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Clinical and endoscopic characteristics of post-colonoscopy colorectal cancers detected within 10 years after a previous negative examination*

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Authors

Kenta Kodama**,[1,2], Shin-ei Kudo[1], Hideyuki Miyachi**,[1], Kunihiko Wakamura[1], Yasuharu Maeda[1], Katsuro Ichimasa[1], Yushi Ogawa[1], Yuta Kouyama[1], Masahiro Abe[1], Yohei Ogura[1], Taishi Okumura[1], Kenichi Mochizuki[1], Yosuke Minegishi[1], Misaki Ishiyama[1], Yuichi Mori[1], Masashi Misawa[1], Toyoki Kudo[1], Takemasa Hayashi[1], Fumio Ishida[1], Daisuke Watanabe[3,4]

Institutions

1 Digestive Disease Center, Showa University Northern Yokohama Hospital, Yokohama, Japan
2 Division of Gastroenterology, Japanese Red Cross Society Fukushima Hospital, Fukushima, Japan
3 Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
4 Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, United States

Corresponding author

Shin-ei Kudo, MD, PhD, Digestive Disease Center, Showa University Northern Yokohama Hospital, 35-1 Chigasaki Chuo, Tsuzuki-ku, Yokohama City, Kanagawa 224-8503, Japan
Fax: +81-45-949-7535
kudos@med.showa-u.ac.jp

ABSTRACT

Background and study aims We sometimes encounter colorectal cancer (CRC) that is discovered during the time interval between initial colonoscopy and the recommended follow-up examination. Although several studies reported such cases of CRC, most were based on registry data, which implied that the endoscopic quality was not consistent or guaranteed. We aimed to clarify these clinical and endoscopic characteristics at our high-volume center where a retrospective survey could be precisely performed.

Patients and methods We retrospectively analyzed patients with CRC who underwent endoscopic resection or surgery from April 2002 to December 2010, categorizing them into two groups: a "study group" of patients with a negative colonoscopy during the previous 10 years, and a "control group" of patients without a previous colonoscopy or with a previous colonoscopy more than 10 years prior.

Results A total of 2042 patients had CRC, among which 55 patients were classified into the study group and the remaining 1989 into the control group. The CRC cases in the study group showed a significant association with smaller (< 30 mm) tumor size (odds ratio [OR] 2.3; 95% confidence interval [CI] 1.3–4.0) and proximal tumor site (OR 1.7; 95% CI 0.9–2.9). In addition, right-sided and depressed-type T1 CRCs were significantly more common in the study group.

Conclusions Tumor size and location were associated with CRCs detected within 10 years after the negative examination. In addition, depressed-type T1 CRCs were more common. Therefore, we should pay more attention to small, right-sided, or depressed-type tumors in daily colonoscopy.

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** These authors contributed equally.

Introduction

Colorectal cancer (CRC) is the major cause of death by malignancy in Japan as well as in western countries [1]. On the other hand, adenomas are accepted as precursor lesions for most CRC cases [2]. To date, most deaths from CRC are currently prevented by regular colonoscopy coupled with the removal of adenomas. In fact, adenomas can be decreased by 76% to 90%, with a significant reduction in CRC mortality, in patients who undergo a clearing colonoscopy [3, 4].

In routine clinical practice, a CRC is sometimes discovered during the time interval between initial colonoscopy and the recommended follow-up examination. Such CRCs that are found before the expected interval after the initial colonoscopy are named interval colorectal cancers, or post-colonoscopy CRCs (PCCRCs), while the World Endoscopy Organization (WEO) consensus states that the term "interval cancers" should be used only for screening and surveillance colonoscopy programs [5]. Although associations between PCCRC and several clinical risk factors have been reported [6–8], these results were mainly based on registry-based administrative data such as the Ontario Cancer Registry [8], the Canadian Institute for Health Information-Discharge Abstract Database [9], or Manitoba's provincial physicians' billing claims database [10]. Little information has been reported at a high-volume center where a retrospective survey could be precisely performed.

Although the annual 2-day fecal immunochemistry test (FIT) method is commonly used in population-based CRC screening programs in Japan, total colonoscopy has recently been used in situations such as CRC screening during medical check-up examinations. A 10-year screening interval is recommended after a negative initial colonoscopy [11], while this strategy may not work efficiently when considering the presence of PCCRC. In addition, we also considered that it would be more informative to elucidate the characteristics of PCCRC that were identified during the 10-year interval. Therefore, the aim of this study was to evaluate the characteristics of PCCRC that were observed during the 10-year interval based on large cohort data obtained at our flagship gastrointestinal center in order to provide endoscopists with useful information for daily practice.

Patients and methods

Patients and clinical data

We retrospectively analyzed patients with CRC who underwent endoscopic resection or surgery at our hospital from April 2002 to December 2010. Hereditary CRC and appendiceal cancer were excluded from the final analysis. Written informed consent was obtained from all patients before initial colonoscopy or surgery. Patients whose previous colonoscopy was not completed were excluded. When identification of the appendiceal orifice or intubation of the terminal ileum was endoscopically recorded, the colonoscopy was considered to be completed. In this study, we regarded PCCRC as "interval type PCCRC," which was identified before the next recommended screening or surveillance examination, referring to the WEO Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Can-

cer [5]. For the analysis, all eligible patients with CRC were divided into two groups as follows: a "study group" was defined as patients with CRC with a negative colonoscopy during the previous 1 to 10 years, and a "control group" was defined as all patients except for those in the study group, that is patients with CRC without a previous colonoscopy, or with a previous colonoscopy less than one year previously and more than 10 years prior. Therefore, preoperative examination would not be included in the study group. In this study, a negative colonoscopy indicated that the examination results revealed no or only a few benign polyps (hyperplastic polyps of 10 mm or less in size in the rectum or sigmoid colon) that were diagnosed by magnifying observation.

Information on age, sex, and tumor size, location, and stage [12] was reviewed in the electronic record system. In cases of T1 CRC, morphology of the lesions was also reviewed. The morphology was classified as depressed-, flat- or protruded-type according to Kudo's morphological development classification [13–15]. Accordingly, in this study, mixed-type T1 cancers such as "IIa+IIc" or "Is+IIc" were classified as "depressed-type".

Preparation and colonoscopy

Before the examination, patients underwent bowel preparation with 2 to 3 L of polyethylene glycol solution. Diazepam or midazolam and butyl-scopolamine or glucagon were used intravenously for sedation and prevention of peristalsis, respectively. Colonoscopy was performed using a magnifying colonoscope (CF-240ZI, CF-H260AZI, PCF-240ZI; Olympus Corp., Tokyo, Japan). All detected neoplasms were diagnosed based on the pit pattern classification system described by Kudo et al. [16]. Each diagnosis was recorded into the database just after colonoscopy. Lesion size, location, and morphology were also measured and recorded.

Pathological evaluation

The specimens were examined by one pathologist based on the World Health Organization criteria and the Japanese Society for Cancer of the Colon and Rectum guidelines, as previously described [12]. Briefly, all resected lesions were retrieved and immediately fixed in a 10% buffered formalin solution for 24 to 48 hours. Among them, T1 CRC lesions were carefully observed with a focus on the pit pattern using a stereomicroscope. Subsequently, they were cut at the point where the deepest invasion area could be exposed on the cut end surface. The other histological specimens were cut into parallel 2- to 3-mm-thick sections. Tumor size was measured after formalin fixation.

Statistical analysis

We analyzed clinicopathological factors using a Fisher exact test and Welch's **t**-test. A $P < 0.05$ was considered significant. Multivariate logistic regression analysis was performed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) after accounting for potential confounders. All data were presented as the mean ± standard deviation. We conducted all ana-

lyses using JMP software version 10.0.2 (SAS Institute, Cary, North Carolina, United States).

Ethical considerations

This study was approved by the institutional review board of Showa University Northern Yokohama Hospital (approval number: 19H068).

Results

A total of 46,891 colonoscopies were performed during the study period (April 2002 to December 2010). Among them, 2050 CRC (excluding hereditary CRC) patients were identified, and then eight appendix cancer cases were excluded. Of these 2042 subjects, 53 patients who underwent another colonoscopy within 10 years after the previous negative colonoscopy were classified as the study group, while the remaining 1989 patients were assigned to the control group (▶Fig. 1). The indications of colonoscopy in the study group are shown in ▶Table 1. The interval of colonoscopies in the study group was 756.7 ± 642.1 days. Typical cases in the study group are shown in ▶Fig. 2 and ▶Fig. 3.

Demographic and tumor characteristics among the study and control groups

Matching the 55 patients of the study group with the 1989 patients of the control group, in the study group mean age and tumor size were 68.9 ± 11.3 years and 26.3 ± 20.2 mm, respectively, and in the control group mean age and tumor size were 65.6 ± 11.8 years and 40.7 ± 24.1 mm, respectively (▶Table 2 and ▶Supplementary Table 1). There were more males than females in both groups (study group: 66.0% vs. 34.0%; control group: 56.6% vs. 43.4%; $P = 0.22$). In the study group, although the rectum was the most common location (n = 14, 26.4%), 12 colorectal neoplasms (22.6%) were also located in the ascending colon. Regarding tumor stage, T1 stage was most common in the study group (n = 22, 41.5%), while T3 stage occurred most frequently in the control group (n = 907, 45.6%). Additionally, when the study period was divided into two terms (12–36 and 36–120 months) within the study group, tumor size was significantly smaller in the 12- to 36-month subgroup (23.8 ± 15.7 mm) than in the 36- to 120-month subgroup (45.7 ± 38.1 mm), and no significant differences were observed in age (years old), sex (male/female), tumor location (C,A,T/D,S,R), or tumor stage (T1/Others).

Risk factors for CRC in patients with a prior negative colonoscopy

To determine demographic and tumor factors associated with CRC in patients with a prior negative colonoscopy, we performed a multivariate logistic analysis of the study group compared with the control group (▶Table 3). Age, sex, and tumor stage were not significantly associated with CRC in the study group. In contrast, the study group showed a strong association with smaller (<30 mm) tumor size (OR 2.8; 95% CI 1.4–5.3). In addition, the proximal tumor site was also independently associated with CRC in the study group (OR 2.0; 95% CI 1.2–3.5).
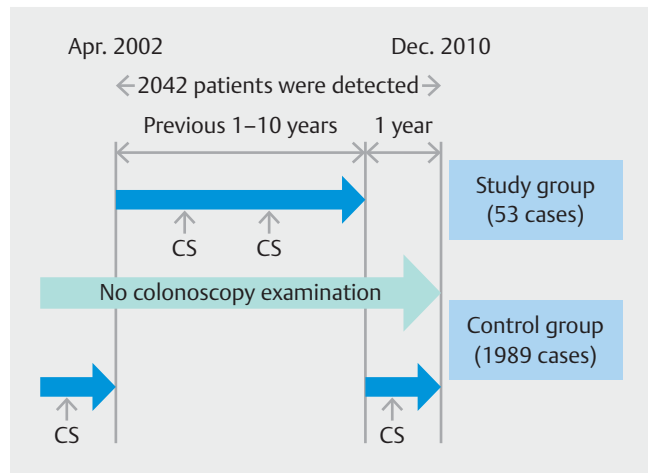

▶ Fig. 1 Study algorithm. A total of 46891 colonoscopies were performed between April 2002 and December 2010. Among them, 2050 patients with CRC were identified, and eight cases of appendiceal cancer were excluded. Among these 2042 subjects, 53 patients who underwent another colonoscopy within 10 years after the previous negative colonoscopy were classified as the study group, while the remaining 1989 patients were assigned to the control group.

▶ Table 1 Indications for colonoscopy in the study group (n = 53).

Indication for colonoscopy (current history)	n (%)
Positive fecal occult blood test	16 (30.2%)
Surveillance after endoscopic treatment for polyps	9 (17.0%)
Surveillance after surgery for colorectal cancers	8 (15.1%)
Hematochezia	7 (13.2%)
Anemia	4 (7.5%)
Medical checkup (no symptoms)	4 (7.5%)
Abdominal bloating	2 (3.8%)
Constipation	2 (3.8%)
Abdominal pain	1 (1.9%)

Morphological and distributional features of T1 tumors in patients with a prior negative colonoscopy

Finally, we compared the characteristics of the location and morphology of T1 CRC between the Study and control group. As shown in ▶Table 4, T1 CRC in the study group was located more frequently in the proximal colon than in the distal sites (50.0% vs. 26.2%, $P < 0.05$). In addition, depressed-type T1 CRC was more common in the study group than in the control group (50.0% vs. 22.5%, $P < 0.05$).
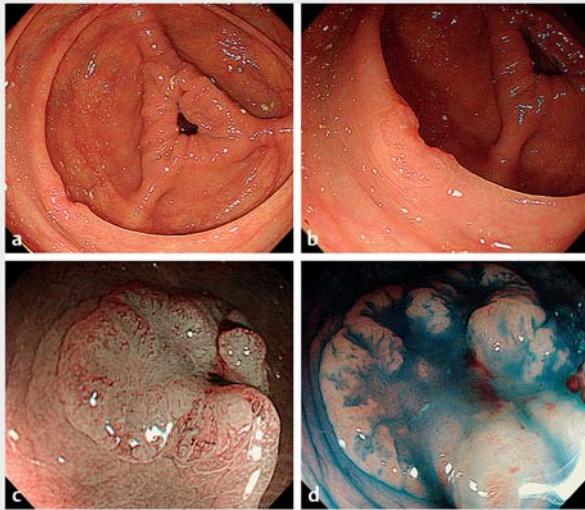
▶ **Fig. 2** A typical case of post-colonoscopy colorectal cancer. An 80-year-old male patient underwent follow-up colonoscopy 716 days after his negative colonoscopy examination, and a 10 × 9 mm colorectal cancer (IIa + IIc type) was identified in the distal ascending colon. The pathological diagnosis was T1 carcinoma (SM 1250 μm), well-differentiated adenocarcinoma, ly0, v2, pN0. **a** White-light normal observation. **b** White-light observation with slight magnification. **c** Narrow band Imaging observation with magnification. **d** Indigo carmine-sprayed observation with magnification.
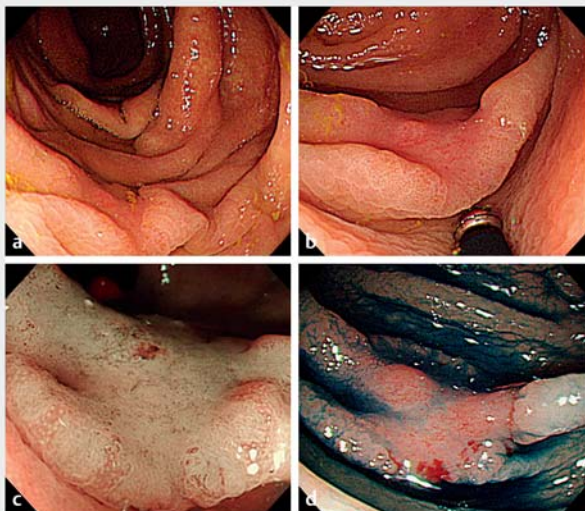
▶ **Fig. 3** Another typical case of post-colonoscopy colorectal cancer. An 80-year-old male patient underwent follow-up colonoscopy 840 days after his negative colonoscopy examination, and a 14 × 9 mm colorectal cancer (LST-NG pseudo-depressed type) was found in the proximal ascending colon. The pathological diagnosis was T1 carcinoma (SM 1450 μm), well-differentiated adenocarcinoma, ly0, v0, pN0. **a** White-light normal observation. **b** White-light observation with moderate magnification. **c** Narrow band Imaging observation with magnification. **d** Indigo carmine-sprayed observation with magnification.

▶ **Table 2** Patient and tumor characteristics in the study and control groups.

	Study group (n = 53)	Control group (n = 1989)	P value
Age (y)	68.9 ± 11.3	65.6 ± 11.8	< 0.05
Sex			0.22
▪ Male	35 (66.0 %)	1,125 (56.6 %)	
▪ Female	18 (34.0 %)	864 (43.4 %)	
Tumor size (mm)	26.3 ± 20.2	40.7 ± 24.1	< 0.05
Tumor location			0.0636
▪ C	3 (5.7 %)	106 (5.3 %)	
▪ A	12 (22.6 %)	286 (14.4 %)	
▪ T	7 (13.2 %)	181 (9.1 %)	
▪ D	4 (7.5 %)	95 (4.8 %)	
▪ S	13 (24.5 %)	585 (29.4 %)	
▪ R	14 (26.4 %)	736 (37.0 %)	
Tumor stage (T)			0.0587
▪ T1	22 (41.5 %)	569 (28.6 %)	
▪ T2	8 (15.1 %)	298 (15.0 %)	
▪ T3	18 (34.0 %)	907 (45.6 %)	
▪ T4	5 (9.4 %)	215 (10.8 %)	

C, cecum; A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; R, rectum.

Discussion

We sometimes encounter cases of CRC that are discovered during the time interval between the initial negative colonoscopy and the recommended follow-up examination. Such CRCs are termed as PCCRCs [17]. Although some studies discussed the appropriate interval for screening of CRCs after the initial negative examinations [4, 18], and several researchers have defined PCCRCs as lesions discovered 6 to 36 months after the initial negative colonoscopy [19, 20], the consensus statements by Rutter et.al. [5] are widely accepted. Accordingly, we regarded PCCRC as "interval type PCCRC" which was identified before the next recommended screening or surveillance examination. Moreover, while the prevalence and risk factors of PCCRC have been described in previous studies [21, 22], no definitive consensus has been consolidated. In addition, the occurrence of PCCRC is strongly related to the sensitivity and quality of colonoscopy [23, 24], while most of the previous reports were based on registry-based data implying that the endoscopic quality was not consistent or guaranteed. In this study, we have clarified the clinical and endoscopic characteristics of PCCRC at our high-volume center, through which a retrospective survey could be precisely performed. As a result, strong relationships between PCCRC and tumor size/location were re-

▶Table 3 Multivariable ORs and 95 %CIs of patient and tumor characteristics in the study group compared with the control group.

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
Age		N.S		N.S.
▪ ≥60	2.1 (1.0–4.2)		1.6 (0.8–3.4)	
▪ <60	1.0 (ref)		1.0 (ref)	
Sex		N.S.		N.S.
▪ Male	1.5 (0.8–2.6)		1.4 (0.8–3.4)	
▪ Female	1.0 (ref)		1.0 (ref)	
Tumor size		0.0036		0.0027
▪ <30	2.3 (1.3–4.0)		2.8 (1.4–5.3)	
▪ ≥30	1.0 (ref)		1.0 (ref)	
Tumor location		0.0189		0.0154
▪ C or A or T	1.7 (0.9–2.9)		2.0 (1.2–3.5)	
▪ D or S or R	1.0 (ref)		1.0 (ref)	
Tumor stage		N.S.		N.S.
▪ T1	1.7 (1.0–3.0)		0.9 (0.5–1.7)	
▪ T2 or T3 or T4	1.0 (ref)		1.0 (ref)	

OR, odds ratio; CI, confidence interval; C, cecum; A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; R, rectum.

▶Table 4 Distributional and morphological features of T1 CRC in the study group compared with the control group.

	Study group	Control group	*P* value
Tumor location			< 0.05
▪ C, A, T	11 (50.0 %)	149 (26.2 %)	
▪ D, S, R	11 (50.0 %)	420 (73.8 %)	
Tumor morphology			< 0.05
▪ Depressed type	11 (50.0 %)	128 (22.5 %)	
▪ Protruded/flat type	11 (50.0 %)	441 (77.5 %)	

C, cecum; A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; R, rectum

cognized. In addition, right-sided and depressed-type T1 CRC lesions were more frequently found in the PCCRC group.

Proximal sites could be an independent predictor of PCCRC (OR 2.0, 95 %CI 1.2–3.5, *P* = 0.0154), consistent with previous studies [19, 25, 26]. Three reasons were indicated. First, the biological features of tumors in the right-sided colon might differ from those in the left side. That is, the serrated pathway for carcinogenesis of CRC or microsatellite instability (MSI)/CpG island methylator phenotypes (CIMP) might be associated with this feature. Regarding the serrated pathway, it is well known that sessile serrated lesions with sessile configuration and in-

conspicuous borders are often found in the right-sided colon [27, 28]. These have as high as or higher malignant potential than conventional adenomas [29]. However, we would like to emphasize that depressed-type T1 CRC was more often found than the other types. Therefore, treating small, right-sided, not only sessile but also depressed-type lesions is necessary to reduce PCCRC occurrence. Arain et al. showed that interval cancers that are more likely to arise in the right-sided colon had a higher MSI and CIMP signature than non-interval cancers [30]. Second, proximal colorectal tumors with advanced histology were frequently small, or had a non-polypoid appearance [31]. Third, anatomical features might be related to overlooking a tumor, because tumors in the hepatic flexure are sometimes difficult to observe. In fact, PCCRC is more common in the hepatic flexure [26].

In addition, our study found that tumor size (<30 mm) was a significant predictor of PCCRC. Previous studies also showed that tumor size was an independent risk factor for PCCRC [32, 33]. The incidence of PCCRC has been reported to be based on the following three factors: (1) an overlooked tumor; (2) incomplete resection; or (3) specific biological characteristics. Given that several studies have demonstrated that most PCCRC cases were associated with the first two factors (1 or 2), and that the quality of colonoscopy was of the utmost importance [34], we should pay more attention to small-sized lesions in clinical settings.

We also evaluated the macroscopic appearance of T1 PCCRC and revealed that depressed-type T1 CRC was more common than the other types. The information of macroscopic appearance has been scarcely reported because most studies concerning PCCRC relied on registry-based administrative data. However, consistent with our findings, le Clercq et al. also stated that a flat appearance was an independent risk factor for PCCRC (OR 1.70, 95 %CI 1.18–2.43) [20]. This might be because, like small-sized tumors, non-polypoid (flat or depressed) tumors could be more easily overlooked in routine practice [35], could be more difficult to resect [36], and could have more progressive potential [37] than polypoid tumors. Although overlooked tumors or incomplete resection were two major causes of PCCRC, as mentioned above, specific biological characteristics including de novo pathway [14, 15] could also be important to prevent cancer death from PCCRC. Our results suggested that depressed-type T1 CRC might be a feature of PCCRC (▶Fig. 2 and ▶Fig. 3), and hence more frequent colonoscopies would be required, rethinking current surveillance recommendations or guidelines in the future.

There are several limitations in this study. First, this present study was a single-center retrospective cohort study, and hence all limitations of retrospective studies apply. It was difficult to collect the perfect history or indication of colonoscopy data for all patients, especially those in the control group. However, the large sample size and unified evaluation methods could provide significant reliability. In the case of multicenter studies, it would often be difficult to align the quality of the examinations. Second, although most patients in this study underwent colonoscopy regularly, the evaluation of CRC occurrence relied on patients' self-intent. If patients did not undergo colonosco-

py, we were not able to perform a colonoscopy on them. Third, in this retrospective study, patients undergoing colonoscopy 1 to 10 years previously at another facility could be classified into the control group, which means that some patients with CRC in the control group might have a history of colonoscopy at another facility. Fourth, not all patients complied with our follow-up schedule after their initial negative colonoscopy. Finally, this retrospective study mainly focused on the clinical and endoscopic characteristics of PCCRCs and their comparison with non-PCCRCs, and many of the patient who received colonoscopy at our hospital were referral cases from other hospitals with wide variety of indications but some with unclear initial colonoscopy date, which makes calculation of incidence of PCCRCs in terms of event (s) per 1000 person-years not feasible and it may not be possible to classify the PCCRCs into any single category as per defined by WEO expert consensus [38]. Nevertheless, in this study, we still provided valuable clinical characteristic of PCCRC.

Conclusions

In conclusion, our study revealed that PCCRCs are more likely to be smaller in size (< 30 mm) and at a proximal site. Therefore, we must pay attention to small tumors in the right-sided colon to avoid the occurrence of PCCRC. Our large, single-center, cohort study validates previous national cohort studies and provides useful information for endoscopists. In addition, this is the first report to reveal that identifying right-sided, depressed-type T1 CRC is of great importance to reduce PCCRC occurrence.

Acknowledgements

Competing interests

The authors declare that they have no conflict of interest.

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▶ **Supplementary Table 1** Comparison of patient and tumor characteristics between the 12– to 36-month subgroup and the 36– to 120-month subgroup within the study group.

	12- to 36-month group (n=47)	36- to 120-month group (n=6)	*P* value
Age (y)	69.0±11.5	68.5±10.5	N.S
Sex (male/female)	32/15	3/3	N.S
Tumor size (mm)	23.8±15.7	45.7±38.1	<0.05
Tumor location (C,A,T/D,S,R)	19/28	3/3	N.S
Tumor stage (T1/others)	20/27	2/4	N.S

C, cecum; A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; R, rectum