



Post-colonoscopy colorectal cancers in average-risk Korean subjects with a normal initial colonoscopy

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ABSTRACT

Background/Aims: There are relatively few studies regarding the incidence of post-colonoscopy colorectal cancer (PCCRC) in Asian countries. We evaluated the characteristics of PCCRC in average-risk Korean subjects.

Materials and Methods: This study included subjects who were ≥ 50 years of age and had undergone a first completed colonoscopy between January 2001 and December 2004, at which no baseline adenoma had been detected, followed by a second colonoscopy 1–5 years later. The incidences and characteristics of advanced neoplasia in these subjects were assessed.

Results: A total of 343 subjects underwent follow-up colonoscopy within 5 years. Seventy-three (21.3%) subjects were found to have at least one adenoma on follow-up colonoscopy. Advanced adenoma was found in eight (2.3%) subjects, and non-advanced adenomas were found in 65 (19.0%). Five (1.5%) subjects were diagnosed with invasive CRC following a normal colonoscopy. The putative reason for PCCRCs was missed lesions in two (40.0%) subjects and a new cancer in three (60.0%).

Conclusion: The risk of advanced neoplasia (including PCCRCs) within 5 years after a normal baseline colonoscopy in our cohort was not low. Considering that 40% of PCCRCs were attributable to missed lesions, our results emphasize the need for technical improvement of colonoscopic examinations to improve adenoma detection.

Keywords: Colonoscopy, colonic neoplasms, colorectal cancer

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide. The incidence of CRC has rapidly increased in recent decades in many Asian countries (1). In Korea, CRC is the second most common cancer in males and the third most common in females (2). Although mortality rates because of some common cancers, including stomach cancer and cervical cancer, have continuously decreased, those of CRC have continued to increase (2). On the basis of the cancer-related death statistics reported by the South Korea National Statistical Office from 1983 to 2000 and a projection of cancer mortality for 2001 and 2005, the National Cancer Center of Korea reported a 35% increase in mortality because of CRC in males and females (3). Because of the burden of CRC in Korea, a national CRC screening program that involves annual fecal occult blood testing was initiated in 2004 (4).

Among several screening methods, colonoscopy is widely accepted as an alternative screening test of choice for average-risk individuals because it enables removal of precancerous polyps at the time of detection (5). The recently published Asia–Pacific consensus report recommends a repeat colonoscopy at a 10-year interval after a normal colonoscopy (6). This 10-year interval is based on the estimates of the sensitivity of colonoscopy and the presumed time required for the natural progression of an adenoma to carcinoma (5,7). However, colonoscopy is imperfect and can fail to detect colorectal adenoma or even cancer. A meta-analysis of six tandem colonoscopy studies involving a total of 465 patients demonstrated that the pooled miss rate for polyps of any size was 22%, with a 2.1% miss rate for adenomas of ≥ 10 mm (8).

Emerging evidence indicates that the incidence of interval cancers markedly varies, ranging from 1 in 130 to

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1 in 1,000 colonoscopies or 1 in 13 to 1 in 45 of all diagnosed CRCs (9). While the term "interval CRC" appears to be suitable for CRCs identified in the interval between screening and surveillance, the term "post-colonoscopy CRC (PCCRC)" describes CRCs found after a colonoscopic examination, regardless of whether the indication for colonoscopy is screening or diagnosis (10). Few published studies have evaluated the incidence of PCCRC after a negative colonoscopy in Asian countries. This study aimed to evaluate the characteristics of CRCs identified at a second colonoscopy within 5 years after a normal initial colonoscopy in average-risk Korean subjects.

MATERIALS AND METHODS

Study population

This retrospective analysis of prospectively collected data was performed using information from the endoscopy, clinical records, and pathology database system of our hospital. Subjects were eligible if they were 50 years or older and had undergone a first completed colonoscopy between January 2001 and December 2004, at which no baseline adenoma was detected, followed by a second colonoscopy 1–5 years later. The influence of more than one repetitive colonoscopy in some patients was not considered in this study. We excluded the following cases: those with a prior history of CRC; surgical resection of the colon or rectum; inflammatory bowel disease; a family history of familial adenomatous polyposis, hereditary non-polyposis CRC, or familial CRC; and incomplete examination of the entire colon because of poor bowel preparation or technical difficulties during the procedure.

Study procedures

Subjects were administered polyethylene glycol–electrolyte lavage solution on the day before colonoscopy for bowel preparation and meperidine for sedation. All colonoscopies were performed using a standard Olympus single-channel colonoscope (Olympus Optical; Tokyo, Japan) by four experienced colonoscopists each of whom performs >500 colonoscopies per year. Examinations were considered complete when the colonoscope reached the cecum. During the examination, the location and size of all polyps were noted and recorded in a computerized database. The size of each polyp was estimated using open-biopsy forceps. The colon was divided into the distal (rectum, sigmoid colon, and descending colon) and proximal (splenic flexure, transverse colon, hepatic flexure, ascending colon, and cecum) regions.

All polyps detected during the follow-up colonoscopy, with the exception of tiny hyperplastic polyps in the rectum and distal sigmoid colon, were removed using biopsy forceps, conventional polypectomy, or endoscopic mucosal resection, and the obtained samples were sent for histological evaluation. The Vienna classification was used for histological classification of colorectal neoplasias (11). For invasive cancer, the TNM classification system was used for post-operative pathological staging

according to the 7th edition of the American Joint Committee on Cancer staging criteria. Patients with multiple lesions were classified according to the most advanced lesion. Advanced adenomas were defined as those with a size of ≥ 10 mm, tubulovillous (villous component of $>20\%$) or villous histology, and/or high-grade dysplasia. Because Western pathologists identify intramucosal carcinoma as adenoma with high-grade dysplasia (12), we also defined invasive carcinoma as a lesion extending into the submucosa or beyond.

Statistical analysis

Values were expressed as mean \pm standard deviation (SD). Continuous data were compared using an independent sample t-test, whereas categorical data were analyzed using χ^2 or Fisher's exact tests. Data were processed and analyzed using SPSS version 12.0 (SPSS Inc.; Chicago, IL, USA). A p value of <0.05 was considered to indicate statistical significance for all tests.

Ethics statement

This study protocol was approved by the Institutional Research Ethics Board of our institution (IRB No: UC11RISI0146) and adhered to the principles of the Declaration of Helsinki. All of the study subjects completed an informed consent form before participating in the study. The informed consent was confirmed by the Research Ethics Board.

RESULTS

Among subjects who had undergone a first completed colonoscopy between January 2001 and December 2004, 343 subjects who underwent a second colonoscopy 1–5 years later were enrolled (Table 1). The mean age of the subjects was 60.3 ± 7.2 years, and males comprised 39.9% of the study population. The average colonoscopy interval was 41.3 months

Table 1. Baseline clinical characteristics of patients

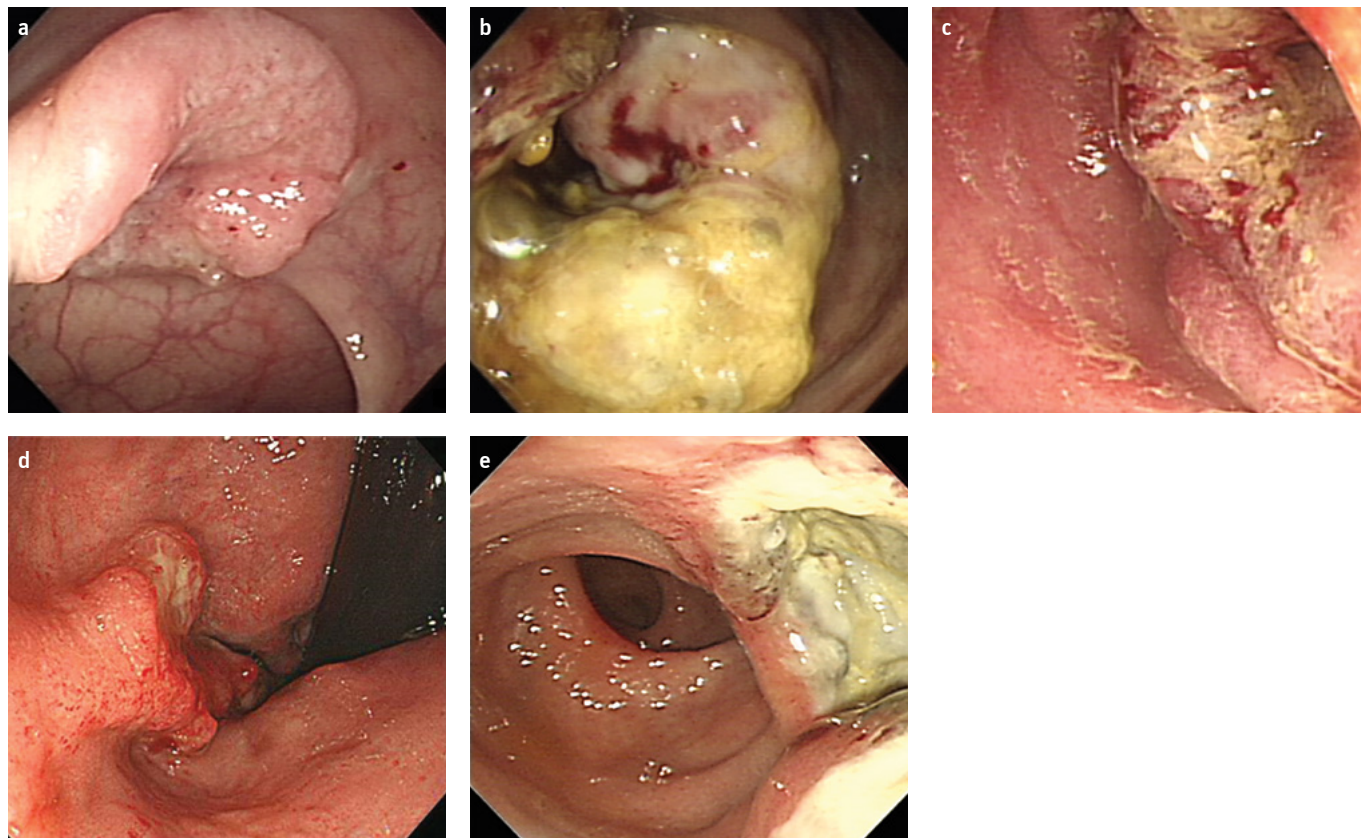
Characteristics	Value
Age, years	60.3 \pm 7.2
50–59	171 (49.8)
60–69	132 (38.5)
70–79	38 (11.1)
80–89	2 (0.6)
Male sex	137 (39.9)
Interval of colonoscopy (months)	41.3 \pm 14.2
Indication of index colonoscopy	
Abdominal pain or discomfort	154 (44.9)
Screening	83 (24.2)
Changes in bowel habits	78 (22.7)
Blood in stool	21 (6.1)
Anemia evaluation	7 (2.1)

Data are presented as Mean \pm SD or numbers (%).

Table 2. Characteristics of five patients diagnosed with invasive cancer during the 5-year follow-up period

Case number	Age/sex	Indication	Location	Months since initial colonoscopy	Macroscopic type	Stage
1	61/M	Routine surveillance	Rectum	60	Ila+Ilc (depressed)	I
2	74/F	Abdominal pain	Ascending	34	Ulcerofungating	III
3	60/M	Changes in bowel habits	Sigmoid	44	Ulcerofungating	III
4	51/M	Abdominal pain	Rectum	50	Ulceroinfiltrative	III
5	80/M	Blood in stool	Rectum	35	Ulceroinfiltrative	IV

M: male; F: female

**Figure 1. a-e.** Colonoscopic views of the five post-colonoscopy CRCs. Case 1 (a), Case 2 (b), Case 3 (c), Case 4 (d), and Case 5 (e).

(range, 12–60 months). The most frequent indication for a first colonoscopy was abdominal pain or discomfort (44.9%), followed by screening (24.2%), changes in bowel habits (22.7%), blood in stool (6.1%), and anemia evaluation (2.1%). The most common indication for follow-up colonoscopy was abdominal pain or discomfort (38.2%), followed by routine surveillance (36.1%), changes in bowel habits (16.9%), blood in stool (7.9%), and anemia evaluation (0.9%).

Of the 343 subjects, 73 (21.3%) were found to have at least one adenoma on follow-up colonoscopy. Advanced adenoma was found in eight (2.3%) subjects, and non-advanced adenomas were found in 65 (19.0%). Thirty-two (9.3%) subjects had more than one adenoma in the colon. Of the eight advanced adenomas, four (50.0%) were located in the proximal colon. Five (1.5%) subjects were diagnosed with an invasive CRC following a normal colonoscopy (Table 2). Figure 1 shows the colono-

scopic appearance of these five PCCRC cases. In four (80.0%) subjects, the indications for colonoscopy at which the cancer was detected were symptoms suggestive of CRC and the other was routine surveillance. The mean age of patients found to have cancer was 65.2 ± 11.6 years. The average interval from the first colonoscopy to cancer detection was 44.6 months (range, 34–60 months). There were no significant differences in age, sex, and indications for colonoscopy at the time of initial examination between patients with and without PCCRC. Of PC-CRC cases, one (20.0%) was submucosal cancer and the other four (80.0%) were advanced cancers. Four (80.0%) were located on the left side of the colon. According to the American Joint Committee in Cancer staging criteria, one patient had stage I disease, three had stage III, and one had stage IV disease. The patient with stage IV disease subsequently died because of CRC during the follow-up period. According to Pabby et al. (13), each case of post-colonoscopy CRC was assigned to one of the

two categories: missed (if cancer was found within 3 years of the prior colonoscopy and the examination at which cancer was diagnosed and there was no evidence of a significant adenoma in the same segment of the colorectum at the prior examination) or new cancers (if ≥ 3 years had elapsed since the prior colonoscopy, and no significant adenoma was detected in the same segment at that examination). The putative reasons for PCCRCs were missed lesions in two (40.0%) cases and new cancer in three (60.0%). Of the two cases classified as probable missed lesions, the diagnosis may have been delayed in one case, in which the cancer was located in the lower rectum, because of the absence of rectal retroflexion.

DISCUSSION

In this study, we found that the risk of occurrence of advanced neoplasia, including PCCRC, within 5 years was 3.8% among average-risk Korean subjects with no baseline adenoma. Emerging evidence indicates that the risk of advanced adenoma 5 years after a normal baseline colonoscopy is low, and the interval of surveillance colonoscopy could be determined according to the baseline risk stratification. Imperiale et al. (14) reported that the risk of advanced adenoma determined on re-screening among 1256 subjects with no colorectal neoplasia on initial screening colonoscopy was 1.3%. Leung et al. (15) demonstrated that the risk of advanced adenoma for asymptomatic average-risk Chinese subjects aged 55–75 years at 5 years was 1.4%. In one prospective study, the 5-year incidences of advanced adenoma in the normal (no baseline adenoma), low-risk (1–2 adenomas of <10 mm), and high-risk (an advanced adenoma or ≥ 3 adenomas) groups were 2.4%, 2.0%, and 12.2%, respectively (16). However, no invasive cancer was identified in these cohorts. A recent Japanese multicenter retrospective cohort study demonstrated that the cumulative incidence of advanced neoplasia among 2006 patients over 40 years without adenoma during the mean follow-up period of 5.1 years was 2.4% (17). Of 52 advanced neoplasia cases, four (8%) were submucosal cancer and seven (13%) were advanced cancer. The relatively high risk of advanced neoplasia in our study could be attributable to its different design (i.e., involving clinic-based data) and population (i.e., screening and diagnostic indications) and the small sample size.

Recent large population-based studies that evaluated the incidence and risk of interval CRCs at colonoscopy reported that the incidence varies from 2.9% to 7.9% (18–23). In addition, these studies demonstrated the protective effect of colonoscopy against CRC; however, they also reported that the efficacy of this technique in the proximal colon was limited. This large variation in incidence rates could be attributed to the different methodological designs (i.e., retrospective vs. prospective and claims-based administrative vs. clinical data), differences in the definitions of interval cancers, differences in study populations (screening vs. diagnostic indication), and differences in endoscopic techniques (10). In a pooled analysis of eight large North American prospective studies that involved 9167 participants

with a median follow-up of 47.2 months, the incidence of interval cancer was low (0.6%, or 1.71 per 1000 person-years of follow-up) (24). However, assuming that the incidence of new cases of CRC is approximately 1,000,000 per year worldwide and considering that 1 of 30 diagnosed CRCs is an interval cancer, the occurrence of $>30,000$ interval cancers might be annually expected (9). In both our study and a prior Japanese multicenter retrospective study (17), the incidences of PCCRC were lower (1.5% and 0.55%, respectively) compared with those in Western studies. This discrepancy could be a result of our retrospective, clinic-based study design, use of different study populations, and/or ethnic differences.

Two important reasons for the occurrence of interval CRCs are technical failure of colonoscopy and distinct molecular biological characteristics, inducing the more-aggressive clinical behavior of precursor lesions (9). Pabby et al. (13) developed an algorithm to classify each case of interval CRCs into one of the following four etiologies: 1) incomplete adenoma resection (cancer at the site of a previous adenoma), 2) failed biopsy detection (cancer in an area of suspected neoplasia with negative biopsy specimens), 3) missed cancer, or 4) new cancer. In this study, each case of PCCRC was classified into missed or new cancer because our cohort included only patients with no baseline adenoma. Of the five patients with PCCRC, two were ascribed to missed lesions and three to new lesions. Although it is impossible to evaluate the exact frequency of missed lesions during colonoscopy, recent studies suggest that 23%–58% of PCCRCs are attributable to missed lesions (18,20,24,25). The reasons for missed lesions include incomplete bowel preparation, suboptimal withdrawal time and technique, and differences in the knowledge and training of endoscopists regarding the recognition of subtle-appearing precursor lesions, such as flat and depressed adenoma or sessile serrated adenomas/polyps (SSA/P) (9). Kaminski et al. (26) demonstrated that the endoscopist's adenoma detection rate (ADR) is an independent predictor of the risk of interval CRC after screening colonoscopy. In this study, endoscopists with an ADR in the lower ranges (e.g., $<11\%$, 11% – 14.9% , and 15% – 19.9%) had a 10-fold greater risk of interval CRCs than those with an ADR of $\geq 20\%$. In this study, the endoscopist's ADR could not be used to predict the risk of PCCRCs because all endoscopists were experienced. Of our cases classified as probable missed lesions, rectal retroflexion was not performed in one case in which the cancer was located very low in the rectum, which could explain the missed lesion. Previous studies of the value of routine retroflexion have reported inconsistent results. While Varadarajulu et al. (27) revealed the highest yield of routine retroflexion wherein six had tubular adenomas detected only by retroflexion maneuver among 590 patients, other researchers have reported that routine retroflexion did not enable detection of clinically important neoplasia (28,29). Because the absence of rectal retroflexion can lead to missed lesions, careful rectal examination that includes rectal retroflexion could facilitate the detection of rectal neoplasia.

Another potential explanation for PCCRCs is the more-aggressive biological behavior of some types of cancer. There are few data available regarding the contribution of biological factors to the occurrence of PCCRCs. Recent studies have demonstrated that microsatellite instability and the cytosine–phosphate–guanine island methylator phenotype, which are more common among cancers in the proximal colon, are associated with interval cancers (30,31). However, additional research is necessary because these studies were performed on the same sample of 63 CRCs from a predominant male population of veterans. In addition, certain phenotypes of non-polypoid colorectal neoplasms, particularly the lateral spreading tumors of the non-granular type and depressed lesions, and SSA/P could be common precursor lesions of PCCRCs that were classified as new cancer because they exhibit a more-aggressive biological behavior (32,33). Further molecular research is required to understand the biology of these lesions. However, substantial differences in biological behavior appear unlikely because the survival of patients with PCCRC does not appear to differ from that of those without PCCRC (34).

There were several limitations to our study. First, it was a single-center, retrospective cohort study with a relatively small sample size. Furthermore, the indications for colonoscopy at the time of initial examination were not only screening but also diagnosis. Second, we did not evaluate the risk of colorectal advanced neoplasia after polypectomy, patient-related risk factors (physical activity, smoking status, body mass index, etc.), and endoscopist-related risk factors (ADR and withdrawal time). Enough withdrawal time is one of the most important factors to improve ADR (35). Although information regarding withdrawal time is not available in considerable number of included patients during the study period, all colonoscopies were performed by experienced colonoscopists who keep spending a mean of 6 or more minutes on withdrawal. Third, the majority of patients in our study were aged 50–70 years. The inclusion of a small number of patients aged ≥ 70 years could limit the generalizability of our results.

In conclusion, the risk of advanced neoplasia, including PCCRCs, within 5 years after a normal baseline colonoscopy in average-risk Korean subjects was not low. To recommend surveillance colonoscopy at a 10-year interval after normal colonoscopy, a further large, prospective study is necessary. Considering that 40% of PCCRCs could be attributed to missed lesions, our results emphasize the requirement for technical improvements of colonoscopic examinations to improve adenoma detection.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Institutional Research Ethics Board of Uijeongbu St. Mary's Hospital / (Project No: UC11RIS10146)

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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