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Comparison of Targeted vs Random Biopsies for Surveillance of Ulcerative Colitis-Associated Colorectal Cancer

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e23. Learning Objective: Upon completion of this evaluation, successful learners will be able to manage patients with ulcerative colitis who are at high risk for the development of colorectal cancer.

See Covering the Cover synopsis on page 1043.

BACKGROUND & AIMS: A random biopsy is recommended for surveillance of ulcerative colitis (UC)-associated colorectal cancer. However, a targeted biopsy might be more effective. We conducted a randomized controlled trial to compare rates of neoplasia detection by targeted vs random biopsies in patients with UC. **METHODS:** We performed a study of 246 patients with UC for 7 years or more, seen at 52 institutions in Japan from October 1, 2008 through December 31, 2010. Patients were randomly assigned to the random group (4 random biopsies collected every 10 cm in addition to targeted biopsies, n = 122) or the target group (biopsies collected from locations of suspected neoplasia, n = 124). The primary end point was the number of neoplastic lesions detected in a single surveillance colonoscopy. We estimated the ratio and difference in the mean number of neoplastic lesions between the groups. We also evaluated the non-inferiority between the groups as an exploratory study. A non-inferiority margin of 0.65 (0.13 of 0.20) was considered for the ratio of the mean number of neoplastic lesions between groups. **RESULTS:** The mean number of biopsies found to contain neoplastic tissue per colonoscopy was 0.211 (24 of 114) in the target group and 0.168 (18 of 107) in the random group (ratio of 1.251; 95% confidence interval, 0.679–2.306). The lower limit was above the non-inferiority margin of 0.65. Neoplasias were detected in 11.4% of patients in the target group and 9.3% of patients in

the random group ($P = .617$). Larger numbers of biopsy samples per colonoscopy were collected in the random group (34.8 vs 3.1 in the target group; $P < .001$), and the total examination time was longer (41.7 vs 26.6 minutes in the target group; $P < .001$). In the random group, all neoplastic tissues found in random biopsies were collected from areas of the mucosa with a history or presence of inflammation. **CONCLUSIONS:** In a randomized controlled trial, we found that targeted and random biopsies detect similar proportions of neoplasias. However, a targeted biopsy appears to be a more cost-effective method. Random biopsies from areas without any signs of present or past inflammation were not found to contain neoplastic tissues. Clinical Trial Registry: UMIN000001608.

Keywords: Dysplasia; Random Biopsy; Colonoscopy; IBD.

In long-standing ulcerative colitis (UC), the risk for colorectal cancer (CRC) increases as disease duration increases. The cumulative risk reaches 7.5%−18.4% at 30 years after onset of the disease.[1–3] We previously showed that at an advanced stage, UC-associated CRC has poorer survival rates than sporadic CRC.[4] Therefore, early detection of UC-associated CRC is essential for successful management of long-standing UC. However, it is not always easy to endoscopically identify UC-associated CRC or dysplasia, as these lesions can be either invisible or very difficult to identify.[5] Therefore, the guidelines recommend use of non-targeted biopsy (random biopsy) for surveillance colonoscopy, in which either 4 biopsy specimens for every 10 cm or ≥33 biopsy specimens are obtained.[6–9] However, random biopsy has been recognized to be costly and time-consuming[10] and targeted biopsy has recently received much attention as an alternative.[11–13] Studies have found that 61%−84% of neoplastic lesions could be visualized by recent endoscopy[14–16] and, therefore, the guidelines suggest the possible use of targeted biopsy in place of random biopsy to improve the efficacy of surveillance.[17,18] In targeted biopsy, specimens are obtained only when endoscopic findings indicate the possibility of neoplasia, leading to a smaller number of samples and resulting in a more cost-effective method. However, very few studies have so far directly and prospectively compared the efficacy of targeted biopsy with that of random biopsy, and it still remains controversial as to whether targeted biopsy should completely replace random biopsy. Therefore, the Research Group for Intractable Inflammatory Bowel Disease of the Ministry of Health, Labour and Welfare of Japan and the Japanese Society for Cancer of the Colon and Rectum (JSCCR) conducted a randomized controlled trial to compare the 2 different biopsy methods. The aim of the present study was to evaluate whether targeted biopsy would show the comparable neoplasia detection rates with a random biopsy.

Methods

Study Design and Oversight

This trial was designed as an exploratory multicenter randomized controlled trial to provide an estimate of the mean number of neoplastic biopsy samples per colonoscopy for a targeted biopsy and a random biopsy in cancer surveillance for long-standing UC patients (Figure 1). The non-inferiority was additionally evaluated with a non-inferiority margin of 0.65 for the ratio of mean number of neoplastic lesions identified between groups. The protocol was set up by the Research Group for Intractable Inflammatory Bowel Disease of the Ministry of Health, Labour and Welfare of Japan and JSCCR. This study was approved by the ethics committee of JSCCR and the Institutional Review Boards of all participating institutions and was conducted in accordance with the Declaration of Helsinki. All participants gave their written informed consent for study participation. An independent data and safety monitoring committee assessed the study data. All serious adverse events were reported to an independent data and safety monitoring committee. The trial is registered at the UMIN Clinical Trial Registry as UMIN000001608 (http://www.umin.ac.jp/ctr/index-j.htm) and the study protocol has been described previously.[19]

Sites and Patients

All of the participating sites (52 Japanese institutions) were members of the Research Group for Intractable Inflammatory Bowel Disease of the Ministry of Health, Labour and Welfare of Japan or JSCCR. We recruited UC patients (left-sided colitis and pancolitis) for whom 7 years or more had passed since onset of the disease. Inclusion and the exclusion criteria are shown in Supplementary Table 1.[20,21]

Study Interventions

We randomly assigned the patients to the targeted biopsy group (target group) or the step biopsy group (random group) after confirming the inclusion and exclusion criteria with the Data Center, Department of Preventive Medicine and Public Health, Keio University. Using stratified allocation, the Data Center defines the facilities and the severity of UC as stratification factors to randomly assign the patients into the target group or the random group. Unique random sequence, which had been generated by the Data Center, was sequentially applied to each patient allocation. The detailed procedures of randomization were not disclosed to researchers at the participating sites. The results of the assignment were not blinded to researchers. In the target group, specimens were obtained by a targeted biopsy. In addition, at least 1 biopsy sample was obtained in the lower rectum, even when no findings suggesting the presence of neoplasia existed. In the random group, 4 random biopsies were obtained every 10 cm. In addition, a targeted biopsy was performed in regions suspected of neoplasia. Panchromoendoscopy was not performed routinely because the study was concluded before the SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection

Abbreviations used in this paper: CRC, colorectal cancer; JSCCR, Japanese Society for Cancer of the Colon and Rectum; UC, ulcerative colitis.

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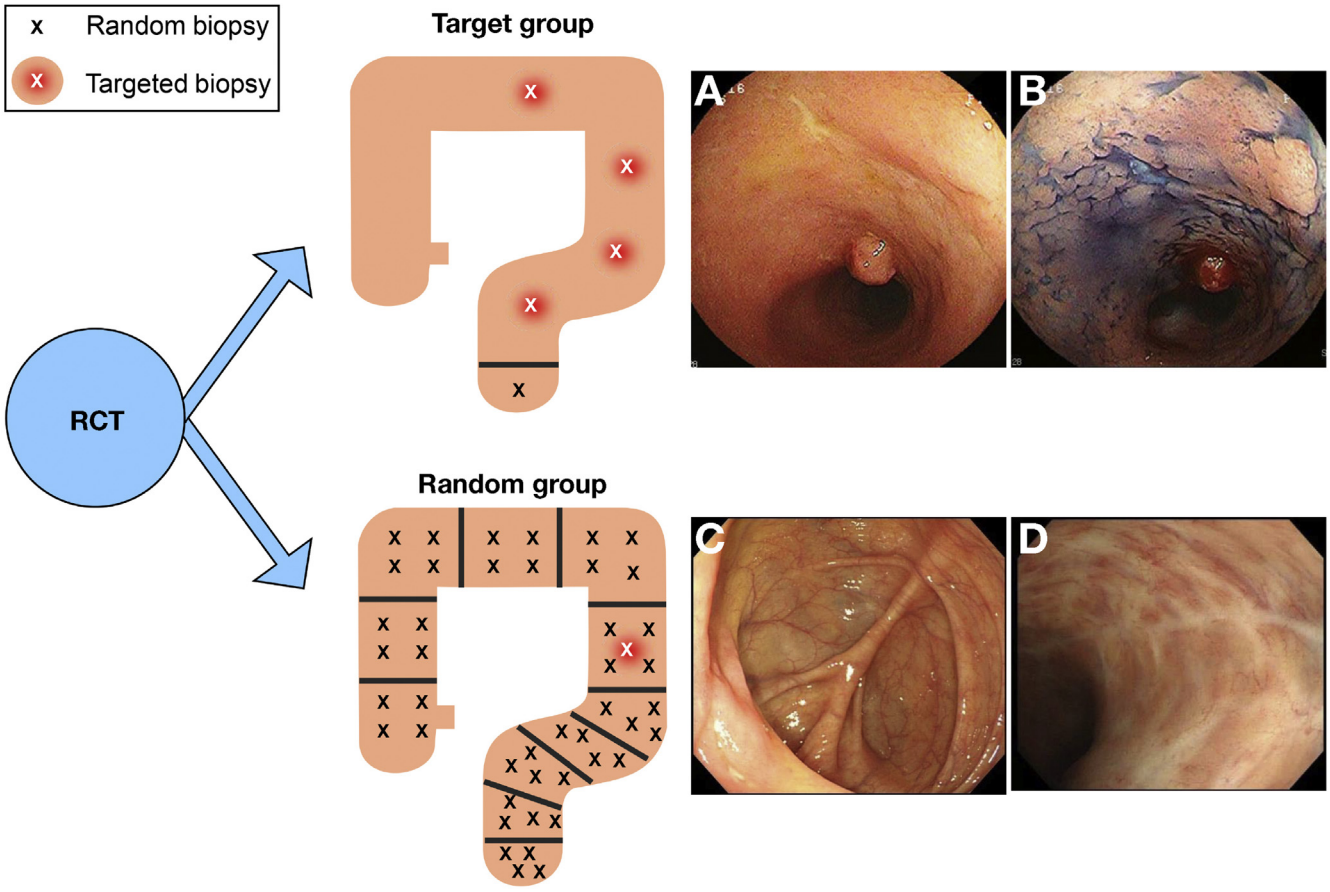


Figure 1. Study design. The patients were randomly assigned to either the targeted biopsy group (target group) or the random biopsy group (random group). In the target group, specimens were obtained by a targeted biopsy. In addition, at least 1 biopsy sample was obtained in the lower rectum, even though there were no findings suspicious for neoplasia. In the random group, 4 random biopsies were obtained every 10 cm. In addition, a targeted biopsy was performed from regions suspicious of neoplasia. (*A*) Two dysplastic lesions were detected by targeted biopsies. A biopsy specimen from the flat elevated lesion on 1 o'clock direction showed high-grade dysplasia, while that from the polypoid lesion in the center revealed low-grade dysplasia. (*B*) Indigo carmine dye spraying enhanced dysplastic lesions detected by white light endoscopy shown in (*A*). (*C*) Areas showing clear vascular patterns without any evidence of present or past inflammation, which could be omitted when performing a random biopsy. (*D*) Areas with ulcer scars, which may be better surveyed by a random biopsy.

and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) statements had been published. However, in both groups, normal endoscopy and chromoendoscopy were performed for any lesions suspected of being neoplasia. Although high-definition colonoscopy was only employed at the endoscopists' discretion and based on the institutions' availability, the majority of institutions utilized high-definition white-light endoscopes in 100% of cases, while the rest of the institutions used them whenever they were available. The number of targeted biopsy samples was not particularly limited, but the characteristics of the biopsied areas were noted to be protruding lesions, flat lesions, depressed lesions, or others.

Outcomes

The primary end point was the number of neoplastic lesions detected in a single surveillance colonoscopy. The secondary end points were the detection rate of patients with neoplasia, examination time, number of biopsies in each examination, incidence of complications requiring special treatments, and risk factors for neoplasia. At the time of registration and after the performance of surveillance colonoscopy, the patient clinical data were reported to the Data Center. Each participating institution submitted 4 unstained sections of all biopsy specimens to the Data Center, which were stained for H&E, p53, and Ki67. All biopsied specimens were centrally evaluated histopathologically by 3 specialized pathologists. The pathologic findings were categorized as the absence of neoplasia, low-grade dysplasia, and high-grade dysplasia.[22] In the event of a discrepancy among the pathologists, the final diagnosis was made based on a discussion. The final pathologic diagnoses were sent to each institution.

Statistical Methods

As noted previously in the study protocol, we set the total sample size for this study at 200 to estimate the difference in the primary end point with the one side length of the 95% confidence interval (CI) precision of 0.11.[19] Mean number of neoplasias per colonoscopy was expected to be the same between the groups, and non-inferiority would be accepted

statistically if the mean number of neoplasias in the target group was at least 65% (0.13 of 0.2) of the mean number of neoplasias per colonoscopy in the random group.

Analyses were performed in the full analysis set. In the primary end point assessment, we estimated the ratio and difference in mean number of neoplastic lesions between the random biopsy and target biopsy groups with a 95% CI. The 95% CIs of the ratio and the difference in mean number were calculated based on the Poisson distribution. For the secondary end points, Wilcoxon rank sum test and χ^2 test were used, as appropriate. The non-inferiority *P* value was 1-sided and the other *P* values were 2-sided; those <.025 for 1-sided tests and <.05 for 2-sided tests were considered to be statistically significant. All analyses were performed with SAS software, version 9.4 (SAS Institute Inc, Cary, NC) and R, version 3.1.2.

Table 1. Patient Characteristics and Clinical Characteristics

Characteristic	Target group (n = 114)	Random group (n = 107)
Age, *y*, mean (SD)	50.7 (13.9)	48.5 (13.6)
Sex, n		
Male	72	75
Female	42	32
Duration of disease, n		
<10 y	17	21
≥10 y	97	86
Disease extent, n		
Left-sided colitis	44	27
Pancolitis	64	75
Others	6	5
Simple clinical activity index, n		
Score ≤8	114	107
Score >8	0	0
Activity index of Truelove and Witts, n		
Mild	114	107
Moderate	0	0
Severe	0	0
Body mass index, kg/m^2, mean (SD)	22.9 (3.1)	22.4 (3.1)
Stool frequency, n/*d*, mean (SD)	2.0 (1.3)	2.1 (1.1)
Hospitalizations for UC, n, mean (SD)	1.3 (1.4)	1.9 (1.9)
History of steroid use in the past year, n		
Present	20	16
Absent	93	90
History of use of immunomodulatory drugs in the past year, n		
Present	29	34
Absent	84	73
Primary sclerosing cholangitis, n		
Present	0	0
Absent	114	106
Family history of cancer, n		
Present	19	22
Absent	95	84
Family history colorectal cancer, n		
Present	5	4
Absent	108	100
Maintenance therapy at the time of examination, n		
Present	108	101
Absent	5	4

Results

A total of 250 patients were assessed for eligibility (Supplementary Appendix). Four patients were determined to be ineligible and 246 patients underwent randomization. One hundred and twenty-four patients were assigned to the target group and 122 patients to the random group. Twenty-five patients were ineligible for the full analysis set, therefore, 114 patients in the target group and 107 patients in the random group were ultimately analyzed. The baseline characteristics of the 2 groups were similar (Table 1). Patients from 34 institutions were enrolled in this study between October 1, 2008 and December 31, 2010.

A total of 42 biopsy samples were found to demonstrate neoplasia (Figures 3 and 4, Table 2, and Supplementary Figure 1). The number of low-grade dysplasias was 23 in the target group and 18 in the random group, and the number of high-grade dysplasias was 1 in the target group

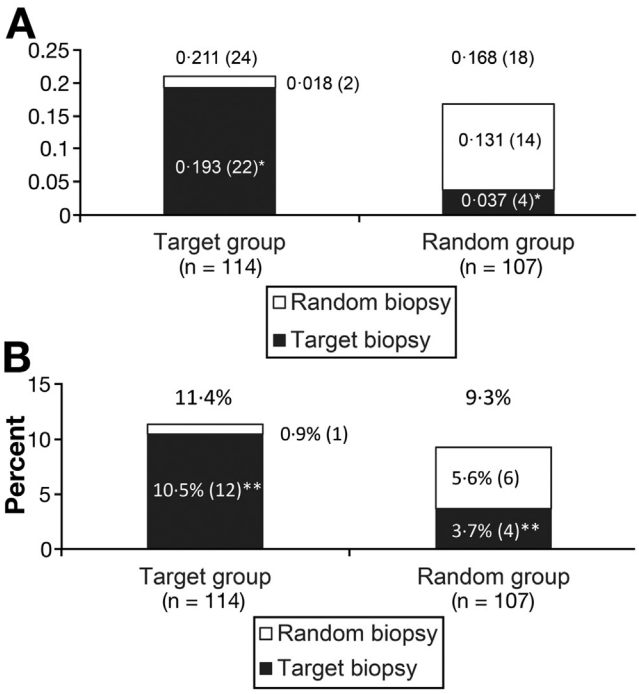
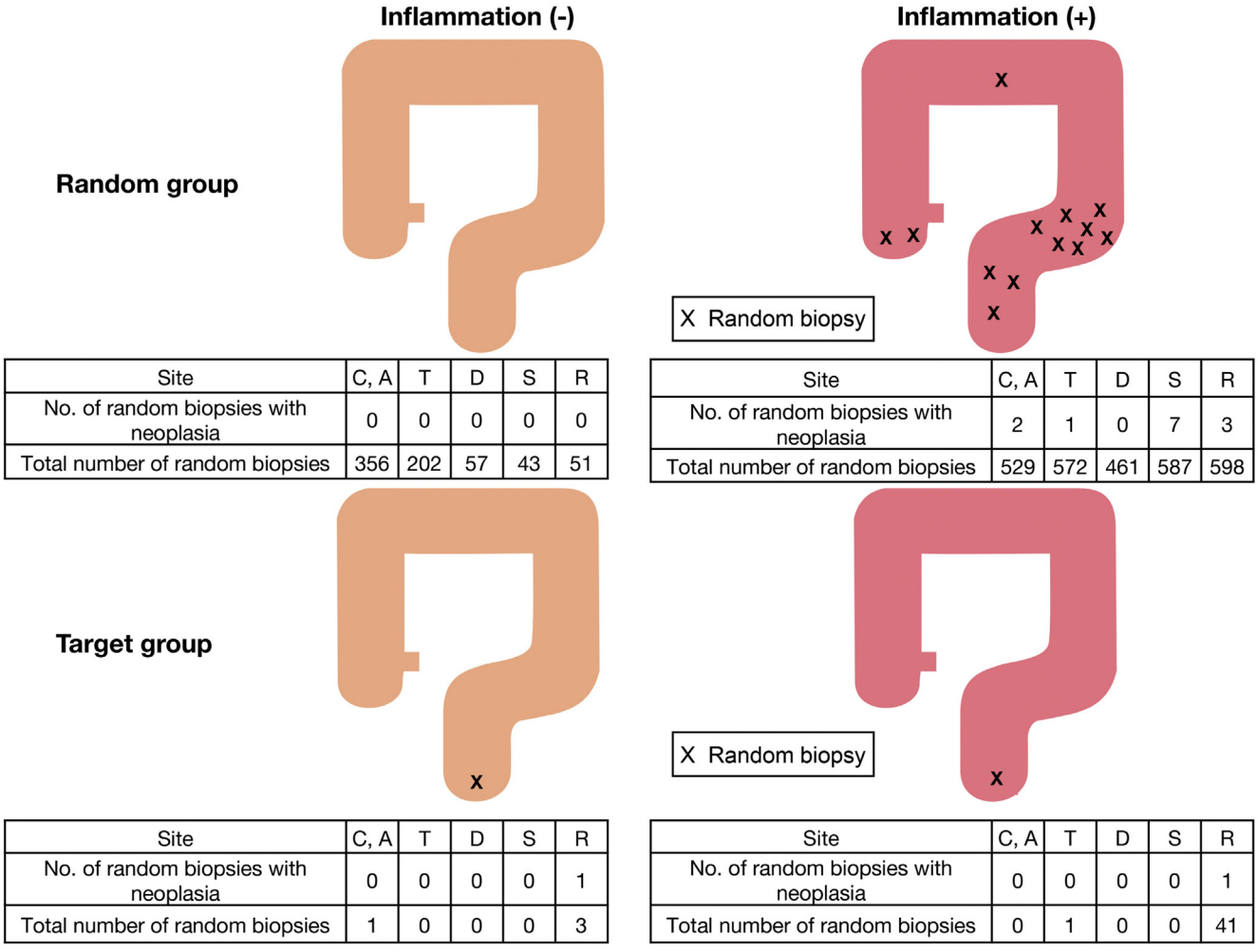


Figure 2. The mean number of biopsy samples with neoplasia (*A*) and the detection rate of patients with neoplasia (*B*). (*A*) The mean number of biopsy samples with neoplasia in each surveillance colonoscopy was 0.211 (24 of 114) in the target group and 0.168 (18 of 107) in the random group, thus showing no significant difference ($P = .423$). Focusing on a targeted biopsy, there was a significant difference between the 2 groups. The target group showed a significantly higher mean number of samples with neoplasia detected by a targeted biopsy than the random group (0.193 vs 0.037; $P < .001$). (*B*) The detection rate of patients with neoplasia was 11.4% (13 of 114) and 9.3% (10 of 107) in the target group and random group, respectively, showing no significant difference. A higher percentage of patients had a diagnosis of neoplasia based on the findings of a targeted biopsy in the target group than in the random group ($P = .052$).

and 0 in the random group. The mean number of biopsy samples with neoplasia in each surveillance colonoscopy was 0.211 (24 of 114) in the target group and 0.168 (18 of 107) in the random group, showing no statistical significance (Figure 2). The ratio between the groups was 1.251 (95% CI, 0.679 to 2.306). The lower limit was above the non-inferiority margin of 0.65 (Supplementary Figure 2). The difference between the 2 groups was 0.042 (95% CI, −0.209 to 0.294). The target group showed a significantly higher mean number of samples with neoplasia detected by targeted biopsy than the random group (0.193 vs 0.037; $P < .001$). The detection rate of the patients with neoplasia was 11.4% (13 of 114) in the target group and 9.3% (10 of 107) in the random group, showing no significant difference ($P = .617$). However, there was a significant difference in the detection rate of patients with neoplasia by targeted biopsy. A higher percentage of patients had a diagnosis of neoplasia by targeted biopsy in the target group than in the random group (10.5% vs 3.7%; $P = .052$).

There was a close relationship between neoplasia and inflammation (Figure 3). In the random group, all neoplastic random biopsy samples were obtained from mucosa with either history or presence of inflammation (100% [13 of 13]), except for 1 sample with unknown inflammation status. In other words, no neoplastic random biopsy samples were obtained from mucosa without either history or presence of inflammation in the random group (0% [0 of 709]. However, in the target group, 1 random biopsy sample obtained from the rectum without inflammation showed neoplasia.

The proportion of neoplasia among the biopsied samples was significantly higher in the target group (6.9% [24 of 350]) than in the random group (0.5% [18 of 3725]; $P < .001$). Mean number of biopsy samples in each colonoscopy was significantly larger in the random group than in the target group (34.8 vs 3.1; $P < .001$). The total examination time was significantly longer in the random group than in the target group (41.7 vs 26.6 minutes;



Site	C, A	T	D	S	R
No. of random biopsies with neoplasia	0	0	0	0	0
Total number of random biopsies	356	202	57	43	51

Site	C, A	T	D	S	R
No. of random biopsies with neoplasia	2	1	0	7	3
Total number of random biopsies	529	572	461	587	598

Site	C, A	T	D	S	R
No. of random biopsies with neoplasia	0	0	0	0	1
Total number of random biopsies	1	0	0	0	3

Site	C, A	T	D	S	R
No. of random biopsies with neoplasia	0	0	0	0	1
Total number of random biopsies	0	1	0	0	41

Figure 3. Distribution of random biopsied samples with neoplasia. In the random group, all neoplastic samples taken by a random biopsy were obtained from mucosal regions with either history or presence of inflammation. In other words, all random biopsied samples obtained from mucosal regions without history or presence of inflammation were non-neoplasia in the random group. However, in the target group, 1 sample obtained by random biopsy from a mucosa in the rectum without inflammation showed neoplasia.

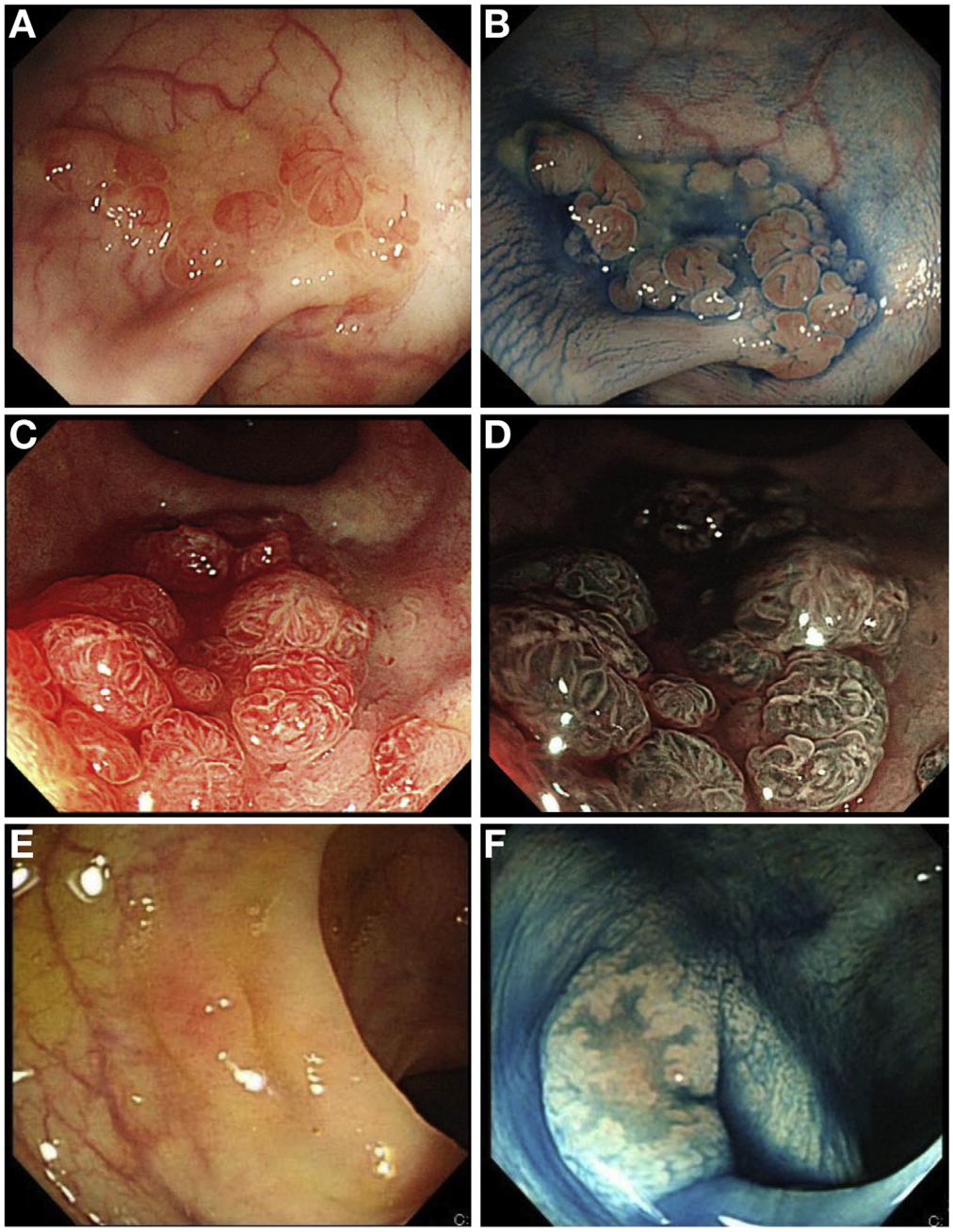


Figure 4. Endoscopic appearances of neoplastic lesions. Neoplastic lesions detected by targeted biopsies. (*A, B*) A flat granular lesion (0−IIa, low-grade dysplasia) (*A*: white light; *B*: indigo carmine dye spraying). (*C, D*) A coarse nodular lesion (0−IIa, low-grade dysplasia) (*C*: white light; *D*: narrow band imaging). (*E, F*) A flat depressed lesion (0−IIc, low-grade dysplasia) (*E*: white light; *F*: indigo carmine dye spraying).

$P < .001$). In total, the number of neoplastic lesions in the right, transverse, descending, sigmoid colon, and rectum was 5, 5, 3, 19, and 10, respectively (Supplementary Figure 3). In the target group, 77.3% of the neoplastic lesions (17 of 22) were protruded lesions, 4.5% (1 of 22) were flat lesions and 18.2% (4 of 22) were stenosis (Supplementary Figure 4, Supplementary Table 2). Physician experience with surveillance colonoscopy was comparable between the 2 groups (mean, 12.7 [SD 5.7] years in the target group and mean, 13.7 [SD 6.1] years in the random group; $P = .201$). There were no complications requiring any special treatments in either group. Univariate analysis revealed the duration of the disease to be a risk factor for neoplasia (Supplementary Table 4).

Discussion

The target group was non-inferior to the random group with respect to the mean number of neoplasia detected per colonoscopy. Furthermore, the overall detection rates of neoplasia per patient showed no significant difference between the 2 groups, and detection rates in the present study were in line with results reported previously (range, 8.7%−12.3%).[2,16] The examination time was significantly longer in the random group (41.7 vs 26.6 minutes; $P < .001$) and mean number of biopsy samples per each examination was significantly larger in the random group than in the target group (34.8 vs 3.1; $P < .001$). Recent guidelines recommend the use of a target biopsy, however, there has been no concrete evidence to show that a target biopsy should

Table 2. Results of Ulcerative Colitis Surveillance in Target vs Random Group

Variable	Target group (n = 114)	Random group (n = 107)
Neoplastic lesions per colonoscopy, n	0.211	0.168
Patients with neoplasia detected, n (%)	13 (11.4)	10 (9.3)
The proportion of neoplasia per biopsy specimen		
Neoplastic lesions, n (%)	24 (6.9)	18 (0.5)
Biopsy specimens taken, n	350	3725
Neoplastic lesions detected, n	24	18
By targeted biopsy	22	4
By random biopsy	2	14
Location, n (%)		
Ascending, cecum	2 (8.3)	3 (16.7)
Transverse	2 (8.3)	3 (16.7)
Descending	3 (12.5)	0 (0)
Sigmoid	12 (50.0)	7 (38.9)
Rectum	5 (20.8)	5 (27.8)
Configuration, n (%)		
Protruded	17 (77.3)	—
Flat	1 (4.5)	—
Stricture	4 (18.2)	—
Total examination time, *min*	26.6	41.7
Low-grade dysplasia, n	23	18
High-grade dysplasia, n	1	0
Invasive cancer, n	0	0

replace a random biopsy completely. To date, several randomized controlled trials have evaluated the different methods of surveillance.[12,23–26] Kiesslich et al[12,23] found that chromoendoscopy or chromoendoscopy-guided endomicroscopy can improve the efficacy of surveillance. van den Broek et al[24] found autofluoroscence imaging improved detection of neoplasia in surveillance. However, these studies did not directly compare the efficacy of a random biopsy with a target biopsy. The present study performed a direct comparison between targeted biopsy and random biopsy in a randomized controlled trial and found that both procedures show comparable rates of neoplasia detection. Furthermore, no severe complications occurred that required treatment in either group. Taken together, it is suggested that a targeted biopsy may be more cost-effective and may be used as an alternative to performing a random biopsy in the surveillance of UC.

The use of targeted biopsy by omitting a random biopsy may increase the potential risk of missing neoplastic lesions because neoplastic lesions are sometimes difficult to identify. However, contrary to our expectations, the target group showed an even larger mean number of neoplastic samples per colonoscopy (0.211 vs 0.168) and a higher detection rate of patients with neoplasia (11.4% vs 9.3% per patient), although these differences did not reach statistical significance. Furthermore, focusing on the detection rate of neoplasia by a targeted biopsy, the target group showed a significantly higher mean number of samples with neoplasia per colonoscopy than the random group (0.193 vs 0.037; $P < .001$). In addition, a higher percentage of patients had a diagnosis of neoplasia by a targeted biopsy in the target group than in the random group (10.5% vs 3.7%; $P = .052$). The precise reason for these differences is unclear. However, one possible reason may be that, in the random group, bleeding due to a random biopsy may disturb precise endoscopic examinations, thereby making a targeted biopsy more difficult. Another possibility is that a random biopsy takes a larger number of biopsies and needs a longer examination time, which may distract endoscopists from performing meticulous examinations. Therefore, endoscopists might overlook some suspicious lesions that would normally be obtained by a targeted biopsy.

Previous studies found that 1088–2707 random biopsies are necessary to find 1 dysplasia,[16,25,27] while another study showed that no neoplasia was found in 2904 random biopsy samples.[11] On average, Rutter et al[10] reported that 1266 random biopsies are necessary to detect 1 neoplasia. In the present study, about 250 random biopsies were needed to find 1 neoplasia in the random group. On the other hand, only 14 targeted biopsies were needed to find neoplasia in the target group. Other studies also show that a smaller number of specimens are needed to find 1 neoplasia by a targeted biopsy.[11,16] These results show that a targeted biopsy appears to be a more useful and effective method for time and cost-effectiveness.

Endoscopic inflammation seemed to be important to improve the efficacy of a random biopsy. In the random group, all 13 neoplastic random biopsy samples were obtained from mucosa with the presence or history of inflammation. In other words, not even a single sample from mucosa without the presence or history of inflammation showed neoplasia (0% [0 of 709]), which suggests the possibility that random biopsy from mucosa without the presence or a history of inflammation can be omitted. If we follow this method, we could have decreased the number of random biopsies from 3456 to 2747 in the present study. However, it should also be noted that 1 of the 2 random biopsy samples that demonstrated neoplasia in the target group was taken from rectal mucosa without inflammation. According to the present protocol, 1 random biopsy was to be taken from the rectum in the target group because neoplasia is frequently located in the rectum in UC. This protocol was originally carried out in our previous study.[13] Taken together, these results suggest that when performing a targeted biopsy, an additional random biopsy from the rectum is recommended, even when there is no evidence or a history of any inflammation.

A clinicopathologic analysis revealed that the location of neoplasia shows a distal predominance, the majority of neoplastic lesions detected by a targeted biopsy were protruded lesions, and the risk factor for neoplasia was the duration of the disease, all of which is in line with previous studies.[1,2,4]

There are several limitations in the present study. First, surveillance colonoscopy was conducted once for each patient during the study period. No data on subsequent colonoscopy after 1 or 2 years were collected. Therefore, this may raise some concern that neoplastic lesions may

have been missed during surveillance colonoscopy, which might have been detected during subsequent colonoscopy. Second, we did not incorporate pancolonic chromoendoscopy in our protocol because it was not generally recommended at the time we made the protocol. Our protocol paper was published in August 2010, which was before the British Society of Gastroenterology guideline was published. However in the recent SCENIC statements, many experts recommend the use of chromoendoscopy,[28] and probably panchromoendoscopy is now one of the choices for UC surveillance. The incorporation of pancolonic chromoendoscopy might have changed our result. At the same time, however, controversy still existed regarding the use of chromoendoscopy because one recent large cohort paper from the Netherlands demonstrated that chromoendoscopy did not increase the dysplasia detection rate.[29] Lastly, the number of patients in this trial was another limitation. We could not plan this trial in an ideal setting, as non-inferiority because of difficulty in recruiting patients. However, the mean number of neoplastic lesions of the target group was larger than that of the random group, and the 1-sided P value for non-inferiority was $<.05$, from which we can consider our hypothesis was supported.

In conclusion, a targeted biopsy is as effective as a random biopsy for the detection of neoplasia in surveillance for UC. Considering cost-effectiveness, a targeted biopsy seems to be more effective than a random biopsy. When performing a targeted biopsy, it is recommended that a random biopsy sample be taken from the rectum. On the other hand, when performing a random biopsy, obtaining biopsy specimens from areas without any signs of present or past inflammation can be omitted, which can reduce the number of unnecessary biopsies and increase the efficacy of the random biopsy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.08.002.

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Conflicts of interest
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