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# Outcomes of endoscopic submucosal dissection for superficial esophageal cancer in an elderly population: a retrospective single center cohort study



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ABSTRACT

**Background and study aims** Endoscopic submucosal dissection (ESD) is increasingly being used to treat superficial esophageal cancer in the elderly. However, data on clinical outcomes in this age group are limited. The aim of this study was to evaluate the safety and efficacy of ESD in treatment of superficial esophageal cancer and its effect on long-term outcome in the elderly.

**Patients and methods** In total, 664 consecutive patients with a histological diagnosis of squamous cell carcinoma or high-grade intraepithelial neoplasia who underwent ESD between April 2008 and March 2016 at our institution were enrolled. Clinical outcomes and prognostic factors were compared retrospectively between those aged 75 years or older (n = 162) and those aged younger than 75 years (n = 502).

**Results** There was no significant difference in post-ESD bleeding (0 vs. 0.8 %, $P = 0.27$) and perforation rates (1.8 vs. 1.2 %, $P = 0.47$) between the two age groups; however, stricture rate was higher in younger patients than in elderly patients (20.8 % vs 11 %; $P = 0.036$). There was no significant difference in the rate of locoregional recurrence between the two groups. Overall survival was significantly different between the two groups, but cause-specific survival was similar.

**Conclusion** These findings confirm the efficacy of ESD for superficial esophageal cancer in selected elderly patients (75 years or older) who were fit for the treatment because they can achieve similar long-term survival to younger patients.

## Introduction

Endoscopic submucosal dissection (ESD) is now widely accepted as a less invasive treatment for superficial esophageal cancer [1,2] and is increasingly being used in elderly patients. However, it is unclear whether older patients with comorbidity are suitable candidates for ESD. Life expectancy of both western and eastern populations is increasing, and so increasing numbers of elderly patients are developing esophageal cancer. The safety and efficacy of ESD in elderly individuals is important. However, there are no data on the clinical outcomes of this procedure in elderly patients with superficial esophageal cancer.

Esophageal tumors that can be treated by ESD and those that need to be treated by esophagectomy differ in their level of invasiveness. Therefore, the likelihood of longer survival and maintenance of good quality of life should be considered when choosing between ESD and esophagectomy or chemoradiation therapy in patients with these tumors. Attention tends to be focused on risk of locoregional metastasis at the expense of benefit in terms of quality of life, and there are few relevant data in the elderly. The aim of this study was to evaluate the safety and

efficacy of ESD and the prognosis in elderly patients with superficial esophageal cancer.

## Patients and methods

### Patients

In total, 664 consecutive patients with a histological diagnosis of squamous cell carcinoma or high-grade intraepithelial neoplasia who underwent ESD between April 2008 and March 2016 at our institution were retrospectively identified and enrolled in the study. There were no exclusion criteria, but 26 patients were lost to follow-up among the elderly patients and 63 patients were lost among the younger patients. Elderly patients were defined as patients aged 75 years or older based on the Japan Geriatrics Society recommendation in 2017. The study was approved by our institutional review board (No. 1421).

### Endoscopic submucosal dissection

During the study period, the ESD procedures were performed by endoscopists with varying degrees of experience (including operators with less than 10 years of experience performing esophageal ESD or experience of less than 100 cases) under conscious sedation mainly. A single-channel upper gastrointestinal endoscope with a water-jet system (EG-450RD5, Fujifilm, Tokyo, Japan; GIF-Q260J, Olympus Medical Systems, Tokyo, Japan) was used, with a transparent cap attached to the tip of the endoscope. A Flex or Dual knife (Olympus Medical Systems) and a standard electrosurgical generator (ICC 200 or VIO300D, Erbe Elektromedizin GmbH, Tübingen, Germany) were used. We sprayed the site with iodine, and marking dots were then placed outside the margins of the tumor. Next, a solution containing a mixture of 10% glycerin and a small amount of indigo carmine and epinephrine was injected into the submucosal layer. An incision was then made on the distal side of the lesion and another on the proximal side. Submucosal dissection was performed from the proximal area to the distal area. and the lesion was removed en bloc. During dissection, endoscopic hemostatic procedures were performed, when necessary. An intralesional injection of triamcinolone acetonide (Kenacort; Bristol-Myers Squibb Co., Tokyo, Japan), diluted with saline to a concentration of 4 mg/mL was administered if deemed necessary by the operator, and was administered mainly for lesions with a circumferential mucosal defect of more than three-quarters of the circumference. In cases of full circumferential mucosal defect, oral steroids were administered. The resected specimen was sliced into 2-mm thick sections for histological examination.

### Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) was used to identify comorbid conditions [3,4]. Cancer, which was weighted as a double score, was defined as a cancer that developed in any organ other than the esophagus. Baseline patient characteristics were retrieved from the medical records.

### Definitions

Residual/locally recurrent lesions were defined as cancers that occurred at the site of excision of the primary lesion. Tumor location was classified as being in the cervical, upper, middle, or lower esophagus including the abdominal esophagus. Histopathological examination was performed in accordance with the recommendations of the Japanese classification for esophageal cancer [5]. Tumor size, depth, and lymphovascular involvement were assessed histologically, and curative resection was defined as lesions with a depth of invasion limited to within the lamina propria mucosa, negative horizontal margin, and no lymphovascular involvement. Adverse events (AE) included post-ESD bleeding, perforation, stricture, and ESD-related mortality. Post-ESD bleeding was diagnosed based on onset of clinical symptoms such as hematemesis, melena, or a decrease in hemoglobin level > 2 g/dL after ESD. Perforation was diagnosed when extraluminal organs around the esophagus were visualized during ESD or when significant pneumomediastinum was observed on computed tomography (CT) or radiography. An esophageal stricture was deemed to be present when the endoscope (diameter 9.2 mm) could not pass through the post-ESD ulcer scar. Procedure time was defined as the interval between incision and removal of the resected specimen. Locoregional and distant recurrence was defined as lymph node swelling ≥ 10 mm or neoplastic lesion in another organ as detected by CT, endoscopic ultrasound (EUS), or positron emission tomography.

### Follow-up surveillance

Patients who had been diagnosed with tumor invasion extending into the epithelium /lamina propria mucosa (EP/LPM) underwent follow-up endoscopic examination at 6-month intervals. Patients who had been diagnosed with invasion up to the muscularis mucosa (MM) or deeper were informed of the need for additional treatment and the associated benefits and risks. If patients opted to be followed up without any additional treatment or chemoradiotherapy, then CT, EUS, endoscopy, and cervical and abdominal ultrasonography were performed every 6 months. When surgery was performed, follow-up CT was performed at 6-month intervals and endoscopic examination was performed annually.

### Study parameters

The primary endpoint in this study was to elucidate cause-specific survival in elderly patients compared with younger patients. Secondary endpoints were short- and long-term outcomes of ESD, including AEs as the safety parameters, local recurrence rate, overall survival, and cause of death. AEs included perforation, post-ESD bleeding, and esophageal stricture. Prognostic factors associated with survival were also measured.

### Statistical analysis

Categorical variables were compared between the two groups using Pearson's chi-square test or Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. Kaplan-Meier curve analysis was used to compare overall survi-

▶ **Table 1** Clinical characteristics of patients who underwent endoscopic submucosal dissection.

| | Elderly | Young | *P* value |
|---|---|---|---|
| Number of patients (lesions) | 162 (209) | 502 (691) | |
| Median age, years (range) | 79 (75 – 96) | 65 (41 – 74) | < 0.0001 |
| Sex | | | 0.68 |
| ▪ Male | 148 (91.4) | 431 (85.9) | |
| ▪ Female | 14 (8.6) | 71 (14.1) | |
| CCI | | | 0.056 |
| ▪ ≤ 2 | 137 (84.6) | 452 (90.0) | |
| ▪ ≥ 3 | 25 (15.4) | 50 (10.0) | |
| Congestive heart failure | 5 (3.1) | 4 (0.8) | 0.048 |
| Cerebrovascular accident | 13 (8.0) | 24 (4.8) | 0.118 |
| Dementia | 5 (3.1) | 1 (0.2) | 0.001 |
| Pulmonary disease | 11 (6.8) | 19 (3.8) | 0.109 |
| Liver disease | 2 (1.2) | 9 (1.8) | 0.628 |
| Diabetes | 27 (16.7) | 56 (11.2) | 0.065 |
| Renal disease | 7 (4.3) | 14 (2.8) | 0.333 |
| Cancer of another organ | 47 (29.0) | 117 (23.3) | 0.143 |
| Severe liver disease | 2 (1.2) | 13 (2.6) | 0.313 |

Values are number (%) unless otherwise indicated.
CCI, Charlson Comorbidity Index

▶ **Table 2** Technical results.

| | Elderly | Young | *P* value |
|---|---|---|---|
| Number of patients (lesions) | 162 (209) | 502 (691) | |
| Median tumor size, mm (range) | 19 (2 – 80) | 19 (2 – 115) | 0.63 |
| Location | | | 0.827 |
| ▪ Ce | 10 (4.8) | 24 (3.5) | |
| ▪ Ut | 31 (14.8) | 132 (19.1) | |
| ▪ Mt | 115 (55.0) | 361 (52.2) | |
| ▪ Lt/Ae | 53 (25.4) | 174 (25.2) | |
| ESD under general anesthesia | 31 (14.8) | 144 (20.8) | 0.055 |
| Median procedure time, min (range) | 40 (7 – 250) | 45 (3 – 255) | 0.68 |
| Mucosal defect | | | 0.40 |
| ▪ ≤ 3/4 | 178 (85.2) | 581 (84.1) | |
| ▪ > 3/4 | 31 (14.8) | 110 (15.9) | |

Values are number (%) unless otherwise indicated.
Ce, cervical esophagus; Ut, upper esophagus; Mt, middle esophagus; Lt, lower esophagus; Ae, abdominal esophagus; ESD, endoscopic submucosal dissection

val and cause-specific survival between elderly patients and younger patients. The log-rank test was used to compare the survival curves. Cox proportional hazards modeling was used to evaluate potential prognostic factors and their association with survival time. Variables that were significant in the univariate analysis were included in the multivariate analysis. $P < 0.05$ was considered statistically significant. Overall Survival (OS) was measured from the date of the first ESD to the date of death or most recent confirmation of survival. All statistical analyses were performed using Stata software (version 11, Stata Corp LP, College Station, Texas, United States).

# Results

## Patient demographics and clinical characteristics

Baseline demographic characteristics are presented in ▶ **Table 1** and ▶ **Table 2**. There was no statistically significant difference in patient sex, size, or location of the tumor, number of ESD procedures performed under general anesthesia, or procedure time between the two age groups. A Charleston comorbidity index (CCI) ≤ 2 was less common in the elderly patients than in the younger patients, but not significantly so. Among the CCI items, congestive heart failure and dementia were significantly more common in the elderly, but the numbers were minimal.

## Short-term outcomes

Short-term outcomes are shown in ▶ **Table 3** and ▶ **Table 4**. Although post-ESD bleeding and perforation rates were not significantly different between the two age groups, stricture rate was higher in younger patients than in elderly patients (20.8 % vs 11 %; $P = 0.036$). The rate of additional treatments in patients with T1a-MM or deeper was significantly lower in elderly patients than in younger patients (31.8 % vs 68 %). Mortality rate, including deaths from primary cancer, was not significantly higher in elderly patients compared with younger patients. There was no difference in locoregional recurrence rate between the groups.

## Long-term data

Kaplan-Meier curves for overall survival are shown in ▶ **Fig. 1**. There were significant differences between the groups according to age ($P = 0.037$, log-rank test). In elderly and younger patients, 3-year survival rates were 92.3 % and 96.1 %, respectively, and 5-year survival rates were 83.6 %, and 91.2 %, respectively. The Kaplan-Meier curves for cause-specific survival rate at 3 years was 98.5 % in both age groups and at 5 years was 97.3 % in elderly patients and 97.5 % in younger patients (▶ **Fig. 2**). The follow-up rate in elderly and younger patients was 83.3 % and 87.1 % respectively.

▶ **Table 3** Pathological result and rate of patients with additional treatments.

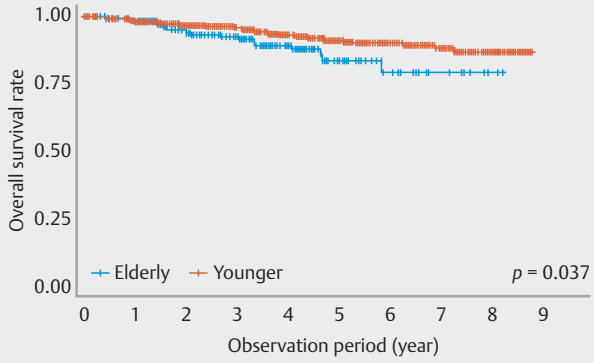
| | Elderly | Young | *P* value |
|---|---|---|---|
| Number of patients (lesions) | 162 (209) | 502 (691) | |
| Tumor depth | | | 0.165 |
| ▪ EP/LPM | 165 (79.0) | 538 (77.9) | |
| ▪ MM/SM1 | 26 (12.4) | 113 (16.3) | |
| ▪ SM2 | 18 (8.6) | 40 (5.8) | |
| Ly | 11 (5.3) | 55 (8.0) | 0.12 |
| V | 11 (5.3) | 42 (6.1) | 0.40 |
| Curative resection | 163 (78) | 520 (75.3) | 0.46 |
| MM or deeper | 44 (21.1) | 143 (20.7) | 0.49 |
| Additional treatment | 14 (31.8) | 104 (72.7) | <0.0001 |
| Surgery | 1 | 32 | 0.0014 |
| CRT | 13 | 72 | 0.042 |

Values are number (%) unless otherwise indicated.
EP, intraepithelial cancer; LPM, tumor invading the lamina propria mucosa; MM, invading the muscularis mucosa; SM1, invading the submucosal layer to 200 µm or less; SM2, invading deeper submucosal lesions; Ly, lymphatic involvement; V, venous involvement; CRT, chemoradiotherapy

▶ **Table 4** Outcomes of endoscopic submucosal dissection.

| | Elderly | Young | *P* value |
|---|---|---|---|
| Number of lesions (lesions) | 162 (209) | 502 (691) | |
| Adverse events | | | |
| ▪ Post-ESD bleeding | 0 (0) | 4 (0.6) | 0.27 |
| ▪ Perforation | 3 (1.4) | 6 (0.9) | 0.47 |
| ▪ Stricture | 23 (11) | 144 (20.8) | 0.036 |
| ESD-related mortality | 0 (0) | 0 (0) | 1.00 |
| Death | 17 (10.5) | 36 (7.2) | 0.175 |
| Primary cancer: other cancer | 3:8 | 10:20 | – |
| Locoregional recurrence | 5 | 10 | 0.415 |
| Median follow-up interval, months (range) | 41.5 (0.23 – 100.1) | 50.8 (0.17 – 107) | 0.0001 |
| Cause-specific survival | | | |
| ▪ 5-year | 97.3 | 97.5 | 0.91 |

Values are number (%) unless otherwise indicated.
ESD, endoscopic submucosal dissection




▶ **Fig. 1** Comparison of overall survival between elderly patients and younger patients.


▶ **Fig. 2** Comparison of cause-specific survival between elderly patients and younger patients.

### Risk factors

Univariate Cox proportional hazards modeling revealed depth of invasion and lymphovascular invasion to be independent prognostic factors; in multivariate analysis, no specific factor was identified as an independent predictor of prognosis (▶ **Table 5**).

## Discussion

With the current view, our concern was to clarify the impact of ESD on survival in elderly patients. The main finding of this study is that long-term outcomes are favorable in elderly patients with esophageal carcinoma who undergo ESD. Recently, Cummings et al. compared short-term outcomes, recurrence rate, and survival after endoscopic versus surgical treatment of early esophageal cancers in an older population [6]. They found that the 2-year survival rate following endoscopic treatment was 84 %, which was significantly higher than that after surgery. Depth of tumor invasion, age, and endoscopic therapy were also reported to be predictors of overall mortality. Unfortunately, that study documented only 2-year survival, so the long-term survival rate could not be investigated. To our know-

▶ **Table 5** Potential predictors of cause-specific survival.

| | | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|
| | **Patients, n** | **All-cause specific mortality, n** | **HR** | **95 % CI** | ***P* value** | **HR** | **95 % CI** | ***P* value** |
| Age, years | | | | | | | | |
| ▪ <75 | 502 | 10 | 1 | | | 1 | | |
| ▪ ≥75 | 162 | 3 | 1.08 | 0.30 – 3.94 | 0.91 | 1.26 | 0.34 – 4.63 | 0.73 |
| Tumor size, mm | | | | | | | | |
| ▪ ≤20 mm | 312 | 5 | 1 | | | | | |
| ▪ >20 mm | 352 | 8 | 1.42 | 0.46 – 4.34 | 0.54 | | | |
| Depth of invasion | | | | | | | | |
| ▪ EP/LPM | 473 | 3 | 1 | | | 1 | | |
| ▪ MM or deeper | 191 | 10 | 7.44 | 2.05 – 27.03 | 0.002 | 4.06 | 0.83 – 19.9 | 0.085 |
| CCI | | | | | | | | |
| ▪ ≤2 | 589 | 10 | 1 | | | | | |
| ▪ ≥3 | 75 | 3 | 2.39 | 0.66 – 8.68 | 0.19 | | | |
| LVI | | | | | | | | |
| ▪ Negative | 579 | 6 | 1 | | | 1 | | |
| ▪ Positive | 85 | 7 | 7.19 | 2.42 – 21.4 | <0.0001 | 2.92 | 0.76 – 11.3 | 0.12 |
| Congestive heart failure | | | | | | | | |
| ▪ Negative | 655 | 13 | 1 | | | | | |
| ▪ Positive | 9 | 0 | 1.25e-14 | 0 | 1.00 | | | |
| Dementia | | | | | | | | |
| ▪ Negative | 658 | 13 | 1 | | | | | |
| ▪ Positive | 6 | 0 | 3.41e-14 | 0 | 1.00 | | | |

CI, confidence interval; CCI, Charlson Comorbidity Index; EP, intraepithelial cancer; HR, hazards ratio; LPM, tumor invading the lamina propria mucosa; MM, invading the muscularis mucosa; LVI, lymphovascular involvement;

ledge, the current report is the first to determine long-term outcomes of ESD in a geriatric population.

Safety of ESD in the elderly was confirmed to be similar to that in the younger population, which is consistent with a previous report from a single center indicating no increase in the AE rate in elderly patients undergoing ESD for early gastric cancer [7] or endoscopic mucosal resection for Barrett's esophagus [8]. However, the current study was influenced by a degree of selection bias, in that patients with respiratory failure as a consequence of aspiration pneumonia, those in whom use of sedative drugs during ESD would have been difficult, and those with Child-Pugh class C liver cirrhosis were excluded.

In our study, long-term overall survival was significantly lower in elderly patients than in younger patients, but cause-specific survival was similar; this could simply reflect the fact that elderly patients are at increased risk of susceptibility to other cancers or diseases. In fact, the percentage of the elderly and younger patients who died from other cancers or disease was 8.6 % and 5.2 %, respectively. Therefore, ESD likely contributes to longer survival by preventing death from the primary cancer. However, it should be noted that the survival rates were derived from a population that has one of the longest life expectancies and a country that has large numbers of skillful endoscopists.

Risk of lymph node metastasis in patients with a histological tumor grade of T1a-MM or T1b-SM2 is about 10 % to 54 % [9, 10], so additional treatment is generally recommended in these patients. In the current study, more younger patients than elderly patients underwent additional treatment (68 % vs 31.8 %), most likely because the latter group are generally hesitant to undergo chemotherapy and/or radiation therapy because of comorbidities or advanced age. In a review of the Nationwide Inpatient Sample and Surveillance, Epidemiology, and End Results-Medicare data on outcomes of esophagectomy in 27,957 patients aged 65 years or older, Finlayson et al. found that operative mortality significantly increased from 8.8 % in

patients aged 65 to 69 years to 13.4 % in those aged 70 to 79 years and to 19.9 % in those aged older than 80 years [11]. Furthermore, in a study by Takeuchi et al., patients aged 71 years or older had worse survival and experienced more toxicity than younger patients when treated with the cisplatin and 5-fluorouracil regimen and radiation [12]. Low percentages of additional treatment would be expected in the elderly in such circumstances. However, recurrence rate during follow-up was no different from that in younger patients. This finding suggests that need for additional treatment should be reassessed in elderly patients, taking into account the higher mortality rate after esophagectomy and systemic toxicity associated with chemoradiation therapy.

Age, depth of tumor invasion, and CCI score were not identified to be independently associated with survival in a Cox proportional hazards model. A previous study of ESD in patients with gastric cancer aged 85 years or older showed that presence of comorbidities, regardless of severity, predicted a poor prognosis [7]. Sekiguchi et al. also reported that prognosis in elderly patients was mostly determined by factors other than gastric cancer, and that lesion characteristics and curability by ESD were not prognostic factors [7]. Another report by Lu et al. recommended individualized treatment in accordance with further age subgrouping and pretreatment in line with the CCI [13]. Therefore, we should consider additional treatment strategies after a thorough assessment of an individual patient's functional status and wishes.

This study has some limitations, particularly its single-center retrospective design. In addition, a degree of selection bias was introduced at two points in the study, the first being when the decision was taken regarding whether or not to perform ESD and the second being when the decision was made about whether to proceed to additional treatment. However, these judgments reflect the situation in everyday clinical practice. Another limitation is that there were some missing data on survival. Also, we did not have data for the prognostic nutrition index or American Society of Anesthesiologists' Physical Status in this retrospective study, which should be investigated in future studies.

## Conclusion

In conclusion, this study has elucidated the safety and efficacy of ESD for superficial esophageal cancer in patients aged 75 years or older. These patients had a relatively low risk of death from esophageal cancer. In addition, for selected elderly patients who were fit for treatment despite calendar age, ESD is feasible because they can achieve similar long-term survival to young patients.

## Competing interests

None

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