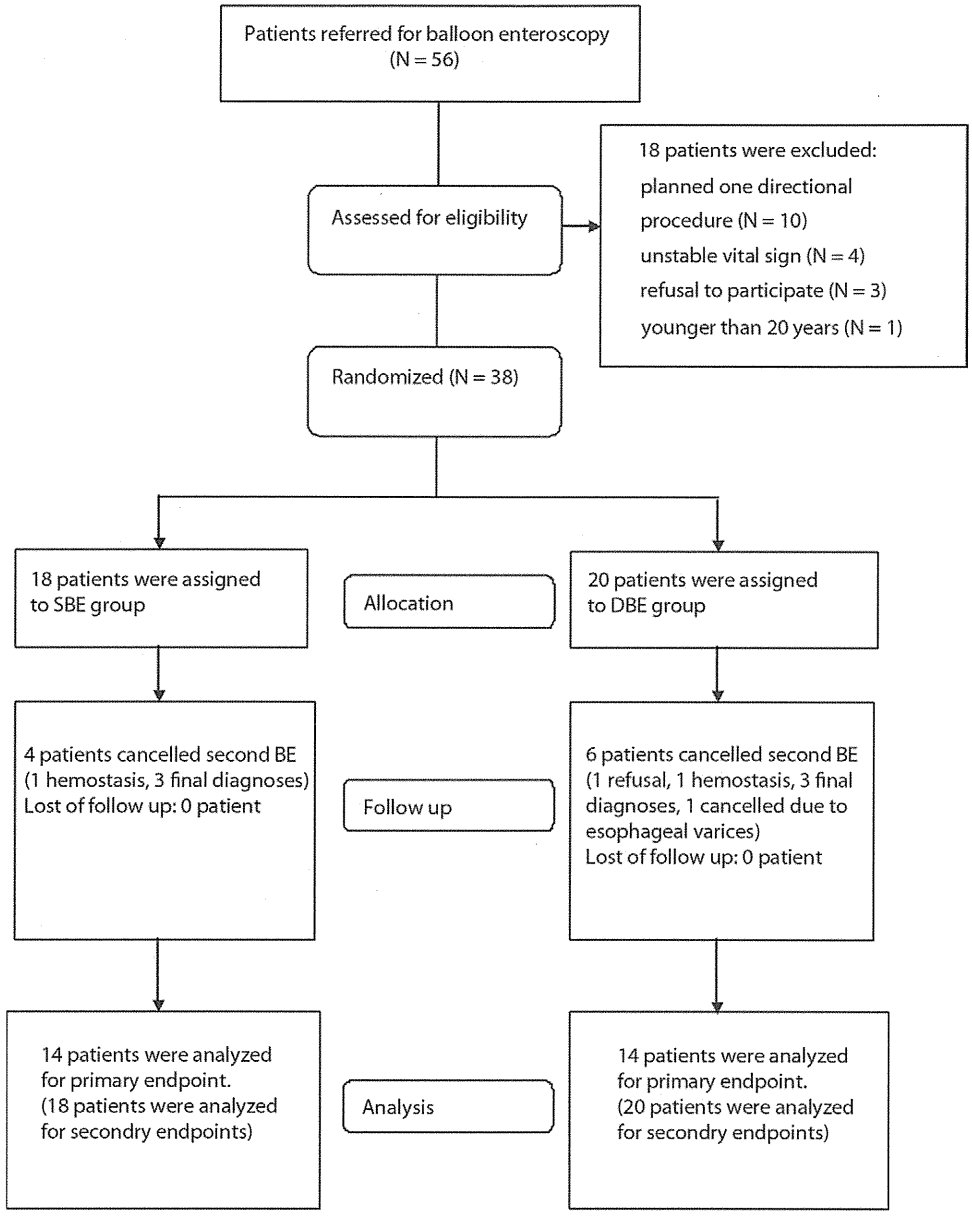

Figure 1. Study flow diagram.

Categorical data including total enteroscopy rate and diagnosis rate were compared using the Fisher exact test. Continuous variables were compared using the Student t test. Examination time, insertion time, and X-ray fluoroscopy time were compared with the Mann-Whitney U test.

Differences with $P < .05$ were considered statistically significant. All statistical analyses were performed by using JMP software (version 8.0 and 9.1; SAS Institute, Cary, NC).

RESULTS

Participant flow and baseline characteristics

This study started in April 2008 and was terminated in April 2010 because of an obvious disadvantage for the SBE group when interim analysis showed the statistically significant difference in the total enteroscopy rate between the SBE and DBE groups. Between the recruitment periods, a total of 56 patients were referred to our department for BE. Of them, 18 patients were excluded because of refusal to participate (n = 3) or meeting exclusion criteria (n = 15). Endoscopic findings of the 10 patients excluded because of planned 1-route BE were ileal ulcer in 2, malignant lymphoma in 2, lipoma, Crohn's disease, angioectasia, radiation enteritis, edematous jejunum in 1 each, and a suspected tumor in the afferent loop of Roux-Y reconstruction in the remaining patient. A total of 38 patients were enrolled in the study (Fig. 1). Eighteen patients were assigned to the SBE group and 20 patients to the DBE

TABLE 1. Baseline of characteristics of the study patients

	SBE group	DBE group	*P* value
No. of patients	18	20	
Male/female	13/5	15/5	.99†
Age, y*	64.9 ± 14.7	62.7 ± 16.1	.66‡
BMI, kg/m^2*	23.4 ± 3.2	23.3 ± 4.9	.95‡
History of abdominal surgery, no. (%)	8 (44)	8 (40)	.99†
Indications			
Obscure GI bleeding, no. (%)	10 (56)	13 (65)	.74†
Suspected small-intestine tumor, no. (%)	4 (22)	4 (20)	.99†
Suspected inflammatory bowel disease, no. (%)	4 (22)	3 (15)	.69†
Patients who underwent bidirectional BE, no. (%)	14 (78)	14 (70)	.72†
Patients underwent per-oral BE only, no. (%)	1 (6)	3 (15)	.61†
Patients underwent per-anal BE only, no. (%)	3 (17)	3 (15)	.99†

SBE, Single-balloon endoscopy; *DBE;* double-balloon endoscopy; *BMI,* body mass index; *BE,* balloon endoscopy.
*Mean ± standard deviation.
†Fisher exact test.
‡Student *t* test.

group. The second BE was canceled in 4 patients in the SBE group and 6 patients in DBE group because of interventions (hemostasis) in 2, final diagnoses in 6 (3 ileal ulcers, 1 malignant lymphoma, 1 intussusception, 1 jejunitis), patient refusal in 1, and the presence of esophageal varices in 1 patient. The diagnosis rate was not significantly different between the excluded patients who underwent 1-route BE and the included patients in whom the second BE was canceled ($P = .58$ by the Fisher exact test). In the SBE group, 14 patients underwent bidirectional BE (the second BE). In the DBE group, 14 patients underwent bidirectional BE. Finally, a total of 28 patients (14 SBE and 14 DBE) were analyzed for our primary study outcome measurements. For secondary outcome measurements, all randomized patients (N = 38) were analyzed.

Table 1 shows the baseline characteristics of the study patients. There was no significant difference between the SBE and DBE groups.

Total enteroscopy rate and endoscopic procedure results

Table 2 summarizes the total enteroscopy rate and endoscopic procedure results. The total enteroscopy rate was 0% in the SBE group and 57% in the DBE group ($P = .002$). Although SBE had a longer examination time and X-ray fluoroscopy time, none of the SBE group completed total enteroscopy (185.9 ± 34.9 minutes vs 160.7 ± 29.0 minutes for examination time, $P = .03$ and 14.5 ± 7.0 minutes vs 9.3 ± 5.0 minutes for fluoroscopy time, $P = .03$, respectively).

In terms of complications, 1 patient in the DBE group had Mallory-Weiss syndrome, and 1 patient in the SBE group had hyperamylasemia. Both patients recovered without surgery within 3 days.

Diagnostic and therapeutic yields of BE

The diagnostic yield for each study group is summarized in Table 3. There was no difference in overall diagnosis rate between the SBE and DBE groups (61.1% vs 50.0%, $P = .53$). The most prevalent finding was ulcerative lesions, followed by angiodysplasia. The order of the prevalence of small intestine diseases was also the same in the SBE and DBE groups.

The clinical outcomes of the study patients are shown in Table 4. Again, there was no difference in therapeutic outcome between SBE and DBE groups (27.8% vs 35.0%, $P = .73$).

DISCUSSION

The current study clearly shows that DBE had a higher total enteroscopy rate with a shorter procedure time than SBE. Our results seem reasonable because with DBE, it is easier to grip the small intestine at the tip of the endoscope than with SBE, which makes it possible for us to insert the endoscopy deeply without redundant loops. In terms of DBE, the total enteroscopy rate was ranged widely between 0% and 86%.[8-18] This is because of the difference in previous experience with BE and patient settings. The average total enteroscopy rate was calculated as 42.3%

TABLE 2. Total enteroscopy rate and endoscopic procedural outcomes of the bidirectional enteroscopic procedure

	SBE group	DBE group	*P* value
No. of patients	14	14	
Total enteroscopy achieved, no. (%)	0 (0)	8 (57)	.002†
Total examination time, min*	185.9 ± 34.9	160.7 ± 29.0	.03‡
Total X-ray fluoroscopic time, min*	14.5 ± 7.0	9.3 ± 5.0	.03‡
Per-anal procedure			
Examination time, min	93.1 ± 22.6	90.4 ± 13.7	.70
X-ray fluoroscopic time, min	7.7 ± 6.5	5.4 ± 3.6	.25
Per-oral procedure			
Examination time, min	92.8 ± 20.6	70.4 ± 26.5	.019
X-ray fluoroscopic time, min	6.8 ± 3.4	3.9 ± 2.1	.014

All variables are mean ± standard deviation.
SBE, Single-balloon endoscopy; *DBE,* double-balloon endoscopy.
*Sum of per-anal approach and per oral approach.
†Fisher exact test.
‡Mann-Whitney *U* test.

TABLE 3. Comparison of diagnostic yield between SBE and DBE

	SBE group	DBE group	*P* value*
No. of patients	18	20	
Angiodysplasia	3 (17)	3 (15)	.99
Ulcers or erosions	5 (28)	5 (25)	.99
Tumors or polyps	1 (6)	2 (10)	.99
Diverticulosis	1 (6)	0 (0)	.47
Normal findings	7 (39)	10 (50)	.53
Severe adhesion	1 (6)	0 (0)	.47

Values shown are number (%).
SBE, Single-balloon endoscopy; *DBE,* double-balloon endoscopy.
*Fisher exact test.

TABLE 4. Clinical outcome of the study patients

	SBE group	DBE group	*P* value*
No. of patients	18	20	
Endoscopic hemostasis	2 (11)	2 (10)	.99
Surgery	1 (6)	1 (5)	.99
Endoscopic polypectomy	0 (0)	1(5)	.99
Medication	2 (11)	3 (15)	.99
Observation	13 (72)	13 (65)	.73

Values shown are number (%).
SBE, Single-balloon endoscopy; *DBE,* double-balloon endoscopy.
*Fisher exact test.

(140/331), indicating that skill in performing DBE at our institution was better than average. On the other hand, we could not complete a total enteroscopy using SBE. So far, there are a few articles regarding total enteroscopy rate of SBE. Apart from the article by Ohtsuka et al,[4] the total enteroscopy rate with SBE was between 5% and 25%.[19-21] Aktas et al[20] reported that total enteroscopy was achieved in 3 in 61 patients (5%). Kawamura et al[22] reported that total enteroscopy was achieved in 1 of 8 patients (12.5%). Tsujikawa et al[21] and Ramchandani et al[19] reported that their total enteroscopy rate was 25%. However, their study patients were much younger than our patients. Ohtsuka et al[4] reported a very high total enteroscopy rate of 71%. However, there are several unclear factors in the report. They attempted a total enteroscopy in only 7 of 30 patients. There were no data on the diagnostic yield for their study patients. In addition, they used carbon dioxide gas for insufflation instead of air, which is the major difference from our study. One randomized, controlled trial showed that carbon dioxide improves intubation depth in DBE.[23] However, whether carbon dioxide is also useful for SBE is unclear. Finally, even if we added the study by Ohtsuka et al, the average total enteroscopy rate with SBE was calculated as 16.7% (20/120), which is lower than that with DBE.

Recently, a European multicenter trial found that that the total enteroscopy rate was higher with DBE than with SBE (66% vs 22%).[24] Although their total enteroscopy rate with SBE was higher than that in our study, the superiority of DBE over SBE regarding total enteroscopy was the same as that in our study. In their study, SBE was performed by

using a double-balloon system manufactured by Fujifilm Medical Co Ltd, which is different from the original SBE system manufactured by Olympus Medical Systems in terms of endoscope flexibility and balloon pressure.

In contrast to the total enteroscopy rate, we showed that the diagnostic yield and therapeutic yield were the same with SBE and DBE. Our study indicated that we can use either SBE or DBE for diagnosing small-bowel diseases. It seems contradictory to our primary outcome measurement, ie, the superiority of DBE for total enteroscopy. The reason for the complicated finding was the low prevalence of small-bowel diseases in patients who underwent bidirectional BE. In fact, only 47% of the patients undergoing bidirectional BE had small-bowel diseases, whereas 80% of the patients undergoing 1-route (oral or anal) BE had abnormal findings in the small intestine. Shishido et al[25] reported the same trend in patients with obscure GI bleeding. For our study, we designed a study protocol in which we canceled the second BE (opposite-direction approach from the first BE) when we found clinically significant lesions on the first BE, which is a comparable standard clinical decision. In addition, all study patients underwent CE and/or abdominal CT examination before BE so that we could determine the first insertion route that seemed nearer to suspected lesions. Among our study patients, 26% underwent only 1-route BE. Therefore, we think that more patients are needed to reach a statistically significant difference in the diagnostic rates between the SBE and DBE groups.

There were some limitations of this study. First, the number of study participants was relatively small. To minimize the disadvantage of one of the study groups (SBE group), we conducted an interim analysis, which was determined according to the method of Pocock. In the first interim analysis, we found an obvious difference in the total enteroscopy rate between the SBE and DBE groups, and therefore we terminated the study. Second, we have more experience with DBE than with SBE. When we started this study, we had performed 248 DBEs and 10 SBEs. As we develop more experience with performing SBE, the total enteroscopy rate by using SBE may increase. However, this study clearly indicates that endoscopists experienced in performing DBE should not switch to SBE to examine the small intestine.

In conclusion, total enteroscopy is easier to conduct with DBE than with SBE. We should use DBE in patients requiring total enteroscopy.

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An effective training system for endoscopic submucosal dissection of gastric neoplasm

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submitted 15. March 2011
accepted after revision
08. July 2011

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DOI http://dx.doi.org/10.1055/s-0031-1291383
Endoscopy 2011; 43: 1033–1038

ISSN 0013-726X

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Background and study aims: A standard training system for endoscopic submucosal dissection (ESD) remains to be established. In this study, we evaluated the validity of our training program for gastric ESD.

Patients and methods: Four trainees performed gastric ESD for a total of 117 lesions in 107 patients (27 to 30 consecutive lesions per trainee) at a tertiary referral center during 2 years in the training program. Trainees, who already had the fundamental skills and knowledge needed for ESD, each assisted at 40 gastric ESD procedures, then in 20 cases applied post-ESD coagulation (PEC) to gastric mucosal defects; they then began to perform ESD, starting with gastric antral lesions. Treatment outcomes, including mean procedure time, and rates of en bloc resection, en bloc plus R0 resections, complications, and self-completion, were evaluated, for the initial 15 and subsequent 12 to 15 cases.

Results: Overall rates of en bloc resection and en bloc plus R0 resection were as high as 100% and 96.6%, respectively. Regarding complications, seven cases of delayed hemorrhage (6.0%) and three cases of perforation (2.6%) occurred; all complications were solved endoscopically. The most frequent reason for operator change was lack of submucosal dissection skill. The self-completion rate was more than 80% even in the early period, and did not increase for later cases.

Conclusions: Our training system enabled novice operators to perform gastric ESD without a decline in clinical outcomes. Key features of this training are prior intensive learning and actual ESD during the learning period under expert supervision.

Introduction

Endoscopic submucosal dissection (ESD) is an excellent treatment for early gastric cancer (EGC) because large tumors or lesions with ulcer findings can be successfully resected in an en bloc fashion [1,2]. However, compared with conventional endoscopic mucosal resection (EMR), ESD is technically more difficult and can result in more complications [3]. Therefore establishment of an effective and feasible training system to develop ESD skills in endoscopists without increasing the likelihood of complications is warranted, although there are several reports claiming that even novice operators can perform safer ESD procedures under appropriate supervision [4–7]. The aim of the present study was to evaluate the validity of our training program for gastric ESD.

Patients and methods

The study protocol was approved by the institutional review board of the NTT Medical Center Tokyo (No. 10–663).

Patients

A total of 341 patients had 413 gastric neoplasms treated by ESD between July 2007 and July 2009 at the NTT Medical Center Tokyo, Japan; among these, 107 patients had 117 gastric neoplasms that were resected by the four novice ESD operators (trainees A, B, C, and D; **Table 1**). Medical records for the initial 27 or 30 consecutive ESDs for each novice operator were retrospectively reviewed (operator A performed only 27 ESDs at our hospital). Characteristics of the 117 lesions are shown in **Table 2**.

According to the Gastric Cancer Treatment Guidelines issued by the Japanese Gastric Cancer Association, guideline criteria for lesions suitable for

Table 1 Training in endoscopic submucosal dissection (ESD) of gastric neoplasm. Profiles of novice operators prior to ESD practice.

	Operator			
	A	B	C	D
Years after graduation	4	4	6	5
EGDs performed, n	1200	1700	2900	1100
Gastric EMRs performed, n	12	4	19	8
Total colonoscopies performed, n	400	250	1200	150

EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection.

ESD are intestinal-type mucosal EGC, smaller than 2 cm, and without ulcers or scars [9]. However, at our hospital, the indication for ESD included "lesions with expanded criteria" [8] as follows: intestinal-type mucosal EGC, larger than 2 cm, and without ulcers or scars; an intestinal-type mucosal EGC smaller than 3 cm, and with ulcers or scars; and diffuse-type mucosal EGC, smaller than 2 cm, and without ulcers or scars.

Our ESD training system

Before starting our ESD training program, trainees were required to have performed more than 1000 esophagogastroduodenoscopies (EGDs). In addition, knowledge of the complications of ESD and possession of necessary skills, including those for accurate gastric biopsy and precise diagnosis of the cancer outline, were also required.

After meeting these requirements, as confirmed by a single specialist (K.O., who had performed more than 700 gastric ESDs), each trainee assisted at 40 gastric ESD procedures. The trainees observed the specialist's techniques and learned how to use ESD devices and to choose the local injection liquid. Next, the trainees coagulated vessels on post-ESD ulcer floors in 20 lesions. Through this step, the trainees also learned how to keep a stable operative field.

The trainees then started ESD in lesions of the gastric antrum, and after two procedures in the antrum, they advanced to ESD of lesions in the gastric angle or the lesser curvature of the gastric body under close supervision by the specialist. Then, finally, each trainee was allowed to perform gastric ESD in any location. The whole procedures were recorded on DVD, and trainees were required to review their procedures afterwards. When novice operators could not accomplish ESD, due to inability to continue the procedure as judged by the specialist or due to complications, the specialist took over the operation.

ESD procedure

All patients provided written informed consent before treatment. ESD was performed with patients under conscious sedation with flunitrazepam and buprenorphine, and a video endoscope (GIF-Q260J; Olympus Optical Co., Ltd., Tokyo, Japan) and a high frequency power supply unit (VIO 300 D or ICC 200; ERBE, Tübingen, Germany) were used.

The ESD procedure was as follows. First, marks were placed 5 mm outside the tumor edge using a Flex Knife (Olympus Optical). Diluted epinephrine in saline solution (1 : 100 000) was injected into the submucosal layer around the lesion, and the mucosa 5 mm outside of the marks was cut using the IT-Knife 2 (Olympus Optical). After incision of the mucosa, submucosal dissection of the lesion was performed using the IT-Knife 2. After resection of the lesion, all visible vessels on the ulcer floor were coagulated with hot biopsy forceps (Hoya Co., Ltd., Pentax Life Care Div., Japan).

Patients who did not develop complications started a soft diet on day 1 after ESD and were discharged 5 days after the procedure.

Table 2 Training in endoscopic submucosal dissection (ESD) of gastric neoplasm. Pathological characteristics of 117 lesions from 107 patients resected by novice operators. Locations of the first 15 lesions and second 15 lesions are shown.

	Operator				Total
	A	B	C	D	
Number of lesions resected	27*	30	30	30	117
Diameter of resected specimens, mean (SD), mm	38.6 (12.7)	41.6 (11.6)	41.1 (12.3)	40.2 (10.8)	40.4 (11.8)
Diameter of lesions, mean (SD), mm	13.9 (8.5)	17.0 (11.1)	15.7 (7.0)	15.7 (9.3)	15.6 (9.1)
Macroscopic type					
I	0	1	1	1	3
IIa	11	20	18	16	65
IIb	3	1	0	0	4
IIc	13	8	11	13	45
Location of the lesion					
Antrum					56
1st set of 15 lesions	11	7	6	6	
2nd set of lesions	7	3	7	9	
Angle or lesser curvature of the middle third of the stomach					38
1st set of 15 lesions	3	5	6	8	
2nd set of lesions	3	5	3	5	
Other					23
1st set of 15 lesions	1	3	3	1	
2nd set of lesions	2	7	5	1	

SD, standard deviation.

* Trainee A carried out 27 procedures at our hospital; thus the first set included 15 lesions and the second 12 lesions.

Table 3 Endoscopic submucosal dissection (ESD) results in the first and second set of 15 lesions for four trainee operators. A total of 117 lesions in 107 patients were resected.

	Operator				1st set totals	2nd set totals*	Overall total
	A	B	C	D			
Lesions, n							117
1st set	15	15	15	15	60		
2nd set	12	15	15	15		57	
Expanded criteria lesions, n							33
1st set	2	4	2	3	11		
2nd set of patients	5	6	5	6		22	
En bloc resection, n (%)							117 (100)
1st set	15 (100)	15 (100)	15 (100)	15 (100)	60 (100)		
2nd set	12 (100)	15 (100)	15 (100)	15 (100)		57 (100)	
En bloc plus R0 resection, n (%)							113 (96.6)
1st set	15 (100)	15 (100)	15 (100)	13 (86.7)	58 (96.7)		
2nd set	12 (100)	15 (100)	14 (93.3)	14 (93.3)		55 (96.5)	
Complications, n (%)							
Delayed hemorrhage							7 (6.0)
1st set	1 (6.7)	1 (6.7)	1 (6.7)	1 (6.7)	4 (6.7)		
2nd set	0	1 (6.7)	0	2 (13.3)		3 (5.3)	
Perforation							3 (2.6)
1st set	1 (6.7)	1 (6.7)	0	0	2 (3.3)		
2nd set	0	1 (6.7)	0	0		1 (1.8)	
Procedure time, mean (SD), min							83.9 (53.8)
1st set	66 (34)	80 (63)	68 (43)	85 (37)	75 (45)		
2nd set	100 (62)	90 (66)	83 (61)	102 (56)		94 (60)	
Self-completion, n (%)							94 (80.3)
1st set	12 (80)	13 (86.7)	13 (86.7)	13 (86.7)	51 (85)		
2nd set	10 (83.3)	9 (60)	11 (73.3)	13 (86.7)		43 (75.4)	

SD, standard deviation.
* Trainee A had only 12 lesions in the second set.

Complications

Perforation and delayed hemorrhage were regarded as major complications. Delayed hemorrhage was defined as post-ESD bleeding presenting with hematemesis or melena, requiring emergent endoscopic treatment. Perforation was defined as a hole penetrating the gastric wall detected during the ESD procedure or the presence of free air observed on post-ESD X-ray.

Data analysis

To assess the validity of our ESD training system, we analyzed the following data for the 117 ESD resections performed by the trainees: en bloc resection rate, en bloc plus R0 resection rate, operation time, self-completion rate, and complication rate. All patients with lesions that had a positive vertical margin later underwent surgery. Operation time was defined as the period between identification of the target lesion and completion of blood vessel coagulation on the post-ESD ulcer floor. The 30 lesions resected by each trainee (27 for trainee A) were divided into two groups: the first 15 resections and the second 15 (second 12 cases for trainee A), and the results were compared between these two periods to assess the learning curve.

Statistical analysis

Categorical data were compared using the $\chi 2$ test (with Yates' correction) and Fisher's exact test. Continuous data were compared using Student's t test. P values <0.05 were considered significant, and all tests were two-sided. Data are expressed as the mean (standard deviation [SD]). All statistical analyses were performed with PASW Statistics 18 for Windows (SPSS Japan, Tokyo).

Results

The overall rates of en bloc resection and en bloc plus R0 resection were 100% (117/117) and 96.6% (113/117), respectively, and the mean (SD) procedure time was 83.9 (53.8) minutes. A total of 33 lesions (28.2%) were resected according to the expanded criteria, and all other lesions were resected according to the guideline criteria. Regarding complications, there were seven instances of delayed hemorrhage (6.0%) and three occurrences of perforation (2.6%), but all complications were solved endoscopically. The results of ESD by the four operators are shown in **Table 3**. Even in the first 15 cases, the novice operators performed ESD in various locations (**Fig. 1**) and achieved good clinical outcomes.

The overall self-completion rate was as high as 80.3% (94/117). Even in the first 15 procedures, the self-completion rate was higher than 80% for each of the four novice operators, and the self-completion rate did not increase further in the second set of procedures (n=15 for trainees C, D, and E; n=12 for trainee A) (**Fig. 2**). However, regarding guideline criteria lesions in the angle or lesser curvature in the middle third, novice operators were able to achieve self-completion in the second set of procedures. ESD results for guideline criteria lesions and expanded criteria lesions for each trainee are shown in **Table 4**. Self-completion rate went down and procedure time was longer for expanded criteria lesions, but the rates of en bloc resection and complication were almost the same for the two categories.

The comparison of successful self-completion and failed self-completion procedures is shown in **Table 5**. In cases of failed

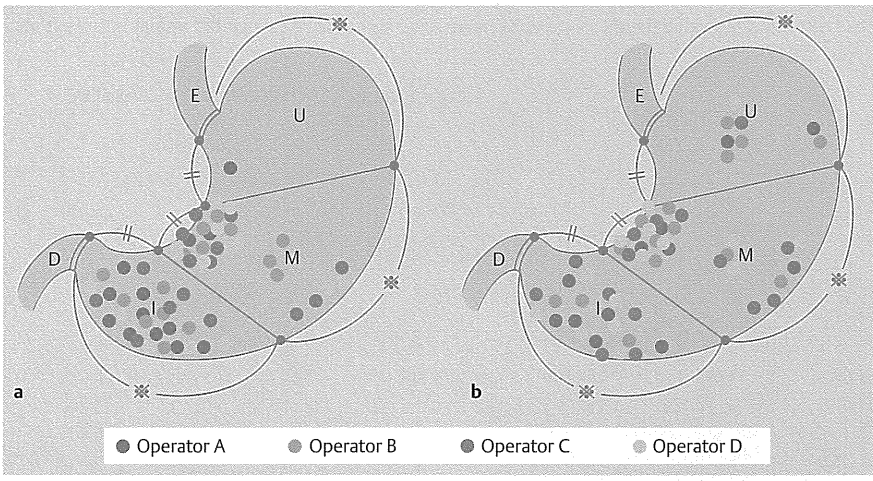

Fig. 1 Training in endoscopic submucosal dissection (ESD) of gastric neoplasm. Location of the lesions for which ESD was performed by four trainee operators: a the first 15 procedures; b the second 15 procedures (second 12 procedures for trainee operator A). E, esophagus; U, upper third; M, middle third; L, lower third; D, duodenum.

Table 4 Endoscopic submucosal dissection (ESD) results for guideline criteria lesions (GCLs) and expanded criteria lesions (ECLs) for four trainee operators.

	Operator								Total		Overall total
	A		B		C		D				
	GCL	ECL	GCL	ECL	GCL	ECL	GCL	ECL	GCL	ECL	
Lesions, n	20	7	20	10	23	7	21	9	84	33	117
En bloc resection, n (%)	20 (100)	7 (100)	20 (100)	10 (100)	23 (100)	7 (100)	21 (100)	9 (100)	84 (100)	33 (100)	117 (100)
En bloc plus R0 resection, n (%)	20 (100)	7 (100)	20 (100)	10 (100)	23 (100)	6 (86)	21 (100)	6 (66.7)	84 (100)	29 (87.9)	113 (96.6)
Complications, n (%)											
Delayed hemorrhage	1 (5.0)	0	1 (5.0)	1 (10.0)	1 (4.3)	0	2 (9.5)	1 (11.1)	5 (6.0)	2 (6.1)	7 (6.0)
Perforation	0	1 (14.3)	2 (10.0)	0	0	0	0	0	2 (2.4)	1 (3.0)	3 (2.6)
Procedure time, mean (SD), min	66 (37)	127 (59)	70 (61)	115 (62)	51 (26)	156 (32)	84 (43)	115 (53)	67 (44)	126 (54)	83.9 (53.8)
Self-completion, n (%)	17 (85.0)	5 (71.4)	17 (85.0)	5 (50.0)	22 (95.7)	2 (28.6)	19 (90.5)	7 (77.8)	75 (89.3)	19 (57.6)	94 (80.3)

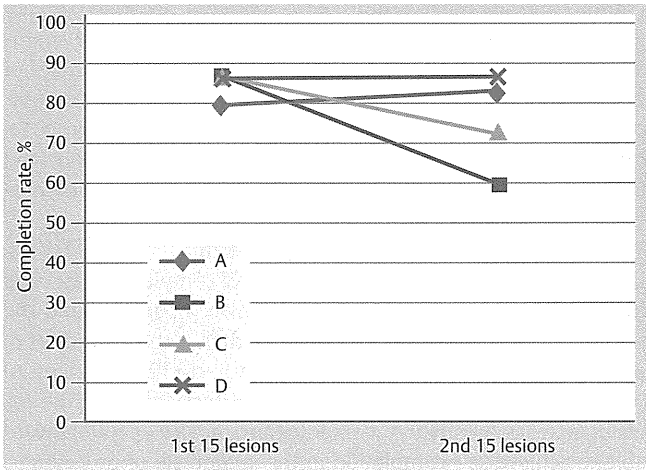

Fig. 2 Training in endoscopic submucosal dissection (ESD). Rate of resection completion without change of operator to the supervising expert: the first 15 and the second 15 procedures (second 12 for trainee A).

Table 5 Endoscopic submucosal dissection (ESD) of 117 lesions in 107 patients by four ESD trainees: comparison of procedures with successful and failed self-completion

	Self-completion	Self-completion failure	*P* value*
Procedure time, mean (SD), min	67.9 (39.4)	149.6 (55.6)	<0.001
Diameter of resected specimens, mean (SD), mm	39.3 (11.4)	45.0 (12.4)	0.038
Diameter of lesions, mean (SD), mm	14.9 (9.0)	17.9 (9.7)	0.156
Location			<0.001
Antrum	55	1	
Angle or lesser curvature in the middle third	29	9	
Other	10	13	

SD, standard deviation.
* *P* values by χ^2 test and unpaired *t* test.

	Operator				Total, n (%)
	A[1]	B	C	D	
Perforation					3 (2.6)
1st 15 lesions	1	1	0	0	
2nd 15 lesions	0	1	0	0	
Inability to continue operation					
Inability to achieve hemostasis					6 (5.1)
1st 15 lesions	1	0	0	1	
2nd 15 lesions	1	1	1	1	
Lack of submucosal dissection skill					15 (12.8)
1st 15 lesions	1	1	2	1	
2nd 15 lesions	1	4	4	1	

[1] Trainee A had only 12 lesions in the second set.

Table 6 Endoscopic submucosal dissection (ESD) of 117 lesions in 107 patients by four ESD trainee operators: reasons for change of operator (take over by expert).

self-completion the procedure time was longer and resected specimens were larger than in successfully self-completed procedures. Moreover, there were significantly fewer antral lesions in self-completion failures than in self-completion successes. The reasons for the operator change are shown in **Table 6**. Inability to continue the operation was attributed to two categories: inability to achieve hemostasis and lack of submucosal dissection skill. Lack of submucosal dissection skill included inability to cut off ulceration scar, inability to reach the appropriate depth of the submucosal layer, and inability to approach the lesion at a short distance. The most frequent reason for inability to continue operation was lack of submucosal dissection skill.

Discussion

To date, many reports on ESD have been published from Japan or other countries in East Asia [4, 8–10], but there are few data from Western countries [11–14]. This is partly because the incidence of EGC is much lower in the Western world, and also because ESD is technically difficult and requires intensive training [11]. However, the advantage of ESD is quite significant, and ESD should eventually become popular worldwide. Therefore, an effective training system must be established. Several reports have referred to the learning curve for gastric ESD [6, 7,15–19]. Gotoda et al. pointed out that a trainee requires at least 30 cases to gain early proficiency in this technique [19]. Yamamoto et al. revealed that novice operators can safely perform gastric ESD under the supervision of an expert [6], but in their study ESD was performed according to the guideline indication criteria and, as Probst et al. pointed out, most of the EGCs diagnosed in Europe do not meet the guideline criteria [11]. If trainees in the Western world are restricted to guideline criteria lesions, they may have little opportunity to perform gastric ESD. To expand the use of gastric ESD worldwide, it is necessary to establish a training system that can apply in the West as well as in the East. For this reason, it was considered important to confirm the feasibility of our training system in which expanded criteria lesions were included.

As a result of our approach, novice operators were able to successfully and safely accomplish ESD for EGC, including for expanded criteria lesions, under close supervision by an expert, confirming the feasibility of our training system [9]. Even in the initial 15 procedures, trainees were able to safely perform ESD and the rate of en bloc plus R0 resection was very high [6, 9]. We speculate that this was partly due to the close supervision, which made it possible to stop novice operators before they started using a dangerous technique, but mainly due to our unique training system which obliged trainees especially to acquire the skill of keeping a stable field during endoscopy. The ability to keep a stable operative field is the most important point in performing ESD. As mentioned above, beginners were required to meet certain conditions before performing ESD. Among these, coagulating vessels on post-ESD ulcer floors in 20 lesions was the most important, because it helped novice operators to learn to keep a stable operative field and to achieve hemostasis. The ability to perform exact gastric biopsy is also an important requirement. Because they acquired essential skills before starting to carry out ESD, novice operators could perform ESD even for expanded criteria lesions from the initial stage, albeit under close supervision. Essential requirements for trainees starting ESD remain to be established, but our system can be one of the standards. ESD failure simply because of lack of skill of novice operators is not acceptable from the ethical standpoint.

Regarding the learning curve, the self-completion rate did not increase in the second set of 15 cases, although this may be partly due to the increase in the number of expanded criteria lesions and the decrease in antral lesions in the later period. Excellent clinical outcomes were maintained throughout the training period, but even after 30 cases, novice operators could not always complete gastric ESD without help from the expert. However, our study demonstrated that, under our training system, novice operators could resect antral lesions from the beginning, and guideline criteria lesions in the angle or lesser curvature in the middle third, in the second set of cases, without worsening clinical outcomes. Additionally, they must achieve self-completion for lesions in the antrum and guideline criteria lesions in the angle or lesser curvature in the middle third after the first 30 ESD operations.

The most frequent reason for operator change was lack of submucosal dissection skill. Lesions with ulcers or scars do not lift with submucosal injection, and therefore ESD for this kind of lesion is rather difficult. This type of ESD should be performed by experts. The approach to lesions on the lesser curvature in the middle third of the stomach is sometimes problematic, and novice operators often find it difficult to perform ESD for such lesions. To overcome this difficulty, certain techniques such as air deflation or scope twisting are helpful, and a multi-bending endoscope (M-scope, GIF-2T260M; Olympus Optical) is also useful [20]. In many cases of failed self-completion, novice operators could not reach the appropriate depth in the submucosal layer beneath the fat layer. In the greater curvature of the stomach body, the upper layer of the submucosal layer is rich in fat tissue containing many penetrating vessels [6]. If an operator cannot reach the appropri-

ate depth beneath the fat layer, bleeding continues during submucosal dissection. It is important to reach an appropriately deep layer by cutting the fat layer, but this step is relatively difficult for beginners.

In the upper third of the stomach, beginners often find it difficult to achieve hemostasis during operation. Submucosal artery diameters are larger in the upper third of the stomach than in the antrum, and bleeding during ESD procedures occurs more frequently in that location [21]. To achieve hemostasis quickly, it is necessary to identify the bleeding point accurately using an endoscope with a waterjet function [22].

Hands-on training on ex vivo animal models may help novice operators learn how to approach lesions in the lesser curvature [15–18]; however, ex vivo animal models do not help in acquiring the skills of hemostasis and approaching a deep enough level of the submucosal layer, because bleeding does not occur. In vivo animal models might be more valuable for attaining a higher self-completion rate in the early period; however, as Parra-Blanco et al. pointed out, there are several differences between porcine and human stomachs [17]. We suggest that at an institution that has no ESD experts, novice operators should be trained with a combination of animal models and human practice. Using animal models that simulate human cases should be helpful. The creation of animal perforation models can also help in learning to deal with that complication. Of course, many ESD experts in Japan can contribute to training in countries where there is no ESD expert [5].

The present study has several limitations in that it is a retrospective single-center study and the numbers of participating endoscopists and cases are small. In addition, we should investigate how many gastric ESD procedures novice operators need to undertake in order to perform ESD without expert supervision, because even at the end of 30 cases in this study, expert assistance was still needed in a remaining 20% of ESDs. If the expert had permitted trainees to continue the procedure even in difficult situations, the self-completion rate would have reached almost 100% in this study, although the mean operation time would have been much more prolonged. However, we had to consider the ethical aspect that the final goal in clinical practice was not to train novice operators but to cure the patients safely. In this context, in self-completed procedures novice operators handled an endoscope by themselves for the entire operation time, so we believe excellent outcomes reflected their proficiency, but more investigation is necessary.

In conclusion, our training system enabled novice operators to perform ESD for EGC, including for expanded criteria lesions, without a decline in clinical outcomes, although the experience of 30 procedures was not enough for them to complete all gastric ESDs without expert help.The keys to improving the learning curve were good hemostasis technique and a sufficient level of submucosal dissection skill.

Competing interests: None

Acknowledgment

The content of this paper was presented in part at the 18th United European Gastroenterology Week Meeting, October 23–27 2010, in Barcelona, Spain.

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Abdominal Imaging

Published online: 7 July 2011

Abdom Imaging (2012) 37:29–34
DOI: 10.1007/s00261-011-9777-y

Diagnostic yield of capsule endoscopy for gastric diseases

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Abstract

Background and aim: Capsule endoscopy (CE) for the stomach has not yet been in practical use. Likewise as in colon, CE for colorectal cancer screening, the less invasive nature of CE may be suitable for gastric screening. The aim of this study is to estimate a diagnostic yield of CE for gastric diseases.

Methods: This study involved 55 patients who participated in other clinical studies regarding obscure overt gastrointestinal bleeding or iron deficiency anemia. All patients underwent esophagogastroduodenoscopy and CE within 2 weeks. Sensitivity and specificity of CE for diffuse and localized gastric lesions were calculated, respectively.

Results: Gastroscopy revealed 38 diffuse lesions (14 antral gastritis, 19 pangastritis, and 5 diffuse antral vascular ectasia) and 25 localized lesions (14 erosions, 2 cancers, and 9 polyps). CE had a higher sensitivity for gastric diffuse lesions compared with localized lesions. For diffuse lesions, sensitivity and specificity of CE were 70% and 82%, respectively. For localized lesions, sensitivity and specificity of CE were 28% and 63%, respectively. All cancers could not be detected by CE.

Conclusions: Currently, the diagnostic yield of CE for gastric diseases is not high enough for gastric screening. Additional improvements including preparations, position change, or the invention of new technologies are required.

Key words: Capsule endoscopy—Gastric diseases—Diagnostic yield—Gastric passage time—Screening endoscopy

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Three different types of capsule endoscopy (CE) have been developed, capsule endoscopy for the esophagus, the small intestine, and the colon [1–3]. One of the most important advantages of CE is it is a noninvasive procedure. CE requires neither sedation nor air insufflation. The noninvasive nature of CE implies that it should be suitable for mass screening. Indeed, CE for the esophagus (PillCam® ESO, Given imaging Ltd., Yoqneam, Israel) has been used for periodic screening for Barrett esophagus [4]. High sensitivity and specificity of PillCam® ESO for esophageal adenocarcinoma has been reported [5]. Although the sensitivity of CE (PillCam® COLON) for colorectal cancer was not as high as that of colonoscopy procedures, CE is intended for use in mass screening for colorectal cancer [3].

In Japan, screening endoscopy for gastric cancer is common among asymptomatic subjects, because of the high incidence of gastric cancer [6–8]. In general, simpler and less invasive procedures achieve a higher screening rate among asymptomatic individuals. Therefore, the advent of capsule endoscopy for the stomach is expected. In this study, we aimed to estimate a baseline diagnostic yield of capsule endoscopy for gastric diseases.

Methods

Subjects

Between January 2007 and March 2008, patients participating in other clinical studies regarding obscure overt gastrointestinal bleeding (overt OGIB) or iron deficiency anemia (IDA) were consecutively enrolled in the present study. Diagnosis of OGIB was made by excluding patients with a bleeding source which could be found by esophagogastroduodenoscopy (EGD) and colonoscopy [9]. When the following lesions were found by EGD or colonoscopy, patients were excluded; invasive cancers diagnosed by endoscopy or CT scan or surgery, ulcers at active stages based on the classification

of Sakita and Miwa, vascular or diverticular lesions with bleeding at endoscopy [10]. IDA was diagnosed as all the following criterias being fulfilled; hemoglobin (Hb) concentration < 13.5 g/dl, serum ferritin < 65 ng/dl, mean corpuscular volume < 80 fl and mean corpuscular hemoglobin concentration < 28 pg. Patients with a cardiac pacemaker installed or a past history of bowel obstruction were excluded. Finally, a total of 55 patients (Age 63.8 ± 13.3 years, 33 males) were analyzed in this study. All patients provided written informed consent.

Capsule endoscopy procedures

We used Pillcam® SB (Given Imaging Ltd., Yoqneam, Israel) for all study patients. All patients underwent CE within 2 weeks after EGD. The preparation for CE involved fasting for 12 h and the administration of 40 mg of simethicone just before CE. Drinking was permitted 2 h after CE ingestion and eating was allowed after 5 h. During the examination, patients could move freely. CE was performed for about 8 h after ingesting, and sensor array and recording devices were removed.

Three experienced endoscopists independently reviewed all capsule endoscopy videos without any information on the gastroscopy findings of each patient. CE images were reviewed using Rapid® 5 Access software (Given Imaging Ltd., Yoqneam, Israel). The reading speed of the capsule endoscopy videos was 15–20 frames per second in the dual-view mode. After independent reviewing, the reviewers checked CE findings together and finally reached a consensus.

Diagnostic criteria of gastric diseases by gastroscopy and capsule endoscopy

In this study, detectability of the following lesions were analyzed; endoscopic gastritis, diffuse antral vascular ectasia (DAVE), gastric ulcers at the healing stage or scar stage, gastric erosions, gastric polyps, and gastric cancer at the early stage. Definition of each disease based on the gastroscopy findings was as follows: gastritis: visible blood vessels under gastric mucosa or disappearance of gastric folds with or without thickened mucus [11]; DAVE: diffusely distributed spotty or confluent erythemas in the antrum or longitudinal angioid stripes radiating from the prepyloric region (Fig. 1A, B) [12, 13]; gastric ulcer: a defect of the gastric wall that extends through the muscularis mucosae into the deeper layers of the wall [14]; gastric erosions: superficial lesions confined to the mucosa [14]; gastric polyps: luminal lesions projecting above the plane of the mucosal surface [15]; gastric cancer at the early stage: tumor with invasion limited to the mucosa or submucosa of the stomach irrespective of lymph node involvement [16]. All gastric ulcers and cancers were confirmed by histological analysis.

We used the same definitions of each disease when we reviewed the capsule endoscopy videos. For cases of gastritis, when CE showed any of the following findings, we considered that the patient had gastritis, rough reddish mucosa, disappearance of gastric fold, and thickened mucus in the stomach.

Statistical analysis

Gastric lesions detected by EGD were categorized into two groups, diffuse lesions including antral gastritis, corpus gastritis, and DAVE or localized lesions including gastric erosions, ulcers at the healing or scar stage, cancers at the early stage and polyps. Sensitivity and specificity of CE for gastric diffuse and localized lesions were calculated, respectively. The findings obtained by EGD were used as a gold standard.

Study subjects were divided into three groups according to gastric passage time: group A (n = 18); 0–14 min, group B (n = 18); 15–54 min, group C (n = 19); 55 min or over. Detectability of gastric localized lesions and diffuse lesions were compared between each group.

All statistical analyses were performed with the JMP 7 statistical software program (SAS Institute Inc., North Carolina, USA). In all analyses, means were compared with unpaired Student's t test, and frequency distributions, with Fisher's exact probability test or Chi-squared test. Parametric data was expressed as mean ± standard deviation. A P value < 0.05 was considered statistically significant. McNemar test was used in assessment of the difference in sensitivity and specificity between gastric diffuse and localized lesions.

Results

Baseline characteristics of the study patients

Baseline clinical characteristics of the study patients were summarized in Table 1. Of the 55 patients, 27 patients (49%) had overt OGIB and 28 patients (51%) had IDA. Twenty-two patients (40%) had past history of abdominal surgery including gastrectomy, cholecystectomy, appendectomy, and uterine myomectomy. During the recording period, CE reached to the cecum in 33 patients (60%). Mean passage time of each time was as follows: esophagus; 13.7 ± 6.9 s, stomach; 53.1 ± 10.3 min, small intestine; 303.7 ± 16.5 min. Among the study patients, gastric images could not be taken by CE in three patients, because CE passed the stomach within one second in two patients and there was food residue in the stomach of one patient. No capsule retention occurred.

Gastroscopy revealed 38 diffuse lesions (14 antral gastritis, 19 pan gastritis, and 5 DAVE) and 25 localized lesions (14 erosions, 2 cancers, and 9 polyps).

Regarding localized lesions, there were two gastric cancers. One was early gastric cancer (type 0-IIa) in the

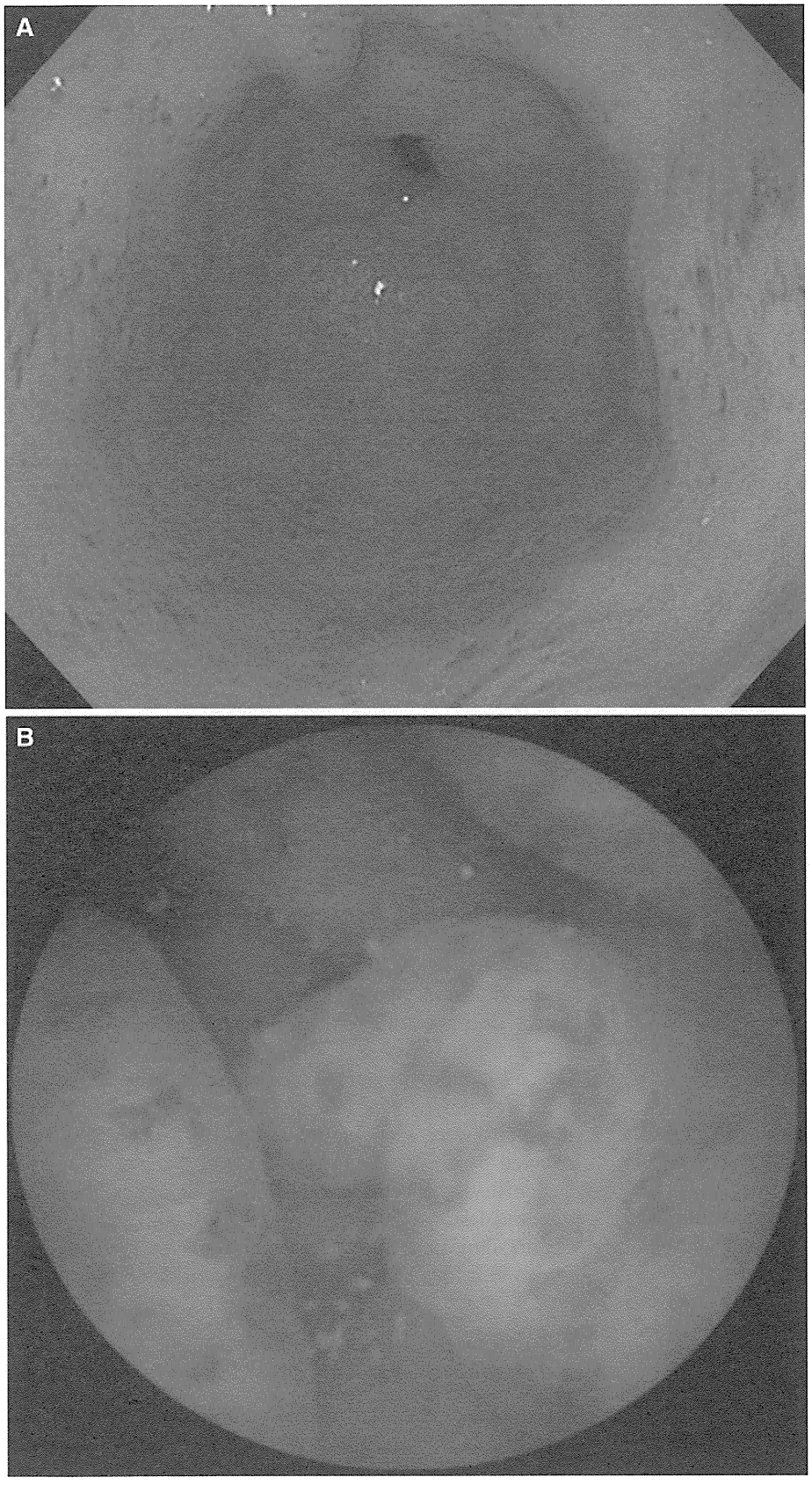

Fig. 1. Endoscopic photographs of diffuse antral vascular ectasia (DAVE): **A** Gastroscopy; **B** Capsule endoscopy.

Table 1. Baseline of characteristics of the study patients (N = 55)

Age (years)[a]	63.8 ± 13.3
Male/female	33 (60%)/22 (40%)
Indications of CE	
Obscure gastrointestinal bleeding	27 (49%)
Iron deficiency anemia	28 (51%)
Daily using drugs	
NSAIDs	5 (9%)
Antiplatelet agent	13 (24%)
Past history of abdominal surgery	22 (40%)
% of capsule obtained cecum image	60%
CE passage time[a]	
Esophagus (s)	13.7 ± 6.9
Stomach (min)	53.1 ± 10.3
Small intestine (min)	303.7 ± 16.5
Gastroscopy findings (patients)	
Pangastritis	22 (20%)
Antral gastritis	11 (10%)
DAVE	5 (9%)
Cancer	2 (4%)
Polyp	9 (16%)
Erosion	14 (25%)
Ulcer	0 (0%)

[a] Mean ± SD
CE, Capsule endoscopy; NSAIDs, Non-steroidal anti-inflammatory drugs; DAVE, Diffuse antral vascular ectasia

Table 2. Concordance of gastric diffuse lesions between CE and EGD

	EGD			
	Gastritis	DAVE	No lesion	Total
CE				
Gastritis	23	1	3	27
DAVE	1	4	0	5
No lesion	6	0	14	20
Unknown	3	0	0	3
Total	33	5	17	55

CE, Capsule endoscopy; EGD, Esophagogastroduodenoscopy; DAVE, Diffuse antral vascular ectasia

Table 3. Sensitivity and Specificity of CE findings of diffuse lesions

	Sensitivity	Specificity	PPV	NPV
Gastric antrum (%)	71	82	90	61
Gastric body (%)	64	73	61	83

CE, Capsule endoscopy; PPV, Positive predictive value; NPV, Negative predictive value

Table 4. Concordance of localized gastric lesions between CE and EGD

	EGD					
	Cancer	Polyp	Ulcer	Erosion	No lesion	Total
CE						
Cancer	0	0	0	0	0	0
Polyp	0	2	0	3	1	6
Ulcer	1	0	0	0	0	1
Erosion	1	1	0	5	7	14
No lesion	0	6	0	6	19	31
Unknown	0	0	0	0	3	3
Total	2	9	0	14	30	55

CE, Capsule endoscopy; EGD, Esophagogastroduodenoscopy

anterior wall of the lower gastric body and the other was residual stomach cancer (type 4). As a matter of fact, one patient with early gastric cancer underwent gastroscopy at a local hospital prior to CE. We conducted gastroscopy after CE because there was blood in the stomach at CE, and confirmed the presence of gastric cancer in the patient. In another case with residual stomach cancer, the cancer was not detected at the time of pre-CE gastroscopy, but the serum level of CEA was elevated after CE. We conducted a second gastroscopy, and found residual stomach cancer.

Sensitivity and specificity of CE for gastric diseases

For diffuse lesions, 23 of the 33 patients with gastritis were diagnosed correctly and the remaining six patients were diagnosed as having normal gastric mucosa by CE. Four out of five patients with DAVE were diagnosed correctly by CE (Table 2). Sensitivity and specificity of CE for diffuse lesions were 70% and 82%, respectively. In the antrum, sensitivity and specificity for diffuse lesions were 71% and 82%. In the corpus, sensitivity and specificity were 64% and 73%. There was no difference in sensitivity and specificity between the antrum and the corpus (Table 3).

As for localized lesions, 2 of the 9 patients with polyps were diagnosed correctly and erosions were detected in 5 of the 14 patients. Unfortunately, CE could not detect gastric cancers at all (Table 4). Sensitivity and specificity of CE for localized lesions were 28% and 63%, respectively. In the antrum, sensitivity and specificity for localized lesions were 33% and 85%. In the corpus, sensitivity and specificity were 23% and 88%. Concerning erosions, sensitivity of CE was 41% and specificity was 63%. 67% of erosions were seen in the antrum. Sensitivity of CE for polyps was 20% and specificity was 84%. 90% of polyps were seen in the body. No cancer could be detected by CE.

Sensitivity for diffuse lesions was higher than for localized lesions (70% vs. 28%, P = 0.002), while there was no significant difference among specificity for diffuse lesions and localized lesions (82% vs. 63%, P = 0.17).

Association between gastric passage time and diagnostic yield of capsule endoscopy

We analyzed the relation between passage time of the stomach and concordance rate of gastric diseases between gastroscopy and CE. For gastric diffuse lesions, median gastric passage time was 32 min in the correctly detected group and 15 min in the incorrectly detected group (P = 0.27). The concordance rate in group B

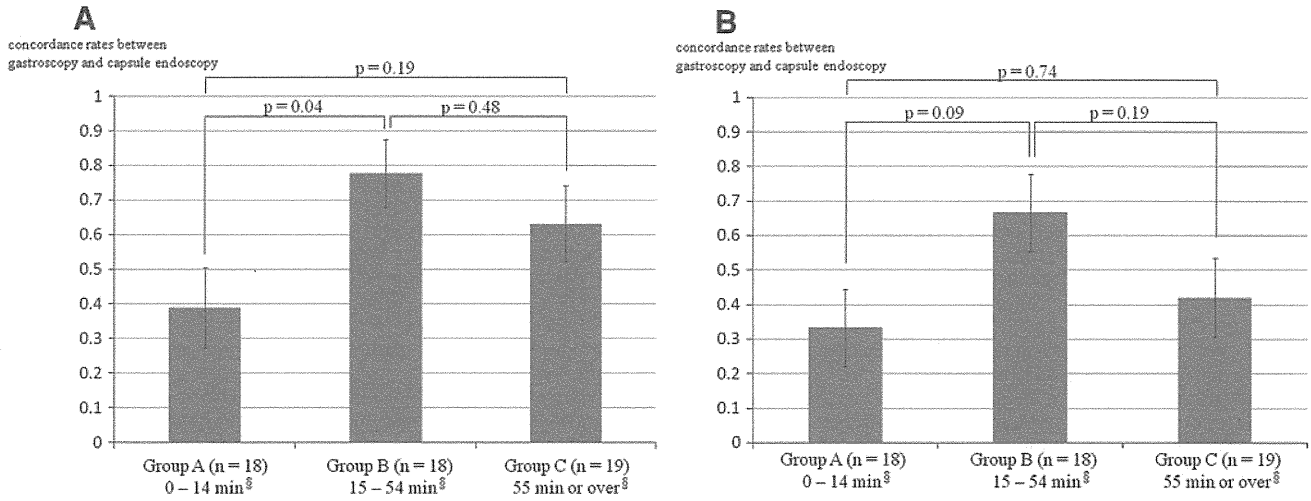

Fig. 2. Association between gastric passage time and concordance rates of gastroscopy and capsule endoscopy. **A** Gastric diffuse lesions (including gastritis and diffuse antral vascular ectasia); **B** Gastric localized lesions (including gastric cancer, gastric ulcer, gastric erosion, and gastric polyp), §Gastric passage time of capsule endoscopy.

(15–54 min) was significantly higher than in group A (78% vs. 39%, $P = 0.04$) (Fig. 2A). For gastric localized lesions, median gastric passage time was 30 min in the correctly diagnosed group and 23 min in the incorrectly diagnosed group. Although it did not reach a statistical significance, concordance rate in group B was higher than in group A, similarly (67% vs. 33%, $P = 0.09$) (Fig. 2B). Group A had a lower concordance rate for both gastric localized and diffuse lesions than group B or group C.

Discussion

This study reveals that current capsule endoscopy is not sufficient enough to diagnose gastric diseases. The present study estimated that sensitivity and specificity of CE were 70% and 82% for diffuse lesions, and 28% and 63% for localized lesions, respectively. In order to apply CE for gastric screening, both sensitivity and specificity should be markedly improved. For example, photofluorography is widely performed in Japan. The sensitivity and the specificity of photofluorography for gastric cancer were better than those of CE, which ranged from 68% to 88% and 81% to 92%, respectively [17].

In particular, the study also showed that sensitivity for localized gastric lesions was lower than that for diffuse gastric lesions. Although CE has low sensitivity for localized gastric lesions, most of the localized lesions including gastric cancers and ulcers are accompanied by with gastritis. Our finding implies that CE could select subjects with a higher risk of gastric cancer by detecting gastritis.

In addition, the study showed that shorter passage time of the stomach was associated with a lower concordance rate between CE and gastroscopy for diffuse as well as localized gastric lesions. Our study indicated that more than 15 min of the gastric surveillance time was necessary to obtain a higher detectability of gastric lesions. For screening of the small intestine, several methods for minimizing gastric passage time were reported, such as keeping a right lateral position or using metoclopramide [18]. A standard method of keeping CE in the stomach is also required. Use of gastrointestinal antispasmodics or a body position such as the left lateral position or supine position is expected to extend gastric passage time. It will also be very important to apply new technology in CE for gastric screening, such as the magnetically navigated capsule which Rey JF et al. [19] reported. We used Pillcam® SB in this study; however, the next generation PillCam® SB 2, which has wider angle of view (154°) and captures nearly twice the mucosal area is now available. It is estimated that the diagnostic yield of gastric diseases will increase with PillCam® SB 2. Furthermore, the sensitivity could be improved by using two imagers, one at each end, in the manner of CE for the esophagus and the colon.

The trial was restricted to patients with OGIB and IDA, and cases with more easily viewable lesions such as advanced cancers or ulcers at the active phase were excluded. Therefore, the current study may underestimate the diagnostic yield of CE for localized gastric lesions.

Conclusion

The study shows that although CE had a higher sensitivity for diffuse gastric lesions compared with localized lesions, diagnostic yield of CE for gastric diseases was not high enough to apply CE for gastric screening. Additional improvements including preparations, position change, or the invention of new technologies are required to apply CE to screen for gastric diseases.

Conflicts of interest None.

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