Clinical outcomes of endoscopic submucosal dissection in elderly patients with early gastric cancer

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Objectives **Endoscopic submucosal dissection (ESD) has advantages over conventional endoscopic mucosa resection. The number of elderly patients (more than 75 years old) with early gastric cancer (EGC) has been steadily increasing. We sought to assess clinical outcomes of ESD for EGC in elderly.**

Methods **ESD was performed for patients with EGC, who fulfilled the criteria for ESD: mucosal cancer without ulcer findings irrespective of tumor size; mucosal cancer with ulcer findings 3 cm or less in diameter; and minute submucosal invasive cancer 3 cm or less in size. Two hundred and sixty elderly patients ($\geq$ 75 years old) with 279 lesions, and 401 non-elderly patients with 434 lesions were enrolled to this study. The patients underwent ESD and then received periodic endoscopic follow-up and metastatic surveys for 6–89 months (median: 30 months). Resectability (en-bloc or piecemeal resection), curability (curative or noncurative resection), completeness (complete or incomplete resection), complications, and survival rates were assessed.**

Rersults **The one-piece resection rate was significantly lower in elderly patients (93.9%) than in non-elderly patients (97.9%). The complete resection rate was significantly lower in elderly patients (87.4%) than in non-elderly patients (96.6%). Pneumonia, but not bleeding or perforation, developed in association with ESD more frequently in the elderly patients by 2.2%. Local tumor recurrence was quite rare, and the overall and disease-free survival rates were acceptable irrespective of age.**

Conclusion **En-bloc and complete resections were achieved less frequently in elderly patients, but the long-term outcomes in elderly EGC patients may be excellent, and ESD is a feasible treatment in the elderly.** ***Eur J Gastroenterol Hepatol*** **22:311–317 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Early gastric cancer (EGC) is defined as gastric cancer that is confined to the mucosa or submucosa (T1 cancer), irrespective of the presence of regional lymph node metastases [1]. Currently, almost 10 000 cases of EGC are being detected each year in Japan, accounting for 40–50% of all gastric cancers [2]. Of note, the number of elderly patients with EGC has been steadily increasing in Japan [2,3]. Endoscopic mucosal resection (EMR) is widely accepted as a standard treatment for EGC with nominal risk of lymph node metastasis, as it is minimally invasive, safe, and convenient [4,5]. However, the snaring procedure is not reliable for lesions larger than 20 mm in diameter or lesions with ulcer findings [6,7]. Conventional EMR is associated with a high risk of local recurrence (range: 2–35%) in such cases, especially when resections are not accomplished *en bloc* or the margins are not clear [8].

Endoscopic submucosal dissection (ESD) has been developed to dissect directly along the submucosal layer using specialized devices, including an insulation-tipped diathermy knife (IT knife) [9,10]. Preliminary studies have been published showing the advantage of ESD over conventional EMR for removing larger or ulcerated EGC lesions in an en-bloc manner [6,10–12]. Thus, ESD allows precise histological assessment of the resected specimens, and it may prevent residual disease and local recurrence [5,7,8]. Although the early results of ESD are promising, except for a higher risk of procedure-related

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complications [8,11–13], there is little information on the clinical outcomes of ESD for elderly patients with EGC. The purpose of this study was to evaluate the feasibility and efficacy of ESD and its clinical outcomes for elderly patients with EGC.

Patients and methods

Patients

A total of 713 EGCs in 661 consecutive patients were treated by ESD at the hospitals of Nagasaki University School of Medicine from January 2001 to December 2007. The patients were enrolled based on the guideline criteria for EMR, which were established by the Japanese Gastric Cancer Association, have been generally accepted, and it states that: (i) elevated EGCs less than 2 cm in diameter and (ii) small (≤ 1 cm) depressed EGCs without ulceration are absolutely indicated for EMR [14]. The lesions which fulfilled the expanded criteria proposed by Gotoda *et al.* [5,15], wherein differentiated gastric cancers (well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma) with no lymphatic–vascular involvement, correlating with a nominal risk of lymph node metastasis, were defined as: mucosal cancer without ulcer findings, irrespective of tumor size; mucosal cancer with ulcer findings 3 cm or less in diameter; and minute ($< 500\,\mu$m from the muscularis mucosae) submucosal invasive cancer 3 cm or less in size, were also treated by ESD. Patients with EGCs who did not fall into these categories were excluded from the study and urged to undergo gastrectomy with lymph node removal. Patients with severe, concomitant heart, respiratory, renal, and liver diseases, and those with a bleeding tendency, were excluded from the study. The performance status of each patient was less than 2 on the Eastern Cooperative Oncology Group scale [3]. Patients were divided into an elderly (75 years old or older) group and a non-elderly group (younger than 75 years old). We did not check *Helicobacter pylori* positivity and did not perform its eradication systematically. Written informed consent was obtained from all the patients before ESD.

Endoscopic submucosal dissection

EGCs were first identified and demarcated using white-light endoscopy and chromoendoscopy with indigo–carmine solution, and then marking around the lesions was carried out with spotty cautery using a needle-knife. Glyceol (10% glycerol and 5% fructose; Chugai Pharmaceutical Co., Tokyo, Japan) was then injected into the submucosal layer to lift the mucosa. A circumferential mucosal incision was made around the lesion using the IT knife (Olympus Optical Co. Ltd., Tokyo, Japan). Submucosal dissection was performed for complete removal of the lesion using the IT knife and the Hook knife (Olympus). High-frequency generators (ICC200 or VIO 300D; ERBE Elektromedizin GmbH, Tübingen, Germany) were used during marking, incision of the gastric mucosa, and exfoliation of the gastric submucosa. The patients who had received anticoagulant and/or antiplatelet drugs underwent ESD after they had discontinued these for at least 7 days.

Procedure-related bleeding after ESD was defined as bleeding that required transfusion or surgical intervention, or bleeding that caused the hemoglobin level to decrease by 2 g/dl [13]. Perforation was diagnosed endoscopically or by the presence of free air on an abdominal plain radiograph or computed tomogram (CT). The procedure-related pneumonia that occurred for the first time after ESD was diagnosed with the chest radiography or thoracic CT.

Histopathological evaluation

The location of EGC was classified into upper, middle, and lower thirds of the stomach. The macroscopic type of EGC was divided into the elevated type and the flat/depressed type. The excised specimens were sectioned perpendicularly at 2-mm intervals. Histology was classified into differentiated adenocarcinoma (well or moderately differentiated adenocarcinoma or papillary adenocarcinoma) or undifferentiated adenocarcinoma (poorly differentiated adenocarcinoma or signet-ring cell carcinoma). The tumor size, the depth of invasion, the presence of ulcerative changes, lymphatic and vascular involvement, and tumor involvement to the lateral and vertical margins were assessed.

En-bloc resection was defined when the lesions were resected in one piece [15]. When the lesion required removal in multiple segments, the piecemeal-resected specimens were reconstructed as completely as possible. The curability of ESD was classified as curative or noncurative [15,16]. Resections were deemed curative when the removal was achieved with tumor-free lateral and vertical margins, and there was no submucosal invasion deeper than 500 μm from the muscularis mucosae and no lymphatic and vascular involvement. Noncurative resection was defined as resection that did not meet the curative criteria, or when compartments of undifferentiated carcinoma were identified. Resection was considered complete when the tumor was removed *en bloc* with tumor-free lateral and vertical margins and no lymph–vascular infiltration [11]. Cases in which tumors were resected in multiple segments or resections with the horizontal/vertical margins positive for cancer invasion were classified as incomplete resection [11].

Follow-up

Endoscopic examinations were scheduled at 1, 3, 6, and 12 months after ESD and then annually thereafter. Biopsy specimens during each follow-up endoscopy were taken from the treatment-related scar or any other suspicious abnormalities to assess the presence of local recurrent

tumor or metachronous cancer of the stomach. To detect lymph node and distant metastases, contrast-enhanced CT and ultrasound sonography of the abdomen and chest radiography was performed annually. Procedure-related mortality was defined as any death within 30 days after ESD [13]. The cumulative disease-specific and overall survivals were estimated.

Statistical analysis

The significance of differences in the patients' characteristics and clinicopathological features, resectability (*en bloc* or piecemeal), curability (curative or noncurative), and completeness (complete or incomplete) of ESD was determined using the Fisher's exact test, the χ^2 test, Mann–Whitney's *U* test, or Student's *t*-test, as appropriate. Factors associated with the resectability, curability, and completeness of ESD were analyzed using logistic regression analysis. Odds ratios (ORs), together with 95% confidence intervals (CI), were calculated to estimate the relative risk of piecemeal resection, noncurative resection, or incomplete resection and their associations with various parameters. Long-term outcomes were calculated using the Kaplan–Meier method and analyzed using the log-rank test. *P* values less than 0.05 were considered statistically significant.

Results

The patients' median age was 72 years (mean: 71 years; range: 38–92 years), and the male/female ratio was 2.6 : 1 (475 : 186). There were 260 elderly patients with a total of 279 lesions, and 401 non-elderly patients with a total of 434 lesions. The elderly group included 100 women, whereas the non-elderly group included 86 women; the sex difference between the groups was significant ($P < 0.0001$). Of the 661 patients with 713 EGCs treated by ESD, 551 patients with a total of 589 EGC lesions who met the eligibility criteria received endoscopic follow-up for 6–89 months (median: 30 months). At the time of ESD, 76 patients had multiple concurrent EGCs. There were 346 lesions that fulfilled the generally accepted indications: (i) elevated EGCs less than 2 cm in diameter, and (ii) small ($\leq$ 1 cm) depressed EGCs without ulceration [6]. At the same time, these lesions must be differentiated from adenocarcinoma confined to the mucosa with no lymphatic or vascular involvement. A total of 243 lesions did not fulfill the guideline criteria, but did meet the expanded inclusion criteria. The 124 remaining patients who did not meet the expanded criteria after histopathological assessment of the resected specimens (the exclusion group) were urged to undergo surgery.

Table 1 compares the clinicopathological characteristics, including sex, tumor size, macroscopic appearance, location of tumors, ulcer findings, depth of invasion, and indication criteria between the elderly and non-elderly groups. No statistically significant differences between the groups were observed in tumor size, macroscopic appearance, tumor location, and invasion depth. There were significant differences between the groups in sex, macroscopic appearance, and ulcer findings.

Table 1 Comparison of clinicopathological characteristics between elderly ($\geq$ 75 years old) and non-elderly (<75 years old) patients

Group (no. of lesions)	Total (713)	Elderly (279)	Non-elderly (434)	*P* value
Sex (female/male)	197 : 516	106 : 173	91 : 343	$P<0.0001$
Macroscopic appearance				
Elevated	368	157	211	$P<0.05$
Flat/depressed	343	120	223	
Unknown	2	2		
Tumor size (mm)				
Median	18	18	18	
Mean	19	20	19	NS
Range	2–80	3–75	2–80	
Unknown	7	1	6	
Location				
Upper	117	44	73	
Middle	338	129	209	NS
Lower	254	105	149	
Unknown	4	1	3	
Ulcer findings				
Present	61	10	51	$P<0.0001$
Absent	652	269	383	
Invasion depth (μm)				
m; mucosal cancer	591	222	369	NS
sm1; submucosal invasive cancer (<500 μm)	52	26	26	
sm2; submucosal invasive cancer ($\geq$ 500 μm)	70	31	39	
Inclusion criteria				
Guideline criteria	346	125	221	NS
Expanded criteria	243	98	145	
Exclusion	124	56	68	

On the whole, en-bloc resection was achieved in 687 of 713 (96.3%) cases. There was a significant difference in the one-piece resection rates between the elderly and non-elderly groups ($P < 0.01$, Table 2); the elderly patients were at higher risk of piecemeal resection. Of the 589 lesions, eight could not be evaluated for curability because of difficulties in histopathological assessment; these were attributed to the burn effect or insufficient reconstruction of the piecemeal fragments. Thus, 550 (93.4%) of 589 lesions were defined as having been resected curatively, and complete resection was achieved in 538 (91.3%). Table 2 also compares the curability of ESD between the elderly and non-elderly groups. The curative resection rates were insignificant with 91.5 and 94.5% in the elderly and non-elderly group, respectively. The complete resection rate was significantly higher in the non-elderly group (93.7%) than that in the elderly group (87.4%). Thus, the elderly patients were at significantly higher risk of incomplete resection.

Then, logistic regression analyses were performed with respect to respectability, curability, and completeness of ESD (Table 3). The variables included sex, tumor size, tumor location, macroscopic appearance, and the presence of ulcer findings. In the non-elderly group, the upper location of EGCs significantly contributed to

piecemeal resection, whereas the presence of ulcer findings had a significant impact on ESD curability and completeness (Table 3). In contrast, no significant factors were associated with the ESD resectability, curability, and completeness in the elderly group (Table 3). The piecemeal resection had significantly negative impact on curability (OR: 21.69; 95% CI: 5.94–79.22; $P < 0.0001$) and completeness (OR: 176.92; 95% CI: 21.05–1486.88; $P < 0.0001$) of ESD in the non-elderly and elderly group, respectively.

Table 2 Comparison of en-bloc, curative and complete resection rates between elderly (≥ 75 years old) and non-elderly (<75 years old) patients

Group (no. of lesions)	Total (713)	Elderly (279)	Non-elderly (434)	*P* value
Resectability				
En-bloc resection	687	262	425	*P*<0.01
Piecemeal resection	26	17	9	
En-bloc resection rate (%)	96.4	93.9	97.9	
Curability				
Curative	550	204	346	
Noncurative	31	19	12	NS
Not evaluated	8		8	
Curative resection rate (%)	93.4	91.5	94.5	
Completeness				
Complete	538	195	343	
Incomplete	43	28	15	*P*<0.01
Not evaluated	8		8	
Complete resection rate (%)	91.3	87.4	93.7	

Of the patients with noncurative resections, eight underwent gastrectomy with the removal of lymph nodes; of these, four had local recurrence, whereas the remainder had no residual or recurrent tumor and no lymphatic involvement. Four patients with noncurative resection were successfully treated using argon plasma coagulation for margins with cancerous glands, and two underwent repeat ESD with one-piece curative resection.

Table 4 summarizes the complications related to ESD. Procedure-related bleeding was observed in 18 patients (2.5%). The bleeding rates were similar in the two groups. All of the hemorrhagic episodes were successfully managed by endoscopic clipping or coagulation. Perforations related to ESD occurred in 29 patients (4.1%); they could also be managed by conservative medical treatment after endoscopic closure with clipping. There was no significant difference in the perforation rates between the groups. However, six patients, all of whom belonged to the elderly group, developed pneumonia after the procedure, and recovered well with antibiotic treatment. None of the non-elderly group developed pneumonia; the difference in the complication rates (2.2 vs. 0.0%) was significant ($P < 0.01$). In this regard, there was no significant difference in operation times of ESD between the non-elderly and elderly groups as a whole (median: 122 and 123 min, respectively). Nevertheless, the

Table 3 Association between the clinicopathological characteristics of early gastric cancer lesions and resectability, curability, or completeness of endoscopic submucosal dissection

	Resectability		Curability		Completeness	
Factors	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
In non-elderly (<75 years old) patients						
Sex						
Female	1 (reference)		1 (reference)		1 (reference)	
Male	1.20 (0.33–4.33)	0.78	0.82 (0.22–3.10)	0.77	0.99 (0.36–2.76)	0.98
Tumor size	1.05 (1.01–1.10)	0.03	1.00 (0.94–1.07)	0.91	1.04 (0.99–1.08)	0.06
Tumor location						
Lower	1 (reference)		1 (reference)		1 (reference)	
Middle	0.74 (0.23–2.34)	0.61	0.74 (0.21–2.61)	0.67	0.82 (0.29–2.28)	0.67
Upper	1.07 (0.26–4.44)	0.92	0.85 (0.16–4.51)	0.85	2.77 (0.91–8.44)	0.07
Macroscopic appearance						
Flat/depressed	1 (reference)		1 (reference)		1 (reference)	
Elevated	0.58 (0.21–1.64)	0.31	3.09 (0.82–11.60)	0.11	1.09 (0.47–2.54)	0.84
Ulcer findings						
Absent	1 (reference)		1 (reference)		1 (reference)	
Present	2.39 (0.65–8.87)	0.19	5.44 (1.55–19.19)	0.01	3.04 (1.05–8.80)	0.04
In elderly (≥ 75 years old) patients						
Sex						
Female	1 (reference)		1 (reference)		1 (reference)	
Male	0.87 (0.27–2.83)	0.81	0.60 (0.20–1.79)	0.36	0.65 (0.27–1.55)	0.33
Tumor size	1.02 (0.97–1.07)	0.43	1.03 (0.99–1.08)	0.19	1.02 (0.99–1.06)	0.20
Tumor location						
Lower	1 (reference)		1 (reference)		1 (reference)	
Middle	1.24 (0.51–3.03)	0.53	1.04 (0.27–4.01)	0.95	0.82 (0.29–2.28)	0.67
Upper	3.85 (0.96–15.40)	0.06	3.85 (0.96–15.08)	0.06	2.77 (0.91–8.44)	0.07
Macroscopic appearance						
Flat/depressed	1 (reference)		1 (reference)		1 (reference)	
Elevated	0.65 (0.19–2.23)	0.49	2.28 (0.76–6.88)	0.56	1.03 (0.43–2.46)	0.95
Ulcer findings						
Absent	1 (reference)		1 (reference)		1 (reference)	
Present	6.12 (0.59–63.76)	0.13	0.03 (0.002–318)	0.98	2.89 (0.29–29.04)	0.37

CI, confidence interval; OR, odds ratio.

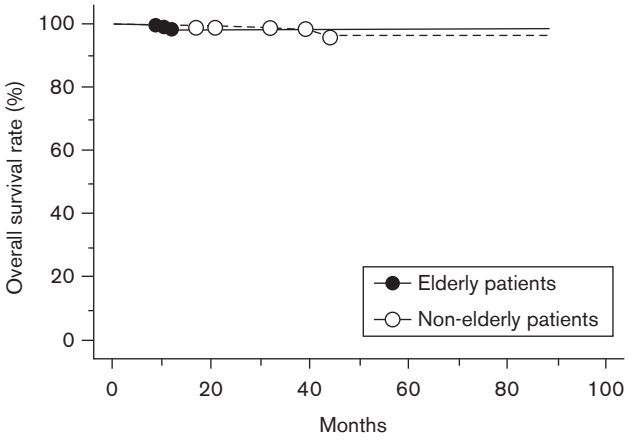
Table 4 Comparison of complications related to endoscopic submucosal dissection between elderly (≥ 75 years old) and non-elderly (< 75 years old) patients

Group (no. of lesions)	Total (713)	Elderly (279)	Non-elderly (434)	*P* value
Procedure-related bleeding				
Present	18	7	11	NS
Absent	695	272	423	
Incidence (%)	2.5	2.5	2.5	
Procedure-related perforation				
Present	29	14	15	NS
Absent	684	265	419	
Incidence (%)	4.1	5.0	3.5	
Procedure-related pneumonia				
Present	6	6	0	
Absent	707	273	434	$P<0.01$
Incidence (%)	0.8	2.2	0.0	

operation times for the patients complicated with pneumonia were significantly longer than those for the uncomplicated patients (median: 175 and 122 min, respectively). The procedure-related mortality rate was 0% in both groups.

Among the 551 EGC patients enrolled based on the proposed criteria, 75 with a follow-up period of less than 1 year were excluded from the analysis of local recurrence in accordance with an earlier report [10]. Thus, 510 lesions in 476 patients were eligible for the analysis of clinical results including local recurrence, metachronous gastric cancer, and survival times. These included 195 lesions in the elderly group and 315 in the non-elderly group. The median follow-up periods were 31 and 33.5 months for the elderly and non-elderly groups, respectively; the difference between the groups was not statistically significant. Local tumor recurrence occurred in two lesions (0.6%) of EGC patients from the non-elderly group and in two (1.0%) from the elderly group; the difference between the groups was not statistically significant. There was one of 484 (0.2%) recurrent tumors among the lesions with curative, but piecemeal resection; whereas three of 26 recurrent tumors (11.5%) developed from the lesions with noncurative resection. Thus, EGC patients with noncurative resection were at significantly higher risk of local recurrence ($P < 0.0001$). Tumor recurrence was observed between 13 and 24 months after ESD, and each patient underwent gastrectomy with D2 lymph node dissection. All of the recurrent tumors were limited to the mucosal layer without lymphatic and vascular involvement, and no lymph node metastases were observed in any of the cases. Metachronous gastric cancers that were not local recurrences developed in 12 patients in the non-elderly group and two in the elderly group during a median follow-up of 14 months (range: 12–42 months); the difference in the incidences was not significant. None of the patients had metastases to the lymph nodes or distant organs, such as the liver and lungs, during the study period.

Fig. 1



The overall survival curves for elderly (≥ 75 years old) and non-elderly (< 75 years old) patients with early gastric cancer treated by endoscopic submucosal dissection.

Of the 476 patients who met the proposed criteria, two patients whose vital status was unknown and eight patients who underwent gastrectomy were excluded from the disease-specific and overall survival analyses. On the whole, 190 and 55 patients could be followed up for more than 3 and 5 years, and 3-year and 5-year overall survival rates were 98.5 and 97.1%, respectively. The 3-year overall survival rates were adequate: 98.4% in the elderly group and 98.6% in the non-elderly group (Fig. 1). The 5-year overall survival rates were 98.4% in the elderly group and 96.6% in the non-elderly group; the difference between the groups was not significant (Fig. 1). None of the patients died of gastric cancer during this study, and the 3-year and 5-year disease-specific survival rates were 100% in both groups.

Discussion

Despite the increasing use of ESD for elderly patients with EGC, the clinical outcomes have not been fully evaluated in such a cohort. Hirasaki *et al.* [3] reported no significant differences between elderly and non-elderly groups in the short-term results, including the one-piece resection rate, the complete resection rate, and the procedure-related bleeding, and perforation rates. However, their study included only a small number of elderly patients with EGC; 53 of a total of 144 patients treated by ESD [3]. Moreover, there has been no information on the longer-term outcomes, such as local tumor recurrence and prognosis after ESD for EGC, in the elderly to date. In the present larger consecutive series, the 3-year survival rate after ESD in the elderly group (> 98%) was comparable with that in the non-elderly group. In a multicenter study of endoscopic resection for EGC, Oda *et al.* [17] reported a comparable 3-year overall survival between the EMR and ESD groups (99.7 and 98.5%,

respectively). The 5-year overall survival rate after ESD reached 98.4% in the elderly patients, which was equivalent to that after EMR documented in earlier reports [17,18]. Of note, the disease-specific survival rates after ESD were 100%, similar to those after EMR in 12 major Japanese institutions [17]. This is the first study to clarify the prognosis of EGC patients after ESD with respect to their age, though the follow-up periods are still limited compared with those following surgical treatment. EGC has excellent clinical outcomes, with 10-year and 20-year survival rates as high as 95% after gastrectomy with removal of lymph nodes [17]. Confirmation of whether ESD can equal surgery, irrespective of age, will require further long-term prospective studies.

The present results confirmed that local recurrence of gastric cancer after ESD was rare irrespective of age when curative resection was achieved; local recurrence occurred in only four patients (two from the elderly group and two from the non-elderly group). In contrast, about 10% of all of the patients with noncurative resection had local recurrence. This implies that EGC patients with noncurative ESD require close follow-up surveillance for cancer recurrence after ESD. In this study, the four patients with tumor recurrence were referred to surgery. These lesions, however, at least in the elderly, could be treated endoscopically. Earlier studies have shown that endoscopic therapies allow curative resection of locally recurrent EGC [16,19]. In contrast, patients with curative ESD may also require periodic endoscopic surveys for new EGC lesions. In this study, 14 metachronous gastric cancers developed after ESD. Similarly, another study of the clinical outcomes of ESD for EGC documented 14 (6.2%) metachronous lesions among 225 EGCs after ESD [7]. The incidence of metachronous gastric cancer varies from 1.8 to 8.1% after EMR [17,20,21]; thus, the necessity for continued surveillance is an intrinsic drawback of endoscopic therapies, irrespective of curability.

The en-bloc resection rate in this study was no less than 96% as a whole, which was comparable with that in a large series from the Japanese Cancer Institute reported by Oda *et al.* [13]. According to their analyses, upper and middle location, tumor size more than 21 mm, and positive ulcer findings were associated with piecemeal resection [13]. Oka *et al.* [11] reported a marked decrease in en-bloc resection rates from 92.9% for EGC without ulcer findings to 19.2% for tumors with ulceration. Larger and/or ulcerative lesions are considered to be significant risk factors for unsuccessful resection. In fact, upon logistic regression analysis, the tumor size was significantly associated with the ESD respectability in the non-elderly patients (Table 3). The upper location of EGCs seemed to make it difficult to conduct ESD in an en-bloc manner despite insignificance (Table 3). Again, we found that the one-piece resection rate was higher for EGC lesions in the non-elderly group (97.9%) than in the elderly group (93.9%). In the present series, however, the incidence of positive ulcer findings in the elderly group was significantly lower (3.6%; 10 of the 279 EGC lesions) than in the non-elderly group (11.8%; 51 of the 434 lesions), whereas there was no statistically significant difference in the size of EGCs between the groups. Nevertheless, resectability of the lesions in the elderly group was still acceptable, with the one-piece resection rate reaching 94%, considering that the en-bloc resection rates are much lower for conventional EMR, even for smaller lesions without ulceration [11,16,17]. Kojima *et al.* [18] reviewed articles on EMR for EGC, and en-bloc resection was carried out in 75.8% of the cases (486 of 641). However, the one-piece resection rates by EMR varied from 56.0 to 86.4% among the Japanese major institutes [17].

En-bloc resection of ESD provides much higher complete resection rates than piecemeal resection, permitting precise histopathological examination of curability to guide further management and to stratify a patient's risk for developing metastasis [5,8]. In fact, resectability of ESD was significantly associated with curability and/or completeness of ESD (Table 3). The complete resection rate for EGCs in the non-elderly group was comparable with earlier results [11,13]; no less than 94% of the lesions were resected in an en-bloc manner with tumor-free lateral and vertical margins and no lymphatic–vascular involvement. As the complete resection rate of the lesions in the elderly group was rather lower (87.4%), we performed logistic regression analyses in the elderly and non-elderly patients with EGCs treated by ESD (Table 3). In the non-elderly group, the presence of ulcer findings was the sole significant contributor for incomplete and curative resection. In contrast, there were no significant contributors to noncurative or incomplete resection in the elderly group. Thus, we do not really know where the lower complete resection rate in the aged patients derives from. Nevertheless, complete removal of EGCs with standard EMR was achieved in no more than 73.9% of cases in a large series from Japan [17]. In addition, the much lower rates (46.9–62.8%) for EMR were derived from series with expanded indications, as adopted in this study [17].

ESD had relatively high complication rates for procedure-related bleeding (2.5%) and perforation (4.1%) in this study. These complication rates were comparable in the elderly and non-elderly groups. Of note, pneumonia developed more frequently in the elderly patients (2.2%), whereas it did not occur in any of the non-elderly patients. However, all patients with pneumonia were successfully treated with antibiotics. Thus, pneumonia possibly because of aspiration can be another problem

after ESD in the elderly [22]. The risk of aspiration may increase if it is a longer duration endoscopic procedure [22]. In fact, operation times of ESD in patients with the procedure-related pneumonia were much longer than those in the uncomplicated patients in this study. It is still not clear whether the use of prophylactic antimicrobial therapy is beneficial in such settings. A low frequency of bacteremia has been reported after EMR [23]. Investigation of antibiotic prophylaxis is required for patients who undergo ESD, especially in the elderly who have underlying diseases more frequently.

Gotoda *et al.* [15] have also included poorly differentiated adenocarcinoma or signet-rig cell carcinoma of the stomach without ulceration and a size below 2 cm in their expanded criteria. In certain cases of such undifferentiated tumors, however, it is difficult to define the extent of tumor invasion. A curative treatment might also have been possible in this group of patients, but these patients were referred to surgery in this study. Again, when the lesion required removal in multiple segments, the piecemeal-resected specimens were reconstructed as completely as possible. Nevertheless, we might not be able to assess tumor-free margins absolutely in a few cases, and hence, we analyzed the completeness of ESD. Cases in which tumors were resected in multiple segments or resections with the horizontal/vertical margins positive for cancer invasion were classified as incomplete resection [11].

In conclusion, ESD provides lower en-bloc and curative resection rates for EGC lesions in elderly patients than in non-elderly patients. However, resectability and curability were acceptable in the elderly group when compared with standard EMR. Clinical outcomes of ESD, including local tumor recurrence and prognosis, may be adequate for EGCs irrespective of age.

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Conflicts of interest: none declared.

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