

**Table 3** Multivariate logistic regression analysis

	$\beta$ -coefficient	Odds ratio (95% CI)	<i>p</i> value
Margin elevation	7.838	6.221 (3.938–9.825)	<0.0001
Tumor size (more than 30 mm)	6.570	4.937 (3.066–7.951)	<0.0001
Remarkable redness	3.411	2.087 (1.367–3.186)	0.0006
Uneven surface	3.343	2.306 (1.413–3.764)	0.0008

CI confidence interval

Evaluated items in multiple logistic regression analysis were followed: tumor size more than 30 mm, macroscopic type (IIa + IIc), remarkable redness, uneven surface margin elevation, ulceration and enlarged folds. Only the statistically significant items are listed in the table

**Table 4** Proposed depth-predicting score

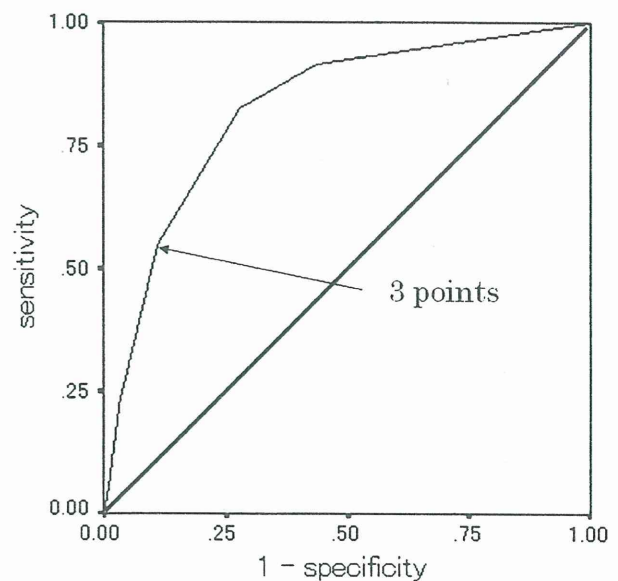
Factor	Points	
	Present	Absent
Margin elevation	2	0
Tumor size (more than 30 mm)	2	0
Remarkable redness	1	0
Uneven surface	1	0

83.7–88.8%), and 81.1% (95% CI 78.5–83.8%), respectively (Fig. 7).

Finally, we applied the suggested DPS model to the 211 validation lesions without any histological information. When we considered 3 points or more as SM2, the sensitivity, specificity, and accuracy of the proposed DPS, assigned by the three endoscopists, were 29.7–45.9, 93.1–93.7, and 82.5–84.8%, respectively. When we divided the validation group into “IIa” and “IIc/IIa + IIc”, the sensitivity, specificity, and accuracy were 50.0–83.3, 92.6–96.3, and 91.7% (by all three endoscopists) for IIa lesions and 25.8–38.7, 92.5–93.3, and 78.8–82.1% for IIc/IIa + IIc lesions (Table 5).

**Discussion**

Patients’ quality of life is one of the most important issues in EGC treatment, because the prognosis of EGC is favorable [13]. Differentiating endoscopically resectable M-SM1 gastric cancers from surgically resectable SM2 lesions is of great significance, given the low risk of lymph node metastases with the former. In conventional endoscopic diagnosis for these EGCs, however, endoscopists have had to empirically estimate the depth of invasion, as no objective criteria existed.



**Fig. 7** Receiver operating characteristic curve for depth-predicting score (DPS) and the sensitivity of SM2: the arrow (3 points) shows the cutoff point between M-SM1 and SM2

**Table 5** Diagnostic sensitivity and specificity by depth-predicting score according to macroscopic type in the validation group

	IIa	IIc/IIa + IIc	Total
<b>Endoscopist 1</b>			
Sensitivity	50.0% (3/6)	25.8% (8/31)	29.7% (11/37)
Specificity	96.3% (52/54)	92.5% (111/120)	93.7% (163/174)
Accuracy	91.7% (55/60)	78.8% (119/151)	82.5% (174/211)
<b>Endoscopist 2</b>			
Sensitivity	83.3% (5/6)	38.7% (12/31)	45.9% (17/37)
Specificity	92.6% (50/54)	93.3% (112/120)	93.1% (162/174)
Accuracy	91.7% (55/60)	82.1% (124/151)	84.8% (179/211)
<b>Endoscopist 3</b>			
Sensitivity	50.0% (3/6)	35.8% (11/31)	37.8% (14/37)
Specificity	96.3% (52/54)	92.5% (111/120)	93.7% (163/174)
Accuracy	91.7% (55/60)	80.8% (122/151)	83.9% (177/211)

The first aim of this retrospective study was to analyze the differences in conventional endoscopic features between M-SM1 and SM2 EGCs. We found that tumor size more than 30 mm, margin elevation, uneven surface, and remarkable redness were significantly associated with an increased risk of SM2 invasion according to logistic regression analysis.

There have been few reports about the usefulness of conventional endoscopy for predicting depth of invasion. The overall accuracy rates for determining depth of invasion of EGCs were between 63 and 73% by non-objective criteria [11, 14, 15]. Namieno et al. [16] concluded that

macroscopic appearance, histological differentiation, and tumor size were associated with submucosal invasion. However, they did not analyze the morphologic features of the tumors.

Although we used endoscopy in the present study, EUS can also show the depth of invasion clearly. The introduction of high-frequency thin probes has allowed target scanning with high resolution under endoscopic control [8, 9]. In spite of some excellent accuracy data [17], there have been no significant differences between EUS and endoscopy in terms of depth accuracy [14].

Considering the need for simple and objective diagnosis, we proposed an endoscopic determination for the depth of invasion of differentiated EGCs by the DPS described here, based on our analysis of the derivation group. The DPS could be used to determine an appropriate treatment strategy for the validation group with 82.5–84.8% accuracy. Based on macroscopic type, the accuracy for elevated lesions tended to be better than that for the depressed and combined lesions.

Although specificity was good in steering M-SM1 cancers toward endoscopic treatment, low sensitivity was a weak point of the DPS. Selected endoscopic features may not reflect microscopic SM2 invasion. Also, each variable was considered as only either present or absent. If the significance of each finding had been taken into consideration, the sensitivity and accuracy of the score may have increased. However, this would have complicated the DPS, and was therefore not done.

EUS could be omitted for lesions with a DPS of less than 2 points and endoscopic resection performed, except for large ulcerative lesions more than 30 mm in diameter. Lesions with a DPS of 3 points or more may be considered as candidates for additional EUS, potentially providing more precise prediction. By using this simple diagnostic model, appropriate treatment strategies can be determined for differentiated M-SM1 EGCs, while saving time and cost as compared to EUS being done for all cases.

The limitation of this investigation was the retrospective design at a single institution. Further research in a prospective study is needed to investigate the utility of the DPS in combination with EUS for lesions with a DPS of 3 points or greater.

In conclusion, the proposed DPS may be useful in making treatment decisions for differentiated M-SM1 EGCs.

**Acknowledgments** The authors had the generous support and encouragement of Dr. Hitoshi Kondo (The Center for Digestive Diseases, Tonan Hospital, Japan). Also, we wish to thank Dr. Jeffery Paul Gaboury (Department of Surgery, University of Saskatchewan, Canada) and Dr. Satchan Takaya (Division of Infectious Diseases, University of Saskatchewan, Canada) for correcting the English used in this manuscript.

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## Clinical impact of a strategy involving endoscopic submucosal dissection for early gastric cancer: determining the optimal pathway

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Received: 16 June 2010 / Accepted: 30 September 2010 / Published online: 17 February 2011  
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### Abstract

**Background** Endoscopic submucosal dissection (ESD) is a technique developed to enable the endoscopic resection (ER) of large and ulcerative neoplastic lesions that were previously unresectable using conventional endoscopic mucosal resection (EMR). We investigated the clinical outcomes of ER of early gastric cancer (EGC) before and after the introduction of ESD, with particular attention to surgery and its potential consequences.

**Methods** We reviewed 2,785 consecutive surgical patients with EGC and 2,469 consecutive lesions treated by ER with curative intent between 1990 and 2005. The study was divided into an EMR period (1990–1999) and an ESD period (2000–2005). We analyzed the clinical outcomes of endoscopic and surgical resections and defined ‘potentially avoidable surgery’ as cases of surgery performed for lesions curable by ER.

**Results** The rate of potentially avoidable surgery was 3.8% (52/1,369) in the EMR period and 0.2% (3/1,416) in the ESD period ( $P < 0.001$ ). For ER patients, the rate of overall non-curative ER was 36.9% (154/417) in the EMR group and 17.0% (348/2,052) in the ESD group ( $P < 0.001$ ). The rate of non-curative ER for lesions

defined as having ‘positive or difficult to estimate horizontal margins only’ decreased significantly, from 26.1% (109/417) in the EMR group to 1.4% (29/2,052) in the ESD group ( $P < 0.001$ ). Conversely, the rate of non-curative ER for lesions defined as having ‘possible lymph node metastasis’ significantly increased in the ESD group (15.5%; 319/2,052) compared to that in the EMR group (10.8%; 45/417) ( $P < 0.01$ ).

**Conclusions** The application of a pathway involving ESD resulted in a significant decrease in the rate of potentially avoidable surgery, highlighting the advantages associated with performing ESD.

**Keywords** Early gastric cancer · Lymph node metastasis · Endoscopic submucosal dissection · Potentially avoidable surgery · Non-curative endoscopic resection

### Abbreviations

ER	Endoscopic resection
EGC	Early gastric cancer
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
sm2	Submucosal deep invasion
sm1	Submucosal superficial invasion

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### Introduction

Therapeutic endoscopic resection (ER) has been performed for early gastric cancer (EGC) since the mid 1980s and is now accepted as the standard treatment for those patients with negligible risk of lymph node metastasis [1–8]. The conventional method by which EGCs were removed was by endoscopic mucosal resection (EMR). The limitations

of applying EMR to all potentially endoscopically resectable lesions were size, location, and scarring from previous ulceration, so that only piecemeal removal was possible in such cases [9–11]. Unfortunately, piecemeal resection of EGC is associated with both difficulties in accurate histological assessment and a higher rate of local recurrence [12, 13]. Consequently, surgery was often chosen as the initial preferred method of treatment for lesions which were difficult to resect by EMR and those associated with difficulty in estimation of tumor depth.

A major breakthrough was achieved at the turn of the twenty-first century, with the advent of endoscopic submucosal dissection (ESD) [14–20]. ESD is a technique developed to enable the resection of large and ulcerative lesions, regardless of tumor location, that are unable to be removed using the conventional EMR procedure. The other major advantage of ESD is its ability to achieve a higher rate of en-bloc resection, thus providing more accurate histological assessment as compared to EMR [12, 21]. For the aforementioned reasons, ESD has translated into lower rates of local recurrence of gastric cancer as compared with EMR [22, 23]. The gastric cancer treatment guidelines of the Japanese Gastric Cancer Association for lesions that are considered curative by EMR are shown in Table 1 [24]. Based on the risk of lymph node metastasis determined from a large cohort of surgically treated cases of EGCs, ESD is now regarded as a curative procedure for lesions selected using the National Cancer Center expanded criteria (Table 2) [25].

**Table 1** JGCA guideline criteria for endoscopic resection

Differentiated adenocarcinoma
Intramucosal cancer
≤20 mm in size without ulceration

JGCA Japanese Gastric Cancer Association

**Table 2** NCC expanded histopathological criteria for curative endoscopic resection

Early gastric cancer with negligible risk of lymph node metastasis
Differentiated adenocarcinoma
No lymphatic or venous invasion
Intramucosal cancer regardless of tumor size without ulceration
Or intramucosal cancer ≤30 mm in size with ulceration
Or submucosal superficial cancer (sm1) ≤30 mm in size
Resection margin
Tumor-free horizontal margin
Tumor-free vertical margin

NCC National Cancer Center

An important advantage of ESD is that it can also be considered as improving diagnostic assessment due to the suboptimal accuracy of the endoscopic staging of EGC, which is sometimes difficult because EGC shows unclear margins due to gastritis, and depth diagnosis is not always accurate [26–28]. Thus, the use of ESD has enabled us to achieve enhanced diagnosis of lesions where it may have been difficult to estimate the tumor depth or where there was a technical difficulty in resection with EMR. The treatment strategy in which additional surgery is performed after confirmation of the histological assessment of the ER specimen has already been established as one of the therapies for EGC [29–31]. We hypothesized that ESD might reduce the rate of potentially avoidable surgery by its improvement of diagnostic and therapeutic capacity compared to that of EMR. We retrospectively investigated the relationship between the surgical and endoscopic treatment of EGC before and after the introduction of ESD, with particular attention to the rate of surgical resection and its potential consequences.

## Patients and methods

We retrospectively reviewed the clinical records and endoscopic and histological reports of 2,785 consecutive patients with EGC treated by surgery with curative intent and 3,102 consecutive EGC lesions treated by ER at the National Cancer Center Hospital, Tokyo, between 1990 and 2005. Informed consent was obtained from all patients in accordance with the institutional protocol. Our primary aim in this study was to retrospectively compare the rate of potentially avoidable surgery before and after the introduction of ESD and to compare the rates of non-curative ER and rates of complications between the EMR and ESD groups. All patients and lesions were discussed and the treatment strategies were determined in weekly multidisciplinary conferences involving endoscopists, surgeons, radiologists, and pathologists. The study was divided into an EMR period (1990–1999), during which the main endoscopic modality of treatment for EGC was EMR, based on the guideline criteria of the Japanese Gastric Cancer Association (Table 1) [24] and an ESD period (2000–2005), during which ESD became the predominant method by which EGCs were endoscopically resected, based on the National Cancer Center expanded criteria (Table 2) [25].

For surgical patients, we defined cases of ‘potentially avoidable surgery’ as those cases with surgically resected histopathological specimens within the guideline criteria of the Japanese Gastric Cancer Association [24]. In other words, the patients with potentially avoidable surgery were those who underwent surgery for lesions curable by ER.



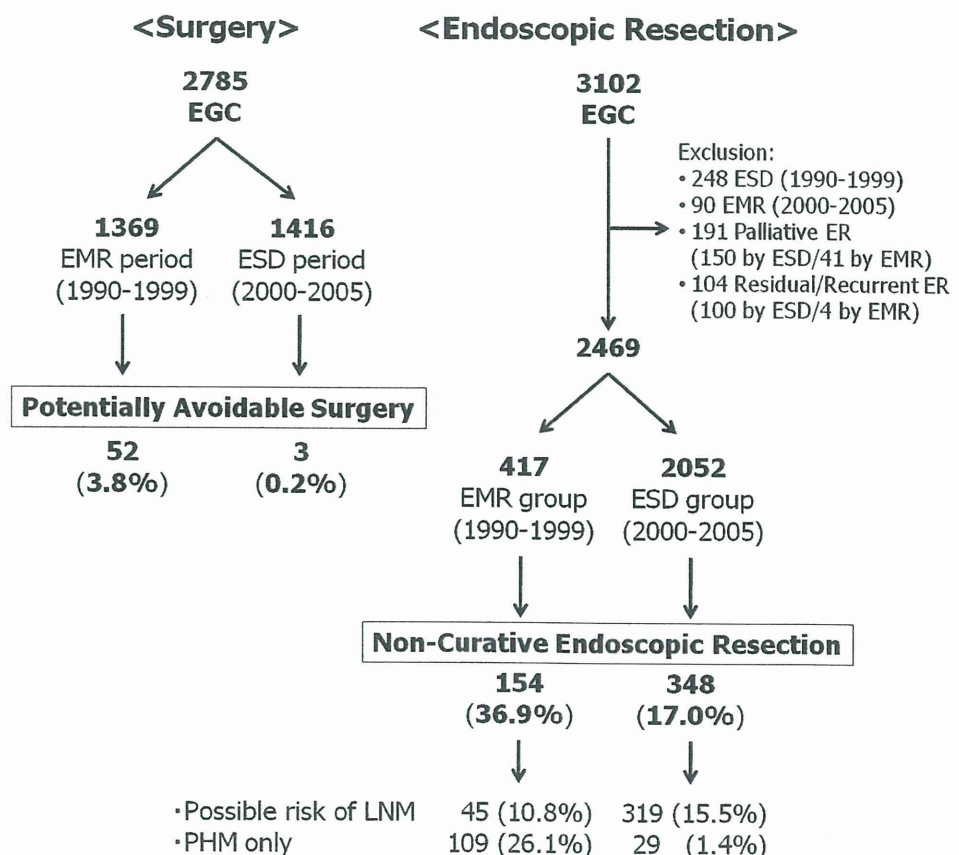
In the ER patients, 2,469 lesions, after exclusions, were treated by ER with curative intent; 417 lesions from the EMR group included only those lesions that were treated by EMR during the EMR period, while 2,052 lesions from the ESD group involved only those lesions that were treated by ESD during the ESD period. Another 248 lesions that were treated by ESD in the EMR period and 90 lesions that were treated by EMR in the ESD period, all with curative intent, were excluded from this study (Fig. 1). In addition, other EGCs were excluded from this study because ERs were performed for palliative purposes or because the ERs were performed for residual/recurrent lesions from previous endoscopic treatments. Palliative ERs were performed in patients who refused or were unfit for surgery because of comorbidities and for those lesions found during pre-therapeutic staging to have submucosal deep invasion (sm2) or deeper invasion, as well as those lesions with undifferentiated adenocarcinomas as revealed by biopsies. Palliative ERs included 191 lesions (150 by ESD and 41 by EMR) and residual/recurrent ERs included 104 lesions (100 by ESD and four by EMR) during each respective period (Fig. 1).

The curability of ER was divided into categories of curative and non-curative; the non-curative category

included lesions that could not be precisely evaluated histologically based on the National Cancer Center expanded criteria and the tumor margins [25]. Non-curative ER was separated into two groups based on histological results: 'non-curative with positive or difficult to estimate horizontal margins only' and 'non-curative with a possible risk of lymph node metastasis irrespective of horizontal margin', based on submucosal deep invasion (sm2:  $\geq 500 \mu\text{m}$ ), positive lymphatic and/or venous invasion, intramucosal cancer more than 3 cm in size in the presence of ulceration, submucosal superficial invasion (sm1:  $< 500 \mu\text{m}$ ) in a lesion greater than 3 cm in size, predominantly undifferentiated type adenocarcinoma, and positive vertical margin (Table 3). Therefore, non-curative ERs with a possible risk of lymph node metastasis were cases of ER carried out in patients who went on to require additional surgery. In other words, these patients were those who underwent ER for lesions curable by surgery. Complications including perforation and delayed bleeding that required blood transfusion were also investigated in the EMR and ESD groups.

Clinical outcomes were analyzed using the  $\chi^2$  test and Fisher's exact test (Statview; Abacus Concepts, Berkeley, CA, USA), and  $P < 0.05$  was considered statistically significant.

**Fig. 1** Outline of the study, including rates of potentially avoidable surgery and non-curative endoscopic resection based on the histological results. *EGC* Early gastric cancer, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *ER* endoscopic resection, *LNM* lymph node metastasis, *PHM* positive or difficult to estimate horizontal margin



**Table 3** Non-curative endoscopic resection

Non-curative with possible risk of lymph node metastasis
Submucosal deep invasion (sm2)
Positive lymphatic and/or venous invasion
Intramucosal cancer >30 mm in size with ulceration
Submucosal superficial invasion (sm1) >30 mm in size
Predominantly undifferentiated type adenocarcinoma
Positive vertical margin
Non-curative with positive or difficult to estimate horizontal margins only

**Table 4** Rates of potentially avoidable surgery

	EMR period (1990–1999)	ESD period (2000–2005)	<i>P</i>
Treated surgically	1,369	1,416	
Guideline lesion	52 (3.8%)	3 (0.2%)	<0.001
Technical difficulty	21	0	<0.001
Incorrect assessment	31	3	<0.001

EMR endoscopic mucosal resection, ESD endoscopic submucosal dissection

## Results

### Potentially avoidable surgery

The study results are outlined in Fig. 1. The rate of potentially avoidable surgery was 3.8% (52/1,369) in the EMR period and 0.2% (3/1,416) in the ESD period ( $P < 0.001$ ) (Table 4). There were two possible contributory factors to potentially avoidable surgery: technical difficulty with ER and incorrect pre-therapeutic assessment of EGC. EMR was not possible in 21 patients where technical difficulty arose from there being a remnant stomach due to prior surgery; scarring from previous ulceration close to the lesion; and the location of the lesion, in particular those very close to the pylorus and the gastroesophageal junction. Thirty-one patients did not undergo EMR due to incorrect pre-therapeutic endoscopic findings suggesting submucosal invasion and unclear margins. In the ESD group, all attempted lesions were treated successfully with ESD, and, in the ESD period, there were three surgical patients with incorrect preoperative assessments with lesions thought to have submucosal invasion (Table 4).

Non-curative ER with possible risk of lymph node metastasis and positive or difficult to estimate horizontal margins only

The rate of overall non-curative ER was 36.9% (154/417) in the EMR group and 17.0% (348/2,052) in the ESD group

**Table 5** Rates of non-curative endoscopic resection

	EMR group % (n = 417)	ESD group % (n = 2,052)	<i>P</i>
Non-curative with possible LNM	10.8 (45)	15.5 (319)	<0.01
Non-curative with PHM only	26.1 (109)	1.4 (29)	<0.001
Total	36.9 (154)	17.0 (348)	<0.001

EMR endoscopic mucosal resection, ESD endoscopic submucosal dissection, LNM lymph node metastasis, PHM positive or difficult to estimate horizontal margin

**Table 6** Causes of non-curative endoscopic resection

	EMR group % (n = 417)	ESD group % (n = 2,052)	<i>P</i>
sm2 cancer	8.9 (37)	7.5 (153)	NS
Positive lymphatic and/or venous invasion	5.3 (22)	5.4 (110)	NS
Intramucosal cancer >30 mm in size with ulceration	0 (0)	1.7 (34)	<0.004
sm1 cancer >30 mm in size	0 (0)	2.3 (48)	<0.0003
Predominantly undifferentiated type	1.4 (6)	3.8 (79)	<0.01
Positive vertical margin	4.6 (19)	2.2 (46)	<0.007
Positive horizontal margin	31.4 (131)	3.0 (62)	<0.001

In some patients there was more than one cause

EMR endoscopic mucosal resection, ESD endoscopic submucosal dissection, sm2 submucosal deep invasion, sm1 submucosal superficial invasion, NS not significant

( $P < 0.001$ ) (Fig. 1) (Table 5). Reasons for non-curative ER are summarized in Table 6. The rates of sm2 invasion and positive lymphatic and/or venous involvement did not differ between the two groups. However, rates of intramucosal cancer more than 3 cm in size with ulceration, sm1 lesions more than 3 cm in size, and predominantly undifferentiated type adenocarcinoma in the ESD group significantly increased compared to those in the EMR group. The rate of positive vertical margins significantly decreased in the ESD group. In Table 6, we have listed the causes of non-curative endoscopic resection. Lesions considered non-curative with possible risk of lymph node metastasis may have been considered as such for one or a combination of overlapping criteria. To put this another way, the rate of non-curative ER with possible risk of lymph node metastasis regardless of horizontal margin increased in the ESD group (15.5%; 319/2,052) compared to that in the EMR group (10.8%; 45/417) ( $P < 0.01$ ) (Table 5). Conversely, the rate of non-curative ER with positive or difficult to estimate horizontal margins only dramatically decreased in the ESD group (1.4%; 29/2,052)



compared to that in the EMR group (26.1%; 109/417) ( $P < 0.001$ ) (Table 5).

### Complications

The rate of perforation in the EMR group (6.0%; 25/417) was significantly higher compared to that in the ESD group (3.0%; 62/2,052) ( $P < 0.003$ ). All perforations were detected endoscopically during the procedure, except for one patient in the ESD group with a delayed perforation who had a gastric tube after esophagectomy. Seven patients in the EMR group and one patient in the ESD group underwent emergency surgery because the perforations were difficult to manage endoscopically using endoclips. Blood transfusion was required in one patient in each group.

### Discussion

This retrospective study shows that the rate of potentially avoidable surgery decreased significantly and the overall non-curative ER rate also decreased with the development of ESD. In the ESD group, the rate of non-curative endoscopically resected specimens with positive or difficult to estimate horizontal margins only significantly decreased compared with that in the EMR group, but the rate of non-curative ERs with possible risk of lymph node metastasis increased significantly.

The rate of potentially avoidable surgery was 3.8% (52/1,369) during the EMR period and 0.2% (3/1,416) during the ESD period ( $P < 0.001$ ) (Table 4). We believe this may be as a result of two factors, the technical progress of ER and improved diagnostic accuracy. The progress of ER with EMR, and now ESD, over the past two decades has involved major breakthroughs in endoscopy and has revolutionized the treatment of EGC. The advent of ESD has enabled us to achieve a higher rate of en-bloc resection in situations not possible before. These include remnant stomachs, scarring from previous gastric ulceration, and certain technically difficult locations. Despite the recent development of new technology such as narrow band and autofluorescence imaging [32, 33], there have been no significant changes in our ability to diagnose the depth of invasion of EGC [27, 28]. Other studies have reported that the endoscopic staging of EGC is not always accurate and is correct in only 80–90% of cases, even with endoscopic ultrasonography [26, 34–36]. In our study, we found that incorrect preoperative assessments such as endoscopic overstaging leading to potentially avoidable surgery dropped significantly with the use of ESD (Table 4), but we believe that the increased use of ESD for enhanced diagnosis, rather than improvements in other diagnostic modalities, resulted in this reduction.

For reference, the rate of surgery for lesions included within the National Cancer Center expanded criteria was 4.7% (67/1,416) during the ESD period (data not shown). These lesions consisted of 18 intramucosal cancers >20 mm without ulceration, 33 intramucosal cancers  $\leq$ 30 mm in size with ulceration, and 16 sm1 cancers  $\leq$ 30 mm in size. It is believed that surgery on some of these lesions was potentially avoidable, but a direct comparison using the guideline criteria of the Japanese Gastric Cancer Association and the National Cancer Center expanded criteria cannot be made because of differences between the two sets of criteria.

The rate of non-curative ER, secondary to positive or difficult to estimate horizontal margins only, in the ESD group (1.4%; 29/2,052) significantly decreased compared to that in the EMR group (26.1%; 109/417) ( $P < 0.001$ ) (Table 5). This reflects the inability of EMR to resect large lesions en bloc, the lesion often being resected in multiple fragments, making it difficult to ensure complete resection [9–11]. The other main problem that arises with performing EMR, even for small lesions, is the uncertainty regarding inaccurate resection margins. Several previous articles have reported higher rates of local recurrence caused by piecemeal resection and positive tumor margins [12, 13, 22, 23, 37]. The development of ESD has addressed these problems, as it enables an en-bloc resection with tumor-free margins.

On the other hand, the rate of non-curative ERs with possible risk of lymph node metastasis (which should ideally be managed by gastrectomy with lymph node dissection) increased in the ESD group (15.5%:319/2,052) compared to that in the EMR group (10.8%:45/417) ( $P < 0.01$ ) (Table 5). This five percent difference could have occurred due to several reasons, but the primary cause was most likely the increase in the number of patients who underwent diagnostic ESD for borderline lesions which were either difficult to resect technically by EMR or difficult to estimate tumor depth accurately. Specifically, the introduction of the National Cancer Center expanded criteria and the ability of ESD to resect larger lesions are two possible reasons for the increase in the number of intramucosal cancers more than 3 cm in size with ulceration and sm1 lesions more than 3 cm in size for which ER was undertaken. An increase in the number of lesions with predominantly undifferentiated adenocarcinoma also occurred, most likely because the heterogeneity of gastric carcinoma may increase in larger-size lesions. Thus, this five percent rise in the rate of non-curative ERs with possible risk of lymph node metastasis has to be weighed against the potential advantages in undertaking ESD and the significantly reduced rate of potentially avoidable surgery. Oda et al. [31] reported that the actual rate of lymph node metastases, as determined from surgically resected



specimens, in a group of cases of 'non-curative ESD with possible risk of lymph node metastasis', was 6.3%. This emphasizes the fact that this cohort of patients should receive additional surgery.

In the present study, the rate of perforation in the EMR group (6.0%) was significantly higher compared to that in the ESD group (3.0%) although it is widely recognized that the rate of perforation with ESD is higher than that with EMR [22]. There is no evident explanation for this result, but one possible reason may be that EMR procedures were performed more aggressively because of curative intent in the EMR group.

The surgically resected stomach never returns to its natural state. Currently, the pathway whereby we use ESD as the optimal therapeutic strategy for the treatment of EGC seems to reduce the rate of potentially avoidable surgery and allows us to more appropriately select those cases that would benefit from additional surgery, as it enables more accurate histological assessment, particularly in difficult EGC cases. As a result, this pathway has brought about major benefits for patients by reducing potentially avoidable surgery, because with this strategy the final diagnosis is obtained with higher reliability due to precise feedback from histological assessments. However, it would be prudent to advise caution in performing ESD for EGC unless the indications have been carefully reviewed in the individual to ensure that the EGC is within the established selection criteria. We would emphasize that recognition of resectability and curability are two very different matters. It is also important to recognize the role of ESD in providing enhanced diagnostic information, thus contributing to the optimal therapy being undertaken for the appropriate indication.

#### Limitations

This study was retrospective and there were differences in criteria for ER between the two groups. In addition, the transitional phase was at the turn of the twenty-first century, but it was not clearly delineated as both procedures were being used at that time. However, we believe that by analysis by procedure (EMR and ESD) we have minimized the impact of this last factor.

#### Conclusions

We believe that a pathway of undertaking ESD in lesions where it may be difficult to estimate the depth of invasion and in technically difficult cases results in a significant decrease in the rate of potentially avoidable surgery, this being due to the advantages associated with not only a potentially curative procedure, but also one which provides

enhanced diagnostic information and consequently enables more appropriate therapy.

**Acknowledgments** We thank Dr. Sunil Dolwani and Dr. Marcus Chin for their writing assistance.

**Conflict of interest** None.

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## CASE STUDIES

# Endoscopic submucosal dissection with electro-surgical knives in a patient on aspirin therapy (with video)

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**Background:** The electro-surgical knives required to perform endoscopic submucosal dissection (ESD) have recently passed the 510(k) premarketing evaluation by the U.S. Food and Drug Administration and are now available for purchase in the United States. Challenges to ESD being more widely performed in the United States include the lack of intensive hands-on training programs and a low incidence of appropriate, highly dysplastic gastric lesions on which an ESD-trained endoscopist can begin performing this procedure in patients. Furthermore, there are no guidelines regarding the safety of continuing antiplatelet therapy in patients undergoing ESD.

**Objective:** To report on the first gastric ESD performed in the United States by using recently approved electro-surgical knives on a patient who was maintained on aspirin therapy.

**Design:** Case report.

**Setting:** Large academic medical center.

**Patient:** One patient with a 2-cm high-grade dysplasia (HGD) lesion in the posterior antrum who had indwelling coronary stents and was maintained on aspirin therapy throughout the periprocedural period.

**Interventions:** High-definition white-light and narrow-band imaging endoscopy, endosonography, and ESD by using recently approved electro-surgical knives.

**Main Outcome Measurements:** Complete resection of the HGD gastric lesion.

**Results:** En bloc complete resection of the HGD gastric lesion was achieved without any immediate or delayed bleeding or perforation. No residual or recurrent dysplasia was found on 1- or 3-month follow-up endoscopies.

**Limitations:** Generalizations cannot be made from this single case.

**Conclusions:** After receiving intensive hands-on training in both ex vivo and in vivo animal models, gastric ESD was successfully performed by 2 U.S. endoscopists by using recently approved electro-surgical knives in a patient maintained on aspirin therapy without any complications.

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Endoscopic submucosal dissection (ESD) is an accepted endoscopic therapy for highly dysplastic gastric lesions in Japan and parts of Asia and South America.<sup>1-5</sup> Despite nearly a decade of experience in Asian countries,

*Abbreviations:* ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NBI, narrow-band imaging.

*DISCLOSURE:* The following authors disclosed financial relationships relevant to this publication: Dr. Emura: consultant for Olympus. Dr. Yeaton: consultant for Olympus and Gore. The other authors disclosed no financial relationships relevant to this publication.

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0016-5107/\$36.00

doi:10.1016/j.gie.2010.06.008

Received April 21, 2010. Accepted June 3, 2010.

the expertise to perform ESD in the stomach, or in other parts of the luminal GI tract, is largely lacking in Western countries.<sup>6</sup> This disparity in experience is likely because of the relatively low prevalence of highly dysplastic gastric

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lesions and early gastric carcinomas found in patients living in Western countries.<sup>7</sup> Furthermore, because ESD of esophageal or colorectal lesions is even more challenging than gastric ESD, performing ESD in these locations is considered to be inappropriate for inexperienced operators.<sup>6</sup>

Eastern endoscopists rely on advanced optical imaging techniques (such as chromoendoscopy and narrow-band imaging [NBI]) to identify lesions containing high-grade dysplasia (HGD) or early gastric adenocarcinomas that are suitable for endoscopic resection. Although increasing, experience with these advanced optical imaging technologies is not widespread among Western gastroenterologists.<sup>8</sup> Furthermore, there are no training programs in the United States that offer the intensive hands-on instruction required to learn ESD. A final, yet critically important, issue is that the specialized electrosurgical knives required to perform ESD have only recently passed the 510(k) premarketing evaluation by the U.S. Food and Drug Administration, and as such they have only recently been made available for consumer purchase and use in the United States.

The American Society for Gastrointestinal Endoscopy practice guidelines<sup>9-11</sup> and other sources<sup>12</sup> have recommended, in the absence of a preexisting bleeding disorder, that aspirin or nonsteroidal anti-inflammatory drug therapy may be continued in patients undergoing endoscopic procedures. However, if a procedure with a higher risk of bleeding is planned, an individualized approach has been recommended.<sup>12</sup> For patients undergoing higher-risk endoscopic procedures, it has been recommended that clopidogrel be discontinued 7 to 10 days before their procedures.<sup>10</sup> Finally, American Society for Gastrointestinal Endoscopy guidelines do state that patients on combination antiplatelet therapy (eg, aspirin and clopidogrel) may be at increased risk of bleeding as a result of endoscopic procedures.<sup>10</sup>

At present, there are no published reports describing the use of the recently approved electrosurgical knives to perform ESD in individuals on antiplatelet therapy in the United States.

## CASE REPORT

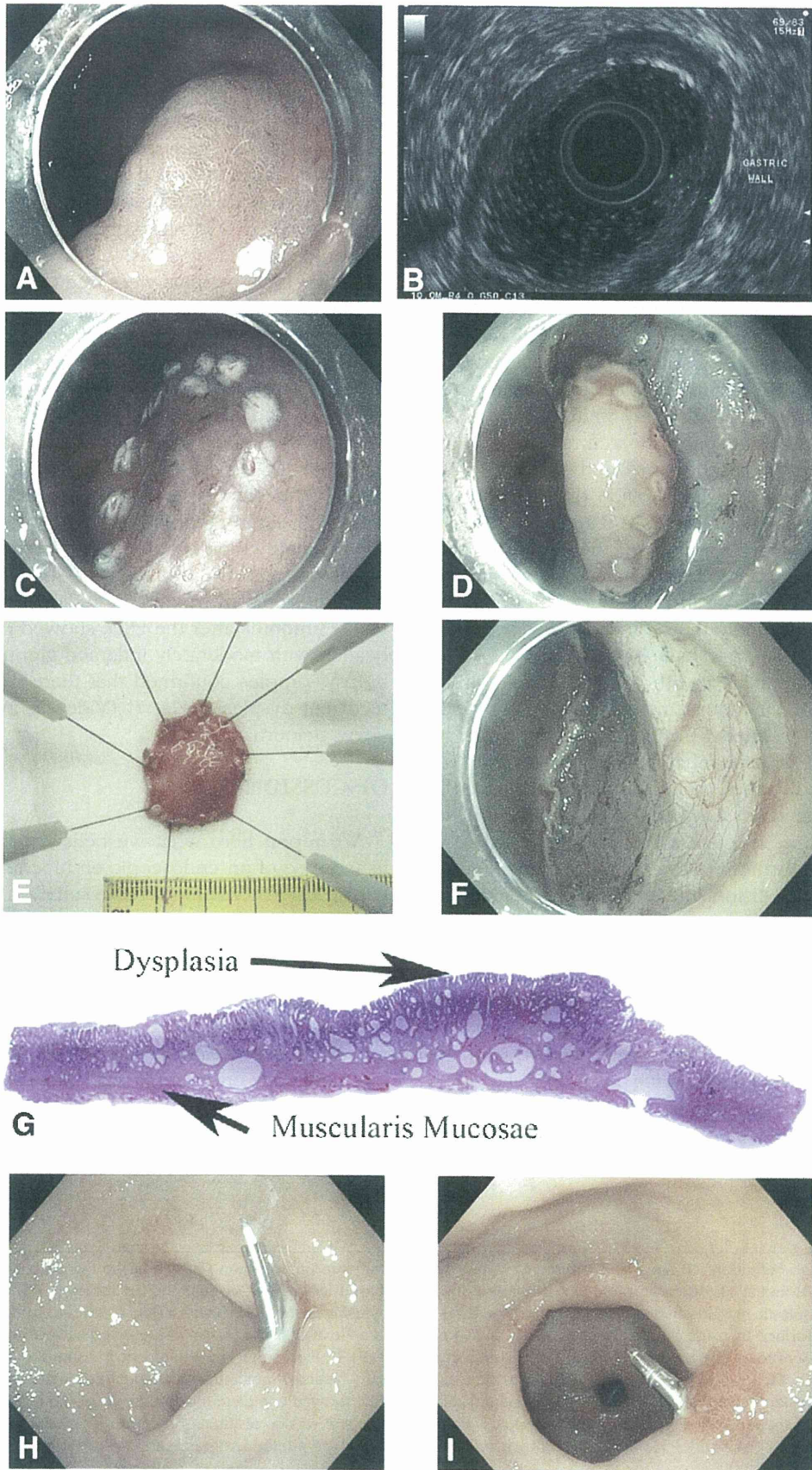
A 66-year-old Chinese woman with known gastric intestinal metaplasia was referred for dyspepsia and a history of a gastric polyp. She had a history of diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease with 2 metal stents that had been placed in her right coronary artery 5 years ago in China. One year ago, she underwent cardiac catheterization for chest pain that demonstrated nonobstructive coronary artery disease, and the patient was maintained on aspirin 81 mg/day and clopidogrel 75 mg/day. An initial EGD was performed by using high-definition white light, NBI, and chromoendoscopy by using 0.8% indigo carmine (GIF-H180) gastroscope using the Evis Exera II platform; Olympus America, Center Valley, Pa), which demonstrated a 20-mm raised lesion

(Paris 0-IIa),<sup>13</sup> along the posterior wall of the antrum that had dysplastic features. Biopsy samples were taken that confirmed HGD. There were a few other small dysplastic areas identified in other portions of the body and antrum that were found to contain low-grade dysplasia (LGD) on biopsy specimens. The patient's case was presented at a multidisciplinary GI-oncology tumor board at the University of Virginia Hospital. The consensus recommendation was to offer the patient either a subtotal gastrectomy, given the multifocal LGD with focal HGD, or a staging EUS examination followed by ESD of the lesion containing HGD and frequent endoscopic surveillance of the LGD lesions. The patient chose to pursue endoscopic therapy with subsequent close surveillance. Radial EUS demonstrated a lesion in the distal antrum that was confined to the mucosa, and no pathological perigastric lymph nodes were identified, which further confirmed that this lesion was appropriate for ESD.

Given the patient's coronary artery disease and indwelling coronary stents, it was decided that she should continue her aspirin therapy throughout the peri-procedural period and stop her clopidogrel at least 4 days before her procedure. ESD was performed at the University of Virginia Hospital by 2 interventional endoscopists (A.Y.W., P.Y.), who each perform more than 500 interventional endoscopies yearly. Both U.S.-based endoscopists first received hands-on instruction by using an *ex vivo* and an *in vivo* porcine model from a visiting professor (H.K.) from Korea who had performed more than 150 gastric ESDs. Further didactic and hands-on training by using an *in vivo* animal model was obtained by attending an intensive 3-day course in gastric ESD held in Bogotá, Colombia (taught by F.E. and I.O., who are both Japanese-trained endoscopists, who together have performed well over 1000 gastric ESDs).<sup>14</sup> This course culminated with a hands-on practical examination and a written examination followed by observing a live gastric ESD procedure in a human patient, after which university certification in ESD was awarded. Subsequently, both U.S. endoscopists performed at least 5 additional successful ESDs using an *in vivo* or an *ex vivo* porcine model before performing this procedure. Institutional credentialing in ESD and informed consent was obtained before performing the procedure.

A span of 4 months elapsed before the ESD could be performed because we were awaiting 510(k) approval of the necessary electrosurgical knives. The procedure was performed with the patient under general endotracheal anesthesia, and preprocedural intravenous ampicillin (2 g) and gentamicin (60 mg) were administered given the patient's diabetes and the potential risks of bleeding and perforation. Intravenous esomeprazole (40 mg) was also administered preprocedurally. A diagnostic gastroscope (GIF-H180; Olympus America) and a processor capable of high-definition white-light imaging and NBI (Evis Exera II; Olympus America) were used during ESD. An ESD cap (D201-11804; Olympus America) was attached to the distal







end of the gastroscope and secured with clear plastic tape. Electrocautery was provided by using an electrosurgical generator (ESG-100, Olympus America). Submucosal injections were performed by using a 1:100,000 solution of epinephrine in normal saline solution tinted with a few drops of 0.8% indigo carmine (a total of 100 mL of this solution was used in divided doses during ESD).

Under high-definition white light and NBI, a 20-mm, raised lesion (Paris 0-IIa),<sup>13</sup> without ulceration or mucosal tenting, was seen in the distal, posterior antrum. NBI without optical magnification allowed clear delineation of the highly dysplastic borders of the lesion. The stomach was lavaged by using simethicone washes, and all the fluid was evacuated. Under high-definition NBI visualization, a HookKnife (KD-620LR; Olympus America) was used to mark a circular border approximately 5 mm outside of the area of HGD by using soft coagulation current set at 20 W. A double marking was placed in the distal/anterior border (at the 12 o'clock position) to provide directionality for subsequent histopathology. The final diameter of the circumscribed lesion was 30 mm. After the circumferential marking was completed, the lesion was lifted by using the dilute epinephrine/indigo carmine/saline solution. The circumferential incision into the submucosa was begun by using a straight needle-knife (KD-10Q-1; Olympus America), and it was completed with a combination of the IT-knife2 (KD-611L; Olympus America) and the FlexKnife (KD-630L; Olympus America) by using a pulse cut slow mode set at 60 W. In sequential fashion, the submucosal dissection was performed with the IT-knife2 and the FlexKnife, by using either a forced coagulation current set at 20 to 50 W or a pulse cut slow current set at 40 to 60 W to carefully dissect through the submucosal plane. During the circumferential incision and the submucosal dissection, any mild oozing encountered was controlled with the short blades of the IT-knife2, by using a forced coagulation current set at 50 W, and when a visible vessel was exposed, it was coagulated by using coagulation forceps (Coagrasper, FD-410LR; Olympus America) with the soft coagulation current set at 50 W. There was no significant bleeding or perforation encountered during this procedure, which was performed in 1 hour and 45 minutes. After ESD was completed, there remained a 30-mm submucosal antral ulcer. Two endoclips (long upper QuickClip2, HX-201LR-135L.B;

Olympus America) were used to mechanically obliterate 2 nonbleeding visible vessels seen in the ulcer base to reduce the risk of delayed bleeding.

The resected specimen measured approximately 30 mm when stretched and pinned to a Styrofoam board covered with gauze wetted with saline solution. This specimen was fixed while attached to the Styrofoam and then serially sectioned to evaluate for oncologic resection. Histopathology showed HGD in a background of intestinal metaplasia without evidence of invasive carcinoma. The deep and circumferential margins were free of dysplasia.

The patient was admitted for observation for 3 days after her ESD. She was kept on nothing by mouth for the first night, and then clear liquids were initiated uneventfully the following day. She experienced no new abdominal pain, had no signs of melena or hematemesis, and serial hemoglobin values remained stable. A planned follow-up EGD performed 2 days after her ESD showed early granulation tissue in the ulcer. The patient maintained her aspirin therapy throughout her procedure, and she resumed clopidogrel 7 days after the ESD procedure. A follow-up EGD 1 month later showed a 5-mm clean-based, residual ulcer with an adherent endoclip. Another EGD, 3 months after the ESD, showed complete mucosal healing with moderately inflamed granulation tissue, and biopsy samples confirmed that there was no residual or recurrent dysplasia (Fig. 1) (Video 1, available online at [www.giejournal.org](http://www.giejournal.org)).

## DISCUSSION

We report here what we believe to be the first published case of an endoscopic en bloc resection of a large gastric lesion containing HGD via ESD in the United States, which was performed by using newly approved electrosurgical knives in a patient maintained on aspirin therapy. Given the differences in histopathological interpretation between Japanese and Western pathologists, this lesion would have likely been called a well-differentiated, mucosally-based early gastric cancer in Japan.<sup>15,16</sup> Given our complete endoscopic resection of this lesion, and because the anticipated risk of lymph node metastasis for this lesion is nearly 0% (according to large published Japanese series on early gastric cancer),<sup>1,17</sup> it would be

**Figure 1.** **A**, High-definition NBI endoscopy demonstrated a dysplastic 20-mm raised lesion (Paris 0-IIa) in the distal antrum along the posterior wall. **B**, Radial EUS demonstrated that this was a mucosally-based lesion with no submucosal invasion. **C**, NBI was used to delineate the dysplastic margins and circumferential marking was made by using a HookKnife (with a double mark to provide orientation). **D**, ESD was performed by using a straight needle-knife, an IT-knife2, and a FlexKnife. The lesion was resected en bloc and affixed to wet gauze on top of Styrofoam (**E**), leaving behind a 30-mm submucosal ulcer (**F**). **G**, Final surgical pathology demonstrated complete resection of the HGD lesion. **H**, A follow-up EGD 1 month later demonstrated a nearly healed 5-mm antral ulcer with a retained endoclip; there was no recurrent or residual dysplasia. **I**, Another EGD, 3 months after the ESD, showed complete mucosal healing with moderately inflamed granulation tissue and a retained endoclip. Biopsy samples confirmed that there was no residual or recurrent dysplasia. (Special thanks to Edward B. Stelow, MD, and Dirk P. Stanley, MD, for their assistance in obtaining a photomicrograph of the relevant histopathology for this case.)



reasonable to perform surveillance endoscopy on an annual basis primarily to detect metachronous HGD and early gastric cancer.<sup>18</sup> Use of NBI was important in initially identifying the highly dysplastic lesion, subsequently in delineating the dysplastic margins for ESD, and finally in surveying for recurrent or metachronous dysplasia on follow-up endoscopy.

The types of current and wattage used to perform ESD will vary depending on the electrosurgical generator and may at times need to be optimized according to the patient and the lesion. At the National Cancer Center in Tokyo, Japan, when using the ESG-100 generator, the recommended standard setting for circumferential dissection is a pulse cut slow current set at 40 W, and for submucosal dissection either a forced coagulation current set at 50 W or a pulse cut slow current set at 40 W is used. Although techniques are emerging that may enable reliable endoscopic apposition of the post-ESD defect,<sup>19</sup> at present, the standard approach at most high-volume ESD centers is to coagulate or clip exposed visible vessels and not to attempt to close the submucosal defect.<sup>20</sup>

Because the electrosurgical knives needed to perform ESD have received 510(k) approval, these tools can now be purchased in the United States. However, despite having the proper tools to perform this advanced procedure, challenges to performing ESD in the United States include the lack of training programs based in the United States and the relatively low prevalence of early gastric cancers or highly dysplastic gastric lesions on which a trained endoscopist can begin to perform this procedure in patients. Although there is the potential to perform ESD in the esophagus and colorectum, procedures in these locations are more challenging because of the thinner walls of these organs, and as such, these locations are considered to be inappropriate areas in which to begin performing ESD.<sup>6</sup>

In addition to training programs in Japan and other East Asian countries (South Korea and Taiwan), there are specialized centers to obtain exposure to and training in ESD in South America (eg, Colombia), where the incidence of gastric cancer is very high.<sup>4,21</sup> A training model similar to the one used by the U.S. endoscopists in this report has been shown to be effective in teaching this procedure.<sup>22</sup> Yamamoto et al<sup>23</sup> studied ESD training by observing 3 Japanese residents, trained in routine endoscopy, perform 30 consecutive, supervised ESDs of small mucosally-based lesions. These authors found that the self-completion rate and operation time were significantly worse for the submucosal dissection part of the procedure than for the circumferential mucosal incision portion. Two of the 3 trainee operators studied showed a flat learning curve for submucosal dissection, and complications were related mainly to uncontrollable hemorrhage.<sup>23</sup> This steep learning curve was further highlighted by Teoh et al,<sup>24</sup> who reported a prospective study of 24 endoscopists participating in a Chinese ESD training program by using a

porcine model to teach esophageal and gastric ESD. These investigators found that during gastric ESD, 15 participants (65%) encountered perforations, and bleeding occurred during 57% of ESDs. A significantly higher proportion of perforations occurred with the use of noninsulated knives.<sup>24</sup>

We advise that endoscopists interested in performing gastric ESD should first pursue intensive hands-on training in both ex vivo and in vivo models supervised by an expert in ESD, followed by observing live gastric ESD procedures in patients. This basic training should be followed up by self-study and by successfully performing ESD procedures in both ex vivo and in vivo animal models before performing ESD on a patient. Although in vivo training is more costly and requires animal protocols and special handling, we believe that the experience of performing this procedure in a living animal is invaluable because it offers the opportunity to encounter and treat ESD-associated bleeding, which is paramount to acquiring proficiency in this procedure. Furthermore, skill in coagulating or clipping exposed visible vessels is mandatory, because routine coagulation of visible vessels may prevent delayed bleeding after ESD.<sup>20</sup> Despite advanced hemostasis techniques, the common practice in most high-volume ESD centers is to stop antiplatelet and antithrombotic therapy before performing ESD.<sup>25</sup> In this article, we report on what we believe to be the first ESD performed in the United States in a patient on continuous aspirin therapy. Although generalizations cannot be drawn from a single case, by ceasing clopidogrel but continuing aspirin therapy, ESD was not complicated by immediate or delayed bleeding, and the patient did not experience any cardiovascular complications.

As with all new procedures, specialized institutional credentialing must be obtained before performing this procedure, and careful informed consent is necessary. As more endoscopists become trained in ESD in the United States, a national training program may be feasible, and investigation into the utility of ESD in the esophagus and colorectum for HGD and early carcinomas will be necessary. Last, specialized Current Procedural Terminology codes will be required because this procedure is much more than an upper endoscopy but not quite a subtotal gastrectomy.

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# Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria

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**Background:** Criteria for endoscopic resection in patients with early gastric cancer (EGC) have been expanded recently by the National Cancer Centre (NCC). This study compared long-term outcomes in patients with EGC who underwent endoscopic treatment according to guideline criteria with those treated according to expanded criteria.

**Methods:** Baseline and outcome data from patients undergoing curative endoscopic resection for EGC between January 1999 and December 2005 were collected from electronic medical records. Survival time hazard ratios and 95 per cent confidence intervals were calculated using the Cox proportional hazards model.

**Results:** Of 1485 patients who had a curative resection, 635 (42.8 per cent) underwent resection according to traditional criteria and 625 (42.1 per cent) according to expanded criteria. There was no significant difference in overall survival between the groups.

**Conclusion:** Patients who have treatment following the expanded criteria have similar long-term survival and outcomes to those treated according to guideline criteria.

Paper accepted 22 January 2010

Published online 18 March 2010 in Wiley InterScience (www.bjs.co.uk). DOI: 10.1002/bjs.7033

## Introduction

In Japan, endoscopic mucosal resection (EMR) has been the treatment of choice for small early gastric cancer (EGC) for the past two decades<sup>1,2</sup>. Owing to the technical limitations of EMR, traditional indications for endoscopic resection of EGC according to the Gastric Cancer Treatment Guidelines of the Japanese Gastric Cancer Association (JGCA) were restricted to resection of small intramucosal EGCs (smaller than 20 mm) with intestinal-type histology and no ulceration.

The low risk of lymph node involvement in EGC confined to the superficial layers of the submucosa indicated that cure can be achieved by local resection, even of lesions larger than 20 mm, as long as the lesion is removed *en bloc*<sup>3</sup>. Endoscopic submucosal dissection (ESD) has become established as a technique that allows *en bloc* resection regardless of size. Revised criteria were proposed by the National Cancer Centre (NCC) in Tokyo (from January 1999) to expand the indications for endoscopic

treatment and avoid unnecessary radical surgery, which until recently was the 'gold standard' for larger lesions<sup>4,5</sup>.

This study compared the long-term outcome of patients with EGC who underwent endoscopic treatment based on either guideline of JGCA criteria or expanded NCC criteria.

## Methods

Consecutive patients who had endoscopic resection for EGC between January 1999 and December 2005 were studied. Informed consent was obtained from all patients in accordance with the institutional protocol. The procedure was carried out under conscious sedation using a combination of midazolam and pentazocine. Patients who were assessed histologically as having had a non-curative resection owing to positive lateral margins and/or deep submucosal invasion, regardless of positive vertical margins and/or lymphatic-vascular infiltration and/or diffuse-type histology, and those who had undergone endoscopic



resection as a palliative treatment for advanced cancer were excluded.

Curability was based on the histological criteria for curative endoscopic resection (Table 1) according to the Japanese Classification of Gastric Carcinoma<sup>6</sup>. Pathological assessment of the resected specimen included: size, location, macroscopic appearance, presence of ulceration, histological type, depth of invasion, lymphatic and vascular involvement, and resection margin status. Tumours smaller than 20 mm without ulceration were included in the JGCA criteria group and those larger than 20 mm in the NCC expanded criteria group. Patients with multiple EGCs were analysed as a separate group.

Baseline and outcome data were collected from electronic medical records. Incomplete and missing data were retrieved from different sources such as telephone contact with patients, family and referring physicians, and checked with statistical data kept by the local government registry.

All patients with curative resection who met JGCA criteria were followed up by annual upper gastrointestinal surveillance endoscopy to identify local recurrence and/or metachronous gastric cancer. Patients who met NCC criteria were additionally followed by thoracic and abdominal computed tomography and/or endoscopic ultrasonography every 6 months. Patients were followed from the date of first treatment until 31 July 2007.

**Statistical analysis**

Survival time was calculated as the interval between the date of the first treatment and the date of death or the last date confirmed as alive for survivors. Survival curves were calculated using the Kaplan–Meier method. To compare overall survival by treatment method, a Cox proportional hazards model was used to estimate hazard ratios and 95 per cent confidence intervals (c.i.). Age, sex and past history of cancer were included as co-variables in the multivariable analyses. All *P* values reported are two sided and *P* < 0.050 was considered statistically significant.

**Table 1** Histological criteria for curative endoscopic resection

Factors for no risk of lymph node metastasis
Intestinal-type histology
No lymphatic or vascular infiltration
Intramucosal cancer regardless of tumour size without ulcer finding or intramucosal cancer less than 30 mm in size with ulcer finding or minute submucosal invasive cancer (sm1) less than 30 mm in size
Factors for resection margin
Tumour-free horizontal margin
Tumour-free vertical margin

Statistical analyses were performed with SAS® software version 9.1 (SAS Institute, Cary, North Carolina, USA).

**Results**

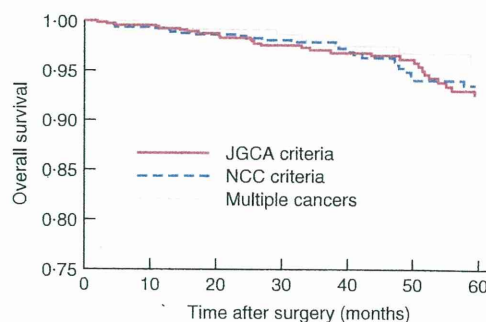
Some 1786 lesions were resected curatively among 1485 patients; 635 patients (42.8 per cent) were treated according to the guideline of JGCA criteria and 625 (42.1 per cent) in accordance with the expanded NCC criteria; 225 patients (15.2 per cent) had multiple EGCs with both criteria. Baseline characteristics by treatment allocation are shown in Table 2.

Follow-up was complete for all 1485 patients, with a median observation period of 44.1 months. During follow-up, 77 patients died (5.2 per cent). Only one patient treated according to JGCA criteria died from metachronous invasive gastric cancer, which was detected 5 years later. Locally recurrent gastric cancer was found in another patient who underwent piecemeal endoscopic resection. This patient underwent ESD for local recurrence 18 months after the first endoscopic resection and was alive with no evidence of recurrence after 57 months. There was

**Table 2** Baseline patient characteristics by treatment group

	JGCA criteria (n = 635)	NCC criteria (n = 625)	Multiple cancers (n = 225)
Mean age (years)	66.4	66.5	68.6
Men	479 (75.4)	505 (80.8)	180 (80.0)
Past history of cancer	154 (24.3)	87 (13.9)	95 (42.2)
Mean tumour size (mm)	10.8	23.8	12.4

JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre.



No. at risk	0	10	20	30	40	50	60
JGCA criteria	635	631	584	455	346	264	186
NCC criteria	625	621	559	433	314	242	156
Multiple cancers	225	223	210	180	156	126	89

**Fig. 1** Survival by treatment group. JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre

**Table 3** Hazard ratio for all-cause mortality according to treatment group

	No. of deaths	5-year survival rate (%)	Hazard ratio	
			Crude	Adjusted*
JGCA criteria	36	92.4	1.00	1.00
NCC expanded criteria	31	93.4	0.93 (0.57, 1.50)	1.10 (0.67, 1.81)
Multiple cancers	10	95.6	0.63 (0.31, 1.26)	0.46 (0.23, 0.94)

Values in parentheses are 95 per cent confidence intervals. JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre. \*Multivariable Cox proportional hazards model, adjusted for age, sex and past history of cancer.

no significant difference in the rate of local and/or systemic recurrence between the JGCA and the NCCH groups.

Survival curves are shown in *Fig. 1*. The 5-year survival rate was 92.4 per cent in the JGCA group, 93.4 per cent in the NCCH group and 95.6 per cent among those with multiple cancers. There was no significant difference in overall survival (*Table 3*). In multivariable analysis, the hazard ratio for survival of patients in the NCC group compared with those in the JGCA group was 1.10 (95 per cent c.i. 0.67 to 1.81).

## Discussion

Radical surgery with complete removal of first- and second-tier lymph nodes is accepted as a standard treatment for patients with EGC. A 5-year survival rate of around 90 per cent has been achieved in oriental and Western patients<sup>7–9</sup>. In patients with cancer limited to the mucosa, the incidence of lymph node metastasis is less than 3 per cent. This risk increases to 20 per cent when the cancer invades the submucosa<sup>10</sup>.

Radical surgery may not be the optimal treatment approach in all patients with EGC because it carries a significant risk of morbidity and mortality, and is associated with a significant reduction in quality of life<sup>11–13</sup>. Patients with no risk of lymph node metastasis can be treated safely by endoscopic resection<sup>14</sup>.

Accepted indications for EMR of EGC have been (1) well differentiated elevated cancers less than 2 cm in diameter and (2) small (maximum 1 cm) depressed lesions without ulceration. These indications were established because of the technical limitations of EMR. In larger lesions, EMR has a high risk of recurrence as a result of incomplete resection when piecemeal EMR is used for larger lesions<sup>15</sup>. Specimens obtained by piecemeal EMR are difficult to analyse and there is a high risk of inadequate histological staging<sup>16</sup>. From a histological point of view, *en bloc* removal should be considered essential for endoscopic resection of larger lesions to ensure accurate histological staging. The treatment strategy for EGC has

been revolutionized recently by the ESD procedure. This method is superior to other endoscopic techniques used for EGC as it makes *en bloc* resection possible, allowing precise histological staging and minimizing recurrence risk compared with standard EMR techniques<sup>17</sup>.

Kojima and colleagues<sup>18</sup> have reviewed the outcomes of EMR from 12 major institutions in Japan. Long-term outcomes after EMR for small differentiated mucosal EGC less than 2 cm in diameter have been reported to be comparable to those following gastrectomy<sup>19</sup>, but the long-term outcome of endoscopic resection of large EGCs has not been reported.

The present study has demonstrated that there is no difference in 5-year survival and local and/or systemic recurrence rates between patients treated according to JGCA or NCC criteria. The hazard ratio for overall survival showed no significant difference between the two groups.

Final staging can be carried out accurately only by formal histological analysis, especially with regard to potential lymphovascular infiltration. Therefore, *en bloc* resection is a prerequisite for accurate staging and prediction of a patient's risk of lymph node metastasis.

Expanded NCC criteria for patients with EGC are safe and practicable. As a result of the ability to achieve *en bloc* resection by ESD, more patients may benefit from endoscopic resection, further reducing the need for radical surgery.

## Acknowledgements

The authors declare no conflict of interest.

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## ENDOSCOPY MINISERIES

**Endoscopic resection of gastrointestinal lesions:  
Advancement in the application of endoscopic  
submucosal dissection**Abby Conlin,\* Tonya Kaltenbach,<sup>†</sup> Chika Kusano,<sup>‡</sup> Takahisa Matsuda,<sup>§</sup> Ichiro Oda<sup>§</sup> and Takuji Gotoda<sup>‡</sup>

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**Key words**

chromoendoscopy, colonic, endoscopic, esophageal, gastric, gastrointestinal, IT-2, resection.

Accepted for publication 14 May 2010.

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**Abbreviations**

GIT, gastrointestinal tract; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LST, laterally spreading tumor; LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor non-granular type.

**Abstract**

Curative endoscopic resection is now a viable option for a range of neoplastic lesions of the gastrointestinal tract (GIT) with low invasive potential. Risk of lymph node metastasis is the most important prognostic factor in selecting appropriate lesions for endoscopic therapy, and assessment of invasion depth is vital in this respect. To determine appropriate treatment, detailed endoscopic diagnosis and estimation of depth using magnifying chromoendoscopy is the gold standard in Japan. En bloc resection is the most desirable endoscopic therapy as risk of local recurrence is low and accurate histological diagnosis of invasion depth is possible. Endoscopic mucosal resection is established worldwide for the ablation of early neoplasms, but en bloc removal using this technique is limited to small lesions. Evidence suggests that a piecemeal resection technique has a higher local recurrence risk, therefore necessitating repeated surveillance endoscopy and further therapy. More advanced endoscopic techniques developed in Japan allow effective en bloc removal of early GIT neoplasms, regardless of size. This review discusses assessment of GIT lesions and options for endoscopic therapy with special reference to the introduction of endoscopic submucosal dissection into Western countries.

**Introduction**

The presence of lymph node metastasis is an important prognostic factor in gastrointestinal malignancy.<sup>1,2</sup> Lesions known to have a low risk of lymph node metastasis can be considered for curative endoscopic resection, thus avoiding radical surgery. Endoscopic mucosal resection (EMR) is now a well-established technique worldwide for the treatment of benign and small malignant lesions in the gastrointestinal tract (GIT).<sup>3</sup> Endoscopic submucosal dissection (ESD) is a more advanced technique and was pioneered by Japanese endoscopists.<sup>4</sup> It has become standard treatment in Japan for superficial esophageal and early gastric cancers and has recently been implemented in major centers to achieve en bloc resection of colorectal lesions that would otherwise necessitate piecemeal or surgical resection. Few centers offer ESD in the West, and there are currently no publications of significant patient cohorts. In the following article we give an

overview of endoscopic resection of GIT lesions and consider the application of ESD in Western countries.

**Assessment of GIT lesions****Histological assessment**

Early or superficial gastrointestinal cancer is confined to the mucosa and submucosa, irrespective of the presence of lymph node metastasis.<sup>5</sup> Comparison between Eastern and Western publications has been difficult in the past due to a divergence in the histological definition of gastrointestinal neoplasia. One of the main differences was that lesions with high-grade intraepithelial neoplasia and no invasion of the lamina propria were defined as high-grade dysplasia in the West, but as intramucosal carcinoma in Japan. In an attempt to overcome these discrepancies, the Vienna Workshop produced a consensus classification, revised in 2002,