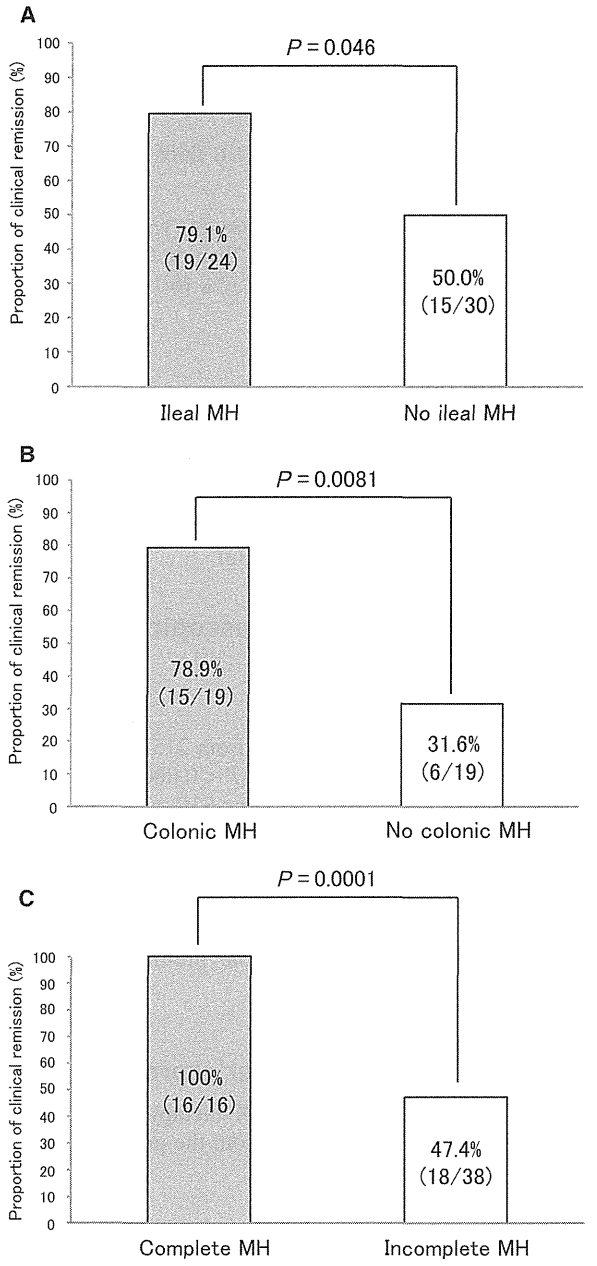

Figure 3 Proportion of clinical remissions at follow-up endoscopy. (A) Comparison of groups with ileal mucosal healing (MH) and with no ileal MH. (B) Comparison of groups with colonic MH and with no-colonic MH. (C) Comparison of groups with complete and incomplete MH. The proportion of clinical remission was significantly higher in the ileal-MH group compared to the no-ileal-MH group (79.1% [19/24] *vs* 50.0% [15/30]). The proportion of clinical remission was significantly higher in the colonic-MH group compared to the no-colonic-MH group (78.9% [15/19] *vs* 31.6% [6/19]). The proportion of clinical remission was significantly higher in the complete-MH group compared to the incomplete-MH group (100% [16/16] *vs* 47.4% [18/38]).

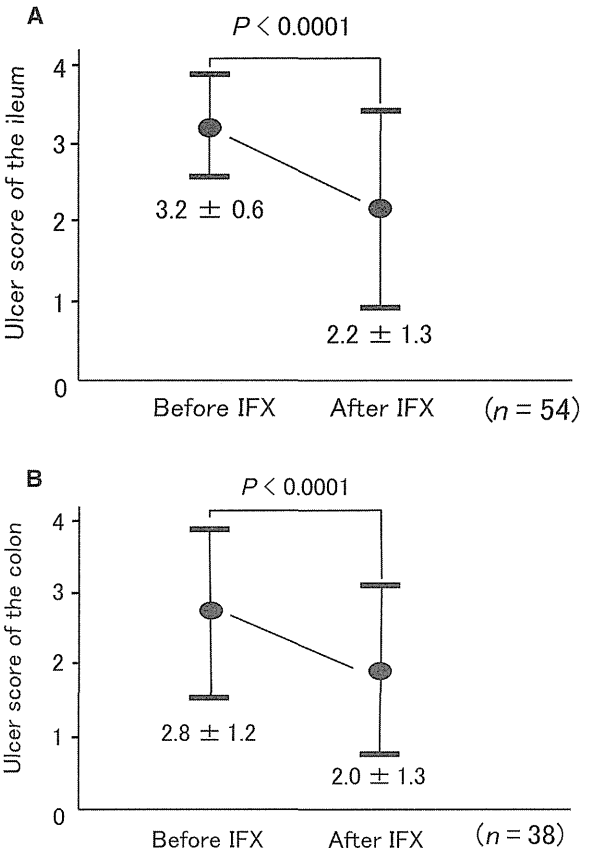

Figure 4 Serial changes of scores for (A) ileal ulcer and (B) colonic ulcer before and after infliximab (IFX) therapy. There are significant changes in the ileal ulcer score and in the colonic ulcer score.

log–rank test showed the difference between the two groups to be significant ($P = 0.025$) (Fig. 5a). The clinical remission rate showed no significant difference between the colonic-MH group and the no-colonic-MH group ($P = 0.593$). The clinical remission rate showed no significant difference between the ileal-MH group and the no-ileal-MH group ($P = 0.268$).

Correlation between MAS for strictures and MH at the time of follow-up endoscopy

The MAS-free rate for strictures was higher in the complete-MH (CMH) group than in the incomplete-MH group, and the log–rank test shows the difference between the two groups to be significant ($P = 0.044$) (Fig. 5b). The surgical site was the ileum in five (71%), ileum/ascending colon anastomosis in one, and ileum/ascending colon in one patient. The MAS-free rate was higher in the ileal-MH group than in the no-ileal-MH group, and the log–rank test showed

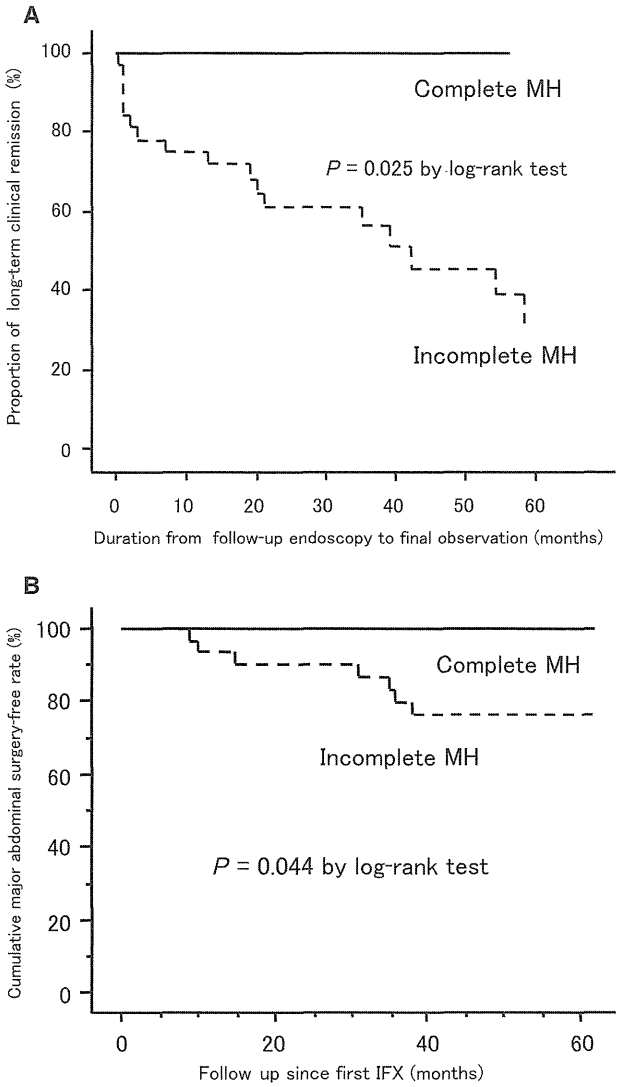

Figure 5 (A) Correlation between the long-term clinical remission rate, evaluated based on the Crohn's disease activity index on the day of final clinical observation, and complete mucosal healing (CMH) at the time of the follow-up endoscopy. The clinical remission rate is higher in the CMH group than in the incomplete-MH group, and the log–rank test shows the difference between the two groups to be significant ($P = 0.025$). (B) Correlation between complete mucosal healing (CMH) and major abdominal surgery (MAS) for strictures. The MAS-free rate is higher in the CMH group than in the incomplete-MH group, and the log–rank test shows the difference between the two groups to be significant ($P = 0.044$).

that the difference between the two groups was significant ($P = 0.030$). The MAS-free rate showed no significant difference between the colonic-MH group and the no-colonic-MH group ($P = 0.717$).

DISCUSSION

THE PRESENT STUDY is the first clinical study to investigate the significance of ileal MH, and complete MH (MH of both ileal and colonic lesions) during IFX maintenance therapy. Ileal MH and complete MH were significantly correlated with clinical remission at follow-up endoscopy. Complete MH correlated significantly with long-term clinical remission. In addition, a lack of complete MH was a predictive factor for MAS as a result of strictures.

There have been few reports of small intestinal mucosal healing as a result of IFX, but Alkiviadis *et al.* reported that the only change found to show endoscopically significant improvement in patients with CD of the small bowel was the number of large ulcers.[23] Imaeda *et al.* recently reported that, among CD patients on maintenance IFX using balloon-assisted endoscopy and colonoscopy, they could not make any comparison because there were no descriptions regarding small intestinal mucosal healing.[24] Following IFX therapy, there was not only improvement in colonic ulcer lesions, but also significant improvement in ileal lesions. This appears to be an important finding, as there have been no published reports of evaluation of mucosal healing separately for the small and large intestine. It was also found that the ileal stenosis score did not show much worsening following IFX therapy.

D'Haens *et al.* reported a strong correlation between post-IFX therapy changes in Crohn's disease endoscopic index of severity (CDEIS) and CDAI.[11] The present study found a strong correlation between complete MH and clinical remission at the follow-up endoscopy. Therefore, evaluation for ileal MH alone or colonic MH alone is insufficient; ideally, both ileal MH and colonic MH should be evaluated.

With respect to long-term prognosis, the clinical relapse rate was low in patients who achieved complete MH, and the rate of surgery as a result of stricture was lower in patients who achieved complete MH. Schnitzler *et al.*[15] and Baert *et al.*[18] reported on MH and the subsequent long-term prognosis, but there have been no reports concerning the importance of complete MH. Accordingly, we think that our present study provides valuable new information.

In the present study, follow-up endoscopy was carried out an average of 18.7 months after IFX induction. As there was no substantial discrepancy compared to the large-scale studies reported by Rutgeerts *et al.* and Baert *et al.*,[10,18] we believe that follow-up endoscopy 1–2 years after starting treatment is appropriate.

In previous reports on MH with IFX (Table 2), different endoscopic scores were used to define MH.[10,15,17–19,24] Most reports define MH as an absence of ulcerations. The CDEIS

Table 2 Present and previous studies on mucosal healing of CD with infliximab

Author	Year	Time to follow-up endoscopy (months)	Duration of IFX treatment (months)	Proportion of MH (%)	Endoscopic index	Definition of MH
Rutgeerts *et al.*[10]	2006	13.5	13.5	50	CDEIS	Absence of mucosal ulceration
Björkesten *et al.*[17]	2011	3, 12	12	45.0, 90.0	Mucosal activity score	Mucosal activity score 0–2
Laharie *et al.*[19]	2011	ND	28	60	CDEIS, SES-CD	Absence of mucosal ulceration
Imaeda *et al.*[24]	2013	>6	40	25.6	Rutgeerts' score	Rutgeerts' score 0 or 1
Schnitzler *et al.*[15]	2009	6.7	68.7	45.4	Original activity index	Complete mucosal healing
Baert *et al.*[18]	2010	24	48	72	SES-CD	SES-CD 0
Present study	2013	18.7	46	29.6	Fukuoka index	Fukuoka index 0 or 1

CD, Crohn's disease; CDEIS, Crohn's disease endoscopic index of severity; IFX, infliximab; MH, mucosal healing; ND, not described; SES-CD, simple endoscopic score for Crohn's disease.

is an endoscopic score focusing on the ileum and colon. The calculations required for assessing the CDEIS score are complicated. In contrast, the Fukuoka index[16] can assess lesions in the small and large intestine, and the calculations are easy. The Fukuoka index ulcer score is similar to a four-point scale,[25] which is a simplified index of the simple endoscopic score for Crohn's disease (SES-CD).[26] The four-point scale includes both ulcers and stenosis, and evaluation may be ambiguous. Therefore evaluation of ileal ulcerations using the Fukuoka index is highly significant.

Ono *et al.*[22] reported that concomitant endoscopic balloon dilation (EBD) for intestinal strictures reduced the rate of surgery. Although IFX promotes the healing of lesions, complications because of intestinal strictures have been reported.[27,28] We also previously reported worsening of intestinal stenosis with MH by IFX induction.[16] New strictures after IFX induction, as identified by double contrast radiography or endoscopy, have been reported in 8% of cases.[22] In the present study, the incidence of small intestinal stenosis was investigated. Prior to IFX therapy, severe stenosis of ≥2 points in the ileum was seen in 43% (23/54). Following IFX maintenance therapy, development of new stenosis or worsening of stenosis was seen in 11% (6/54). The study subjects showed a high rate of stenosis and, for that reason, it is impossible to evaluate all small intestinal lesions by DBE by the anal approach, and this is another limitation of the present study.

Endoscopic evaluation of MH before the advent of DBE was limited to the part of the terminal ileum that could be observed by ileocolonoscopy. DBE is a more advanced technique than ileocolonoscopy, which enables observation of the entire small intestine.[29] However, in actual practice, adhesions or strictures of the ileum after laparotomy in CD patients can severely limit the range of observation. Manes *et al.* also reported that, for half of the patients, the range from Bauhin's valve that could be observed was ≤50 cm, and that DBE for CD was technically difficult.[30]

In the initial endoscopic observation, the percentage of patients with an ileal ulcer score of ≥3 points was high (89%, 48/54). The mean ileal ulcer score was 3.2 points, meaning that there were many patients with mild endoscopic severity. In addition, the endoscopic examination was carried out on the basis of the information gained from small intestinal double-contrast imaging, and it can be said that it was possible to endoscopically observe the lesions with the most severe inflammation.

Many of the initially selected patients were later excluded from this study. In 26 patients, endoscopy was carried out, but the presence of stenosis prevented observation of the deep portion of the small intestine on the adoral side of the stenosis, and the observable range was thus insufficient. Eighty-one patients did not consent to endoscopic examination. Patients with serious complications at baseline and patients who did not respond to IFX therapy were excluded. The study patients were thus limited to those who achieved induction of remission and underwent endoscopy. It could thus be said that there was a selection bias for well-treated patients. However, the activity of the small intestinal lesions was high, and endoscopic observation of these lesions generated results that show that it is possible to predict the subsequent clinical course. Thus, this study has considerable significance. The present study has other limitations, such as being a retrospective, single-center study. In addition, a validated endoscopic score was not used.

We conclude that, in CD patients on IFX maintenance therapy, complete MH after 1–2 years was a predictive factor for long-term clinical remission for up to 4 years after starting IFX. A lack of complete MH was a predictive factor for MAS for strictures. Mucosal healing of ileal lesions was associated with long-term clinical remission after infliximab

maintenance treatment. The present findings suggest that endoscopic evaluation of ileal MH is useful for the long-term prognosis of CD patients.

ACKNOWLEDGMENT

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CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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GASTROENTEROLOGY

Second peak in the distribution of age at onset of ulcerative colitis in relation to smoking cessation

Haruhiko Takahashi,* Toshiyuki Matsui,* Takashi Hisabe,* Fumihito Hirai,* Noritaka Takatsu,* Kozue Tsurumi,* Takao Kanemitsu,* Yuho Sato,* Ken Kinjyo,* Yutaka Yano,* Yasuhiro Takaki,* Takashi Nagahama,* Kenshi Yao† and Masakazu Washio‡

Departments of *Gastroenterology and †Endoscopy, Fukuoka University Chikushi Hospital, Chikushino-City, and ‡Department of Community Health and Clinical Epidemiology, St. Mary's College, Kurume Fukuoka, Japan

Key words
age distribution, smoking cessation, ulcerative colitis.

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Correspondence
Toshiyuki Matsui, Department of Gastroenterology, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikushino, Fukuoka 818-8502, Japan. Email: matsui@fukuoka-u.ac.jp

Abstract

Background and Aim: The prevalence of ulcerative colitis (UC) is increasing steadily in Japan. In Western countries, a bimodal distribution, with UC onset peaks in youth and middle age, is observed, and smoking cessation is reported as a risk factor for UC. However, there are few reports on a bimodal distribution of onset age among Japanese patients. Therefore, the distribution of onset age and factors related to late onset (i.e. onset at 50 years old or later) were investigated in UC patients in Japan.

Methods: A questionnaire survey of UC patients was conducted to investigate the distribution of the age of onset and factors that may be related to UC onset in a Japanese university hospital.

Results: Among 465 UC patients, 343 patients responded. In the distribution of onset age, a large peak was seen in patients aged 10–20s, and small peaks were seen at age 40–44 years and then in 50–60s. In addition, the onset age was older in the UC patients diagnosed in 2001 or later than in those diagnosed in 2000 or earlier. Late onset was more common among the UC patients diagnosed in 2001 or later (*vs* 2000 or earlier: interaction odds ratio = 4.98, 95% CI: 2.21–11.25, $P < 0.01$) and among former smokers (*vs* never-smokers: interaction odds ratio = 2.93, 95% CI: 1.40–6.14, $P < 0.01$) on multivariate analysis.

Conclusions: Similar to UC patients in Western countries, a bimodal distribution of onset age was also observed in Japanese UC patients, and smoking cessation may partly contribute to the increase in late-onset UC patients in recent years in Japan.

Introduction

The prevalence and morbidity rates of inflammatory bowel disease (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD), are lower in Japan than in Western countries, but they are increasing steadily.[1] Factors related to this are thought to include Westernization of the diet and other living habits in Asian countries.[2,3] Research in recent years has shown that genetic factors and various environmental factors may also contribute to IBD onset.[2–5]

IBD is thought to occur more commonly in young people, but as society ages, there are increases in the number of patients with onset at older age and in the number of patients under long-term observation, and elderly patients with IBD are encountered with greater frequency. Older age at onset has been seen in UC in particular in recent years, and it has been pointed out that, in Western countries, the distribution of onset age has shown bimodality, with onset at a young age and at a fairly old age.[5–11]

UC is increasing in many parts of the Asia-Pacific region and is diagnosed at a slightly older age than in the West.[2,3,12–14] In Asia, there is rarely a second incidence peak as in the West.[2,3,12]

Among the onset factors, smoking in particular is said to be an important factor in the onset of UC and its clinical course in Western countries and Asia-Pacific countries, and several case–control studies and cohort studies have been reported.[2–4,12,13,15–19] In Japan, on the other hand, very few reports have closely examined the most recent prevalence and incidence rates and their generational changes.

Therefore, the distribution of onset age of UC, generational changes in age at onset, and factors related to the onset age of UC were investigated in the UC outpatients of our university hospital in Fukuoka, Japan.

Methods

A questionnaire survey was distributed at the time of outpatient visits and by mail to 465 UC patients seen as outpatients at our hospital between April 2006 and March 2010. The subjects of the present analysis were the 343 patients who responded. The diagnosis of UC was based on clinical, endoscopic, and histological criteria. The protocol of this study was approved by theInstitutional

Review Board of Fukuoka University Chikushi Hospital. All participants provided their written, informed consent to participate.

The questionnaire was administered with the aim of investigating onset factors, with question items limited to smoking habit, alcohol consumption, and family history of IBD. Subjects were divided into three groups by smoking habit before the diagnosis of UC: never-smokers, former smokers, and current smokers. For the former smokers, information about duration since they stopped smoking, duration of past smoking, and the number of cigarettes they smoked a day was obtained.

The duration of non-smoking since they stopped smoking among former smokers was classified into three categories (1 year or less, 1–9 years, and 10 years or more). Intensity of smoking was measured by the Brinkman index (BI) (never-smokers, BI = 1–499, BI = 500–999, BI = 1000, or greater). The BI was determined as the number of cigarettes per day multiplied by the number of years smoking.[20]

The patients were similarly divided into three groups by alcohol drinking habit before the diagnosis of UC: never-drinkers, former drinkers, and current drinkers.

In the present study, UC patients were considered to have a family history if they had a relative within the third degree of kinship who had CD or UC.

The age at onset and clinical features were based mainly on the individual clinical survey of their medical records. The distribution of the age at onset was investigated for all subjects and for men and women separately. Patients were divided into two date groups according to onset (2000 or earlier and 2001 or later), and the generational changes in age at onset and related factors were compared between these two groups.

Comparisons were also made between the two groups of 20–49 years old and ≥ 50 years old. As 50 years of age showed a small peak in the overall distribution of age at onset, 50 years of age was used as a cut-off point. In addition, the correlations between smoking habit and disease extent and severity, and the relationships between age at onset and disease extent, severity, and course (surgery and hospitalization rates) were investigated.

Statistical analysis. All statistical analyses were conducted using the Statistical Analysis System (SAS) package (SAS Institute, Cary, NC, USA). In comparisons between groups, Student's *t*-test (for continuous variables) and the χ^2 test (for categorical variables) were used to compare the two groups. Unconditional logistic regression was used to compute the odds ratios (ORs) and their 95% confidence intervals (CIs) with adjustments for covariates. The dose-dependent trend was tested by evaluating the regression coefficient when the categories were treated as equally spaced numerical variables in the logistic regression model. Differences were assessed with two-side tests, with an alpha level of 0.05.

Results

The clinical backgrounds of the subjects ($n = 343$) are shown in Table 1. The distribution of age at onset in all patients is shown in Figure 1. A large peak was seen in the 10–20s, and small peaks were seen at age 40–44 years and then at age 50–64 years.

Table 1 Clinical background of subjects ($n = 343$)

Sex (male : female)	173:170
Age at onset (year)	34.7 ± 15.8
Mean year at onset	2001.7 ± 7.6
Smoking status	
Never-smoker	215 (62.7%)
Former smoker	74 (21.6%)
Current smoker	54 (15.7%)
Drinking status	
Never-drinker	218 (63.6%)
Former drinker	9 (2.6%)
Current drinker	116 (33.8%)
Has family history	31 (9.0%)

Each set of value represents the mean ± SD or number (%).

Figure 1 also shows a comparison of male and female patients. The mean (± standard deviation [SD]) age at onset of UC was significantly higher in male patients than in female patients (36.5 ± 16.0 years *vs* 32.8 ± 15.4 years, $P = 0.03$). There was also a significant difference between men and women in the distribution of age at onset ($P = 0.04$). The proportion of old patients tended to be greater in male patients than in female patients (22.0% *vs* 15.4%, $P = 0.07$).

Table 2 shows the generational changes in age at onset and related factors in both groups. The mean year of onset was 2001.7 ± 7.6 years; thus, the subjects were divided into two groups according to onset (2000 or earlier and 2001 or later). The mean (± SD) age of onset was significantly younger in the 127 patients diagnosed in 2000 or earlier than in the 216 UC patients diagnosed in 2001 or later (30.8 ± 12.1 years *vs* 36.9 ± 17.2 years; $P < 0.01$). In addition, the proportion of late-onset patients (≥ 50 years) was significantly smaller in the patients diagnosed in 2000 or earlier than in the patients diagnosed in 2001 or later (6.3% *vs* 25.9%, $P < 0.01$). There was also a significant difference between the two groups in the distribution of age at onset ($P < 0.01$). In the investigation of onset factors, the 2001 or later onset group had a significantly larger proportion of smokers before onset than the 2000 or earlier onset group ($P = 0.03$). No significant differences were seen in alcohol consumption and family history.

Table 3 shows the cumulative effects of the interactions between onset age and smoking status, drinking status, and family history of UC at onset limited to adult UC patients (≥ 20 years). Even after controlling for all factors in the table, the late-onset patients (≥ 50 years) were more common among the patients with onset in 2001 or later (interaction odds ratio [ORi] = 4.98, 95% CI: 2.21–11.25, $P < 0.01$) and among former smokers (ORi = 2.93, 95% CI: 1.40–6.14, $P < 0.01$) on multivariate analysis.

As shown in Table 4, compared with never-smokers, former smokers were more common among late-onset adult UC patients than early-onset adult patients even after controlling for sex (sex-adjusted ORi = 3.42, 95% CI: 1.69–6.93). In addition, former smokers with longer years had higher ORi (*vs* never-smokers, 1 year or less: sex-adjusted ORi = 2.34, -------; *P* for trend < 0.01). Furthermore, the BI was positively associated with late onset (*vs* never smokers, BI = 1–499: sex-adjusted ORi = 2.55, 95% CI: 1.19–5.47; BI = 500–999: sex-adjusted ORi = 8.02, 95% CI: 2.14–30.10; BI = 1000 or greater; sex-adjusted ORi = 22.33, 95% CI: 2.33–214.43; *P* for trend < 0.01).

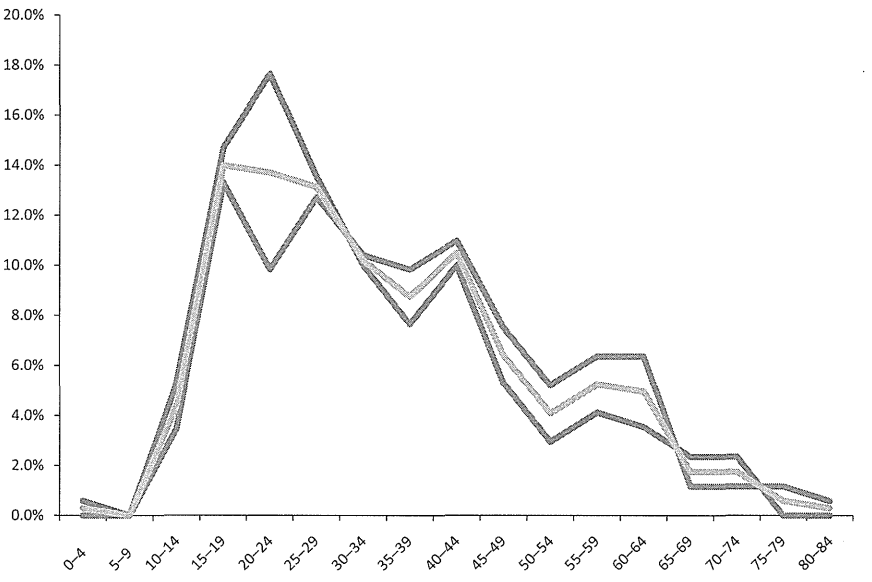

Figure 1 Distribution of age at onset in all subjects (n = 343). A large peak is seen in the 10–20s, and small peaks are seen at age 40–44 years and then at age 50–64 years. Distribution of age at onset in men and women (173 men, 170 women). The mean age at onset is 36.5 ± 16.0 years for men and 32.8 ± 15.4 years for women (P = 0.03). There is a significant difference in the distribution of age at onset. ═, male; ═, female, ═, total.

Table 2 Comparison of distribution of age at onset and onset factors by generation

	Onset in 2000 or earlier (n = 127)	Onset in 2001 or later (n = 216)	P-value
Age at onset (year)	30.8 ± 12.1	36.9 ± 17.2	< 0.01**
Men	49 (39.2%)	124 (56.9%)	< 0.01**
Distribution of age at onset (year)			
< 10	1 (0.8%)	0 (0%)	
10–19	24 (18.9%)	40 (18.6%)	
20–29	40 (31.5%)	50 (23.1%)	
30–39	25 (19.7%)	40 (18.5%)	
40–49	29 (22.8%)	30 (13.9%)	< 0.01**
50–59	6 (4.7%)	26 (12.0%)	
60–69	2 (1.6%)	21 (9.7%)	
70–79	0 (0%)	8 (3.7%)	
≥ 80	0 (0%)	1 (0.5%)	
Proportion ≥ 50	8 (6.3%)	56 (25.9%)	< 0.01**
Smoking status before onset			
Never-smoker	91 (71.7%)	124 (57.3%)	
Former smoking	17 (13.3%)	57 (27.1%)	0.03*
Current smoker	19 (15.0%)	35 (16.2%)	
Drinking status before onset			
Never-drinker	83 (65.4%)	135 (62.4%)	
Former drinking	2 (1.6%)	8 (3.2%)	0.65
Current drinker	42 (33.0%)	73 (34.4%)	
Has family history	14 (11.0%)	17 (7.8%)	0.29

*P < 0.05; **P < 0.01.
Each set of value represents the mean ± SD or number (%).
Student's t-test or χ^2 test.

Although not shown in a table, the age at onset by smoking habit was 31.2 ± 14.7 years in never-smokers, 46.1 ± 13.9 years in former smokers, and 32.7 ± 15.1 years in current smokers. The age at onset was thus significantly higher in former smokers (P < 0.01). There was no correlation between age at onset and disease extent, severity, or course (surgery rate and hospitalization rate), and there was no correlation between smoking habit and disease extent or severity.

Discussion

The present study is the first large-scale report to show a bimodal distribution of onset age and relationship with smoking cessation in Japanese UC patients.

The mean age of onset in the years since 2001 was 36.9 years, which is older than the age of onset in the years 2000 and earlier. The results of a multivariate analysis of people with early onset (20–49 years) and people with late onset (≥ 50 years) showed that the risk of onset after smoking cessation was about three times higher in people with late onset. Moreover, the risk of onset at an older age has increased fivefold since 2001, suggesting the possibility that smoking cessation is a risk for late onset. When the BI was high, the risk of late onset was also high, and there was a risk of late onset even 10 years after smoking cessation.

On the other hand, the rate of current smokers did not differ between the patients with onset in 2001 or later and those with onset in 2000 or earlier (15.6% *vs* 12.8%). These findings suggest that smoking cessation may partly contribute to an increase in late-onset UC patients and to the bimodal distribution of the age at onset in recent years in Japan. Moreover, these trends strengthened with the later generational changes in this study.

In a survey of IBD patients in Japan by Asakura *et al.*,[1] the prevalence of IBD was 63.6/100 000 persons for UC and 21.2/100 000 persons for CD in 2005. These rates are lower than those in Western countries, but they are increasing steadily. Fujimoto *et al.*[21] reported that the proportion of UC patients aged ≥ 60 years

Table 3 Comparison of smoking and drinking status and family history of adult patients at the diagnosis of ulcerative colitis according to the onset age

Age category	20–49 years old (n = 215)	50–89 years old (n = 64)	OR (95% CI)	Adjusted OR (95% CI)
Female	109 (50.7%)	26 (40.6%)	1.00 (reference)	1.00 (reference)
Male	106 (49.3%)	38 (59.4%)	1.50 (0.85–2.65)	0.91 (0.45–1.80)
Year of diagnosis				
2000 or earlier	93 (43.3%)	8 (12.5%)	1.00 (reference)	1.00 (reference)
2001 or later	122 (56.7%)	56 (87.5%)	5.34 (2.43–11.74)**	4.98 (2.21–11.25)**
Smoking status				
Never-smoker	136 (63.3%)	26 (40.6%)	1.00 (reference)	1.00 (reference)
Former smoker	45 (22.3%)	29 (46.9%)	3.27 (1.76–6.08)**	2.93 (1.40–6.14)**
Current smoker	34 (14.4%)	9 (12.5%)	1.35 (0.56–3.27)	1.22 (0.46–3.27)
Drinking status				
Never-drinker	136 (63.3%)	35 (54.7%)	1.00 (reference)	1.00 (reference)
Former drinker	4 (1.9%)	5 (7.8%)	4.86 (1.24–19.04)*	3.37 (0.78–14.62)
Current drinker	75 (34.9%)	24 (37.5%)	1.24 (0.69–2.25)	1.00 (0.51–1.96)
Family history of IBD				
No	196 (91.2%)	58 (90.6%)	1.00 (reference)	1.00 (reference)
Yes	19 (9.4%)	6 (9.4%)	0.94 (0.36–2.46)	0.56 (0.20–1.57)

*P < 0.05; **P < 0.01.
Each set of value represents number (%).
95% CI, 95% confidence interval; adjusted OR, odds ratio adjusted for factors in the table; OR, odds ratio.

Table 4 Cumulative effects of interaction between onset age and sex, smoking status, duration of quit smoking, Brinkman index at the onset of ulcerative colitis risk: case-only analysis among adult never and former smokers

Factors	Early onset adult UC patients, 20–49 years old (n = 181)	Late onset adult UC patients, 50–89 years old (n = 55)	Sex-adjusted ORi (95% CI)
Gender			
Female	101 (50.8%)	24 (43.6%)	1.00 (reference)
Male	80 (44.2%)	31 (56.4%)	0.61 (0.33–1.13)
Smoking status			
Never smokers	136 (75.1%)	26 (47.3%)	1.00 (reference)
Former smokers	45 (24.9%)	29 (52.7%)	3.42 (1.69–6.93)**
Duration of quit smoking			
Never smokers	136 (75.1%)	26 (47.3%)	1.00 (reference)
1 year or less	10 (5.5%)	6 (10.9%)	3.20 (1.04–9.98)*
1–9 years	23 (12.7%)	10 (18.2%)	2.34 (0.94–5.83)***
10 years or more	12 (6.6%)	13 (23.6%)	5.84 (2.23–15.31)**
			P for trend < 0.01
Brinkman index (BI)			
Never smokers	136 (75.1%)	26 (47.3%)	1.00 (reference)
1–499	39 (21.6%)	18 (32.7%)	2.55 (1.19–5.47)*
500–999	5 (2.8%)	7 (12.7%)	8.02 (2.14–30.10)**
1000 or greater	1 (0.6%)	4 (7.3%)	22.33 (2.33–214.43)**
			P for trend < 0.01

*P < 0.05; **P < 0.01; ***P < 0.1.
Each set of value represents number(%).
95% CI, 95% confidence interval; ORi, interaction odds ratio.

increased 6.5-fold from 1981 to 2000. These results indicate that UC does not occur more commonly in young people.

UC is increasing in many parts of the Asia-Pacific region and is diagnosed at a slightly older age than in the West.[2,3,12,13] Looking at the distribution of age at onset of UC in Western countries, a bimodal distribution is seen, with young people in their 20–30s and older people in their 50–70s.[4–7] In contrast, there is rarely a second incidence peak in Asian populations.[2,3,12] In a recent Korean study, Yang *et al.*[14] were able to demonstrate this smaller second peak in incidence for UC, similar to that seen in the present study.

In Asia, some studies have shown that smoking has a protective effect in the development of UC.[2,3,12,22] Other possible environmental factors associated with UC in the Asian population include a

Western diet. Several studies have shown genetic polymorphisms associated with UC in the Asian population.[2,3,12]

The results of the present investigation are similar to those of Western countries and other Asian countries, suggesting that there may be bimodality in the age at onset and an increase in patients with onset at older age among Japanese as well. The effect of an aging society is not the only factor involved in this. Environmental factors such as diet, smoking habit, and alcohol consumption are also thought to be related to onset. Smoking in particular has been said for some time to be an important environmental factor.

A relationship between IBD and smoking was first reported in 1982 by Harries *et al.*,[15] who reported that there were fewer smokers among UC patients than among healthy people. Later, smoking habit was thought to an important factor in the onset of UC and its clinical course in Western countries and Asia-Pacific countries, and several case–control studies and cohort studies have been reported.[16–19,22–24]

Aldhous *et al.*[17] found that a group of former smokers had significantly higher age at onset than current smokers and never-smokers (46.5 years *vs* 31.1 years or 29.4 years, $P < 0.01$). They also showed a bimodal distribution of age at onset and a significantly higher proportion of former smokers in the group with onset at age ≥ 50 years. These results are the same as those of the present investigation. Moreover, the second peak in age at onset is conjectured to be formed by smoking cessation in middle-aged people,[23,24] and the high proportion of onset at older age in men in particular is conjectured to be because the smoking cessation rate is higher in men than in women.[24] There are several reports that the proportion of onset at an elderly age increases with later generations, a tendency that is particularly strong in men.[6–8,10,11,24] The proportion of late onset (≥ 50 years) in this study was 38/173 (22.0%) in men and 26/170 (15.4%) in women. Although the difference was not significant, the incidence rate had a male preponderance. This is thought to be because of the high smoking cessation rate in men. In Japan, the "People's Health Promotion Campaign for the 21st Century" (Healthy Japan 21) was formulated in 2000 as a measure to promote health and vitality in all citizens. Programs in Healthy Japan 21 are implemented with cigarette smoking as a priority issue. To prevent lifestyle-related diseases, a health promotion law was enacted in 2002 that incorporates the concept of health promotion through lifestyle improvements in the areas of nutrition, exercise, and alcohol and tobacco consumption. Since that time, the smoking rate has remained relatively flat in women (1990–2010: 14.3–12.1%), but it declined over time in men (1990–2010: 58.8–36.6%).[25]

In the present study, no correlation was seen between smoking habit and disease extent or severity, and no correlation was seen between age at onset and disease extent, severity, or course (surgery and hospitalization rates). There are many reports of greater severity at time of onset[26] and more extensive disease[11,26] in early-onset patients than in late-onset patients, but there are also reports showing no difference,[17,19] and no consensus has been reached.

Similar to the report by Higuchi *et al.*,[27] when the BI was high, the risk of late onset was also seen to be high, and there was a risk of late onset even 10 years after smoking cessation. Thus, it was found that smoking cessation was a risk for the onset of UC, regardless of the length of time between smoking cessation and onset.

While smoking is thus thought to have a positive effect for UC patients, the mechanism is not clear. Since smoking is known to increase risks for cardiovascular events such as myocardial infarction and stroke, lung diseases such as emphysema, and lung cancer and other malignancies, it is difficult to recommend smoking to our UC patients. The mechanisms are likely to be complex and require further investigation.

In the present study, there was no causal association between family history of IBD and onset, but Ha *et al.*[19] reported that, while smoking cessation was an onset factor in the older onset group ($P < 0.001$), family history was an onset risk in the young onset group ($P = 0.008$). In Japan, Ishige *et al.*[28] found that family history of IBD was significantly higher in a young onset group when young onset was defined as onset at age ≤ 16 years. Various studies have been conducted in recent years with gene analysis of IBD patients, and we look forward to elucidation of this in the coming years.

The present study has several limitations. First, the number of UC patients was small because the participants in the present study were not from hospitals all over the Japan but from one university hospital in Fukuoka, Japan. Second, the present study was not a case–control study. Thus, one can evaluate the risk of UC onset but not the interaction between factors related to UC onset. Further studies are needed.

In conclusion, a bimodal distribution of the age at onset in UC patients was seen in our hospital, similar to the distribution in Western countries. Moreover, these trends strengthened with the later generational changes. The present results also suggest that smoking cessation may contribute as a factor in the second peak.

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Characterization of gut microbiota profiles by disease activity in patients with Crohn's disease using data mining analysis of terminal restriction fragment length polymorphisms

AKIRA ANDOH[1], TOSHIO KOBAYASHI[2], HIROYUKI KUZUOKA[3], TOMOYUKI TSUJIKAWA[4], YASUO SUZUKI[5], FUMIHITO HIRAI[6], TOSHIYUKI MATSUI[6], SHIRO NAKAMURA[7], TAKAYUKI MATSUMOTO[7] and YOSHIHIDE FUJIYAMA[4]

[1]Division of Mucosal Immunology, Graduate School of Medicine, Shiga University of Medical Science, Otsu, Shiga 520-2192; [2]Miyagi University, Sendai, Miyagi 982-0215; [3]Research and Development Laboratories, EN Otsuka Pharmaceutical Co., Ltd., Hanamaki, Iwate 025-0312; [4]Department of Medicine, Shiga University of Medical Science, Otsu, Shiga 520-2192; [5]Department of Internal Medicine, Sakura Medical Center, Toho University, Sakura, Chiba 285-8741; [6]Department of Gastroenterology, Chikushi Hospital, Fukuoka University, Chikushino, Fukuoka 814-0180; [7]Division of Lower Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo 663-8131, Japan

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Abstract. The gut microbiota plays a significant role in the pathogenesis of Crohn's disease (CD). In this study, we analyzed the disease activity and associated fecal microbiota profiles in 160 CD patients and 121 healthy individuals. Fecal samples from the CD patients were collected during three different clinical phases, the active (n=66), remission-achieved (n=51) and remission-maintained (n=43) phases. Terminal restriction fragment length polymorphism (T-RFLP) and data mining analysis using the Classification and Regression Tree (C&RT) approach were performed. Data mining provided a decision tree that clearly identified the various subject groups (nodes). The majority of the healthy individuals were divided into Node-5 and Node-8. Healthy subjects comprised 99% of Node-5 (91 of 92) and 84% of Node-8 (21 of 25 subjects). Node-3 was characterized by CD (136 of 160 CD subjects) and was divided into Node-6 and Node-7. Node-6 (n=103) was characterized by subjects in the active phase (n=48; 46%) and remission-achieved phase (n=39; 38%) and Node-7 was characterized by the remission-maintained phase (21 of 37 subjects; 57%). Finally, Node-6 was divided into Node-9 and Node-10. Node-9 (n=78) was characterized by subjects in the active phase (n=43; 55%) and Node-10 (n=25) was characterized by subjects in the remission-maintained phase (n=16; 64%). Differences in the gut microbiota associated with disease activity of CD patients were identified. Thus, data mining analysis appears to be an ideal tool for the characterization of the gut microbiota in inflammatory bowel disease.

Correspondence to: Professor Akira Andoh, Division of Mucosal Immunology, Graduate School, Shiga University of Medical Science, Seta Tsukinowa, Otsu, Shiga 520-2192, Japan
E-mail: andoh@belle.shiga-med.ac.jp

Key words: data mining, microbiota, terminal restriction fragment length polymorphism, inflammatory bowel disease

Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), is a chronic intestinal disorder of unknown etiology (1-4). The pathogenesis of IBD involves an aberrant response by the mucosal immune system toward luminal antigens, such as dietary factors and/or commensal microbiota in genetically susceptible individuals (2,5-8). In particular, the commensal microbiota is regarded as the major environmental factor associated with IBD (5,7,9-12). IBD is mainly localized to those intestinal areas in which the majority of the bacteria are congregated, namely, the distal small intestine and the colon. The commensal microbiota is essential for the development of experimental colitis in various animal models of IBD (6,9).

The global composition of the gut microbiota, rather than the presence of certain pathogens, is most relevant to the etiology and pathogenesis of IBD (dysbiosis hypothesis) (5,13-16). Molecular approaches targeting the 16S ribosomal (r)DNA have been used to define significant changes in the diversity and composition of the gut microbiota in IBD (17). For example, a marked decrease in the relative abundance of members of the phylum Firmicutes, particularly *Clostridium* clusters IV and XIV, has been reported in IBD (5,17,18). The etiological significance of this finding is supported by a recent study by Atarashi *et al* (19), which demonstrated that the genus *Clostridium* plays a significant role in the induction of colonic regulatory T cells, which play a central role in maintaining immune homeostasis. Other reports indicated

that *Faecalibacterium prausnitzii*, a member of *Clostridium* cluster IV, is also clinically significant (20-22).

It was previously demonstrated, using terminal restriction fragment length polymorphism (T-RFLP) analysis, that the fecal microbiota profile of CD patients differs from that of healthy individuals (14,18). This difference was observed even in patients with inactive disease (18). However, no differences associated with the activity of the disease were detected in the fecal microbiota profiles of CD patients with active and inactive disease. To further investigate the fecal microbiota of CD patients, we performed a data-mining analysis on the T-RFLP results from the analysis of fecal samples collected at three clinical time points (prior to induction therapy, immediately after the achievement of remission and ≥6 weeks later, while under continuous remission).

Materials and methods

Patients and samples. The patients and fecal samples used in this study were the same as those used in our previous study (14). In total, 66 patients with active CD [CD activity index (CDAI)>150 as reported by Best *et al* (23)] were recruited. The diagnosis of CD was based on clinical, endoscopic and pathological criteria. A total of 121 healthy individuals residing close to each center were also enrolled.

Fecal samples were collected from each patient at three different clinical phases: i) active disease at entry (active phase), ii) immediately after achievement of remission (CDAI<150; remission-achieved phase) and iii) maintained remission for ≥6 weeks (remission-maintained phase). The average period of remission between ii) and iii) was 15.7±10.8 weeks (mean ± SD). Samples from patients with ileostomy, patients who received surgical treatment or those who failed to achieve remission during the course of the study were excluded.

This study was approved by the Institutional Review Boards and the patients provided written informed consent prior to enrolment.

DNA extraction. Each fecal sample (0.5 g) was suspended in 5 ml of Tris-EDTA buffer (pH 7.5) and centrifuged. This washing step was repeated 4 times. The sample was then resuspended in 5 ml of the same buffer containing lysozyme (5 mg/ml; Sigma, St. Louis, MO, USA), *N*-acetylmuramidase (0.5 mg/ml; Sigma) and achromopeptidase (0.5 mg/ml; Sigma). The following manipulations of DNA extraction were performed as previously described (24) and the final concentration of the DNA sample was adjusted to 20 ng/μl.

Polymerase chain reaction (PCR) amplification and T-RFLP analysis. The 16S rRNA gene was amplified from human fecal DNA using the 27 forward 5'-AGAGTTTGATCCTGG CTCAG-3' and 1492 reverse 5'-GGTTACCTTGTTACG ACTT-3' primers (25,26). The 5'-ends of the forward primers were labeled with 6'-carboxyfluorescein, which was synthesized by Applied Biosystems (Tokyo, Japan). The PCR amplifications of the DNA samples (10 ng of each DNA) were performed as previously described (25,26). The amplified 16S rDNA genes were purified using polyethylene glycol (PEG 6000) and redissolved in 20 μl distilled water.

The restriction enzymes were selected according to Matsumoto *et al* (25). The purified PCR products (2 μl) were digested with 20 U *Hha*I and *Msp*I at 55˚C for 1 h. The length of the T-RF fragments was determined with an ABI PRISM® 3100 or ABI 3130xl genetic analyzer (Applied Biosystems) in GeneScan mode. Standard size markers, such as GS500 ROX and GS1000 ROX (Applied Biosystems), were used. The fragment sizes were estimated using the local Southern method in GeneScan 3.1 software (Applied Biosystems). As the apparent size of identical T-RFs may vary by 1-2 bp among different gels and/or lanes of the same gel, major T-RFs similar in size by 1-2 bp were summarized to operational taxonomic units (OTUs). The major T-RFs were identified by computer simulation, which was performed using a T-RFLP analysis program (27), a phylogenetic assignment database for T-RFLP analysis of human colonic microbiota (25) and Microbiota Profiler (InfoCom T-RFLP Database & Analysis Software, Infocom Co., Tokyo, Japan). T-RFs with a peak height <25 fluorescence units were excluded from the analysis. Cluster analyses were performed using BioNumerics software (Applied Maths, Kortrijk, Belgium) based on the *Hha*I or *Msp*I T-RFLP patterns. The distances were calculated to determine any similarity among the samples and were graphically represented by constructing a dendrogram. Pearson's similarity coefficient analysis and the unweighted pair-group methods with arithmetic means were used to establish the type of dendrogram.

Data mining. Data mining analysis was performed using SPSS Clementine 14 software (IBM, Tokyo, Japan). A dividing system using the Classification and Regression Tree (C&RT) approach, which is the most typical method for constructing decision trees, using the Gini coefficient (28) between geographic districts and OTU data was applied. The records were divided into two subsets, so that the records within each subset were more homogeneous compared to the previous subset. C&RT is quite flexible and allows unequal misclassification costs to be considered, unlike other growing systems of data mining.

Results and Discussion

Data mining provided a decision tree as shown in Fig. 1, which clearly identified the various subject groups (nodes). A decision tree is a decision-supporting pathway that forms a tree-like graph. Each OTU was expressed as a restriction enzyme and RF length (bp), e.g., the *Hha*I 32-bp OTU was abbreviated as Hh32 and the *Msp*I 225-bp OTU was abbreviated as M225. Node-0 (the left end of the decision tree) is referred to as the root node, which is the starting point for tree construction and the decision tree grew toward the right to divide the subjects. As shown in Fig. 1, Node-0 was divided into Node-1 and Node-2 by Hh93, with a cut-off value of 0.086. This cut-off value was calculated from Hh93 data for all the subjects using the Gini coefficient and the C&RT method. Similar steps were repeated to fully construct the decision tree. The details of the decision tree and the pathway to the next node clearly indicated the species and quantities of OTUs, which contributed to the division of the various subject groups.

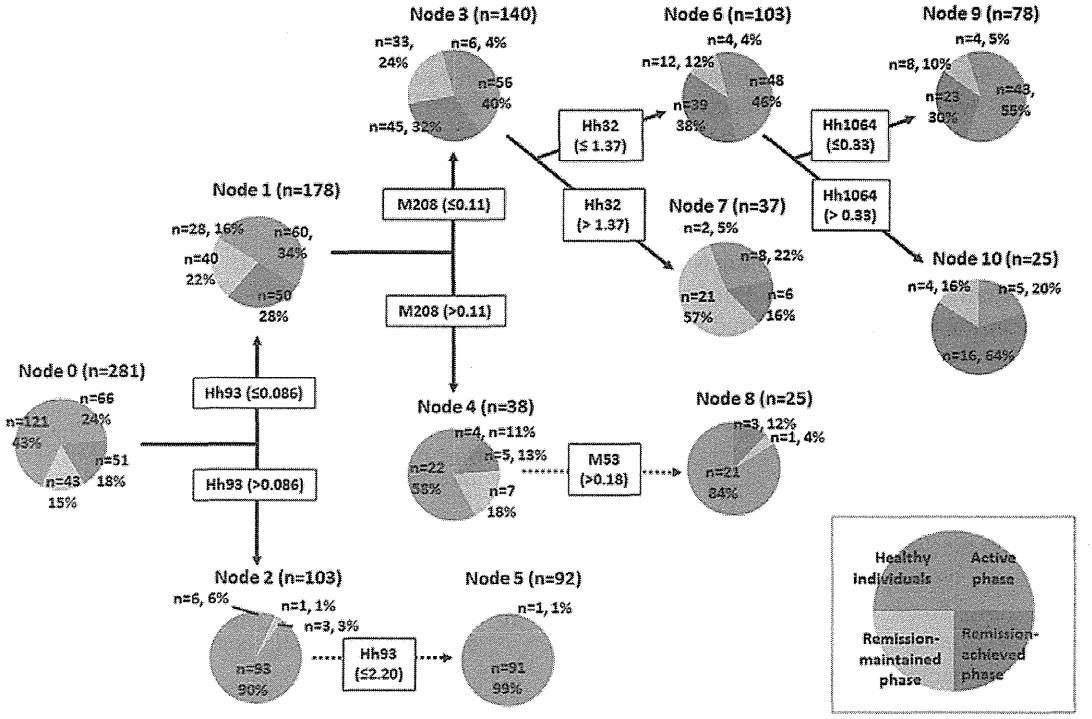

Figure 1. Decision tree constructed using the Classification and Regression Tree (C&RT) approach. Each operational taxonomic unit (OTU) is expressed as a restriction enzyme and RF length (bp), e.g. *Hha*I 93-bp OTU is abbreviated as Hh93 and *Msp*I 208-bp OTU is abbreviated as M208. The cut-off value of each dividing OTU was calculated from the OTU data of all the subjects, using the Gini coefficient with the C&RT method. Similar steps were repeated for the construction of a decision tree. Node-0 (the left end of the decision tree) is referred to as the root node, which is the starting point for tree construction. The details of the decision tree and the pathway indicate the species and quantities of OTUs, which contribute to dividing the various subject groups. RF, restriction fragment.

Node-1 included almost all the CD subjects and a small number of healthy subjects. By contrast, Node-2 consisted primarily of healthy subjects. These data indicate that Hh93 plays a significant role in the discrimination of healthy individuals from those with CD. Hh93 also played a role in the discrimination of the healthy individuals of Node-2 into Node-5. The database assignment of Hh93 included *Desulfovibrio* (a genus of sulfate-reducing bacteria) and *Lawsonia*; however, the pathological roles of these bacteria in human disease have not been clearly determined.

Node-1 was divided into Node-3 and Node-4 by M208, with a cut-off value of 0.11. Node-3 was characterized by CD patients in all phases; however, Node-4 consisted of 22 healthy individuals (58%) and 16 subjects with CD (42%), indicating that the gut microbiota profile of certain CD patients resembles that of healthy individuals. The database assignment of M208 included *Coprococcus*, *Roseburia*, *Dorea* and *Blautia*; however, the role of these bacteria has not been fully elucidated. M53 (*Faecalibacterium*), which had a cut-off value >0.18, led to further segregation of healthy individuals from Node-4 into Node-8.

As shown in Fig. 1, Node-3 included 56 CD subjects in the active, 45 in the remission-achieved and 33 in the remission-maintained phase. Node-3 was divided into Node-6 and Node-7 based on Hh32 (*Faecalibacterium*, *Bacteroides*), with a cut-off of 1.37. Node-6 included 48 subjects in the active phase (46%) and 39 subjects in the remission-achieved phase (38%), indicating that there are no significant differences in fecal microbiota profiles between CD patients in the active and remission-achieved phases. By contrast, Node-7 was characterized by 21 subjects in the remission-maintained phase (57%), indicating that the gut microbiota profile tends to change according to the duration of remission maintenance. Hh32 is assigned to *Faecalibacterium* and remission maintenance may stimulate the growth of this bacterium, which exhibits strong anti-inflammatory activity (20-22).

We previously reported the results of cluster analyses of the gut microbiota profiles of the same samples used in the present study (14). However, disease-associated differences were not identified, possibly due to the several limitations of the cluster analysis. For example, the cluster analysis only shows some classified groups and it does not produce clearly defined reasons for the creation of these groups. In addition, the obtained clusters lack flexibility, meaning that a slight modification of the data affects cluster formation. Furthermore, data mining constructs a decision tree, which is a set rule that predicts target variables and enables the creation of classification trees by repeated data division. During this process, a tree branch is formed and every branch determines the classification criteria for the dividing data. Therefore, exploration of a dataset by data mining enables the researcher to predict the most significant predictor variable. Additionally, once the decision tree is constructed, all the subsequent new records may be run with the same data mining tree, as long as the basic concepts of the data remain active. The main difference between data mining and cluster analysis is the capacity for handling data noise. Data mining skips characteristic noise and selects a series of related fields; however, cluster processing respects all

data, without consideration of any numerical noise. Thus, in the present study it was possible to demonstrate geographical differences in the human gut microbiota in Japan.

In conclusion, to the best of our knowledge, this study is the first to identify disease activity and associated differences in the gut microbiota profiles of CD patients, which differ from those of healthy individuals. Among the CD patients, the gut microbiota profiles may differ according to disease activity. These results indicate that data mining is an ideal tool for characterizing human gut microbiota. Further investigations of the gut microbiota profiles associated with CD may lead to improved diagnostics and the development of novel therapeutic agents.

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Original Article

Long-term outcome of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease

Fumihito Hirai, Takahiro Beppu, Noritaka Takatsu, Yutaka Yano, Kazeo Ninomiya, Yoichiro Ono, Takashi Hisabe and Toshiyuki Matsui

Department of Gastroenterology, Fukuoka University Chikushi Hospital, Chikushino, Japan

Background and Aim: Endoscopic balloon dilation (EBD) is an alternative to surgery for small bowel strictures of patients with Crohn's disease (CD). However, little is known about the long-term efficacy of EBD. The aim of the present study was to clarify the long-term outcome of EBD for small bowel strictures in patients with CD.

Methods: Subjects comprised 65 patients with CD who underwent EBD for small intestinal strictures and were followed up for at least 6 months. All subjects had obstructive symptoms as a result of small bowel strictures. Short-term success was defined as technical success and the disappearance of obstructive symptoms. The short-term success rate of EBD, its safety profile, the cumulative surgery-free rate and the cumulative redilation-free rate were investigated.

Results: Short-term success rate was 80.0% (52/65). Complications were encountered in six of the 65 patients (9.2%). Seventeen patients (26.2%) underwent surgery during the observation period of this study. Cumulative surgery-free rate after initial EBD was 79% at 2 years and 73% at 3 years, respectively. EBD successful cases showed significantly higher surgery-free rates than unsuccessful cases ($P < 0.0001$). In 52 of the successful cases, the cumulative redilation-free rate after initial EBD was 64% at 2 years and 47% at 3 years, respectively.

Conclusion: EBD for small bowel strictures secondary to CD provides not only short-term success but also long-term efficacy. However, the high redilation rate is one of the clinical problems of this procedure.

Keywords: balloon-assisted enteroscopy, Crohn's disease, endoscopic balloon dilation, small bowel stricture

INTRODUCTION

CROHN'S DISEASE (CD) is a chronic inflammatory disorder of the gastrointestinal tract characterized by transluminal inflammation. In consideration of the long-standing and relapsing nature of this disease, frequent surgeries should be avoided in order to reduce the risk of short bowel syndrome or malnutrition. However, up to 80% of CD patients require at least one surgical resection within 10 years of being diagnosed.[1] It was also reported that the cumulative surgery rate after diagnosis was 46–62% at 5 years and 61–75% at 10 years.[2–4] Moreover, after the initial surgery, almost half the patients underwent re-surgery.[5,6] Intestinal strictures are one of the most common intestinal complications in patients with CD. Severe intestinal strictures require surgical intervention, including intestinal resection or strictureplasty.[7,8] However, surgical intervention increases the risk of recurrent strictures.[9] Endoscopic balloon dilation (EBD) is a well-established therapeutic option for Crohn's strictures, enabling avoidance of surgery.[10–20] According to a systematic review, the technical success rate of EBD was 71–100%, and clinical efficacy was observed in 53–100% of the reported cases.[21] In recent years, there have been several reports on EBD for small bowel strictures using balloon-assisted enteroscopy (BAE).[22–26] However, all these reports involved small cohorts and the long-term efficacy was not sufficiently evaluated. Therefore, it is unclear how EBD for small bowel strictures affects the long-term course of CD. The current study was conducted to clarify the long-term outcome of EBD for small bowel strictures in patients with CD.

Corresponding: Fumihito Hirai, Department of Gastroenterology, Fukuoka University Chikushi Hospital, 1-1-1, Zokumyoin, Chikusino, Fukuoka 818-8502, Japan. Email: fuhirai@cis.fukuoka-u.ac.jp
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METHODS

Patients

PATIENTS WITH CD who had obstructive symptoms as a result of small bowel strictures and met the indications for EBD were included in this study. Patients with strictures

of the ileo-colonic anastomosis only were excluded, as were patients whose post-EBD observation periods were less than 6 months. Indications for EBD using double balloon enteroscopy (DBE) for small bowel strictures at our hospital are as follows: (i) small bowel strictures causing obstructive symptoms; (ii) stricture length ≤5 cm; (iii) no associated fistula or abscess; (iv) no deep ulcer; and (v) no severe curvature of the stricture.[25] We confirmed the site, length, number and severity of the strictures by small bowel enteroclysis and abdominal computed tomography (CT) prior to DBE. Between April 2005 and September 2012, EBD using DBE was attempted at our hospital in 75 patients who we thought met our inclusion criteria. However, fistulas and deep ulcers were later detected by DBE in 10 of these patients. Of these, two were fistulas and eight were deep ulcers that could not be identified prior to DBE. Hence, a total of 65 patients were evaluated in the present study. Baseline characteristics, details of stricture site and concomitant treatment of subjects are shown in Table 1.

Dilation methods and definition of short-term success

Endoscopic balloon dilation was carried out using a DBE (EN-450 T5; Fujifilm Medical Co., Tokyo, Japan) and a 12–18-mm through-the-scope (TTS) balloon catheter (CRE™ balloon catheter; Boston Scientific Co., Natick, MA, USA). The balloon was inflated to a pressure of 1–7 atm, the pressure being maintained for 30 seconds to 2 minutes. During the procedure, we usually use carbon dioxide insufflation in order to avoid retention of a large amount of air.[27] EBD was carried out under conscious sedation produced by midazolam and buprenorphine.

Short-term success was defined by the disappearance of obstructive symptoms (e.g. abdominal pain, bloating and vomiting) after technically adequate dilation. As patients are hospitalized at our institution for 2 days after EBD, we could determine whether their obstructive symptoms had disappeared. In patients who had multiple strictures, when the small bowel stricture that was deemed responsible for the obstructive symptoms was dilated by EBD, we judged it as short-term success. Moreover, we investigated the factors influencing short-term success by comparing successful and unsuccessful cases.

Table 1 Characteristics of patients, stricture site and concomitant treatment at initial EBD

	n = 65
Characteristic	
Gender (M : F)	51 : 14
Age (years)	36.0 ± 10.5
Disease duration (years)	13.1 ± 8.6
History of surgery (yes/no)	40/25
Disease site (ileitis/ileo-colitis)	40/25
Stricture site	
Location (jejunum/ileum/anastomosis)	6/49/10
Strictures (single/multiple)	25/40
Length (<3 cm / ≥3 cm)	49/16
Prestenotic dilatation (yes/no)	46/19
Concomitant treatment†	
Anti-TNF-α antibody (yes/no)	32/33
Steroid (yes/no)	5/60
Immunomodulator (yes/no)	28/37
Enteral nutrition‡ (yes/no)	25/40

†Patients who received two or three treatments were included.
‡Patients who received ≥600 kcal/day of enteral nutrition were included.
EBD, endoscopic balloon dilation; TNF, tumor necrosis factor.

Safety profile

In order to assess the safety profile of EBD, we analyzed the rate and details of post-EBD complications that needed additional treatment.

Long-term outcomes

Long-term results were assessed as the cumulative surgery-free rate and the cumulative redilation-free rate of the subjects. Secondary EBD was usually carried out for redilation in patients with relapse of obstructive symptoms. However, even in patients without recurrence of obstructive symptoms, we pre-emptively carried out secondary EBD if we found re-strictures through which the enteroscope could not be passed in follow-up DBE, to avoid relapse of the obstructive symptoms. We also investigated the factors influencing redilation by comparing patients with and without a need for redilation.

Ethical considerations

Complete information regarding DBE, EBD and conscious sedation was provided to all patients. Written informed consent was obtained from all patients before the procedures were carried out.

Statistical analysis

Student's *t*-test was used for comparison of unpaired continuous variable data. Chi-squared test or Fisher's exact test was used for comparison of frequencies. The Kaplan–Meier method and log–rank test were used for analysis of the cumulative surgery-free rate and the cumulative redilation-free rate. SPSS version 16.0 was used for

statistical analysis. *P*-value <0.05 was considered statistically significant.

RESULTS

Short-term outcome

TECHNICALLY SUCCESSFUL EBD occurred in 52 cases. All 52 cases had confirmed disappearance of obstructive symptoms. However, in two cases in the technically unsuccessful group, obstructive symptoms disappeared probably as a result of an additional elemental diet. As a result, EBD using DBE was successful in 52 of the 65 cases (80.0%). In most of the short-term successful cases (48/52, 92.3%), the scope could be passed through the stricture site after the initial EBD. Of the 13 unsuccessful cases, the scope could not be inserted up to the stricture site in eight cases, and the guidewire or through-the-scope (TTS) balloon could not be maintained at the correct position of the stricture in five cases. There were no significant differences in clinical features and concomitant treatment between the two groups (data not shown). Patients with long strictures measuring ≥3 cm were significantly more frequently observed in EBD unsuccessful cases (53.8%, 7/13) than in EBD successful cases (17.3%, 9/52) ($P = 0.02$). There were no significant differences in other stricture-related factors between the two groups (Table 2).

Safety profile

Complications occurred in six EBD successful cases (9.2%) only. One patient experienced hemorrhage that required blood transfusion and one patient developed acute pancreatitis. Both patients recovered immediately following conservative therapy. Perforation was observed in one patient only (1.5%) who recovered following emergency surgery (partial ileal resection). The other three patients showed hyperamylasemia, all of them recovering after nil per os for a few days.

Table 2 Comparison of stricture-related factors between EBD successful and unsuccessful cases

	Successful cases (n = 52)	Unsuccessful cases (n = 13)	*P*-value
Location			
Naïve lesion	44	11	0.94
Anastomotic lesion	8	2	
Strictures			
Single	21	4	0.75
Multiple	31	9	
Length of stricture			
<3 cm	43	6	0.02
≥3 cm	9	7	
Prestenotic dilatation			
Existent	37	9	0.89
Non-existent	15	4	

EBD, endoscopic balloon dilation.

Long-term outcome

Seventeen patients (26.2%) underwent surgery during the observation period of 41.8 ± 24.9 months after initial EBD. Cumulative surgery-free rate among all the subjects was 79% and 73% at 2 and 3 years, respectively (Fig. 1). Nine (17.3%) of 52 EBD successful cases underwent surgery. Although six patients underwent surgery as a result of the persistence of obstructive symptoms, the reasons for surgery were newly diagnosed fistula in two patients and rectal cancer in the remaining patient. In contrast, eight (61.5%) of the 13 EBD unsuccessful cases underwent surgery, the reason for surgery in all eight cases being small bowel obstruction. Figure 2 shows a comparison of the cumulative surgery-free rate between EBD successful and unsuccessful cases. EBD successful cases showed a significantly higher surgery-free rate than EBD unsuccessful cases ($P < 0.0001$).

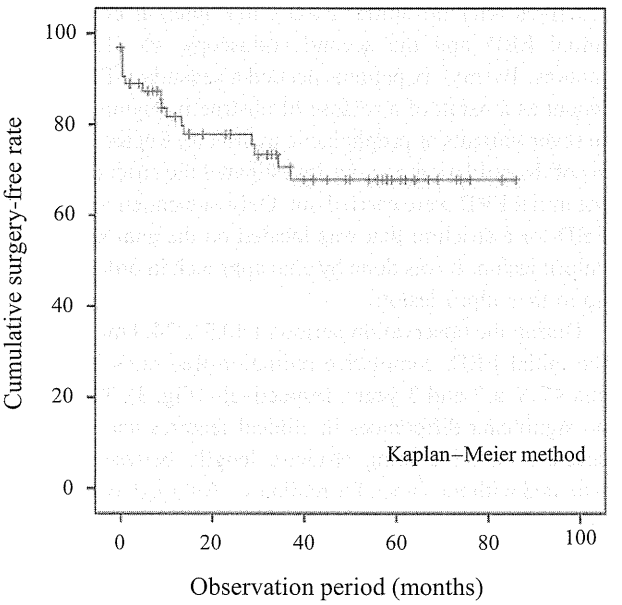

Figure 1 Cumulative surgery-free rate among all the subjects was 79% and 73% at 2 and 3 years, respectively, with an observation period of 41.8 ± 24.9 months after initial endoscopic balloon dilation.

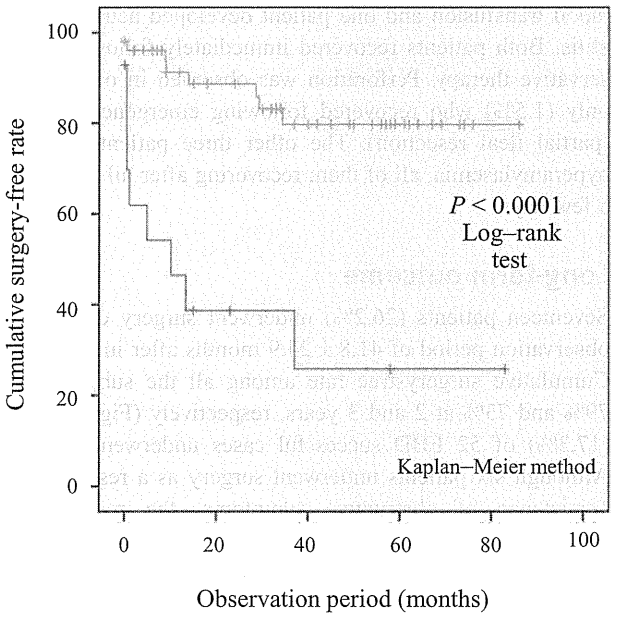

Figure 2 Cumulative surgery-free rate of successful endoscopic balloon dilation (EBD) cases was 80% at 3 years after initial EBD. Successful cases after initial EBD (green line) showed significantly higher surgery-free rates than EBD unsuccessful cases (blue line) ($P < 0.0001$).

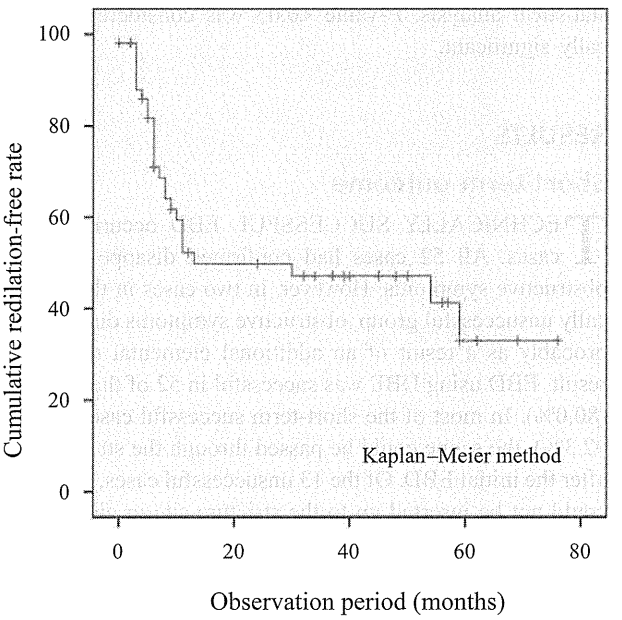

Figure 3 Cumulative redilation-free rate of endoscopic balloon dilation (EBD) successful cases was 64% and 47% at 2 and 3 years, respectively, during the observation period of 40.3 ± 24.8 months after initial EBD.

In the 52 EBD successful cases, 45 patients (86.5%) were re-examined endoscopically to confirm the condition of the strictures after the initial EBD. Time interval between the initial EBD and the second endoscopy was 12.0 ± 13.6 months. Twenty-six patients needed a secondary EBD, 19 of whom as a result of a relapse of obstructive symptoms, and in seven patients as prophylactic treatment. Regarding analysis of the redilation rate, we investigated the strictures where the initial EBD were carried out. Only one patient underwent EBD for a stricture that was located on the anal side of the culprit lesion. It was done by anal approach in order to insert up to the culprit lesion.

During the observation period of 40.3 ± 24.8 months after the initial EBD, cumulative redilation-free rates were 64% and 47% at 2 and 3 years, respectively (Fig. 3). There were no significant differences in clinical features and details of stricture site, including stricture length, between patients with and without a need for redilation. Although two patients with redilation and three patients without redilation started anti-tumor necrosis factor-α antibody as a result of active small bowel lesion after the initial EBD, there were no significant differences regarding concomitant treatment between the two groups (Tables 3,4). There were also no significant differences in terms of the initial dilation methods between the two groups (Table 5).

Table 3 Baseline characteristics and concomitant treatment of patients with and without redilation

	With redilation (n = 26)	Without redilation (n = 26)	P-value
Characteristic			
Gender (M : F)	18 : 8	23 : 3	0.17
Age (years)	35.8 ± 10.7	35.7 ± 8.9	0.96
Disease duration (years)	13.2 ± 8.1	12.7 ± 9.5	0.84
History of surgery (yes/no)	14/12	15/11	1
Disease site (ileitis/ileo-colitis)	14/12	17/9	0.4
Concomitant treatment†			
Anti-TNF-α antibody (yes/no)	13/13	17/9	0.26
Steroid (yes/no)	3/23	2/24	0.64
Immunomodulator (yes/no)	14/12	12/14	0.58
Enteral nutrition‡ (yes/no)	10/16	14/12	0.27

†Patients who received two or three treatments were included.
‡Patients who received 600 kcal/day or more of enteral nutrition were included.
TNF, tumor necrosis factor.

Table 4 Stricture-related factors in patients with and without redilation

	With redilation (n = 26)	Without redilation (n = 26)	P-value
Location			
Naïve lesion	19	23	0.3
Anastomotic lesion	7	3	
Strictures			
Single	15	15	1
Multiple	11	11	
Length of stricture			
<3 cm	20	24	0.25
≥3 cm	6	2	
Prestenotic dilatation			
Existent	15	22	0.25
Non-existent	11	4	

Table 5 Comparison of the initial dilation methods between patients with and without redilation

	With redilation (n = 26)	Without redilation (n = 26)	P-value
Intubation route			
Antegrade	4	5	1
Retrograde	22	21	
Dilation pressure			
<3 atm	13	15	0.58
≥3 atm	13	11	
Dilation time			
<1 min	6	8	0.75
≥1 min	20	18	
Diameter of balloon catheter			
≥15 mm	6	7	0.81
<15 mm	20	19	

DISCUSSION

ENDOSCOPIC BALLOON DILATION is an alternative to surgery for gastrointestinal strictures in patients with CD. Although EBD for Crohn's strictures has been frequently used since the 1990s,[10–20] the procedure has mainly been applied to strictures of the upper gastrointestinal tract, naïve colonic and ileo-colonic anastomoses, which can be approached by gastrointestinal scopes or colonoscopes. Since the development of BAE, it been widely used for the diagnosis and treatment of small bowel diseases,[28] but the procedure is also being carried out for small bowel strictures as a result of CD. However, previous studies evaluating this procedure have involved small cohorts only.[22–25] To our knowledge, the current study includes the largest cohort regarding EBD for small bowel strictures.

To date, it is unclear how the safety and efficacy of EBD should be evaluated. There is no established definition of its short-term success, different definitions being used in different studies. In the present study, short-term success was defined as technical success and disappearance of obstructive symptoms. According to this definition, a high short-term success rate (80.0%) was confirmed. If short-term success were defined as being able to pass the scope through the stricture site, the short-term success rate was 73.8%, which was as high as that reported in previous reports.[22–25] In comparative analysis, EBD unsuccessful cases were more likely to have long strictures measuring ≥3 cm in length. As long strictures are a potential factor in the failure of EBD, we should pay attention to the length of the stricture when selecting subjects for EBD.

One of the major concerns of EBD is perforation. The perforation rate was previously reported as 0–9%,[10–20,22–25] the rate in our study being 1.5%. The other complications observed included one case of hemorrhage, one case of pancreatitis and three cases of hyperamylasemia, all of which recovered with conventional therapy. Thus, we believe that EBD is a safe, less-invasive method of treating small bowel strictures. However, in our case series, the EBD procedure had to be abandoned in 10 cases as a result of contraindications that could not be identified prior to DBE. Precise examination before EBD is therefore important in order to confirm the indications before starting the procedure.

The current study focused mainly on the long-term efficacy of EBD. The cumulative surgery-free rate was 79% and 73% at 2 and 3 years, respectively. This rate was similar to the results reported in previous studies evaluating EBD for naïve colonic and ileo-colonic anastomoses.[10–20] Therefore, EBD using DBE for small bowel strictures had almost the same efficacy as EBD using conventional scopes in terms of avoiding surgery. EBD successful cases had a lower surgery rate (17.3%) than EBD unsuccessful cases (61.5%) during the follow-up period of 41.8 ± 24.9 months after EBD. Given the results of the current study, EBD for small bowel strictures in patients with CD seems to be effective not only over the short-term but also over the long-term, at least over an observation period of approximately 4 years after the initial EBD.

The relapse rate of obstructive symptoms post-EBD has been reported as being 22 to 31%.[22–25] Hence, there are some EBD successful cases that require redilation in order to avoid surgery. To date, there are no data regarding how often redilation needs to be carried out. In the present study, half the cases required redilation, and the cumulative redilation-free