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Endoscopic submucosal dissection *versus* esophagectomy for t1 esophageal squamous cell carcinoma: a propensity score-matched analysis

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Abstract

Background: Endoscopic submucosal dissection (ESD) has been a preferred treatment option for superficial esophageal squamous cell carcinoma (SESCC).

Objectives: To compare the outcomes of ESD and esophagectomy in the treatment of SESCC, especially for lesions invading muscularis mucosa or submucosa (pT1a-MM/T1b).

Design: We retrospectively analyzed data from patients with SESCC who underwent ESD or esophagectomy between 2015 and 2021.

Methods: After propensity score matching, overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS), and treatment-related events were compared between the ESD and esophagectomy groups. Furthermore, we performed a Cox regression analysis to identify factors associated with survival.

Results: OS and DSS were significantly higher in the ESD group ($n = 508$) than that in the esophagectomy group ($n = 466$). After matching, 404 patients (202 per group) were included in the study. No significant differences were found between the ESD and esophagectomy groups in OS ($p = 0.566$), RFS ($p = 0.586$), and DSS ($p = 0.912$). The ESD group showed less blood loss, shorter procedure duration and hospital stay, lower hospital cost, and fewer adverse events. However, a lower R0 resection rate was observed in the ESD group compared to the esophagectomy group. Subgroup analysis showed comparable survival outcomes between the two groups. In Cox regression analysis, age was the independent factor associated with OS.

Conclusion: In the treatment of SESCC, ESD showed sufficient safety and advantages. Even for pT1a-MM/pT1b SESCC, ESD may be an alternative treatment to esophagectomy.

Keywords: endoscopic submucosal dissection, esophagectomy, outcomes, superficial esophageal squamous cell carcinoma

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Introduction

Esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer-related deaths worldwide.[1] It is histologically divided into two main categories: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma. ESCC accounts for the predominant histological type worldwide, especially in some high-risk regions (e.g. China).[1,2] Due to its highly aggressive nature, ESCC has a poor prognosis. If earlier management could be achieved, the survival would improve significantly.[3]

Esophagectomy combined with regional lymph node dissection is the standard treatment for superficial ESCC (SESCC). However, the considerable morbidity and mortality associated with

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esophagectomy cannot be ignored. In addition, it was reported to have a negative impact on postoperative quality of life.[4,5] Endoscopic submucosal dissection (ESD) has become a treatment option for SESCC. According to the National Comprehensive Cancer Network guidelines, ESD is the preferred treatment for T1a SESCC and an option for T1b SESCC.[6] The Japanese and European guidelines also recommend ESD as the first-line treatment for SESCC confined to intraepithelium and lamina propria (pT1a-M1/M2), and an alternative therapy for mucosal muscle and submucosal (pT1a-MM/T1b) cancers.[7,8] Many studies have demonstrated that ESD can provide comparable survival outcomes to esophagectomy in the treatment of SESCC.[9–11] However, with the increased risk of lymph node metastasis, esophagectomy remains the recommended treatment for lesions invading into the muscularis mucosa or submucosa.[12,13] Risk factors reported for lymph node metastasis in esophageal cancer include the depth of invasion, degree of differentiation, and lymphovascular invasion (LVI).[14,15] Due to the limitations of current examination techniques, it is difficult to accurately assess the depth of tumor invasion.[16,17] In contrast, ESD enables accurate evaluation of the invasion depth by performing en bloc resection. Based on the histopathological findings, the risk of lymph node metastasis can also be well assessed.[4] Therefore, it is valuable to define the feasibility of ESD in the treatment of SESCC.

Recent evidence showed similar long-term outcomes between patients receiving ESD *versus* surgery.[10,18,19] However, there are still limited studies that compare ESD and esophagectomy in pT1a-MM/pT1b tumors, which were considered as the relative indications for ESD. Thus, this study aimed to evaluate the clinical outcomes of ESD and esophagectomy in patients with T1 ESCC.

Methods

Study design and patients

This was a retrospective cohort study, we analyzed all consecutive patients who underwent ESD or esophagectomy for SESCC at The First Affiliated Hospital of USTC between January 2015 and December 2021. The exclusion criteria were as follows: (1) patients who lacked complete clinical data; (2) patients with other gastrointestinal cancer; (3) patients combined with severe diseases of other organs; (4) patients with neoadjuvant therapy; (5) patients who were failed in endoscopic treatment; and (6) patients were lost to follow-up. Finally, 508 patients in the ESD group and 466 patients in the esophagectomy group were enrolled. Before treatment, the patients underwent an intensive evaluation, and informed consent was obtained from all individuals. The study protocol was approved by the Medical Ethics Committee of the First Affiliated Hospital of USTC (approval number: 2022-RE-077).

Propensity score matching (PSM) was performed to minimize selection bias. The balanced variables include age, gender, cigarette, alcohol, family history, and the tumor information (location, diameter, morphology, histologic type, and invasion depth). The study flowchart is shown in Figure 1.

Data collection

Patients' data were obtained from electronic medical records. We collected the baseline information and treatment-related events, including age, gender, cigarette, alcohol, family history, tumor characteristics (location, diameter, morphology, histologic type, invasion depth, and LVI), estimated blood loss, procedure duration, hospital stay, hospital cost, resection margin, adverse events, and presence of adjuvant therapy (repeat endoscopy/surgery, radiotherapy, and chemotherapy). Survival information was inquired by telephone. When we failed to contact the patient themselves, we obtained data from the patients' families through telephone follow-up.

Definitions and outcome assessment

In terms of the macroscopic tumor types, we classified types I (protruding) and IIa (slightly elevated) as elevated types, and types IIb (flat), IIc (slightly depressed), and III (depressed) as flat/depressed types. The depth of invasion was classified into M1 (confined to the intraepithelium), M2 (confined to the lamina propria), MM (confined to the muscularis mucosa), and SM (submucosal invasion).[20]

R0 resection was defined as horizontal or vertical margins (VMs) without the presence of tumor cells. Recurrence was defined as a new malignant lesion that was detected at least 6 months after the ESD/esophagectomy treatment. Stricture was defined as the occurrence of dysphagia requiring intervention.

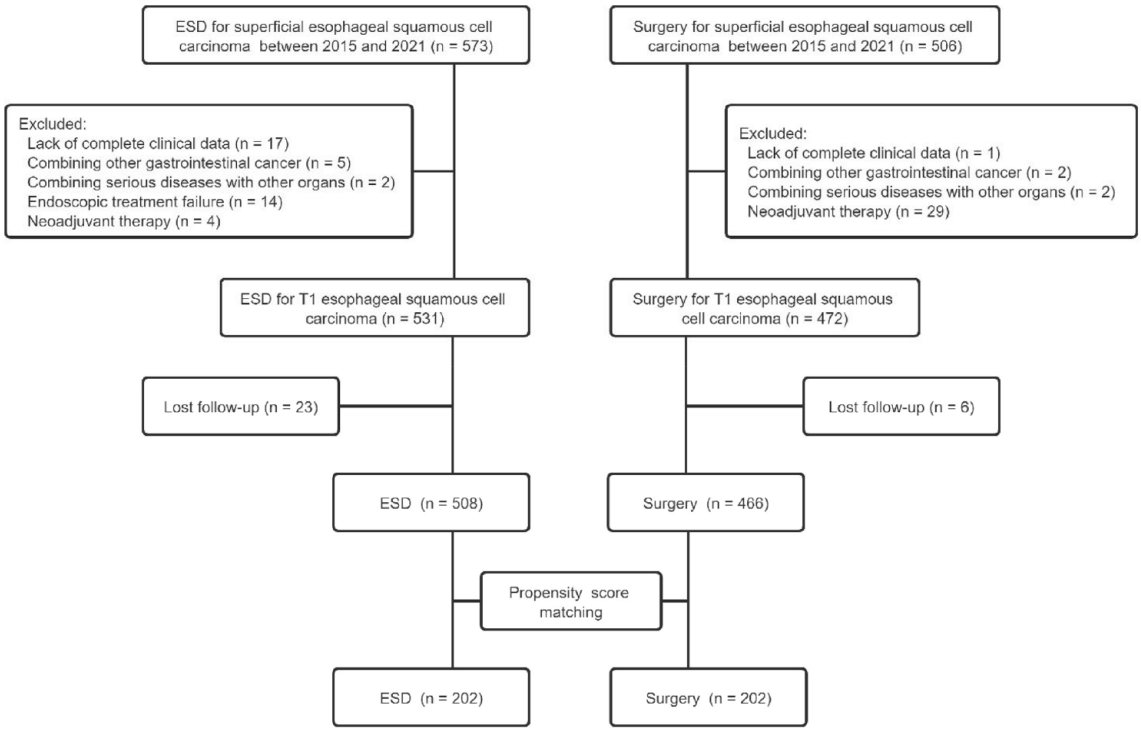

Figure 1. Flowchart of the study population.
ESD, endoscopic submucosal dissection.

The primary endpoint was overall survival (OS). The secondary endpoint included disease-specific survival (DSS), recurrence-free survival (RFS), and treatment-related events (estimated blood loss, procedure duration, hospital stay, hospital cost, resection margin, adverse events, and presence of adjuvant therapy). OS was defined as the time from ESD/esophagectomy to death from any cause. DSS was defined as the time from ESD/esophagectomy to death from ESCC. RFS was defined as the time from ESD/esophagectomy to the first recurrence or death.

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) or median with interquartile range, and categorical variables were expressed as numbers (%). A Student's t-test was used to assess normally distributed continuous variables, while a Mann–Whitney U test was used for continuous non-normal data. We used the chi-square test to identify differences between groups for categorical variables. However, when the expected frequency in a cell was less than 5, Fisher's exact test was chosen. The Kaplan–Meier method was used to estimate survival analyses, and the log-rank test was used to compare survival outcomes. To identify the independent factors of survival, univariate and multivariate Cox proportional hazards models were performed. Variables considered clinically relevant, or with a p value of <0.10 in univariate analyses were subsequently entered into multivariate analyses. 1:1 PSM was used to minimize selection bias, with a caliper width of 0.20 SDs of the logit of the estimated propensity score. All statistical analyses were performed using SPSS software (version 26.0, IBM Corp, Armonk NY, USA) and Prism software (version 9.0, Inc., San Diego, CA, USA). A $p < 0.05$ was considered statistically significant in all analyses. The reporting of this study conforms to the STROBE statement.[21]

Results

Baseline characteristics

Baseline characteristics of the total and matched patients are shown in Table 1. There were no significant differences between the ESD and esophagectomy groups in age, gender, cigarette,

Table 1. Baseline characteristics of patients before and after propensity score-matched cohort.

	Before matching			After matching		
	ESD *N* = 508	**Esophagectomy *N* = 466**	***p* Value**	**ESD *N* = 202**	**Esophagectomy *N* = 202**	***p* Value**
Age (mean ± SD; years)	64.76 ± 8.41	65.62 ± 8.09	0.105	64.95 ± 8.42	64.82 ± 8.19	0.876
Gender, *n* (%)			0.744			0.512
Male	367 (72.4%)	341 (73.2%)		146 (72.3%)	140 (69.3%)	
Female	141 (27.6%)	125 (26.8%)		56 (27.7%)	62 (30.7%)	
Lifestyle, *n* (%)						
Cigarette	122 (24.0%)	109 (23.4%)	0.819	34 (16.8%)	28 (13.9%)	0.408
Alcohol	120 (23.6%)	107 (23.0%)	0.808	37 (18.3%)	26 (12.9%)	0.131
Family history, *n* (%)	19 (3.7%)	13 (2.8%)	0.406	4 (2.0%)	5 (2.5%)	0.736
Tumor location, *n* (%)			<0.001			0.188
Upper	69 (13.6%)	73 (15.7%)		26 (12.9%)	25 (12.4%)	
Upper-middle	4 (0.8%)	3 (0.6%)		3 (1.5%)	1 (0.5%)	
Middle	219 (43.1%)	265 (56.9%)		96 (47.5%)	117 (57.9%)	
Middle-lower	25 (4.9%)	11 (2.4%)		10 (5.0%)	5 (2.5%)	
Lower	191 (37.6%)	114 (24.5%)		67 (33.1%)	54 (26.7%)	
Tumor diameter (mean ± SD; cm)	3.48 ± 2.12	2.95 ± 1.66	<0.001	3.38 ± 2.02	3.08 ± 1.72	0.111
Tumor morphology, *n* (%)			0.064			0.498
Elevated	98 (19.3%)	69 (14.8%)		35 (17.3%)	30 (14.9%)	
Flat or depressed	410 (80.7%)	397 (85.2%)		167 (82.7%)	172 (85.1%)	
Depth of tumor invasion, *n* (%)			<0.001			0.066
M1/M2	435 (85.6%)	119 (25.5%)		133 (65.8%)	115 (56.9%)	
MM/SM	73 (14.4%)	347 (74.5%)		69 (34.2%)	87 (43.1%)	
High-grade dysplasia	337 (66.3%)	98 (21.0%)	—	98 (48.5%)	75 (37.1%)	—
Squamous cell carcinoma			0.012			0.389
Well/moderately differentiated	144 (28.4%)	274 (58.8%)		84 (41.6%)	108 (53.5%)	
Poorly differentiated	27 (5.3%)	94 (20.2%)		20 (9.9%)	19 (9.4%)	
LVI, *n* (%)	1 (0.2%)	11 (2.2%)	0.002	1 (0.5%)	3 (1.5%)	0.315

Upper-middle or Middle-lower, lesions involving two segments; M1, confined to the intraepithelium; M2, confined to the lamina propria; MM, confined to the muscularis mucosa; SM, submucosal invasion.
ESD, endoscopic submucosal dissection; LVI, lymphovascular invasion; SD, standard deviation.

alcohol, family history, and tumor morphology. Regarding tumor location, the ESD group had more lesions in the lower esophagus, and the esophagectomy group showed more middle esophageal lesions. Deep tumor infiltration, poorly differentiated lesions, and LVI were more common in the esophagectomy group, while tumor diameter was much larger in the ESD group. After PSM, all baseline characteristics were not statistically different between the two groups.

Clinical outcomes

The clinical outcomes before and after PSM are summarized in Table 2. Compared with the esophagectomy group, the ESD group showed less blood loss, shorter procedure duration and hospital stay, lower hospital cost, and fewer adverse events. However, the lower R0 resection rate was also found in the ESD group. No statistically significant difference in adjuvant therapy between the two groups. In the matched cohort, those variables that had statistical significance before matching still showed significant differences. Furthermore, adjuvant treatment became different between the ESD group and the esophagectomy group.

Bleeding, stricture, pulmonary events, and anastomotic leakage were common adverse events in the two groups. In addition, adverse events in the esophagectomy group also included chylothorax, vocal cord palsy, wound dehiscence, and Ileus. Four patients in the esophagectomy group died of adverse events, while no fatal adverse events occurred in the ESD group.

Survival analysis

The Kaplan–Meier survival curves for OS, RFS, and DSS in the total and matched cohorts are presented in Figure 2. For the 1-, 3-, and 5-year OS rates, there were 99.8%, 98.7%, and 98.0% in the ESD group *versus* 98.4%, 95.7%, and 93.3% in the esophagectomy group, respectively. For the 1-, 3-, and 5-year RFS rates, there were 99.1%, 97.7%, and 97.0% in the ESD group *versus* 98.1%, 95.4%, and 93.0% in the esophagectomy group, respectively. Regarding the 1-, 3-, and 5-year DSS rates, there were 99.8%, 99.5%, and 99.5% in the ESD group *versus* 98.7%, 97.3%, and 97.3% in the esophagectomy group, respectively. With a median follow-up period of 30 months (range, 4–78 months) in the ESD group and 28 months (range, 4–87 months) in the esophagectomy group, the RFS was comparable between the two groups. Compared with the esophagectomy group, the ESD group showed better outcomes in terms of OS and DSS. After matching, the 1-, 3-, and 5-year OS rates were 99.5%, 98.6%, and 98.6% in the ESD group, while that were 99.0%, 97.4%, and 94.3% in the esophagectomy group. The 1-, 3-, and 5-year RFS rates were 98.9%, 96.7%, and 96.7% *versus* 99.0%, 96.5%, and 94.3% for the ESD and esophagectomy groups, respectively. The 1-, 3-, and 5-year DSS rates were 100.0%, 99.2%, and 99.2% *versus* 99.0%, 98.2%, and 98.2% for the ESD and esophagectomy groups, respectively. There was no statistical difference in the OS, RFS, and DSS between the ESD and esophagectomy groups.

Subgroup analysis

We divided all patients into two subgroups basing on the depth of tumor invasion, the pT1a-M1/M2 and pT1a-MM/pT1b groups. Recurrence and survival outcomes are listed in Supplemental Table 1. For the pT1a-M1/M2 group, all-cause mortality, recurrence rate, and disease-specific mortality were comparable between the ESD and esophagectomy groups. The same results were shown in pT1a-MM/pT1b group.

A subgroup analysis of pT1a-MM/pT1b ESCC was performed to compare the ESD and esophagectomy groups (Table 3). No significant differences were found between the two groups concerning age, gender, tumor morphology, differentiation, LVI, and rate of adverse events. Patients who underwent ESD had larger tumor diameter, lower hospital costs, and shorter procedure duration and hospital stay, but lower R0 resection rate and more adjuvant treatments. After matching, tumor location, diameter, and adjuvant therapy became comparable, while adverse events showed statistically significant difference in the two groups.

The Kaplan–Meier survival curves of the pT1a-MM/pT1b subgroup are shown in Figure 3. At the end of follow-up, no significant differences were found in OS ($p = 0.721$), RFS ($p = 0.595$), and DSS ($p = 0.931$) between the ESD and esophagectomy groups.

Table 2. Clinical outcomes in the two cohorts.

	Before matching			After matching		
	ESD *N* = 508	**Esophagectomy *N* = 466**	***p* Value**	**ESD *N* = 202**	**Esophagectomy *N* = 202**	***p* Value**
Estimated blood loss (ml)			<0.001			<0.001
⩽50	506 (99.6%)	30 (6.4%)		200 (99.0%)	13 (6.4%)	
>50	2 (0.4%)	436 (93.6%)		2 (1.0%)	189 (93.6%)	
Procedure duration (min), median (IQR)	85 (55–100)	255 (215–290)	<0.001	85 (53–100)	266 (220–300)	<0.001
Hospital stay (day), median (IQR)	10.4 (8.0–12.0)	20.4 (14.5–22.0)	<0.001	10.7 (7.5–12.0)	21.1 (15.0–24.0)	<0.001
Hospital cost (USD), median (IQR)	3308.4 (2703.8–3541.9)	9084.5 (7484.8–9731.8)	<0.001	3345.9 (2721.9–3610.4)	8786.8 (7046.5–9310.9)	<0.001
Resection margin			<0.001			<0.001
R0 resection	478 (94.1%)	464 (99.6%)		189 (93.5%)	202 (100.0%)	
R1 resection	30 (5.9%)	2 (0.4%)		13 (2.5%)	0 (0.0%)	
Adverse events, *n* (%)			<0.001			<0.001
Bleeding	2 (0.4%)	2 (0.4%)		0 (0.0%)	1 (0.5%)	
Stricture	9 (1.8%)	6 (1.3%)		3 (1.5%)	3 (1.5%)	
Pulmonary events	11 (2.2%)	29 (6.2%)		3 (1.5%)	12 (5.9%)	
Anastomotic leakage	2 (0.4%)	13 (2.8%)		1 (0.5%)	5 (2.5%)	
Chylothorax	0 (0.0%)	1 (0.2%)		0 (0.0%)	0 (0.0%)	
Vocal cord palsy	0 (0.0%)	1 (0.2%)		0 (0.0%)	1 (0.5%)	
Wound dehiscence	0 (0.0%)	4 (0.9%)		0 (0.0%)	2 (1.0%)	
Ileus	0 (0.0%)	1 (0.2%)		0 (0.0%)	1 (0.5%)	
Adjuvant therapy, *n* (%)			0.479			0.001
Repeat endoscopy/ esophagectomy	5 (1.0%)	4 (0.9%)		3 (1.5%)	0 (0.0%)	
Radiotherapy	11 (2.2%)	3 (0.6%)		9 (4.5%)	0 (0.0%)	
Chemotherapy	1 (0.2%)	5 (1.1%)		1 (0.5%)	1 (0.5%)	

EDS, endoscopic submucosal dissection; IQR, interquartile range.

Cox regression analysis

In the univariate analysis, factors associated with OS included age [hazard ratio (HR) = .26, 95% confidence interval (CI): 1.13–1.42, $p < 0.01$] and tumor invasion depth (HR = 8.19, 95% CI: 1.02–66.00, $p = 0.048$). In multivariate analysis, age (HR = 1.28, 95% CI: 1.13–1.44, $p < 0.01$) was the independent risk factor for OS (Table 4). We also performed Cox regression analysis on RFS and DSS. The results showed that age (HR = 1.17, 95% CI: 1.07–1.29, $p < 0.01$) and depth of infiltration (HR = 4.84, 95% CI:

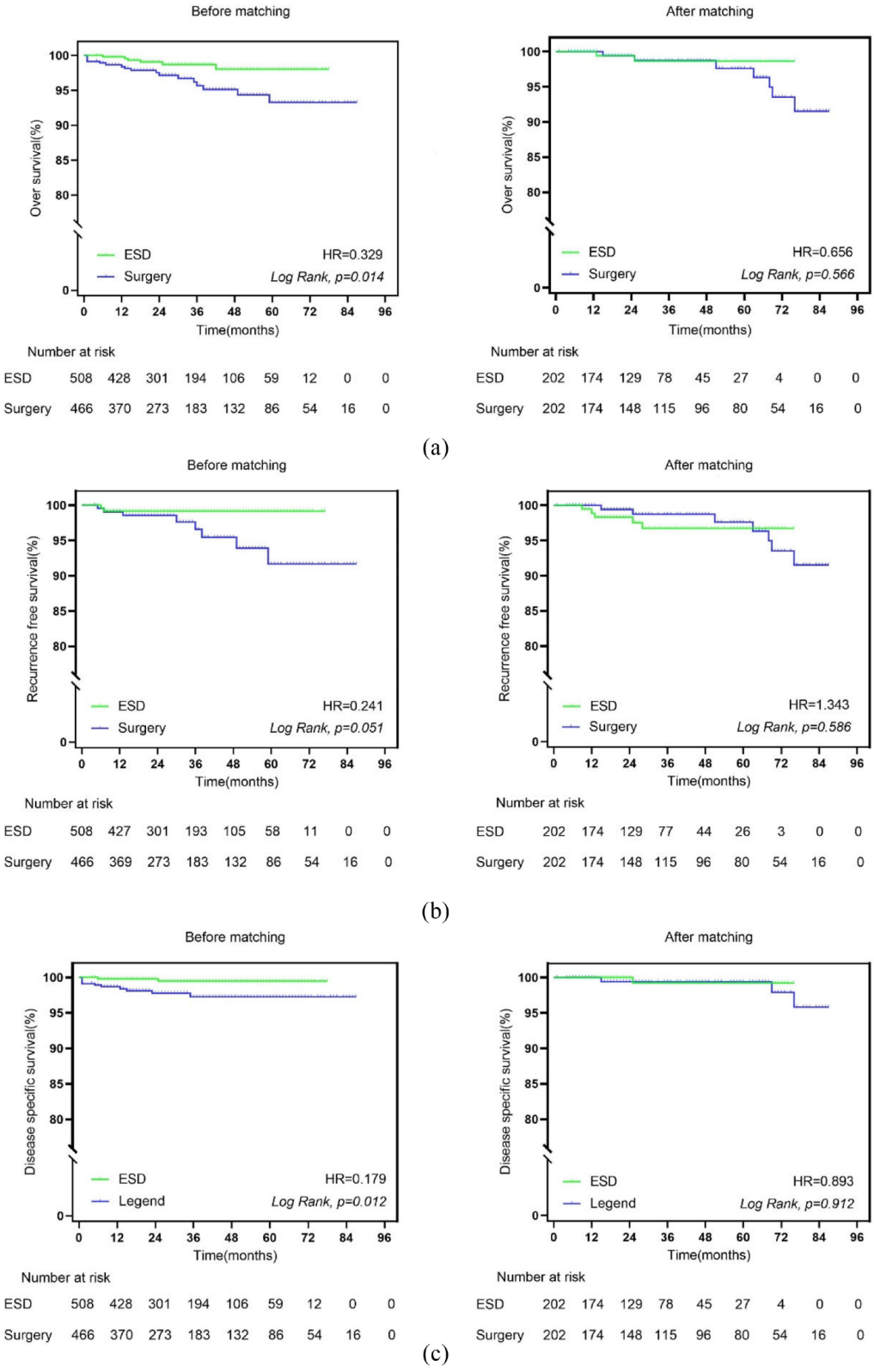

Figure 2. Kaplan–Meier survival curves of OS, RFS, and DSS in total enrolled and matched patients between endoscopic submucosal dissection and esophagectomy groups: (a) OS, (b) DSS, and (c) RFS.
DSS, disease-specific survival; OS, overall survival; RFS, recurrence-free survival.

Table 3. Baseline characteristics and clinical outcomes in pT1a-MM/pT1b esophageal cancer patients.

	Before matching			After matching		
	ESD *N* = 73	**Esophagectomy *N* = 347**	***p* Value**	**ESD *N* = 69**	**Esophagectomy *N* = 87**	***p* Value**
Age (mean ± SD; years)	65.78 ± 8.59	65.63 ± 8.02	0.887	65.68 ± 8.40	64.08 ± 8.03	0.217
Gender, *n* (%)			0.877			0.436
Male	53 (72.6%)	255 (73.5%)		50 (72.5%)	58 (66.7%)	
Female	20 (27.4%)	92 (26.5%)		19 (27.5%)	29 (33.3%)	
Tumor location, *n* (%)			0.022			0.638
Upper	7 (9.6%)	58 (16.7%)		7 (10.2%)	10 (11.5%)	
Upper-middle	2 (2.7%)	2 (0.6%)		1 (1.5%)	1 (1.1%)	
Middle	34 (46.6%)	198 (57.1%)		33 (47.8%)	51 (58.6%)	
Middle-lower	3 (4.1%)	7 (2.0%)		3 (4.3%)	3 (3.5%)	
Lower	27 (37.0%)	82 (23.6%)		25 (36.2%)	22 (25.3%)	
Tumor diameter (mean ± SD; cm)	3.84 ± 2.10	3.01 ± 1.72	<0.001	3.77 ± 2.11	3.39 ± 1.92	0.230
Tumor morphology, *n* (%)			0.185			0.951
Elevated	16 (21.9%)	54 (15.6%)		14 (20.3%)	18 (20.7%)	
Flat or depressed	57 (78.1%)	293 (84.4%)		55 (79.7%)	69 (79.3%)	
High-grade dysplasia	8 (11.0%)	44 (12.7%)	—	6 (8.7%)	23 (26.4%)	—
Squamous cell carcinoma			0.413			0.628
Well/moderately differentiated	50 (68.5%)	218 (62.8%)		49 (71.0%)	52 (59.8%)	
Poorly differentiated	15 (20.5%)	85 (24.5%)		14 (20.3%)	12 (13.8%)	
LVI, *n* (%)	1 (1.4%)	9 (2.6%)	0.533	1 (1.5%)	6 (6.9%)	0.134
Procedure duration (min), median (IQR)	90.88 (60.0–108.0)	253.5 (215.0–290.0)	<0.001	89.36 (60.0–105.5)	275.48 (220.0–316.0)	<0.001
Hospital stay (day), median (IQR)	10.5 (7.0–12.0)	20.2 (14.0–22.0)	<0.001	10.0 (7.0–11.0)	21.0 (16.0–24.0)	<0.001
Hospital cost (USD), median (IQR)	3346.7 (2775.5–3694.4)	9107.4 (7483.2–9754.7)	<0.001	3125.6 (2678.5–3554.2)	8373.1 (6507.1–8721.3)	<0.001
R1 resection, *n* (%)	6 (8.2%)	1 (0.29%)	<0.001	5 (7.2%)	0 (0.0%)	0.036
Adverse events, *n* (%)	4 (5.5%)	39 (11.2%)	0.140	3 (4.3%)	12 (13.8%)	0.047
Adjuvant therapy, *n* (%)	9 (12.3%)	7 (2.0%)	<0.001	5 (7.2%)	1 (1.1%)	0.122

ESD, endoscopic submucosal dissection; LVI, lymphovascular invasion.

1.05–22.36, $p = 0.044$) were associated with RFS, while only age (HR = 1.16, 95% CI: 1.00–1.35, $p = 0.046$) was the independent risk factor for DSS (Tables 5 and 6).

Discussion

Due to advances in endoscopic diagnostic techniques, esophageal cancer is being increasingly detected at its early stage. In recent years, ESD

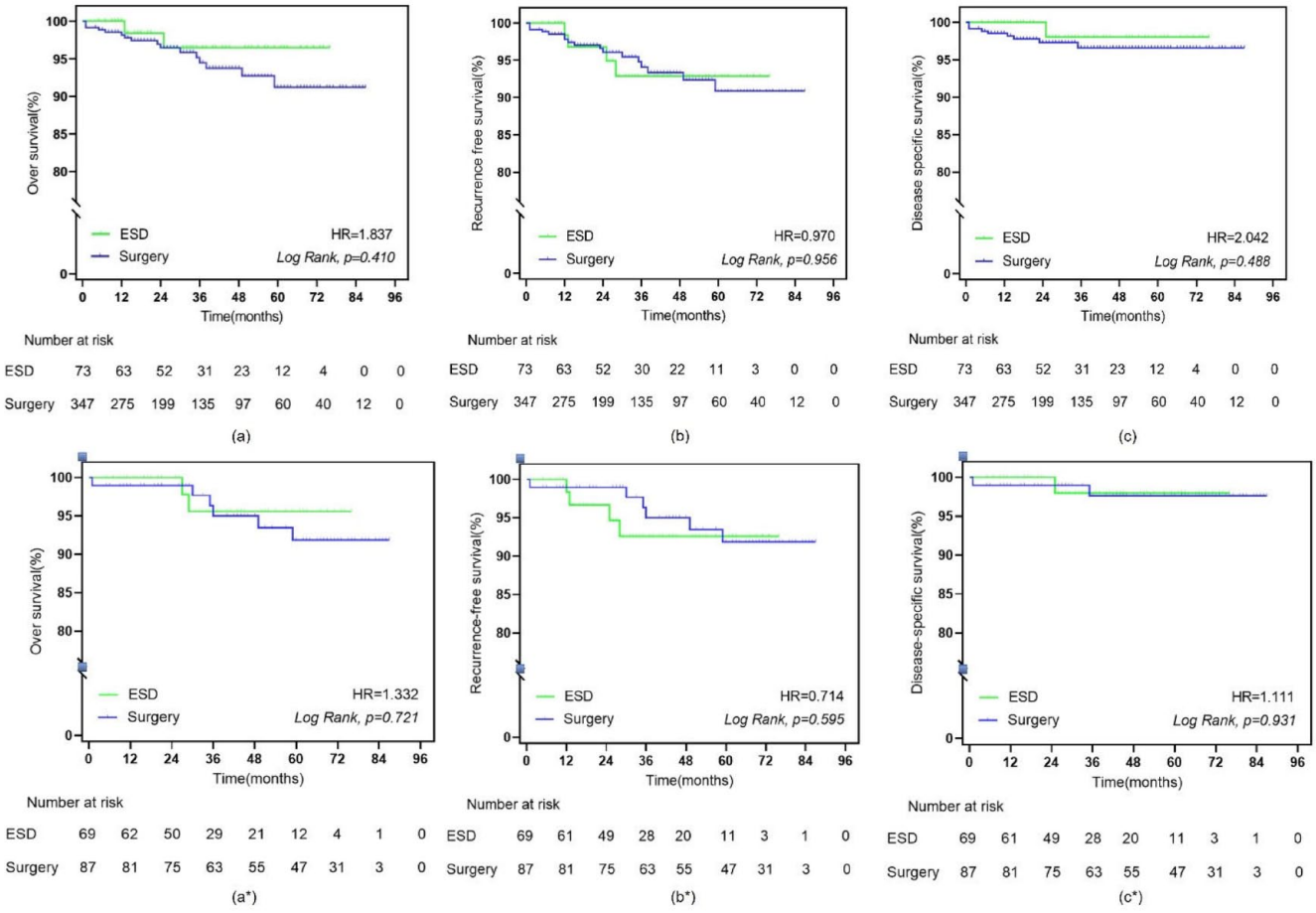

Figure 3. Kaplan–Meier survival curves of OS, RFS, and DSS in pT1a-MM/pT1b subgroup. Before matching: (a) OS, (b) RFS, and (c) DSS. After matching: (a*) OS, (b*) RFS, and (c*) DSS.
DSS, disease-specific survival; OS, overall survival; RFS, recurrence-free survival.

has emerged as an alternative treatment for superficial esophageal cancer. Many studies have demonstrated the efficacy and safety of ESD in the treatment of SESCC.[22,23] After long-term follow-up, a European multicenter study showed excellent results for ESD in the treatment of SESCC, with a disease recurrence rate of 2.9% and a mortality rate of 0%.[12] Hatta et al. recently investigated the risk of metastatic recurrence after endoscopic resection for ESCCs with an invasion depth between pT1a-MM and pT1b-SM. According to the depth of invasion, LVI, and VM, patients were stratified into three categories: category A, pT1a-MM with negative LVI and VM; category B, pT1b SM1 with negative LVI and VM; and category C, others (pT1b-SM2, LVI, or positive/unclear VM). In categories A and B, the 5-year metastatic recurrence rates were 2.6% and 4.3%, respectively. In category C, the 5-year metastatic recurrence rate was 9.1% in patients with additional treatment. They further found that the 5-year DSS were 99.6%, 100.0%, and 90.3% in categories A, B, and C. After additional treatment, a 5-year DSS of 100% was achieved in both categories A and B, even in category C, the 5-year DSS could reach 96%.[24] In our study, ESD showed favorable outcomes similar to these previous reports, with a 5-year OS of 98.6%, a 5-year RFS of 96.7%, and a 5-year DSS of 99.2%.[12,22,23]

However, with a risk of lymph node metastasis, esophagectomy is still considered the only curative treatment when lesions invade the muscularis mucosa and submucosa layer.[25,26] An accurate evaluation of tumor invasion depth is crucial, as it has shown to correlate significantly with the risk of lymph node metastasis. Endoscopic ultrasound

Table 4. Univariate and multivariate regression analyses of OS for PSM patients.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Treatment method (ESD *versus* esophagectomy)	0.38 (0.08–1.85)	0.231		
Age	1.26 (1.13–1.42)	<0.001	1.28 (1.13–1.44)	<0.001
Gender, male = 1	1.26 (0.32–5.06)	0.741		
Cigarette, no = 1	0.78 (0.10–6.26)	0.816		
Alcohol, no = 1	0.04 (0.01–14.25)	0.439		
Family history, no = 1	0.04 (0.01–79.59)	0.530		
Tumor location				
Upper	1.00	—		
Upper-middle	0.01 (0.02–16.28)	0.990		
Middle	0.66 (0.07–5.94)	0.710		
Middle-lower	2.98 (0.19–47.80)	0.990		
Lower	1.18 (0.12–11.39)	0.884		
Tumor diameter	1.14 (0.88–1.47)	0.320		
Tumor morphology				
Elevated	1.00			
Flat or depressed	0.47 (0.10–2.31)	0.355		
Tumor infiltration depth				
M1/M2	1.00			
MM/SM	8.19 (1.02–66.00)	0.048	6.68 (0.82–54.31)	0.076
Histologic type				
High-grade dysplasia	1.00			
Well/moderately differentiated	1.91 (0.37–9.87)	0.442		
Poorly differentiated	4.35 (0.61–30.96)	0.142		
LVI, yes = 1	0.05 (0.01–1.82)	0.870		
Estimated blood loss, >50	2.81 (0.58–13.73)	0.200		
Resection margin, no = 1	0.05 (0.01–19.02)	0.694		

CI, confidence interval; ESD, endoscopic submucosal dissection; HR, hazard ratio; LVI, lymphovascular invasion; PSM, propensity score matching.

(EUS) is widely used to assess the invasion depth, but was reported to have a relatively low diagnostic accuracy.[27,28] Ishihara et al. explored the performance of EUS after conventional endoscopy for the diagnosis of ESCC invasion depth. They found that additional EUS did not improve the diagnostic performance of non-magnifying and magnifying endoscopy in evaluating the invasion depth of T1 ESCC.[17] Because the current diagnostic tools are limited, some discrepancies have been found in T-staging between the clinical and pathological results. Therefore, we compared the

Table 5. Univariate and multivariate regression analyses of RFS for PSM patients.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Treatment method (ESD *versus* esophagectomy)	0.91 (0.29–2.90)	0.872		
Age	1.18 (1.08–1.30)	< 0.001	1.17 (1.07–1.29)	<0.001
Gender, male = 1	1.83 (0.58–5.77)	0.303		
Cigarette, no = 1	0.56 (0.07–4.31)	0.574		
Alcohol, no = 1	0.04 (0.01–43.95)	0.366		
Family history, no = 1	0.05 (0.01–74.45)	0.719		
Tumor location				
Upper	1.00			
Upper-middle	0.01 (0.08–5.42)	0.987		
Middle	0.52 (0.11–2.61)	0.430		
Middle-lower	1.45 (0.13–16.05)	0.761		
Lower	0.59 (0.10–3.52)	0.560		
Tumor diameter	1.04 (0.80–1.37)	0.762		
Tumor morphology				
Elevated	1.00			
Flat or depressed	0.43 (0.12–1.61)	0.210		
Tumor infiltration depth				
M1/M2	1.00			
MM/SM	5.36 (1.17–24.61)	0.031	4.84 (1.05–22.36)	0.044
Histologic type				
High-grade dysplasia	1.00			
Well/moderately differentiated	1.85 (0.48–7.19)	0.373		
Poorly differentiated	2.96 (0.49–17.75)	0.235		
LVI, yes = 1	0.05 (0.01–3.86)	0.854		
Estimated blood loss, 50	1.17 (0.37–3.75)	0.789		
Resection margin, no = 1	0.05 (0.01–23.43)	0.648		

CI, confidence interval; ESD, endoscopic submucosal dissection; HR, hazard ratio; LVI, lymphovascular invasion; OS, overall survival; PSM, propensity score matching; RFS, recurrence-free survival.

outcomes of ESD and esophagectomy by performing an overall analysis of patients with T1 ESCC based on postoperative pathological findings.

Previous studies have compared the outcomes of endoscopic treatment and surgical resection for the SESCC, and showed no difference in survival or risk of cancer recurrence or metastasis in

Table 6. Univariate and multivariate regression analyses of DSS for PSM patients.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Treatment method (ESD *versus* esophagectomy)	0.38 (0.04–3.62)	0.396		
Age	1.16 (1.00–1.35)	0.048	1.16 (1.00–1.35)	0.046
Gender, male = 1	0.87 (0.09–8.33)	0.900		
Cigarette, no = 1	1.91 (1.20–18.33)	0.577		
Alcohol, no = 1	0.04 (0.01–61.26)	0.595		
Family history, yes = 1	0.05 (0.01–2.13)	0.838		
Tumor location				
Upper	1.00			
Upper-middle	1.01 (0.01–2.18)	—		
Middle	2.38 (0.01–3.59)	—		
Middle-lower	1.02 (0.01–2.83)	—		
Lower	4.73 (0.06–7.13)	—		
Tumor diameter	1.12 (0.74–1.70)	0.584		
Tumor morphology				
Elevated	1.00			
Flat or depressed	0.47 (0.05–4.57)	0.515		
Tumor infiltration depth				
M1/M2	1.00			
MM/SM	3.59 (0.37–34.81)	0.270		
Histologic type				
High-grade dysplasia	1.00			
Well/moderately differentiated	0.44 (0.04–4.88)	0.505		
Poorly differentiated	0.19 (0.01–2.98)0.817	0.234		
LVI, yes = 1	0.05 (0.01–2.01)	0.910		
Estimated blood loss, >50	2.88 (0.30–27.84)	0.362		
Resection margin, no = 1	0.05 (0.01–59.42)	0.797		

CI, confidence interval; ESD, endoscopic submucosal dissection; DSS, disease-specific survival; HR, hazard ratio; LVI, lymphovascular invasion; PSM, propensity score matching.

patients with T1a or T1b SESCC receiving ESD *versus* esophagectomy. A meta-analysis showed similar OS (86.4% *versus* 81.8%, HR = 0.66, 95% CI: 0.39–1.11), RFS, and DSS between the ESD and esophagectomy groups, while fewer adverse events were found in the ESD group (19.8% *versus* 44.0%, odds ratio = 0.3, 95% CI: 0.23–0.39).[5] In pT1a-M3/pT1b SESCC, patients who were treated with ESD had comparable OS ($p = 0.419$), DSS ($p = 0.436$), and PFS ($p = 0.176$) to those

treated with esophagectomy.[29] An et al.[11] conducted a study to compare ESD with esophagectomy under different depth of tumor invasion, and found that there were no significant differences in OS ($p = 0.417$), DSS ($p = 0.423$), and RFS ($p = 0.726$) between the two groups. It should be noted that preoperative assessment is challenging on the depth of tumor infiltration. Thus, defining an appropriate treatment strategy for SESCC can be difficult. To our knowledge, studies with sufficient samples and putting patients in comparable clinical circumstances to discuss the outcomes of ESD and surgery are still limited. By performing propensity-matched analysis of pT1 ESCC and pT1a-MM/pT1b ESCC subgroups, we explored the role of ESD in patients with T1 lesions.

In this study, the ESD group had significantly less blood loss than the esophagectomy group. The procedure duration (median, 75 *versus* 276) and the hospital stay (median, 9 *versus* 18) were also significantly shorter in the ESD group. As a result, the hospital cost (median, $3095.7 *versus* $8588.6 USD) in the ESD group was significantly lower than that in the surgery group. Furthermore, there were fewer adverse events but a lower R0 resection rate in the ESD group.[30,31] We recommend additional treatment for patients who underwent ESD in our study with positive margins, but the final decision was based on the patient's physical condition and preference.[32] Concerning survival outcomes, we found that the ESD group had better OS ($p = 0.014$) and DSS ($p = 0.012$), while RFS ($p = 0.051$) was comparable between the two groups. These results may be due to the more pT1a-MM/pT1b patients, poorly differentiated lesions, and LVI in the esophagectomy group.

To make a more precise comparison, PSM was used to balance the tumor characteristics (including location, diameter, morphology, histologic type, and invasion depth). After matching, the ESD group still showed significant advantages in terms of operation time (median, 77 *versus* 256), hospital stay (median, 9 *versus* 18), and hospital cost (median, 3093.5 *versus* 8204.7). More adverse events (even two perioperative deaths) were observed in the esophagectomy group.[30] Although the R0 resection rate was lower in the ESD group, it could be well managed with close follow-up or adjuvant therapy. Our results are similar to those reported previously.[4,19,33] In the matched cohorts, there was no significant difference in OS ($p = 0.566$), RFS ($p = 0.586$), and DSS ($p = 0.912$) between the two groups.[9,29] Subgroup analysis based on the depth of invasion was used to compare survival outcomes. In the pT1a-M1/M2 and pT1a-MM/pT1b subgroups, there were no significant differences between the ESD and esophagectomy groups in terms of all-cause mortality, recurrence rate, and disease-specific mortality. According to the guidelines, ESD is a preferred treatment for esophageal lesions confined to the epithelium and lamina propria mucosa.[6–8] For lesions with a deeper invasion, there is still no definite treatment to be recommended. Therefore, we further performed a detailed subgroup analysis of pT1a-MM/pT1b ESCC. The results showed that patients had comparable OS, RFS, and DSS between the ESD and esophagectomy groups.

Cox regression analysis was used to identify risk factors associated with OS, RFS, and DSS. According to a nomogram prognostic model, the independent factors associated with prognosis included age (HR: 1.990; 95% CI: 1.288–3.074; $p = 0.002$), Karnofsky performance status score, T stage, chemotherapy, body mass index, cervical esophageal carcinoma index, and neutrophil to lymphocyte ratio.[34] In multivariate analysis, we have not found an association between the treatment method (ESD *versus* esophagectomy) and survival outcomes (including OS, RFS, and DSS). Results showed that age was the independent risk factor for OS.[35] Regarding RFS, age and the depth of tumor invasion were independent factors. In terms of DSS, only age was the influential factor. We can observe that age was the common risk factor for OS, RFS, and DSS, which is consistent with the previous study.[36] Since elderly patients tend to have many comorbidities and poor physical status, a comprehensive evaluation should be conducted by clinicians to select the appropriate treatment for them.

ESD also has its drawback. It can only remove the primary lesion, not the metastatic lymph nodes. Although EUS has a relatively lower accuracy for evaluating the depth of invasion, it can be a valuable tool for identifying lymph node metastases.[37] Furthermore, additional esophagectomy or chemoradiotherapy after ESD is safe and effective for lesions with a high risk for metastatic recurrence.[26] Recently, excellent results have been reported on adjuvant therapy after ESD.[38]

Therefore, it is reasonable to recommend ESD as the primary treatment for T1 ESCC.

This study has some limitations. First, selection bias is unavoidable for a retrospective study, although a PSM analysis was performed to minimize potential bias. Second, compared with the esophagectomy group, there were fewer T1b ESCC in the ESD group. Thus, we also performed a subgroup analysis of pT1a-MM/pT1b patients. Third, we enrolled the study subjects based on postoperative pathological results. Due to the limitation of current diagnostic tools, there was a discrepancy between preoperative diagnosis and postoperative pathological findings. Fourth, we did not analyze in detail the patients who received adjuvant therapy after ESD/esophagectomy to further evaluate their prognosis, and there is no standard in which type of additional therapy should be chosen for them. Since a prospective randomized trial is not ethical, further studies on comparing ESD with esophagectomy and the efficacy of each additional treatment are needed.

Conclusions

In conclusion, the long-term outcomes after ESD for SESCC were comparable with esophagectomy. Patients who underwent ESD had less blood loss, shorter procedure duration and hospital, lower hospital cost, and fewer adverse events. Even in pT1a-MM/pT1b ESCC, ESD has shown favorable results. Therefore, with sufficient safety and advantages, it is reasonable to recommend ESD as the primary treatment for T1 ESCC.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Medical Ethics Committee of the First Affiliated Hospital of USTC (approval number: 2022-RE-077). Since this is a retrospective study using clinical routine treatment or diagnostic medical records and no human immunodeficiency virus positive cases were involved, the First Affiliated Hospital of USTC Medisch Ethische Institutional approved the waiver of the participants' consent.

Consent for publication

Not applicable.

Author contribution(s)

Meng Qian: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Visualization; Writing – original draft; Writing – review & editing.

Shuo Feng: Visualization; Writing – review & editing.

Hangcheng Zhou: Data curation; Visualization.

Lijie Chen: Data curation; Visualization.

Song Wang: Conceptualization; Investigation; Methodology; Resources; Supervision; Validation; Visualization; Writing – review & editing.

Kaiguang Zhang: Conceptualization; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – review & editing.

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The authors declare that there is no conflict of interest.

Availability of data and materials

The data analyzed in this study are available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

References

1. Sung H, Ferlay J, Siegel RL, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71: 209–249.
2. Zhang X, Wang Y and Meng L. Comparative genomic analysis of esophageal squamous

cell carcinoma and adenocarcinoma: new opportunities towards molecularly targeted therapy. *Acta Pharm Sin B* 2022; 12: 1054–1067.

3. di Pietro M, Canto MI and Fitzgerald RC. Endoscopic management of early adenocarcinoma and squamous cell carcinoma of the esophagus: screening, diagnosis, and therapy. *Gastroenterology* 2018; 154: 421–436.
4. Takahashi K, Hashimoto S, Mizuno KI, *et al*. Management decision based on lymphovascular involvement leads to favorable outcomes after endoscopic treatment of esophageal squamous cell carcinoma. *Endoscopy* 2018; 50: 662–670.
5. Yeh JH, Huang RY, Lee CT, *et al*. Long-term outcomes of endoscopic submucosal dissection and comparison to surgery for superficial esophageal squamous cancer: a systematic review and meta-analysis. *Therap Adv Gastroenterol* 2020; 13: 1756284820964316.
6. Ajani JA, D'Amico TA, Bentrem DJ, *et al*. Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2019; 17: 855–883.
7. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, *et al*. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European society of gastrointestinal endoscopy (ESGE) guideline - update 2022. *Endoscopy* 2022; 54: 591–622.
8. Kitagawa Y, Uno T, Oyama T, *et al*. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. *Esophagus* 2019; 16: 25–43.
9. 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: 624–633.
10. Yamauchi K, Iwamuro M, Nakagawa M, *et al*. Long-term outcomes of endoscopic versus surgical resection for MM-SM1 esophageal squamous cell carcinoma using propensity score analysis. *Esophagus* 2021; 18: 72–80.
11. An W, Liu MY, Zhang J, *et al*. Endoscopic submucosal dissection versus esophagectomy for early esophageal squamous cell carcinoma with tumor invasion to different depths. *Am J Cancer Res* 2020; 10: 2977–2992.
12. Berger A, Rahmi G, Perrod G, *et al*. Long-term follow-up after endoscopic resection for superficial esophageal squamous cell carcinoma: a multicenter Western study. *Endoscopy* 2019; 51: 298–306.
13. Molena D and DeMeester SR. When less is just less: endoscopic therapy for submucosal T1b esophageal cancer. *Gastrointest Endosc* 2020; 92: 40–43.
14. Zheng H, Tang H, Wang H, *et al*. Nomogram to predict lymph node metastasis in patients with early oesophageal squamous cell carcinoma. *Br J Surg* 2018; 105: 1464–1470.
15. Jiang KY, Huang H, Chen WY, *et al*. Risk factors for lymph node metastasis in T1 esophageal squamous cell carcinoma: a systematic review and meta-analysis. *World J Gastroenterol* 2021; 27: 737–750.
16. He LJ, Xie C, Wang ZX, *et al*. Submucosal saline injection followed by endoscopic ultrasound versus endoscopic ultrasound only for distinguishing between T1a and T1b esophageal cancer. *Clin Cancer Res* 2020; 26: 384–390.
17. Ishihara R, Mizusawa J, Kushima R, *et al*. Assessment of the diagnostic performance of endoscopic ultrasonography after conventional endoscopy for the evaluation of esophageal squamous cell carcinoma invasion depth. *JAMA Netw Open* 2021; 4: e2125317.
18. Kamarajah SK, Phillips AW, Hanna GB, *et al*. Is local endoscopic resection a viable therapeutic option for early clinical stage T1a and T1b esophageal adenocarcinoma?: a propensity-matched analysis. *Ann Surg* 2022; 275: 700–705.
19. Joseph A, Draganov P, Maluf-Filho F, *et al*. Outcomes for endoscopic submucosal dissection of pathologically staged T1b esophageal cancer: a multicenter study. *Gastrointest Endosc* 2022; 96: 445–453.
20. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th edition: part II and III. *Esophagus* 2017; 14: 37–65.
21. von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; 4: e296.
22. Nishizawa T and Suzuki H. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Cancers (Basel)* 2020; 12: 2849.
23. Oda I, Shimizu Y, Yoshio T, *et al*. Long-term outcome of endoscopic resection for intramucosal esophageal squamous cell cancer: a secondary analysis of the Japan esophageal cohort study. *Endoscopy* 2020; 52: 967–975.

24. Hatta W, Koike T, Takahashi S, *et al.* Risk of metastatic recurrence after endoscopic resection for esophageal squamous cell carcinoma invading into the muscularis mucosa or submucosa: a multicenter retrospective study. *J Gastroenterol* 2021; 56: 620–632.

25. Draganov PV, Wang AY, Othman MO, *et al.* AGA institute clinical practice update: endoscopic submucosal dissection in the United States. *Clin Gastroenterol Hepatol* 2019; 17: 16–25.e11.

26. Ishihara R, Arima M, Iizuka T, *et al.* Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. *Dig Endosc* 2020; 32: 452–493.

27. Choi J, Chung H, Lee A, *et al.* Role of endoscopic ultrasound in selecting superficial esophageal cancers for endoscopic resection. *Ann Thorac Surg* 2021; 111: 1689–1695.

28. Dumoulin FL, Hildenbrand R, Oyama T, *et al.* Current trends in endoscopic diagnosis and treatment of early esophageal cancer. *Cancers (Basel)* 2021; 13: 752.

29. Wang CY, Chen BH, Lee CH, *et al.* cT1N0M0 esophageal squamous cell carcinoma invades the muscularis mucosa or submucosa: comparison of the results of endoscopic submucosal dissection and esophagectomy. *Cancers (Basel)* 2022; 14: 424.

30. Lee HD, Chung H, Kwak Y, *et al.* Endoscopic submucosal dissection versus surgery for superficial esophageal squamous cell carcinoma: a propensity score-matched survival analysis. *Clin Transl Gastroenterol* 2020; 11: e00193.

31. Liu Z and Zhao R. Endoscopic submucosal dissection vs. surgery for superficial esophageal squamous cancer: a systematic review and meta-analysis. *Front Oncol* 2022; 12: 816832.

32. National Health Commission of the People's Republic of China. Chinese guidelines for diagnosis and treatment of esophageal carcinoma 2018 (English version). *Chin J Cancer Res* 2019; 31: 223–258.

33. Song BG, Kim GH, Cho CJ, *et al.* Close observation versus additional surgery after noncurative endoscopic resection of esophageal squamous cell carcinoma. *Dig Surg* 2021; 38: 247–254.

34. Xiao L, Lyu J, Chen M, *et al.* The development of a nomogram and the prognostic prediction value of patients with esophageal squamous cell carcinoma undergoing radical radiotherapy. *Future Sci OA* 2022; 8: FSO781.

35. Yang Y, Chen M, Xie J, *et al.* Treatment patterns and outcomes of elderly patients with potentially curable esophageal cancer. *Front Oncol* 2022; 12: 778898.

36. Rahman SA, Walker RC, Maynard N, *et al.* The AUGIS survival predictor: prediction of long-term and conditional survival after esophagectomy using random survival forests. *Ann Surg* 2021. Epub ahead of print February 2021. DOI: 10.1097/sla.0000000000004794.

37. Ahmed O, Ajani JA and Lee JH. Endoscopic management of esophageal cancer. *World J Gastrointest Oncol* 2019; 11: 830–841.

38. Minashi K, Nihei K, Mizusawa J, *et al.* Efficacy of endoscopic resection and selective chemoradiotherapy for stage I esophageal squamous cell carcinoma. *Gastroenterology* 2019; 157: 382–390.e383.