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

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

Established gastric cancer treatment guidelines (1) indicate that “the standard operation for advanced gastric cancer is gastrectomy with D2 lymph node dissection” and that “advanced gastric cancer involving the upper third portion is recommended for treatment by total gastrectomy including splenectomy for dissection of lymph nodes located at the splenic hilus”. Pancreaticosplenectomy with lymph node dissection at the splenic hilus and around the splenic artery for advanced gastric cancer has often been performed. However, pancreaticosplenectomy is not recommended for gastric cancer

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patients without direct invasion of the pancreas because this procedure does not increase their survival rate (2, 3). Furthermore, it was reported that splenectomy may increase postoperative morbidity (3, 4). Therefore, gastrectomy with spleen preservation was indicated as a potential less-invasive operation for patients without lymph node metastasis to the splenic hilus. Currently, gastrectomy with spleen preservation for early gastric cancer is a common procedure, and a randomized prospective controlled trial for proximal gastric cancer designed by the Japan Clinical Oncology Group 0110 (JCOG 0110) (5), which will reveal the clinical significance of splenectomy in patients with advanced tumors without lymph node metastasis to the splenic hilus or along the splenic artery, is underway. Currently, however, the indications for splenectomy in proximal gastric cancer remain controversial.

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

Patients and Methods

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

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

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

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

Results

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

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

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

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

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

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

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

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

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

CI, Confidence interval.

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

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

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

splenectomy were 84% and 84% in stage I, 57% and 60% in stage II, 28% and 52% in stage III, and 18% and 7% in stage IV, respectively. No significant differences were observed between the two groups.

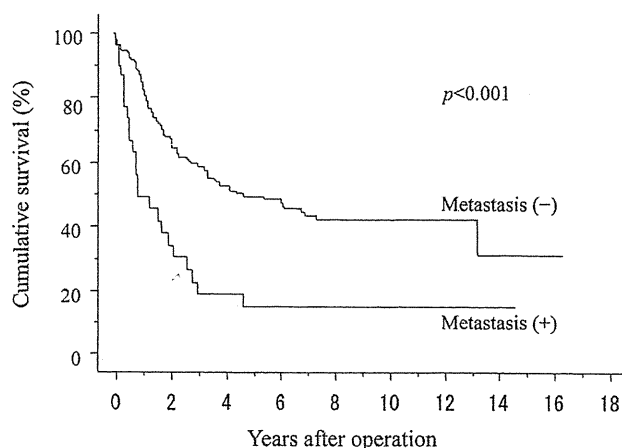


Figure 1. Survival curves of patients who underwent total gastrectomy and splenectomy with or without lymph node metastasis to the splenic hilus.

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

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

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

Discussion

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

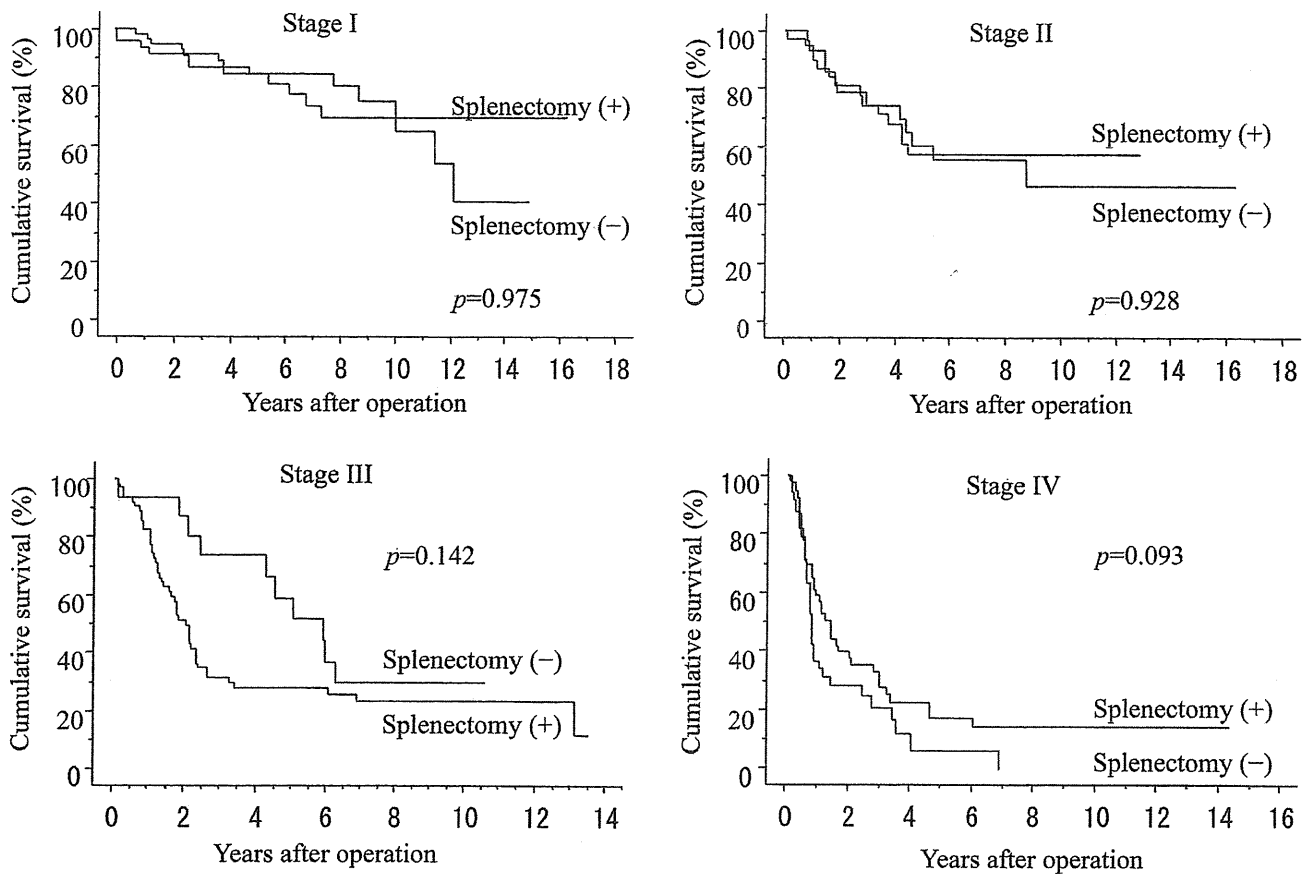


Figure 2. Survival curves of patients who underwent total gastrectomy with or without splenectomy in each stage.

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

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

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

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

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Risk of perforation during endoscopic submucosal dissection using latest insulation-tipped diathermic knife (IT knife-2)

Endoscopic submucosal dissection (ESD) enables en bloc resection of lesions regardless of tumor size or location. The insulation-tipped (IT) diathermic knife (Olympus Medical Systems Corp., Tokyo, Japan) is a proven endoscopic device for ESD [1,2]. ESD gastric perforations using the IT knife usually happen during submucosal dissection [3]. However, we present an ESD perforation case that occurred when an IT knife-2, an improved version of the IT knife [4], was being used for circumferential mucosal incision.

A 59-year-old man presented a superficial depressed-type 20-mm lesion (● Fig. 1), histologically diagnosed as a well-differentiated adenocarcinoma. Under sedation and following submucosal injection of normal saline solution, an initial incision was performed using a needle knife (Olympus Medical Systems Corp.). After the tip of the IT knife-2 had been inserted into the initial incision (● Fig. 2a), an unexpected perforation occurred during the circumferential mucosal incision (● Fig. 2b, ● Video 1). The resection was discontinued and the perforation was successfully closed using endoscopic clips (● Fig. 3).

A recent study evaluated the use of the IT knife-2 over the original IT knife, reporting a significantly shorter operating time with no significant changes in the en bloc resection and complication rates [4]. The addition of a three-pronged blade directly beneath the insulation tip of the IT knife-2 seems to be the reason for an increased cutting ability from a vertical view, an enhanced lateral cutting capability, and a greater facility to hook the tissue edge prior to cutting (● Fig. 4a and b). However, it is our belief that the perforation reported here would not have occurred if the original IT knife had been used at the time. Therefore, more gentle manipulation than that required with the original IT knife should be adopted during circumferential mucosal incision, especially by endoscopists who are inexperienced in the use of this recently developed device.

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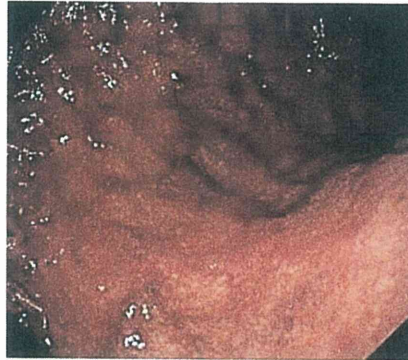


Fig. 1 Endoscopic finding of early gastric cancer. A superficial depressed lesion located in the posterior wall of the lower gastric body was revealed by conventional endoscopy.

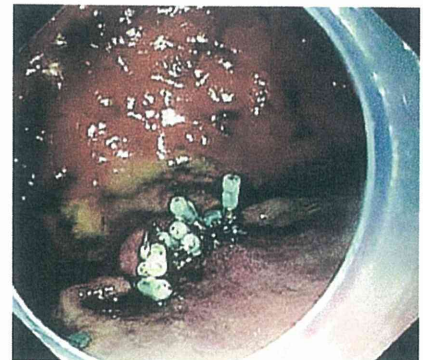


Fig. 3 Closure of the perforation was successfully performed using endoscopic clips.



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

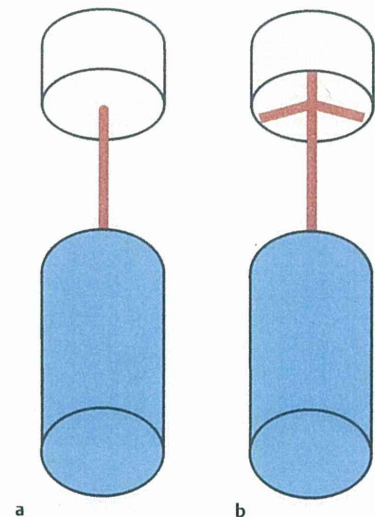


Fig. 4 The difference between the original IT knife and the IT knife-2. **a** There is no blade underneath the insulation tip of the original IT knife. **b** The IT knife-2 has a three-pronged blade directly beneath the insulation tip.

Video 1

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

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Mixed-histologic-type submucosal invasive gastric cancer as a risk factor for lymph node metastasis: feasibility of endoscopic submucosal dissection

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Background and study aims: The clinicopathologic features of gastric cancers containing a mixture of differentiated-type and undifferentiated-type components remain uninvestigated. We evaluated the risk of lymph node metastasis and the feasibility of endoscopic submucosal dissection (ESD) for the treatment of mixed-histologic-type gastric cancers.

Patient and methods: We histologically classified 376 cases of gastric cancer with submucosal invasion into four types (differentiated type, differentiated-type-predominant mixed type, undifferentiated-type-predominant mixed type, and undifferentiated type) and studied the clinicopathologic relations of each type to lymph node metastasis. Lymphatic invasion was evaluated by D2–40 immunostaining.

Results: The overall prevalence of lymph node metastasis in gastric cancer with submucosal invasion was 16.5% (62/376). The prevalence of lymph node metastasis was 36.5% (23/63) in undifferentiated-type-predominant mixed type, which was significantly higher than those in the

other three types ($P < 0.001$ vs. differentiated type, $P = 0.013$ vs. differentiated-type-predominant mixed type, and $P = 0.003$ vs. undifferentiated type). Lymphatic invasion, a depth of invasion of 500 μm or more from the lower margin of the muscularis mucosae (SM2), tumor size above 30 mm, and undifferentiated-type-predominant mixed histologic type were independent risk factors for lymph node metastasis. Submucosal cancers without these four risk factors were free of lymph node metastasis (0/41; 95% confidence interval 0%–8.6%).

Conclusions: Undifferentiated-type-predominant mixed-type gastric cancer with submucosal invasion carries a high risk of lymph node metastasis. ESD can be indicated for gastric cancer with submucosal invasion provided that the following conditions indicating a low risk of metastasis are met: a depth of invasion of no more than 500 μm or more from the lower margin of the muscularis mucosae (SM1), no lymphatic invasion, a tumor size of no more than 30 mm, and a proportion of undifferentiated components below 50%.

Introduction

Early gastric cancer is defined as a carcinoma that is confined to the mucosa or submucosa (depth of invasion from the lower margin of the muscularis mucosae $< 500 \mu\text{m}$, SM1; depth of invasion from the lower margin of the muscularis mucosae $\geq 500 \mu\text{m}$, SM2), irrespective of the presence or absence of lymph node metastasis [1]. Pathologically, gastric cancer can be broadly divided into two types according to the presence or absence of tubular structures: these are the differentiated type and the undifferentiated type [1]. Characteristically, undifferentiated gastric cancer carries a higher risk of lymph node metastasis than does differentiated gastric cancer [2–5]. However, in some cases gastric cancer includes a mixture of differentiated and undifferentiated components.

Gastric cancers that include a mixture of differentiated and undifferentiated components are classified according to the predominant histologic type by the Japanese Classification of Gastric Carcinoma [1].

Many studies have examined lymph node metastasis in early gastric cancer. The incidence of lymph node metastasis in intramucosal gastric cancer is estimated to be 2% [2,3,6,7]. Lymph node metastasis is present in about 20% of all cases of gastric cancer with submucosal invasion [4,5,8–10]. Cancer with SM2 invasion, undifferentiated-type cancer, and lymphatic invasion are independent risk factors for lymph node metastasis [2,4,5]. However, the advent of new devices such as insulation-tipped knives, the development of techniques for endoscopic submucosal dissection (ESD) [11], and a better understanding

of the characteristics of lesions with an extremely low risk of lymph node metastasis have provided technical and theoretical bases for the en bloc resection of lesions larger than those resectable by conventional endoscopic mucosal resection (EMR) [2, 4, 12–15]. ESD is now indicated for the treatment of differentiated-type early gastric cancers with SM1 invasion that are 30 mm or less in diameter [2, 4]. The indications for endoscopic resection are now gradually being extended to submucosal invasive gastric cancers that previously required surgical resection. To our knowledge, however, no previous study has evaluated the clinicopathologic features, prevalence of lymph node metastasis, lymphatic invasion, and ulceration of early gastric cancer containing both differentiated-type and undifferentiated-type components. Indications for the endoscopic treatment of mixed-histologic-type early gastric cancers have also not been evaluated.

Materials and methods

The study group comprised 376 patients with primary gastric cancer invading the submucosa (99 patients with SM1 invasion and 277 with SM2 invasion) who underwent surgical resection and a D2 lymphadenectomy according to the Japanese Classification of Gastric Carcinoma at Kitasato University East Hospital from 1995 through 2006. All lesions were thinly sliced at intervals of 3 to 5 mm. One section each of all dissected lymph nodes (at least 15 nodes per case) was stained with hematoxylin and eosin. The cut sections were examined histologically to assess the presence or absence of metastasis. To assess histologic type, all specimens were reviewed to determine the percentages of differentiated-type components (well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma) and undifferentiated-type components (poorly differentiated adenocarcinoma and signet-ring cell carcinoma) [1]. The lesions were classified into the following four categories according to the proportions of intramucosal undifferentiated-type components: differentiated type (A), differentiated-type-predominant mixed type (B), undifferentiated-type-predominant mixed type (C), and undifferentiated type (D). The percentages of undifferentiated-type components were 0% in A, more than 0% but less than 50% in B, 50% or more but less than 100% in C, and 100% in D. A representative case of mixed-type gastric cancer is shown in **Fig. 1**.

The patterns of submucosal invasion were classified into four types (**Fig. 2**).

The horizontal length of submucosal invasion was measured histologically on the sections with greatest invasion (**Fig. 3**).

The number of lymphatic invasion sites and the number of lymphatic invasion sites per millimeter of submucosal invasion were calculated. Data on patient sex and age and tumor location, macroscopic type, and size were collected from the patients' medical records and pathology reports.

Immunohistochemistry

Lymphatic invasion by cancer cells was identified immunohistochemically using D2–40 antibody (DakoCytomation, Glostrup, Denmark) and an EnVision+ kit (DakoCytomation). One representative slide including the site of deepest invasion was selected for each case. Sections 4 μ m thick were cut from the formalin-fixed, paraffin-embedded tissue. The sections were mounted on coated slides and deparaffinized in xylene. Nonspecific reactions were blocked with 0.3% hydrogen peroxide in methanol for 15

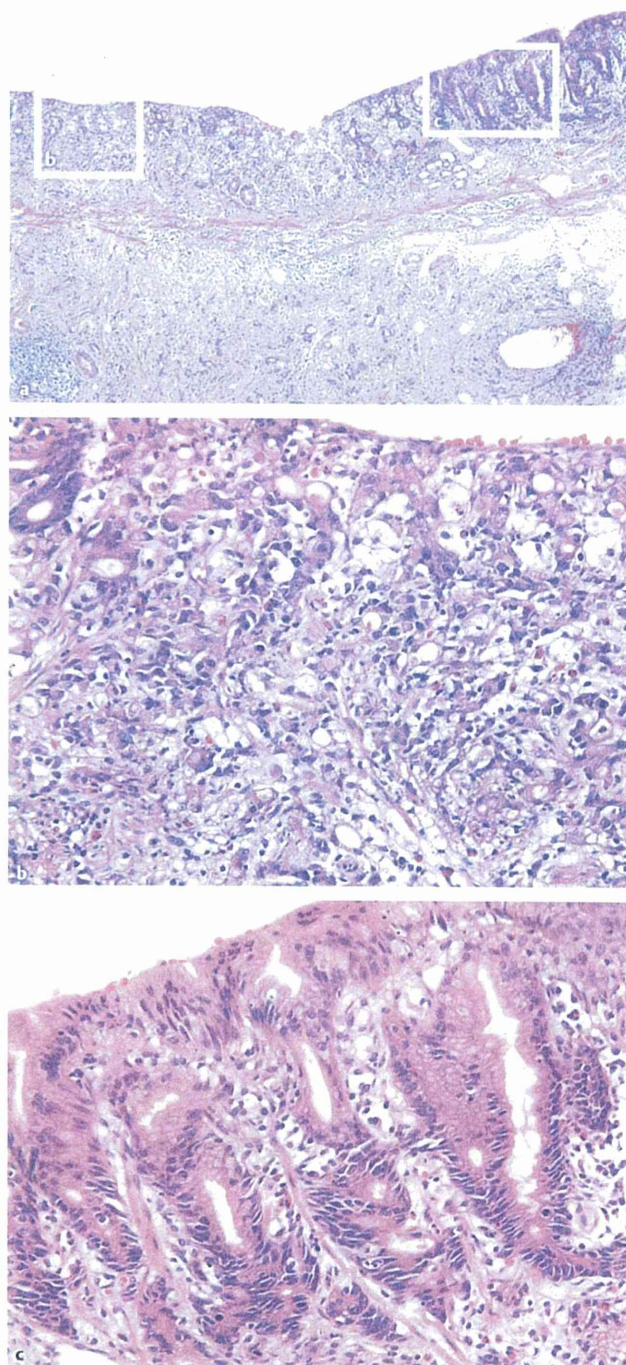


Fig. 1 Representative case of mixed-type (differentiated and undifferentiated) gastric carcinoma. **a** In the lamina propria, the right half of the tumor consists of the differentiated type and the left half of the undifferentiated type. The submucosal invasion consists of the undifferentiated type. **b** Box b in **a**, at higher magnification. **c** Box c in **a**, at higher magnification.

minutes and the blocking solution of the EnVision+ kit. Then, the sections were incubated with the D2–40 antibody at a 1:50 dilution in phosphate-buffered saline for 1 hour at room temperature. After incubation, staining was performed according to the manufacturer's instructions. 3-3'-Diaminobenzidine was used as the final chromogen, and nuclei were counterstained

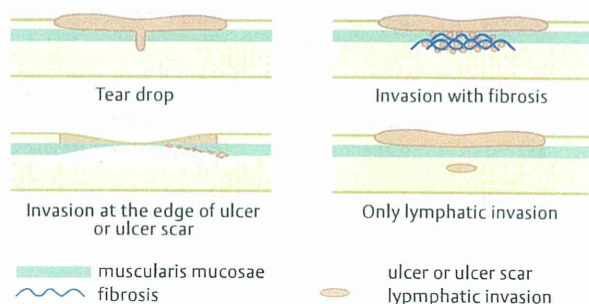


Fig. 2 Patterns of submucosal invasion.

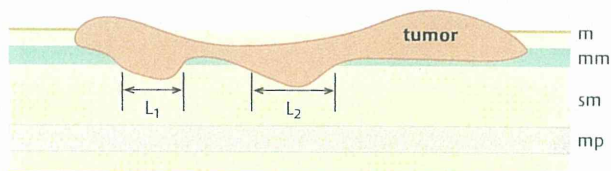


Fig. 3 Definition of horizontal length of submucosal invasion. $L = L_1 + L_2 + \dots + L_n$, horizontal length of submucosal invasion; m, mucosa; mm, muscularis mucosae; sm, submucosa; mp, muscularis propria.

with Mayer's hematoxylin to facilitate histopathologic assessment. Two pathologists (N.H. and T.M.) checked the slides to identify and count the number of lymphatic invasion sites, which appeared as cancer cell nests surrounded by D2-40-positive lymphatic endothelium (● Fig. 4).

Ethical approval

This work using pathological samples in Kitasato University East Hospital (with the informed consent of patients) was approved by our Medical School and University Ethics Committee.

Statistical analysis

To assess differences in tumor size and horizontal length of submucosal invasion among the four histologic groups (A, B, C, D), the Kruskal–Wallis test was used, followed by evaluation with the Mann–Whitney *U* test for multiple comparisons. Resulting *P* values were corrected according to the Bonferroni method. The χ^2 test was used to compare other clinicopathologic features. Multivariate logistic-regression analysis was performed with SPSS (version 11.0 in 2001; SPSS, Chicago, Illinois, USA). *P* values of less than 0.05 were considered to indicate statistical significance.

Results

The prevalence of lymph node metastasis was 16.5% (62/376) overall, 4.0% (4/99) in patients with SM1 invasion, and 20.9% (58/277) in those with SM2 invasion. Univariate analysis demonstrated that tumor size (> 30 mm), lymphatic invasion, histologic type, depth of invasion (SM2), and histologic type of the invasion front (undifferentiated type) differed significantly between patients with and those without lymph node metastasis (● Table 1).

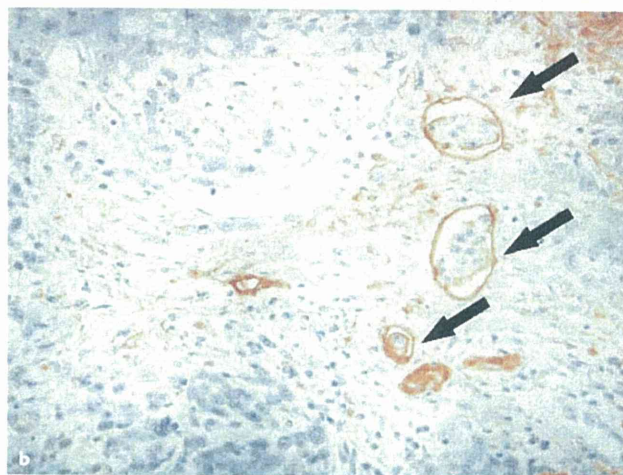
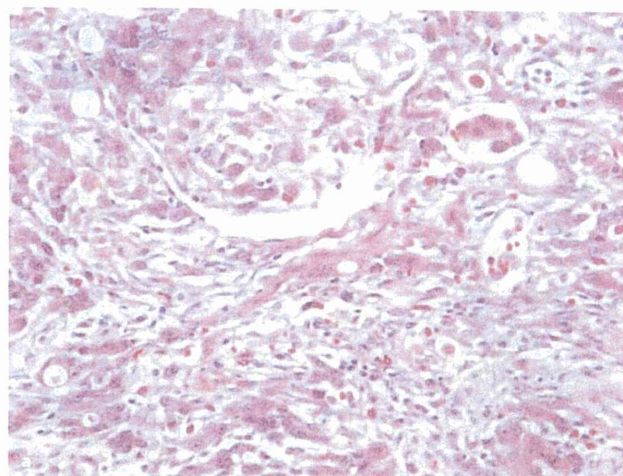


Fig. 4 a Submucosal invasion front of an undifferentiated-type gastric carcinoma. b Lymphatic invasion of cancer cells after D2-40 immunostaining. Cancer cells can be easily identified in lymphatic vessels (arrows).

Multivariate analysis of these risk factors indicated that lymphatic invasion, depth of invasion (SM2), tumor size (> 30 mm), and histologic type (C, undifferentiated-type-predominant mixed type) were independent risk factors for lymph node metastasis (● Table 2).

Relation between histologic type and lymph node metastasis

The prevalence of lymph node metastasis was 5.4% (7/129) in differentiated type (A), 19.2% (20/104) in differentiated-type-predominant mixed type (B), 36.5% (23/63) in undifferentiated-type-predominant mixed type (C), and 15.0% (12/80) in undifferentiated type (D). The prevalence of lymph node metastasis was highest in undifferentiated-type-predominant mixed type (C) ($P < 0.001$ vs. A, $P = 0.019$ vs. B, and $P = 0.0029$ vs. D) (● Table 3).

Submucosal cancers with a depth of invasion of SM1, no lymphatic invasion, a tumor size equal to or less than 30 mm, and consisting of less than 50% of undifferentiated components were free of lymph node metastasis (0/41; 95% confidence interval 0%–8.6%).

	n	Lymph node metastasis, n (%)		p-value
		Present	Absent	
Sex				
Male	271	39 (14.4)	232	0.078
Female	105	23 (21.9)	82	0.284
Age				
< 60	229	34 (14.8)	195	
≥ 60	147	28 (19.0)	119	
Location				0.171
Upper third	217	32 (14.7)	185	
Middle third	56	9 (16.1)	47	
Lower third	103	21 (20.4)	82	
Macroscopic type				0.758
Elevated	72	11 (15.3)	61	
Depressed	304	51 (16.8)	253	
Tumor size				< 0.001
≤ 30 mm	193	18 (9.3)	175	
> 30 mm	183	44 (24.0)	139	
Pattern of submucosal invasion*				0.473
1	3	0 (0.0)	3	
2	347	58 (16.7)	289	
3	24	3 (12.5)	21	
4	2	1 (50.0)	1	
Histologic type †				< 0.001
A	129	7 (5.4)	122	
B	104	20 (19.2)	84	
C	63	23 (36.5)	40	
D	80	12 (15.0)	68	
Lymphatic invasion				< 0.001
Yes	131	45 (34.4)	86	
No	245	17 (6.9)	228	
Histologic type of invasion front				< 0.001
Differentiated	183	17 (9.3)	166	
Undifferentiated	193	45 (23.3)	148	
Depth of invasion ‡				< 0.001
SM1	99	4 (4.0)	95	
SM2	277	58 (20.9)	219	

* 1, teardrop type; 2, invasion with fibrosis; 3, invasion at the edge of ulcer or ulcer scar; 4, only lymphatic invasion.

† A, differentiated type; B, differentiated-type-predominant mixed type; C, undifferentiated-type-predominant mixed type; D, undifferentiated type.

‡ SM1, depth of invasion from the muscularis mucosae < 500 μm; SM2, depth of invasion from the muscularis mucosae ≥ 500 μm.

Table 1 Relations between clinicopathologic factors and regional lymph node metastases in 376 cases of gastric cancer with submucosal invasion: results of univariate analysis.

Clinicopathologic feature	Relative risk (95% CI)	SE	P value
Lymphatic invasion (presence vs. absence)	5.28 (2.73–10.22)	0.337	< 0.001
Depth of invasion (SM2 vs. SM1)	3.41 (1.14–10.23)	0.560	0.029
Tumor size (> 30 vs. ≤ 30 mm)	2.58 (1.35–4.91)	0.329	0.004
Histologic type (C vs. non-C)	2.35 (1.12–4.96)	0.380	0.024

CI, confidence interval; SE, standard error.

Table 2 Risk factors for regional lymph node metastasis in 376 cases of gastric cancer with submucosal invasion: results of multivariate analysis.

Relations of histologic type and tumor size to lymphatic invasion

The prevalence of lymphatic invasion was highest in undifferentiated-type-predominant mixed type (C) ($P < 0.001$ vs. A, $P = 0.02$ vs. B, and $P = 0.03$ vs. D). Tumor size (47.2 ± 34.5 mm) and the width of submucosal invasion (8.6 ± 7.4 mm) were greatest in undifferentiated-type-predominant mixed type (C) and differed significantly from the respective values in differentiated type (A, 31.5 ± 20.5 , $P = 0.018$; 4.7 ± 5.1 ; $P < 0.001$) (Table 3). The number of lymphatic invasion sites per millimeter of submucosal invasion did not differ significantly among the histologic types. However, the presence of one or more lymphatic invasion sites per millimeter of submucosal invasion was associated with a higher prevalence of lymph node metastasis ($P = 0.030$) (Table 4).

Discussion

In the present study, we histologically classified early gastric cancers according to the percentage of undifferentiated components and found that the prevalence of lymph node metastasis was higher with the undifferentiated-type-predominant mixed type (C) than with the other histologic types. We also found that lymphatic invasion, SM2 invasion, tumor size, and undifferentiated-type-predominant mixed type were independent risk factors for lymph node metastasis in patients who had gastric cancer with submucosal invasion.

Previous clinicopathologic studies of gastric cancer, head and neck cancer, and breast cancer have demonstrated that lymphatic invasion is an extremely important risk factor for lymph node metastasis [16–18]. The advent of D2–40 immunostaining has

Table 3 Relations of histologic type and size of tumor to lymphatic invasion in 376 cases of gastric cancer.

Tumor type	Presence of lymph node metastasis, n (%)	Presence of lymphatic invasion, n (%)	Tumor size, mm, mean \pm SD	Horizontal length of submucosal invasion, mm, mean \pm SD	Number of lymphatic invasion sites, /mm, mean \pm SD
A (n = 129)	7 (5.4)	24 (18.6)	31.5 \pm 20.5	4.7 \pm 5.1	0.50 \pm 0.48
B (n = 104)	20 (19.2)	40 (38.5)	39.5 \pm 25.9	6.0 \pm 5.5	1.1 \pm 2.3
C (n = 63)	23 (36.5 [*])	36 (57.1 ^{**})	47.2 [†] \pm 34.5	8.6 [‡] \pm 7.4	1.2 \pm 2.7
D (n = 80)	12 (15.0)	31 (38.8)	37.0 \pm 22.2	6.7 \pm 6.1	0.46 \pm 0.69

P values were determined using the Mann-Whitney U test with Bonferroni correction.

^{*}P < 0.001 vs. A, P = 0.013 vs. B, P = 0.003 vs. D (χ^2 test).

^{**}P < 0.001 vs. A, P = 0.019 vs. B, P = 0.029 vs. D (χ^2 test).

[†]P = 0.018 vs. A.

[‡]P < 0.001 vs. A.

	n	Lymph node metastasis		P value
		Present	Absent	
Number of lymphatic invasion sites \geq 1	24	13 (54.1 [*])	11	< 0.001
Number of lymphatic invasion sites < 1	107	33 (30.8)	74	
Cases without lymphatic invasion	245	16 (6.9)	229	

^{*}P = 0.030 vs. number of lymphatic invasion sites < 1.

Table 4 Relation between lymph node metastasis and number of lymphatic invasion sites per millimeter of horizontal length of submucosal invasion in 376 cases of gastric cancer.

facilitated the identification of lymph vessels, and many studies have reported that immunostaining is useful for the evaluation of gastric cancer [19–23]. We therefore clinicopathologically studied the relationship of the histologic type of gastric cancer to lymph node metastasis from the viewpoints of lymphatic invasion and histogenesis.

Undifferentiated-type-predominant mixed type (C) had the highest prevalence of lymphatic invasion. The presence of lymphatic invasion was characterized by a high prevalence of lymph node metastasis. In this study, the existence of one or more lymphatic invasion sites per millimeter of submucosal invasion was associated with an increased prevalence of lymph node metastasis. The higher prevalence of lymph node metastasis in undifferentiated-type-predominant mixed type (C) than in the other groups was attributed to the significant differences in the presence of lymphatic invasion among these groups.

The fact that the highest prevalence of lymphatic invasion is seen in undifferentiated-type-predominant mixed type (C) gastric cancer might be related to the size of the tumor and the horizontal length of the submucosal invasion, which were larger in this group than in the others. Lymph vessels are densely present from the muscularis mucosae to the upper layer of the submucosa [19]. With tumor-cell proliferation and extension to the muscularis mucosae and submucosa, the incidence of lymphatic invasion increases.

Gastric cancer generally shows greater histologic diversity than other types of cancer. Even tumors confined to the mucosa show histologic diversity, which tends to increase with deeper invasion and increased tumor diameter [24,25]. This notion is supported by the findings of Inoshita et al., who studied histologic diversity in gastric cancer. In elderly patients, they found that the differentiated type predominates in early gastric cancer, but that histologic diversity increases with progression to advanced cancer, resulting in higher proportions of undifferentiated type [26]. Peng and Honda et al. reported that undifferentiated-type gastric cancer with tubular components (C: undifferentiated-type-predominant mixed type) and undifferentiated-type gastric cancer (D) arise from different genetic pathways. They proposed that mixed-type gastric cancer can arise from either differentiated

cells or undifferentiated cells [27,28]. Studies of mucin phenotype have reported that some cases of differentiated-type gastric cancer with gastric phenotype are transformed into undifferentiated-type gastric cancer during tumor growth and development, increasing the risk of lymph node metastasis [29–34]. However, further studies are needed to delineate the relation between histogenesis and the risk of metastasis.

At present, the indications for endoscopic resection include the treatment of submucosal cancers that meet the following four conditions: a tumor size of 30 mm or less, SM1 invasion, differentiated type, and no lymphatic invasion [2,4]. In our study, lymph node metastasis was not associated with submucosal cancers that met all of the following criteria: SM1 invasion, no lymphatic invasion, a tumor size of 30 mm or less, and less than 50% undifferentiated-type components (0/41; 95% confidence interval, 0% to 8.6%). Such cancers can be curatively treated by local endoscopic resection.

Gastric cancer is associated with underlying conditions such as acid-induced changes and chronic gastritis caused by persistent *Helicobacter pylori* infection. Disease progression is often accompanied by the formation of an ulcer or ulcer scar. It is challenging to predict preoperatively the percentage of undifferentiated components and to accurately diagnose the depth of tumor invasion on the basis of the fine surface characteristics of gastric cancers. In particular, the accuracy of endoscopic ultrasonography for predicting whether a tumor is confined to the mucosa or invades the submucosa is only about 80% [35]. Submucosal tumor invasion is frequently discovered on histopathologic examination after endoscopic resection. If an early gastric cancer is found to have SM1 invasion on histopathologic examination after endoscopic resection, the presence of a tumor that is 30 mm or greater in size, lymphatic invasion, or a 50% or higher percentage of undifferentiated components suggests an increased risk of lymph node metastasis. Additional surgical resection with lymph node dissection should therefore be considered.

Undifferentiated early gastric cancer has a high risk of lymph node metastasis [2–5]. To date, surgical resection has been the treatment of choice, but the feasibility of endoscopic resection is now being considered. Park et al. reported that endoscopic resec-

tion can be indicated for undifferentiated-type cancers that are 15 mm or less in diameter and have a submucosal invasion depth of up to 500 µm because these characteristics are associated with a low risk of lymph node metastasis [36]. In their study, however, histologic types and lymphatic invasion were not adequately evaluated. In our study, the incidence of lymph node metastasis was higher in undifferentiated-type-predominant mixed type (C) than in pure undifferentiated type (D) gastric cancer. Endoscopic resection should therefore not be conducted in patients with undifferentiated-type gastric cancer without detailed histopathologic studies, including assessments of histologic diversity and lymphatic invasion.

We believe that confirmation of lymphatic invasion by means of D2–40 immunostaining may lead to more accurate identification of cases at high risk of lymph node metastasis.

We conclude that histologically mixed-type gastric cancer with submucosal invasion can be considered for endoscopic resection provided that the following four conditions indicating a low risk of metastasis are met: a lower than 50% proportion of undifferentiated components, a tumor size of 30 mm or less, SM1 invasion, and no lymphatic invasion. Given the limited number of cases in this study, these findings should be confirmed by more data in the future.

Acknowledgment

We are indebted to the members of the Department of Pathology, Kitasato University East Hospital, for their excellent technical assistance.

Competing interests: None

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Prospective clinical trial of magnetic-anchor-guided endoscopic submucosal dissection for large early gastric cancer (with videos)

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Background: The treatment of early gastric cancer (EGC) by endoscopic submucosal dissection (ESD) has been rapidly gaining popularity in Japan. However, the procedure needs a high quality of skill. To facilitate complicated ESD by using a single working-channel gastroscope (“one-hand surgery method”), the magnetic-anchor-guided ESD (MAG-ESD) controlled by an extracorporeal electromagnet was reported to be successful in a porcine model.

Objectives: The purpose of this prospective clinical trial was to evaluate the feasibility of MAG-ESD for large EGC located on the gastric body in human beings.

Design: Prospective clinical trial at a single center.

Setting: National Cancer Center Hospital, Tokyo, Japan.

Subjects: From January 2005 to May 2006, 25 patients with EGC >20 mm in diameter, located in the gastric body, and intestinal-type histology were enrolled. Patients with a cardiac pacemaker, advanced malignancy in other organs, severe cardiac and/or pulmonary diseases, and uncontrolled hypertension and/or diabetes mellitus were excluded from this study.

Interventions: Similar to a standard ESD, the MAG-ESD procedure was performed with the patient under conscious sedation by intravenous injection of midazolam (3–5 mg) and pentazocine (15 mg).

Main Outcome Measurements: Unfavorable events and other intraoperative complications caused by the magnetic anchor or the magnetic force were recorded and evaluated. Two GI endoscopists (T.G., I.O.) assessed whether the magnetic anchor facilitated gastric ESD according to 2 criteria: “supportive” and “not supportive.” The en bloc resection rate, complications, total operation time, bleeding, perforation, and recurrence rate were also evaluated. The total operation time was measured from insertion to withdrawal of the endoscope, including the retrieving of the magnetic anchor or anchors.

Results: All tumors were resected en bloc, without any perforations or severe uncontrollable bleeding. All magnetic anchors were safely retrieved. Two endoscopists assessed that the MAG system was supportive in 23 patients. None of the patients experienced physiologic and mental abnormalities as a result of long-term magnetic-field exposure. During a median follow-up of 20 months (15–32 months), neither delayed adverse effects nor allergies caused by the stainless steel of the magnetic anchor were observed.

Conclusions: MAG-ESD is a feasible and safe method that allowed an excellent visualization by suitable tissue tension and facilitated gastric ESD in patients with EGC. The system should be miniaturized to make it applicable in daily clinical practice. (Gastrointest Endosc 2009;69:10-5.)

Abbreviations: EGC, early gastric cancer; ESD, endoscopic submucosal dissection; IT-knife, insulation-tipped diathermic knife; MAG-ESD, magnetic-anchor-guided endoscopic submucosal dissection.

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It has been reported that endoscopic submucosal dissection (ESD) of early gastric cancer (EGC) improves the rate of successful en bloc resection.^{1,2} An ESD by using an insulation-tipped diathermic knife (IT-knife), developed at the National Cancer Center Hospital, was the first of such techniques.^{3,4} Other endoscopic devices for ESD have been developed.⁵⁻⁷ ESD has been rapidly gaining popularity in Japan, primarily because of its ability to remove larger EGC en bloc, thus reducing a local recurrence caused by a piecemeal resection.⁸ However, it is still an

investigational technique and requires a high level of skill from the endoscopists.⁹⁻¹¹

Endoscopic resection should be safe, effective, and applicable to a wide variety of clinical situations. In particular, when EGC is located in the gastric body, an ESD is more complicated, and the rate of a complete resection is lower than in the gastric antrum.¹² The more difficult extension of the wall and the collection of fluid, including blood and/or gastric juice, hinder the performance of the ESD procedure. Optimal extension of the wall and visualization of the lesion is mandatory for a safe and feasible ESD.

To facilitate a complicated standard ESD procedure performed by using a single working-channel gastroscope (one-hand surgery), the magnetic-anchor-guided ESD (MAG-ESD) controlled by an extracorporeal electromagnet, was developed.¹³ We reported that MAG-ESD facilitated the ESD procedure in the porcine model. The purpose of this prospective clinical trial was to evaluate the feasibility of MAG-ESD for large EGC in human beings.

PATIENTS AND METHODS

Patients

The purpose of this prospective clinical trial was to evaluate the feasibility of MAG-ESD. Twenty-five patients with EGC >20 mm diameter, located in the gastric body, were enrolled. The patients were first seen on an outpatient basis, and the tumor was assessed by a gastroscopy. From January 2005 to May 2006, all patients with EGC >20 mm in diameter, located in the gastric body, and with intestinal-type histology underwent an ESD on an inpatient basis at the National Cancer Center Hospital, Tokyo, Japan. The ethics committee approved the study, and a detailed written informed consent was obtained from each patient. The presented study was conducted according to the Declaration of Helsinki.

The patients with a cardiac pacemaker, advanced malignancy in other organs, severe cardiac and/or pulmonary diseases, uncontrolled hypertension, and/or diabetes mellitus were excluded from this study. Pregnant or lactating women, and those who wished to become pregnant during the study were also excluded. Patients with tumors with recurrent disease, fibrosis, deeper invasion, or diffuse-type histology were excluded.

Standard ESD

The standard ESD procedure was initially started by using a standard gastroscope with a single working channel (GIF Q260 or Q240; Olympus Optical Co, Ltd, Tokyo, Japan).¹⁴ Marking dots were placed approximately 5 mm outside the margin of the lesions by using a needle-knife (KD-1L-1; Olympus) and forced coagulation current 20 W (IC C200; ERBE, Tübingen, Germany). First, injection

Capsule Summary

What is already known on this topic

- Endoscopic submucosal dissection (ESD) is useful in the en bloc removal of large gastric lesions, thus reducing the risk of a local recurrence caused by piecemeal resection.
- Magnetic-anchor-guided ESD (MAG-ESD), controlled by an extracorporeal electromagnet, facilitates the standard ESD procedure performed by using a single working-channel gastroscope.

What this study adds to our knowledge

- In 25 patients with gastric cancer lesions >20 mm in diameter who underwent magnetic-anchor-guided ESD, all tumors were resected en bloc, without any perforations or severe uncontrollable bleeding, and all magnetic anchors were safely retrieved.
- No patient experienced physiologic or mental abnormalities as a result of long-term magnetic field exposure.

of diluted epinephrine (1:100,000) was performed to raise the submucosal layer and to insert the tip of the IT-knife into the submucosal layer. Then, a small initial incision was made by a standard needle-knife by using 80 W effect 3 Endocut (ICC200; ERBE). Mucosal cutting at the periphery of the marking dots was circumferentially performed with an IT-knife (KD-610L; Olympus) with 80 W Endocut. After additional submucosal injection of diluted epinephrine, the submucosal layer below the lesion was directly dissected by using the same IT-knife. The final aim was to achieve en bloc resection.

All patients were sedated by intravenous injection of midazolam (3–5 mg) and pentazocine (15 mg), and, if necessary, conscious sedation was maintained with an additional injection of midazolam.

Magnetic anchor and extracorporeal electromagnetic control system

The magnetic anchor (Pentax Co, Tokyo, Japan) consists of 3 parts: a hand-made magnetic weight, made of magnetic stainless steel (SYS420F), microforceps, and a connecting thread. A 1.0 × 1.0 × 1.5-cm weight was designed to facilitate gastric ESD by use of an extracorporeal hands-free electromagnet, whereby magnetic forces allow a suitable counter-traction for submucosal dissection (Fig. 1). The anchor weight used for this procedure was approximately 6 g.

The magnetic control system (Fig. 2) consists of an electromagnet with up-and-down motion; a movable examination table was made by Tamakawa Co (Sendai, Japan) for use in a standard endoscopic room. The magnetic control system consisted of a 0.68 kOe/100A extracorporeal

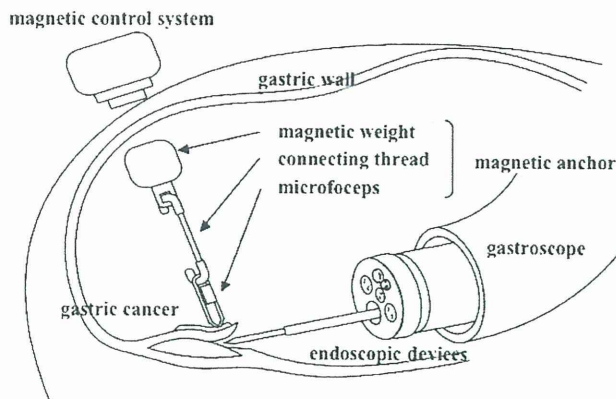


Figure 1. Concept of the MAG-ESD.

electromagnet, 350 mm in diameter, positioned at 10 cm from the center of the magnetic yoke. In this manner, the position of the electromagnet was adjusted according to the patient's physique. The examination table was able to move freely to be able to control the magnetic weight so as to achieve ideal mucosal lifting to allow the gastric submucosal dissection.

MAG-ESD

According to the standard ESD, after circumferential mucosal cutting by using an IT-knife, the procedure was switched to an MAG-ESD, controlled by a high-power electromagnet placed outside the body of the patient (Fig. 3). First, an overtube (Sumitomo Bakelite, Tokyo, Japan) was inserted into the esophagus. Second, a tube catheter was passed through the working channel of the gastroscop. A magnetic anchor, with a magnetic weight, a microforceps, and a connecting thread, was attached to the tip of the catheter. The gastroscop that carries the magnetic anchor was reinserted. Inside the stomach, the magnetic weight was pushed out from the catheter. According to the direction of gravity, the microforceps connected to the magnetic weight was placed at the mucosal edge (Video 1, available online at www.giejournal.org). The submucosal dissection by using an IT-knife was performed by suitable tissue tension with hands-free stabilization and visualization (Video 2, available online at www.giejournal.org).

If experienced endoscopists, who have performed more than 100 gastric ESDs, requested additional magnetic anchors to maneuver the traction direction of the exfoliated gastric tissue, then any numbers of magnetic anchors were attached. To maintain suitable tissue tension, either the patients were rotated or the direction of the magnetic anchor was repositioned by using the movable examination table. After endoscopic resection, both the resected tissue and the magnetic anchor or anchors were retrieved into the overtube by using a grasping forceps and were removed from the stomach.

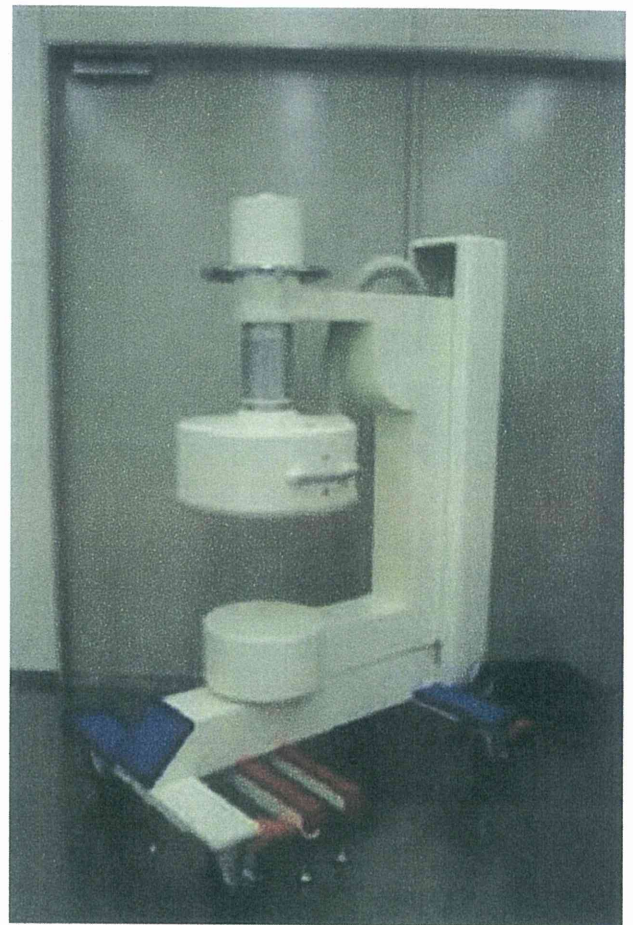


Figure 2. Extracorporeal electromagnetic control system.

Assessments

The demographic and clinical features of each patient were recorded in a case report form. Unfavorable events and other intraoperative complications caused by the magnetic anchor or the magnetic force were recorded and evaluated. We defined serious adverse events as those that lead to death, threat to life, notable disability, prolonged hospital stay, or hospitalization. Patients were followed-up until adverse events either dissipated or returned to pretreatment levels. Two GI endoscopists (T.G., I.O.) assessed, according to the 2 criteria, whether the magnetic anchor facilitated a gastric ESD. Once the dedicated endoscopists evaluated that the MAG-traction-facilitated gastric ESD compared with the standard gastric ESD technique, it was defined as "supportive." When the ESD procedure was not effectively influenced by using the MAG system, it was defined as "not supportive." The en bloc resection rate, complications, total operation time, bleeding, perforation, and recurrence rate were also evaluated. The total operation time was measured from gastroscop insertion to withdrawal, including retrieving the magnetic anchor or anchors.

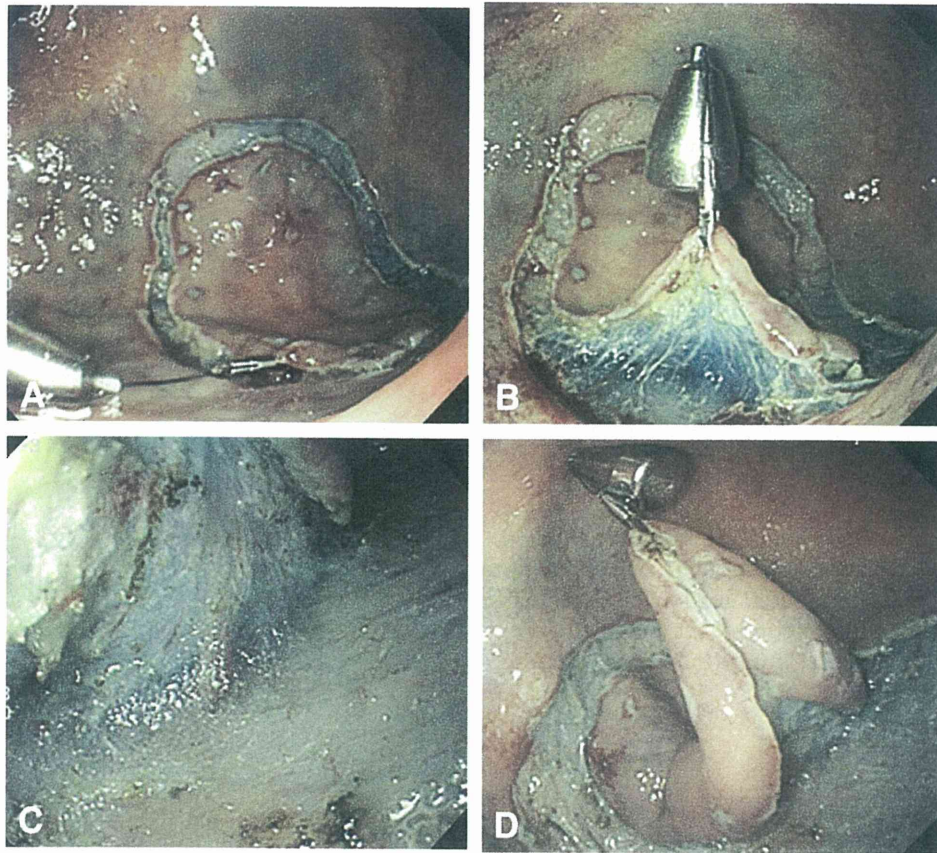


Figure 3. Magnetic-anchor-assisted ESD for large EGC. **A,** Fitting the magnetic anchor onto the tip of the gastric mucosa before applying the magnetic force. **B,** Lifting of the gastric tissue and stretched submucosal layer under strong counter-traction by the magnetic anchor. **C,** Good visualization of vessel in submucosal layer under counter-traction by magnetic force. **D,** Controllable traction by the magnetic anchor with a magnetic field.

RESULTS

The MAG-ESD technique was performed in 25 patients (M/F, 17/8; median age 70 years, range 48-85 years; median tumor size, 30 mm, range 20-70 mm).

The results of the MAG-ESDs are shown in Table 1. All tumors were resected en bloc, without any perforations or severe uncontrollable bleeding. The median size of resected specimen was 55 mm (33-125 mm). The median procedure time was 80 minutes (50-240 minutes). One resection was histologically confirmed as being noncurative because of deep submucosal invasion with positive vertical margins and lymphatic-vessel involvement. This patient underwent additional radical surgery.

One magnetic anchor was required in 21 cases, and 2 magnetic anchors were used in 4 cases. All magnetic anchors were safely retrieved. Two endoscopists assessed that the MAG system was supportive in 23 patients. In particular, the MAG system effectively facilitated an ESD for all 9 tumors located on the greater curvature of the gastric body. However, the magnetic anchor was not helpful in 2 patients. In one case, it was difficult to inflate the gastric lumen because of air leakage through the hiatus hernia.

TABLE 1. Results of 25 patients treated by MAG-ESD

En bloc resection rate	25/25 (100%)
Median resection size (mm)	55 (range 33-125)
Complications	0/25 (0%)
Median time consumption (min)	80 (range 50-240)
Exposure time for magnetic field (min)	30 (range 10-110)
Endoscopist's assessment	
Supportive	23
Not supportive	2

In another case, it was impossible to pull the gastric tissue toward the proper direction, even after changing the patient's position.

None of the patients experienced physiologic and mental abnormalities as a result of long-term magnetic-field exposure, neither before nor after the procedure. After a mean of 30 minutes (range 10–110 minutes) of exposure

to the magnetic field, no adverse effects of standard ESD procedure were observed regarding pulmonary and cardiac function. During a median follow-up of 20 months (range 15–32 months), neither delayed adverse effects nor allergies were observed because of the stainless steel of the magnetic anchor.

Eight weeks after an MAG-ESD, all artificial defects caused by ESD were completely cured. Neither recurrent cancer nor distant metastases were observed in any of the patients during follow-up.

DISCUSSION

The present study is, to our knowledge, the first clinical trial by using MAG-ESD for EGC in human beings. The feasibility of the technique for gastric cancer treatment was already evaluated in an animal study. The MAG-ESD technique permits excellent visualization of the submucosal layer, because it is possible to achieve suitable tissue tension. This simplifies a gastric ESD, even for large lesions located in the gastric body. The long-term exposure to the magnetic field did not cause any unwanted physiologic or mental effects. Furthermore, no delayed complications or allergies related to the stainless steel of the magnetic anchor were observed. All the tumors were resected en bloc, without any perforation or severe uncontrollable bleeding.

Endoscopic resection is comparable in many respects to conventional surgery, with the advantages of being less invasive and more cost efficient.^{15,16} Endoscopic removal of cancer was initially attempted by using colorectal polypectomy with a high-frequency electric surgical cautery.¹⁷ The use of endoscopic polypectomy to treat pedunculated or semipedunculated EGC was first described in 1974 in Japan. In 1984, the technique of EMR, the so-called strip biopsy, was devised for endoscopic snare polypectomy.¹⁸ Today, EMR is established and widely accepted as a minimally invasive treatment for EGC.¹⁹ Although several techniques have been reported to make EMR procedures easier and safer,^{20,21} these cannot be used to remove, en bloc, lesions larger than 2 cm in diameter.^{22,23} Piecemeal resection may cause the pathologist to inadequately stage the specimen. Furthermore, there is a high risk of a recurrence after a piecemeal resection.^{24,25}

An ESD is superior to a standard EMR and provides en bloc specimens with a standard single-channel gastro-scope. After an endoscopic resection, pathologic assessment of depth of cancer invasion, degree of cancer differentiation, and lymphatic or blood-vessel involvement allows an accurate prediction of the risk of lymph-node metastasis.²⁶ The risk of developing lymph-node or distant metastasis is then weighed against the risk of surgery.²⁷⁻²⁹

Endoscopic resection should be safe, effective, and applicable to a wide variety of clinical situations. However, an ESD still requires an experienced endoscopist with a high level of skill, especially when using a single working-chan-

nel gastroscope. Recently, the technique of percutaneous traction-assisted EMR by using a laparoscopic port to create a strong counter-traction was reported.³⁰⁻³² However, all previous trials showed that the technique was complicated, invasive, and did not make ESD easier.

Magnets and magnetic fields were used to direct the catheter tip during catheter procedures.³³ A magnetic anchoring system was used to achieve laparoscopic surgery by using a single trocar.³⁴ Very recently, the feasibility of using magnetically anchored instruments was reported as a promising technique to facilitate natural orifice transluminal endoscopic surgery in a porcine model.³⁵ These magnets may also provide a way to alter tissue contours without any direct contact. A direct-current-generated magnetic field, as used in magnetic resonance imaging, is regarded as the least invasive or even the most appropriate noninvasive procedure that can be medically applied.

In 21 of our patients, only one magnetic anchor was needed to achieve the desired result, either by rotating the patient or by moving the examination table. In 4 cases, 2 magnetic anchors were required. In 2 cases, a second magnetic anchor was helpful. With the other 2 cases, however, the second anchor did not help, because the MAG system did not provide adequate visualization for submucosal dissection or allow suitable maneuvering of the endoscopic devices. This was caused by underinflation of the gastric cavity. Therefore, to obtain better visualization during an MAG-ESD, the prevention of air leakage because of a hiatus hernia should be achieved.

Another limitation of this procedure was that the extracorporeal electromagnetic control system is too large and cumbersome. Although it was possible to achieve hands-free fixation of the mucosa by using the magnetic anchor tractioned with the extracorporeal electromagnet, the system should be miniaturized to allow wider clinical application.

In conclusion, this prospective clinical trial proved that MAG-ESD can feasibly be used in human beings. The MAG-ESD technique was able to obtain excellent visualization by suitable tissue tension and to facilitate the procedures. Further innovations are warranted to apply the MAG procedure in daily clinical practice.

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