ORIGINAL PAPER

SUITABILITY OF SURVEILLANCE COLONOSCOPY FOR PATIENTS WITH ULCERATIVE COLITIS TO DETECT COLORECTAL CANCER: CURRENT GUIDELINES MISS SOME EARLY-STAGE CASES

Toru Kamiya[1], MD; Takafumi Ando[1], MD, PhD; Osamu Watanabe[1], MD, PhD;
Masanao Nakamura[1], MD, PhD; Takeshi Yamamura[2], MD, PhD;
Ryoji Miyahara[1], MD, PhD; Yoshiki Hirooka[2], MD, PhD;
and Hidemi Goto[1,2], MD, PhD

[1]Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine,
Nagoya, Japan
[2]Department of Endoscopy, Nagoya University Hospital, Nagoya, Japan

ABSTRACT

Surveillance colonoscopy (SC) is considered important for the early detection and treatment of colorectal cancer (CRC) in patients with ulcerative colitis (UC). Here, we investigated whether current guidelines are appropriate in preventing UC patients from being diagnosed with CRC at an incurable stage. Among 1583 patients under treatment for UC, 27 patients were diagnosed with CRC. Of these, we excluded two patients who had not undergone colonoscopy before CRC diagnosis. We then divided the remaining patients into three groups based on colonoscopy interval (A, 1 year or less; B, between 1 and 2 years; and C, 2 years or longer). Fifteen patients had tubular adenocarcinomas, and 10 had other types (8 poorly differentiated adenocarcinomas, 1 mucinous adenocarcinoma, 1 endocrine cell carcinoma). Five (20%) of 25 patients developed CRC within 8 years after the onset of UC, of which one case was detected at stage IV. Six patients were classified into group A, 8 into group B, and 11 into group C. On distribution by histologic type, tubular adenocarcinomas were detected in stages 0 - II in 100% in group A, 100% in group B, and 57.1% in group C. In contrast, other types of carcinomas were detected in stage 0 - II in 100% in group A, 40% in group B, and 0% in group C. Current guideline recommendations for SC are not sufficient for the detection of early stage CRC in patients with UC. SC should be commenced earlier than recommended in the current guidelines and repeated annually.

Key Words: surveillance colonoscopy, ulcerative colitis, colorectal cancer

INTRODUCTION

Colorectal cancer (CRC) was first recognized as a complication of ulcerative colitis (UC) by Crohn and Rosenberg in 1925.[1] A meta-analysis of 116 studies reported that the overall prevalence of CRC in any UC patient was 3.7%, and that cumulative probabilities were 2% at 10 years, 8% at 20 years, and 18% at 30 years.[2] Another study with a 15-year follow-up

period reported that CRC was diagnosed in 9 (1.3%) of 681 patients with inflammatory bowel disease (IBD), including UC and Crohn's disease patients.[3] Accordingly, UC patients are advised to undergo surveillance colonoscopy (SC) aimed at detecting dysplasia or asymptomatic early CRC at a surgically curable stage.[4-6]

With regard to surveillance, several institutions in Western countries have independently issued and updated surveillance guidelines aimed at detecting CRC in UC patients, including the British Society of Gastroenterology (BSG), American Gastroenterological Association (AGA), and European Crohn's Colitis Organization (ECCO).[7-9] These guidelines all indicate that SC is required for extensive colitis, i.e. pancolitis and left-sided colitis, but not for proctitis. The BSG and ECCO recommend starting SC approximately 10 years after the onset of colitic symptoms,[7,9] while the AGA recommends starting no later than 8 years after the onset of symptoms.[8] Guidelines issued by an institution in Japan recommended that SC should be started at 8–10 years after disease onset.[10] Overall, these guidelines recommend that SC should be started after 8–10 years of disease in the case of extensive UC. Recommended intervals after the first SC differ, however: the AGA recommends the next SC within 1 to 2 years after the initial SC, and then every 1 to 3 years;[8] the Japanese guideline recommends annual or biannual SC after the initial SC;[10] while the BSG and ECCO guidelines both recommend yearly, 3-yearly or 5-yearly SC depending on the risk of CRC in individual patients.[7,9] This variation in recommended intervals indicates a lack of consensus on the best interval between SC in these patients.[7-10]

Recent population-based and referral center cohorts have shown that while the incidence and prevalence UC in Asia is rising, they remain lower than in the West.[11] The incidence rate of CRC among UC patients in Japan was reported to differ from those in Western countries.[2,3,12] Of note, UC phenotype or disease course might differ according to ethnicity and region, and guidelines from Western countries might not be appropriate for detecting CRC at a curable stage in UC patients in Japan. To date, however, no well-designed clinical study has evaluated SC protocols in Japan or overseas, and the legitimacy of the current SC guidelines for UC patients requires verification.

Here, we retrospectively evaluated patients treated for UC-associated CRC in a network of hospitals in Japan, and aimed to determine whether the current guidelines are appropriate to prevent the development of incurable advanced colorectal cancer in these patients.

METHODS

With approval by the ethics committee of each institution, we retrospectively examined 1583 UC patients experienced at our hospital (Nagoya University Hospital) and three related hospitals (Toyohashi National Hospital, Toyohashi City Hospital, and Yamashita Hospital) from October, 1998 to July, 2011. A total of 27 patients under treatment for UC were diagnosed with CRC, all by colonoscopy. During these colonoscopies, targeted biopsies of suspicious lesions for cancer or dysplasia were performed. Of these 27 patients, we excluded 2 who had not undergone colonoscopy before CRC diagnosis, and investigated the diagnostic course of CRCs associated with UC in the remaining 25 (Table 1). We defined 'colonoscopy interval' as the duration between the time when CRC was diagnosed and the time when the last colonoscopy had been performed before CRC diagnosis. For these 25 cases, the former endoscopic findings had shown no suspicious lesions for cancer or dysplasia except for one patient, case no. 5, who had been diagnosed with dysplasia 6 months previously. Fourteen patients had relapsing-remitting disease and 11 had chronic continuous disease. With regard to disease extension, 18 cases were of the pancolitis type, 7 were left-sided colitis, and none were of the proctitis type. We divided the

patients into three groups based on CS interval (A, 1 year or less; B, between 1 and 2 years; and C, 2 years or longer) (Table 2), and examined incidence by interval. Patients were staged according to the Union for International Cancer Control's (UICC) TNM classification.[13]

Table 1 Patient characteristics

Case no.	Sex	Age at onset of UC (years)	Age at cancer diagnosis (years)	UC duration at cancer diagnosis	Extent of UC	Clinical course	Colono-scopy interval	Location	Histologic type	TNM classification (UICC2002)
1	F	22	30 (1999)	7y6m	pancolitis	chronic continuing	5m	R	por	I (T1N0M0)
2	F	49	71 (2000)	22y	pancolitis	relapsing-remitting	14y	C	por	III B (T4N1M0)
3	F	31	46 (2000)	13y8m	pancolitis	relapsing-remitting	1m	R	tub	I (T1N0M0)
4	F	36	56 (2002)	20y10m	pancolitis	relapsing-remitting	4y	R	por	III B (T4N1M0)
5	F	19	43 (2003)	23y10m	pancolitis	chronic continuing	6m	C	tub	I (T2N0M0)
6	F	16	27 (2004)	11y10m	pancolitis	chronic continuing	2y	S	ecc	IV (TXNXM1)
7	M	26	36 (2005)	10y10m	pancolitis	chronic continuing	3y	S	tub	0 (TisN0M0)
8	M	41	70 (2008)	3y6m	left-sided	relapsing-remitting	1y	D	tub	0 (TisN0M0)
9	M	17	30 (2009)	12y10m	pancolitis	relapsing-remitting	1y5m	T	por	II A (T3N0M0)
10	F	29	67 (2009)	39y3m	pancolitis	chronic continuing	2m	R	tub	I (T2N0M0)
11	F	30	42 (2010)	11y11m	left-sided	chronic continuing	1y2m	R	por	III A (T2N1M0)
12	F	54	69 (2010)	15y1m	pancolitis	chronic continuing	2y	S	tub	I (T1N0M0)
13	F	44	49 (2008)	4y7m	left-sided	relapsing-remitting	1y	S	tub	I (T1N0M0)
14	F	22	49 (2009)	27y3m	left-sided	chronic continuing	1y2m	T	tub	I (T1N0M0)
15	M	63	71 (2010)	7y11m	pancolitis	chronic continuing	1y1m	R	por	I (T1N0M0)
16	M	35	47 (2010)	12y	pancolitis	chronic continuing	2y	R,D	por	IV (T4N2M1)
17	F	56	70 (2003)	14y3m	pancolitis	relapsing-remitting	–	A	tub	IV (T4N2M1)
18	F	26	41 (1999)	13y7m	pancolitis	chronic continuing	11y	R	tub	III C (T4N2M0)
19	M	17	23 (2004)	6y	pancolitis	relapsing-remitting	–	R	muc	IV (T4N2M1)
20	M	29	38 (2009)	9y6m	pancolitis	relapsing-remitting	2y1m	R	tub	0 (TisN0M0)
21	M	27	60 (2004)	33y3m	pancolitis	relapsing-remitting	–	S,T	por	IV (T4N2M1)
22	M	18	47 (2011)	29y1m	pancolitis	relapsing-remitting	1y1m	R	tub	0 (TisN0M0)
23	F	35	42 (2001)	8y1m	left-sided	relapsing-remitting	5y1m	V	tub	IIA (T3N0M0)
24	M	31	60 (2003)	29y10m	left-sided	relapsing-remitting	14y	R	tub	IIIA (T3N1M0)
25	F	28	58 (2008)	30y	left-sided	relapsing-remitting	–	S	tub	IIA (T3N0M0)

Table 2 Characteristics according to SC interval

	Group A	Group B	Group C	Total	
No. of patients	6	8	11	25	$P=0.433$
Male/female ratio	1:5	4:4	5:6	10:15	
Age at cancer diagnosis (yr) (mean±SD)	50.8±15.2	47.8±15.9	50.5±15.3	49.7±14.8	$P=0.912$
UC duration at cancer diagnosis (mo) (mean±SD)	185±167	191±93	216±116	201±119	$P=0.855$
Extent					
Pancolitis	4	7	8	19	$P=0.659$
left-sided	2	1	3	6	
Clinical course					
chronic continuing	3	6	2	11	$P=0.044$
relapsing-remitting	3	2	9	14	

RESULTS

Among the 25 patients with UC-associated CRC, cancers were detected at stage 0 in 4, stage I in 8, stage II in 3, stage III in 5, and stage IV in 5 (Tables 1, 3). CRC was detected within 8 years after UC onset in five patients, one of whom was at stage IV (Table 1). Histologically, 15 CRCs were tubular adenocarcinomas and 10 were other types of carcinoma (8 poorly differentiated adenocarcinomas, 1 mucinous adenocarcinoma, and 1 endocrine cell carcinoma) (Table 1). Six patients were classified into group A, consisting of one with stage 0 disease and five in stage I (Table 4A). Eight patients were classified into group B, consisting of one patient in stage 0, three in stage I, one each in stages II and III, and two in stage IV. Eleven patients were classified into group C, consisting of two patients each in stages 0 and II, four in stage III, and three in stage IV. Cancers in Stage 0, I, or II, which are generally treated by radical excision, were diagnosed in 100% of patients in group A, versus only 62.5% in group B and 36.4% in group C (p=0.037). Further, on distribution by histologic type, tubular adenocarcinomas were detected in stages 0-II in 100% of patients in groups A and B versus 57.1% in group C (Table 4B). Moreover, other types of carcinoma were detected in stages 0-II in 100% of patients in group A, versus 40% in group B and 0% in group C (Table 4C). Tubular adenocarcinomas were detected at a significantly earlier stage (stages 0-II) than other types of carcinoma (Table 5, p=0.012).

Table 3   Characteristics according to CRC stage

	Stage 0	Stage I	Stage II	Stage III	Stage IV	
No. of patients	4	8	3	5	5	P=0.026
Male/female ratio	4:0	1:7	1:2	1:4	3:2	
Age at cancer diagnosis (yr) (mean±SD)	47.8±15.6	53.0±14.6	43.3±14.0	54.0±12.7	45.4±20.4	P=0.795
UC duration at cancer diagnosis (mo) (mean±SD)	159±132	209±143	203±139	236±86	185±125	P=0.920
Extent						
pancolitis	3	7	1	3	5	P=0.232
left-sided	1	1	2	2	0	
Clinical course						
chronic continuing	1	6	0	2	2	P=0.207
relapsing-remitting	3	2	3	3	3	

Table 4   Clinical stage according to SC interval

A) All cases

	Group A	Group B	Group C	Total
Stage 0	1	1	2	4
Stage I	5	3		8
Stage II		1	2	3
Stage III		1	4	5
Stage IV		2	3	5
discovery rate of Stage 0-II	100%*	62.5%*	36%*	60%

* p=0.037 (χ^2 test)

B) Tubular adenocarcinoma cases

	Group A	Group B	Group C	Total
Stage 0	1	1	2	4
Stage I	4	2		6
Stage II			2	2
Stage III			2	2
Stage IV			1	1
discovery rate of Stage 0-II	100%*	100%*	57%*	80%

* p=0.117 (χ^2 test)

C) Other types of carcinoma

	Group A	Group B	Group C	Total
Stage 0				0
Stage I	1	1		2
Stage II		1		1
Stage III		1	2	3
Stage IV		2	2	4
discovery rate of Stage 0-II	100%*	40%*	0%*	30%

* p=0.117 (χ^2 test)

Table 5 Clinical stage according to histological type

	Tubular adenocarcinoma	Other type of carcinoma	Total
Stage 0	4	0	4
Stage I	6	2	8
Stage II	2	1	3
Stage III	2	3	5
Stage IV	1	4	5
discovery rate of Stage 0-II	80%*	30%*	60%

* p=0.012 (χ^2 test)

DISCUSSION

We investigated 25 patients with UC who developed CRC. Fifteen cases were tubular adenocarcinoma and 10 were other types of carcinoma. Five (20%) of 25 patients developed CRC within 8 years after the onset of UC. Tubular adenocarcinomas were detected in stages 0-II in 100% of patients under surveillance at intervals of 2 years or less. For other types of carcinoma, in contrast, although CRCs were detected in stage 0-II in 100% of patients under annual surveillance, they were detected in stages 0-II in only 40% of those under surveillance intervals of 1 to 2 years. This indicates that an SC interval of 2 years was sufficient to detect CRCs at stages 0-II in UC patients who developed tubular adenocarcinomas, but was not sufficient for those who developed other types of carcinoma.

An association between UC and CRC was first reported in the 1920s.[1] Several later studies also described this association, and it is now generally accepted.[2,3] The incidence of CRC in UC patients increases with the prolongation of disease course. This cumulative increase in probability appears to justify the start of SC at some point in the course of UC, with repeat SC at appropriate intervals. However, an optimal starting point and intervals have yet to be generally defined. Earlier and more frequent SC increases the probability of detecting CRC at an early stage, but also increases medical workload, and the risk of complications and inconvenience to the UC patient. Eaden *et al.* reported that the incidence of CRC increased 10 years after the onset of

UC,[2] and current guidelines recommend starting SC at 8–10 years after the start of colitis or at 10 years after the onset of colitic symptoms.[7-10] Specifically, the AGA recommends starting SC at 8–10 years after the onset of colitis;[8] the BSG and ECCO recommend that all patients with extensive UC undergo SC approximately 10 years after the onset of colitic symptoms;[7,9] and the Japanese guideline recommends starting SC at 8–10 years after UC onset.[10] In our study, however, 5 (20%) of 25 patients developed CRC within 8 years after the onset of UC, one case of which was found at stage IV. This indicates that starting SC at 8 years after the onset of UC is not sufficient for all UC patients.

With regard to SC interval, the AGA recommends annual or biannual SC following the first SC for UC patients, and after two negative examinations (no dysplasia or cancer), further SC should be performed every 1 to 3 years.[8] In contrast, the BSG and ECCO recommend SC should be conducted yearly, 3-yearly or 5-yearly according to the duration and extent of UC and additional risk factors.[7,9] Strikingly, these guidelines recommend that low-risk groups undergo SC every 5 years.[7,9] The UICC TNM classification system, the most commonly used staging algorithm for colon cancer, categorizes patients on the basis of three variables (tumor, node, and metastasis);[13] when CRC patients are staged according to this classification, it is critical to find CRC at stage 0, I, or II, not only to facilitate curative resection (stage 1, 99.5%; stage II, 97.0%) but also a good 5-year survival rate (stage 0, 94.3%; stage 1, 90.6%; stage II, 81.2%).[14] According to the TNM system, although tubular adenocarcinomas were detected in stages 0-II in 100% of our group B patients, other types of carcinomas were detected in stage 0-II in only 40% of this group. Given our current inability to predict which UC patients will develop adenocarcinomas or other types of carcinomas, our data indicate that SC at intervals longer than 1 year is inappropriate for some UC patients.

Reported risk factors for CRC include early-age onset of UC,[15,16] family history of CRC,[17,18] and primary sclerosing cholangitis.[19,20] In our 25 patients, 4 were diagnosed with UC before age 20 years, whereas 12 were diagnosed at 30 years or older. Only 3 of the 25 patients had a family history of CRC, and none had primary sclerosing cholangitis. Although preliminary, these findings suggest that the known risk factors for CRC do not assist in deciding which patients should receive more frequent SC.

Several limitations of this study warrant mention. First, sample size was small. Second, the study was conducted under a retrospective design. A conclusive understanding of the appropriate starting time and interval for SC in UC patients will require prospective studies in larger UC populations. Finally, despite evidence that cancers can be detected at an earlier stage in patients undergoing SC, confirmation of an effect on survival in patients with extensive colitis requires further study.

In conclusion, this study shows that SC at a two-year interval is appropriate for the early detection of tubular adenocarcinomas, but that other types of carcinoma require annual SC. Because we cannot distinguish UC patients by CRC type, any protocol which starts SC later than 8 years after UC onset and repeats it at longer than 1-year intervals is inappropriate. None of the current guidelines is appropriate for detecting all CRCs in UC patients at their respective curable stages. Studies aimed at distinguishing UC patients who will likely develop a specific type of CRC will aid in the establishment of appropriate guidelines for SC for UC patients.

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