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Retrospective Study

Feasibility of gastric endoscopic submucosal dissection in elderly patients aged ≥ 80 years

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Abstract

BACKGROUND

Endoscopic resection, especially endoscopic submucosal dissection (ESD), is increasingly performed in elderly patients with early gastric cancer, and lesions beyond the expanded indications are also resected endoscopically in some patients. It is essential to assess whether gastric ESD is safe and suitable for elderly patients and investigate what type of lesions carry an increased risk of ESD-related complications.

AIM

To assess the efficacy and feasibility of gastric ESD for elderly patients, and define high-risk lesions and prognostic indicators.

METHODS

Among a total of 1169 sessions of gastric ESD performed in Kanagawa Cancer Center Hospital from 2006 to 2014, 179 sessions (15.3%) were performed in patients aged ≥ 80 years, and 172 of these sessions were done in patients with a final diagnosis of gastric cancer. These patients were studied retrospectively to

Machida N, Ogata T, Oshima T, and Maeda S edited the manuscript; all authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

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statement: This study has been approved by the research ethics committee of Kanagawa Cancer Center, which complies with International Guidelines for Ethical Review of Epidemiological Studies.

Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. According to "Ethical Guidelines for Medical and Health Research Involving Human Subjects" published by Japanese Ministry of Health, Labor and Welfare, opt-out is accepted for practical procedure to obtain informed consent from the recruited patients, in retrospective study without any invasion or newly investigated information after recruitment. For our study, we have put information concerning the study on Kanagawa Cancer Center HP, to give recruited patients a chance to refuse entry to the study.

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evaluate short-term outcomes and survival. The short-term outcomes included the rates of *en bloc* resection and curative resection, complications, and procedure-related mortality. Curability was assessed according to the Japanese Gastric Cancer Treatment Guidelines 2010. Fisher's exact test was used to statistically analyze risk factors. Clinical characteristics of each group were compared using Fisher's exact test and Mann-Whitney *U* test. Survival rates at each time point were based on Kaplan-Meier estimation. Overall survival rates were compared between patients with gastric cancer in each group with use of the log-rank test. To identify prognostic factors that jointly predict the hazard of death while controlling for model overfitting, we used the least absolute shrinkage and selection operator (LASSO) Cox regression model including factors curative/noncurative, age, gender, body mass index, prognostic nutritional index, Charlson comorbidity index (CCI), Glasgow prognostic score, neutrophil-to-lymphocyte ratio, and antithrombotic agent use. We selected the LASSO Cox regression model that resulted in minimal prediction error in 10-fold cross-validation. $P < 0.05$ was considered statistically significant.

RESULTS

The *en bloc* dissection rate was 97.1%, indicating that a high quality of treatment was achieved even in elderly patients. As for complications, the rates of bleeding, perforation and aspiration pneumonitis were 3.4%, 1.1% and 0.6%, respectively. These complication rates indicated that ESD was not associated with a particularly higher risk in elderly patients than in nonelderly patients. A dissection incision > 40 mm, lesions associated with depressions, and lesions with ulcers were risk factors for post-ESD bleeding, and location of the lesion in the upper third of the stomach was a risk factor for perforation in elderly patients ($P < 0.05$). Location of the lesion in the lower third of the stomach tended to be associated with a higher risk of bleeding. The overall survival (OS) did not differ significantly between curative and noncurative ESD ($P = 0.69$). In patients without additional surgery, OS rate was significantly lower in patients with a high CCI (≥ 2) than in those with a low CCI (≤ 1) ($P < 0.001$).

CONCLUSION

Gastric ESD is feasible even in patients aged ≥ 80 years. Observation without additional surgery after noncurative ESD is reasonable, especially in elderly patients with CCI ≥ 2 .

Key Words: Endoscopic submucosal dissection; Elderly; Charlson comorbidity index; Early gastric cancer; Complications; Prognostic indicators

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Core Tip: This was a retrospective study to evaluate the efficacy and feasibility of gastric endoscopic submucosal dissection in elderly patients aged ≥ 80 years. The rates of *en bloc* dissection, bleeding, perforation and aspiration pneumonitis were 97.1%, 3.4%, 1.1% and 0.6%, respectively. These rates are similar to the rates in nonelderly patients reported previously. Risk factors for bleeding were incision > 40 mm, lesions associated with depressions, and ulcerative lesions. A risk factor for perforation was location in the upper third of the stomach. Charlson comorbidity index ≥ 2 was an indicator of poor prognosis regardless of curability.

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INTRODUCTION

Early gastric cancer (EGC) is defined as gastric cancer confined to the mucosa and submucosa[1]. Increasing numbers of EGCs are being detected in Japan[2,3], and EGCs currently account for $> 60\%$ of all detected cases of gastric cancer[4]. Since the development of endoscopic submucosal dissection (ESD), the treatment of EGC has changed dramatically[5,6]. Various techniques have considerably reduced the technical limitations of endoscopic resection (ER), and EGCs can now be freely resected, independently of size and shape[6-8]. Many EGCs that would have been surgically resected previously are now resected endoscopically. The most attractive point of ESD as compared with open surgery is its lower invasiveness and the ability to avoid deterioration in the quality of life.

The elderly population is increasing rapidly in Japan. The average life span is 80.50 years for men and 86.83 years for women, according to statistics reported by the Ministry of Health, Labour and Welfare, Japan in 2014. Surgery carries an increased risk in elderly patients because of poor physical status or serious underlying diseases [9,10]. Thus ER, especially ESD, is being increasingly performed in elderly patients[10-14]. Because this trend is expected to continue, it is necessary to assess whether ESD is actually safe and suitable for elderly patients. In addition, more clearly defining high-risk lesions associated is prerequisite to safe treatment.

MATERIALS AND METHODS

Patients

A total of 1169 sessions of ESD were performed to treat gastric diseases (mainly EGCs and gastric adenomas, as well as some non-neoplastic lesions) in Kanagawa Cancer Center Hospital between January 2006 and December 2014, and 179 (15.3%) of these sessions were performed in a total of 131 patients who were aged ≥ 80 years. Among the resected specimens, gastric cancers were finally diagnosed in 175 lesions treated by 172 sessions of ESD in 124 patients. These cases were studied retrospectively.

ESD procedure

Around-the-lesion biopsy was performed beforehand to confirm the margin of the lesions, if necessary. On the day of ESD, the margin was identified again using white light endoscopy, chromoendoscopy with indigo carmine solution, and narrow-band imaging. All-around-the-lesion marking was carried out with the use of small multiple cautery units. Submucosal injection was performed to lift the mucosal layer. Glyceol (10% glycerol and 5% fructose; Chugai Pharmaceutical Co., Tokyo, Japan) or MucoUp (0.4% sodium hyaluronate; Johnson & Johnson, New Brunswick, NJ, United States) with a small amount of indigo carmine was used as the injection solution. A circumferential mucosal incision and submucosal dissection were performed using a needle knife (Olympus Optical Co. Ltd., Tokyo, Japan). The high-frequency generators used were ICC200 or VIO300D (ERBE Elektromedizin GmbH, Tübingen, Germany).

Short-term outcomes

The short-term outcomes included the rates of *en bloc* resection and curative resection, complications, and procedure-related mortality. Curability was assessed according to the Japanese Gastric Cancer Treatment Guidelines 2010[15]. A curative resection was defined as satisfying all the following conditions: *en bloc* resection, negative horizontal and vertical margin, no lymphovascular infiltration, and absolute or expanded indication for ER. Differentiated type intramucosal cancer ≤ 20 mm in size without ulceration was categorized as a lesion of absolute indication. A lesion of expanded indications was as follows: Differentiated type intramucosal cancer > 20 mm in size without ulceration; differentiated type intramucosal cancer ≤ 30 mm in size with ulceration; differentiated type submucosal superficial cancer ≤ 30 mm in size; and undifferentiated type intramucosal cancer ≤ 20 mm in size without ulceration.

As for complications, bleeding, perforation and aspiration pneumonitis were assessed. Bleeding was defined as the occurrence of melena or hematemesis; detection of ongoing hemorrhage; or the presence of coagulated blood in the stomach with apparent bleeding spots on endoscopic examination, which was basically performed routinely in all patients on the next day of ESD. Perforation was confirmed by observation of mesenteric fat during ESD or by detection of free air on X-ray films. Aspiration pneumonitis was diagnosed on the basis of clinical findings and X-ray films. Procedure-related mortality was defined as death within 30 d due to complica-

ations. In patients who had complications, patient-related factors, such as World Health Organization performance status and underlying disease, as well as lesion-related factors, such as location, size, and macroscopic aspects were investigated.

Long-term outcomes

For evaluation of long-term outcomes, a patient who had experienced noncurative ESD within the last 5 years ($n = 1$) and patients who underwent additional surgery after ESD ($n = 3$) were excluded from the target of analysis. Overall survival (OS) was evaluated starting from the date of ESD to the date of death or the last verified date of survival. To determine the prognostic indicators for elderly patients with EGC treated by ESD, we also evaluated the clinical characteristics of the patients who did not undergo additional surgery after ESD ($n = 120$), using age, gender, body mass index (BMI), prognostic nutritional index (PNI), Charlson comorbidity index (CCI), Glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio (NLR), and use of antithrombotic agents.

Statistical analysis

To estimate affecting factors related to complications, relative risks were calculated. Fisher's exact test was used to statistically analyze risk factors. Clinical characteristics of each group were compared using Fisher's exact test and Mann-Whitney *U* test. Survival rates at each time point were based on Kaplan-Meier estimation. OS rates were compared with the log-rank test between patients with gastric cancer in each group. To identify prognostic factors that jointly predict the hazard of death while controlling for model overfitting, the least absolute shrinkage and selection operator (LASSO) Cox regression model including factors curative/noncurative, age, gender, BMI, PNI, CCI, GPS, NLR and antithrombotic agent use was used (R package glmnet) [16]. We selected the LASSO Cox regression model that resulted in minimal prediction error in 10-fold cross-validation. $P < 0.05$ was considered statistically significant.

All statistical analyses were conducted using the EZR software, version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[17] and R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). The statistical review of the study was performed by a biomedical statistician.

RESULTS

Short-term outcomes

Short-term outcomes are shown in Table 1. Within 172 sessions of ESD, two different specimens of multiple lesions were resected at the same time in three sessions; only one specimen was resected for each treatment in 168 sessions; and one lesion was unresectable in one session. A total of 174 specimens were thus resected from 175 lesions in 172 sessions of ESD. The *en bloc* dissection rate and the curative dissection rate were 97.1% and 77.1%, respectively. Six lesions (3.4%) had postoperative bleeding, two (1.1%) had intraoperative perforation, and one patient (0.6%) had aspiration pneumonitis after ESD. Blood transfusion was required in one patient. There were no procedure-related deaths.

The characteristics of the treated lesions and patients are shown in Table 2. Macroscopically, flat-type shaped lesions (85.7%) predominated over protruded-type lesions (13.7%). There was one advanced type 1 lesion, which was misdiagnosed as EGC type 0-I before treatment. Of 124 recruited patients, 38 (30.6%) had circulatory underlying diseases, nine (7.3%) had respiratory underlying diseases, and 22.6% of the patients were receiving at least one antithrombotic agent.

In the present study of elderly patients, lesions that did not meet the indication criteria were also treated. The details of noncurative lesions and noncurative factors are shown in Table 3. Among 40 noncurative lesions, 32 (80.0%) were differentiated type, and eight (20.0%) were undifferentiated type. The noncurative factors were depth of invasion in 30.0%, oversize in 20.0%, positive ulceration associated with undifferentiated components in 12.5%, and positive or uncertain lymph vascular invasion in 35.0% of the noncurative lesions.

The patients with complications are summarized in Table 4. One patient had both postoperative bleeding and aspiration pneumonitis, and the others had one complication each. None of patients with postoperative bleeding was receiving any antithrombotic agents.

Table 1 Short-term outcomes of ESD, *n* (%)

Location of the lesions (<i>n</i> = 175) ¹	
Upper third	33 (18.9)
Middle third	57 (32.6)
Lower third	85 (48.6)
Size of dissected specimen (<i>n</i> = 174) ²	
Range	9-110 mm
Median	30 mm
Average	33.4 mm
ESD quality (<i>n</i> = 175) ²	
En bloc dissection	170 (97.1)
Fractional dissection	4 (2.3)
Not dissected endoscopically	1 (0.6)
Curability (<i>n</i> = 175) ¹	
Curative dissection	135 (77.1)
Non-curative dissection	40 (22.9)
Complications	
ESD sessions (<i>n</i> = 172) with any complication	8 (4.7)
Bleeding (<i>n</i> = 175) ¹	6 (3.4)
Perforation (<i>n</i> = 175) ¹	2 (1.1)
Aspiration pneumonitis (<i>n</i> = 172) ³	1 (0.6)
Procedure-related death (<i>n</i> = 172) ³	0

¹Location, Endoscopic submucosal dissection (ESD) quality (*en bloc* or fractional dissection rate), curability (curative or noncurative dissection rate), and complications of bleeding and perforation calculated with respect to the total number of 175 treated lesions.

²Size of dissected specimen measured only in endoscopically resected cases (*n* = 174).

³Number of ESD sessions (total *n* = 172) associated with aspiration pneumonitis. ESD: Endoscopic submucosal dissection.

The relation of complications to lesion location and size of resected specimen is summarized in Table 5. Lesion location in the lower third of the stomach and a resected specimen size > 40 mm tended to have higher bleeding rates. Lesion location in the upper third of the stomach and a resected specimen size > 40 mm tended to be associated with higher perforation rates.

The relative risks of lesion location and resected specimen size are shown in Table 6. Resected specimens > 40 mm, macroscopic shape with depressive component, and presence of ulceration were determined to be risk factors for bleeding ($P < 0.05$). Location of the lesion in the upper third of the stomach was determined to be a risk factor for perforation ($P < 0.05$).

Long-term outcomes

Survival curves according to the curability are shown in Figure 1. The patients were divided into two groups: Those who underwent only curative ESD (curative ESD group, *n* = 87), and those who underwent noncurative ESD without additional surgery (noncurative ESD group, *n* = 33). Patients who had undergone dissection more than once were classified as noncurative when ESD was noncurative at least once. A total of 32 patients (26.7%) died during a median follow-up period of 2005 d (range, 83-4774 d). Twenty-four of the patients who died were in the curative ESD group and eight were in the noncurative ESD group. The cause of death was gastric cancer in none of them. The OS rate did not differ significantly between the curative and the non-curative ESD groups ($P = 0.69$).

Prognostic factors for OS using LASSO in the patients who did not undergo additional surgery (*n* = 120) are shown in Table 7. Among these clinical characteristics, gender and CCI, one of most widely used and validated comorbidity scoring system to

Table 2 Characteristics of treated lesions and patients, *n* (%)

(A) Lesions (<i>n</i> = 175)	
Macroscopic type	
Protruded type (0-I, 0-I+IIa, 0-I+IIb, 0-I+IIc)	24 (13.7)
Flat type (0-IIa, 0-IIa+IIc, 0-IIb, 0-IIc, 0-IIc+IIa)	150 (85.7)
Advanced (type 1)	1 (0.6)
Ulceration	
UL (+)	22 (12.6)
UL ()	153 (87.4)
Depth of invasion	
M	152 (86.9)
\geq SM	23 (13.1)
(B) Patients (<i>n</i> = 124)	
Underlying disease	
Circulatory	38 (30.6)
Respiratory	9 (7.3)
Renal	0
Antithrombotic agent	
Taking	28 (22.6)

UL: Ulceration; M: Mucosa; SM: Submucosa.

measure comorbidity status, were significantly associated with OS. As median CCI in each group was 1, patients were divided in two groups according to CCI ≤ 1 or > 1 . The survival curve of patients with low CCI ≤ 1 ($n = 100$) and those with high CCI ≥ 2 ($n = 20$) are shown in [Figure 2](#). The OS rate was significantly different between the two groups ($P < 0.001$).

DISCUSSION

In Japan, the morbidity rate of gastric cancer has been rapidly decreasing according to the Center for Cancer Control and Information Services, National Cancer Center, Japan. Nonetheless, the number of EGCs treated endoscopically has dramatically increased. The increased use of ER seems to be attributed to three reasons. The first reason is the expansion of the indications for ER. Because ER is a local resection procedure without lymphadenectomy, the indications for ER are limited to conditions expected to have no lymph node metastasis[15]. Previous studies of patients who underwent surgery for gastric cancer have evaluated conditions associated with no lymph node metastasis. The second reason is progress in endoscopic techniques[6-8]. The final reason is the minimal invasiveness of ESD. ESD is far less invasive than open surgery, and can prevent symptoms associated with a small capacity of stomach after surgery.

Although minimal invasiveness is undoubtedly attractive for elderly patients because they have higher incidences of underlying diseases than younger patients have and are sometimes in poor general condition[9,10], the feasibility of ESD remains to be fully evaluated. In our study, complications occurred only in 4.7% of patients, without any procedure-related deaths. In previous studies of elderly patients, the rate of bleeding ranged from 2.5% to 9.6%[10-14], except for the study by Hirasaki *et al*[10], which reported a bleeding rate of 43.4%[3], and the rates of perforation and of pneumonia ranged from 1.5% to 5.0% and 0.5% to 2.2%, respectively. In most of these studies, ESD was not associated with particularly higher risk in elderly than in nonelderly patients. Indeed, the rates of bleeding and perforation among patients of all ages were reported to range from 3.7% to 15.6% and 1.2% to 6.7%, respectively[18-22].

Table 3 Details of noncurative lesions, and estimated noncurative factors of 40 noncurative lesions

(A) Details of noncurative lesions (n = 40)				
	Depth of invasion			
	M	SM1	SM2	\geq MP
Histological type				
Differentiated (tub1, tub2, pap)	19	4	8	1
Undifferentiated (por, sig, muc)	4	2	2	0
(B) Estimated non-curative factors of 40 non-curative lesions, n (%)				
Depth of invasion				
\geq SM2, differentiated			8 (20)	
\geq SM, undifferentiated			4 (10)	
Lesion size				
≥ 30 mm, differentiated, UL (+)			2 (5)	
≥ 30 mm, differentiated, SM1			1 (2.5)	
≥ 20 mm, undifferentiated			5 (12.5)	
Ulceration				
UL (+) with undifferentiated components			5 (12.5)	
Lymphovascular invasion				
Ly +/-uncertain			7 (17.5)	
V +/-uncertain			7 (17.5)	
Surgical margin				
Positive			7 (17.5)	
Uncertain			21 (52.5)	
Not dissected endoscopically			1 (2.5)	

M: Mucosa; SM: Submucosa; MP: Muscularis propria; UL: Ulceration; Ly: Lymphatic invasion; V: Venous invasion.

In nonelderly patients, Lin *et al*[23] reported that the rates of bleeding, perforation and procedure-related pneumonia were 2.9%, 1.1% and 0.4%, respectively, in their meta-analysis of nine previous studies of gastric ESD. These previous reports and present study suggest that the rates of complications of ESD in elderly patients are not particularly higher than the rates in nonelderly or patients of all ages. Accordingly, we argue that gastric ESD is feasible even in elderly patients aged ≥ 80 years.

However, some studies have reported that ESD carries a higher risk in elderly patients than in younger patients[13,21]. Toyokawa *et al*[13] reported that the bleeding rate was significantly higher in the elderly group (age ≥ 75 years) than in the nonelderly group (age < 75 years). However, in multivariate analysis, high age was not in itself an independent predictor of bleeding, and the reason why the bleeding rate was higher in the elderly group was unclear. It was also reported by Toyokawa *et al* [21] in another report that age ≥ 80 years was associated with a significantly higher risk of delayed bleeding after ESD, and they concluded that the use of antiplatelet agents or anticoagulants was not the reason for delayed bleeding in elderly patients. Also in that study, they could not specify the reason why delayed bleeding was predominant in elderly patients over nonelderly patients. In our institution, endoscopic examination on the next day of ESD was routinely performed, and coagulation of visible vessels at the ulcer floor was carried out. This endoscopic examination may have contributed to low incidence of bleeding in our present study. In any case, attentive precautionary endoscopic hemostasis after dissection is crucial for aged patients, as they demonstrate age-related physiological decline with higher incidence of underlying diseases and worse overall condition[13].

Even if gastric ESD is feasible in elderly patients, complications can have severe consequences. To acknowledge the characteristics of lesions associated with higher

Table 4 Details of patients who had complications of endoscopic submucosal dissection

Age (yr)	Gender	Ps	Underlying disease	Past history	Location ¹	Size (mm)	Macroscopic type	Final pathology	Curability	Specimen (mm)	Complications
83	F	1		Post-BHA	L, Ant	40	0-IIc, UL (+)	Tub2 > por2, M, ly0, v0, HM0, VM0	Noncurative	60	Bleeding G2
83	M	0			L, Ant	10	0-IIc, UL (+)	Tub1 > tub2, M, ly0, v0, HM0, VM0	Curative	20	Bleeding G2
92	M	0		Laryngeal cancer	U, Post	50	Type1	Surgical resection: pap > tub, SS, ly0, v1, NX, HMX	Noncurative	52 ²	Perforation G3
89	M	3		Brain cancer	M, Les	33	0-IIc, UL (+)	Sig/por2, M, ly0, v0, HM0, VM0	Noncurative	68	Bleeding G3, pneumonitis G2
83	F	2	AD, Depression		U, Les	15	0-IIa	Tub1, M, ly0, v0, HM0, VM0	Curative	30	Perforation G2
82	F	0			(1) L, Ant	(1) 20	(1) 0-IIc	(1) Tub2 > tub1 > por, M, ly0, v0, HM0, VM0	(1) Curative	54	Bleeding G2
					(2) L, Ant	(2) 10	(2) 0-IIc	(2) Tub1-tub2, M, ly0, v0, HM0, VM0	(2) Curative		
84	M	2	AP, COPD		L, Les	15	0-IIc	Por1, M, ly0, v0, HMX, VMX	Noncurative	40	Bleeding G2
80	M	0		Colon cancer, EGC	L, Les	16	0-IIa+IIc, UL (+)	Tub1 > tub2 > por, M, ly0, v0, HM0, VM0	Curative	47	Bleeding G2

¹Location divided into three regions of the stomach; U (upper third), M (middle third), and L (lower third), respectively.

²Size of all-around incision of endoscopic submucosal dissection measured in a surgically resected specimen.

PS: Performance status; BHA: Bipolar hip arthroplasty; AD: Alzheimer disease; UL: Ulceration; AP: Angina pectoris; COPD: Chronic obstructive pulmonary disease; EGC: Early gastric cancer; M: Mucosa; SM: Submucosa; SS: Subserosa; ly: Lymphatic invasion; v: Venous invasion; HM: Horizontal margin; VM: Vertical margin; N: Lymph node metastasis; L: Lower third; M: Middle third; U: Upper third.

risks in elderly patients is essential to a safe procedure. Kim *et al*[22] reported that the risk of perforation associated with ESD is higher for lesions located in the gastric body than those located in the antrum. Toyokawa *et al*[21] reported that ESD carried a high risk of perforation when EGCs located in the upper third of the stomach were dissected. Our results that lesion location in the upper third of the stomach was a significant risk factor, and lesion size > 40 mm tended toward a higher risk of perforation in elderly patients seem to be consistent with previous studies performed in patients of all ages.

As for bleeding, Chung *et al*[18] reported that the risk of delayed bleeding after ESD was significantly higher for lesions located in the upper portion of the stomach. In contrast, in our study focusing on elderly patients, lesions located in the lower portion of the stomach tended to have a higher risk of bleeding. As for macroscopic shape, lesions with depressive components such as 0-IIc, 0-IIa + IIc, 0-IIc + IIa, and 0-I + IIc and lesions with ulceration were associated with bleeding after ESD. In contrast, treatment with antithrombotic agents was not associated with bleeding. We speculate that strong peristaltic contractions of the gastric antrum increased the risk of bleeding in the lower portion of the stomach. In addition, a resected lesion size > 40 mm in diameter was determined to be a risk factor for bleeding. Moreover, the median lesion size in patients with bleeding was 50.5 mm (range, 20-68 mm), which was about 70% larger than median lesion size of 30 mm (range, 9-110 mm) in the study group as a whole. We therefore recommend meticulous preventive endoscopic hemostasis after resecting lesions > 40 mm, especially those located in the lower third of the stomach, and lesions with depressive aspects or ulceration, when treating elderly patients.

Table 5 Relations of complications to location or dissected size of endoscopic submucosal dissection specimens, *n* (%)

	Bleeding (+)	Bleeding (-)	Perforation (+)	Perforation (-)	Total
	<i>n</i> = 6	<i>n</i> = 169	<i>n</i> = 2	<i>n</i> = 173	<i>n</i> = 175
Location					
Upper third	0	33 (100)	2 (6.1)	31 (93.9)	33
Middle third	1 (1.6)	56 (98.4)	0	57 (100)	57
Lower third	5 (5.9)	80 (94.1)	0	85 (100)	85
Size of specimen					
≤ 20 mm	1 (3.3)	29 (96.7)	0	30 (100)	30
21-40 mm	1 (1.0)	102 (99.0)	1 (1.0)	102 (99.0)	103
41-60 mm	3 (8.1)	34 (91.9)	1 (2.7) ¹	36 (97.3)	37
≥ 61 mm	1 (20.0)	4 (80.0)	0	5 (100)	5

¹Not endoscopically dissected case.

Size of all-around incision of endoscopic submucosal dissection measured in a surgically resected specimen.

To prevent aspiration during ESD, an overtube was inserted in all patients. Accordingly, the rate of aspiration pneumonitis was as low as 0.6%. In contrast, Isomoto *et al*[12] reported that aspiration pneumonitis occurred in 2.2% of patients aged ≥ 75 years, which was more frequent than in younger patients. In contrast, Lee *et al*[24] reported that the risk of aspiration might be increased by endoscopic procedures with a longer duration.

In the present study of elderly patients, lesions that did not meet the indication criteria were also treated. Accordingly, the curative dissection rate of ESD was only 77.1%. Abe *et al*[14] reported that the curative rate of ESD was 77.9% in their multicenter study of ESD in patients aged ≥ 80 years, consistent with our results. The question arises whether dissecting lesions beyond expanded indications was meaningless? Kang *et al*[25] recently reported that even if the lesions are beyond expanded indications, ESD reduces the risk of death from gastric cancer, although it does not completely cure the disease in some patients. In our study, the disease-specific 5-year survival rate and 5-year OS rate in the noncurative ESD group were as high as 100% and 76.9%, respectively. These rates were higher than 5-year survival rate of patients with EGC who did not undergo resection (62.8%) as reported by Tsukuma *et al*[26]. Furthermore, the OS of the noncurative ESD group was equivalent to that of the curative ESD group. Although the number of patients in our study was small, and our results may have been influenced by selection bias, our findings suggest that ESD might be effective for EGC beyond expanded indications. Indeed, although 32 of 120 recruited patients died during the follow-up period, none of them died of gastric cancer. The causes of death in the other patients were malignancy in other organs in seven patients, respiratory diseases in five patients, and uncertain in 20 patients.

Tsukuma *et al*[26] reported that the median interval required for EGC to progress to an advanced stage was 44 mo. Moreover, older patients tended to have shorter intervals to the development of advanced disease, and it was 36 mo in patients aged > 75 years[27]. We thus consider it reasonable to endoscopically resect lesions beyond expanded indications if surgery is unacceptable, with the goal of preventing symptoms that may develop in the future, in patients who are expected to survival for longer than 36 mo.

In this study, local recurrence developed in only one (3.0%) of 33 patients in the noncurative ESD group. Similarly, Abe *et al*[14] reported that local recurrence developed in 3.3% and distant metastasis developed in 5.5% of patients who did not undergo additional surgery after noncurative ESD. Kusano *et al*[28] reported that survival was improved by additional surgery following noncurative ER in elderly patients. In contrast, Ahn *et al*[29] reported that the mortality rate was significantly higher in the presence of lymphovascular invasion than in the absence of such invasion in patients with differentiated EGC who underwent nonsurgical follow-up after noncurative ER. Thus, if possible, additional surgery is advisable after noncurative ESD, even in elderly patients, especially when lymphovascular invasion is

Table 6 Relative risks of location and size for bleeding or perforation

(A) Relative risk of location lower third, size > 40 mm, macroscopic shape, presence or absence of ulceration, and depth of invasion for bleeding			
	Bleeding (+)	Relative risk	P value
Location			
Lower third	5.9% (5/85)	5.3	0.11
Upper third, middle third	1.1% (1/90)		
Dissected size			
≥ 41 mm	9.5% (4/42)	6.3	0.030
≤ 40 mm	1.5% (2/133)		
Macroscopic shape			
Depressive component (+)	8.2% (6/73)		0.005
Depressive component ()	0% (0/102)		
Ulceration			
UL (+)	18.2% (4/22)	13.9	0.003
UL ()	1.3% (2/153)		
Depth of invasion			
≥ SM	3.9% (6/152)		1
M	0% (0/23)		
(B) Relative risk of location upper third, size > 40 mm, macroscopic shape, presence or absence of ulceration, and depth of invasion for perforation			
	Perforation (+)	Relative risk	P value
Location			
Upper third	6.3% (2/32)		0.033
Middle third, lower third	0% (1/143)		
Dissected size			
≥ 41 mm	2.4% (1/42)	3.2	0.423
≤ 40 mm	0.8% (1/133)		
Macroscopic shape			
Depressive component (+)	0% (0/73)	-	0.511
Depressive component ()	2.0% (2/102)		
Ulceration			
UL (+)	0% (0/22)	-	1
UL ()	1.3% (2/153)		
Depth of invasion			
≥ SM	0.7% (1/152)	6.6	0.246
M	4.3% (1/23)		

UL: Ulceration; M: Mucosa; SM: Submucosa.

confirmed histologically.

CCI was developed to assess the risk of death from comorbidities and has been widely used to evaluate clinical outcomes, such as prognosis or complications. CCI was calculated as the sum of the scores assigned to several comorbidities (myocardial infarction, congestive heart failure, cerebrovascular disease, uncomplicated diabetes, moderate-to-severe chronic kidney disease, moderate-to-severe liver disease, solid tumor, leukemia *etc.*) based on the original definition[30]. In our study, curability of ESD was not associated with OS rate. CCI was indicated to be the only factor

Table 7 Prognostic factors for overall survival ($n = 120$)

	Cox LASSO
Curability	
Noncurative	-
Patient	-
Age	-
Gender: Male	0.416
BMI	-
PNI	-
CCI > 1	0.477
GPS	-
NLR	-
Antithrombotic agent (+)	-

LASSO: Least absolute shrinkage and selection operator; BMI: Body mass index; PNI: Prognostic nutritional index; CCI: Charlson comorbidity index; GPS: Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio.

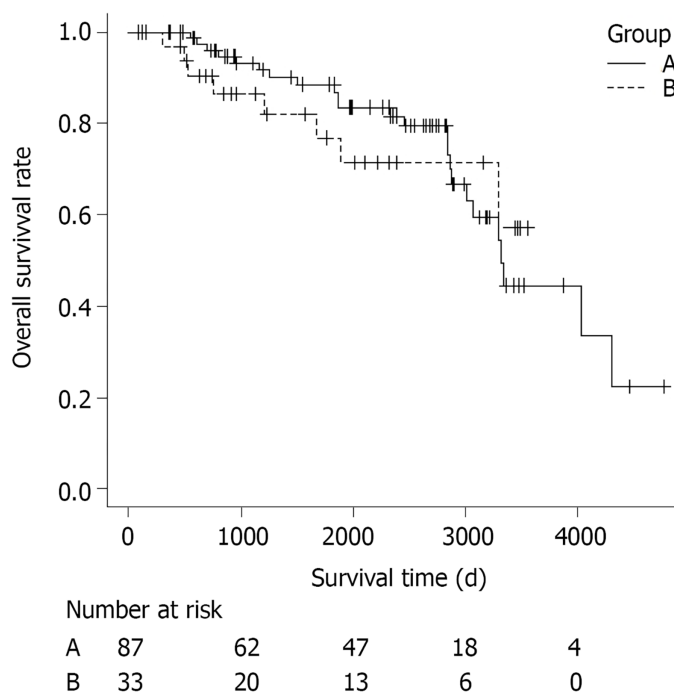


Figure 1 Overall survival of curative and noncurative patients. Group A: Curative endoscopic submucosal dissection (ESD) group ($n = 87$); Group B: Noncurative ESD group ($n = 33$). A total of 32 patients (26.7%) died during a median follow-up of 2005 d (range, 83–4774 d). Twenty-four of the patients who died were in the curative ESD group and eight were in the noncurative ESD group. The cause of death was gastric cancer in none of them. The overall survival rate did not differ significantly between the curative and noncurative ESD groups ($P = 0.69$).

associated with prognosis, among various clinical characteristics such as BMI, PNI, GPS and NLR. However, Iwai *et al*[31] reported that $CCI \geq 3$ and $PNI < 47.7$ were both significantly associated with lower OS rate. Whether nutritional status is truly a predictor of long-term prognosis is controversial. According to our results, we suggest that observation without additional surgery after noncurative ESD may be considered, especially in elderly patients with $CCI > 1$.

The limitation of our study was that it was retrospective. Although complications are expected to differ depending on concomitant diseases, we cannot confirm the patients' characteristics in detail. Moreover, we had only a few cases of bleeding and perforation, as this was a single-center study with a limited number of recruited

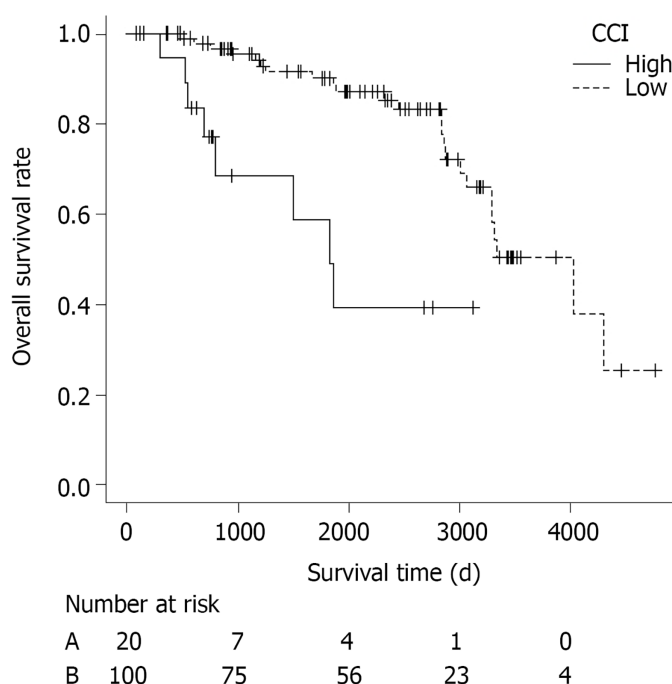


Figure 2 Overall survival of patients with high and low Charlson comorbidity index. Charlson comorbidity index (CCI) High: Patients with CCI ≥ 2 ($n = 20$); CCI Low: Patients with CCI ≤ 1 ($n = 100$). Overall survival rate was significantly different between the two groups ($P < 0.001$).

patients, and our results may have been influenced by selection bias. Therefore, a multicenter prospective trial needs to be performed to confirm the risk factors of ESD related to underlying disease.

CONCLUSION

Gastric ESD is feasible and permissible in elderly patients aged ≥ 80 years. To ensure a safe procedure, meticulous preventive endoscopic hemostasis is recommended after resecting specimens > 40 mm or lesions with depressive aspects or ulceration, especially those located in the lower third of the stomach, when treating aged patients. Concerning their long-term prognosis, male gender and CCI > 1 are negative predictors.

ARTICLE HIGHLIGHTS

Research background

Endoscopic submucosal dissection (ESD) is increasingly performed in elderly patients with early gastric cancer (EGC).

Research motivation

Whether gastric ESD is safe and suitable for elderly patients, type of lesions which carry an increased risk of procedure-related complications, indicators of prognosis for elderly patients after ESD are unclear.

Research objectives

To investigate short-term and long-term outcomes of gastric ESD for elderly patients, and to determine the risk factors of procedure-related complications and the indicators of prognosis.

Research methods

This study included patients aged ≥ 80 years who underwent ESD for EGC in Kanagawa Cancer Center Hospital. These patients were studied retrospectively to evaluate short-term outcomes and survival of gastric ESD.

Research results

The *en bloc* dissection rate was as high as 97.1%, and the complication rates of bleeding, perforation and aspiration pneumonitis were as low as 3.4%, 1.1% and 0.6%, respectively, which were similar to the rates of ESD for nonelderly patients. A dissection incision > 40 mm, lesions associated with depressions, and lesions with ulcers were risk factors for bleeding, and location of the lesion in the upper third of the stomach was a risk factor for perforation ($P < 0.05$). The overall survival (OS) did not differ significantly between curative and noncurative ESD groups ($P = 0.69$). In patients without additional surgery, OS rate was significantly lower in patients with a high Charlson comorbidity index (CCI) ≥ 2 than in patients with a low CCI ≤ 1 ($P < 0.001$).

Research conclusions

Gastric ESD is feasible even in elderly patients aged ≥ 80 years. Meticulous preventive endoscopic hemostasis after resecting specimens > 40 mm, or lesions associated with depressions or ulcers is recommended. CCI is a prognostic indicator. Observation without additional surgery after noncurative ESD is reasonable, especially in elderly patients with CCI ≥ 2 .

Research perspectives

As our institution is a hub hospital specializing in cancer treatment, relatively healthy patients without severe underlying diseases tend to visit the hospital. Therefore, a selection bias of target patients may have existed in our study. A multicenter prospective trial with a large number of patients is desirable to confirm the feasibility of gastric ESD in patients with various health problems, and the risk factors and the prognostic indicators related to each underlying disease.

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