

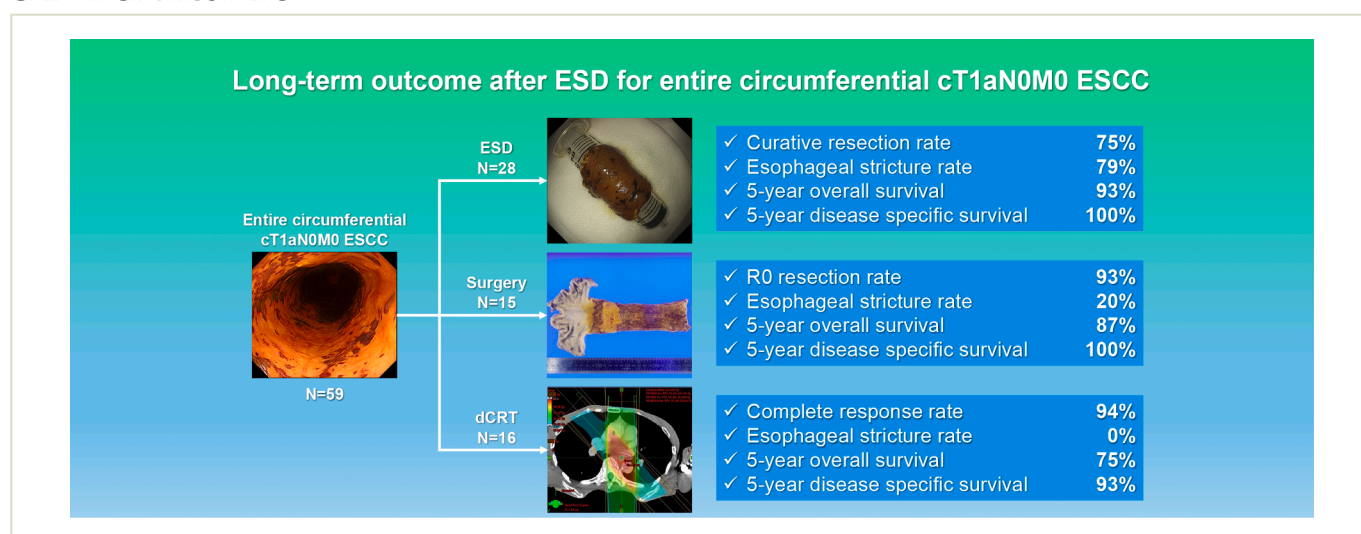


Long-term outcome after endoscopic submucosal dissection for entire circumferential cT1aN0M0 esophageal squamous cell carcinoma

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GRAPHICAL ABSTRACT



Background and Aims: Endoscopic submucosal dissection (ESD) is the standard treatment for cT1a esophageal squamous cell carcinoma (ESCC); however, its indication for the entire circumferential (EC) lesion remains controversial because of the stricture risk after ESD. Therefore, several treatments are administered on the basis of the physician's choice; the clinical course, however, remains unclear. This retrospective study aimed to clarify the long-term outcomes after ESD in patients with circumferential cT1aN0M0 ESCC compared with those after esophagectomy or chemoradiotherapy.

Methods: Patients with circumferential cT1aN0M0 ESCC treated with ESD, chemoradiotherapy, or esophagectomy as the initial treatment between January 2010 and December 2018 were included. The 5-year overall survival (OS), 5-year disease-free survival (DFS), esophageal stricture, refractory stricture, curative ESD resection, and complete response (CR) rates to chemoradiotherapy were evaluated.

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Results: Of the 59 eligible patients, 28, 15, and 16 patients received ESD, chemoradiotherapy, and esophagectomy, respectively, as the initial treatment. During a median follow-up period of 95 months, the 5-year OS/DFS was 93%/89% after ESD, 87%/87% after esophagectomy, and 75%/69% after chemoradiotherapy. The curative resection rate of ESD was 72%. The esophageal stricture/refractory stricture rates were 79%/46% after ESD, 20%/13% after esophagectomy, and 0%/0% after chemoradiotherapy. The CR rate to chemoradiotherapy was 94%.

Conclusions: The long-term outcomes of each treatment group for EC cT1aN0M0 ESCC were elucidated. The esophageal stricture and refractory stricture rates after ESD were higher than those in other patients. Further investigations in large cohorts are necessary to clarify the indication criteria for ESD in patients with lesions. (Gastrointest Endosc 2026;104:376-84.)

(footnotes appear on last page of article)

INTRODUCTION

Recent improvements in endoscopic diagnosis have enabled the early detection of many superficial esophageal squamous cell carcinomas (ESCCs). Endoscopic submucosal dissection (ESD), an endoscopic resection method for superficial ESCC, is a minimally invasive and highly effective en bloc complete resection treatment.¹ Currently, the entire circumferential (EC) ESCC (EC-ESCC) can be resected en bloc using ESD.^{2,3} However, refractory strictures often occur after ESD for EC-ESCC, which impairs quality of life.

The ESD/EMR guidelines for esophageal cancer in Japan recommend each treatment strategy based on endoscopic diagnosis for the tumor depth, circumference, and longitudinal extension.⁴ However, the indication of ESD for an EC-ESCC remains controversial because the risk of severe esophageal stricture after ESD is high, which occasionally limits the choice of additional treatment for noncurative resection after ESD.⁵⁻¹⁴ Thus, it is weakly recommended to perform ESD upon implementing prophylactic treatment against esophageal stricture for EC-ESCC with cT1a-epithelium (EP)/lamina propria mucosae (LPM) with a longitudinal extension of 50 mm or less, which is regarded as having a relatively low risk of noncurative resection and refractory stricture after ESD. In contrast, ESD is not recommended for EC-ESCC with cT1a-EP/LPM with a longitudinal diameter >50 mm or for cT1a-mucularis mucosae (MM)/T1b-SM1 (submucosal invasion depth within 200 μ m), regardless of the longitudinal diameter, because of the high risk of noncurative resection and refractory stricture after ESD. Definitive chemoradiotherapy (dCRT) and esophagectomy are the primary treatments for these lesions. However, the long-term clinical course of cT1a EC-ESCC after initial treatment (ESD, surgery, and dCRT) remains unclear, and there are no clear criteria for the initial treatment of cT1a EC-ESCC. Currently, the guidelines are not always applied in clinical practice, and the initial treatment for EC-ESCC varies among institutions. This study, therefore, aimed to clarify the long-term outcomes after ESD in patients with cT1aN0M0 EC-ESCC compared with those after surgery or dCRT.

MATERIALS AND METHODS

Patients

We retrospectively enrolled patients who met the following criteria: (1) histopathologically diagnosed with primary ESCC; (2) located at the thoracic esophagus; (3) diagnosed with an EC or subcircumferential lesion that is expected to result in an EC mucosal defect if ESD is performed; (4) tumor depth is limited to cT1a in pretreatment endoscopic findings (it can be difficult to distinguish between clinical muscularis mucosae (cMM) and cSM1 cancers during preoperative diagnosis using endoscopy; these 2 entities were therefore treated as being in the same category as cT1a)⁴; (5) absence of lymph node metastasis (LNM) or distant metastasis using contrast-enhanced CT; and (6) underwent ESD, surgery, or dCRT as the initial treatment between January 2010 and December 2018 at the National Cancer Center Hospital East. The following exclusion criteria were applied: (1) previous treatment for esophageal cancer (except for a final diagnosis of pT1a-MM or a shallower cancer without lymphovascular invasion), (2) synchronous or metachronous multiple cancers within the previous 5 years (except for stage I cancer), and (3) inability to be followed up for more than 12 months.

The optimal treatment for each patient was determined by a multidisciplinary tumor board comprising endoscopists, surgeons, medical oncologists, and radiation oncologists at our hospital. All patients were informed of the treatment's efficacy, invasiveness, and potential adverse events (AEs), and each made their decision voluntarily.

ESD procedure and prophylactic treatment against esophageal stricture after ESD

ESD was performed as previously reported.¹⁵ We used a single-channel endoscope (GIF-Q260J; Olympus, Tokyo, Japan) with an electrosurgical unit (ICC-200 and VIO-300; ERBE, Tübingen, Germany) and electrosurgical knife (Dual Knife KD-650L/IT Knife Nano KD-612; Olympus).

To prevent post-ESD strictures, steroid injections into the ulcer bed after ESD were introduced, starting in December 2009 at our institution, and furthermore, oral steroid

administration was introduced in addition to local injections, beginning in November 2012, except for those in whom steroid therapy was contraindicated. For steroid injections, 1 part triamcinolone acetonide (Kenacort, 50 mg/5 mL; Bristol-Myers Squibb Co, Tokyo, Japan) was diluted with 1 part saline solution to 5 mg/mL. We injected the solution for every 0.2 mL into the residual submucosal tissue, and either 50 or 100 mg of triamcinolone acetonide was injected in total at the discretion of the operator. As an oral steroid, prednisolone was initiated at 30 mg/d on the third post-ESD day, decreasing gradually (30, 30, 25, 25, 20, 15, 10, and 5 mg for 7 days each), and terminated after 8 weeks.

Surgical procedures

The surgical methods were thoracoscopic subtotal esophagectomy, mediastinoscopic subtotal esophagectomy, or other nonopen esophagectomies with 3-field or 2-field lymphadenectomy and reconstruction using a gastric tube or colon. No preoperative chemotherapy or chemoradiotherapy was administered. Additional surgery was performed after ESD using the same procedure.

CRT procedures

The dCRT consisted mainly of cisplatin (70 mg/m²/d, days 1 and 29) and fluorouracil (700 mg/m²/d, days 1-4 and 29-32, continuous intravenous infusion [civ]) with concurrent radiotherapy using x-rays or protons (50.4 Gy/28 F or 60 Gy/30 F). In patients receiving 60 Gy/30 F, local irradiation was performed using either x-rays or protons. In cases receiving 50.4 Gy/28 F, prophylactic irradiation to the regional lymph nodes was initially administered at a dose of 41.4 Gy/23 F using x-rays, followed by a localized boost of 9 Gy/5 F to the primary tumor site. In patients with cardiac or renal dysfunction, nedaplatin (80 mg/m²/d, days 1 and 29) and fluorouracil (800 mg/m²/d, days 1-4 and 29-32, civ) or fluorouracil alone (800 mg/m²/d, days 1-4 and 29-32, civ) were used as chemotherapy.

After completion of dCRT, in the 2 or more consecutive endoscopic examinations performed at intervals of ≥ 4 weeks, patients were determined to have complete response (CR) if all of the following findings were fulfilled: (1) all endoscopic findings suggestive of neoplastic lesions (erosive changes with irregularities, ulcerative lesions, and obvious bumps) have disappeared; (2) histopathologic biopsy of the site where the primary tumor was located before dCRT shows no evidence of cancer; (3) the entire esophagus can be observed by endoscopy; and (4) there are no endoscopic findings suggestive of active esophagitis.

Additional CRT after ESD consisted of cisplatin (70 mg/m²/d, days 1 and 29) and fluorouracil (700 mg/m²/d, days 1-4 and 29-32, civ) with concurrent radiotherapy using x-rays (41.4 Gy/23 F) covering regional lymph nodes.

Histopathologic examinations

Histopathologic evaluation was performed for all cases in which ESD or surgery was performed on the basis of the Japanese classification of esophageal cancer.¹⁶

Additional treatment after ESD was indicated if one of the following findings was met by histopathologic evaluation after ESD: (1) the tumor depth was deeper than the MM, (2) it was positive for vascular or lymphatic invasion, or (3) it was positive or difficult to evaluate for a vertical margin. In the ESD group, "curative resection" was defined when none of the aforementioned findings were met on histopathologic evaluation after resection. Patients eligible for additional treatment were recommended additional surgery or CRT, and the treatment method was selected at the patient's discretion.

Follow-up after treatments

In the ESD group, an endoscopy was performed 2 to 6 weeks after ESD to evaluate ulcer healing and assess esophageal stricture. In the dCRT and surgery groups, an endoscopy was performed in patients who experienced dysphagia to evaluate esophageal stricture. Esophageal stricture was defined as when an endoscope (GIF-Q260; Olympus) could not pass through the post-ESD region, the irradiation area, or the post-operative anastomosis. For patients with esophageal strictures in all the groups, endoscopic balloon dilation (EBD) was repeated every 2 to 4 weeks until relief of dysphagia or improvement of the stricture. All patients requiring ≥ 6 EBD procedures were defined as having refractory esophageal strictures.

After the completion of treatment, an endoscopy with iodine staining was performed to detect local recurrence and metachronous ESCC, and contrast-enhanced CT of the neck, chest, and abdomen was performed to identify lymph node and distant recurrence. In the ESD (including additional surgery or CRT after ESD), surgery, and dCRT groups, endoscopy and CT were performed every 3 to 12 months.

Ethical considerations

This was a single-center retrospective study, and the study protocol was approved by the Institutional Review Board of the National Cancer Center (approval number: 2017-434, approval date: March 7, 2018).

Statistical analysis

The primary outcome was 5-year overall survival (OS) in each treatment group. Other outcomes included 5-year disease-specific survival (DSS), 5-year disease-free survival (DFS), 5-year cumulative recurrence rate (CRR), AEs, esophageal stricture rate, refractory stricture rate, curative resection rate in the ESD group, and CR rate in the dCRT group.

The AEs of ESD, dCRT, and additional CRT after ESD were evaluated using the Common Terminology Criteria for Adverse Events version 5.0, whereas the AEs of esophagectomy were assessed using the Clavien-Dindo classification version 2.0.¹⁷ Acute AEs of dCRT were defined as events that occurred within 3 months of dCRT initiation, and late AEs as events that occurred 3 months after dCRT initiation. Acute AEs of surgery were defined as events that occurred

TABLE 1. Background characteristics of patients with entire circumferential esophageal squamous cell carcinoma in each treatment group

Characteristics	ESD (n = 28)	Surgery (n = 15)	dCRT (n = 16)	Total (n = 59)
Sex, male/female	23/5	13/2	14/2	50/9
Age, median (range)	73 (60-83)	68 (61-83)	68 (38-78)	69 (38-83)
Tumor location				
Ut	1	1	2	4 (7%)
Mt	17	9	9	35 (59%)
Lt	10	5	5	20 (34%)
Longitudinal length of tumor (mm) median (range)	50 (30-100)	90 (40-150)	90 (50-170)	70 (30-170)
Clinical depth of invasion				
cEP/LPM	19	8	6	33 (56%)
cMM/SM1	9	7	10	26 (44%)
	ESD (n = 28)	Surgery (n = 15)	dCRT (n = 16)	Total (n = 59)
Combination of longitudinal length and depth of invasion				
cEP/LPM				
≤5 cm Group A	10	0	1	11
5-10 cm Group C	9	5	3	17
>10 cm	0	2	2	4
Total	19	7	6	32
cMM/SM1				
≤5 cm Group B	7	2	0	9
5-10 cm Group D	2	3	6	11
>10 cm	0	3	4	7
Total	9	8	10	27

cEP, Clinical epithelium; cMM, clinical muscularis mucosae; dCRT, definitive chemoradiotherapy; ESD, endoscopic submucosal dissection; LPM, lamina propria mucosae; Lt, lower thoracic esophagus; Mt, middle thoracic esophagus; SM, submucosal layer; Ut, upper thoracic esophagus.

within a month of the surgery date, and late AEs as events that occurred after a month of the surgery date.

OS was defined as the period from the starting date of each treatment to death from any cause and was censored at the last contact date for a living patient. DSS was defined as the period from the date of starting each treatment to death from primary ESCC and was censored at the last contact date with a living patient or the date of death from any cause. DFS was defined as the period from the date of starting each treatment to either the first recurrence event or death from any cause and was censored at the last contact date for a living patient. Recurrence was defined as a distant metastasis, LNM, or major local recurrence. Major local recurrence was defined as a recurrence that required more invasive treatment than repeated endoscopic resection. CRR was defined as the CRR in each treatment group from the date of treatment initiation.

The ESD group was divided into 4 groups (groups A-D) according to clinical tumor depth and longitudinal length, and the curative resection, esophageal stricture, and refractory stricture rates were evaluated in each group (group A: clinical epithelium [cEP]/LPM with ≤5 cm; group B: cMM/submuco-

sal layer 1 [SM1] ≤5 cm; group C: cEP/LPM >5 cm; and group D: cMM/SM1 >5 cm).

Statistical analyses were performed using Easy R software for R (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a modified version of the R Commander, designed to add statistical functions frequently used in biostatistics.

RESULTS

Patient characteristics and initial treatment

Sixty-seven patients with ESCC met the inclusion criteria, and 8 were excluded. Ultimately, 59 patients were included (Supplementary Fig. 1, available online at www.giejournal.org, Table 1). Male patients were predominant, with a median age of 69 years (range, 38-83). The median longitudinal tumor length was 70 mm (range, 30-170). The clinical tumor depth was cEP/LPM in 33 patients and cMM/SM1 in 26 patients.

Regarding the initial treatment, 28, 15, and 16 patients underwent ESD, surgery, and dCRT, respectively. The median longitudinal tumor length in the ESD group (50 mm)

tended to be shorter than that in the surgery (90 mm) and dCRT (90 mm) groups. Regarding the clinical tumor depth, cEP/LPM accounted for a larger proportion of the tumors in the ESD (68%; 19/28) than those in the surgery (53%; 8/15) and dCRT (43%; 6/14) groups. In patients with a longitudinal tumor length >10 cm, surgery or dCRT was chosen, regardless of tumor depth.

Details of initial treatment

The en bloc resection rate was 100% in the ESD group (Table 2). As prophylactic treatment against stricture, local steroid injection was performed in all 28 patients (100%), and oral steroid administration was performed in 23 of the 28 patients (82%).

Among the 15 patients in the surgery group, 12 underwent thoracoscopic esophagectomy, and 3 underwent mediastinoscopic esophagectomy. Three-field lymph nodes dissection was the most common (87%). Most patients underwent gastric pull-up reconstruction ($n = 13$), and the colon was used as a conduit in the remaining patients ($n = 2$).

The most common chemotherapy regimen in the dCRT group was cisplatin and fluorouracil (76%), followed by nedaplatin and fluorouracil (12%) and fluorouracil alone (12%). Of the 16 patients, 15 received 2 courses, and 1 received 1 course. Regarding radiation therapy, 9 patients were treated with x-rays and 7 with protons.

Short-term outcomes

As shown in Table 3, the curative resection, esophageal stricture, and refractory stricture rates were 72%, 79%, and 46%, respectively, in the ESD group. These rates were 80%, 70%, and 30%, respectively, in group A; 43%, 86%, and 43%, respectively, in group B; 89%, 78%, and 56%, respectively, in group C; and 100% each in group D (Supplementary Table 1, available online at www.giejournal.org). The curative resection rate was 84% (16/19) for cEP/LPM lesions, whereas it was lower at 56% (5/9) for cMM/SM1 lesions. AEs included 1 patient each with perforation during ESD and bleeding after ESD (Supplementary Table 2, available online at www.giejournal.org). Among the 28 patients in the ESD group, esophageal stricture developed in 22 patients (79%), all of whom required a median of 7 (range, 1-37) EBD sessions. Ultimately, 4 patients (14%) had a dysphagia score of ≥ 2 , and esophageal stricture did not improve. Of these, 2 patients underwent placement of a biodegradable stent, and 1 patient required gastrostomy. In the remaining 1 patient, symptoms were monitored while continuing regular EBD.

The R0 resection rate in the surgical group was 93%. Esophageal stricture occurred in 3 patients (20%), and refractory stricture occurred in 2 patients (13%). Acute AEs after surgery included grade ≥ 2 anastomotic leak in 6 patients (40%), grade 2 recurrent nerve palsy in 2 patients (13%), and grade 2 chylothorax in 2 patients (13%). In the surgery group, esophageal stricture occurred in 3 of 15 patients (20%), who also required a median of 16 (range, 1-24)

TABLE 2. Details of ESD, surgery, surgery after ESD, dCRT, and additional CRT after ESD

Treatment group and details	No. of patients (%)
ESD group ($n = 28$)	
En bloc resection (%)	28 (100)
Prophylactic treatment against esophageal stricture (%)	
Local steroid injections	28 (100)
Oral steroid administration	23 (82)
Surgery group ($n = 15$)	
Operative methods	
Thoracoscopic subtotal esophagectomy	12 (80)
Mediastinoscopic subtotal esophagectomy	2 (13)
Other	1 (7)
Lymphadenectomy	
3-field	13 (87)
2-field	2 (13)
Abdominal approach	
Laparoscopy	12 (80)
Open	3 (20)
Reconstruction method	
Gastric tube	13 (87)
Colon	2 (13)
Adjuvant chemotherapy	0 (0)
Additional surgery after ESD ($n = 1$)	
Operative methods	
Open subtotal esophagectomy	1 (100)
Lymphadenectomy	
Three-field	1 (100)
Abdominal approach	
Laparoscopy	1 (100)
Reconstruction method	
Gastric tube	1 (100)
dCRT group ($n = 16$)	
Chemotherapy regimen	
Cisplatin + fluorouracil	12 (76)
Nedaplatin + fluorouracil	2 (12)
Fluorouracil	2 (12)
Radiation therapy	
X-ray	9 (56)
50.4 Gy	5
60 Gy	2
Proton	7 (44)
50.4 Gy	1
60 Gy	6
Regimen course	
2 courses	15 (91)

(continued on the next page)

TABLE 2. Continued

Treatment group and details	No. of patients (%)
1 course	1 (9)
Additional CRT after ESD (n = 3)	
Chemotherapy regimen	
Cisplatin + fluorouracil	3 (100)
Radiation therapy	
X-ray	3 (100)
41.4 Gy	3 (100)
Regimen course	
2 courses	2 (67)
1 course	1 (33)

CRT, Chemoradiotherapy; dCRT, definitive chemoradiotherapy; ESD, endoscopic submucosal dissection.

EBD sessions. Ultimately, 1 of the 3 patients had a dysphagia score of ≥ 2 without symptomatic improvement and underwent placement of a biodegradable esophageal stent.

The CR rate in the dCRT group was 94%. Acute AEs after dCRT included grade ≥ 2 esophagitis in 9 (57%), anorexia in 4 (25%), leukopenia in 13 (82%), thrombocytopenia in 2 (13%), and renal dysfunction in 1 (6%) patient.

Clinical course and long-term outcome

Overall, the median follow-up period after the initial treatment was 95 months (range, 1-154). In the ESD group, 21 patients were judged to have undergone curative resection, with the other 7 patients judged to have undergone noncurative resection by histopathologic examination after ESD (Supplementary Fig. 2, available online at www.giejournal.org). Of the 21 patients who underwent curative resection, 1 experienced liver metastasis 4 years after ESD and died of the primary disease. Of the 7 patients who underwent noncurative resection, 3 underwent additional treatment, and no recurrence was observed in all 7 patients.

In the surgery group, 2 patients had pathologic LNM in the resected specimen. None of the patients experienced any recurrence (Supplementary Fig. 3, available online at www.giejournal.org).

In the dCRT group, CR was achieved in 15 patients (CR rate: 94%) (Supplementary Fig. 4, available online at www.giejournal.org). One patient in non-CR underwent salvage ESD. Histopathologic examination after ESD revealed vascular invasion; however, the patient was observed without additional treatment and survived without recurrence. Of the 15 patients with CR, 3 had distant recurrences: 1 had lung metastasis, 1 had lung and LNM (supraclavicular lymph nodes and mediastinal lymph nodes), and 1 had iliac LNM. These patients died from the primary disease (Supplementary Table 3, available online at www.giejournal.org).

The 5-year OS rate was 92.9% (95% CI, 74.3-98.2) in the ESD group, 86.7% (95% CI, 56.4-96.5) in the surgery group, and 75.0% (95% CI, 46.3-89.8) in the dCRT group (Fig. 1). The 5-year DSS rate was 100% (95% CI, not available [N/A]), 100% (95% CI, N/A), and 93.3% (95% CI, 61.3-99.0), respectively. The 5-year DFS rate was 89.3% (95% CI, 70.4-96.4), 86.7% (95% CI, 56.4-96.5), and 68.8% (95% CI, 40.5-85.6), respectively (Fig. 2). The 5-year CRR was 3.7% (95% CI, 0.5-23.5), 0.0% (95% CI, N/A), and 14.1% (95% CI, 3.7-46.0), respectively.

DISCUSSION

In this study, we investigated the clinical course and long-term outcomes of each initial treatment group for cT1aN0M0 EC-ESCC. Half of the EC-ESCC lesions underwent ESD as initial treatment, and almost all lesions ≤ 5 cm underwent ESD. In contrast, all lesions >10 cm underwent surgery or dCRT. The ESD group showed moderate short-term outcomes, with good en bloc and curative resection rates (100% and 75%, respectively); however, the esophageal and refractory stricture rates were higher. The surgery and dCRT groups showed good short-term outcomes, with 93% R0 resection and 94% CR.

In the ESD group, the curative resection rate was higher for cEP/LPM (groups A and C) than for cMM/SM1 (groups B and D). The esophageal and refractory stricture rates tended to be higher when the longitudinal tumor length was >5 cm. Accordingly, if stricture prevention methods are improved, group C can be the first to be expanded for ESD. The indication for ESD in cMM/SM1 cases should be carefully considered. In particular, all cMM/SM1 lesions >5 cm developed refractory stricture; therefore, ESD may not be indicated, and surgery or dCRT should be selected. However, their long-term outcomes were unclear.⁴ In this study, we clarified the short-term outcomes and long-term prognosis of surgery and dCRT for cT1aN0M0 EC-ESCC. The surgery group showed good long-term outcomes with high curative efficacy. However, some postoperative AEs occurred, and loss of the esophagus decreases postoperative quality of life. In the dCRT group, the CR rate was high, without esophageal strictures. dCRT is a good option for patients with poor operative tolerance for whom ESD is not indicated. However, the long-term outcomes were worse in the dCRT group than in the other treatment groups. Possible reasons for this are that the CRT group included a large number of cMM/SM1 lesions, the lack of histopathologic evaluation that may have hindered accurate assessment of tumor depth, and all recurrent cases were distant metastases that could not be cured by salvage treatment.

Although the results suggest that ESD may be expanded to include EC-ESCC, several problems need to be resolved. First, accurately diagnosing the depth of EC-ESCC is difficult. To diagnose superficial ESCC, in addition to

TABLE 3. Short-term outcomes for each treatment group

Outcomes	ESD group (n = 28)	Surgery group (n = 15)	dCRT group (n = 16)
Curative/R0 resection or CR (%)	21/28 (75)	14/15 (93)	15/16 (94)
Esophageal stricture (%)	22/28 (79)	3/15 (20)	0/16 (0)
Refractory esophageal stricture (%)	13/28 (46)	2/15 (13)	0/16 (0)

CR, Complete response; dCRT, definitive chemoradiotherapy; ESD, endoscopic submucosal dissection.

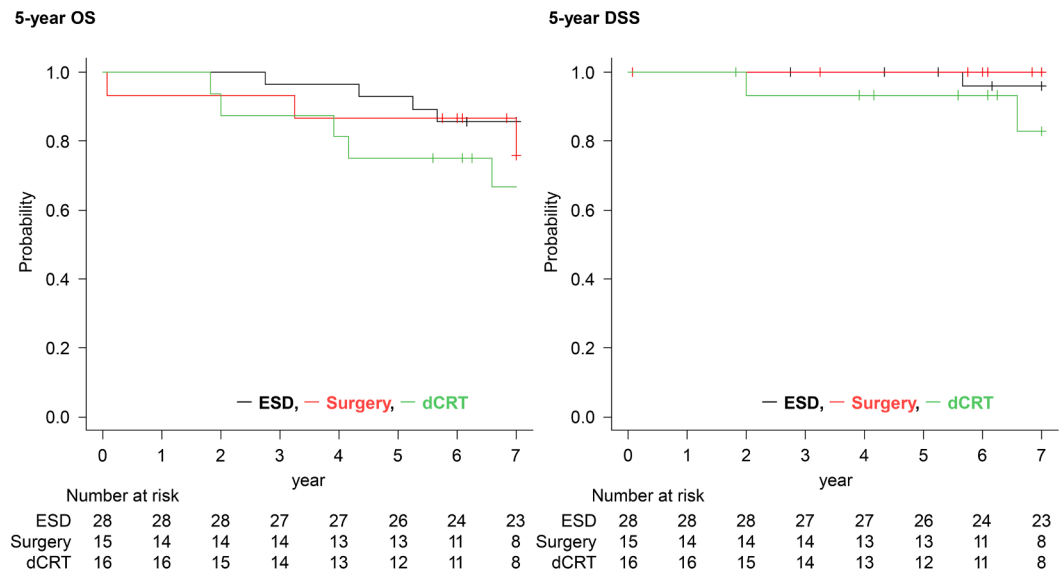


Figure 1. Five-year OS and 5-year DSS rate of each treatment group. dCRT, Definitive chemoradiotherapy; DSS, disease-specific survival; ESD, endoscopic submucosal dissection; OS, overall survival.

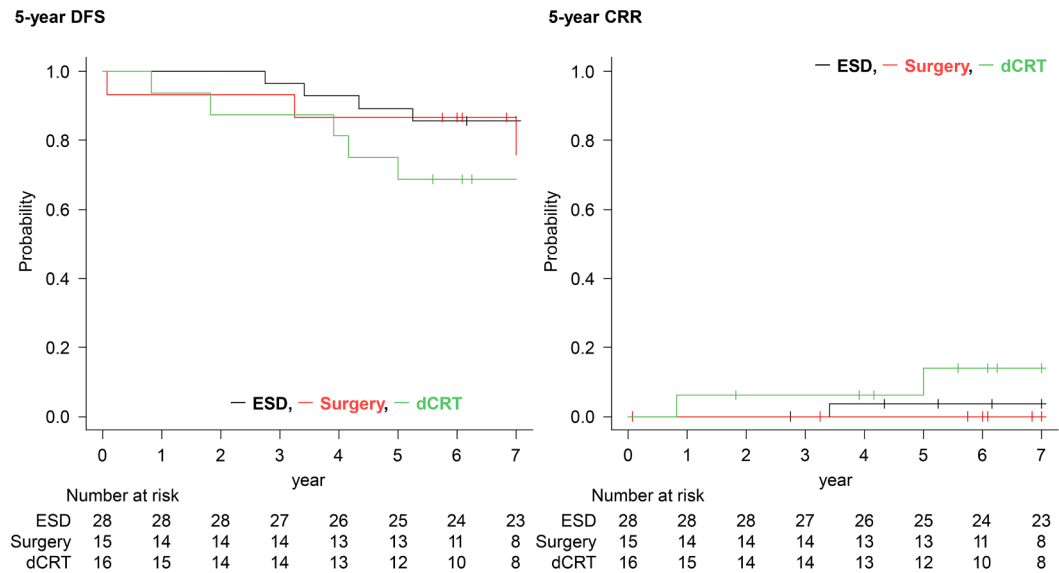


Figure 2. Five-year DFS rate and 5-year CRR of each treatment group. CRR, Cumulative recurrence rate; dCRT, definitive chemoradiotherapy; DFS, disease-free survival; ESD, endoscopic submucosal dissection.

nonmagnifying endoscopy, vessel classification in magnifying endoscopy is reportedly useful, but the diagnosis of cMM/SM1 is particularly difficult.¹⁸ The effect of EUS on cMM/SM1 cases has also been examined, but its addition was not associated with improvements in diagnostic accuracy.¹⁹ The diagnostic accuracy of the invasion depth of

cMM/SM1 with a large circumference was even lower (50%),²⁰ an issue that must be improved in the future.

Another problem is esophageal stricture after ESD. Although local steroid injection and oral steroid administration are generally used to prevent esophageal stricture after ESD for EC-ESCC, the stricture rate is reportedly high.^{10,11} Increasing the dose of oral steroids,²¹ changing the timing of steroid infusion,⁶ and changing the method of intraluminal administration, such as the filling method,²² reportedly prevent stricture after ESD. In addition to these improvements, new preventive approaches, including detachable stents,²³ polyglycolic acid sheets,²⁴ tissue-engineered cell sheets,²⁵ and swallowed topical tacrolimus,²⁶ have been reported. Establishing evidence for these novel strategies is warranted. To expand the indications for ESD of EC-ESCC, improving the method for preventing strictures after ESD is a future issue. On the basis of these findings, the treatment strategy for EC-ESCC can be summarized in [Supplementary Figure 5](#) (available online at www.giejournal.org). Group A represents the best indication for ESD. If prevention methods for strictures are improved, group C may serve as an expanded indication for ESD. In group B, the indication for ESD should be carefully determined because of the low curative resection rate and the risk of refractory stricture. For group D, ESD would be generally not indicated, and surgery or dCRT should be considered instead.

Finally, this study had several limitations. First, this was a single-center retrospective study. Treatment strategies were decided on the basis of the discussions at the multidisciplinary conference and the patient's preferences, taking into account each patient's age, medical history, performance status, and the risk of stricture and noncurative resection according to the length and tumor depth. Therefore, potential selection bias cannot be completely excluded. Consequently, caution is warranted when interpreting comparisons of long-term outcomes because patient characteristics were unbalanced among the treatment groups. Second, the number of patients was small. Similar to the first limitation, this is also one of the reasons why caution should be exercised when interpreting the results. Third, the prevention of esophageal stricture or EBD procedures has not all been carried out uniformly because of factors such as changes in the times, the patient's medical history, and the director's judgment. These factors may have influenced the outcomes related to esophageal stricture. To solve these problems, a multiinstitutional prospective observational study (UMIN000043763) evaluating the clinical course after ESD, surgery, and CRT for superficial EC-ESCC is currently being conducted by our group.

In conclusion, the long-term outcomes of each treatment group for cT1aN0M0 EC-ESCC were elucidated. If the diagnostic, technical, and oncological problems are resolved, ESD indications for EC-ESCC may expand. Thus, further in-

vestigations with a larger cohort are necessary to clarify the indication criteria for ESD in patients with lesions.

PATIENT CONSENT

All data were collected from medical records, and all procedures were performed after obtaining written informed consent from all patients.

DISCLOSURE

All authors disclosed no financial relationships.

DIVERSITY, EQUITY, AND INCLUSION

The authors are committed to promoting diversity, equity, and inclusion in research. This study was conducted with respect for all participants, without discrimination based on sex, age, ethnicity, or socioeconomic status. All eligible patients were included according to the study criteria.

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Abbreviations: AE, adverse event; cEP, clinical epithelium; civ, continuous intravenous infusion; cMM, clinical muscularis mucosae; CR, complete response; CRR, cumulative recurrence rate; dCRT, definitive chemoradiotherapy; DFS, disease-free survival; DSS, disease-specific survival; EBD, endoscopic balloon dilation; EC, entire circumferential; EP, epithelium; ESCC, esophageal squamous cell carcinoma; ESD, endoscopic submucosal dissection; LNM, lymph node metastasis; LPM, lamina propria mucosae; MM, muscularis mucosae; N/A, not available; OS, overall survival; SM1, submucosal layer 1.



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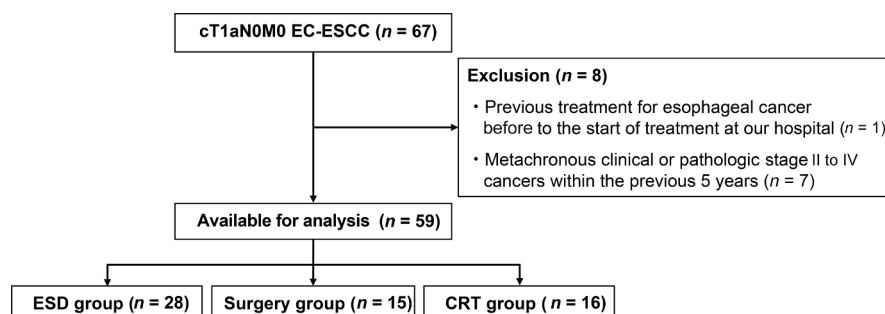
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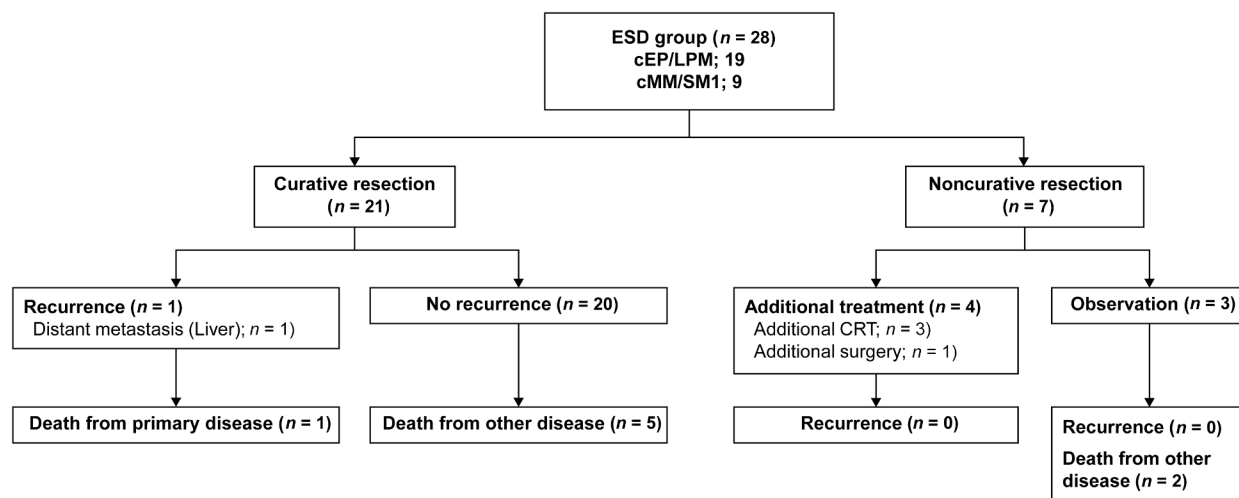
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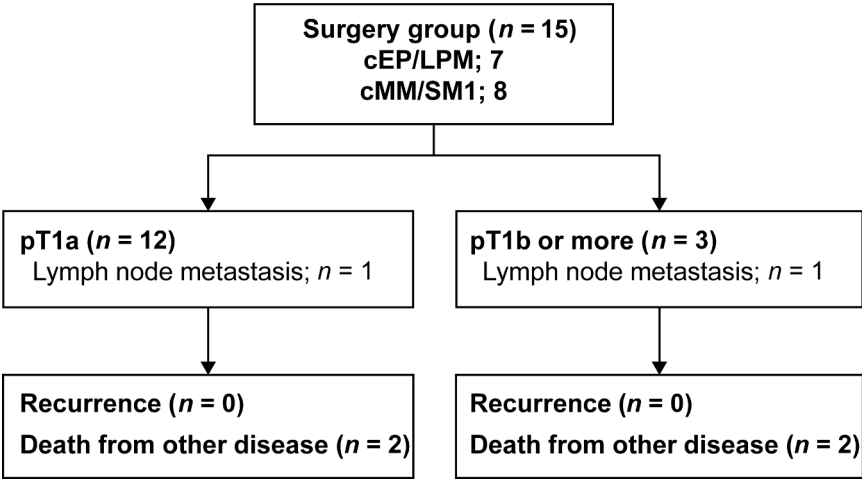




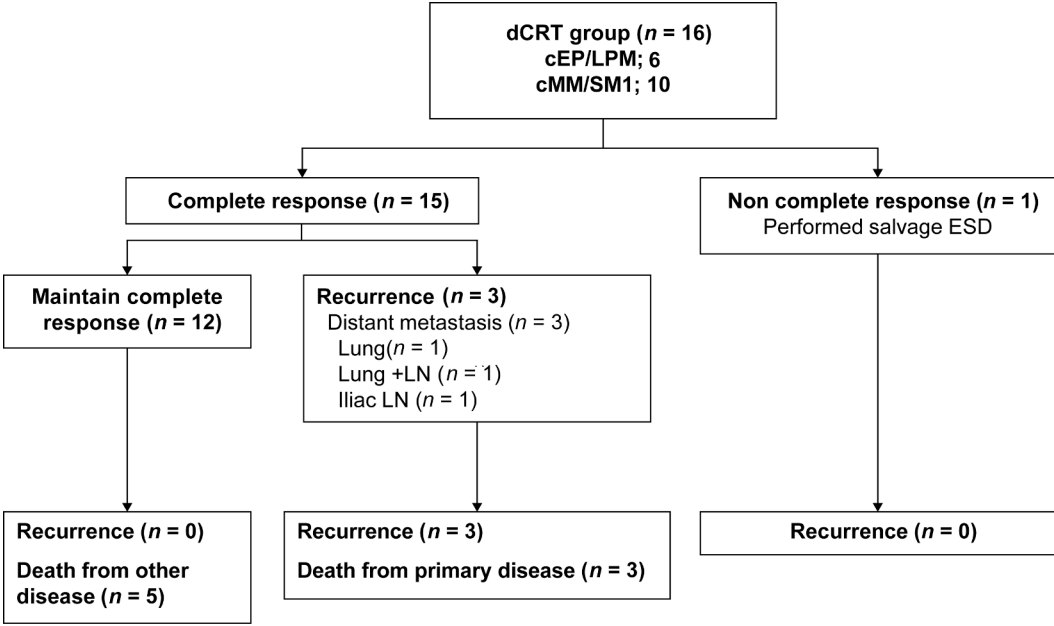
Supplementary Figure 1. The study flow diagram. *CRT*, Chemoradiotherapy; *EC-ESCC*, entire circumferential esophageal squamous cell carcinoma; *ESD*, endoscopic submucosal dissection.



Supplementary Figure 2. Clinical course of the ESD group. *cEP*, Clinical epithelium; *cMM*, clinical muscularis mucosae; *CRT*, chemoradiotherapy; *ESD*, endoscopic submucosal dissection; *LPM*, lamina propria mucosae; *SMI*, submucosal layer.



Supplementary Figure 3. Clinical course of the surgery group. *cEP*, Clinical epithelium; *cMM*, clinical muscularis mucosae; *LPM*, lamina propria mucosae; *SMI*, submucosal layer.



Supplementary Figure 4. Clinical course of the dCRT group. *cEP*, Clinical epithelium; *cMM*, clinical muscularis mucosae; *dCRT*, definitive chemo-radiotherapy; *ESD*, endoscopic submucosal dissection; *LN*, lymph node; *LPM*, lamina propria mucosae; *SMI*, submucosal layer.

		Depth of tumor	
		cEP/LPM	cMM/SM1
Length	≤5cm	Best ESD candidates	Limited indication
	>5cm	Potential for expanded indication	Not suitable for ESD

Supplementary Figure 5. A color box diagram of groups A, B, C, and D stating candidacy for ESD or surgery or dCRT. Group A: best indication for ESD, group B: limited indication for ESD, group C: potential for expanded indication for ESD if stricture prevention improves, group D: not suitable for ESD, and surgery or dCRT should be considered. *cEP*, Clinical epithelium; *cMM*, clinical muscularis mucosae; *ESD*, endoscopic submucosal dissection; *LPM*, lamina propria mucosae; *SMI*, submucosal layer.

SUPPLEMENTARY TABLE 1. Short-term outcome of each group of ESD group

ESD group (n = 28)	No. of patients (%)
Curative resection (%)	
Depth of invasion	
cEP/LPM	16/19 (84)
cMM/SM1	5/9 (56)
Group	
≤5 cm and cEP/LPM (group A)	8/10 (80)
≤5 cm and cMM/SM1 (group B)	3/7 (43)
>5 cm and cEP/LPM (group C)	8/9 (89)
>5 cm and cMM/SM1 (group D)	2/2 (100)
Esophageal stricture (%), refractory stricture (%)	
Depth of invasion	
cEP/LPM	14/19 (74), 8/19 (42)
cMM/SM1	8/9 (89), 5/9 (56)
Group	
≤5 cm and cEP/LPM (group A)	7/10 (70), 3/10 (30)
≤5 cm and cMM/SM1 (group B)	6/7 (86), 3/7 (43)
>5 cm and cEP/LPM (group C)	7/9 (78), 5/9 (56)
>5 cm and cMM/SM1 (group D)	2/2 (100), 2/2 (100)

cEP, Clinical epithelium; cMM, clinical muscularis mucosae; ESD, endoscopic submucosal dissection; LPM, lamina propria mucosa; SM, submucosal layer.

SUPPLEMENTARY TABLE 2. Adverse events for each treatment group

Adverse events	No. of patients (%)			
	Grade 2	Grade 3	Grade 4	Grade 5
ESD group (n = 28)				
During ESD perforation	1 (4)	0 (0)	0 (0)	0 (0)
Post-ESD bleeding	1 (4)	0 (0)	0 (0)	0 (0)
Surgery group (n = 15)				
Acute				
Anastomotic leak	3 (20)	3 (20)	0 (0)	0 (0)
Recurrent nerve palsy	2 (13)	0 (0)	0 (0)	0 (0)
Chylothorax	2 (13)	0 (0)	0 (0)	0 (0)
Late				
Hiatal hernia	0 (0)	1 (7)	0 (0)	0 (0)
Additional surgery after ESD (n = 1)				
Acute				
Anastomotic leak	0 (0)	0 (0)	0 (0)	0 (0)
Recurrent nerve palsy	0 (0)	0 (0)	0 (0)	0 (0)
Chylothorax	0 (0)	0 (0)	0 (0)	0 (0)
Late				
Hiatal hernia	0 (0)	0 (0)	0 (0)	0 (0)
dCRT group (n = 16)				
Acute				
Esophagitis	7 (44)	2 (13)	0 (0)	0 (0)
Anorexia	3 (19)	1 (6)	0 (0)	0 (0)
Leukopenia	10 (63)	1 (6)	2 (13)	0 (0)
Thrombocytopenia	2 (13)	0 (0)	0 (0)	0 (0)
Renal dysfunction	1 (6)	0 (0)	0 (0)	0 (0)
Late				
Pleural effusion	0 (0)	0 (0)	0 (0)	0 (0)
Pericardial effusion	0 (0)	0 (0)	0 (0)	0 (0)
Pneumonitis	0 (0)	0 (0)	0 (0)	0 (0)
Additional CRT after ESD (n = 3)				
Acute				
Esophagitis	1 (33)	0 (0)	0 (0)	0 (0)
Anorexia	1 (33)	0 (0)	0 (0)	0 (0)
Leukopenia	2 (67)	1 (33)	0 (0)	0 (0)
Thrombocytopenia	0 (0)	1 (33)	0 (0)	0 (0)
Renal dysfunction	0 (0)	0 (0)	0 (0)	0 (0)
Late				
Pleural effusion	0 (0)	0 (0)	0 (0)	0 (0)
Pericardial effusion	0 (0)	0 (0)	0 (0)	0 (0)
Pneumonitis	0 (0)	0 (0)	0 (0)	0 (0)

CRT, Chemoradiotherapy; dCRT, definitive chemoradiotherapy; ESD, endoscopic submucosal dissection.

SUPPLEMENTARY TABLE 3. Details of recurrence cases (*n* = 4)

Age	Sex	Initial treatment	Size	Depth	Ly/V	Additional treatment after ESD	Time to Rec (mo)	Site of Rec	Treatment for Rec	Clinical course
63	M	ESD	58	cSM1	0/0	Obs	41	Liver	Chemo	Death from ESCC
61	M	dCRT	120	cMM	N/A	N/A	60	LN (Iliac)	Chemo	Death from ESCC
66	M	dCRT	70	cSM1	N/A	N/A	10	Lung	BSC	Death from ESCC
76	M	dCRT	90	cSM1	N/A	N/A	91	Lung LN	BSC	Death from ESCC

BSC, Best supportive care; *Chemo*, chemotherapy; *cMM*, clinical muscularis mucosae; *cSM*, clinical submucosal layer; *dCRT*, definitive chemoradiotherapy; *ESCC*, esophageal squamous cell carcinoma; *ESD*, endoscopic submucosal dissection; *LN*, lymph node; *Ly*, lymphatic invasion; *M*, male; *N/A*, not available; *Obs*, observation; *Rec*, recurrence; *V*, vascular invasion.