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CLINICAL—ALIMENTARY TRACT

Efficacy of Endoscopic Resection and Selective Chemoradiotherapy for Stage I Esophageal Squamous Cell Carcinoma

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BACKGROUND & AIMS: Esophagectomy is the standard treatment for stage I esophageal squamous cell carcinoma (ESCC). We conducted a single-arm prospective study to confirm the efficacy and safety of selective chemoradiotherapy (CRT) based on findings from endoscopic resection (ER). **METHODS:** We performed a prospective study of patients with T1b (SM1–2) N0M0 thoracic ESCC from December 2006 through July 2012; 176 patients underwent ER. Based on the findings from ER, patients received the following: no additional treatment for patients with pT1a tumors with a negative resection margin and no lymphovascular invasion (group A); prophylactic CRT with 41.4 Gy delivered to locoregional lymph nodes for patients with pT1b tumors with a negative resection margin or pT1a tumors with lymphovascular invasion (group B); or definitive CRT (50.4 Gy) with a 9-Gy boost to the primary site for patients with a positive vertical resection margin (group C). Chemotherapy comprised 5-fluorouracil and cisplatin. The primary end point was 3-year overall survival in group B, and the key secondary end point was 3-year overall survival for all patients. If lower limits of 90% confidence intervals for the primary and key secondary end points exceeded the 80% threshold, the efficacy of combined ER and selective CRT was confirmed. **RESULTS:** Based on the results from pathology analysis, 74, 87, and 15 patients were categorized into groups A, B, and C, respectively. The 3-year overall survival rates were 90.7% for group B (90% confidence interval, 84.0%–94.7%) and 92.6% in all patients (90% confidence interval, 88.5%–95.2%). **CONCLUSIONS:** In a prospective study of patients with T1b (SM1–2) N0M0 thoracic ESCC, we confirmed the efficacy of the combination of ER and selective CRT. Efficacy is comparable to that of surgery, and the combination of ER and selective CRT should be considered as a minimally invasive treatment option. UMIN-Clinical Trials Registry no.: UMIN000000553.

Keywords: Esophageal Neoplasms; Nonsurgical Treatment; Minimally Invasive; Histologic Evaluation.

The survival rate for esophageal cancer patients is very poor (overall 0.88 mortality/incidence ratio and an estimated 400,000 deaths and 456,000 new cases

Abbreviations used in this paper: **AE, adverse event; CI, confidence interval; CRT, chemoradiotherapy; ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; ESD, endoscopic submucosal dissection; LVI, lymphovascular invasion; OS, overall survival.**

Most current article

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Esophagectomy is the standard treatment for stage I esophageal squamous cell carcinoma (ESCC).

NEW FINDINGS

The combination of diagnostic endoscopic resection (ER) and selective chemoradiotherapy (CRT) achieved effective survival compatible to esophagectomy and could be minimally invasive treatment strategy.

LIMITATIONS

This study is not a randomized controlled trial to directly compare the efficacy and safety of surgery. This study included only patients with shallow submucosal (SM1-2) invasive tumor.

IMPACT

This treatment strategy might be a standard option for clinically suspected T1b (SM1–2) N0M0 ESCC as a minimally invasive approach that can be tailored to each patient.

worldwide in 2012[1]) because most patients are diagnosed at an advanced stage; therefore, early detection is critical for improving patient survival. Recent endoscopic imaging technologies have enabled the early detection of esophageal squamous cell carcinoma (ESCC),[2] but raise new questions related to how early ESCC is managed because it can be treated with different therapeutic modalities, such as endoscopic resection (ER), surgical resection, and chemoradiotherapy (CRT).

Clinical stage I (T1N0M0) ESCC can be treated with surgery, with a 5-year survival rate of 70%–80%[3–5]; however, at times the pathologic diagnosis after surgical resection reveals mucosal (T1a) cancer without lymph node metastasis,[3] which indicates that some stage I ESCC patients have the potential to be treated using less-invasive procedures, such as ER alone. Conversely, CRT is also a curative treatment option for stage I ESCC; however, local control of CRT was not good, even in stage I ESCC.[6]

ER has the advantage of being able to evaluate the actual depth of tumor invasion and the presence or absence of lymphovascular invasion (LVI) using the resected specimen. In addition, it has a local therapeutic effect by removing the primary tumor. ER is now one of the standard treatments for T1a ESCC and can remove the shallow submucosal (T1b: SM1–2) ESCC.

If clinically suspected shallow T1b (SM1–2) ESCC is histologically diagnosed as T1a after ER, the patient can be followed up without additional treatment, such as surgery or CRT. If the removed ER specimen was diagnosed as pathologic T1b (pT1b) with a negative margin, the patient has a low risk of local recurrence but a high risk of lymph node metastasis (20%–40%).[7–10] Furthermore, even in pT1a ESCC cases, the presence of LVI is known to increase the incidence of lymph node metastasis.[8–11] For patients with pT1b or pT1a ESCC involving LVI, subsequent CRT with elective nodal irradiation might reduce lymph node metastasis. If the ER specimen showed positive vertical margins, the patient has a risk of local recurrence. For these patients, definitive CRT or surgery is indicated. This strategy of selective CRT based on diagnostic ER could be an ideal minimally invasive treatment for clinical stage I ESCC, however, this strategy has not been proven prospectively.

Based on these possible strategies, we conducted a multicenter, single-arm prospective confirmatory study to evaluate the efficacy and safety of selective CRT based on diagnostic ER for clinical T1b (SM1–2) ESCC.

Methods

Study Design and Participants

This was a multi-institutional, single-arm prospective confirmatory study conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Studies Involving Human Subjects. The Institutional Review Boards of all participating hospitals approved the study protocol. The staging and evaluation of the depth of cancer invasion were based on the Japanese Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus[12] (Supplementary Figure 1).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: histologically proven squamous cell carcinoma or basaloid cell carcinoma based on biopsy and main tumor depth of invasion noted as cSM1–2 by endoscopic ultrasound. Other detailed eligibility and exclusion criteria are provided in the Supplementary Material.

Because patient recruitment and accrual were slow, the study protocol was revised in August 2008 and the eligibility criteria were expanded to include patients with basaloid cell carcinoma and multiple Lugol-voiding lesions.

Procedures

ER was indicated within 30 days after registration and was conducted in an inpatient setting (details of the ER procedure are provided in the Supplementary Material). Based on the histologic evaluation, additional treatment was selected according to the following criteria: group A, tumors limited to pT1a with negative resection margins and no LVI were followed up without additional treatment; group B, prophylactic CRT was indicated for patients with tumors at pT1b (SM1–2) with negative resection margins or pT1a with LVI; and group C, definitive CRT for patients with tumors with positive vertical resection margins or uncollectible or uncertain margins for determining cancer-free status. Figure 1 shows the study flow diagram.

CRT was initiated between 29 and 70 days after ER, and within 14 days of the examination if the following criteria were met: Eastern Cooperative Oncology Group Performance Status, 0 or 1; scarring of the artificial ulcer after ER, and white blood cell count $\geq 3.5 \times 10^9$ cells/L; platelet count $\geq 100 \times 10^9$ cells/L; hemoglobin ≥ 100 g/L; alanine transaminase and aspartate transaminase ≤ 100 IU/L; total bilirubin ≤ 25.7 μmol/L; and estimated creatinine clearance ≥ 60 mL/min.

The chemotherapy regimen comprised continuous intravenous administration of 5-fluorouracil (700 mg/m^2/d, days 1–4

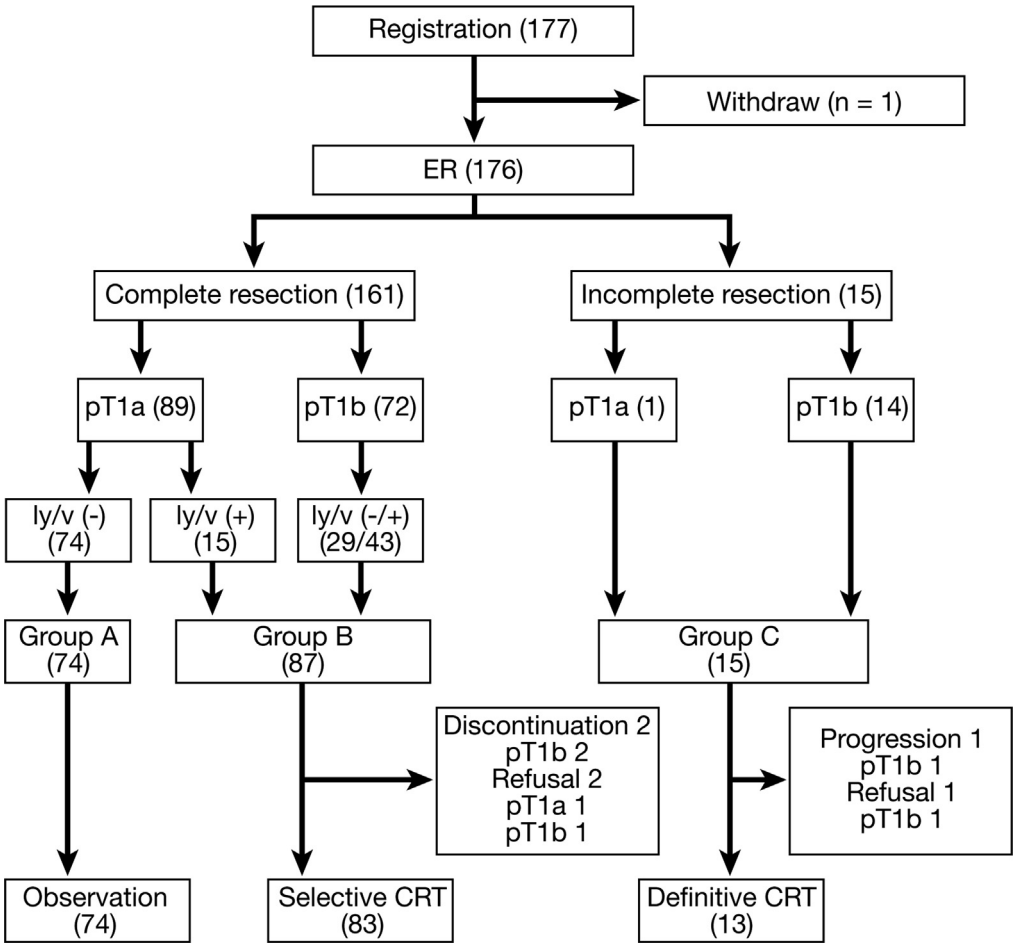

Figure 1. Patient flow diagram. ly/v, lymphovascular invasion.

and 29–32) and bolus injection of cisplatin (70 mg/m^2/d, days 1 and 29). Chemotherapy and radiotherapy were initiated simultaneously on day 1; there was no scheduled intermission for radiotherapy. The dosage of radiotherapy was 41.4 Gy in 23 fractions over 5 weeks for prophylactic CRT (group B) and 50.4 Gy in 28 fractions over 6 weeks for definitive CRT (group C), delivered with megavoltage equipment ($\geq$6 MV). The Supplementary Material provides the radiotherapy details.

Pretreatment diagnostic radiographs, radiotherapy planning materials, and charts of the total radiotherapy course were collected for quality assurance. Quality assurance reviews were conducted regularly at the radiotherapy support center in Tokyo, Japan, with feedback sent to each institution by the radiotherapy study coordinator (NK).

Outcomes

Initially, the primary end point was 3-year overall survival (OS) in patients with negative resection margins and pT1b (SM1–2) ESCC to evaluate whether the low-dose CRT (41.4 Gy) strategy is equivalent to surgery. OS was defined as the time from enrollment to death from any cause or to the last contact with a surviving patient. When the study was designed, the prognosis of mucosal cancer with LVI was not clearly understood; therefore, those patients were not initially included in the primary analyses. However, after the study was initiated, few studies on lymph node metastasis of Tis/T1a ESCC after surgery had reported that the risk of lymph node metastasis was high, even in pT1a with LVI similar to pSM1–2,[8–11] therefore, the protocol for the current study was amended in December 2009 to include patients with pT1a ESCC with LVI for analysis of the primary end point.

Key secondary end point was 3-year OS in all the enrolled patients to evaluate whether this step-up strategy is equivalent to surgery. Other secondary end points were progression-free survival, adverse events (AEs) of ER, and AEs of CRT. AEs and adverse reactions were evaluated using the Common Terminology Criteria for Adverse Events 3.0. After completion of the protocol treatment, patients were followed up without any treatment Follow-up was planned for every 4 months after ER for 3 years in all enrolled patients with physical examination; upper gastrointestinal endoscopy; computed tomography of the neck, chest, and abdomen; and the tumor marker (SCC). After 3 years, follow-up was continued at least every 6 months to determine patient survival and disease recurrence. Progression was defined by imaging or clinical deterioration. An increase in the tumor marker alone without evidence of recurrence from radiographs was not considered to be progression. Metachronous development of clinical T1a ESCC in other sites was also not considered to be progression because it could be curatively removed using ER. If the patient relapsed during the observation period, subsequent treatment, including salvage surgery or chemotherapy, could be decided by his or her physician.

Table 1. Patient and Lesion Characteristics

Characteristic	Data
Median age, *y* (IQR) (range)	63 (59–67) (42–75)
Sex, n	
Male	147
Female	30
ECOG Performance Status, n	
0	177
1	0
Histologic type, n	
SCC	177
Multiple lesions, n	
Yes	19
1 lesion/2 lesions	12/7
No	158
Tumor location, n	
Upper	16
Middle	120
Lower	41
Macroscopic type, n	
0–I	19
0–IIa	30
0–IIb	4
0–IIc	124
Clinical diagnosis of invasion, n	
SM1	114
SM2	63
Diameter of tumor, *cm*, median (IQR) (range)	2.5 (1.7–3.0) (0.5–5.0)
Circumference of tumor, n	
≤1/4	72
>1/4, ≤1/2	82
>1/2, ≤3/4	23

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Table 2. Results of Endoscopic Resection for the Main Primary Tumor (n = 176)

Variable	Data
Method of ER, n	
EMR	35
ESD	141
Type of resection, n	
En bloc resection	161
Piecemeal resection	15
Diameter of mucosal defect, *cm*, median (IQR) (range)	4.0 (3.0–5.0) (1.0–10.0)
Circumference of mucosal defect, n	
≤1/4	23
>1/4, ≤1/2	74
>1/2, ≤3/4	59
>3/4	20
Pathologic invasion, n	
EP (M1)	3
LPM (M2)	31
MM (M3)	56
SM1	17
SM2	69
LVI, n	
Positive	68
Negative	108
Lateral resection margin, n	
Positive or uncertain	29
Negative	147
Vertical resection margin, n	
Positive or uncertain	15
Negative	161

EMR, endoscopic mucosal resection.

Statistical Analyses

This study was designed to investigate whether the 3-year OS of patients in group B was comparable to or better than that of surgery. The 3-year OS of all of the enrolled patients was evaluated as the key secondary end point. It is clinically preferable to evaluate the OS after 5 years rather than after 3 years; however, we deemed it important to obtain results as soon as possible and, thus, designated the primary end point as 3-year OS. To be clear, follow-up was conducted for another 2 years after the primary analysis, and clinically relevant 5-year OS will be evaluated 5 years after registration in the study.

Based on the results among the surgically treated patients with pT1b (pSM1–3) esophageal cancer, the 3-year OS threshold was estimated to be 80%.[3,4] The expected 3-year OS was set as 90% based on the Japan Clinical Oncology Group Study (JCOG9708) of stage I ESCC patients treated with CRT,[6] and the expected OS in the current study was estimated to be better than that in previous reports because patients with deeper SM (SM3) ESCC were not enrolled; therefore, the required sample size was 82 for the primary analysis (group B), with a one-sided α of .05 and power of 90%. To maintain the power for the key secondary end point with the same expected outcome and a 3-year OS threshold rate of 80%, the total sample size was 137 patients with a one-sided $\alpha = .05$ and power of at least 90%, considering that the patients in group B would constitute approximately 60% of all the enrolled patients. We continued to accrue patients in the study until at least 82 were enrolled in group B. Only when a lower limit of a 90% confidence interval (CI) exceeded the threshold of 80% for the primary end point, could the test for the key secondary end point be conducted using the hierarchical method with the study-wise α error at a nominal level (1-sided 5%). The Kaplan–Meier method was used to estimate OS, and Greenwood's formula was used to estimate CI for the 3-year OS. If the lower limits of 90% CI in both the primary and key secondary end points exceeded the 80% threshold, a diagnostic ER plus selective CRT would be considered as a new treatment option.

Demographic data on the patients, procedures, and ER pathologic data and on the ER and CRT outcomes and safety data were collected. SAS, version 9.2 (SAS Institute, Cary, NC) was used to perform all statistical analyses. This trial was registered with the UMIN-Clinical Trials Registry (UMIN000000553). All authors had access to the study data and have reviewed and approved the final manuscript.

Results

In this study, 177 patients were enrolled from 23 institutions between December 21, 2006 and July 13, 2012.

Table 3. Adverse Events Associated With Endoscopic Resection and Chemoradiotherapy

Variable	Grade 1, n	Grade 2, n	Grade 3, n	Grade 4, n	Grade 3–4, %
AEs associated with ER					
Intraoperative					
Hypoxia	—	1	0	0	0
Perforation, esophagus	0	2	0	0	0
Hemorrhage/bleeding associated with surgery	—	—	0	0	0
Intraoperative injury, esophagus	3	0	0	0	0
From the end of ER to discharge					
Fever	17	1	0	0	0
Heartburn	13	1	0	-	0
Pain, esophagus	60	8	0	0	0
Hemorrhage/bleeding associated with surgery	—	—	0	0	0
From discharge to CRT start					
Stricture/stenosis, esophagus	16	18	1	0	0.6
AEs associated with CRT					
Acute AEs					
Neutrophils	29	37	22	0	22.9
Hemoglobin	19	9	1	0	1.0
Platelets	27	7	4	0	4.2
Creatinine	30	3	0	0	0
Hyponatremia	47	-	7	0	7.3
Fever	8	2	0	0	0
Esophagitis	29	21	4	0	4.2
Dysphagia	23	11	2	0	2.1
Anorexia	27	26	7	0	7.3
Nausea	27	14	2	0	2.1
Mucositis/stomatitis	17	4	1	0	1.0
Pain, esophagus	17	8	1	0	1.0
Infection with grade 3 or 4 neutrophils	—	0	1	0	1.0
Late AEs					
Cardiac ischemia/ infarction	0	1	1	1	2.1
Pericardial effusion (non-malignant)	5	—	0	0	0
Pneumonitis	26	3	1	0	1
Pleural effusion (non-malignant)	5	2	0	0	0

NOTE. AEs were evaluated using Common Terminology Criteria for Adverse Events 3.0.

One patient withdrew consent before treatment, therefore, 176 patients underwent ER. Patients and lesion characteristics are presented in Table 1.

The results of ER for primary lesions are shown in Table 2. Endoscopic mucosal resection and endoscopic submucosal dissection (ESD) were performed on 35 and 141 patients, respectively. En bloc resection was possible in 161 (91.0%) patients. Pathologic invasion of epithelial layer/lamina propria mucosae/muscularis mucosae/SM1/SM2 (Supplementary Figure 1) was found in 3, 31, 56, 17, and 69 cases, respectively. Sixty-eight (38.6%) patients had LVI.

AEs of ER are summarized in Table 3. Although no grade $\geq$3 AEs were reported either intraoperatively or postoperatively during hospitalization, 1 patient suffered from grade 3 esophageal stenosis after discharge, despite repeated endoscopic balloon dilation; additional selective CRT was refused. Among the patients with grade 1–2 stenosis after ER, there was no case in which the stricture became worse during or after CRT.

The study flow diagram is shown in Figure 1. Among the patients who achieved complete resection, 89 (55.3%) were diagnosed with pT1a ESCC. Seventy-four of these patients without LVI were followed up without needing additional treatment (group A). Prophylactic CRT (group B, primary analysis) was indicated in 15 patients with pT1a ESCC who had LVI and 72 (44.7%) with pT1b ESCC with complete resection. Definitive CRT (group C, Figure 1) was indicated in only 15 patients.

The median period from ER to the start of additional CRT was 54 days (range, 34–71 days), and there was no difference between groups B and C (median, 54 vs 50 days).

No patient died from treatment-related causes within 30 days after the last day of treatment.

Four patients in group B and 2 patients in group C did not receive the protocol treatment (refusal as a result of AEs, n = 3; discontinuation as a result of AEs, n = 2; disease progression, n = 1). Finally, treatment safety was analyzed in 96 patients who underwent selective CRT. All patients completed the planned radiotherapy. Although all patients completed the first course of chemotherapy, 13 who received prophylactic CRT and 2 who received definitive CRT did not receive a second course of chemotherapy because of AEs (leukocytopenia, n = 10; anorexia and fatigue, n = 2; visual impairment, n = 1; treatment refusal, n = 2). Table 3 summarizes the acute and late AEs

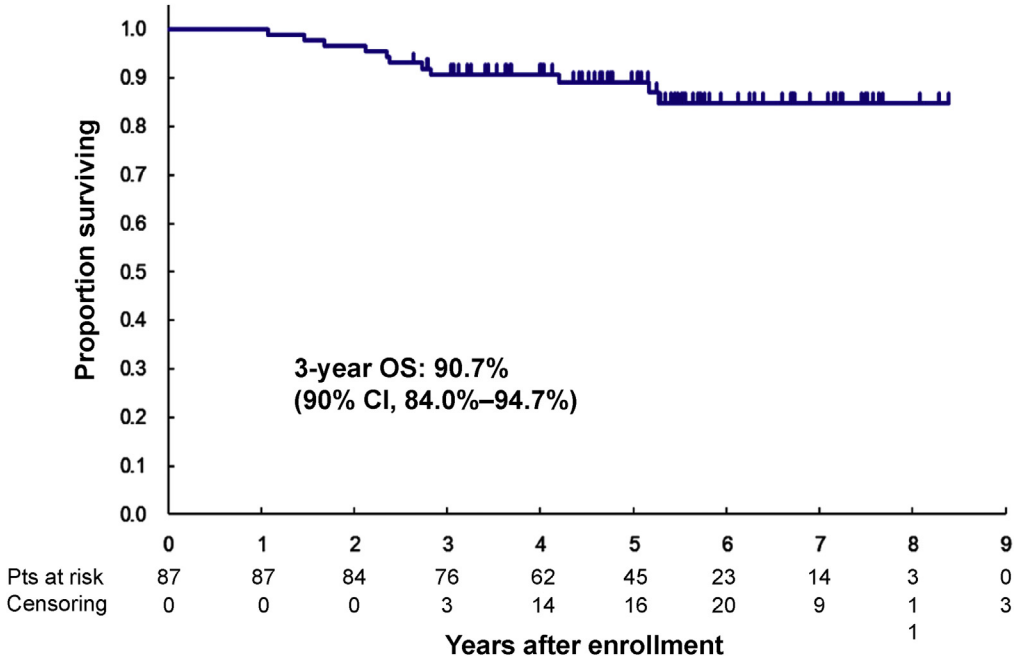

Figure 2. OS of patients with selective CRT (group B, n = 87). Patient enrollment period was between December 21, 2006 and July 13, 2012. Data cutoff day was July 14, 2015. Pts, patients.

from CRT. There were no grade 4 acute AEs reported. Although cardiac- and lung-associated late AEs at grades ≥2 were observed in 8 (8.3%) patients, and 1 patient suffered grade 4 cardiac ischemia, none died from these AEs.

The data cutoff was July 14, 2015. The 3-year OS rate among the 87 patients in group B was 90.7% (90% CI, 84.0%–94.7%; Figure 2). The key secondary end point of 3-year OS among all of the enrolled patients was 92.6% (90% CI, 88.5%–95.2%; Figure 3). The lower limits of 90% CI in both the primary and key secondary end points exceeded the 80% threshold, therefore, the hypothesis of this study was proven.

Metastatic recurrence was observed in 15 (8.5%) of all the enrolled patients, including 1, 10, and 4 patients in groups A, B, and C, respectively. The recurrence sites were cervical, thoracic, and abdominal lymph nodes in 2, 8, and 6 patients, respectively. Organ metastasis appeared in 5 patients, 4 of which were simultaneous with lymph node metastasis with the liver in 2 patients, with the lung in 2 patients, with the pleura in 1 patient, and with bone in 1 patient. Seven patients with recurrent cancer in only the lymph nodes underwent salvage surgery, and 2 were alive at the final follow-up. Three (1.7%) patients had local recurrence, 2 of which were resectable using local treatment, including ER. The 3-year progression-free survival rate for all of the enrolled patients was 89.7% (95% CI, 84.2%–93.4%; Figure 4), which did not include the recurrence that could be treated with curative resection.

Eighteen patients died during the study period up to the cutoff date. Eleven patients died of esophageal cancer, comprising 1, 7, and 3 patients in groups A, B, and C, respectively. Five patients died of other causes (brain hemorrhage, bile duct cancer, acute pancreatitis, and pneumonia in 2, 1, 1, and 1, respectively). Two patients died of unknown causes.

Quality assurance data on radiotherapy were determined to be fully evaluable in 96 patients. Eighty-six (90%) patients were assessed as acceptable per protocol or acceptable with variation. Among the 10 (10%) patients assessed as having unacceptable variations, anterior–posterior opposite portals were used in 9 for the middle or lower thoracic primary site, and the clinical target volume coverage was inadequate in 1 patient.

Discussion

The current study showed that the new treatment strategy of selective CRT based on histologic evaluation using diagnostic ER provided survival rates comparable to those of surgery. In addition, the 3-year OS among all the enrolled patients was equal to that of surgery; therefore, the nonsurgical treatment strategy of CRT selection based on a diagnostic ER should be considered for standard minimally invasive treatment.

Clinically, it is recommended that the majority of patients with ESCC that is suspected to have invaded the submucosa undergo surgery, even those without lymph node metastasis; however, some patients revealed mucosal cancer after histologic evaluation. Indeed, about one-half of the patients with clinical T1b (SM1–2) ESCC were diagnosed with pT1a ESCC in this study. For these patients, surgery might be an overly aggressive curative treatment, and ER can be the first choice for treatment to preserve the organ.

Conversely, accurate discrimination of tumor invasion into the submucosa vs into the mucosa has been clinically challenging. Furthermore, compared to surgery, ER is evidently less invasive, therefore, this line of treatment

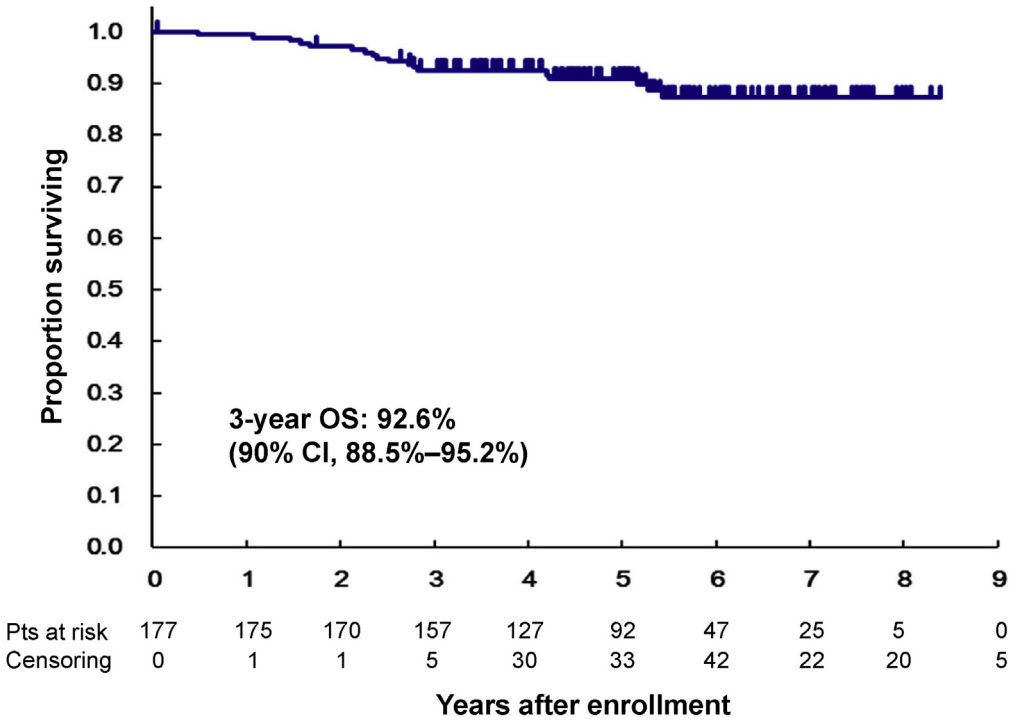

Figure 3. OS of all the enrolled patients (key secondary end point, n = 177). Pts, patients.

should be considered as not only that of choice but also as a tool for the histologic evaluation of tumor invasion, which can help advise and allow for the selection of the next appropriate treatment in ESCC patients.

Selective CRT after ER has several merits over definitive CRT. First, complete removal of the primary tumor might reduce local failure after CRT. Second, the irradiation boost dosage to the primary site can be reduced, with an expected decrease in radiation-related AEs. In contrast, definitive CRT is indicated to achieve a complete response because of the risk of local recurrence in patients if the tumor shows positive vertical resection margins or is uncollectible or uncertain for cancer-free margins.

The efficacy of adding CRT after ER has been reported[13–15]; however, these were single-institution retrospective analyses. Shimizu et al[13] have reported that the 5-year OS of the

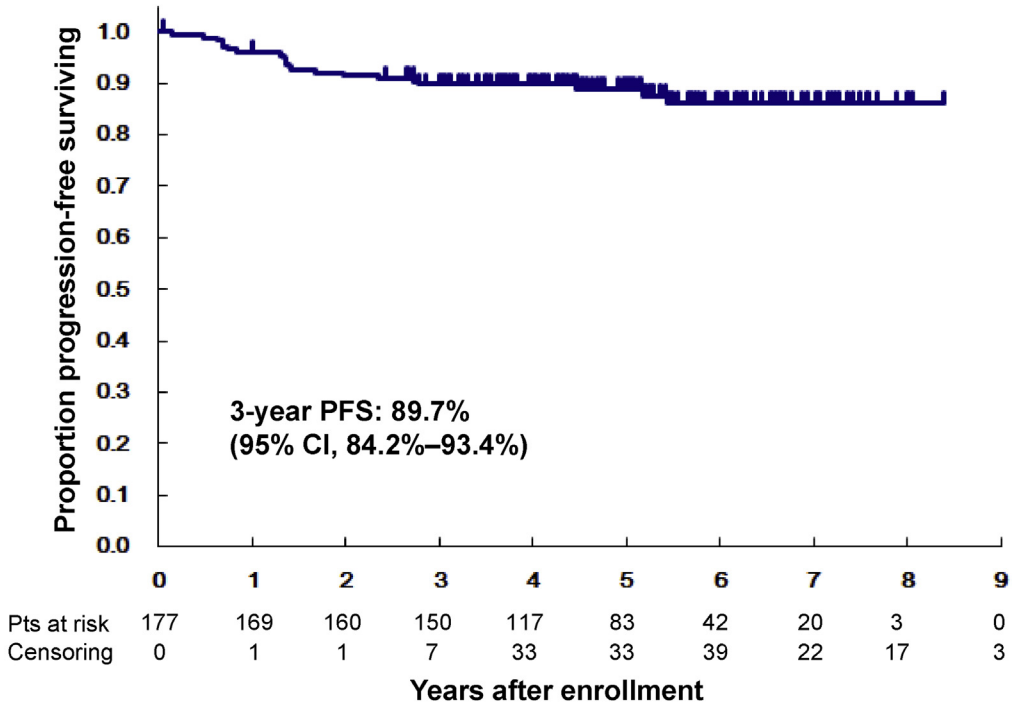

Figure 4. PFS of all the enrolled patients (secondary end point, n = 177). PFS, progression-free survival; Pts, patients.

patients who received ER combined with CRT for ESCC that invaded from the muscularis mucosae to the upper submucosa was equivalent to that from surgery (100% and 87.5%, respectively). Kawaguchi et al[14] have reported that the 3-year OS of ESD followed by CRT for patients with a tumor that invaded the submucosal layer (T1b) or muscularis mucosae with LVI was higher than that from definitive CRT (90.0% vs 63.2%, respectively). Local recurrence in the definitive CRT group (19%) was significantly higher than that in the ESD–CRT group (0%) ($P = .029$). Yoshimizu et al[15] have also reported that the 5-year relapse-free survival in the ER–CRT group was significantly more favorable than that in the definitive CRT group (85.1% vs 59.2%, respectively; $P < .05$). Taken together, the OS from ER followed by CRT has the potential to be equivalent to that of surgery and the relapse-free survival rate is better than that of definitive CRT.

As a primary treatment, definitive CRT can be indicated in patients with clinically suspected stage I (T1bN0M0) ESCC. Kato et al[6] have reported the CR rate of definitive CRT for clinical stage I ESCC as 87.5% (63 of 72); however, 30.6% (22 of 72) of the patients developed local failure. Among those with local failure, 72.7% (16 of 22) underwent salvage endoscopic treatment and the other patients underwent salvage surgery. This finding suggests that despite the high CR rate, local control was insufficient with definitive CRT compared to that with resection, which is a major problem associated with definitive CRT. A combination treatment strategy using diagnostic ER and selective CRT might resolve this issue.

The safety of diagnostic ER and selective CRT was clinically acceptable because no severe AEs were observed from these treatments in this study. Only 1 patient developed grade 3 esophageal stenosis, which was a possible risk from ER because a mucosal defect more than three-fourths of the circumference of the resected area after ESD potentially develops stenosis. To prevent this situation, we recommend prophylactic balloon dilation.[16] Consequently, the stenosis rate was quite low. Other effective methods, such as steroid injection at the mucosal defect[17,18] and oral intake of steroids, were reported[19] that could control this AE. Neutropenia, platelet counts, and esophagitis were slightly higher in selective CRT than those noted in the results of a previous report (JCOG9708),[6] which could have been caused by differences in the radiation field; however, those AEs could also be medically controlled. With late AEs, severe pericardial and pleural effusion are less frequent than reported previously,[20,21] which might be related to the multifield planning technique and reduced irradiation dosage (41.4 and 50.4 Gy).

This study had several limitations. First, survival rates were not directly compared with those of surgery, and a randomized controlled study would be ideal for that purpose; however, obtaining informed consent from some patients might be difficult because the level of invasiveness between surgery and ER with or without CRT is different. Another limitation is that although the surgical studies included all T1b (SM1–3) ESCC patients, this study included only patients with shallow T1b (SM1–2) ESCCs that the endoscopists determined to be completely resectable. To confirm the efficacy of this treatment strategy, the expected and threshold OS rates were set at levels higher than those of surgery. Because the 3-year OS rate was higher than the expected and threshold values in both patients with prophylactic CRT and all of the enrolled patients, this strategy should be considered as a standard minimally invasive treatment.

Conclusions

Our study suggests that the new strategy of selective CRT based on diagnostic ER might be a standard treatment option for clinically suspected T1b (SM1–2) N0M0 ESCC as a minimally invasive approach that can be tailored to each patient.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.04.017.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–E386.
2. Muto M, Minashi K, Yano T, et al. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol 2010;28:1566–1572.
3. Igaki H, Kato H, Tachimori Y, et al. Clinicopathologic characteristics and survival of patients with clinical stage I squamous cell carcinomas of the thoracic esophagus treated with three-field lymph node dissection. Eur J Cardiothorac Surg 2001;20:1089–1094.
4. Ozawa S, Tachimori Y, Baba H, et al. Comprehensive registry of esophageal cancer in Japan, 2004. Esophagus 2012;9:75–98.
5. Tachimori Y, Ozawa S, Numasaki H, et al. Comprehensive registry of esophageal cancer in Japan, 2011. Esophagus 2018;15:127–152.
6. Kato H, Sato A, Fukuda H, et al. A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol 2009;39:638–643.
7. Tachimori Y, Ozawa S, Fujishiro M, et al. Comprehensive registry of esophageal cancer in Japan, 2006. Esophagus 2013;11:21–47.
8. Eguchi T, Nakanishi Y, Shimoda T, et al. Histopathological criteria for additional treatment after endoscopic mucosal resection for esophageal cancer: analysis of

464 surgically resected cases. Mod Pathol 2006;19:475–480.
9. Kim DU, Lee JH, Min BH, et al. Risk factors of lymph node metastasis in T1 esophageal squamous cell carcinoma. J Gastroenterol Hepatol 2008;23:619–625.
10. Tomita N, Matsumoto T, Hayashi T, et al. Lymphatic invasion according to D2-40 immunostaining is a strong predictor of nodal metastasis in superficial squamous cell carcinoma of the esophagus: algorithm for risk of nodal metastasis based on lymphatic invasion. Pathol Int 2008;58:282–287.
11. Shimada H, Nabeya Y, Matsubara H, et al. Prediction of lymph node status in patients with superficial esophageal carcinoma: analysis of 160 surgically resected cancers. Am J Surg 2006;191:250–254.
12. Japanese Society for Esophageal Diseases. Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus, Ninth Edition: preface, general principles, part I. Esophagus 2004;1:61–88.
13. Shimizu Y, Kato M, Yamamoto J, et al. EMR combined with chemoradiotherapy: a novel treatment for superficial esophageal squamous-cell carcinoma. Gastrointest Endosc 2004;59:199–204.
14. Kawaguchi G, Sasamoto R, Abe E, et al. The effectiveness of endoscopic submucosal dissection followed by chemoradiotherapy for superficial esophageal cancer. Radiat Oncol 2015;10:31.
15. Yoshimizu S, Yoshio T, Ishiyama A, et al. Long-term outcomes of combined endoscopic resection and chemoradiotherapy for esophageal squamous cell carcinoma with submucosal invasion. Dig Liver Dis 2018;50:833–838.
16. Ezoe Y, Muto M, Horimatsu T, et al. Efficacy of preventive endoscopic balloon dilation for esophageal stricture after endoscopic resection. J Clin Gastroenterol 2011;45:222–227.
17. Hashimoto S, Kobayashi M, Takeuchi M, et al. The efficacy of endoscopic triamcinolone injection for the prevention of esophageal stricture after endoscopic submucosal dissection. Gastrointest Endosc 2011;74:1389–1393.
18. Hanaoka N, Ishihara R, Takeuchi Y, et al. Intralesional steroid injection to prevent stricture after endoscopic submucosal dissection for esophageal cancer: a controlled prospective study. Endoscopy 2012;44:1007–1011.
19. Yamaguchi N, Isomoto H, Nakayama T, et al. Usefulness of oral prednisolone in the treatment of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. Gastrointest Endosc 2011;73:1115–1121.
20. Ishikura S, Nihei K, Ohtsu A, et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2003;21:2697–26702.
21. Kato K, Muro K, Minashi K, et al. Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). Int J Radiat Oncol Biol Phys 2011;81:684–690.

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Conflicts of interest
The authors disclose no conflicts.

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Supplemental Material

Depth of Endoscopic Ultrasound and Endoscopic Resection Specimens

Clinically, an accurate distinction between muscularis mucosae (MM) and SM1 lesions is often difficult, even when using endoscopic ultrasound, which is a challenge for making treatment decisions. If a distinction between MM and SM1 is difficult, the estimated depth is considered to be large to subsequently avoid insufficient treatment, and the larger depth was accepted in this study. In ER specimens, SM infiltration was categorized into 2 stages, depending on the extent of infiltration, as follows from the Japanese Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus: cancer infiltration limited within a depth $\leq$200 μm from the lower surface of the MM were classified as pSM1 and those extending $>$200 μm were classified as pSM2.

Pathologic Depth of Invasion and Abbreviations

Based on the guidelines for clinical and pathologic studies on carcinoma of the esophagus,[12] the pathologic depth of invasion is described using the following abbreviations: EP (mucosal epithelium); LPM (lamina propria mucosae); and MM. Submucosal infiltration is divided into 3 stages, depending on the depth of infiltration in the surgical resected specimen. These are abbreviated as follows: SMI is cancer infiltrating the superficial one-third of the submucosal layer; SM2 is cancer infiltrating the middle one-third of the submucosal layer; and SM3 is cancer infiltrating the deep one-third of the submucosal layer. Because this classification is applicable to surgical samples but not to ER samples, a lesion with a depth $\leq$200 μm from the lower surface of the MM is classified as pSM1, and a depth $>$200 μm as pSM2 (Supplementary Figure 1).

Inclusion Criteria

The inclusion criteria for this study were as follows: histologically proven squamous cell carcinoma or basaloid cell carcinoma on the basis of biopsy; location within the thoracic esophagus; main tumor depth of invasion as cSM1–2 confirmed by endoscopic ultrasound; a maximum of 2 intra-esophageal tumors, all of which are limited to the epithelium (cEP) and/or lamina propria (cLPM); stage cN0/M0 confirmed by computed tomography; main tumor size and circularity $\leq$5 cm and less than three-fourths, respectively; absence of ulcerative lesions in tumors; absence of multiple Lugol-voiding lesions; absence of synchronous cancer confirmed by an otorhinolaryngologist or head and neck surgeon for patients with multiple Lugol-voiding lesions; absence of intra-esophageal metastasis; no previous treatment with chemotherapy or radiation against any other malignancies, and no previous treatment for esophageal cancer except ER (diagnosed as pEP, pLPM, or pMM tumors without lymphovascular invasion); age between 20 and 75 years; an Eastern Cooperative Oncology Group Performance Status of 0 or 1; sufficient organ functions; and provision of written informed consent for participation in the trial.

Exclusion Criteria

The exclusion criteria were as follows: iodine allergy; discontinuation of anticoagulant or antiplatelet medication was impossible; synchronous or metachronous multiple cancers within the previous 5 years except intramucosal tumors cured with local therapy; pregnancy or breast feeding; severe mental disease; systemic steroid therapy; positive hepatitis B virus surface antigen; active bacterial or fungal infection; history of myocardial infarction within 3 months of study enrollment or unstable angina pectoris; uncontrollable hypertension; uncontrollable diabetes mellitus or insulin therapy; or interstitial pneumonia, lung fibrosis, or severe emphysema observed on chest x-ray.

The Procedure of Endoscopic Resection

Any protocol of conventional ER, such as the 2-channel method, cap method, and esophageal endoscopic mucosal resection tube method, was allowed based on the physician's choice; however, ESD using an incision knife was allowed only for persons certified to perform endoscopy. After completion of ER, immediate iodine staining chromoendoscopy was performed to confirm whether the lateral resection margin was negative. If no residual lesion was observed by chromoendoscopy, the lateral margin was determined to be negative. For ER quality control, all ER procedures were recorded and reviewed by all investigators. According to the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus, the resected specimen was stained with iodine solution and sliced at 2-mm intervals. All resected specimens were evaluated by experienced pathologists at each institution. The vertical or lateral margin was determined to be negative if cancer was not observed in any of the cross sections. If both the vertical and lateral margins of the sections were negative, the resection was considered complete.

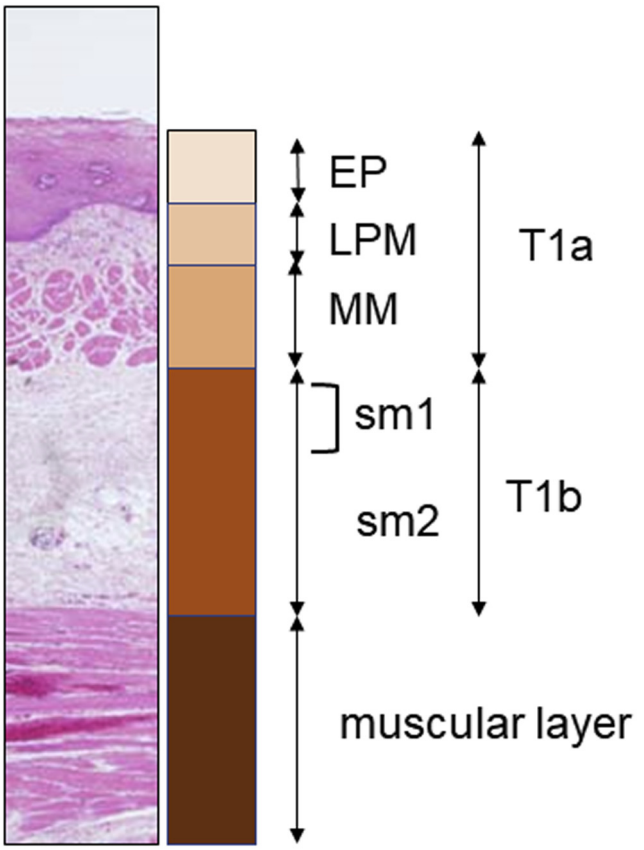
Some patients were assessed as having positive histologic lateral resection margins, even though they were endoscopically negative; however, they were at low risk for local recurrence, and if local recurrence does develop, we can curatively remove the cancer using ER. A positive histologic lateral resection margin was not used for decisions indicating definitive CRT.

Endoscopic follow-up was necessary the day after ER to confirm the absence of hemorrhage or perforation, and $\geq$29 days after ER to confirm scarring of the ulcer. Proton pump inhibitors or H_2 blockers were administered for at least 4 weeks after ER.

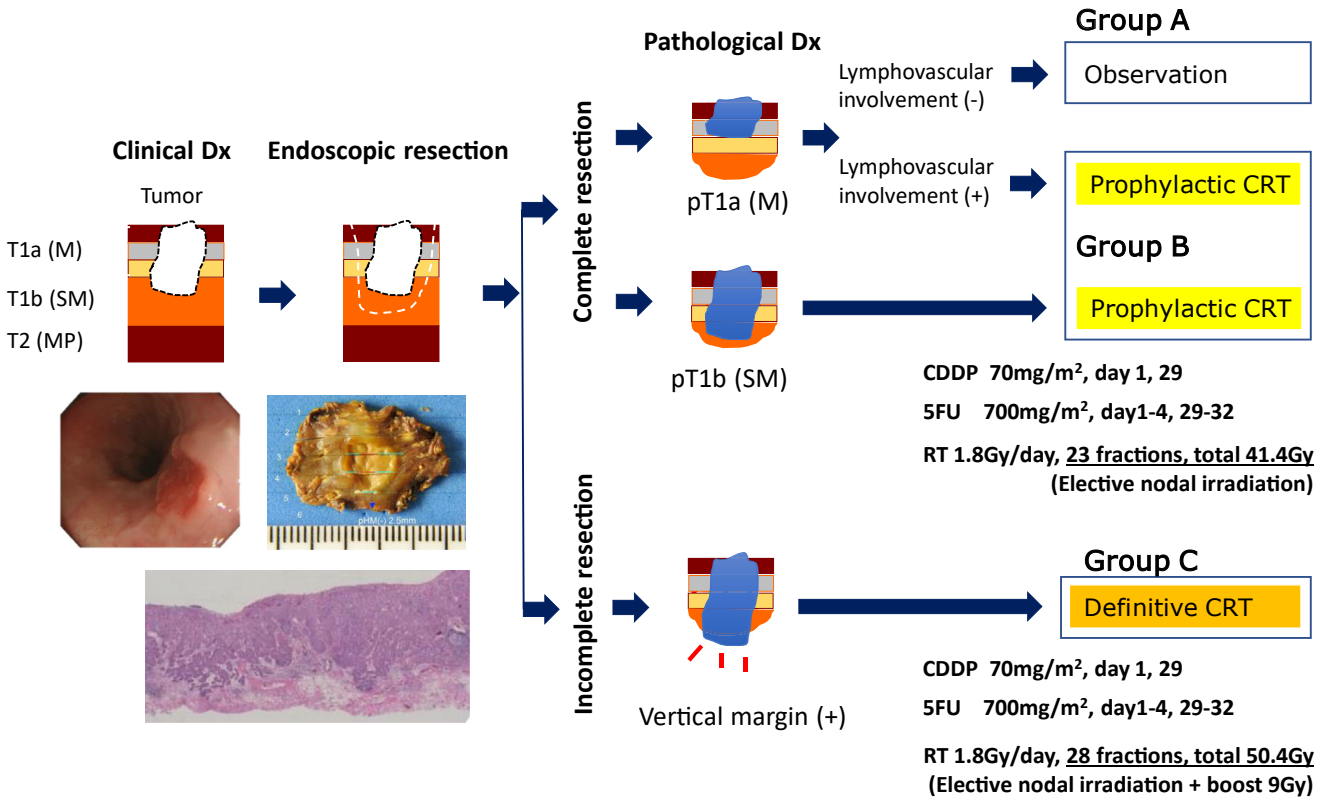
Details of Radiotherapy

CT-based 3-dimensional treatment planning was required for all the enrolled patients. The area of prophylactic irradiation covered regional lymph nodes because of the risk of lymph node metastasis. Among these, supraclavicular, upper mediastinal, and subcarinal lymph nodes were irradiated in patients with primary lesions located in the upper thoracic esophagus. Mediastinal and perigastric

lymph nodes were included in the field of irradiation when treating tumors in the middle or lower thoracic esophagus, whereas, celiac lymph nodes were included in treating primary tumors in the lower esophagus. In definitive CRT (group C), after the total dose of 41.4 Gy was delivered to regional lymph nodes, a boost dose of 9 Gy was administered to the primary site because of a positive margin after ER. To avoid excessive dose delivery to the heart, the multiple-field technique was required in cases of irradiation to the middle or lower mediastinal lymph nodes.



Supplementary Figure 1. Subclassification for superficial cancer by endoscopic resection. Superficial cancer was classified as mucosal cancer (T1a) and submucosal cancer (T1b). In addition, mucosal cancer was divided into 3 categories according to the depth of invasion as follows: cancer invasion limited to within the EP, LPM, and lamina MM. In endoscopically resected specimens, a tumor invading the submucosa to a depth $\leq$200 μm from the lamina MM was classified as T1b–SM1, while a tumor extending to a depth $>$200 μm was classified as T1b–SM2 because the distance of the submucosal layer is unknown.



Supplementary Figure 2. Study flow diagram. Patients clinically diagnosed with T1b (SM1–2) N0M0 thoracic ESCC enrolled in the trial and underwent ER. Based on the pathologic diagnosis, treatments were indicated as follows: group A, no additional treatment for pT1a with negative resection margins and no LVI; group B, selective CRT with 41.4 Gy delivered to locoregional lymph nodes for pT1b with negative resection margins or pT1a with LVI; and group C, definitive CRT (41.4 Gy) with a 9-Gy boost to the primary site for patients with positive vertical resection margins. Chemotherapy comprised 5-fluorouracil (700 mg/m^2/d, days 1–4 and 29–32, continuous intravenous infusion) and cisplatin (70 mg/m^2/d, days 1 and 29).