Table 3. Hazard ratio (HR) and 95% confidence intervals (CIs) of overall survival according to the risk of lymph node metastasis

| | Number of subject | Number of deaths (death from gastric cancer) | Five-year survival rate (%) | Crude | | Multivariable adjusted[a] | |
|---|---|---|---|---|---|---|---|
| | | | | HR | 95% CI | HR | 95% CI |
| Curative ER | 308 | 33 | 84 | 1.00 | | 1.00 | |
| Non-curative ER-A with surgery | 29 | 1 (0) | 96 | 0.36 | 0.05–2.66 | 0.54 | 0.07–4.07 |
| Non-curative ER-B with surgery | 9 | 1 (0) | 89 | 0.96 | 0.13–7.01 | 1.09 | 0.15–8.14 |
| Non-curative ER-A without surgery | 38 | 14 (3) | 52 | 4.72 | 2.52–8.85 | 3.31 | 1.67–6.58 |
| Non-curative ER-B without surgery | 44 | 10 (1) | 71 | 1.55 | 0.75–3.22 | 1.17 | 0.56–2.47 |

ASA, American Society of Anesthesiologist; ER, endoscopic resection.

[a]Adjusted for age, sex, ASA score, clinical stage of cancer in past history, and past history of diseases (cardiovascular diseases, diabetes mellitus, respiratory diseases, and others).

margin (13,14). Long-term survival of EGC patients undergoing ER with expanded criteria has been equal to those undergoing ER with original guidelines (15). Expanded criteria for ER of larger tumors may benefit elderly patients with EGC (16).

As a general rule, additional surgery should be recommended for patients when curative ER is not achieved (17), as EGC surgical outcomes are known to be excellent (11). Our study provides long-term survival data of EGC in an elderly cohort. We demonstrate the efficacy of curative ER for EGC, showing a similar 5-year survival rate among elderly patients with curative ER and non-curative ER with surgery. We found that when curative ER was not achieved, elderly patients appeared to benefit from subsequent surgical gastrectomy. Furthermore, patients who had a non-curative ER without surgery and were established to have a high risk of lymph node metastasis had the lowest overall 5-year survival rate of 52%.

It was reported that lymphovascular involvement and massive submucosal penetration had a significant association with lymph node metastasis in EGC (18). From our data, there were significant difference in overall and disease-free survival between the patients with curative ER and non-curative ER-A without surgery group. Lymphovascular involvement or massive submucosal penetration was more frequent in surgical patients than in non-surgical patients. It is likely that the physician suggested additional surgery to these patients with high risk of lymph node metastasis. Considering the patient's age and the risk of lymph node metastasis in this recommendation.

Notably, the patients with the non-curative ER without surgery did not undergo additional surgery primarily due to subjective measures. Thus, although the treating physician routinely discussed and recommended radical surgery to all patients with non-curative ER, individual factors such as comorbid disease, reason for non-curative ER, age, and patient preference ultimately influenced treatment decisions. These conditions are subjective and cannot be expressed numerically, and are an inherent limitation of our retrospective study.

In conclusion, following non-curative ER for ECG, especially with lymphovascular involvement or massive submucosal penetration, additional surgery is recommended in elderly patients.

## CONFLICT OF INTEREST

**Guarantor of the article**: Chika Kusano, MD, PhD.

**Specific author contributions**: Conceptualization, data analysis, and script preparation: Chika Kusano and Motoki Iwasaki; endoscopic diagnosis and treatment: Takuji Gotoda and Ichiro Oda; data collection: Chika Kusano, Ichiro Oda, and Takuji Gotoda; critical reviewer of the paper: Ichiro Oda, Takuji Gotoda, Tonya Kaltenbach, and Abby Conlin. All authors have read and approved the submitted version of the paper.

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**Potential competing interests**: None.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Endoscopic resection (ER) has been accepted as standard treatment for early gastric cancers, which have a low risk of lymph node metastasis.
- ✓ Additional surgery with lymph node dissection should be recommended for patients when curative ER is not achieved.
- ✓ Deciding whether or not to pursue gastric surgery or not is particularly complex in elderly patients who often have comorbidities and limited life expectancy.

### WHAT IS NEW HERE

- ✓ A significant difference in overall and disease-free survival was evident between the patients with curative endoscopic resection (ER) and non-curative ER without surgery (hazard ratio (95% confidence interval): 1.89 (1.08–3.28), 2.30 (1.35–3.94)).
- ✓ Overall and disease-free survival of non-curative ER with "positive lymphatic or/and venous invasion" or "submucosal deep (sm2) invasion" are lowest.
- ✓ After non-curative ER for early gastric cancer, especially with lymphovascular involvement or massive submucosal penetration in historical findings, additional surgery is necessarily even in elderly patients.

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ORIGINAL ARTICLE

# Correlation between endoscopic macroscopic type and invasion depth for early esophagogastric junction adenocarcinomas

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**Abstract**

*Background* Although correlations between endoscopic macroscopic type and tumor depth have been reported for superficial esophageal squamous cell carcinoma and early gastric and early colorectal adenocarcinomas, there is no published study investigating the correlation between endoscopic macroscopic type and invasion depth for mucosal (M) and submucosal (SM) adenocarcinomas located at the esophagogastric junction (EGJ). We decided to analyze, therefore, the relationship between endoscopic macroscopic type and tumor depth for such cancers.

*Methods* We retrospectively reviewed 73 early EGJ adenocarcinomas (M/SM = 33/40; differentiated/undifferentiated type = 70/3) in 73 consecutive patients treated endoscopically and/or surgically between January 2000 and December 2008. The mean age of the patients was 63.9 years (range 37–85 years) and the male/female ratio was 62:11. EGJ adenocarcinoma was defined as junctional carcinoma (type II) according to the Siewert classification.

*Results* We found polypoid type lesions (0-I) in 14 patients, non-polypoid type without mixed type (0-IIa, 0-IIb, or 0-IIc) in 39, and mixed type (0-IIa + IIc or 0-IIc + IIa) in 20 patients. Non-polypoid type without mixed type (31%; 12/39) lesions had a significantly lower risk for SM invasion compared to polypoid type (79%; 11/14; $p < 0.01$) and mixed type (85%; 17/20; $p < 0.01$) lesions. In polypoid type lesions, the risk of SM invasion was significantly lower for the pedunculated subtype (0-Ip) than for the sessile subtype (0-Is) lesions (0%; 0/2 vs. 92%; 11/12; $p < 0.05$). M lesions (mean size 14.5 ± 7.5 mm) were significantly smaller than SM lesions (24.5 ± 7.7 mm; $p < 0.01$).

*Conclusions* Determination of endoscopic macroscopic type may be useful in accurately diagnosing early EGJ adenocarcinoma invasion depth.

**Keywords** Esophagogastric junction · Adenocarcinoma · Endoscopic macroscopic type · Depth of invasion

## Introduction

Accurate endoscopic diagnosis of invasion depth for gastrointestinal cancer is essential for making the proper decision on treatment strategy. The use of endoscopic resection in treating early gastrointestinal cancer has become more widespread recently. As a result, the differential endoscopic diagnosis of mucosal (M) and submucosal (SM) depth of invasion has become increasingly important for determining the indications for endoscopic resection [1–3].

Endoscopy examination is the primary modality for diagnosing gastrointestinal cancer and is also helpful in diagnosing invasion depth. Correlations between endoscopic macroscopic type and invasion depth have been

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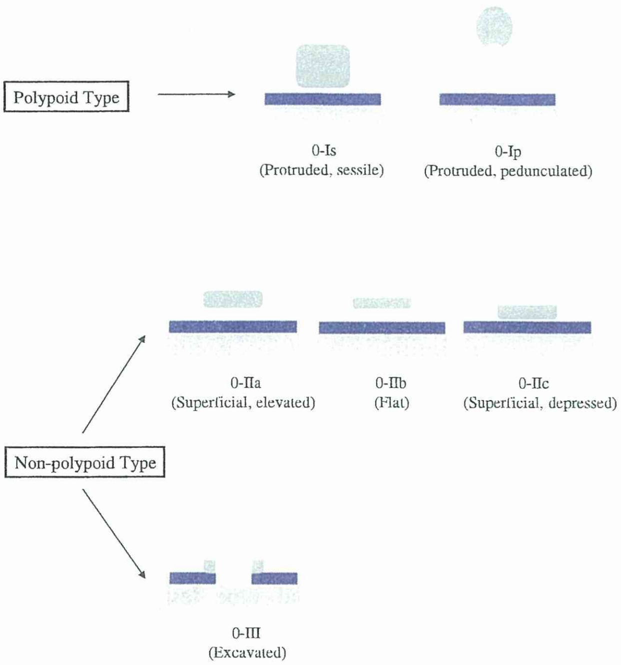


**Fig. 1** Classification of endoscopic macroscopic types of early esophagogastric junction adenocarcinomas

reported for superficial esophageal squamous cell carcinoma and early gastric and early colorectal adenocarcinomas in *The Paris endoscopic classification of superficial neoplastic lesions* [4], and in an even more recent evaluation, of endoscopic macroscopic types in early Barrett's neoplasia, such correlations have also been reported [5]. There has been no previously published study, however, investigating the correlation between endoscopic macroscopic type and invasion depth for M and SM adenocarcinomas located at the esophagogastric junction (EGJ). The intention of this study was to clarify the relationship between endoscopic macroscopic type and invasion depth for such early EGJ adenocarcinomas.

## Patients and methods

A total of 73 early EGJ adenocarcinomas in 73 consecutive patients treated endoscopically and/or surgically between January 2000 and December 2008 at the National Cancer Center Hospital in Tokyo, Japan, were retrospectively analyzed in this study. EGJ adenocarcinoma was defined as a junctional carcinoma (type II) according to the Siewert classification [6]. An upper gastrointestinal endoscopy examination was performed on each patient before treatment.

We reviewed the clinical records and endoscopic and pathological reports for every patient and analyzed the relationships between invasion depth of early EGJ adenocarcinomas and the following clinicopathological findings: age, gender, initial treatment, histological type, histological findings with regard to a diagnosis of Barrett's cancer, center of tumor location, tumor size, and endoscopic macroscopic type.

Invasion depth for early EGJ adenocarcinomas was divided into M and SM and initial treatment was divided into endoscopic resection and surgical resection. Histological type was diagnosed based on the predominant tumor pattern in the M layer and then divided into two types: differentiated type and undifferentiated type, according to the *Japanese classification of gastric carcinoma* [7]. The histological findings with regard to a diagnosis of Barrett's cancer were classified as Barrett's cancer and non-Barrett's cancer, with Barrett's cancer diagnosed whenever a tumor was continuously located on Barrett's esophagus. The center of tumor location was divided into quarters (12:01–3:00, 3:01–6:00, 6:01–9:00, and 9:01–12:00 o'clock), using

**Table 1** Clinicopathological findings of 73 patients with esophagogastric junction adenocarcinoma

| | |
|---|---|
| Age, mean ± SD (years) | 63.9 ± 12.0 |
| Sex (%) | |
| Male | 62 (85) |
| Female | 11 (15) |
| Invasion depth (%) | |
| Mucosal | 33 (45) |
| Submucosal | 40 (55) |
| Initial treatment (%) | |
| Endoscopic resection | 40 (55) |
| Surgical resection | 33 (45) |
| Histological type (%) | |
| Differentiated type | 70 (96) |
| Undifferentiated type | 3 (4) |
| Histological finding (%) | |
| Barrett's cancer | 42 (58) |
| Non-Barrett's cancer | 31 (42) |
| Tumor location, quarter (%) | |
| 12:01–3 o'clock | 50 (68) |
| 3:01–6 o'clock | 10 (14) |
| 6:01–9 o'clock | 3 (4) |
| 9:01–12 o'clock | 10 (14) |
| Tumor size, mean ± SD (mm) | 20.0 ± 9.1 |
| Endoscopic macroscopic type (%) | |
| 0-I | 14 (19) |
| 0-IIa | 8 (11) |
| 0-IIb | 1 (1) |
| 0-IIc | 30 (41) |
| 0-IIa + IIc | 17 (23) |
| 0-IIc + IIa | 3 (4) |
| 0-III | 0 (0) |

*SD* Standard deviation

Table 2 Correlation between clinicopathological findings and invasion depth

| | Invasion depth | | $p$ value |
|---|---|---|---|
| | Mucosal ($n = 33$) | Submucosal ($n = 40$) | |
| Age, mean ± SD (years) | 63.3 ± 11.5 | 64.3 ± 12.5 | NS |
| Sex (%) | | | |
| Male | 28 (45) | 34 (55) | NS |
| Female | 5 (45) | 6 (55) | |
| Histological type (%) | | | |
| Differentiated type | 33 (47) | 37 (53) | NS |
| Undifferentiated type | 0 (0) | 3 (100) | |
| Histological findings (%) | | | |
| Barrett's cancer | 23 (55) | 19 (45) | NS |
| Non-Barrett's cancer | 10 (32) | 21 (68) | |
| Tumor location, half (%) | | | |
| 12:01–6 o'clock | 28 (47) | 32 (53) | NS |
| 6:01–12 o'clock | 5 (38) | 8 (62) | |
| Tumor size, mean ± SD (mm) | 14.5 ± 7.5 | 24.5 ± 7.7 | <0.01 |
| Endoscopic macroscopic type (%) | | | |
| Polypoid type (0-I) | 3 (21) | 11 (79) | <0.01* |
| Non-polypoid type without mixed type (0-IIa, 0-IIb or 0-IIc) | 27 (69) | 12 (31) | |
| Mixed type (0-IIa + IIc or 0-IIc + IIa) | 3 (15) | 17 (85) | <0.01* |

*SD* Standard deviation, *NS* not significant

* Significantly different from non-polypoid type without mixed type

the forward endoscopic EGJ view. Tumor size was defined as the length of the major axis. Endoscopic macroscopic type was classified based on the Paris classification and divided into polypoid (0-I) and non-polypoid (0-IIa, 0-IIb, 0-IIc and 0-III) types (Fig. 1) [4]. A mixed type was diagnosed whenever a lesion consisted of at least two distinct endoscopic macroscopic types. Polypoid type lesions were then subdivided into sessile (0-Is) and pedunculated (0-Ip) subtype lesions.

Data were analyzed using the $\chi^2$ test, Fisher's exact test, or Student's $t$ test as appropriate. Value differences in which $p < 0.05$ were considered statistically significant.

## Results

Clinicopathological findings are shown in Table 1. The mean age ± standard deviation (SD) of the patients was 63.9 ± 12.0 years and the male/female ratio was 5.64 (62:11). Relationships between clinicopathological findings and invasion depth are shown in Table 2. M lesions (mean size 14.5 ± 7.5 mm) were significantly smaller than SM lesions (24.5 ± 7.7 mm; $p < 0.01$). Non-polypoid type without mixed type (0-IIa, 0-IIb or 0-IIc) lesions had a significantly lower risk for SM invasion than polypoid type (0-I) and mixed type (0-IIa + IIc or 0-IIc + IIa) lesions (Table 2; see images in Figs. 2, 3, 4). When polypoid type lesions were subdivided into sessile (0-Is) and pedunculated (0-Ip) subtypes, the risk of SM invasion was significantly lower for the pedunculated subtype than for the sessile subtype (0%; 0/2 vs. 92%, 11/12; $p < 0.05$) (see images in Figs. 4, 5).

## Discussion

There has been a dramatic increase in the incidence of EGJ adenocarcinomas in the United States and other Western countries over the past two decades [8–12]. It has also been reported from a large referral center in Japan that the proportion of EGJ adenocarcinomas among all gastric adenocarcinomas detected in Japanese patients has been increasing in recent years [13].

Remarkable progress has been made during the past decade in the development and refinement of endoscopic resection methods, from conventional endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD) [14–20], which has been applied to early EGJ adenocarcinomas [21]. Consequently, accurate differential endoscopic diagnosis of M and SM invasion depth in early EGJ adenocarcinomas has become more important for determining the indications for such procedures.

Endoscopic ultrasonography (EUS) is one of the current modalities used for diagnosing tumor invasion depth. Using conventional EUS (7.5 MHz), advanced T3/T4 carcinomas can be distinguished from T1/T2 carcinomas in

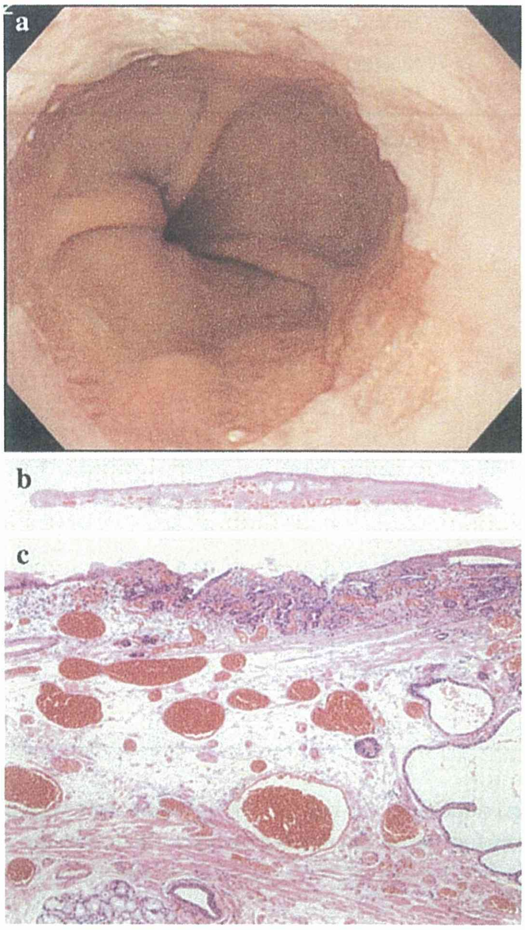

**Fig. 2** **a** Endoscopic image reveals a non-polypoid type without mixed type, slightly depressed (0-IIc) lesion at the esophagogastric junction (EGJ). **b**, **c** Histological features of the resected specimen indicate a well-differentiated adenocarcinoma confined to the mucosal layer that had spread to the subepithelial layer of the esophagus (**b** H&E, panoramic view), (**c** H&E, ×40)

more than 80% of cases; however, accurate differentiation between M and SM invasion depth is difficult [22–24]. EUS using a miniprobe (20 MHz) has reportedly demonstrated a high diagnostic accuracy of approximately 80% for differentiating between M and SM early EGJ adenocarcinomas. There was no significant difference, however, between EUS diagnostic accuracy and that of high-resolution video endoscopy [23]. Consequently, endoscopy can also be helpful in diagnosing invasion depth, but such diagnosis is subjective in nature so there is a need for objective criteria.

In the present study, we analyzed the relationship between the invasion depth of early EGJ adenocarcinomas and relevant clinicopathological findings, including endoscopic macroscopic type. We found that M lesions were

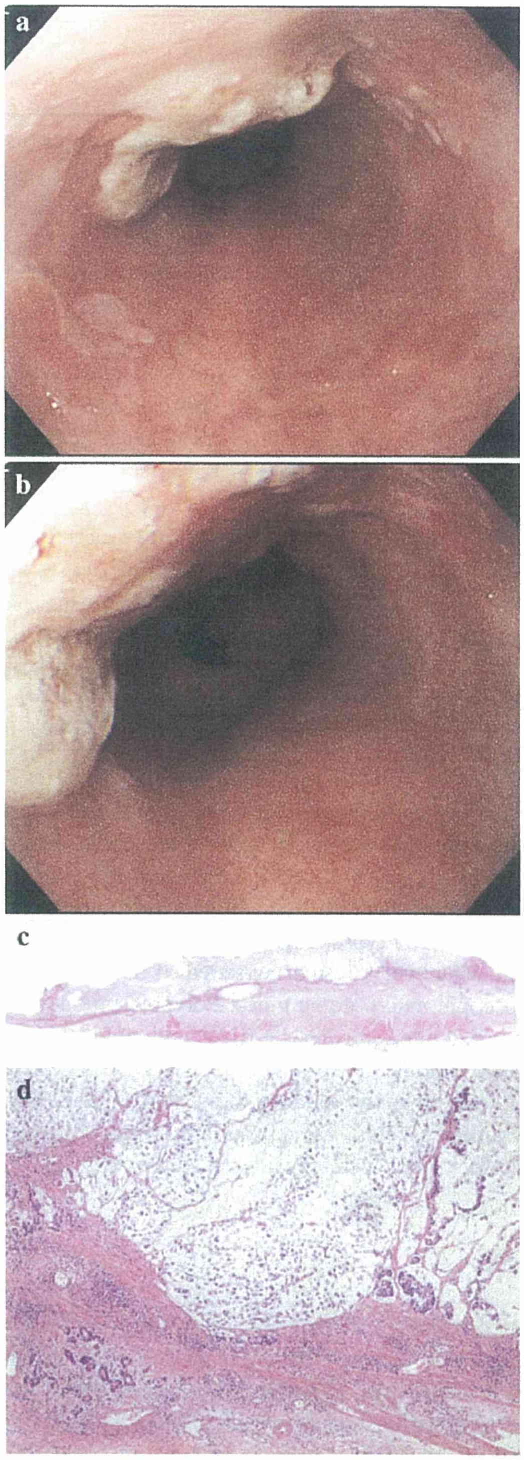

**Fig. 3** **a**, **b** Endoscopic images reveal a mixed type, elevated lesion with a central depression (0-IIa + IIc) at the EGJ. **c**, **d** Histological features of the resected specimen indicate a mucinous adenocarcinoma in the mucosal layer and a poorly differentiated adenocarcinoma that had invaded the submucosal layer (**c** H&E, panoramic view), (**d** H&E, ×100)

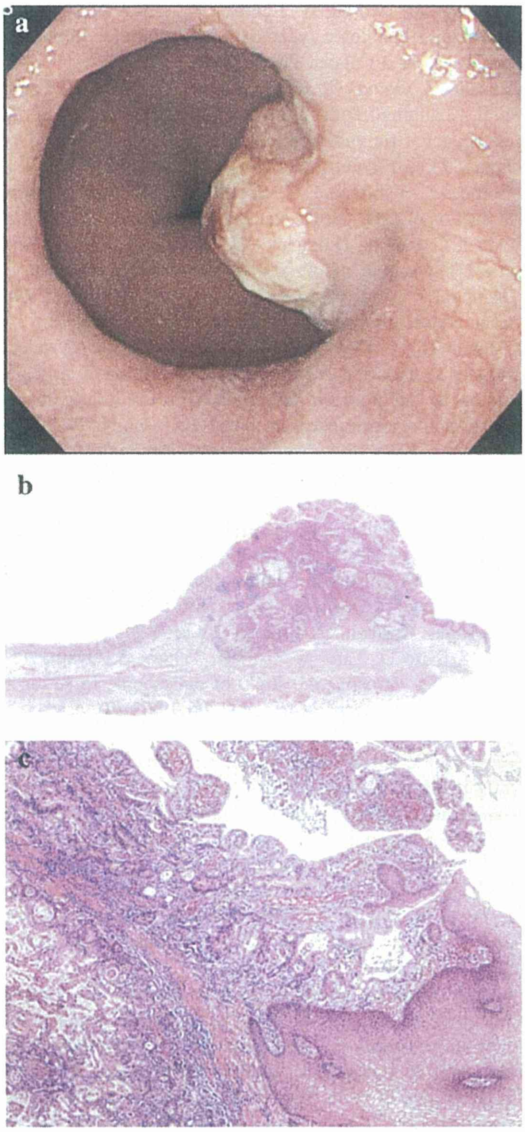

Fig. 4 a Endoscopic image reveals a polypoid type, sessile subtype (0-Is) lesion at the EGJ. b, c Histological features of the resected specimen indicate a well-differentiated adenocarcinoma that had invaded the submucosal layer (b H&E, panoramic view), (c H&E, ×100)

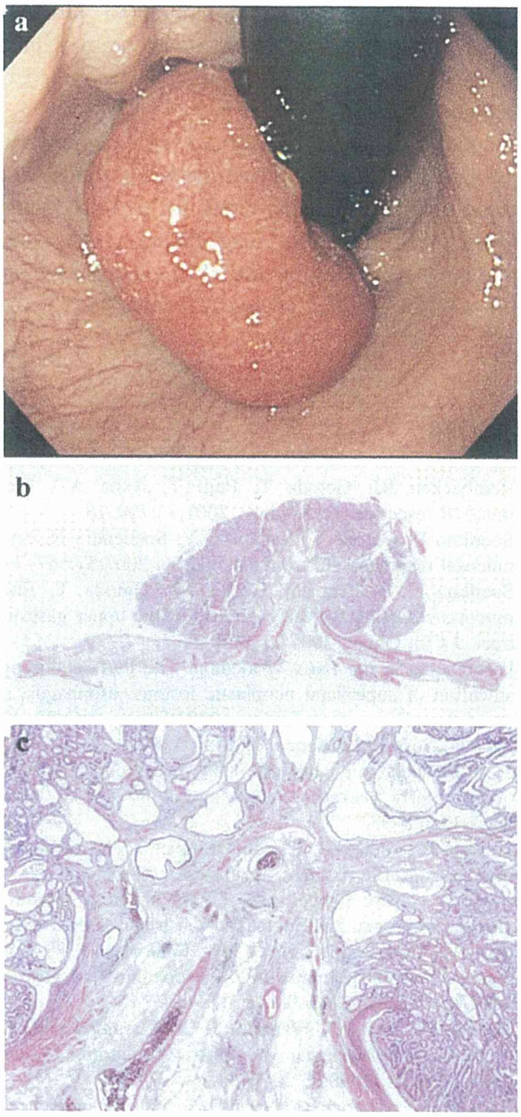

Fig. 5 a Endoscopic image reveals a polypoid type, pedunculated subtype (0-Ip) lesion at the EGJ. b, c Histological features of the resected specimen indicate a well-differentiated adenocarcinoma confined to the mucosal layer (b H&E, panoramic view), (c H&E, ×100)

significantly smaller than SM lesions. Non-polypoid type without mixed type (0-IIa, 0-IIb or 0-IIc) lesions had a significantly lower risk for SM invasion compared to polypoid type (0-I) and mixed type (0-IIa + IIc or 0-IIc + IIa) lesions. In the polypoid type lesions, the risk for SM invasion was significantly lower for the pedunculated subtype (0-Ip) than for the sessile subtype (0-Is) lesions. These results were similar to those in previously published reports of other gastrointestinal neoplasias [4, 5].

One limitation of the present study is that it was a retrospective investigation from a single center, with a relatively small number of reported cases, so a large prospective study will be needed to confirm our findings on the correlation of endoscopic macroscopic type with invasion depth for early EGJ adenocarcinomas. Another limitation of our study was that invasion depth for early EGJ adenocarcinomas was divided into M and SM, but SM was not further subdivided into SM1 and SM2, because the definition of SM1 for EGJ adenocarcinomas is still undecided at the present time. SM1 for gastric cancer and esophageal cancer is defined as a tumor that invades less than 500 μm and less than 200 μm, respectively, into the submucosa from the muscularis mucosa and is associated with a lower risk of lymph-node metastasis compared with SM2 [4]. Additional investigation as to an accurate definition of SM1 and the risk of lymph-node metastasis for EGJ adenocarcinomas is also necessary.

In conclusion, this retrospective study demonstrated that there were certain correlations between endoscopic macroscopic type and invasion depth for early EGJ adenocarcinomas. As a result, determination of endoscopic macroscopic type may be useful in accurately diagnosing invasion depth for EGJ adenocarcinomas.

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ORIGINAL ARTICLE

# Depth-predicting score for differentiated early gastric cancer

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**Abstract**
*Background* Intramucosal and minute submucosal (M-SM1; <500 μm in depth) differentiated gastric cancers, which have a negligible risk of lymph node metastasis, are the targets for endoscopic resection. However, there have been few reports about the endoscopic distinction between these cancers and cancers with deeper submucosal invasion (SM2; ≥500 μm in depth). The aim of this retrospective study was to analyze the differences in the endoscopic features between M-SM1 and SM2 cancers, and to develop a simple scoring model to predict the depth of these early gastric cancers.
*Methods* We analyzed 853 differentiated early gastric cancers treated endoscopically or surgically as a derivation group. Endoscopic images were reviewed to determine the relationship between depth of invasion and the following endoscopic features: tumor location, macroscopic type, tumor size, and endoscopic findings (remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds). Secondly, we created a depth-predicting model based on the obtained data and applied the model to 211 validation samples.
*Results* On logistic regression analysis, tumor size more than 30 mm, remarkable redness, uneven surface, and margin elevation were significantly associated with deeper submucosal cancers. A depth-predicting score was created by assigning 2 points for margin elevation and tumor size more than 30 mm, and 1 point for each of the other endoscopic features. When validation lesions of 3 points or more were diagnosed as deeper submucosal cancers, the sensitivity, specificity, and accuracy as evaluated by three endoscopists were 29.7–45.9, 93.1–93.7, and 82.5–84.8%, respectively.
*Conclusions* The depth-predicting score could be useful in the decisions on treatment strategy for differentiated M-SM1 early gastric cancers.

**Keywords** Early gastric cancer · Depth · Diagnosis · Endoscopy

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## Introduction

Endoscopic resection in patients with early gastric cancer (EGC) is less invasive and more economical than conventional surgery. The negligible incidence of lymph node metastasis in certain stages of EGC means that, in selected cases, patients can be cured with such therapies. Gotoda et al. [1] concluded that among 5265 patients who underwent gastrectomy, there was no lymph node involvement in differentiated mucosal (M) gastric cancers without lymphatic or vessel invasion when the cancers were smaller than 3 cm in diameter with ulceration, or any size without ulceration. Differentiated minute submucosal (SM1, <500 μm in depth) cancers without lymphatic or venous involvement and cancers smaller than 3 cm also showed no lymph node involvement [1]. The endoscopic submucosal dissection (ESD) technique using an insulation-tipped diathermic knife or other endo-knives could technically achieve one-piece resection for such lesions [2–7]. It is important to distinguish M-SM1 cancers from deeper submucosal (SM2; $\geq$500 μm in depth) cancers, which have the possibility of lymph node metastasis, for making the proper decision on treatment strategy.

Thus, preoperative determination of the depth of invasion is important. Although the usefulness of endoscopic ultrasonography (EUS) has been reported, with this modality it is impossible to distinguish M-SM1 from SM2 definitively [8, 9]. Conventional endoscopy is the initial route of EGC detection, but there have been few reports comparing the endoscopic features of EGC stages M-SM1 and SM2. Furthermore, no objective criteria regarding the depth of invasion exist, and many endoscopists diagnose based on their own experiences. The aim of this retrospective study was to analyze the differences in the endoscopic features between M-SM1 and SM2, and to develop a simple model to predict the depth of these EGCs.

## Materials and methods

### Analyzed lesions and review methods

A total of 880 consecutive differentiated EGCs were treated endoscopically or surgically between 2001 and 2003 at the National Cancer Center Hospital in Tokyo. Twenty-seven lesions were excluded because precise endoscopic findings could not be depicted [eight detected in remnant stomach, six after esophagectomy, six local recurrences after endoscopic mucosal resection (EMR), five with insufficient endoscopic images, one with a tattoo, and another with an endo-clip artifact].

The remaining 853 differentiated EGCs (M 592, SM1 111, SM2 150, mean patient age of 65.6 years, 686 male and 167 female patients) were analyzed as a derivation group. An endoscopist (S.A.), experienced with more than 5000 gastroscopies, reviewed conventional endoscopic images without histological information about depth. The following characteristics were evaluated: tumor location (upper, middle, and lower), tumor size (mm), macroscopic type, and five other endoscopic findings that are widely accepted as markers of deeper submucosal invasion among Japanese endoscopists, with some minor variations (remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds) [10, 11].

Subsequently, we made a simple and practical scoring model (depth-predicting score, DPS) to distinguish M-SM1 from SM2 cancers, based on the analyzed data in the derivation group. Three endoscopists (S.A., T.K., and K.T., each experienced with more than 5000 gastroscopies) evaluated the endoscopic findings and investigated the sensitivity, specificity, and accuracy of our DPS in our validation set, consisting of 211 differentiated EGCs treated between January and June in 2000 at our hospital.

Conventional white-light endoscopy (video-endoscope Q240 or Q260; Olympus Medical Systems, Tokyo, Japan) was used for pretreatment endoscopic examination. In addition, surface details were enhanced by indigo-carmine chromoendoscopy.

### Definitions

The EGC macroscopic and histological types in the enrolled patients were decided according to the *Japanese classification of gastric carcinoma* [12]. We divided the macroscopic types into three groups: IIa (elevated lesions such as 0 I, 0 IIa, and 0 I + IIa), IIc (depressed lesions such as 0 IIc, 0 IIc + III, and 0 III + IIc), and IIa + IIc (combined type, such as 0 IIa + IIc and 0 IIc + IIa). Histological type was diagnosed based on the predominant tumor pattern and then divided into two types; differentiated type and undifferentiated type. Well differentiated, moderately differentiated, and papillary adenocarcinoma were defined as differentiated type.

We described five endoscopic features in this study. Remarkable redness was defined as a reddish area similar to regenerative epithelium (Fig. 1). Nodulations in the tumor's surface were considered an uneven surface (Fig. 2). Margin elevation referred to the finding of a protruding edge surrounding the tumors, including submucosal tumor like component with a limited amount of air insufflation (Fig. 3a, b). Either a scar or an ulcerative area within the tumors was evaluated as ulceration (Fig. 4). Finally, enlarged folds included any thickened or merged convergent folds (Fig. 5).

### Statistical methods

To identify the variables that were significantly more common in SM2, the endoscopic data were initially

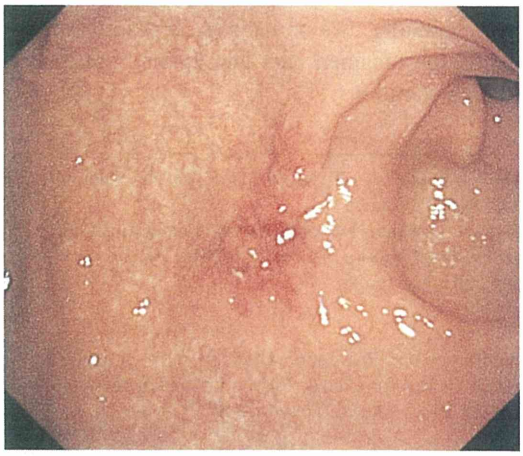

**Fig. 1** Remarkable redness: endoscopic picture shows unusual redness inside the lesion

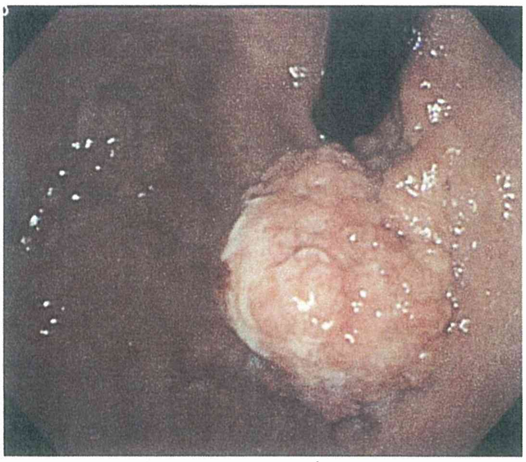

**Fig. 2** Uneven surface: nodular mucosa can be seen

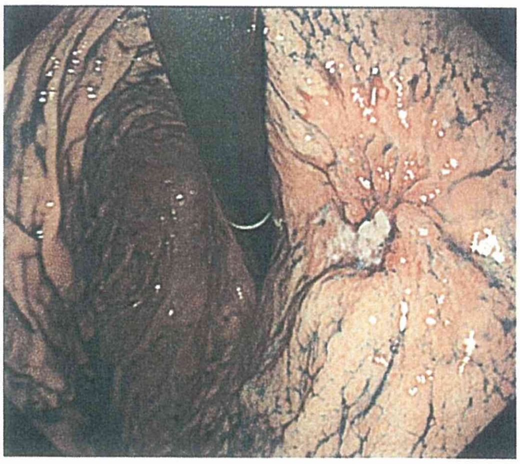

**Fig. 4** Ulceration: endoscopic picture of ulceration

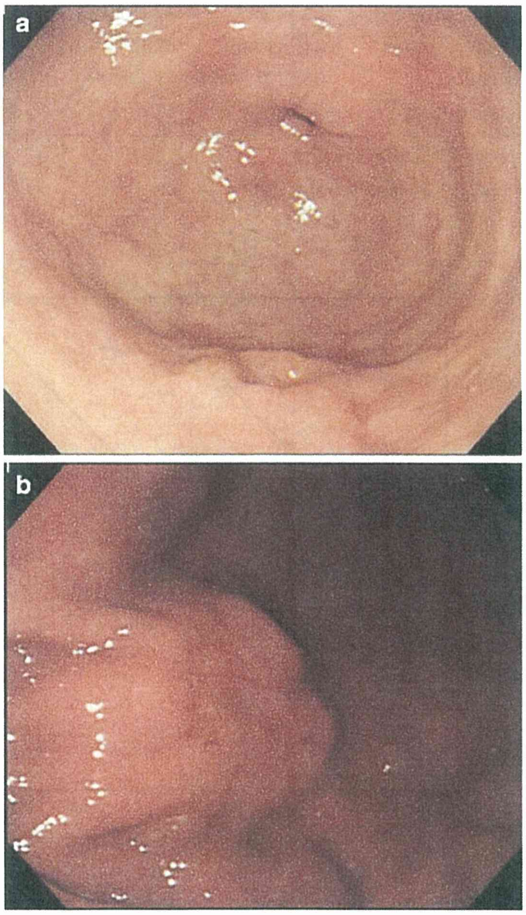

**Fig. 3** **a** Margin elevation: endoscopic picture of surrounding elevation. **b** Margin elevation: endoscopic picture of submucosal tumor like component can be demonstrated from the view with a limited amount of air insufflation

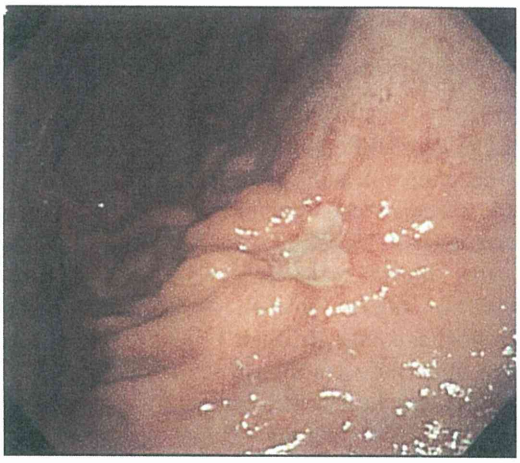

**Fig. 5** Enlarged folds: thickened or merged folds can be seen toward the inside of the lesion

evaluated with Student's $t$ test for tumor size and the $\chi^2$ test for other endoscopic features. We then entered the candidate variables into a logistic regression analysis. Endoscopic features independently and statistically associated with SM2 penetration were selected as examination items for the DPS. The relative weighting of each DPS variable was based on its $\beta$-coefficient in the logistic regression analysis. The significance level was set at 5% for each analysis. A $p$ value of $<0.05$ was considered significant.

## Results

### Analysis of endoscopic features

Table 1 shows the histological and therapeutic characteristics of both the derivation and validation groups. There were no significant differences between the two groups in the depth of invasion, histological type, or treatment strategies.

**Table 1** Histological and therapeutic characteristics

| | Derivation group ($n = 853$) | Validation group ($n = 211$) | $p$ value |
|---|---|---|---|
| Depth (M-SM1/SM2) | 703/150 | 175/36 | NS* |
| Histological type | | | |
| Well | 732 | 185 | NS* |
| Moderately | 109 | 25 | |
| Papillary | 12 | 1 | |
| Treatment | | | |
| EMR/ESD | 632 | 171 | NS* |
| Surgery | 221 | 40 | |

*M-SM1* intramucosal and minute submucosal (<500 μm in depth) cancers, *SM2* deeper submucosal (≥500 μm in depth) cancers, *well* well-differentiated adenocarcinoma, *moderately* moderately differentiated adenocarcinoma, *papillary* papillary adenocarcinoma, *EMR*, endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *NS* not significant

* $\chi^2$ test

In the derivation group, there was no significant difference in tumor location between M-SM1 and SM2. SM2 gastric cancers were significantly larger and were characterized as IIa + IIc. According to the endoscopic features, we also found statistically significant differences in remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds (Table 2).

The tumor size cutoff was set at 30 mm with a cross point between the receiver operating characteristic (ROC) curve against SM2 and the 45° line, which represented the ROC curve of a test whose decision ability is no better than chance (Fig. 6). Tumor size more than 30 mm was determined as a variable in multivariate analysis.

In the logistic regression analysis, tumor size (more than 30 mm), macroscopic type, and endoscopic features which were significantly more common in SM2 by univariate analysis were investigated. As a result, margin elevation, tumor size (more than 30 mm), remarkable redness, and uneven surface were significantly associated with SM2 EGCs (Table 3).

## Establishment of depth-predicting score

The DPS was created based on the above results. One point was given for remarkable redness and uneven surface, while margin elevation and tumors more than 30 mm were scored with 2 points because the relative magnitude of the $\beta$-coefficient was roughly twice that of other variables. Thus, the range of the resulting DPS was 0–6 points (Table 4). A total of 3 points was defined as the cutoff between M-SM1 and SM2. This was done in order to balance the power for SM2 selection and minimize the population for overtreatment. The sensitivity, specificity, and accuracy of the proposed DPS were 57.3% (95% confidence interval [CI] 49.4–65.3%), 86.2% (95% CI

**Table 2** Endoscopic comparison between M-SM1 and SM2 in derivation group

| | M-SM1 ($n = 703$) | SM2 ($n = 150$) | $p$ value |
|---|---|---|---|
| Location | | | |
| U | 134 | 38 | |
| M | 257 | 35 | NS* |
| L | 312 | 77 | |
| Tumor size (mm) | | | |
| Mean, range | 19.2 (3–120) | 31.6 (5–120) | <0.0001** |
| Macroscopic type | | | |
| IIa | 178 | 30 | |
| IIc | 458 | 88 | |
| IIa + IIc | 67 | 32 | <0.0001* |
| Endoscopic features | | | |
| Remarkable redness | 160 (22.8%) | 70 (46.7%) | <0.0001* |
| Uneven surface | 72 (10.2%) | 47 (31.3%) | <0.0001* |
| Margin elevation | 110 (15.6%) | 82 (54.7%) | <0.0001* |
| Ulceration | 152 (21.6%) | 57 (38.0%) | <0.0001* |
| Enlarged folds | 7 (1.0%) | 11 (7.3%) | <0.0001* |

*U* upper, *M* middle, *L* lower

* $\chi^2$ test, ** Student's $t$ test

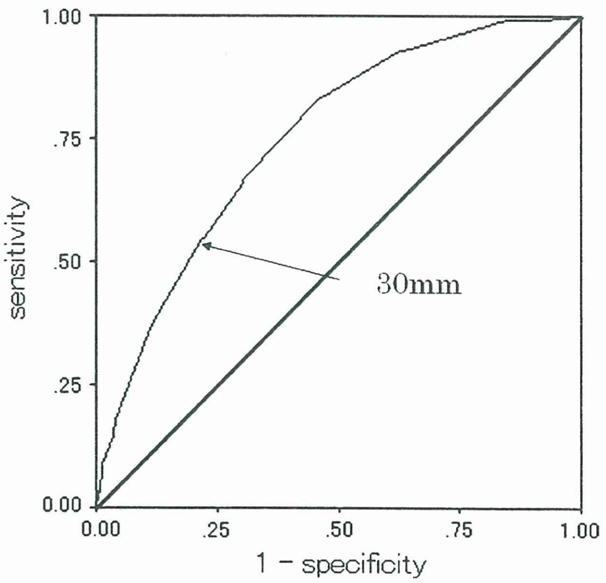


**Fig. 6** Receiver operating characteristic curve for tumor size and the sensitivity of submucosal cancers ≥500 μm in depth (SM2): the *arrow* (30-mm diameter) shows the cutoff point between intramucosal and minute submucosal <500 μm in depth (M-SM1) and SM2 cancers

**Table 3** Multivariate logistic regression analysis

| | β-coefficient | Odds ratio (95% CI) | *p* 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).

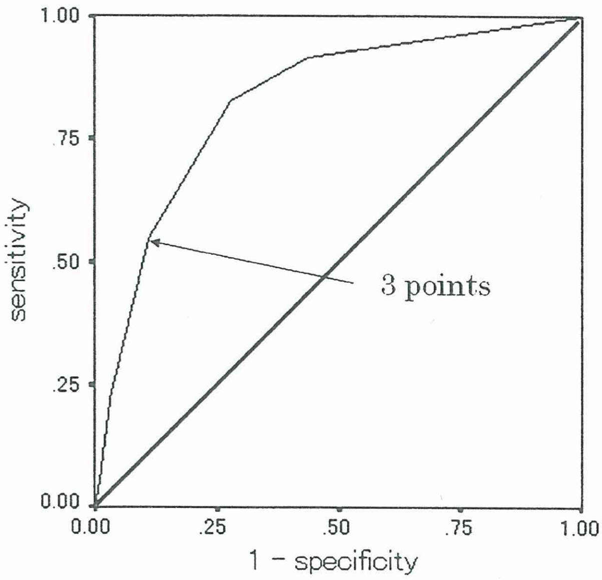


**Fig. 7** Receiver operating characteristic curve for depth-predicting score (DPS) and the sensitivity of SM2: the *arrow* (3 points) shows the cutoff point between M-SM1 and SM2

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

| | IIa | IIc/IIa + IIc | Total |
|---|---|---|---|
| Endoscopist 1 | | | |
| 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) |
| Endoscopist 2 | | | |
| 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) |
| Endoscopist 3 | | | |
| 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) |

## 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.

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.

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ORIGINAL ARTICLE

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

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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: ≥500 μm), positive lymphatic and/or venous invasion, intramucosal cancer more than 3 cm in size in the presence of ulceration, submucosal superficial invasion (sm1: <500 μm) 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.

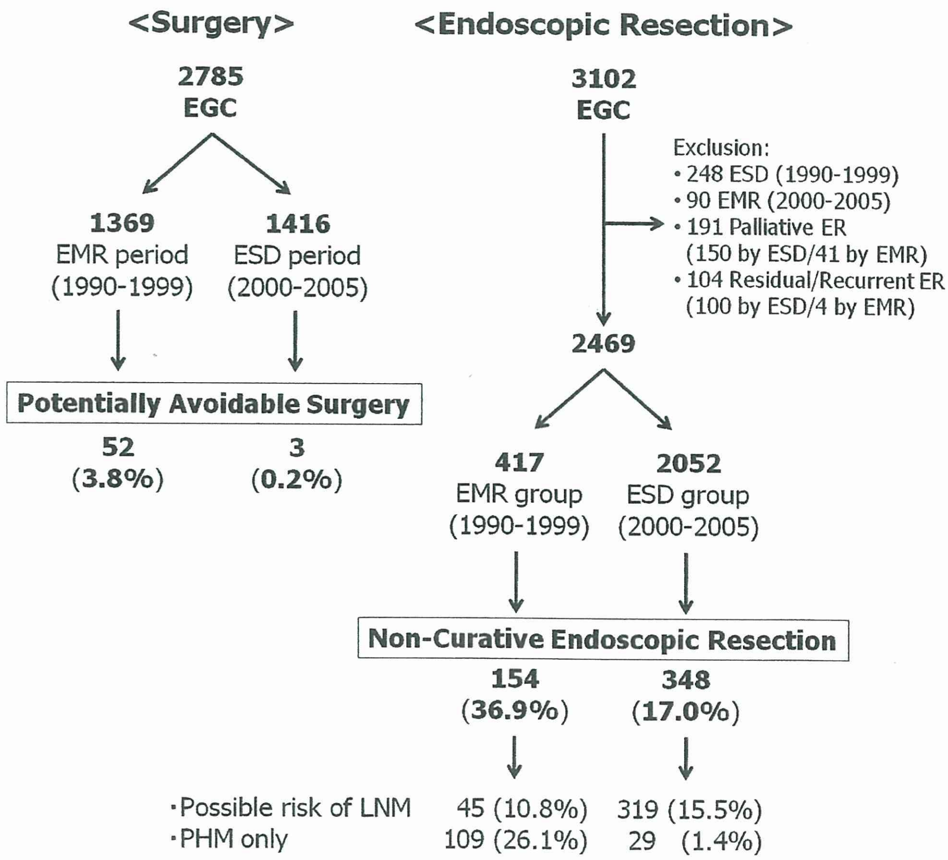


**Fig. 1** Outline of the study, including rates of potentially avoidable surgery and non-curative endoscopic resection based on the histological results. *EGC* Early gastric cancer, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *ER* endoscopic resection, *LNM* lymph node 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) | *P* |
|---|---|---|---|
| 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 ($P < 0.001$) (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)

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

| | EMR group % ($n$ = 417) | ESD group % ($n$ = 2,052) | *P* |
|---|---|---|---|
| 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) | *P* |
|---|---|---|---|
| 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 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 ≤30 mm in size with ulceration, and 16 sm1 cancers ≤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.

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**Conflict of interest** None.

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