【 ORIGINAL ARTICLE 】

Combined Use of Computed Tomography Enterography/Enteroclysis and Capsule Endoscopy Improves the Accuracy of Diagnosis of Small Bowel Bleeding

Madoka Unno[1], Shinichi Hashimoto[1], Kensaku Shimizu[2], Hideko Onoda[3], Masahiro Tanabe[3], Tomohiro Shirasawa[1], Atsushi Goto[1], Koichi Hamabe[1], Takeshi Okamoto[1], Jun Nishikawa[4], Katsuyoshi Ito[3] and Isao Sakaida[1]

Abstract:

Objective   CT enterography/enteroclysis (CTE) is listed in the clinical practice guidelines as a method for diagnosing small bowel bleeding, as is capsule endoscopy (CE), but there are no real-world data yet available on CTE in Japan. This study aimed to investigate the diagnostic ability of CTE and long-term prognosis after CTE in Japan.

Patients   We conducted a retrospective cohort study of patients suspected of having small bowel bleeding who underwent both CTE and CE within 30 days between April 2008 and March 2019. The number of patients free from rebleeding for up to 24 months was thus determined.

Results   Seventy-one patients were extracted from the database. The 43 patients (60.6%) with a definite and suspicious source of bleeding in the small bowel were detected by CTE. When the 31 patients with a definite source of bleeding in the small bowel were analyzed, the sensitivity of CTE was 19/31 (61.3%) and that of CE was 24/31 (77.4%), thus indicating no significant difference (p=0.332). However, the sensitivity when CTE and CE were used in combination was 30/31 (96.8%), which was significantly higher than that of CE alone (p=0.0412). No rebleeding was observed in the CTE and CE negative group (p=0.0965).

Conclusion   The combined use of CTE and CE increased the detection rate of small bowel bleeding. Therefore, in patients with suspected tumor/polyp lesions, not only CE, but also CTE should be performed. This study provides the first real-world data on the diagnostic accuracy of CTE for small bowel bleeding in Japan.

Key words: CT enterography, CT enteroclysis, small bowel bleeding, obscure gastrointestinal bleeding, capsule endoscopy

(Intern Med 60: 2545-2555, 2021)
(DOI: 10.2169/internalmedicine.6785-20)

Introduction

Obscure gastrointestinal bleeding (OGIB) was formerly defined as gastrointestinal bleeding of unknown cause even after examination by esophagogastroduodenoscopy (EGD) and colonoscopy (CS) (1), and it accounted for about 5% of all diagnoses of gastrointestinal bleeding (2, 3). Despite this small proportion, bleeding recurs in about half of all cases of OGIB (4), often resulting in clinical problems. In recent years, with the popularization of device-assisted enteroscopy (DAE) (5) and capsule endoscopy (CE) (6), it has become possible to diagnose and treat small bowel lesions in many cases. Thus, cases previously classified as OGIB have been

renamed as suspected small bowel bleeding, and the definition of OGIB has been changed to cases in which the source of bleeding cannot be detected even after searching throughout the entire gastrointesitinal tract, including the small bowel (7, 8).

Computed tomography (CT) is useful for diagnosing gastrointestinal bleeding (9), and the advent of CT enteroclysis and CT enterography (CTE), in which CT images are taken while the small bowel is dilated with a contrast medium, has increased the number of reports of the diagnosis of small bowel diseases (10, 11).

The clinical practice guidelines for small bowel bleeding in different countries include not only CE and DAE but also CTE. However, the American College of Gastroenterology (ACG) and the American Society for Gastrointestinal Endoscopy (ASGE) list CE and CTE together (7, 8), and the European Society of Gastrointestinal Endoscopy (ESGE) lists CE as the first choice for screening (12). Thus, a globally unified algorithm has not yet been established.

Although CT is the first choice in Japan (13), as far as we have searched, there are no reports of real-world data on suspected small bowel bleeding using CTE in Japan. This study aimed to analyze the positioning of CTE by comparing it with CE in the algorithm for suspected small bowel bleeding.

Materials and Methods

Patients

In this retrospective cohort study, data from patients who visited Yamaguchi University Hospital and underwent small bowel examination (CTE, CE, or DAE) for gastrointestinal bleeding between April 2008 and March 2019 were prospectively and consecutively extracted from the medical records. Data from patients who did not undergo EGD and/or CS before small bowel examination, patients in whom the source of bleeding was found with EGD and CS, patients lacking important clinical data, and patients in whom CE did not reach the small bowel were excluded. The remaining patients were defined as having suspected small bowel bleeding, and among them, patients in whom both CTE and CE were performed, and the interval between the implementation of CTE and CE was 30 days or less, were included as the subjects in this study. All researchers involved in this study conducted the study in accordance the World Medical Association's Declaration of Helsinki (1964, and its later amendments). The study was reviewed and approved by the Ethical Committee on Human Research at Yamaguchi University Hospital.

Patient background

Clinical information regarding gastrointestinal bleeding and the patient backgrounds was collected from medical records. Patient background data were collected on age, sex, lowest hemoglobin level, platelet count, history of abdomi-

nal operation, history of blood transfusion before examination, time from day of bleeding to first small bowel examination, capsule retention, and complications associated with CTE. Data on the comorbidities of hypertension, ischemic heart disease, atrial fibrillation, chronic heart failure or cardiac operation, cerebrovascular disease, chronic kidney disease, hemodialysis, diabetes mellitus, and liver cirrhosis were also collected, as were data on oral administration of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelet drugs, anticoagulants, and prednisolone.

Classification of the bleeding pattern and diagnosis groups

Overt ongoing bleeding was defined as melena or hematochezia observed within 24 hours before small bowel examination, whereas overt previous bleeding was defined as melena or hematochezia observed 24 hours or more before small bowel examination. Occult bleeding was defined as bleeding without melena or hematochezia, but with iron deficiency and/or a positive fecal occult blood test (14).

Patients were classified into diagnosis groups according to the location of the source of bleeding. Patients in whom the source of bleeding was between the ampulla of Vater and the ileocecal valve were classified into the small bowel bleeding group, and those in whom the source of bleeding was located at other sites were classified into the non-small bowel bleeding group. Those in whom the source of bleeding was not determined were classified into the OGIB group (8).

Reference standard

As the reference standard, the final diagnosis was determined by agreement between U.M. (with more than 5 years of experience in gastroenterology) and S.H. (with more than 20 years of experience in gastroenterology), based on all examination findings, such as CE, DAE, angiography, and CT angiography (CTA) performed in each case, and surgical findings, surgically resected specimens, and EGD and CS performed again after small bowel examination. When their judgments differed, they discussed their findings until a consensus decision was reached.

In addition, because whether the lesion listed as the final diagnosis was actually involved in bleeding is very important regarding examination accuracy, the lesions that were very likely the source of bleeding were defined as definite and those that were suspected as the source of bleeding were defined as suspicious, as reported by Shinozaki et al. (14).

The criteria for the endoscopic findings of CE, DAE, EGD, and CS, were created with reference to the reports of Shinozaki et al. (14) and Niikura et al. (15), with some modifications. For ulcer/erosion, lesions ≥10 mm and those <10 mm but with obvious bleeding or exposed vessels were defined as definite, whereas the others were defined as suspicious. For vascular lesions, those classified as type 1a according to the Yano-Yamamoto classification and without

bleeding were defined as suspicious, and the others were de-
fined as definite (16). For tumor/polyp, lesions with ulcers
and those with a diameter exceeding 20 mm or with bleed-
ing were defined as definite, and the others were defined as
suspicious. Diverticulum only, small red spots, and erosions
not greater than 1 mm were excluded as the source of
bleeding. For CTA and angiography, if extravasation and ab-
normal blood vessels in the intestinal wall were observed,
these were classified as definite, and other findings were
classified as undiagnosable. Based on the above, the patients
with definite or suspicious lesions were defined as the diag-
nosable group. As a result, all criteria except those defining
the diagnosable group apply to the OGIB group.

CTE findings

The medical records were examined, and the findings as
reported by more than two radiographic interpreters of the
Department of Radiology at Yamaguchi University Hospital
at the time of examination were considered to represent the
diagnosis. The radiologists judging CTE were informed of
the purpose of the examination, i.e., a thorough inspection
of the gastrointestinal tract for the source of gastrointestinal
bleeding. The final diagnosis and CTE findings were com-
pared to determine whether the findings detected by CTE
were true positives or false positives. M.U. and S.H. made
the judgments individually, and when their judgments dif-
fered, they discussed their findings until a consensus deci-
sion was reached.

Details of small bowel examination and therapeutic procedure

Patients undergoing CT enterography consumed contrast
medium 1 hour before the procedure. For CT enteroclysis, a
16 Fr balloon-tipped nasoduodenal tube (gastroenterography
balloon catheter, 1,500 mm; Create Medic, Yokohama, Ja-
pan) was placed in the duodenojejunal flexure via a transna-
sal endoscope, and contrast medium was injected. The con-
trast medium used was polyethylene glycol solution
(Nifrec®, EA Pharma, Tokyo, Japan) or amidotrizoic acid
adjusted to isotonicity (Gastrographin®, Bayer, Osaka, Ja-
pan). The dose of contrast medium was set between 400 and
1,800 mL depending on each individual case, taking into
consideration the patient's body build and the possibility of
intestinal stenosis.

The patients were examined with multislice CT scanners
(SOMATOM Definition, SOMATOM Sensation 64, SOMA-
TOM Force; Siemens Healthcare, Erlangen, Germany, or
Optima CT660; GE Healthcare, Milwaukee, USA). The en-
tire abdomen and pelvis were scanned using breath-hold ac-
quisition. Unenhanced CT and contrast-enhanced CT were
performed using the following scanning parameters: dual-
energy mode (100 and 150 kVp using a 0.6 mm tin filter)
with the SOMATOM Force, or 120 kVp with the other CT
scanners; milliampere-seconds were automatically calculated
based on the localizer image; collimation 0.6-1.25 mm;
pitch factor 0.6-1.375; and reconstruction interval 1-2 mm.

Coronal image reconstruction with maximum intensity pro-
jection was performed using a computer workstation. The
total contrast agent volume (range, 76-135 mL) was indi-
vidualized depending on the patient's body weight and was
administered intravenously over 30 seconds using a power
injector. Contrast-enhanced CT images were acquired ap-
proximately 40, 70, and 120 seconds after injection with or
without bolus tracking. Late-phase images (120 seconds af-
ter injection) were not obtained in eight patients. When the
contrast medium was amidotrizoic acid, only plain CT was
captured.

PillCam SB1/2/3 capsules (Medtronic Japan, Tokyo, Ja-
pan) were used for CE. The patients were instructed to fast
for 12 hours before the examination. For DAE, an EN-450T,
EN-580T, or EN-580XP enteroscope (Fujifilm, Tokyo, Ja-
pan) or a SIF-Q260 enteroscope (Olympus, Tokyo, Japan)
was used.

Before CTE, CE, or DAE was performed, the patients
were given a thorough explanation, including the risks, and
their written consent was obtained.

Specific treatment was defined as the performance of en-
doscopic argon plasma coagulation, clip placement, polypec-
tomy/endoscopic mucosal resection, arterial embolization
during angiography, and surgical operation, and only cases
of withdrawal from NSAIDs, antiplatelet drugs, anticoagu-
lants, or prednisolone were excluded.

Rebleeding-free interval

Patients who could be followed up for at least 1 month
from the first small bowel examination were investigated for
rebleeding. With reference to the report by Shin et al. (17),
rebleeding was defined as melena or hematochezia during
the follow-up period, a decrease in hemoglobin level of 2 g/
dL or more from baseline, or the need for blood transfusion.
The study period was the period from the day the first small
bowel examination was performed to 24 months later.

Statistical analysis

For each patient background factor in each diagnosis
group, the unpaired t-test or the Mann-Whitney U test was
used for continuous variables, and the χ^2 test or Fisher's ex-
act test was used for categorical variables. To calculate a di-
agnostic yield for CTE, the number of patients with a posi-
tive CTE finding was divided by the total number of pa-
tients. The comparison of CT enteroclysis and CT enterogra-
phy sensitivity were analyzed by Fisher's exact test. The
comparison of CTE and CE sensitivity were analyzed by
McNemar's test. The comparison of CTE sensitivity when
either CTE or CE was performed first was analyzed by
Fisher's exact test. In the investigation of the rebleeding-free
rate, the Kaplan-Meier method and log-rank test were used
to estimate the rebleeding events at 1 to 24 months. Differ-
ences were considered statistically significant at a value of
$p<0.05$. All statistical analyses were performed with EZR,
which is for R (under the GNU General Public Li-
cense) (18). More precisely, it is a modified version of R

```
┌─────────────────────────────────────────────────────────────────────────────────────┐
│ Patients in whom small bowel examination was performed for gastrointestinal           │
│ bleeding between 2008 and 2019 (n = 320)                                              │
└─────────────────────────────────────────────────────────────────────────────────────┘
                                    │
                                    │        ┌──────────────────────────────────────────────┐
                                    │        │ · No history of EGD (n = 29), CS (n = 46), and both EGD and │
                                    ├───────▶│   CS (n = 7) before small bowel examination    │
                                    │        │ · Source of bleeding identified with EGD or CS (n = 8) │
                                    │        │ · No data on onset date of bleeding (n = 2)    │
                                    │        │ · No data on comorbidities and oral administration of drugs (n = 2) │
                                    ▼        └──────────────────────────────────────────────┘
┌─────────────────────────────────────────────────────────────────────────────────────┐
│ Patients with suspected small bowel bleeding (n = 226)                                │
└─────────────────────────────────────────────────────────────────────────────────────┘
                                    │
                                    │        ┌──────────────────────────────────────────────┐
                                    │        │ · No implementation of CTE and/or CE (n = 131) │
                                    ├───────▶│ · Both CTE and CE were performed, but with an interval of ≥30 │
                                    │        │   days (n = 21)                                │
                                    │        │ · CE stagnated in the stomach and did not reach the small bowel │
                                    ▼        │   (n = 3)                                      │
┌─────────────────────────────────────────────────────────────────────────────────────┐
│ Patients undergoing CTE and CE within 30 days (n = 71)                                │
└─────────────────────────────────────────────────────────────────────────────────────┘
            │                              │                             │
            ▼                              ▼                             ▼
┌──────────────────────┐   ┌─────────────────────────────┐   ┌──────────────────────┐
│ Small bowel bleeding │   │ Non-small bowel bleeding    │   │ OGIB group (n = 14)  │
│ group (n = 43)       │   │ group (n = 14)              │   │                      │
└──────────────────────┘   └─────────────────────────────┘   └──────────────────────┘
```
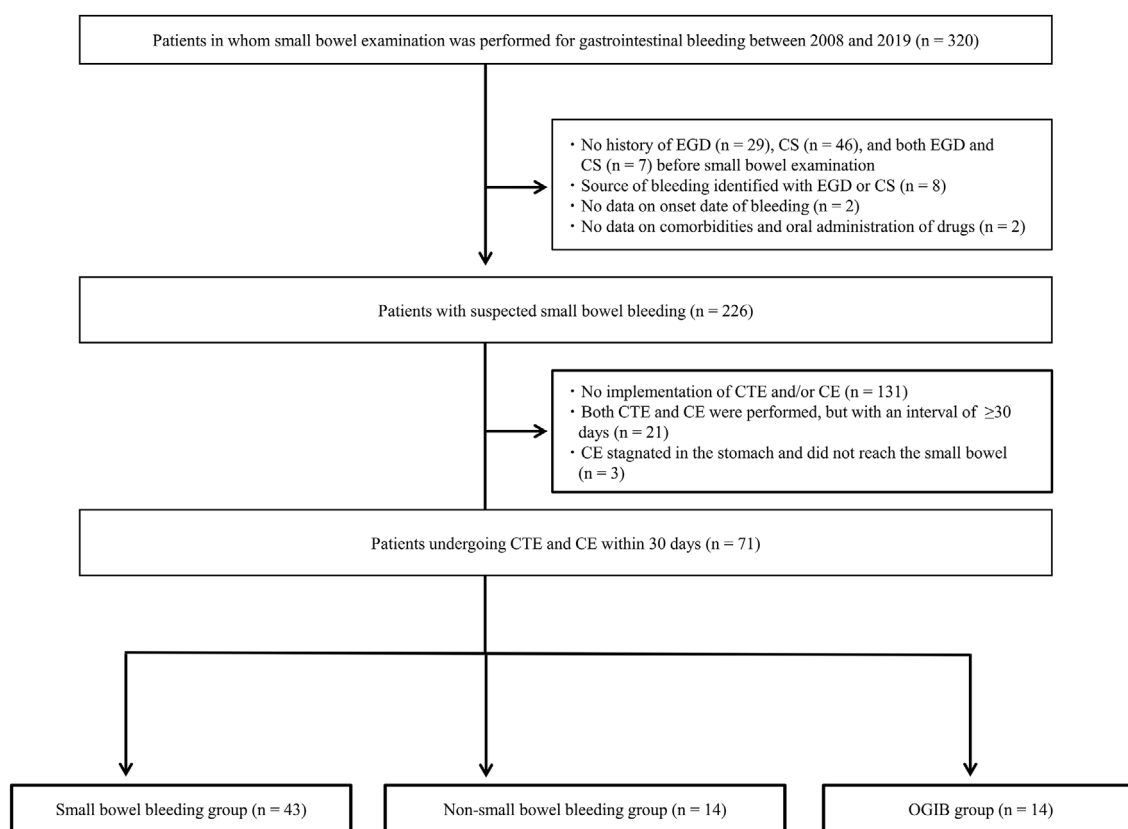
Figure 1.   Patient flow in this study. CE: capsule endoscopy, CS: colonoscopy, CTE: computed tomography enterography/enteroclysis, EGD: esophagogastroduodenoscopy, OGIB: obscure gastrointestinal bleeding

commander designed to add statistical functions frequently used in biostatistics.

Results

Patients

Of the patients extracted from the database, 320 were applicable. After excluding 94 patients for the reasons presented in Fig. 1, the remaining 226 patients were determined to have suspected small bowel bleeding. Among them, 71 patients in whom both CTE and CE were performed and the interval between the two examinations was within 30 days were extracted. These 71 patients were divided into three diagnosis groups based on the reference standard as follows: 43 (60.6%) in the small bowel bleeding group, 14 (19.7%) in the non-small bowel bleeding group, and 14 in (19.7%) in the OGIB group (Fig. 1).

Clinical features and patient background according to the diagnosis group

The small bowel bleeding group had the highest rates of use of DAE and of specific treatment implementation versus the non-small bowel bleeding group and OGIB group (74.4% vs. 57.1% vs. 35.7%, p=0.029 and 39.5% vs. 28.6% vs. 0.0%, p=0.019, respectively) (Table 1). The non-small bowel bleeding group had the highest rate of liver cirrhosis

versus the small bowel bleeding group and the OGIB group (28.6% vs. 9.3% vs. 0.0%, p=0.046) (Table 2). Other items did not differ significantly between the three groups.

Content of final diagnosis

The source of bleeding was identified as the final diagnosis in 57 of 71 patients (80.3%). These 57 patients comprised 22 (38.6%) with ulcer/erosion, 21 (36.8%) with vascular lesion, and 14 (24.6%) with tumor/polyp. Among them, 41 patients (71.9%) were determined to have definite lesions, and 16 (28.1%) had suspicious lesions. Among the definite lesions, ulcer/erosion was the most common, whereas vascular lesion, especially type 1a angioectasia, was the most common among the suspicious lesions (Table 3).

Comparison between the CTE findings and the final diagnosis

Forty-eight sites of suspected sources of bleeding were detected by CTE in 45 of the 71 patients, for a diagnostic yield of 63.4%. Among these 48 sites, a final diagnosis of the lesions was made in 30 patients, giving a true-positive rate of 62.5% (30/48). The most common finding of CTE was contrast enhancement of the intestinal wall, and other findings including vasodilatation/arteriovenous malformation (AVM), tumor/polyp, wall thickness, and stenosis were also detected by CTE. Final diagnoses corresponding to contrast enhancement were non-specific ulcers, NSAIDs ulcers, cap-

Table 1.   Clinical Features by Diagnosis Group.

Factor		Diagnosis group			p value
		Small bowel bleeding	Non-small bowel bleeding	OGIB	
n (%)		43 (60.6)	14 (19.7)	14 (19.7)	
Subtype of bleeding (%)					
	Overt ongoing	5 (11.6)	3 (21.4)	0 (0.0)	0.344
	Overt previous	36 (83.7)	10 (71.4)	12 (85.7)	
	Occult	2 (4.7)	1 (7.1)	2 (14.3)	
Time to first small bowel examination (median, quartile, days)		27.00 (18.00, 70.50)	35.00 (11.50, 55.75)	17.50 (8.75, 40.50)	0.406
CTE and CE interval (median, quartile, days)		2.00 (1.00, 10.50)	2.00 (0.00, 6.75)	2.50 (0.25, 4.75)	0.479
Follow-up period within 24 months (median, quartile, months)		8.00 (2.00, 24.00)	16.50 (6.75, 23.50)	24.00 (3.00, 24.00)	0.727
CTE					
Enteroclysis (%)		22 (51.2)	6 (42.9)	7 (50.0)	0.863
Enterography (%)		21 (48.8)	8 (57.1)	7 (50.0)	
Contrast medium (%)					
	Amidotrizoic acid	2 (4.7)	1 (7.1)	2 (14.3)	0.473
	Polyethylene glycol solution	41 (95.3)	13 (92.9)	12 (85.7)	
Finding (%)					
	Negative	13 (30.2)	5 (35.7)	8 (57.1)	0.192
	Positive	30 (69.8)	9 (64.3)	6 (42.9)	
CE					
Completion rate (%)					
	No	7 (16.3)	1 (7.1)	3 (21.4)	0.565
	Yes	36 (83.7)	13 (92.9)	11 (78.6)	
Retention (%)					
	No	42 (97.7)	14 (100.0)	14 (100.0)	0.719
	Yes	1 (2.3)	0 (0.0)	0 (0.0)	
DAE (%)					
	No	11 (25.6)	6 (42.9)	9 (64.3)	0.029
	Yes	32 (74.4)	8 (57.1)	5 (35.7)	
Final diagnosis	Confidence level (%)				
	Suspicious	12 (27.9)	4 (28.6)	0(0)	1
	Definite	31 (72.1)	10 (71.4)	0 (0)	
Treatment	Specific treatment (%)				
	No	26 (60.5)	10 (71.4)	14 (100.0)	0.019
	Yes	17 (39.5)	4 (28.6)	0 (0.0)	

CE: capsule endoscopy, CTE: computed tomography enterography/enteroclysis, DAE: device-assisted enteroscopy, OGIB: obscure gastrointestinal bleeding

illary hemangiomas, and gastric antral vascular ectasias. Examples of image findings in a CTE-positive case are presented in Fig. 2. Type 1b angioectasia and AVM were detected in the cases of vasodilatation/AVM by CTE. In the cases of tumor/polyp by CTE, polypoid (or protruded) lesions were actually detected in the lesions for which a final diagnosis could be made (9/11, 81.8%) (Table 4).

Diagnostic ability of CTE for sources of suspected small bowel bleeding

When the combination of definite and suspicious lesion was defined as the bleeding source, the sensitivity of CTE for diagnosing sources was 52.6%, specificity was 57.1%, positive predictive value was 83.3%, negative predictive value was 22.9%, and the rate of true diagnosis was 53.5%. When only definite lesions were defined as the bleeding source, the respective rates were 61.0%, 53.3%, 64.1%, 50.0%, and 57.7% (Table 5). In the 41 patients with definite

lesions, CT enteroclysis was performed in 23 cases, 16 of which (69.6%) were positive, and CT enterography was performed in 18 cases, of which 9 (50%) were positive. Although CT enteroclysis had a higher positive rate, no significant difference was observed (p=0.332). Of the 5 cases that demonstrated occult bleeding, a fecal occult blood test was positive in 3 cases, and the final diagnosis was reached in 1 case with NSAIDs ulcer, which was positive for both CTE and CE. The source of bleeding was unknown in the remaining two cases.

Comparison of sensitivity of CTE and CE for small bowel lesions

To compare the sensitivity of CTE and CE for small bowel lesions, 31 patients in the small bowel bleeding group with definite lesions were investigated. The sensitivity of CTE was 19/31 (61.3%), whereas that of CE was 24/31 (77.4%) (p=0.332). However, the sensitivity of the combined

Table 2.   Patient Background by Diagnosis Group.

Factor		Diagnosis group			p value
		Small bowel bleeding	Non-small bowel bleeding	OGIB	
n (%)		43 (57.6)	14 (19.7)	14 (19.7)	
Age (mean±SD, yrs)		67.79±10.70	67.79±11.56	63.07±16.40	0.433
Sex (%)	Male	19 (44.2)	6 (42.9)	9 (64.3)	0.389
	Female	24 (55.8)	8 (57.1)	5 (35.7)	
Lowest hemoglobin (mean±SD, g/dL)		7.77±2.64	6.51±2.22	8.61±2.98	0.109
Platelet count (mean±SD, ×10⁴/μL)		24.26±7.45	24.36±16.05	20.70±5.06	0.446
History of abdominal surgery (%)	No	25 (58.1)	6 (42.9)	10 (71.4)	0.309
	Yes	18 (41.9)	8 (57.1)	4 (28.6)	
Transfusion (%)	No	14 (34.1)	3 (23.1)	8 (61.5)	0.102
	Yes	27 (65.9)	10 (76.9)	5 (38.5)	
Comorbidity and drugs					
Hypertension (%)	No	27 (62.8)	8 (57.1)	10 (71.4)	0.729
	Yes	16 (37.2)	6 (42.9)	4 (28.6)	
Ischemic heart disease (%)	No	26 (60.5)	9 (64.3)	10 (71.4)	0.758
	Yes	17 (39.5)	5 (35.7)	4 (28.6)	
Atrial fibrillation (%)	No	41 (95.3)	13 (92.9)	12 (85.7)	0.473
	Yes	2 (4.7)	1 (7.1)	2 (14.3)	
Chronic heart failure/cardiac operation (%)	No	38 (88.4)	13 (92.9)	12 (85.7)	0.831
	Yes	5 (11.6)	1 (7.1)	2 (14.3)	
Cerebrovascular disease (%)	No	41 (95.3)	12 (85.7)	12 (85.7)	0.362
	Yes	2 (4.7)	2 (14.3)	2 (14.3)	
Chronic kidney disease (%)	No	40 (93.0)	12 (85.7)	13 (92.9)	0.681
	Yes	3 (7.0)	2 (14.3)	1 (7.1)	
Hemodialysis (%)	No	42 (97.7)	14 (100.0)	14 (100.0)	0.719
	Yes	1 (2.3)	0 (0.0)	0 (0.0)	
Diabetes mellitus (%)	No	39 (90.7)	10 (71.4)	13 (92.9)	0.134
	Yes	4 (9.3)	4 (28.6)	1 (7.1)	
Liver cirrhosis (%)	No	39 (90.7)	10 (71.4)	14 (100.0)	0.046
	Yes	4 (9.3)	4 (28.6)	0 (0.0)	
Aspirin (%)	No	34 (79.1)	12 (85.7)	13 (92.9)	0.469
	Yes	9 (20.9)	2 (14.3)	1 (7.1)	
NSAIDs (%)	No	36 (83.7)	12 (85.7)	11 (78.6)	0.867
	Yes	7 (16.3)	2 (14.3)	3 (21.4)	
Thienopyridine (%)	No	41 (95.3)	14 (100.0)	11 (78.6)	0.053
	Yes	2 (4.7)	0 (0.0)	3 (21.4)	
Cilostazol (%)	No	42 (97.7)	14 (100.0)	14 (100.0)	0.719
	Yes	1 (2.3)	0 (0.0)	0 (0.0)	
Warfarin/DOAC (%)	No	39 (90.7)	12 (85.7)	12 (85.7)	0.81
	Yes	4 (9.3)	2 (14.3)	2 (14.3)	
Prednisolone (%)	No	40 (93.0)	14 (100.0)	14 (100.0)	0.361
	Yes	3 (7.0)	0 (0.0)	0 (0.0)	

DOAC: direct oral anticoagulants, NSAIDs: nonsteroidal anti-inflammatory drugs, OGIB: obscure gastrointestinal bleeding

use of CTE and CE was 30/31 (96.8%), which was significantly higher than that of CE alone (p=0.0412) (Table 6). Among these 31 patients, 6 cases were positive by CTE and negative by CE. The final diagnosis of these cases consisted of 3 cases of GIST, 1 case of metastatic tumor, and 2 cases of NSAIDs ulcer. The CTE findings of these cases were a tumor in 3 cases, stenosis in 1 case, and contrast enhancement of the intestinal wall in 2 cases. Among these 31 cases, CTE was performed first in 13 cases and CE was performed first in 18 cases, and the sensitivities of CTE were 46.2% (6/13) and 72.2% (13/18), respectively, which showed no significant difference (p=0.262).

Rebleeding-free interval

The rebleeding rate in the OGIB group was significantly lower than that of the diagnosable group (patients with definite and suspicious lesions) (p=0.0337) (Fig. 3a). Investigations of the sources of rebleeding showed that the patients with a vascular lesion tended to have a higher rebleeding rate, but the differences were not significant: ulcer/erosion

Table 3. Content of Final Diagnosis.

Diagnosis		n	%
Total lesions		57	100
	Ulcer/erosion	22	38.6
	Vascular lesion	21	36.8
	Tumor/polyp	14	24.6
Definite lesions		41	71.9
Ulcer/erosion	NSAIDs	10	
	Ileal duplicated-related ulcer	1	
	Diverticulum-related ulcer	1	
	Nonspecific ulcer	6	
Vascular lesion	Type 1a with oozing	2	
	Type 1b with oozing	3	
	Type 1b without oozing	4	
	AVM	2	
	GAVE with oozing	1	
Tumor/polyp	GIST	4	
	Malignant lymphoma	2	
	Lipoma	1	
	Metastatic colon cancer	1	
	Capillary hemangioma	1	
	Pyogenic granuloma	1	
	Gastric polyp	1	
Suspicious lesions		16	28.1
Ulcer/erosion	NSAIDs	1	
	Duodenal ulcer	2	
	Nonspecific ulcer	1	
Vascular lesion	Type 1a without oozing	8	
	Hemorrhoid	1	
Tumor/polyp	Lipoma	1	
	Gastric abscess	1	
	Non-neoplastic polyp	1	

AVM: arteriovenous malformation, GAVE: gastric antral vascular ectasia, GIST: gastrointestinal stromal tumor, NSAID: nonsteroidal anti-inflammatory drug

vs. vascular lesion, p=0.117; vascular lesion vs. tumor/polyp, p=0.203; and tumor/polyp vs. ulcer/erosion, p=0.937 (Fig. 3b). The rebleeding rate in the group with positive findings by CTE was not higher than that of the others without CTE findings (p=0.675) (Fig. 3c). The rebleeding rate in the group with positive findings by CE was not higher than that of others without CE findings (p=0.278) (Fig. 3d). Rebleeding was not observed for 24 months in the group negative for both CTE and CE findings, but there was no significant difference between the groups with or without findings by CTE and CE (p=0.0965) (Fig. 3e).

Adverse events of CTE and CE

CTE-related adverse events were observed in 3 of 71 patients (4.2%). Vomiting was observed in three and nosebleeding associated with nasoduodenal tube insertion in one patient, but no serious events, such as intestinal obstruction and intestinal perforation, were observed. For CE, retention was observed in only one patient, but the retained capsule was recovered following spontaneous passage. Pre-examination with a patency capsule was not performed in this patient because at the time of CE, the patency capsule was not covered by insurance in Japan.

Discussion

This study is the first report, to our knowledge, to provide real-world data on the diagnostic ability of CTE for suspected small bowel bleeding in Japan. The following five points were clarified. First, CTE had a diagnostic yield of 63.4% and a true-positive rate of 62.5%. Second, the diagnostic ability of CTE for suspected small bowel bleeding was investigated, and both sensitivity and specificity were found to be low. Third, when the sensitivity of CTE and that of CE for small bowel definite lesions were compared, no
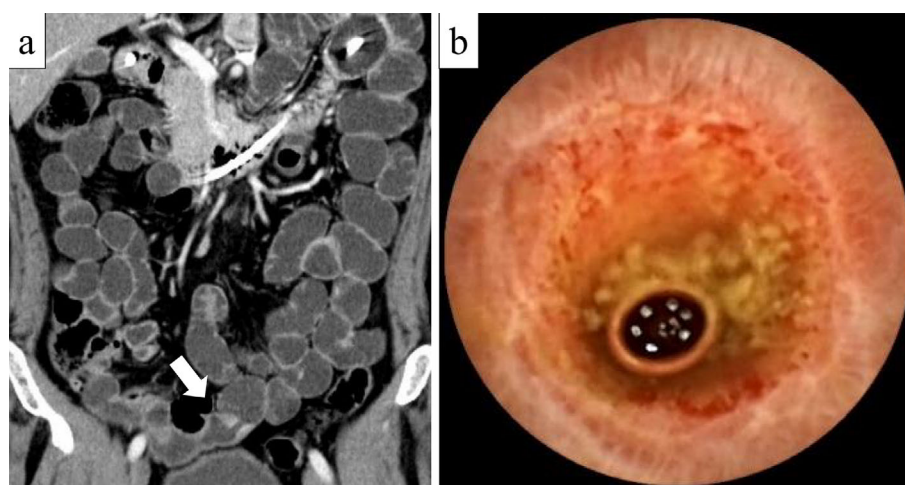

Figure 2. Images from a 63-year-old man with anemia and positive fecal occult blood test. (a) Image from CT enteroclysis shows contrast enhancement and stenosis of the ileum (arrow). (b) Capsule endoscopy shows a nonsteroidal anti-inflammatory drug-induced ulcer.

Table 4.   CTE Findings and Final Diagnosis of Lesions.

CTE findings	n	Final diagnosis					
		Definite lesion	n	Suspicious lesion	n		n	True positive rate (%)
Total	48		25		5		18	62.5
Contrast enhancement	16	Non-specific ulcer	4	-	0	FP	7	56.3
		NSAIDs ulcer	3					
		Capillary hemangioma	1					
		GAVE with oozing	1					
Vasodilatation/AVM	15	Type 1b	4	Type 1a	3	FP	6	60.0
		AVM	2					
Tumor/polyp	11	GIST	4	Gastric abscess	1	FP	2	81.8
		ML	1	Non-neoplastic polyp	1			
		Lipoma	1					
		Gastric polyp	1					
Wall thickness	5	Non-specific ulcer	2	-	0	FP	3	40.0
Stenosis	1	NSAIDs ulcer	1	-	0	FP	0	100.0

AVM: arteriovenous malformation, CTE: computed tomography enterography/enteroclysis, FP: false positive, GAVE: gastric antral vascular ectasia, GIST: gastrointestinal stromal tumor, ML: malignant lymphoma, NSAID: nonsteroidal anti-inflammatory drug

Table 5.   Diagnostic Ability of CTE for the Source of Suspected Small Bowel Bleeding.

CTE findings	Definite+suspicious lesion n=57	Others n=14	Total n=71
Positive	30	6	36
Negative	27	8	35
			95% CI
Positive rate	0.507 (36/71)		0.386 - 0.628
Prevalence rate	0.803 (57/71)		0.691 - 0.888
Sensitivity	0.526 (30/57)		0.390 - 0.660
Specificity	0.571 (8/14)		0.289 - 0.823
Positive predictive value	0.833 (30/36)		0.672 - 0.936
Negative predictive value	0.229 (8/35)		0.104 - 0.401
True diagnosis rate	0.535 (38/71)		0.413 - 0.655
CTE findings	Definite lesion n=41	Others n=30	Total n=71
Positive	25	14	39
Negative	16	16	32
			95% CI
Positive rate	0.549 (39/71)		0.427 - 0.668
Prevalence rate	0.577 (41/71)		0.454 - 0.694
Sensitivity	0.610 (25/41)		0.445 - 0.758
Specificity	0.533 (16/30)		0.343 - 0.717
Positive predictive value	0.641 (25/39)		0.472 - 0.788
Negative predictive value	0.500 (16/32)		0.319 - 0.681
True diagnosis rate	0.577 (41/71)		0.454 - 0.694

CTE: computed tomography enterography/enteroclysis, CI: confidential interval

significant difference was observed, but the combined use of CTE and CE significantly increased the sensitivity compared to that of CE alone. Fourth, when both CTE and CE were negative, rebleeding was not observed for 24 months. Fifth, no serious adverse events related to CTE were observed.

According to the meta-analysis reported by Wang et al., the diagnostic yield of CTE was 40% on average, but individual reports showed large differences, ranging from 13% to 83% (9, 19-28), likely because the rates of ulcer/erosion, vascular lesion, and tumor/polyp in the target cohort and the criteria for determining the source of bleeding were different in each report. Several studies comparing CTE with CE and

Table 6.   Sensitivity of CTE and CE for Definite Small Bowel Lesions (n=31).

CTE	CE		CTE+CE	CE	
	Positive	Negative		Positive	Negative
Positive	13	6	Positive	24	6
Negative	11	1	Negative	0	1
p=0.332 (McNemar's test)			p=0.041 (McNemar's test)		

CE: capsule endoscopy, CTE: computed tomography enterography/enteroclysis
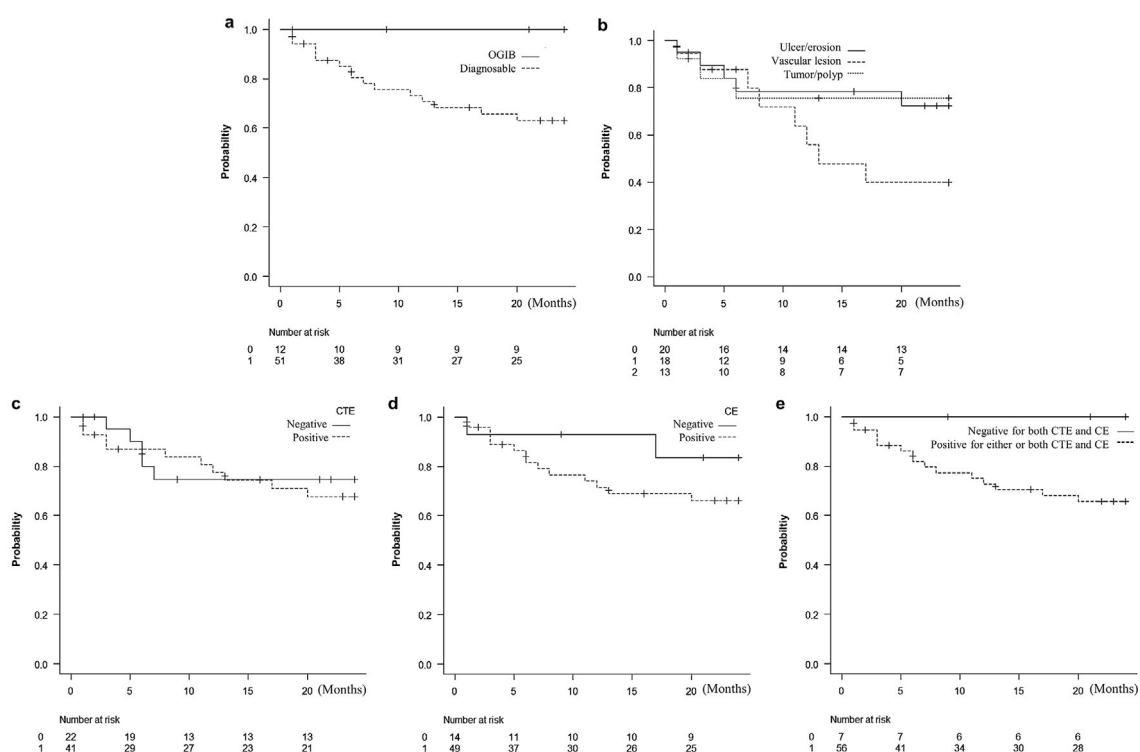
Figure 3.   Rebleeding-free interval after initial small bowel examination. (a) Diagnosable group, OGIB, (b) Lesion group (ulcer/erosion, vascular lesion, tumor/polyp), (c) CTE-positive, negative, (d) CE-positive, negative, (e) Positive for either or both CTE and CE, negative for both CTE and CE. CE: capsule endoscopy, CTE: computed tomography enterography/enteroclysis, OGIB: obscure gastrointestinal bleeding

DAE reported that the diagnostic yield of CTE was lower (21-23, 27), whereas in one report, the diagnostic yield of CTE exceeded that of CE; presumably, the improved diagnostic ability of CTE in this report was due to the large proportion of tumor/polyp lesions in the target cohort (26). In the present study as well, among the 11 patients diagnosed as having tumor/polyp lesions by CTE, tumor/polyp was confirmed in 9 (81.8%), indicating a high true-positive rate. In addition, there are several reports indicating that CTE with amidotrizoic acid results in greater detection of tumors and stenosis in the small bowel (11, 29). On the other hand, among the 22 cases with ulcer/erosion, 9 cases (40.9%) were detected by CTE, and 16 cases (72.7%) were detected by CE, indicating that CE has a higher detection rate for ulcer/erosion than CTE. From the above, in patients with suspected tumor/polyp lesions, not only CE but

also CTE should be performed. However, the most common finding of CTE in the present study was contrast enhancement of the intestinal wall, but the positive predictive value of this finding was 56.3%. We previously investigated CTE findings of drug-induced small bowel lesions and classified the contrast enhancement of the intestinal wall into three categories, and we are planning to apply this classification to small bowel intestinal bleeding in the future (30).

With regard to the criteria for determining the source of bleeding, when minute lesions, such as type 1a angioectasia, are included as the source of bleeding, the diagnostic yield will increase. However, it cannot be determined whether these lesions are actually involved in bleeding, thus making it difficult to accurately evaluate the diagnostic ability. As a result, we divided the diagnostic lesions into definitive and suspicious lesions. The sensitivity and specificity of CTE for

lesions suspected of causing small bowel bleeding were low, possibly due to the difficulty of detecting minute lesions on the mucosal surface with CTE. Although the sensitivity of CTE alone for definite lesions of small bowel bleeding was lower than CE, the combined use of CTE and CE increased the sensitivity to 96.8%. The significantly increased sensitivity, compared with 77.4% for CE alone, clearly showed the usefulness of combining CTE with CE.

Because no rebleeding was observed at 24 months in any of the patients classified as having OGIB and there was a significant difference compared with the diagnosable group (patients with definite and suspicious lesions), the setting of the reference standard is considered valid. Although the patients with a vascular lesion tended to have a higher rebleeding rate, specific treatment was performed in 2/22 cases (9.1%) of ulcer/erosion, 9/21 cases (42.9%) of vascular lesions, and 10/14 cases (71.4%) of tumor/polyp. The low specific treatment rate for ulcer/erosion was a result of the definition that patients with withdrawal from NSAIDs and antiplatelet drugs were not included in the specific treatment. There were many cases of vascular lesions that were not sufficiently treated. Regarding the relationship between the CTE findings and the rebleeding-free rate, there were no significant differences in CTE diagnostic results, with Shin et al. (17) reporting similar results. In CE, rebleeding was less frequent in the negative group, but the difference was not significant. Previous reports have shown rebleeding rates of 5.6-11% even after negative CE findings (31, 32), and Shinozaki et al. showed that vascular lesions rebled after a short time (14). In the present study, no rebleeding was observed when both CTE and CE were negative, suggesting that the combined use of CTE and CE can detect most lesions that cause rebleeding.

Low invasiveness is also an important factor for screening modalities. The incidence rate of CTE-related adverse events was 4.2%, and no serious events, such as intestinal obstruction and intestinal perforation, were observed. CE is also a test with low invasiveness, and the combined use of CTE and CE can be useful in this respect.

According to the guidelines of each academic society, CE is consistently listed as an important screening method for suspected small bowel bleeding, but CTE is positioned differently in each guideline, indicating that the evidence for the usefulness of CTE for suspected small bowel bleeding is still considered to be insufficient (7, 8, 12). The ESGE guideline states only that CTE may be considered when CE is negative and rebleeding is observed (12). The ACG guideline states that CTE should be considered prior to CE when there is a possibility of gastrointestinal stenosis (8), and the ASGE guideline states that CTE should be considered prior to CE in cases of suspected stenosis or surgically altered anatomy of the gastrointestinal tract (7). Certainly, in cases of massive bleeding or unstable blood pressure, CT angiography or angiography should be considered (7, 8). In contrast, in the Japanese Gastroenterological Endoscopy Society guideline, CT is the first-line method (13), as Japan has the

highest number of CT scanners in the world and CT use is very common and can be implemented quickly (33). However, until now, there have been no reports of real-world data on suspected small bowel bleeding using CTE in Japan, and therefore the data from the present study are important.

This study is associated with some limitations. First, this was a single-center, retrospective study, and the number of cases was small; thus, the implementation of a prospective multicenter study in the future is desirable. Second, this study targeted patients who underwent both CTE and CE, but there may have been some selection bias because CTE is not performed in many patients with kidney dysfunction, and CTA is often performed for overt ongoing bleeding. Third, as this study includes both CT enteroclysis and CT enterography, it may include the effects of these two different diagnostic abilities. In the future, it will be necessary to carry out research that unifies the methods. Fourth, the study period was long, and the performance of CE and CT scanners may have improved during that time. Regarding CE, of the 31 cases with definitive small bowel lesions, the SB1 was used in 8 cases, the SB2 in 21 cases, and the SB3 in 2 cases. The sensitivity was 7/8 (87.5%) with SB1 and 17/23 (73.9%) with SB2/3, and no clear difference in diagnostic ability was observed. However, it is highly possible that diagnostic ability will differ depending on the performance of the CT equipment and endoscopes; thus, the construction of a database involving multiple institutions would be desirable so that many cases can be investigated within a short period of time.

In conclusion, this study showed that the combined use of CTE and CE increased the diagnostic rate for suspected small bowel bleeding and might improve long-term prognosis. Furthermore, this study provides the first real-world data from Japan regarding the diagnostic ability of CTE for suspected small bowel bleeding. To our knowledge, only one report included more than 60 cases among the studies of patients undergoing both CTE and CE for suspected small bowel bleeding (21-26, 28). In addition, there are two reports on the long-term prognosis after CTE, but in one of them, CE was performed in combination with CTE in only 15% of the target cases (17, 26). Therefore, the present study is also considered to be valuable from these aspects.

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

References

1. Raju GS, Gerson L, Das A, Lewis B. American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. Gastroenterology **133**: 1697-1717, 2007.
2. Longstreth GF. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol **92**: 419-424, 1997.
3. Katz LB. The role of surgery in occult gastrointestinal bleeding. Semin Gastrointest Dis **10**: 78-81, 1999.
4. Thompson JN, Salem RR, Hemingway AP, et al. Specialist investigation of obscure gastrointestinal bleeding. Gut **28**: 47-51, 1987.

5. Yamamoto H, Sekine Y, Sato Y, et al. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc **53**: 216-220, 2001.

6. Iddan G, Meron G, Glukhovsky A, Swain P. Wireless capsule endoscopy. Nature **405**: 417, 2000.

7. Gurudu SR, Bruining DH, et al.; ASGE Standards of Practice Committee. The role of endoscopy in the management of suspected small-bowel bleeding. Gastrointest Endosc **85**: 22-31, 2017.

8. Gerson LB, Fidler JL, Cave DR, Leighton JA. ACG Clinical Guideline: diagnosis and management of small bowel bleeding. Am J Gastroenterol **110**: 1265-1287; quiz 1288, 2015.

9. Ettorre GC, Francioso G, Garribba AP, Fracella MR, Greco A, Farchi G. Helical CT angiography in gastrointestinal bleeding of obscure origin. AJR Am J Roentgenol **168**: 727-731, 1997.

10. Filippone A, Cianci R, Milano A, Valeriano S, Di Mizio V, Storto ML. Obscure gastrointestinal bleeding and small bowel pathology: comparison between wireless capsule endoscopy and multidetector-row CT enteroclysis. Abdom Imaging **33**: 398-406, 2008.

11. Maglinte DD, Sandrasegaran K, Lappas JC, Chiorean M. CT enteroclysis. Radiology **245**: 661-671, 2007.

12. Pennazio M, Spada C, Eliakim R, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy **47**: 352-376, 2015.

13. Yamamoto H, Ogata H, Matsumoto T, et al. Clinical practice guideline for enteroscopy. Dig Endosc **29**: 519-546, 2017.

14. Shinozaki S, Yamamoto H, Yano T, et al. Long-term outcome of patients with obscure gastrointestinal bleeding investigated by double-balloon endoscopy. Clin Gastroenterol Hepatol **8**: 151-158, 2010.

15. Niikura R, Yamada A, Nagata N, et al. New predictive model of rebleeding during follow-up of patents with obscure gastrointestinal bleeding: a multicenter cohort study. J Gastroenterol Hepatol **31**: 752-760, 2016.

16. Yano T, Yamamoto H, Sunada K, et al. Endoscopic classification of vascular lesions of the small intestine (with videos). Gastrointest Endosc **67**: 169-172, 2008.

17. Shin JK, Cheon JH, Lim JS, et al. Long-term outcomes of obscure gastrointestinal bleeding after CT enterography: does negative CT enterography predict lower long-term rebleeding rate? J Gastroenterol Hepatol **26**: 901-907, 2011.

18. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant **48**: 452-458, 2013.

19. Wang Z, Chen JQ, Liu JL, Qin XG, Huang Y. CT enterography in obscure gastrointestinal bleeding: a systematic review and meta-analysis. J Med Imaging Radiat Oncol **57**: 263-273, 2013.

20. Miller FH, Hwang CM. An initial experience: using helical CT imaging to detect obscure gastrointestinal bleeding. Clin Imaging **28**: 245-251, 2004.

21. Rajesh A, Sandrasegaran K, Jennings SG, et al. Comparison of capsule endoscopy with enteroclysis in the investigation of small bowel disease. Abdom Imaging **34**: 459-466, 2009.

22. Zhang BL, Jiang LL, Chen CX, Zhong BS, Li YM. Diagnosis of obscure gastrointestinal hemorrhage with capsule endoscopy in combination with multiple-detector computed tomography. J Gastroenterol Hepatol **25**: 75-79, 2010.

23. Voderholzer WA, Ortner M, Rogalla P, Beinhölzl J, Lochs H. Diagnostic yield of wireless capsule enteroscopy in comparison with computed tomography enteroclysis. Endoscopy **35**: 1009-1014, 2003.

24. Khalife S, Soyer P, Alatawi A, et al. Obscure gastrointestinal bleeding: preliminary comparison of 64-section CT enteroclysis with video capsule endoscopy. Eur Radiol **21**: 79-86, 2011.

25. Hara AK, Walker FB, Silva AC, Leighton JA. Preliminary estimate of triphasic CT enterography performance in hemodynamically stable patients with suspected gastrointestinal bleeding. AJR Am J Roentgenol **193**: 1252-1260, 2009.

26. Huprich JE, Fletcher JG, Fidler JL, et al. Prospective blinded comparison of wireless capsule endoscopy and multiphase CT enterography in obscure gastrointestinal bleeding. Radiology **260**: 744-751, 2011.

27. Yen HH, Chen YY, Yang CW, Liu CK, Soon MS. Clinical impact of multidetector computed tomography before double-balloon enteroscopy for obscure gastrointestinal bleeding. World J Gastroenterol **18**: 692-697, 2012.

28. Saperas E, Dot J, Videla S, et al. Capsule endoscopy versus computed tomography or standard angiography for the diagnosis of obscure gastrointestinal bleeding. Am J Gastroenterol **102**: 731-737, 2007.

29. Barlow JM, Goss BC, Hansel SL, et al. CT enterography: technical and interpretive pitfalls. Abdom Imaging **40**: 1081-1096, 2015.

30. Kishi T, Shimizu K, Hashimoto S, et al. CT enteroclysis/enterography findings in drug-induced small-bowel damage. Br J Radiol **87**: 20140367, 2014.

31. Macdonald J, Porter V, McNamara D. Negative capsule endoscopy in patients with obscure GI bleeding predicts low rebleeding rates. Gastrointest Endosc **68**: 1122-1127, 2008.

32. Lai LH, Wong GL, Chow DK, Lau JY, Sung JJ, Leung WK. Long-term follow-up of patients with obscure gastrointestinal bleeding after negative capsule endoscopy. Am J Gastroenterol **101**: 1224-1228, 2006.

33. Ohmiya N. Management of obscure gastrointestinal bleeding: comparison of guidelines between Japan and other countries. Dig Endosc **32**: 204-218, 2020.