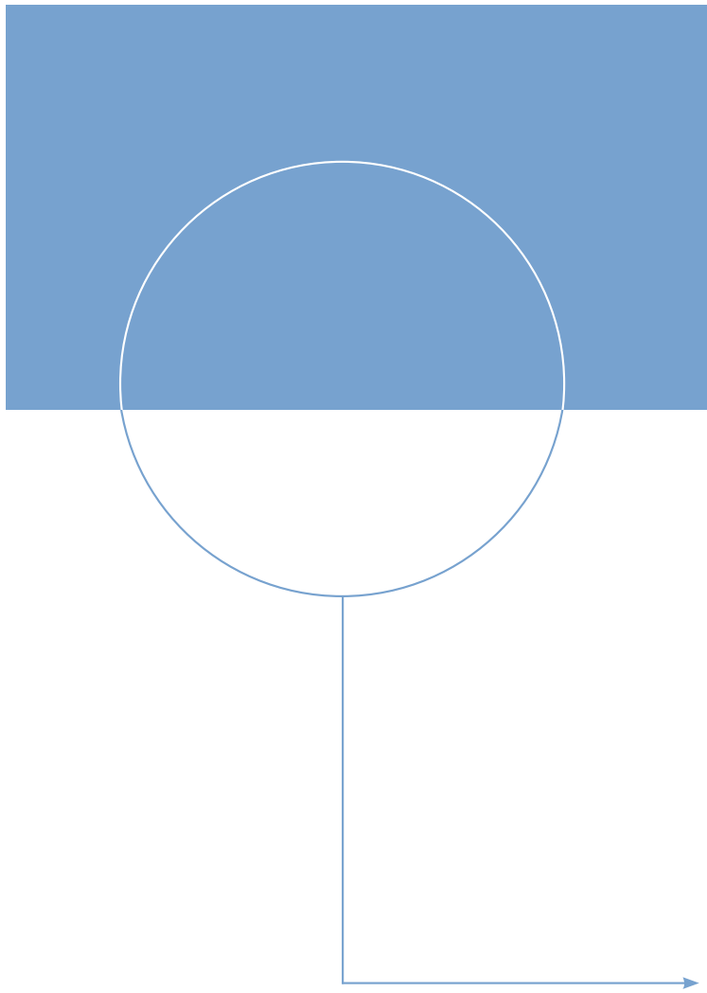

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Post-Colonoscopy Colorectal Cancer - How is the Quality of Colonoscopy at St. Olavs hospital, Trondheim University Hospital?

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Medicine

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Preface

This thesis was written as a part of the 6-year medical study at the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology. The work started back in the autumn of 2018, when two medical students took their first steps into the world of research, with the aim of investigating the quality of colonoscopies at St. Olavs hospital, Trondheim University Hospital. With great help from our supervisors at the Department of Gastroenterology and Hepatology, Tom Christian Martinsen and Gunnar Qvigstad, as well as Tore Stornes and Lars Cato Rekstad at the Department of Gastrointestinal Surgery, the study method was developed, and the project was planned.

The journey of finding, registering and analyzing data, as well as writing this thesis, has taught us a lot about scientific research, gastroenterology and gastrointestinal surgery. Furthermore, after reading countless medical records and colonoscopy reports, it has given us a unique insight into the work as a doctor. This project, which has resulted in our first scientific paper, has therefore given us valuable competence at various areas of the work as a clinician, which we greatly appreciate.

We would like to express our gratitude to our supervisors for their excellent guidance, engagement and support during the work of this project. We are grateful to have been given the opportunity to learn about scientific research, gastroenterology and gastrointestinal surgery from a group with so much expertise. They have inspired us to develop our scientific, problem-oriented mindset, as well as inspired us to further research in the future.

Dennis Ross and Ingeborg Aune Jørgensen
Trondheim, August 2020

Abstract

Background and aims

Colonoscopy is considered the gold standard in diagnosing colorectal cancer (CRC). However, lesions can be missed and give rise to post-colonoscopy colorectal cancers (PCCRCs), which in recent years have been increasingly recognized as an important measure of colonoscopy quality. The aim of this study was to investigate the quality of colonoscopies performed at St. Olavs hospital, Trondheim University Hospital, by calculating the proportion of PCCRC cases, and examine associated characteristics of these patients, colonoscopies and tumors.

Methods

We conducted a retrospective quality assessment of 17 670 colonoscopies performed over the period of 2010 to 2014 at St. Olavs hospital, Trondheim University Hospital, and registered the proportion of PCCRCs developed within 5 years after an index colonoscopy without detected tumors. Only PCCRCs with histologically verified adenocarcinoma were included. Furthermore, we calculated the proportion of CRCs diagnosed in 2013 and 2014 that were PCCRCs developed within 3 years after an index colonoscopy. To characterize the PCCRC patients, we registered data regarding the patients, index colonoscopies and tumors.

Results

In a total of 17 670 colonoscopies, 74 (0.42%) PCCRC cases were identified. Adenoma detection rate (ADR) was 39.2% at the index colonoscopies prior to the PCCRCs. Forty-seven (63.5%) PCCRCs were proximal cancers (right or transverse colon). Concerning staging, 42 (56.8%) cancers were localized (stage I or II). Among the PCCRCs, 48 (64.9%) occurred in women and 26 (35.1%) in men. Furthermore, 24.3% had a first degree relative with CRC and 8.1% had a previous history of inflammatory bowel disease (IBD). Patients in an endoscopic follow-up program at the time of cancer diagnosis had a significantly lower mean age at cancer diagnosis (71.4 vs 76.1 years, $p = 0.022$) and the mean tumor size was smaller (24.2 vs 42.0 mm, $p < 0.001$) compared to those who were not. In 2013 and 2014, approximately 4% of diagnosed CRCs were PCCRCs occurred within 3 years after an index colonoscopy.

Conclusions

This study provides an important measure of colonoscopy quality, that is, cancer after a colonoscopy in which no cancer was found. Our findings are representative for the total quality of all colonoscopies performed at St. Olavs hospital, Trondheim University Hospital, over the period of 2010 to 2014. Proximal location, early stage, female gender, IBD and a family history of CRC are all factors that seem to be associated with PCCRC. These characteristics may help endoscopists to identify patients with increased risk of missed lesions. Thorough examination of the proximal colon and a proper anamnesis regarding family history may be of special importance.

Abbreviations used in this paper: PCCRC, post-colonoscopy colorectal cancer; CRC, colorectal cancer; ADR, adenoma detection rate; CIR, cecal intubation rate; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; HNPCC, hereditary nonpolyposis colorectal cancer; FAP, familial adenomatous polyposis; CEA, carcinoembryonic antigen.

Background and aims

Colorectal cancer (CRC) is the second most common malignancy in Norway, both in men and women, after prostate- and breast cancer, respectively [1]. In 2018, 4428 new cases of CRC were registered in Norway, of these, 3068 colon cancers and 1360 rectal- and rectosigmoid cancers [1]. Colonoscopy is considered the gold standard in diagnosing CRC and gives the opportunity to obtain biopsies and provide treatment of precancerous lesions [2]. However, lesions may be missed during colonoscopy, and thus give rise to post-colonoscopy colorectal cancers (PCCRCs) [3].

The etiology of PCCRCs comprises three main categories: missed lesions, incomplete polypectomies and new cancers [3]. Missed lesions constitute about two thirds of all cases [4] and can arise due to inadequate examination (poor bowel preparation or incomplete colonoscopy) or failure to recognize precancerous or cancerous lesions. Older age, comorbidities and diverticulosis are associated with suboptimal bowel preparation and higher risk of incomplete colonoscopy, thereby increasing the risk of missed lesions [4]. The remaining third develop either as cancers occurring after incomplete polypectomies or as new cancers [4].

The quality of colonoscopy depends on the skills of the endoscopist, which can be measured as adenoma detection rate (ADR) or polyp detection rate (PDR), cecal intubation rate (CIR) and withdrawal time. In addition, patient related factors like bowel preparation, pain during examination and comorbidity may affect the accuracy of this procedure [5, 6]. ADR is a

frequently used measure of colonoscopy quality, and European guidelines recommend an ADR ≥ 25% [6]. In the forthcoming Norwegian screening program an ADR of minimum 20% is mandatory [7]. Likewise, a CIR >90% is considered a minimum rate, with a target rate >95% [6, 8]. In recent years, the PCCRCs have been increasingly recognized as an important measure of colonoscopy quality [3].

The present study was conducted at St. Olavs hospital, Trondheim University Hospital, which, in terms of number of procedures, is the largest colonoscopy center in Norway [5] with 17 670 examinations performed on 14 381 adult patients between January 1, 2010 and December 31, 2014. CRC screening is not yet a public health service in Norway [9], so all patients were examined due to symptoms, signs or findings from other examinations or as part of surveillance.

The aim of this study was to investigate the quality of colonoscopies performed between 2010 and 2014 at St. Olavs hospital, Trondheim University Hospital. We aimed to identify the proportion of PCCRC cases and, in addition, examine associated characteristics of these patients, colonoscopies and tumors.

Materials and methods

We used the electronic database at St. Olavs hospital, Trondheim University Hospital, to identify all patients who had been in contact with the hospital in the period between January 1, 2010 and December 31, 2019 with the ICD-10 codes C18-C20 (colorectal cancer). This yielded a total number of 4120 patients. From these, we manually identified those who fulfilled the following 5 criteria for being defined as a PCCRC case in this study:

1. Index colonoscopy performed between January 1, 2010 and December 31, 2014 (the "5-year colonoscopy period") at St. Olavs hospital, Trondheim University Hospital, Department of Gastroenterology.
2. Histologically verified CRC (colorectal adenocarcinoma) diagnosed between January 1, 2010 and December 31, 2019 (the "10-year CRC period").
3. CRC developed in an endoscopically visualized area at index colonoscopy.
4. CRC developed in a colorectal segment without precancerous or cancerous lesions at the index colonoscopy.
5. ≤60 months between index colonoscopy and histologically verified CRC.

Patients with non-adenocarcinoma, tumors without mucosal affection and tumors of the appendix were excluded. Also, CRC patients with unsuccessful polypectomy at index colonoscopy, which later developed to PCCRC, and those with CRC developed in non-visualized bowel segments at index colonoscopy, were excluded.

- ➔ Example 1: Index colonoscopy performed in 2014. CRC diagnosed in 2016. Cancer defined as a PCCRC due to index colonoscopy within the 5-year colonoscopy period, cancer within the 10-year cancer period and ≤60 months between index colonoscopy and CRC.
- ➔ Example 2: Index colonoscopy performed in 2015. CRC diagnosed in 2016. Cancer not defined as a PCCRC due to no index colonoscopy performed within 5-year colonoscopy period.
- ➔ Example 3: Index colonoscopy performed in 2009. CRC diagnosed in 2010. Cancer not defined as a PCCRC due to no index colonoscopy performed within the 5-year colonoscopy period.
- ➔ Example 4: Index colonoscopy performed in 2011. CRC diagnosed in 2019. Cancer not defined as a PCCRC due to >60 months between index colonoscopy and CRC.
- ➔ Example 5: Index colonoscopy performed in 2012. CRC diagnosed in 2014. Cancer defined as a PCCRC due to index colonoscopy within the 5-year colonoscopy period, cancer within the 10-year cancer period and ≤60 months between index colonoscopy and CRC.

Figure 1. Timeline showing the defined colonoscopy- and CRC periods, as well as examples of included and excluded patients assuming that criteria 3 and 4 are fulfilled. Red = 10-year cancer period (CRC diagnosed). Green = 5-year colonoscopy period (index colonoscopy performed).

In this study, there were three outcomes. Firstly, of 17 670 colonoscopies performed at St. Olavs hospital, Trondheim University Hospital, between 2010 and 2014, we wanted to examine how many PCCRCs developed within five years after an index colonoscopy. Secondly, we aimed to calculate the proportion of CRCs diagnosed in 2013 and 2014 that were PCCRCs developed within 3 years after an index colonoscopy. Other years could not be assessed due to the possibility of an index colonoscopy performed within 3 years, but outside the 5-year colonoscopy period. Finally, we wanted to examine the characteristics of patients, index colonoscopies and tumors in the PCCRC cases.

Of special note, the term “index colonoscopy” in this paper refers to colonoscopies performed between 2010 and 2014 on patients who later developed PCCRC, and all subsequent colonoscopy data are related to these.

Table 1. In every PCCRC case, the following data was registered.

Index colonoscopy	Referent and date of referral. Date of index colonoscopy. Indication for colonoscopy (surveillance[a], symptoms, findings from other examinations[b]). Quality of bowel preparation. Polyps. Adenomas, and if they were advanced[c]. Cecum reached, and reason if not reached[d]. Inflammation/active IBD. Biopsy taken.
Pathology	Cancer date. Cancer localization. ICD-10 code. Dukes' stadium. TNM stadium. Tumor size. Differential grade. Mucinous or Signet ring-cell carcinoma. Distant metastases. Synchronous tumors.
Treatment	Operation. Operation date. Type of procedure. R-stage. Lymphatic or vascular infiltration.
Risk factors	First degree relative with CRC. HNPCC. FAP. IBD. PSC. Previous cancer, both CRC specifically and other cancers.
Others	Gender. Date of birth. Date of death. Cancer-specific death. Patient compliance[e]. How the cancer diagnosis was made. If the patient was in an endoscopic follow-up program at the time of diagnosis, and if it was adhered to.

[a] **Surveillance:** Due to earlier detected polyps, cancer, IBD, HNPCC, FAP or in relation to other medical workup.
[b] **Findings from other examinations:** Anemia, occult fecal blood, CT findings or increased CEA.
[c] **Advanced adenoma:** Adenoma ≥10 mm, high-grade dysplasia, tubulovillous or villous growth pattern or ≥3 adenomas.
[d] **Cecum reached:** If previous right-sided hemicolectomy, a full colonic examination was registered as cecum reached.
[e] **Patient compliance:** Number of times where the patients have not met to colonoscopy after the index colonoscopy.

To characterize the PCCRC patients, we registered different variables, listed in Table 1. Of special note, cancers were assigned as being right-sided when located in cecum, ascending colon or hepatic flexure, while proximal cancers also included the transverse colon. For patients who had more than 1 colonoscopy performed within the 5-year colonoscopy period, data from the most recent examination were used for further analysis.

Patients who developed synchronous PCCRCs were registered, and the tumor with the largest size was used for further analysis. PCCRCs that occurred in polyps were also registered, and the endoscopically measured polyp size was used as the tumor size. In patients with rectal cancer who received neoadjuvant treatment, the tumor staging was registered using radiological measurements obtained before initiation of therapy.

All statistical analysis was performed using the statistical software IBM SPSS 26.0. Differences in the numerical variables were examined through the independent-samples t test. The Chi-squared test was used for comparing categorical variables. For test significance, p values <0.05 were considered significant.

This study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (reference number 2019/831) and the Faculty of Medicine and Health Sciences at the Norwegian University of Science and Technology.

Results

In a total of 17 670 colonoscopies, 74 (0.42%) PCCRC cases were identified. Fifty-three (71.6%) cases were diagnosed within 4 years, while 34 (45.9%) were diagnosed within 3 years. One patient developed 2 PCCRCs within the study period and was included twice. Based on the number of individuals examined between 2010 and 2014, the PCCRC rate was 0.51% (73 of 14 381). Descriptive statistics regarding patient characteristics are presented in Table 2.

In 2013 and 2014 a total of 219 and 218 new cases of CRC were registered at St. Olavs hospital, Trondheim University Hospital, respectively [10]. In the same years we found that 8 and 9 PCCRC cases occurred within 3 years after an index colonoscopy, giving a PCCRC rate of 3.7% in 2013 and 4.1% in 2014.

Indications for index colonoscopy were surveillance in 44 cases (59.5%) and new symptoms and/or findings from other examinations in 39 cases (52.7%). ADR was 39.2% at the index colonoscopy and no statistically significant difference between males and females was observed (50.0% vs 33.3%, $p = 0.161$). Furthermore, there was no difference in ADR between patients with adequate bowel preparation and those without bowel preparation description (41.5% vs 37.5%, $p = 0.731$). Advanced adenomas were detected in 23.0%. Further details are given in Table 3.

Among the PCCRC cases, 48 (64.9%) occurred in women. Forty-seven (63.5%) PCCRCs were proximal cancers located in the right or transverse colon. Concerning staging, 42 (56.8%) cancers were localized (stage I or II). See Table 4 for further tumor characteristics.

Thirty-six (48.6%) PCCRCs were diagnosed in patients being in an endoscopic follow-up program at the time of cancer diagnosis (see Table 2), with a significantly lower mean age at cancer diagnosis (71.4 vs 76.1 years, $p = 0.022$) and smaller tumor size (24.2 vs 42.0 mm, $p < 0.001$) compared to those who were not in a surveillance program. Also, there was a significant difference in number of deaths (all causes) in the two groups, being higher in the group without an endoscopic follow-up program (16 vs 6, $p = 0.017$). Comparative statistics regarding these patient groups are given in Table 5.

Six patients had IBD – 5 with ulcerative colitis (of which 1 had PSC), and 1 with Crohn´s disease. All patients with IBD had right-sided PCCRC. The patients with ulcerative colitis had all a history of extensive or pancolitis, while the patient with Crohn´s disease had no history of colorectal disease. Regarding the patients with ulcerative colitis (see Table 6), the mean time from IBD diagnosis to PCCRC was 20.6 years (ranging from 11.8 to 25.9 years), and the mean time from index colonoscopy to PCCRC was 2.9 years. The mean age at PCCRC diagnosis was

62.8 years in patients with ulcerative colitis compared to 73.8 years in the total group. Only 2 of the 5 patients with ulcerative colitis developing PCCRC were endoscopically followed according to current ECCO guidelines [11].

Table 2. Patient characteristics in PCCRC cases.

Characteristics	PCCRC cases (n=74)
No. of patients	73
Age at index colonoscopy, *y*, mean ± SD	71.0 ± 8.6
Age at PCCRC diagnosis, *y*, mean ± SD	
All patients	73.8 ± 8.8
Male	75.0 ± 11.3
Female	73.2 ± 7.1
Time from index colonoscopy to PCCRC, *y*, mean ± SD	2.9 ± 1.4
No. of PCCRCs diagnosed within, n (%)	
1 year	12 (16.2)
2 years	19 (25.7)
3 years	34 (45.9)
4 years	53 (71.6)
5 years	74 (100)
Gender, n (%)	
Male	26 (35.1)
Female	48 (64.9)
Risk factors, n (%)	
Previous colorectal cancer	21 (28.4)
First degree relative with CRC	18 (24.3)
Inflammatory bowel disease	6 (8.1)
Hereditary non-polyposis colorectal cancer	1 (1.4)
Patient in a follow-up program at the time of cancer diagnosis, n (%)	36 (48.6)
Program followed as planned, n (%)	26 (35.1)
Reason for being in a follow-up program, n (%)	
Polyp	27 (36.5)
Post-operative CRC surveillance	5 (6.8)
High risk [a]	4 (5.4)

[a] Patients with IBD, PSC or HNPCC.

Table 3. Characteristics of index colonoscopies prior to PCCRC.

Characteristics	Index colonoscopies (n=74)
Indication for index colonoscopy, n (%)	
Surveillance	44 (59.5)
Symptoms and/or findings from other examinations	39 (52.7)
Bowel preparation, n (%)	
Adequate	41 (55.4)
Inadequate	1 (1.4)
Not described	32 (43.2)
Cecum intubated, n (%)	
Yes	72 (97.3)
Index colonoscopy findings, n (%)	
Adenoma	29 (39.2)
Advanced adenoma[a]	17 (23.0)

[a] Adenoma ≥10 mm, high-grade dysplasia, tubulovillous or villous growth pattern or ≥3 adenomas.

Table 4. Tumor characteristics in PCCRC cases.

Characteristics	PCCRC cases (n=74)
Tumor size, *mm*, mean ± SD (range)[a]	33.4 ± 20.1 (10-100)
Tumor location, n (%)	
Right colon[b]	34 (45.9)
Transverse colon	13 (17.6)
Left colon[c]	22 (29.7)
Rectum	5 (6.8)
Stage, n (%)	
Localized (stage I or II)	42 (56.8)
Regional (stage III)	21 (28.4)
Metastatic (stage IV)	11 (14.9)
Tumor differential grade, n (%)	
Well differentiated	4 (5.4)
Moderately differentiated	43 (58.1)
Poorly differentiated	15 (20.3)
Undifferentiated	1 (1.4)
Unknown	11 (14.9)
Cancer located in polyp, n (%)	10 (13.5)
Synchronous tumors, n (%)	3 (4.1)

[a] One tumor size unknown, n=73.
[b] Cecum, ascending colon or hepatic flexure.
[c] Splenic flexure, descending or sigmoid colon.

Table 5. Comparison between PCCRC cases diagnosed within and without a follow-up program.

Characteristics	Within a follow-up program (n=36)	Without a follow-up program (n=38)
Age at index colonoscopy, *y*, mean ± SD*	68.9 ± 7.4	72.9 ± 9.3
Age at PCCRC diagnosis, *y*, mean ± SD*	71.4 ±7.8	76.0 ±9.2
Time from index colonoscopy to PCCRC, *y*, mean ± SD	2.6 ±1.6	3.1 ±1.2
Tumor size, *mm*, mean ± SD (range)*	24.2 ±13.3 (10-55)	41.2 ±21.7 (10-100)
Dead, n (%)*	6 (16.7)	16 (42.1)

* Statistically significant difference between the two groups ($p < 0.05$).

Table 6. Characteristic of patients with ulcerative colitis (all had a history of extensive or pancolitis).

Characteristics	Patients with ulcerative colitis (n=5)
Age at index colonoscopy, *y*, mean ± SD	60.0 ±15.2
Age at PCCRC diagnosis, *y*, mean ± SD (range)	62.8 ±15.6 (39-81)
Time from index colonoscopy to PCCRC, *y*, mean ± SD	2.9 ±1.4
Time from IBD diagnosis to PCCRC, *y*, mean ± SD	20.6 ±5.6

Discussion

In this quality assessment of 17 670 colonoscopies performed over the period of 2010-2014, 74 PCCRC cases developed within 5 years, giving a PCCRC rate of 0.42%. Of these, 47 cancers (63.5%) were proximally located, indicating that these parts of the colon are more difficult to examine accurately. In 2013 and 2014, approximately 4% of diagnosed CRCs were PCCRCs occurred within 3 years after an index colonoscopy.

Previous studies have reported diverging results regarding the proportion of PCCRCs in relation to colonoscopies, partly due to differences in population and methodology. Richter et al [12] showed that 0.09% of colonoscopies resulted in a PCCRC within 5 years. Although our result (0.42%) may seem high compared to this, the colonoscopies in our study were performed solely in patients with symptoms or risk factors, while the study by Richter, after excluding high-risk patients with IBD and HNPCC, was conducted in a population with a colonoscopy screening program, and thus had a higher proportion of low-risk individuals. By comparison, a Swedish study [13], also after excluding high-risk patients, found that 0.44% of colonoscopies resulted in a PCCRC within 3 years. In our study, all patients who underwent colonoscopy, regardless of previous CRC or high-risk groups like IBD and HNPCC, were included, making our result representative for the total quality of all colonoscopies performed at St. Olavs hospital.

We found that 3.7% and 4.1% of CRCs diagnosed at St. Olavs hospital in 2013 and 2014, respectively, were PCCRCs occurred within 3 years after an index colonoscopy. These findings agree with a systematic review and meta-analysis performed by Singh et al [4], showing that approximately 3.7% (ranging from 1.8-9.0%) of patients with CRC have performed a prior colonoscopy within 6-36 months in which CRC was not diagnosed. Considering the fact that cancers arisen within 3-4 years after colonoscopy most likely are not new cancers [3], our findings represent the proportion of missed CRCs diagnosed within three years after an index colonoscopy in which the endoscopist has visualized the mucosa and classified it as tumor free.

Using the frequently applied surrogate markers for colonoscopy quality, the index colonoscopies performed in our study were acceptable, with an ADR of 39.2%, a CIR of 97.3% and only one case of inadequate bowel preparation. However, it is worth noting that, due to our study design, we were only able to evaluate the quality of colonoscopies where the mucosa in which the cancer arose, was inspected. Cases where a cancer occurred in a non-inspected colorectal area, due to an incomplete index colonoscopy (poor bowel preparation or incomplete examination), were excluded. Hence, the calculated CIR and degree of bowel preparation are

biased, being too high. Regardless of this, although several colonoscopy reports (43.2%) lacked description of bowel preparation (Table 3), the overall quality seems good. However, the patients still developed PCCRC, emphasizing the importance of PCCRC as a clinical endpoint when evaluating colonoscopy quality.

Our findings in regard to cancer location agree with previous research showing that PCCRCs more often than other CRCs are located in the proximal colon [4, 12, 14-18]. There are most likely several reasons for this [19]. Firstly, an adequate bowel preparation is more difficult to achieve in the proximal colon, making it easier to miss small lesions. However, in this study, only one index colonoscopy was reported as inadequate. Secondly, it may be difficult to both reach and identify landmarks at the proximal colon with the endoscope. Due to our study design, however, all PCCRCs arose in a segment that was visualized at an index colonoscopy, making this a less likely explanation as well. Finally, tumors of the proximal colon more often arise from flat lesions [20], making them more difficult to detect during colonoscopy. Of special note, we found a surprisingly high proportion of cancer located in the transverse colon (17,6%) compared to the normal distribution of CRCs [21-23], suggesting that complete and accurate examination of this segment may be especially difficult.

Of all PCCRC cases, 24.3% had a first degree relative with CRC. This is a high proportion, both compared to patients with detected CRCs as well as patients without CRC [14]. Other studies [4, 14] have found similar results, indicating that patients with PCCRC are more likely to have a family history of CRC. This suggests that hereditary factors may be a part of the tumorigenesis in a subset of PCCRCs, emphasizing the importance of obtaining a proper anamnesis regarding family history to identify patients with increased risk of developing PCCRC.

We found a large proportion of women (48 of 74) among our PCCRC cases. Although women accounted for 54.8% of the 17 760 colonoscopies performed, the proportion of women who developed PCCRC was still higher than expected. Some studies [15, 18] suggest that women are more prone to develop PCCRCs, but a meta-analysis [4] found no association between gender and PCCRC. Data from Gastronet [8], the Norwegian quality registry of gastrointestinal endoscopy, showed that women are more prone to experience pain during examination. This may compromise the accuracy of the endoscopist while performing the colonoscopy, wanting to complete the procedure as soon as possible, with a shorter withdrawal time. In turn this gives a shorter bowel inspection time, increasing the risk of missing cancer or precancerous lesions. In our study, no registration of withdrawal time was done, meaning that

the actual inspection time of the colon and rectum was unknown, allowing a possibility for shorter examinations in individuals difficult to examine and with pain.

Among the identified PCCRC cases, a high proportion (8.1%) had IBD. In a nationwide population-based study, Erichsen et al [15] found that 6.5% of patients with PCCRC after index colonoscopies performed 1-5 years before diagnosis had IBD. In the same study, of nearly 36 000 patients with no colonoscopy before CRC diagnosis, only 0.5% had IBD. Morris et al [19] suggests that patients with IBD may have an increased risk for PCCRC due to malignancy being more difficult to detect in an inflammatory colon and because the cancer may have a different underlying morphology. Furthermore, they suggest that IBD-related cancer may be more aggressive with a quicker development.

The strengths of our study include the fact that it was performed at the largest colonoscopy lab in Norway [5], with a high number of performed colonoscopies having the possibility of giving rise to PCCRCs. Also, previous studies and reports have used surrogate markers to describe the quality of colonoscopy [5, 6, 24, 25], but our study provides one of the most important clinical endpoints, that is, cancer after a colonoscopy in which no tumor was found [3, 5]. Unlike other studies based on large databases [4, 17], data on patient level were manually obtained from each patient's medical record, which provided the opportunity to characterize the patients in great detail.

The present study design implies that the PCCRC cases would result either from missed lesions or new cancers, arising in endoscopically visualized colorectal mucosa. Other studies [3] have included a broader spectrum of cancers as part of the PCCRC term, for instance cancers arisen after incomplete resections of identified lesions or detected, but not resected, lesions. In our study these cancers were excluded because the primary goal was to detect the number of endoscopically missed lesions. Cancers arising from incomplete polypectomies or non-resected lesions are not endoscopically missed, but rather managed improperly.

On the other hand, there are some limitations to the methodology. Those who performed an index colonoscopy at St. Olavs hospital, but later moved outside the region and developed PCCRC, or those who died within the 5-year follow-up period, were lost. Furthermore, we have used quite strict time criteria, which may give an incorrect time between index colonoscopy and CRC. For instance, a patient with tumor free colonoscopies performed in both 2014 and 2016 who developed PCCRC in 2018 was registered with 4 years from index colonoscopy to PCCRC. The mean time from index colonoscopy to PCCRC in our study (2.9 years) may therefore be falsely too long.

Our study has other limitations as well. Firstly, due to its retrospective nature, the results fully rely on documentation in the patients' medical records, with possibilities that our data contain errors. Secondly, we performed a single center study with a relatively low number of CRC cases and therefore also a low number of PCCRC cases. Hence, the results may be inaccurate. Thirdly, the data were manually obtained, allowing the possibility for personal errors. Even though the data was cross-checked several times, we acknowledge that this does not replace automatic processes based on registers and databases. Finally, due to our study design and lack of a screening program at the time of the colonoscopies, our results may not be comparable to other PCCRC studies nor generalizable to populations where colonoscopy screening of asymptomatic average-risk individuals is more widely employed.

In conclusion, we found that 0.42% of all colonoscopies resulted in a PCCRC within 5 years. Approximately 4% of CRCs diagnosed in 2013 and 2014 at St. Olavs hospital had an index colonoscopy performed within 3 years before the diagnosis. Proximal location, early stage, female gender, IBD and a family history of CRC are all factors that seem to be associated with PCCRC. Of special note, compared to the normal distribution of CRC, many PCCRCs occurred in the transverse colon, suggesting that this segment may require especially thorough examination.

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