

## A multicenter survey of enteroscopy for the diagnosis of intestinal follicular lymphoma

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**Abstract.** The importance of enteroscopy examinations to investigate the entire length of the small intestines has been emphasized in follicular lymphoma patients with intestinal involvement. The aim of the present study was to determine the current state of enteroscopy examinations, including the performance rate, and the prevalence of small intestinal lesions in a patient population in Japan. A retrospective multicenter survey of 17 institutions collected the case information

of 110 follicular lymphoma patients with gastrointestinal involvement. The results of the enteroscopy examinations were reviewed, and in order to identify potential factors affecting the performance rate of enteroscopy, patient gender, age at lymphoma diagnosis, histopathological grade, clinical stage, the date of the initial diagnosis and the annual volume of enteroscopy at the institution were compared between the patients who underwent one or more enteroscopy procedures and the patients who did not undergo enteroscopy. A total of 34 patients (30.9%) underwent enteroscopy, and 24 of these (70.6%) presented with involvement in the jejunum and/or ileum. It was found that more patients diagnosed in recent years and more patients treated at an ultra-high volume institution ( $\geq 101$  enteroscopy examinations/year) underwent an enteroscopy. In conclusion, although the prevalence of small intestinal lesions was high (70.6%) in the follicular lymphoma patients presenting with intestinal involvement, the performance rate of enteroscopy was only 30.9%, and thus the majority of the patients have not undergone enteroscopy examinations. Further investigation is required to define the clinical significance of enteroscopy at the initial diagnostic work-up and during the follow-up period of these patients.

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## Introduction

Follicular lymphoma is the most common subtype of indolent non-Hodgkin's lymphoma. Widespread nodal involvement is a typical presentation of this disease, with the majority of patients presenting with Ann Arbor stage III or IV, whereas only 5-10% of patients present with early stage I or II (1-3). Follicular lymphoma arising in the intestine has recently been drawing attention for its distinct clinical features, which are different from their nodal counterpart. Several studies have suggested that the majority of patients with intestinal follicular lymphoma present with localized disease and show favorable clinical courses (3-5).

Intestinal follicular lymphomas were initially introduced as a disease predominantly involving the duodenum (6). The representative macroscopic features of the duodenal lesions are multiple small, whitish polypoid lesions (5). The detection of such duodenal lesions by esophagogastroduodenoscopy is the initial diagnostic clue in the cases of the majority of the patients with this disease entity. Since the development of novel enteroscopy devices such as double-balloon enteroscopy and video capsule enteroscopy, recent studies have revealed the frequent involvement of the jejunum and ileum in these patients. Among follicular lymphoma patients presenting with intestinal involvement, the reported percentage of cases with multiple follicular lymphoma lesions in the jejunum and/or ileum has ranged from 66.7 to 100% (3,7-11).

These results emphasize the importance of enteroscopy examinations to precisely evaluate the extent of the intestinal lesions in follicular lymphoma patients. However, the majority of the previous studies were conducted in a single tertiary-care center, and to the best of our knowledge, the number of patients with this disease entity who underwent enteroscopy examinations in actual clinical settings has never been determined. A retrospective multicenter survey was therefore conducted to reveal the present status of enteroscopy examinations among follicular lymphoma patients presenting with intestinal involvement. The purposes of the present study were to determine the current state of enteroscopy examinations, including the performance rate, and to determine the prevalence of small intestinal lesions in a patient population in Japan.

## Patients and methods

**Patients.** A database search performed at the Department of Pathology at the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Okayama, Japan) identified 110 follicular lymphoma patients with gastrointestinal involvement who were treated at Okayama University Hospital or one of 16 collaborating institutions (listed in the Acknowledgements section) between July 1990 and October 2013. A subset of the 110 patients examined also participated in a number of our previous studies (4,6,12-19).

The diagnosis of follicular lymphomas was made according to World Health Organization (WHO) classifications (1,20). A histological diagnosis was based on morphological and immunophenotypical analyses of endoscopically biopsied specimens or surgically resected specimens. Histopathological grading was also determined according to WHO criteria (1). Patients with grade 3 follicular lymphoma were excluded from this study

since these cases are generally managed based on treatment strategies established for diffuse large B-cell lymphomas (1). Clinical data regarding the patients' endoscopic, radiological and biological examinations were obtained from retrospectively reviewed clinical records. The Lugano staging system for the classification of gastrointestinal lymphoma was used to determine each patient's clinical stage (21,22).

The present study was approved by the Ethical Committee of the Okayama University Hospital and adhered to the Declaration of Helsinki.

**Analyses.** Based on the clinical records of the enrolled patients, the patients were divided into two groups: The Ent group was composed of the patients who underwent any type of enteroscopy, such as per oral/per anal double-balloon enteroscopy and video capsule enteroscopy, and the No-Ent group was comprised of the patients who had never undergone enteroscopy. First, to determine the prevalence of follicular lymphoma lesions in the small intestine and their endoscopic features, the study evaluated the Ent group patients' modalities of enteroscopy performed, the macroscopic appearance of the lesions and the affected regions of the small intestine. Subsequently, to identify potential factors affecting the performance rate of enteroscopy among follicular lymphoma patients with gastrointestinal involvement, patient gender, age at lymphoma diagnosis, histopathological grade, clinical stage, the date of the initial diagnosis and the annual volume of enteroscopy examinations at the institution where the patient was treated were evaluated.

The annual volume of enteroscopy is presented as the total number of enteroscopy examinations performed at the participating institution in 2013. The 17 institutions were then divided into the following four groups in accordance with the annual number of enteroscopies performed: Low-volume institutions, 0-25 examinations/year (9 institutions); middle-volume institutions, 26-50 examinations/year (3 institutions); high-volume institutions, 51-100 examinations/year (3 institutions); and ultra-high volume institutions, >101 examinations/year (2 institutions).

**Statistical analysis.** For the comparisons of the two groups, statistical analyses, including t-tests,  $\chi^2$  tests and F-tests were performed using JMP 8.0.1 software (SAS Institute, Cary, NC, USA).  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

Among the 110 patients, 34 patients (30.9%) had undergone one or more enteroscopy examinations at the initial diagnostic work-up and/or during the follow-up period (Table I). A total of 21 patients underwent video capsule enteroscopy, 17 patients underwent double-balloon enteroscopy, 1 patient underwent per-oral single balloon enteroscopy and 1 patient underwent per-oral push enteroscopy. A total of 6 patients underwent a video capsule enteroscopy plus a double-balloon enteroscopy. Of the 10 patients in whom the small intestine was investigated only by double-balloon enteroscopy, 3 underwent only a per-oral enteroscopy, 2 underwent only a per-anal enteroscopy and the remaining 6 underwent a per-oral plus a per-anal enteroscopy. Eventually, the entire length of the

Table I. Prevalence and endoscopic features of follicular lymphoma lesions in the small intestine

Feature	No. of patients
Total no. of patients	34
Modality of enteroscopy	
VCE	21
DBE	17
SBE	1
Push enteroscopy	1
Affected regions of the small intestine	
Jejunum only	16
Ileum only	2
Jejunum plus ileum	6
None	10
Macroscopic appearance	
Whitish granules <sup>a</sup>	22
Ulcer	2
Stenosis	2
Ulcerative tumor	1
Wall thickening	1

<sup>a</sup>20 cases showed only whitish granular lesions. VCE, video capsule enteroscopy; DBE, double-balloon enteroscopy; SBE, single-balloon enteroscopy.

small intestine was examined in 28 patients by video capsule enteroscopy and/or the combination of per-oral plus per-anal double-balloon enteroscopy.

The enteroscopy examinations revealed only jejunal involvement in 16 patients and only ileal involvement in 2 patients. A total of 6 patients presented with small intestinal lesions in the jejunum plus the ileum, whereas 10 patients exhibited no involvement in the small intestine. Finally 24/34 patients (70.6%) exhibited involvement in the jejunum and/or ileum. Among the 34 patients who underwent enteroscopy, 32 patients (94.1%) presented with duodenal involvement and 22/32 patients (68.8%) with involvement in the jejunum and/or ileum.

In terms of the macroscopic appearance, 22 patients showed whitish granules in the jejunum and/or ileum (Figs. 1 and 2). Such whitish granules, which are quite similar to the well-known features observed in duodenal follicular lymphoma (1,5), were the only presenting feature in 20 patients. In the remaining 4 patients, 1 presented with an ulcerative tumor (Fig. 3), another with luminal stenosis, the third with whitish granules, wall thickening and ulcers, and the fourth with whitish granules, luminal stenosis and ulcers.

The patients were subdivided into the following two groups according to the status of their small intestinal examinations: The Ent group, i.e., the patients who underwent enteroscopy (n=34), and the No-Ent group, i.e., the patients who did not undergo an enteroscopy (n=76). The clinical characteristics of each group are provided in Table II. The comparisons of the two groups revealed that patient age (P=0.886), gender (P=1.000), histological grade (P=0.674) and clinical stage (I and II1 vs. II2 and IV; P=0.663) did not differ significantly

between the groups, whereas more patients diagnosed in recent years (since 2008) underwent enteroscopy examinations compared with the patients diagnosed previously (in 2007 or earlier; P<0.001). Additionally, more patients treated at an ultra-high volume institution were examined by enteroscopy compared with the patients treated at other institutions (low-, middle- and high-volume institutions; P=0.003).

## Discussion

The primary purpose of the present study was to investigate the performance rate of enteroscopy in follicular lymphoma patients presenting with gastrointestinal involvement. To the best of our knowledge, this study is the first to reveal the performance rate in actual clinical settings. In this study, 34/110 patients (30.9%) underwent enteroscopy examinations. The statistical analysis disclosed that the small intestines were more frequently investigated in patients diagnosed in recent years (since 2008) and in patients treated at the institutions where a considerable number of enteroscopy examinations was performed ( $\geq 101$  examinations/year). Conversely, the number of enteroscopy examinations was fewer in patients diagnosed in earlier years, particularly in 2007 or prior to this, and in patients treated at institutions where <100 examinations were performed per year.

In Japan, double-balloon enteroscopy was introduced in the fall of 2003 (23) and video capsule enteroscopy was introduced in the fall of 2007 (24). It is likely that the availability of enteroscopy devices at the initial staging of follicular lymphoma patients affected the performance rate of the enteroscopic examinations. Another possible reason is that the high prevalence of the intestinal lesions was recognized in 2008. However, it is noteworthy that enteroscopy examinations were not performed at the initial work-up or even in the follow-up period in 41 of the 44 patients (93.2%) who were diagnosed in 2007 or earlier.

As aforementioned, previous studies documented that the jejunum and/or ileum was affected in 66.7 to 100% of follicular lymphoma patients presenting with intestinal involvement (3,4,7-11). The present study showed a similar prevalence, as the jejunum and/or ileum was affected in 24/34 patients (70.6%). Consequently, all the follicular lymphoma patients presenting with intestinal involvement can be regarded as candidates for enteroscopy examinations, regardless of the availability of enteroscopy devices in the institution and regardless of the phase of the patient's clinical course (i.e., at the initial work-up or during follow-up period).

In the present study, the jejunum and/or ileum was affected in 24 patients. Among them, 20 patients (83.3%) developed whitish granules as the only presenting feature. Other studies have described the small intestinal lesions observed by enteroscopy as 'multiple white nodules', 'multiple small granules', 'small whitish polyps', 'whitish granular lesions' or 'polypoid lesions' (5,8,9,11). The present study and previous reports indicated that the whitish granules, which are similar to the typical endoscopic features of duodenal follicular lymphoma, are the predominant morphology of the jejunal and ileal involvement as well. Nakamura *et al* noted that the jejunal lesions are easily identified as follicular lymphoma lesions as physiological lymphoid structures rarely exist in the jejunum, whereas ileal lesions are occasionally difficult to differentiate from physiological lymphoid follicles (11). In such cases, histological

Table II. Clinical backgrounds of the Ent and No-Ent patients.

Parameter	Enteroscopy	No enteroscopy	P-value
No. of patients	34	76	
Male/female, n	15/19	34/42	1.000
Age at diagnosis of FL, years	63.0±2.0	63.4±1.4	0.886
WHO grade, n			0.674
Grade 1	31	72	
Grade 2	3	4	
Lugano system staging, n			0.663
I	19	39	
II1	5	10	
II2	3	4	
IV	7	23	
Date of initial diagnosis, n			<0.001 <sup>a</sup>
1990-2003	2	20	
2004-2007	1	21	
2008-present	31	35	
Annual volume of enteroscopy at the institution, n			0.003 <sup>b</sup>
0-25	6	27	
26-50	3	6	
51-100	3	17	
101+	22	26	

<sup>a</sup>1990-2007 vs. 2008-present; <sup>b</sup>0-100 vs. ≥101.

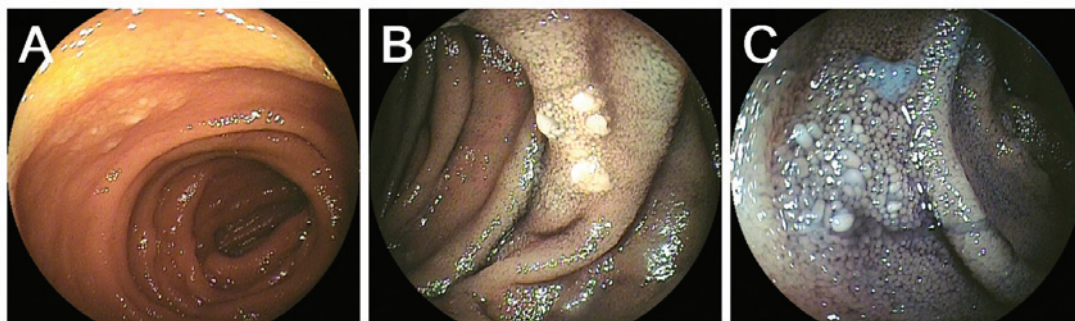


Figure 1. Images of enteroscopy results for a 73-year-old male with stage I follicular lymphoma. Per-oral double-balloon enteroscopy images showing whitish granules in the (A) duodenum and (B) jejunum. (C) The whitish granules are emphasized by indigo carmine spraying.

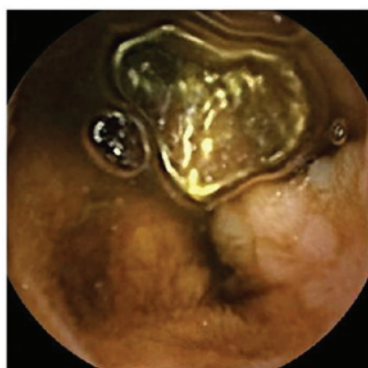


Figure 2. An image of enteroscopy results for a 61-year-old female with stage I follicular lymphoma. Video capsule enteroscopy image revealing whitish granules in the jejunum in addition to the duodenal lesions.

examinations with the immunostaining of biopsied specimens are required for an accurate diagnosis.

The present study also found that 4 patients exhibited macroscopic features other than whitish granules, namely ulcerative lesions, luminal stenosis, tumorous lesions accompanied by ulcers and/or wall thickening. These morphologies were probably formed during the progression of the disease and as a result of an increased number of infiltrated lymphoma cells within the small intestinal wall (7,25). Biopsy examinations are generally useful for such lesions showing atypical macroscopic features, not only for the accurate pathological diagnosis of follicular lymphomas, but also for the detection of the histological transformation from grades 1 and 2 to grade 3, which generally facilitates the prompt initiation of treatment.



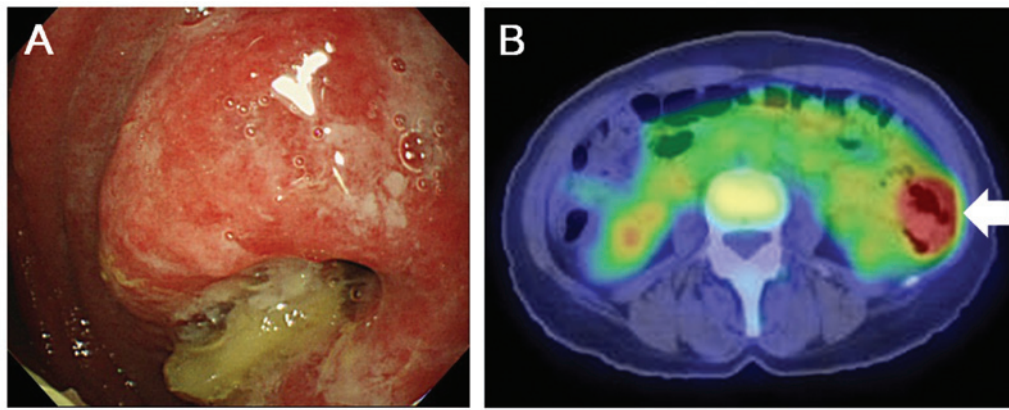


Figure 3. Images of enteroscopy results for a 49-year-old female with stage I follicular lymphoma. (A) An ulcerative tumor was observed in the jejunum by the per-oral single-balloon enteroscopy examination. This case also had duodenal involvement showing whitish granules. (B) A diffusely thickened wall was detected by computed tomography scan, and an accumulation of tracer was observed in the jejunal lesion (arrow) by positron emission tomography.

No standardized treatment strategies have been established for limited-stage gastrointestinal follicular lymphoma. The initial treatment may be radiotherapy, systemic chemotherapy, monoclonal antibody monotherapy, a combination of these therapies or a 'watch and wait' policy (3-5). Several studies have stated that the watch and wait strategy can be an acceptable initial approach due to the indolent nature of this disease entity (2,3,12,26-28). On the other hand, for limited-stage follicular lymphoma of nodal origin, radiotherapy is recommended as the preferred treatment with curative potential (2,29). In the study by Schmatz *et al*, it was reported that all the patients with primary intestinal follicular lymphoma treated by radiotherapy alone (n=19) experienced complete remission, and none of these patients developed a local recurrence during a median follow-up time of 37 months (3). Radiotherapy may thus be one of the treatment options for limited-stage gastrointestinal follicular lymphoma, as well as for nodal cases. In such situations, surveillance of the jejunum and ileum prior to local treatment is particularly vital, since the majority of treatment failures occur outside the involved field of radiotherapy (30).

At the present time, double-balloon enteroscopy and video capsule enteroscopy are the two major devices that enable the direct visualization of the entire length of the small intestines. Video capsule enteroscopy is more convenient for patients than double-balloon enteroscopy; the capsule-type device is easily swallowed, and the full length of the small intestines can be examined at a single examination session. Moreover, sedation and exposure to X-ray is not required during a video capsule enteroscopy procedure. On the other hand, although the double-balloon enteroscopy generally requires sedation, exposure to X-rays, and per-oral and per-anal examinations to observe the entire small intestine, it provides the great advantage of biopsy sampling. A biopsy is particularly valuable for the diagnostic work-up of ileal lesions of follicular lymphoma and for the detection of histological transformation, as aforementioned.

The results of the present study revealed that the majority of the patients (76/110, 69.1%) had not undergone enteroscopy examinations at the initial work-up and/or in the follow-up period, despite the high prevalence of small intestinal lesions among these patients. At the present time, the

clinical significance of enteroscopy examinations in follicular lymphoma patients remains a subject of debate, as it has not been revealed whether or not small intestinal lesions detected by enteroscopy affect the prognoses of follicular lymphoma patients. We believe that, in follicular lymphoma patients presenting with gastrointestinal involvement (particularly in patients at limited stages), the entire gastrointestinal tract should be screened by video-capsule enteroscopy, esophago-gastroduodenoscopy and colonoscopy at the initial diagnostic work-up.

Double-balloon enteroscopy is required to take biopsy samples in cases of lesions with atypical morphology or ileal lesions mimicking physiological lymphoid follicles, in order to make an accurate pathological diagnosis and to detect the histological transformation. We contend that this policy is acceptable, as the histological transformation to grade 3 follicular lymphoma generally requires the prompt initiation of treatment. Other topics to debate concerning enteroscopy examinations include whether enteroscopy should be repeated during the follow-up period and whether a biopsy is required at each enteroscopy examination to screen for transformation. Further studies should address these questions.

The present study has certain limitations. First, among the 34 patients who underwent enteroscopy, 24 patients (70.6%) presented with jejunal and/or ileal involvement, but not all of the 34 patients had the entire small intestine examined. For example, 1 patient underwent per-oral push enteroscopy, 3 patients underwent per-oral enteroscopy only, and two patients underwent only a per-anal enteroscopy. As a result, an underestimation of the prevalence of small intestinal lesions may have occurred. Second, the enteroscopy examinations were performed under different conditions, since the patients were treated at various institutions. It is possible that differences in methodology among the participating institutions affected the detection of small intestinal lesions.

In conclusion, this multicenter survey revealed that 34/110 (30.9%) follicular lymphoma patients presenting with intestinal involvement underwent enteroscopy examinations, and that jejunal and/or ileal involvement was frequently identified (24/34 patients, 70.6%). The clinical significance of precisely evaluating the extent of the intestinal lesions by enteroscopy should be determined hereafter.

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