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. Due to its highly aggressive nature, ESCC has a poor prognosis. If earlier management could be achieved, the survival would improve significantly.

Esophagectomy combined with regional lymph node dissection is the standard treatment for superficial ESCC (SESCC). However, the considerable morbidity and mortality associated with...
esophagectomy cannot be ignored. In addition, it was reported to have a negative impact on postoperative quality of life.\textsuperscript{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.\textsuperscript{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.\textsuperscript{7,8} Many studies have demonstrated that ESD can provide comparable survival outcomes to esophagectomy in the treatment of SESCC.\textsuperscript{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.\textsuperscript{12,13} Risk factors reported for lymph node metastasis in esophageal cancer include the depth of invasion, degree of differentiation, and lymphovascular invasion (LVI).\textsuperscript{14,15} Due to the limitations of current examination techniques, it is difficult to accurately assess the depth of tumor invasion.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).

#### 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, and invasion depth). 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).\textsuperscript{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.
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           |                |        |                |                |        |
| 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. For 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. 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. 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 ESCC. 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.
Cox regression analysis
In the univariate analysis, factors associated with OS included age (hazard ratio (HR) = 0.26, 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:

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 \( \text{[ml]} \) | <0.001 | <0.001 |
| \( \leq 50 \) | 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 \( \text{[min], median [IQR]} \) | <0.001 | <0.001 |
| \( 85 \) [55–100] | 255 (215–290) | 85 [53–100] | 266 [220–300] | <0.001 |
| Hospital stay \( \text{[day], median [IQR]} \) | <0.001 | <0.001 |
| \( 10.4 \) [8.0–12.0] | 20.4 [14.5–22.0] | 10.7 [7.5–12.0] | 21.1 [15.0–24.0] | <0.001 |
| Hospital cost \( \text{[USD], median [IQR]} \) | <0.001 | <0.001 |
| \( 3308.4 \) [2703.8–3541.9] | 9084.5 [7484.8–9731.8] | 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) = 0.26, 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 | p Value |
|--------------------------|----------------|----------------|---------|
|                          | ESD            | Esophagectomy  |         |
| Age (mean ± SD; years)   | 65.78 ± 8.59   | 65.63 ± 8.02   | 0.887   |
| Gender, n (%)            | 0.877          |                |         |
| Male                     | 53 (72.6%)     | 255 (73.5%)    |         |
| Female                   | 20 (27.4%)     | 92 (26.5%)     |         |
| Tumor location, n (%)    | 0.022          |                |         |
| Upper                    | 7 (9.6%)       | 58 (16.7%)     |         |
| Upper-middle             | 2 (2.7%)       | 2 (0.6%)       |         |
| Middle                   | 34 (46.6%)     | 198 (57.1%)    |         |
| Middle-lower             | 3 (4.1%)       | 7 (2.0%)       |         |
| Lower                    | 27 (37.0%)     | 82 (23.6%)     |         |
| Tumor diameter (mean ± SD; cm) | 3.84 ± 2.10 | 3.01 ± 1.72 | <0.001 |
| Tumor morphology, n (%)  | 0.185          |                |         |
| Elevated                 | 16 (21.9%)     | 54 (15.6%)     |         |
| Flat or depressed        | 57 (78.1%)     | 293 (84.4%)    |         |
| High-grade dysplasia     | 8 (11.0%)      | 44 (12.7%)     |         |
| Squamous cell carcinoma  | 0.413          |                |         |
| Well/moderately differentiated | 50 (68.5%) | 218 (62.8%) |         |
| Poorly differentiated    | 15 (20.5%)     | 85 (24.5%)     |         |
| LVI, n (%)               | 1 (1.4%)       | 9 (2.6%)       | 0.533   |
| Procedure duration (min), median (IQR) | 90.88 (60.0–108.0) | 253.5 (215.0–290.0) | <0.001 |
| Hospital stay (day), median (IQR) | 10.5 (7.0–12.0) | 20.2 (14.0–22.0) | <0.001 |
| Hospital cost (USD), median (IQR) | 3346.7 (2775.5–3694.4) | 9107.4 (7483.2–9754.7) | <0.001 |
| R1 resection, n (%)      | 6 (8.2%)       | 1 (0.29%)      | <0.001 |
| Adverse events, n (%)    | 4 (5.5%)       | 39 (11.2%)     | 0.140   |
| Adjuvant therapy, n (%)  | 9 (12.3%)      | 7 (2.0%)       | <0.001 |

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
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.\textsuperscript{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%.\textsuperscript{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 SM\textsubscript{1} with negative LVI and VM; and category C, others (pT1b-SM\textsubscript{2}, 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%.\textsuperscript{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%.\textsuperscript{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.\textsuperscript{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

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Kaplan-Meier_survival_curves.pdf}
\caption{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.}
\end{figure}
(EUS) is widely used to assess the invasion depth, but was reported to have a relatively low diagnostic accuracy.\textsuperscript{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.\textsuperscript{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

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

| 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.
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

| 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)    | 0.234         |                      |               |
| 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.
treated with esophagectomy. An et al. 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 versus the hospital cost (median, $3095.7 versus $8588.6 USD) in the ESD group. Furthermore, there were fewer adverse events but a lower R0 resection rate in the ESD group.30,31 We recommend additional treatment for patients who underwent ESD in our study with positive margins, but the final decision was based on the patient’s physical condition and preference. Concerning survival outcomes, we found that the ESD group had better OS ($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. 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.
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 Institutionel 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.

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

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