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Long-Term Outcomes of Endoscopic Submucosal Dissection for Special Type of Esophageal Cancer

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Keywords
Special type of esophageal cancer · Superficial esophageal cancer · Endoscopic submucosal dissection

Abstract
Background: Esophageal cancers other than two types, squamous cell carcinoma (SCC) and adenocarcinoma, are commonly referred to as special type of esophageal cancer (STEC). Studies on STECs have been limited because of its low prevalence. Therefore, we aimed to clarify the clinicopathological findings and the long-term outcomes of STECs that were managed with ESD. ***Methods:*** We reviewed 713 patients with 1,089 lesions who underwent ESD for primary esophageal cancer except Barrett's esophageal cancer. Patients were classified into the SCC group and the STEC group, respectively. Their clinicopathological findings and long-term outcomes including disease-specific survival (DSS) were collected and examined. ***Results:*** A total of 19 consecutive patients (1.7%) were diagnosed with STEC. Nine patients were diagnosed with basaloid carcinoma, 6 with adenosquamous carcinoma, 2 with mucoepidermoid carcinoma, 2 with salivary duct-type carcinoma, and 1 with neuroendocrine cell carcinoma. There was significantly more pT1b esophageal cancer (47.4% vs. 11.0%, $p < 0.01$) and lymphovascular invasion (31.6% vs. 10.2%, $p = 0.011$) in the STEC group. Metastatic relapse and disease-specific mortality were significantly higher in the STEC group (both 15.8% vs. 1.2%, $p < 0.01$), and the STEC group had shorter DSS with 5-year DSS rates of 90.9%. In a subgroup analysis of patients with pT1a esophageal cancer, the 5-year DSS rate was shorter in the STEC group ($p < 0.01$). In the multivariate analysis, STEC (HR = 0.24) and tumor depth (HR = 12.60) were the factors associated with DSS. ***Conclusion:*** STECs are suggested to have high malignant potential and to be an independent negative prognostic factor for DSS.

Introduction

Esophageal cancer is classified into various histological types according to the Japanese Classification of Esophageal Cancer [1] and WHO classification of digestive system tumors [2]. The two major histological types of esophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma [3]. Although SCC is the most common type of primary esophageal cancer worldwide, ade-

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nocarcinoma occurs more frequently in Western countries [4, 5]. In Japan, SCC accounts for 90% of esophageal cancers and adenocarcinoma, including Barrett's esophageal cancer, represents about 5% [6]. Esophageal cancers other than these two major types are rare and commonly referred to as special type of esophageal cancer (STEC). STECs are characterized by specific immunohistochemical profiles, poor prognosis due to highly aggressive biological behavior, and difficult histological confirmation by endoscopic biopsy [7–15].

Favorable short- and long-term outcomes of endoscopic submucosal dissection (ESD) have been reported for esophageal SCC and Barrett's esophageal carcinoma [16–24], and ESD is a useful and well-established treatment modality for superficial esophageal cancer [25]. Because of the low prevalence of STECs and infrequent detection at an early stage, studies of the outcomes of endoscopic resection for STECs, particularly with regard to long-term outcomes, have thus far been limited compared with those of the common types of esophageal cancer.

In this study, we retrospectively compared the clinicopathological findings of STECs and esophageal SCCs that were managed with ESD. We also compared the long-term clinical outcomes of ESD between patients with STEC and those with SCC.

Materials and Methods

Study Population and Design

This study reviewed 772 patients with 1,171 lesions who underwent ESD for primary esophageal cancer at Toranomon Hospital, Tokyo, Japan, between May 1, 2010, and January 1, 2018. Patients diagnosed with Barrett's esophageal cancer and those with a history of chemotherapy and/or radiation therapy were excluded. This left 713 consecutive patients with 1,089 lesions eligible for further analysis. When synchronous and metachronous esophageal cancers were taken into account, there were 879 cases for which ESD was performed.

In accordance with the Japanese Classification of Esophageal Cancer [1], patients diagnosed with SCC were classified into the SCC group and patients diagnosed with STECs were classified into the STEC group. Their clinicopathological findings and clinical outcomes, such as the last follow-up date, any recurrence, long-term mortality, and cause of death, were collected from patient records. Follow-up data were obtained until December 31, 2021.

Metachronous cancer was defined as esophageal cancer detected after ESD. To account for lead-time bias, for metachronous cancer, the findings of the patient and the lesion at the time of initial treatment were evaluated. For synchronous cancer, the deepest lesion was evaluated.

Indication for ESD and Clinical Course

The indications for lesion treatment were determined based on the preoperative findings of endoscopy, endoscopic ultrasound, and biopsy. Indications for ESD were based on the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus [26]. In ESD, complete resection (R0 resection) is defined as en bloc resection with tumor-free margins, and curative resection was defined based on the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus, with the resected specimen meeting the requirements for R0 resection and showing no invasion of the lymph duct or venous duct or invasion of the muscularis mucosae (pT1a-MM) or deeper [26]. Adjuvant therapy such as surgical treatment or chemoradiation therapy was recommended for noncurative resection. Cases of pT1a-MM without lymphovascular invasion (LVI) were defined as noncurative resection, and patients were fully informed of the risks and benefits when deciding whether to undergo treatment or not.

In all cases, ESD was performed inpatient. ESD was usually performed while the patient was conscious but sedated with a mixture of diazepam (5–10 mg/kg body weight) and pethidine hydrochloride (35–70 mg/kg body weight). However, if the ESD was expected to be difficult because the tumor extended to the cervical esophagus or occupied the entire circumference, the patient was placed under general anesthesia. The length of hospital stay set by the clinical pathway for ESD was 8 days. However, since the pathological results were basically explained to the patient during the hospital stay, the hospitalization period may be extended by several days until the pathological results were available.

Clinical findings during follow-up were analyzed; noncurative ESD cases generally underwent endoscopy, computed tomography (CT), and endoscopic ultrasonography once every 6 months for at least 5 years after ESD and thereafter endoscopy twice a year and CT and endoscopic ultrasonography once a year. The presence of lymph node (LN) or distant metastasis was determined by pathological evaluation in surgical resection or by CT, endoscopic ultrasonography, and/or fluorodeoxyglucose-positron emission tomography.

For patients who had lost outpatient follow-up, the long-term outcome data were retrieved by request from the referring physicians or through a telephone interview. Survival time was calculated as the interval between the date of the first treatment and the date of death or the last date on which the patient was confirmed to be alive.

Adjuvant Therapy

Within 60 days after ESD, concomitant CRT was started in accordance with the regimen in the JCOG 0508 study [27]. The chemotherapy regimen comprised continuous 5-fluorouracil (700 mg/m^2/day, days 1–4 and 29–32) and cisplatin (70 mg/m^2/day, days 1 and 29). The radiotherapy dose was 41.4 Gy/23 Fr/5 weeks (5 days/week) for cases with a negative resection margin and 50.4 Gy/28 Fr/5 weeks (5 days/week) with a boost in the primary site for cases with a positive resection margin.

For esophagectomy after primary ESD, the main method was thoracoscopic-laparoscopic esophagectomy combined with three-field (cervical-thoracic-abdominal) LN dissection. The number of dissected LNs depended on the surgeon.

Histopathological Assessment of Resected Specimens

All ESD specimens were fixed in 10% formalin, stained with hematoxylin and eosin, and pathologically assessed based on the Japanese Classification of Esophageal Cancer [1]. ESD specimens were sectioned serially at 2-mm intervals. Each slice was evaluated

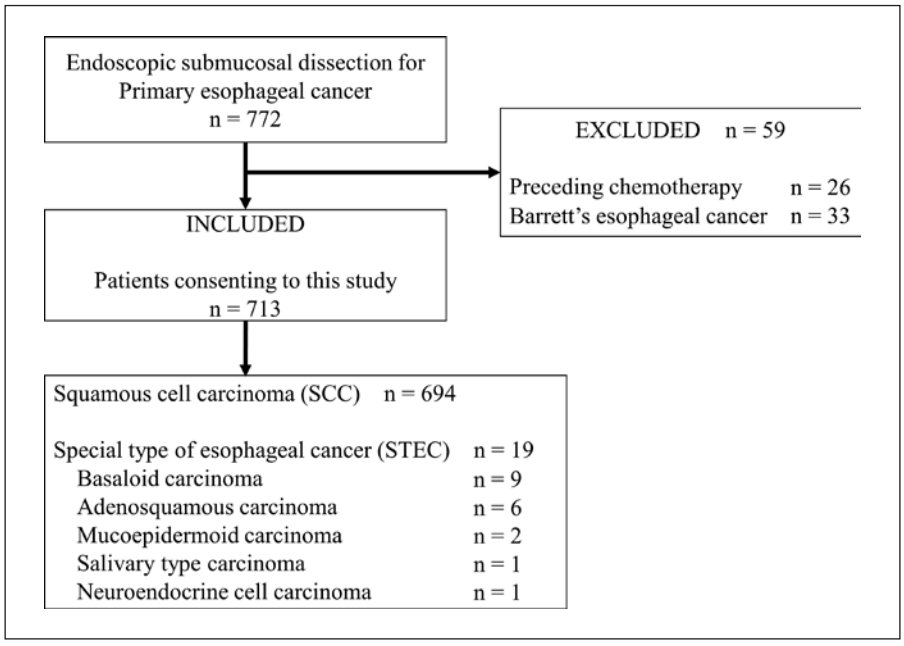

Fig. 1. Study flowchart showing the 713 patients who consented to the study divided between the STEC group (n = 19) and SCC group (n = 694).

in terms of histological type, tumor size, depth of invasion, resection margins, and LVI by specialist pathologists from the Japanese Society of Pathology. According to the Japanese Classification of Esophageal Cancer [1], STECs were divided into five types as follows: basaloid carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, neuroendocrine carcinoma, and salivary duct-type carcinoma. In this study, SCCs with basaloid carcinoma component were classified as basaloid carcinoma and SCCs with mucoepidermoid component were classified as mucoepidermoid carcinoma. Salivary duct-type carcinoma included adenoid cystic carcinoma and carcinoma with salivary duct-like differentiation.

Endoscopic Findings

The location, size, and macroscopic features of each lesion were determined from images obtained by white-light endoscopy and chromoendoscopy (1% Lugol's iodine solution) and saved in the medical records. Diagnoses were retrospectively obtained based on the Japanese Classification of Esophageal Cancer [1] by two board-certified fellows of the Japan Gastroenterological Endoscopy Society. The tumor morphological type was evaluated by classifying types I, 0-I, and 0-IIa into elevated type, types 0-IIc, 0-IIc + 0-IIa, and 0-III into depressed type, and 0-IIb into flat type based on the Paris classification [28].

Study Endpoints

The primary study endpoint was disease-specific survival (DSS). The secondary endpoints were overall survival (OS), prevalence of STECs, and clinicopathological characteristics.

Statistical Analysis

Data are presented as the median and interquartile range. The χ^2 and Fisher's exact tests were used for the intergroup comparison of qualitative variables, whereas the Mann-Whitney U test was used for the comparison of quantitative variables. A Cox proportional-hazards model was used for multivariate analysis. Survival was calculated using the Kaplan-Meier method with a log-rank test. Survival time was calculated from the date of the first ESD for the esophageal cancer until the date of death or the last date on which patients were confirmed to be alive before the endpoint date, whichever came first. All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). A p value <0.05 was considered statistically significant.

Ethical Approval

This study was approved by the Ethics Committee of our hospital (approval number 2268) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The requirement for written informed consent was waived by the Ethics Committee of Toranomon Hospital Certified Review Board, Federation of National Public Service Personnel Mutual Aid Associations, in view of the retrospective observational nature of the research and because it used only information recorded in the medical records and not samples. However, by disclosing information related to clinical research on our Website, we offered patients the opportunity to withhold consent for their anonymized information to be used for research purposes via the opt-out route.

Results

Basic Characteristics and Clinical Course

Figure 1 shows the study flowchart of the inclusion and exclusion criteria used in this study. Table 1 lists the basic characteristics of the study population.

Table 1. Basic characteristics

	STEC (*N* = 19)	SCC (*N* = 694)	*p* value
Age, median (IQR), years	72 (67–75)	69 (63–75)	0.177
Sex, male:female, %	19:0, 100	596:99, 85.9	0.078†
Brinkman index, median (IQR)	760 (112.5–1,200)	600 (187.5–1,000)	0.469
Alcohol consumption, median (IQR), g/day	60 (27–65)	40 (20–60)	0.286
CCI, *n* (%)			0.014*
Mild (0–2)	12 (63.2)	561 (80.8)	
Moderate (3–4)	4 (21.1)	109 (15.7)	
Severe (≥5)	3 (15.8)	24 (3.5)	
Mean CCI ± SD	2.63±0.702	1.36±0.058	0.088†
Performance status			1.000
ECOG 0/1, *n* (%)	19 (100)	690 (99.4)	
ECOG ≥2, *n* (%)	0 (0)	4 (0.6)	
Medication			
Anticoagulant	4 (21.1)	110 (15.9)	0.526
Corticosteroid	0 (0)	9 (1.3)	1.000
Immunosuppressive	0 (0)	4 (0.6)	1.000

IQR, interquartile range; SCC, squamous cell carcinoma; STEC, special type of esophageal cancer. * $p < 0.05$, † $p < 0.1$.

A total of 19 consecutive patients with 19 lesions (1.7%) were diagnosed with STEC (online suppl. Table; see www.karger.com/doi/10.1159/000529590 for all online suppl. material). There was no significant difference in age, alcohol consumption, Brinkman index (the number of cigarettes smoked per day multiplied by the number of years of smoking), Eastern Cooperative Oncology Group (ECOG) performance status, or medication between the STEC and SCC groups. All patients were male in the STEC group, and the male to female ratio tended to be higher in the STEC group than in the SCC group ($p = 0.078$). There was a significant difference between the two groups in the severity of the Charlson Comorbidity Index (CCI), and there were four times as many patients with severe CCI scores in the STEC group than in the SCC group (15.8% vs. 3.5%). Mean CCI score tended to be higher in the STEC group than in the SCC group (2.63 vs. 1.36).

Clinicopathological Findings of Tumors and Procedure-Related Outcomes

Table 2 shows the clinicopathological findings of tumors and procedure-related outcomes. There was no significant difference between the two groups in tumor location, morphological type, or size. Three lesions (15.8% [3 of 19]) in the STEC group had submucosal tumor-like morphology.

Of the 18 STECs for which biopsies were performed preoperatively, 17 (94.4%) were diagnosed as SCC or squamous intraepithelial neoplasia; only 1 lesion, adenosquamous carcinoma, was diagnosed as adenocarcinoma on preoperative biopsy. Preoperative magnifying endoscopy with narrow-band imaging was performed in 17 lesions and endoscopic ultrasound in 15 lesions. Preoperative depth prediction was cEP-lamina propria mucosa in 8 lesions, cMM-SM1 in 10 lesions, and cSM2 in 1 lesion, respectively.

Nine patients were diagnosed with basaloid carcinoma, 6 with adenosquamous carcinoma, 2 with mucoepidermoid carcinoma, 1 with salivary duct-type carcinoma, and 1 with neuroendocrine cell carcinoma. The lesion diagnosed as salivary duct-type carcinoma had a dilated salivary duct-like structure surrounded by elastic fibers, with comedo necrosis and an immunophenotype different from that of normal SCC. Complete resection rates were high and not significantly different between the STEC and SCC groups (94.7% vs. 94.2%, respectively). On the other hand, tumor depth was significantly greater in the STEC group and the percentage of lesions that invaded the submucosa (SM) (pT1b) was significantly higher (47.4% [9 of 19] vs. 11.0% [76 of 694], respectively; $p < 0.01$). There was also significantly more LVI in the STEC group. In the STEC group, 1 lesion (10% [1 of 10]) in T1a and 5 lesions (55.6% [5 of 9]) in T1b showed LVI. These factors resulted in a significantly lower rate of curative resection. There was no significant difference between the groups in the median procedure time, rate of complications, or length of hospital stay. Table 3 gives the clinical and tumor data for all patients with disease-specific death.

Table 2. Clinicopathological findings of tumors and procedure-related outcomes

Variable	STEC (*N* = 19)	SCC (*N* = 694)	*p* value
Pathological type, *n* (%)			
Basaloid SCC	9 (47.4)		
Adenosquamous carcinoma	6 (31.6)		
Mucoepidermoid carcinoma	2 (10.5)		
NEC	1 (5.3)		
Salivary gland type carcinoma	1 (5.3)		
Location, *n* (%)			0.137
Ce	0 (0)	51 (7.3)	
Ut	2 (10.5)	94 (13.5)	
Mt	9 (47.4)	401 (57.8)	
Lt	8 (42.1)	148 (21.3)	
Morphological type, *n* (%)			0.106
Elevated	5 (26.3)	84 (12.1)	
Flat	4 (21.1)	266 (38.3)	
Depressed	10 (52.6)	344 (49.6)	
Elevated versus others			0.076†
Tumor size, median (IQR), mm	18 (10–27)	21 (13–32)	0.420
Depth of invasion, *n* (%)			<0.01*
EP-LPM	4 (21.1)	525 (75.6)	
MM-SM1	10 (52.6)	117 (16.9)	
SM2 or deeper	5 (26.3)	52 (7.5)	
pT1a versus pT1b	10 (52.6)	618 (89.0)	<0.01*
LVI, *n* (%)	6 (31.6)	71 (10.2)	0.011*
Lymphatic invasion, *n* (%)	4 (21.1)	53 (7.6)	0.058†
Vascular invasion, *n* (%)	3 (15.8)	42 (6.1)	0.112
Margin			
Horizontal margin positive or unknown, *n* (%)	1 (5.3)	32 (4.6)	0.598
Vertical margin positive or unknown, *n* (%)	1 (5.3)	10 (1.4)	0.259
Complete resection, *n* (%)	18 (94.7)	654 (94.2)	1.000
Curative resection, *n* (%)	4 (21.1)	501 (72.2)	<0.01*
Median procedure time, median (IQR), min	41 (30–65.8)	43 (29–65)	0.361
Complication, *n* (%)	0 (0)	29 (4.2)	1.000
Bleeding, *n* (%)	0 (0)	6 (0.9)	1.000
Perforation, *n* (%)	0 (0)	8 (1.1)	1.000
Pneumonia, *n* (%)	0 (0)	19 (2.7)	1.000
Hospital stay, median (IQR), days	10 (8–13.5)	8 (8–11)	0.858
Adjuvant therapy, *n* (%)	7 (36.8)	96 (13.8)	0.012*
CTx	1/7 (14.3)	1/96 (1.1)	
RT	1/7 (14.3)	0/96 (0)	
CRT	2/7 (28.6)	58/96 (61.1)	
SR	3/7 (42.9)	37/96 (37.9)	
Metachronous esophageal cancer, *n* (%)	4 (21.1)	110 (15.6)	0.526
Metastatic relapse, *n* (%)	3 (15.8)	9 (1.3)	<0.01*
Disease-specific mortality, *n* (%)	3 (15.8)	9 (1.3)	<0.01*
All-cause mortality, *n* (%)	4 (21.1)	86 (12.4)	0.284
Observation period, median (IQR), months	61 (42–77)	62.5 (39–92)	0.496

Ce, cervical part of the thoracic esophagus; CRT, chemoradiation therapy; CTx, chemotherapy; EP, epithelium; IQR, interquartile range; LPM, lamina propria mucosa; Lt, lower part of the thoracic esophagus; MM, muscularis mucosa; Mt, middle part of the thoracic esophagus; RT, radiation therapy; SCC, squamous cell carcinoma; SM, submucosa; SR, surgical resection; STEC, special type of esophageal cancer; Ut, upper part of the thoracic esophagus. * $p < 0.05$, † $p < 0.1$.

Table 3. Clinical course of the 12 patients with disease-specific death

Case	Pathological type	Observation period, months	Age at initial treatment, years	Sex	Tumor depth	LVI	Adjuvant therapy after ESD	Recurred site	Subsequent treatment after recurrence	Time to recurrence, months
1	STEC/NEC	77	72	M	SM2	V1	CPT-11 + CDDP	Liver	VP16 + CBDCA	62
2	STEC/ASC	60	60	M	SM2	Ly1	SR	LN	LND	42
3	STEC/BSCC	94	70	M	MM	No	CRT (FP-RT)	Liver, Lung	NDP/5-FU, PTX	78
4	SCC	106	88	M	SM2	Ly1, V1	No	LN	RT	64
5	SCC	74	56	M	LPM	No	No	Lung	Partial PNx, FP	26
6	SCC	34	74	M	SM2	No	CRT (FP-RT)	Penis	No	32
7	SCC	63	61	M	SM2	Ly1, V1	CRT (FP-RT)	LN	Esophagectomy	53
8	SCC	30	79	M	SM2	Ly1, V1	CRT (FP-RT)	LN, Lung	LND, partial PNx	9
9	SCC	7	70	M	SM2	Ly1, V1	SR	No	No	
10	SCC	23	78	F	MM	No	No	LN	FP	16
11	SCC	33	59	M	SM1	No	No	LN	CRT (FP-RT)	25
12	SCC	18	82	M	SM2	Ly1, V1	CRT (FP-RT)	LN	No	16

ASC, adenosquamous cell carcinoma; BSCC, basaloid squamous cell carcinoma; CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan; CRT, chemoradiation therapy; F, female; FP, 5-fluorouracil plus cisplatin; LN, lymph node; LND, lymphadenectomy; LPM, lamina propria mucosa; LVI, lymphovascular invasion; Ly, lymphatic invasion; M, male; MM, muscularis mucosa; NDP/5-FU, 5-fluorouracil plus nedaplatin; NEC, neuroendocrine cell carcinoma; PNx, pneumonectomy; PTX, paclitaxel; RT, radiation therapy; SCC, squamous cell carcinoma; SM, submucosa; SR, surgical resection; STEC, special type of esophageal cancer; V, vascular invasion; VP16, etoposide.

Long-Term Outcomes

After the initial ESD, the median follow-up period was 61 months in the STEC group and 62.5 months in the SCC group. Significantly more patients in the STEC group received adjuvant therapy (36.8% [7/19] vs. 13.8% [96/694], respectively; $p = 0.012$). Regarding adjuvant therapy, surgical resection was performed in 3 patients (42.9%) in the STEC group and 37 (37.9%) in the SCC group. Metastatic relapse and disease-specific mortality were significantly higher in the STEC group (both 15.8% [3/19] vs. 1.2% [8/694], $p < 0.01$). On the other hand, there was no significant difference in the incidence of metachronous esophageal cancer between the groups (21.1% [4/19] vs. 15.6% [110/694], respectively; $p = 0.526$). The histological type of all metachronous cancers was SCC and all lesions were treated with ESD. Two metachronous cancers in the STEC group and 9 in the SCC group invaded the SM.

Figure 2 shows the Kaplan-Meier survival curves for OS and DSS. At the end of follow-up, no significant difference was found in the OS rate ($p = 0.17$; Fig. 2a), with 5-year OS rates of 90.9% (95% confidence interval [95% CI]: 73.8–100.0) in the STEC group and 91.3% (95% CI: 88.9–93.7) in the SCC group. The STEC group had shorter DSS than the SCC group ($p < 0.01$; Fig. 2b), with 5-year DSS rates of 90.9% (95% CI: 73.8–100.0) and 99.2% (95% CI: 98.4–100), respectively. In a subgroup analysis of patients with pT1a and pT1b esophageal cancer (10 and 618 patients with pT1a esophageal cancer and 9 and 76 patients with pT1b esophageal cancer in the STEC and SCC groups, respectively; Fig. 2c, d), no significant difference was found in the 5-year DSS rate of pT1b patients between the two groups (83.3% [95% CI: 53.5–100.0] vs. 93.7% [95% CI: 87.6–99.8], respectively; $p = 0.23$). However, the 5-year DSS rate of pT1a patients was shorter in the STEC group than in the SCC group ($p < 0.01$).

Factors Associated with OS

Table 4 lists the univariate and multivariate analysis results of OS and DSS in all study populations. In the univariate analysis, the factors associated with OS were age, CCI, tumor depth, and LVI. In the multivariate analysis, age (hazard ratio [HR] = 1.06, 95% CI: 1.03–1.09), CCI (HR = 1.19, 95% CI: 1.06–1.34), and tumor depth (HR = 2.27, 95% CI: 1.22–4.20) remained the factors associated with OS.

In the univariate analysis, pathological type, tumor depth, and LVI were the factors associated with DSS. In the multivariate analysis, pathological type (HR = 0.24, 95% CI: 0.06–0.97) and tumor depth (HR = 12.60, 95% CI: 2.55–62.32) were still the factors associated with DSS.

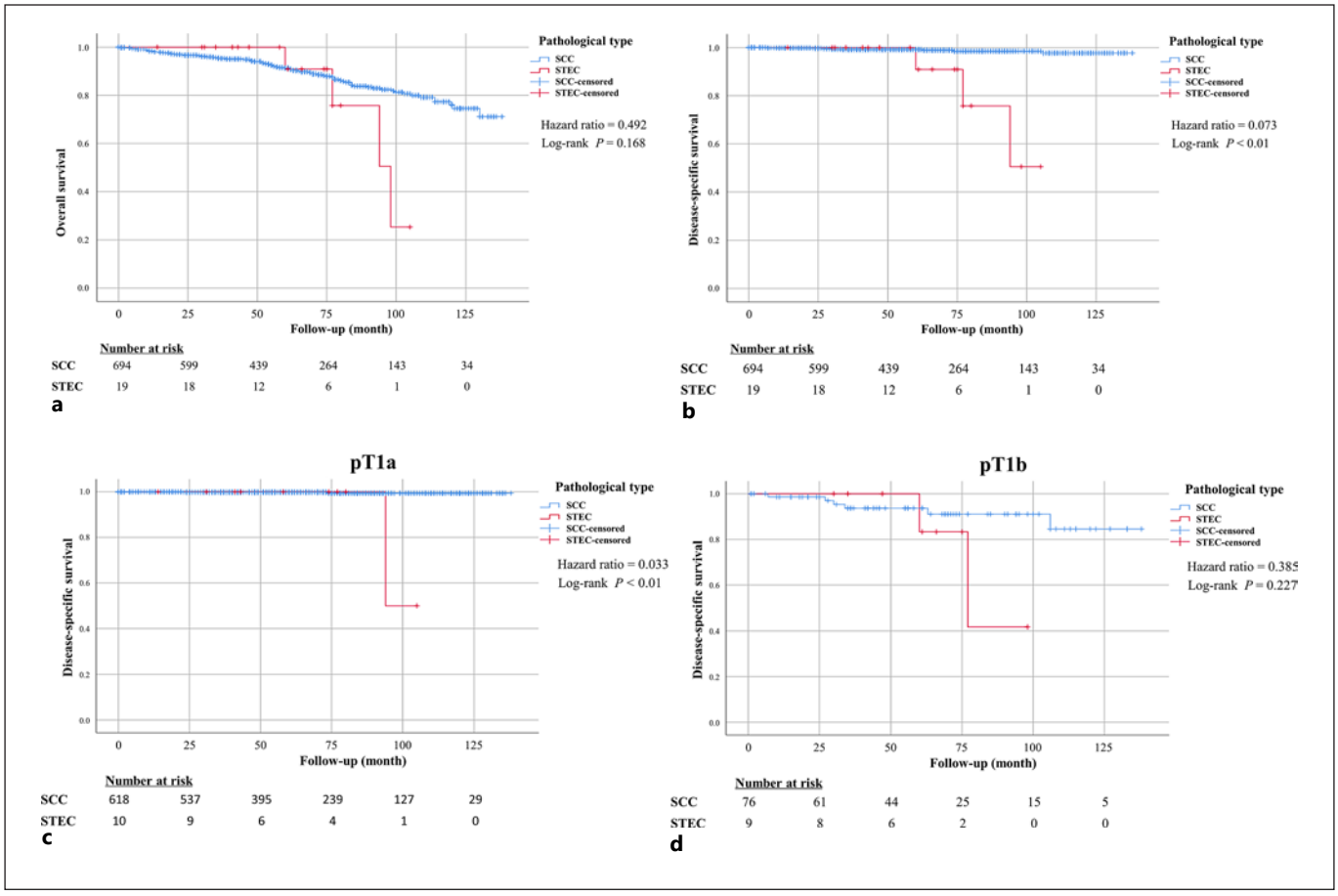

Fig. 2. Kaplan-Meier survival curves for the special type of esophageal cancer (STEC) and squamous cell carcinoma (SCC) groups. Total study population. **a** Overall survival. **b** DSS. DSS for the subgroup of patients with pT1a and pT1b diseases. **c** pT1a. **d** pT1b.

Discussion

In this study, we sought to identify the clinical presentation of STECs and the long-term outcomes of ESD by comparing our STEC data with those of common types of superficial esophageal SCC. No study has examined the long-term outcomes of ESD for STEC because of its rarity. The strength of this study is the relatively large number of cases that we collected and reviewed to compare the long-term outcomes of ESD for STECs with those of SCC and to examine prognostic factors. We showed that STEC is an independent negative prognostic factor for DSS after ESD. We also performed a stratified analysis by tumor depth and showed that STECs have a poor prognosis, even in superficial esophageal cancers that remain in the mucosal layer.

No consistent hypothesis of the histogenesis of STEC has been developed yet. Nonetheless, several origins have been postulated, such as esophageal submucosal gland cells, ductal cells, or pluripotent basal epithelial cells [8–11, 29]. Therefore, they are considered to originate deeper than the common types of esophageal epithelial tumors and to tend to invade downward. It has also been suggested that ordinary SCC may develop various types of differentiation as it progresses and that this process may lead to SCCs becoming STECs [29, 30], which are rarely detected in the early stages of disease. On the other hand, it is important to understand the clinical presentation of STECs at an early stage because recent advances in endoscopic technology are expected to permit the detection of epithelial esophageal tumors at earlier stages. In this study, 1.7% of patients who underwent ESD were diagnosed with STECs. This was comparable to the previously reported rate for all esophageal cancers, including advanced cancer [6–11]. This shows that a certain number of STECs are also present among superficial esophageal

Table 4. Results of univariate and multivariate analyses of overall survival and DSS for all patients

Variable	Univariate analysis			Multivariate analysis		
	p value	HR	95% CI	*p* value	HR	95% CI
Overall survival						
Age (continuous)	<0.01*	1.07	1.04–1.10	<0.01*	1.06	1.03–1.09
Sex (female vs. male)	0.61	0.85	0.45–1.59			
CCI (continuous)	<0.01*	1.29	1.16–1.45	<0.01*	1.19	1.06–1.34
Pathological type (SCC vs. STEC)	0.17	0.49	0.18–1.35	0.75	1.18	0.41–3.38
Tumor depth (pT1b vs. pT1a)	<0.01*	3.01	1.90–4.77	<0.01*	2.27	1.22–4.20
LVI (no vs. yes)	<0.01*	0.46	0.28–0.76	0.30	0.71	0.37–1.35
DSS						
Age (continuous)	0.17	1.05	0.98–1.13			
Sex (female vs. male)	0.59	0.57	0.07–4.42			
CCI (continuous)	0.26	0.75	0.45–1.25			
Pathological type (SCC vs. STEC)	<0.01*	0.07	0.02–0.27	0.044*	0.24	0.06–0.97
Tumor depth (pT1b vs. pT1a)	<0.01*	23.44	6.34–86.60	<0.01*	12.60	2.55–62.32
LVI (no vs. yes)	<0.01*	0.09	0.03–0.30	0.33	0.50	0.13–2.02

95% CI, 95% confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; STEC, special type of esophageal cancer. * $p < 0.05$.

cancers that are clinically diagnosed as eligible for endoscopic resection. It is interesting that all metachronous cancers in the STEC group were SCC. This may support the hypothesis of the differentiation of ordinary SCC into various types of STECs in the process of progression rather than simply the low frequency of STECs.

Histological confirmation by preoperative biopsy is often difficult for STECs. It is because that the lesion is predominantly located in the deeper layers and tends to be diagnosed as SCC only with hematoxylin and eosin staining. In this study, 94.4% of STECs were diagnosed as SCC on preoperative biopsy and in most cases were only diagnosed as STEC on pathological analysis after ESD. Therefore, it is not easy to assume STEC preoperatively because of its rarity and pathological features. Although the endoscopic findings of STECs were not significantly different from those of SCCs, there was a tendency for more cases to have an elevated appearance. We consider this to be due to the fact that STECs tend to show submucosal tumor-like elevation with downward invasion.

STECs have been reported to have a high rate of LN metastasis and a generally poor prognosis compared with the common types of esophageal cancer [7–11]. However, these studies included advanced cancer, and no studies have focused on superficial esophageal cancer. In the present study, more patients had submucosal and LVI in the STEC group than in the SCC group, and only 21% of the patients met the criteria for curative endoscopic resection. It can be inferred that STECs are associated with a high incidence of LVI, even in superficial esophageal cancers for which endoscopic resection is indicated. Furthermore, although adjuvant therapy was performed in 36.8% of the patients in the STEC group, both metastatic recurrence and disease-specific death occurred in about 15% of them, which is quite high for superficial esophageal cancer. These results suggest that superficial STEC also has a more aggressive biological behavior compared with conventional SCC.

ESD is indicated for esophageal SCCs with depths down to the muscularis mucosae (cT1a), and adjuvant therapy is recommended for patients with pT1b and/or LVI [25, 26]. On the other hand, the current guidelines do not provide detailed information on the indications for treatment or the adjuvant therapy for histological types other than the common types. As for preoperative diagnosis, magnifying endoscopy with narrow-band imaging classifications for predicting the histological invasion depth of superficial esophageal SCCs have been proposed [31–34]. For adenocarcinoma, the Japan Esophageal Society proposed a classification of Barrett's esophagus in recent years [35, 36], but no consistent findings have been reported on the clinical presentation of early-stage STECs. At present, STECs are described only in the magnifying endoscopic classification of the Japan Esophageal Society as the occasional presence of reticular pattern vessels [34]. In addition, it is difficult to histologically confirm STECs on preoperative biopsy, so it is difficult to assume the presence of STECs before treatment starts. As a result, STECs are often diagnosed on postop-

erative pathology, and information about the long-term outcomes of STECs is important when considering the treatment of superficial esophageal cancer.

In terms of long-term outcomes, our results showed that age, CCI, and tumor depth were independent negative prognostic factors for OS, whereas tumor depth and histological type were identified as independent negative prognostic factors for DSS. The Brinkman index has been suggested to be involved in the metachronous carcinogenesis of superficial esophageal SCC, and the ECOG performance status in OS [37, 38]. However, in the present study, neither the background Brinkman index nor ECOG performance status showed significant differences between the two groups. The 5-year DSS rate exceeded 90% in both groups, but subgroup analysis by depth showed that STECs with pT1a had a lower DSS rate than SCCs and that the 5-year DSS rate for STECs with pT1b was 83.3%. In addition, of the 13 STEC patients with pT1a and no LVI, disease-specific death was observed in 1 patient (7.7%) after 94 months of follow-up. This suggests that adjuvant therapy should even be considered in STEC patients with pT1a and no LVI. Because pathological type is an independent prognostic factor, it should be taken into account when considering the indication for endoscopic resection and for subsequent adjuvant therapy.

This study has some limitations. First, it was a single-center study with a retrospective and a small number of STEC cases. Because STEC is a rare type of cancer, a future multicenter study is desirable. Second, the baseline characteristics differed between the STEC and SCC groups, especially tumor depth, which is a prognostic factor for esophageal cancer. Given the pathogenesis of STEC, it is assumed that STEC tends to be detected in more advanced state than ordinary SCC. In fact, the STEC group had a significantly higher percentage of lesions invading the SM and had more LVI at the time of initial ESD. However, STEC was identified as an independent negative prognostic factor for DSS in multivariate analysis. Furthermore, in the subgroup analysis by tumor depth, STEC showed a lower DSS in cases of pT1a, which would be considered noneligible for additional treatment in the ordinary SCC. Therefore, both the malignancy of STEC itself and its tendency to be detected in an advanced state were considered to contribute to its poor prognosis. Third, there has been no consensus on the selection criteria for patients receiving adjuvant therapy after ESD. In this study, adjuvant therapy was recommended in patients that did not meet the cure criteria but was not strictly enforced if complete resection was achieved, taking into account age and comorbidities. In addition, the type of adjuvant therapy was not standardized and was based on patients' background. Fourth, the influence of metachronous esophageal cancers was not considered, and 11 lesions had invaded the submucosal layer. However, lead-time bias must be considered when examining long-term prognosis and, in this study, lesions treated for the first time were included in the evaluation.

In conclusion, although STECs are rare types of superficial esophageal cancers, endoscopic treatment was performed in 1.7% of cases with the exception of Barrett's esophageal cancer. STECs are suggested to have high malignant potential with a tendency for submucosal and LVI, even at an early stage. STEC was an independent negative prognostic factor for DSS, suggesting that adjuvant therapy should be considered after ESD, even for pT1a cancer without vascular invasion.

Statement of Ethics

This study protocol was reviewed and approved by Institutional Review Board of Toranomon Hospital, approval number [2268]. The need for informed consent was waived by the Ethics Committee of Toranomon Hospital Certified Review Board, Federation of National Public Service Personnel Mutual Aid Associations. However, patients were given the opportunity to opt out via the hospital's Website.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, methodology, writing – original draft, and writing – review and editing: Yugo Suzuki. Investigation: Yugo Suzuki, Akira Matsui, Daisuke Kikuchi, Kenichi Ohashi, and Shu Hoteya. Approval of final manuscript: Yugo Suzuki, Kosuke Nomura, Akira Matsui, Daisuke Kikuchi, Kenichi Ohashi, and Shu Hoteya.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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