Title:

Safety and usefulness of endoscopic submucosal dissection for early esophageal cancers in elderly patients 80 years or older

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Background and Aim: Endoscopic submucosal dissection (ESD) for early gastrointestinal (GI) cancers is widely performed as a standard treatment in Japan. Given the increasing life expectancy worldwide, it is naturally regarded that the rate of elderly patients diagnosed with early GI cancer has increased. Available guidelines do not specifically outline how to manage endoscopic therapy for the elderly. The aim of this study was to assess the safety and usefulness of ESD for superficial esophageal squamous cell carcinoma (SESCC) in elderly patients.

Methods: We retrospectively investigated 393 consecutive patients, who underwent 426 ESD for 444 SESCCs from January 2011 to August 2016 at our institution. For this study, patients were divided into 2 groups based on their age; ≥ 80 years (Group aged ≥80 years, n = 42) and < 80 years (Group aged <80 years, n = 351). Patient demographics, sedation methods, technical outcomes, adverse events, sedatives, dosages given, overall survival and disease specific survival were then examined.

Results: The ESD procedure time was significantly longer for group aged ≥80 years than for group aged <80 years (110 minutes [range, 29-260] vs 85 minutes [24-504], p=0.006), however there was no significant differences between other technical items and adverse events. The 3-year overall survival and disease specific survival were favorable in both groups.

Conclusions: Esophageal ESD for elderly patients aged ≥80 years can be safely performed. Mid-term outcome was favorable. Our study suggests that esophageal ESD might be a usefulness treatment for SESCCs.

Key Words: esophageal cancer, endoscopic submucosal dissection, elderly patient

Introduction

Endoscopic submucosal dissection (ESD) for early gastrointestinal (GI) cancers is widely performed as a standard treatment in Japan [1-5]. ESD enables en-bloc resection of large or scarring lesions, which are difficult to remove in one piece with conventional endoscopic mucosal resection (EMR) [6, 7]. In the esophagus, ESD for early cancers has been reported to have a significantly higher success rate for en-bloc resection compared to EMR [8]. Although endoscopic therapy is less invasive than surgery, ESD is technically challenging and often takes a prolonged amount of time to complete. Given the current increased life expectancy worldwide, it is naturally regarded that the rate of elderly patients diagnosed with early GI cancer has increased. It is therefore necessary to clearly define how to treat elderly patients safely via endoscopic treatment, as they frequently have severe comorbidities and limited physical function. Available guidelines do not specifically outline how to manage endoscopic therapy for the elderly [9-13]. Although we have reported that ESD for early gastric cancer can be performed safely if the general condition of the elderly patient is encouraging, there have however, been a few outcomes including long-term results for elderly patients having undergone ESD for the treatment of superficial esophageal squamous cell carcinoma (SESCC) [14-16]. The aim of this study was to assess the safety and usefulness of ESD for SESCC in elderly patients.

Patients and methods

We retrospectively investigated 393 consecutive patients, who underwent 426 ESD for 444 SESCCs from January 2011 to August 2016 at our institution. In order to examine the safety and effectiveness of ESD in elderly patients aged 80 years or older, we compared patients' characteristics, lesion characteristics, ESD

results, administered drugs, dosage of the drugs, pathological results of SESCCs, the need for additional treatment, as well as comparing long-term outcome of patients aged 80 years or older (group aged ≥80 years, n = 42) with those less than 80 years of age (group aged <80 years, n = 351). Patients with multiple lesions required longer treatment time, they were nevertheless included in this study, according to actual clinical practice. Seven esophageal ESD cases, which were performed as an additional treatment after CRT/RT, were excluded as well as patients with severe comorbidities to be unfit for ESD procedure. Written informed consent was obtained from all patients, and the study was approved by the institutional review board at our hospital.

Definition and therapeutic indications

All the information on SESCC described in this study is based on the clinical pathology guidelines for esophageal cancer issued by the Japan Esophageal Society [17, 18]. Based on the guidelines for the Diagnosis and Treatment of Carcinoma of the Esophagus, we decided to adapt ESD for SESCCs to include the relative indication of lesions invading up to the muscularis mucosae or only slightly infiltrating the submucosa up to 200 μm (MM/SM1), as well as lesions limited to the mucosal epithelium or the lamina propria mucosa (EP/LPM) [19]. In our hospital, EMR was basically performed lesions 15mm or less in size while ESD was applied for lesions more than 15mm in size, particularly over 20mm. Circumferential lesions were basically excluded from ESD indication during this period. Lesions which clinically diagnosed to invade extensively (more than 200 μm) into the submucosa were also excluded from ESD indication. However, staging ESD was performed for some of them after it was discussed at a multidisciplinary conference.

Endoscopic treatment

In this study, endoscopists practicing at our center as attending doctors were defined as experts, whereas endoscopists, who were residents and trainees, were defined as non-experts. ESD was either performed, by the experts or non-experts under an expert's supervision, using the electrosurgical generators (VIO300D; ERBE Elektromedizin, Tübingen, Germany or ESG100; Olympus Co., Ltd., Tokyo, Japan). Furthermore, ESD was executed using the IT knife nano (Olympus) and Dual knife (Olympus) as previously reported [20]. If there were no adverse events after the treatment, patients were discharged on post-operative day five.

Sedation method and monitoring

Sedation methods included intravenous sedation or general anesthesia (GA). Depending on the lesion and the patient's condition, the attending physician selected the appropriate sedation method. When intravenous anesthesia is not appropriate, then GA was chosen in the operating. The intravenous anesthesia was composed of pentazocine hydrochloride or fentanyl, which was administered with propofol. We used electrocardiogram monitoring, oxygen saturation levels, non-invasive blood pressure measurements, continuous breath sound measurements using an acoustic respiration monitor or capnograph, as well as bispectral index (BIS) monitoring, in all cases [21, 22]. During deep sedation by administering a sedative and analgesic, the numerical value of BIS was kept basically between 60 and 80. The patient was given oxygen at a rate of 2-3 L/min, using a nasal cannula.

Additional treatment and follow-up methods

When ESD results diagnosed tumor depth to be EP/LPM/MM, and showed negative findings for lymphovascular invasion and vertical margin (VM), we followed up with upper GI endoscopy and blood tests every 6 to 12 months without additional treatment. If the ESD result was diagnosed the depth of the lesion to be SM, lymphovascular invasion or positive findings of VM, additional treatment such as surgery or chemoradiotherapy (CRT) / radiotherapy (RT) were considered. When local recurrence occurred, additional EMR/ESD was considered. When lymph node metastasis or distant metastasis occurred, additional surgery or CRT/RT or chemotherapy was considered. There were cases having severe comorbidities in the elderly patients that were followed up without additional treatment. New lesions, which were detected during follow-up period after endoscopic resection, were described as metachronous ones in this study.

Statistical analysis

Variables in the present study were described in terms of mean, standard deviation, median, and range, as deemed appropriate. Clinical outcomes were analyzed using the $\chi 2$-test, Fisher's exact test, Student's t-test, and the Mann–Whitney U-test. Follow-up period was defined as the time from the date of the initial ESD to the date of the last evaluation. Survival curves and cumulative incidence were calculated using the Kaplan–Meier method and compared using the log-rank test. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were carried out using statistical analysis software (SPSS, version 20; SPSS Japan Inc., Tokyo, Japan).

Results

Patient characteristics and endoscopic findings

A total of 393 consecutive patients suffering from 444 SESCCs, underwent ESD at our hospital. For this study, patients were divided into 2 groups based on their age; ≥ 80 years (Group aged ≥80 years, n = 42) and < 80 years (Group aged <80 years, n = 351) (Table 1). The proportion of class III of the classification of the American Society of Anesthesiologists in group aged ≥80 years and group aged <80 years were 5% (I-II/III, 40/2) and 2% (I-II/III, 345/6), respectively (p = 0.03). The median tumor size of SESCCs in group aged ≥80 years and group aged <80 years was 26 mm (range, 7 - 61 mm) and 22 mm (1 - 85 mm) (p = 0.007) and circumference of lesions was wider in group aged ≥80 years.

Technical results and sedatives

The results of ESD for SESCCs were shown in Table 2. The ESD procedure time was significantly longer for group aged ≥80 years than for group aged <80 years (110 minutes [range, 29-260] vs. 85 minutes [24-504], p=0.006), however there was no significant differences between other technical items and adverse events such as delayed bleeding and perforation. Delayed bleeding occurred in each one case without antithrombotic drug of both groups, Forty-one (91%) patients from group aged ≥80 years and 361 (95%) patients from group aged <80 years were sedated using intravenous anesthesia in the endoscopic examination room, while 4 (9%) and 20 (5%) patients were sedated by GA. The median dosage of administered drugs in group aged ≥80 years and group aged <80 years were as follows; propofol was 6.0 mg/kg/h (2.9-11.1) and 7.0 mg/kg/h (0.41-31) (p = 0.001), pentazocine was 0.21 mg/kg/h (0.08-0.84) and 0.28 mg/kg/h (0.05-1.2)

(p = 0.049), and fentanyl was 1.3 μg/kg/h (0.73-2.9) and 1.9 μg/kg/h (0.62-7.0) (p = 0.005).

Pathological results and additional treatments

Tumor depth and tumor margins were similar results between two groups (Table 3). The positive rate of lymphovascular invasion was 1 case (2%) and 31 cases (8%) (p = 0.03). Three lesions (6%) and 55 lesions (14%), respectively, were positive for submucosal or lymphovascular invasion or vertical margin (p = 0.02). No patient underwent additional treatment after ESD in group aged ≥80 years while 55 cases (14%) received additional therapies in group aged <80 years including radiation therapy for 1 case (0.3%), chemoradiotherapy for 52 cases (13%) and surgery for 2 cases (0.8%)(Table 3, Fig. 1).

Metachronous lesions, recurrences and survivals

The observation period after ESD was 35.4 ± 14.6 months and 41.5 ± 17.8 months in group aged ≥80 years and group aged <80 years, respectively (Table 4). In 3 of group aged ≥80 years and 54 cases of group aged <80 years, metachronous esophageal cancer was revealed during the observation period. 3-year cumulative occurrence rate was 8% and 14% in group aged ≥80 years and group aged <80 years, respectively (p=0.74). Endoscopic resection has been performed for all metachronous esophageal cancers, and the period from the initial ESD up to the treatment was 20 ± 6.7 months and 24 ± 15 months in group aged ≥80 years and group aged <80 years, respectively. In group aged <80 years, only one patient (0.3%) underwent CRT as additional treatment after ESD procedure because pathological result revealed submucosal invasion. There were no cases of deaths from metachronous esophageal cancer. In 3 of group aged ≥80 years compared to 28 cases of group aged <80 years, metachronous head and neck cancers were detected during the observation period (Table 4). 3-year cumulative occurrence rate was 8% in both group aged ≥80 years and group aged <80

years (p=0.97). Additional treatment was performed in all cases. There were no cases of deaths from metachronous head and neck cancers.

No recurrence were seen and no patients died of esophageal cancer in group aged ≥80 years. There were five patients with recurrence which were lymph node metastasis in 4 cases and lymph node metastasis with liver metastasis in 1 case, and finally 2 patients died of esophageal cancer in group aged <80 years. There was no significant difference between the two groups in the overall survival rate and disease specific survival rate (Fig. 2).

DISCUSSION

Treatment results in the short term were comparable between elderly patients aged ≥80 years and those aged <80 years. There were no significant differences in complications, such as delayed bleeding, perforation, pneumonia and hospitalization period. In addition, the 3-year overall survival rate as a mid-term outcome was favorable in group aged ≥80 years and group aged <80 years, 98% and 96%, respectively.

Elderly patients were noted to suffer more from chronic diseases such as hypertension, heart disease, and cerebrovascular disorder. There are also cases, in which lifestyle diseases developed and the performance status worsened. In this study, the proportion of type III from the classification of the American Society of Anesthesiologists and the coexistence rate of hypertension / cardiovascular disease, were significantly higher in the group ≥80 years of age. However, there was no difference in the short-term results, which indicates that esophageal ESD can safely be performed in the elderly, unless they have serious comorbidities.

Although the procedure time in the group aged ≥80 years was significantly longer in comparison to

group aged <80 years because of larger tumor size and wider circumference of lesion, the technical results including en-bloc resection, perforation and delayed bleeding were comparable. Therefore, we believe that esophageal ESD can perform safely for the elderly patients aged ≥80 years in the technical aspects. Generally, it is thought that the risk of aspiration pneumonia increases with elderly patients during endoscopic treatment; we reported that pneumonia was seen as a complication in only 2% of ESD of gastric cancer in elderly patients aged ≥85 years at our institution [14]. Although the number of cases may be small in this study, pneumonia was not observed as a complication in the group aged ≥80 years.

There was no significant difference in sedation methods between the groups, nevertheless the amount of propofol and fentanyl used was smaller in the elderly group. It has been previously reported that the dosage of propofol required for sedation is smaller in elderly compared to non-elderly patients [23]. For elderly patients, even with the same dosage, there is a possibility of excessive sedation compared to non-elderly patients, as such, careful drug administration is necessary.

The proportion of esophageal cancer invading the submucosa or the proportion of lymphovascular invasion or positivity for margin in the group aged ≥80 years was 13%, in comparison to that of group aged <80 years, which was 18%. The treatment for esophageal cancer, except for endoscopic resection, provides patients the huge physical burden. There are some opportunities to attempt staging ESD for lesions that might be slightly deep, as such the curative resection rate for those become to be low. This might be considered as one of the reasons why the curative resection rate is low in the group aged ≥80 years. In the previous report, ESD for SESCCs was performed and the rate of submucosal invasion was 13-18% [3, 16].

The proportion for which CRT was performed as an additional treatment was higher in the group

aged <80 years, than that of elderly patients (0% vs 13%, $p < 0.001$). Although there were 2 patients who required to receive additional treatment due to pathological result, they had no recurrence in the follow up period fortunately. Regarding additional treatments such as CRT, surgical resection and others, for the elderly, is often decided by comprehensively judging their physical condition and background. If additional treatments were performed, they would suffer from adverse events [24]. The extent to which the risk of recurrence is tolerated is controversial for the elderly patients.

The 3-year overall survival and disease specific survival were favorable in both groups, even for patients aged ≥80 years. Within 3 years, metachronous multiple esophageal cancer was found in 9-14%. Metachronous head and neck cancer was found in 8%, which was comparable to that of multiple-esophageal cancers reported in previous reports. There was a slightly higher tendency for head and neck cancer [25]. Follow-up of upper gastrointestinal endoscopy after treatment of early esophageal cancer is important.

There are several limitations to this study. It is a retrospective study at a single institute. The sample size of the elderly group was relatively small and the standard of additional treatment was not defined. Furthermore, median follow-up period is approximately 3 years, which might be not enough to evaluate the long-term outcome..

Conclusion

In conclusion, esophageal ESD for elderly patients aged ≥80 years can be safely performed, unless they have serious comorbidities. Although a small number of deaths from esophageal cancer were observed, mid-term outcome was favorable. Our study suggests that esophageal ESD might be a useful treatment for

superficial esophageal cancer.

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Table 1. Patient and lesion characteristics

	aged ≥ 80 years	aged < 80 years	*P* value
No. of patients	42	351	
No. of lesions	47	397	
No. of ESD† sessions	45	381	
Age, years, mean±SD‡	82.3±2.2	67.1±6.2	
Sex, n (%)			
Male	36 (86%)	286 (81%)	0.44
Female	6 (14%)	65 (19%)	
Body weight, kg, mean±SD‡	58.1±6.8	59.6±8.5	0.17
ASA* classification, n (%)			
I-II	40 (95%)	345 (98%)	0.03
III	2 (5%)	6 (2%)	
Comorbidities**			
Hypertension, no. (%)	28 (67%)	133 (38%)	<0.001
Hyperlipidemia	7 (17%)	36 (10%)	0.04
Cardiovascular disease	7 (17%)	34 (10%)	0.02
Diabetes	7 (17%)	32 (9%)	0.01
Respiratory disease	4 (10%)	18 (5%)	0.045
Cerebrovascular disease	1 (2%)	12 (3%)	0.58
Renal failure	1 (2%)	9 (3%)	0.90
Antithrombotic drugs, no. (%)	4 (10%)	22 (6%)	0.19
Tumor size, mm, median (range)	26 (7-61)	22 (1-85)	0.007
Location of lesions, n (%)			
Cervical (Ce)	0 (0%)	5 (1%)	0.07[a]
Upper thoracic (Ut)	8 (17%)	40 (10%)	
Middle thoracic (Mt)	24 (51%)	244 (62%)	
Lower thoracic (Lt)	9 (19%)	95 (24%)	
Abdominal (Ae)	6 (13%)	13 (3%)	
Circumference of lesions, n (%)			
<1/2	30 (64%)	295 (74%)	0.02[b]
1/2-3/4	16 (34%)	95 (24%)	
>3/4	1 (2%)	7 (2%)	
Macroscopic type, n (%)			
0-IIa***	0 (0%)	17 (4%)	0.01[c]
0-IIb***	1 (2%)	15 (4%)	
0-IIc***	45 (95%)	346 (87%)	
combined	1 (2%)	19 (5%))	

† Endoscopic submucosal dissection

‡ Standard deviation

* Classification of the American Society of Anesthesiologists

** Including overlapping cases

*** Type 0-IIa: Slightly elevated type, Type 0-IIb: Flat type, Type 0-IIc: Slightly depressed type

[a] Ce-Ut vs Mt-Ae

[b] <1/2 vs ≥1/2

[c] 0-IIc vs the others

Table 2. Technical results and administered drugs

	aged ≥ 80 years	aged < 80 years	*P* value
Operators, n* (%)			
Experts	29 (62%)	273 (69%)	0.13
Non-experts	18 (38%)	124 (31%)	
En-bloc resection, n* (%)	47 (100%)	396 (99.7%)	0.62
Procedure time**, min, median (range)	110 (29-260)	85 (24-504)	0.006
Delayed bleeding, n* (%)	1 (2%)	1 (0.3%)	0.20
Intraoperative perforation, n* (%)	0 (0%)	5 (1%)	0.25
Pneumonia, n† (%)	0 (0%)	1 (0.3%)	0.58
Hospitalization, days, mean±SD***	7.4±0.6	7.7±1.2	0.32
Sedation method, n† (%)			
Intravenous anesthesia	41 (91%)	361 (95%)	0.066
GA‡	4 (9%)	20 (5%)	
Dosage of Drugs§, mg/kg/h, median (range)			
Propofol	6.0 (2.9-11.1)	7.0 (0.41-31)	0.001
Pentazocine	0.21 (0.08-0.84)	0.28 (0.05-1.2)	0.049
Fentanyl	1.3 (0.73-2.9)	1.9 (0.62-7.0)	0.005

* Number of lesions

**From insertion to withdrawal of the endoscope.

*** Standard deviation

† Number of endoscopic submucosal dissection sessions

‡ GA: general anesthesia

§ Drugs for intravenous anesthesia

Table 3. Pathological results of SESCC† and additional treatment

	aged ≥ 80 years (n=47§)	aged < 80 years (n=397§)	*P* value
Tumor depth, n (%)			
EP‡	11 (24%)	88 (22%)	0.95*
LPM‡	24 (51%)	209 (53%)	
MM‡	9 (19%)	60 (15%)	
Submucosa, SM1‡	1 (2%)	10 (2%)	
Submucosa, SM2‡	2 (4%)	30 (8%)	
Lymphovascular invasion, n (%)			
Present	1 (2%)	31 (8%)	0.03
Absent	46 (98%)	366 (92%)	
Horizontal margin, n (%)			
Positive	3 (6%)	19 (5%)	0.52
Negative	44 (94%)	378 (95%)	
Vertical margin, n (%)			
Positive	0 (0%)	3 (1%)	0.36
Negative	47 (100%)	394 (99%)	
SM or lymphovasucular invasion (+) or VM** (+)	3 (6%)	55 (14%)	0.02
Additional treatment, n (%)			
Radiotherapy	0 (0%)	1 (0.3%)	0.58
Chemoradiotherapy	0 (0%)	48 (12%)	<0.001
Operation	0 (0%)	2 (0.5%)	0.48

§ Number of lesions

† SESCC, superficial esophageal squamous cell carcinoma

‡ EP, Carcinoma in situ (Tis); LPM, Lamina propria mucosae; MM, Muscularis mucosae; SM1, The upper third of the submucosal layer; SM2, The middle third of the submucosal layer

* EP+LPM vs MM+SM1+SM2

** VM, vertical margin

Table 4. Long-term outcome

	aged ≥ 80 years (n=42§)	aged < 80 years (n=351§)	*P* value
Follow-up period, months, mean±SD	35.4±14.6	41.5±17.8	0.045
Local recurrence, n (%)	0 (0%)	0 (0%)	---
Metastasis†, n (%)			
Lymph node	0 (0%)	5 (1%)	0.23
Distant*	0 (0%)	1 (0.3%)	0.58
Cause of Death, n (%)			
Esophageal cancer	0 (0%)	2 (0.6%)	0.44
Non-esophageal cancer	0 (0%)	5 (1.4%)	0.23
Others	1 (2.4%)	8 (2.3%)	0.95
Survival rate			
3-year overall, %	94	97	0.71
3-year disease-specific, %	100	99	0.69
Metachronous esophageal cancer†			
No. of lesions, n	3	54	
3-year cumulative occurrence rate, %	9	14	0.74
Metachronous head and neck cancer†			
No. of lesions, n	3	28	
3-year cumulative occurrence rate, %	8	8	0.97

§ Number of patients

† The lesion was detected after esophageal endoscopic submucosal dissection.

* Lymph node metastasis coexist.

** disease specific survival

(supplementary file)

Table 5. Clinical information of patients with recurrence

Age	Sex	Size (mm)	Depth	Lymphovascular invasion	Additonal treatment (post-ESD)	Recurrence	Additonal treatment (post-recurrence)	Outcome
54	M	23 26	MM MM	ly (-), v (-) ly (-), v (-)	-	lymph node and liver	-	dead**
61	M	55	MM	ly (+), v (-)	CRT	lymph node	CRT*	dead**
62	M	28	MM	ly (+), v (+)	RT	lymph node	OP	alive
63	M	32	MM	ly (+), v (-)	CRT	lymph node	OP and CT	alive
71	M	37	SM2	ly (+), v (-)	CRT	lymph node	CT	alive

Vertical margin was negative in all cases.

M, Male; MM, Muscularis mucosae; SM2, The middle third of the submucosal layer; ly, Lymphatic invasion; v, Vascular invasion; CRT, Chemoradiotherapy; RT, Radiotherapy; OP, Operation; CT, Chemotherapy;

* Chemoradiotherapy for cervical lymph node metastasis; ** dead of esophageal cancer

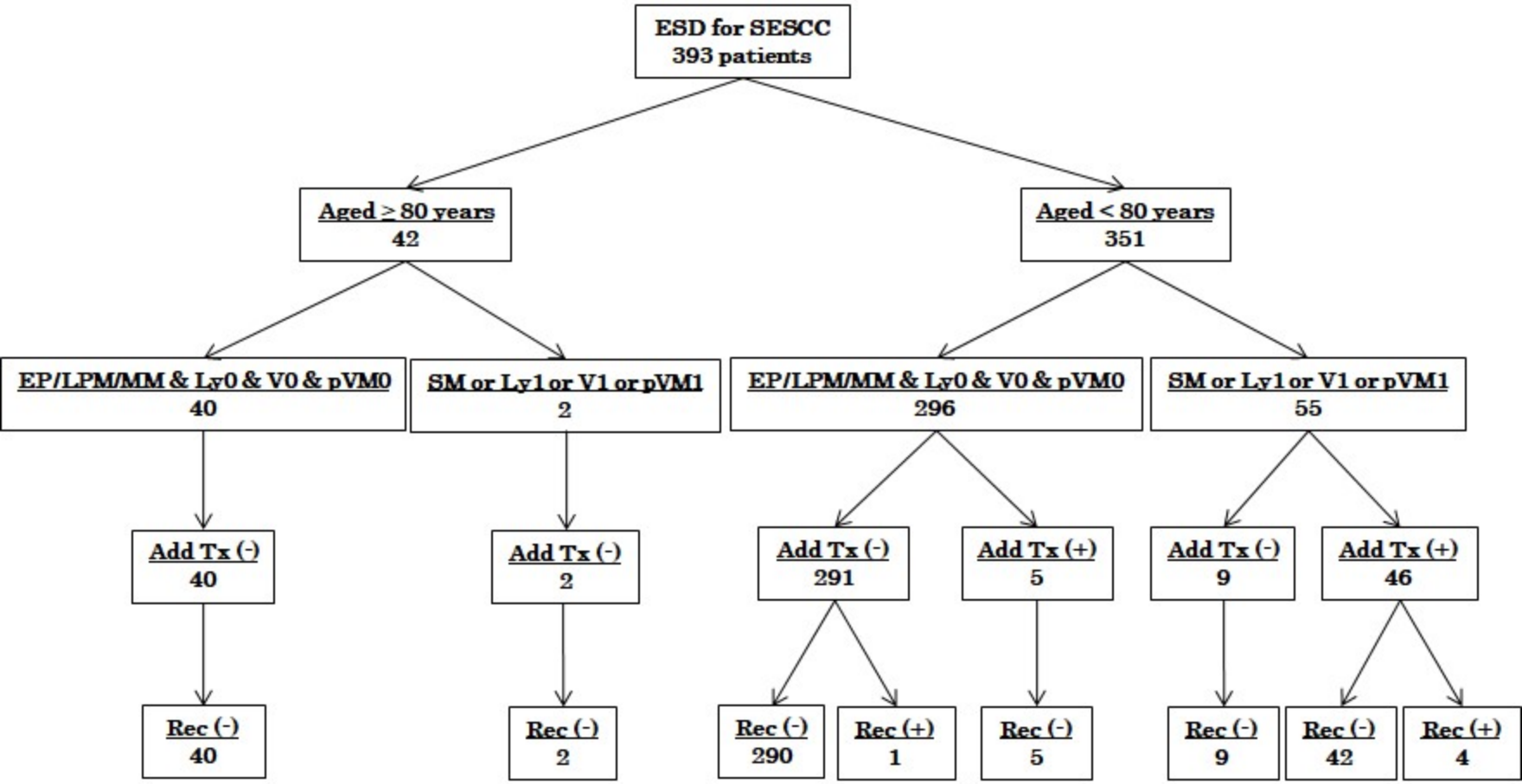
Figure legend:

Figure 1 Patient flow diagram
Flow diagram of patients who received endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. When patients have multiple lesions including metachronous esophageal cancers, the most advanced lesions are described as main lesion

Figure 2 Overall and disease-specific survivals
There is no significant difference between group aged ≥80 years and group aged <80 years using Kaplan–Meier estimates

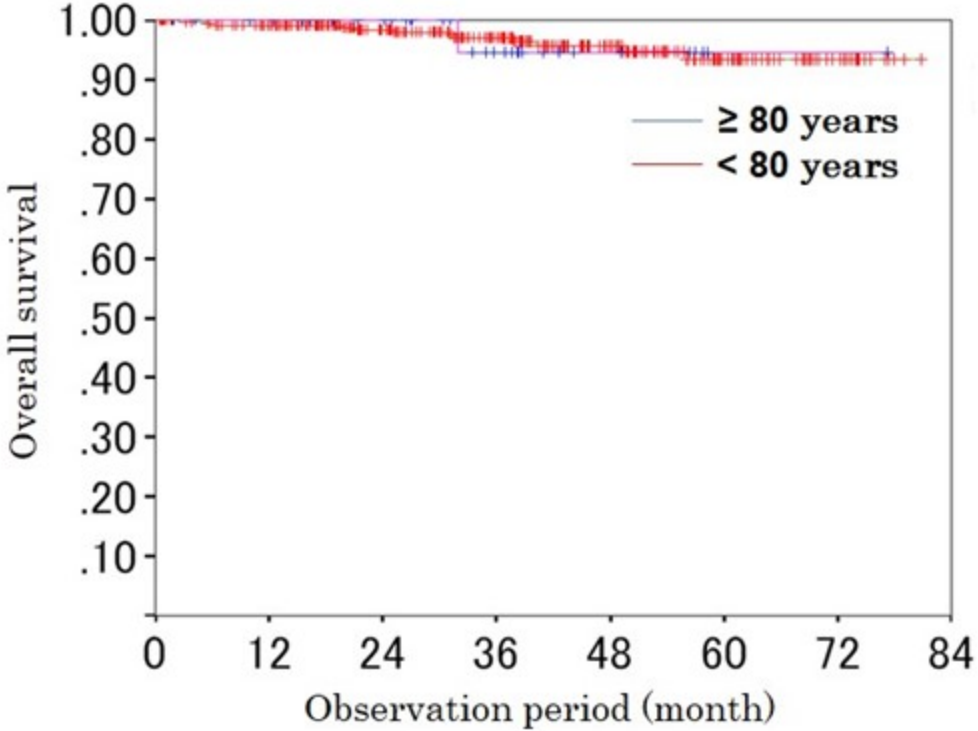
(supplementary file)
Figure 3 Metachronous cancer of the esophagus and head & neck
There is no significant difference between group aged ≥80 years and group aged <80 years using Kaplan–Meier estimates

<January 2011 - August 2016>



SESCC, superficial esophageal squamous cell carcinoma; Add Tx, Additional treatment; Rec, recurrence; EP, Carcinoma in situ (Tis); LPM, Lamina propria mucosae; MM, Muscularis mucosae; SM, Submucosal layer; Ly, Lymphatic invasion; V, vascular invasion ; pVM, pathological vertical margin

Figure 1. Patient flow diagram



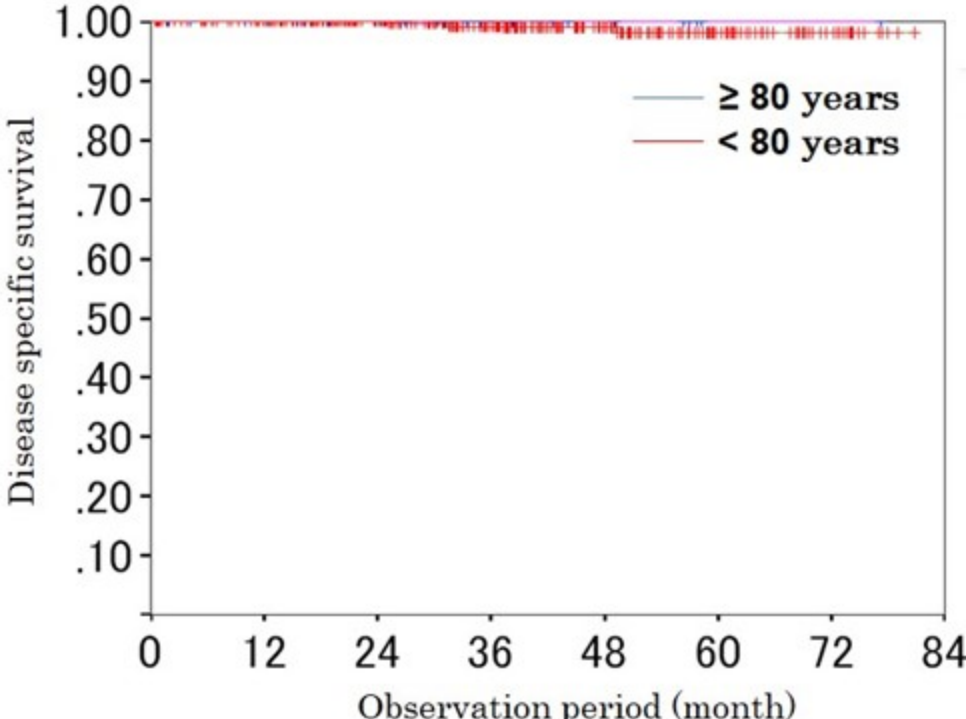
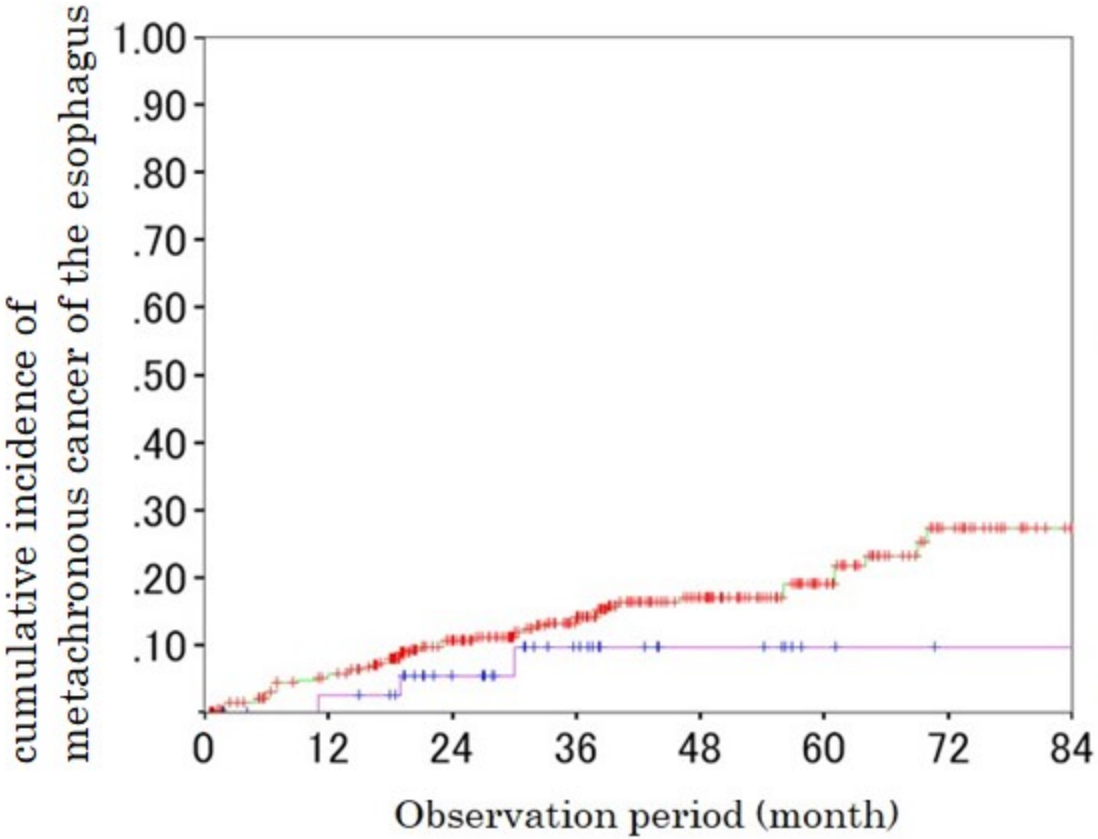


Figure 2. Overall and disease-specific survivals



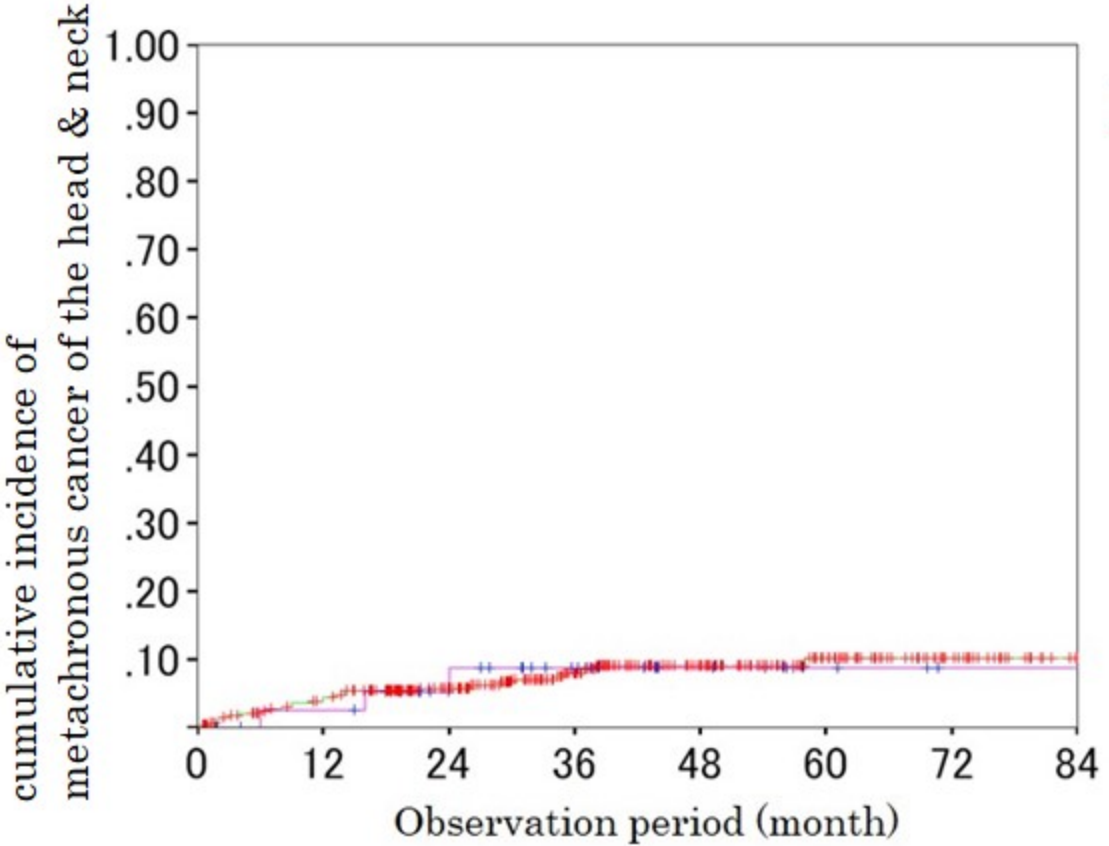


Figure 3. Metachronous cancer of the esophagus and head & neck