

Clinical and endoscopic predictors of colorectal adenoma recurrence after colon polypectomy

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Background/aims: Colonic adenoma is a well-known precancerous lesion of colon cancer. Therefore, the early detection of advanced colonic neoplasm is critical. This study aimed to determine whether findings at baseline colonoscopy are independent predictors of subsequent recurrence of adenoma in Korean patients. **Materials and Methods:** Patients who underwent complete colonoscopy ≥ 2 times at the Seoul Metropolitan Government-Seoul National University, Boramae Medical Center were included. Follow-up colonoscopy was done more than 1 year after removal. Colonoscopic findings at baseline examinations were compared for patients with and without adenoma recurrence. **Results:** Of the 167 patients enrolled, 78 had recurrent adenoma at follow-up colonoscopy. Male patients had a higher risk of recurrence than female patients. Patients with ≥ 10 mm adenoma at baseline colonoscopy were more likely to have recurrent adenomas than those with < 10 mm adenoma. Patients with ≥ 4 adenoma at baseline colonoscopy had also an increased risk for recurrent adenomas. Multivariable analysis showed that ≥ 10 mm sized (Odds ratio 2.76, 95% confidence interval 1.07-7.11, $p=0.035$) and ≥ 4 adenomas (Odds ratio 2.58, 95% confidence interval 1.02-6.54, $p=0.045$) at baseline colonoscopy were independent predictors of adenoma recurrence at subsequent colonoscopy. **Conclusion:** The presence of adenoma ≥ 10 mm or ≥ 4 adenomas at baseline colonoscopy were significant predictors of recurrent adenoma.

Key words: Adenoma, colonoscopy, size, number, recurrence

Kolon polipektomisinden sonra kolorektal adenom reküransinin klinik ve endoskopik prediktörleri

Giriş ve Amaç: Kolonik adenom prekanseröz bir oluşumdur. Kolon kanserlerinin ileri evreye geçmeden önlenmesi için prekanseröz lezyonların erken tanısı önemlidir. Bu çalışmada bazal kolonoskopik bulgulardan adenomanın saptanmasının daha sonra neoplastik nüksün ortaya çıkmasında belirleyici olup olmadığını ortaya koymak amaçlanmıştır. **Gereç ve Yöntem:** Seul Büyükşehir Hükümet-Seul Ulusal Üniversitesi Boramae Tıp Merkezinde iki veya fazla kez tam kolonoskopi yapılan hastalar çalışmaya alındı. Takip kolonoskopisi polip çıkarılmasından en az 1 yıl sonra yapılmıştı. Adenom reküransı olan ve olmayan hastalarda bazal incelemedeki kolonoskopik bulgular karşılaştırılmıştır. **Bulgular:** Çalışmaya alınan 167 hastanın 78'inde takip kolonoskopide reküran adenom vardı. Erkek hastalardaki risk kadınlardan fazla idi. Bazal kolonoskopide ≥ 10 mm adenomu olanlarda < 10 mm olanlara göre reküran adenom ihtimali daha fazla idi. Ayrıca, bazal kolonoskopide ≥ 4 adenomu olan hastaların reküran adenom riski daha yüksekti. Çok değişkenli analiz sonucuna göre bazal kolonoskopide çapı ≥ 10 mm (OR 2.76, 95% C.I. 1.07-7.11, $p=0.035$) olan ve ≥ 4 adet (OR 2.58, 95% C.I. 1.02-6.54, $p=0.045$) polip olan hastalarda ileriki kolonoskopide adenom reküransı açısından bağımsız risk faktörü olduğu belirlendi. **Sonuç:** Bazal kolonoskopide çapı ≥ 10 mm olan ve ≥ 4 adet adenom olmasının, hastalarda reküran adenom açısından anlamlı risk faktörü olduğu belirlendi.

Anahtar kelimeler: Adenom, kolonoskopi, boyut, sayı, rekürans

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Manuscript received: 18.06.2012 **Accepted:** 23.08.2012

Turk J Gastroenterol 2013; 24 (6): 476-482
doi: 10.4318/tjg.2013.0610

INTRODUCTION

Colonic adenoma is a well-documented precancerous lesion of colon cancer. Thus, the early detection of advanced colonic neoplasms is of considerable importance. According to a previous study, colon cancer can be prevented in about 90% of cases by the complete colonoscopic resection of colonic adenoma (1). The incidence of colonic adenoma has increased rapidly in Korea. In a recent multicenter study, the prevalence rate of colonic neoplasm in asymptomatic Korean adults was 33.2%, which was similar in Western countries (2, 3). However, patients with removed adenoma remain at high risk of developing new adenomas or cancer in the subsequent years, which justified follow-up colonoscopy (4). Because of the cost of surveillance colonoscopy and the risk of complications of colonoscopy, the main issue is to determine the period of follow-up examination and define the risk groups of patients who may benefit from intensive surveillance.

Recent literature suggested that some adenoma characteristics, such as the number, size, and histologic features of adenoma, may confer a high risk of recurrence of adenoma at follow-up colonoscopy (5). The period between baseline colonoscopy and follow-up colonoscopy should be dependent on histologic findings. According to several guidelines published in the West, individuals who have advanced or multiple adenomas (≥ 3) should have colonoscopy at 3 years and those who with 1 or 2 small tubular adenomas are recommended for repeat at 5 to 10 years. Nevertheless, the appropriate intervals required for surveillance colonoscopy remain debatable. In a previous study, it was found that the overall recurrence rate of adenomas in patients that underwent colonoscopy at 1 and 3 years was greater than in those that underwent colonoscopy only at 3 years after colonoscopy (42% vs. 32%) (6).

There was some evidence that patients with colon polyps had high risks of occurrence of another polyp in the follow-up (7), but whether the characteristics of the adenoma detected at the initial colonoscopy help define the risk of adenoma recurrence was not fully understood.

The purpose of this study was to evaluate the clinical and endoscopic adenoma characteristics at baseline colonoscopy to predict recurrence of adenoma at follow-up colonoscopy.

MATERIALS and METHODS

Study Population

The study enrolled 325 patients who were older than 40 years, underwent colonoscopy for the first time from January 2000 to October 2007 at Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center, and who had colorectal adenomas that were diagnosed on pathology after polypectomy. We excluded 92 patients with advanced cancer, inflammatory bowel disease, intestinal tuberculosis, and hereditary polyposis syndrome. Of the remaining 233 patients, 66 patients underwent follow-up colonoscopy within 12 months due to either suspicion of missed adenoma or symptoms including bleeding, bowel habit change, abdominal pain or weight loss. Ultimately, the study population comprised 167 asymptomatic patients, who underwent a follow-up colonoscopy after 1 year or more.

Methods

Colonoscopy was performed with a standard colonoscope (CF-Q240AL, Olympus Optical, Tokyo, Japan) by two experienced endoscopists who had each performed more than 300 cases annually for at least 5 years. All patients were given a routine bowel preparation with ingestion of 4 L of polyethylene glycol 8 hours before the procedure. Meperidine (50 mg) and midazolam (3 mg) were administered to all patients just before colonoscopy. Colonoscopic withdrawal time was more than 6 minutes in all cases.

We analyzed patients' age and gender, number, size, location, and morphology of adenomatous polyp at baseline colonoscopy as well as the existence of villous histology and the degree of dysplasia on pathology. Advanced adenoma was defined as an adenoma of diameter ≥ 10 mm or a villous component or severe dysplasia. Polyp size was defined as the diameter of the largest adenoma in millimeters (mm), and polyp location was classified as 'proximal colon' in cases with one or more polyps involving the proximal area of the transverse colon or 'distal colon' when all polyps were located in the descending or sigmoid colon or rectum. For patients with multiple adenomas, the most affected adenoma was used to classify the size, location, morphology, and histology. Follow-up colonoscopy was performed at least 1 year after the baseline colonoscopy to find recurrent adenomas. The primary end point was adenoma recur-

rence at follow-up colonoscopy. The baseline colonoscopic characteristics of adenomas were compared between patients with recurrent adenoma and those without recurrent adenoma at follow-up colonoscopy. This retrospective study was approved by the Institutional Review Board (IRB) of SMG-SNU Boramae Medical Center, and informed consents were waived by IRB after a full explanation of the study protocol.

Statistical Analysis

Univariable and multivariable analysis were performed to identify predictors of adenoma recurrence. The student’s t test or the Mann-Whitney U-test was used to analyze continuous variables, and the χ^2 test or Fisher’s exact test was used to analyze categorical variables. Multivariable analysis was performed using multiple binary logistic regression analysis to identify independent predictors of adenoma recurrence at follow-up colonoscopy. The Kaplan-Meier and log rank tests were used to compare cumulative group recurrence rates. Statistical analysis was performed using SPSS version 15.0 for Windows (SPSS, Chicago, IL, USA), and *p*-values of <0.05 were considered statistically significant.

RESULTS

The Characteristics of Adenomas Detected at Baseline Colonoscopy

Of the 167 patients, 121 were male and 46 were female. The mean age was 60.6±9.6 years (mean± standard error of mean; range 40-87). Mean adenoma size detected at baseline colonoscopy was 8.0±5.8 mm. Patients were categorized into three groups based on adenoma size. 44 patients (26.3%) had an adenoma < 5 mm, 73 (43.7%) had one adenoma 5~9 mm in size, and 50 (29.9%) patients had one ≥10 mm. The mean number of adenomas detected was 2.2±1.5, and 30 (18.0%) patients had ≥4 adenomas. 79 (47.3%) patients had a proximal adenoma. The majority of adenomas were tubular; 4 (2.4%) patients had an adenoma with a villous or mixed histology. High-grade dysplasia was detected in 31 (18.6%) patients (Table 1).

The Predictors of Adenoma Recurrence at Follow-up Colonoscopy

Patients with recurrent adenoma at follow-up colonoscopy (the recurrence group) were older than those without adenoma (the non-recurrence group), but this was not a statistically significant difference (62.0±8.8 years vs. 59.4±10.2 years,

Table 1. Patient and adenoma characteristics associated with recurrence among subjects with adenomas at baseline colonoscopy

	Total (n=167)	No recurrence of adenoma (n=89)	Recurrence of adenoma (n=78)	<i>p</i> -value
Age, years old, mean (SD)	60.6 (9.6)	59.4 (10.2)	62.0 (8.8)	0.092
<50, No (%)	21 (12.6)	16 (18.0)	5 (6.4)	0.144
50-59, No (%)	59 (35.3)	30 (33.7)	29 (37.2)	0.196
60-69, No (%)	60 (35.9)	29 (32.6)	31 (39.7)	0.205
≥70, No (%)	27 (16.2)	14 (15.7)	13 (16.7)	0.215
Male, No (%)	121 (72.5)	58 (65.2)	63 (80.8)	0.024
Baseline colonoscopic findings				
Size, No (%)				
< 5 mm	44 (26.3)	30 (33.7)	14 (17.9)	0.018
5 – 9 mm	73 (43.7)	38 (42.7)	35 (44.9)	0.075
≥ 10 mm	50 (29.9)	21 (23.6)	29 (37.2)	0.012
Number of adenomas, No (%)				
≥ 4	30 (18.0)	10 (11.2)	20 (25.6)	0.016
Proximally located, No (%)	79 (47.3)	41 (46.1)	38 (48.7)	0.732
High-grade dysplasia, No (%)	31 (18.6)	16 (18.0)	15 (19.2)	0.835
Villous histology, No (%)	4 (2.4)	3 (3.4)	1 (1.3)	0.624
Interval of surveillance period, months, mean (SD)	18.9 (12.0)	19.3 (13.6)	18.5 (10.1)	0.655

SD, Standard deviation

$p=0.092$). Men had a significantly higher recurrence rate than women (80.8% were men in the recurrence group vs. 65.2% in the non-recurrence group, $p=0.024$). Patients with a small (<5 mm) adenoma at baseline constituted a smaller percentage of the recurrence group than the non-recurrence group (17.9% vs. 33.7%) and those with a large (≥ 10 mm) adenoma at baseline constituted a larger percentage of the recurrence group (37.2% vs. 23.6) ($p=0.012$). In addition, the patients in the recurrence group had more adenomas at baseline than the patients in the non-recurrence group (patients with ≥ 4 adenomas, 25.6% vs. 11.2%, $p=0.016$). No such differences were found with respect to histologic findings (a villous component or high-grade dysplasia), and adenoma locations were similar in the two groups. Furthermore, mean follow-up durations for the two groups were similar (18.5 vs. 19.3 months, $p=0.655$, Table 1).

Multivariable analysis revealed that adenoma size at baseline was an independent predictor of adenoma recurrence at surveillance colonoscopy, after adjusting for age, gender, and histologic findings (p for trend=0.037). In particular, the recurrence risk in patients with a ≥ 10 mm sized adenoma was 2.76 times greater than in those with a <5-mm adenoma (95% CI 1.07-7.11; $p=0.035$), and patients with more than 4 adenomas had 2.58 times greater risk of recurrence than those with less than 4 adenomas (95% CI 1.02-6.54; $p=0.045$, Table 2).

Cumulative Adenoma Recurrence Rates at Follow-up Colonoscopy

The mean time between baseline and follow-up colonoscopy for all study subjects was 18.9 ± 12.0 months, and recurrence occurred in 78 (46.7%) patients. The cumulative recurrence rates were 13.5% at 12 months and 47.1% at 24 months after baseline colonoscopy (Figure 1).

Patients with ≥ 4 adenomas had a significantly higher recurrence rate than those with <4 adenomas by the log rank test ($p=0.026$, Figure 2). The cumulative recurrence rates in those with ≥ 4 adenomas at 12 months and at 24 months after base-

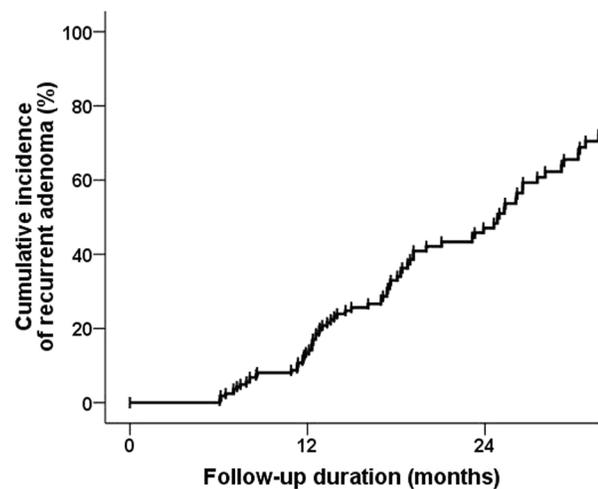


Figure 1. Cumulative incidences of the recurrence of adenoma at surveillance colonoscopy.

Table 2. Independent predictors of adenoma recurrence at surveillance colonoscopy according to baseline colonoscopic findings: multivariable analysis

	OR	95% CI	p-value
Age			
<50	1		
50-59	3.04	0.93-9.95	0.066
60-69	3.12	0.96-10.18	0.059
≥ 70	2.59	0.68-9.88	0.165
			* p for trend =0.27
Male	0.66	0.30-1.43	0.287
Findings at baseline colonoscopy			
Size			
< 5 mm	1		
5 – 9 mm	1.58	0.69-3.63	0.277
≥ 10 mm	2.76	1.07-7.11	0.035
			* p for trend =0.037
No of adenoma, ≥ 4	2.58	1.02-6.54	0.045
Villous histology	0.11	0.01-1.29	0.078
High-grade dysplasia	0.97	0.41-2.32	0.972

OR: Odds ratio. CI: Confidence interval.

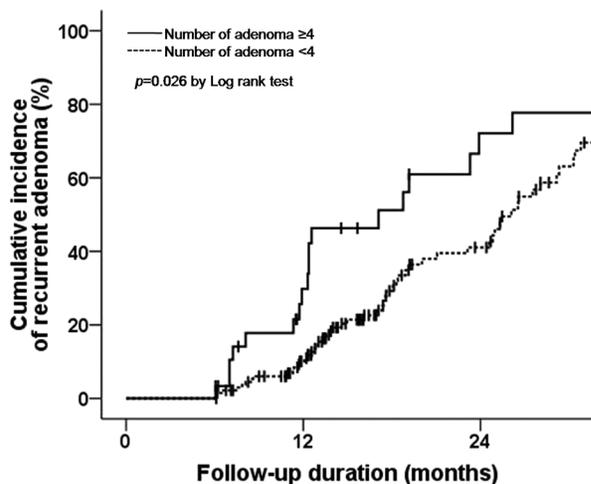


Figure 2. Comparison of cumulative incidences of the recurrence of adenoma at surveillance colonoscopy between patients with detected <4 and ≥4 adenomas at baseline colonoscopy.

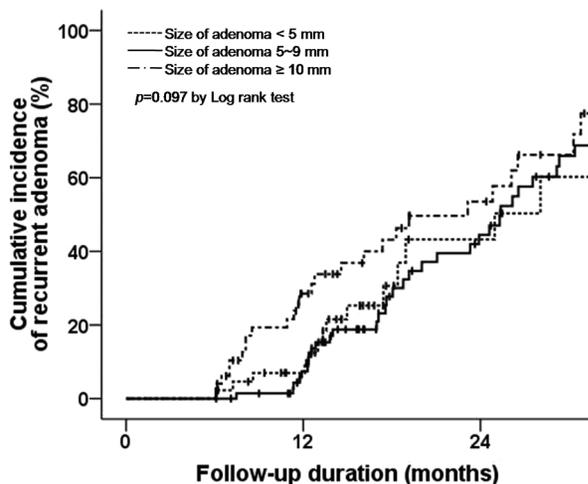


Figure 3. Comparison of cumulative incidences of the recurrence of adenoma at surveillance colonoscopy among patients with adenoma sized <5 mm, 5-9 mm, and ≥10 mm.

line colonoscopy were 29.8% (10.1% in those with <4 adenomas, and 72.1% (41% in those with <4 adenomas), respectively. Although adenoma size at baseline exam was found to significantly affect recurrence, the cumulative recurrence rates among the 3 groups categorized by the size of adenoma (<5 mm, 5-9 mm, ≥10 mm) did not differ significantly ($p=0.097$, Figure 3). In detail, cumulative recurrence rates at 12 months after baseline exam were 9.6% in patients with an adenoma <5 mm, 7.4% in those with one 5-9 mm in size, and 28.5% in those with and adenoma ≥10 mm. At 24 months after baseline, cumulative recurrence rates were 43.2% in patients with an adenoma <5 mm, 44.5% in those with an adenoma 5~9 mm in

size, and 53.5% in subjects with an adenoma ≥10 mm.

DISCUSSION

In accordance with the adenoma-carcinoma sequence, adenomas are considered as precursor lesions for the colorectal cancers (8). Size and the existence of villous structure were found to be the most important factors defining the risk of high-grade dysplasia or invasive carcinoma in adenoma patients (9, 10). The prevalence of colorectal adenoma has been calculated to be 24 to 29% in colonoscopic series (11). The detection rates of metachronous adenomas in follow-up studies varied widely (12 - 60%) depending on the time interval of the examinations and on the characteristics of patients and adenomas at the baseline examination (12-14). Patients in whom adenomas had been removed have a high risk for recurrence of adenoma, and so are recommended to undergo repeat colonoscopy according to a clinical practice guideline for polypectomy surveillance.

The U.S. Multi-Society Task Force on Colorectal Cancer and the American Cancer Society jointly developed a consensus update for postpolypectomy surveillance guideline in 2006 (4). According to this guideline, patients were stratified as having high risk or low risk for subsequent recurrence of advanced adenoma on the basis of adenoma characteristics at baseline colonoscopy. The guideline defined patients with 3 or more adenomas, those with large adenoma (≥10 mm in diameter), or those with villous component or high-grade dysplasia as the high-risk group. Individuals classified as the high-risk group are recommended to have follow-up colonoscopy in 3 years, where as those in the low-risk group (with <2 adenoma, <10 mm in diameter) are to have repeated colonoscopy in 5 to 10 years. The guidelines also recommend 10-year follow-up colonoscopy for those with no adenomatous polyps.

Some studies have found that a proximal colon location indicates a high risk of recurrence (15). However, some of the above findings have not been borne out by larger studies. For example, one large-scale randomized prospective study conducted on 1418 patients found that those with more than 3 adenomas had 6.8 times greater risk of developing advanced adenoma at follow-up after adjusting for other factors (1). In contrast, another study conducted on 2079 patients concluded that adenoma size and number did not significantly predict recurrence by multivariable analysis (16).

The present study was performed to identify the risk factors of adenoma recurrence after polypectomy, which has not been fully investigated in Korean. In the present study, a large (≥ 10 mm) adenoma at baseline was found to be associated with a high recurrence risk, as has been reported previously. However, 3 or more adenomas at baseline were not found to affect recurrence (≥ 3 adenoma, 39.7% in the recurrence group vs. 27.0% in the non-recurrence group, $p=0.080$, data not shown). Rather, we found that an adenoma number of ≥ 4 was significantly associated with recurrence (Table 1). Furthermore, a villous histology is a well-established risk factor, but because this was only found in 2.4% of our study population, we were unable to confirm the relation. In a previous Korean study, villous adenoma was detected in only 8.2% of the cohort (17). Accordingly, villous adenoma cannot be considered a prime predictor of recurrence in Korea due to its low prevalence.

Age at diagnosis has been reported as a risk factor of colonic adenoma, and patients aged over 60 years old are at the high risk of adenoma recurrence (9). In the present study, the recurrence risk was found to be 3.04 times higher in 50-59-year-olds and 3.12 times higher in 60-69-year-olds than in <50-year-olds (Table 2), which concurs with other studies. However, in the present study, multivariable analysis failed to demonstrate that age was a significant risk factor of adenoma recurrence (OR 2.59, 95% CI 0.68-9.88 for <50-year-olds vs. >70-year-olds, Table 2). Because we might have included greater proportions of ambulatory and healthy individuals than the general elderly population, our result suggested that an aggressive surveillance colonoscopy in the healthy elderly could be recommendable.

According to our result, the high-grade dysplasia, a well-described risk factor of colorectal cancer, did not affect significantly the adenoma recurrence (Table 2). Since our study population consisted of relatively high proportion of patients with high-

grade dysplasia (18.6%, Table 1) compared to previous studies (1, 18, 19), recurrent adenomas were detected frequently in those with and without high-grade dysplasia (Table 1). Moreover, according to previous pooled analysis, the risk of nonadvanced neoplasm was not significantly related with high-grade dysplasia (20). In the same context with previous studies, advanced neoplasms (2 adenomas with high-grade dysplasia and 1 adenocarcinoma) developed only among those with high-grade dysplasia in the present study (data not shown).

Although the recommended surveillance intervals are 5 years in asymptomatic individuals and 3 years in those at high risk of colonic polyps or cancer, many clinicians perform colonoscopy more frequently (21). The recurrence rates of adenoma at 3-4 years after polypectomy have been reported to be 35 - 48.6% (14, 22), and the cumulative recurrence rates of adenoma in Koreans have been reported to be 13.8% at 1 year and 44.6% at 2 years after polypectomy (8). In the present study, the cumulative recurrence rates were also found to be high (13.5% at 1 year and 47.1% at 2 years after polypectomy, Figure 1). Thus, recent studies indicate that patients at high risk of adenoma recurrence may be considered for follow-up colonoscopy within 2 years of polypectomy (23). Especially, an importance of the first-year follow-up colonoscopy is being emphasized (24).

In brief, we found that the risk of adenoma recurrence at follow-up colonoscopy after polypectomy was significantly higher for patients with more than 4 adenomas and for those with an adenoma of ≥ 10 mm. Finally, our results suggest that more aggressive surveillance colonoscopy than indicated by the existing guidelines may be need for patients with high-risk factors for adenoma recurrence.

Conflict of interest: No author has conflicts of interest or financial arrangement that could potentially influence the described research.

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