



Comparison of Colonoscopy Surveillance Outcomes Between Young and Older Colorectal Cancer Patients

ORIGINAL
ARTICLE

Sung Bae Kim^{1,2}, Hyun Jung Lee^{1,2}, Soo Jung Park^{1,2}, Sung Pil Hong^{1,2}, Jae Hee Cheon^{1,2}, Won Ho Kim^{1,2}, Tae Il Kim^{1,2,3}

¹Department of Internal Medicine, ²Institute of Gastroenterology, ³Cancer Prevention Center, Yonsei University College of Medicine, Seoul, Korea

Background: Young-onset colorectal cancer is uncommon, but the incidence is increasing. Despite several guidelines for colonoscopic surveillance following colorectal cancer resection, there is little consistency regarding the timing and age-adjusted strategies of surveillance colonoscopy after surgery of young-onset colorectal cancer. The aim of this study was to compare the outcomes of surveillance colonoscopy between sporadic colorectal cancer patients with young and older age after curative resection.

Methods: We retrospectively reviewed 569 colorectal cancer patients who underwent curative resection between January 2006 and December 2010. The primary outcome was comparison of the development of metachronous advanced neoplasia during surveillance colonoscopy between young and older colorectal cancer patients.

Results: There were 95 patients in the young age group and 474 patients in the older age group. The mean time interval from surgery to the development of metachronous advanced neoplasia was 99.2 ± 3.7 months in the young age group and 84.4 ± 2.5 months in the old age group ($P = 0.03$). In the multivariate analysis, age (OR, 3.56; $P = 0.04$) and family history of colorectal cancer (OR, 2.66; $P = 0.008$) were associated with the development of metachronous advanced neoplasia. None of the young patients without both family history of colorectal cancer and high-risk findings at index colonoscopy showed advanced neoplasia during the follow-up period.

Conclusions: Age and family history of colorectal cancer are independent risk factors for the occurrence of advanced neoplasia after curative colorectal cancer resection, suggesting age-adjusted strategies of surveillance colonoscopy.

(*J Cancer Prev* 2017;22:159-165)

Key Words: Surveillance, Colonoscopy, Colorectal neoplasms, Age of onset

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and a significant cause of cancer-related death.¹ It is well known that the incidence of CRC increases with age, and most patients are diagnosed at over 50 years of age.¹⁻³ However, a recent epidemiologic study showed that over the past few decades, the incidence of CRC has continuously increased in the younger population, aged under 50 years, in contrast to a slight decline in patients older than 50 years.⁴ Despite the rising incidence, the clinicopathological features and prognosis of young-onset CRC remain controversial.^{5,6}

Colonoscopic surveillance after curative resection of CRC is important to prevent the development of metachronous CRC in the remnant colon and rectum.^{7,8} Current National Comprehensive Cancer Network (NCCN) and the USA Multi-Society Task Force guidelines suggest colonoscopic surveillance within 1 year after curative resection of CRC in patients who underwent complete colonoscopy prior to surgery and within 3 to 6 months in those with incomplete preoperative colonoscopy due to obstruction. The subsequent follow-up interval is determined according to the findings of the first follow-up surveillance including the size, number, and pathologic features of adenomas. If the colonoscopy result is negative for any adenomatous or serrated polyps, the

Received August 17, 2017, Accepted August 30, 2017

Correspondence to: Tae Il Kim

Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-1965, Fax: +82-2-393-6884, E-mail: Taeilkim@yuhs.ac, ORCID: Tae Il Kim, <http://orcid.org/0000-0003-4807-890X>

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second surveillance colonoscopy is recommended after 3 years.^{7,9}

Current colonoscopic surveillance guidelines after CRC surgery do not consider age, despite the fact that age is a significant factor in the development of adenomatous polyps or advanced neoplasia.¹⁰ NCCN guidelines mention that more frequent colonoscopies may be indicated in patients who present with colon cancer before 50 years of age.⁹ However, there has been insufficient evidence to support the need for a more intensive colonoscopy strategy in young patients without inherited syndromes, such as Lynch syndrome, familial adenomatous polyposis, and inflammatory bowel disease (IBD). For this reason, heterogeneous follow-up strategies continue to be pursued in colonoscopic surveillance following curative resection.

Therefore, we compared surveillance colonoscopic outcomes between the young and the older CRC patients after curative resection and investigated independent factors associated with the development of metachronous advanced neoplasia to determine whether the young CRC patients may require more surveillance colonoscopies.

MATERIALS AND METHODS

1. Patients

Between January 2006 and December 2010, a total of 795 patients fulfilling the following criteria were initially included in this retrospective review: (1) curative surgical resection due to CRC; (2) available index colonoscopy records; and (3) available records from more than one follow-up surveillance colonoscopy at Severance Hospital in Korea. Patients meeting the following criteria were excluded: (1) stage 4 CRC or palliative resection ($n = 3$); (2) total colectomy or transanal excision ($n = 2$); (3) hereditary CRC ($n = 11$); (4) IBD ($n = 1$); (5) history of another malignancy ($n = 27$); (6) first follow-up colonoscopy performed more than 2 years after curative resection for CRC ($n = 171$); and (7) follow-up period of less than 1 year after surgery ($n = 3$). Following the exclusion of 226 patients based on our exclusion criteria, a total of 569 patients were finally reviewed. Surveillance colonoscopy records were collected up to three times after surgery during follow-up periods.

This study was approved by the Institutional Review Board (IRB) of Severance Hospital, Yonsei University in Seoul, Korea (IRB No. 4-2015-1170).

2. Definition

Young-onset was defined as age under 50 years at the time of diagnosis.^{6,9,11} Tumor staging was performed according to the

American Joint Commission on Cancer standards contemporaneous to the treatment period. Body mass index (BMI) was categorized as follows: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5-22.9 kg/m²), overweight (BMI 23.0-24.9 kg/m²), and obese (BMI > 25.0 kg/m²). Family history of CRC was defined as prior diagnosis of CRC in first-degree relatives.

Index colonoscopy was defined as a recent complete colonoscopy with satisfactory preparation prior to surveillance colonoscopy, including postoperative colonoscopy within 6 months in patients who were unable to undergo preoperative complete colonoscopy due to obstruction.¹² Tumor location was categorized under right colon (cecum, ascending colon), transverse colon, left colon (descending colon, sigmoid colon), or rectum.

Advanced adenoma was defined as an adenoma with (1) villous histology features, (2) a size larger than 10 mm, (3) high-grade dysplasia, and (4) of the serrated sessile type. Advanced neoplasia was defined as adenocarcinoma including intramucosal carcinoma and advanced adenoma. The high-risk patient group was considered to include patients with (1) advanced neoplasia and (2) more than three adenomas. The low-risk patient group was defined as the patients without high-risk findings. Metachronous advanced neoplasia did not include anastomosis site recurrence or locoregional recurrence.^{10,13}

3. Primary and secondary outcomes

The primary outcome was comparison of the development of metachronous advanced neoplasia during surveillance colonoscopic between young and older patients. The secondary outcome was evaluation of risk factors for postoperative metachronous advanced neoplasia development.

4. Statistical analysis

Data are expressed as the median (interquartile range), number, or number (%), as appropriate. Factors associated with metachronous adenoma and advanced neoplasia were investigated using the Cox regression. Any variables identified as significant ($P < 0.05$) in the univariate analysis were included in the multivariate analysis.

For comparison of the cumulative probability of metachronous lesions, Kaplan-Meier estimator survival analysis was used; the recurrence curves of each group were compared by using a log-rank test. For comparing outcomes, the chi-square test or Fisher's exact test was used for categorical data, and the Student's *t*-test was used for continuous variables. Data analysis was performed using PASW software ver. 18.0 (IBM Co., Armonk, NY, USA). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

1. Baseline characteristics

Baseline characteristics of the 569 patients are shown in Table 1. The median age at the time of surgery was 43.7 years (28.0-49.0 years) in the young age patients, compared to 63.3 years (50.0-85.0 years) in the older age patients ($P = 0.001$). In the older age group, a male predominance (65.2%) was revealed compared to the young age group (53.7%; $P = 0.03$). The proportion of patients with a family history of CRC was 11.6% in the young age group and 8.9% in the older age group, with no statistically significant difference. The index colonoscopy findings including existence of synchronous adenoma and advanced neoplasia is

more common in old age group significantly ($P = 0.001$; $P = 0.03$). In this context, high-risk patients were more common in the older age group ($P = 0.003$). The young age group showed a high proportion of poor differentiation, mucinous histology (5.3%), and lymphovascular invasion (30.5%) in the resected specimens ($P = 0.03$; $P = 0.02$). BMI, alcohol history, smoking history, location of tumor, pathologic tumor stage, and preoperative carcinoembryonic antigen titer were not significantly different between the age groups.

2. Surveillance colonoscopy outcomes

During the follow-up period, surveillance colonoscopy was performed once in 158 patients (27.8%), twice in 312 patients

Table 1. Baseline clinical, endoscopic, and pathological characteristics of the patients

Variable	Age group ^a		Pvalue
	Young age (n = 95)	Older age (n = 474)	
Age at surgery (yr)	43.7 (28.0-49.0)	63.3 (50.0-85.0)	0.001
Sex (male : female)	51 (53.7) : 44 (46.3)	309 (65.2) : 165 (34.8)	0.03
Family history of colorectal cancer	11 (11.6)	42 (8.9)	0.40
Body mass index (kg/m ²)			0.19
Below weight (< 18.5)	4 (4.2)	9 (1.9)	
Normal (18.5-22.9)	45 (47.4)	185 (39.0)	
Overweight (23.0-24.9)	22 (23.2)	130 (27.4)	
Obese (> 25.0)	24 (25.3)	150 (31.7)	
Alcohol	54 (56.8)	235 (49.6)	0.20
Smoking	38 (40.0)	184 (38.8)	0.83
Index colonoscopy finding			
Adenoma positive patient	31 (32.6)	269 (56.8)	0.001
Advanced neoplasia ^b positive patient	19 (20.0)	147 (31.0)	0.03
Adenoma size (mm) (max)	13.0 ± 13.4	10.3 ± 7.9	0.09
High-risk patient ^c	20 (21.1)	175 (36.9)	0.003
Location of tumor			0.37
Right colon (cecum, ascending colon)	20 (21.1)	113 (23.8)	
Transverse colon	5 (5.3)	23 (4.9)	
Left colon (descending colon, sigmoid colon)	33 (34.7)	195 (41.1)	
Rectum	37 (38.9)	142 (30.0)	
AJCC stage			0.08
I	28 (29.5)	154 (32.5)	
II	28 (29.5)	180 (38.0)	
III	39 (41.1)	140 (29.5)	
Differentiation			0.03
Well	25 (26.3)	110 (23.2)	
Moderate	60 (63.2)	346 (73.0)	
Poor	5 (5.3)	10 (2.1)	
Mucinous	5 (5.3)	8 (1.7)	
Lymphovascular invasion	29 (30.5)	94 (19.8)	0.02
CEA (ng/mL)	4.6 ± 8.4	4.5 ± 9.3	0.96

Values are presented as median (range), number (%), or mean ± SD. The sum of the percentages does not equal 100% because of rounding. AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen. ^aAge group defined as young age (< 50 years) and older age (≥ 50 years). ^bThis was defined as adenoma with (1) villous histology feature, (2) size larger than 10 mm, (3) high-grade dysplasia, (4) serrated sessile type, and (5) adenocarcinoma. ^cThese were defined as patients with advanced neoplasia or adenoma numbers more than three.

(54.8%), and three times in 99 patients (17.4%). The median time interval from the surgery to the first surveillance colonoscopy was 13.0 months. The mean periods of time from the first colonoscopy examinations to the second and the second to the third were 34.0 months and 28.0 months, respectively. There were no significant differences in the surveillance colonoscopy

Table 2. Comparison of total number and interval of follow-up colonoscopies between the young age and older age patients

Variable	Age group ^a		P-value
	Young age (n = 95)	Older age (n = 474)	
No. of follow-up colonoscopy			0.18
1	21 (22.1)	137 (28.9)	
2	52 (54.7)	260 (54.9)	
3	22 (23.2)	77 (16.2)	
Interval to follow-up colonoscopy			
First (mo)	14.0 (12.0-15.0)	13.0 (12.0-16.0)	0.70
Second (mo)	35.0 (29.0-37.0)	34.0 (26.0-37.0)	0.22
Third (mo)	26.5 (15.7-35.8)	29.0 (19.0-37.0)	0.73

Values are presented as number (%) or median (interquartile range).
^aAge group defined as young age (< 50 years) and older age (≥ 50 years).

numbers and intervals between the young and older age groups (Table 2).

During follow-up surveillance colonoscopy, the metachronous adenoma positive rate was 16.8% in the young age group and 44.1% in the older age group ($P = 0.001$). The proportion of high-risk patients and number of advanced neoplasia were also higher in the older age group ($P = 0.007$ and 0.02). However, there were no significant differences in the positive rate of metachronous advanced neoplasia between the age groups ($P = 0.09$) (Table 3).

3. Factors associated with metachronous advanced neoplasia

Cancer-related factors; patient-related factors including age, sex, BMI, alcohol history, smoking history, and family history of CRC; and index colonoscopy results, such as the existence of synchronous adenoma or advanced neoplasia, size and number of adenomas, and high-risk findings were analyzed to determine independent factors associated with the development of metachronous advanced neoplasia. Among the factors, age ($P = 0.03$), family history of CRC ($P = 0.01$), and high-risk findings on index colonoscopy ($P = 0.03$) were found to be associated with the

Table 3. Comparison of the adenoma incidence rate between the young age and older age patients

Variable	Age group ^a		P-value
	Young age (n = 95)	Older age (n = 474)	
First surveillance colonoscopy (95 : 474) ^b			
Adenoma positive patient	8 (8.4)	137 (28.9)	0.001
Advanced neoplasia ^c positive patient	1 (1.1)	16 (3.4)	0.33
Polyp size (max) (mm)	5.0 ± 2.2	5.9 ± 3.2	0.44
High-risk ^d patient	1 (1.1)	35 (7.4)	0.02
Second surveillance colonoscopy (74 : 337) ^b			
Adenoma positive patient	9 (12.2)	107 (31.9)	0.001
Advanced neoplasia ^c positive patient	1 (1.4)	17 (5.1)	0.22
Polyp size (max) (mm)	4.1 ± 2.5	5.8 ± 5.0	0.32
High-risk ^d patient	2 (2.7)	26 (7.7)	0.13
Third surveillance colonoscopy (22 : 77) ^b			
Adenoma positive patient	4 (18.2)	37 (48.1)	0.01
Advanced neoplasia ^c positive patient	1 (4.5)	6 (7.8)	0.69
Polyp size (max) (mm)	10.8 ± 12.9	5.7 ± 3.0	0.49
High-risk ^d patient	1 (4.5)	12 (15.6)	0.29
Total surveillance colonoscopy (95 : 474) ^b			
Adenoma positive patient	16 (16.8)	209 (44.1)	0.001
Advanced neoplasia ^c positive patient	3 (3.2)	39 (8.2)	0.09
No. of advanced neoplasia ^c	0.03 ± 0.18	0.09 ± 0.30	0.02
High-risk ^d patient	4 (4.2)	68 (14.3)	0.007

Values are presented as number (%) or mean ± SD. ^aAge group defined as young age (< 50 years) and older age (≥ 50 years). ^bSubtotal of young age group : older age group. ^cThis was defined as adenoma with (1) villous histology features, (2) size larger than 10 mm, (3) high-grade dysplasia, (4) serrated sessile type, and (5) adenocarcinoma. ^dThese were defined as patients with advanced neoplasia or adenoma numbers more than three.

development of metachronous advanced neoplasia in univariate analysis. The mean time interval from surgery to the development of metachronous advanced neoplasia was 99.2 ± 3.7 months in the young age group and 84.4 ± 2.5 months in the old age group. Figure 1 shows the rate of development of metachronous advanced neoplasia between the young and older age groups with Kaplan-Meier survival analysis. Subsequently, multivariate Cox regression analysis, including age group, family history of CRC, and high-risk group, revealed older age ($P = 0.04$; OR, 3.56; 95% CI, 1.08-11.74) and family history of CRC ($P = 0.008$; OR, 2.66; 95% CI, 1.29-5.48) as the independent risk factors associated with metachronous advanced neoplasia (Table 4).

4. Outcomes according to risk factors

To identify young patients with a lower risk of metachronous advanced neoplasia in the surveillance colonoscopy, patients were divided into those with either a family history of CRC within first-degree relatives or high-risk index colonoscopic findings and those meeting neither of these two criteria. We identified 89 patients (15.6%) in the former group and 480 patients (84.4%) in the latter group. The mean time interval from surgery to the development of metachronous advanced neoplasia in each of the groups was 71.4 ± 4.3 months and 94.5 ± 3.4 months, respectively ($P = 0.001$). With further classification according to the age at diagnosis, 82 patients (86.3%) were categorized as young patients without a family history of CRC or high-risk features in the index colonoscopy. None of these patients had developed metachronous advanced neoplasia within 161 colonoscopic examinations during follow-up over a mean time period of 44.5 ± 21.5 months.

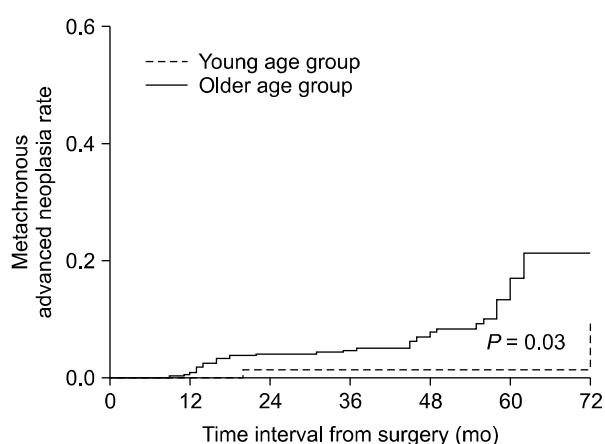


Figure 1. Cumulative probability of metachronous advanced neoplasia during follow-up surveillance colonoscopy. Comparisons of metachronous advanced neoplasia between patients aged under 50 years ($n = 95$) and over 50 years ($n = 474$).

DISCUSSION

The number of cases of young-onset CRC has been steadily increasing worldwide. Several studies have suggested that these patients may be characterized by more advanced stage disease and a higher incidence of poorly differentiated pathology, as well as a high proportion of hereditary CRC and IBD, compared to older CRC patients.^{5,11,14} The definition of young-onset CRC is still the subject of debate, and the cutoff age varies, ranging from 30 to 50 years. In this study, we used 50 years as the cutoff age because most guidelines recommend screening colonoscopy in average-risk patients at the age of 50 years, and NCCN guidelines also mention that more frequent colonoscopy may be indicated in patients who present with CRC before that age.^{9,11}

It is well known that one of the primary benefits of surveillance colonoscopy after curative resection for CRC is the detection of metachronous advanced neoplasia.¹⁵ Indeed, patients with hereditary CRC or IBD require a more frequent and intensive surveillance strategy, but there is a lack of evidence regarding the timing of the surveillance colonoscopy and whether more frequent colonoscopic surveillance is needed in young-onset CRC patients without risk factors such as hereditary CRC or IBD after curative resection in real life.¹⁶⁻¹⁸ To solve this

Table 4. Univariate and multivariate analysis for the factors associated with metachronous advanced neoplasia

Variable	Univariate	Multivariate	
	P-value	P-value	OR (95% CI)
Patient factor			
Age group ^a (young vs. older age)	0.03	0.04	3.56 (1.08-11.74)
Family history	0.01	0.008	2.66 (1.29-5.48)
Sex	0.29		
Body mass index	0.11		
Alcohol	0.44		
Smoking	0.42		
Cancer factor			
Location	0.06		
Stage	0.50		
Differentiation	0.65		
Lymphovascular invasion	0.06		
Preoperative CEA	0.92		
Polyp factor			
Adenoma	0.07		
Advanced neoplasia	0.05		
Size (max)	0.24		
Number	0.21		
High-risk group	0.03	0.09	1.71 (0.91-3.19)

CEA, carcinoembryonic antigen. ^aAge group defined as young age (< 50 years) and older age (≥ 50 years).

problem, we focused on comparison of the development of metachronous advanced neoplasia during surveillance colonoscopy between young and older CRC patients without hereditary CRC or IBD.

The percentage of young-onset patients in our study population was 16.7%, and this value is similar to that of a previous study conducted in Asia.¹⁴ Some reports have suggested that young-onset and right-sided colon cancer is more common in males, but our study population showed a significant male predominance in older patients, with no difference in tumor location. Higher proportions of poor differentiation or mucinous pathology and lymphovascular invasion in the young patients were also consistent with the findings of previous studies.^{19,20} As mentioned above, NCCN guideline suggests more frequent surveillance colonoscopy in young age patients.⁹ However, the timing and number of colonoscopic examinations did not show any differences between the age groups. This result suggested that there is a distinction between guideline and clinical practice.

In the first surveillance colonoscopy, the positive rates of adenoma, advanced neoplasia, and metachronous cancer were 25.5%, 3.0%, and 0%. These findings are similar to the previous study results in which 3.2% of patients developed advanced adenoma and none had newly developed cancer 1 year after undergoing CRC resection.^{21,22} Overall surveillance colonoscopy results comparing age groups revealed that the positive rates of metachronous adenoma, advanced adenoma, and high-risk colonoscopic findings were significantly higher in the older age group. Our results were consistent with the suggestion in the previous studies that older age is a common risk factor for the development of metachronous advanced adenoma in surveillance colonoscopy after CRC resection.^{10,21,23,24}

The identification of high-risk patients who require intensive surveillance colonoscopy is a critical issue, and several studies have suggested various risk factors such as aging, synchronous advanced neoplasia, male sex, tumor location, and history of diabetes.^{21,24} In the present study, older age, first-degree family history of CRC, and high-risk colonoscopic findings at index colonoscopy were associated with the development of metachronous advanced neoplasia in univariate analysis. Young patients were definitely at lower risk compared to older patients according to the univariate and multivariate analysis. We also divided patients according to two significant factors in the univariate analysis to more selectively define patients at low risk for the development of metachronous advanced neoplasia. Patients without both family history of CRC and high-risk index colonoscopy findings showed a significantly lower risk for the

development of metachronous advanced neoplasia. Moreover, none of the young patients in our study without these two risk factors developed metachronous advanced neoplasia. In our experience, young patients had a low probability of developing metachronous advanced neoplasia, especially those with no family history of CRC and low-risk index colonoscopy findings. As a result, the benefits of an intensive surveillance colonoscopy strategy in this patient group have a relatively low impact on the detection and prevention of metachronous advanced neoplasia.

As a limitation of our study, the timing of surveillance colonoscopy was not equal in all patients, because of the inherent retrospective design of the study. However, we restricted the inclusion criteria to patients with the first surveillance colonoscopy within 2 years after surgery. In addition, in both age groups, the number and intervals of follow-up colonoscopies did not differ significantly.

In conclusion, the present study showed that age is independent factor for the development of metachronous advanced neoplasia after surgery compared to older onset patients. In particular, young patients without a family history of CRC and high-risk index colonoscopy findings have an extremely low rate of metachronous advanced neoplasia. Therefore, colonoscopy surveillance strategy should be adjusted with independent risk factors, including age and family history of CRC.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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