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TOWARDS FURTHER PENETRATION OF ESD TECHNIQUES – WHAT IS THE ROLE OF JAPANESE ESD EXPERTS?

LEARNING CURVE FOR ENDOSCOPIC SUBMUCOSAL DISSECTION OF EARLY GASTRIC CANCER BASED ON TRAINEE EXPERIENCE

ICHIRO ODA, TOMOYUKI ODAGAKI, HARUHISA SUZUKI, SATORU NONAKA AND SHIGETAKA YOSHINAGA

Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

Background and Aim: There have been few previous reports on endoscopic submucosal dissection (ESD) learning curve for early gastric cancer (EGC) so we retrospectively assessed this subject based on experience of our trainees.

Methods: Trainees in our center start performing ESDs for lesions in lower third of stomach with hands-on support by experts during first 10 cases and then perform ESDs by themselves primarily with verbal guidance from experts. They are gradually assigned to perform ESDs in middle and upper thirds of stomach. From January 1999 to December 2008, 464 EGC patients, who underwent ESD performed by 13 trainees, were assessed by dividing ESD cases into five training periods (A, 1-10; B, 11-20; C, 21-30; D, 31-40; and E, 41-50). We compared data from B to C, D and E.

Results: Lesions in lower third were A/59%, B/57%, C/55%, D/36% and E/40% with B significantly higher than D ($p<0.01$) and E ($p<0.05$). Mean tumor sizes were A/13.9±7.5mm, B/18.3±11.4mm, C/19.0±12.5mm, D/19.3±11.7mm and E/16.8±10.3mm. En-bloc resection rate was 100% in every period. Delayed bleeding / perforation rates were A/0%/1.8%, B/2.8%/1.9%, C/1.9%/2.9%, D/1.1%/0% and E/2.1%/2.1%, respectively. Lower third procedure times were A/76±39, B/90±61, C/70±48, D/60±50 and E/55±26 minutes with B significantly longer than D and E ($p<0.05$). Middle and upper third procedure times were A/104±80, B/115±68, C/106±67, D/134±86 and E/96±55 minutes.

Conclusion: Step-by-step training was highly effective with 100% en-bloc resection rate and few complications. Learning curve point for our trainees to acquire performing ESD in lower third of stomach was 30 cases.

Key words: early gastric cancer, endoscopic submucosal dissection, learning curve, training.

INTRODUCTION

Endoscopic submucosal dissection (ESD) is widely accepted for treating early gastric cancer (EGC) with a negligible risk of lymph node metastasis.[1–3] ESD requires a high level of technical expertise, however, so it is technically challenging especially for less experienced endoscopists. ESD trainees at the National Cancer Center Hospital (NCCH) in Tokyo, Japan, follow a step-by-step process for learning ESD techniques as shown in Table 1. The first step entails acquiring a basic knowledge and understanding of EGC and ESD in particular diagnosis of EGC and the indications for ESD. The next step is for trainees to observe expert endoscopists in action as they perform various ESD procedures. The third step involves trainees acquiring first-hand experience by assisting during actual ESD followed by ESD training using animal models as the fourth step. In the final step, it is important for trainees to start by performing ESD on lesions easier to treat including those that are located in the lower third of the stomach, smaller in size and without ulcer fibrosis. Trainees perform ESD with direct hands-on support from highly qualified endoscopists for the first 10 ESD procedures and then start to perform ESD by themselves with mostly verbal guidance from the expert endoscopists. As their ESD techniques improve, trainees are gradually assigned to perform ESD on lesions located in the middle and upper thirds of the stomach and larger in size.

Few studies have previously reported on the subject so we decided to assess the ESD learning curve for EGC based on the experience of our ESD trainees.[4,5]

PATIENTS AND METHODS

From January 1999 to December 2008, 13 trainees performed their initial gastric ESD and conducted more than 30 subsequent ESD at NCCH. The previous mean ± standard deviation endoscopy experience of the 13 trainees prior to performing their first ESD was 5.2 ± 2.2 years. During this period, 630 patients with solitary EGC clinically diagnosed before treatment as intestinal type EGC with a negligible risk of lymph node metastasis underwent ESD performed by the 13 trainees. After excluding 104 cases with pathological ulcer findings and 62 other cases involving some trainees who had performed more than 50 ESD, we retrospectively assessed 464 EGC cases by dividing the ESD into five equal training periods: A, 1–10 cases; B, 11–20 cases; C, 21–30 cases; D, 31–40 cases; and E, 41–50 cases. Clinicopathogical findings including age, sex, tumor location and tumor size were investigated as well as technical results regarding the en bloc resection rate, procedure time, delayed bleeding rate and perforation rate.

Tumor locations were divided into the lower third of the stomach and the middle and upper thirds of the stomach

Correspondence: Ichiro Oda, Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Email: ioda@ncc.go.jp

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Table 1. Phased learning of gastric ESD techniques

1. Acquire basic knowledge about EGC and ESD
2. Observe experts in action
3. Train using animal model
4. Perform ESD procedures†

†Starting with ESD for lesions located in the lower third of the stomach, small lesions in size and lesions without ulcer fibrosis.
EGC, early gastric cancer; ESD, endoscopic submucosal dissection.

combined based on the Japanese classification of gastric carcinoma.[6] Tumor sizes were estimated endoscopically. An en bloc resection was defined as a one-piece resection while delayed bleeding was defined as a clinical indication of bleeding evidenced by hematemesis or melena requiring endoscopic treatment and occurring within 30 days of an ESD. We also recorded the incidence of perforations as observed during the procedure or evidenced clinically following an ESD.

We compared data from period B to periods C, D and E because highly qualified endoscopists provided hands-on support to trainees through most of the process of performing the various ESD procedures during period A. Data were analyzed using the χ^2-test, Fisher's exact test or Student's *t*-test as appropriate (STATA version 10.0; StataCorp, College Station, TX, USA) with value differences of $P < 0.05$ considered statistically significant.

RESULTS

Clinicopathogical findings of EGC resected by 13 trainees are shown in Table 2. The proportion of lesions located in the lower third of the stomach was 59%, 57%, 55%, 36% and 40% in periods A, B, C, D and E, respectively. Lesions located in the lower third of the stomach were significantly less frequent in periods D ($P < 0.01$) and E ($P < 0.05$) than in period B. Table 3 indicates the technical results of the ESD performed by the 13 trainees for all 464 cases. The en bloc resection rate was 100% in all five periods and there were no significant differences in any of the technical results between period B and periods C, D and E. When procedure times for the 13 trainees were analyzed by tumor location (Table 4), the procedure times for lesions located in the lower third of the stomach were 76 ± 39, 90 ± 61, 70 ± 48, 60 ± 50 and 55 ± 26 min in periods A, B, C, D and E, respectively, with the procedure times significantly shorter in periods D ($P < 0.05$) and period E ($P < 0.05$) than in period B. Procedure times for lesions located in the middle and upper thirds of the stomach were 104 ± 80, 115 ± 68, 106 ± 67, 134 ± 86 and 96 ± 55 in periods A, B, C, D and E, respectively.

DISCUSSION

Gastric ESD has a number of advantages including higher rates of en bloc resection and a lower incidence of local recurrence in comparison to endoscopic mucosal resection (EMR).[7–13] When compared to surgery, ESD preserves the stomach and, therefore, improves a patient's overall quality of life. Although many endoscopists are interested in learning how to perform ESD, the procedure requires a high level of expertise and is technically challenging especially for less experienced endoscopists. There have been few reports regarding the learning curve for ESD[4,5] and they have focused on determining the learning curve point for gastric ESD based on all data from the time this procedure was first introduced at their hospital. Choi *et al.* examined the learning curve for the circumferential incision and snare technique reporting an increase in the en bloc resection rate from 45% to 85% after 40 cases. There were three perforations in the first 20 procedures (15%), but only one in the following 60 procedures. They concluded that 20–40 procedures was the learning curve point for this particular technique.[4] Kakushima *et al.* demonstrated that a reduction in procedure time was an indicator for becoming proficient in this skill.[5]

There is no other published report of a similar size series to the best of our knowledge on establishing the learning curve point based on the experience of trainee endoscopists under the direction of highly skilled endoscopists. We developed and introduced the ESD procedure for clinical use on patients in the mid-1990s and have gained substantial experience and expertise in performing ESD over the years. As a result, we have had several expert endoscopists specializing in ESD at NCCH throughout the study period. We assessed the ESD learning curve for EGC based on the experience of our ESD trainees. The step-by-step training program at NCCH has been very effective as evidenced by the trainees achieving an en bloc resection rate of 100% with comparatively few complications. It should be noted that a basic level of diagnostic endoscopy with detection and characterization of lesions as well as being able to perform targeting biopsy and experience in therapeutic endoscopic procedures including hemostasis, polypectomy and EMR are required before starting to learn how to perform ESD. Actually, the 13 trainees in this study had a mean of 5.2 ± 2.2 years of basic diagnostic and therapeutic endoscopic experiences prior to performing their first ESD. As Kakushima *et al.* reported, we used procedure time as an indicator of ESD proficiency and determined that 30 cases was the learning curve point to acquire the basic technical skills for successfully performing ESD in the lower third of the stomach. The procedure time for lesions located in the middle and upper thirds of the stomach was 96 ± 55 min in period E compared to 115 ± 68 min in period B, although there was no significant difference probably due to the relatively small number of cases. In our estimation, performing at least 40 ESD would be the minimum learning curve point for performing ESD in the middle and upper thirds of the stomach. It should be noted that we excluded 104 EGC with ulcer fibrosis because of increased technical difficulty and longer procedure time in performing ESD and such cases were too few in number to accurately assess the learning curve for EGC with ulcer fibrosis.

Limitations included this study being a retrospective investigation from a single center between January 1999 and December 2008. There have been various improvements over the years in endoscopes, cutting instruments, injection solutions, electrosurgical units, training animal models and other equipment which probably have affected the ESD learning curve point.[14–22] We assume that such improvements have contributed to improving the learning curve process and further advances should shorten the learning curve point in the future.

Table 2. Clinicopathogical EGC findings

	Period A ($n = 114$)	Period B ($n = 108$)	Period C ($n = 105$)	Period D ($n = 89$)	Period E ($n = 48$)	Total ($n = 464$)
Age, mean ± SD (years)	65.7 ± 9.6	68.1 ± 8.7	66.8 ± 9.3	66.4 ± 8.7	66.8 ± 7.9	67.0 ± 9.0
Sex (%)						
Male	91 (80)	84 (78)	84 (80)	67 (75)	35 (73)	361 (78)
Female	23 (20)	24 (22)	21 (20)	22 (25)	13 (27)	103 (22)
Tumor location (%)						
Lower third	67 (59)	62 (57)	58 (55)	32 (36)†	19 (40)†	238 (51)
Middle and upper thirds	47 (41)	46 (43)	47 (45)	57 (64)	29 (60)	226 (49)
Tumor size, mean ± SD (mm)	13.9 ± 7.5	18.3 ± 11.4	19.0 ± 12.5	19.3 ± 11.7	16.8 ± 10.3	17.4 ± 11.0

†Lesions located in the lower third of the stomach were significantly less frequent in period D ($P < 0.01$) and period E ($P < 0.05$) than in period B.
EGC, early gastric cancer; SD, standard deviation.

Table 3. ESD technical results

	Period A ($n = 114$)	Period B ($n = 108$)	Period C ($n = 105$)	Period D ($n = 89$)	Period E ($n = 48$)	Total ($n = 464$)
En bloc resection rate (%)	114 (100)	108 (100)	105 (100)	89 (100)	48 (100)	464 (100)
Procedure time, mean ± SD (min)	88 ± 61	101 ± 65	86 ± 60	108 ± 83	80 ± 50	93 ± 66
Delayed bleeding rate (%)	0 (0)	3 (2.8)	2 (1.9)	1 (1.1)	1 (2.1)	7 (1.5)
Perforation rate (%)	2 (1.8)	2 (1.9)	3 (2.9)	0 (0)	1 (2.1)	8 (1.7)

ESD, endoscopic submucosal dissection; SD, standard deviation.

Table 4. ESD procedure times by tumor location

	Period A ($n = 114$)	Period B ($n = 108$)	Period C ($n = 105$)	Period D ($n = 89$)	Period E ($n = 48$)	Total ($n = 464$)
Procedure time, mean ± SD (min)						
Lower third ($n = 238$)	76 ± 39	90 ± 61	70 ± 48	60 ± 50†	55 ± 26†	75 ± 50
Middle and upper thirds ($n = 226$)	104 ± 80	115 ± 68	106 ± 67	134 ± 86	96 ± 55	113 ± 75

†Procedure times were significantly shorter in period D ($P < 0.05$) and period E ($P < 0.05$) than in period B.
EGC, early gastric cancer; ESD, endoscopic submucosal dissection; SD, standard deviation.

In conclusion, the step-by-step training system in our center has been highly effective with an en bloc resection rate of 100% and a low complication rate. As a result of this program, the learning curve point for our trainees to acquire the basic technical skills for successfully performing ESD in the lower third of the stomach was 30 cases.

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CONFLICT OF INTEREST

None declared.

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CASE REPORT

A case of lymph node metastasis following a curative endoscopic submucosal dissection of an early gastric cancer

Hisaharu Oya · Takuji Gotoda · Tetsu Kinjo · Haruhisa Suzuki · Shigetaka Yoshinaga · Hirokazu Taniguchi · Ryoji Kushima · Makoto Saka · Hitoshi Katai · Ichiro Oda

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Abstract Currently in Japan, differentiated gastric submucosal invasive cancers <500 μm (SM1) with negative lymphovascular involvement are included in expanded pathological criteria for curative endoscopic treatment. This is based on a retrospective examination of surgical resection cases in which patients suitable for such expanded criteria were determined to have a negligible risk of lymph node metastasis. We performed endoscopic submucosal dissection on a 65-year-old male with early gastric cancer in April 2005, and pathology revealed a well-differentiated adenocarcinoma, 21 × 10 mm in size, SM1 invasion depth and negative lymphovascular invasion as well as tumor-free margins, so the case was diagnosed as a curative resection. This case, however, resulted in lymph node metastasis that was diagnosed by endoscopic ultrasonography with fine-needle aspiration biopsy in May 2009. Distal gastrectomy with D2 lymph node dissection was then performed, confirming lymph node metastasis from the original gastric cancer.

Keywords Early gastric cancer · Lymph node metastasis · Expanded criteria · ESD · SM1

H. Oya · T. Gotoda · T. Kinjo · H. Suzuki · S. Yoshinaga · I. Oda (✉)
Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: ioda@ncc.go.jp

T. Gotoda
Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, Japan

H. Taniguchi · R. Kushima
Pathology Division, National Cancer Center Hospital, Tokyo, Japan

M. Saka · H. Katai
Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan

Introduction

Endoscopic resection is the preferred treatment method for the local dissection of early cancer with a negligible risk of lymph node metastasis. For early gastric cancer (EGC), it is possible to achieve nearly 100% curability by radical surgery; therefore, it is an absolute requirement to maintain such a level of curability with endoscopic resection. In Japan, the Gastric Cancer Treatment Guideline (3rd version) specifies that the pathological criteria for curative endoscopic resection are limited to small intramucosal differentiated-type gastric cancer ≤20 mm in size without an ulcer finding [1]. Recently, the pathological criteria for curative endoscopic resection of EGC have been expanded to cover other lesions with a negligible risk of lymph node metastasis [2]. These expanded criteria include larger lesions, lesions with ulceration and lesions that invade the submucosa <500 μm (SM1).

Together with advances in treatment equipment used for endoscopic resection in recent years, endoscopic submucosal dissection (ESD) provides a higher en bloc resection rate, thus allowing for more accurate and detailed pathological evaluation compared to endoscopic mucosal resection (EMR) [3–8]. Due to the refinement of ESD and the acceptance of the expanded pathological criteria for curative endoscopic resection, which in turn resulted in expanded clinical indications for endoscopic resection, the

number of patients who are treated by endoscopic resection has increased dramatically.

We experienced for the first time a case of lymph node metastasis following ESD resulting in a pathologically curative resection of SM1 EGC and report this case here.

Case report

A 65-year-old man was admitted in 2005 because EGC was detected by screening endoscopy. There were no abnormalities in the physical examination or laboratory data, and no medical history of malignant tumors. The lesion was a type 0–IIc well-differentiated adenocarcinoma, 20 mm in size with an ulcer scar on the anterior wall near the pylorus (Fig. 1a, b). ESD was performed on this lesion, resulting in an en bloc resection. Precise pathological examination of 2-mm slices from the entire specimen revealed a type 0–IIc lesion 21 × 10 mm in size with an ulcer scar that was predominantly a well-differentiated adenocarcinoma with an intramucosal, but not a submucosal poorly differentiated adenocarcinoma component in the proximal portion of the lesion. The poorly differentiated adenocarcinoma component was separate from the ulcer scar. The tumor involved SM1 invasion with negative lymphovascular involvement and horizontal/vertical margins, so it was determined that the resection was curative based on the expanded pathological criteria (Fig. 2a–c). Thereafter, we performed computed tomography (CT) or endoscopic ultrasonography (EUS) on an alternating basis every 6 months as well as endoscopy every year. In December 2007, CT detected an enlarged lymph node near the pylorus (12 × 9 mm) (Fig. 3), and the laboratory data indicated an increase in CEA of 12.4 ng/ml (normally <5.0 ng/ml). EUS was unable to detect the enlarged lymph node, so we continued EUS follow-up every 2 or 3 months. In July 2008, EUS revealed a 12-mm enlarged lymph node at the same site indicated by CT in December 2007. This enlarged lymph node had some highly echoic spots, so it was thought to be an inflammatory reaction, and we continued EUS follow-up every 2 or 3 months. Although the size of the lymph node did not change, a new 6-mm enlarged lymph node near the original site was detected by EUS in May 2009 (Fig. 4a), and the CEA level had increased to 17.5 ng/ml by then. For diagnosis of the enlarged lymph nodes, EUS with fine-needle aspiration biopsy (EUS-FNA) was carried out, and a pathological examination revealed an adenocarcinoma (Fig. 4b). No other lesions were detected; therefore, lymph node metastasis was diagnosed as resulting from the SM1 EGC originally treated by ESD. In July 2009, a distal gastrectomy with D2 lymph node dissection was carried out, and postoperative pathological examination revealed no local recurrent tumor at the ESD site in the stomach. Metastasis was limited to the lymph node near the pylorus (Fig. 5a, b). No recurrence has been subsequently detected following the gastrectomy.

Discussion

We previously reported a group of patients with negligible risk of lymph node metastasis based on the pathological examination of over 5,000 surgical EGC cases that developed into the current expanded pathological criteria for curative endoscopic resection of EGC [2]. The expanded criteria include differentiated adenocarcinomas with negative lymphovascular involvement that are either intramucosal cancer without ulcer findings regardless of tumor size, intramucosal cancer with ulcer finding ≤3 cm in size

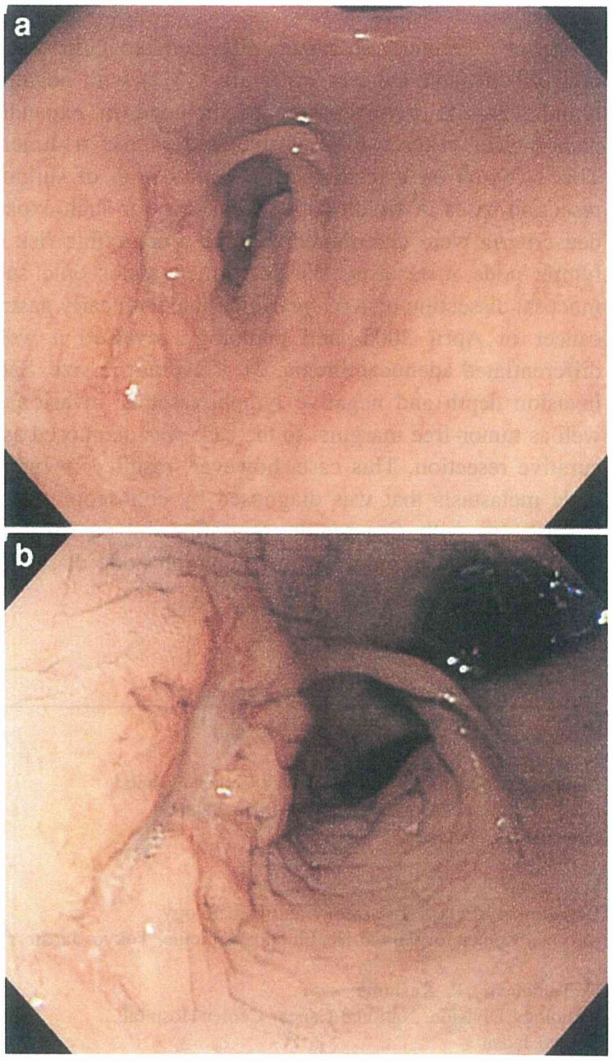

Fig. 1 **a** Endoscopy detected a type 0–IIc lesion 20 mm in size with an ulcer scar on the anterior wall near the pylorus. **b** Chromoendoscopy using indigo-carmine clearly revealed the margin of the lesion

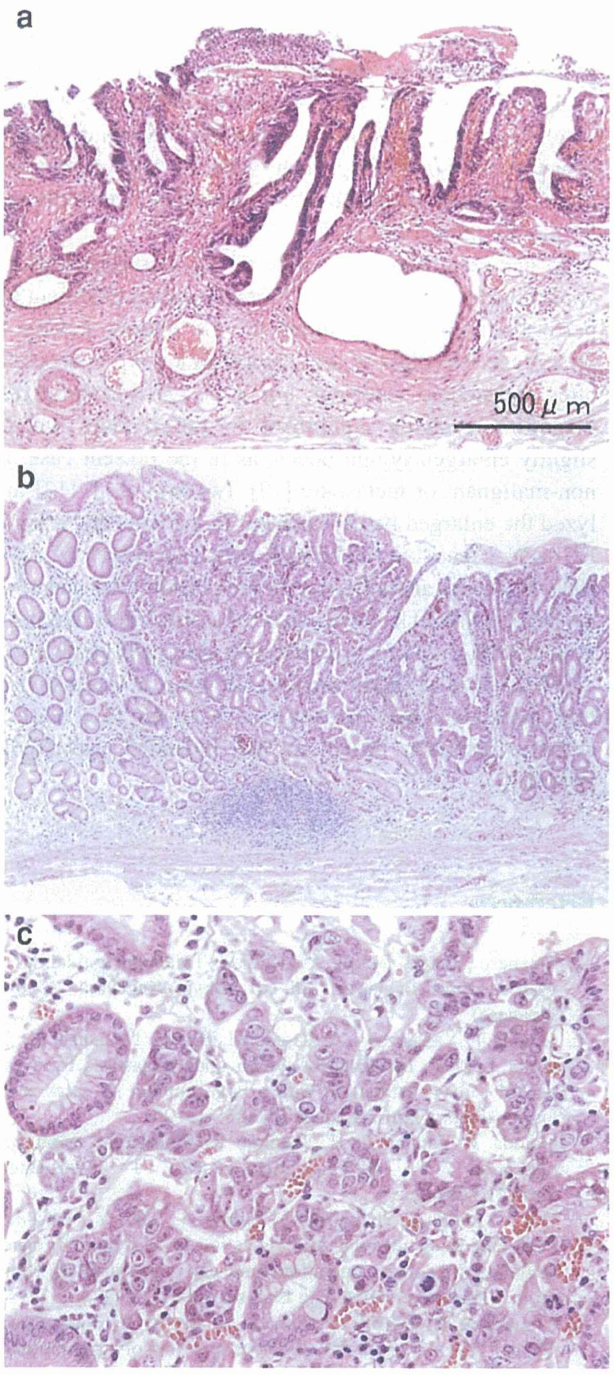

Fig. 2 **a** Pathological examination revealed a type 0–IIc lesion with ulcer scar, 21 × 10 mm in size, that had invaded <500 μm with negative lymphovascular involvement and horizontal/vertical margins. **b**, **c** Resected specimen predominantly revealed a well-differentiated adenocarcinoma with a poorly differentiated adenocarcinoma component in just the intramucosal proximal portion of the lesion

or SM1 cancer ≤3 cm in size. Patients who were treated following these expanded criteria have had similar long-term outcomes to those treated according to traditional

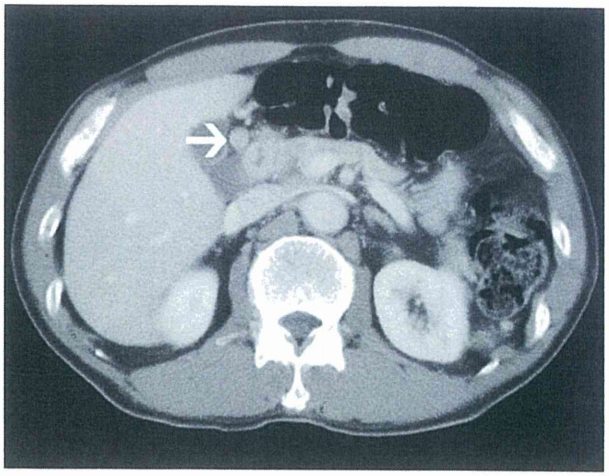

Fig. 3 CT in December 2007 detected an enlarged suprapyloric lymph node measuring 12 × 9 mm in size

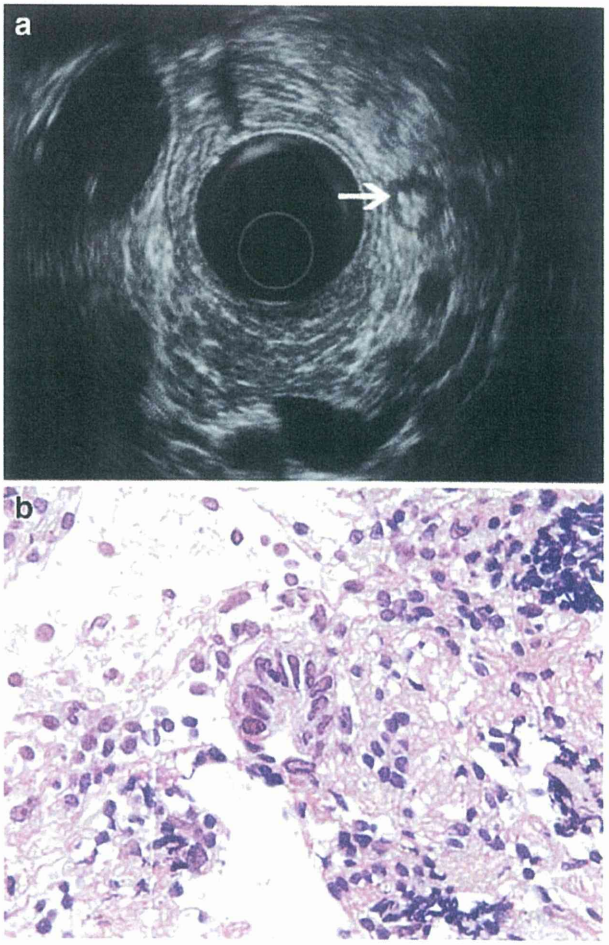

Fig. 4 **a** EUS in May 2009 revealed an enlarged lymph node measuring 12 mm in size at the site previously revealed by CT as well as another lymph node measuring 6 mm in size at a site close to the first one. **b** An adenocarcinoma with an enlarged nucleus and border irregularities was pathologically revealed by EUS-FNA

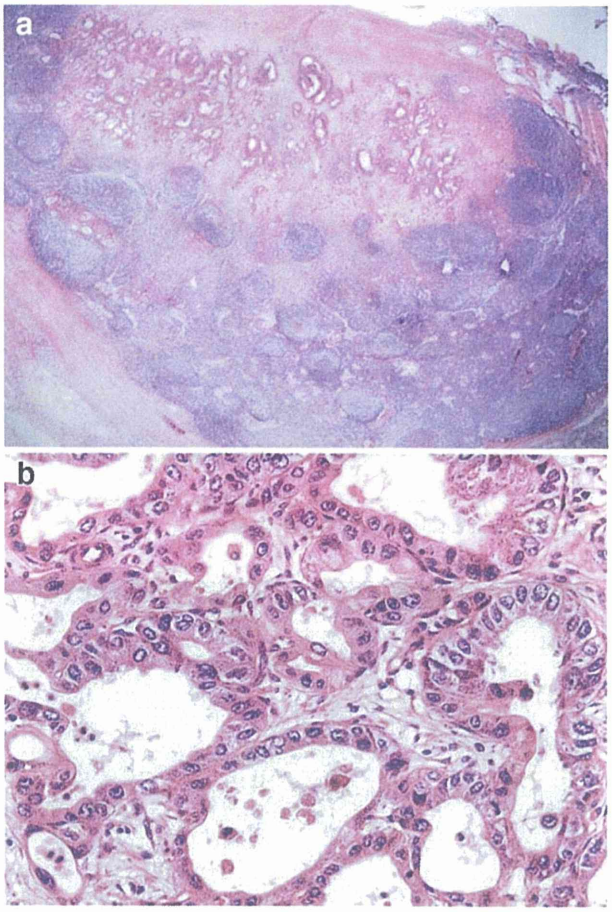

Fig. 5 Lymph node resected by surgery revealed a well-differentiated adenocarcinoma

guideline criteria (5-year survival rate of expanded criteria vs. traditional guideline criteria: 93.4 vs. 92.4%) [9]. In recent years, Nagano et al. [10] reported two cases of lymph node metastasis of SM1 cancer; however, one patient was previously treated by endoscopic piecemeal resection, and submucosal lymphatic involvement was observed in the other case. No lymphovascular involvement was observed in the present case, however, and this is the first case of a curative resection based on the SM1 expanded criteria in which lymph node metastasis was observed during careful follow-up.

We speculate that there are two possible explanations for such lymph node metastasis. First, we have previously reported that SM1 gastric cancer differentiated adenocarcinomas with negative lymphovascular involvement $\leq$3 cm in size had a 0% rate (0/145) of lymph node metastasis with a 95% confidence interval (CI) upper limit of 2.5% [2]. The risk of lymph node metastasis for such SM1 gastric cancer is slightly higher, however, than for the expanded criteria for intramucosal cancer. Second, the resected specimen revealed a predominantly well-differentiated adenocarcinoma, but a poorly differentiated adenocarcinoma component also was identified in the proximal portion of the lesion, although it was not in the area of SM1 infiltration and separate from the ulcer scar. A similar case of lymph node metastasis following ESD has been reported involving such a mixed type adenocarcinoma, and the patient subsequently died of liver metastasis 33 months after ESD [11].

In our case, lymph node metastasis was pathologically confirmed by EUS-FNA, and radical surgical treatment was performed, thus far resulting in the patient having no recurrence. Needless to say, careful follow-up is necessary after endoscopic resection, but it is difficult for current diagnostic imaging equipment to differentiate whether slightly enlarged lymph nodes, as in the present case, are non-malignant or metastatic [12]. Iwashita et al. [13] analyzed the enlarged lymph nodes of 62 patients and reported EUS-FNA sensitivity to be 97% with a specificity of 100%. EUS-FNA was also effective in the present case; therefore, we believe that EUS-FNA can be of assistance in making an accurate diagnosis for patients with enlarged lymph nodes.

We have to maintain careful follow-up, keeping in mind that metastasis may possibly occur even in a case of curative resection based on the expanded pathological criteria.

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ORIGINAL ARTICLE

A Multicenter Survey of the Management After Gastric Endoscopic Submucosal Dissection Related to Postoperative Bleeding

Osamu Goto · Mitsuhiro Fujishiro · Ichiro Oda · Naomi Kakushima · Yorimasa Yamamoto · Yosuke Tsuji · Ken Ohata · Takashi Fujiwara · Junko Fujiwara · Naoki Ishii · Chizu Yokoi · Shinichi Miyamoto · Toshiyuki Itoh · Shinji Morishita · Takuji Gotoda · Kazuhiko Koike

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Abstract

Background and Aims Bleeding is a major complication after gastric endoscopic submucosal dissection (ESD). An evidence-based strategy for postoperative care related to delayed bleeding is required. We conducted a multicenter survey to assess the current status of management after gastric ESD.

Methods A total of 1,814 gastric epithelial neoplasms in 2009 at ten tertiary referral centers were enrolled. The current status of the management after gastric ESD (use of an antisecretory drug, food intake, and second-look endoscopy) at participating hospitals was assessed. Furthermore, the rate of post-ESD bleeding and the differences in each parameter were retrospectively analyzed.

Results Postoperative bleeding occurred in 100 cases (5.5%), which included 62 cases of bleeding within 24 h after ESD. In all of the hospitals, proton pump inhibitors (PPIs) were used. The median administration period was 56 days (range 14–60 days). Food intake was resumed from postoperative day (POD) 1 in 4 hospitals and from POD 2 in 6 hospitals. Second-look endoscopy was performed for almost all cases, fewer cases, and rarely or none in 6, 2, and 2 hospitals, respectively. The day of second-look endoscopy varied among hospitals. There was no statistical relationship between the postoperative bleeding rate and the differences in these three parameters.

O. Goto (✉) · K. Koike
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, Japan
e-mail: ogotou-gi@umin.ac.jp

M. Fujishiro
Department of Endoscopy and Endoscopic Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

I. Oda
Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

N. Kakushima
Endoscopy Division, Shizuoka Cancer Center, Shizuoka, Japan

Y. Yamamoto
Department of Gastroenterology, Cancer Institute Hospital, Tokyo, Japan

Y. Tsuji · K. Ohata
Department of Gastroenterology, NTT Medical Center Tokyo, Tokyo, Japan

T. Fujiwara · J. Fujiwara
Department of Gastroenterology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

N. Ishii
Department of Gastroenterology, St Luke's International Hospital, Tokyo, Japan

C. Yokoi · T. Gotoda
Department of Gastroenterology, National Center for Global Health and Medicine, Tokyo, Japan

S. Miyamoto · T. Itoh
Department of Gastroenterology, The University of Kyoto, Kyoto, Japan

S. Morishita
Department of Gastroenterology, Tokyo Koseinenkin Hospital, Tokyo, Japan

Conclusions Post-ESD management (duration of PPI use, resumption of food intake, and performance of second-look endoscopy) varied among the medical centers; thus, randomized controlled trials are required for an optimal strategy after gastric ESD.

Keywords Endoscopic submucosal dissection · Gastric epithelial neoplasms · Postoperative bleeding · Second-look endoscopy

Introduction

Endoscopic submucosal dissection (ESD) for gastric epithelial neoplasms has been established as a minimally invasive endoluminal surgery [1–6]. However, there has been no consensus about an optimal strategy during the perioperative period, and the management of the patients who undergo ESD varies among hospitals.

Even in terms of preventing postoperative bleeding, which is one of the major complications to be avoided [7, 8], individual approaches are taken at each hospital; these are based more on experience than evidence. Although several suggestions have been made, e.g., the optimal use of an antisecretory drug [9], optimal duration [10], and the necessity of second-look endoscopy [11], the findings supporting these suggestions are mostly obtained by limited data from a single center, and the validity of these finding is unknown. In addition, other parameters may influence postoperative bleeding.

The establishment of an optimal strategy for secure ESD should be investigated by well-designed prospective studies in the future. To do so, we should understand the current status of postoperative care first, because we cannot design a suitable study if we remain ignorant of the prevailing strategy. Therefore, data collection about the management after gastric ESD was conducted at ten high-volume hospitals to assess the current status of prevention for postoperative bleeding.

Methods

A total of 1,814 patients who underwent gastric ESD at ten high-volume tertiary referral hospitals between January and December 2009 were enrolled. The following hospitals participated in this study: The University of Tokyo, Tokyo; National Cancer Center Hospital, Tokyo; Shizuoka Cancer Center, Shizuoka; Cancer Institute Hospital, Tokyo; NTT Medical Center Tokyo, Tokyo; Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo; St Luke's International Hospital, Tokyo; National Center for Global Health and Medicine, Tokyo; The University of Kyoto, Kyoto; and Tokyo Koseinenkin Hospital, Tokyo.

The questionnaire on the postoperative management for post-ESD bleeding was sent to the delegates of each hospital. The contents of the questionnaire are shown in Fig. 1.

Hospital: _____ Delegate: _____

Q1. How many gastric ESDs have been performed at your hospital so far?
_____ **cases**
Q2. How many gastric ESDs were performed in 2009?
_____ **cases**
Q3. What type of antisecretory drugs were administered? (Choose one)
☐**Proton-pump inhibitor**
☐**H2-blocker**
☐**Others**
Q4. How long were antisecretory drugs administered?
Until _____ **days after ESD**
Q5. When was oral intake resumed after the operation?
From postoperative day _____
Q6. How frequently was second-look endoscopy performed? (Choose one)
☐**90-100% of cases**
☐**50-90% of cases**
☐**10-50% of cases**
☐**0-10% of cases**
Q7. When was second-look endoscopy performed? (Choose one)
☐**Postoperative day** _____
☐**Irregular**
☐**Not performed**
Q8. How many cases of postoperative bleeding occurred?
_____ **cases**
Q9. How many episodes of postoperative bleeding occurred within 24 hours after the operation?
_____ **cases**
Q10. In the cases checked by second-look endoscopy, how many cases of postoperative bleeding occurred after that?
_____ **cases**

Fig. 1 The questionnaire regarding the management after gastric endoscopic submucosal dissection (ESD) and postoperative bleeding. Data were gathered from ten hospitals

In brief, the figure shows the total number of cases, the number of cases seen between January and December 2009, the management after ESD relevant to postoperative bleeding (use of an antisecretory drug, resumption of food intake, and frequency of second-look endoscopy), and the number of cases of postoperative bleeding. The survey was completed by August 2010 and the data were sent back to the principal investigator (O.G.) for analysis.

Postoperative bleeding was defined as apparent hematemesis or melena or a >2 g/dL decrease in the level of hemoglobin in addition to changes in vitals after ESD, in which bleeding from the mucosal defect or blood in the stomach was confirmed by emergency endoscopy. Second-look endoscopy was defined as the scheduled esophagogastroduodenoscopy that was conducted to check the mucosal defect and to perform hemostasis or prophylactic coagulation for the prevention of postoperative bleeding.

ESD was performed for possible node-negative early gastric cancers (EGCs) according to the criteria for node-negative EGCs by Gotoda et al. [12] and for gastric adenoma that was difficult to distinguish from adenocarcinoma or which the patient strongly desired to have resected. All patients provided informed written consent before undergoing treatment.

The patients were hospitalized for ESD and were usually allowed to resume eating soft foods after ESD. The patients taking anticoagulants and/or antiplatelet drugs were generally instructed to stop for the perioperative period, but this duration and whether other drugs, e.g., heparin, were taken instead depended on the endoscopist in charge. When bleeding or non-bleeding visible vessels were seen on the mucosal defect during the final step of the operation, hemostasis or prophylactic coagulation was performed with, e.g., clips or hemostatic forceps before the withdrawal of the endoscope [13]. When perforations occurred, the schedules including food intake were changed in accordance with the patient's condition.

For statistical analyses, postoperative bleeding rates were compared among two or three groups for each parameter (duration of antisecretory drug use, resumption of food intake, and frequency of second-look endoscopy): a short (until postoperative day [POD] 14), middle (until approximately POD 28), or long (until approximately POD 56) duration group with respect to the use of proton pump inhibitors (PPIs); early (from POD 1) or late (from POD 2) resumption group in terms of food intake; and major (90–100%), intermediate (10–90%), or minor (0–10%) proportion group in terms of second-look endoscopy.

Univariate analysis was performed for the duration of antisecretory drug use and the frequency of second-look endoscopy by one-way analysis of variance (ANOVA), and for the resumption of food intake by Student's *t*-test. Statistical significance was set at a *P*-value of less than 0.05.

Results

The median number of gastric ESDs in total at each hospital was 668.5 (range 130–4,142). In 2009, the total number of gastric ESDs in the participating hospitals was 1,814, and the median number was 113 (range 33–411). Postoperative bleeding occurred in 100 cases (5.5%), which included 62 (3.4%) patients who bled within 24 h after the operation. The median rate of postoperative bleeding at each hospital was 4.3% (range 0–11.3%). Bleeding before second-look endoscopy occurred in 79 cases (including cases at the hospitals where second-look endoscopy was not routinely performed), and bleeding occurred in 21 cases after second-look endoscopy.

The results of the questionnaires related to the parameters of postoperative bleeding are shown in Fig. 2. At all of the hospitals, a PPI was used as an antisecretory drug. The median duration of PPI administration was 56 days (range 14–60), and the period had a trimodal tendency of approximately 2, 4, and 8 weeks at 1, 3, and 6 hospital(s), respectively. Food intake was resumed by POD 2 at all of the hospitals (from POD 1 at 4 and from POD 2 at 6 hospitals). Second-look endoscopy was performed in almost all cases (90–100%), fewer cases (10–50%), and rare cases or none (0–10%) at 6, 2, and 2 hospitals, respectively. The day of second-look endoscopy varied among the hospitals (POD 1, POD 2, irregular, and none at 5, 1, 3, and 1 hospital[s], respectively).

Table 1 shows the comparison of postoperative bleeding rates among the groups for the three parameters. There were no statistical differences among the parameters.

Discussion

In the present analysis, we elucidated the current status of post-ESD management at the major hospitals where gastric ESD is routinely performed. By investigating each parameter related to postoperative bleeding, this study may be of some help for establishing an optimal strategy regarding post-ESD management and for designing further prospective studies.

In terms of antisecretory drugs, all of the participating hospitals used PPIs for at least 2 weeks, which might be the influence of a prospective randomized controlled trial by Uedo et al., which elucidated the superiority of PPIs to an H_2-receptor antagonist in the prevention of postoperative bleeding [9]. However, the duration of PPI administration varies among hospitals. The previous study showed that the artificial ulcer after a gastric ESD heals within 8 weeks under PPI administration [10]. In addition, more than 90% of peptic ulcers heal with the use of PPIs for 8 weeks [14, 15]. These factors may be the reasons for why PPIs are

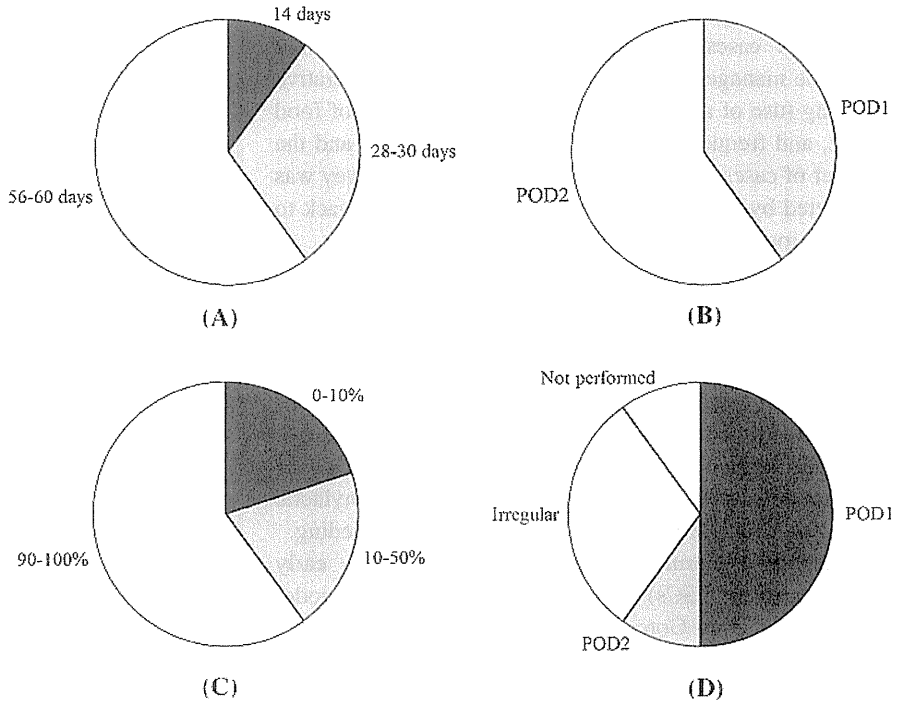

Fig. 2 Management after gastric ESD. Variability existed among the participating ten hospitals (the period of proton pump inhibitor [PPI] administration, the start point of food intake, and frequency and the day of second-look endoscopy). **a** Duration of PPI administration. **b** The start point of food intake. **c** Frequency of second-look endoscopy. **d** The day of second-look endoscopy. *POD* postoperative day

Table 1 The relationship between postoperative bleeding and the parameters regarding postoperative management

	Number of hospitals (*n*)	Mean postoperative bleeding rate (% ± standard deviation [SD])	*P*-value
Use of PPI[a]			
Short duration	1	2.6	0.6975
Middle duration	3	6.3 ± 4.6	
Long duration	6	4.7 ± 3.5	
Food intake[b]			
Early resumption	4	5.4 ± 5.0	0.7904
Late resumption	6	4.7 ± 2.7	
Second-look endoscopy[c]			
Major proportion	6	4.9 ± 4.5	0.8300
Intermediate proportion	2	3.9 ± 1.8	
Minor proportion	2	6.3 ± 1.7	

[a] Short, for 2 weeks; middle, for approximately 4 weeks; long, for approximately 8 weeks

[b] Early, from postoperative day 1; late, from postoperative day 2

[c] Major, 90–100%; intermediate, 10–90%; minor, 0–10%

used for approximately 2 months in a majority of the hospitals. However, Lee et al. revealed that the necessary and sufficient duration of PPIs for iatrogenic gastric ulcers caused by endoscopic resection might not be 8 weeks [16]. The present findings that postoperative bleeding did not increase even though PPIs were administered for only 2 or 4 weeks suggest that the duration of PPIs may be shortened compared to that observed in patients with peptic ulcers. Further studies are required in order to find an optimal duration and dose of PPIs.

Similarly, refeeding was permitted prior to POD 3 at all of the hospitals. Because there have been few studies relevant to food intake after bleeding peptic ulcers [17], even less is known about its relationship to the iatrogenic ulcer, and the decision to initiate is based mainly on the experience at each hospital or the individual endoscopist in charge. The present survey speculates that extended periods of fasting may not be required, which is beneficial in terms of shorter hospital stay and patient comfort. In fairly rare cases, however, microperforation or delayed perforation occurs. Therefore, the decision for refeeding should be carefully made after confirming that there is no occult perforation by X-ray or by the cautious surveillance of the patient's condition.

Goto et al. [11] suggested that second-look endoscopy might be unnecessary after gastric ESD in a retrospective, single-center analysis. In this multicenter study, the shortcomings described above have been overcome to some extent. The present study also showed no significant difference in postoperative bleeding in terms of the frequency of second-look endoscopy, speculating that second-look endoscopy may contribute little to the prevention of postoperative bleeding. This speculation can be supported by the fact that two-thirds of postoperative bleeding cases (62 out of 100) occurred within 24 h after the operation,

because these cases cannot be prevented by scheduled endoscopy.

Despite the data being obtained consecutively, there were certain limitations. This is a survey by questionnaire and an underpowered analysis with some possible biases. For example, patients with a high-risk lesion, e.g., large lesions or lesions with a scar, would be likely to experience a long period of PPI administration, to have a long fasting time, and to undergo second-look endoscopy. In addition, the identification of necessities such as short PPI administration, short fasting period, or no second-look endoscopy should be performed by non-inferiority studies. Furthermore, the data shown in Table 1 were not allocated by whether second-look endoscopy was performed for each case, but, rather, by how frequently it was performed at each hospital. Considering these limitations, our data indicated that a prospective comparative study was worth conducting in order to clarify whether it was possible to shorten the length of PPI administration or fasting time and to omit second-look endoscopy.

In conclusion, this multicenter survey clarified that post-ESD management (duration of PPI use, resumption of food intake, and performance of second-look endoscopy) varied among the medical centers. To establish an optimal strategy after gastric ESD, randomized controlled trials are required, especially for parameters in which it may not be necessary.

Conflict of interest None.

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ORIGINAL ARTICLE

Discrepancies in histologic diagnoses of early gastric cancer between biopsy and endoscopic mucosal resection specimens

Madoka Takao · Naomi Kakushima · Kohei Takizawa · Masaki Tanaka · Yuichiro Yamaguchi · Hiroyuki Matsubayashi · Kimihide Kusafuka · Hiroyuki Ono

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Abstract
Background A preoperative histologic diagnosis of neoplasia is a requirement for endoscopic resection (ER). However, discrepancies may occur between histologic diagnoses based on biopsy specimens versus ER specimens. The aim of this study was to assess the rate of discrepancy between histologic diagnoses from biopsy specimens and ER specimens.
Methods A total of 1705 gastric lesions, from 1419 patients with a biopsy diagnosis of neoplasia, were treated by ER from September 2002 to December 2008. We compared the histologic diagnosis from the biopsy sample and the final diagnosis from the ER specimen to assess the discrepancy rate. Clinicopathological characteristics of the lesions that were related to the histologic discrepancies were also studied.
Results An ER diagnosis of gastric cancer was made in 49% (118/241) of lesions diagnosed as borderline lesions from biopsy specimens; this included adenomas and lesions difficult to diagnose as regenerative or neoplastic. The size, existence of a depressed area, and ulceration findings were significant factors observed in these lesions. An ER diagnosis of differentiated type cancer was obtained for 17% (12/63) of lesions diagnosed as undifferentiated type cancer from the biopsy specimens; for these lesions, the color and a mixed histology were significant factors related to the histologic discrepancies.
Conclusion A biopsy diagnosis of borderline lesions or undifferentiated type cancer is more likely to disagree with the diagnosis from ER specimens. Endoscopic characteristics should be considered together with the biopsy diagnosis to determine the treatment strategy for these lesions.

Keywords Endoscopic mucosal resection (EMR) · Endoscopic submucosal dissection (ESD) · Early gastric cancer (EGC)

M. Takao · N. Kakushima (✉) · K. Takizawa · M. Tanaka · Y. Yamaguchi · H. Matsubayashi · H. Ono
Division of Endoscopy, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi, Suntougun, Shizuoka 411-8777, Japan
e-mail: kakushin-tky@umin.ac.jp

K. Kusafuka
Division of Pathology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi, Suntougun, Shizuoka 411-8777, Japan

Introduction

Endoscopic resection (ER) is an effective treatment for early-stage gastrointestinal neoplasms [1]. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are popular ER techniques that are widely used for the treatment of early gastric cancer (EGC). In Japan, the EGC criteria for ER are based on technical limitations and the possibility of nodal metastasis. The criteria for EGC lesions indicated for ER proposed by the Japanese Gastric Cancer Association include those with a preoperative diagnosis of differentiated type intramucosal cancer without ulcer findings, differentiated type intramucosal cancer that is no larger than 3 cm in diameter with ulcer findings, differentiated type minute invasive submucosal cancer (invasion less than 500 μm below the muscularis mucosa) that is no larger than 3 cm in diameter, and undifferentiated type intramucosal cancer that is no larger than 2 cm in diameter without ulcer findings [2]. Therefore, a preoperative histologic diagnosis based on biopsy samples is required before planning ER.

However, the diagnosis based on the biopsy samples sometimes does not correspond with the endoscopic diagnosis. Biopsy-based diagnoses are subject to the limitations of superficiality and sampling errors, sometimes leading to misjudgments in the treatment for the lesion. For EGC, a biopsy diagnosis of differentiated type adenocarcinoma is one of the requirements for ER. There are few studies examining the discrepancy between the histologic types of EGC diagnosed from biopsy samples versus the diagnosis from ER specimens. The aim of this study was to evaluate the discrepancy rate of diagnoses between biopsy samples and ER specimens, and to evaluate the clinicopathological characteristics of gastric lesions that were diagnosed differently with the two modalities.

Patients and methods

A total of 1705 gastric lesions from 1419 patients, who were treated by ER from September 2002 to December 2008 at a single prefectural cancer center, were included. The indications for ER at our institution include lesions with the findings of EGC that meet the Japanese EGC criteria for ER, diagnosed by endoscopy and chromoendoscopy, or a gastric neoplasia suspected of being EGC. For lesions suspicious for EGC endoscopically, a diagnostic ER was performed for lesions with a preoperative biopsy diagnosis of borderline lesion or neoplasia. As for elderly patients or EGC patients considered to be inoperable because of having an inadequate general condition for surgery, ER was selected for some EGC lesions that were diagnosed as an indication for surgery. In such patients, preoperative computed tomography was performed before the ER to confirm that distant metastasis was absent.

Clinicopathological data were retrieved from charts and endoscopic and pathology reports. Discrepancies between the histologic diagnoses based on biopsy specimens and those based on ER specimens were assessed (study 1). Three gastrointestinal pathologists at our hospital were involved in the histologic diagnosis in this study. Generally, the pathologists did not refer to the biopsy samples when they diagnosed the ER specimens. However, when a discrepancy occurred between the final diagnosis and the preoperative diagnosis, such as no tumor being found in the ER specimen or lesions changing in histologic type, there was a discussion between the pathologists with reference to the previous biopsy specimen. The histologic diagnosis of biopsy specimens was carried out according to the classification of the Japanese Gastric Cancer Association [3, 4]. Biopsy histology is classified into five groups: normal or benign changes (hyperplasia/metaplasia) without atypia (group I); lesions with atypia resulting from regeneration (group II); borderline lesions including adenomas and lesions difficult to diagnose as regenerative or neoplastic (group III); lesions strongly suspected of carcinoma (group IV); and definite carcinomas irrespective of invasion (group V). For lesions with a biopsy diagnosis of definite carcinoma, the histologic type diagnosed by biopsy was compared to the final diagnosis obtained from ER specimens (study 2). All of the recognizable histologic types of cancer observed in the biopsy specimen (in one biopsy sample or 2 or more samples), were recorded. The diagnosis of mixed type histology was documented beginning from the histology of the major component; for example, well differentiated carcinoma > moderately differentiated carcinoma.

The ER methods used included EMR and ESD using an insulated-tip knife 1 or 2 (IT-knife 1, IT-knife 2). The details of ESD using the IT-knife 1 or 2 were described previously [5]. Written informed consent was collected from all patients undergoing endoscopy with biopsy sampling and before ER. This retrospective study was approved by the institutional review board of our hospital (No. 22-J127-22-1-3). Statistical analysis was done using the χ^2test, and a P value of ≤ 0.05 was considered significant.

Results

Clinicopathological data on the 1705 lesions are shown in Table 1. The method of ER was ESD in 99.5% (1697/1705) of the lesions. All lesions had a biopsy diagnosis of group III or more. The breakdown for groups III, IV, and V was 14, 6, and 80%, respectively. Among the 1360 lesions diagnosed as definite cancer (group V) from biopsy specimens, 1291 lesions were diagnosed as differentiated type cancer and 69 were diagnosed as undifferentiated type cancer.

Study 1: the discrepancy rate between histologic diagnoses based on biopsy specimens and those based on ER specimens

The discrepancies between the histologic diagnosis from biopsy specimens and the final diagnosis from ER specimens are shown in Table 2. Among 235 lesions with a biopsy diagnosis of group III (borderline lesions), 48% (112/235) were diagnosed as cancer. For lesions with biopsy diagnoses of group IV and group V, the final diagnosis was cancer in 93.6% (103/110) and 98.6% (1341/1360) of lesions, respectively. For lesions with upgraded histology, the final diagnosis of cancer was made by both cellular and structural atypia. In most cases, there were similar histologic findings in the ER specimen and biopsy sample. In nine lesions, no neoplastic change was found in

Table 1 Clinicopathological characteristics of 1419 patients (1705 lesions)

Sex (male/female)	1095/324
Age, years, median (range)	71 (36–93)
Location[a], *n* (%)	
Upper third	343 (20.1)
Middle third	744 (43.7)
Lower third	618 (36.2)
Lesion diameter, mm, median (range)	18 (1–110)
Gross type, *n* (%)	
Elevated type	800 (46.9)
Flat type	9 (0.5)
Depressed type	840 (49.3)
Recurrence after ER	56 (3.3)
Biopsy histology, group classification, *n* (%)	
Group III	235 (13.8)
Group IV	110 (6.5)
Group V	1360 (79.7)
Histological type of cancer, forceps biopsy, *n* (%)	
Differentiated	1291 (95.0)
Undifferentiated	69 (5.0)
ER method, *n* (%)	
ESD	1697 (99.5)
EMR	8 (0.5)

ER endoscopic resection, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

[a] According to Ref. [17]

Table 2 Results of biopsy histology (group classification according to Ref. [3]) and final histology after endoscopic resection

Biopsy histology (%)	Histology after endoscopic resection		
	Nonneoplastic	Adenoma	Cancer
Group III ($n = 235$)	2 (0.8)	121 (51.5)	112 (47.7)
Group IV ($n = 110$)	0 (0)	7 (6.4)	103 (93.6)
Group V ($n = 1360$)	7 (0.5)	12 (0.9)	1341 (98.6)
Total	9	140	1556

the ER specimen. Seven of these lesions had a biopsy diagnosis of group V; six had a diameter smaller than 5 mm and one lesion was re-diagnosed as regenerative atypia based on the ER specimen.

Univariate analyses of clinicopathological factors associated with the final histology after ER in group III lesions are shown in Table 3. The factors shown in Table 3 were derived from endoscopic findings. Lesions with a diameter of 2 cm or more, the presence of a depressed area within the lesion, and the presence of ulcer findings within the lesion were significant factors related to lesions with a final diagnosis of cancer ($P < 0.05$).

Table 3 Univariate analysis of factors associated with the final histology after endoscopic resection in group III lesions (group classification according to Ref. [3])

	Histology after endoscopic resection		
	Adenoma ($n = 121$)	Cancer ($n = 112$)	*P* value
Location[a] (*n*)			
Upper third	15	16	NS
Middle third	47	56	
Lower third	59	40	
Tumor diameter (cm)			
<2	82	52	0.001
≧2	39	60	
Depressed area (*n*)			
Present	10	35	<0.0001
Absent	111	77	
Ulcer findings (*n*)			
Present	4	12	0.0255
Absent	117	100	

NS not significant

[a] According to Ref. [17]

Study 2: comparison of the biopsy diagnosis of histologic cancer type and the final diagnosis from ER specimens

The final diagnoses of 1360 lesions that had a biopsy diagnosis of definite cancer (group V) are shown in Table 4. For lesions with a biopsy diagnosis of differentiated type cancer, 97% (1253/1291) had a concordant final diagnosis of differentiated type cancer. For lesions with a biopsy diagnosis of undifferentiated type cancer, 17% (12/69) had a discrepant final diagnosis of differentiated type cancer; 8 of these lesions were diagnosed as mixed histology of differentiated and undifferentiated type cancer, and 4 lesions were diagnosed as pure differentiated type cancer without having the component of the biopsy histology.

Univariate analyses of clinicopathological factors associated with the final histologic type of cancer among lesions diagnosed as undifferentiated type adenocarcinoma by biopsy are shown in Table 5. The factors shown in Table 5, except for histologic type, were derived from endoscopic findings. The color of the lesion (normal to reddish) and the presence of mixed histology of differentiated and undifferentiated type within the lesion were significant factors related to discrepancies in the histologic type of cancer diagnosed from biopsy versus ER specimens.

A representative case of EGC with a discrepant diagnosis between biopsy and ER specimens is shown in Fig. 1a, b. The endoscopic diagnosis was a depressed type intramucosal cancer, 13 mm in diameter. The biopsy

Table 4 Biopsy histology type and final histology after endoscopic resection

Biopsy histology type (%)	Histology after endoscopic resection			
	Non-neoplastic	Adenoma	Differentiated	Undifferentiated
Differentiated (n = 1291)	7 (0.5)	12 (0.9)	1253 (97.1)	19 (1.5)
Undifferentiated (n = 69)	0 (0)	0 (0)	12 (17)	57 (83)
Total	7	12	1265	76

Table 5 Univariate analyses of factors associated with the final histology after endoscopic resection in lesions diagnosed as undifferentiated type adenocarcinoma by biopsy

Factors	Histology after endoscopic resection		
	Differentiated (n = 12)	Undifferentiated (n = 57)	P value
Marginal area (n)			
Well-demarcated	5	39	NS
Poorly demarcated	7	18	
Surface color (n)			
Normal mucosa or reddish	10	29	0.0039
Whitish discoloration	2	28	
Ulcer findings (n)			
Present	2	10	<0.0001
Absent	10	47	
Histologically mixed type (n)			
Yes	8	13	0.0027
No	4	44	

Histologically mixed type is defined as a lesion with both differentiated and undifferentiated type cancer

NS not significant

specimen showed poorly differentiated type cancer (Fig. 1c). Although undifferentiated type EGC is not an indicated lesion for ER, ESD was performed due to the patient's advanced age and comorbidities; the ESD specimen is shown in Fig. 1d. The final diagnosis was an intramucosal cancer, 13 × 8 mm, moderately differentiated adenocarcinoma, with no lymphovascular infiltration (Fig. 1e). Therefore, the treatment was considered to be a curative resection.

Discussion

One of the advantages of ER is that a precise pathological evaluation can be obtained from the whole lesion resected in one piece. Forceps biopsy is sometimes inadequate for a correct histologic diagnosis and the foci of dysplasia may not be identified [6, 7]. In our present study, among 1705 lesions with a biopsy diagnosis of group III or more, nine cases (0.5%) had a final diagnosis of non-neoplastic tissue based on the ER specimen. Possible reasons for this discrepancy are that either the lesion was removed by biopsy or the biopsy diagnosis was an overestimation. The reasons why we conducted ER for the two lesions with a biopsy diagnosis of group III that were finally diagnosed as non-neoplastic were that the endoscopic finding of one of these lesions was a depressed type suspicious for EGC, and the biopsy of the other lesion showed high-grade gastric epithelial dysplasia.

The clinical management of gastric lesions with a biopsy diagnosis of borderline lesions, including adenomas and lesions difficult to diagnose as regenerative or neoplastic (so-called group III lesions), may differ among institutions. Repeat biopsy, follow-up, or ER may be options. Previous studies reported that 5.1–74% of group III lesions had a final diagnosis of cancer after ER [8–11]. In our present study, half of the group III lesions had a final diagnosis of cancer, and the rest were diagnosed as tubular adenomas. One of the reasons for the wide detection range of cancer from group III lesions is that the diagnosis for group III includes not only adenomas but also lesions difficult to diagnose as regenerative or neoplastic. In fact, group III includes lesions of categories 2 and 3 according to the revised Vienna classification of gastrointestinal epithelial neoplasia [12]. To address the need for a clinically meaningful classification, the Japanese Gastric Cancer Association recently published the 14th edition of the *Japanese classification of gastric carcinoma* (in Japanese) [13] and revised the group classification of gastric biopsy specimens, which is now closer to the Vienna classification.

For lesions diagnosed as adenomas from biopsy specimens and finally diagnosed as cancer from ER specimens, the endoscopic features indicative of cancer were a larger size, the presence of a depressed area within the lesion, and the presence of an ulcer or ulcer scar within the lesion. These endoscopic features have been reported previously [14–16], and the results of our study are compatible with these reports.

Considering the histologic type of cancer, the discrepancy rate for diagnosis was different between lesions diagnosed as differentiated type or undifferentiated type cancer. For lesions with a biopsy diagnosis of differentiated type cancer, 97% showed concordant histology, whereas only 83% of lesions with a biopsy diagnosis of undifferentiated type cancer had concordant histology. Analysis indicated that the presence of mixed histology with

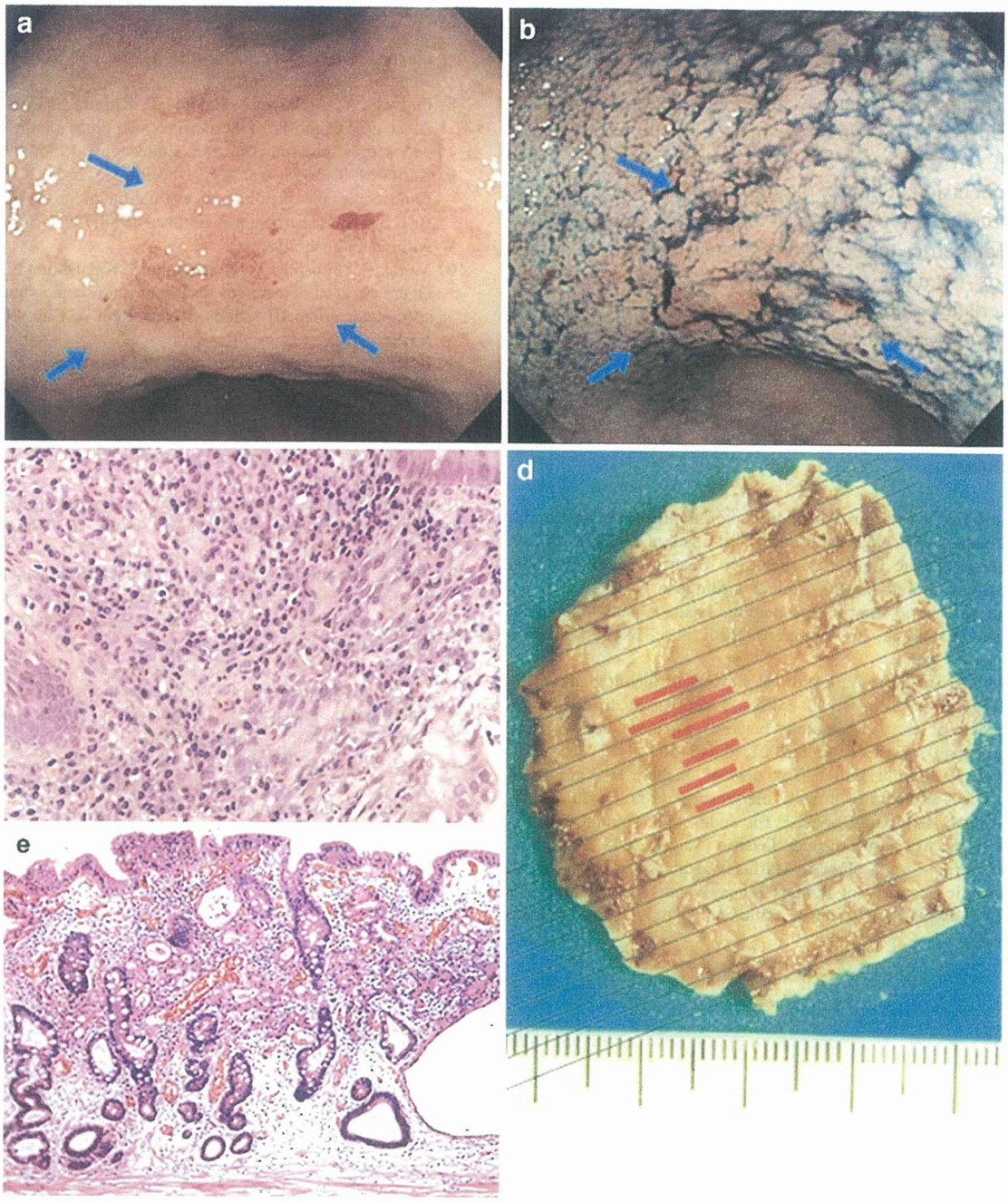

Fig. 1 **a** A slightly depressed area *(arrows)*, 13 mm in diameter, is observed in the gastric angle. **b** After chromoendoscopy with indigo carmine, an endoscopic diagnosis of a depressed type intramucosal cancer *(arrows)* was made. **c** The biopsy specimen showed poorly differentiated type cancer (H&E, ×10). **d** The specimen from the endoscopic submucosal dissection showed mucosal cancer in the *red lined* areas. **e** The final diagnosis was an intramucosal cancer, 13 mm in diameter, moderately differentiated adenocarcinoma, with no lymphovascular infiltration (H&E, ×40)

differentiated and undifferentiated types within the lesion was one of the features indicative of histologic type discrepancies, and these histologic type discrepancies might be due to the heterogeneity of gastric cancer. Also, biopsy specimens with tissue that was crushed due to technical problems would be inadequate to detect duct formation of the cancer cells, and a finding of no ductal formation would lead to the diagnosis of poorly differentiated adenocarcinoma.

The limitation of the present study is that it was a retrospective analysis with data derived from a database of ER performed for gastric neoplasms. Therefore, some