Diagnosis and treatment of small bowel diseases are advanced by capsule endoscopy and double-balloon enteroscopy

Hidemi Goto

Abstract In 2001, new endoscopic procedures for the small bowel, capsule endoscopy (CE) and double-balloon enteroscopy (DBE), were introduced into regular clinical practice. These methods were significant breakthroughs for imaging examination of the small bowel. The methods have different characteristics with regard to their approach into the target organ; however, common to both is the feature of enabling rapid total observation of the small bowel. CE is the first safe, non-invasive well-tolerated procedure and can be performed in any condition. The examination time is about 8 h and the patient can spend the time freely. CE can demonstrate active bleeding or neoplasm in the small bowel, which other modalities cannot detect. DBE, which was developed by Yamamoto, employs two balloons combined with an overtube and allows deeper insertion into the small bowel, and can be a modality for examination of the entire small bowel with combined oral and anal approaches. This modality enables biopsy specimens to be taken, polyps to be resected and hemostatic procedures to be performed throughout the small bowel. These two methods, CE and DBE, are considered to be excellent tools for the diagnosis and treatment of small bowel disorders and further clinical study of unknown small bowel disorders using these two modalities and algorithms for the management of small bowel disorders are required.

Keywords Capsule endoscopy · Double-balloon enteroscopy · Small bowel

Abbreviations
VCE Capsule endoscopy
DBE Double-balloon enteroscopy
PE Push enteroscopy
OE Intra-operative enteroscopy

Introduction

The development of capsule endoscopy (CE) [1] and double-balloon enteroscopy (DBE) [2] in 2001 introduced a great change in diagnostic and therapeutic possibilities for patients with suspected small bowel disorders. The important characteristics of CE are that it is discomfort-free and the entire small bowel can be examined in any condition [3]. The usefulness of CE for mid-gastrointestinal (mid-GI) bleeding [4], in particular, has been proven by many studies [5, 6]. One study suggested that the diagnostic yield of mid-GI bleeding was higher in those with a short interval than in those with a longer interval between the last overt bleeding and CE [7]. DBE, however, which was developed by Yamamoto, employs two balloons combined with an overtube and allows deeper insertion into the small bowel, and can be a modality for examination of the entire small bowel with combined oral and anal approaches. This modality enables biopsy specimens to be taken, polyps to be resected [8] and hemostatic procedures to be performed throughout the small bowel. These two methods, CE and DBE, are considered to be excellent tools for the diagnosis and treatment of small bowel diseases and
also for complementary procedures. Therefore, comparative study is necessary to determine the appropriate roles of CE and DBE and their indications in the evaluation of small bowel disorders.

Small bowel disorders

The disorders that occur in the small bowel include many different abnormalities and their details have been clarified over several years because of the progress of small bowel endoscopy. As far as we know, small bowel disorders include five categories: bleeding, neoplasm, stenosis, inflammation, and functional disorders of the small bowel. They are often related to each other, as shown in Fig. 1.

The core disorder is small bowel bleeding, which is related to the other four types of disorder. The symptom of bleeding is important for diagnosis because it may be the first sign in a patient. Mid-GI bleeding between the major papilla and the ileum end often remains undiagnosed with conventional imaging modalities such as gastroscopy, colonoscopy, computed tomography (CT), enteroclysis, scintigraphy and angiography. The major origins of such bleeding are in the small bowel. Ohmiya et al. [9] analyzed the diagnoses of 277 patients with suspected small bowel bleeding in a multicenter study as follows: chronic inflammatory diseases ($n = 67, 24.2\%$), vascular diseases ($n = 66, 23.8\%$), tumors or polyps ($n = 54, 20.6\%$), drug or radiation injury ($n = 19, 6.9\%$), other small bowel diseases ($n = 20, 7.2\%$), upper GI diseases ($n = 25, 9.0\%$), colorectal diseases ($n = 25, 9.0\%$) and biliary disease ($n = 1$, biliary tumor, 0.4\%). Small bowel diseases, which had not been identified by conventional gastroscopy or colonoscopy, were confirmed in 226 patients (82% in patients with positive findings, 47% in patients with suspected small bowel bleeding).

A small bowel tumor is difficult to diagnose when it has a small size, and it is often found accidentally or owing to symptoms associated with a progressive stage. Mitsui et al. [10] reported that the most common tumor found was malignant lymphoma (21.5%), followed by gastrointestinal stromal tumor (18.8%), Peutz–Jeghers syndrome (15.3%), familial adenomatous polyposis (9.7%) and carcinoma (9.7%) in a multicenter DBE study.

Small bowel stenosis can be caused by various mechanisms, namely, mechanical obstruction, non-mechanical obstruction and vascular ischemia. A patient sometimes has no symptoms with small bowel stenosis, but it can often be identified by CT or abdominal ultrasound at that stage. There is also stenosis caused by abdominal adhesion without direct damage of the small bowel. Ohmiya et al. [11] listed Crohn’s disease (CD), malignant tumor, ischemic enteritis, intussusception, inflammatory adhesions and NSAID-induced diaphragm disease as causes of stenosis.

Inflammatory bowel disease often causes diffuse lesions in the small bowel. Since each lesion is very small but...
multifocal and spread in a broad area, confirmation of diagnosis can be undertaken with examination of a partial site only; however, it is sometimes difficult to distinguish between neoplasm and inflammation because they have similar clinical features. Repeated or additional examinations are needed.

Functional disorders in the small bowel consist of motor disturbance [12] and absorption abnormality [13]. There may usually be a primary site in the small bowel, but it has not been clearly identified yet. Non-invasive visual observation throughout the small bowel in CE and pathologic findings from biopsy specimens in DBE may be useful for the diagnosis of protein-losing enteropathy.

Examinations of the small bowel

Table 1 shows the examinations used to inspect the small bowel. The modalities that mainly enable exploration of the mucosa of the small bowel are very useful in detecting small bowel lesions, and endoscopic and fluoroscopic examinations in particular are used with them. Abdominal ultrasound [14], CT and magnetic resonance (MR) imaging [15, 16] are also considered useful tools. We are able to examine the functional characteristics of small bowel disorders using protein-losing tests, including $^{99m}$Tc-HSA-D scintigraphy and $a_1$-antitrypsin clearance, as well as absorption tests. Moreover, the tests are more effective in collaboration with an endoscopic modality. Since small bowel disorders have various patterns of clinical characteristics, multiple modalities are required for accurate diagnosis. Therefore, we should select a suitable modality during diagnosis for the target lesion.

Small bowel endoscopy

Even if the abnormal site is suspected to be in the small bowel, conventional endoscopy has investigational limitations due to its length, partially because the small bowel in human adults has a median length of 575 cm [17]. Push enteroscopy (PE) and intra-operative enteroscopy (OE) have mainly been used for examination of small bowel diseases since 2000; however, PE has a limitation by its ability to explore only the proximal small intestine in variable distances [18]. OE was found to be the most reliable procedure for total visualization of the small bowel [19], although this technique has not become sufficiently widespread because passage of the enteroscope is assisted by a surgeon during open laparotomy. Endoscopists have not selected this option regularly owing to its inherently invasive procedure.

In 2001, new endoscopic procedures for the small bowel, CE and DBE, were introduced into regular clinical practice.

Capsule endoscopy

The advent of CE in 2001 has dramatically changed the diagnosis and management of many diseases of the small bowel. The video capsules used (M2A and PillCam SB, Given Imaging, Ltd, Yokneam, Israel), measuring 26 × 11 mm, are propelled by peristalsis without prokinetics. The technical procedures and evaluation of the capsule images were described previously [20]. Subsequently, other types of CE, EndoCapsule [21], OMOM and MiroCam, were introduced, which have functions similar to that of the CE of Given Imaging. Regarding the CE procedure, many endoscopists have selected bowel preparation without prokinetics and cathartics. There are many studies in the literature that compared small bowel observations in patients with and without bowel preparation [22, 23]. Several studies reported that an additional cathartic enhanced the rate of arrival in the colon [24, 25]; however, cathartic use for the small bowel has not yet been recognized as a standard procedure for CE [26].

CE interpretation software can convey information about CE transit into the lumen. Approximately 40–60 min

Table 1 Examinations to investigate the small bowel

<table>
<thead>
<tr>
<th>Examination</th>
<th>Details</th>
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<tbody>
<tr>
<td>Endoscopy</td>
<td>CE, DBE, push enteroscopy, intra-operative endoscopy, spiral enteroscopy</td>
</tr>
<tr>
<td>Fluoroscopy</td>
<td>Double-contrast method, endoscopic retrograde ileography</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>B-mode, enhanced image, Doppler</td>
</tr>
<tr>
<td>CT</td>
<td>Coronal imaging, CT enterography</td>
</tr>
<tr>
<td>MRI</td>
<td>MR enterography, diffusion imaging</td>
</tr>
<tr>
<td>Angiography</td>
<td>Arteriography, venography</td>
</tr>
<tr>
<td>Isotope</td>
<td>Meckel diverticulum scintigraphy, bleeding scanning, FDG-PET</td>
</tr>
<tr>
<td>Protein-losing test</td>
<td>$^{99m}$Tc-HSA-D scintigraphy, $a_1$-antitrypsin clearance</td>
</tr>
<tr>
<td>Absorption test</td>
<td>$d$-Xylose absorption test, PFD test, fatty stool</td>
</tr>
</tbody>
</table>
is often reported as the average gastric transit time. Early passage through the stomach is important for CE as it allows more time to check the small bowel. Small bowel transit time is generally thought to be approximately four and a half hours on average.

CE has a significant role in the diagnosis of obscure gastrointestinal hemorrhage and inflammatory bowel disease and has a higher diagnostic yield than other diagnostic modalities. Furthermore, CE has gained an important role in the management and surveillance of suspected small bowel neoplasms and in patients with polyposis syndromes [27]. In addition, CE has a role in the work-up of symptomatic celiac disease and in the assessment of drug therapeutic efficacy and adverse small bowel effects [28].

Thanks to the introduction of CE, the algorithm for examining the small bowel has changed [29, 30]. CE has become widespread throughout the world and, since its introduction into clinical practice in 2001, it has become more readily available because it can be used in all kinds of medical institutions, from family doctors’ clinics to general hospitals. However, problems with CE have been elucidated during its introduction and development. An important problem is related to the CE interpretation technique. The interpretation time, which was initially 60–90 min, has been shortened to 30 min. The improvement has been attained in part by software to support CE interpretation. The performance of the CE workstation has been improved by a “Suspected Blood Indicator” function [31], which indicates a bleeding site using an image reddened by bleeding, and a pick-up review function for serious findings. A physician is required to allow more time for CE interpretation in addition to their normal clinical routine. Therefore, their interpretation may be inadequate when the results of CE interpretation are requested within a short period. Since CE is performed under physiological conditions without air supply, a CE finding is often different from that obtained by standard endoscopy for the same lesion. Diagnosis is requested whenever only a part of a lesion is shown in the images. Furthermore, CE interpretation requires training and it is estimated that the assessment of 10 cases is adequate training for CE interpretation [32]; however, to improve the performance of interpretation, it is necessary to interpret CE routinely thereafter. When a doctor without experience interprets CE images, it takes longer to interpret and a lesion may be overlooked. Therefore, a special system for CE interpretation is considered essential [33].

Although CE is a relatively non-invasive method, it is contraindicated in patients with swallowing disorders, known gastrointestinal obstruction, strictures and in patients with implanted electromedical devices; however, the safety of CE for patients with a pacemaker has been reported [34]. Capsule retention was defined as a capsule remaining in the digestive tract for a minimum of 2 weeks or a capsule remaining in the bowel lumen unless medical, endoscopic or surgical intervention was instituted. Capsule retention is the most feared complication of CE with a frequency of 1.5–5% [35]. Other contraindications include pregnancy and children less than 10 years of age.

### Double-balloon enteroscopy

Until the end of the twentieth century, PE was the most commonly used method for the endoscopic investigation of the small bowel. Modern diagnostic and therapeutic DBE allows for a deeper and more thorough evaluation of the small bowel than PE [36], enabling the detection of more pathological lesions. In addition, DBE has for the first time enabled endoscopists to observe the whole small bowel at one time, and has provided endoscopic interventions such as cauterization of bleeding lesions, polypectomy, balloon dilation for stenosis, placement of small bowel stents and foreign-body extraction [37].

The DBE system (FUJIFILM Corp., Kanagawa, Japan) consists of a video endoscope with a biopsy channel with an internal diameter of 2.2 mm (EN-450P5) or 2.8 mm (EN-450T5), a flexible overtube and a balloon controller. DBE is usually preceded by CE because DBE would induce mucosal artifacts that could be misinterpreted by CE. In addition, DBE can be carried out from oral and/or anal approaches with reference to the results of CE such as transit time and localization of lesions [38, 39]. Preparation, sedation and analgesia for both approaches were described previously [36–39]. The method of confirming inspection throughout the small bowel and localize lesions for laparoscopic surgery involves marking using sterilized Indian ink. The pathological findings from biopsy specimens at DBE in addition to the endoscopic, chromendooscopic and ultrasonographic findings with a miniature probe can influence the subsequent treatment, including surgery.

For example, DBE is considered to be a safe and useful tool for the diagnosis and the endoscopic treatment of Peutz–Jeghers polyps throughout the small bowel. Double-balloon enteroscopic polypectomy may preclude complications of Peutz–Jeghers syndrome, including intussusception, bleeding and tumorigenesis, thereby obviating the need for multiple laparotomies. In patients with stricture with CD or drug-induced enteropathy, enteroscopic dilation can be carried out using through-the-scope balloon catheters to a maximum dilation of about 20 mm when passage of the enteroscope (distal-tip diameters of EN-450P5 and T5 are 8.5 and 9.4 mm, respectively) through the stricture is impossible. A stricture with a deep open ulcer or fistula is considered a contraindication for balloon dilation. Passage
through the stricture is attempted immediately after the dilation and the endoscopist can interpret easy passage as a mark of technical success.

The DBE procedure also has some problems. One is the requirement for assistance for the procedure and the examination time taking over an hour. For this reason, it is sometimes hard work for one examination only. The other concerns the technique for use of the endoscope [40]. The endoscopist sometimes has difficulty in controlling the endoscope in the deep small bowel owing to the bending loops of the device. When performing this procedure, it is necessary that total colonoscopy is completed with all patients and there is a learning curve of procedure training. An easier method is expected such as automatic insertion.

Comparison and combination of capsule endoscopy and double-balloon enteroscopy

CE and DBE were introduced clinically during the same period and each has specific capabilities that the other does not have. They are said to be complementary [41], and there have been some comparative diagnostic yield analyses of mid-GI bleeding between CE and DBE. We previously described that diagnostic rates of CE and DBE were not significantly different [42], but in another study, however, CE detected significantly more small bowel abnormalities than DBE [43]. These data are shown in Table 2. There is no major difference in diagnosis. The timing of the test may be very important and it is suggested that the optimal time to perform CE or DBE is within a few days of the occurrence of bleeding, possibly within 2 weeks [44]. DBE may be indicated in patients with a positive finding on CE requiring a biopsy or therapeutic intervention, if suspicion of a small bowel lesion is high despite a negative CE, and in patients with active bleeding. Regarding the concordance of the diagnoses, Westerhof et al. [45] described that DBE confirmed the findings of CE in the majority of cases in many studies; however, the concordance between findings of CE with those of DBE varied between 29 and 92%.

The technical skill and the understanding of small bowel disorders by learning are also important for the diagnostic yield. Nakamura et al. [42] reported that CE is superior in the detection of very small lesions in a preliminary study. Subsequently, Ohmiya et al. [8] stated that the two modalities are almost equal in the diagnosis of small bowel bleeding because of the improved performance of DBE and detailed interpretation of CE in a multicenter study. CE should be recommended as the first tool for mid-GI bleeding and DBE should be the gold standard for it. Several algorithms for it including other modalities are to be found in the literature; however, evidence for managing bleeding has yet to be obtained in sufficient quantity from prospective studies. With regard to the diagnosis of small bowel diseases, many endoscopists have stated that both CE and DBE showed a high diagnostic yield without serious complications [46–49]. There is no statistically significant difference in diagnostic yield between the two modalities.

On the other hand, Ross et al. [50] reported that DBE detected small bowel mass lesions missed by CE. Unlike vascular lesions, neoplasm, which causes major symptoms, is generally a single lesion in the whole small bowel. At the CE image capture rate of two frames per second, a single lesion is more likely to be missed than multifocal lesions. Mass lesions located in the proximal small bowel may be missed on the basis of a capsule’s advance or rotation. As the CE passes along the duodenal sweep rapidly, it may increase in speed and result in a lesion being missed. In addition, much residue, large folds, cincturing of bowel by tumors and blood around the lesion may obscure visualization of an underlying mass lesion. It was suggested that additional endoscopic evaluation of the small bowel by DBE or CE should be performed in patients with ongoing mid-GI bleeding and negative or non-specific findings on CE.

DBE generally utilizes both oral and anal routes for the investigation of small bowel diseases. It is often difficult

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>CE Diagnostic yield (%)</th>
<th>DBE Diagnostic yield (%)</th>
<th>Total observation rate (%)</th>
<th>Characteristic</th>
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<tr>
<td>Matsumoto</td>
<td>2005</td>
<td>13</td>
<td>38</td>
<td>46</td>
<td>84</td>
<td>Comparison in the same range</td>
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<td>Hadithi</td>
<td>2006</td>
<td>35</td>
<td>80</td>
<td>60</td>
<td>85</td>
<td>Higher diagnostic rate</td>
</tr>
<tr>
<td>Nakamura</td>
<td>2006</td>
<td>32</td>
<td>59</td>
<td>43</td>
<td>90</td>
<td>Preliminary study</td>
</tr>
<tr>
<td>Ohmiya</td>
<td>2007</td>
<td>74</td>
<td>50</td>
<td>53</td>
<td>–</td>
<td>Multicenter study in Japan</td>
</tr>
<tr>
<td>Fujimori</td>
<td>2007</td>
<td>45</td>
<td>40</td>
<td>50</td>
<td>–</td>
<td>Including follow-up data</td>
</tr>
<tr>
<td>Kameda</td>
<td>2008</td>
<td>62</td>
<td>72</td>
<td>66</td>
<td>73</td>
<td>Single-blinded study</td>
</tr>
<tr>
<td>Arakawa</td>
<td>2009</td>
<td>74</td>
<td>54</td>
<td>64</td>
<td>68</td>
<td>Largest number of subjects</td>
</tr>
</tbody>
</table>
to complete total enteroscopy using only one approach. To manage small bowel lesions accurately and rapidly, to reduce the examination time and to reduce invasiveness for the patient, the initial selection of the DBE route is essential. CE transit time is considered to be an effective indicator for the route selection of DBE in small bowel investigation with mid-GI bleeding. Nakamura et al. [51] reported that the route selection for DBE was most accurate when the cut-off value for the selection was half of the small bowel transit time in the CE complete examination for mid-GI bleeding.

A current issue about the usage of CE and DBE is indications for suspected and established CD. CE has been shown by meta-analysis to be a more sensitive method to investigate patients for small bowel CD, with an incremental yield above 30% versus other imaging modalities [52]. However, the rate of retention in CE is the highest in patients with established CD. Mensink et al. [53] stated that DBE is a useful diagnostic tool for the evaluation of small bowel lesions in CD patients and the significance of these findings is emphasized by the fact that adjustment of therapy in the majority of these patients leads to significant and sustained clinical improvement. Oshitani et al. [54] suggested that special attention should be paid to mesenteric longitudinal ulcers during insertion and the overtube balloon of DBE should not be inflated if a clear intestinal view is not possible, from the experience of perforation during DBE. At present, endoscopic evaluation for CD is considered to be important for subsequent management and this suggestion has been reported in many articles; however, it has not been standardized yet and the establishment of an algorithm for the management of CD aiming at endoscopic remission is expected, mainly using CE and DBE.

**Conclusion**

CE and DBE are major complementary methods for small bowel examination in the twenty-first century. CE seems to be superior as the first examination and DBE is useful for detailed examination and endoscopic therapy, but further clinical study for unknown or unsolved small bowel disorders using these two modalities is required.

**References**


