The Usefulness of Double-balloon Enteroscopy in Gastrointestinal Stromal Tumors of the Small Bowel with Obscure Gastrointestinal Bleeding

Masami Nakatani, Yasuhiro Fujiwara, Yasuaki Nagami, Satoshi Sugimori, Natsuhiko Kameda, Hirohisu Machida, Hirotoki Okazaki, Hirokazu Yamagami, Tetsuya Tanigawa, Kenji Watanabe, Toshio Watanabe, Kazunari Tominaga, Eiji Noda, Kiyoshi Maeda, Masahiko Ohshawa, Kenichi Wakasa, Kosei Hirakawa and Tetsuo Arakawa

Abstract

Objective Gastrointestinal stromal tumors (GISTs) are the most frequently occurring mesenchymal tumors of the GI tract. Double-balloon enteroscopy (DBE) and capsule endoscopy (CE) promise the detection and accurate diagnosis of small bowel diseases in patients with obscure GI bleeding (OGIB). The aim of the present study was to analyze the clinical characteristics of small bowel GISTs and the usefulness of DBE, CE and computed tomography (CT).

Methods Among 705 cases with OGIB examined between December 2003 and January 2011, 12 (1.7%) cases of small bowel GIST were identified. We analyzed endoscopic appearance, tumor-size and location, detection rate by DBE, CE and CT and clinical course in each of these cases.

Results Of the 12 patients with GIST, eight were men. The mean patient age was 53.6 years. The presenting symptoms in most patients included tarry stools and/or anemia. Six patients required blood transfusions. The detection rates of DBE, CE and CT were 92%, 60% and 67%, respectively. All cases, except for one incomplete study, were identified using DBE; however, one case was not diagnosed as a tumor because of the presence of extramural growth. A pathological diagnosis of GIST was obtained using biopsies during DBE in three (45%) of seven cases. Lower detection rates were found in cases with intramural and extramural growth, larger tumors (>35 mm) detected by CE and intraluminal growth and smaller tumors (<35 mm) detected by CT.

Conclusion DBE or a combination of CE and CT are thus considered to be useful for detecting small bowel GISTs.

Key words: gastrointestinal stromal tumor, small bowel, double balloon enteroscopy, capsule endoscopy, CT

(Intern Med 51: 2675-2682, 2012)
(DOI: 10.2169/internalmedicine.51.7847)

Introduction

Gastrointestinal (GI) bleeding is a common emergency condition. In approximately 3% to 5% of patients with GI bleeding, the bleeding source cannot be identified using esophagogastroduodenoscopy (EGD) and/or colonoscopy (1, 2). Bleeding points are found in the small bowel in cases with obscure GI bleeding (OGIB) (3-5). Our previous study showed that 13 (1.2%) of 1,044 cases with acute
Materials and Methods

Patients

We retrospectively examined 705 patients referred to our department for suspected OGIB between December 2003 and January 2011. All patients had been examined with EGID and colonoscopy but had no obvious lesions responsible for GI bleeding. In our department, the general diagnostic algorithm used for OGIB is as follows. In cases with overt-ongoing OGIB bleeding, oral DBE is first performed, followed by anal DBE. CE is first performed in cases with overt-previous bleeding of OGIB or occult OGIB. When lesions are detected with CE, DBE is performed to make a final diagnosis and as treatment to control bleeding. Enhanced abdominal CT is performed in some cases; however, the timing of examination varies in each case. During the study period, 487 cases were examined with CE and 389 were examined with DBE. We identified 12 (1.7%) cases of small bowel GISTs among the 705 patients with OGIB and analyzed the clinical characteristics of each case, including tumor size and location, detection rate of each modality, endoscopic appearance of DBE and/or CE, treatment, pathological assessment of the resected tissue (obtained during surgery) and prognosis during follow-up. Two cases of small bowel GISTs without GI bleeding were diagnosed pathologically during the same study period in our hospital. These cases were not surgically resected or examined with DBE or CE. Therefore, we did not include these cases in the present analysis.

Double-balloon enteroscopy

DBE was performed using a DBE system (Fujinon-Toshiba ES System, Saitama, Japan) according to the methods described by Yamamoto et al. (11). This technique uses a specially designed videobructoscope with an outer diameter of 8.5 or 9.4 mm and a working length of 200 cm with an attachable balloon at the tip. The videobructoscope is used together with a soft overtube (length, 145 cm) that has another balloon on the distal end. The balloons can be inflated and deflated with a single touch using a specially designed pump while the balloon pressure is accurately monitored. Most patients underwent DBE via antegrade and retrograde approaches to evaluate the entire small intestine while under sedation with 3 to 5 mg of midazolam and 35 mg of pethidine hydrochloride. DBE was first performed via an antegrade approach, and a mark was left by a tattoo injection (East Indian ink) at the deepest point of the small intestine for use in the retrograde approach. In the retrograde approach, reaching the tattoo indicated a complete small bowel examination. For the antegrade approach, preparation was limited to fasting after midnight on the evening before the examination. However, for the retrograde approach, preparation included both overnight fasting and ingestion of 2 L of an electrolyte lavage preparation (Niflec, Ajinomoto Pharma, Tokyo, Japan) in the morning. In some cases, biopsy specimens were obtained during DBE using biopsy forceps.

Capsule endoscopy

The CE procedure was performed using a Pill Cam capsule (M2A, Given Imaging, Yoqneam, Israel) (19). Specific preparation for video CE (VCE) was limited to fasting after midnight on the evening before the examination (minimum fast: eight hours). A standard 8-sensor array connected to the recorder was used. After ingesting the capsule, the patients fasted for another two hours during which time they were only permitted to ingest water. Four hours after capsule ingestion, the patients were permitted to eat, and eight hours after capsule ingestion, the sensor array and recorder were disconnected. Data were then downloaded and interpreted by experienced endoscopists. Abdominal radiography was performed to document the disappearance of the CE capsule, if necessary.

Definition of tumor growth

The tumor growth patterns were subdivided into intraluminal, intramural and extramural growth patterns. An intraluminal growth pattern was defined as a tumor that grew primarily into the intestinal lumen, while an extramural growth pattern was defined as a tumor that grew primarily into the outside of the intestine through the serosa. An intra-
mural growth pattern was defined as a tumor located primarily in the intestinal layer that grew both into the luminal side and outside of the intestine.

**Pathologic examination**

The biopsy specimens or surgically resected tissues were fixed in formalin, embedded in paraffin and cut into 4-μm-thick sections. A pathological diagnosis of GIST was made based on the shape of the tumor cells, including spindle-cell types, epithelioid types or rarely mixed types, and immunohistochemical staining for c-kit, CD34, smooth-muscle actin and S-100 proteins using specific antibodies. The number of mitotic cells in a high-power field was counted using surgically resected tissues and hematoxylin and eosin staining. The overall categorization of risk groups was completed on the basis of size and mitotic activity according to the risk classification of Fletcher et al. (20).

**Data collection during follow-up**

The clinical data of each case were collected after surgery from the patients’ medical records. Recurrence, prognosis (survival) and the use of imatinib after surgical tumor resection were examined during follow-up (4-50 months; mean: 27 months).

**Statistical analysis**

The detection rates of small bowel GISTs classified according to tumor growth patterns and size were analyzed using the chi-square test. A p-value <0.05 was considered to be statistically significant.

**Results**

Of the 12 patients with small bowel GISTs, eight were men and four were women. Their ages ranged from 33 to 67 years, and the mean age was 53.6 years. Most patients presented with tarry stools (overt OGIB type) and anemia (mean hemoglobin level: 9.6 g/dL). Six patients required blood transfusions. No patient was diagnosed as having neurofibromatosis type I. Four cases were first detected with CE, five with DBE and three with CT. Tumors were detected in six (60%) of 10 cases using CE, 11 (92%) of 12 cases using DBE, including one case with an incomplete study due to intestinal adhesion, and eight (67%) of 12 cases using CT. Taken together, four cases were found with DBE that were missed with CE, three cases were found with CT and one case was found with CE and CT that was missed with DBE. The tumors...
were located in the 3rd part of the duodenum (n=1) or the upper part of the jejunum (n=11). The endoscopic appearance of 11 tumors revealed round tumors with ulceration (Fig. 1A, B) in six cases and umbilication (Fig. 1C, D) in five cases; however, one case showed only a hole with an irregular edge and did not show protruded lesions on DBE (Fig. 2A, B). This case was identified on CT as a tumor with extramural growth (Fig. 2C) and an enhanced pattern (Fig. 2D). Although biopsy examinations were performed during DBE in seven of 11 cases, a final pathological diagnosis of GIST was made in three (43%) cases. No serious adverse events such as retention, perforation or acute pancreatitis were observed during the CE and DBE procedures in the present 12 cases. The clinical characteristics of the study subjects and the detected lesions are summarized in Table 1.

Surgical resection was performed in all patients, and laparoscopy-assist partial resection was performed in six patients. The shapes of the resected tumors were round (n=6) or nodular (n=6) and the growth patterns were intraluminal (n=6), intramural (n=5) or extramural (n=1). The size of each tumor ranged from 14 to 80 mm in diameter (mean diameter: 36 mm). The tumors were classified into very low risk (n=2), low risk (n=5), intermediate risk (n=2) or high risk (n=3) according to the mitotic rate and tumor size. Peritoneal metastasis was found in one case (case 6) during surgery. Treatment with imatinib was administered in four cases (cases 2, 6, 9 and 10). Recurrence was noted in one case (case 2, intermediate risk) with liver metastasis occurring 16 months after surgery; however, all patients remained alive during the follow-up (4-50 months; mean: 27 months). The characteristics of the small bowel GISTs and the clinical courses of the patients are summarized in Table 2.

We next examined the factors associated with detection of GISTs using DBE, CE and CT. DBE detected tumors in all cases except one with an incomplete study, and the detection rates of CE and CT were lower than that of DBE. The detection rates according to tumor growth pattern and tumor size are shown in Fig. 3. The detection rate of CE was dependent on the growth pattern, resulting in lower rates in cases with intramural or extramural growth patterns. In contrast, the detection rate of CT was relatively lower in cases with intraluminal growth patterns (Fig. 3A). However, the detection rate of CT was significantly higher for small-size tumors (< 35 mm) compared with that for large tumors (≥35 mm), whereas the detection rate of CE was significantly lower for larger tumors than for smaller tumors (Fig. 3B).

**Discussion**

The present study demonstrated the clinical characteristics and usefulness of DBE, CE and CT in 12 cases of small bowel GISTs in patients with OGIB. Although all lesions, except for one case of incomplete study, were detected with DBE, one lesion was not confirmed as a tumor due to having an extramural growth pattern. The detection rates of CE and CT were lower than that of DBE. Such low detection rates were caused by tumor growth patterns as well as tumor size. All patients were treated with surgical resection and remained alive during the follow-up period.
### Table 1. The Clinical Characteristics of the Study Subjects and the Detected Lesions

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Gender</th>
<th>Type of OGIB</th>
<th>Symptoms</th>
<th>Location of the lesion</th>
<th>Hb (g/dL)</th>
<th>Blood transfusion</th>
<th>Endoscopic appearance</th>
<th>Detection of the lesions</th>
<th>Diagnosis of BX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CE</td>
<td>DBE</td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>M</td>
<td>Overt</td>
<td>Tarry stool abdominal pain</td>
<td>Jejunum upper part</td>
<td>13.1</td>
<td>Yes</td>
<td>Round tumor with mucosal ulceration</td>
<td>NT</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>M</td>
<td>Overt</td>
<td>Tarry stool</td>
<td>Jejunum upper part</td>
<td>8.1</td>
<td>No</td>
<td>Round tumor with mucosal ulceration</td>
<td>Yes*</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>F</td>
<td>Overt</td>
<td>Tarry stool</td>
<td>Jejunum upper part</td>
<td>10.6</td>
<td>Yes</td>
<td>Round tumor with umbilication</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>M</td>
<td>Occult</td>
<td>Anemia</td>
<td>Jejunum upper part</td>
<td>12.8</td>
<td>No</td>
<td>Round tumor with umbilication</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>M</td>
<td>Overt</td>
<td>Tarry stool</td>
<td>Jejunum upper part</td>
<td>6.3</td>
<td>Yes</td>
<td>Round tumor with mucosal ulceration</td>
<td>NT</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>F</td>
<td>Overt</td>
<td>Tarry stool</td>
<td>Jejunum upper part</td>
<td>8.9</td>
<td>No</td>
<td>Round tumor with umbilication</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>M</td>
<td>Overt</td>
<td>Tarry stool</td>
<td>Jejunum upper part</td>
<td>11.1</td>
<td>No</td>
<td>Round tumor with umbilication</td>
<td>Yes*</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>M</td>
<td>Occult</td>
<td>No symptom</td>
<td>Jejunum upper part</td>
<td>11.9</td>
<td>No</td>
<td>Round tumor with umbilication</td>
<td>Yes*</td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td>F</td>
<td>Overt</td>
<td>Tarry stool</td>
<td>Jejunum upper part</td>
<td>8.6</td>
<td>No</td>
<td>Hole with irregular edge</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>M</td>
<td>Overt</td>
<td>Tarry stool</td>
<td>Duodenum 3rd part</td>
<td>7.0</td>
<td>Yes</td>
<td>Round tumor with mucosal ulceration</td>
<td>Yes*</td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>M</td>
<td>Overt</td>
<td>Tarry stool</td>
<td>Jejunum upper part</td>
<td>7.6</td>
<td>Yes</td>
<td>Round tumor with mucosal ulceration</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>57</td>
<td>F</td>
<td>Overt</td>
<td>Tarry stool</td>
<td>Jejunum upper part</td>
<td>8.6</td>
<td>Yes</td>
<td>Round tumor with mucosal ulceration</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: CE: capsule endoscopy, DBE: double balloon enteroscopy, BX: biopsy, NT: not tested, GIST: gastrointestinal stromal tumor
* the modality that first detected the tumors; # not completely tested due to the presence of adhesions

In the present study, 12 (1.7%) cases of small bowel GISTs were found among 705 cases with OGIB. Similarly, the prevalence of small bowel GIST in the era of CE and DBE is reported to be 2.6% (27 of 1,035 cases) with DBE in Japan (21), 1.5% (20 of 1,332 cases) with CE in Korea (22) and 0.7% (36 of 5,129 cases) with CE in Europe (23). Although the reasons for performing small bowel examinations were different in each study, OGIB was the most common feature of the patients with small bowel tumors, especially those with small bowel GISTs (12). This finding might be associated with the macroscopic appearance of GISTs, e.g. as ulcers or erosions on tumors. In this study, the small bowel GISTs were located in the upper jejunum (92%) and duodenum (8%), while no GISTs were found in the ileum. Other studies have also reported a predominance of small bowel GISTs in the jejunum (60-87%) (21, 23).

Two studies compared the detection rates and diagnostic yields between CE and DBE in patients with suspected small bowel diseases. Kameda et al. prospectively examined 32 patients with OGIB using CE and DBE. They found that CE yielded more abnormal findings than DBE (CE 90.6%, DBE 65.6%); however, they observed no significant differences in diagnostic yield between DBE and CE (24). On the other hand, Fukumoto et al. analyzed 66 patients and found that the detection rate of CE and DBE was 55.3% and 60.5%, respectively, and concluded that CE and DBE are nearly equal in their ability to detect small bowel lesions when the entire small bowel is examined (13). In the present study, the detection rate of small bowel GISTs was higher with DBE than with CE. The discrepancy between the findings of the two studies and those of the present study might be due to the small bowel lesions examined because most of the endoscopic findings of these two studies were of erosions or ulcers.

DBE is useful for detecting small bowel tumors because the DBE procedure has several merits, e.g. direct detailed examination, the ability to determine the extent of lesions using selective contrast agents, tattooing to prepare the surgical resection and biopsy examination (25). The diagnostic yields of pathological diagnoses of GIST made according to biopsies do not seem to be effective compared with other...
Table 2. The Characteristics of the Small Bowel Gastrointestinal Stromal Tumors (GISTs) and the Clinical Courses of the Patients

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Resected tumors</th>
<th>Metastasis</th>
<th>Size (mm)</th>
<th>Mitotic rate (per 50 HPF)</th>
<th>Risk classification</th>
<th>Follow-up after the operation (months)</th>
<th>Recurrence (period, months)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Partial jejunectomy</td>
<td>Round Intraluminal No 30 5 Low 50 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Partial jejunectomy</td>
<td>Nodular Intramural No 75 3 Intermediate 41 Liver metastasis (16 months) Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Partial jejunectomy</td>
<td>Nodular Intramural No 80 40 High 40 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Laparoscopy-assisted partial jejunectomy</td>
<td>Round Intraluminal No 30 3 Low 25 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Laparoscopy-assisted partial jejunectomy</td>
<td>Round Intramural No 33 1 Low 22 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Partial jejunectomy</td>
<td>Round Intraluminal Peritoneum 32 5 Low 21 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Laparoscopy-assisted partial jejunectomy</td>
<td>Round Intraluminal No 14 2 Very low 20 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Partial jejunectomy</td>
<td>Round Intraluminal No 18 0 Very low 16 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Laparoscopy-assisted partial jejunectomy</td>
<td>Nodular Extramural No 70 10 High 11 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Partial duodenectomy</td>
<td>Nodular Intramural No 70 36 High 10 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Laparoscopy-assisted partial jejunectomy</td>
<td>Nodular Intramural No 50 1 Intermediate 10 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Laparoscopy-assisted partial jejunectomy</td>
<td>Nodular Intraluminal No 42 5 Low 4 No Alive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: HPF: high-power field

Figure 3. Detection rates according to tumor growth patterns and tumor size. Detection with CE was lower in cases with intramural and extramural growth, while lower detection was observed with CT in cases with intraluminal growth (A). The detection rates of CE and CT were dependent on tumor size: a lower detection of small-size tumors was observed with CT and a lower detection of large-size tumors was observed with CE (B). White box: DBE; black box: CE; and dotted box: CT. *p < 0.05 versus detection of a smaller tumor (< 35 mm) using the same diagnostic tool.

small bowel tumors such as cancer or lymphoma. A previous report showed that a positive diagnosis of GIST was made in 40.9% of cases (nine out of 22) according to biopsy examination during DBE (21), which is similar to the results of the present study.

The reasons for the lower detection rates of CE and CT observed in this study have been discussed. In general, CE is a safe, accurate and painless method; however, incomplete
examination of the entire small intestine and poor images caused by residues or active bleeding are responsible for undetectable lesions. In addition, the present results suggest that tumor growth patterns, e.g. intramural and extramural growth and large size, are associated with lower detection rates of CE. Abdominal CT is useful for diagnosing small bowel tumors, especially those of a larger size and with extramural growth, in addition to providing high sensitivity for detecting abdominal metastasis. Although Wu et al. reported a series of 100 small bowel GISTs and found that the sensitivity of detection was 91% (26), other studies have shown low diagnostic yields before the use of CE or DBE (22, 23). The present study showed that the detection rate of CT was low for tumors with intraluminal growth and smaller size (< 35 mm); however, we emphasize that CT was extremely useful for diagnosing GISTs with extramural growth.

Fan et al. reported the prognostic factors and outcomes of resected patients with small bowel GISTs (27). They found that recurrence was noted in 19 (16.7%) patients and that 12 (10.5%) patients died of GIST with a median time from recurrence to death of 14 months. They identified tumor size (low risk) as a prognostic indicator of small bowel GISTs (27). In the present study, only one patient (8.3%) experienced recurrence (liver metastasis) 14 months after resection; however, all patients remained alive during the follow-up period. This might be related to the efficacy of imatinib treatment. In addition, since the size of the GISTs in this study was relatively small (mean diameter: 36 mm) compared to that of previous reports (28, 29), small bowel GISTs were detected at an earlier stage with DBE or CT. This finding might be related to the presence of bleeding symptoms or a low prevalence of extramural growth because previous reports have shown a higher prevalence of extramural growth in small bowel GISTs (28, 29).

The present study has some limitations. First, the number of small bowel GISTs was small. This might affect the statistical analysis. Second, since the present study was a retrospective study, the timing and order of examination with each modality varied in each case, although the general diagnostic algorithm described in the Methods section was followed. In addition, the results of examination with each modality were not blinded, which might have affected the detection rates. Finally, there are several other diagnostic modalities for small bowel tumors such as small bowel series or enteroclysis, magnetic resonance imaging (MRI) or angiography. Although the usefulness of barium contrast studies was established in the era before CE and DBE, we examined only a few cases with OGIB using small bowel series. In the future, we should combine positron emission tomography (PET), CT or MRI enterography/enteroclysis and endoscopic ultrasonography to make detailed diagnoses of small bowel GISTs.

In conclusion, we demonstrated the clinical characteristics and usefulness of CE, DBE and CT for small bowel GISTs in patients with OGIB. DBE was found to be useful; however, other diagnostic modalities should also be combined, especially in patients with small bowel GISTs with extramural growth. The combination of CE and CT is also useful for detecting small bowel GISTs.

The authors state that they have no Conflict of Interest (COI).

References


© 2012 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html