TABLE II – GASTRIC CANCER INCIDENCE RATES ACCORDING TO SERUM PG I LEVEL

Group	I-50	I-30	I-0	p (trend)
Serum PG I level (ng/mL)	>50	≤50 and >30	≤30	
Subjects	3267	1352	590	
Person-years	31748.0	13099.0	5579.0	
Age [mean (SD)]	49.1 (4.7)	49.1 (4.8)	49.3 (4.9)	
Follow-up years [mean (SD)]	9.7 (0.8)	9.7 (0.9)	9.5 (1.1)	
Total gastric cancer				
Age [mean (SD)]	50.1 (4.4)	51.0 (3.1)	51.7 (3.3)[1]	
Follow-up years [mean (SD)]	6.6 (2.3)	5.2 (3.0)	6.2 (2.3)	
Cases/incidence rate[2]	27/85	17/130	19/341	
HR (95%CI)	1	1.51 (0.83–2.78)	3.54 (1.95–6.40)	<0.0001
Intestinal-type gastric cancer				
Age [mean (SD)]	50.0 (3.8)	50.7 (3.2)	52.3 (3.4)[1]	
Follow-up years [mean (SD)]	6.3 (2.5)	5.7 (2.3)	5.7 (2.3)	
Cases/incidence rate[2]	12/38	15/115	15/269	
HR (95%CI)	1	3.01 (1.41–6.42)	6.19 (2.88–13.32)	<0.0001
Diffuse-type gastric cancer				
Age [mean (SD)]	50.2 (4.9)	53.0 (1.4)	49.5 (1.3)	
Follow-up years [mean (SD)]	6.8 (2.2)	2.0 (0.7)	8.0 (1.6)	
Cases/incidence rate[2]	15/47	2/15	4/72	
HR (95%CI)	1	0.32 (0.07–1.40)	1.38 (0.45–4.20)	0.23
Lung cancer				
Age [mean (SD)]	48.0 (4.6)	51.0 (4.6)	55	
Follow-up years [mean (SD)]	7.9 (0.6)	6.7 (2.1)	7	
Cases/incidence rate[2]	15/47	4/31	1/18	
HR (95%CI)	1	0.65 (0.21–1.95)	0.38 (0.50–2.89)	0.72

[1]*vs.* I-50 group, $p < 0.05$.–[2]Per 100,000 person-years.

TABLE III – GASTRIC CANCER INCIDENCE RATES ACCORDING TO SERUM PG I AND *H. pylori* ANTIBODY LEVELS

Group			I-50	I-30	I-0	p (trend)
Serum PG I level (ng/mL)			>50	≤50 and >30	≤30	
H. pylori-positive	Total	Case/subjects	26/2302	14/855	15/499	
		Incidence Rate[1]	117	170	320	
		HR (95%CI)	1	1.43 (0.75–2.74)	2.52 (1.33–4.80)	0.0059
	High titer	Case/subjects	14/557	6/173	6/109	
		Incidence Rate[1]	262	363	596	
		HR (95%CI)	1	1.39 (0.53–3.62)	2.27 (0.86–5.98)	0.3755
	Low titer	Case/subjects	12/1745	8/682	9/390	
		Incidence Rate[1]	71	122	244	
		HR (95%CI)	1	1.65 (0.67–4.03)	2.97 (1.24–7.10)	0.0077
Indeterminate		Case/subjects	0/328	2/179	2/47	
		Incidence Rate[1]	0	112	430	
		HR (95%CI)	(1)[2]	3.88 (0.35–42.83)	11.92 (1.06–133.57)	0.0942
H. pylori-negative		Case/subjects	1/637	1/318	2/44	
		Incidence Rate[1]	16	32	472	
		HR (95%CI)	1	1.99 (0.12–31.80)	27.34 (2.4–302.42)	0.0127

[1]Per 100,000 person-years.–[2]In reality, the cancer incidence in the subgroup was null; thus, comparison of the cancer risk was impossible. Therefore we tentatively presumed that a single cancer case derived from the subgroup during the study period and the HR was calculated in each subgroup of the same antibody level according to Cox proportional-hazards model.

stratified by serum *H. pylori* antibody levels and the same analysis was applied (Table III). The cancer incidence rate and HR in the same antibody level group increased as the PG I level decreased, reaching the highest level in group I-0. Despite the small number of *H. pylori*-negative and indeterminate subjects in group I-0, the cancer incidence rate was quite high in these groups, that is 472/100,000 and 430/100,000 person-years, respectively. The overall incidence rate of these 91 subjects with an antibody level ≤50 U/mL (*H. pylori*-negative and indeterminate groups) in group I-0 was 439/100,000 person-years, which was higher than that of the *H. pylori*-positive subjects in group I-0. When the *H. pylori*-positive group was divided into high- and low-titer subgroups, the cancer incidence rate of group I-0 in the high-titer subgroup was the highest, and that in the low-titer subgroup was the lowest of the 4 subgroups of I-0 (Table III). In contrast, the cancer incidence rate was low in the antibody-negative subjects with a PG I level >30 ng/mL. Furthermore, among the antibody-negative subjects with a PG I >70 ng/mL, who accounted for 4.5% ($n = 233$) of the cohort, no one developed cancer (not shown in Table III).

PG I/II ratio and cancer development

Table IV shows the relationship between the serum PG I/II ratio and cancer development. Subjects were classified into 3 groups according to the PG I/II ratio; group III-3 with a PG I/II ratio >3.0, group III-2 with a PG I/II ratio >2.0 and ≤3.0, and group III-0 with a PG I/II ratio ≤2.0. The Kaplan-Meier analysis showed that after 3 years of follow-up there was a stepwise increase in cancer development with reduction in the PG I/II ratio (Fig. 2*b*). The cancer incidence rates were 60/100,000 person-years in group III-3, 209/100,000 person-years in group III-2, and 302/100,000 person-years in group III-0; the highest and most significant HR was observed in group III-0 (HR = 4.89, 95% CI: 2.66–8.99). The observed significant negative correlation between cancer incidence rate and the PG I/II ratio was noted to be unrelated to histopathological cancer type. Next, the same analysis was used to assess the groups stratified by *H. pylori* antibody level. As shown in Table V, in all of the groups except the indeterminate group there was a stepwise increase in the cancer incidence rate and HR with a reduction in the PG I/II ratio, reaching the highest level in

TABLE IV – GASTRIC CANCER INCIDENCE RATES ACCORDING TO PG I/II RATIO

Group	III-3	III-2	III-0	*p* (trend)
PG I/II ratio	>3.0	≤3.0 and >2.0	≤2.0	
Subjects	3453	939	817	
Person-years	33353.0	9112.5	7960.5	
Age [mean (SD)]	48.7 (4.8)	49.8 (4.5)[1]	50.7 (4.3)[1]	
Follow-up years [mean (SD)]	9.7 (0.9)	9.7 (0.8)	9.5 (1.1)	
Total gastric cancer				
Age [mean (SD)]	51.3 (3.9)	50.5 (4.3)	50.8 (3.2)	
Follow-up years [mean (SD)]	5.7 (2.3)	6.0 (2.7)	6.3 (2.7)	
Cases/incidence rate[2]	20/60	19/209	24/302	
HR (95%CI)	1	3.70 (1.97–6.95)	4.89 (2.66–8.99)	<0.0001
Intestinal-type gastric cancer				
Age [mean (SD)]	51.8 (3.4)	50.1 (3.8)[1]	51.4 (3.3)	
Follow-up years [mean (SD)]	5.3 (2.5)	6.4 (2.7)	5.8 (2.5)	
Cases/incidence rate[2]	13/39	12/132	17/214	
HR (95%CI)	1	3.76 (1.71–8.27)	5.36 (2.54–11.33)	<0.0001
Diffuse-type gastric cancer				
Age [mean (SD)]	50.6 (4.8)	51.1 (5.3)	49.3 (2.7)	
Follow-up years [mean (SD)]	6.5 (1.8)	5.4 (2.7)	7.8 (2.8)	
Cases/incidence rate[2]	7/21	7/77	7/88	
HR (95%CI)	1	3.60 (1.26–10.30)	4.04 (1.40–11.67)	0.016
Lung cancer				
Age [mean (SD)]	48.6 (4.7)	52.3 (4.6)	45	
Follow-up years [mean (SD)]	7.8 (0.6)	6.2 (2.3)	8.1	
Cases/incidence rate[2]	16/48	3/33	1/13	
HR (95%CI)	1	0.70 (0.20–2.41)	0.27 (0.04–2.05)	0.61

[1]*vs.* III-3 group, $p < 0.05$.–[2]Per 100,000 person-years.

TABLE V – GASTRIC INCIDENCE RATES ACCORDING TO PG I/II AND *H. pylori* ANTIBODY LEVELS

Group			III-3	III-2	III-0	*p* (trend)
PG I/II ratio			>3.0	≤3.0 and >2.0	≤2.0	
H. pylori-positive	Total	Case/subjects	18/1991	17/903	20/762	
		Incidence Rate[1]	94	197	277	
		HR (95%CI)	1	2.05 (1.06–3.99)	2.77 (1.46–5.26)	0.0025
	High titer	Case/subjects	8/400	7/241	11/198	
		Incidence Rate[1]	208	304	591	
		HR (95%CI)	1	1.47 (0.53–4.04)[4]	2.83 (1.13–7.07)	0.0139
	Low titer	Case/subjects	10/1591	10/662	9/589	
		Incidence Rate[1]	55	158	168	
		HR (95%CI)	1	2.26 (0.91–5.59)	2.28 (0.95–5.48)	0.0187
Indeterminate		Case/subjects	2/500	1/22	1/32	
		Incidence Rate[1]	40	457	317	
		HR (95%CI)	1	13.30 (1.81–97.80)	11.59 (1.05–127.90)	0.182
H. pylori-negative		Case/subjects	0/962	1/14	3/23	
		Incidence Rate[1]	0	744	1448	
		HR (95%CI)	(1)[2]	83.39 (7.47–931.40)	131.98 (11.95–1457.36)	0.0001

[1]Per 100,000 person-years.–[2]In reality, the cancer incidence in the subgroup was null; thus, comparison of the cancer risk was impossible. Therefore we tentatively presumed that a single cancer case derived from the subgroup during the study period and the HR was calculated in each subgroup of the same antibody level according to Cox proportional-hazards model.

group III-0. Despite the small number, the cancer incidence rate of subjects with a PG I/II ratio ≤3.0 were quite high in the *H. pylori*-negative and indeterminate groups. The overall cancer incidence rate in the 91 subjects with a PG I/II ratio ≤3.0 (groups III-2 and III-0) and an antibody titer ≤50 U/mL (*H. pylori*-negative and indeterminate groups) was 659/100,000 person-years, which was higher than that of *H. pylori*-positive subjects in group III-2 or III-0. Within the *H. pylori*-positive group, the cancer incidence rate in group III-0 was higher in the high-titer subgroup than in the low-titer subgroup. Meanwhile, the cancer incidence rate among subjects with a PG I/II ratio >3.0 (group III-3) in the *H. pylori*-negative or indeterminate group was quite low.

PG II levels and cancer risk

The subjects were also divided into 3 groups according to PG II level: group II-0 with a PG II ≤10 ng/mL, group II-10 with a PG II >10 ng/mL and ≤30 ng/mL, and group II-30 with a PG II >30 ng/mL, and the relationship between serum PG II level and cancer development was analyzed. As shown in Table VI, there was a stepwise increase in the cancer incidence rate and the HR with an increase in the PG II level ($p = 0.025$). This significant, dose-dependent, positive association between cancer development and PG II level was observed only in diffuse-type cancer; a significant HR increase was noted with a PG II >30 ng/mL (HR = 15.67, 95% CI: 1.88–130.64). The Kaplan-Meier analysis showed that after 3 years of follow-up, the diffuse-type cancer development was the highest in group II-30, followed by group II-10, then group II-0; the incidence rates were 119/100,000 person-years, 35/100,000 person-years and 7/100,000 person-years, respectively (Fig. 2*c*). The subjects stratified by serum *H. pylori* antibody level were analyzed in the same manner (Table VII). In the *H. pylori*-positive group, the development of diffuse-type cancer tended to increase with an increase in the PG II level, reflecting cancer development in the high-titer subgroup. About 42.9% (9/21) of diffuse-type cancers developed in the high-titer subgroup. There was

TABLE VI – GASTRIC CANCER INCIDENCE RATES ACCORDING TO SERUM PG II LEVEL

Group	II-0	II-10	II-30	p (trend)
Serum PG II level (ng/mL)	≤10	≤30 and >10	>30	
Subjects	1435	3247	527	
Person-years	14068.5	31302.0	5055.5	
Age [mean (SD)]	48.2 (4.8)	49.6 (4.6)[1]	49.8 (4.6)[1]	
Follow up-years [mean (SD)]	9.7 (0.9)	9.6 (0.9)	9.6 (0.9)	
Total gastric cancer				
Age [mean (SD)]	51.6 (3.4)	51.2 (3.4)	47.9 (4.7)[1]	
Follow-up years [mean (SD)]	5.0 (2.5)	6.2 (2.4)	7.7 (2.5)	
Cases/incidence rate[2]	7/50	45/147	10/198	
HR (95%CI)	1	2.67 (1.21–5.97)	3.57 (1.36–9.40)	0.025
Intestinal-type gastric cancer				
Age [mean (SD)]	51.5 (3.0)	51.6 (3.6)	46.8 (1.5)[1]	
Follow up-years [mean (SD)]	4.7 (2.8)	6.1 (2.3)	8.1 (1.9)	
Cases/incidence rate[2]	6/43	32/102	4/79	
HR (95%CI)	1	2.14 (0.89–5.14)	1.63 (0.46–5.78)	0.224
Diffuse-type gastric cancer				
Age [mean (SD)]	51.8 (2.4)	50.4 (3.9)	48.8 (6.4)	
Follow up-years [mean (SD)]	5.1 (2.5)	6.9 (2.2)	7.3 (3.1)	
Cases/incidence rate[2]	1/7	14/35	6/119	
HR (95%CI)	1	5.95 (0.78–45.39)	15.67 (1.88–130.64)	0.018
Lung cancer				
Age [mean (SD)]	51.0 (4.6)	48.5 (5.0)	48.3 (4.2)	
Follow up-years [mean (SD)]	7.5 (0.6)	7.5 (1.3)	7.8 (0.6)	
Cases/incidence rate[2]	4/284	13/42	3/59	
HR (95%CI)	1	1.48 (0.48–4.56)	2.12 (0.47–9.52)	0.805

[1]*vs.* II-0 group, $p < 0.05$.–[2]Per 100,000 person-years.

TABLE VII – DIFFUSE-TYPE GASTRIC CANCER INCIDENCE RATES ACCORDING TO SERUM PG II AND *H. pylori* ANTIBODY LEVELS

Group			II-0	II-10	II-30	p (trend)
Serum PG II level (ng/mL)			≤10	≤30 and >10	>30	
H. pylori-positive	Total	Case/subjects	3/691	11/2533	5/432	
		Incidence Rate[1]	45	44	123	
		HR (95%CI)	1	0.96 (0.25–13.05)	3.26 (0.63–43.72)	0.147
	High titer	Case/subjects	0/67	6/647	3/125	
		Incidence Rate[1]	0	99	258	
		HR (95%CI)	(1)[2]	0.43 (0.05–3.59)	0.83 (0.09–7.97)	0.752
	Low titer	Case/subjects	3/624	5/1886	2/307	
		Incidence Rate[1]	50	28	69	
		HR (95%CI)	1	0.61 (0.11–9.26)	1.16 (0.25–13.05)	0.176
Indeterminate		Case/subjects	1/323	0/215	0/16	
		Incidence Rate[1]	31	0	0	
		HR (95%CI)	1	0	0	
H. pylori-negative		Case/subjects	1/668	0/325	0/6	
		Incidence Rate[1]	15	0	0	
		HR (95%CI)	1	0	0	

[1]Per 100,000 person-years.–[2]In reality, the cancer incidence in the subgroup was null; thus, comparison of the cancer risk was impossible. Therefore we tentatively presumed that a single cancer case derived from the subgroup during the study period and the HR was calculated in each subgroup of the same antibody level according to Cox proportional-hazards model.

a marked stepwise increase in the incidence rate with an increase in the PG II level, reaching a high rate of 258/100,000 person-years in groupII-30. This incidence rate was the highest among the subgroups stratified by serum PG II and antibody levels. Conversely, the cancer incidence rate tend to be low in subjects with low serum levels of both PG II and *H. pylori* antibodies.

Other cancer and non-neoplastic disorders developed during the study

During the study period of 10 years, 71 cases of newly developed cancers other than gastric cancer were detected; they were cancer of the bladder ($n = 6$), colon ($n = 14$), esophagus ($n = 5$), head and neck ($n = 12$), kidney ($n = 4$), liver ($n = 4$), lung ($n = 22$), pancreas ($n = 1$), prostate ($n = 2$) and testis ($n = 1$). In addition, there were 2 cases of non-Hodgkin's lymphoma. Fifty-six of these 73 subjects (76.7%) died from these malignant disorders. There was no significant correlation between the development of any of these neoplasms and serum PG or *H. pylori* antibody level. As a reference, the incidence of lung cancer according to serum PG or *H. pylori* antibody level is shown in Tables I, II, IV and VI. In addition, 51 subjects died during the study from various non-neoplastic disorders such as heart disease ($n = 11$), cerebral vascular accident ($n = 10$), chronic liver disease ($n = 4$), traumatic injuries due to accident in the workplace ($n = 6$), or suicide ($n = 9$).

Discussion

In the present study, a cohort of 5,209 healthy, asymptomatic, middle-aged subjects, in whom serum *H. pylori* antibody titer and PG levels had been assessed, was followed for a mean of 9.7 years, and the incidence rate of gastric cancer was estimated in the groups stratified by the levels of each of these serologic markers. It was found that *H. pylori*-infected subjects had a high risk of stomach cancer regardless of histological type, in good agreement with the results of previous studies dealing with the role of *H. pylori* in stomach carcinogenesis.[3–12] Furthermore, there was a stepwise increase in cancer development with an increase in the

antibody level. Previous studies analyzing the association between gastric cancer risk and serum *H. pylori* antibody level have reported contradictory results.[2,4,43,44] While it has been reported that there is no association between a high antibody level and cancer risk,[43] Yamaji *et al.* indicated that there is a possible association between low antibody levels and cancer risk in elderly subjects.[44] Moreover, a positive association between antibody levels and cancer risk has been suggested by 2 nested case-control studies.[2,4] The present longitudinal cohort study clearly demonstrated that there is a positive, dose-dependent association between the two in asymptomatic, middle-aged, male subjects. In general, the *H. pylori* antibody level is considered to be correlated with the severity of inflammation in stomachs infected with *H. pylori*[35,36]; the persistence of severe gastritis appears to lead to the rapid progression to atrophy and cancer. Indeed, in previous studies involving an *in vivo* carcinogenesis model using Mongolian gerbils, the *H. pylori* antibody level was higher in tumor-bearing animals than in tumor-free animals under similar conditions.[33,34,45] The results of the present study, together with those in the experimental animal model, strongly indicate the possibility that an enhancement of the host-immune response contributes to *H. pylori*-induced stomach carcinogenesis. The importance of these results lies in the potential use of *H. pylori* antibody levels or other markers for genetic predisposition affecting inflammation, such as proinflammatory cytokine gene polymorphisms, as indicators of risk for cancer.[46,47] Further studies are required to look for a link between the immune factors and host genetic cancer susceptibility.

The results of this study demonstrated that an increase in risk of gastric cancer occurred with a reduction in the serum PG I level or the PG I/II ratio. The risk of cancer was significantly elevated in subjects with a serum PG I level ≤30 ng/mL (HR = 3.54, 95% CI: 1.95–6.40) or with a PG I/II ratio ≤3.0 (HR = 4.25, 95% CI: 2.47–7.32). This negative, dose-dependent association between cancer risk and these serologic markers was observed mainly in intestinal-type cancer. Previous studies have indicated that a reduction in the serum PG I level or the PG I/II ratio is closely correlated with the progression of gastric atrophy.[24,25,39] Thus, the present results are in agreement with the clinicopathological and epidemiological studies that have indicated that many gastric cancers, especially the intestinal-type, develop in stomach mucosa affected by severe and extensive CAG, and that subjects with extensive CAG are at high risk of gastric cancer.[1,16–20] Using the combination of the *H. pylori* antibody level and the PG I level or the PG I/II ratio, a subgroup with an especially high cancer incidence rate could be identified. These results are in line with the results of previous nested case-control studies that showed that subjects with elevated *H. pylori* antibody and low PG I had the highest risk of cancer.[27,30] Furthermore, in the *H. pylori*-positive group, the cancer incidence rate was higher in subjects with a lower PG I level or a lower PG I/II ratio. In fact, as the antibody level increased, the incidence rate increased, so that the high-titer subgroup with PG I ≤30 ng/mL had the highest incidence rate (596/100,000 person-years), which was similar to that in the high antibody titer subgroup with PG I/II ≤2.0 (591/100,000 person-years). These results strongly suggest that the presence of *H. pylori*-related gastritis, which is associated with severe inflammation as indicated by a high antibody level, together with the consequent extensive atrophy as indicated by a low serum PG I level or PG I/II ratio, is associated with a particularly high risk of gastric cancer. Although only 12.7% (8/63) of gastric cancers developed in the *H. pylori*-negative and indeterminate groups during the observation period, the cancer incidence rate in these subgroups was considerably elevated with a low PG I level or a low PG I/II ratio. In the *H. pylori*-negative and indeterminate groups, there were 91 subjects (1.7% of the cohort) with a PG I ≤30 ng/mL (group I-0), and the same number of subjects with a PG I/II ratio ≤3.0; the cancer incidence rates of these subjects were 439/100,000 person-years and 659/100,000 person-years, respectively. The incidence rate increased with lower serum PG and/or antibody levels, reaching the highest incidence rate of 1,448/100,000 person-years in the *H. pylori*-negative group III-0 and 472/100,000 person-years in the *H. pylori*-negative group I-0. It is widely accepted that in the *H. pylori*-infected stomach, chronic inflammation induces mucosal atrophy together with intestinal metaplasia. With the extension of intestinal metaplasia the serum PG levels are reduced, and spontaneous eradication of the bacterium is induced, showing a low or null specific antibody level.[48,49] Thus, the 1.7% of subjects in the cohort with a low serum PG I level or a low PG I/II ratio who had negative or indeterminate *H. pylori* antibody levels were considered to have metaplastic gastritis. The results strongly support the hypothesis that the presence of metaplastic gastritis is associated with a high risk of gastric cancer and that *H. pylori* infection is not directly involved in stomach carcinogenesis but has an indirect relationship as a driving force of the atrophy-metaplasia-dysplasia-cancer sequence.[1]

In contrast, the subjects with a high PG I or a high PG I/II ratio in the *H. pylori*-negative group or the indeterminate group were at low risk. In particular, cancer development was not observed during the study period in the *H. pylori*-negative group among subjects with a PG I >70 ng/mL or a PG I/II ratio >3.0. These subgroups are considered to consist primarily of *H. pylori*-free subjects with nonatrophic stomach. The present results strongly indicate the possibility that in the current epidemiological environment of Japan it is quite rare for gastric cancer to develop in *H. pylori*-free healthy stomachs.

Previous studies have indicated that *H. pylori* infection alters the expression of PG II in the stomach mucosa[50]; serum PG II levels are higher in *H. pylori*-related nonatrophic gastritis and lower in atrophic gastritis. The increase in serum PG II levels is reported to be correlated with histological changes reflecting the severity of mucosal inflammation,[51,52] and the eradication of *H. pylori* reverses serum PG II elevation.[53–55] Therefore, the PG II level is considered an index of *H. pylori*-induced gastric inflammation in the nonatrophic stomach. In the present study, the development of diffuse-type cancer, but not intestinal-type, significantly increased with the PG II level; the risk of cancer was significantly elevated in subjects with a PG II level >30 ng/mL (HR = 3.81, 95% CI: 1.10–13.21). These results are in agreement with the previously proposed hypothesis that chronic active inflammation directly induces diffuse-type cancer without passing through atrophic gastritis with intestinal metaplasia.[6,31,56,57] Moreover, stratification using the combination of serum *H. pylori* antibody and PG II levels showed that this type of cancer tends to develop in subjects with high serum levels in both of the tests. *H. pylori*-induced, severe, chronic inflammation is believed to trigger a series of molecular intracellular events that lead to various genetic alterations in the stomach mucosa.[31,32] In addition, there is an increasing body of evidence, including ours, that CpG island methylation is induced by *H. pylori* infection in the stomach mucosa,[58–60] and inactivation of the E-cadherin gene by DNA methylation is reported to be highly prevalent in diffuse-type cancer.[61] The present results strongly support the notion that severe *H. pylori*-induced inflammation, together with a strong host immune response, induces a series of genetic and epigenetic events that directly lead to the development of diffuse-type cancer.

In conclusion, our results show that the serum PG and/or *H. pylori* antibody levels provide an index of gastric cancer development, and that based on these markers the risk for gastric cancer can be objectively determined in each individual with *H. pylori*-related gastritis from the general population. The Japanese anti-gastric cancer strategy has given priority to secondary prevention, based on mass screening using barium X-ray examination as a filter test, over primary prevention. To improve the efficiency of the screening programs, it is necessary to establish a new test for high-risk subjects, and various trials have been conducted in a number of countries including Japan.[62–66] Our results clearly indicate that serum PG and/or *H. pylori* antibody levels can be used as objective markers to differentiate individuals at high and low risk for gastric cancer, and they can provide data that could be a basis for cancer control. The measurement of these serum markers is

simple, reproducible, easy to accept, relatively inexpensive, and can be used to screen a large population.[39] Therefore, by adding these serum tests to a mass screening program greater efficacy can be expected. Since the atrophy-metaplasia-dysplasia-cancer sequence caused by *H. pylori* infection is the main route of stomach carcinogenesis not only in Japan but also in China, Korea, Eastern Europe, Central America, and South America, the detection and strict follow-up of the high-risk population using these serum markers can be considered an effective strategy for the control of gastric cancer worldwide.

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Digestive Endoscopy

Technical feasibility of endoscopic submucosal dissection for early gastric cancer in patients taking anti-coagulants or anti-platelet agents

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ABSTRACT

Background: Endoscopic submucosal dissection is a novel technique that is expected to be a curative treatment for early gastric cancers. Anti-coagulants and anti-platelet agents are widely used, especially in elderly patients, to prevent thromboembolic disease. However, the feasibility of endoscopic submucosal dissection for such patients has not been investigated.

Aims: To determine the feasibility of endoscopic submucosal dissection for patients using anti-coagulant and anti-platelet agents via retrospective investigation of clinical outcomes.

Methods: Of 408 patients with 444 early gastric cancers consecutively treated by endoscopic submucosal dissection from January 2000 to December 2007 in our hospital, 47 patients with 56 early gastric cancers were receiving anti-coagulants or anti-platelet agents. All patients were classified into groups for high and low risk of thromboembolism. In 44 low-risk patients, these agents were stopped for 1 week before and after treatment. Only three high-risk patients underwent intravenous heparin replacement during the cessation period.

Results: Comparison with other patients showed no significant differences in complete en-bloc resection (96.4%) or perforation (1.8%). Postoperative bleeding requiring endoscopic treatment occurred for six early gastric cancers (10.7%) in the anti-coagulant and anti-platelet group; this frequency was slightly higher than that observed for other patients (5.2%). The healing of endoscopic submucosal dissection ulcers was not delayed by anti-coagulant and anti-platelet treatment (91% in the scarring stage) when checked at the 8th week after endoscopic submucosal dissection.

Conclusion: The clinical outcomes of endoscopic submucosal dissection for early gastric cancers in patients receiving anti-coagulants or anti-platelet agents indicated that endoscopic submucosal dissection for low-risk patients could be a reliable technique with equivalent efficacy and risk in comparison with that for other early gastric cancer patients.

1. Introduction

Successful outcomes for endoscopic mucosal resection (EMR) have resulted in its implementation as the standard treatment for small and non-ulcerative early gastric cancers (EGCs), as it is less invasive than surgical gastrectomy [1,2]. Recently, owing to establishment of criteria for node-negative tumours [3] and development of endoscopic submucosal dissection (ESD) [4–10], endoluminal treatments have also been recommended for large-sized or ulcerative EGCs.

ESD has become a more acceptable option than gastrectomy, especially for elderly patients who often have several comorbidities [11], such as medication with anti-coagulants or anti-platelet agents for primary and secondary prevention of cerebro- and cardiovascular disease. These agents are considered to enhance the tendency to bleed, which may result in increased intra- and post-ESD bleeding. Additionally, ESD-induced ulcers may delay the healing process due to their inhibition of the regeneration of epithelial cells. Thus, the cessation during the perioperative period has been principally recommended without solid evidence; this practice may cause life threatening cerebro- and cardiovascular events.

Because the feasibility of ESD for patients receiving anti-coagulant and anti-platelet therapy has not been investigated in detail, we here investigated the clinical outcomes of ESD in EGC patients receiving these drugs.

2. Methods

Amongst 408 patients with 444 EGCs consecutively treated by ESD from January 2000 to December 2007 in the University of Tokyo hospital, 47 patients (males: 37; females: 10) with 56 EGCs were receiving anti-coagulants or anti-platelet agents. All patients were

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Table 1
Summary of anti-platelet agents and anti-coagulants in 47 patients[a].

	N
Anti-coagulants	
Warfarin	5
Anti-platelet agents	
Aspirin	35
Ticlopidine	11
Icosapentate ethyl	9
Cilostazol	6
Dipyridamole	2
Prostaglandin	2
Others	4

[a] Some patients were receiving more than one agent.

classified into groups for high and low risk of thromboembolism as classified by the American Society for Gastrointestinal Endoscopy. High-risk criteria included conditions of atrial fibrillation associated with valvular heart disease, mechanical valve in the mitral position, and mechanical valve with prior thromboembolic event. In this study, patients with coronary stents, including drug-eluting stents that require double anti-platelet therapy, were also included in the high-risk group. Other patients were assigned to the low-risk group [12].

We defined the following as anti-platelet agents: cyclooxygenase inhibitors (e.g., aspirin), phosphodiesterase inhibitors (e.g., cilostazol), purinergic receptor antagonists (e.g., ticlopidine), serotonin receptor antagonists (e.g., sarpogrelate), and eicosapentaenoic acid preparations (e.g., icosapentate) [13]. These agents were principally stopped for 1 week before and after treatment if the patients were considered to be at low risk for thromboembolism. For patients at high risk for thromboembolism, intravenous heparin was administered until 6 h before treatment and restarted once haemostasis was confirmed by stable vital signs and laboratory data, and after consultation with the prescribing doctors.

All indicated lesions were preoperatively confirmed to be adenocarcinomas or lesions suspected to be adenocarcinomas by endoscopic biopsy. In our study, no lymphovascular invasion in addition to the following were criteria for node-negative EGCs [3]: intramucosal intestinal-type cancer without ulcerative findings, regardless of size (M-UI[−]); intramucosal intestinal-type cancer with ulcerative findings, 3 cm or less in size (M-UI[+]); SM1 (slight invasion into submucosa less than 500 μm from muscularis mucosa) intestinal-type cancer, 3 cm or less in size (SM1).

The above preoperative diagnosis was principally predicted by white-light conventional and choromoendoscopy with indigo carmine. Endoscopic ultrasonography was additionally performed for lesions suspected to present submucosal invasion and/or ulcers. Some lesions that did not meet the above criteria preoperatively were also resected by ESD if they were technically resectable upon consideration of patient comorbidities and/or requests [14]. The ESD procedure was performed as previously reported elsewhere [5,6,8]. All patients provided written informed consent before receiving treatment.

Table 2
Summary of comorbidities of patients receiving anti-coagulants or anti-platelet agents.

Comorbidity	N
Ischaemic heart disease	21
Cerebral vascular disturbance	12
Arteriosclerosis obliterans	5
Atrial fibrillation	3
Abdominal aortic aneurysm	1
Unknown	12

Table 3
Clinicopathological findings of early gastric cancers resected by endoscopic submucosal dissection in patients receiving anti-coagulants or anti-platelet agents.

Findings	N = 56
Mean size of resected mucosa (mm, mean ± S.D.)	21.3 ± 16.2
Location	
Upper	11 (19.6%)
Middle	20 (35.7%)
Lower	22 (39.3%)
Remnant	3 (5.4%)
Macroscopic type	
Protruded	19 (33.9%)
Flat or depressed	31 (55.4%)
Mixed	6 (10.7%)
Depth of invasion	
M	42 (75%)
SM1	6 (10.7%)
SM2	8 (14.3%)
Histological type	
Diffuse	5 (8.9%)
Intestinal	51 (91.1%)
Angiolymphatic invasion	
Yes	7 (12.5%)
No	49 (87.5%)

Endoscopic characteristics of the lesions were classified according to the Paris endoscopic classification [15]. Histological assessment was performed according to the revised Vienna classification of gastrointestinal epithelial neoplasia [16].

The parameters assessed in this study were en-bloc resection, en-bloc resection with tumour-free lateral and basal margins (R0 resection), and frequency of complications; these included postoperative bleeding and perforation as well as ulcer healing after ESD. These parameters were compared amongst patients who were using or not using anti-coagulants or anti-platelet agents and who were treated during the same period in our hospital. Statistical analyses were conducted using the χ^2-test with Yates' modification and Student's t-tests. $P \leq 0.05$ was considered significant.

3. Results

The mean age of the 47 patients was 72.4 ± 7.7 years (range, 57–90 years), which was significantly higher than that of the other 361 patients in the same period (mean age, 66.3 ± 9.9 years). All of these 47 patients were receiving anti-platelet agents, and warfarin was additionally prescribed to five patients. In three patients, intravenous heparin replacement was performed during the cessation period due to high risk for thromboembolism. Intravenous heparin was restarted in these three high-risk patients at 18, 14 and 11 h after ESD, respectively. The most common anti-platelet agent was aspirin (74%), followed by ticlopidine (23%) (Table 1). Thirty-five patients had apparent comorbidities requiring these agents. The most common comorbidity was ischaemic heart disease (45%), followed by cerebral vascular disturbance (26%). Twelve patients

Table 4
Clinical outcomes according to use of anti-coagulants or anti-platelets.

	With anti-coagulants or anti-platelet agents	Without anti-coagulants or anti-platelet agents	P-value
En-bloc resection (%)	96.4 (54/56)	94.3 (366/388)	NS
Plus R0 resection	82.1 (46/56)	93.0 (361/388)	NS
Postoperative bleeding (%)	10.7 (6/56)	5.2 (20/388)	NS
Perforation (%)	1.8 (1/56)	4.4 (17/388)	NS

NS, not significant.

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Table 5
Characteristics of tumours and patients experiencing postoperative bleeding.

Case no.	Age (years)	Sex	Location	Diameter of lesions (mm)	Diameter of specimen (mm)	Depth of invasion	Scar	Pathological feature	Timing of bleeding	Anti-coagulants	Anti-platelet drugs	Restart of drugs	Comorbidity
1	64	F	Middle	47	113	M	+	Intestinal	Within 24 h	–	Aspirin, ticlopidine, Icosapentate	19th day	Cerebral vascular disturbance
2	76	M	Lower	17	36	M	–	Intestinal	Within 24 h	–	Icosapentate	Not restarted	Hypertension
3	65	M	Lower	5	20	M	–	Intestinal	7th day	–	Aspirin	28th day	Ischaemic heart disease
4	81	M	Lower	16	24	M	–	Intestinal	2nd day	–	Cilostazol	21st day	Hypertension
5	70	M	Middle	20	26	SM1	–	Intestinal	3rd day	–	Aspirin	Not restarted	Ischaemic heart disease
6	67	M	Upper	35	50	SM1	–	Intestinal	14th day	–	Aspirin, ticlopidine[a]	3rd day	Ischaemic heart disease

[a] A patient with a coronary stent in the high-risk group. Intravenous heparin was alternatively administered.

receiving anti-platelet agents had no certain comorbidities such agents (Table 2). One patient was receiving aspirin in spite of liver cirrhosis with thrombocytopenia.

Histopathological findings of the 56 resected lesions are summarised in Table 3. There were no significant differences in mean size, location, macroscopic type, depth, histological type, and lymphovascular invasion of the lesions in the two groups (P = not significant).

The frequency of en-bloc and en-bloc plus R0 resections as well as complications are summarised in Table 4. The frequency of en-bloc resection was 96.4%, and that of en-bloc resection plus R0 resection was 82.1%. A mean change in haemoglobin levels -0.44 ± 0.77 g/dL (range, -1.9 to $+1.2$ g/dL) was observed between pre- and post-ESD, and the haemoglobin level dropped by more than 1 g/dL in 9 (19%) of 47 patients. Postoperative bleeding requiring endoscopic treatment occurred in six EGCs (10.7%) in five low-risk patients and one high-risk patient. Postoperative bleeding was observed within 24 h in two patients, within 24–72 h in two patients, and at more than 72 h in two patients. Only one high-risk patient had postoperative bleeding after restarting anti-platelet agent treatment, and in five low-risk patients, bleeding occurred during the cessation period of these agents (Table 5). Perforation during ESD occurred in one low-risk patient (1.8%). There were no significant differences in the frequency of complications in the two types of patients evaluated in the same period.

Twenty-two low-risk patients underwent follow-up endoscopy at the 8th week after ESD in our hospital following our usual follow-up schedule. Examination of the 22 low-risk patients revealed 20 reddish scars without ulcers and 2 reduced ulcers surrounded by regenerative mucosa. There seemed to be no delay of healing for gastric ulcers created by ESD in low-risk patients when compared to the other patients without anti-coagulants or anti-platelet agents, as previously described elsewhere [17].

4. Discussion

As the populations of developed countries age, older high-risk patients with EGCs are being treated with ESD. Our previous study demonstrated the technical feasibility of ESD treatment for these patients, with outcomes comparable to those in younger patients [11]. However, elderly patients have higher incidences of comorbidities including cerebro- and cardiovascular diseases that require anti-coagulants or anti-platelet agents, as shown in the present study. Increased treatment of EGCs in elderly patients with ESD techniques will therefore result in increased likelihood of gastroenterologists encountering patients receiving those agents.

From this study, a reliable outcome can be expected for ESD in patients receiving such agents, assuming that a sufficient cessation period is secured. However, a longer cessation period could increase the risk of thromboembolism, although we did not observe any cases of cerebro- or cardiovascular events during cessation. Some cases of adverse events during cessation have been reported in Japan [18]; therefore, shorter cessation periods are preferable even for patients at low risk for thromboembolism. However, shorter cessation periods may also cause significant increases in postoperative bleeding and delayed healing of artificial ulcers. To balance the risk of thromboembolism in the perioperative period with complications related to the agents, it is necessary to definitely identify the optimal cessation time.

Although this study revealed similar clinical outcomes of ESD for EGCs in patients taking and not taking anti-coagulants or anti-platelet agents, several limitations must be considered when interpreting the data. These include the retrospective design and the insufficient number of patients to analyse risk factors for complications. In particular, there was a very limited number of patients

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at high risk for thromboembolism who required intravenous heparin; this implies that our study may actually only represent the feasibility of ESD for EGCs in patients at low risk for thromboembolism.

A non-concurrent, long-term follow-up study of EGC revealed that median duration of the early stage was estimated as 44 months and the cumulative 5-year corrected survival was estimated as 62.8% in unresected patients [19]. Because the treatment strategy should be determined by weighing risks against obtainable benefits, it might be one of options for high-risk patients to be followed without any treatment for EGC. The limited number of such patients in the present study may indicate that primary physicians managing the high-risk patients made the treatment decision before consulting endoscopic surgeons, as we did not intentionally exclude high-risk patients from ESD treatment in this study.

In summary, ESD for EGC can be performed with satisfactory outcomes with permissible risk even in patients receiving anti-coagulants or anti-platelet agents when a sufficient cessation period of these agents is obtained. The indication criteria for ESD may therefore be expanded to such patients, at least to those with a low risk of thromboembolism. However, further studies with a larger number of high-risk cases are needed to conclusively assess the feasibility of ESD for EGCs in this subgroup.

Conflict of interest statement
None declared.

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GASTROENTEROLOGY

Is it possible to predict the procedural time of endoscopic submucosal dissection for early gastric cancer?

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Key words
early gastric cancer, endoscopic submucosal dissection, operation schedule, predictive formula of procedural time, procedural time.

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Abstract

Background and Aim: Endoscopic submucosal dissection (ESD) has been expected to be a possible curative treatment, especially for node-negative early gastric cancer (EGC). We investigated the influential factors on the procedural time of gastric ESD with a Flex knife for the estimation.

Methods: In 222 intestinal-type EGC resected by ESD experts with established techniques, age, sex, location, circumference, gross type, tumor size, tumor depth, ulcerative findings, the period of ESD, the operator, and the experience of the operator were retrospectively analyzed. Predictors with a significant difference, as determined by multivariate analysis, were used to compose a predictive formula of procedural time.

Results: Location, gross type, tumor depth, ulcerative findings, and tumor size were considered influential factors on the procedural time by univariate analysis. Location in the upper-third of the stomach, presence of ulcerative findings, and > 20 mm in size were independent factors, as determined by multivariate analysis. Procedural time (min) was nearly equal to the maximal tumor size (mm) multiplied by 2.5, and an additional 40 min was required if the tumor was located in the upper-third of the stomach or had ulcerative findings (in both situations, an additional 80 min was needed).

Conclusion: The procedural time of ESD with a Flex knife for EGC can be predicted by tumor size, location, and existence of ulcerative findings. The estimation of procedural time may be very useful to determine the operation schedule.

Introduction

Endoscopic submucosal dissection (ESD) is a recently-developed endoluminal surgical technique for intramucosal neoplasms of the gastrointestinal tract, characterized by a circumferential mucosal incision and submucosal dissection beneath the lesion.[1-3] It is expected to be a possible curative method, especially for node-negative early gastric cancer (EGC),[4,5] with the advantage of preserving the whole stomach.

One of the shortcomings of ESD is, however, that it takes longer to resect the lesion, compared to other endoscopic treatments.[5,6] In Japan, ESD is usually performed in the left lateral decubital position under only intravenous administration of some sedatives or analgetics without an anesthesiologist. When the operation is prolonged, this can lead to accompanying complications, for example, postoperative aspiration pneumonia, deep vein thrombosis, or cardiorespiratory instability due to an overdose of anesthetic drugs. If the procedural time can be predicted, it would be very useful for arranging the operation schedule to prevent possible complications. Although some reports refer to the factors that prolong ESD,[7-10] to our knowledge, there has been no investigation about the prediction of the procedural time so far. Therefore, we retrospectively assessed the influential factors on the procedural time of ESD for EGC from our consecutive data and validated the possibility of whether the procedural time of ESD can be predicted before it takes place.

Methods

From August 2003, when the technical methodology of ESD was established in our hospital (The University of Tokyo, Tokyo, Japan) to January 2008, 347 consecutive EGC were resected by ESD. In this study, 222 lesions with a histological diagnosis of intestinal-type EGC were retrospectively investigated. Those excluded included 47 lesions resected by beginners who performed gastric ESD for 30 cases or less; 42 lesions resected in the initial phase of experts, where the total number of resection reached up to 30; eight lesions with a histological diagnosis of diffuse-type EGC, because these lesions were principally resected by gastrectomy in our hospital due to the possibility of the rapid growth of residual cancer cells, or the difficulty in the demarcation of the tumor, or the difficulty to distinguish ulcerative findings caused by biopsy from those by the tumor in some cases; six

Table 1 Univariate analysis of predictors for procedural time

	n	Mean procedural time (min)	*P*-value
Sex (male : female)	183 : 39	77.7 : 69.2	0.3898
Location (U : M : L)	65 : 79 : 78	99.9 : 73.6 : 59.1	< 0.0001*
Circumference (AW : GC: LC: PW)	42 : 29 : 91 : 60	80.2 : 58.3 : 75.1 : 83.8	0.2256
Gross type (0–I/IIa : 0–IIb/IIc : combined)	68 : 136 : 18	82.7 : 68.9 : 107.2	0.0116**
Tumor depth (mucosa : submucosa)	169 : 53	70.7 : 94.0	0.0077
Ulcerative findings (presence : absence)	42 : 180	98.3 : 71.1	0.0041
Period of ESD (early : late)†	136 : 86	78.1 : 73.3	0.5377
Operator (A : B : C : D)	54 : 121 : 36 : 11	86.4 : 72.9 : 77.9 : 57.3	0.3174
Experience of ESD (51 or more : 31–50)	191 : 31	76.9 : 71.8	0.6332
	Mean ± SD	*r*	
Age (years)	68.1 ± 9.3	0.083	0.2203
Tumor size (mm)	21.7 ± 15.2	0.506	< 0.0001

*Significantly different between upper-third (U) and middle-third (M), and between U and lower-third (L) by Fisher's Fisher's protected least significance difference (PLSD). **Significantly different between flat/depressed and combined by Fisher's PLSD. AW, anterior wall; GC, greater curve; LC, lesser curve; PW, posterior wall. †Early, 2003–2005; Late, 2006–2008.

lesions in a remnant stomach after gastrectomy or in a gastric tube after esophagectomy, because the number was small and the specific conditions might affect subsequent analyses; and 22 lesions from patients whose medical records were insufficient for retrospective analyses.

All patients provided written, informed consent before undergoing treatment. All lesions were resected by four very experienced ESD experts, each of whom had performed ESD with a Flex knife for more than 30 cases of EGC or gastric adenoma.[11–13] The technical outcomes and major complication rates of ESD for these cases were as follows: en bloc resection rate, 97.3%; complete resection rate (the rate of en bloc resection with tumor-free lateral and basal margins), 88.3%; delayed bleeding rate, 6.3%; and perforation rate, 2.7%.

ESD was indicated according to the criteria of node-negative EGC by Gotoda *et al.*[14] The ESD techniques have been described elsewhere.[1–3] In brief, a Flex knife (KD-630L; Olympus, Tokyo, Japan)[3,15] was used as the main electrosurgical knife, and other knives, such as an insulation-tipped (IT) knife,[1,2] a hook knife,[16] or a needle knife, were used when required. An endoscope with a water-jet system (GIF-Q260J; Olympus, Japan) was mainly used in the study. A mixture of 10% glycerin mixed with a 5% fructose and 0.9% saline preparation (Glyceol; Chugai Pharmaceutical, Tokyo, Japan) containing 0.005% indigo carmine and 0.0005% epinephrine was used to make a submucosal fluid cushion.[17] Hyaluronic acid was added to the injection solution for resection of a difficult lesion.[18] Hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan) were used for hemostasis.[19]

Procedural time was defined as the duration from circumferential marking around the lesion to the completion of hemostasis on the mucosal defect after resection. To determine the influential factors on procedural time, the following variables were analyzed: age, sex, location (upper-third, middle-third, or lower-third), circumference (anterior wall, posterior wall, lesser curve, or greater curve), gross type (0–I/IIa, 0–IIb/IIc, or combined type), tumor size (maximal diameter of the resected tumor actually measured), tumor depth (mucosal tumor or submucosal invasive tumor), ulcerative findings in the submucosal layer (endoscopical presence or absence), the period of ESD (early [2003–2005], late [2006–2008]), the operator (A, B, C, and D), and the experience of ESD (more than 50 cases or 31–50 cases).

Table 2 Multivariate analysis of predictors for procedural time over 120 min

		Odds ratio (95% confidence interval)	*P*-value
Location	Lower	1	
	Middle	1.006 (0.288–3.513)	0.9920
	Upper	4.649 (1.393–15.513)	0.0124
Gross type	0–I/IIa	1	
	0–IIb/IIc	0.345 (0.109–1.089)	0.0695
	Combined	2.600 (0.691–9.784)	0.1575
Tumor depth	Mucosa	1	
	Submucosa	0.665 (0.229–1.929)	0.4527
Ulcerative findings	Absence	1	
	Presence	4.914 (1.480–16.318)	0.0093
Tumor size	≤ 20 mm	1	
	> 20 mm	8.261 (2.786–24.493)	0.0001

A preliminary univariate analysis was performed using Pearson's correlation coefficient for age and tumor size; Student's *t*-test for sex, tumor depth, ulcerative findings, the period of ESD, and the experience of ESD; and one-way ANOVA for location, circumference, gross type, and the operator. Predictors with a significant difference or correlation, as determined by univariate analysis, were included in the multivariate analysis using a logistic regression model. Predictors with a significant difference, as determined by multivariate analysis, were included in a step forward linear regression model to compose a predictive formula of procedural time. A *P*-value of < 0.05 in each analysis was considered statistically significant.

Results

The univariate analysis of variables for the procedural time is shown in Table 1. Location, gross type, tumor depth, ulcerative findings, and tumor size were considered influential factors on

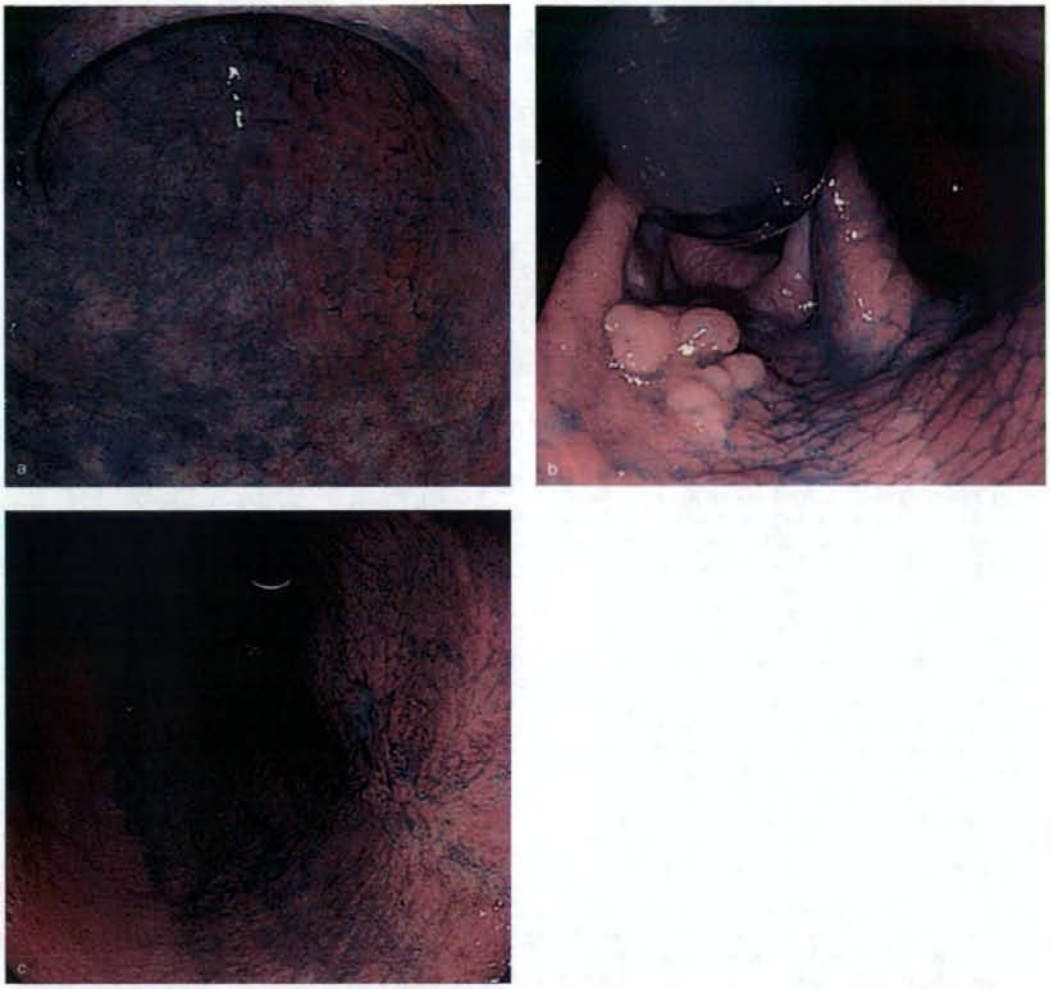

Figure 1 Representative cases for a comparison between predictive and actual procedural time. (a) 50 mm in maximal diameter located in the lower-third of the stomach without ulcerative findings. Predictive time is 125 min and the actual time is 130 min. (b) 15 mm in maximal diameter located in the upper-third of the stomach without ulcerative findings. Predictive time is 77.5 min and the actual time is 80 min. (c) 15 mm in maximal diameter located in the middle-third of the stomach with ulcerative findings. Predictive time is 77.5 min and the actual time is 90 min.

procedural time with a significant difference or correlation. The multivariate analysis using these variables revealed that the location in the upper-third of the stomach, presence of ulcerative findings, and > 20 mm in size were independent factors with a significant difference (Table 2), with a procedural time exceeding 120 min considered a long time.[10]

To compose a predictive formula of procedural time, categorical data were changed as follows: location in the upper-third of the stomach, 1; the middle or the lower third of the stomach, 0; presence of ulcerative findings, 1; and the absence of ulcerative findings, 0. After these variables were included in a linear regression model, the following formula was obtained: predictive procedural time (min) = 2.384 × (tumor size, mm) + 38.568 × (location) + 40.333 × (ulcerative findings) ($R^2 = 0.767$, $P = < 0.0001$). The simplified predictive formula is shown in Table 3 with some examples of clinical cases (Fig. 1).

Table 3 Predictive formula of procedural time and some examples for a comparison between predictive and actual procedural time

	Predictive procedural time (min) = 2.5 × (tumor size, mm)				
Case	Tumor size (mm)	Location	+ 40 × (Location)† Ulcerative findings	+ 40 × (Ulcerative findings)‡ Predictive time (min)	Actual time(min)
a	50	Lower	Absence	125	130
b	15	Upper	Absence	77.5	80
c	15	Middle	Presence	77.5	90

†Upper-third = 1, middle- or the lower-third = 0; ‡Presence = 1, absence = 0.

Discussion

In the present study, we elucidated that the prediction of procedural time was possible by determining tumor size, location, and ulcerative findings. The findings that these parameters affected the procedural time of gastric ESD were consistent with previous reports[7–10] and our own experiences. Oda *et al.* reported that these factors were equal to characteristics technically difficult to resect, by investigating the en bloc resection rate, and that ESD was prolonged depending on the presence of these factors, with no statistical analysis.[7] Although Onozato *et al.*[8] and Imagawa *et al.*[9] also demonstrated that procedural time was significantly prolonged, influenced by tumor size, location, and ulcerative findings, these data were only from univariate analyses. The present study is considered to be valuable with regard to the disclosure of the determinant factors, as determined by multivariate analysis.

In the predictive formula of procedural time, each coefficient of predictors indicates a degree of influence on procedural time. The formula implies that procedural time (min) is nearly equal to maximal tumor size (mm) multiplied by 2.5, and an additional 40 min is required when the tumor is located in the upper-third of the stomach or has ulcerative findings (in both situations, an additional 80 min is needed). By quantifying the influence of these parameters, we can easily calculate the predictive procedural time.

The prediction of procedural time is useful for the patient. We can arrange some safer conditions for the patient when ESD is expected to take a long time. First, treatment by an ESD expert can contribute to a faster operation. Second, the use of intermittent compression of the calf with an external pressure cuff may prevent deep vein thrombosis. Third, the attendance of an anesthesiologist can make the operator concentrate on the treatment. Fourth, airway management by the insertion of an endotracheal tube assists secure ventilation and may prevent intraoperative aspiration or postoperative pneumonia.

Because the primary objective of this study is to elucidate predictors of procedural time before ESD, we used factors that could be known before ESD. In practice, intraoperative conditions, such as unexpected massive bleeding, perforation, piecemeal resection, patient's compliance to venous anesthesia, and the application of an electrocautery snare in the final step of dissection, are expected to be influential on the actual procedural time to some extent. However, this study revealed a strong correlation with actual time ($R^2 = 0.767$) by using only three preoperative parameters.

Some shortcomings may be raised in the generalization our findings. First, these outcomes were obtained from ESD experts; second, a Flex knife was used as a main electrosurgical knife (resection with an IT knife is supposed to be quicker); and third, there are some technical differences, including equipment, among hospitals. The most important thing in this study, however, lies in the predictability of the procedural time before ESD. Accumulation of the predictive formula with various conditions in various hospitals is expected to confirm the possibility to predict procedural time.

In summary, we found a formula to predict the procedural time of gastric ESD, based on tumor size, location, and ulcerative findings. This may be useful in determining an appropriate operation schedule for the patient when the operation is expected to take a long time.

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Outcomes of endoscopic submucosal dissection for early gastric cancer with special reference to validation for curability criteria

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Background and study aims: Endoscopic submucosal dissection (ESD) is a novel, promising endoscopic technique for gastrointestinal neoplasms. We aimed to elucidate the feasibility of ESD as curative treatment for intestinal-type early gastric cancer (EGC) potentially without lymph-node metastases.

Patients and methods: For the short-term analysis, 276 consecutive, intestinal-type EGCs, which fulfilled the criteria for node-negative EGC in 231 patients who had undergone ESD from January 2000 to March 2007, were retrospectively investigated. For the long-term analysis, 212 lesions checked by endoscopy later than 1 year or recurrence within 1 year after ESD were assessed for local recurrence, and 208 patients followed for over 1 year or to death within 1 year after ESD were assessed for metastases and survival. All lesions/patients were divided into three groups: intramucosal cancer without ulcerative findings (M-UI[−]); intramucosal cancer with ulcerative findings, ≤3 cm (M-UI[+]); and slight invasive cancer into submucosa (< 500 µm), ≤3 cm (SM1).

Results: En bloc and complete resection rates were 96.7% and 91.7%, respectively. During a median follow-up of 36 months (range 2–93 months), two local recurrences occurred (0.9%), which were detected at 2 and 6 months after ESD, respectively. During a median follow-up of 38 months (range 6–97 months), the 5-year overall and disease-specific survival rates were 96.2% and 100%, respectively, with neither lymph node nor other-organ metastasis; one patient died due to other disease 6 months after ESD. No disease-related death occurred. No significant differences were found between the groups in short- and long-term analyses.

Conclusions: The prognostic analyses demonstrated the validity of the criteria of node-negative intestinal-type EGC as curability criteria for ESD. ESD can be proposed as an alternative method to gastrectomy for the treatment of these EGCs.

Introduction

Endoscopic submucosal dissection (ESD), which is characterized by circumferential mucosal incision and submucosal dissection beneath the lesion, is a recently developed endoscopic method used mainly for intramucosal neoplasms of the gastrointestinal tract [1–3]. This technique enables en bloc resection even for large or ulcerative lesions.

However, "resectability of the primary site" is quite different from "curability of the entire lesion," because an endoluminal approach can only completely resect a primary site. Although the "tentative" curability criteria for ESD in the treatment of early gastric cancer (EGC) has been established by the condition of absence of nodal metastasis in the surgically resected stomach and regional lymph nodes [4], there are, at least, three considerable drawbacks to curability criteria. First, investigation of metastatic lymph nodes in the operative cases in the study [4] may be insufficient, because the nodal metastases were only investigated at one central section of each lymph node stained by hematoxylin and eosin. Second, cancer cells may remain in the gastric wall between the primary site and the lymph nodes, which may result in a intraluminal recurrent tumor, such as a submucosal tumor, after ESD. Finally, the tumor may have metastasized to organs other than lymph nodes, because nodal metastasis is not the only way to metastasize.

Accordingly, the prognostic analyses in patients with EGC who have undergone ESD are warranted, to evaluate whether the condition of node-negative EGC can be regarded as a curability criterion for ESD. In prognosis studies of patients with gastrectomy, the 5-year disease-specific

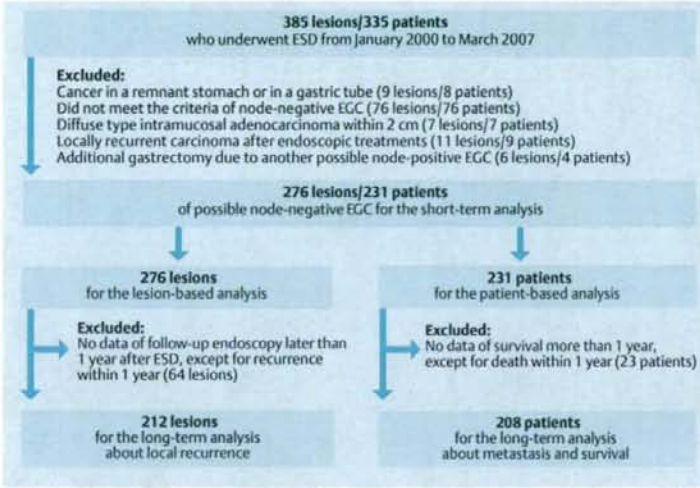

Fig. 1 Flowchart showing the patient inclusion in this study: 276 lesions from 231 patients were eligible for the short-term analysis, and 212 lesions from 208 patients were eligible for the long-term analysis.

survival rate was 99% in mucosal cancer groups and 96% in submucosal cancer groups [5–7]. However, little is known about the prognosis of endoscopic resection, particularly ESD [8–10]. Therefore, we performed this retrospective, long-term analysis to investigate the feasibility of ESD as curative treatment for possible node-negative EGC.

Patients and methods

From January 2000 to March 2007, 335 patients with 385 EGCs underwent ESD in our hospital after giving informed consent. All the indicated lesions were preoperatively either proven or suspected as adenocarcinoma by endoscopic biopsy. The following criteria, which are without angiolymphatic invasion, were the curability criteria for ESD used in our hospital, and reported by Gotoda et al. as node-negative EGCs [4]:

- intramucosal intestinal-type cancer without ulcerative findings, regardless of size (M-UI[−])
- intramucosal intestinal-type cancer with ulcerative findings, 3 cm or less in size (M-UI[+])
- SM1 (slight invasion into submucosa less than 500 µm from muscularis mucosa) intestinal-type cancer, 3 cm or less in size (SM1).

The original criteria by Gotoda et al. also included small intramucosal diffuse-type cancers without ulcer findings. In our hospital, however, these cancers are principally resected by gastrectomy for reasons such as difficulty in demarcation of the tumor margin, possibility of rapid growth of residual cancer cells, or difficulty in deciding on ulcerative status in some cases.

The above histological diagnosis was principally predicted by white-light conventional endoscopy and chromoendoscopy with indigo carmine. Endoscopic ultrasonography was also performed for lesions with suspicion of submucosal invasion and/or ulcerative lesions. After ESD, some of the lesions were excluded from further assessment; a total of 276 lesions in 231 patients, which met the above curability criteria, were eligible to be assessed for this study (**Fig. 1**). Excluded were: nine lesions in eight patients in a remnant stomach after gastrectomy or in a gastric tube after esophagectomy because a previous operation might have changed the angiolymphatic flow and the previous carcinoma might have influenced the patient's survival; 76 lesions in 76 patients that did not meet the criteria of node-negative EGC; seven diffuse-type adenocarcinomas within 2 cm in seven patients; 11 locally recurrent carcinomas in nine patients; and six lesions in four patients, in whom post-ESD lesions were resected by additional gastrectomy due to another possible node-positive EGC because the outcome of current ESD could not reflect the survival of these patients accurately. Clinicopathological features of the eligible lesions are shown in **Table 1**.

For the short-term analysis, all the EGCs (246 M-UI[−]s, 17 M-UI[+]s, 13 SM1s) were analyzed in terms of en bloc resection (resection in a one-piece fashion with endoscopically no residual tumor), complete resection (resection in a one-piece fashion with histologically no tumor on the lateral and vertical margins), and two major complications (delayed bleeding and perforation). Additionally, the subanalysis targeting the M-UI(-) group (179 small tumors [≤2 cm in size] and 67 large tumors [>2 cm in size]) was performed to verify the technical feasibility of ESD for large tumors.

For the long-term analysis, 212 lesions (76.8% of the 276 lesions), which were checked by esophagogastroduodenoscopy at least once later than 1 year post-ESD or had recurred within 1 year, were analyzed for local recurrence. In the subanalysis, the frequency of local recurrence was compared between the lesions with and without en bloc/complete resection. In terms of metastases and survival, data from 208 patients (90.0% of the 231 patients) whose survival information was obtained later than 1 year or whose death occurred within 1 year, were analyzed. For the 117 patients who had no medical records for the most recent year up to the end of March 2008, the following questionnaire was sent in order to obtain the necessary information.

- When did you have your last endoscopy?
- Was the local recurrence identified by endoscopy?
- When did you have your last abdominal computed tomography (CT) scan?
- Was any metastasis identified by CT?

At total of 78 patients (66.7%) had responded to our questionnaire by the end of April 2008, and the obtained data were included in the analyses.

	Total	Cancer type		
		M-UI(-)	M-UI(+)	SM1†
Number of patients	231	203	15	13
Age, mean ± SD, years	66.8 ± 9.6	66.7 ± 9.4	67.0 ± 13.7	68.8 ± 8.3
Sex, male/female	192/39	168/35	13/2	11/2
Number of lesions	276	246	17	13
Location				
Upper	43	36	2	5
Middle	89	79	4	6
Lower	144	131	11	2
Circumference				
Anterior wall	51	48	1	2
Posterior wall	71	61	3	7
Lesser curve	112	98	11	3
Greater curve	42	39	2	1
Macroscopic type				
Protruded or elevated	81	75	2	4
Flat or depressed	171	151	15	5
Combined	24	20	0	4

† Slight invasion into submucosa < 500 µm from muscularis mucosa.

Table 1 Clinicopathological features of possible node-negative cancers resected by endoscopic submucosal dissection.

	Total	Cancer type			*P*-value
		M-UI(-)	M-UI(+)	SM1‡	
Number of lesions	276	246	17	13	
En bloc resection rate, %	96.7	97.6	88.2	92.3	0.0731
Complete resection rate, %*	91.7	92.3	82.4	92.3	0.3575
Delayed bleeding rate, %†	5.1	4.5	11.8	7.7	0.3770
Perforation rate, %	4.0	3.7	5.9	7.7	0.7063

* En bloc with histologically tumor-free on the edge of lateral/vertical surgical margins.
† The rate of cases needing emergency endoscopy due to hematemesis or melena.
‡ Slight invasion into submucosa < 500 µm from muscularis mucosa.

Table 2 Short-term outcomes of endoscopic submucosal dissection for possible node-negative early gastric cancers.

ESD techniques have been described precisely elsewhere [2,3,11–13]. In brief, a flex-knife (KD-630L; Olympus, Tokyo, Japan) was used as the main electrosurgical knife [3,11]. An insulation-tipped diathermic knife (IT knife) [12] or a hook-knife [13] was used as the lesion required. These knives were used for cutting the surrounding non-neoplastic mucosa and for submucosal dissection beneath the lesion. A mixture of 10% glycerin plus 5% fructose and 0.9% saline preparation (Glyceol, Chugai Pharmaceutical Co., Tokyo, Japan) or 20% glucose, which contained 0.005% indigo carmine and 0.0005% epinephrine, was injected into the submucosa under the lesion to make a submucosal fluid cushion [14]. Hyaluronic acid was added to the injection solution for lesions with ulcerative findings or those located in a difficult area [15]. Hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan) were used for bleeding during the procedure or for ablation of visible vessels on the mucosal defect after resection [16]. An electrocautery snare 15 mm (SD-210L-15, Olympus) or 25 mm (SD-210L-25, Olympus) in diameter was used at the final step of ESD when appropriate, following consideration of several factors (e.g. procedure time, technical difficulty, complications, patient's comorbidity).

If the patient's symptoms, laboratory findings, and chest and abdominal radiographs were unremarkable the day after ESD, a light meal was permitted, and the patient was then discharged within 1 week. If complications occurred, the schedules were changed according to the individual patient's condition. Follow-up endoscopy for surveillance of recurrence was carried out at 2 months after ESD in the first year, and annually thereafter. If tumor-free margins of the resected specimens had not been obtained at ESD, an additional endoscopy at 6 months post-ESD was scheduled. Abdominal CT was also performed annually, or more frequently, according to the judgment of doctors in charge. For the statistical analyses, the chi-squared test was used for the analysis of short-term outcomes, and Fisher's exact probability test was used for the subanalyses. The Kaplan-Meier method was used for the analysis of long-term outcomes. If we could not calculate the difference between the groups due to no event in either group, the chi-squared test or Fisher's exact probability test was used to assess those differences in proportions. Statistical significance was set at a *P*-value of less than 0.05.

Results

The short-term outcomes of ESD are summarized in ○ **Table 2**. In total, favorable outcomes could be shown in the en bloc resection rate (96.7%) and the complete resection rate (91.7%). Delayed bleeding rate (5.1%) and perforation rate (4.0%) were also acceptable and all complications were managed without surgical intervention. In the analyses according to EGC group, there were no significant differences between the groups. Even in the subanalysis of tumor size in the M-UI(-) group, there were no significant differences in the resectability and complication rates (○ **Table 3**).

	≤ 2 cm	> 2 cm	*P*-value
Number of lesions	179	67	
En bloc resection rate, %	97.8	97.0	0.6650
Complete resection rate, %*	93.3	89.6	0.4200
Delayed bleeding rate, %†	5.0	3.0	0.7320
Perforation rate, %	3.4	4.5	0.7075

* En bloc with histologically tumor-free on the edge of lateral/vertical surgical margins.
† The rate of cases needing emergency endoscopy due to hematemesis or melena.

Table 3 Short-term outcomes of endoscopic submucosal dissection for intramucosal cancers without ulcerative findings.

For the lesion-based long-term analysis during a median endoscopic follow-up of 36 months (range 2–93 months), locally recurrent carcinoma occurred in two of 212 lesions (0.9%). Both cases had been resected in an en bloc fashion without tumor-free lateral margins. In one case, local recurrence was diagnosed at 2 months after ESD for M-UI(-). Additional ESD was performed in an en bloc fashion without tumor-free lateral margins; local recurrence was indicated again after a further 7 months, but no further treatment was performed because of coexisting uncontrollable hepatocellular carcinoma, which caused death at 25 months after the initial ESD. In the other case, local recurrence was diagnosed at 6 months after ESD for M-UI(+). Additional ESD was performed with complete resection and no further recurrence was seen after a further 10 months. No recurrence was seen in lesions that underwent complete resection. Between the lesions with and without en bloc resection, there was no significant difference in local recurrence rate (1.0% [2/203] vs. 0% [0/9]; $P > 0.9999$), whereas in the lesions with incomplete resection local recurrence was significantly more frequent than in the lesions with complete resection (8.7% [2/23] vs. 0% [0/189]; $P = 0.011$).

For the patient-based long-term analysis during a median follow-up of 38 months (range 6–97 months), no metastasis to lymph nodes or other organs was seen and nine patients died due to diseases other than gastric cancer. Of those, one patient died 6 months after ESD. The 3- and 5-year overall/disease-specific survival was 96.2%/100% and 96.2%/100%, respectively, with no significant differences between the three groups (**Fig. 2**).

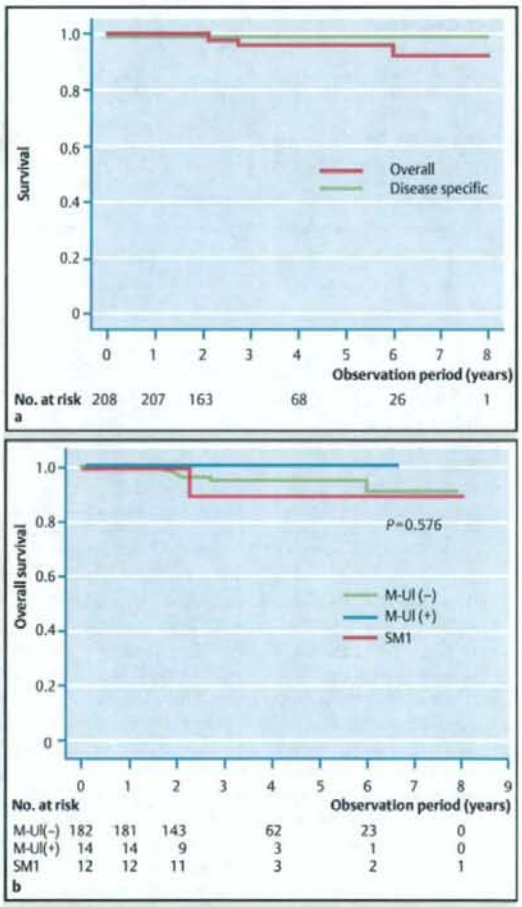

Fig. 2 Kaplan-Meier estimation of survival for early gastric cancer patients: **a** in total; **b** in the three groups. There was no significant difference between the groups.

Discussion

In the present study, the overall rates of en bloc resection and complete resection, which were major parameters for the evaluation of the short-term outcomes of ESD, were high (96.7% and 91.7%). In addition, technical feasibility to expand the indication criteria for ESD to include large intramucosal intestinal-type EGCs without ulcerative findings and small intramucosal intestinal-type EGCs with ulcerative findings may be acceptable in terms of short-term outcomes. Furthermore, the favorable short-term outcomes have led to excellent long-term prognoses in this study. In particular, the 3- and 5-year disease-specific survival rates (100%, 100%) are as high as those in reported data for gastrectomy [5–7]. When considering the preservation of stomach physiology in cases of ESD, it is quite obvious that ESD will win an advantage over gastrectomy.

In small EGCs, some reports have demonstrated the long-term efficacy of endoscopic resection, showing satisfactory data of 3- or 5-year disease-specific survival rates (> 99%) [8,9]. The comparative studies between endoscopic mucosal resection (EMR) and ESD have revealed some advantages and disadvantages of ESD and EMR [9,10]. Further studies will be needed to elucidate the best endoscopic treatments for small EGCs in each case.

Additionally, another advantage of ESD, to minimize local recurrence even when piecemeal resection is performed, was noticed in this study. From this study, only two cases with en bloc resection resulted in local recurrence, whereas none of nine lesions that underwent piecemeal resection recurred. On the contrary, previous studies of EMR have revealed that piecemeal resection could be a major causal factor for local recurrence [1,17,18]. Procedural differences between EMR and ESD may influence the re-

sults, which means that circumferential mucosal incision around the tumor with an appropriate margin during ESD may prevent the occurrence of residual cancer cells even when ESD is completed in a piecemeal fashion. Further studies are warranted to determine whether en bloc resection by ESD is essential for a favorable prognosis. However, from the aspect of precise histological investigation, piecemeal resection should be avoided even when ESD is applied [19], and the number of pieces should be kept to a minimum.

In contrast to intestinal-type EGC, ESD for diffuse-type EGC should be discussed cautiously [20,21]. Even though Gotoda et al. [4] reported that there was no lymph node metastasis in diffuse-type EGCs of less than 2 cm in size without ulcerative findings, the results were based on relatively small numbers (141 cases), and there remain a number of identified difficulties in using ESD for this indication (e.g. difficulty in demarcation of tumor margin, possibility of rapid growth of residual cancer cells, and uncertainty over ulcerative findings). More evidence is needed to clarify the use of ESD in this indication.

The limitations of this study are its retrospective design and single-center analysis, with recall bias to some extent, although the results were obtained from consecutive data. To increase the follow-up rate, questionnaires were sent to those patients lost during follow-up. However, there are approximately 20% of local recurrence and 10% of survival data still missing. A prospective, multicenter study will be necessary to confirm our results.

In conclusion, the present study with favorable long-term prognoses corroborated the feasibility of ESD for possible node-negative intestinal-type EGC and the validity of the criteria of node-negative intestinal-type EGC as curability criteria for ESD. We would propose that ESD can become an alternative method to gastrectomy in cases of possible node-negative intestinal-type EGC, with an invaluable advantage over gastrectomy of preservation of the stomach.

Competing interests: None

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