ORIGINAL

Morphological Characteristics and Location of Missed, Advanced Colorectal Neoplasms after Colonoscopy

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Abstract : This retrospective study aimed to clarify the clinical characteristics of advanced colorectal neoplasms after colonoscopy, likely to have been missed on the previous colonoscopy. We reviewed a total of 5,768 consecutive colonoscopies performed from April 2010 to September 2013 in 4,841 patients, and analyzed advanced colorectal neoplasms after colonoscopy, particularly focusing on their morphological characteristics and locations, as compared with primary lesions, defined as lesions detected in their first colonoscopy or in a subsequent colonoscopy >5 years after the previous one. Of the 5,768 examinations, 922 advanced neoplasms (including 217 cancers with ≥T2) were detected, and 167 lesions (18.1%) were diagnosed within 5 years after a previous colonoscopy (post-colonoscopy advanced neoplasms). The incidence of right-sided lesions in the post-colonoscopy advanced neoplasms (48.5%, 81/167) was significantly higher than in the primary lesions (34.0%, 257/755 ; $p<0.001$). We excluded 217 cancers with ≥T2 from the morphological analysis to characterize early-stage post-colonoscopy advanced neoplasms. The incidence of non-polypoid lesions in the post-colonoscopy advanced neoplasms (25.6%, 41/160) was significantly higher than that in the primary lesions (12.3%, 67/545 ; $p<0.001$). These findings suggest that extra attention should be paid to non-polypoid, right-sided advanced colorectal neoplasms during screening and surveillance colonoscopy. J. Med. Invest. 63 : 163-170, August, 2016

Keywords **:** *Colorectal cancer, interval cancer, colon polyp, laterally spreading tumor*

INTRODUCTION

In recent years, the incidence and mortality of colorectal cancer (CRC) have increased, and it is now one of the most frequently diagnosed cancers in Japan (1). CRC can be effectively prevented by removing precancerous lesions diagnosed upon colonoscopy (2-5). Indeed, the incidence and mortality of CRC have decreased in United States as the screening rate of CRC using colonoscopy has increased (6). The risk of CRC after a previous negative colonoscopy is very low. Nevertheless, considerable numbers of CRCs are diagnosed several years after colonoscopy (7-15) ; such lesions are called "interval cancer" or "post-colonoscopy colorectal cancer" (16). A number of researches have suggested that a deficiency in colonoscopy quality rather than accelerated tumor biology is the cause of the majority of interval cancers occurring within 3-5 years after a negative colonoscopy (6, 10, 16-20). Hence, interval cancer represents a clinical problem urgently requiring a solution. Although the distribution and predictors of interval cancers after negative colonoscopy have been extensively studied, the morphology of interval cancers in the early stage has not yet been studied in detail.

Advanced adenoma is considered to represent the pre-stage of life-threatening cancer and may be the most valid neoplastic surrogate marker for present and future colorectal cancer risks (21). Advanced colorectal neoplasia is a concept that merges invasive cancer with advanced adenoma and is defined as cancer or adenoma that is at least 10 mm in diameter and has high-grade dysplasia with histological characteristics of villous or tubulovillous lesions, or a combination thereof (22). As a general rule, the Paris classification is usually used to depict the morphology of colorectal neoplasms (23) ; however, different neoplastic growth types are sometimes included in the same category of the Paris classification. For example, even if lesions were classified as IIa in the Paris classification, the biological behavior would differ between lesions with and without a granular surface. Therefore, the pragmatic classification of superficial neoplastic colorectal lesions is commonly used in clinical practice (24). In the present study, using this classification, we investigated the morphology and locations of post-colonoscopy advanced neoplasms (PCANs), excluding ≥ T2 tumors, as a means to characterize the early stage of PCANs, which are considered likely to have been missed on the previous screening colonoscopy.

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METHODS

Study design

This is a single-center, retrospective study of prospectively collected data from April 2010 to September 2013. Data were obtained from the endoscopic database in Kyoto Second Red Cross Hospital, Kyoto, Japan. Consecutive colonoscopies performed during this period were included in this study. Informed consent was obtained from all individual participants in the study, and the study protocol was approved by the institutional review board of Kyoto Second Red Cross Hospital and conducted in accordance with the Declaration of Helsinki (as revised in Tokyo, 2004). Patients were excluded from our analysis based on the following criteria : inflammatory bowel diseases, familial adenomatous polyposis, colonoscopy within 6 months, unknown history of previous colonoscopy, and unknown family history. We analyzed the differences in morphological characteristics and location of advanced neoplasms between

PCANs and primary lesions, defined as lesions detected in their first colonoscopy or in a subsequent colonoscopy performed more than 5 years after the previous one. According to the pragmatic classification, advanced neoplasms were divided into five groups (Fig. 1), namely polypoid, flat, depressed, laterally spreading tumor granular type (LST-G), and laterally spreading tumor non-granular type (LST-NG) lesions. Advanced cancers are difficult to classify because of substantial changes in the original morphology ; therefore, advanced cancers classified as T2 or higher stages according to the American Joint Committee on Cancer/TMN system (25) were excluded from the final analysis.

Terminology

In the majority of studies reported, interval cancer or post-colonoscopy colorectal cancer is defined as cancer lesions detected after a previous colonoscopy within a 6- to 60-month period (16). In reference to this definition, in the present study, we defined PCANs as advanced neoplasms detected after a previous colonoscopy within a 0.5- to 5.5-year period. We also analyzed PCANs by subdividing the lesions into two groups : lesions detected between 0.5 and 3.5 years (PCAN ≤ 3 years), and between 3.5 and 5.5 years (PCAN 4-5 years) after colonoscopy.

Laterally spreading tumors (LSTs) are neoplasms with a lateral tumor growth of at least 10 mm in diameter, and are divided into LST-G lesions, having a granular surface (0-IIa, 0-Is+IIa, and 0-IIa+Is), and LST-NG lesions, which lack a granular surface (0-IIa, 0-IIa+IIc, and 0-IIc+IIa) (26). Flat lesions are defined as 0-IIa lesions smaller than 10 mm in diameter. Depressed lesions are expressed as 0-IIc, 0-IIa+IIc, and 0-Is+IIc lesions smaller than 10 mm in diameter. Polypoid lesions are defined as 0-Is and 0-Ip lesions. Advanced neoplasia includes advanced adenoma (defined as tubular adenoma ≥ 10 mm, adenoma with a villous histology, and/or adenoma with high-grade dysplasia) or cancer with ≥ T1 (defined as malignant cells beyond the muscularis mucosa). Adenoma with high-grade dysplasia includes mucosal cancer. Traditional serrated adenoma was included in the adenoma category. The right-sided colon is defined as the oral side from the splenic flexure, and the rest of the colon is defined as the left-sided colon.

Colonoscopy

The patients were instructed to take magnesium citrate the day before colonoscopy as preparatory medication. On the morning before the colonoscopy, polyethylene glycol was used to clean the bowel ; when inadequate, an enema was given. All colonoscopies were carried out or supervised by experienced endoscopists. As a general rule, all polyps, except hyperplastic polyps < 5 mm, were removed by cold polypectomy or endoscopic mucosal resection during the procedure, while all ≥ T2 cancers and the majority of T1 cancers were resected by surgical intervention. Midazolam was used only when a patient complained of severe pain.

Data collection and statistical analysis

We used an endoscopic database, recorded in Solemio ENDO® filing system Ver. 3.2 (Olympus Medical Systems Inc., Tokyo, Japan), for data collection. Each endoscopist input the following data shortly after each colonoscopic procedure : age, sex, family history of CRC, past history of colonoscopy, indication of colonoscopy, and the morphology and location of the detected lesions. The morphology of the polyps was reviewed by experienced endoscopists after the procedure. Each endoscopist input data regarding the past history of colonoscopy by referring to the medical records of the patients for the last 10 years, and also by asking the patients whether they had previously undergone colonoscopy elsewhere. We excluded patients who had previously undergone colonoscopy at different hospitals, as we were unable to obtain exact information on the results. After the histopathological findings were analyzed, the endoscopists added the pathological data to the database.

Differences in the patient characteristics, including sex, family history, or indication of colonoscopy, and in the characteristics of the future advanced neoplasms including location, histology, and morphology among each category were analyzed using the χ^2 test. Analysis of variance was also used for continuous variables such as age. Statistical analyses were done using IBM SPSS statistics version 22 (IBM SPSS, Armonk, NY, USA), with $p < 0.05$ considered statistically significant.

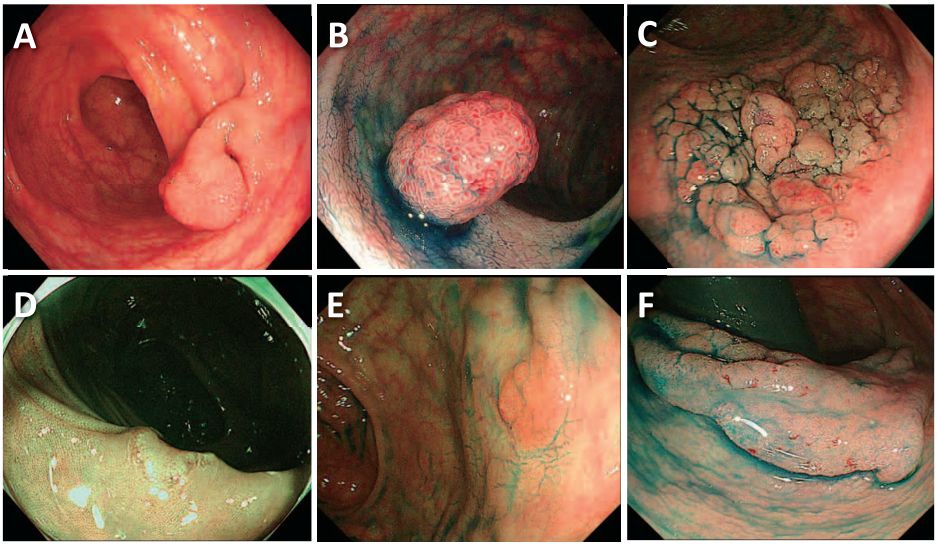

Fig. 1. Typical endoscopic images of 6 different types of advanced neoplasms. (A) Polypoid lesion (pedunculated type ; 0-Ip), (B) polypoid lesion (sessile type ; 0-Is), (C) laterally spreading tumor granular type lesion (LST-G ; 0-IIa+Is), (D) depressed lesion (0-IIc), (E) flat lesion (0-IIa), and (F) laterally spreading tumor non-granular type lesion (LST-NG ; 0-IIa). A, B, and C were classified as the polypoid group, and D, E, and F were classified as the non-polypoid group in the present study.

RESULTS

Patient characteristics

Data on consecutive colonoscopies (n=10,632) performed in 7,251 patients were collected, out of which 5,768 colonoscopies for 4,841 patients met all inclusion/exclusion criteria and were analyzed (Fig. 2). A total of 2,979 patients did not undergo colonoscopy during the past 5.5 years or were tested for the first time (Table 1). About one-third of these patients underwent colonoscopy because of a positive fecal occult blood test (35.7% ; 1063/2979 cases). Half of the patients who underwent repeated colonoscopy within the 0.5- to 5.5-year period were subjected to surveillance colonoscopy after polypectomy (50.2% ; 1399/2789 cases), which was similar to the proportion of patients within the 0.5- to 3.5-year period who were subjected to surveillance colonoscopy (52.8% ; 1284/2431 cases) (Table 1). Older age and male sex were associated with repeated colonoscopy within both the 0.5- to 5.5-year and 0.5- to 3.5-year periods ($p<0.001$ for both), as was a family history of CRC ($p=0.002$ and $p=0.02$, respectively).

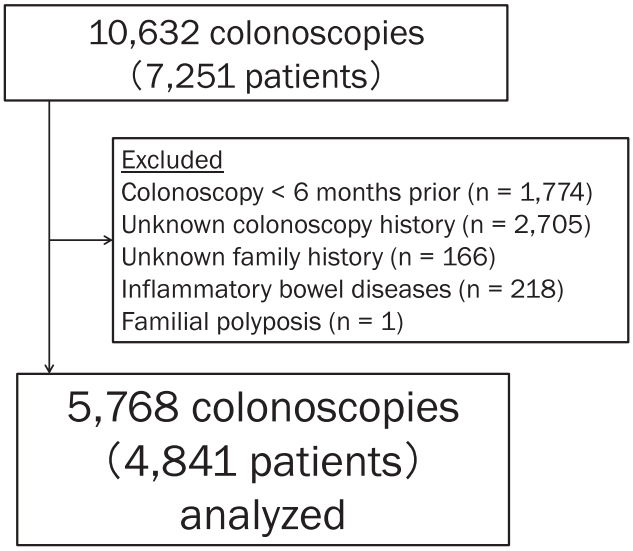

Fig. 2. Study flow.

Location and histological features of advanced neoplasms

Overall, 922 advanced neoplasms (including 217 cancers with ≥ T2, 41 cancers with T1, and 173 mucosal cancers) were detected during the study period, out of which 755 lesions were diagnosed as primary lesions (Table 2). We detected 142 lesions of PCANs during 0.5 to 3.5 years after colonoscopy (PCAN ≤ 3 y), and the number of PCANs increased to 167 lesions when collected from 0.5 to 5.5 years after colonoscopy (PCAN ≤ 5 y). To test whether PCANs with a relatively long interval after colonoscopy displayed distinct characters, we analyzed PCANs detected 3.5-5.5 years after the previous colonoscopy. However, there were no significantly differences in the distribution of their location ($p=0.560$) and histological features ($p=0.207$) between the PCAN 0.5-3.5 y and PCAN 3.5-5.5 y groups (data not shown). Based on these findings, we analyzed the characteristics of PCANs by comparing the differences between primary lesions and PCAN ≤ 3 y or PCAN ≤ 5 y.

First, we analyzed the location of PCANs. As shown in Table 2, the incidence of advanced neoplasms in the right-sided colon was significantly higher in the PCAN ≤ 5 y (48.5%, $p<0.001$) and PCAN ≤ 3 y (45.8%, $p<0.01$) groups compared with that in the primary group (34.0%). Especially, the incidence of advanced neoplasms in the transverse colon was doubled in the PCAN ≤ 5 y group when compared with that in the primary group (19.8% vs. 9.3%, $p<0.001$), whereas the incidence was reversed in the rectum between the PCAN ≤ 5 y (9.0%) and primary groups (19.6%, $p<0.01$). Similar differences were observed when comparing the PCAN ≤ 3 y and primary groups (Table 2).

We detected a total of 258 cancers with ≥ T1 during the test period (246 primary lesions in 234 patients and 12 PCAN ≤ 5 y lesions in 12 patients ; Table 2). Among the 258 cancers with ≥ T1, 210 out of 246 (85.4%) in the primary group and 7 out of 12 (58.3%) in the PCAN ≤ 5 y group were ≥ T2. As expected, the percentage of cancers with ≥ T1 in the PCAN ≤ 5 y group (7.2%, 12/167 lesions) was significantly lower compared with that in the primary group ($p<0.001$). Because of the small number of cancers with ≥ T1 in the PCAN ≤ 5 y group (12 lesions), we could not statistically compare the histological characteristics of cancers with ≥ T1 between PCANs and primary lesions. However, well-differentiated adenocarcinoma was the most dominant type for both the PCANs and primary lesions (Table 2), whereas poorly differentiated and mucinous adenocarcinomas were detected only in the primary lesions.

Table 1. Characteristics of the study patients

	Total (% of total cases)	Previous colonoscopy		
		None or > 5.5 y (% of 2,979 cases)	0.5-3.5 y (% of 2,431 cases)	0.5-5.5 y (% of 2,789 cases)
Cases	5,768	2,979	2,431	2,789
Male (%)	3,344 (58.0%)	1,555 (52.2%)	1,544 (63.5%)[a]	1,772 (63.5%)[a]
Age (years old, mean±SD)	63.7±12.4	62.0±13.7	65.5±10.4[a]	65.5±10.5[a]
Family history of CRC	502 (8.7%)	226 (7.6%)	234 (9.6%)[b]	276 (9.9%)[c]
Indications				
Fecal occult blood	1,298 (22.5%)	1,063 (35.7%)	157 (6.5%)	235 (8.4%)
Bloody stool	480 (8.3%)	390 (13.1%)	66 (2.7%)	90 (3.2%)
Abdominal symptoms	490 (8.5%)	366 (12.3%)	84 (3.5%)	124 (4.4%)
Surveillance after CRC operation	534 (9.3%)	13 (0.4%)	502 (20.6%)	521 (18.7%)
Surveillance after polypectomy	1,461 (25.3%)	62 (2.1%)	1,284 (52.8%)	1,399 (50.2%)
Medical examination	886 (15.4%)	708 (23.8%)	129 (5.3%)	178 (6.4%)
Others	619 (10.7%)	377 (12.7%)	209 (8.6%)	242 (8.7%)

[a]Significantly different compared with patients who did not undergo colonoscopy during the past 5.5 years or were tested for the first time ($p<0.001$).
[b]Significantly different compared with patients who did not undergo colonoscopy during the past 5.5 years or were tested for the first time ($p=0.02$).
[c]Significantly different compared with patients who did not undergo colonoscopy during the past 5.5 years or were tested for the first time ($p=0.002$).
SD, standard deviation ; CRC, colorectal cancer

Table 2. Localization and histological features of 922 advanced neoplasms

Location or histology	Primary lesions (% of 755 lesions)	PCAN ≤ 3 y (% of 142 lesions)	PCAN ≤ 5 y (% of 167 lesions)
Right-sided colon	257 (34.0%)	65 (45.8%)[b]	81 (48.5%)[a]
Cecum	51 (6.8%)	6 (4.2%)	7 (4.2%)
Ascending colon	136 (18.0%)	34 (23.9%)	41 (24.6%)
Transverse colon	70 (9.3%)	25 (17.6%)[b]	33 (19.8%)[a]
Left-sided colon and rectum	498 (66.0%)	77 (54.2%)[b]	86 (51.5%)[a]
Descending colon	52 (6.9%)	15 (10.6%)	17 (10.2%)
Sigmoid colon	298 (39.5%)	49 (34.5%)	54 (32.3%)
Rectum	148 (19.6%)	13 (9.2%)[b]	15 (9.0%)[b]
Adenoma with low-grade dysplasia	66 (8.7%)	16 (11.3%)	21 (12.6%)
Villous adenoma	18 (2.4%)	12 (8.5%)[a]	16 (9.6%)[a]
Traditional serrated adenoma	9 (1.2%)	1 (0.7%)	1 (0.6%)
Adenoma with high-grade dysplasia (including mucosal cancer)	382 (50.6%)	103 (72.5%)[a]	115 (68.9%)[a]
≥ T1 cancer	246 (32.6%)	8 (5.6%)[a]	12 (7.2%)[a]
Well-differentiated	198	5	8
Moderately differentiated	39	3	4
Poorly differentiated	6	0	0
Mucinous adenocarcinoma	3	0	0
Unknown	34 (4.5%)	2 (1.4%)	2 (1.2%)

PCAN ≤ 3 y, post-colonoscopy advanced neoplasms detected 0.5-3.5 years after a previous negative colonoscopy ; PCAN 4-5 y, post-colonoscopy advanced neoplasms detected 3.5-5.5 years after a previous negative colonoscopy ; PCAN ≤ 5 y, post-colonoscopy advanced neoplasms detected 0.5-5.5 years after a previous negative colonoscopy. PCAN ≤ 5 y includes PCAN ≤ 3 y and PCAN 4-5 y lesions.
[a]Significantly different compared with primary advanced neoplasms ($p < 0.001$).
[b]Significantly different compared with primary advanced neoplasms ($p < 0.01$).

As for the advanced adenomas, the incidences of adenomas with high-grade dysplasia and villous adenomas were significantly higher in the PCAN ≤ 3 y and PCAN ≤ 5 y groups compared with in the primary group ($p < 0.001$; Table 2).

Macroscopic morphology of advanced neoplasms

Next, we excluded the 217 cancers with ≥ T2 from the 922 advanced neoplasms, and the 705 remaining advanced neoplasms (545 primary lesions and 160 PCANs) were subjected to analysis of the tumor morphology (Table 3). The 705 advanced neoplasms were macroscopically divided into two groups : the polypoid and non-polypoid groups. Generally, many LST-G lesions possess a polypoid component ; therefore, LST-G was included as a subgroup of the polypoid group in this study. The non-polypoid group included three types of lesions : flat, depressed, and LST-NG lesions. The incidence of non-polypoid lesions was significantly higher in the PCAN ≤ 3 y (25.2%, $p < 0.001$) and PCAN ≤ 5 y groups (25.6%, $p < 0.001$) than in the primary group (12.3%). Among the subgroups of the non-polypoid group, the incidences of flat lesions (< 10 mm) were significantly higher ($p < 0.001$) in the PCAN ≤ 3 y (9.4%) and PCAN ≤ 5 y (10.0%) groups compared with that in the primary group (2.2%). A significantly higher incidence of LST-NG in PCANs was observed only when comparing between the PCAN ≤ 5 y and primary groups ($p < 0.05$). We also examined the distribution of tumor morphology between the PCAN ≤ 3 y and PCAN 4-5 y groups, and confirmed that there was no significant difference ($p = 0.771$).

Cases with ≥ T1 cancer detected within 5 years after colonoscopy

Among the 258 cancers with ≥ T1 detected during the test period, 12 lesions were detected within 5 years after colonoscopy (so-called "interval cancers" ; Table 4). As described above, 7/12 lesions (58.3%) were ≥ T2 cancers, and one case had distant metastasis

Table 3. Morphological characteristics of 705 advanced neoplasms, excluding ≥ T2 cancers

Macroscopic morphology	Primary lesions (% of 545 lesions)	PCAN ≤ 3 y (% of 139 lesions)	PCAN ≤ 5 y (% of 160 lesions)
Polypoid group	478 (87.7%)	104 (74.8%)[a]	119 (74.4%)[a]
Polypoid	443 (81.3%)	98 (70.5%)[b]	113 (70.6%)[b]
LST-G	35 (6.4%)	6 (4.3%)	6 (3.8%)
Non-polypoid group	67 (12.3%)	35 (25.2%)[a]	41 (25.6%)[a]
Flat (< 10 mm)	12 (2.2%)	13 (9.4%)[a]	16 (10.0%)[a]
Depressed	9 (1.7%)	3 (2.2%)	3 (1.9%)
LST-NG	46 (8.4%)	19 (13.7%)	22 (13.8%)[c]

LST-G, laterally spreading tumor granular type ; LST-NG, laterally spreading tumor non-granular.
[a]Significantly different compared with primary advanced neoplasms ($p < 0.001$).
[b]Significantly different compared with primary advanced neoplasms ($p < 0.01$).
[c]Significantly different compared with primary advanced neoplasms ($p < 0.05$).

Table 4. Cases with ≥ T1 cancer detected within 5 years after colonoscopy

Age (y)	Sex	Location	Morphology†	Histology	Stage‡	Previous colonoscopy	Findings of previous colonoscopy (location)
62	F	A	2	Wel	III	4 years ago	Negative
61	M	A	0-IIc	Mod	I	One year ago	Small adenoma (D)[a]
80	M	A	2	Mod	II	5 years ago	Negative
82	F	T	2	Wel	IV	3 years ago	Negative
72	F	T	2	Mod	I	One year ago	Small adenoma (S)[b] and SSA/P (A)[b]
43	M	S	0-Ip	Wel	I	2 years ago	Negative
65	M	S	0-IIa+IIc (LST-NG)	Wel	I	3 years ago	Small adenoma (T)[a]
78	F	R	2	Wel	II	One year ago	T3 cancer (S)[c]
60	M	R	0-Is	Wel	I	3 years ago	Small adenoma (S)[a]
50	F	R	0-IIa+Is (LST-G)	Mod	I	3 years ago	Negative
67	M	R	2	Mod	III	4 years ago	Small adenoma (S)[d]
77	M	R	2	Wel	II	5 years ago	Small adenoma (S)[b]

A, ascending colon ; T, transverse colon ; D, descending colon, S, sigmoid colon ; R, rectum, Wel, well-differentiated adenocarcinoma ; Mod, moderately differentiated adenocarcinoma ; LST-NG ; laterally spreading tumor non-granular type ; SSA/P, sessile serrated adenoma/polyp.
† Morphology was categorized according to the Paris classification. ‡ Cancer stage was decided according to the American Joint Committee on Cancer/TNM system. [a]Removed by cold polypectomy. [b]Removed by endoscopic mucosal resection. [c]Removed by surgical intervention. [d]Not removed.

(Stage IV). Five of these 12 lesions (42%) were right-sided. As for the previous colonoscopic findings, 5/12 cases (42%) were negative, whereas small adenomas or sessile serrated adenoma/polyps (SSA/Ps) were detected in another segment from interval cancers in 6/12 cases (50%).

DISCUSSION

Screening and removal of precancerous lesions upon colonoscopy are indispensable for the prevention of CRC (2-5). Analysis of 5,768 colonoscopies for 4,841 patients in this study showed that 246 cancers with ≥ T1 were detected in 234 (7.8%) of the 2,979 patients undergoing colonoscopy for the first time or repeated colonoscopy after more than a 5.5-year interval, whereas this incidence was decreased to 0.4% (12 cases) of the 2,789 patients undergoing a repeated colonoscopy within 5.5 years (PCAN ≤ 5 y). Among the 12 cancers with ≥ T1 in the PCAN ≤ 5 y group, 7 lesions were ≥ T2 cancers. The remaining 160 PCANs were still early-stage cancers. Thus, our results confirm the importance of colonoscopy to reduce the risk for life-threatening CRC.

At the same time, however, a significant number of advanced neoplasms could be detected as PCANs. It might be difficult to determine whether the detected PCANs were caused by missed lesions or rapid growth of the lesions. In this regard, a number of recent researches have suggested that most cases of interval cancers are caused by missed lesions in the previous colonoscopy (6, 10, 16-20). Therefore, it is particularly important to reveal the crucial factors related to why the lesions were missed at the previous colonoscopy. Several studies have shown that the prevalence of right-sided CRC is not successfully reduced after colonoscopy as compared with left-sided CRC (3, 4, 27-29). In agreement with those reports, the incidence of right-sided lesions was significantly higher in PCANs than in primary lesions in the present study. To more strictly examine missed, advancedre neoplasms after colonoscopy, we also analyzed PCANs detected within 3.5 years after the previous colonoscopy (PCAN ≤ 3 y). However, even in this case, the incidence of right-sided lesions was significantly higher in PCANs compared with that in primary lesions. The different biological features of right-sided lesions and higher probability of missing lesions in the right-sided colon may explain the lack of reduction in right-sided CRC (6, 16, 17).

Although the distribution and risk factors of interval cancers after negative colonoscopy have been extensively studied, the macroscopic tumor morphology has not been investigated in detail. This investigation is particularly important from the viewpoint of oversight. Non-polypoid neoplasms are typically located in the right-sided colon (30, 31). The importance of non-polypoid lesions was advocated by Kudo *et al.* in the 1990s in Japan (32), and non-polypoid neoplasms are now relatively common even in Western countries (33-39). Meanwhile, LST has been recognized as a type of non-polypoid lesion (31, 40-43). As for the molecular biological mechanism, non-polypoid neoplasms differ from polypoid lesions. Especially, one study suggested that depressed and LST-NG lesions less frequently show *KRAS* mutations compared to polypoid lesions (44), whereas these mutations are relatively common in LST-G (41). Based on these findings, in this study, LST-G was classified into the polypoid group, because the characteristics of LST-G are consider to differ from those of other non-polypoid lesions.

As a result, we found that the incidence of non-polypoid lesions was significantly higher in the PCAN ≤ 5 y group than in the primary group. Especially, the rates of flat lesions (< 10 mm) and LST-NGs were higher in the PCAN ≤ 5 y group than in the primary group. The morphology of early-stage *de novo* cancer has been considered to frequently be non-polypoid, especially the depressed type (45) ; these cancers can rapidly grow and invade deep into the tissue, while the tumors still appear small. In this study, there was no significant difference in the incidence of depressed polyps between primary lesions and PCANs ; we identified 3 (1.9%) and 9 lesions (1.7%) of depressed polyps in the 545 primary lesions and 160 PCANs, respectively. In contrast, LST-NG lesions represented the majority of non-polypoid PCANs in the present study. LST-NG lesions can be easily missed upon colonoscopy because of their flat shape, indicating that LST-NG lesions might be an important candidate precursor for interval CRC.

SSA/P is also typically located in the right-sided colon and has been recently recognized as a precursor to CRC (46). Accordingly, the difficulty of SSA/P detection via colonoscopy is noted as one of the factors impeding early prevention of interval cancers in the right-sided colon. However, SSA/P was not included as an endpoint in this study.

We also analyzed PCANs detected 3.5 to 5.5 years after the previous colonoscopy (PCAN 4-5 y) to test whether PCANs displayed somewhat different characteristics depending on the interval after

colonoscopy. The location and morphological features of the PCAN ≤ 3 y group were similar to those of the PCAN 4-5 y group, suggesting that most PCANs were likely to be missed, slowly growing lesions.

Despite the fact that the proportions of non-polypoid and right-sided lesions in PCANs are high, polypoid and left-sided lesions are still considered important, as they account for the highest number of total lesions. In the present study, more than half of all cancers with ≥ T1 detected within 5 years after colonoscopy were left-sided lesions. Hence, we should still pay close attention to left-sided and polypoid lesions in order to prevent interval CRC.

Recently, several instruments and techniques to identify and prevent missed lesions located behind the folds have been reported, including cap-assisted colonoscopy (47), the retroflection technique (48, 49), and various novel types of colonoscopies to improve the polyp detection rate (50). These techniques may prove to be useful especially in the right-side colon, as the frequency of folds in the right-sided colon tends to be high. Furthermore, image-enhanced endoscopy has also been discussed for the detection of colorectal polyps (51-53). The rate of missed lesions may decrease in the future using these novel endoscopies and techniques.

This study has several limitations. First, it is a retrospective, single-center study. Second, patients who undergo repeated colonoscopy are often at relatively high risk for CRC and may hence not represent the general population. Third, the quality of the previous colonoscopy (e.g. preparation status) could not be evaluated in this study. However, despite these limitations, the results of this study provide important information about the characteristics of lesions detected after colonoscopy. In particular, careful attention should be paid to non-polypoid and right-sided lesions during screening and surveillance colonoscopy.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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