procedure that was finished without a change of supervisor. The learning curve was assessed as the change in self-completion rate and required operation time for each 10 procedures of each operator. Reasons for a change of supervisor during each mucosal incision and submucosal dissection were analyzed with reference to the operation record and video recordings, and were categorized according to the above-mentioned assistant policy.

Statistical analysis

JMP version 6.0 (SAS Institute, Cary, North Carolina, USA) was used for data analysis. Summarized numerical data were expressed as medians (interquartile ranges). The Mann–Whitney U-test was used for comparison of procedure time between mucosal incision and submucosal dissection. The χ^2 test was used for comparison of self-completion rates between mucosal incision and submucosal dissection. Significant differences were taken to be indicated by a *P*-value below 0.05.

Results

Assessment of feasibility

The overall complete resection rate was 93% (84 of 90 procedures). A total of four complications were experienced (4.4%), comprising two cases of delayed hemorrhage and two perforations. The perforations were repaired successfully with endoscopic clips as soon as the operators changed. The distribution of complete resection and complication rates was similar between operators (**Table 4**).

Analysis of difficulty

The self-completion rate for submucosal dissection was significantly lower than that for mucosal incision, and operation time was significantly longer (**Table 4**).

Concerning the learning curve, the self-completion rate for mucosal incision for all operators exceeded 80% in the third group of 10 cases, whereas for submucosal dissection two of three operators stayed around 50%, even for the final 10 cases (**Fig. 1**). Median operation time for mucosal incision did not change markedly and remained around 30 minutes for all operators. Median operation time for submucosal dissection became shorter than 30 minutes for one operator whose self-completion rate increased, but did not improve for the other two operators (**Fig. 2**).

The reasons for incompletion of the procedures are listed in **Table 5**. For mucosal incision, "inability to continue the procedure" was the most frequent reason for a change of supervisor. According to the video recordings, this was mainly an inability to achieve a mucosal incision owing to unfamiliarity with use of the IT knife. For submucosal dissection, "overtime," "inability to achieve hemostasis," and "inability to continue the procedure" led to discontinuation of the procedure for about 40% of the lesions. Video recordings revealed that "overtime" was usually caused by spending too long on hemostasis, and "inability to continue the procedure" was largely the result of interference with the procedure and loss of orientation caused by hemorrhage and clotting: in other words, the main difficulty for completion of submucosal dissection was uncontrollable hemorrhage.

Discussion

In the present case series study, we found that ESD for EGC measuring less than 2 cm, performed by supervised residents, was practicable, with a complete resection rate of 93% and a complication rate of 4%, which is similar to findings in previous studies of experienced endoscopists [10]. Difficulties arose more frequently during submucosal dissection than mucosal incision, and most of these were related to uncontrollable hemorrhage.

It has been reported that closely supervised trainees can perform advanced surgery such as esophagogastrectomy, hepatectomy [11], or pancreatectomy [12] with similar outcomes to consultant surgeons. In these studies, surgeons with a large workload encouraged trainees to be accept more opportunities to participate in such complex operations, with appropriate supervision, because this improved their learning of the surgical methods and did not jeopardize patient care. We believe that this concept can be applied to endoscopic procedures, and our results support this conclusion. Needless to say, this cannot be achieved without the availability of a highly experienced supervisor, because a significant number of cases were not completed by the resident alone and complications such as perforations were generally managed by the supervisor.

The requirements and criteria for starting to perform ESD have not been clarified to date. In our center, endoscopists who intend to start ESD should attend the pre- and post-treatment conference, and take part in actual ESD procedures as an assistant for at least 1 year before beginning the procedure themselves. In addition to gastroenterologists, surgeons and pathologists participate in these conferences, and thus new endoscopists can learn how to diagnose the extent and depth of the tumor, establish the optimum treatment strategy, and manage the patients appropriately according to the histopathological findings in resected specimens. By assisting experienced endoscopists, trainees acquire the skills needed to troubleshoot various situations. Moreover, obtaining expertise in hemostasis before starting ESD is recommended since most of the difficulties surrounding the procedure were related to uncontrollable hemorrhage.

In the present study, patients with small EGCs were selected. We suspect that if a novice endoscopist performs ESD for large lesions, it could involve an extremely long operation time, and it is too difficult for them to acquire the basic techniques during their restricted time in clinical practice. For this reason, we recommend that supervision should be started with small lesions, so that trainees have the opportunity to learn the entire ESD procedure. After this, it is easier to move on to larger lesions, because the procedure for large lesions consists of repeating certain basic procedures.

Choi et al. [13] have investigated the learning curve for ESD, and reported an increase in the en bloc resection rate from 45% to 85% after experience of 40 cases. They have concluded that trainees need to perform 20–40 procedures to be able to use the technique effectively, although their method consisted of mucosal incision and snaring rather than ESD. Gotoda et al. [14] have found that experience of at least 30 cases is required for a beginner to gain early proficiency in this technique. In our study, two of the three operators could not achieve a sufficient self-completion rate for submucosal dissection after 30 cases. The fact that two of the three operators could not achieve a sufficient self-completion rate for ESD by the 30th case suggests that more extensive experience is required before endoscopists can be considered to be proficient. Our study did not include hands-on training

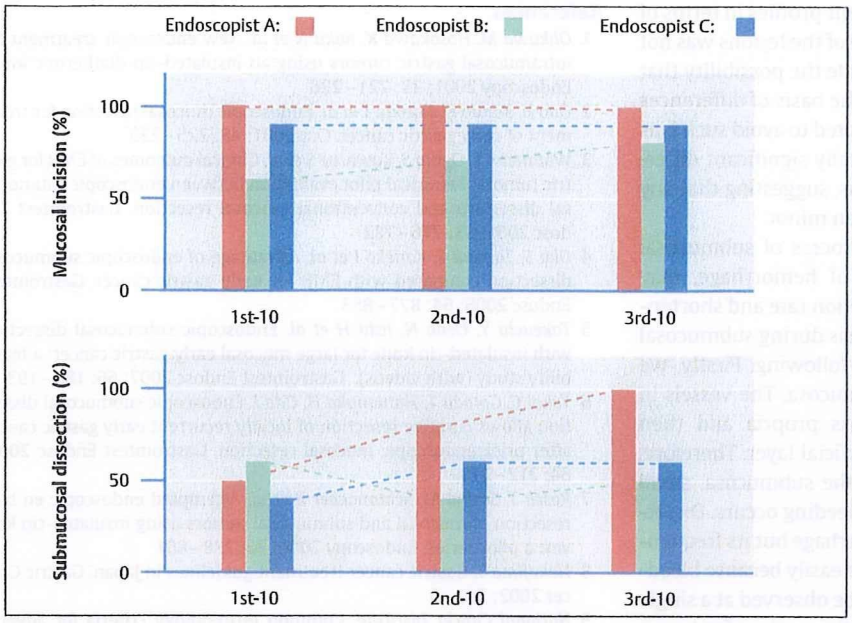

Fig. 1 Learning curves for self-completion rate for mucosal incision and endoscopic submucosal dissection.

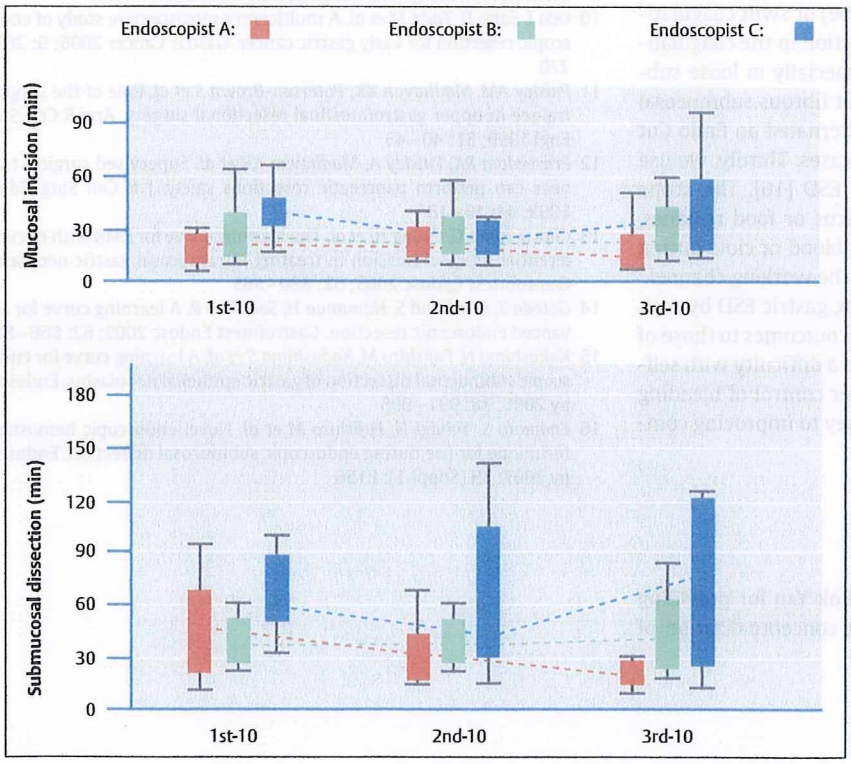

Fig. 2 Learning curves for operation time for mucosal incision and endoscopic submucosal dissection.

on ex vivo animal models such as the Erlangen Active Simulator for Interventional Endoscopy (EASIE) or living animals, which might have improved the learning curve of our three endoscopists. Nevertheless, we feel that incorporation of supervised clinical procedures is imperative.

The baseline profile of our operators, such as graduation year or number of cases experienced, was not associated with learning speed. Kakushima et al. [15] have indicated that a change in en bloc complete resection and complication rates did not represent operator proficiency with ESD under supervision, but that a decrease in operation time is a marker of proficiency. We evaluated self-completion rate as a parameter of expertise and it was associated with a decrease in procedure time, and as a result it may be a marker of proficiency. Differences in learning speed have been attributed to variations in individual talent. However, clarifying the objective parameters that reflect the actual expertise of a trainee and setting up relevant acquisition conditions are important for the establishing of a training system for advanced therapeutic procedures. Because our data are limited by the number of participating endoscopists and procedures, further investigations using common evaluation parameters are required.

The three residents in this study had different profiles in terms of their endoscopic experience. The allocation of the lesions was not randomized and we therefore cannot exclude the possibility that some lesions may have been allocated on the basis of differences in profile between the residents. We attempted to avoid such bias as much as possible and found no statistically significant differences in the size of lesions or their locations, suggesting that any bias due to residents' profiles may have been minor.

Our results suggest that improving the process of submucosal dissection, especially the controllability of hemorrhage, may have contributed to the decrease in completion rate and shortening of operation time. To facilitate hemostasis during submucosal dissection, we attempted to improve the following. Firstly, we tried to dissect a deeper layer of the submucosa. The vessels in the gastric wall penetrate the muscularis propria and then branch in the submucosa toward the superficial layer. Therefore, when we dissect the superficial layer of the submucosa, small branched vessels are disrupted and more bleeding occurs. Dissection of deeper layers causes spurting hemorrhage but its frequency becomes less, and it can be stopped more easily because bleeding from the stump of the vessel trunk can be observed at a single point. Secondly, during submucosal dissection, we prefer to use the coagulation mode of the electrosurgical unit, e.g., a forced coagulation mode of 50 W for the ICC200 (Erbe) or swift coagulation of 100 W, for the VIO300D (Erbe). Dissection in the coagulation mode can cut and prevent bleeding, especially in loose submucosal tissue, but sometimes it cannot cut fibrous submucosal tissue in the gastric body; therefore, we alternated an Endo Cut mode with the coagulation mode in such cases. Thirdly, we use an endoscope with waterjet function for ESD [16]. The scope was developed originally to clean out mucus or food residues, but it can be used for washing out of shed blood or clots during ESD without withdrawing the device from the working channel.

In conclusion, with appropriate supervision, gastric ESD by residents is practicable, with equivalent clinical outcomes to those of experienced endoscopists, although there is a difficulty with self-completion of submucosal dissection. Better control of bleeding during submucosal dissection may be the key to improving completion rates and procedure times.

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Competing interests: None

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Risk factors for cardiac and pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment

Authors S. Coda[1], I. Oda[1], T. Gotoda[1], C. Yokoi[1], T. Kikuchi[1], H. Ono[2]

Institutions
[1] Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan
[2] Division of Endoscopy, Shizuoka Cancer Center Hospital, Shizuoka, Japan

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Corresponding author
I. Oda, MD
Endoscopy Division, National Cancer Center Hospital
5-1-1 Tsukiji, Chuo-ku
Tokyo 104-0045
Japan
Fax: +81-3-35423815
ioda@ncc.go.jp

Background and study aims: Bleeding and perforation are major complications of endoscopic submucosal dissection (ESD) for early gastric cancer (EGC), but post-ESD stenosis represents a severe delayed complication that can result in clinical symptoms such as dysphagia and nausea. The aims of this study were to determine the risk factors and evaluate the clinical treatment for post-ESD stenosis.

Methods: A total of 2011 EGCs resected by ESD at our institution between 2000 and 2005 were reviewed retrospectively. Resection was defined as cardiac when any mucosal defect was located in the squamocolumnar junction, and as pyloric when any mucosal defect was located < 1 cm from the pylorus ring. Post-ESD stenosis was defined when a standard endoscope could not be passed through the stenosis. We examined the incidence of post-ESD stenosis, its relationship with relevant factors, and the clinical course of post-ESD stenosis patients.

Results: Post-ESD stenosis occurred with seven of 41 cardiac resections (17%) and eight of 115 pyloric resections (7%). Circumferential extent of the mucosal defect of > 3/4 and longitudinal extent > 5 cm were each significantly related to occurrence of post-ESD stenosis with both cardiac and pyloric resections. All 15 affected patients were successfully treated by endoscopic balloon dilation.

Conclusions: A circumferential extent of the mucosal defect of > 3/4 or longitudinal extent of > 5 cm in length were both demonstrated to be risk factors for post-ESD stenosis, in both cardiac and pyloric resections, and endoscopic balloon dilation was shown to be effective in treating post-ESD stenosis.

Introduction

Currently, endoscopic resection is a widely accepted treatment for early gastric cancer (EGC) when the risk of lymph node metastasis is diagnosed as being very low or negligible [1–3]. Endoscopic submucosal dissection (ESD) is a new endoscopic resection method that facilitates one-piece resection even in patients with large or ulcerative lesions, thereby reducing local recurrence [4–9].

Although bleeding and perforation remain the most common complications, post-ESD stenosis represents a severe delayed complication that may result in clinical symptoms such as dysphagia and nausea. It is thought that post-ESD stenosis is caused by the removal of a large area when lesions are located near either the cardia or the pylorus, but only one case series about post-ESD stenosis in gastric ESDs has been reported so far [10]. The aims of this study were to determine the risk factors for post-ESD stenosis and evaluate the clinical treatment of post-ESD stenosis patients.

Patients and methods

We performed ESD with curative intent on 2011 EGCs in 1819 consecutive patients at the National Cancer Center Hospital in Tokyo between January 2000 and December 2005. Written informed consent was obtained from all patients before their ESD procedures. The median age of patients was 68 years (range 27–94) and the male/female ratio was 3.92 (1449/370). The ECG lesions were located in the upper third of the stomach in 326 instances, the middle third in 887, and the lower third in 798. Resection was defined as cardiac when any mucosal defect was located in the squamocolumnar junction, and as pyloric when any mucosal defect was located < 1 cm from the pylorus ring.

Table 1 Characteristics of patients with cardiac and pyloric resections.

	Cardiac resection n = 41	Pyloric resection n = 115
Age, median years (range)	68 (41 – 85)	70 (37 – 90)
Gender, n (%)		
Male	36 (88)	75 (65)
Female	5 (12)	40 (35)
Concomitant disease, n (%)		
Diabetes mellitus	4 (10)	8 (7)
Liver cirrhosis	0 (0)	5 (4)
Chronic heart failure	2 (5)	3 (3)
Autoimmune disease	0 (0)	3 (3)
Chronic renal failure	0 (0)	2 (2)
Circumferential extent of mucosal defect, n (%)		
≤ 1/2	28 (68)	81 (70)
1/2 – 3/4	6 (15)	16 (14)
> 3/4	7 (17)	18 (16)
Longitudinal extent of mucosal defect, n (%)		
≤ 5 cm	39 (95)	109 (95)
> 5 cm	2 (5)	6 (5)
Location of mucosal defect (center), n (%)		
Lesser curve	32 (78)	32 (28)
Anterior wall	3 (7)	32 (28)
Greater curve	2 (5)	22 (19)
Posterior wall	4 (10)	29 (25)
Perforation*, n (%)		
No	37 (90)	113 (98)
Yes	4 (10)	2 (2)
Lesion macroscopic type, n (%)		
Elevated	14 (34)	32 (28)
Depressed	24 (59)	65 (56)
Elevated and depressed	3 (7)	18 (16)
Depth of invasion, n (%)		
Mucosal	29 (71)	99 (86)
Submucosal	12 (29)	16 (14)
Ulcer finding, n (%)		
Absence	37 (90)	94 (82)
Presence	4 (10)	21 (18)

*All patients with perforations were successfully treated by endocopic clipping.

ESD procedures were performed with sedation using midazolam and pentazocine and began with identification of the lesion margins which were then marked with a needle knife. Submucosal injections were used to lift the mucosa followed by a circumferential mucosal incision around the lesion. Finally, submucosal dissection of the lesion was performed with an insulation-tipped knife (Olympus Medical Systems, Tokyo, Japan) [5]. The curative success of the ESDs was subsequently determined pathologically. As a general rule, we performed an additional gastrectomy with lymph node dissection after a noncurative ESD in which a resected specimen was diagnosed as indicating a possible risk of nodal metastasis, such as showing submucosal deep invasion or positive lymphatic invasion. [11] When a resected specimen was diagnosed as showing a curative resection, we usually performed an endoscopy to check the healing progress of the ESD mucosal defect 2 – 3 months later. If patients had undergone cardiac or pyloric resection or had any clinical symptoms, we carried out endoscopy earlier than 2 – 3 months after ESD. We then followed up the patients every 6 months or annually.

Post-ESD stenosis risk factors

Post-ESD stenosis was diagnosed by endoscopy and defined as existing when a standard 10-mm diameter endoscope could not be passed through an existing stenosis.

We reviewed the clinical records, endoscopic images, and endoscopic and pathological reports for all patients. Patients with cardiac and pyloric resection lesions were divided into two groups, that is, with and without post-ESD stenosis. The two groups were compared with regard to age, gender, concomitant disease that might affect ESD ulcer healing, circumferential extent of the mucosal defect, longitudinal extent of the mucosal defect, gastric location of the center of the mucosal defect, occurrence of perforation during ESD, macroscopic type of the lesion, depth of invasion, and finding of the presence of an ulcer.

The extent of the circumferential mucosal defect was classified into ≤ 1/2, 1/2 – 3/4 or > 3/4. The extent of the longitudinal mucosal defect was divided into ≤ 5 cm and > 5 cm. The gastric location of the center of the mucosal defect was categorized as lesser curve, anterior wall, greater curve, or posterior wall. These classifications were made by an experienced endoscopist who reviewed endoscopic images without being aware of the clinical outcomes.

Table 2 Risk factors for post-ESD stenosis following cardiac resection.

	Post-ESD stenosis		*P* value
	None n = 34	Present n = 7	
Age, mean years (range)	68 (41 – 85)	73 (54 – 80)	n. s.
Gender, n (%)			
Male	31	5 (14)	n. s.
Female	3	2 (40)	
Concomitant disease, n (%)			
Diabetes mellitus	3	1 (25)	n. s.
Chronic heart failure	2	0 (0)	n. s.
Circumferential extent of mucosal defect, n (%)			
≤ 3/4	34	0 (0)	< 0.01
> 3/4	0	7 (100)	
Longitudinal extent of mucosal defect, n (%)			
≤ 5 cm	34	5 (13)	0.03
> 5 cm	0	2 (100)	
Location of mucosal defect (center), n (%)			
Lesser curve	26	6 (19)	n. s.
Anterior wall	3	0 (0)	
Greater curve	2	0 (0)	
Posterior wall	3	1 (25)	
Perforation*, n (%)			
No	30	7 (19)	n. s.
Yes	4	0 (0)	
Lesion macroscopic type, n (%)			
Elevated	12	2 (14)	n. s.
Depressed	19	5 (21)	
Elevated and depressed	3	0 (0)	
Depth of invasion, n (%)			
Mucosal	24	5 (17)	n. s.
Submucosal	10	2 (17)	
Ulcer finding, n (%)			
Absent	31	6 (16)	n. s.
Present	3	1 (25)	

n. s., not significant.
*All patients with perforations were successfully treated by endocopic clipping.

Macroscopic lesion types were classified endoscopically as elevated type, depressed type, or elevated and depressed type, based on data collected from the endoscopic reports. Depth of invasion and the presence of an ulcer were determined pathologically, according to the findings from the pathological reports.

Clinical treatment of post-ESD stenosis patients

The clinical treatment of post-ESD stenosis patients was also investigated in our study. Endoscopic balloon dilation was indicated for post-ESD stenosis patients complaining of any clinical symptoms. A 15 – 18-mm or 18 – 20-mm wire-guided balloon dilator (CRE Wire-Guided Balloon Dilation Catheter; Boston Scientific, Natick, Massachusetts, USA) was used without fluoroscopic guidance. Endoscopic balloon dilation was performed once or twice a week as necessary whenever the degree of post-ESD stenosis was severe. The interval was extended gradually to every 2 weeks and then every month as the patient's condition improved, and endoscopic balloon dilation was continued until the patient's post-ESD stenosis and clinical symptoms were resolved completely.

Data were analyzed using the chi-squared test, Fisher's exact test or the Student *t* test as appropriate (Statview; Abacus Concepts, Berkeley, California, USA). Value differences of $P < 0.05$ were considered statistically significant.

Results

Post-ESD stenosis risk factors

Post-ESD stenosis was associated with 15 of the 2011 lesions (0.7%) previously treated by ESD, in 15 of the 1819 patients. Of the other 1804 patients, 209 underwent gastrectomies because the ESDs were noncurative, while 84 received their first follow-up endoscopy examinations at other hospitals with no subsequent referrals to our hospital. None of the remaining 1511 patients showed signs of post-ESD stenosis, either at the first follow-up endoscopy after ESD at our hospital to check the healing progress of the mucosal defect or at any of their subsequent follow-up examinations.

All 15 post-ESD stenosis cases were induced by ESDs involving either the cardiac or pyloric resections that had comprised 41 of the 326 upper third lesions (13%) and 115 of the 798 lower third lesions (14%), respectively (**Table 1**). Post-ESD stenosis occurred following seven of the 41 cardiac resections (17%) and eight of the 115 pyloric resections (7%). All of the post-ESD stenosis patients were diagnosed before undergoing a routine first follow-up endoscopy examination, because each of the seven stenosis patients who had undergone cardiac resection experienced dysphagia while all eight of the pyloric resection stenosis patients suffered from severe nausea, with six of them actually vomiting due to the large amount of residual food in their stomachs.

Table 3 Risk factors for post-ESD stenosis following pyloric resection.

	Post-ESD stenosis		*P* value
	None n = 107	Present n = 8	
Age, mean years (range)	70 (37–90)	74 (51–83)	n.s.
Gender, n (%)			
Male	70	5 (7)	n.s.
Female	37	3 (8)	
Concomitant disease, n (%)			
Diabetes mellitus	8	0 (0)	n.s.
Liver cirrhosis	5	0 (0)	n.s.
Chronic heart failure	3	0 (0)	n.s.
Autoimmune disease	3	0 (0)	n.s.
Chronic renal failure	2	0 (0)	n.s.
Circumferential extent of mucosal defect, n (%)			
≤ 3/4	97	0 (0)	< 0.01
> 3/4	10	8 (44)	
Longitudinal extent of mucosal defect, n (%)			
≤ 5 cm	107	2 (2)	< 0.01
> 5 cm	0	6 (100)	
Location of mucosal defect (center), n (%)			
Lesser curve	29	3 (9)	n.s.
Anterior wall	29	3 (9)	
Greater curve	21	1 (5)	
Posterior wall	28	1 (3)	
Perforation*, n (%)			
No	105	8 (7)	n.s.
Yes	2	0 (0)	
Lesion macroscopic type, n (%)			
Elevated	28	4 (13)	n.s.
Depressed	62	3 (5)	
Elevated and depressed	17	1 (6)	
Depth of invasion, n (%)			
Mucosal	93	6 (6)	n.s.
Submucosal	14	2 (13)	
Ulcer finding, n (%)			
Absent	88	6 (6)	n.s.
Present	19	2 (10)	

n.s., not significant.
*All patients with perforations were successfully treated by endocopic clipping.

The median period from ESD to the diagnosis of post-ESD stenosis was 22 days (range 16–33) in the cardiac resection patients and 27 days (range 15–46) in the pyloric resection patients.
The data for post-ESD stenosis following cardiac and pyloric resections are shown in ▶ **Table 2** and ▶ **Table 3**, respectively. A circumferential mucosal defect > 3/4 in extent and a longitudinal mucosal defect > 5 cm in extent were each significantly related to the development of post-ESD stenosis in both cardiac and pyloric resections.

Clinical treatment of post-ESD stenosis patients

Each of the 15 post-ESD stenosis patients required endoscopic balloon dilation treatment. The clinical symptoms related to the stenosis were completely resolved in every patient in response to either single (one patient) or repeated (14 patients) endoscopic balloon dilation sessions. The median number of dilations and the median period from the first to the last dilation are shown in ▶ **Table 4**. No complications were observed after any endoscopic balloon dilation treatments.
Two patients, one each with post-ESD stenosis following cardiac resection and pyloric resection, underwent an additional gastrectomy with lymph node dissection following endoscopic balloon dilation treatment because their resected ESD specimens were subsequently pathologically diagnosed as showing a possible risk of lymph node metastasis. Those two patients were excluded from the analysis of follow-up data after repeated endoscopic balloon dilation treatment. During the median follow-up period of 36 months (range 2–63 months) for the other 13 post-ESD stenosis patients, the patency of the cardiac and pyloric lumens was well maintained and there were no further symptoms. The patient with the 2-month follow-up period subsequently received medical care at another institution with no further referral to our hospital.

Discussion

In the past, the accepted indications for conventional endoscopic mucosal resection (EMR) of EGC were a small intramucosal cancer ≤ 2 cm in size, of a differentiated histological type, and without an ulcer finding. This was because of technical limitations associated with the EMR procedure [4]. More recently, however, indications for the endoscopic resection of EGC have been expanded, based on a very low or negligible risk of lymph node metastasis

	Cardiac resection	Pyloric resection	*P* value
Number of dilations, median (range)	5 (1 – 14)	9 (7 – 40)	n. s.
Period of dilation treatments, median days (range)	42 (1 – 120)	50 (28 – 198)	n. s.

n. s., not significant

Table 4 Endoscopic balloon dilation treatment in patients with post endoscopic submucosal dissection (ESD) stenosis following cardac and pyloric resections.

as determined from a large number of surgical EGC cases [3,4,12]. The expanded indications include lesions > 20 mm and ulcerated lesions that would otherwise be difficult to resect by means of conventional EMR. Both kinds of lesions were previously resected by surgery, but the relatively new ESD technique has been developed to achieve the one-piece resection of even large and ulcerated lesions [4 – 9].

The number of EGC patients who undergo endoscopic resection is increasing in Japan because of the expanded indications and technical improvements mentioned above. Consequently, the number of endoscopic resection-related complications has also increased, so endoscopists must be aware of both the risk factors and the incidence of complications as well as knowing how to effectively treat such complications. Although cases of bleeding and perforation related to ESD of EGC have previously been reported [5,13,14], so far only one case series about post-ESD stenosis in gastric ESDs has been published [10].

This is the first study to determine the incidence of post-ESD stenosis in EGC lesions and the associated risk factors. The present study has shown that a circumferential mucosal defect of extent > 3/4 and a longitudinal mucosal defect of extent > 5 cm were each significantly related to the development of post-ESD stenosis in both cardiac and pyloric resections. Similar results have been reported in a study investigating esophageal stenosis after EMR of superficial esophageal cancer [15]. Knowledge of the risk factors associated with the subsequent development of post-ESD stenosis will allow endoscopists to better anticipate the likelihood of this complication.

Bleeding and perforation are complications that usually happen during ESD or within 24 hours after the procedure [5,13,14] so immediate treatment is normally required in such cases. In contrast, however, it is thought that post-ESD stenosis manifests itself several weeks after ESD, during the actual healing process. In this study, the median period from ESD to the diagnosis of post-ESD stenosis was 22 days in cardiac resection stenosis cases and 27 days in pyloric resection stenosis cases. Appropriate endoscopic follow-up to check for the subsequent presence of post-ESD stenosis, therefore, is recommended for patients with either of the identified risk factors for this complication. In order to minimize or prevent post-ESD stenosis-related symptoms from occurring, however, it may be advisable to start balloon dilation before the stenosis actually develops in such patients.

The clinical significance of post-ESD stenosis is that it decreases a patient's quality of life. In the present study, all 15 post-ESD stenosis patients developed a clinical symptom that was successfully relieved by either single (one patient) or repeated (14 patients) endoscopic balloon dilation treatment, and the patency of the cardiac and pyloric lumens was well maintained during a sufficiently lengthy follow-up period. Based on our findings, endoscopic balloon dilation can be regarded as an effective therapy for post-ESD stenosis although the number of patients was limited in this study. Similar effectiveness of endoscopic balloon dilation for the treatment of esophageal stenosis after EMR of superficial esophageal cancer has also been reported [15]. Patients with stenosis following pyloric resection required more balloon dilation procedures over a longer period compared with those with cardiac resections, although there was no significant difference between the two groups, probably once again because of the small number of patients involved (**Table 4**). In our study there were no complications after any of the balloon dilations, but the number of patients was limited and perforations related to endoscopic balloon dilation have been reported [10], so enhanced efforts should be made to preclude the development of post-ESD stenosis in the first place. In this regard, there is a recent case report of a biodegradable esophageal stent effective for patients with esophageal stenosis after ESD [16] that may be useful in preventing post-ESD stenosis from developing in patients with cardiac or pyloric resections.

In conclusion, the results of this retrospective study demonstrate that cardiac or pyloric resections in which the extent of the mucosal defect is > 3/4 circumferentially or > 5 cm longitudinally carry a risk for the occurrence of post-ESD stenosis, and that endoscopic balloon dilation can be an effective treatment for such post-ESD stenosis.

Competing interests: None

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Risk of perforation during endoscopic submucosal dissection using latest insulation-tipped diathermic knife (IT knife-2)

Endoscopic submucosal dissection (ESD) enables en bloc resection of lesions regardless of tumor size or location. The insulation-tipped (IT) diathermic knife (Olympus Medical Systems Corp., Tokyo, Japan) is a proven endoscopic device for ESD [1,2]. ESD gastric perforations using the IT knife usually happen during submucosal dissection [3]. However, we present an ESD perforation case that occurred when an IT knife-2, an improved version of the IT knife [4], was being used for circumferential mucosal incision.

A 59-year-old man presented a superficial depressed-type 20-mm lesion (**Fig. 1**), histologically diagnosed as a well-differentiated adenocarcinoma. Under sedation and following submucosal injection of normal saline solution, an initial incision was performed using a needle knife (Olympus Medical Systems Corp.). After the tip of the IT knife-2 had been inserted into the initial incision (**Fig. 2a**), an unexpected perforation occurred during the circumferential mucosal incision (**Fig. 2b**, **Video 1**). The resection was discontinued and the perforation was successfully closed using endoscopic clips (**Fig. 3**).

A recent study evaluated the use of the IT knife-2 over the original IT knife, reporting a significantly shorter operating time with no significant changes in the en bloc resection and complication rates [4]. The addition of a three-pronged blade directly beneath the insulation tip of the IT knife-2 seems to be the reason for an increased cutting ability from a vertical view, an enhanced lateral cutting capability, and a greater facility to hook the tissue edge prior to cutting (**Fig. 4a** and **b**). However, it is our belief that the perforation reported here would not have occurred if the original IT knife had been used at the time. Therefore, more gentle manipulation than that required with the original IT knife should be adopted during circumferential mucosal incision, especially by endoscopists who are inexperienced in the use of this recently developed device.

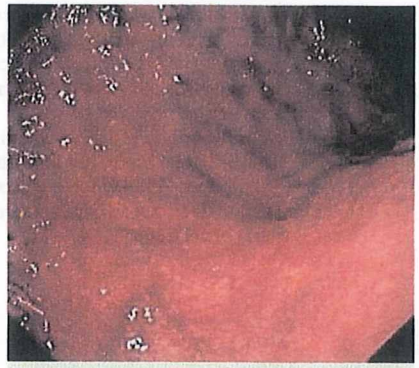

Fig. 1 Endoscopic finding of early gastric cancer. A superficial depressed lesion located in the posterior wall of the lower gastric body was revealed by conventional endoscopy.

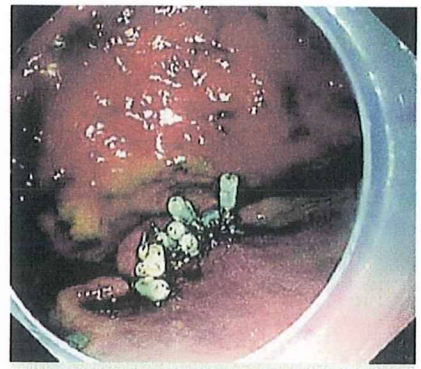

Fig. 3 Closure of the perforation was successfully performed using endoscopic clips.

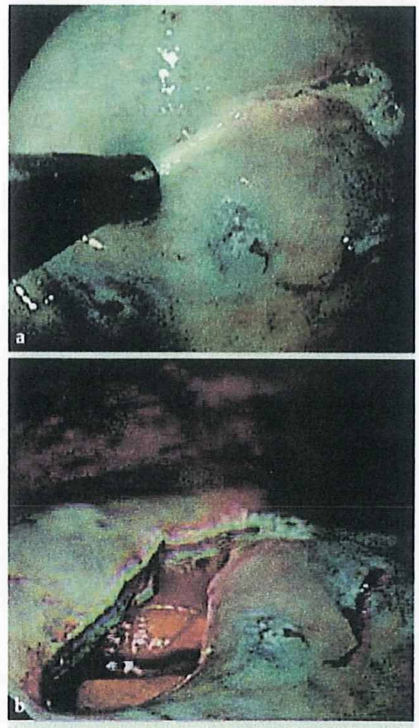

Fig. 2 Circumferential mucosal incision. **a** Circumferential mucosal incision had just begun using the insulation-tipped (IT) knife-2 from the point of small initial incision made with a needle knife. **b** Perforation occurred at the beginning of the circumferential mucosal incision.

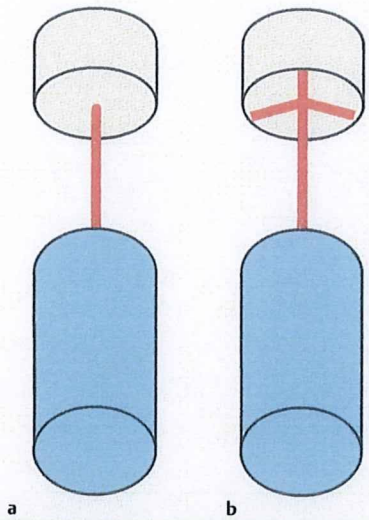

Fig. 4 The difference between the original IT knife and the IT knife-2. **a** There is no blade underneath the insulation tip of the original IT knife. **b** The IT knife-2 has a three-pronged blade directly beneath the insulation tip.

Video 1

Endoscopic submucosal dissection gastric perforation using the IT knife-2 during circumferential mucosal incision.

Endoscopy_UCTN_Code_CPL_1AH_2AZ

S. A. Con[1,2], **I. Oda**[1], **H. Suzuki**[1], **C. Kusano**[1], **S. Kiriyama**[1], **T. Gotoda**[1]

[1] Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

[2] Surgery and Endoscopy Divisions, Centro Digestivo Doctores Con-Medi-plaza, San Jose, Costa Rica

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Corresponding author

I. Oda, MD

Endoscopy Division

National Cancer Center Hospital

5-1-1 Tsukiji

Chuo-ku

Tokyo 104–0045

Japan

Fax: +81-3-35423815

ioda@ncc.go.jp

Mixed-histologic-type submucosal invasive gastric cancer as a risk factor for lymph node metastasis: feasibility of endoscopic submucosal dissection

Authors N. Hanaoka[1], S. Tanabe[1], T. Mikami[2], I. Okayasu[2], K. Saigenji[1]

Institutions
[1] Department of Gastroenterology, Kitasato University School of Medicine, Sagamihara-City, Kanagawa, Japan
[2] Department of Pathology, Kitasato University School of Medicine, Sagamihara-City, Kanagawa, Japan

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Corresponding author
N. Hanaoka, MD
Department of Gastroenterology
Kitasato University School of Medicine
2-1-1 Asamizodai
Sagamihara-City
Kanagawa 228-8520
Japan
Fax: +81-42-7484288
noboley1121@aol.com

Background and study aims: The clinicopathologic features of gastric cancers containing a mixture of differentiated-type and undifferentiated-type components remain uninvestigated. We evaluated the risk of lymph node metastasis and the feasibility of endoscopic submucosal dissection (ESD) for the treatment of mixed-histologic-type gastric cancers.

Patient and methods: We histologically classified 376 cases of gastric cancer with submucosal invasion into four types (differentiated type, differentiated-type-predominant mixed type, undifferentiated-type-predominant mixed type, and undifferentiated type) and studied the clinicopathologic relations of each type to lymph node metastasis. Lymphatic invasion was evaluated by D2–40 immunostaining.

Results: The overall prevalence of lymph node metastasis in gastric cancer with submucosal invasion was 16.5% (62/376). The prevalence of lymph node metastasis was 36.5% (23/63) in undifferentiated-type-predominant mixed type, which was significantly higher than those in the other three types ($P < 0.001$ vs. differentiated type, $P = 0.013$ vs. differentiated-type-predominant mixed type, and $P = 0.003$ vs. undifferentiated type). Lymphatic invasion, a depth of invasion of 500 µm or more from the lower margin of the muscularis mucosae (SM2), tumor size above 30 mm, and undifferentiated-type-predominant mixed histologic type were independent risk factors for lymph node metastasis. Submucosal cancers without these four risk factors were free of lymph node metastasis (0/41; 95% confidence interval 0%–8.6%).

Conclusions: Undifferentiated-type-predominant mixed-type gastric cancer with submucosal invasion carries a high risk of lymph node metastasis. ESD can be indicated for gastric cancer with submucosal invasion provided that the following conditions indicating a low risk of metastasis are met: a depth of invasion of no more than 500 µm or more from the lower margin of the muscularis mucosae (SM1), no lymphatic invasion, a tumor size of no more than 30 mm, and a proportion of undifferentiated components below 50%.

Introduction

Early gastric cancer is defined as a carcinoma that is confined to the mucosa or submucosa (depth of invasion from the lower margin of the muscularis mucosae < 500 µm, SM1; depth of invasion from the lower margin of the muscularis mucosae ≥ 500 µm, SM2), irrespective of the presence or absence of lymph node metastasis [1]. Pathologically, gastric cancer can be broadly divided into two types according to the presence or absence of tubular structures: these are the differentiated type and the undifferentiated type [1]. Characteristically, undifferentiated gastric cancer carries a higher risk of lymph node metastasis than does differentiated gastric cancer [2–5]. However, in some cases gastric cancer includes a mixture of differentiated and undifferentiated components. Gastric cancers that include a mixture of differentiated and undifferentiated components are classified according to the predominant histologic type by the Japanese Classification of Gastric Carcinoma [1].

Many studies have examined lymph node metastasis in early gastric cancer. The incidence of lymph node metastasis in intramucosal gastric cancer is estimated to be 2% [2,3,6,7]. Lymph node metastasis is present in about 20% of all cases of gastric cancer with submucosal invasion [4,5,8–10]. Cancer with SM2 invasion, undifferentiated-type cancer, and lymphatic invasion are independent risk factors for lymph node metastasis [2,4,5]. However, the advent of new devices such as insulation-tipped knives, the development of techniques for endoscopic submucosal dissection (ESD) [11], and a better understanding

of the characteristics of lesions with an extremely low risk of lymph node metastasis have provided technical and theoretical bases for the en bloc resection of lesions larger than those resectable by conventional endoscopic mucosal resection (EMR) [2,4,12–15]. ESD is now indicated for the treatment of differentiated-type early gastric cancers with SM1 invasion that are 30 mm or less in diameter [2,4]. The indications for endoscopic resection are now gradually being extended to submucosal invasive gastric cancers that previously required surgical resection. To our knowledge, however, no previous study has evaluated the clinicopathologic features, prevalence of lymph node metastasis, lymphatic invasion, and ulceration of early gastric cancer containing both differentiated-type and undifferentiated-type components. Indications for the endoscopic treatment of mixed-histologic-type early gastric cancers have also not been evaluated.

Materials and methods

The study group comprised 376 patients with primary gastric cancer invading the submucosa (99 patients with SM1 invasion and 277 with SM2 invasion) who underwent surgical resection and a D2 lymphadenectomy according to the Japanese Classification of Gastric Carcinoma at Kitasato University East Hospital from 1995 through 2006. All lesions were thinly sliced at intervals of 3 to 5 mm. One section each of all dissected lymph nodes (at least 15 nodes per case) was stained with hematoxylin and eosin. The cut sections were examined histologically to assess the presence or absence of metastasis. To assess histologic type, all specimens were reviewed to determine the percentages of differentiated-type components (well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma) and undifferentiated-type components (poorly differentiated adenocarcinoma and signet-ring cell carcinoma) [1]. The lesions were classified into the following four categories according to the proportions of intramucosal undifferentiated-type components: differentiated type (A), differentiated-type-predominant mixed type (B), undifferentiated-type-predominant mixed type (C), and undifferentiated type (D). The percentages of undifferentiated-type components were 0% in A, more than 0% but less than 50% in B, 50% or more but less than 100% in C, and 100% in D. A representative case of mixed-type gastric cancer is shown in **Fig. 1**.

The patterns of submucosal invasion were classified into four types (**Fig. 2**).

The horizontal length of submucosal invasion was measured histologically on the sections with greatest invasion (**Fig. 3**).

The number of lymphatic invasion sites and the number of lymphatic invasion sites per millimeter of submucosal invasion were calculated. Data on patient sex and age and tumor location, macroscopic type, and size were collected from the patients' medical records and pathology reports.

Immunohistochemistry

Lymphatic invasion by cancer cells was identified immunohistochemically using D2–40 antibody (DakoCytomation, Glostrup, Denmark) and an EnVision+ kit (DakoCytomation). One representative slide including the site of deepest invasion was selected for each case. Sections 4µm thick were cut from the formalin-fixed, paraffin-embedded tissue. The sections were mounted on coated slides and deparaffinized in xylene. Nonspecific reactions were blocked with 0.3% hydrogen peroxide in methanol for 15 minutes and the blocking solution of the EnVision+ kit. Then, the sections were incubated with the D2–40 antibody at a 1:50 dilution in phosphate-buffered saline for 1 hour at room temperature. After incubation, staining was performed according to the manufacturer's instructions. 3-3'-Diaminobenzidine was used as the final chromogen, and nuclei were counterstained

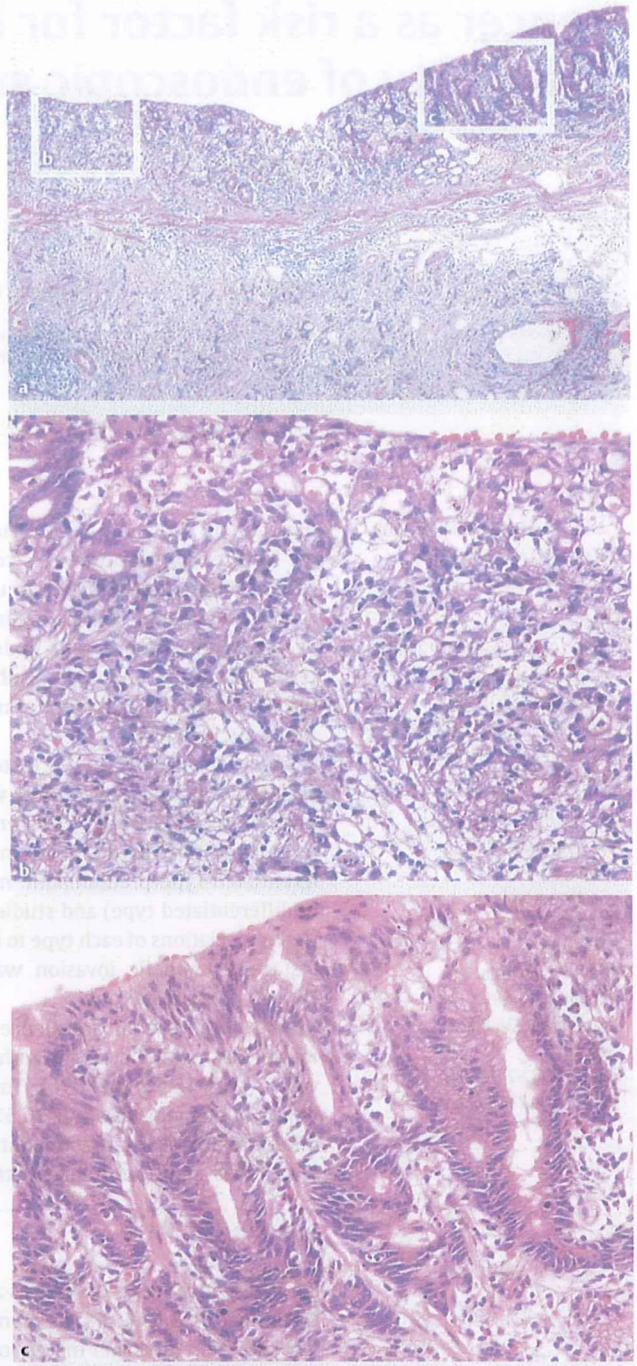

Fig. 1 Representative case of mixed-type (differentiated and undifferentiated) gastric carcinoma. **a** In the lamina propria, the right half of the tumor consists of the differentiated type and the left half of the undifferentiated type. The submucosal invasion consists of the undifferentiated type. **b** Box **b** in **a**, at higher magnification. **c** Box **c** in **a**, at higher magnification.

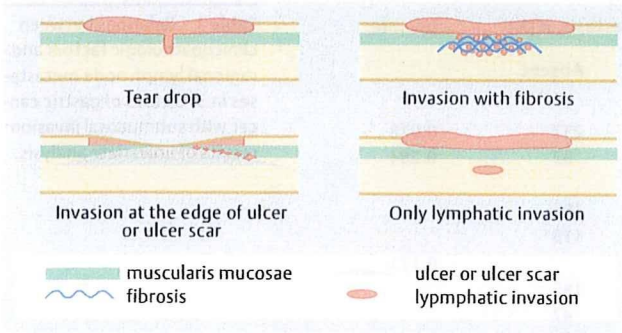

Fig. 2 Patterns of submucosal invasion.

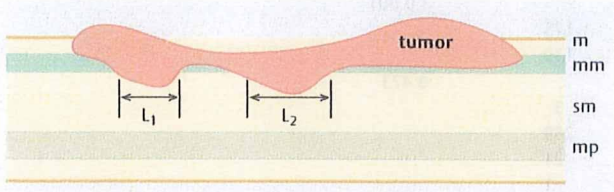

Fig. 3 Definition of horizontal length of submucosal invasion. $L = L_1 + L_2 + \ldots + L_n$, horizontal length of submucosal invasion; m, mucosa; mm, muscularis mucosae; sm, submucosa; mp, muscularis propria.

with Mayer's hematoxylin to facilitate histopathologic assessment. Two pathologists (N.H. and T.M.) checked the slides to identify and count the number of lymphatic invasion sites, which appeared as cancer cell nests surrounded by D2–40-positive lymphatic endothelium (● **Fig. 4**).

Ethical approval

This work using pathological samples in Kitasato University East Hospital (with the informed consent of patients) was approved by our Medical School and University Ethics Committee.

Statistical analysis

To assess differences in tumor size and horizontal length of submucosal invasion among the four histologic groups (A, B, C, D), the Kruskal–Wallis test was used, followed by evaluation with the Mann–Whitney *U* test for multiple comparisons. Resulting *P* values were corrected according to the Bonferroni method. The x^2 test was used to compare other clinicopathologic features. Multivariate logistic-regression analysis was performed with SPSS (version 11.0 in 2001; SPSS, Chicago, Illinois, USA). *P* values of less than 0.05 were considered to indicate statistical significance.

Results

The prevalence of lymph node metastasis was 16.5% (62/376) overall, 4.0% (4/99) in patients with SM1 invasion, and 20.9% (58/277) in those with SM2 invasion. Univariate analysis demonstrated that tumor size (> 30 mm), lymphatic invasion, histologic type, depth of invasion (SM2), and histologic type of the invasion front (undifferentiated type) differed significantly between patients with and those without lymph node metastasis (● **Table 1**).

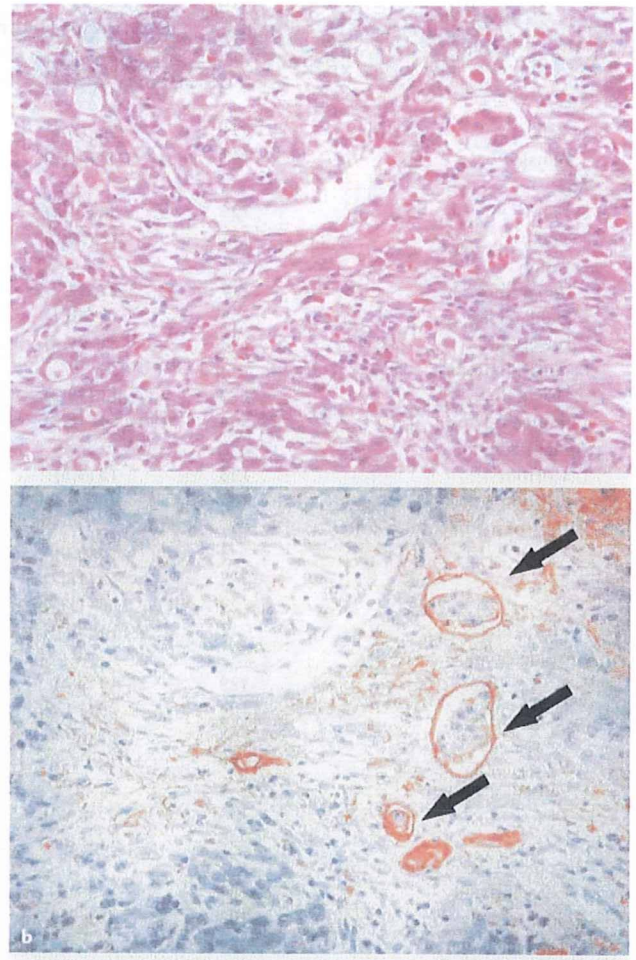

Fig. 4 **a** Submucosal invasion front of an undifferentiated-type gastric carcinoma. **b** Lymphatic invasion of cancer cells after D2–40 immunostaining. Cancer cells can be easily identified in lymphatic vessels (arrows).

Multivariate analysis of these risk factors indicated that lymphatic invasion, depth of invasion (SM2), tumor size (> 30 mm), and histologic type (C, undifferentiated-type-predominant mixed type) were independent risk factors for lymph node metastasis (● **Table 2**).

Relation between histologic type and lymph node metastasis

The prevalence of lymph node metastasis was 5.4% (7/129) in differentiated type (A), 19.2% (20/104) in differentiated-type-predominant mixed type (B), 36.5% (23/63) in undifferentiated-type-predominant mixed type (C), and 15.0% (12/80) in undifferentiated type (D). The prevalence of lymph node metastasis was highest in undifferentiated-type-predominant mixed type (C) ($P < 0.001$ vs. A, $P = 0.019$ vs. B, and $P = 0.0029$ vs. D) (● **Table 3**).

Submucosal cancers with a depth of invasion of SM1, no lymphatic invasion, a tumor size equal to or less than 30 mm, and consisting of less than 50% of undifferentiated components were free of lymph node metastasis (0/41; 95% confidence interval 0%–8.6%).

	n	Lymph node metastasis, n (%)		p-value
		Present	Absent	
Sex				
Male	271	39 (14.4)	232	0.078
Female	105	23 (21.9)	82	0.284
Age				
< 60	229	34 (14.8)	195	
≥ 60	147	28 (19.0)	119	
Location				0.171
Upper third	217	32 (14.7)	185	
Middle third	56	9 (16.1)	47	
Lower third	103	21 (20.4)	82	
Macroscopic type				0.758
Elevated	72	11 (15.3)	61	
Depressed	304	51 (16.8)	253	
Tumor size				< 0.001
≤ 30 mm	193	18 (9.3)	175	
> 30 mm	183	44 (24.0)	139	
Pattern of submucosal invasion*				0.473
1	3	0 (0.0)	3	
2	347	58 (16.7)	289	
3	24	3 (12.5)	21	
4	2	1 (50.0)	1	
Histologic type †				< 0.001
A	129	7 (5.4)	122	
B	104	20 (19.2)	84	
C	63	23 (36.5)	40	
D	80	12 (15.0)	68	
Lymphatic invasion				< 0.001
Yes	131	45 (34.4)	86	
No	245	17 (6.9)	228	
Histologic type of invasion front				< 0.001
Differentiated	183	17 (9.3)	166	
Undifferentiated	193	45 (23.3)	148	
Depth of invasion‡				< 0.001
SM1	99	4 (4.0)	95	
SM2	277	58 (20.9)	219	

Table 1 Relations between clinicopathologic factors and regional lymph node metastases in 376 cases of gastric cancer with submucosal invasion: results of univariate analysis.

* 1, teardrop type; 2, invasion with fibrosis; 3, invasion at the edge of ulcer or ulcer scar; 4, only lymphatic invasion.
† A, differentiated type; B, differentiated-type-predominant mixed type; C, undifferentiated-type-predominant mixed type; D, undifferentiated type.
‡ SM1, depth of invasion from the muscularis mucosae < 500 µm; SM2, depth of invasion from the muscularis mucosae ≥ 500 µm.

Clinicopathologic feature	Relative risk (95 % CI)	SE	P value
Lymphatic invasion (presence vs. absence)	5.28 (2.73 – 10.22)	0.337	< 0.001
Depth of invasion (SM2 vs. SM1)	3.41 (1.14 – 10.23)	0.560	0.029
Tumor size (> 30 vs. ≤ 30 mm)	2.58 (1.35 – 4.91)	0.329	0.004
Histologic type (C vs. non-C)	2.35 (1.12 – 4.96)	0.380	0.024

CI, confidence interval; SE, standard error.

Table 2 Risk factors for regional lymph node metastasis in 376 cases of gastric cancer with submucosal invasion: results of multivariate analysis.

Relations of histologic type and tumor size to lymphatic invasion

The prevalence of lymphatic invasion was highest in undifferentiated-type-predominant mixed type (C) ($P < 0.001$ vs. A, $P = 0.02$ vs. B, and $P = 0.03$ vs. D). Tumor size (47.2 ± 34.5 mm) and the width of submucosal invasion (8.6 ± 7.4 mm) were greatest in undifferentiated-type-predominant mixed type (C) and differed significantly from the respective values in differentiated type (A, 31.5 ± 20.5, $P = 0.018$; 4.7 ± 5.1; $P < 0.001$) (**Table 3**). The number of lymphatic invasion sites per millimeter of submucosal invasion did not differ significantly among the histologic types. However, the presence of one or more lymphatic invasion sites per millimeter of submucosal invasion was associated with a higher prevalence of lymph node metastasis ($P = 0.030$) (**Table 4**).

Discussion

In the present study, we histologically classified early gastric cancers according to the percentage of undifferentiated components and found that the prevalence of lymph node metastasis was higher with the undifferentiated-type-predominant mixed type (C) than with the other histologic types. We also found that lymphatic invasion, SM2 invasion, tumor size, and undifferentiated-type-predominant mixed type were independent risk factors for lymph node metastasis in patients who had gastric cancer with submucosal invasion.

Previous clinicopathologic studies of gastric cancer, head and neck cancer, and breast cancer have demonstrated that lymphatic invasion is an extremely important risk factor for lymph node metastasis [16 – 18]. The advent of D2 – 40 immunostaining has

Table 3 Relations of histologic type and size of tumor to lymphatic invasion in 376 cases of gastric cancer.

Tumor type	Presence of lymph node metastasis, n (%)	Presence of lymphatic invasion, n (%)	Tumor size, mm, mean ± SD	Horizontal length of submucosal invasion, mm, mean ± SD	Number of lymphatic invasion sites, /mm, mean ± SD
A (n = 129)	7 (5.4)	24 (18.6)	31.5 ± 20.5	4.7 ± 5.1	0.50 ± 0.48
B (n = 104)	20 (19.2)	40 (38.5)	39.5 ± 25.9	6.0 ± 5.5	1.1 ± 2.3
C (n = 63)	23 (36.5*)	36 (57.1**)	47.2† ± 34.5	8.6‡ ± 7.4	1.2 ± 2.7
D (n = 80)	12 (15.0)	31 (38.8)	37.0 ± 22.2	6.7 ± 6.1	0.46 ± 0.69

P values were determined using the Mann-Whitney U test with Bonferroni correction.
*$P < 0.001$ vs. A, $P = 0.013$ vs. B, $P = 0.003$ vs. D (x^2 test).
**$P < 0.001$ vs. A, $P = 0.019$ vs. B, $P = 0.029$ vs. D (x^2 test).
†$P = 0.018$ vs. A.
‡$P < 0.001$ vs. A.

Table 4 Relation between lymph node metastasis and number of lymphatic invasion sites per millimeter of horizontal length of submucosal invasion in 376 cases of gastric cancer.

	n	Lymph node metastasis		*P* value
		Present	Absent	
Number of lymphatic invasion sites ≥ 1	24	13 (54.1*)	11	< 0.001
Number of lymphatic invasion sites < 1	107	33 (30.8)	74	
Cases without lymphatic invasion	245	16 (6.9)	229	

*$P = 0.030$ vs. number of lymphatic invasion sites < 1.

facilitated the identification of lymph vessels, and many studies have reported that immunostaining is useful for the evaluation of gastric cancer [19–23]. We therefore clinicopathologically studied the relationship of the histologic type of gastric cancer to lymph node metastasis from the viewpoints of lymphatic invasion and histogenesis.

Undifferentiated-type-predominant mixed type (C) had the highest prevalence of lymphatic invasion. The presence of lymphatic invasion was characterized by a high prevalence of lymph node metastasis. In this study, the existence of one or more lymphatic invasion sites per millimeter of submucosal invasion was associated with an increased prevalence of lymph node metastasis. The higher prevalence of lymph node metastasis in undifferentiated-type-predominant mixed type (C) than in the other groups was attributed to the significant differences in the presence of lymphatic invasion among these groups.

The fact that the highest prevalence of lymphatic invasion is seen in undifferentiated-type-predominant mixed type (C) gastric cancer might be related to the size of the tumor and the horizontal length of the submucosal invasion, which were larger in this group than in the others. Lymph vessels are densely present from the muscularis mucosae to the upper layer of the submucosa [19]. With tumor-cell proliferation and extension to the muscularis mucosae and submucosa, the incidence of lymphatic invasion increases.

Gastric cancer generally shows greater histologic diversity than other types of cancer. Even tumors confined to the mucosa show histologic diversity, which tends to increase with deeper invasion and increased tumor diameter [24,25]. This notion is supported by the findings of Inoshita et al., who studied histologic diversity in gastric cancer. In elderly patients, they found that the differentiated type predominates in early gastric cancer, but that histologic diversity increases with progression to advanced cancer, resulting in higher proportions of undifferentiated type [26]. Peng and Honda et al. reported that undifferentiated-type gastric cancer with tubular components (C: undifferentiated-type-predominant mixed type) and undifferentiated-type gastric cancer (D) arise from different genetic pathways. They proposed that mixed-type gastric cancer can arise from either differentiated cells or undifferentiated cells [27,28]. Studies of mucin phenotype have reported that some cases of differentiated-type gastric cancer with gastric phenotype are transformed into undifferentiated-type gastric cancer during tumor growth and development, increasing the risk of lymph node metastasis [29–34]. However, further studies are needed to delineate the relation between histogenesis and the risk of metastasis.

At present, the indications for endoscopic resection include the treatment of submucosal cancers that meet the following four conditions: a tumor size of 30 mm or less, SM1 invasion, differentiated type, and no lymphatic invasion [2,4]. In our study, lymph node metastasis was not associated with submucosal cancers that met all of the following criteria: SM1 invasion, no lymphatic invasion, a tumor size of 30 mm or less, and less than 50% undifferentiated-type components (0/41; 95% confidence interval, 0% to 8.6%). Such cancers can be curatively treated by local endoscopic resection.

Gastric cancer is associated with underlying conditions such as acid-induced changes and chronic gastritis caused by persistent *Helicobacter pylori* infection. Disease progression is often accompanied by the formation of an ulcer or ulcer scar. It is challenging to predict preoperatively the percentage of undifferentiated components and to accurately diagnose the depth of tumor invasion on the basis of the fine surface characteristics of gastric cancers. In particular, the accuracy of endoscopic ultrasonography for predicting whether a tumor is confined to the mucosa or invades the submucosa is only about 80% [35]. Submucosal tumor invasion is frequently discovered on histopathologic examination after endoscopic resection. If an early gastric cancer is found to have SM1 invasion on histopathologic examination after endoscopic resection, the presence of a tumor that is 30 mm or greater is size, lymphatic invasion, or a 50% or higher percentage of undifferentiated components suggests an increased risk of lymph node metastasis. Additional surgical resection with lymph node dissection should therefore be considered.

Undifferentiated early gastric cancer has a high risk of lymph node metastasis [2–5]. To date, surgical resection has been the treatment of choice, but the feasibility of endoscopic resection is now being considered. Park et al. reported that endoscopic resec-

tion can be indicated for undifferentiated-type cancers that are 15 mm or less in diameter and have a submucosal invasion depth of up to 500 µm because these characteristics are associated with a low risk of lymph node metastasis [36]. In their study, however, histologic types and lymphatic invasion were not adequately evaluated. In our study, the incidence of lymph node metastasis was higher in undifferentiated-type-predominant mixed type (C) than in pure undifferentiated type (D) gastric cancer. Endoscopic resection should therefore not be conducted in patients with undifferentiated-type gastric cancer without detailed histopathologic studies, including assessments of histologic diversity and lymphatic invasion.

We believe that confirmation of lymphatic invasion by means of D2-40 immunostaining may lead to more accurate identification of cases at high risk of lymph node metastasis.

We conclude that histologically mixed-type gastric cancer with submucosal invasion can be considered for endoscopic resection provided that the following four conditions indicating a low risk of metastasis are met: a lower than 50% proportion of undifferentiated components, a tumor size of 30 mm or less, SM1 invasion, and no lymphatic invasion. Given the limited number of cases in this study, these findings should be confirmed by more data in the future.

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Competing interests: None

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Prospective clinical trial of magnetic-anchor–guided endoscopic submucosal dissection for large early gastric cancer (with videos)

Takuji Gotoda, MD, Ichiro Oda, MD, Katsunori Tamakawa, PhD, Hirohisa Ueda, PhD, Toshiaki Kobayashi, MD, PhD, Tadao Kakizoe, MD, PhD

Tokyo, Japan

Background: The treatment of early gastric cancer (EGC) by endoscopic submucosal dissection (ESD) has been rapidly gaining popularity in Japan. However, the procedure needs a high quality of skill. To facilitate complicated ESD by using a single working-channel gastroscope ("one-hand surgery method"), the magnetic-anchor-guided ESD (MAG-ESD) controlled by an extracorporeal electromagnet was reported to be successful in a porcine model.

Objectives: The purpose of this prospective clinical trial was to evaluate the feasibility of MAG-ESD for large EGC located on the gastric body in human beings.

Design: Prospective clinical trial at a single center.

Setting: National Cancer Center Hospital, Tokyo, Japan.

Subjects: From January 2005 to May 2006, 25 patients with EGC >20 mm in diameter, located in the gastric body, and intestinal-type histology were enrolled. Patients with a cardiac pacemaker, advanced malignancy in other organs, severe cardiac and/or pulmonary diseases, and uncontrolled hypertension and/or diabetes mellitus were excluded from this study.

Interventions: Similar to a standard ESD, the MAG-ESD procedure was performed with the patient under conscious sedation by intravenous injection of midazolam (3–5 mg) and pentazocine (15 mg).

Main Outcome Measurements: Unfavorable events and other intraoperative complications caused by the magnetic anchor or the magnetic force were recorded and evaluated. Two GI endoscopists (T.G., I.O.) assessed whether the magnetic anchor facilitated gastric ESD according to 2 criteria: "supportive" and "not supportive." The en bloc resection rate, complications, total operation time, bleeding, perforation, and recurrence rate were also evaluated. The total operation time was measured from insertion to withdrawal of the endoscope, including the retrieving of the magnetic anchor or anchors.

Results: All tumors were resected en bloc, without any perforations or severe uncontrollable bleeding. All magnetic anchors were safely retrieved. Two endoscopists assessed that the MAG system was supportive in 23 patients. None of the patients experienced physiologic and mental abnormalities as a result of long-term magnetic-field exposure. During a median follow-up of 20 months (15–32 months), neither delayed adverse effects nor allergies caused by the stainless steel of the magnetic anchor were observed.

Conclusions: MAG-ESD is a feasible and safe method that allowed an excellent visualization by suitable tissue tension and facilitated gastric ESD in patients with EGC. The system should be miniaturized to make it applicable in daily clinical practice. (Gastrointest Endosc 2009;69:10-5.)

Abbreviations: EGC, early gastric cancer; ESD, endoscopic submucosal dissection; IT-knife, insulation-tipped diathermic knife; MAG-ESD, magnetic-anchor-guided endoscopic submucosal dissection.

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It has been reported that endoscopic submucosal dissection (ESD) of early gastric cancer (EGC) improves the rate of successful en bloc resection.[1,2] An ESD by using an insulation-tipped diathermic knife (IT-knife), developed at the National Cancer Center Hospital, was the first of such techniques.[3,4] Other endoscopic devices for ESD have been developed.[5-7] ESD has been rapidly gaining popularity in Japan, primarily because of its ability to remove larger EGC en bloc, thus reducing a local recurrence caused by a piecemeal resection.[8] However, it is still an

investigational technique and requires a high level of skill from the endoscopists.[9-11]

Endoscopic resection should be safe, effective, and applicable to a wide variety of clinical situations. In particular, when EGC is located in the gastric body, an ESD is more complicated, and the rate of a complete resection is lower than in the gastric antrum.[12] The more difficult extension of the wall and the collection of fluid, including blood and/or gastric juice, hinder the performance of the ESD procedure. Optimal extension of the wall and visualization of the lesion is mandatory for a safe and feasible ESD.

To facilitate a complicated standard ESD procedure performed by using a single working-channel gastroscope (one-hand surgery), the magnetic-anchor–guided ESD (MAG-ESD) controlled by an extracorporeal electromagnet, was developed.[13] We reported that MAG-ESD facilitated the ESD procedure in the porcine model. The purpose of this prospective clinical trial was to evaluate the feasibility of MAG-ESD for large EGC in human beings.

Capsule Summary

What is already known on this topic

- Endoscopic submucosal dissection (ESD) is useful in the en bloc removal of large gastric lesions, thus reducing the risk of a local recurrence caused by piecemeal resection.
- Magnetic-anchor–guided ESD (MAG-ESD), controlled by an extracorporeal electromagnet, facilitates the standard ESD procedure performed by using a single working-channel gastroscope.

What this study adds to our knowledge

- In 25 patients with gastric cancer lesions >20 mm in diameter who underwent magnetic-anchor–guided ESD, all tumors were resected en bloc, without any perforations or severe uncontrollable bleeding, and all magnetic anchors were safely retrieved.
- No patient experienced physiologic or mental abnormalities as a result of long-term magnetic field exposure.

PATIENTS AND METHODS

Patients

The purpose of this prospective clinical trial was to evaluate the feasibility of MAG-ESD. Twenty-five patients with EGC >20 mm diameter, located in the gastric body, were enrolled. The patients were first seen on an outpatient basis, and the tumor was assessed by a gastroscopy. From January 2005 to May 2006, all patients with EGC >20 mm in diameter, located in the gastric body, and with intestinal-type histology underwent an ESD on an inpatient basis at the National Cancer Center Hospital, Tokyo, Japan. The ethics committee approved the study, and a detailed written informed consent was obtained from each patient. The presented study was conducted according to the Declaration of Helsinki.

The patients with a cardiac pacemaker, advanced malignancy in other organs, severe cardiac and/or pulmonary diseases, uncontrolled hypertension, and/or diabetes mellitus were excluded from this study. Pregnant or lactating women, and those who wished to become pregnant during the study were also excluded. Patients with tumors with recurrent disease, fibrosis, deeper invasion, or diffuse-type histology were excluded.

Standard ESD

The standard ESD procedure was initially started by using a standard gastroscope with a single working channel (GIF Q260 or Q240; Olympus Optical Co, Ltd, Tokyo, Japan).[14] Marking dots were placed approximately 5 mm outside the margin of the lesions by using a needle-knife (KD-1L-1; Olympus) and forced coagulation current 20 W (IC C200; ERBE, Tübingen, Germany). First, injection of diluted epinephrine (1:100,000) was performed to raise the submucosal layer and to insert the tip of the IT-knife into the submucosal layer. Then, a small initial incision was made by a standard needle-knife by using 80 W, effect 3 Endocut (ICC200; ERBE). Mucosal cutting at the periphery of the marking dots was circumferentially performed with an IT-knife (KD-610L; Olympus) with 80 W Endocut. After additional submucosal injection of diluted epinephrine, the submucosal layer below the lesion was directly dissected by using the same IT-knife. The final aim was to achieve en bloc resection.

All patients were sedated by intravenous injection of midazolam (3–5 mg) and pentazocine (15 mg), and, if necessary, conscious sedation was maintained with an additional injection of midazolam.

Magnetic anchor and extracorporeal electromagnetic control system

The magnetic anchor (Pentax Co, Tokyo, Japan) consists of 3 parts: a hand-made magnetic weight, made of magnetic stainless steel (SYS420F), microforceps, and a connecting thread. A 1.0 × 1.0 × 1.5-cm weight was designed to facilitate gastric ESD by use of an extracorporeal hands-free electromagnet, whereby magnetic forces allow a suitable counter-traction for submucosal dissection (Fig. 1). The anchor weight used for this procedure was approximately 6 g.

The magnetic control system (Fig. 2) consists of an electromagnet with up-and-down motion; a movable examination table was made by Tamakawa Co (Sendai, Japan) for use in a standard endoscopic room. The magnetic control system consisted of a 0.68 kOe/100A extracorporeal

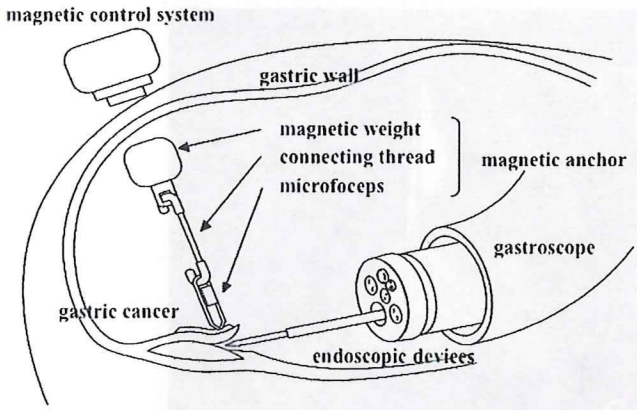

Figure 1. Concept of the MAG-ESD.

electromagnet, 350 mm in diameter, positioned at 10 cm from the center of the magnetic yoke. In this manner, the position of the electromagnet was adjusted according to the patient's physique. The examination table was able to move freely to be able to control the magnetic weight so as to achieve ideal mucosal lifting to allow the gastric submucosal dissection.

MAG-ESD

According to the standard ESD, after circumferential mucosal cutting by using an IT-knife, the procedure was switched to an MAG-ESD, controlled by a high-power electromagnet placed outside the body of the patient (Fig. 3). First, an overtube (Sumitomo Bakelite, Tokyo, Japan) was inserted into the esophagus. Second, a tube catheter was passed through the working channel of the gastroscope. A magnetic anchor, with a magnetic weight, a microforceps, and a connecting thread, was attached to the tip of the catheter. The gastroscope that carries the magnetic anchor was reinserted. Inside the stomach, the magnetic weight was pushed out from the catheter. According to the direction of gravity, the microforceps connected to the magnetic weight was placed at the mucosal edge (Video 1, available online at www.giejournal.org). The submucosal dissection by using an IT-knife was performed by suitable tissue tension with hands-free stabilization and visualization (Video 2, available online at www.giejournal.org).

If experienced endoscopists, who have performed more than 100 gastric ESDs, requested additional magnetic anchors to maneuver the traction direction of the exfoliated gastric tissue, then any numbers of magnetic anchors were attached. To maintain suitable tissue tension, either the patients were rotated or the direction of the magnetic anchor was repositioned by using the movable examination table. After endoscopic resection, both the resected tissue and the magnetic anchor or anchors were retrieved into the overtube by using a grasping forceps and were removed from the stomach.

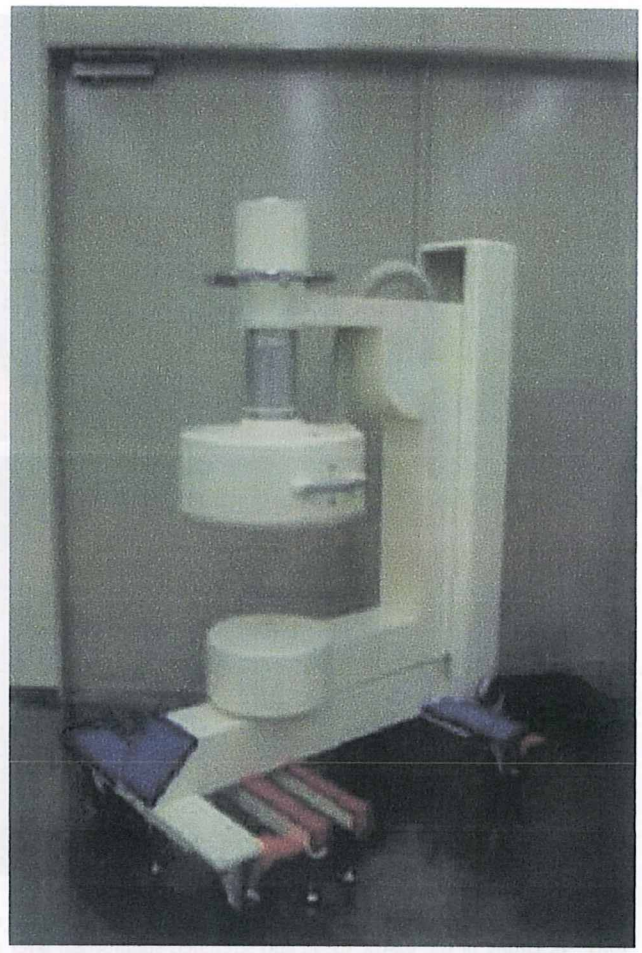

Figure 2. Extracorporeal electromagnetic control system.

Assessments

The demographic and clinical features of each patient were recorded in a case report form. Unfavorable events and other intraoperative complications caused by the magnetic anchor or the magnetic force were recorded and evaluated. We defined serious adverse events as those that lead to death, threat to life, notable disability, prolonged hospital stay, or hospitalization. Patients were followed-up until adverse events either dissipated or returned to pretreatment levels. Two GI endoscopists (T.G., I.O.) assessed, according to the 2 criteria, whether the magnetic anchor facilitated a gastric ESD. Once the dedicated endoscopists evaluated that the MAG-traction–facilitated gastric ESD compared with the standard gastric ESD technique, it was defined as "supportive." When the ESD procedure was not effectively influenced by using the MAG system, it was defined as "not supportive." The en bloc resection rate, complications, total operation time, bleeding, perforation, and recurrence rate were also evaluated. The total operation time was measured from gastroscope insertion to withdrawal, including retrieving the magnetic anchor or anchors.