Appropriate indications for endoscopic submucosal dissection of early gastric cancer according to tumor size and histologic type

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Background: Endoscopic submucosal dissection (ESD) is increasingly being performed for early gastric cancers (EGCs) that are larger than 2 cm and those that are not intestinal-type (IT) cancers by Lauren's classification. The technical feasibility of ESD for these EGCs has not been fully evaluated.

Objective: To identify appropriate expanded indications for ESD of EGC.

Design and Setting: A retrospective analysis of prospectively collected data was performed on consecutive patients who underwent ESD at a single tertiary center.

Patients and Methods: In total, 487 EGCs in 461 patients treated by ESD were classified by size and histologic type: IT EGCs 2 cm or less (257 lesions in 235 patients), IT EGCs larger than 2 cm (172 lesions in 168 patients), and non-IT EGCs (58 lesions in 58 patients).

Main Outcome Measurements: Curative resections were assessed among the 3 groups, and logistic regression analysis was used to analyze factors related to curative resection.

Results: The rates of curative resection significantly decreased from IT EGCs 2 cm or less (88.7%) to IT EGCs larger than 2 cm (73.3%) to non-IT EGCs (37.9%). Tumor size (>3 cm), ulceration, histologic type (non-IT), and piecemeal resection were independently unfavorable factors in curative resection.

Limitations: Small sample size and short-term duration of follow-up study.

Conclusions: ESD with curative intent is technically most feasible for nonulcerative and IT EGCs smaller than 3 cm. (Gastrointest Endosc 2010;71:920-6.)

EMR has become a major treatment option for early gastric cancer (EGC). Currently accepted indications for EMR are well-differentiated, elevated lesions less than 2 cm and small (≤1 cm) depressed lesions without ulceration.[1] However, clinical observations suggest that the accepted indications for EMR are too strict and may lead to unnecessary surgery.[2] The introduction of endoscopic submucosal dissection (ESD) has allowed en bloc resection of EGCs larger than 2 cm as well as ulcerated EGCs.[3] ESD also allows precise histologic assessment of resected specimens and may prevent residual disease and local recurrence.[3,4] Gotoda et al[5] reported surgical data showing that EGC subgroups had no risk of lymph node metastasis. Thus, the results allowed the development of expanded criteria for ESD. ESD is increasingly performed for EGCs larger than 2 cm. Recently, EMR of undifferentiated EGC has been reported to be feasible.[6-9] These prospects were based on studies that evaluated the risk of lymph node metastasis based on surgical data. However, the actual feasibility of EMR for undifferentiated EGCs cannot be

Abbreviations: APC, argon plasma coagulation; DT, diffuse type; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; IT, intestinal type; MT, mixed type.

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considered solely on the basis of surgical data. The technical feasibility of ESD for these EGCs was not fully clarified, especially with reference to size and histologic type. Thus, we analyzed the technical feasibility of ESD in 487 EGCs, in which 257 lesions were not suitable for EMR based on traditional indications of EMR.

Capsule Summary

What is already known on this topic

- Endoscopic submucosal dissection (ESD) has facilitated en bloc resection of early gastric cancers (EGCs) larger than 2 cm and/or ulcerated lesions.

What this study adds to our knowledge

- In a retrospective study of ESD performed in 487 EGCs, the rates of curative resection progressively decreased from intestinal–type lesions measuring 2 cm or less (88.7%) to those more than 2 cm (73.3%) to nonintestinal-type lesions (37.9%).
- Tumor size (>3 cm), ulceration, nonintestinal histologic type, and piecemeal resection were independently unfavorable factors in curative resection.

PATIENTS AND METHODS

Study subjects

Of 696 patients with 735 EGCs treated by ESD between November 2003 and June 2008, 235 patients had a diagnosis of tubular adenoma based on resected specimens and were excluded from this study. Thus, 461 patients with 487 EGCs were included in the study and received endoscopic follow-up for 1 to 68 months (median 33 months).

The study was approved by our hospital ethics committee and institutional review board. Written informed consent was obtained from all patients before ESD.

The resected lesions were classified by size and histologic subtype based on Lauren's classification.[10] The intestinal type (IT) is characterized by cohesive neoplastic cells that form glandlike tubular structures, and, histologically, the IT includes papillary, well-, and moderately differentiated or mucinous adenocarcinoma without signet ring cell carcinoma. The diffuse type (DT) lacks gland formation and consists primarily of signet ring cell carcinoma and poorly differentiated adenocarcinoma, according to the World Health Organization's classification.[11] The mixed type (MT) consisted histologically of nonhomogeneous mixtures of IT and DT lesions. Compared with the IT, the MT exhibits more aggressive biological behavior, including invasion depth, lymphatic invasion, and lymph node metastasis.[12-14]

Thus, the resected EGCs were divided into 3 groups: the small IT EGC group consisting of IT EGCs 2 cm or less in diameter (257 lesions in 235 patients), the large IT EGC group consisting of IT EGCs less than 2 cm in diameter (172 lesions in 168 patients), and the non-IT EGC group consisting of both DT and MT EGCs, regardless of tumor size (58 lesions in 58 patients).

EUS and CT were performed in all patients before performing ESD to exclude lymph node metastasis or distant metastasis.

ESD methods

All patients were sedated with an intravenous injection of 5 to 7.5 mg midazolam (Roche Korea Co, Ltd, Seoul, South Korea), with monitoring of cardiorespiratory function during the procedure. EGCs were first identified and demarcated by using white-light endoscopy and chromoendoscopy with indigo-carmine solution, and then the lesions were marked with argon plasma coagulation (APC). Sodium alginate (1% sodium alginate and normal saline solution; Taejoon Pharmaceutical, Seoul, South Korea) was then injected into the submucosal layer to lift the mucosa. A circumferential mucosal incision and ESD were performed by using an IT knife (Olympus Optical Co Ltd, Tokyo, Japan), a Flex knife (Olympus Optical Co Ltd), or a Fork knife (Kachu Technology Co, Seoul, South Korea). High-frequency generators (ICC200 or VIO 300D; ERBE Elekromedizin, Tubingen, Germany) were used during marking, incision, and ESD. ESD was performed by an experienced endoscopist (J.Y.C.).

Definitions

En bloc resection refers to a resection in 1 piece. Curative resection was defined as achieving tumor-free lateral and vertical margins after tumor removal, with no submucosal invasion deeper than 500 μm from the muscularis mucosae and no lymphatic or vascular involvement. Noncurative resections were defined as those that did not meet the curative criteria. Procedure-related bleeding after ESD was defined as bleeding that required transfusion or that caused the hemoglobin level to fall by 2 g/dL. Perforation was diagnosed endoscopically or by the presence of free air on abdominal plain radiography or CT.

Follow-up

Endoscopic examinations were scheduled at 1, 3, 6, and 12 months after ESD. Additional examinations were conducted at 6-month intervals during the second year and annually thereafter. Biopsy specimens during each follow-up endoscopy were taken from the treatment-induced scar and any suspicious abnormalities to assess the presence of local recurrent tumor or metachronous cancer of the stomach. Contrast-enhanced abdominal CT and chest radiographs were performed at 6-month inter-

TABLE 1. Comparison of the clinicopathologic features in the small intestinal-type, large intestinal-type, and nonintestinal-type early gastric cancer groups

Endoscopic and histologic findings	Small IT EGC group, no. (%) (IT ≤2 cm) (n = 257)	Large IT EGC group, no. (%) (IT >2 cm) (n = 172)	Non-IT EGC group, no. (%) (DT or MT) (n = 58)
Histologic subtype			
	WD 173 (67.3), MD 84 (32.7)	WD 107 (62.2), MD 65 (37.8)	PD 22 (37.9), SRC 15 (25.9), MT 21 (36.2)
Tumor size	12.7 ± 4.6 cm*	32.6 ± 12.8 cm†	23.8 ± 13.6 cm
Tumor location			
Upper	21 (8.2)‡	18 (10.5)	9 (15.5)
Middle	62 (24.1)‡	54 (31.4)	26 (44.8)
Lower	174 (67.7)‡	99 (58.1)	22 (39.7)
Macroscopic type			
Elevated	81 (31.5)	71 (41.3)†	11 (19)
Flat/ depressed	176 (68.5)	101(58.7)†	47 (81)
Ulcer			
Absent	184 (71.6)	118 (68.6)	33 (56.9)
Present	73 (28.4)	54 (31.4)	25 (43.1)
Depth of invasion			
Mucosa	236 (91.8)*	144 (83.7)†	31 (53.4)
Submucosa (<500 μm)	14 (5.4)*	20 (11.6)†	8 (13.8)
Submucosa (≥500 μm)	7 (2.7)*	8 (4.7)†	19 (32.8)
No lymphatic invasion	249 (96.9)‡	164 (95.3)†	44 (75.9)
No vascular invasion	251 (97.7)‡	165 (95.9)	52 (89.7)

IT, Intestinal-type; *EGC*, early gastric cancer; *DT*, diffuse-type; *MT*, mixed-type; *WD*, well-differentiated adenocarcinoma; *PD*, poorly differentiated adenocarcinoma; *MD*, moderately differentiated adenocarcinoma; *SRC*, signet ring cell carcinoma.
*$P < .05$ compared with large IT EGC group and non-IT EGC group.
†$P < .05$ compared with non-IT EGC group.
‡$P < .05$ compared with non-IT EGC group.

vals or more frequently after ESD, according to the judgment of the attending physician (J.Y.C.).

Statistical analysis

Significant differences in patient characteristics, clinicopathologic features, and therapeutic efficacies among the 3 groups were determined by using the Fisher exact test, the χ^2 test, the χ^2 test for trends, the Kruskal-Wallis test, or analysis of variance, as appropriate. P values $<.05$ were deemed to indicate statistical significance. Factors associated with ESD curability were analyzed by using a logistic regression analysis. Odds ratios and 95% confidence intervals were calculated to estimate the relative risk of noncurative resection and their association with various parameters (age, sex, tumor size, tumor location, macroscopic appearance, the presence of ulcer, histologic type, and the presence of an en bloc resection).

RESULTS

Clinicopathologic characteristics

The mean (± standard deviation) age of the 461 patients was 62.0 (± 10.1) years. The patients consisted of 324 men and 137 women. No significant difference was found in age or sex among the 3 EGC groups: 257 were in the small IT EGC group, 172 were in the large IT EGC group, and 58 were in the non-IT EGC group. Table 1 summarizes the clinicopathologic features of the EGCs by

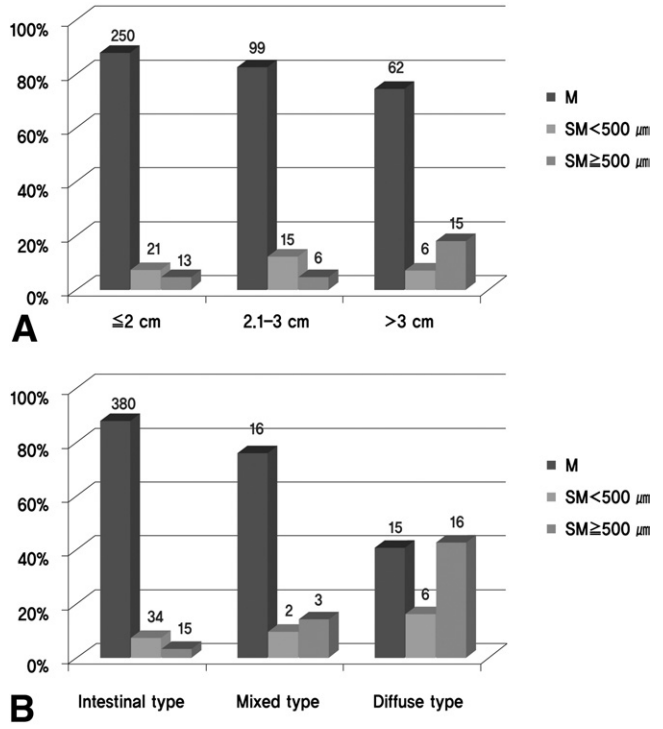

Figure 1. Relationship between depth of invasion and tumor size (**A**) and histologic subtype (**B**), according to Lauren's classification. As tumor size increased, SM invasion of 500 μm or more increased accordingly (P for trend $<$ .001). The risk of SM invasion of 500 μm or more increased gradually from IT to MT to DT EGCs (P for trend $<$ .001). SM, submucosa; M, mucosa.

the 3 EGC groups. The small IT EGC group showed a significantly lower rate of submucosal invasion than the other groups. The rate of lymphatic invasion in the non-IT EGC group was significantly higher than in the other groups. Figure 1 shows the degree of invasion depth, according to tumor size and histologic type, by Lauren's classification.

Therapeutic efficacy

No significant difference was found in the rate of en bloc resection among the 3 groups (Table 2). The rates of curative resection gradually decreased from the small IT to the large IT to the non-IT EGC group. Table 3 summarizes the rates of curative resection according to histologic type, presence of ulceration, and tumor size. Nonulcerative and IT EGCs smaller than 3 cm showed significantly higher rates of curative resection compared with those in the other subgroups.

Factors related to therapeutic outcome

Independent factors for curative resection were tumors larger than 3 cm, ulceration, histologic type, and piecemeal resection (Table 4).

Complications

Although the non-IT EGC group showed a higher procedure-related bleeding rate (12.1%; 7 patients) than the small and large IT EGC groups (4.3%, 11 patients and 2.9%, 5 patients, respectively), this difference was not statistically significant. Perforation occurred in 4 (1.6%), 2 (1.2%), and 3 (5.2%) patients in the small IT, large IT, and non-IT EGC groups, respectively. No significant difference was found among the 3 groups in the rate of perforation. There were no treatment-related deaths.

ESD clinical outcomes

Noncurative resection was observed in 29, 46, and 36 patients in the small IT, large IT, and non-IT EGC groups, respectively. Treatment of patients with noncurative resection by surgery or endoscopic treatment was selected on an empirical basis. Surgery after noncurative ESD was recommended for patients with non-IT EGC, massive submucosal cancer, tumor-involved vertical margins, or the presence of lymphovascular invasion. Salvage operations were performed in 6, 10, and 23 patients in the noncurative small IT, large IT, and non-IT EGC groups, respectively. Of the operated cases, 12 (30.7%) had residual cancer cells in surgical specimens, and 3 (7.6%, 1 large IT and 2 non-IT EGC cases) had lymph node metastasis. Endoscopic treatments, such as APC and repeat ESD, were performed in the remaining 72 cases, including those who refused surgery or were precluded from surgery because of advanced age, serious comorbidity, or poor general condition.

Table 5 summarizes the number of patients who were evaluated and assessed for local recurrence and metastatic disease at 3 and 5 years from each group and the proportion found to have local recurrence and metastatic disease at those time points. Although the large IT EGC group showed a higher incidence of local tumor recurrence tumor at 3 years (6.7%) than the small IT and non-IT EGC groups (1.5% and 0%, respectively), the difference was not statistically significant. However, a significant difference was found in the local recurrence rate between the curative (0.6%, 2 patients) and noncurative resection groups (5.8%, 6 patients; P = .001). Tumor recurrence occurred within 24 months after ESD, and 4 patients underwent gastrectomy for D2 lymph node dissection. No lymph node metastases were observed in their recurrent tumors. The other 4 patients underwent repeat ESD or ablation therapy with APC. No other patients had metastases to either the lymph nodes or distant organs such as the liver and lung during the study period. Metachronous gastric cancers that were not local recurrences developed in 4 patients with curative resection after ESD, with a median follow-up period of 13.5 months (range 12-17 months). There were no gastric cancer–related deaths; however, 6 patients died of other causes: 2 cerebrovascular accidents, 2 pancreatic cancers, 1 aortic aneurysm rupture, and 1 lung cancer.

TABLE 2. Comparison of therapeutic efficacies in small intestinal-type, large intestinal-type, and nonintestinal-type early gastric cancer groups

	Small IT EGC group, no. (%) (n = 257)	Large IT EGC group, no. (%) (n = 172)	Non-IT EGC group, no. (%) (n = 58)
En bloc resection	234 (91.1)	146 (84.9)	48 (82.8)
Curative resection	228 (88.7)*	126 (73.3)†	22 (37.9)
Free lateral margins	236 (91.8)*	134 (77.9)	42 (72.4)
Free vertical margins	250 (97.3)‡	162 (94.2)†	44 (75.9)

IT, Intestinal-type; *EGC*, early gastric cancer.
*$P < .05$ compared with large IT EGC group and non-IT EGC group.
†$P < .05$ compared with non-IT EGC group.
‡$P < .05$ compared with non-IT EGC group.

TABLE 3. Histologic type, tumor size, presence of ulcer, and complete resection rate with endoscopic submucosal dissection: curative-to-noncurative ratio (%)

	Intestinal type		Nonintestinal type	
Size (cm)	Ulcer (−)	Ulcer (+)	Ulcer (−)	Ulcer (+)
≤2.0	171:13 (92.9)	57:16 (78.1)*	11:6 (64.7)*	2:8 (20)†
2.1-3.0	57:7 (89.1)	29:11 (72.5)*	4:2 (66.7)*	2:8 (20)†
>3.0	31:23 (57.4)†	9:5 (64.3)*	2:8 (20)†	1:4 (20)†

*$P < .01$, compared with intestinal-type early gastric cancers that showed no ulceration and were less than 2 cm in diameter.
†$P < .001$ compared with intestinal-type early gastric cancers that showed no ulceration and were less than 2 cm in diameter.

DISCUSSION

ESD is accepted as the optimal therapeutic strategy for EGC, especially in Korea and Japan, because it preserves the stomach and maintains the quality of life. There has been an increasing number of reports regarding the potential expansion of the indications for EGC. However, the technical feasibility of ESD for EGCs, which were not suitable for EMR based on traditional indications for EMR, has not been fully evaluated. This study indicated that it was technically difficult to curatively remove EGCs that were larger than 3 cm, ulcerative lesions, or DT lesions.

Controversy remains regarding whether EGC size has a significant impact on ESD outcomes. Isomoto et al[15] reported that tumor size had no significant impact on curative resection. However, our study revealed that lesions larger than 3 cm represented an independent factor for noncurative resection. Similarly, Imagawa et al[16] reported that the rate of curative resection differed significantly depending on the size of the lesion (>2 cm vs ≤2 cm, 59% vs 89%; $P < .0001$). Moreover, invasion depth was well correlated with tumor size (P for trend < .001) in our study. From a technical perspective, a large lesion has a larger vascular network than smaller lesions, which increases the possibility of bleeding during ESD and, thus, an interrupted procedure. Actually, tumor size has been significantly associated with piecemeal resection, which yields much lower curative resection rates than en bloc resection.[15,17] In addition, a significant correlation has been found between tumors larger than 3 cm and an increased risk of lymph node metastases.[5] Given the above-mentioned results, EGC size seems to have a significant impact on ESD outcomes.

Our results also demonstrate that the presence of ulceration interfered with curative resection; similar findings have been reported in previous studies.[18-20] Submucosal dissection is technically challenging during an ESD procedure, and it is likely that ulcerative lesions were more difficult to dissect, which precluded curative resection.

The histologic type, based on Lauren's classification, had significant impact on curative resection. In this study, the rates of curative resection were significantly lower in non-IT EGCs than in IT EGCs. The rate of SM invasion 500 μm or more increased from IT to MT to DT. Two non-IT EGC patients of 3 EGCs with a salvage operation had lymph node metastasis despite negative findings on both EUS and CT. The cases of lymph node metastasis suggest that non-IT EGC can present a difficult challenge to therapeutic success as well as technical feasibility.

Accuracy for nodal staging is greater with EUS than CT.[21,22] The accuracy of EUS for gastric cancer ranges from 50% to 90% for nodal staging.[22,23] The major drawback of EUS is high operator dependency. Currently, no satisfactory radiologic methods exist to recognize lymph node metastases. Thus, ESD may be suitable for larger lesions (>3 cm), ulcerative lesions, or non-IT EGCs from the viewpoint of ESD with diagnostic intent. How-

TABLE 4. Association of clinicopathologic characteristics of the 487 early gastric cancer lesions with curative resection from endoscopic submucosal dissection

Factors	Univariate analysis, OR (95% CI)	*P* value	Multivariate analysis, OR (95% CI)	*P* value
Age	1.00 (0.98–1.02)	.48		
Sex				
Male	1 (reference)			
Female	1.30 (0.83–2.06)	.24		
Tumor size, cm				
<2.0	1			
2.1-3.0	0.586 (0.344–0.999)	.050	0.743 (0.400–1.379)	.346
>3.0	0.192 (0.112–0.329)	<.001	0.179 (0.096–0.335)	<.001
Tumor location				
Upper	1 (reference)			
Middle	1.645 (0.836–3.234)	.14	1.412 (0.622–3.206)	.409
Lower	3.705 (1.931–7.110)	<.001	2.075 (0.940–4.579)	.071
Macroscopic appearance				
Elevated	1 (reference)			
Flat/depressed	0.716 (0.450-1.141)	.160		
Ulcer				
Absent	1 (reference)		1 (reference)	
Present	0.411 (0.265-0.637)	<.001	0.373 (0.219–0.634)	<.001
Histologic type				
Intestinal type	1 (reference)		1 (reference)	
Mixed	0.233 (0.096–0.569)	.001	0.278 (0.097–0.793)	.017
Diffuse	0.090 (0.042–0.189)	<.001	0.089 (0.038–0.206)	<.001
Resection type				
En bloc resection	1 (reference)		1 (reference)	
Piecemeal resection	0.17 (0.09–0.31)	<.001	0.209 (0.109–0.402)	<.001

OR, Odds ratio; *CI*, confidence interval.

ever, ESD requires a high level of expertise and experience. Moreover, considerable variation may occur in accurate pathologic staging after ESD between high- and low-volume hospitals. Adequate strategies for additional treatment after noncurative ESD are also not well established.

Interestingly, ESD was performed in particular groups, such as large non-IT and ulcerated non-IT EGCs, because of failure to accurately predict the histology and tumor size by using pre-ESD diagnostic modalities. In this study, there were histologic discrepancies between endoscopic biopsy specimens and ESD resected specimens in more than one third of non-IT EGC cases. The resected specimens showed a larger size than expected based on the initial endoscopic findings despite chromoendoscopy. This suggests that pre-ESD diagnostic modalities may lead to unnecessary ESD, particularly in patients with non-IT EGC.

In conclusion, ESD with curative intent is technically the most feasible option for nonulcerative and IT EGCs less than 3 cm. However, our study was limited to a single center, which potentially limits the generalizability of our results. Further studies are needed to validate expanded indications for ESD in patients with EGCs.

TABLE 5. Comparison of local recurrence and metastatic disease at 3 and 5 years after endoscopic submucosal dissection in the small intestinal-type, large intestinal-type, and nonintestinal-type early gastric cancer groups

	Small IT n/N	Large IT n/N	Non-IT n/N
3 y after ESD	131/142	90/99	15/16
Local recurrence	2 (1.5%)	6 (6.7%)	0
Metastatic disease	0	0	0
5 y after ESD	20/22	9/9	2/2
Local recurrence	0	0	0
Metastatic disease	0	0	0

IT, Intestinal-type; *n*, number of patients evaluated; *N*, number of patients assessable; *ESD*, endoscopic submucosal dissection.

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