Enteroscopic and radiologic diagnoses, treatment, and prognoses of small-bowel tumors

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Background: Small-bowel tumors (SBTs) represent a diagnostic challenge.

Objective: To evaluate the usefulness of contrast-enhanced CT (CECT), fluoroscopic enteroclysis (FE), videocapsule endoscopy (VCE), and double-balloon endoscopy (DBE) and the outcome after treatment.

Design: Single-center, retrospective study.

Setting: Tertiary-care referral hospital.

Patients: Between June 2003 and May 2011, 159 consecutive patients with SBTs (93 malignant and 66 benign) were enrolled.

Main Outcome Measurements: Comparison of diagnostic yields among CECT, FE, VCE, and DBE and the prognosis.

Results: CECT and FE had significantly lower diagnostic yields of SBTs ≤10 mm, but VCE and DBE had high yields of SBTs regardless of size. CECT had a significantly lower diagnostic yield of epithelial tumors compared with subepithelial tumors. When stratified by the site, the diagnostic yield of VCE for SBTs located only in the distal duodenum/the proximal jejunum (73%) was significantly lower than that for SBTs located in other areas (90%). Comparisons among the 4 methods revealed that VCE and DBE had significantly higher diagnostic yields than CECT, and DBE had significantly higher diagnostic yields than VCE, but a combination of CECT and VCE had a diagnostic yield similar to that of DBE. The histologic diagnostic yield of SBTs by DBE was 92%, and 25% of SBTs were enteroscopically treated. Metastatic tumors had the poorest overall survival, followed by adenocarcinomas and malignant lymphomas.

Limitations: Retrospective comparative study.

Conclusion: For the detection of SBTs, a combination screening method by using VCE and CECT is recommended. DBE is useful for histologic diagnosis and endoscopic treatment. (Gastrointest Endosc 2012;76:344-54.)

Small-bowel tumors (SBTs) are uncommon, insidious in presentation, and frequently represent a diagnostic challenge. The rarity of SBTs generally delays their recognition and treatment, which may lead to difficulty in clinical management. Malignant tumors arising from the small bowel have a poorer prognosis compared with tumors from other parts of the GI tract.[1]

Until recently, the small bowel was the only part of the alimentary tract not completely accessible by endoscopy. Only indirect evaluation was possible by using small-

Abbreviations: CECT, contrast-enhanced CT; DBE, double-balloon endoscopy or enteroscopy; FE, fluoroscopic enteroclysis; SBT, small-bowel tumor; VCE, videocapsule endoscopy.

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bowel follow-through barium examination or enteroclysis, but patient discomfort, the high radiation dose, and labor intensiveness limit these barium studies.[2] CT often is used as a front-line tool in the evaluation of abdominal symptoms. CT, CT enterography, and CT enteroclysis can identify masses, but these methods occasionally lack the sensitivity to diagnose small tumors and have a limited capacity to differentiate between tumor types.[3] The advent of videocapsule endoscopy (VCE)[4] and double-balloon endoscopy (DBE)[5] is a significant breakthrough for the visual diagnosis of diseases located deep in the small bowel. VCE allows painless endoscopic imaging of the whole small bowel, but it is contraindicated for patients with suspected or documented intestinal obstruction.[6] DBE is more labor intensive, but it enables tissue sampling and interventional therapies throughout the small bowel.[7] A multicenter European study indicated that VCE identified 124 SBTs (2.4%) in 5129 patients undergoing VCE, and 80.6% of the tumors were identified solely based on the VCE findings.[8] A Japanese multicenter study reported that DBE identified 144 SBTs (13.9%) in 1035 patients undergoing DBE.[9] To our knowledge, no comparisons of DBE with other modalities for the detection of SBTs have been performed in a large cohort. In our previous study of Peutz-Jeghers syndrome, fluoroscopic enteroclysis (FE) identified fewer small-intestine polyps than did DBE, whereas VCE had detection rates similar to those of DBE regardless of the polyp size.[10] In this study, we compared the diagnostic yields of SBTs among CT, FE, VCE, and DBE, stratified by size or tumor types, by using a larger cohort of patients than had been described in previous reports. We further assessed the outcomes after surgical, enteroscopic, and medical treatment.

Take-home Message

- The diagnostic yield of the combination examination by both contrast-enhanced CT and videocapsule endoscopy is high, similar to that of double-balloon endoscopy.
- The histologic diagnostic yield of small-bowel tumors by double-balloon enteroscopy is more than 90%, and 25% of small-bowel tumors are enteroscopically treated.

PATIENTS AND METHODS

Patients

Of the 806 patients who were admitted to Nagoya University Hospital to undergo DBE between June 2003 and May 2011, 159 consecutive patients (20%) with SBTs were enrolled. SBTs were designated as tumors or polyps between the third portion of the duodenum and the distal ileum. Regarding patients with lymphangioma, only patients with symptomatic lymphangioma were enrolled. The indications for DBE in patients without symptoms consist of follow-up, check-up, and others. Follow-up examinations were performed in patients who were already diagnosed as having GI diseases, such as familial adenomatous polyposis and Peutz-Jeghers syndrome. Surveillance protocols of familial adenomatous polyposis and Peutz-Jeghers syndrome included annual EGD and enteroclysis once every 2 to 4 years, respectively, before using VCE and DBE. Check-ups indicated SBTs that were encountered at health check-up examinations in asymptomatic participants, such as follicular lymphoma diagnosed at EGD for screening of gastric carcinoma. Others indicated SBTs that were encountered at examinations for evaluating symptoms irrelevant to SBTs. The enrolled patients had not undergone prior DBE. These 159 patients underwent a total of 218 DBE examinations; for diagnosis, 129 patients underwent the examination via the oral route, and 89 patients underwent the examination via the anal route. Of these 159 patients, 121 underwent 121 contrast-enhanced CT (CECT) examinations, 80 patients underwent 80 FE examinations, and 101 patients without obstructive symptoms underwent 101 VCE examinations before (n = 91) or after (n = 10) DBE. VCE was performed after DBE when SBTs were inaccessible at DBE or needed to be followed up after treatment. All patients underwent CECT in our hospital. Almost all patients underwent FE and VCE in our hospital, but some were done in other hospitals. The median intervals (range) between CECT and DBE, FE and DBE, and VCE and DBE were 6 days (0-1097 days), 12.5 days (0-408 days), and 5 days (0-1379 days), respectively. The median follow-up after the first DBE was 22.5 months (range 0-90 months). This study was reviewed and approved by the Institutional Review Board of Nagoya University School of Medicine. Informed consent was obtained from all patients.

CT

CT was performed with a multidetector row helical CT scanner (Aquilion; Toshiba Medical Systems Co, Ltd, Tokyo, Japan) equipped with a gantry rotation time of 0.5 seconds. During scanning, each patient received 100 mL of nonionic intravenous contrast medium containing 370 mg I/mL (iopamidol; Iopamiron, Nihon Schering, Co, Ltd, Osaka, Japan) for patients with body weights of 60 kg or more or 350 mg I/mL (iohexol; Omnipaque 350, Daiichi Pharmaceutical Co, Ltd, Tokyo, Japan) for patients with body weights less than 60 kg, by using an automated power injector at a rate of 1.5 mL/second. The entire abdomen of each patient was scanned in a craniocaudal direction. Coronal reconstructions at 2 mm also were obtained.

DBE, FE, and VCE

DBE,[11] FE,[12] and VCE (PillCam SB and SB2; Given Imaging, Ltd, Yokneam, Israel or Endocapsule; Olympus Medical Systems Corp, Tokyo, Japan)[10,13] were performed as previously described. VCE was performed between

TABLE 1. Final diagnosis of small-bowel tumors or polyps

Final diagnosis	No.	%	Sex			Age at diagnosis
			Male	Female	M/F ratio	Mean ± SD (range)
Total	159		102	57	1.8	56 ± 18 (15-86)
Malignant tumors	93	58	62	31	2.0	60 ± 13 (15-84)
Malignant lymphoma*	47	30	28	19	1.5	60 ± 14 (15-80)
GI stromal tumor	15	9	6	9	0.7	59 ± 15 (35-81)
Metastasis or invasion of cancer†	15	9	14	1	14.0	64 ± 12 (43-84)
Adenocarcinoma‡	13	8	11	2	5.5	56 ± 12 (34-80)
Carcinoid tumor	3	2	3	0	n.d.	62 ± 1 (61-63)
Benign tumors or polyps	66	42	40	22	1.8	50 ± 21 (15-86)
Hamartoma§	28	18	18	10	1.8	45 ± 22 (15-82)
Adenoma‖	14	9	7	7	1.0	40 ± 20 (19-76)
Aberrant pancreas	8	5	4	4	1.0	59 ± 18 (25-85)
Hemangioma	5	3	2	3	0.7	62 ± 20 (43-86)
Lipoma	4	3	3	1	3.0	61 ± 19 (37-73)
Lymphangioma¶	3	2	2	1	2.0	66, 71, 82
Inflammatory fibroid polyp	2	1	2	0	n.d.	48, 62
Leiomyoma	2	1	2	0	n.d.	64, 69

M, Male; *F,* female; *SD,* standard deviation; *n.d.,* not determined.
*Follicular lymphoma (n = 28), diffuse large B-cell lymphoma (n = 11), mucosa-associated lymphoid tissue lymphoma (n = 5), mantle cell lymphoma (n = 1), unknown (n = 3).
†Metastasis from lung cancer (adenocarcinoma, n = 4; squamous cell carcinoma, n = 1; small cell cancer, n = 1), gastric adenocarcinoma (n = 2), pancreatic carcinoma (n = 2), colonic adenocarcinoma (n = 1), renal cell carcinoma (n = 1), pelvic adenocarcinoma (n = 1), malignant melanoma (n = 1), invasion from cholangiocarcinoma (n = 1).
‡Familial adenomatous polyposis (n = 2), Peutz-Jeghers syndrome (n = 1), Crohn's disease (n = 1), included.
§Peutz-Jeghers syndrome (n = 17), included. Adenomatous components of hamartomatous polyps were included here.
‖Familial adenomatous polyposis (n = 9) and Gardner syndrome (n = 2), included.
¶Symptomatic lymphangiomas only.

June 2004 and February 2011 on patients who had not undergone bowel preparation. Bioptic, polypectomy, or EMR specimens at DBE were reviewed histologically.

Measurement and estimation of tumor size

The tumor size at FE was computed by dividing the length by 1.1 (the x-ray enlargement factor) or was measured with an installed scale by using digital radiography. The tumor size at CECT was measured with an installed scale. At VCE, the tumor size was estimated as previously described.[10] At DBE, the tumor size was estimated according to the width of the biopsy forceps or the diameter of the polypectomy snare or was measured on the scale after retrieval. When the tumor was surgically resected, tumor size was measured on the scale before formalin fixation. When the SBTs were resected surgically or at DBE, we adopted the actual sizes of the retrieved SBTs instead of the estimated sizes from the small-bowel imaging studies.

Interpretation of findings

The final diagnoses and localization of the SBTs were determined by using a combination of CECT, FE, VCE, and DBE including biopsy, polypectomy, surgery, or EMR, and the diagnostic yields were calculated. The findings that detected SBTs were considered diagnostically positive, even if only a part of the SBTs was observed. These findings did not include the mere presence of blood, extraluminal compression, or the dilated lumen on the proximal side. The CECT findings were evaluated by two independent blinded radiologists. The FE findings were prospectively evaluated by a single blinded gastroenterologist with more than 8 years of experience before performing the VCE and DBE examinations. VCE findings were prospectively evaluated by two blinded endoscopists, each with more than 8 years of experience in conventional endoscopy before performing the DBE examinations. These two endoscopists sometimes perform DBE

TABLE 2. Indications

Final diagnosis	No.	OGIB	%	SBO	%	Pain	%	Mass	%	No symptoms			%
										Follow-up	Check-up	Others	
Total	159	50	31	18	11	21	13	1	1	12	19	38	43
Malignant tumors	93	33	35	15	16	13	14	1	1	2	16	13	33
Malignant lymphoma	47	8	17	5	11	8	17	0	0	1	16	9	55
GI stromal tumor	15	12	80	1	7	1	7	0	0	0	0	1	7
Metastasis or invasion of cancer	15	5	33	5	33	2	13	1	7	0	0	2	13
Adenocarcinoma	13	6	46	3	23	2	15	0	0	1	0	1	15
Carcinoid tumor	3	2	67	1	33	0	0	0	0	0	0	0	0
Benign tumors or polyps	66	17	26	3	5	8	12	0	0	10	3	25	58
Hamartoma	28	5	18	3	11	7	25	0	0	8	0	5	46
Adenoma	14	0	0	0	0	0	0	0	0	2	1	11	100
Aberrant pancreas	8	1	13	0	0	0	0	0	0	0	1	6	88
Hemangioma	5	3	60	0	0	0	0	0	0	0	0	2	40
Lipoma	4	3	75	0	0	0	0	0	0	0	0	1	25
Lymphangioma	3	2	67	0	0	1	33	0	0	0	0	0	0
Inflammatory fibroid polyp	2	1	50	0	0	0	0	0	0	0	1	0	50
Leiomyoma	2	2	100	0	0	0	0	0	0	0	0	0	0

OGIB, Obscure GI bleeding; *SBO,* small-bowel obstruction.

after reading VCE. The number of positive findings obtained with each technique was tabulated to calculate the diagnostic yield.

Statistical analysis

The numbers in the text were expressed as the means (± standard deviation), and comparisons were analyzed by using the Mann-Whitney *U* test. The comparisons of the diagnostic yields of SBTs at CT, FE, VCE, and DBE (stratified by size or tumor type) were assessed by using χ^2 statistics. The proportions of patients with positive findings at two examinations were compared, and a significant difference between the tests was calculated by using the exact McNemar test. The comparisons of the diagnostic yields of VCE stratified by tumor site and the histologic and VCE diagnostic yields between epithelial and subepithelial SBTs were assessed by using the Fisher exact test. The cumulative overall survival curves after medical, enteroscopic, and surgical treatments were constructed by using the Kaplan-Meier method, and the differences were evaluated by using the log-rank test. Differences were considered significant when the *P* values were less than .05, except in comparisons of the diagnostic yields among the 4 different examination methods, in which *P* values less than .0083 were considered significant.

RESULTS

Clinicopathologic characteristics of small-bowel tumors

The clinical characteristics of patients with SBTs are presented in Tables 1 through 4. The incidence of SBTs was higher in men than in women, except for GI stromal tumors and hemangioma ($P = .0160$). The age at diagnosis for benign SBTs was lower than the age at diagnosis for malignant SBTs ($P = .0046$). Malignant SBTs were more significantly symptomatic compared with benign SBTs ($P = .0024$), but 34% of the malignant SBTs and 57% of the benign SBTs were asymptomatic. Small-bowel obstruction was more common with malignant SBTs compared with benign SBTs ($P = .0241$). The incidence of obscure GI bleeding was not significantly different between malignant and benign SBTs ($P = .1720$). The lowest hemoglobin level was observed in GI stromal tumors, followed by metastasis or invasion of cancer and hemangioma. The diagnostic delay that means median intervals between the onset of symptoms and the time of diagnosis is presented in Table 5. In patients with metastasis or invasion of cancer, the median intervals between the times of diagnoses of primary tumors and the secondary small-bowel

TABLE 3. Hemoglobin level and blood transfusion

Final diagnosis	No.	Hb level, g/dL Mean ± SD (range)	Blood transfusions: RBC used None	1-5	6-10	>10
Total	159	10.8 ± 3.1 (4.0-16.4)	134	9	7	10
Malignant tumors	93	10.4 ± 3.2 (4.0-16.4)	72	5	7	9
Malignant lymphoma	47	11.8 ± 2.6 (4.2-16.4)	45	1	0	1
GI stromal tumor	15	7.7 ± 2.2 (4.4-13.4)	5	4	4	2
Metastasis or invasion of cancer	15	9.2 ± 3.4 (4.4-14.9)	9	0	2	4
Adenocarcinoma	13	10.3 ± 2.9 (4.0-13.9)	11	0	1	1
Carcinoid tumor	3	4.7, 7.2, 15.2	2	0	0	1
Benign tumors or polyps	66	11.5 ± 2.8 (5.6-16.3)	61	4	0	1
Hamartoma	28	12.2 ± 2.5 (7.4-15.9)	28	0	0	0
Adenoma	14	11.2 ± 2.5 (7.0-16.3)	14	0	0	0
Aberrant pancreas	8	11.4 ± 3.3 (7.8-15.1)	7	1	0	0
Hemangioma	5	9.5 ± 4.3 (5.8-14.1)	3	1	0	1
Lipoma	4	10.1 ± 2.6 (6.7-13.0)	3	1	0	0
Lymphangioma	3	5.6, 12.0, 13.5	2	1	0	0
Inflammatory fibroid polyp	2	9.2, 14.6	2	0	0	0
Leiomyoma	2	11.1, 11.4	2	0	0	0

Hb, Hemoglobin; *RBC,* red blood cells; *SD,* standard deviation.

lesions was 16 weeks (range −15 to 96 weeks; −15 means that the small-bowel lesion was diagnosed 15 weeks before the primary lung cancer was diagnosed). Although 71% (195/276 lesions) of the overall SBTs were located in the distal duodenum and/or jejunum, carcinoid tumors were located in the ileum ($P = .0070$). GI stromal tumors ($P = .0154$) and adenomas ($P = .0097$) were mainly located in the duodenum and/or jejunum.

Diagnostic yields of CECT, FE, VCE, and DBE

The recording time of VCE and the duration of DBE examinations were 483 ± 56 (282-825) minutes and 76.4 ± 37.8 (10-315) minutes, respectively. The success rates for total enteroscopy at VCE and DBE were 80 of 101 (79%) and 42 of 53 (79%) in attempted cases, respectively. The recording time of VCE examinations between successful cases (482 ± 62 minutes) and unsuccessful cases (487 ± 24 minutes) was not significantly different ($P = .3977$). The diagnostic yields of CECT, FE, VCE, and DBE for SBTs stratified by size and tumor types (epithelial or subepithelial origin) are shown in Table 6. The diagnostic yield of VCE performed after DBE was 100% (10/10). The SBTs detected at CT, FE, VCE, and DBE were 47 ± 30 mm (5-120 mm), 45 ± 29 mm (3-120 mm), 26 ± 25 mm (2-115 mm), and 30 ± 28 mm (2-120 mm) in size, respectively. CECT and FE had significantly lower diagnostic yields of tumors that were 10 mm or smaller in diameter ($P < .0001$), but VCE and DBE had high diagnostic yields regardless of tumor size. Regarding SBTs larger than 10 mm in diameter, CECT had a significantly lower diagnostic yield of epithelial tumors (58%) compared with subepithelial tumors (92%, $P = .0003$), whereas FE and DBE had high diagnostic yields regardless of tumor type. VCE had a slightly lower diagnostic yield of subepithelial tumors (78%) compared with epithelial tumors (91%) >10 mm in diameter, which was not significant ($P = .3020$). Comparisons among CECT, FE, VCE, and DBE examinations showed that diagnostic yields of VCE and DBE were significantly higher than those of CECT ($P = .00008$ and $.00000001$; odds ratio 6.75 and 14.00, respectively; Tables 7A and B), and the diagnostic yield of DBE was significantly higher than that of VCE ($P = .0004$; odds ratio 17.00; Table 7C). When stratified by tumor site, the diagnostic yield of VCE for SBTs located only in the distal duodenum and/or the proximal jejunum (37/51; 73%) was significantly lower than that for SBTs located in the other areas of the small bowel (45/50; 90%; $P = .0400$). Of the SBTs that were overlooked by VCE, 14 (74%) were localized only in the duodenum or the proximal jejunum. The diagnostic yield of FE was not significantly different from those of the other tested examination methods. The diagnostic yield of a

TABLE 4. Location of small-bowel tumors or polyps

Final diagnosis	No. patients	No. tumors/ polyps	Duodenum	Jejunum			Ileum	
				Roux-en-Y limb	Proximal	Distal	Proximal	Distal
Total	159	276	53	2	106	34	44	37
Malignant tumors	93	153	28	1	56	20	26	22
Malignant lymphoma	47	96	22	—	33	10	16	15
GI stromal tumor	15	18	2	—	9	6	1	0
Metastasis or invasion of cancer	15	17	1	1	5	2	4	4
Adenocarcinoma	13	18	3	—	9	2	2	2
Carcinoid tumor	3	4	0	—	0	0	3	1
Benign tumors or polyps	66	123	25	1	50	14	18	15
Hamartoma	28	79	12	1	27	12	14	13
Adenoma	14	20	11	—	8	0	0	1
Aberrant pancreas	8	8	1	—	5	1	1	0
Hemangioma	5	5	0	—	2	1	2	0
Lipoma	4	4	0	—	4	0	0	0
Lymphangioma	3	3	1	—	2	0	0	0
Inflammatory fibroid polyp	2	2	0	—	1	0	0	1
Leiomyoma	2	2	0	—	1	0	1	0

—, not operated.

combination examination that used CECT and VCE (91%), which is considered to be a candidate screening method for SBTs, was not significantly different from that of DBE (99%; $P = .0771$; Table 7D). The histology of bioptic, polypectomy, or EMR specimens under DBE is shown in Table 8. Histologic diagnostic yields of epithelial and subepithelial SBTs were 98% and 90%, respectively ($P = .0982$).

Treatment and prognosis

The therapeutic interventions during or after DBE in 159 patients with SBTs are shown in Table 9. Of the 23 malignant lymphomas that were >30 mm in diameter, 11 (48%) were resected surgically because of small-bowel obstruction or bleeding and were followed with chemotherapy, and the other malignant lymphomas were treated with chemotherapy only. Twenty-four malignant lymphomas that were 30 mm or less in diameter were follicular lymphomas and were treated with chemotherapy or were followed watchfully without treatment. Of the 93 malignant SBTs, only 1 case with in situ adenocarcinoma was resected successfully at DBE. With respect to prognosis, metastatic tumors exhibited the poorest overall survival, followed by adenocarcinoma, malignant lymphoma, and GI stromal tumors ($P < .0001$; Fig. 1).

Complications

Of the 159 patients who underwent DBE, 2 had perforation episodes, and 1 developed acute pancreatitis, with complication rates of 1.3% and 0.6%, respectively. The perforation occurred at the contra-ampullary side of the second portion of the duodenum in a patient with hemophilia and a bleeding carcinoid tumor, which required an emergency surgical omental patch. The other perforation occurred after polypectomy of a 50-mm polyp with a 100-mm stalk invaginating from the terminal ileum to the ascending colon in a patient with Peutz-Jeghers syndrome, which required emergency surgical wedge resection. The complicating nonnecrotizing pancreatitis occurred in a patient with a medical history of multiple laparotomy due to invagination of Peutz-Jeghers polyps, and the patient recovered on conservative therapy within 2 weeks. Of the 101 patients without obstructive symptoms who underwent VCE, capsule retention occurred in 3 patients (3.0%). The capsules lodged at the location of the adenocarcinoma (n = 2) and the malignant lymphoma (n = 1) but were successfully removed by DBE in all of these patients. There were no complications associated with CECT or FE, such as dye reactions, acute renal failure, or aspiration pneumonia.

TABLE 5. Diagnostic delay (week)

Final diagnosis	No.	Median (range)
Total	80	18.5 (0-1162)
Malignant tumors	60	21 (1-940)
Malignant lymphoma	18	17.5 (2-419)
GI stromal tumor	14	76 (5-940)
Metastasis or invasion of cancer	14	6.5 (1-163)
Adenocarcinoma	11	39 (2-527)
Carcinoid tumor	3	12 (2-28)
Benign tumors or polyps	20	15.5 (0-1162)
Hamartoma	8	20 (0-108)
Aberrant pancreas	1	4
Hemangioma	3	8 (7-18)
Lipoma	3	23 (3-39)
Lymphangioma	2	586 (10-1162)
Inflammatory fibroid polyp	1	13
Leiomyoma	2	107.5 (2-213)

DISCUSSION

The diagnostics and therapeutics of SBTs have evolved since the advent of VCE and DBE.[8,9] In this study, which compared 4 diagnostic small-bowel techniques in patients with SBTs, DBE and VCE had higher diagnostic yields than CECT, presumably because CECT frequently failed to depict small SBTs and even large epithelial SBTs; DBE had higher diagnostic yields than VCE presumably because VCE sometimes failed to depict SBTs located in the proximal portion of the small bowel. To our knowledge, no comparisons of DBE with other modalities for the detection of SBTs have been performed in large cohorts of patients. A multicenter European study based on VCE reported that the diagnostic yields of small-bowel series/small-bowel enteroclysis, abdominal CT scanning, push enteroscopy, and DBE were 7 of 51 (14%), 10 of 21 (48%), 24 of 40 (48%), and 4 of 6 (67%), respectively, before and after VCE. This European study involved 69 patients with SBTs identified by VCE, although statistical analysis was not performed.[8] A meta-analysis of 24 VCE studies with 530 patients showed that the yield of VCE for the identification of small-bowel disease is significantly greater (ie, double the yield) than other methods, such as small-bowel follow-through, push enteroscopy, and colonoscopy with ileal intubation, but a VCE miss rate of 18.9% for SBTs (n = 106) was higher than the miss rate of 5.9% and 0.5% for vascular lesions and ulcers, respectively.[14] These two studies, which were based on VCE findings, were not fully compared to balloon-assisted or intraoperative enteroscopy; therefore, the miss rate of VCE might have been underestimated. In this study, a VCE miss rate of 18.8% for 101 SBTs was consistent with previous reports. Ross et al[15] reported that prior VCE identified mass lesions in only 5 of 15 patients (33%) with SBTs identified by a subsequent DBE. To our knowledge, this study is the first to statistically demonstrate that a high miss rate of VCE for SBTs is caused by the occasional inability to detect SBTs located in the duodenum and/or the proximal jejunum. This oversight may be caused by the shortcomings of the present version of VCE, including the impossibility of air insufflation and too-rapid passage of VCE through the duodenum and proximal jejunum at a rate of a single 0.5-second image.[16] Small-bowel transit time and a motility study using a magnet tracking system revealed that short bursts of very fast movements (>15 cm/minute) occurred for approximately 45 minutes after pyloric passage, probably reflecting phase III of the migrating motor complexes, and the contraction frequency gradually decreased during the first 2 hours after pyloric passage.[17] Differential luminal calibers and sharp turns at ligamentous insertions may cause the oversight. The diagnostic yield of VCE would be higher if a faster adaptable frame rate system and a wider angle of view, such as what is installed in a second-generation colon capsule endoscopy, were introduced. However, for the time being, the detection of SBTs by VCE alone remains a challenge. Therefore, this study also proposed a combination SBT screening method by using VCE and CECT, which resulted in a diagnostic yield as high as the diagnostic yield of DBE. Because CECT had lower detection rates of small (<10 mm) SBTs and large epithelial SBTs, CT enterography or CT enteroclysis would definitely be recommended if possible.[18,19] This study has some inherent bias in that its database used direct referrals for DBE. Some patients with CT-diagnosed or VCE-diagnosed tumors would not have been referred to our hospital for DBE; therefore, this study might overrepresent nondiagnostic CT/FE/VCE studies.

Although small-bowel obstruction was more commonly associated with malignant SBTs than benign SBTs, there were no characteristic symptoms of SBTs. Carcinoid syndrome, including diarrhea and flushing in the face and upper trunk lasting seconds to minutes, affected up to 10% of patients with carcinoid tumors, but in the Japanese population, small-bowel carcinoid tumors are rare compared with the number in the white population.[1,9] In this study, the 3 patients with carcinoid tumors did not have carcinoid syndrome complications. Disclosure of medical history, including previous tumor development in other organs; familial polyposis syndrome, such as familial adenomatous polyposis and Peutz-Jeghers syndrome; von Recklinghausen disease; and inflammatory bowel diseases such as Crohn's disease are essential to the interview process because these histories can suggest the presence

TABLE 6. Diagnostic yields of tumors or polyps (%)

Size	Origin	CECT*	FE*	VCE†	DBE‡
≤10 mm	Epithelial	0/9 (0)	0/2 (0)	6/8 (75)	19/19 (100)
	Subepithelial	5/21 (24)	4/8 (50)	24/29 (83)	32/33 (97)
>10 mm	Epithelial	18/31 (58)§	29/30 (97)	29/32 (91)	41/42 (98)
	Subepithelial	55/60 (92)	38/40 (95)	25/32 (78)	60/64 (94)

CECT, Contrast-enhanced abdominal CT; *FE,* fluoroscopic enteroclysis; *VCE,* videocapsule endoscopy; *DBE,* double-balloon endoscopy or enteroscopy.
*$P < .0001$, tumors ≤10 mm compared with >10 mm.
†$P = .8784$, tumors ≤10 mm compared with >10 mm.
‡$P = .9214$, tumors ≤10 mm compared with >10 mm.
§$P = .0003$, epithelial tumors >10 mm compared with subepithelial tumors >10 mm.

TABLE 7A. Comparison of diagnostic yields of VCE and CECT*†

	VCE		
	Positive	Negative	Total
CECT			
Positive	36	4	40
Negative	27	7	34
Total	63	11	74

VCE, Videocapsule endoscopy; *CECT,* contrast-enhanced abdominal CT.
*$P = .00008$, odds ratio 6.75, exact McNemar test.
†The diagnostic yield of VCE (85%) was significantly higher than that of CECT (54%).

TABLE 7B. Comparison of diagnostic yields of DBE and CECT*†

	DBE		
	Positive	Negative	Total
CECT			
Positive	76	3	79
Negative	42	1	43
Total	118	4	122

DBE, Double-balloon endoscopy or enteroscopy; *CECT,* contrast-enhanced abdominal CT.
*$P = .00000001$, odds ratio 14.00, exact McNemar test.
†The diagnostic yield of DBE (97%) was significantly higher than that of CECT (65%).

TABLE 7C. Comparison of diagnostic yields of DBE and VCE*†

	DBE		
	Positive	Negative	Total
VCE			
Positive	81	1	82
Negative	17	2	19
Total	98	3	101

DBE, Double-balloon endoscopy or enteroscopy; *VCE,* videocapsule endoscopy.
*$P = .0004$, odds ratio 17.00, exact McNemar test.
†The diagnostic yield of DBE (97%) was significantly higher than that of VCE (81%).

TABLE 7D. Comparison of diagnostic yields of DBE and a combination test (CECT and VCE)*†

	DBE		
	Positive	Negative	Total
CECT + VCE			
Positive	66	1	67
Negative	7	0	7
Total	73	1	74

DBE, Double-balloon endoscopy or enteroscopy; *CECT,* contrast-enhanced abdominal CT; *VCE,* videocapsule endoscopy.
*$P = .0771$, odds ratio 7.00, exact McNemar test.
†The diagnostic yield of both CECT and VCE (91%) was not significantly different from that of DBE (99%).

of a metastatic tumor, adenocarcinoma, and GI stromal tumor in the small bowel.

After patients are suspected of harboring SBTs based on medical histories and imaging modalities, histologic confirmation will be required for determining the treatment. In this study, DBE enabled accurate histologic diagnosis in 92% of the 128 patients by using bioptic, polypectomy, and EMR specimens. The Japanese Study Group for DBE reported that DBE aided in histologic diagnosis in most cases with SBTs by 85 biopsies, except for GI stromal tumor cases. Of the 22 participants with GI stromal tumors who underwent a biopsy, only 9 participants (41%) were positively diagnosed by the biopsy specimens.[9] This study also demonstrated low histologic diagnostic yields in sub-

TABLE 8. Histology of bioptic, polypectomy, or EMR specimens at DBE

Final diagnosis	No.	Diagnostic yield	%
Total	128	118	92
Malignant tumors	77	73	95
Malignant lymphoma	47	47	100
GI stromal tumor	6	4	67
Metastasis or invasion of cancer	10	8	80
Adenocarcinoma	12	12	100
Carcinoid tumor	2	2	100
Benign tumors or polyps	51	45	88
Hamartoma	25	24	96
Adenoma	14	14	100
Aberrant pancreas	6	3	50
Hemangioma	1	1	100
Lipoma	1	1	100
Lymphangioma	1	1	100
Inflammatory fibroid polyp	1	0	0
Leiomyoma	2	1	50

DBE, Double-balloon enteroscopy.

epithelial tumors, such as GI stromal tumors (4/6; 67%), aberrant pancreas (3/6; 50%), and leiomyoma (1/2; 50%). Another critical point is that GI stromal tumor is prone to massive bleeding, seeing that we measured the lowest hemoglobin level in GI stromal tumors among SBTs. Even a biopsy from a GI stromal tumor central ulceration may provoke massive bleeding; therefore, we took only 1 biopsy specimen from patients with ulceration or avoided biopsies when the lesion was diagnosed as the obvious origin of bleeding and the indication for surgical resection. Biopsy specimens are especially useful in the histologic diagnosis of malignant lymphoma and metastasis because chemotherapy may be chosen without surgery. The other advantage of DBE is endoscopic treatment. Malignant SBTs were unfortunately and regrettably found in advanced stages of cancer; thus, they were not applicable to endoscopic resection, except for 1 case with jejunal intramucosal adenocarcinoma, which was coincidentally encountered in treating jejuna phlebectasia by endoscopic injection sclerotherapy.[20] Screening of the malignant SBTs in this early stage remains a challenge because these SBTs are asymptomatic and undetectable in a diagnostic combination that uses CECT and VCE. Benign SBTs, such as hamartoma, adenoma, and lipoma, are recommended in-

TABLE 9. Therapeutic intervention during or after DBE

Therapies and final diagnosis	No.
Surgical	58
GI stromal tumor	14
High risk	4
Medium risk	4
Low risk	6
Adenocarcinoma	12
Stage I	2
Stage IIA	4
Stage IIIA	2
Stage IIIB	2
Stage IV	2
Malignant lymphoma	11
Stage I	5
Stage II1	2
Stage IIE	2
Stage IV	1
Unknown	1
Metastasis or invasion	10
Carcinoid tumor	3
Stage IIA	2
Stage IIIA	1
Aberrant pancreas	3
Leiomyoma	1
Hemangioma	1
Invaginated hamartoma	1
Invaginated lipoma	1
Invaginated inflammatory fibroid polyp	1
Endoscopic	43
EMR or polypectomy	39
Hamartoma	24
Adenoma	4
Aberrant pancreas	3
Lipoma	2
Adenocarcinoma in situ	1
Inflammatory fibroid polyp	1

Continued on next page

TABLE 9. Continued

Therapies and final diagnosis	No.
Leiomyoma	1
Hemangioma	1
Malignant lymphoma*	1
Lymphangioma	1
Clipping	2
Hemangioma	2
Electrocoagulation	1
Bleeding from metastasis from lung cancer	1
Balloon dilatation	1
Postchemotherapy scar of metastasis from lung cancer	1
Medical	72
Chemotherapy	50
Monotherapy with rituximab	14
Malignant lymphoma (follicular lymphoma)	14
Stage I	13
Stage IV	1
Monotherapy with imatinib	3
GI stromal tumor	3
High risk	3
Monotherapy with UFT	1
Adenocarcinoma	1
Stage IIA	1
Combination therapy with R-CHOP, etc	23
Malignant lymphoma	23
Stage I	5
Stage II1	4
Stage II2	1
Stage IIE	3
Stage IV	10
Combination therapy with FOLFOX, FOLFIRI, cisplatin, gemcitabine, etc	9
Adenocarcinoma	5
Stage IIIA	1
Stage IIIB	2
Stage IV	1
Metastasis or invasion	4

DBE, Double-balloon enteroscopy; *UFT,* uracil and tegafur; *R-CHOP,* cyclophosphamide, doxorubicin, vincristine, and prednisone including rituximab; *FOLFOX,* oxaliplatin/5-fluorouracil/leucovorin; *FOLFIRI,* irinotecan/5-fluorouracil/leucovorin.
*Diagnostic EMR.

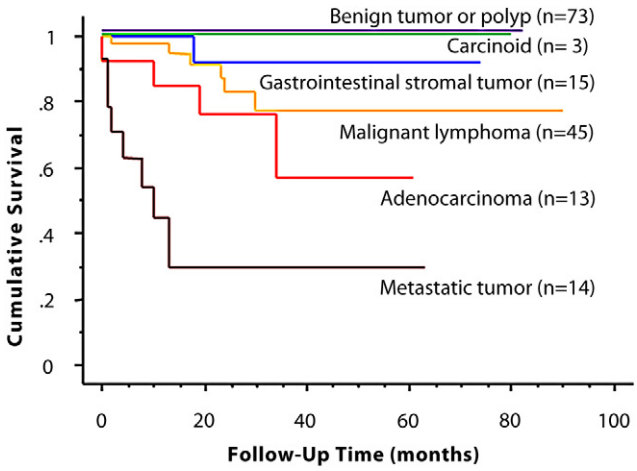

Figure 1. Kaplan-Meier survival curves of small-bowel tumors.

dications for enteroscopic treatment. Even if these SBTs are asymptomatic, enteroscopic treatment might preclude possible complications including intussusception, pain, bleeding, and malignant transformation.[11] In addition, preoperative enteroscopic tattooing also is useful for determining tumor localization, especially in laparoscopic surgery.

With respect to prognosis, metastatic tumors resulted in the poorest overall survival, followed by adenocarcinoma, malignant lymphoma, and GI stromal tumors. Cunningham et al demonstrated that in 73 patients with primary malignant SBTs identified from 1970 to 1991, the median survivals were 13 months for adenocarcinomas and malignant lymphomas, 18 months for sarcomas (which corresponds to the prognosis for GI stromal tumors at present), and 36 months for carcinoid tumors.[21] Although recent advances in chemotherapy may benefit the survival of patients with SBTs, especially malignant lymphoma, the biological malignancy of each SBT is consistent with the results presented in this study. However, our prognosis study has limitations, including small sample size, lack of stage stratification, and discordance of treatment.

In conclusion, VCE is noninvasive but is insufficient for the detection of all SBTs; therefore, a combination screening method that uses both VCE and CECT is recommended. DBE is relatively safe and useful for histologic diagnosis, endoscopic treatment, and preoperative tattooing.

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