

## ORIGINAL ARTICLE

## FEASIBILITY OF ENDOSCOPIC SUBMUCOSAL DISSECTION FOR ELDERLY PATIENTS WITH EARLY GASTRIC CANCERS AND ADENOMAS

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**Background:** Endoscopic submucosal dissection (ESD) has the advantage of permitting en bloc and histologically complete resection for early gastric cancer. Elderly patients often have surgical operative risks due to disease, and the feasibility of this treatment for such patients will improve the quality of life. The aim of the present study is to evaluate the efficacy and safety of ESD in elderly patients.

**Methods:** We reviewed patients who underwent ESD for gastric lesions at Maebashi Red Cross Hospital. Among 251 gastric lesions treated by ESD from 2002 to 2006, 110 lesions were discovered in 93 elderly patients who were 75 years of age or older. The one-piece resection with tumor-free margin rate and the complications were assessed in comparison with younger patients under 75 years old.

**Results:** The average age of the elderly patients was 79.8 years (range 75–92 years). The one-piece resection with tumor-free margin rate was 96.4% (106/110). Immediate bleeding occurred in one lesion (0.9%) and delayed bleeding requiring emergency endoscopy occurred in five lesions (4.5%). Perforation during ESD occurred in two patients (1.8%), and was immediately closed with endoclips and managed by conservative medical treatment. One case (0.9%) complicated with delayed perforation was managed by conservative medical treatment. The one-piece resection with tumor-free margin rate and the complication rate in elderly patients were not significantly different from those of younger patients.

**Conclusion:** The present study shows the technical feasibility of ESD for gastric neoplasms in elderly patients.

**Key words:** complication, early gastric cancer, elderly patient, endoscopic submucosal dissection (ESD), one-piece resection, perforation.

## INTRODUCTION

A one-piece resection is considered to be the gold standard for endoscopic mucosal resection (EMR) as it provides an accurate histological assessment and reduces the risk of recurrence.<sup>1,2</sup> A new technique of endoscopic submucosal dissection (ESD) has the advantage of permitting en bloc and histologically complete resection.<sup>1,3–6</sup> The largest benefit of ESD is that en bloc resection of large or ulcerative lesions in any part of the gastrointestinal tract, mainly the stomach, is possible. However, this method has some disadvantages, including a long performance time and high frequency of complications, as well as the need for a high level of technical skill.<sup>1,3–6</sup>

In Japan, elderly patients over 64 years of age constitute more than 70% of all gastric cancer patients.<sup>7</sup> Although improvements have been made in surgical techniques and perioperative management, a curative but less radical treatment is desirable for the elderly, especially for early stage neoplasms.<sup>8</sup> Among patients who are 75 years or older, the majority have multiple diseases and functional disorders that

would influence daily living.<sup>9</sup> In Japan, the proportion of people who regularly attend hospital for at least one chronic disease is nearly 70% among people who are 75–84 years of age, which is the highest rate compared to other age groups.<sup>7</sup> Thus, one should not only treat each disease but also manage the patient's general function. Elderly patients often have surgical operative risks due to complicated diseases, and the feasibility of ESD for such patients will improve the quality of life.

In the present study, we aimed to evaluate the efficacy and safety of ESD for gastric neoplasms in elderly patients aged 75 years or older. The technical feasibility, the one-piece resection rate, and the complications of ESD in the treatment of gastric neoplasms were compared with those of younger patients.

## METHODS

We reviewed all patients who underwent ESD for gastric lesions at Maebashi Red Cross Hospital in the period between July 2002 and February 2006. Elderly patients aged 75 years or older were 93 patients with 110 lesions. The indications for ESD at our institute were as follows: (i) differentiated adenocarcinoma, intramucosal cancer (m), without ulcer findings (ul(-)), irrespective of the tumor size; (ii) differentiated, m, with ulcer findings (ul(+)),  $\leq 30$  mm in size;

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and (iii) differentiated, minute submucosal penetration (sm1, 500  $\mu$ m penetration into submucosa),  $\leq 30$  mm. ESD was performed not only for treatment purposes but also to make an accurate histological diagnosis of either early gastric cancers or large adenomas. Although the indications for ESD for early gastric cancers were normally based on the criteria, the lesions that did not meet the criteria were also treated with ESD in order to obtain an accurate histological diagnosis.

A data collection sheet was designed to obtain the relevant clinical information about the patient, tumor, procedure and complications, and was reviewed retrospectively. All patients provided written informed consent before receiving the treatment.

Prior to performing ESD, conventional and magnifying endoscopy (Olympus XQ260 and Q240Z; Olympus Optical, Tokyo, Japan), and chromoendoscopy with indigo carmine were routinely performed. The cases in which submucosal invasion was suspected were evaluated by endoscopic ultrasonography (EU-M30S; Olympus). The intravenous administration of pethidine hydrochloride and flunitrazepam/propofol were performed for sedation. First, 35 mg pethidine hydrochloride was given for pain control. From July 2002 to October 2005, flunitrazepam was used, while since November 2005, propofol has been used. Regarding flunitrazepam, it was given at a dosage of 0.01 mg/kg bodyweight at the start of the treatment. Additional administrations of flunitrazepam at 0.003 mg/kg bodyweight were performed when the sedation was weak. In the cases with propofol, it was given at a dosage of 1 mg/kg bodyweight at the start of treatment. Propofol was given at a dosage of 3 mg/kg bodyweight/h. During the administration, patient's consciousness, blood pressure, peripheral oxygen saturation (SpO<sub>2</sub>), heart rate, and electrocardiography (ECG) were monitored. If necessary, O<sub>2</sub> was provided with a nasal catheter. To prevent aspiration pneumonia or deep vein thrombosis, suction of the oral cavity was performed to remove any saliva or exudate and the postural exchange or massage of the lower limbs was performed when the ESD procedures lasted more than 1 h. After the ESD procedures, 2 mg flumazenil were given to antagonize flunitrazepam. In the cases with propofol, the patients were monitored until they obtained complete recovery from sedation.

In patients who took either anticoagulants or antiplatelets daily, they were stopped for 1 week before the treatment whenever possible. Then, after the treatment, anticoagulants or antiplatelets were started from 2 weeks. For those who had a risk of thrombosis and could not stop anticoagulants, intravenous heparin was given instead, until 6 h before the treatment. At 1 h after completing the treatment, follow-up endoscopy was performed to confirm hemostasis. Thereafter, intravenous heparin was given. Anticoagulants were then restarted the next day. We followed, in principle, the guidelines on the management of anticoagulation and antiplatelet therapy for endoscopic procedures either from the American Society for Gastrointestinal Endoscopy (ASGE) in 2002<sup>10</sup> or from the Japan Gastroenterological Endoscopy Society (JGES) in 2005.<sup>11</sup>

The tumors were treated by the standard ESD procedures by using the Flex-knife (KD-630L; Olympus Optical) alone in combination with the Hook knife (KD-620LR; Olympus Optical), and/or insulation-tipped (IT) knife (KD-610L; Olympus). The equipment was a single-channel endoscope (XQ260) with hood (D-201-11804; Olympus) and a high-

frequency generator with an automatically controlled system (Erbotom ICC200 or VIO 300D; ERBE, Tübingen, Germany). Briefly, marking dots were made on the circumference of the lesion. Next, several milliliters of the submucosal injection solution were injected with a 23-gauge disposal injection needle around the lesion to lift it off the muscle layer. Glyceol or sodium hyaluronate with a small amount of indigo carmine and epinephrine was used for submucosal injection solution. Thereafter, the incision of the mucosa outside the marking dots was made by the Flex-knife with the Endocut mode (effect 3, 80 W) to separate the lesion from the surrounding non-neoplastic mucosa. The submucosal connective tissue just beneath the lesion was then gradually dissected with the forced or swift coagulation mode (40 W) from the muscle layer. Where it was difficult to dissect with the Flex-knife, the other knives were used. For a large tumor, these procedures were repeated. Finally, the lesion was cut completely from the muscle layer without snaring. Visible exposed vessels on the artificial ulcer were coagulated with a Coagrasper (FD-410LR; Olympus) with the soft coagulation mode (60 W).

The location of the tumor was divided into the upper, middle and lower thirds of the stomach.<sup>12</sup> A one-piece resection was defined as en bloc resection. Resections were considered to have tumor-free margins when both vertical and horizontal margins were free of tumor cells. Procedure-related bleeding was subdivided into immediate and delayed groups. Immediate bleeding was defined as a large amount of bleeding during the procedure and difficult cases of hemostasis. Delayed bleeding was defined as clinical evidence of bleeding as evidenced by hematemesis or melena at 0–30 days after ESD and requiring endoscopic treatment. We also recorded the incidence of perforation as seen during endoscopy or based on clinical evidence obtained after the procedure. Abdominal X-rays were routinely performed after the procedure for checking the perforation. The physical examination and blood tests were checked based on the use of a clinical pathway. Patients without complications were permitted to take soft food 2 days after ESD and were then discharged after endoscopic follow up at the 7th day. Endoscopic follow-up examinations were performed routinely at 1 week, 3 months, 9 months and every 6 months after ESD, and patients were followed up until 5 years. The parameters assessed in this study were the one-piece resection with tumor-free margin rate and complications of ESD. The one-piece resection and the complication rate of ESD in the elderly were compared with those of younger patients less than 75 years who were treated during the same period in our hospital.

### Statistical analysis

Differences between the groups were analyzed by Fischer's exact probability test and Mann-Whitney's *U*-test, when a significant difference was obtained by the Kruskal-Wallis test. A *P*-value less than 0.05 was considered to be significant.

## RESULTS

### Background and characteristics of the patients

A total of 226 patients with 251 gastric lesions were treated with ESD during the observed period. Elderly patients aged

**Table 1.** Characteristics of gastric lesions treated by ESD among elderly ( $\geq 75$  years) and younger patients ( $< 75$  years)

Characteristics	Elderly ( $\geq 75$ years)	Younger ( $< 75$ years)	<i>P</i>
No. patients ( <i>N</i> )	93	133	
Age			
Mean (range; years)	79.8 $\pm$ 4.0 (75–92)	66.0 $\pm$ 6.4 (47–74)	0.000
Median (years)	79	67	
Sex (male/female)	50/43	106/27	0.001
No. lesions ( <i>N</i> )	110	141	
Location			
U/M/L ( <i>N</i> )	18/45/47	25/35/81	0.086
Macroscopic type			
Elevated/Flat/Depressed ( <i>N</i> )	85/1/24	79/5/57	0.001
Tumor size			
Mean (range; mm)	22.8 $\pm$ 13.2 (5–76)	21.8 $\pm$ 11.9 (5–80)	0.533
$\leq 20$ ( <i>N</i> )	61	70	
21–30	25	33	
31 $\geq$	24	38	
Tumor depth			
m/sm1/sm2 ( <i>N</i> )	102/6/2	114/12/15	0.844
Ulcer findings			
Positive/Negative ( <i>N</i> )	14/96	24/117	0.379

ESD, endoscopic submucosal dissection; L, lower third of stomach; M, middle third of stomach; N, number; U, upper third of stomach.

75 years or older were 93 patients with 110 lesions and younger patients aged less than 75 years were 133 patients with 141 lesions (Table 1). The average age of the elderly patients was 79.8  $\pm$  4.0 years (range 75–92 years). Male/female ratio in the elderly group was 50/43 and the ratio of females was significantly increased in the elderly group in comparison to the younger group ( $P < 0.001$ ). Seventy-four of the 93 elderly patients (79.6%) had comorbid diseases, including 32 cases with hypertension, 15 cases with heart disease (ischemic heart disease, arterial fibrillation etc.), seven with pulmonary disease (emphysema etc.), 16 with neurological diseases (cerebral infarction etc.), 11 with endocrine diseases (diabetes mellitus, hypothyroidism etc.) and nine with other malignancies (prostate cancer etc.). Eighty-three of the 133 younger patients (62.4%) had comorbid diseases, including 36 cases with hypertension, 12 cases with heart disease (ischemic heart disease, arterial fibrillation etc.), four with pulmonary disease (emphysema, bronchial asthma etc.), five with neurological diseases (cerebral infarction etc.), 21 with endocrine diseases (diabetes mellitus, gout etc.), four with chronic renal failure and nine with other malignancies (hepatocellular carcinoma, uterine cervical cancer etc.). The cases complicated with severe comorbid diseases whose prognosis was supposed to be worse than no treatment for gastric cancers were excluded for ESD treatment. Therefore, the cases in which the prognosis of comorbid diseases was considered to be less than several years were excluded for indication. The ratio of patients demonstrating comorbid diseases was significantly higher in the elderly group than in the younger group ( $P < 0.01$ ).

Mean neoplasm diameter was 22.8  $\pm$  13.2 mm (range 5–76 mm), and 49 (44.5%) lesions were larger than 20 mm in the elderly group. The median operation time for elderly patients was 89.1  $\pm$  83.5 min (range 10–400 min) and that for younger patients was 108.9  $\pm$  107.6 min (range 10–600 min). There were no significant differences in the operation time between the two groups. The one-piece resection with tumor-

free margin rate was 96.4% (106/110) in the elderly patients, and 95.0% (134/141) in the younger patients. There were no significant differences in the one-piece resection with tumor-free margin rate between the two groups. The four lesions in the elderly group resulted in a piecemeal resection, and additional endoscopic microwave coagulation therapy was performed. A total of seven patients were considered for additional therapy due to the risk of lymph node metastasis in the elderly patients. They had lymphatic and/or vascular invasion (three patients), massive submucosal invasion with lymphatic and/or vascular invasion (three patients), or undifferentiated type cancer (one patient). Among these seven patients, four patients underwent an additional gastrectomy with a lymph node dissection, which revealed no lymph node metastasis. The other three patients refused surgery due to their age and general health and, instead, were carefully followed. However, a total of 11 patients were considered to require additional therapy among the younger patients and these cases demonstrated lymphatic, vascular invasion, and/or massive submucosal invasion. All 11 of these patients underwent an additional gastrectomy with a lymph node dissection.

### Complications

There was no procedure-related death in this series. Four cases of urinary retention due to adverse effect of flunitrazepam were seen in the elderly patients. In the elderly patients, two cases were complicated with aspiration pneumonia after ESD. Six cases that developed fever after ESD were considered to have been caused by aspiration to the respiratory tract, although no obvious pneumonia shadow had been observed on chest X-ray findings. However, no cases of severe respiratory failure were observed and all cases recovered after either O<sub>2</sub> administration, antibiotics or observations. There were no other complications associated

**Table 2.** One-piece resection rate and complications with ESD among elderly ( $\geq 75$  years) and younger patients ( $< 75$  years)

	Elderly ( $\geq 75$ years) ( <i>n</i> = 110) (93 patients)	Younger ( $< 75$ years) ( <i>n</i> = 141) (133 patients)	<i>P</i>
One-piece resection with tumor-free margin rate (%)	106/110 (96.4%)	134/141 (95.0%)	0.426
Complications (no. patients)			
None	101 (84)	120 (112)	0.075
Bleeding			
Total	6	16 <sup>†</sup>	0.077
Immediate	1	5	
Delayed	5	12	
Perforation			
Total	3	6 <sup>‡</sup>	0.386
Immediate	2	6	
Delayed	1	0	

<sup>†</sup>One case was complicated with both immediate and delayed bleeding.

<sup>‡</sup>One case was complicated with both perforation and delayed bleeding. ESD, endoscopic submucosal dissection.

with sedation. Regarding specific problems which occurred in the elderly patients but not in the younger patients, delirium during the night was observed in four patients. No cases with either urinary retention, aspiration pneumonia or delirium were observed in the younger patients.

There were seven cases who took anticoagulants and 19 cases who took antiplatelets in the elderly group. All except one case stopped anticoagulants or antiplatelets for 1 week before and 2 weeks after the treatment. After artificial heart valve replacement, one patient could not stop the anticoagulants due to a high risk for developing thrombosis. This case was given intravenous heparin instead. There were no cases with complications due to cessation of the anticoagulants or antiplatelets, such as a recurrence of cerebral infarction or myocardial infarction.

Eighty-four patients (90.3%) with 101 lesions did not experience problematic complications related to the ESD procedures, for which the patients either needed additional treatment or required extended hospitalization. Patients without complications were permitted to take soft food 2 days after ESD and then they were discharged after endoscopic follow up on the 7th day. Treatment-related complications are presented in Table 2. Immediate bleeding occurred in one lesion (0.9%) and delayed bleeding requiring emergency endoscopy occurred in five lesions (4.5%) in the elderly group. No patient required laparotomy or blood transfusion after complications. Perforation occurred in two patients (1.8%) during submucosal dissection, and was immediately closed with endoclips. One case (0.9%) complicated with delayed perforation was managed by conservative medical treatment. This case had a past history of a distal gastrectomy 24 years ago. After local recurrence of an incomplete EMR at a previous hospital, she was referred to our hospital. The lesion was fibrotic and electrocoagulation was frequently used for hemostasis during the procedure. Furthermore, the reflux of bile juice may have caused mucosal injury. All perforations were managed endoscopically using endoclips, a patch of omentum or conservative therapy. No patient had to undergo any extra surgery. There was no

significant difference in the results of ESD between elderly patients and younger patients in terms of one-piece resection with tumor-free margin rate, and complication rate (Table 2).

## DISCUSSION

In the present study, ESD enabled us to treat elderly patients with safety and with acceptable complication rates which were the same as for younger patients. Nowadays, we are often faced with the problem of treating elderly patients with gastric neoplasms. Elderly patients often have complicated life-limiting diseases, including malignancies.<sup>7</sup> Therefore, a curative but less radical treatment in the elderly is desired, and endoscopic resection is very attractive in this respect.<sup>8</sup>

A one-piece resection is considered to be the gold standard for EMR as it provides an accurate histological assessment and reduces the risk of recurrence.<sup>1,2</sup> However, it is difficult to resect large and ulcerative lesions en bloc by conventional EMR techniques and therefore a new technique of ESD has been developed.<sup>1,3-6</sup> ESD is curative and is a less radical treatment, and has the advantage of permitting en bloc and histologically complete resection.<sup>1,3-6</sup> However, this method has some disadvantages, including a long performance time and high frequency of complications as well as the need for a high level of technical skill.<sup>1,3-6</sup> However, in the present study, we showed that the one-piece resection with tumor-free margin rate and the complication rate were acceptable in elderly patients, compared with those of younger patients.

No cases demonstrating severe aspiration pneumonia were observed in this study. However, the risk of aspiration pneumonia during ESD seems to increase with age. We should therefore be careful for aspiration pneumonia during the ESD procedure. To prevent aspiration pneumonia, we frequently performed suction of the oral cavity to remove saliva or exudate and carried out postural exchange every 1 h. During these procedures, consciousness, blood pressure, SpO<sub>2</sub> and ECG were all carefully monitored. Fortunately, there were no complications caused by cessation of anticoagulants or

antiplatelet therapy in this study. However, the risk of complications caused by the cessation of anticoagulant medicines depends on the severity of comorbid diseases. Sufficient discussions between the cardiologists or neurologists who administer the anticoagulants or antiplatelets can therefore help us to prevent the occurrence of such complications.

Matsushita *et al.* compared the outcome of elderly patients with gastric cancer with or without treatment and reported longer survival for patients with cancer treatment.<sup>13</sup> For early gastric cancer, the cumulative 5-year risk for progressing to the advanced stage is reported as 63.0%.<sup>14</sup> Thus, although there might be an option of no treatment in elderly patients, it is preferable to treat the lesion within its early stage, if the comorbid diseases of an elderly patient are under control.<sup>15</sup> Gastric adenoma may not be a suitable indication for treatment in elderly patients, as the expected life span of elderly patients would not be affected by the clinical course of adenoma, although gastric adenoma 2 cm or larger are reported to have a risk of developing cancer later on.<sup>16</sup> However, in this study of elderly patients, the complication rate was acceptable and the indications for high-grade adenomas should be expanded for accurate diagnosis and treatment.

Incomplete treatment may occur after ESD. In this study, among the seven patients whose resection was considered non-curative, three patients were followed without additional surgery. In elderly patients, it may be difficult to repeat treatments for local and distant recurrence due to the patient's physical condition or unwillingness. Therefore, it is very important to acquire the specimen in a way that ensures that an accurate histological examination can be carried out, and to obtain definite local control of the tumor. The latter is of special importance in elderly patients whose life expectancy is considered to be several years or longer.

In conclusion, ESD is a feasible method for the treatment of early gastric cancers and high-grade adenomas even in elderly patients. This treatment modality also demonstrates an acceptable rate of complications that can be sufficiently managed endoscopically. This method has helped us to expand our indications for EMR and reduce the need for surgery of early gastric cancers even in elderly patients.

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