

# Safety and efficacy of capsule endoscopy for patients with newly diagnosed Crohn's disease

## A multicenter retrospective study

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### Abstract

Crohn's disease (CD) is a chronic inflammatory disease that develops at a young age and frequently leads to intestinal resection. Capsule endoscopy (CE) can directly and non-invasively inspect the entire small bowel mucosa. We suspected that CE could be a good diagnostic tool for detecting CD in young patients. The aim of this study was to investigate the safety and efficacy of CE in patients with newly diagnosed CD and to evaluate the CE findings, especially in the upper small bowel of young patients. We retrospectively investigated 32 patients with newly diagnosed CD from 5 institutions. Patient characteristics, clinical course, and characteristics of CE findings were analyzed. The total small intestine observation rate was 93%, and the retention rate was 3% (1/32). No abnormality was identified by ileocolonoscopy in 46% (15/32), and transition of small bowel lesions (TSL) was found in 35% (12/34) of the patients. The frequency of longitudinal ulcers and cobblestones in the upper small intestine was significantly higher in younger patients ( $\leq 20$  years). Moreover, positive findings in the upper small intestine were predominantly observed in younger patients ( $\leq 20$  years). CE for patients with newly diagnosed CD was safe and useful, especially for the detection of upper small bowel lesions in young patients.

**Abbreviations:** CD = Crohn's disease, CE = capsule endoscopy, PC = patency capsule, TSL = transition of the small bowel lesion.

**Keywords:** capsule endoscopy, Crohn's disease, upper small intestine, young patients

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### 1. Introduction

Crohn's disease (CD) is a chronic inflammatory disease of unknown cause that develops at a young age. Although the initial phase of this disease is mainly characterized by persistent inflammation of the gastrointestinal tract, intestinal complications, including stenosis, fistula, and perforation can develop. These frequently leads to intestinal resection.<sup>[1]</sup>

Capsule endoscopy (CE) has been used in the diagnosis of CD.<sup>[2-4]</sup> However, most studies have generally assessed the diagnostic yield, not diagnostic accuracy, because there is no gold standard for diagnosis.<sup>[5]</sup> Moreover, due to persistent and progressive inflammation of the gastrointestinal tract, the risk of CE retention is present.<sup>[6]</sup> Therefore, it is necessary to perform a patency capsule (PC) examination prior to CE to verify the patency of the gastrointestinal tract.

On the contrary, many reports have been made on the usefulness of double-balloon endoscopy for CD<sup>[7]</sup>; both oral and anal approaches are required to observe the entire small intestine. However, the oral approach is regarded as particularly

invasive and requires deep sedation.<sup>[8]</sup> The advantage of CE is that it is noninvasive and can directly inspect the total small bowel mucosa for inflammation and ulceration. In particular, CE can detect aphthous lesions that were not detected by other procedures (such as CT enterography, MR enterography, and Radiography).<sup>[9,10]</sup> Watanabe et al proposed that the transition of the small bowel lesion (TSL) is the definite finding for CD. TSL is the erosion in the upper small intestine that changes into small ulcers and longitudinal ulcers<sup>[11]</sup> Esaki et al identified the CE findings to diagnose the early stage of CD, and revealed that circumferential or longitudinal alignment of lesions, especially in the upper small bowel, could be a diagnostic clue in the upper small intestine. Additionally, the CE can clearly depict images.<sup>[12]</sup> Therefore, we suggested that a young patient with suspected CD is a good indication for CE. In this study, we aimed to investigate the safety and efficacy of CE in patients with newly diagnosed CD and to evaluate the CE findings, especially in the upper small bowel of young patients.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]

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## 2. Materials and Methods

### 2.1. Patients

We retrospectively investigated patients with newly diagnosed CD between August 2012 and August 2018 at 5 institutions participating in the Setouchi-Capsule-Endoscopy-Group. A total of 32 patients in each hospital with newly diagnosed CD who underwent CE were enrolled in the study. We defined patients with newly diagnosed CD as follows: the diagnosis had been confirmed by other examinations before CE without any medication, and CD was strongly suspected, and after CE, the diagnosis was confirmed.

The institutional review board of each hospital approved this study, and informed consent was obtained from all patients.

### 2.2. Ethical considerations

The institutional review board of each hospital approved this study, and informed consent was obtained from all patients.

### 2.3. CE examination

CE was performed using PillCam SB2 or SB3 (Given Imaging Ltd., Yokneam, Israel). The images were analyzed with RAPID Reader 6.5 or 8 software on a RAPID workstation (software and workstation from Given Imaging Ltd.).

All the images were reviewed by expert gastroenterologist in each institution.

For each CE, we defined the total small bowel transit time from the beginning of the duodenum to the cecum. The total small bowel transit time was divided into 2 parts: the upper and lower ileum.

### 2.4. Study outcome

First, we investigated the procedure of CE and assessed its safety in enrolled patients. Next, we investigated the characteristics of CE findings, and they were analyzed in all patients, upper small bowel versus lower small bowel, and younger patients ( $\leq 20$  years) versus older patients. Finally, based on the manuscript by Esaki et al,<sup>[12]</sup> we analyzed the detailed findings. Erosions were classified as aphthous, oval, irregular, linear, and ulcers were classified as longitudinal, irregular, oval, or circular. Longitudinal alignment and arranged alignment were also added.

### 2.5. Statistical analysis

AQ3 Continuous and categorical variables were expressed as median (range) and  $n$  (%), respectively. Differences in the clinical outcomes were evaluated using the Mann–Whitney  $U$  test for continuous data and the chi-square test for categorical variables. All statistical analyses were performed using the statistical analysis software JMP Pro, version 15 (SAS Institute Inc., Cary, NC).

States).  $P$  values  $< .05$  were considered statistically significant.

## 3. Results

### 3.1. Clinical characteristics

T1 Table 1 shows the clinical characteristics of the enrolled patients. The median age was 23 years, and the population was relatively young. A definitive diagnosis of CD was made in 84% (27/32) of cases before CE was done. Anal lesions and extraintestinal complications were found in approximately half of the cases. Definite or suspicious findings before CE were obtained from ileocolonoscopy, abdominal CT, EGD, and abdominal US. Patency capsules were performed in 26 patients (81%).

### 3.2. CE procedure and clinical findings

T2 Table 2 shows the details of CE. The total small intestine observation rate was 93%, and the median small intestine transit time was 224 minutes. Adverse events were observed in 2 cases. One patient showed retention of capsules, and patency capsule was not performed in this case. The most common CE findings were erosions ( $n = 23$ ), followed by ulcers ( $n = 21$ ), and cobble stone appearance ( $n = 9$ ). Significant findings were found in the lower small intestine in 20 cases, and TSL was detected in 12 cases. Furthermore, it should be noted that in approximately half of the 15 cases, ileocolonoscopy revealed no abnormalities.

### 3.3. CE findings in positive cases

When the cases were divided into younger ( $\leq 20$  years) and older ( $> 21$  years) patients, erosions were observed in all younger patients, indicating that lesions in the upper small intestine were predominant. The total dominant findings in the small bowel were significantly higher in the lower small intestine than in the upper small intestine (9 vs 20). However, in younger patients, the lesions in the upper small intestine were higher (6 vs 5; Table 3).

### 3.4. Analysis of detailed CE findings

Analysis of detailed findings based on the manuscript by Esaki et al<sup>[12]</sup> showed that circular ulcers were significantly more frequent in older patients (Table 4).

T4 Contrarily, when examined separately for the upper and lower small intestines, the frequency of longitudinal ulcers and cobblestones in the upper small intestine was significantly higher in younger patients (Table 5).

## 4. Discussion

T5 The first aim of this study was to assess the safety of CE for patients with newly diagnosed CD. Only 1 case (3%) that could not be evaluated for patency of the small bowel by PC caused CE retention. In a previous study in Japan, capsule retention was reported to be 7.4% in patients with documented CD and 6.3% in suspected CD,<sup>[13]</sup> which was higher than that in our study. As stated in the clinical practice guidelines for enteroscopy in Japan, the CE procedure is associated with a risk of retention in

**Table 1**  
Clinical characteristics.

| N = 32  |            |
|---|------------|
| Sex   | 17/15      |
| Age (yr, median)                              | 12–68 (23) |
| Definite/Suspicious at the procedure          | 27/5       |
| Perianal lesions                              | 12         |
| Extraintestinal complication                  | 11         |
| Definite or suspicious findings before CE     |            |
| Ileocolonoscopy                               | 27         |
| Abdominal CT                                  | 14         |
| EGD   | 10         |
| Abdominal US                                  | 9          |
| Balloon endoscopy                             | 1          |
| Patency capsule                               |            |
| Performed/not performed                       | 26/6       |
| How to confirm gastrointestinal patency       |            |
| Intact body excretion                         | 16         |
| Patency capsule in the colon with plain X-ray | 8          |
| Computed tomography                           | 2          |

CE = capsule endoscopy.

**Table 2**  
**CE procedure and clinical findings.**

| CE type (Pillcam SB2/SB3)              | 9/23         |
|--|--------------|
| Total enteroscopy                      | 30/32 (93%)  |
| Small bowel passage time (min, mean)   | 44–676 (224) |
| Adverse event                          | 2            |
| Impossible to swallow CE               | 1            |
| Retention                              | 1            |
| Positive findings                      | 29 (90%)     |
| Negative findings* in terminal ileum   | 15 (46%)     |
| Erosion                                | 23           |
| Ulcer                                  | 21           |
| Cobblestone appearance                 | 9            |
| Transition of small bowel lesion (TSL) | 12 (38%)     |
| Dominant findings in the small bowel   |              |
| Upper > Lower                          | 9            |
| Upper < Lower                          | 20           |

CE = capsule endoscopy.

**Table 3**  
**CE findings in positive cases.**

|  | Total<br>(N = 29) | ≤20 yr<br>(N = 11) | >20 yr<br>(N = 18) | P value |
|--|-------------------|--------------------|--------------------|---------|
| Erosion                                | 23                | 11                 | 12                 | .04     |
| Ulcer                                  | 20                | 8                  | 12                 | .38     |
| Cobblestone appearance                 | 9                 | 5                  | 4                  | .19     |
| Transition of small bowel lesion (TSL) | 12                | 5                  | 7                  | .92     |
| Dominant findings in the small bowel   |                   |                    |                    |         |
| Upper > Lower                          | 9                 | 6                  | 3                  | .03     |
| Upper < Lower                          | 20                | 5                  | 15                 |         |

CE = capsule endoscopy.

**Table 4**  
**CE findings in the total cases.**

|                           | Total | ≤20 yrs<br>N = 12 | >20 yrs<br>N = 20 | P value |
|---------------------------|-------|-------------------|-------------------|---------|
| Erosion                   | 23    | 11                | 12                | .04     |
| Aphtha                    | 22    | 10                | 12                | .16     |
| Oval                      | 12    | 6                 | 6                 | .26     |
| Irregular                 | 11    | 4                 | 7                 | .92     |
| Linear                    | 5     | 2                 | 3                 | .90     |
| Longitudinal alignment    | 15    | 5                 | 10                | .65     |
| Circumferential alignment | 7     | 3                 | 4                 | .74     |
| Ulcer                     | 20    | 8                 | 12                | .38     |
| Longitudinal              | 15    | 8                 | 7                 | .08     |
| Irregular                 | 13    | 4                 | 9                 | .51     |
| Oval                      | 8     | 2                 | 6                 | .39     |
| Circular                  | 4     | 0                 | 4                 | .04     |
| Cobblestone appearance    | 9     | 5                 | 4                 | .19     |

CE = capsule endoscopy.

cases of CD (including cases where the diagnosis is suspected). Thus, it is necessary to perform a PC examination prior to CE in order to verify the patency of the gastrointestinal tract.<sup>[6]</sup> A nationwide multicenter prospective study in Japan showed that PC helped preclude CE retention; however, accurate diagnosis of PC location is particularly essential.<sup>[14]</sup>

In this study, the median age of the patients was 23 years, which was relatively young. Since the duration of inflammation is regarded as short in younger cases, we demonstrated that the

risk of CE retention is considered to be relatively low, and CE with PC may be performed actively for newly diagnosed CD in the young.

The next aim of this study was to assess the characteristics of CE findings.

Interestingly, in approximately half of the 15 cases, no abnormalities were identified by ileocolonoscopy. The terminal ileum has been recognized to have a high detection rate for active CD. However, Leighton et al reported that CE detected 16% more lesions in the terminal ileum than ileocolonoscopy.<sup>[15]</sup> They reported that lesions of the terminal ileum detected by CE could not be reached by ileocolonoscopy.

In the North American clinical practice guideline for the use of CE, CE was strongly recommended in patients presenting with clinical features consistent with CD and negative ileocolonoscopy.<sup>[5]</sup> However, it was additionally described that the quality of evidence was very low. Chateau et al reported the characteristics of CD patients that is visible by CE.<sup>[16]</sup> However, the number of patients was relatively small (n = 13), and medication was administered in some cases. In this study, all patients were not given any medication before CD; therefore, the results of this study may increase the reliability of CE at the first diagnosis of CD. The diagnostic criteria for CD in Japan are mainly based on diagnostic imaging finding.<sup>[17]</sup> As the validation study performed by Hisabe et al, the majority of CD diagnoses made in Japan were based on the classical finding of longitudinal ulcer or cobblestone-like appearance which representing an appropriate rationale.<sup>[18]</sup> On the other hand, in the 3 minor findings of the criteria, we can confirm the diagnosis of CD only when all the findings were present. Therefore, when there is only 1 or 2 minor findings, CE is considered useful for supporting early diagnosis of small-bowel type CD.

In this study, we focused on 2 characteristic findings by performing CE for newly diagnosed CD. One is TSL and the other is the finding of upper small intestinal lesions. TSL has not spread

**Table 5**  
**CE findings in upper and lower small intestine.**

|                           | Upper<br>Lower | ≤20 yrs<br>N = 12 | >20 yrs<br>N = 20 | P value |
|---------------------------|----------------|-------------------|-------------------|---------|
| Erosion                   | 19             | 7                 | 12                | .92     |
| Aphthous                  | 21             | 7                 | 14                | .50     |
| Oval                      | 20             | 8                 | 12                | .70     |
| Irregular                 | 7              | 2                 | 5                 | .57     |
| Linear                    | 8              | 4                 | 4                 | .40     |
| Longitudinal alignment    | 7              | 3                 | 4                 | .74     |
| Circumferential alignment | 8              | 2                 | 6                 | .38     |
| Linear                    | 3              | 1                 | 2                 | .87     |
| Circular                  | 5              | 2                 | 3                 | .90     |
| Longitudinal alignment    | 11             | 4                 | 7                 | .92     |
| Circumferential alignment | 10             | 3                 | 7                 | .55     |
| Linear                    | 5              | 2                 | 3                 | .90     |
| Circular                  | 4              | 1                 | 3                 | .57     |
| Ulcer                     | 12             | 6                 | 6                 | .25     |
| Longitudinal              | 16             | 6                 | 7                 | .40     |
| Irregular                 | 7              | 5                 | 2                 | .04     |
| Oval                      | 13             | 6                 | 7                 | .40     |
| Circular                  | 7              | 4                 | 3                 | .13     |
| Cobblestone appearance    | 8              | 1                 | 7                 | .07     |
| Linear                    | 3              | 1                 | 2                 | .87     |
| Circular                  | 6              | 1                 | 5                 | .22     |
| Cobblestone appearance    | 2              | 0                 | 2                 | .16     |
| Linear                    | 2              | 0                 | 2                 | .16     |
| Circular                  | 5              | 4                 | 1                 | .03     |
| Cobblestone appearance    | 6              | 3                 | 3                 | .49     |

CE = capsule endoscopy.

worldwide; however, in our study, TSL was detected in 12 cases (38%). The entire small intestinal mucosa must be continuously observed to diagnose the presence or absence of TSL. Therefore, CE is the only diagnostic equipment to detect TSL. However, the problem with CE is that it is not the gold standard for CD diagnosis,<sup>[4]</sup> and we considered that TSL can be an original finding. A larger number of cases should be collected and analyzed.

Finally, we focused on the findings of the upper small intestinal lesions. We analyzed the detailed findings of the CE in patients under 20 years of age and found that they had significantly more dominant findings in the upper small bowel than in the lower bowel. Moreover, longitudinal ulcer and cobblestone appearance were significantly more frequent in younger patients. These are the most interesting results of this study. The proportion of patients with proximal small bowel involvement in Asians was reported to be higher than that in Western countries.<sup>[19]</sup> We cannot completely explain why the upper small intestine was more dominant in young people in this study. The factors with significant differences were longitudinal ulcer and cobblestone appearance. These are typical findings and well-known CD findings. CD patients with proximal small bowel involvement have been reported to have a poor prognosis, with more frequent relapse and surgery.<sup>[20,21]</sup> We hypothesized that if these young patients are not diagnosed with CD and left without adequate medication, more severe inflammation may occur in the deep small intestine in the future, resulting in an increased risk of bowel resection. Therefore, we think it is very important to detect CD as early as possible in young patients.

Medication for CD was initiated after CE in all the cases entered in this study. In the future, it will be necessary to analyze the long-term results of these cases and verify whether lesions appear in the deep small intestine.

There were some limitations to this study. First, this was a retrospective study, and the sample size was small. CE may have been avoided if other tests suggested the possibility of small bowel stenosis in advance, which may have increased the safety of CE. Therefore, this result may not be directly characteristic of small bowel lesions in the first CD. However, at least all the cases in this study had not been given any medication in the past, so it can be considered that our results showed some characteristics of the first CD.

Next, we included only cases with final diagnosis of CD. Therefore, we could not evaluate false negative or false positive of CE findings in this study. However, each finding in this study has already reported by Esaki et al that high accuracy for performing first diagnosis of CD.<sup>[12]</sup>

Finally, analysis of CE images and diagnosis were performed by the endoscopists in charge of each facility, and it can be mentioned that there are slight variations and differences in the way of reporting findings between facilities. However, all the facilities in this study are under the guidance of the Japan Capsule Endoscopy Society. Moreover, specialists were in charge of the interpretation, so it is considered that a standard was followed.

In conclusion, CE for patients with newly diagnosed CD was considered safe and useful, especially for the detection of upper small bowel lesions in young patients. Further accumulation and follow-up of cases are necessary in the future.

## Author contributions

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