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Do surveillance intervals in patients with more than five adenomas at index colonoscopy be shorter than those in patients with three to four adenomas? A Korean Association for the Study of Intestinal Disease study

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adenoma, colorectal, surveillance.

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Abstract

Background and Aim: There is controversy about the surveillance interval after colonoscopy when 5–10 adenomas have been found on index colonoscopy. This study aimed to investigate the risk of colorectal neoplasm (CRN) according to the number of adenomas at index colonoscopy.

Methods: A retrospective, multicenter study was conducted at 10 university hospitals in Korea. We included 1394 patients with ≥ 3 adenomas at index colonoscopy. The risk of advanced CRN was compared according to the number of adenomas (intermediate risk group, 3–4 small adenomas or at least one ≥ 10 mm, and high risk group, ≥ 5 small adenomas or ≥ 3 at least one ≥ 10 mm).

Results: Overall, 164 (11.8%) developed an advanced CRN after a mean of 4.0 years from baseline colonoscopy. The 3-year and 5-year risk of advanced CRN was 2.1% (95% CI 2.09–2.11) and 14.4% (95% CI 14.36–14.44) in intermediate risk group and 3.2% (95% CI 3.19–3.21) and 23.3% (95% CI 19.15–19.25) in high risk group (P = 0.01). Having ≥ 5 adenomas (OR = 1.57, 95% CI 1.11–2.23, P = 0.01) detected at index colonoscopy was a significant risk factor for developing advanced CRN.

Conclusions: Although risk of advanced CRN in patients with 5–10 adenomas was significantly higher than that in patients with 3–4 adenomas, the cumulative risk at 3 years was low at 3.2%. Thus, we suggest that a 3-year surveillance interval might be appropriate for the patients with 5–10 adenomas, and further prospective studies are needed to investigate whether more intensive surveillance is needed in this group.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in Western countries,[1] and the prevalence of CRC is rapidly increasing in Asian countries.[2] Colonoscopic screening with polypectomy is an effective strategy to reduce the incidence and mortality of CRC.[3,4] In addition, colonoscopy surveillance has been recommended after the removal of colorectal neoplasms (CRNs) because of the increased risk of metachronous CRN during follow up.[5–7]

Current guidelines recommend surveillance intervals based on the findings at baseline colonoscopy. A recent consensus by the US Multi-Society Task Force on Colorectal Cancer identified two major risk groups based on the likelihood of developing an advanced CRN during surveillance.[5] In patients with high-risk adenomas, defined as adenomas with villous histology, high-grade dysplasia (HGD), adenoma ≥ 10 mm, or 3–10 adenomas, surveillance at 3 years is recommended. However, recently updated guidelines of the British Society of Gastroenterology differ from the United States guidelines, by categorizing patients into

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three groups: low risk (1–2 adenomas, < 10 mm), intermediate risk (3–4 small adenomas or 1 adenoma ≥ 10 mm), and high risk (≥ 5 small adenomas or 3 with at least one ≥ 10 mm).[7] These updated guidelines recommend a 1-year surveillance interval in the high-risk group because of concerns of missed lesions at baseline.

As these two guidelines differ in the risk assessment approach when 5–10 adenomas are detected at index colonoscopy, we aimed to investigate the risk of developing CRN after adenoma removal in patients with 5–10 adenomas at index colonoscopy and to compare it with that in patients with 3–4 adenomas.

2. Methods

2.1. Study population. This retrospective, multicenter cohort study included patients with ≥ 3 adenomas or one or more adenomas > 10 mm in diameter at index colonoscopy between January 2007 and December 2008 who had undergone follow-up colonoscopy at intervals of 2.5 years or longer until December 2014, from 10 university hospitals belonging to the Korean Association for the Study of Intestinal Disease. The patients in this study underwent colonoscopy by 32 endoscopists. Their median adenoma detection rate was 31.5 (range 22.2–44.0), and their mean withdrawal time was 9.3 ± 3.5 min.

Patients were excluded if they had > 10 adenomas, a history of CRC, inflammatory bowel disease, a polyposis syndrome (e.g., familial adenomatous polyposis, juvenile polyposis, Peutz-Jeghers syndrome, and Cowden syndrome), incomplete colonoscopy (did not reach the cecum), inadequate bowel preparation (according to the Boston bowel preparation scale [BBPS], who showed less than 1 segment BBPS score or a total BBPS score less than 5], incomplete colorectal polyp resection, CRC in the submucosal layer or deeper invasion, or had undergone surgical resection of the intestine. This study was approved by the institutional review boards at Kangbuk Samsung Hospital and the participating medical centers.

2.2. Data collection and outcome measurement. Data of patients in this study included age, sex, body mass index (BMI), smoking history, family history of CRC, and history of aspirin or nonsteroidal anti-inflammatory drug use. Information on the number, size, histologic characteristics, and location of polyps at index and follow-up colonoscopy was recorded. The polyp size was measured by endoscopists during colonoscopy, and 19 expert pathologists reviewed the histologic characteristics of the polyps.

Advanced adenoma was defined as an adenoma with a diameter ≥ 10 mm or with a villous component or HGD. Pathologic results of intramucosal carcinoma or carcinoma *in situ* were considered indicative of HGD, and hyperplastic or inflammatory polyps were considered normal findings. Serrated adenomas were considered to be adenomas. The location of adenomas was classified as right side (cecum, ascending colon, hepatic flexure, and proximal transverse colon), left side (distal transverse colon, splenic flexure, descending colon, sigmoid, and rectum), or both.

For the outcome measurements, we analyzed all surveillance exams if patients underwent multiple colonoscopies. Overall, CRN was defined as cancer or any adenoma, and advanced CRN was defined as cancer or advanced adenoma. Cancer stage was described according to the American Joint Committee on Cancer, CRC staging, 7th edition. Clinical outcomes were based on the cumulative probabilities of detecting overall and advanced CRN at any surveillance colonoscopies performed ≥ 2.5 years after baseline colonoscopy.

2.3. Statistical analysis. Continuous variables are expressed as mean ± standard deviation, and discrete data are expressed as number and percentage. Differences of baseline characteristics at index colonoscopy and findings on surveillance colonoscopy, including interval duration of colonoscopy, overall/advanced CRN, and location of CRN, were compared with chi-square analysis or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. The absolute risk of both overall and advanced CRN was calculated using the Kaplan–Meier method, and the absolute risk was compared according to the number of adenomas at index colonoscopy using the Breslow test. We used Cox-proportional hazard regression analysis after adjusting for potentially confounding variables including age (per 1 year), sex (male vs. female), family history of CRC (yes vs. no), obesity (BMI ≥ 25.0 kg/m^2 vs. < 5 kg/m^2), smoking status (Current or ex-smoker vs. non-smoker), use of aspirin/NSAIDs (yes vs. no), and adenoma characteristics (HGD vs. LGD, TVA/VA vs. TA, size > 10 mm vs. < 10, number 5–9 vs.3–4) to assess for risk factors for CRN. Correlations between potential predictors and outcomes of interest were estimated by odds ratios (ORs) with 95% confidence intervals (CIs). *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS software (Version 18.0 SPSS Inc., for Windows).

3. Results

3.1. Baseline characteristics of patients. In total, 1394 patients with ≥ 3 adenomas or one or more adenomas > 10 mm in diameter were identified, and we divided these patients into two groups based on the British guidelines: the intermediate-risk group, with 3–4 small adenomas or at least one ≥ 10 mm, and the high-risk group, with ≥ 5 small adenomas or ≥ 3 and at least one ≥ 10 mm, with 768 and 626 patients, respectively. Baseline characteristics of the patients are shown in Table 1. The groups were not equal with regard to sex, age, smoking history, and medication history. There were no significant differences between groups in BMI and family history of CRC. The prevalence of advanced adenoma at index colonoscopy in the high-risk group was significantly higher than that of the intermediate-risk group (84.2% vs.62.1%, $P < 0.001$). Among advanced adenomas, the prevalence of HGD (23.0% vs. 17.8%, $P = 0.02$) and diameter ≥ 10 mm (79.9% vs. 54.6%, $P < 0.001$) was significantly higher in the high-risk group than in the intermediate-risk group.

3.2. Findings on surveillance colonoscopy. Overall, 973 (69.8%) patients developed CRNs and 164 (11.8%) developed advanced CRNs after a mean of 4.0 ± 1.3 years from baseline colonoscopy. Of 164 patients who developed advanced CRNs, 15 (1.1%) had HGD, 33 (2.4%) had villous histology and 144 (10.3%) had adenomas with diameters > 10 mm at surveillance colonoscopy. CRC was diagnosed in one (0.1%) patient in the

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Table 1 Baseline characteristics of patients at index colonoscopy

	Intermediate-risk group (n = 768)	High-risk group (n = 626)	P value
Age	58.5 ± 10.1	60.7 ± 9.7	< 0.001
Male sex	545 (71.0)	496 (79.2)	< 0.001
BMI (kg/m^2)[†]	24.3 ± 3.2	24.4 ± 2.7	0.54
Current or ex-smoker[‡]	223 (31.7)	214 (37.7)	0.03
Family history of CRC[§]	27 (3.8)	23 (4.0)	0.88
Aspirin or NSAID use[§]	89 (12.6)	97 (17.0)	0.03
Location of adenoma			< 0.001
Right	206 (26.8)	80 (12.8)	—
Left	277 (36.1)	92 (14.7)	—
Both	285 (37.1)	454 (72.5)	—
Advanced adenoma	477 (62.1)	527 (84.2)	< 0.001
HGD	137 (17.8)	144 (23.0)	0.02
TVA or VA	156 (20.3)	138 (22.0)	0.46
Size ≥10 mm	419 (54.6)	500 (79.9)	< 0.001

[†]1244 patients.
[‡]1270 patients.
[§]1278 patients.
Data are presented as mean ± standard deviation or number (%).
BMI, body mass index; CRC, colorectal cancer; HGD, high-grade dysplasia; NSAID, nonsteroidal anti-inflammatory drug; TVA, tubulovillous adenoma; VA, villous adenoma.

intermediate-risk group after 2.9 years from the baseline examination. The location was the transverse colon, and the staging was T1N0M0.

The comparison of findings on surveillance colonoscopy between the intermediate-risk and high-risk groups is shown in Table 2. The development of overall (61.8% vs.79.6%, $P < 0.001$) and advanced CRN (9.4% vs.14.7%, $P = 0.003$) was significantly higher in the high-risk group than in the intermediate-risk group.

3.3. Absolute risk and risk factors of developing advanced colorectal neoplasm. The absolute risk of developing overall and advanced CRN at surveillance colonoscopy was compared according to the number of adenomas at index colonoscopy using the Kaplan–Meier method and the Breslow test. There were significant differences in the absolute risk of overall CRN ($P < 0.001$) and advanced CRN ($P = 0.01$) between the groups (Fig. 1). The 3-year and 5-year absolute risk of advanced CRN was 2.1% (95% CI 2.09–2.11) and 14.4% (95% CI 14.36–14.44) in the intermediate-risk group and 3.2% (95% CI 3.19–3.21) and 23.3% (95% CI 19.15–19.25) in the high-risk group, respectively (Table 2, Fig. 1).

On multivariate analysis, the significant risk factors for developing advanced CRN were age (OR = 1.02, 95% CI 1.00–1.04, $P = 0.03$) and adenoma size ≥ 10 mm (OR =1.96, 95% CI 1.32–2.89, $P = 0.001$) at index colonoscopy, after adjusting for sex, BMI, smoking history, family history of CRC, and medication

Table 2 Findings on surveillance colonoscopy

	Intermediate-risk group (n = 768)	High-risk group (n = 626)	P value
Interval duration of colonoscopy (year)	4.0 ± 1.3	3.9 ± 1.2	0.76
Overall CRN	475 (61.8)	498 (79.6)	< 0.001
Advanced CRN	72 (9.4)	92 (14.7)	0.003
Advanced adenoma	71 (9.2)	92 (14.7)	0.002
HGD	6 (0.8)	9 (1.4)	0.23
TVA or VA	17 (2.2)	16 (2.6)	0.72
Size ≥ 10 mm	71 (9.2)	92 (14.7)	0.002
Cancer	1 (0.1)	0	0.99
Location of CRN			0.33
Right	208 (43.8)	231 (46.4)	—
Left	168 (35.4)	154 (30.9)	—
Both	99 (20.8)	113 (22.7)	—
Absolute risk of advanced CRN			0.01
3-year	2.1 (2.09–2.11)	3.2 (3.19–3.21)	—
5-year	14.4 (14.36–14.44)	19.2 (19.15–19.25)	—

Data are presented as mean ± standard deviation or number (%); Absolute risk is presented as % (95% CI). CRN, colorectal neoplasm; HGD, high-grade dysplasia; TVA, tubulovillous adenoma; VA, villous adenoma.

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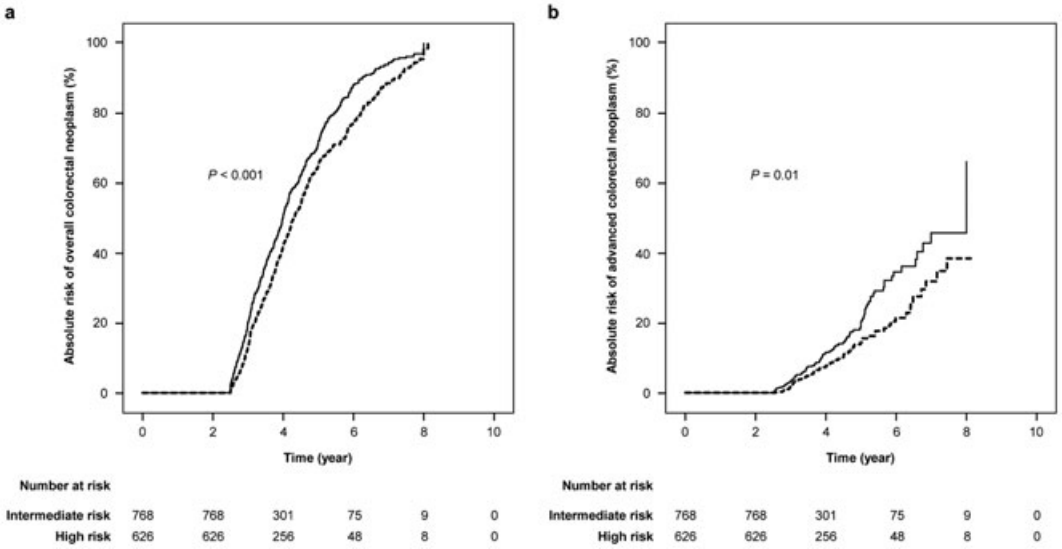

Figure 1 (a) Absolute risk of overall colorectal neoplasm and (b) advanced colorectal neoplasm according to the number of adenomas at index colonoscopy.

history. In addition, having 5–9 adenomas (OR = 1.57, 95% CI 1.11–2.23, $P = 0.01$) detected at index colonoscopy was also a significant risk factor for developing advanced CRN.

3.4. Findings on surveillance colonoscopy in patients with non-advanced adenoma at baseline colonoscopy. To investigate the effect of the number of adenomas in the development of CRN at surveillance colonoscopy regardless of combined advanced histology or size, we performed an analysis of patients with non-advanced adenoma at baseline colonoscopy separately. There were 291 and 99 patients who had 3–4 non-advanced adenomas and 5–9 non-advanced adenomas, all of which were smaller than 10 mm and had no HGD or villous histology. Of 27 (6.9%) patients who developed advanced CRN, 23 (5.9%) had adenomas with diameters > 10 mm at surveillance colonoscopy. The one CRC case that was described previously was diagnosed in the 3–4 non-advanced adenomas group.

When we compare findings on surveillance colonoscopy in the 3–4 non-advanced adenomas and the 5–9 non-advanced adenomas groups, the development of overall (64.3% vs.78.8%, $P < 0.001$) and advanced CRN (6.2% vs. 9.1%, $P = 0.02$) was significantly higher in the 5–9 non-advanced adenomas group (Table 3).

By the Kaplan–Meier method using the Breslow test, there were significant differences in the absolute risk of overall CRN ($P = 0.01$) between the groups (Fig. 2). However, regarding advanced CRN, there were no significant differences between the groups ($P = 0.74$). The 3-year and 5-year absolute risk was 2.1% (95% CI 2.08–2.12) and 7.7% (95% CI 7.65–7.75), respectively, in the 3–4 non-advanced adenomas group and 1.2% (95% CI 1.17–1.22) and 6.4% (95% CI 6.34–6.46), respectively, in the 5–9 non-advanced adenomas group (Table 3).

4. Discussion

In this large, multi-center study, we compared the cumulative risk of developing overall and advanced CRN according to the number

Table 3 Findings on surveillance colonoscopy in patients with non-advanced adenoma at baseline colonoscopy

	3–4 non-advanced adenomas ($n = 291$)	5–9 non-advanced adenomas ($n = 99$)	P value
Interval duration of colonoscopy (year)	4.1 ± 1.4	4.0 ± 1.5	0.007
Overall CRN	187 (64.3)	78 (78.8)	< 0.001
Advanced CRN	18 (6.2)	9 (9.1)	0.02
Advanced adenoma	17 (5.8)	9 (9.1)	0.02
HGD	2 (0.7)	1 (1.0)	0.21
TVA or VA	3 (1.0)	0	0.005
Size ≥ 10 mm	14 (4.8)	9 (9.1)	0.01
Cancer	1 (0.3)	0	0.847
Absolute risk of advanced CRN			0.74
3-year	2.1 (2.08–2.12)	1.2 (1.17–1.22)	—
5-year	7.7 (7.65–7.75)	6.4 (6.34–6.46)	—

Data are presented as mean ± standard deviation or number (%); Absolute risk is presented as % (95% CI). CRN, colorectal neoplasm; HGD, high grade dysplasia; TVA, tubulovillous adenoma; VA, villous adenoma.

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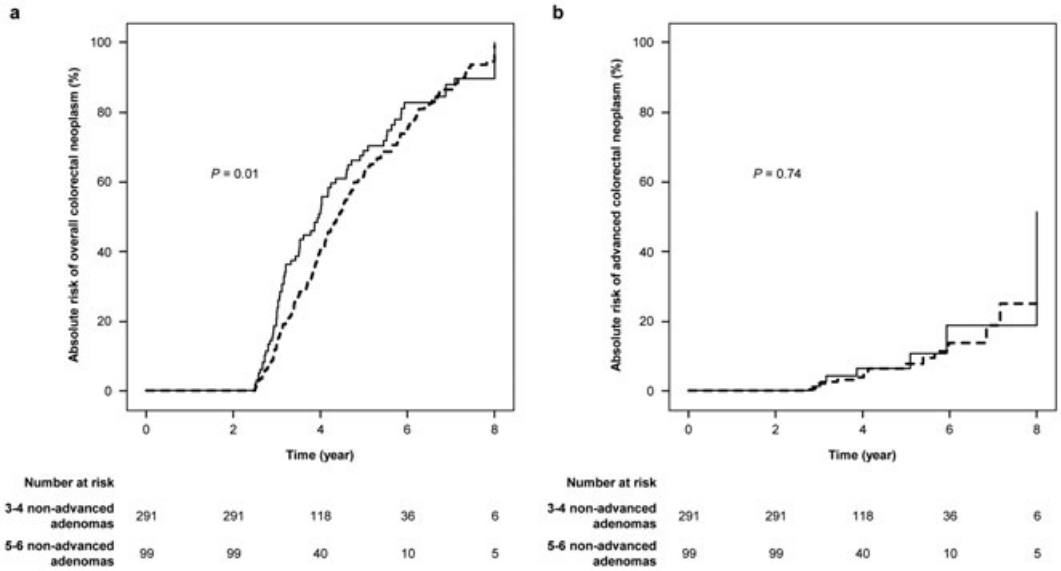

Figure 2 (a) Absolute risk of overall colorectal neoplasm and (b) advanced colorectal neoplasm in patients with non-advanced adenoma at baseline colonoscopy according to the number of adenomas at index colonoscopy.

of adenomas at index colonoscopy. Although there was a statistically significant difference in the cumulative risk of overall and advanced CRN between groups with 3–4 and 5–10 adenomas, the absolute risk of advanced CRN in patients with 5–10 adenomas at 3 years was low at 3.2%.

The number of adenomas at baseline has been found to be an important risk factor for the development of advanced adenoma at follow-up colonoscopy by several studies[8–15] and meta-analyses.[16,17] Although the statistical techniques and participants enrolled differed among studies, the risk of advanced neoplasm increased with the increasing number of adenomas at baseline colonoscopy in most studies. According to a recent meta-analysis,[6] which analyzed one meta-analysis and nine observational studies that included two Korean studies, the subtotal OR and hazard ratio for development of advanced adenoma according to the increased number of adenomas at baseline colonoscopy was 1.93 (95% CI 1.51–2.45) and 2.20 (95% CI 1.49–2.90), respectively. In the subgroup analysis, although the ≥ 2 adenoma group showed a non-significant OR (2.18, 95% CI, 0.86–5.54) compared with the 1 adenoma group, the ≥ 3 adenoma group showed significantly increased OR (2.84, 95% CI 1.26–6.39) and hazard ratio (2.20, 95% CI 1.40–3.46) compared with the 1 adenoma group. A recent meta-analysis from the West[17] corresponds with the previous study, in that patients with ≥ 3 adenomas at baseline had an increased relative risk (RR, 2.52; 95% CI 1.07–5.97) after 3 years compared with patients with 1–2 adenomas at baseline. In addition, the study reported that the RR increased to 5.01 (95% CI, 2.10–11.96) in the ≥ 3 adenoma group, even if all adenomas had a size < 10 mm. Based on these studies, the 2012 United States guidelines[5] recommended a 3-year surveillance interval, similar to that in other patients with advanced neoplasia (adenoma > 10 mm, HGD).

However, the 2010 guidelines of the British Society of Gastroenterology[7] recommend a 1-year surveillance interval in patients with ≥ 5 small adenomas, which differs from the United States guidelines, because of concerns of missed lesions at baseline. Few studies showed the risk of advanced adenoma in patients with ≥ 5 adenomas at baseline colonoscopy. Martinez *et al.*[16] reported pooled data from eight prospective studies; during a median follow up of 47.2 months, advanced adenoma was detected in 16.4%, 20.9%, and 24.9% of patients with 3, 4, and ≥ 5 adenomas at baseline, respectively. Lieberman *et al.*[18] reported the 5-year risk of advanced adenoma in patients with 3–4 and 5–9 adenomas at baseline colonoscopy as 15.9% and 17.2%, respectively. However, the findings of these studies cannot be used to determine whether a surveillance interval of 1 or 3 years is adequate, as they report follow-up results only up to 4 to 5 years. In our study, although the cumulative risk of developing advanced CRN in patients with 5–10 adenomas was higher than that in patients with 3–4 adenomas, the 3-year absolute risk of advanced CRN in patients with 5–10 adenomas was low at 3.2%, which was only 0.9% higher than that in those with 3–4 adenomas. In addition, when we analyzed patients with non-advanced adenoma at baseline colonoscopy separately, there was no difference between the 3–4 adenoma and 5–9 adenoma groups in cumulative risk of advanced CRN.

Regarding the concerns of missed lesions in cases of numerous adenomas at baseline, previous studies have indicated the miss rate of colorectal polyps to be increased significantly when an increased number of adenomas is found at index colonoscopy.[19–22] When five polyps were found, the miss rate of polyps was increased by 4.48 times (95% CI, 1.91–10.5).[20] However, although interval cancers could arise from missed lesions,[23] as most missed polyps were non-neoplastic polyps or hyperplastic neoplasia,[21,22,24] there was no concern of malignant transformation of these polyps in a short period, when quality of colonoscopy was appropriate.[25–27]

Our study had several limitations. First, as this study was retrospective, follow-up colonoscopy was not performed uniformly. Thus, we compared the cumulative risk of CRN using

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the Kaplan–Meier method and the Breslow test, which computed the weighted difference between the observed and the expected number of events at each time point. Second, patients who underwent follow-up colonoscopy within 2.5 years after index colonoscopy were excluded, which could have biased the results by underestimating the incidence of advanced CRN recurrence. Third, because the number of patients with > 10 adenomas at baseline was small, we excluded these patients from our analysis. Further studies with a larger number of such patients are needed.

This is a large, multi-center study, which compared the cumulative risk of developing advanced CRN according to the number of adenomas at index colonoscopy. Our report is the first study to date that investigated the absolute risk of advanced CRN at 3 years in patients with ≥ 5 adenomas at baseline colonoscopy. This is an important topic, as the US and British guidelines differ in the risk assessment approach and suggest different surveillance intervals when ≥ 5 adenomas are detected at index colonoscopy.

In conclusion, the cumulative risk of advanced CRN in patients with 5–10 adenomas at baseline was statistically higher than that in patients with 3–4 adenomas. However, the absolute risk of advanced CRN in patients with 5–10 adenomas at 3 years was low at 3.2%. Thus, the present study suggests that a 3-year surveillance interval might be appropriate for the patients with 5–10 adenomas, same as that in patients with 3–4 adenomas at index colonoscopy. Further prospective studies are needed to investigate whether more intensive surveillance is needed in the 5–10 adenomas group.

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