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【 ORIGINAL ARTICLE 】

The Relationship between Post-colonoscopy Colorectal Cancer and Quality Indicators of Colonoscopy: The Latest Single-center Cohort Study with a Review of the Literature

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Abstract:

Objective This study aims to elucidate the association between the clinical characteristics of post-colonoscopy colorectal cancer (PCCRC) and quality indicators (QIs) of colonoscopy.

Methods Patients with PCCRC who underwent total colonoscopy (TCS) and were histologically diagnosed with adenocarcinoma within six months to five years of the last examination were included in this study. PCCRC and normally detected cancer (NDC) identified within the same period were compared in terms of their clinicopathological characteristics. Furthermore, the QIs at PCCRC detection were compared to those at the last examination.

Results Patients with PCCRC had a significantly higher rate of colon surgery history than those with NDC (PCCRC: 25/76, 32.9%; NDC: 31/1,437, 2.2%; p<0.001), but the invasion depth in these patients was significantly shallower (PCCRC: ≤Tis/≥T1, 37/39; NDC: ≤Tis/≥T1, 416/1,021; p<0.001). Among patients with PCCRC, the T1b group had significantly more non-polypoid growth (NPG)-type cases than PG-type CRC cases (p=0.018). The adenoma detection rate (ADR) of colonoscopists performing TCS was 30.2-52.8%. Furthermore, the ADR of colonoscopists at the time of PCCRC detection (36.7%±5.9%) was significantly higher than that of colonoscopists who performed the last examination (34.9%±4.4%; p=0.034). The withdrawal time for negative colonoscopy (WT-NC) at detection was significantly longer than that at the last examination (at detection: 494.3±253.8 s; at last examination: 579.5±243.6 s; p=0.010).

Conclusion Given that these PCCRC cases were post-colon surgery cases, had a long WT-NC, and were detected by colonoscopists with a high ADR, most cases showed lesions that were missed during the previous colonoscopy. Caution should be practiced in order to avoid missing flat, NPG-type tumors.

Key words: post-colonoscopy colorectal cancer, interval cancer, quality indicator, polypoid growth, adenoma detection rate

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Introduction

The morbidity and mortality of colorectal cancer (CRC) has been increasing (1). Regular screening using colonoscopy is considered important (2, 3). In addition, there is much debate concerning interval cancers, i.e. those diagnosed between examination (4-6). The Colorectal Cancer Screening Committee of the World Endoscopy Organization has defined interval CRC as that diagnosed after a screening or surveillance examination in which no cancer was detected but before the date of the next recommended examina-

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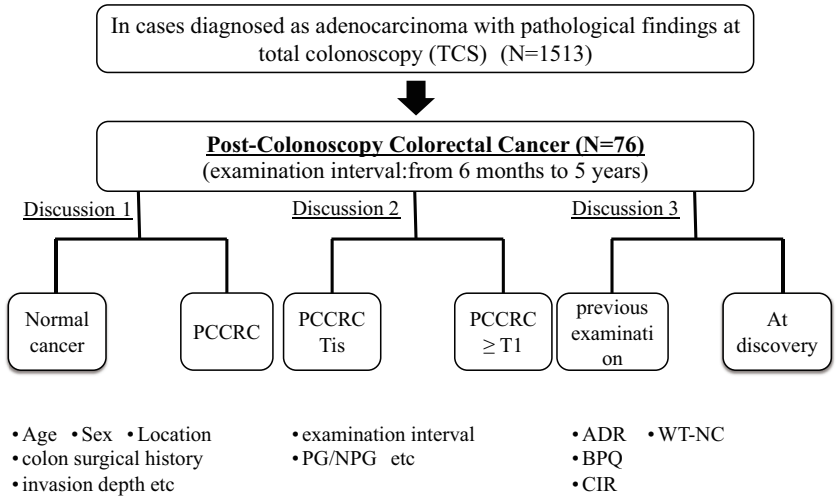

Figure 1. **Flow diagram for the study.**

tion (7).

The new term post-colonoscopy CRC (PCCRC), which specifically refers to CRC detected after a negative colonoscopy, was recently coined. This term seems more appropriate than "interval cancer" and can be applied to all surveillance colonoscopies in addition to screening and surveillance lesions (8). Sanduleanu et al. defined PCCRC as CRC diagnosed within five years after an index colonoscopy. The period between the last examination and the PCCRC diagnosis varies among previous reports, ranging from within 3 years to within 10 years (3, 5, 7, 8).

Eradication of PCCRC is an important goal that would lead to decreased CRC-associated mortality. The main issues that need to be clarified include the lack of standardization in testing intervals and test accuracy and inconsistency in the evaluated speed of tumor growth.

In the present study, we explored the associations between the clinical characteristics of PCCRC and quality indicators (QIs).

Materials and Methods

This study included patients with PCCRC, i.e., those who underwent total colonoscopy (TCS) between October 2008 and August 2017 at our hospital and were histologically diagnosed with adenocarcinoma within six months to five years of the last examination. Three cases of familial polyposis- and hereditary nonpolyposis-type CRC were excluded. Patients in whom colonoscopy could not be completed due to advanced stenotic CRC at the last colonoscopy and those in whom PCCRC was detected from the deep colon that could not be observed postoperatively were also excluded (Fig. 1).

CRC cases were divided into two groups based on the depth of invasion: group A, Tis stage or shallower (≤M); and group B, T1 stage or deeper (≥SM).

The following lesion parameters were compared between the groups: patient age and sex, location of the tumor (right colon: cecum, ascending colon, and transverse colon; left colon: descending and sigmoid colon and rectum), invasion depth, macroscopic morphology, history of colon surgery, number of polyps at the last examination, examination interval, and adenoma detection rate (ADR) of the colonoscopist.

The submucosal invasion depth was measured using a microscope with an ocular lens scale. In specimens where the muscularis mucosa was incompletely disrupted by ulceration or tumor invasion, the muscularis mucosa level was estimated by drawing a line connecting the remaining parts of the muscularis. When the muscularis mucosa was completely disrupted due to tumor invasion, we measured the distance from the tumor surface to the invasive front (9, 10). The growth type of colorectal carcinoma was histologically divided into two types: polypoid growth (PG)-type tumors originating from the intramucosal proliferation of adenoma or carcinoma, and non-polypoid growth (NPG)-type tumors without intramucosal protuberant growth (11).

The parameters for the QI evaluation included the ADR, cecal intubation rate (CIR), bowel preparation quality (BPQ), and withdrawal time in negative colonoscopy (WT-NC). In our hospital, the endoscopy nurse recorded the times for insertion into the cecum and withdrawal. In this study, we calculated the ADR as follows: the number of colonoscopies at which one or more histologically confirmed adenomas were found divided by the total number of colonoscopies performed in the same time period. We evaluated the ADR of the 26 endoscopists in our hospital. As criteria, endoscopists who had performed at least 200 colonoscopies were selected for inclusion. Furthermore, those who performed colonoscopies had to have completed at least 100 total colonoscopic examinations during the study period. WT-NC in this investigation did not include the time taken for procedures such as staining, biopsies, or polyp resection. The Boston Bowel Preparation Scale (BBPS) was used because it is extremely effective for assessing the BPQ. The total BBPS score corresponds to the sum of the segment scores for the right, transverse, and left colons, each as-

Table 1. Clinical Characteristics of Patients and Lesions.

n	1,513
Mean age	70.94±10.45
Sex (M/F)	979/534 (64.7%/35.3%)
Tumor location (C/A/T/D/S/R)	100/236/153/61/534/429 (6.7%/15.6%/10.1%/4.0%/35.3%/28.4%)
Surgical history of colon surgery (Yes/No)	56/1,457 (3.7%/96.3%)
Depth of invasion (M/SM slight/SM massive/Deeper than MP)	453/59/156/845 (29.9%/3.9%/10.3%/55.9%)
Normal cancer/PCCRC	1,437/76 (95.0%/5.0%)

Depth of invasion: M, mucosal cancer; SM slight, tumor infiltration into the submucosal layer <1,000 μm from the muscularis mucosae; SM massive, tumor infiltration into the submucosal layer >1,000 μm from the muscularis mucosae; MP, muscularis propria.
PCCRC: post-colonoscopy colorectal cancer

Table 2. Comparison between Post-colonoscopy colorectal Cancers and Normal Cancers.

	PCCRC	Normal cancer	p value
n	76	1,437	
Mean age	73.21±7.92	70.82±10.56	0.014
Sex (M/F)	55/21 (72.4%/27.6%)	924/513 (64.3%/35.7%)	0.151
Tumor location (L/R)	47/29 (61.8%/38.2%)	977/460 (68.0%/32.0%)	0.264
Surgical history of colon surgery (Yes/No)	25/51 (32.9%/67.1%)	31/1,406 (2.2%/97.8%)	<0.001
Depth of invasion (≤Tis/≥T1)	37/39 (48.7%/51.3%)	416/1,021 (28.9%/71.1%)	<0.001
Histological type			
tub1	51 (67.1%)	809 (56.3%)	0.064
tub2	20 (26.3%)	507 (35.3%)	0.110
pap	1 (1.3%)	42 (2.9%)	0.353
por	3 (3.9%)	38 (2.6%)	0.478
sig	0 (0.0%)	3 (0.2%)	0.857
muc	1 (1.3%)	27 (1.9%)	0.585
nec	0 (0.0%)	1 (0.1%)	0.950

Tumor location: L, left colon (descending colon and sigmoid colon, and rectum); R, right colon (cecum, ascending colon, and Transverse colon).
Histological type: tub1, Well differentiated type (Tubular adenocarcinoma); tub2, Moderately differentiated type (Tubular adenocarcinoma); pap, Papillary adenocarcinoma; por, Poorly differentiated adenocarcinoma; sig, Signet ring cell carcinoma; muc, Mucinous adenocarcinoma; nec, Neuroendocrine carcinoma.
PCCRC: post-colonoscopy colorectal cancer

sessed on a scale of 0-3; the total BBPS score can therefore range from 0 to 9 (12).

The SPSS software program (version 24, SPSS, Chicago, USA) was used for the statistical analyses. Quantitative data were compared using the Mann-Whitney U test. For categorical variables, Fisher's exact test or the chi-square test was used. P values of <0.05 were considered statistically significant.

This study was approved by the Independent Ethics Committee of the Tokyo Medical University Hachioji Medical Center.

Results

There were 76 cases of PCCRC (5.02%) among the 1,513 cases of CRC identified using TCS at our hospital (Table 1). The mean age of patients with PCCRC was 73.2±7.9 years old, and 55 were men and 21 women. CRC was located on the right side in 29 patients and on the left side in 47. The mean examination interval was 792.3±454.8 days. Patients with PCCRC had a significantly higher rate of history of colon surgery than those with NDC (PCCRC: 25/76; NDC: 31/1,437; p<0.001), but the invasion depth in patients with PCCRC was significantly shallower (PCCRC: ≤Tis/≥T1=37/39; NDC: ≤Tis/≥T1=416/1,021; p<0.001). Patients with PCCRC were significantly older at the onset than those with NC (PCCRC: 73.21±7.92 years; NDC: 70.82±10.56 years; p =0.014), but there were no significant differences in the CRC location, male/female ratio, or histological type (Table 2).

Among patients with PCCRC, 37 were classified as group A (37/76, 48.7%) and 39 as group B (39/76, 51.3%). There were no significant differences between groups A and B in terms of the age, sex, tumor location, history of colon surgery, examination interval, or number of polyps at the last examination. Group B had a significantly higher rate of NPG-type tumors than group A (group A: PG=25/NPG=12; group B: PG=5/NPG=12; p=0.009; Table 3). In group B, 22 cases with invasion beyond the muscularis propria (MP) were excluded because it was too difficult to determine

Table 3. Comparison between Shallower than Tis and Deeper than T1 in Post-colonoscopy Colorectal Cancers.

	PCCRC (≤Tis)	PCCRC (≥T1)	p value
n	37	39	
Mean age	72.05±6.29	74.31±9.16	0.213
Sex (M/F)	28/9	27/12	0.530
Tumor location (L/R)	24/13	23/16	0.597
History of colon surgery (Yes/No)	10/27	15/24	0.289
Morphology (PG/NPG)	25/12	5/12	0.009
Mean examination interval (day)	810.92±466.17	774.67±449.04	0.731
Polyp number at last colonoscopy	3.00±3.15	2.36±2.37	0.317
ADR	35.71±5.58%	37.71±6.18%	0.142

Tumor location: L, left colon (descending colon and sigmoid colon, and rectum); R, right colon (cecum, ascending colon, and Transverse colon).
Morphology: PG, polypoid growth; NPG, non-polypoid growth.
PCCRC: post-colonoscopy colorectal cancer, ADR: adenoma detection rate

Table 4. Association with Post-colonoscopy Colorectal Cancer and Quality Indicator.

	n	Previous endoscopy	Discovery time endoscopy	p value
ADR	76	34.92±4.35%	36.74±5.94%	0.034
WT-NC	62	494.26±253.80 s	579.48±243.56 s	0.010
BPQ	62	8.39±0.88	8.54±0.87	0.107
CIR	72	90.3%	93.1%	0.483

ADR: adenoma detection rate, WT-NC: average withdrawal time in negative colonoscopy, BPQ: bowel preparation quality, CIR: cecal intubation rate

whether they were PG- or NPG-type.

The ADR of TCS colonoscopists at our hospital at the time of PCCRC detection was 30.2-52.8% (38.6±6.6%), which was significantly higher than the ADR of colonoscopists who performed the last examination (mean ADR of colonoscopists at detection: 36.7±5.9%; mean ADR of colonoscopists at the last examination: 34.9±4.4%; p=0.034). Furthermore, the WT-NC at PCCRC detection (579.48±243.56 s) was significantly longer than that at the last examination (494.26±253.80 s; p=0.010). No significant differences were found in terms of the BPQ or CIR (Table 4).

Discussion

In this study, most PCCRC cases were due to missed lesions, as many lesions were detected subsequent to colon surgery, had a long WT-NC, and were detected by colonoscopists with a high ADR. Many PCCRC lesions had a shallow invasion depth compared to NC, and many SM invasive cancers among PCCRC (invasion beyond the MP were excluded) were of the NPG-type, suggesting that caution is needed in order to avoid missing flat, NPG-type tumors.

To reduce the number of PCCRC cases, the number of missed tumors must be reduced. Improving the quality of colonoscopy is the most important measure for preventing missed tumors, as these represent the most influential factors for PCCRC development. The American Society for Gastrointestinal Endoscopy (ASGE) reported on QIs and defined the key elements of quality assessment of colonoscopy (13). Lee et al. identified technique, patient safety, and patient experience as the three major elements of a colonoscopy quality assessment (14). Of these, technical measures of the colonoscopy quality are closely associated with the prevention of CRC onset and mortality.

The ADR is the most important QI. Kaminski et al. reported that the risk of the onset of interval cancer for a colonoscopist with an ADR of <20% is >10-fold that for a colonoscopist has an ADR of ≥20% (15). Corley et al. reviewed 314,872 colonoscopies performed by 136 colonoscopists with ADRs ranging from 7.4-52.5% and found that the risk of the onset of interval cancer in the high-ADR group was 0.52-fold that in the low-ADR group, and that each additional percentage of ADR increased the CRC onset risk by 3% and decreased the CRC mortality rate by 5% (16). Based on this report, the ADR is considered to be strongly correlated with interval cancer and an important index for preventing CRC onset and mortality. The ASGE has set the minimum ADR for male patients at 30% and for female patients at 20% (mean, 25%) (13, 14). The ADR of the 26 TCS colonoscopists at our hospital was 30.2-52.8% (mean, 38.6±6.6%); therefore, they all met the minimum standards set by the ASGE. However, the ADR of the colonoscopists at the time of PCCRC detection was significantly higher than that of the colonoscopists at the last examination. The

fact that colonoscopists with a high ADR detected more PCCRC cases suggests the importance of reducing the number of small, missed lesions on routine endoscopy.

The mean WT-NC, BPQ, and CIR were also evaluated in this study as QIs. Barclay et al. reported that the ADR was significantly higher in examinations with a mean WT-NC of ≥6 minutes than in those with a mean WT-NC of <6 min (17). Lee et al. reported that extending the withdrawal time up to 10 minutes significantly increased the ADR; however, the ADR did not improve significantly beyond 10 minutes (18). In the present study, the WT-NC at detection was significantly longer than that at the last examination, but the average WT-NC was 6-10 minutes, which is considered an adequate withdrawal time. To increase the ADR, close observation inside the colon is a more important factor than rapid insertion of the endoscope into the cecum. However, extending the withdrawal time is expected to increase patient discomfort, suggesting the importance of completing close observation within an adequate timeframe. Furthermore, BPQ can increase the examination quality, ensuring sufficient bowel preparation. Lai et al. tested the validity of the BBPS as a BPQ assessment scale and found that good insertion was achieved by 22 endoscopists, with a median score of 6 points and an interquartile range of 6-7, while scores of <5 points indicated an inadequately prepared colon (19). The comparison of the BBPS scores in the present study did not reveal a significant difference between PCCRC detection and the last examination (BBPS score at detection: 8.54±0.87; at last examination: 8.39±0.88); in both the cases, BBPS scores of >8 were maintained, showing that the colonoscopies had been performed after adequate preparation. There were also no significant differences in the CIR at detection or the last examination. Although there were no associations with CIR, there are reports of significant correlations between a low CIR and the onset of interval cancer in the right colon (20). The CIR of all colonoscopists in our hospital was over 95%. Although there was no statistical difference in CIR between previous and discovery time colonoscopy, the CIR for the previous endoscopy was noticeably lower than our rate, due to procedures performed after incomplete preparation and cases in which the cecum was not reached due to inflammation, such as in cases of ischemic colitis, were also included.

The associations between PCCRC and the QIs described above are factors of test accuracy. In addition, the examination intervals and biological factors of PCCRC should be considered. In the present study, we set the period between the last examination and the PCCRC diagnosis at six months to five years, based on the definition of interval cancer established by the World Endoscopy Organization. However, this duration is quite long and lacks uniformity, thereby making generalized comparisons difficult. The probability of missed lesions is higher in cases of short-interval PCCRC than in long-interval cases (Fig. 2); the longer the examination interval, the more likely it is for cases with slow growth detected due to the adenoma-carcinoma sequence to be observed. The National Polyp Study recommends three years as an adequate examination interval after endoscopic resection of adenomatous polyps (21). The European guidelines classify patients who have undergone colonoscopy into three risk groups based on the number, size, and histological type of adenomas and recommend fecal occult blood screening for the low-risk group and colonoscopy after three years and one year for the mid- and high-risk groups, respectively (22). The Japan Polyp Study (JPS) recommends an interval of at least three years before a follow-up examination after colonoscopic removal of newly diagnosed adenomatous polyps (23). In addition, the time when colonoscopy performed is also important. The predictive factors for PCCRC have been reported to include a positive fecal occult blood test and a post-polyp resection (1, 2). Local residual/recurrence is also an issue. In Tis carcinoma, when piecemeal resection is performed or the tumor margin after resection is unclear and the curability cannot be accurately evaluated, colonoscopy should be performed approximately six months after endoscopic treatment (24, 25). The recurrence rate was reported to be 9.1-27.5% at 24 months after piecemeal resection (26, 27). Debates on the best surveillance period are ongoing worldwide, and further investigations will be required for the standardization of examination periods.

Our search of the literature revealed no reports which described that PCCRC were more frequently detected after colon surgery. However, PCCRC is reportedly more likely to develop in patients with a history of abdominal surgery and polypectomy (2, 28). Why PCCRC is more likely to occur in those with a history of colon surgery may be because endoscopists focus on relatively large advanced CRC lesions and may therefore small, precancerous lesions.

Furthermore, the PCCRC cases in this study had a significantly shallower invasion depth than NDC, which is consistent with previous studies that reported that PCCRC tends to be detected at earlier stages than NDC (3, 29, 30). In addition, the morphology of CRC also warrants attention: morphologically, intramucosal lesions growing to a height above the normal surrounding mucosa are classified as PG-type, whereas those that are depressed or of equal height with the surrounding normal mucosa are classified as NPG-type. PG-type SM cancers tend to invade the submucosa ≥20 mm, whereas NPG-type SM cancers tend to invade the submucosa approximately 10 mm (31, 32). Furthermore, interval cancers with SM invasion tend to be small and of the flat NPG-type (30, 33). In the present study, we compared PCCRC cases based on the invasion depth and found that group B had a significantly higher rate of occurrence of NPG-type tumors than group A, suggesting that flat, NPG-type tumors should be investigated carefully, as they can be easily missed. Differentiating between PG and NPG types is also very important in terms of their rapid growth; however, there have been very few cases of fast-growing tumors that were reported in Japan. The only report on the pathological findings of PCCRC and NDC showed that mucinous carci-

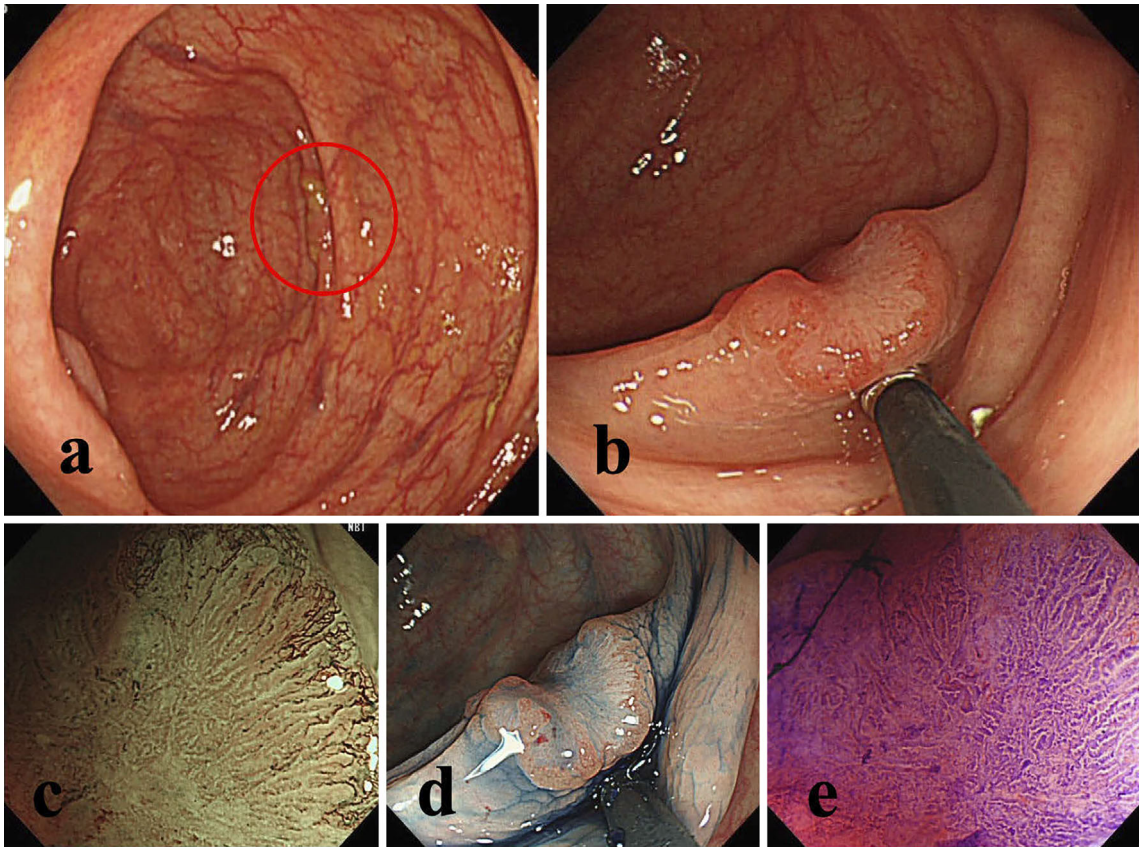

Figure 2. **One example of post-colonoscopy colorectal cancer (missed lesion). a: No clear adenomatous lesions was diagnosed on TCS performed for a positive fecal occult blood test. However, the lesions was found to have been hidden behind the mucosal folds. b: 8-mm IIa+IIc lesions found in the cecum at TCS performed 11 months later for a second positive fecal occult blood test result. c-e: Magnified observation: high irregular pit pattern (Vi) and scheduled for surgery. The invasion depth was SM massive invasion. TCS: total colonoscopy**

nomas were more frequent among PCCRC than among NDC (34). There were no significant histopathological differences between PCCRC and NDC in the present study. If neoplastic lesions demonstrating a high degree malignancy are also considered to be one of the reasons, then the characteristic histopathological findings should also be noted.

As of August 2019, a number of studies from multiple countries have compared the QIs between PCCRC and NDC (Table 5) (1-3, 15, 16, 20, 30, 35-42). Those studies reported the interval PCCRC rates and risk factors, and most noted that an adequate follow-up and high-quality colonoscopy were useful for preventing PCCRC, similar to the present study.

However, several limitations associated with the present study warrant mention. First, this study was a retrospective analysis that was performed at a single center. Therefore, it may be biased to some extent. CRC of various types (residual, recurrent, or fast-growing) and the pathology of PCCRC should be further investigated through large-scale randomized control trials. Second, the diagnosis of the tumor depth is sometimes controversial among pathologists. While expert pathologists diagnose tumors at our hospital, the diagnosis may still vary among pathologists. Third, we used various endoscopic scopes (CF-Q260, CF-H260, PCF-Q260AI, CF-H290, PCF-H290; Olympus Medical Systems, Tokyo, Japan) for the screening and surveillance examinations. As time passes, new endoscopic scopes are introduced. Differences in the capabilities of scopes may introduce a degree of bias. However, the results of the present study can still be considered clinically significant despite these limitations.

Conclusion

This study outlined the relationship between the clinical characteristics of PCCRC and QIs. Missed lesions account for many PCCRC cases. We believe that increasing the quality of medical care and QIs will reduce the number of missed lesions and help prevent PCCRC onset. Reducing the incidence of PCCRC through high-accuracy CRC screening is a major future goal for endoscopists and key to eradicating CRC.

Informed consent was obtained from all the patients.

The authors state that they have no Conflict of Interest (COI).

Table 5. Characteristics of Published Study for Post-colonoscopy Colorectal Cancer.

Reference	Period	Country	Definition of interval CRC	PCCRC rate	Risk factor
(35)	1991-2004	USA	<60 months	5.4	Incomplete polypectomy, right colon,size
(28)	1997-2002	Canada	6-36 months	3.4	older age, diverticular disease, proximal colon, endoscopist's specialty
(36)	1989-2004	USA	<60 months	4.8	proximal colon, MSI, CIMP
(37)	2000-2005	Spain	<36 months	6.7	older age, male sex, the presence of another advanced adenoma at first colonoscopy, history of advanced neoplasia
(15)	2000-2004	Poland	<60 months	42 interval cancer/ 188,788 patients	endoscopist's rate of detection of adenomas
(38)	1992-2008	Canada	6-36 months	7.9	colonoscopy by family physician, famale gender, proximal colon, endoscopist's specialty
(20)	2000-2005	Canada	6-36 months	9	endoscopist's specialty, non-hospital setting
(2)	1994-2005	USA	6-36 months	7.2	proximal tumor location, increased comorbidity, previous diagnosis of diverticulosis, prior polypectomy, endoscopist level (lower polypectomy rate,higher colonoscopy volume)
(1)	2003-2007	Germany	12-100 months	4	female sex, location in the caecum or ascending colon, positive faecal occult blood test, incomplete (caecum not reached)
(39)	1976-2008	China	<60 months	14 interval cancer/ 1,794 patients	incomplete resection of advanced adenomas
(34)	2000-2009	Denmark	12-60 months	2.6	female sex, localized stage at diagnosis, proximal tumor location, high comorbidity burden
(30)	2001-2010	The Netherlands	12-60 months	2.9	proximal colon, small size, flat lesion,inadequate examination/surveillance
(3)	1995-2009	USA	6-60 months	6	proximal colon, earlier-stage cancer, lower risk of death, higher rate of adenoma, family history of CRC
(16)	1998-2010	USA	6-120 months	8.2	adenoma detection rate
(40)	2003-2009	England	6-60 months	12.1	female sex, older age, increased comorbidity, proximal colon, elective procedures, colonoscopy volume
(41)	2001-2008	Australia	<60 months	2.8	diverticulosis, poor bowel preparation
(42)	2001-2012	Denmark	<36 months	9	colonoscopist quality (training, background, certification), diverticulitis, ulcerative colitis, hereditary cancer, proximal colon

PCCRC: post-colonoscopy colorectal cancer, CRC: colorectal cancer

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