Endoscopist	A	B	C
Years since graduation	7	10	5
Number of EGDs performed	2000	3200	1500
Number of EMRs performed for EGC	22	18	10
Number of colonoscopies performed	800	800	250
Number of ERCPs performed	20	65	10

Table 1 Profiles of three operating endoscopists.

EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; EGC, early gastric cancer; ERCP, endoscopic retrograde cholangiopancreatography.

Endoscopists	A	B	C	Total
Number of lesions	n = 30	n = 30	n = 30	n = 90
Median tumor size, mm (IQR)	15 (8.5)	15 (10.25)	13.5 (5.75)	15 (10)
Location of gastric lesions, n (%)				
Upper third	1 (3.3)	5 (17)	1 (3.3)	7 (7.8)
Middle third	13 (43)	11 (37)	14 (47)	38 (42)
Lower third	16 (53)	14 (47)	15 (50)	45 (90)
Type of tumors, n (%)				
Elevated	14 (47)	11 (37)	14 (47)	39 (43)
Depressed	16 (53)	19 (63)	16 (53)	51 (57)

Table 2 Characteristics of the lesions treated by ESD.

IQR: interquartile range

Table 3 Devices and settings of electrical surgical unit for each procedure.

Procedure	Device	ICC200	PSD60
Marking	Needle knife	Forced 20 W	Forced 30 W, effect 1
Mucosal incision	IT knife	Endo Cut 80 – 120 W, effect 3	Endo Cut 120 W, effect 3 (Endo Cut impulse 3, Endo Cut speed 16)
Submucosal dissection	IT knife	Forced coagulation 50 W	Forced coagulation 55 W, effect 2
	IT knife (fibrous submucosal tissue)	Endo Cut 80 – 120 W, effect 3	Endo Cut 120 W, effect 3 (Endo Cut impulse 3, Endo Cut speed 16)
Hemostasis	IT knife (small vessel)	Forced coagulation 50 W	Forced coagulation 55 W, effect 2
	Hemostatic forceps (large vessel)	Soft coagulation 80 W	Soft coagulation 80 W, effect 6

Patients and methods
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This case series was performed in the endoscopic training and learning center of a tertiary cancer referral center.

Participants

A total of three endoscopists were involved in this study. They had experience of at least 1500 regular esophagogastroduodenoscopy procedures and more than 10 endoscopic mucosal resections by the strip biopsy or cap methods (⦿ **Table 1**). Before starting ESD, the operators participated in pre- and postoperative conferences with surgeons, gastroenterologists, radiologists, and pathologists to learn about the diagnosis and management of gastric cancer. They attended ESD procedures performed by senior doctors, as assistants, for at least 1 year, and then attended a lecture about ESD techniques, using a manual and videos, by an experienced endoscopist.

We investigated the records of 30 consecutive ESD procedures performed by each of the three endoscopists, between June 2003 and February 2005, in 87 patients (68 men, 19 women, mean age 67 years). The lesions were allocated to the three endoscopists irrespective of tumor location and size. Lesion characteristics are shown in ⦿ **Table 2**. The indication for ESD in this study was differentiated-type mucosal EGC, without ulcers or scars, smaller than 2 cm, as described in the gastric cancer treatment guidelines issued by the Japanese Gastric Cancer Association [8]. Before treatment, anticipated results, possible risks and complications, and alternative treatments including surgery and no treatment, were explained by the operator to all the patients, who gave their written informed consent. Patients who had severe organ failure or coagulopathy were excluded. The study protocol was approved by the institutional review board at our center.

ESD procedure

All procedures were performed with a videoendoscope (GIF-Q240; Olympus Medical Systems Co., Ltd., Tokyo, Japan) that was fitted with a disposable attachment (D-201 – 11804; Olympus) on its tip. A needle knife (KD-1L-1; Olympus), an insulated-tip (IT) knife (KD-610L; Olympus), and hemostatic forceps (Coagrasper, FD-410LR; Olympus) were used in the procedure. The Intelligent Cut and Coagulation 200 (ICC-200; Erbe Elektromedizin GmbH, Tübingen, Germany) or Power Supply Diathermy 60 (PSD-60; Olympus) was used as an electrical surgical unit; the output settings are summarized in ⦿ **Table 3**. A solution of 2% epinephrine (Bosmin; Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) with 20% concentrated glycerin–fructose (Glyceol; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) was used for submucosal injection.

With the patient under sedation, the ESD procedure was performed as follows [6]. *Marking for removal:* The endoscope was inserted into the stomach, and the extent of the tumor was estimated under chromoendoscopic observation to determine the resection area. Marking dots were drawn circumferentially 3 mm from the tumor boundary by a needle knife. *Mucosal incision:* The epinephrine and glycerol solution was injected into the submucosa just outside the marking dots to elevate the lesion. The procedure was performed with a downward view in the antrum and a retroflex view in the corpus. A precut hole to insert the tip of the IT knife was made outside the region to be resected with the needle knife. The hole was made at the distal side of the lesion in an endoscopic view, and it needed to be sufficiently deep to reach the submucosa. The tip of the IT knife was inserted fully into the submucosa through the precut hole, and the proximal mucosa was cut continuously outside the marking dots using an Endo Cut mode. During mucosal incision, the ceramic tip was in contact with the gastric wall and was pulled with some tension. *Submucosal dissection:* Submucosal dissection was started after completion of the circumferential mucosal cut. The epinephrine and glycerol solution was injected into the submucosa to obtain sufficient mucosal elevation. The IT knife was moved laterally, with the tip continuously touching the gastric wall. Lateral movement was achieved by torquing the scope rather than by using the scope angle. Submucosal dissection was performed with the IT knife using the coagulation mode, or the Endo Cut mode if the submucosa was fibrous. *Hemostasis:* When hemorrhage was noted from small vessels, the bleeding point was coagulated with the blade of the IT knife, using forced coagulation. When hemorrhage from larger vessels was observed, the bleeding point was stopped with the hemostatic forceps using the soft coagulation mode. *Retrieval of the specimen and prevention of delayed hemorrhage:* After removal of the mucosal area, it was retrieved by grasping forceps (FG-47L-1; Olympus). The ulcer base was washed out repeatedly and any adherent clots or suspicious protrusions were coagulated by the hemostatic forceps to avoid delayed hemorrhage. Resected specimens were sent to the department of pathology for histological assessment of completeness of resection and curability.

Assistant policy

The entire procedures were performed under the supervision of an experienced endoscopist (N.U.). The supervisor was changed under the following circumstances: (1) overtime: when time for each mucosal incision and submucosal dissection exceeded 1 hour; (2) inability to achieve hemostasis: when spurting hemorrhage could not be stopped; (3) perforation; and (4) inability to continue the procedure: when the procedure could not be continued for reasons other than inability to achieve hemostasis, or perforation. If an operator changed supervisor, the procedure was regarded as not "self-completed."

All procedures were recorded digitally on video and all events relating to the procedure were recorded on dedicated operation records.

Measured outcome parameters

Complete resection and complication rates were evaluated for assessment of feasibility. Self-completion rate, operation time, learning curve, and reasons for incompletion were analyzed to elucidate procedural difficulties. For assessment the ESD procedure was divided into (i) mucosal incision and (ii) submucosal dissection by completion of the circumferential mucosal cut. Complete resection was defined as en bloc resection without cancer involvement to the lateral and vertical margin of the resected specimen, as shown by histology. Complications included delayed hemorrhage and perforation, which were classified as grade 3 or 4 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 [9]. Operation time was measured from the start of the mucosal incision until the end of tumor removal. "Self-completion" referred to a

Endoscopist	A	B	C	Total	P-value*
Complete resection, n (%)	28 (93)	28 (93)	28 (93)	84 (93)	
Complication, n (%)					
Delayed hemorrhage	1 (3.3)	1 (3.3)		2 (6.7)	
Perforation	1 (3.3)	1 (3.3)		2 (6.7)	
Self-completion, n (%)					
Mucosal incision	30 (100)	20 (67)	27 (90)	77 (86)	0.000
Submucosal dissection	23 (77)	15 (50)	16 (53)	54 (60)	
Median procedure time, minutes (IQR)					
Mucosal incision	19 (13)	23 (19)	33 (26)	23 (20)	0.000
Submucosal dissection	26 (33)	34 (28)	57 (59)	39 (38)	

Table 4 Evaluated parameters for feasibility of ESD.

*P-value for total mean procedure time and total self-completion rate of mucosal incision vs. submucosal dissection.

Procedure	A	B	C	Total (%)
Mucosal incision				
Overtime			2	2 (2)
Inability to achieve hemostasis		1	1	2 (2)
Perforation		1		1 (1)
Inability to continue procedure		8		8 (9)
Submucosal dissection				
Overtime	2	2	6	10 (11)
Inability to achieve hemostasis	1	2	2	5 (6)
Perforation	1			1 (1)
Inability to continue procedure	3	11	6	20 (22)

Table 5 Reasons for change of supervisor.

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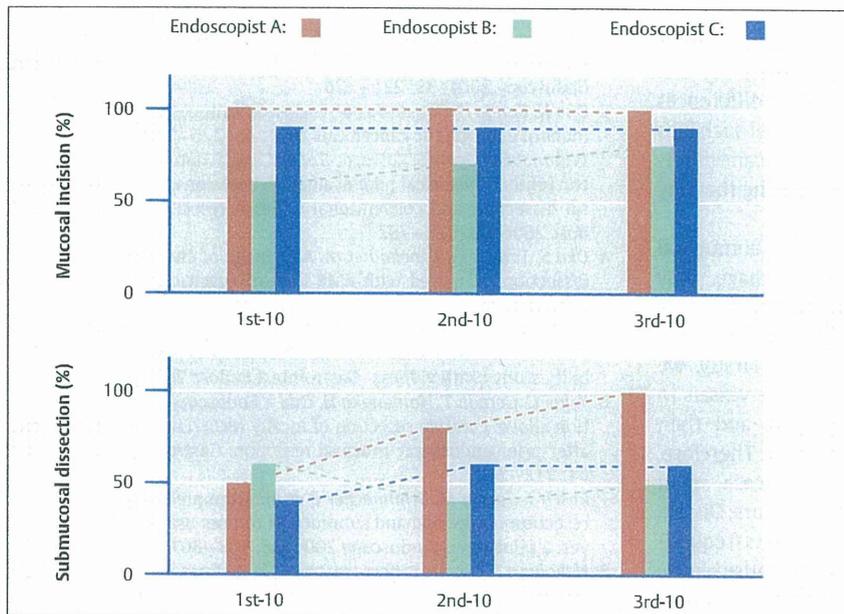
Fig. 1 Learning curves for self-completion rate for mucosal incision and endoscopic submucosal dissection.
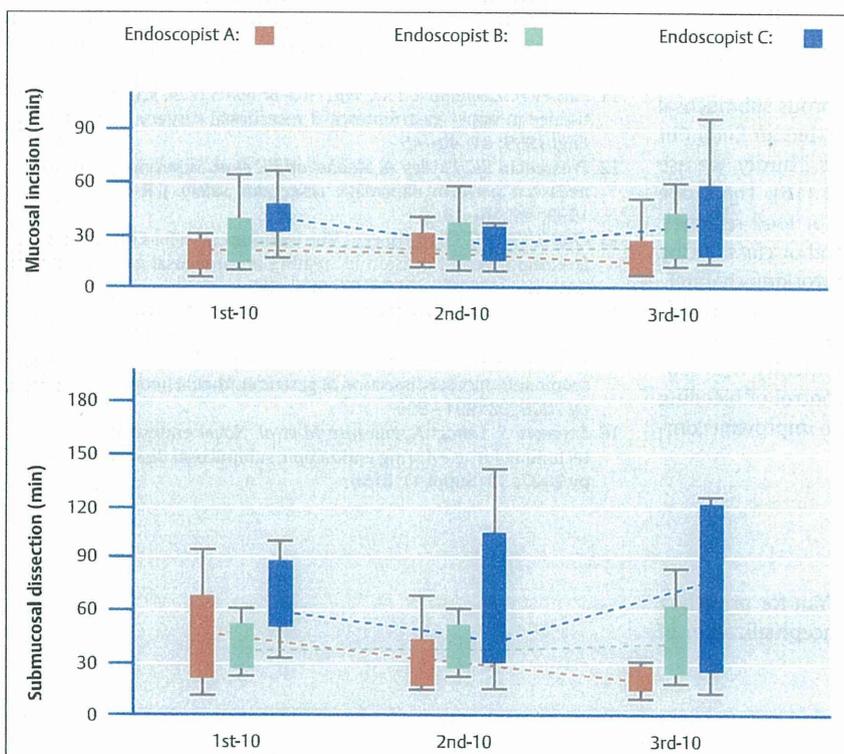

Fig. 2 Learning curves for operation time for mucosal incision and endoscopic submucosal dissection.

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.

Acknowledgments
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References

1 *Ohkuwa M, Hosokawa K, Boku N et al.* New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. Endoscopy 2001; 33: 221–226
2 *Ono H, Kondo H, Gotoda T et al.* Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225–229
3 *Watanabe K, Ogata S, Kawazoe S et al.* Clinical outcomes of EMR for gastric tumors: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. Gastrointest Endosc 2006; 63: 776–782
4 *Oka S, Tanaka S, Kaneko I et al.* Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. Gastrointest Endosc 2006; 64: 877–883
5 *Takeuchi Y, Uedo N, Iishi H et al.* Endoscopic submucosal dissection with insulated-tip knife for large mucosal early gastric cancer: a feasibility study (with videos). Gastrointest Endosc 2007; 66: 186–193
6 *Yokoi C, Gotoda T, Hamanaka H, Oda I.* Endoscopic submucosal dissection allows curative resection of locally recurrent early gastric cancer after prior endoscopic mucosal resection. Gastrointest Endosc 2006; 64: 212–218
7 *Rosch T, Sarbia M, Schumacher B et al.* Attempted endoscopic en bloc resection of mucosal and submucosal tumors using insulated-tip knives: a pilot series. Endoscopy 2004; 36: 788–801
8 *Nakajima T.* Gastric cancer treatment guidelines in Japan. Gastric Cancer 2002; 5: 1–5
9 *National Cancer Institute.* Common terminology criteria for adverse events v. 3.0. Cited 7 Jan 2007. Available from: https://webapps.ctep.nci.nih.gov/webobjs/ctc/webhelp/welcome_to_ctcae.htm
10 *Oda I, Saito D, Tada M et al.* A multicenter retrospective study of endoscopic resection for early gastric cancer. Gastric Cancer 2006; 9: 262–270
11 *Paisley AM, Madhavan KK, Paterson-Brown S et al.* Role of the surgical trainee in upper gastrointestinal resectional surgery. Ann R Coll Surg Engl 1999; 81: 40–45
12 *Praseedom RK, Paisley A, Madhavan KK et al.* Supervised surgical trainees can perform pancreatic resections safely. J R Coll Surg Edinb 1999; 44: 16–18
13 *Choi IJ, Kim CG, Chang HJ et al.* The learning curve for EMR with circumferential mucosal incision in treating intramucosal gastric neoplasm. Gastrointest Endosc 2005; 62: 860–865
14 *Gotoda T, Friedland S, Hamanaa H, Soetikno R.* A learning curve for advanced endoscopic resection. Gastrointest Endosc 2005; 62: 866–867
15 *Kakushima N, Fujishiro M, Kodashima S et al.* A learning curve for endoscopic submucosal dissection of gastric epithelial neoplasms. Endoscopy 2006; 38: 991–995
16 *Enomoto S, Yahagi N, Fujishiro M et al.* Novel endoscopic hemostasis technique for use during endoscopic submucosal dissection. Endoscopy 2007; 39 (Suppl 1): E156

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Treatment strategy for early gastric cancer with the risk of pyloric stenosis after endoscopic resection

We read with great interest the study by Dr. Coda and his colleagues, "Risk factors for cardiac or pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment," regarding early gastric cancer (EGC) [1].

At our center, endoscopic submucosal dissection (ESD) was performed for 433 EGCs (185 located in the lower third of the stomach, 146 in the middle third, and 102 in the upper third) from July 2000 to October 2008, and post-ESD stenosis occurred in five of the 185 pyloric resections. Four of the five had risk factors for post-ESD stenosis, that is a circumferential extent of the mucosal defect of more than ¾ or longitudinal extent of more than 5 cm, as described in the paper of Coda et al. [1].

The authors concluded that endoscopic balloon dilation was useful for pyloric stenosis after ESD. However, we think that balloon dilation is not always appropriate, considering the frequency of procedures needed, and risk of adverse events to the patient. In our series, four patients suffered from nausea and vomiting for a mean of 38 days (range 31 – 70), although the stenoses finally resolved with frequent balloon dilations. Furthermore, one patient sustained a perforation during her first balloon dilation, requiring an emergency operation (**◐ Fig. 1**).

We believe, therefore, that balloon dilation is not always a safe treatment for post-ESD pyloric stenosis.

Coda and colleagues also reported that one of eight patients with pyloric stenosis had to undergo an additional distal gastrectomy with lymph node dissection following balloon dilation. Since the risk of lymph node metastasis is pathologically evaluated from the resected ESD specimens, the indication for ESD with high risk factors for pyloric stenosis should be decided carefully from the viewpoint of minimizing invasiveness.

Considering the above, we have started to recommend laparoscopic distal gastrectomy (LDG) including lymph node dissection for EGC with high risk of post-ESD pyloric stenosis. LDG for EGC is considered
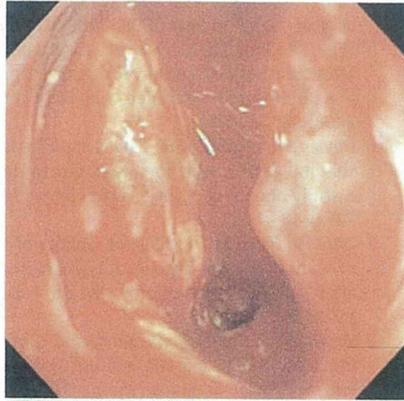

Fig. 1 Endoscopic image of perforation caused by balloon dilation for pyloric stenosis after endoscopic submucosal dissection (ESD). Omental fat tissue was seen in the anterior side of the pyloric ring.

less invasive than open distal gastrectomy and is widely accepted in Korea and Japan. Long-term clinical outcome and survival have not been found to be different for the two surgical methods [2–4]. Our recent cases of EGC with high risk of pyloric stenosis have been successfully resected

by LDG without complication, and with a median hospitalization of 20 days (**◐ Fig. 2a,b**).

We agree that EGC near the cardia should be treated by ESD although this has high risk factors for cardiac stenosis. The standard operation for EGC near the cardia is total gastrectomy, which often makes the quality of life of patients worse because of weight loss, anorexia, dysphagia, and so forth [5–7]. ESD for cardiac lesions could avoid total gastrectomy if resection is curative, and consequently could preserve gastric function, although balloon dilation is required for cardiac stenosis [8].

ESD for EGC with a negligible risk of lymph node metastasis has been recognized as less invasive and more economical than conventional surgery. However, we should take into consideration the benefits and risks of ESD and LDG when deciding upon treatment strategies for EGC, especially in patients with lesions at high risk of post-ESD stenosis.
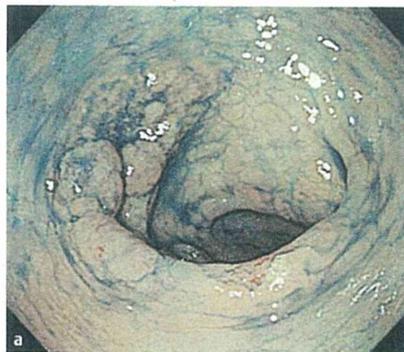
Competing interests: None

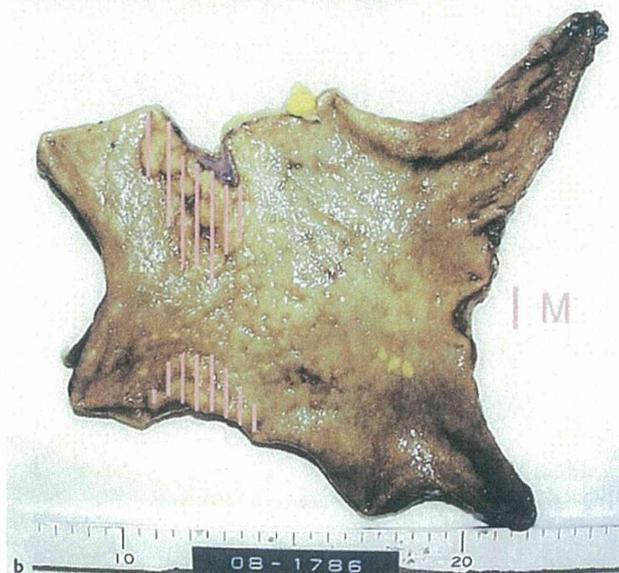**Fig. 2** **a** Antral 0 IIa + IIc lesion with ⅔ circumferential extent. Given the risk of pyloric stenosis after ESD, this lesion was resected by laparoscopic distal gastrectomy (LDG). **b** The resected specimen revealed an intramucosal well-differentiated adenocarcinoma without lymphatic or venous invasion.

References

1 *Coda S, Oda I, Gotoda T et al.* Risk factors for cardiac and pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment. Endoscopy 2009; 41: 421–426

2 *Kitano S, Shiraishi N, Uyama I et al.* A multi-center study on oncologic outcome of laparoscopic gastrectomy for early cancer in Japan. Ann Surg 2007; 245: 68–72

3 *Lee JH, Yom CK, Han HS.* Comparison of long-term outcomes of laparoscopy-assisted and open distal gastrectomy for early gastric cancer. Surg Endosc 2009; 8: 1759–1763 [Epub ahead of print Dec 5 2008]

4 *Kim YW, Baik YH, Yun YH et al.* Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. Ann Surg 2008; 248: 721–727

5 *Wu CW, Chiou JM, Ko FS et al.* Quality of life after curative gastrectomy for gastric cancer in a randomised controlled trial. Br J Cancer 2008; 98: 54–59

6 *Davies J, Johnston D, Sue-Ling H et al.* Total or subtotal gastrectomy for gastric carcinoma? A study of quality of life. World J Surg 1998; 22: 1048–1055

7 *Wu CW, Hsieh MC, Lo SS et al.* Quality of life of patients with gastric adenocarcinoma after curative gastrectomy. World J Surg 1997; 21: 777–782

8 *Yoshinaga S, Gotoda T, Kusano C et al.* Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. Gastrointest Endosc 2008; 67: 202–209

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

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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
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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
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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.

	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)

Table 1 Characteristics of patients with cardiac and pyloric resections.

*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.

	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)	

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

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
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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.

	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)	

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

n.s., not significant.
*All patients with perforations were successfully treated by endoscopic 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 bal-

loon 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
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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 su-

perficial 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

References
1 *Rembacken BJ, Gotoda T, Fujii T et al.* Endoscopic mucosal resection. Endoscopy 2001; 33: 709–718
2 *Soetikno R, Gotoda T, Nakanishi Y et al.* Endoscopic mucosal resection. Gastrointest Endosc 2003; 57: 567–579
3 *Soetikno R, Kaltenbach T, Yeh R et al.* Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol 2005; 23: 4490–4498
4 *Gotoda T, Yamamoto H, Soetikno R.* Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006; 41: 929–942
5 *Oda I, Gotoda T, Hamanaka H et al.* Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. Dig Endosc 2005; 17: 54–58
6 *Yamamoto H, Kawata H, Sunada K et al.* Successful one-piece resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy 2003; 35: 690–694
7 *Oyama T, Kikuchi Y.* Aggressive endoscopic mucosal resection in the upper GI tract – Hook knife EMR method. Minim Invasive Ther Allied Technol 2002; 11: 291–295
8 *Yahagi N, Fujishiro M, Kakushima N et al.* Endoscopic submucosal dissection for early gastric cancer using the tip of an electrosurgical snare (thin type). Dig Endosc 2004; 16: 34–38
9 *Oda I, Saito D, Tada M et al.* A multicenter retrospective study of endoscopic resection for early gastric cancer. Gastric Cancer 2006; 9: 262–270
10 *Tsunada S, Ogata S, Mannen K et al.* Case series of endoscopic balloon dilation to treat a stricture caused by circumferential resection of the gastric antrum by endoscopic submucosal dissection. Gastrointest Endosc 2008; 67: 979–983
11 *Oda I, Gotoda T, Sasako M et al.* Treatment strategy after non-curative endoscopic resection of early gastric cancer. Br J Surg 2008; 95: 1495–1500

12 *Gotoda T, Yanagisawa A, Sasako M et al.* Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219–225

13 *Minami S, Gotoda T, Ono H et al.* Complete endoscopic closure of gastric perforation induced by endoscopic resection of early gastric cancer using endoclips can prevent surgery. Gastrointest Endosc 2006; 63: 596–601

14 *Takizawa K, Oda I, Gotoda T et al.* Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection – An analysis of risk factors. Endoscopy 2008; 40: 179–183

15 *Katada C, Muto M, Manabe T et al.* Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. Gastrointest Endosc 2003; 57: 165–169

16 *Saito Y, Tanaka T, Andoh A et al.* Novel biodegradable stents for benign esophageal strictures following endoscopic submucosal dissection. Dig Dis Sci 2008; 53: 330–333

Frequency of Lymph Node Metastasis to the Splenic Hilus and Effect of Splenectomy in Proximal Gastric Cancer

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Abstract. *Background: The purpose of this study was to investigate the clinicopathological characteristics and frequency of lymph node metastasis to the splenic hilus in proximal gastric cancer and the effect of splenectomy. Patients and Methods: Three hundred and forty-nine patients undergoing total gastrectomy for primary proximal gastric cancer were included. Among these patients, lymph node metastasis to the splenic hilus was histologically assessed in 201 cases. Results: The incidence of lymph node metastasis to the splenic hilus was 31 cases (15.4%). No lymph node metastasis to the splenic hilus was detected in any T1 and T2 tumors located at the lesser curvature and anterior wall. No significant difference was observed between the survival rates of patients with and without splenectomy in each stage. Conclusion: Our findings indicated that gastrectomy with spleen preservation may be recommended at least in patients with T1 or T2 tumors located at the lesser curvature and anterior wall.*

Established gastric cancer treatment guidelines (1) indicate that "the standard operation for advanced gastric cancer is gastrectomy with D2 lymph node dissection" and that "advanced gastric cancer involving the upper third portion is recommended for treatment by total gastrectomy including splenectomy for dissection of lymph nodes located at the splenic hilus". Pancreaticosplenectomy with lymph node dissection at the splenic hilus and around the splenic artery for advanced gastric cancer has often been performed. However, pancreaticosplenectomy is not recommended for gastric cancer patients without direct invasion of the pancreas because this procedure does not increase their survival rate (2, 3). Furthermore, it was reported that splenectomy may increase postoperative morbidity (3, 4). Therefore, gastrectomy with spleen preservation was indicated as a potential less-invasive operation for patients without lymph node metastasis to the splenic hilus. Currently, gastrectomy with spleen preservation for early gastric cancer is a common procedure, and a randomized prospective controlled trial for proximal gastric cancer designed by the Japan Clinical Oncology Group 0110 (JCOG 0110) (5), which will reveal the clinical significance of splenectomy in patients with advanced tumors without lymph node metastasis to the splenic hilus or along the splenic artery, is underway. Currently, however, the indications for splenectomy in proximal gastric cancer remain controversial.

Based on these background data, we performed a retrospective analysis of the frequency of lymph node metastasis to the splenic hilus and the effect of splenectomy on the survival of patients who underwent total gastrectomy for primary proximal gastric cancer.

Patients and Methods

Between January 1991 and December 2006, total gastrectomy was performed in 349 patients with primary proximal gastric cancer in our institute. The mean age of the patients (237 men and 112 women) was 62.9 years (range: 21-90 years). Among the 349 patients, lymph node metastasis to the splenic hilus was histologically assessed in 201 patients who underwent splenectomy or pancreaticosplenectomy. The great pancreatic artery was preserved in patients who underwent pancreas-preserving splenectomy. The rates of lymph node metastasis to the splenic hilus were retrospectively assessed in the patients who underwent splenectomy in accordance with the clinicopathological characteristics. The survival rates of patients with or without splenectomy were assessed. The clinical and pathological diagnoses and classifications were determined according to the Japanese classification of gastric carcinoma (6). Depth of tumor invasion was classified as follows: T1, tumor invasion of the mucosa and/or muscularis mucosa or submucosa; T2, tumor invasion of the muscularis propria or submucosa.

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Table I. *Clinicopathological findings of patients with proximal gastric cancer who underwent total gastrectomy with or without splenectomy.*

	Splenectomy (−) (n=148)	Splenectomy (+) (n=201)	P-value
Age (years; range)	65.0 (29-90)	61.3 (21-88)	0.005
Gender (M/F)	97/51	140/61	0.486
Tumor size (mm; range)	66.5 (1-240)	79.0 (6-385)	0.019
Macroscopic type			<0.001
Early	56	21	
Advanced	92	180	
Histological type			0.632
Differentiated	68	86	
Undifferentiated	80	·115	
Combined resection			
Pancreaticosplenectomy	0	33	
Splenectomy	0	168	
Stage			<0.001
I	64	52	
II	30	36	
III	19	60	
IV	35	53	
Lymph node metastasis			0.001
N0	68	63	
N1	42	51	
N2	34	65	
N3	4	22	
Liver metastasis			0.726
No	144	193	
Yes	4	8	
Peritoneal metastasis			0.007
No	126	173	
Yes	22	28	
Other distant metastasis			0.728
No	145	199	
Yes	3	2	

Statistical analysis was conducted using StatView version 5.0 (SAS Institute, Cary, NC, USA). The significance of differences was determined by the χ^2 test, Student's t-test and logistic regression. The cumulative survival rate was calculated using the Kaplan-Meier method and the log-rank test. The level of significance was set at $p<0.05$.

Results

Clinicopathological factors. The clinicopathological findings of 148 patients without splenectomy and 201 patients with splenectomy are shown in Table I. In the splenectomy group, more advanced tumors were observed. On the other hand, early or extremely severe cases with peritoneal dissemination were recognized in the spleen-preserving group. The clinicopathological findings of the patients with splenectomy are shown in Table II. Overall, 31 patients (15.4%) had metastasis to the lymph nodes of

Table II. *Clinicopathological findings of patients underwent total gastrectomy with splenectomy for proximal gastric cancer.*

	Splenic hilus node metastasis − (n=170)	Splenic hilus node metastasis + (n=31)	P-value
Age (years; range)	62.2 (21-88)	56.7 (33-76)	0.023
Gender (M/F)	123/47	17/14	0.082
Tumor size (mm; range)	75.4 (6-385)	97.2 (9-180)	0.035
Macroscopic type			0.210
Early	20	1	
Advanced	150	30	
Histological type			0.005
Differentiated	80	6	
Undifferentiated	90	25	
Liver metastasis			0.205
No	165	28	
Yes	5	3	
Peritoneal metastasis			<0.001
No	153	20	
Yes	17	11	
Other distant metastasis			0.703
No	169	30	
Yes	1	1	

the splenic hilus. Significant differences were found for age, tumor size, histological type and peritoneal metastasis. In multivariate analysis, age was the only predictive factor (Table III).

The frequency of lymph node metastasis to the splenic hilus was associated with the location and depth of tumor invasion (Table IV). Tumors with lymph node metastasis to the splenic hilus were more frequently located at the greater curvature (38.5%), posterior wall (27.8%), had circumferential involvement (22.8%), and had invaded more deeply than the serosa. Among all T1 and T2 tumors located at the lesser curvature and anterior wall, no lymph node metastasis to the splenic hilus was observed.

Prognosis. In the splenectomy group, the cumulative 5-year survival rate of patients with lymph node metastasis to the splenic hilus was 15%, whereas the corresponding rate in patients without such metastasis was 49% (Figure 1; $p<0.001$). Among 31 patients with lymph node metastasis to the splenic hilus, 23 died of gastric cancer and 1 died of another disease. Regarding recurrence or metastasis, 16 patients had associated peritoneal metastasis, 3 lymph node metastasis and 1 patient each local recurrence, liver metastasis and lung metastasis, respectively.

The survival curves of patients with and without splenectomy in each stage are shown in Figure 2. The cumulative 5-year survival rates of patients with and without

Table III. *Multivariate logistic regression analysis of independent risk factors for lymph node metastasis to the splenic hilus.*

	P-value	Odds ratio	CI
Age (years)			
<60	0.035	2.85	1.08-7.52
≥60	-	1	
Gender			
Male	-	1	
Female	0.406	1.51	0.57-3.95
Tumor size (mm)			
<50	-	1	
≥50	0.064	4.34	0.92-20.51
Macroscopic type			
Early	-	1	
Advanced	0.776	1.37	0.15-12.29
Histological type			
Differentiated	-	1	
Undifferentiated	0.081	2.93	0.88-9.78
Liver metastasis			
No	-	1	
Yes	0.422	2.49	0.27-23.03
Peritoneal metastasis			
No	-	1	
Yes	0.056	2.95	0.97-8.96
Other distant metastasis			
No	-	1	
Yes	0.526	3.44	0.08-155.7

CI, Confidence interval.

Table IV. *Frequency of lymph node metastasis to the splenic hilus associated with location and depth of tumor invasion.*

	M	SM	MP	SS	SE	SI	Total (%)
Less	0/4	0/5	0/10	0/39	1/15	1/3	2/76 (2.6%)
Ant	0/0	0/1	0/2	0/9	1/6	0/1	1/19 (5.3%)
Gre	0/0	0/0	1/2	1/4	2/5	1/2	5 / 1 3 (38.5%)
Post	0/1	0/2	0/4	2/12	4/11	4/6	1 0 / 3 6 (27.8%)
Circ	0/0	0/0	0/1	2/13	9/35	2/8	1 3 / 5 7 (22.8%)
Total	0/5	0/8	1/19	5/77	17/72	8/20	31/201 (15.4%)
	(0%)	(0%)	(5.3%)	(6.5%)	(23.6%)	(40.0%)	(15.4%)

M, Mucosa; SM, submucosa; MP, muscularis propria; SS, subserosa; SE, serosa; SI, invasion of adjacent structures; Less, lesser curvature; Ant, anterior wall; Gre, greater curvature; Post, posterior wall; Circ, circumferential involvement.

Figure 1. *Survival curves of patients who underwent total gastrectomy and splenectomy with or without lymph node metastasis to the splenic hilus.*

Table V. *Postoperative complications following total gastrectomy with or without splenectomy.*

	Splenectomy (−) (n=148)	Splenectomy (+) (n=201)	P-value
Bleeding	0	2 (1.0%)	0.616
Anastomotic leakage	5 (3.4%)	12 (6.0%)	0.389
Pancreatic fistula	0	17 (8.5%)	<0.001
Peritoneal abscess	3 (2.0%)	10 (5.0%)	0.249
Anastomotic stenosis	3 (2.0%)	2 (1.0%)	0.728
Intestinal obstruction	2 (1.4%)	1 (0.5%)	0.788
Cardiac disease	1 (0.7%)	2 (1.0%)	0.749
Pulmonary disease	8 (5.4%)	8 (4.0%)	0.711
Liver dysfunction	1 (0.7%)	2 (1.0%)	0.749
Renal dysfunction	0	0	-
Other	13 (8.8%)	18 (9.0%)	0.956

Morbidity and mortality. The postoperative complications following total gastrectomy with or without splenectomy during the hospitalization are shown in Table V. Postoperative complications were encountered in 32 patients (21.6%) without splenectomy and 55 patients (27.4%) with splenectomy. The major complications were anastomotic leakage, pancreatic fistula and peritoneal abscess. A significant difference in the complications was only observed for pancreatic fistula. Pancreatic fistula was observed in 4 out of 33 patients (12.1%) with pancreaticosplenectomy. Only 1 patient with splenectomy died from postoperative bleeding.

Discussion

The incidence of metastasis to the splenic hilar lymph nodes was reported to be around 10% in proximal gastric cancer (7-9). Lymphangiograms have revealed that the lymphatics

splenectomy were 84% and 84% in stage I, 57% and 60% in stage II, 28% and 52% in stage III, and 18% and 7% in stage IV, respectively. No significant differences were observed between the two groups.
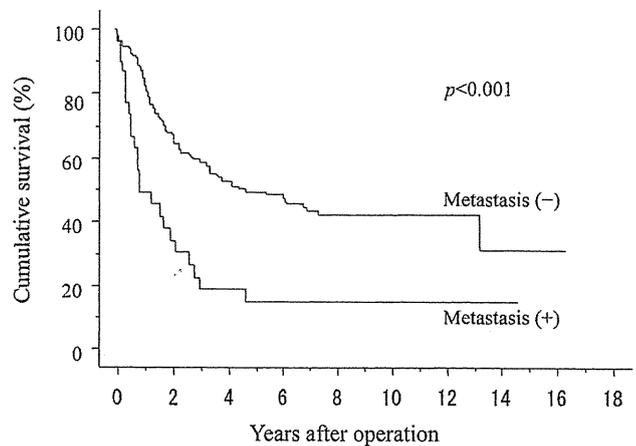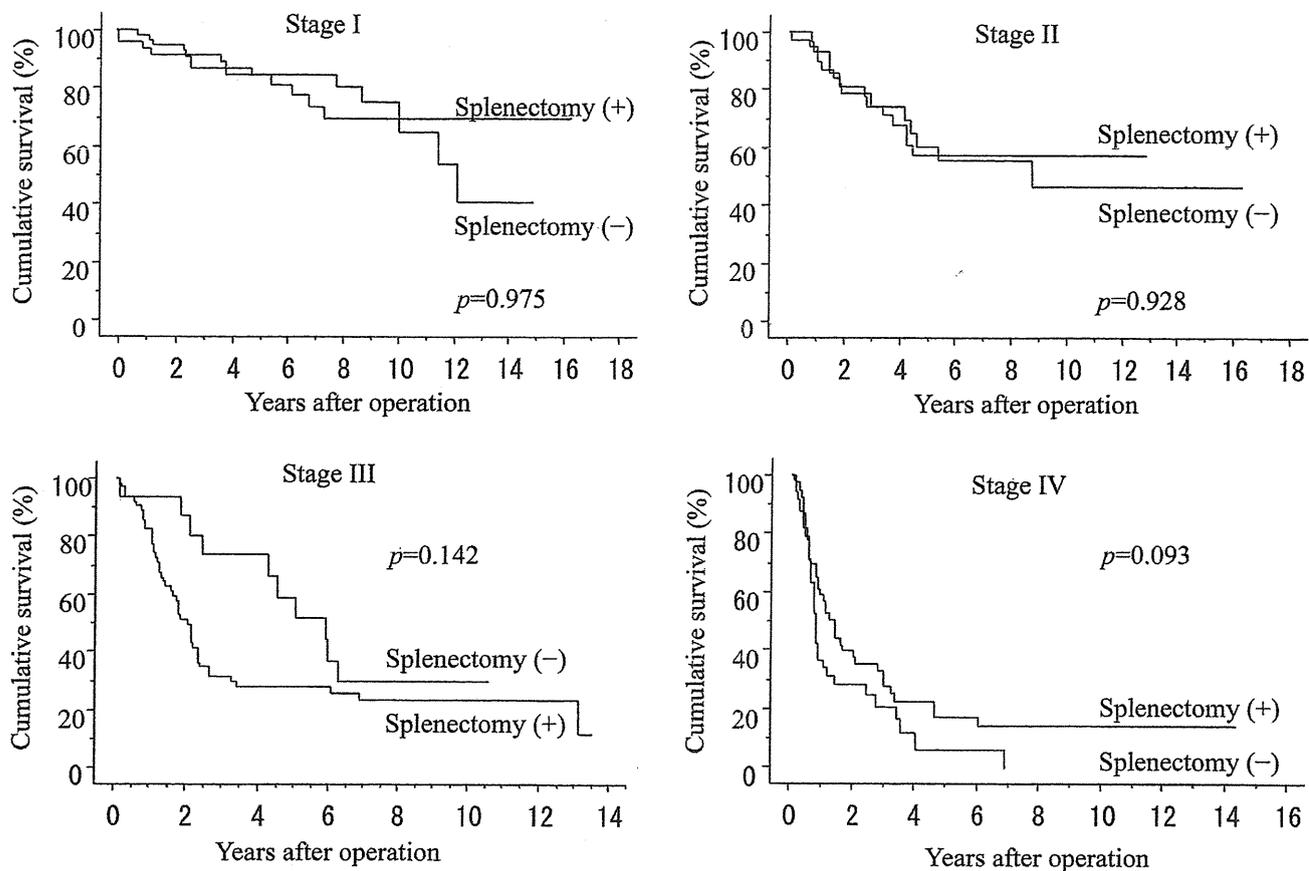
Figure 2. *Survival curves of patients who underwent total gastrectomy with or without splenectomy in each stage.*

from the upper left part of the stomach drain into the splenic hilar nodes and travel to the nodes around the celiac trunk through the splenic artery (10). This drainage route passes along not only the left gastroepiploic artery and short gastric artery, but also the posterior gastric artery, and this anatomical background agrees with the finding that splenic hilar node metastases were more frequent in tumors located at the greater curvature, posterior wall and circumferential involvement.

Although extended lymph node dissection has become a standard surgical procedure for gastric cancer in Japan, it has not shown a clear survival benefit in randomised clinical trials (11, 12) and a meta-analysis (13) in Western countries. The main reason for leaving the spleen is to resect lymph nodes in station 10, because it is impossible to resect them at the splenic hilus without splenectomy. The problems associated with simultaneous splenectomy during surgery for gastric cancer are its contribution to prognosis and the frequency of postoperative complications. A prospective randomised study comparing patients with and without splenectomy in Western countries revealed that splenectomy

did not influence the survival in localized stages of gastric cancer, that is stages IA, IB, II, IIIA (14). A Japanese prospective randomised trial is in progress (5). Although the previous studies did not improve patient survival (3, 15-21), some conferred a survival benefit (10, 22-25). Regarding the survival benefit of splenectomy, previous studies have reported that the spleen in advanced gastric cancer patients produced suppressor T-cells, which might improve the survival *via* tumor-induced immunosuppression (25-28). In the present study, there was no significant difference in survival for each stage between patients with and without splenectomy. Furthermore, among postoperative complications in patients with splenectomy, only pancreatic fistula was more frequent and associated with surgical technique, but did not increase mortality.

In conclusion, from the standpoint of survival benefit, splenectomy did not exhibit any significance for primary proximal gastric cancer. Furthermore, for all T1 and T2 tumors located at the lesser curvature and anterior wall, gastrectomy with spleen preservation may be recommended as a standard operation.

References

1 Japanese Gastric Cancer Association. Gastric Cancer Treatment Guidelines. 2nd ed. Kyoto: The Office of the Japanese Gastric Cancer Association, 2004.

2 Kitamura K, Nishida S, Ichikawa D, Taniguchi H, Hagiwara A, Yamaguchi T and Sawai K: No survival benefit from combined pancreaticosplenectomy and total gastrectomy for gastric cancer. Br J Surg 86: 119-22, 1999.

3 Otsuji E, Yamaguchi T, Sawai K, Ohara M and Takahashi T: End results of simultaneous splenectomy in patients undergoing total gastrectomy for gastric carcinoma. Surgery 120: 40-44, 1996.

4 Sasako M: Risk factors for surgical treatment in the Dutch gastric cancer trial. Br J Surg 84: 1567-1571, 1997.

5 Sano T, Tamamoto S and Sasako M: Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma: Japan Clinical Oncology Group Study JCOG 0110-MF. Jpn J Clin Oncol 32: 363-364, 2002.

6 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 2nd English edition. Gastric Cancer 1: 10-24, 1998.

7 Stefan PM, Peter HC, Stephan EB, Katrin S, Wolfgang S, Jürgen T, Hans PD and Arnulf HH: Splenectomy in proximal gastric cancer: frequency of lymph node metastasis to the splenic hilus. J Surg Oncol 76: 89-92, 2001.

8 Maehara Y, Moriguchi S, Yoshida M, Takahashi I, Korenaga D and Sugimachi K: Splenectomy does not correlate with length of survival in patients undergoing curative total gastrectomy for gastric carcinoma. Cancer 67: 3006-3009, 1991.

9 Maruyama K, Gunven P, Okabayashi K, Sasako M and Kinoshita T: Lymph node metastasis of gastric cancer. General pattern in 1,931 patients. Ann Surg 210: 596-602, 1989.

10 Maruyama K, Okabayashi K and Kinoshita K: Progress in gastric surgery in Japan and its limits of radicality. World J Surg 11: 418-425, 1987.

11 Hartgrink HH, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, Welvaart K, van Krieken JH, Meijer S, Plukker JT, van Elk PJ, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H and Sasako M: Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 22: 2069-2077, 2004.

12 Bonenkamp JJ, Hermans J, Sasako M and van De Velde CJ: Extended lymph-node dissection for gastric cancer. N Engl J Med 25: 908-914, 1999.

13 McCulloch P, Niita ME, Kazi H and Gama-Rodrigues JJ: Gastrectomy with extended lymphadenectomy for primary treatment of gastric cancer. Br J Surg 92: 5-13, 2005.

14 Csendes A, Burdiles P, Rojas J, Braqhetto I, Diaz JC and Maluenda F: A prospective randomized study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma. Surgery 131: 401-407, 2002.

15 Cheong O, Kim BS, Yook JH, Oh ST, Park YK and Ryu SY: Modified radical lymphadenectomy without splenectomy in patients with proximal gastric cancer: comparison with standard D2 lymphadenectomy for distal gastric cancer. J Surg Oncol 98: 500-504, 2008.

16 Fatouros M, Roukos DH, Lorenz M, Arampatzis I, Hottentrott C, Encke A and Kappas AM: Impact of spleen preservation in patients with gastric cancer. Anticancer Res 25: 3023-3030, 2005.

17 Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V and Cook P: Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial.The Surgical Cooperative Group. Lancet 13: 995-999, 1996.

18 Chang HZ, Wen HZ, Yu LH, Chuang QC, Mei JH and Shi RC: Spleen preservation in radical surgery for gastric cardia cancer. Ann Surg Oncol 14: 1312-1319, 2007.

19 Suphan E, Yilmaz E, Yusuf C, Gulen D and Mustafa S: Effect of simultaneous splenectomy on the survival of patients undergoing curative gastrectomy for proximal gastric carcinoma. Surg Today 33: 254-258, 2003.

20 Lee KY, Noh SH, Hyung WJ, Lee JH, Lah KH, Choi SH and Min JS: Impact of splenectomy for lymph node dissection on long-term surgical outcome in gastric cancer. Ann Surg Oncol 8: 402-406, 2001.

21 Griffith JP, Sue-Ling HM, Martin I, Dixon MF, McMahon MJ, Axon AT and Johnston D: Preservation of the spleen improves survival after radical surgery for gastric cancer. Gut 36: 684-690, 1995.

22 Roukos DH: Current advances and changes in treatment strategy may improve survival and quality of life in patients with potentially curable gastric cancer. Ann Surg Oncol 6: 46-56, 1999.

23 Roder JD, Bottcher K, Siewert JR, Busch R, Hermanek P and Meyer HJ: Prognostic factors in gastric carcinoma. Results of German Gastric Cancer Study 1992. Cancer 72: 2089-2097, 1993.

24 Soga J, Ohyama S, Miyashita K, Suzuki T, Nashimoto A, Tanaka O, Sasaki K and Muto T: A statistical evaluation of advancement of gastric cancer surgery with special reference to the significance of lymphadenectomy for cure. World J Surg 12: 398-405, 1988.

25 Toge T, Yanagawa E, Yamaguchi Y, Kuroi K, Sawamura A and Hattori T: Role of the spleen on the immunosuppression in patients with gastric cancer and evaluation of splenectomy in their prognosis. Jpn J Gastroenterol Surg 21: 2478-2481, 1988.

26 Toge T, Hamamoto S, Itagaki E, Yajima K, Tanada M, Nakane H, Kohno H, Nakanishi K and Hattori T: Concanavalin A-induced and spontaneous suppressor cell activities in peripheral blood lymphocytes and spleen cells from gastric cancer patients. Cancer 52: 1624-1631, 1983.

27 Noma K, Yamaguchi Y, Okita R, Matsuura K and Toge T: The spleen plays an immunosuppressive role in patients with gastric cancer: involvement of CD62L+ cells and TGF-beta. Anticancer Res 25: 643-649, 2005.

28 Toge T. Kuroi K, Kuninobu H, Yamaguchi Y, Kegoya Y, Baba N and Hattori T: Role of spleen in immunosuppression of gastric cancer: predominance of suppressor precursor and suppressor inducer T-cells in the recirculating spleen cells. Clin Exp Immunol 74: 409-412, 1988.

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.
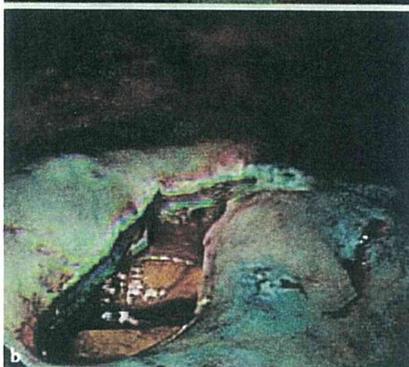

Fig. 2 Circumferential mucosal incision. a Circumferential mucosal incision had just begun using the insulation-tipped (IT) knife-2 from the point of small initial incision made with a needle knife. b Perforation occurred at the beginning of the circumferential mucosal incision.
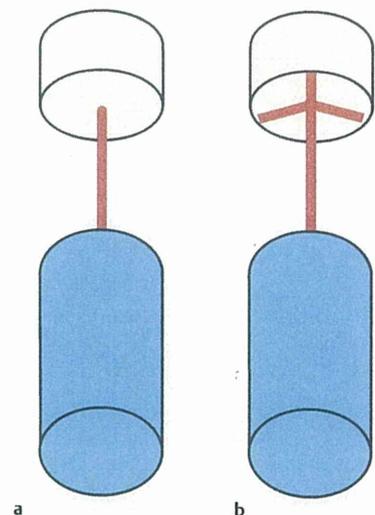

Fig. 4 The difference between the original IT knife and the IT knife-2. a There is no blade underneath the insulation tip of the original IT knife. b The IT knife-2 has a three-pronged blade directly beneath the insulation tip.

Video 1

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

Endoscopy_UCTN_Code_CPL_1AH_2AZ

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References
1 *Hosokawa K, Yoshida S.* Recent advances in
endoscopic mucosal resection for early gas-
tric cancer. Jpn J Cancer Chemother (English
abstract) 1998; 25: 483
2 *Gotoda T, Kondo H, Ono H et al.* A new endo-
scopic mucosal resection (EMR) procedure
using an insulation-tipped diathermic (IT)
knife for rectal flat lesions. Gastrointest En-
dosc 1999; 50: 560–563
3 *Oda I, Ikehara H, Yokoi C et al.* How to cope
with complication throughout the gastroin-
testinal tract. In: Conio M, Siersema P, Repi-
ci A, Pomchon T (eds). Endoscopic mucosal
resection. Oxford, UK: Blackwell Publishing,
2008: 196–211
4 *Ono H, Hasuike N, Inui T et al.* Usefulness of a
novel electrosurgical knife, the insulation-
tipped diathermic knife-2, for endoscopic
submucosal dissection of early gastric can-
cer. Gastric Cancer 2008; 11: 47–52

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