Endoscopic Submucosal Dissection Versus Surgery for Superficial Esophageal Squamous Cell Carcinoma: A Propensity Score-Matched Survival Analysis

Hyun Deok Lee, MD[1], Hyunsoo Chung, MD, PhD[1], Yoonjin Kwak, MD, PhD[2], Jinju Choi, MD[1], Ayoung Lee, MD[1], Jue Lie Kim, MD[1], Soo-Jeong Cho, MD, PhD[1] and Sang Gyun Kim, MD, PhD[1]

INTRODUCTION: **Endoscopic submucosal dissection (ESD) is a preferred treatment option for superficial esophageal squamous cell carcinoma (SESCC). However, only few studies compared long-term survival outcomes of ESD with surgery. This study compared the overall survival (OS), recurrence-free survival, and complication rates of ESD with those of surgery.**

METHODS: **We reviewed patients who underwent ESD (n = 70) or surgery (n = 114) for SESCC at Seoul National University Hospital from 2011 to 2017. A propensity score-matched analysis was used to reduce selection bias. To increase the precision of our results interpretation, subgroups were analyzed according to the depth of tumor invasion.**

RESULTS: **In the matching study, the ESD group (n = 34) showed comparable survival outcomes with the surgery group (n = 34). The 5-year OS rates were 89.4% vs 87.8% for the ESD and the surgery groups, respectively; similarly, the 5-year recurrence-free survival rates were 90.9% and 91.6%, respectively. The ESD group showed a lower early major complication rate (2.9% [1 of 34] vs 23.5% [8 of 34], $P < 0.001$) and shorter hospital stay (median, 3.0 days vs 16.5 days, $P < 0.001$) than the surgery group. In the tumor *in situ* (Tis)-subgroup, ESD showed better OS than esophagectomy ($P = 0.030$). Between-group comparisons of survival outcomes in the T1a and T1b subgroups revealed no significant differences.**

DISCUSSION: **Long-term outcomes of ESD are comparable with surgery for patients with SESCC. For early major complications and duration of hospital stay, ESD was associated with better outcomes than radical surgery. These results support ESD as the preferred treatment option for SESCC.**

INTRODUCTION

Esophageal cancer is ranked the seventh most-common and the sixth most-fatal malignant tumor (1). Esophageal squamous cell carcinoma (SCC), the most prevalent histological type worldwide, is more aggressive than esophageal adenocarcinoma. However, only 22% of early esophageal SCC is detectable (2). The main reason for detection failure is that early esophageal SCC shows flat isochromatic features on conventional endoscopy. In recent years, development and frequent use of Lugol chromoendoscopy and narrow band imaging are contributing to early esophageal SCC detection (3,4). Moreover, advances in endoscopic equipment and technique allowed less invasive treatment of esophageal SCC (5).

Superficial esophageal squamous cell carcinoma (SESCC) is defined as a lesion in which tumor infiltration is limited to the basement membrane (Tis), mucosa (T1a), or submucosal layer (T1b) of the esophageal wall. The National Comprehensive Cancer Network guideline recommends endoscopic submucosal dissection (ESD) as the preferred treatment option for Tis or T1a esophageal SCC (6). European and Japanese guidelines also recommend ESD as the first option for Tis or T1a-LP (confined to lamina propria) tumor, and alternative option for some patients (older patients and/or those with significant comorbidities) in T1a-MM (confined to muscularis mucosae) or T1b-SM1 (submucosa invasion ≤200 μm) tumor (7,8).

These guidelines are mainly based on pathologic studies that evaluated the association between risk of lymph node (LN) metastasis and depth of tumor invasion in surgical specimens (9–11) and clinical studies that focused on long-term outcomes of ESD in

a single group (12–14). However, there are few comparative studies about the long-term outcomes of ESD and surgery in SESCC (15,16). This study aimed to compare the long-term outcomes of ESD with surgical outcomes in SESCC.

METHODS

Study population
We reviewed patients who underwent ESD and surgery for pTis or pT1 esophageal SCC in Seoul National University Hospital from January 2011 to December 2017. The inclusion criteria were as follows: (i) patients who were pathologically staged N0 (pN0) and clinically staged M0 (cM0) for the surgery group and (ii) patients who were clinically staged N0M0 (cN0M0) for the ESD group. The exclusion criteria were as follows: (i) patients with previous treatment history of malignancy within 5 years, (ii) patients with second primary malignancy, (iii) patients with neoadjuvant therapy (neoadjuvant chemotherapy or radiation therapy), and (iv) patients who underwent endoscopic treatment for previous esophageal neoplasm. In the ESD group, patients who underwent rescue esophagectomy immediately after ESD were not excluded for intention-to-treat analysis (Figure 1). The number of annual cases in each procedure for SESCC described in Table 1 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A291). The Institutional Review Board of the Seoul National University Hospital approved this study (Institutional Review Board No. H-1912-031-1086) and granted a waiver of informed consent for the retrospective chart review.

Pretreatment evaluation
All patients in both groups underwent an intensive perioperative evaluation, endoscopy (chromoendoscopy with Lugol solution and/or narrow band imaging endoscopy), endoscopic ultrasound, and chest/abdominal computed tomography (CT). Endoscopic ultrasound was used to assess the depth of tumor invasion and detect mediastinal LN metastasis. Chest/abdominal CT was used to identify possible local LN or distant metastasis. Positron emission tomography was performed when LN metastasis was suspected on CT evaluation.

Procedure and histologic evaluation
Esophageal ESD was performed by experienced endoscopists through a standard technique (17). Intravenous midazolam was used for conscious sedation. After spraying 2% Lugol solution, markings were made 2–3 mm outside the tumor edge using an electrosurgical knife. A mixture of normal saline and indigo carmine was used to lift the submucosal layer of the lesion. After submucosal injection, circumferential mucosal precutting along the marking dot and subsequent dissection of the main lesion were performed. Standard single-channel endoscopes (GIF-H260 or GIF-HQ290; Olympus Optical, Tokyo, Japan) and insulated-tip knife (Helmet Snare; Kachu Technology, Seoul, Korea) were used in this study. Obtained specimen were gently spread and fixed by pins on a board. After fixation using 10% formalin and staining with hematoxylin and eosin, histopathological evaluation was performed on 2-mm thick sections. For the surgery group, Ivor-Lewis or McKeown operation was performed. In some cases, transhiatal esophagectomy was performed. After routine fixation, the surgical specimens were evaluated using 4-mm thick sections.

For pathologic specimen in both groups, tumor histology, grade of differentiation, size, invasion depth, lymphovascular invasion (LVI), and presence of tumor in resection margin were evaluated.

Presence of mediastinal LN metastasis was pathologically evaluated only for the surgical specimen. Staging was determined according to the eighth edition of the American Joint Committee on Cancer staging of esophageal and esophagogastric junction cancers. According to the Japan Esophageal Society guideline, the depth of submucosal invasion was classified into 2 groups: SM1 (submucosa invasion ≤200 μm from the muscularis mucosae) and SM2 (submucosa invasion >200 μm from the muscularis mucosae) (18). Three patients in the surgery group and 2 patients in the ESD group had 2 primary lesions in esophagus. In this case, the deeper invasive lesion was used for analysis.

Follow-up
Post-treatment surveillance of recurrence was intensively performed. For both the ESD and surgery groups, chest CT was performed every 6 months for 2 years and annually thereafter until 5 years. Endoscopic evaluation was performed at 6 months, 1 year, 18 months, 2 years, and annually thereafter for the ESD group. Annual endoscopic evaluation after treatment was performed for the surgery group. For the assessment of recurrent laryngeal nerve injury, nasal laryngoscopy was performed on the third postoperative day in the surgery group to assess vocal cord function. Follow-up data were mainly obtained from medical records. In the case of patients who changed hospitals, the patients' recent status was inquired over the phone.

Investigated variables and outcomes
The following variables were investigated: age, sex, Charlson comorbidity index (CCI), pathologic information (tumor location, size, grade of differentiation, invasion depth, LVI, and tumor presence in resection margin), length of hospital stay, post-treatment adverse event, follow-up period, pattern of cancer recurrence, and cause of death.

Overall survival (OS) and recurrence-free survival (RFS) were evaluated. OS was defined as the period from treatment to death from all causes. RFS was defined as the period from treatment to recurrence of esophageal cancer. Follow-up periods were calculated from the date of ESD or surgery. Survival was assessed on the most recent outpatient visit or telephone evaluation date of May 31, 2019. Patients who failed to follow-up were censored at the time of their last visit to our hospital. Deceased persons were censored on the day of the death. Time to recurrence was calculated from the date of ESD or surgery to the time of the latest endoscopic evaluation in our facility or another hospital.

Adverse events were analyzed in both early and late treatment phases. Early adverse events were defined as events that occurred within 30 days after treatment, whereas late adverse events were defined as those that occurred more than 30 days after. The adverse events of ESD included perforation, bleeding requiring transfusion, and stricture requiring intervention. The postoperative adverse events were as follows: pulmonary (respiratory insufficiency and pneumonia), cardiovascular (arrhythmia), renal (acute kidney injury), and surgical (vocal cord paralysis, wound infection/dehiscence, anastomotic leakage, edematous pylorus narrowing, chyle leakage, bleeding, fistulization, stricture formation, and recurrent ileus). Acute adverse events were graded by the Clavien-Dindo classification.

Statistical analyses
To compare categorical variables, the Pearson χ^2 test or Fisher exact test was used. Comparison of continuous variables were performed using the Student t test or the Mann-Whitney U test.
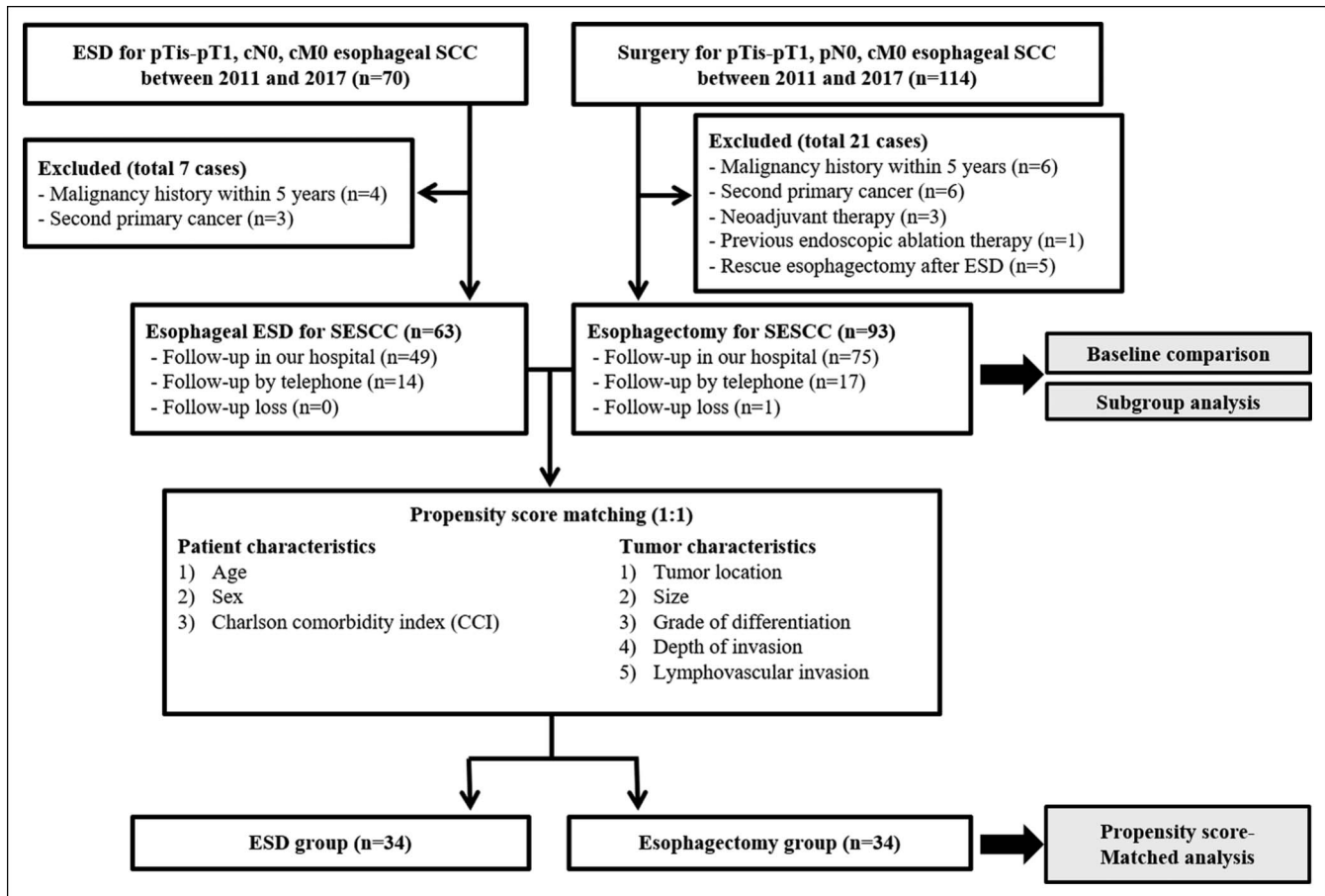
Figure 1. Flow diagram of patients who underwent ESD or surgery for SESCC. ESD, endoscopic submucosal dissection; SCC, squamous cell carcinoma; SESCC, superficial esophageal squamous cell carcinoma.

The Kaplan-Meier method was used for survival analysis. Cox proportional-hazards regression was used to obtain hazard ratios and their confidence intervals. Statistically significant variables were set at P value <0.05 (2 sided). For these, analyses were performed in SPSS version 22.0 for Windows (SPSS, Chicago, IL).

Propensity score (PS)-matching method was used to minimize selection bias. A PS was estimated from a multivariable logistic regression model by including the following covariates: age, sex, CCI, tumor location, size, differentiation grade, invasion depth, and LVI. Presence of a tumor in the resection margin was not selected as a matching covariate because positive resection margin in radical surgery means more diffuse disease than the same condition in ESD. Adjuvant therapy was also not selected as a matching covariate because indication of adjuvant therapy is different in both treatment modalities. The ESD group was then matched to the surgery group in a 1:1 ratio using the Mahalanobis matching within a PS caliper of 0.1. PS matching was performed in R version 3.50 (http://www.r-project.org/).

RESULTS

Patients' clinicopathologic characteristics
Clinicopathologic characteristics of all enrolled and matched patients are shown in Table 1. A total of 63 patients underwent ESD and 93 patients underwent esophagectomy for SESCC. The ESD

group showed smaller tumor size (mean 1.7 vs 2.6 cm), higher proportion of well-differentiated histology (79.4% vs 30.1%), higher proportion of Tis cancer (47.6% vs 14.0%), and higher probability of tumor-positive resection margin (17.5% vs 4.3%). The ESD group also showed higher rate of receiving additional surgery (7.9% vs 0.0%), endoscopic treatment (1.6% vs 0.0%), and chemo/radiation therapy (9.5% vs 2.2%) for noncurative resection. There was no difference in age, sex, CCI, tumor location, and presence of LVI in either group. After balancing major covariates using PS matching, the ESD group show a higher rate of positive resection margin (26.5% vs 0.0%) and frequent adjuvant therapy for noncurative resection (29.4% vs 0.0%).

Survival outcome and cancer recurrence
Table 2 shows the comparison of OS and recurrence in the 2 groups. The median follow-up periods for survival were 34.0 months (interquartile range 21.5–64.0 months) in the ESD group and 47.0 months (interquartile range 29.0–69.0 months) in the surgery group. The overall mortality rate was 1.32/100 person years and 3.44/100 person years in the ESD and surgery groups, respectively. Incidence rates of recurrence were 1.85/100 person years in the ESD group and 3.64/100 person years in the surgery group. After PS matching, overall mortalities in the matched groups were 1.69/100 person years in the ESD group and 3.06/100 person years in the surgery group. Incidence rates of cancer recurrence in

ESOPHAGUS

Table 1. Characteristics of patients with ESD and surgery for superficial esophageal squamous cell carcinoma

	Before propensity score matching			After propensity score matching		
	ESD (n = 63)	Surgery (n = 93)	*P* value	ESD (n = 34)	Surgery (n = 34)	*P* value
Age, mean ± SD, yr	66.6 ± 7.8	67.3 ± 8.2	0.594	67.5 ± 7.4	67.3 ± 7.9	0.900
Sex, n (%)						
Male	59 (93.7)	81 (87.1)	0.282	31 (91.2)	31 (91.2)	1.000
Female	4 (6.3)	12 (12.9)		3 (8.8)	3 (8.8)	
Charlson comorbidity index, n (%)						
0	43 (68.3)	57 (61.3)	0.629	23 (67.6)	22 (64.7)	0.952
1	13 (20.6)	25 (26.9)		6 (17.6)	7 (20.6)	
≥2	7 (11.1)	11 (11.8)		5 (14.7)	5 (14.7)	
Tumor location, n (%)						
Upper	2 (3.2)	4 (4.3)	0.640	1 (2.9)	1 (2.9)	1.000
Middle	27 (42.9)	33 (35.5)		12 (35.3)	12 (35.3)	
Lower	34 (54.0)	56 (60.2)		21 (61.8)	21 (61.8)	
Tumor size, mean ± SD, cm	1.7 ± 0.9	2.6 ± 1.4	**<0.001**	1.9 ± 1.0	2.0 ± 1.2	0.750
Differentiation, n (%)						
G1 (well differentiated)	50 (79.4)	28 (30.1)	**<0.001**	22 (64.7)	23 (67.6)	0.966
G2 (moderately differentiated)	12 (19.0)	60 (64.5)		11 (32.4)	10 (29.4)	
G3 (poorly differentiated)	1 (1.6)	5 (5.4)		1 (2.9)	1 (2.9)	
Depth of invasion, n (%)						
Tis	30 (47.6)	13 (14.0)	**<0.001**	10 (29.4)	11 (32.4)	0.998
T1a-LP	14 (22.2)	16 (17.2)		9 (26.5)	9 (26.5)	
T1a-MM	11 (17.5)	18 (19.4)		7 (20.6)	7 (20.6)	
T1b-SM1	2 (3.2)	8 (8.6)		2 (5.9)	2 (5.9)	
T1b-SM2	6 (9.5)	38 (40.9)		6 (17.6)	5 (14.7)	
LVI positive, n (%)	7 (11.1)	12 (12.9)	0.807	4 (11.8)	3 (8.8)	0.690
Resection margin positive, n (%)	11 (17.5)	4 (4.3)	**0.011**	9 (26.5)	0 (0.0)	**0.001**
Adjuvant therapy, n (%)						
Endoscopic treatment	1 (1.6)	0 (0.0)	**<0.001**	1 (2.9)	0 (0.0)	**0.008**
Radiation therapy	6 (9.5)	1 (1.1)		5 (14.7)	0 (0.0)	
Chemoradiation therapy	0 (0.0)	1 (1.1)		0 (0.0)	0 (0.0)	
Surgery	5 (7.9)	0 (0.0)		4 (11.8)	0 (0.0)	

*Significant *P* values are presented in bold.
ESD, endoscopic submucosal dissection; LVI, lymphovascular invasion; T1a-LP, tumor confined to lamina propria; T1a-MM, tumor confined to muscularis mucosae; T1b-SM1, submucosal invasion ≤200 μm from the muscularis mucosae; T1b-SM2, submucosal invasion > 200 μm from the muscularis mucosae.

matched groups were 2.75/100 person years and 1.54/100 person years in the ESD and surgery groups, respectively.

Figure 2 shows the Kaplan-Meier survival curves of all enrolled and matched patients. In all patients, the 1-year OS rates were 100.0% in the ESD group vs 94.6% in the surgery group and 3-year OS rates were 98.0% in the ESD group vs 87.7% in the surgery group; similarly, 5-year OS rates were 90.7% in ESD and 84.1% in the surgery group. For the 1-, 3-, and 5-year RFS rates, these were as follows: ESD group 95.0%, 92.7%, and 92.7%, whereas the surgery group had 94.3%, 87.1%, and 83.8%, respectively. The difference in OS and RFS between the 2 groups was not statistically significant (OS, *P* = 0.101; RFS, *P* = 0.189, logrank test). In matched patients, the 5-year OS rates were 89.4% vs 87.8% for the ESD and the

surgery groups, respectively. The 5-year RFS rates were 90.9% in the ESD group and 91.6% in the surgery group. There was no statistical difference in OS and RFS between the 2 groups (OS, *P* = 0.408; RFS, *P* = 0.656, logrank test).

Subgroup analysis according to invasion depth was performed for all patients (Figure 3). In Tis esophageal SCC, the ESD group showed better OS outcomes (*P* = 0.030) and comparable RFS. The ESD group also showed comparable survival outcomes in T1a and T1b esophageal SCC.

Hospital stay and adverse events
Table 3 shows the length of hospital stay and adverse events of both treatment modalities. The ESD group showed shorter hospital stay

Table 2. Comparison of overall survival and recurrence in the 2 groups

	Before propensity score matching		After propensity score matching	
	ESD (n = 63)	Surgery (n = 93)	ESD (n = 34)	Surgery (n = 34)
Follow-up period, median (IQR), mo	34.0 (21.5–64.0)	47.0 (29.0–69.0)	33.0 (21.0–62.0)	40.5 (23.0–69.0)
Death, n (%)	3 (4.8)	13 (14.0)	2 (5.9)	4 (11.8)
Overall mortality (/100 persons yr)	1.32	3.44	1.69	3.06
Cause of death, n	Bladder cancer, 2	Esophageal cancer, 5	Bladder cancer, 1	Pneumonia, 2
	Unknown, 1	Liver cirrhosis, 1	Unknown, 1	Unknown, 2
		Pneumonia, 4		
		Unknown, 3		
Recurrence, n (%)	4 (6.3)	13 (14.0)	3 (8.8)	2 (5.9)
Recurrence rate (/100 persons yr)	1.85	3.64	2.75	1.54
Pattern of recurrence, n	Local recurrence, 2	Local recurrence, 1	Local recurrence, 2	LN metastasis, 1
	LN metastasis, 2	LN metastasis, 8	LN metastasis, 1	Distant metastasis, 1
		Distant metastasis, 4		

ESD, endoscopic submucosal dissection; IQR, interquartile range; LN, lymph node.

(median 3 days vs 17.0 days), lower overall adverse events (22.2% vs 47.3%), lower early adverse events (15.9% vs 38.7%), and especially early major complications (3.2% vs 20.4%) than the surgery group. Even after PS matching, the ESD groups showed shorter hospital stay (median 3 vs 16.5 days) and lower early major complications (2.9% vs 23.5%). Stricture requiring intervention was the most common cause of late adverse events in both groups (7.9% in ESD,

whereas 8.6% in surgery). Detailed early complications are listed in Table 2 (see Supplementary Digital Content 2, http://links.lww.com/CTG/A292).

Predictors of OS and cancer recurrence
Cox proportional hazards regression analysis was used for finding the association factor between OS and cancer recurrence (see Table 3,
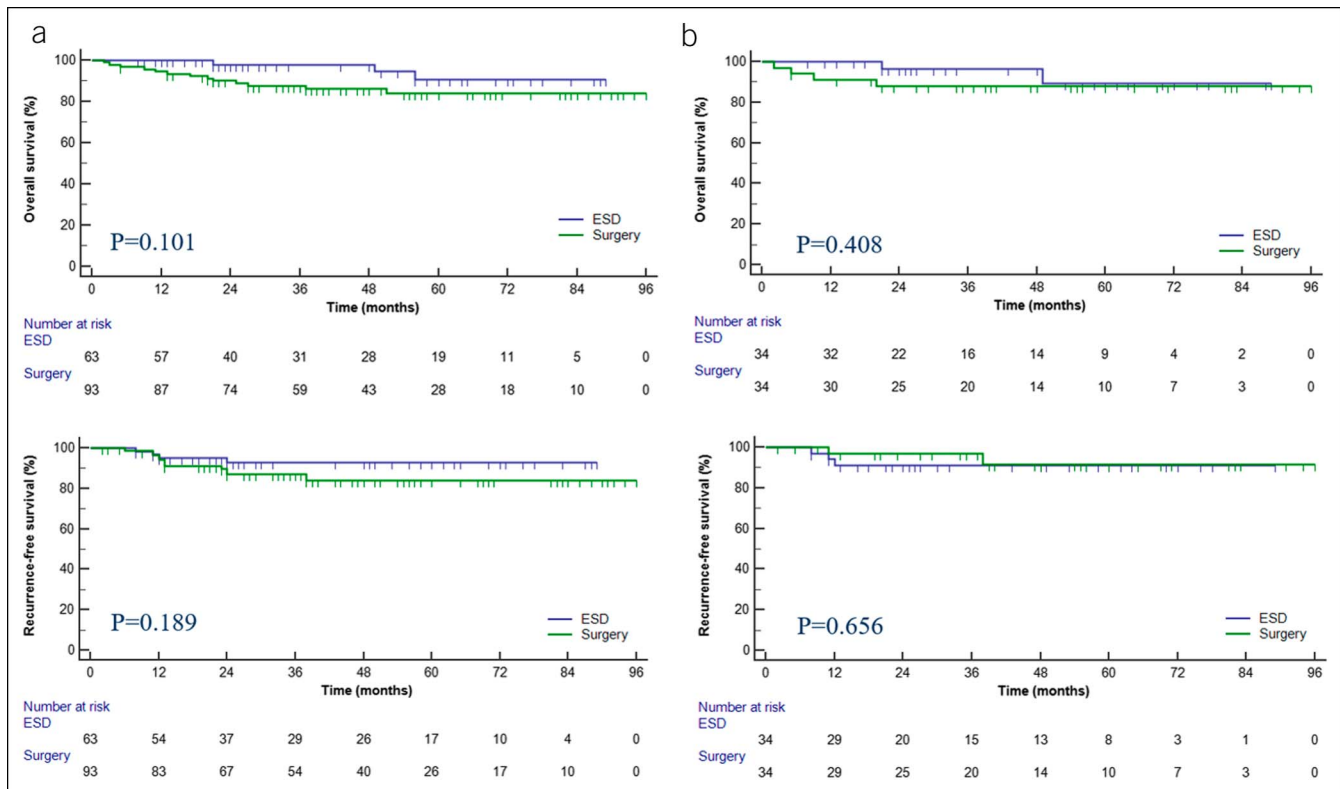

Figure 2. Overall survival and recurrence-free survival of ESD and surgery in all patients (**a**) and in propensity score–matched patients (**b**). *P* values were calculated by the logrank test. ESD, endoscopic submucosal dissection.
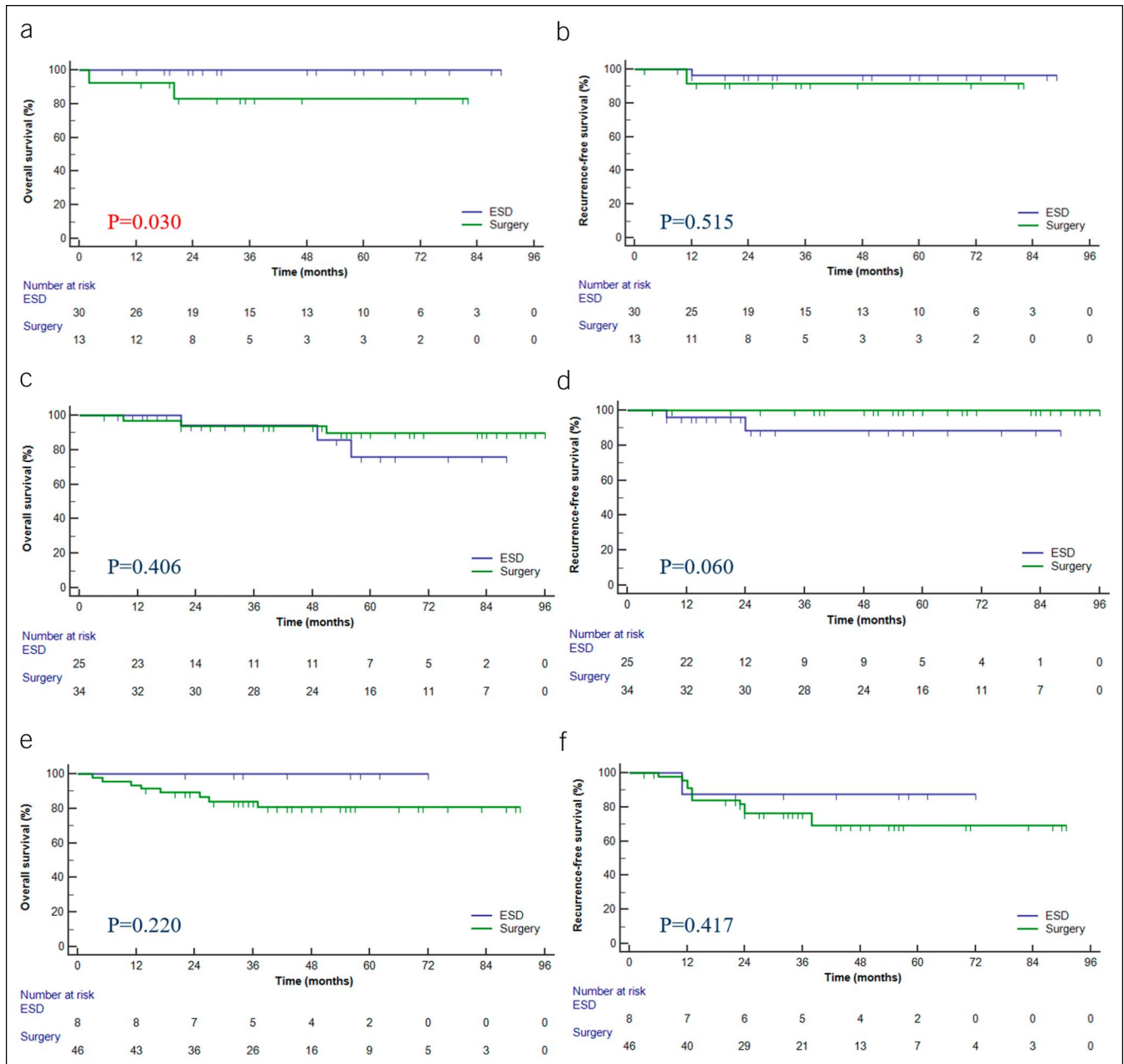
ESOPHAGUS

Figure 3. OS and RFS of the ESD and surgery groups according to the depth of invasion: OS in Tis (**a**); RFS in Tis (**b**); OS in T1a (**c**); RFS in T1a (**d**); OS in T1b (**e**); and RFS in T1b (**f**). *P* values were calculated by the logrank test. ESD, endoscopic submucosal dissection; OS, Overall survival; RFS, recurrence-free survival.

Supplementary Digital Content 3, http://links.lww.com/CTG/A293). Univariate analysis showed that a high CCI ($\geq$2) was significantly associated with poor survival outcomes. On multivariate analysis, high CCI ($\geq$2) and LVI were associated with poor survival outcomes (high CCI [$\geq$2], hazard ratio [HR] 4.068 [1.323–12.510], *P* = 0.014; positive LVI, HR 3.613 [1.100–11.863], *P* = 0.034). Poorly differentiated histology, submucosal invasion, LVI, and residual tumor in resection margin were identified as risk factors for cancer recurrence in univariate analysis. On multivariate analysis, submucosal invasion was associated with cancer recurrence (HR 5.808 [1.880–17.943], *P* = 0.002). There was no statistical difference in mortality and recurrence risk according to treatment modality.

DISCUSSION

In the past, surgery was the main treatment modality for esophageal cancer. This was associated with high mortality and complication rates. Currently, advances in endoscopy have enabled detection and curative resection of early esophageal cancer. Although the current guidelines recommend ESD in Tis-T1a esophageal SCC, few comparative studies support this recommendation (15,16). Considering the high percentage of adverse events in the surgery group, it was difficult to perform a randomized control trial between ESD and surgery in SESCC. Moreover, 2 treatment group showed obvious differences in baseline characteristics. Clinicians tend to choose ESD for

Table 3. Comparison of hospital stay and adverse events in the 2 groups

	Before propensity score matching			After propensity score matching		
	ESD (n = 63)	Surgery (n = 93)	*P* value	ESD (n = 34)	Surgery (n = 34)	*P* value
Hospital stay, median (IQR), d	3.0 (2.0–3.5)	17.0 (14.0–22.0)	**<0.001**	3.0 (2.0–4.0)	16.5 (14.0–23.0)	**<0.001**
Overall adverse events, n (%)	14 (22.2)	44 (47.3)	**0.001**	11 (32.4)	17 (50.0)	0.138
Early adverse events, n (%)	10 (15.9)	36 (38.7)	**0.002**	7 (20.6)	12 (35.3)	0.177
Minor complications[a]	Grade II (8)	Grade I (15)	0.120	Grade II (6)	Grade I (5)	0.549
		Grade II (8)			Grade II (4)	
Major complications[a]	Grade III (2)	Grade III (18)	**0.002**	Grade III (1)	Grade III (7)	**0.027**
		Grade IV (4)			Grade IV (3)	
Late adverse events, n (%)	5 (7.9)	11 (11.8)	0.432	5 (14.7)	7 (20.6)	0.525
	Stricture, 5	Stricture, 8		Stricture, 5	Stricture, 4	
		Fistula, 2			Fistula, 1	
		Recurrent ileus, 2			Recurrent ileus, 2	

*Significant *P* values are presented in bold.
ESD, endoscopic submucosal dissection; IQR, interquartile range.
[a]Early adverse events are graded by Clavien-Dindo classification. Minor complications refer to Grade I and II. Major complications refer to Grade III, IV, and V.

patients with favorable tumor characteristics (small lesion, well differentiated histology, and less deep invasion) or patients who has multiple underlying disease than surgery. Two previous comparative studies used PS-matched analyses for overcoming discrepancies of subjects in 2 treatment options.

Min et al. (15) first reported a comparative study between ESD (n = 191) and surgery (n = 157) in SESCC. Our study has a major difference in the study design from the previous study. Previous study analyzed clinically staged Tis-T1 tumor. Cases with LN metastasis in the surgery group (rate of LN metastasis not available) used for comparison with ESD. ESD is the treatment option for patients with very low probability of LN metastasis. For a more appropriate comparison of the treatment outcomes between ESD and surgery, the latter group was selected based on pathologically negative LN cases. We analyzed pTis-T1, cN0M0 in ESD, and pTis-T1N0M0 in surgery. Our approach is useful for comparing treatment efficacy of ESD with esophagectomy (pN0) as gold standard.

Zhang et al. (16) also reported a comparative study between ESD (n = 322) and surgery (n = 274) for pT1 esophageal SCC. This large retrospective cohort study showed comparative long-term outcomes between ESD and surgery. However, this study compared the ESD group with a high-risk surgery group that identified 13.1% of LN metastasis. To minimize selection bias, the previous study balanced only 5 confounders (age, sex, second malignancy, invasion depth, and adjuvant radiation therapy) between the 2 groups using PS matching. This approach was not enough to correct possible selection bias.

The present study supports the results of previous comparative studies, showing comparable long-term outcomes between ESD and surgery in SESCC. For Tis SESCC, our study yielded better survival outcomes than surgery (*P* = 0.030) and comparable recurrence rates. As far as we know, this is first comparative study that reviled better survival outcomes of ESD in Tis SESCC. ESD for T1a or T1b SESCC showed comparable survival and recurrence rates with surgery. For T1b SESCC, careful interpretation is needed because the small number of ESD subjects compared with surgery subjects. Small sample size with

a relatively low outcome event could suffer type 2 error. This subgroup analysis supported the comparability of long-term outcomes of ESD and surgery in Tis and T1a SESCC.

In our institution, the median length of postoperative stay was 17 days and perioperative mortality within 60 days of SESCC was less than 1% (1/168) during the study period. On the other hand, the ESD group showed short hospital stay (median 3.0 days) and reported no treatment-related mortality. Overall adverse events were more frequent in the surgery group than the ESD group (47.3% vs 22.2%). In the surgery group, late-adverse events had become major causes of death (aspiration pneumonia: 4 cases). For complication and hospital stay, ESD is a better treatment option for SESCC than radical surgery.

In the National Comprehensive Cancer Network and Japanese guidelines, adjuvant therapy after ESD is recommended for T1b or T1a-MM with LVI. However, postoperative adjuvant therapy is recommended only for patients with residual tumor in resection margin. In the ESD group, all patients with T1b underwent adjuvant therapy (5, radiation therapy; 3, esophagectomy). Patients with T1a-MM with LVI underwent radiation therapy (1 of 3) or esophagectomy (2 of 3). In the surgery group, 4 cases of T1b had microscopic residual cancer in epithelium of resection margin. Two patients treated with adjuvant therapy (1, radiation therapy; 1, chemoradiation therapy), but other 2 patients did not want additional therapy because of poor general condition. Subgroup analysis should be performed by considering the additional effect of adjuvant therapy. However, it is hard to perform because of small number of subjects and different indication of adjuvant therapy in both treatment modalities.

This study has some limitations. First, retrospective design comparing 2 groups with obvious differences in baseline characteristics could have the possibility of significant bias. We tried to minimize bias using PS matching method for balancing major covariates and subgroup analysis. Second, this study has a relatively small sample size compared with previous studies. Small sample size with relatively low outcomes could suffer type 2 error. Third, this study used CCI for patient's health status assessment.

CCI is a useful assessment tool for comorbidities and a prognostic indicator of mortality (19,20), but it might be insufficient to reflect the functional status of patients. Finally, the accuracy of the examination may differ between the thickness of the specimens obtained: 4 mm for surgical sections and 2 mm for ESD. Moreover, ESD pathology may have changed in size during fixation.

In conclusion, long-term outcomes of ESD are comparable with surgical outcomes in patients with SESCC. ESD is related to lower early major complication rates and shorter hospital stay. Thus, ESD is a better treatment option for SESCC than radical surgery.

CONFLICTS OF INTEREST

Guarantor of the article: Hyunsoo Chung, MD, PhD.
Specific author contributions: H.D.L., H.C.: study conception and design; H.D.L., J.C.: acquisition of data; Y.K.: review of the pathologic diagnosis; H.D.L., A.L., J.L.K.: analysis and interpretation of data; H.D.L.: drafting of the manuscript; S.-J.C., S.G.K.: critical revision. All authors approved the final draft being submitted.
Financial support: None to report.
Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

✓ The preferred treatment modality for SESCC with a negligible risk of LN metastasis is ESD.
✓ However, this recommendation is based on few comparative studies.

WHAT IS NEW HERE

✓ Long-term OS and RFS of ESD are comparable with surgery.
✓ For tumor *in situ*, ESD yields better OS than surgery and comparable RFS.

TRANSLATIONAL IMPACT

✓ These results support ESD as a first treatment option for SESCC with a negligible risk of LN metastasis.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.
2. Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol 2013;19(34):5598–606.
3. Goda K, Tajiri H, Ikegami M, et al. Clinical impact of narrow-band imaging magnifying endoscopy for "basal layer type squamous cell carcinoma" in the esophagus. Dig Endosc 2011;23(Suppl 1):75–8.
4. Inoue H, Rey J, Lightdale C. Lugol chromoendoscopy for esophageal squamous cell cancer. Endoscopy 2001;33(1):75–9.
5. Noordzij IC, Curvers WL, Schoon EJ. Endoscopic resection for early esophageal carcinoma. J Thorac Dis 2019;11(Suppl 5):S713–S722.
6. Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. 2019;17(7):855.
7. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015;47(9):829–54.
8. Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: Part 1. Esophagus 2019; 16(1):1–24.
9. Kodama M, Kakegawa T. Treatment of superficial cancer of the esophagus: A summary of responses to a questionnaire on superficial cancer of the esophagus in Japan. Surgery 1998;123(4):432–9.
10. Eguchi T, Nakanishi Y, Shimoda T, et al. Histopathological criteria for additional treatment after endoscopic mucosal resection for esophageal cancer: Analysis of 464 surgically resected cases. Mod Pathol 2006;19(3): 475–80.
11. Zhou Y, Du J, Li H, et al. Clinicopathologic analysis of lymph node status in superficial esophageal squamous carcinoma. World J Surg Oncol 2016; 14(1):259.
12. Yamashina T, Ishihara R, Nagai K, et al. Long-term outcome and metastatic risk after endoscopic resection of superficial esophageal squamous cell carcinoma. Am J Gastroenterol 2013;108(4):544–51.
13. Lorenzo D, Barret M, Leblanc S, et al. Outcomes of endoscopic submucosal dissection for early oesophageal squamous cell neoplasia at a Western centre. United Eur Gastroenterol J 2019;7(8):1084–92.
14. Joo DC, Kim GH, Park DY, et al. Long-term outcome after endoscopic submucosal dissection in patients with superficial esophageal squamous cell carcinoma: A single-center study. Gut Liver 2014;8(6):612–8.
15. Min YW, Lee H, Song BG, et al. Comparison of endoscopic submucosal dissection and surgery for superficial esophageal squamous cell carcinoma: A propensity score-matched analysis. Gastrointest Endosc 2018;88(4):624–33.
16. Zhang Y, Ding H, Chen T, et al. Outcomes of endoscopic submucosal dissection vs esophagectomy for T1 esophageal squamous cell carcinoma in a real-world cohort. Clin Gastroenterol Hepatol 2019;17(1):73–81.e3.
17. Fujishiro M, Kodashima S, Goto O, et al. Endoscopic submucosal dissection for esophageal squamous cell neoplasms. Dig Endosc 2009; 21(2):109–15.
18. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th edition: Part I. Esophagus 2017;14(1):1–36.
19. Yamashita K, Watanabe M, Mine S, et al. The impact of the Charlson comorbidity index on the prognosis of esophageal cancer patients who underwent esophagectomy with curative intent. Surg Today 2018;48(6): 632–9.
20. Nakajo K, Abe S, Oda I, et al. Impact of the Charlson comorbidity index on the treatment strategy and survival in elderly patients after non-curative endoscopic submucosal dissection for esophageal squamous cell carcinoma: A multicenter retrospective study. J Gastroenterol 2019; 54(10):871–80.