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Clinical Outcomes and Complications of Endoscopic Submucosal Dissection for Superficial Gastric Neoplasms in the Elderly

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Abstract: The number of elderly people with superficial gastric neoplasms is increasing, but the clinical outcome of endoscopic submucosal dissection (ESD) for treating elderly people with superficial gastric neoplasms remains unclear. We aimed to compare the efficacy and safety of ESD for patients with early gastric cancer (EGC) and precancerous lesions in elderly (≥ 75 years of age) and nonelderly (< 75 years of age) patients.

From October 2005 to December 2014, 83 consecutive patients with EGC and precancerous lesions (86 lesions) who were treated using ESD in our hospital were retrospectively reviewed. There were 44 lesions in 42 elderly patients who were at least 75-years old. The following parameters were compared between the 2 groups: preexisting comorbidities, performance status (PS), lesion inclusion criteria, lesion characteristics, treatment outcomes, surgery time, duration of hospitalization, complications, and intraoperative hemodynamic changes.

Elderly patients had significantly higher preexisting comorbidity rates (90.9% vs 59.5%, $P = 0.001$), expanded lesion criteria rates (43.2% vs 19.0%, $P = 0.016$), and lower best PS rates (38.6% vs 81.0%, $P < 0.001$) than nonelderly patients. Lesion characteristics were similar in the 2 groups. The elderly had higher intraoperative hypotension rates (47.7% vs 21.4%, $P = 0.011$) and oxygen desaturation rates (9.1% vs 0.0%, $P = 0.045$) than nonelderly patients. In addition, the elderly also had a longer surgery time (107.0 ± 51.4 vs 91.5 ± 66.2 minutes, $P = 0.049$) and duration of hospitalization (7.5 ± 3.8 vs 5.9 ± 2.0 days, $P = 0.016$) than nonelderly patients. There were no differences in the prevalence rates of en-bloc resection, complete resection, bleeding, perforation, pneumonia, or intraabdominal free air between the 2 groups.

Although elderly patients who underwent ESD for superficial gastric neoplasms had an increasing risk of intraoperative hypotension and oxygen desaturation, all patients were treated appropriately without postoperative sequelae. ESD is a safe and feasible intervention for elderly patients who have more comorbidity, a worse PS and more expanded lesions.

(*Medicine* 94(44):e1964)

Abbreviations: APC = argon plasma coagulation, ASA = American Society of Anesthesiologists, EGC = early gastric cancer, ESD = endoscopic submucosal dissection, PS = performance status.

INTRODUCTION

Gastric cancer is the 5th most common malignancy and the 3rd leading cause of cancer death worldwide. Half the gastric cancer population lives in Eastern Asia.¹ Early gastric cancer (EGC) is defined as cancer invasion confined to the mucosa or submucosa (T1 cancer), regardless of the presence or the absence of lymph node metastasis.² In the past, gastrectomy with lymph node dissection was the gold standard of treatment for EGC. Endoscopic submucosal dissection (ESD), which originated in Japan to treat EGC, is a novel procedure that has a high en-bloc resection rate, complete resection rate, and low recurrence rate.³ Several retrospective studies have shown that patients with indications for ESD have comparable short-term and long-term outcomes to gastrectomy, but ESD has the advantage of fewer complications, a shorter duration of hospital stay and better quality of life.⁴⁻⁶

Population aging is a major global demographic trend that will intensify during the 21 century. The proportion of the population that is 60 years or older was 8% in 1950, 10% in 2000, and it is projected to reach 21% in 2050 worldwide.⁷ Of note, elderly patients constitute more than 50% of all gastric cancer patients in Taiwan.⁸ For elderly patients with advanced gastric cancer, longer survival was reported for patients who underwent surgery than for those who did not undergo treatment.⁹ For elderly patients with EGC, a multicenter study in Japan showed that both curative ESD and additional surgery after noncurative ESD may contribute to a longer life expectancy.¹⁰

Several reports had compared the clinical outcomes of elderly patients with nonelderly patients who received ESD for EGC. Some reports showed equivalent treatment outcomes and complications between the 2 groups.¹¹⁻¹³ However, a reduced en-bloc resection rate, a reduced complete resection rate, more immediate bleeding, a higher pneumonia risk, and a longer hospital stay have been reported in the elderly population.^{14,15} Sedation-related complications during the time-consuming ESD procedure were rarely reported in the 2 groups.

Editor: Okasha Hussein.

Received: August 1, 2015; revised: September 24, 2015; accepted: October 9, 2015.

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This study is in part supported by grant V104A-017 from Taipei Veterans General Hospital, Taipei, Taiwan.

The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001964

The aim of our study was to compare the clinical outcomes and complications of ESD for EGC and precancerous lesions in elderly patients and nonelderly patients

MATERIALS AND METHODS

Patients

Medical records were retrospectively reviewed from a total of 83 patients with 86 EGC and precancerous lesions who were treated by ESD at Taipei Veterans General Hospital from October 2005 to December 2014. We divided the patients into 2 groups: the elderly group, consisting of patients 75 years of age or older, and the nonelderly group, consisting of patients less than 75 years of age. All patients provided written informed consent to undergo ESD for superficial gastric neoplasms, and the institutional review board at our institution approved this study. The same endoscopist, who specialized in endoscopic tumor treatment, performed all ESDs.

Inclusion Criteria for ESD

ESD was indicated if the lesions fulfilled the guideline criteria or expanded criteria, according to the 2010 Japanese gastric cancer treatment guidelines.¹⁶ Precancerous lesions of the stomach including low-grade or high-grade dysplasia were also included. The standard criteria were defined as mucosal differentiated adenocarcinoma, without ulceration, ≤ 2 cm in diameter and no lymphatic-vascular involvement. The expanded criteria were defined as: mucosal differentiated adenocarcinoma, without ulceration, irrespective of tumor size; mucosal differentiated adenocarcinoma, with ulceration, ≤ 3 cm in diameter; mucosal undifferentiated adenocarcinoma, without ulceration, ≤ 2 cm in diameter; or minute submucosal invasion (SM1, $< 500 \mu\text{m}$ from the muscularis mucosa layer) differentiated adenocarcinoma without ulceration and ≤ 3 cm in diameter.

The macroscopic appearance, histological type, and depth of invasion of each tumor were identified according to the Japanese classification of gastric carcinoma.² The performance status (PS) for each patient was 0 or 1 on the Eastern Cooperative Oncology Group scale.¹⁷ Patients with an American Society of Anesthesiologists (ASA) physical status class were also assessed.¹⁸ If the patients were taking antiplatelet agents (salicylates, clopidogrel, and ticlopidine) or anticoagulants (warfarin) before ESD, these medications were discontinued for at least 1 week preoperatively and resumed 3 days postoperatively under stable conditions. A heparin pump was allowed for bridging until 6 hours before ESD for patients who had a high risk of thrombosis.

Data Analysis

Our analysis of the differences between the 2 groups included preexisting comorbidities (cardiovascular disease, chronic obstructive pulmonary disease, liver cirrhosis, chronic renal dysfunction, cerebral infarction, malignancy other than gastric cancer, hypertension, diabetes, and hyperlipidemia), PS, ASA physical status, lesion inclusion criteria, lesion characteristics, en-bloc resection rates, complete resection rates, surgery time, duration of hospitalization, ESD-related complications, and sedation-related complications.

Anesthesia Procedure

Before ESD, each patient was sedated using a continuous propofol infusion and alfentanil administration, with the assistance of an anesthesiologist. If needed, glycopyrrolate and hyoscine-*N*-butylbromide intravenous injection were used for reduction of secretions and control of gastrointestinal

peristalsis, respectively. Heart rate, blood pressure, electrocardiogram, and percutaneous oxygen saturation were monitored during the procedure. Bispectral index monitor was used to monitor the depth of anesthesia, which was maintained around 60.¹⁹ An end-tidal carbon dioxide monitor was used to detect life-threatening conditions and to circumvent potentially irreversible patient injury. Sedative medication doses were adjusted according to the patient's vital signs, bispectral index, and end-tidal carbon dioxide monitor. We monitored and treated sedation-related complications during the procedure.

ESD Procedure

Patients fasted for at least 6 hours before ESD. One dose of cefazolin (1 gm) was given 30 minutes before ESD. ESD was performed using a single-channel upper gastrointestinal endoscope (GIF-H260 or GIF-Q260, Olympus Medical Systems, Tokyo, Japan). A hood was placed on the tip of the endoscope to maintain a good visual field during submucosal dissection. The lesion was identified and demarcated by white light endoscopy, narrow band imaging, and/or chromoendoscopy with indigo carmine solution. Dots were made 5 to 10 mm outside the margin of the target lesion using argon plasma coagulation (APC). Hyaluronic acid, hydroxypropyl methylcellulose, or glycerol, mixed with diluted epinephrine and indigo carmine, were injected into the submucosal layer to lift the mucosa. The volume of injected fluid varied from 10 to 50 mL, depending on the size of the lesion. An initial cut was made using a dual knife (KD-650L, Olympus Medical Systems, Tokyo, Japan) outside the dotted boundary, and the circumferential mucosal incision was made around the lesion using a dual knife or an IT knife (KD-611L, Olympus Medical Systems, Tokyo, Japan). Submucosal dissection was performed using an IT knife. Repeated submucosal injection may be needed if the cushion dissipated before complete removal of the lesion. Hemostatic forceps (Coagrasper; FD-410LR, Olympus Medical Systems, Tokyo, Japan) were used to control active bleeding or destroy visible vessels at the wound base during and after ESD. An intravenous proton pump inhibitor was administered postoperatively, which was changed to the oral form once patients were able to orally take medication. Patients ingested nothing orally for 24 hours after ESD, followed by a liquid diet on the 2nd day and a soft diet on the 3rd day, if their clinical condition was stable.

Histopathological Evaluation

The resected specimen was oriented immediately and pinned flat onto a cork plate. The oral and anal sides of the specimen were dyed using different colors, and the specimen was immersed in formaldehyde. After fixation, the specimen was sectioned serially at 2-mm intervals and reviewed by the same pathologist. Pathological report included tumor size, location, pathological type, invasion depth, lymphatic-vascular involvement, and status of the margin of resection.

En-bloc resection was defined as lesions resected in 1 piece. Complete resection was defined as en-bloc resection with histological tumor-free peripheral and vertical margins. Piecemeal resection or tumor cell found in margins of specimen was regarded as incomplete resection. Specimens resected in multiple fragments were rearranged on a cork plate according to their original shape, if possible.

ESD-Related Complications

Procedure-related bleeding was defined as bleeding that required transfusion, emergency endoscopy, or surgical

intervention, or that caused a reduction in the hemoglobin level by more than 2 g/dL following the procedure. Procedure-related perforation was defined as endoscopically observed extraluminal space. Postoperative pneumonia was diagnosed by clinical respiratory symptoms/signs, chest radiograph, or chest computed tomography. Asymptomatic intraabdominal free air was detected using a plain frontal supine radiograph or abdominal computed tomography.

Sedation-Related Complications

Intraoperative hypertension was defined as any episode of systolic blood pressure elevation of over 20% from baseline, and it was treated using nicardipine hydrochloride, if necessary. Intraoperative hypotension was defined as any systolic blood pressure below 80 mmHg or at least 1 episode of systolic blood pressure more than 20% below baseline. Once intraoperative hypotension occurred, we immediately increased the intravenous fluid flow rate and reduced the propofol infusion rate. Ephedrine was administered if persistent hypotension occurred. Oxygen desaturation was defined as oxygen arterial saturation <90% for at least 10 seconds. Supplemental oxygen was given to maintain oxygen arterial saturation >95%. If persistent desaturation was noted for more than 3 minutes, the procedure was stopped to secure the airway. Bradycardia was defined as any episode of heart rate less than 40 beats per minute, and it was treated immediately using atropine sulfate. Body movement was defined as irritable status or restlessness of the patient that interrupted the ESD procedure. The propofol infusion rate was titrated to maintain deep sedation for the patients.

Follow-Up

Follow-up endoscopic examinations were arranged at 1, 3, 6, and 12 months after ESD and annually thereafter. Endoscopic biopsy was performed for any lesion suspected to be a local recurrence or metachronous growth. Procedure-related mortality was defined as any death within 30 days after ESD. Disease-specific and overall survivals were estimated.

Statistical Analysis

All continuous variables were analyzed using the Mann–Whitney *U* test and categorical data were examined using the Chi-square test. A 2-tailed *P* value <0.05 was considered significant. All statistical analyses were performed using SPSS software, version 19.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

ESD was performed in 83 patients with 86 EGC and precancerous lesions, who ranged in age from 31 to 95 years old. Forty four lesions were discovered in 42 elderly patients. PS was better in the nonelderly group compared with the elderly group. There were 90.9% patients in the elderly group who had at least 1 form of preexisting comorbidity, which is higher than 59.5% patients in the nonelderly group. The prevalence rates of cardiovascular disease, chronic obstructive pulmonary disease, chronic renal dysfunction, and hypertension were all higher in the elderly group compared with the nonelderly group. There were no differences with respect to gender ratio, antiplatelet agents or anticoagulants use rate or ASA classification between the 2 groups (Table 1).

Of the lesions in the elderly group, 43.2% lesions fulfilled the expanded criteria, while only 19.0% met these criteria in the nonelderly group. The most common histological type was

well-to-moderately differentiated adenocarcinoma, followed by high-grade dysplasia, low-grade dysplasia, and poorly differentiated adenocarcinoma. There were no differences between the 2 groups with respect to tumor location, circumference, macroscopic appearance, or biopsy histological type (Table 2).

The overall en-bloc resection rate was 81.4% and complete resection rate was 76.7%, and there was no difference in these treatment outcomes between the 2 groups (Table 3). There were 20 lesions that were incompletely resected with ESD, including 16 lesions with piecemeal resection and 4 lesions where the margin was positive for cancer or dysplastic cells. Surgery was recommended for all patients with incomplete resection. However, only 2 patients received additional gastrectomy with lymph node dissection, and the pathology report showed no malignant cell or lymphatic-vascular invasion in the resected stomach. For the other 18 patients who refused surgical intervention, 4 patients received palliative APC to destroy potentially residual tumors and 14 patients choose close endoscopic follow-up. One lesion fulfilled the expanded indication, had poorly differentiated adenocarcinoma, and the complete resection showed local recurrence 6 months after ESD. The lesion was treated by palliative APC because of the advanced age of the patient, and no further local recurrence or distant metastasis was noted during the observation period. One other patient was found to have a metachronous lesion 14 months after ESD and the patient underwent surgery to treat this lesion.

Procedure-related bleeding requiring emergency endoscopy occurred in 5 patients (5.8%), and endoscopic hemostasis was achieved in all of them. Among the patients with bleeding, 3 patients received antiplatelet agents or anticoagulants before or after ESD. The postoperative bleeding rate in patients receiving antiplatelet agents or anticoagulants was 25.0% (3/12), which was higher than 2.7% (2/74) in patients who did not receive these drugs (*P* = 0.002). Procedure-related perforation also occurred in 2 patients (2.3%): 1 patient underwent emergency surgical intervention, and the other received immediate endoscopic repair. Both interventions were successful. Three patients got bronchopneumonia and 2 patients were found with asymptomatic intraabdominal free air after ESD. All recovered after intravenous antibiotic therapy and a prolonged period with no oral ingestion of food. There was no difference between the 2 groups in each ESD-related complication. However, in the elderly group, 47.7% of patients had intraoperative hypotension and 9.1% patients had oxygen desaturation during ESD, both of which were higher than in the nonelderly group (21.4% and 0%, respectively). All patients were treated appropriately during ESD and no postoperative sequelae were observed (Table 3). However, the surgery time and duration of hospitalization were longer in the elderly group compared with the nonelderly group (Table 4). There were also no differences in postoperative pathological findings, invasion depth, and the lesion and specimen size between the 2 groups (Table 4).

There were no procedure-related deaths in either group. One patient died 12 months after ESD as a result of pneumonia with respiratory failure. All the other patients (98.8%) survived during the follow-up period (median: 31 months, range: 1–110 months).

DISCUSSION

In the present study, the outcome of ESD for superficial gastric neoplasms in elderly patients was comparable to that in nonelderly patients. Although the elderly patients had more comorbidities, a worse PS and a higher number of expanded lesions, the 2 groups had similar en-bloc resection rates and

TABLE 1. Clinical Characteristics of Elderly (≥ 75 years of Age) and Nonelderly (< 75 years of Age) Patients

Characteristic	Total (N = 86)	Elderly Group (N = 44)	Nonelderly Group (N = 42)	P-Value
Age, years, mean \pm SD (range)	72.7 \pm 11.5 (31–95)	81.6 \pm 3.9 (75–95)	63.4 \pm 9.3 (31–74)	<0.001
Males, n, %	65 (75.6)	36 (81.8)	29 (69.0)	0.168
Best performance status, n, %	51 (59.3)	17 (38.6)	34 (81.0)	<0.001
Antiplatelet agents or anticoagulants, n, %	12 (14.0)	5 (11.4)	7 (16.7)	0.478
ASA classification, n, %				0.267
I	2 (2.3)	0 (0.0)	2 (4.8)	
II	49 (57.0)	23 (52.3)	26 (61.9)	
III	31 (36.0)	18 (40.9)	13 (31.0)	
IV	4 (4.7)	3 (6.8)	1 (2.4)	
Preexisting comorbidities, n, %				
None	21 (24.4)	4 (9.1)	17 (40.5)	0.001
Cardiovascular disease	22 (25.6)	17 (38.6)	5 (11.9)	0.005
Chronic obstructive pulmonary disease	9 (10.5)	8 (18.2)	1 (2.4)	0.017
Liver cirrhosis	2 (2.3)	0 (0.0)	2 (4.8)	0.143
Chronic renal dysfunction	15 (17.4)	13 (29.5)	2 (4.8)	0.002
Cerebral infarction	10 (11.6)	8 (18.2)	2 (4.8)	0.052
Other malignancy	20 (23.3)	14 (31.8)	6 (14.3)	0.054
Hypertension	45 (52.3)	29 (65.9)	16 (38.1)	0.010
Diabetes mellitus	30 (34.9)	19 (43.2)	11 (26.2)	0.098
Hyperlipidemia	14 (16.3)	7 (15.9)	7 (16.7)	0.924

SD = standard deviation.

TABLE 2. Lesion Characteristics

Characteristic	Total (N = 86)	Elderly Group (N = 44)	Nonelderly Group (N = 42)	P-Value
Location				
Fundus	1	0	1	0.112
Body	46	28	18	
Antrum	39	16	23	
Circumference				
GCS	17	10	7	0.556
LCS	29	12	17	
AW	11	6	5	
PW	28	16	12	
Circular	1	0	1	
Macroscopic appearance				
I	10	7	3	0.411
IIa	19	9	10	
IIc	10	6	4	
IIa + IIc	40	19	21	
IIc + IIa	2	0	2	
Others	5	3	2	
Biopsy histological type				
Low-grade dysplasia	6	2	4	0.537
High-grade dysplasia	34	17	17	
Well-to-moderately differentiated	45	25	20	
Poorly differentiated	1	0	1	
EUS staging				
Mucosa	77	37	40	0.091
Submucosa	9	7	2	
Inclusion criteria, n, %				
Guideline criteria	59 (68.6)	25 (56.8)	34 (81.0)	0.016
Expanded criteria	27 (31.4)	19 (43.2)	8 (19.0)	

AW = anterior wall, EUS = endoscopic ultrasound, GCS = greater curvature side, LCS = lesser curvature side, PW = posterior wall.

TABLE 3. Treatment Outcomes and Complications

Characteristic	Total (N = 86)	Elderly Group (N = 44)	Nonelderly Group (N = 42)	P-Value
Resectability, n, %				
En-bloc	70 (81.4)	36 (81.8)	34 (81.0)	0.918
Piecemeal	16 (18.6)	8 (18.2)	8 (19.0)	
Completeness, n, %				
Complete	66 (76.7)	33 (75.0)	33 (78.6)	0.898
Incomplete	20 (23.3)	11 (25.0)	9 (21.4)	
ESD-related complications, n, %				
Bleeding	5 (5.8)	1 (2.3)	4 (9.5)	0.151
Perforation	2 (2.3)	1 (2.3)	1 (2.4)	0.973
Pneumonia	3 (3.5)	3 (6.8)	0 (0.0)	0.089
Intraabdominal free air	2 (2.3)	2 (4.5)	0 (0.0)	0.167
Sedation-related complications, n, %				
Intraoperative hypertension	14 (16.3)	8 (18.2)	6 (14.3)	0.625
Intraoperative hypotension	30 (34.9)	21 (47.7)	9 (21.4)	0.011
Desaturation	4 (4.7)	4 (9.1)	0 (0.0)	0.045
Body movement	5 (5.8)	2 (4.5)	3 (7.1)	0.607
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	–

ESD = endoscopic submucosal dissection.

complete resection rates. The overall en-bloc resection rate was 81.4% and complete resection rate was 76.7% in this study, but they were lower than results reported by Japanese groups.^{11–13} This may be because lesions are repeatedly biopsied in Taiwan, which causes marked submucosal fibrosis and adhesion. The lesions were not easily lifted during submucosal injection, and they were difficult to dissect from the proper muscle layer, which increased the possibility of piecemeal resection and lesion margins that were positive for tumor cells. When endoscopists become more familiar with gross morphology of neoplastic lesions, either through experience or with the aid of image-enhanced endoscopy, repeated or intensive biopsy can be avoided, and a higher en-bloc and complete resection rate can be achieved.

The results of our study showed that there was no difference between the 2 groups in postoperative bleeding rate or

perforation rate, a finding that is in agreement with other reports.^{11–14} The postoperative bleeding rate in patients receiving antiplatelet agents or anticoagulants was higher than patients without them. These results support the finding that post-ESD bleeding was significantly related to oral antithrombotic therapy in previous retrospective studies.^{20,21}

The perforation rate in ESD has been reported to be about 5%.^{22–25} In our study, 2 patients (2.3%) were found with immediate perforation during ESD, which is a better result than previous reports. The 1st patient complicated with perforation was the 3rd patient undergoing ESD in our hospital. As we had little experience with perforation during ESD at that time, the patient was advised to receive surgical repair immediately and he recovered well after the surgery. We have since gained more experience with ESD, and the 2nd patient underwent endoscopic repair smoothly.

TABLE 4. Specimen Characteristics, Surgery Time, and Hospital Day

Characteristic	Total (N = 86)	Elderly Group (N = 44)	Nonelderly Group (N = 42)	P-Value
Pathological finding				
Low-grade dysplasia	4	1	3	0.752
High-grade dysplasia	14	7	7	
Well-to-moderately differentiated	64	34	30	
Poorly differentiated	4	2	2	
Invasion depth				
M	70	33	37	0.183
SM1	9	6	3	
SM2	6	5	1	
Lymphovascular	1	0	1	
Lesion size, mm, mean ± SD	20.8 ± 7.2	22.0 ± 7.7	19.5 ± 6.6	0.083
Specimen size, mm, mean ± SD	39.7 ± 12.1	40.3 ± 12.4	39.0 ± 11.8	0.672
Surgery time, minute, mean ± SD	99.4 ± 59.3	107.0 ± 51.4	91.5 ± 66.2	0.049
Hospital day, day, mean ± SD	6.7 ± 3.1	7.5 ± 3.8	5.9 ± 2.0	0.016

M = mucosal cancer, SD = standard deviation, SM1 = submucosal cancer (<500 μm from the muscularis mucosa layer), SM2 = submucosal cancer (≥500 μm from the muscularis mucosa layer).

There was a tendency for more pneumonia and intraabdominal free air in the elderly group, but there was no statistically significant difference. Isomoto et al¹⁴ found that pneumonia associated with ESD developed 2.2% more frequently in the elderly compared with nonelderly patients. The difference in the pneumonia incidence was believed to result from differences in their ability to expectorate after surgery.¹¹ Of note, the elderly had longer surgery time in our study, which may increase risk of aspiration pneumonia.^{26,27} In addition, the PS has been reported to be a risk factor for complications after open surgery.²⁸ The PS was worse in elderly patients in our study, which may contribute to more side effects after ESD. Intraabdominal free air may also be a complication after ESD. A recent prospective cohort study identified silent free air in 37.3% of patients without perforation after ESD, and a longer procedure time (≥ 105 minutes) was the only independent risk factor.²⁹

This study showed that cardiopulmonary distress presenting with intraoperative hypotension and oxygen desaturation occurred more frequently in elderly than in nonelderly patients. All the events were treated appropriately without severe complications. More comorbidities in the elderly, especially heart, lung, and kidney disease, were believed to be the main cause of more intraoperative events. A retrospective study showed that there was no difference in the sedation-related complications during gastric ESD in the elderly and in a younger group.³⁰ However, most patients enrolled in that study were selected healthy patients with ASA classification I/II, who could not be directly compared with the entirely elderly population. Another study found that bradycardia, but not hypertension, hypotension, or desaturation, was more frequently observed in the elderly than in the nonelderly patients during ESD.³¹ However, the above study used a traditional sedation method of midazolam and pethidine hydrochloride, which was different from our propofol-based sedation method. Propofol has overtaken benzodiazepine sedation in advanced endoscopic procedures because of its short-acting pharmacokinetic characteristics.^{32,33} Sedation via a continuous propofol infusion with opioid administration had been reported to improve outcome in ESD patients compared with intermittent midazolam/propofol injection.³⁴ Under the propofol-based sedation method in ESD, we suggest that hemodynamic changes in elderly patients who have more comorbidities should be closely monitored, and any event that occurs should be treated as soon as possible.

More intraoperative hypotension and desaturation events in the elderly were directly related to a longer surgery time, because intraoperative hemodynamic changes often interrupt the ESD procedure. A higher prevalence rate for hypertension in the elderly may be another reason for a longer surgery time during ESD.¹³ In addition, PS worsening after ESD was observed more frequently in the elderly than the nonelderly in one previous report.¹¹ Clinicians had a tendency to keep elderly patients in the hospital for a longer observation period or for rehabilitation program because of their had worse PS after ESD compared with nonelderly patients.

Limitations of the present study included its retrospective design and small sample size. Additional prospective trials with a larger sample size are needed to make a firm conclusion about the clinical outcomes and complications of ESD in the elderly.

In conclusion, despite the higher prevalence rates of intraoperative hypotension and oxygen desaturation in the elderly, these events were treated appropriately, and ESD was performed safely without postoperative sequelae. ESD is

a feasible and safe intervention for superficial gastric neoplasms in the elderly population.

ACKNOWLEDGMENTS

The authors thank Dr Pei-Chang Lee for his excellent statistical assistance. The authors also thank the grant V104A-017 from Taipei Veterans General Hospital, Taipei, Taiwan.

REFERENCES

- GLOBOCAN 2012. Estimated cancer incidence, mortality and prevalence worldwide in 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. [Accessed July 9, 2015].
- Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer*. 2011;14:101–112.
- Oka S, Tanaka S, Kaneko I, et al. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc*. 2006;64:877–883.
- Goto O, Fujishiro M, Kodashima S, et al. Outcomes of endoscopic submucosal dissection for early gastric cancer with special reference to validation for curability criteria. *Endoscopy*. 2009;41:118–122.
- Choi JH, Kim ES, Lee YJ, et al. Comparison of quality of life and worry of cancer recurrence between endoscopic and surgical treatment for early gastric cancer. *Gastrointest Endosc*. 2015;82:299–307.
- Kim DY, Hong SJ, Cho GS, et al. Long-term efficacy of endoscopic submucosal dissection compared with surgery for early gastric cancer: a retrospective cohort study. *Gut Liver*. 2014;8:519–525.
- United Nations. World Population Ageing 2013. <http://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2013.pdf>. [Accessed July 9, 2015].
- Health Promotion Administration, Ministry of Health, Welfare, Executive Yuan, Taiwan. Cancer registry annual report, 2012, Taiwan, <http://www.hpa.gov.tw/BHPNet/Web/Stat/StatisticsShow.aspx?No=201504290001>. [Accessed July 9, 2015].
- Matsushita I, Hanai H, Kajimura M, et al. Should gastric cancer patients more than 80 years of age undergo surgery? Comparison with patients not treated surgically concerning prognosis and quality of life. *J Clin Gastroenterol*. 2002;35:29–34.
- Abe N, Gotoda T, Hirasawa T, et al. Multicenter study of the long-term outcomes of endoscopic submucosal dissection for early gastric cancer in patients 80 years of age or older. *Gastric Cancer*. 2012;15:70–75.
- Tokioka S, Umegaki E, Murano M, et al. Utility and problems of endoscopic submucosal dissection for early gastric cancer in elderly patients. *J Gastroenterol Hepatol*. 2012;27(Suppl 3):63–69.
- Kakushima N, Fujishiro M, Kodashima S, et al. Technical feasibility of endoscopic submucosal dissection for gastric neoplasms in the elderly Japanese population. *J Gastroenterol Hepatol*. 2007;22:311–314.
- Hirasaki S, Tanimizu M, Nasu J, et al. Treatment of elderly patients with early gastric cancer by endoscopic submucosal dissection using an insulated-tip diathermic knife. *Intern Med*. 2005;44:1033–1038.
- Isomoto H, Ohnita K, Yamaguchi N, et al. Clinical outcomes of endoscopic submucosal dissection in elderly patients with early gastric cancer. *Eur J Gastroenterol Hepatol*. 2010;22:311–317.
- Zhang Y, Huang L, Li L, et al. Endoscopic submucosal dissection for early gastric neoplasms in elderly patients. *J Laparoendosc Adv Surg Tech A*. 2014;24:391–398.
- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer*. 2011;14:113–123.

17. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649–655.
18. American Society of Anesthesiologists Task Force on Sedation, Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology*. 2002;96:1004–1017.
19. Imagawa A, Fujiki S, Kawahara Y, et al. Satisfaction with bispectral index monitoring of propofol-mediated sedation during endoscopic submucosal dissection: a prospective, randomized study. *Endoscopy*. 2008;40:905–909.
20. Ojima T, Takifuji K, Nakamura M, et al. Complications of endoscopic submucosal dissection for gastric noninvasive neoplasia: an analysis of 647 lesions. *Surg Laparosc Endosc Percutan Tech*. 2014;24:370–374.
21. Takeuchi T, Ota K, Harada S, et al. The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo gastric endoscopic submucosal dissection. *BMC Gastroenterol*. 2013;13:136.
22. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut*. 2001;48:225–229.
23. Ohkuwa M, Hosokawa K, Boku N, et al. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy*. 2001;33:221–226.
24. Tsunada S, Ogata S, Ohyama T, et al. Endoscopic closure of perforations caused by EMR in the stomach by application of metallic clips. *Gastrointest Endosc*. 2003;57:948–951.
25. Minami S, Gotoda T, Ono H, et al. Complete endoscopic closure of gastric perforation induced by endoscopic resection of early gastric cancer using endoclips can prevent surgery (with video). *Gastrointest Endosc*. 2006;63:596–601.
26. Lee IL, Wu CS, Tung SY, et al. Endoscopic submucosal dissection for early gastric cancers: experience from a new endoscopic center in Taiwan. *J Clin Gastroenterol*. 2008;42:42–47.
27. Park CH, Kim H, Kang YA, et al. Risk factors and prognosis of pulmonary complications after endoscopic submucosal dissection for gastric neoplasia. *Dig Dis Sci*. 2013;58:540–546.
28. Sierzega M, Kolodziejczyk P, Kulig J. Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach. *Br J Surg*. 2010;97:1035–1042.
29. Watari J, Tomita T, Toyoshima F, et al. The incidence of “silent” free air and aspiration pneumonia detected by CT after gastric endoscopic submucosal dissection. *Gastrointest Endosc*. 2012;76:1116–1123.
30. Gotoda T, Kusano C, Nonaka M, et al. Non-anesthesiologist administered propofol (NAAP) during endoscopic submucosal dissection for elderly patients with early gastric cancer. *Gastric Cancer*. 2014;17:686–691.
31. Chinda D, Sasaki Y, Tatsuta T, et al. Perioperative complications of endoscopic submucosal dissection for early gastric cancer in elderly Japanese patients 75 years of age or older. *Intern Med*. 2015;54:267–272.
32. Heuss LT, Froehlich F, Beglinger C. Nonanesthesiologist-administered propofol sedation: from the exception to standard practice. Sedation and monitoring trends over 20 years. *Endoscopy*. 2012;44:504–511.
33. Kiriya S, Gotoda T, Sano H, et al. Safe and effective sedation in endoscopic submucosal dissection for early gastric cancer: a randomized comparison between propofol continuous infusion and intermittent midazolam injection. *J Gastroenterol*. 2010;45:831–837.
34. Park CH, Min JH, Yoo YC, et al. Sedation methods can determine performance of endoscopic submucosal dissection in patients with gastric neoplasia. *Surg Endosc*. 2013;27:2760–2767.