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Endoscopic submucosal dissection is useful and safe for intramucosal gastric neoplasms in the elderly

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Abstract

Background and study aims : **Endoscopic submucosal dissection (ESD) has recently gained popularity for use against intramucosal gastric neoplasms in Japan, but few studies have examined whether ESD is feasible for elderly patients. This study aims are to evaluate the efficacy and safety of ESD according to age in consecutive elderly patients treated with ESD.**

Patients and methods : **Subjects comprised 116 patients (90 men, 26 women) with 125 lesions treated using ESD from November 2002 to March 2006 at Nagoya City University Hospital and Iwata Municipal Hospital, Japan. Patients were categorized into : Group A, < 65-years-old (n = 34) ; Group B, ≥ 65-years-old but < 75-years-old (n = 41) ; and Group C, ≥ 75-years-old (n = 41). En bloc resection rate and treatment time were examined according to age, tumour size and location, and frequency of complications was examined according to age.**

Results : **Rate of concomitant disease was significantly higher in Group C than in the other groups. En bloc resection rates and median treatment times were 91.4% and 80 min in Group A, 91.1% and 97 min in Group B and 86.7% and 110 min in Group C, respectively. No significant differences were noted between groups, or for en bloc resection rate and treatment time according to tumour size and location, or between groups for frequency of complications.**

Conclusions : **ESD for gastric neoplasms is effective and safe in elderly patients, and may be positively recommended to elderly patients with intramucosal gastric neoplasms.** (Acta gastroenterol. belg., **2007**, 70, **323-330**).

Key words : aged, endoscopy, gastroscopic surgery, gastric cancer, gastric neoplasms.

Introduction

Malignant neoplasms are the leading cause of death in Japan (1). Standardized incidence and mortality rates for gastric cancer are declining in Japan, but the figures remain very high and this pathology represents the second-most common cause of malignant neoplasms in both men and women. Conversely, the number of elderly patients with gastric cancer has been increasing with the rapid aging of the Japanese population. Moreover, cases of early gastric cancer have been increasing by progress in endoscopic diagnosis. Opportunities for endoscopic therapy in elderly patients have thus been increasing and can be expected to keep increasing in the future.

Endoscopic mucosal resection (EMR) has been widely used to treat intramucosal gastric cancer (2,3), as good quality of life can be achieved compared with surgical gastrectomy (4,5). EMR has typically been performed using strip biopsy (6,7) and aspiration mucosectomy (8,9). However, as en bloc resection is often difficult using EMR when dealing with lesions > 10 mm using conventional methods (10), specimens resected piecemeal often cannot be used to judge curability (11) and sometimes result in residual tumour or recurrence after EMR.

The criteria for EMR thus include size limitations for treating lesions. A new EMR technique with submucosal dissection using new devices such as an insulation-tip diathermic knife (IT-knife) (12), hook knife (13), flex knife (14,15) and small-calibre tip transparent hood (ST hood) (16) have recently been developed to achieve reliable en bloc resection, as "endoscopic submucosal dissection (ESD)". ESD allows en bloc resection for intramucosal tumours > 20 mm and reduces local recurrence (17-20), and the technique has been rapidly accepted in Japan. Conversely, high frequencies of complications such as severe bleeding and perforation have been reported for ESD (18,21).

However, although conventional EMR is a well-established method in elderly patients (22), the efficacy and safety of ESD must be assessed separately for the elderly as a new and developing technique. To the best of our knowledge, only 2 studies have specifically examined ESD in the elderly (23,24). Moreover, those studies did not evaluate treatment time or tumour location. Old age cannot be defined exactly because it does not have the same meaning in all societies. However, most developed world countries have accepted the chronological age of 65 years as a definition of 'elderly' or older person because workers become eligible to retire with full Social Security benefits at age 65, and the Japan Geriatrics Society define persons aged 65 to 74 as early old age and ≥ 75-years as late old age.

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Thus, to assess the effects of ESD for the elderly, we divided cases treated with ESD into 3 groups according to age and retrospectively examined en bloc resection rate, treatment time and frequency of complications according to tumour size and location when gastric neoplasms including gastric adenoma and early gastric carcinoma were treated using ESD.

Patients/materials and methods

Patients

A total of 125 lesions in 116 patients (90 men, 26 women) treated using ESD between November 2002 and March 2006 at Nagoya City University Hospital and Iwata Municipal Hospital, Japan, were retrospectively analyzed. Patients were categorized into 3 groups : Group A (non-elderly group), < 65-years-old ; Group B (early old age group), ≥ 65-years-old but < 75-years-old ; and Group C (late old age group), ≥ 75-years-old. Group A comprised 34 patients (28 men, 6 women) with 35 lesions. Group B comprised 41 patients (29 men, 12 women) with 45 lesions. Group C comprised 41 patients (33 men, 8 women) with 45 lesions. All patients in the present study consisted of Japanese population. Informed consent was provided by all patients. The protocol for the research project was approved by a suitably constituted Ethical Committee of the institution. Follow-up endoscopic examinations were performed to check for recurrence every 3 months during the first year after EMR, then annually thereafter.

Based on endoscopic findings, endoscopic ultrasonography (EUS) (UM-2R ; Olympus Optical, Tokyo, Japan) and biopsied specimens, indications for endoscopic treatment were determined. EUS was performed when the lesion was diagnosed as adenocarcinoma based on biopsy findings. Tumours resected in this study comprised early gastric cancers and gastric adenomas, as the main study aim was to evaluate the efficacy and problems of ESD for the treatment of gastric neoplasms including both cancers and adenomas. According to expanded criteria for EMR reported previously (25), the following criteria were fulfilled for all lesions : 1) histopathological diagnosis of differentiated-type adenocarcinoma or adenoma ; 2) lesions within the mucosal layer based on endoscopic findings and EUS ; 3) lesions without ulceration or lesions ≤ 30 mm in diameter with ulceration ; and 4) less than performance status (PS) 2 on the Eastern Cooperative Oncology Group (ECOG) scale without severe concomitant disease. Performance status 2 is defined as ambulatory and capable of all selfcare but unable to carry out any work activities, and up and about more than 50% of waking hours (26).

Location and size of lesions

Location of the resected tumour was categorized into 3 areas : U, upper third of the stomach ; M, middle third of the stomach ; and L, lower third of the stomach. Size was defined as the greatest diameter of the tumour on endoscopic measurement (M2-4K ; Olympus Optical).

ESD

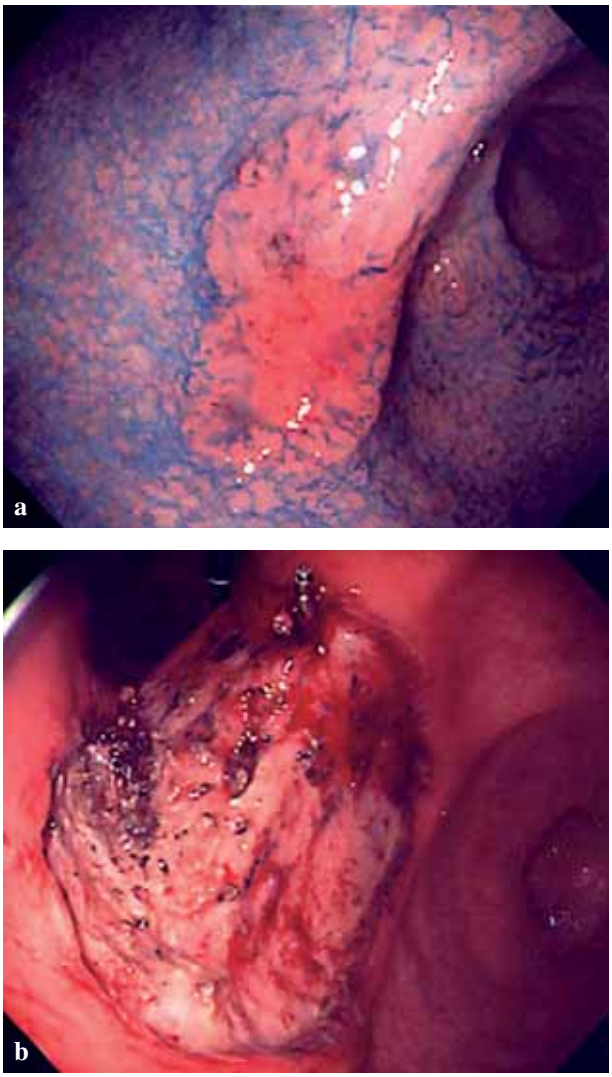
ESD was performed using an IT-knife (12,17,18,27), a flex knife (14) and hook knife (13) as previously reported, through a conventional single-channel endoscope (GIF-Q230, Q240 or H260 ; Olympus Optical), as appropriate. A soft hood (D-201-10704 ; Olympus Optical) was attached to the tip of the endoscope to obtain good endoscopic views. Briefly, several spots were marked 5-10 mm outside the margin of the target lesion using a needle knife (KD-1L ; Olympus Optical) in forced-coagulation mode (30 W) pre-set on the high-frequency generator (Erbtom ICC200 ; Erbe, Tübingen, Germany). Glycerin containing a small amount of indigocarmine dye and 0.5% epinephrine was injected into the submucosal layer around the tumour to lift and detach the mucosal lesion. After cutting mucosa around the marking spots using the IT-knife in endo-cut mode (80 W) or the flex knife (14) in endo-cut mode (60 W), the submucosal layer was dissected using the IT-knife in endo-cut mode (80 W) and the flex knife (14) and hook knife (13) in forced-coagulation mode (60 W). Lesions were thus able to be completely resected in 1 piece (Fig. 1a, b, c). Treatment time was defined as time from marking to the completion of the resection.

Histological assessment of resected lesions

Resected specimens were fixed in formalin and sectioned into 2-mm slices, then embedded in paraffin. Each slice was microscopically assessed for histological type, depth of invasion, presence or absence of lymphatic or venous invasion and completeness of resection according to the Japanese Classification of Gastric Carcinoma (28). En bloc resection was defined when the tumour could be resected in 1 piece and neoplastic components were not shown on either lateral or vertical margins under microscopic examination of specimens. As the presence of submucosal invasion, lymphatic or venous invasion or undifferentiated-type adenocarcinoma are considered to indicate higher risk of lymph node metastases, surgical treatment was strongly recommended (25).

Complications

Bleeding was categorized into 2 types : intraoperative ; and postoperative. Intraoperative bleeding was defined when > 10 min was required to stop bleeding during endoscopic treatment. Postoperative bleeding was defined when hematemesis or melena was detected, or hemostatic treatment with endoscopic clipping, ethanol injection and Argon plasma coagulation (APC) was required after endoscopic treatment. Perforation was diagnosed during endoscopic treatment or according to the presence of free air on plain radiography. If



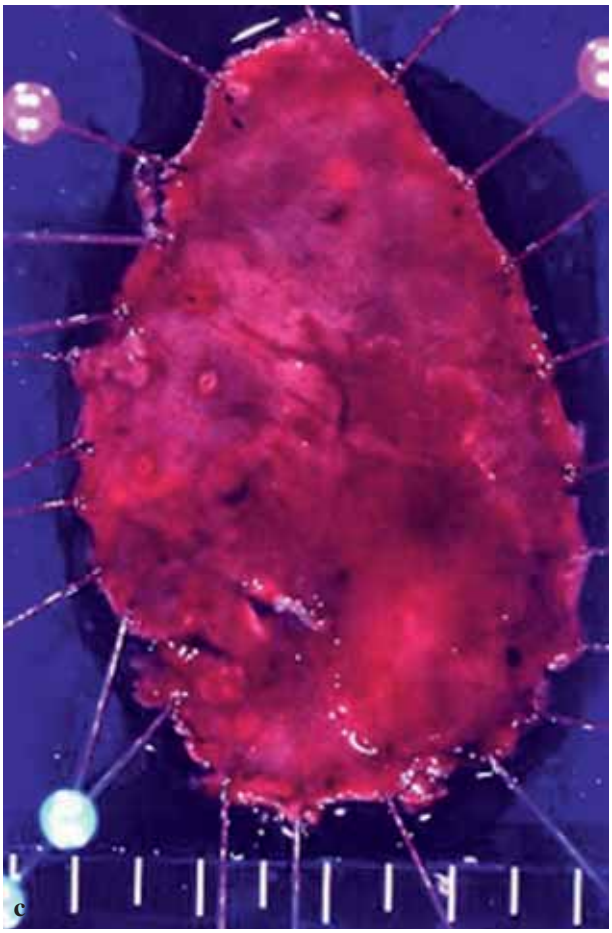


Fig. 1. — ESD. a) Endoscopic examination shows elevated-type early gastric cancer, 40 mm in diameter, located on the lesser curvature of the angle of the stomach ; and b) the view after resection of the mucosal lesions using ESD. c) Lesions were resected in 1 piece, and diagnosis based on histological assessment was intramucosal differentiated adenocarcinoma.

perforation was diagnosed during treatment, endoscopic closure of the perforation was performed by application of metallic clips (29) (Fig. 2a, b). Pneumonia was diagnosed according to fever with respiratory symptoms and/or hypoxia and the presence of consolidation on plain radiography.

Statistics

Values are expressed as medians, interquartile ranges (IQRs) and ranges due to the non-parametric nature of the data. Data were analyzed using the $m \times n$ χ^2 test, Kruskal-Wallis test or Mann-Whitney U-test with Bonferroni correction, as appropriate. Values of $p < 0.05$ were considered statistically significant.

Results

Characteristics

Characteristics of patients in the 3 groups treated with ESD are shown in Table 1. Median age for Groups A, B and C was 61 years (IQR, 6.5 years ; range, 42-64 years), 70 years (IQR, 5 years ; range, 62-74 years) and 78 years (IQR, 4 years ; range, 75-91 years), respectively. Significant differences were thus noted among the 3 groups. Histological diagnosis was adenoma in 11 lesions and adenocarcinoma in 24 lesions for Group A, adenoma in 18 lesions and adenocarcinoma in 27 lesions for Group B, and adenoma in 13 lesions and adenocarcinoma in 32 lesions for Group C. Median tumour size was 17 mm (IQR, 12.5 mm ; range, 8-38 mm) for Group A, 15 mm (IQR, 11 mm ; range, 6-60 mm) for Group B, and 16 mm (IQR, 15 mm ; range, 6-50 mm) for Group C. No significant differences were noted among the 3 groups for gender ratio, histological diagnosis, median tumour size or tumour location.

Concomitant diseases

Concomitant diseases in each group are shown in Table 2. Concomitant disease was present for 12 patients (35.3%) in Group A, 13 patients (31.7%) in Group B and

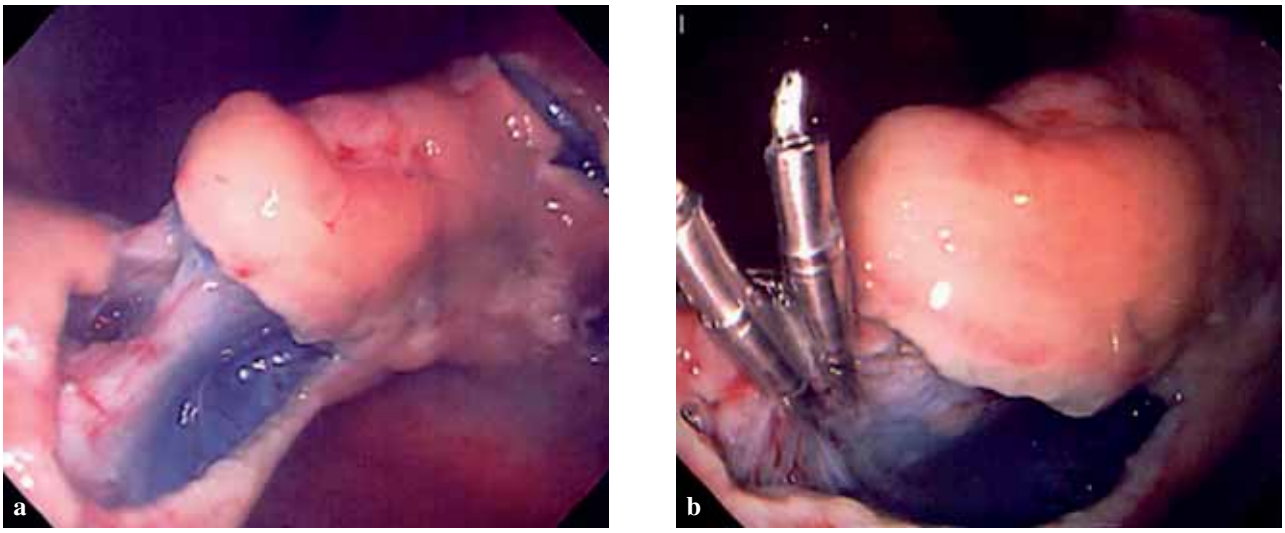


Fig. 2. — Intraoperative perforation with ESD. a) Perforation occurred on the angle of the stomach while cutting the mucosa using an IT-knife. b) The perforation was closed using 2 metal clips, then treatment was continued and the lesion was resected in 1 piece.

Table 1. — **Characteristics in Groups A, B and C**

	A (Age < 65)	B (65 ≤ Age < 75)	C (Age ≥ 75)	*p*
Number of lesions	35	45	45	
Number of patients	34	41	41	
Median age, years (IQR, range)	61 (6.5, 42-64)	70 (5, 65-74)	78 (4, 75-91)	< 0.001
Gender				
Male	28	29	33	= 0.417
Female	6	12	8	
Tumor				
Gastric adenoma	11	18	13	= 0.510
Gastric adenocarcinonia	24	27	32	
Median tumor size, mm (IQR, range)	17 (12.5, 8-38)	15 (11, 6-60)	16 (15, 6-50)	= 0.735
Tumor location				
U	4	7	6	= 0.783
M	16	20	25	
L	15	18	14	

U : upper third of the stomach ; M : middle third of the stomach ; L : lower third of the stomach. Data were analyzed using the $m \times n$ χ^2 test or Kruskal-Wallis test.

27 patients (65.9%) in Group C. Rate of concomitant disease was significantly higher in Group C than in the other groups. Heart disease (arrhythmia, angina, old myocardial infarction, etc.) was present with 1 patient (2.9%) in Group A, 5 patients (12.2%) in Group B and 10 patients (24.4%) in Group C. Rate of heart diseases was significantly higher in Group C than in Group A. Hypertension was identified with 5 patients in Group A, 4 patients in Group B and 10 patients in Group C, but no significant differences were noted among the 3 groups. Significant differences were likewise absent among the 3 groups for rate of respiratory disease, diabetes mellitus, chronic renal damage, cerebrovascular disease, chronic liver damage and anticoagulant therapy.

En bloc resection rates and treatment time according to tumour size

The breakdowns of en bloc resection rates and treatment time by tumour size are shown in Table 3. En bloc resection rate of lesions ≤ 20 mm was > 90% in all groups and no significant differences were noted among groups. Lesions > 20 mm were resected en bloc, comprising 11 of 12 lesions (91.7%) in Group A, 16 of 18 lesions (88.9%) in Group B and 14 of 18 lesions (77.8%) in Group C. No significant differences were noted among the 3 groups.

Median treatment time was 80 min (IQR, 100 min ; range, 10-555 min) in Group A, 97 min in Group B

Table 2. — **Concomitant diseases in Groups A, B and C**

	A (Age < 65)	B (65 ≤ Age < 75)	C (Age ≥ 75)	*p*
Concomitant disease, n (%)	12 (35.3)	13 (31.7)	27 (65.9)*	= 0.003
Heart disease	1 (2.9)	5 (12.2)	10 (24.4)**	= 0.026
Hypertension	5 (14.7)	4 (9.8)	10 (24.4)	= 0.192
Respiratory disease	3 (8.8)	2 (4.9)	3 (7.3)	= 0.791
Diabetes mellitus	2 (5.9)	1 (2.4)	1 (2.4)	= 0.652
Chronic renal damage	2 (5.9)	0 (0)	1 (2.4)	= 0.278
Cerebrovascular disease	0 (0)	0 (0)	3 (73)	= 0.060
Chronic liver damage	1 (2.9)	2 (4.9)	1 (2.4)	= 0.817
Anticoagulant therapy, n (%)	2 (5.9)	5 (12.2)	8 (19.5)	= 0.213

Data were analyzed using the m × n χ^2 test.
* P < 0.01, frequency of underlying disease in Groups A and B vs. Group C
**P < 0.05, frequency of heart disease in Group A vs. Group C.

Table 3. — **En bloc resection rates and treatment time in Groups A, B and C according to tumor size**

	Tumor size (mm)	A (Age < 65)	B (65 ≤ Age < 75)	C (Age ≥ 75)	*p*
En bloc resection rate (%)	≤ 20	21/23 (91.3)	25/27 (92.6)	25/27 (92.6)	= 0.982
	> 20	11/12 (91.7)	16/18 (88.9)	14/18 (77.8)	= 0.498
	Total	32/35 (91.4)	41/45 (91.1)	39/45 (86.7)	= 0.722
Median treatment time, min (IQR, range)	≤ 20	77 (107,10-555)	80 (106, 7-258)	60 (76.5, 16-222)	= 0.851
	> 20	102.5 (53.75, 25-175)	120 (120, 45-640)	123.5 (65.25, 24-380)	= 0.482
	Total	80 (100, 10-555)	97 (105, 7-640)	110 (100, 16-380)	= 0.794

Data were analyzed using the m × n χ^2 test or Kruskal-Wallis test.

(IQR, 105 min ; range, 7-640 min) and 110 min in Group C (IQR, 100 min ; range, 16-380 min), but no significant differences were noted among the 3 groups. Moreover, lesions ≤ 20 mm and > 20 mm likewise displayed no significant differences among the 3 groups in terms of median treatment time.

Clinical course

Clinical courses for Groups A, B and C are shown in Table 4. Local recurrence developed for 1 lesion in Group B and 1 lesion in Group C, but additional ESD was performed for these case and no further recurrence has since developed.

A total of 83 lesions (Group A, 24 lesions ; Group B, 27 lesions ; Group C, 32 lesions) were diagnosed as mucosal limited adenocarcinoma by EUS in addition to endoscopic appearance, but submucosal invasion (> 500 mm in depth) was seen on postoperative histological assessment for 1 lesion in Group A, 2 lesions in Group B and 1 lesion in Group C. Although cut margins were negative, surgical treatment was added for these lesions with deep submucosal invasion.

No significant differences were noted among the 3 groups in terms of recurrence rate and submucosal invasive rate. All cases in the 3 groups were disease-free as of the time of writing.

En bloc resection rates and treatment time according to tumour location

Breakdowns of en bloc resection rates and treatment times by tumour location are shown in Table 5. Even for lesions located in upper third of the stomach, a location in which resection is technically difficult to perform, all 4 lesions (100%) in Group A group, 5 of 7 lesions (71.4%) in Group B and 5 of 6 lesions (83.3%) in Group C were resected en bloc, and no significant differences were found among the 3 groups. For en bloc resection rate in the 2 other areas, no significant differences were seen among the 3 groups.

Median treatment time for lesions located in upper third of the stomach was 162.5 min (IQR, 33.75 min ; range, 130-190 min) in Group A, 150 min (IQR, 114 min ; range, 52-640 min) in Group B and 168.5 min (IQR, 116.75 min, range, 30-380 minutes) in Group C, significantly longer than for lower third of the stomach in each group. However, no significant differences were found among the 3 groups with regard to median treatment time in upper third of the stomach. Median

Table 4. — **Clinical course in Groups A, B and C**

	A (Age < 65)	B (65 ≤ Age < 75)	C (Age ≥ 75)	*p*
Recurrence. n (%)	0/35 (0)	1/45 (2.2)	1/45 (2.2)	= 0.648
↓ Re- ES D				
> Sm_2 invasion, n (%)	1/24 (4.1)	2/27 (7.4)	1/32 (3.1)	= 0.735
↓ Surgical treatment				

Re-ESD : Treated again using ESD.
Data were analyzed using the m × n χ^2 test.

Table 5. — **En bloc resection rates and treatment time in Groups A, Band C according to tumor location**

	Location	A (Age < 65)	B (65 ≤ Age < 75)	C (Age ≥ 75)	*p*
En bloc resection rate (%)	U	4/4 (100)	5/7 (71.4)	5/6 (83.3)	= 0.488
	M	14/16 (87.,5)	19/20 (95.0)	20/25 (80.0)	= 0.333
	L	14/15 (91.4)	17/18 (91.1)	14/14 (86.7)	= 0.634
Median treatment time, min (IQR, range)	U	162,5* (33.75, 130-190)	150* (114, 52-640)	168.5* (116.75, 30-380)	= 0.995
	M	86.5 (73.5, 25-555)	108 (97.5, 25-258)	110 (98, 21-222)	= 0.934
	L	53 (52, 10-150)	51.5 (83.75, 7-220)	61 (74,16-152)	= 0.660

U : upper third of the stomach ; M :middle third of the stomach ; L : lower third of the stomach.
Data were analyzed using m × n χ^2 test, Kruskal-Wallis test or Mann-Whitney U-test with Bonferroni correction.
* $P < 0.05$, treatment time for tumors located in U vs. L in each group.

treatment time in middle and lower third of the stomach did not differ significantly among the 3 groups.

Complications

Complications in Groups A, B and C are shown in Table 6. Intraoperative bleeding occurred for 2 of 35 lesions in Group A, 4 of 45 lesions in Group B and 4 of 45 lesions in Group C. Postoperative bleeding was noted in 1 lesion in Group A, 3 lesions in Group B and 2 lesions in Group C. All bleedings were minor without hypotension and hypoxemia. Perforation was observed in 1 lesion in Group A, 2 lesions in Group B and 1 lesion in Group C. Pneumonia occurred for 1 lesion in each group, but cure was achieved with 4-5 days of intravenous antibiotics and oxygen inhalation. All complications were resolved using conservative treatment without blood transfusion or surgery. No significant differences were noted among the 3 groups for intra- or postoperative bleeding, perforation and pneumonia.

Discussion

EMR has been accepted as a standard treatment for intramucosal gastric neoplasms in Japan due to the reduced invasiveness of therapy. Indications for EMR in cases of early gastric cancer are limited to differentiated IIa type (slightly elevated type) ≤ 20 mm in diameter, or differentiated IIc type (slightly depressed type) without ulcer formation and ≤ 10 mm in diameter (30). This is because tumours fulfilling these criteria are considered to display negligible risk of lymph node metastasis and en bloc resection is possible (31). However, a recent study of a large number of surgically resected cases has shown that intramucosal differentiated adenocarcinomas at any size without ulceration or lymphatic-venous invasion, and intramucosal differentiated adenocarcinomas ≤ 30 mm in diameter with ulceration but without lymphatic-venous invasion are not associated with nodal metastases (25).

ESD allows expansion of the indications for EMR to treat early gastric cancer, as ESD allows resection in 1 piece for large lesions and accurately evaluation of resected specimens (19). ESD has thus seen increasing use in Japan (32). In this study, indications of ESD for gastric neoplasms were expanded as mentioned above. However, as a high frequency of complications such as severe bleeding and perforation has been reported for ESD (18,21) and ESD treatment takes a long time (21), this approach seems to place an increased burden on the patient compared to conventional EMR. The population in Japan is rapidly aging, as with many other countries,

Table 6. — **Complications in Groups A, B and C**

	A (Age < 65)	B (65 ≤ Age < 75)	C (Age ≥ 75)	*p*
Bleeding, n(%)				
intraopcrative	2/35 (5.7)	4/45 (8.9)	4/45 (8.9)	= 0.842
postoperative	1/35 (2.9)	3/45 (6.7)	2/45 (4.4)	= 0.724
Perforation, n (%)	1/35 (2.9)	2/45 (4.4)	1/45 (2.2)	= 0.828
Pneumonia, n (%)	1/35 (2.9)	1/45 (2.2)	1/45 (2.2)	= 0.979

Data were analyzed using the m × n χ^2 test.

and the 2005 Population Census in Japan reported that the population ≥ 65-years-old rose to 21%, representing the highest rate in the world. It is thus necessary to evaluate effects on the elderly for the further spread of ESD. In this study, no significant differences were shown for gender ratio, histological diagnosis, median tumour size or tumour location besides age among the 3 groups. Frequency of concomitant disease for elderly patients ≥ 75-years-old was higher than that for the other groups, as expected, and frequency of heart disease was particularly increased in the late old age. Although no significant differences were noted, hypertension, cerebrovascular disease and anticoagulant therapy tended to be more frequent in the late old age. These data show that treatment for the late old age warrants further attention.

Tumour size and tumour location are important factors affecting the outcomes of EMR and ESD (20,33, 34). We therefore examined results according to tumour size and location in addition to overall outcome among the 3 groups.

No significant differences were noted for en bloc resection rate and treatment time or tumour size for all lesions among the 3 groups (Table 3).

With respect to the 1 lesion in Group B and 1 lesion in Group C that developed local recurrence, both lesions were previously resected in more than 2 pieces using ESD. These lesions were completely resected with second ESD, and no further recurrence has since developed. ESD is thus useful for recurrent lesions after endoscopic procedure.

Invasion into the submucosal layer was seen for 4 of the 83 lesions (4.8%) diagnosed as mucosa-limited adenocarcinoma before the procedure in the present study. Accurately diagnosing the depth of adenocarcinoma before ESD is thus difficult. However, no mucosa-limited lesions have been observed in cases operated on as submucosal invasion since starting this study on ESD. This is attributed to the fact that ESD has been performed initially when the depth of the lesion as either mucosal or submucosal is difficult to determine. ESD is available as a total biopsy for diagnosis of depth, avoiding unnecessary procedures. This approach is particularly useful for feeble patients such as the elderly. ESD to allow en bloc resection for large lesions is thus necessary to expand the indications for EMR. In the present study, treatment time was significantly longer for lesions in upper third of the stomach than for those in lower third of the stomach for each group. However, no significant differences for en bloc resection rate and treatment time according to tumour location were identified among 3 groups. These results show that any lesions can be resected using ESD as easily in the elderly as in younger patients.

Furthermore, no significant differences were noted for complications such as bleeding and pneumonia among groups in the present study. ESD can thus be performed as safely for the elderly as for younger patients. These result support similar findings to those by the recent report (24).

2 patients with more than performance status 3 and severe concomitant disease were excluded from ESD in this study. Such cases may undergo APC (35,36) and be followed as "watch and see" cases, as such patients are considered high risk for ESD and have a limited life expectancy. In fact, one with severe liver cirrhosis in the early old age was ablated with APC and the other in the late old age was followed as "watch and see" due to performance status 4 after cerebral infarction.

In conclusion, ESD for gastric neoplasms can be performed effectively and safely for elderly patients. ESD may be positively recommended for elderly patients with intramucosal gastric neoplasms. However, further development of the devices and techniques used in ESD is necessary for safe ESD, as cases taking a long time are sometimes encountered.

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