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Long-term prognosis after endoscopic resection of T1a-MM/T1b-SM1 esophageal squamous cell carcinoma

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Abstract

The objective of this study was to evaluate the long-term prognosis of T1a-MM/T1b-SM 1 esophageal squamous cell carcinoma (ESCC) after endoscopic resection (ER) and to validate the follow-up policy for pT1a-MM lymphovascular invasion (LVI)-negative ESCC. In this retrospective single-center analysis, patients who underwent ER for superficial ESCC between April 2002 and June 2021 were identified. The overall survival (OS), metastatic recurrence, and recurrence-free survival (RFS) rates were estimated using the Kaplan–Meier method. Cox proportional hazards models for OS, metastatic recurrence, and RFS were used. A total of 104 ESCC patients were eligible for the analysis. Of 104 patients, 81 had pT1a-MM, and 23 had pT1b-SM1. The 5-year OS, RFS, and metastatic recurrence rates of the 56 cases of pT1a-MM LVI-negative ESCC without additional treatment were 0.848 (95% confidence interval [CI]: 0.687–0.931), 0.817 (95% CI: 0.647–0.911), and 0.061 (95% CI: 0.014–0.240), respectively. Cox regression analysis for OS, RFS, and metastatic recurrence showed that only lymphatic invasion was strongly associated with metastatic recurrence (adjusted hazard ratio, 10.3; 95% CI: 2.01–53.3; $P = .005$). The proportion of deaths from other diseases was considerably higher (17/104, 16.3%) than that from ESCC (2/104, 1.9%). This may be related to the high complication rate of malignant tumors in other organs (43.3%, 45/104). The prognosis of ER for pT1a-MM and LVI-negative ESCC is good, and the follow-up policy is valid. Malignant tumors in other organs may be a major prognostic factor for superficial ESCC after ER.

Abbreviations: CI = confidence interval, CRT = radiochemotherapy, CT = computed tomography, ER = endoscopic resection, ESD = endoscopic submucosal resections, ESCC = esophageal squamous cell carcinoma, LVI = lymphovascular invasion, MM = muscularis mucosae, OS = overall survival, RFS = recurrence-free survival, SM = submucosa.

Keywords: endoscopic resection, esophageal squamous cell carcinoma, long-term prognosis, lymphovascular invasion, pT1a-MM/pT1b-SM1

1. Introduction

Endoscopic resection (ER) for superficial esophageal squamous cell carcinoma (ESCC) without lymph node metastasis is a minimally invasive, safe, and potentially curative treatment.[1] Although there are risks associated with ER, such as perforation and post-treatment stenosis, most can be managed endoscopically.[2–4]

According to the guidelines for treating esophageal cancer, ER should be considered in clinically suspected cases of clinical (c) T1a. Surgery, radiochemotherapy (CRT), or radiation therapy may be considered for suspected cT1b-submucosa (SM) 1 or deeper.

After ER, pathological (p) evaluation of lesions with a depth of T1a-epithelium/lamina propria mucosae should be considered for follow-up. Additional surgery, CRT, or radiation

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This was an observational study, and all patients were guaranteed the opportunity to refuse participation by opting out.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of the University of Tokyo (review number: 2058-(3)). All methods were performed in accordance with the relevant guidelines and regulations including the Declaration of Helsinki.

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therapy may be considered if the invasion depth is deeper than pT1b-SM1 or if the invasion depth is pT1a-muscularis mucosae (MM) with lymphovascular invasion (LVI).[5–7] A recent multicenter study reported that selective CRT after endoscopic resection for pT1b-SM1-2 cancer was as effective as surgery.[8] In addition, there have been many reports on the long-term prognosis of superficial ESCC resected endoscopically in recent years in the East and West.[9–15] However, whether additional treatment should be provided for pT1a-MM with LVI-negative status is unclear and controversial. Recently, it has been reported that pT1a-MM with negative LVI and vertical margins has a good prognosis without additional treatment, and follow-up examinations are acceptable.[16,17] There are also reports that follow-up examinations are acceptable even for non-curative resections by pathological evaluation, especially in the elderly population.[18,19] However, it is necessary to verify whether follow-up examination could be performed without additional treatment for p-T1a-MM LVI (-) ESCC.

In this study, we investigated the prognosis of endoscopically resected superficial ESCC of pT1a-MM patients and validated the follow-up policy for pT1a-MM LVI (-) ESCC.

2. Methods

2.1. Ethics statements

This study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of the University of Tokyo [review number: 2058-(3)]. All methods were performed in accordance with the relevant guidelines and regulations including the Declaration of Helsinki. This was an observational study, and all patients were guaranteed the opportunity to refuse participation by opting out.

2.2. Study design

This was a retrospective single-center analysis. We extracted data on superficial ESCC of pT1a-MM and pT1b-SM1, which were endoscopically resected at the University of Tokyo Hospital between April 2002 and June 2021, by reviewing electronic medical records.

The inclusion criteria for this study were as follows: Patients who underwent ER at our hospital and had a pathological diagnosis of ESCC with a depth of pT1a-MM or pT1b- SM1 and; Patients who visited our outpatient clinic after discharge and were followed up at our outpatient clinic.

The exclusion criteria were as follows: Patients with a pathological diagnosis of adenocarcinoma or basaloid carcinoma; Patients who were referred to the referral source even after visiting our outpatient clinic after discharge; Patients who underwent ER for ESCC in the past, where the depth was pT1b-SM2 or deeper; and; Patients who had undergone surgery or CRT for ESCC in the past. However, patients who had been relapse-free for > 10 years were not excluded, even if they had undergone previous treatment.

All esophageal ERs were performed by experienced endoscopists who had performed > 30 gastric endoscopic submucosal resections (ESD).

2.3. Procedure

ER was defined as endoscopic mucosal resection with a cap-fitted panendoscope (EMRC) and ESD. The decision to resect with ESD or EMRC depended on the size of the lesion, and the final decision was made by the endoscopist.

The video processor unit EVIS LUCERA SPECTRUM, EVIS LUCERA ELITE, or EVIS X1 (Olympus Corporation, Tokyo, Japan) and a single-channel upper gastrointestinal endoscope (GIF-Q260J, GIF-H290T; Olympus Co.) were used.

For ESD, hyaluronic acid (MucoUP; Boston Scientific, Tokyo, Japan or Ksmart; Olympus Co.) was used for submucosal injection. A DualKnife (KD-655Q or KD-655L, Olympus Co.), IT-nano knife (KD-612L, Olympus Co.), and Splash M-knife (Pentax Medical, Japan) were used for submucosal dissection.

For EMRC, snare (SD-221L-25, Olympus Co) was used for resection.

2.4. Variables

The following variables were included: Patient demographics (age at the time of ER and sex); Endoscopic findings (resection location, resection specimen diameter, lesion diameter, circumference, or en bloc resection rate); Pathological results (depth of invasion, pathological type, lymphatic invasion, venous invasion, horizontal margin, and vertical margin); and Follow-up data (presence of additional treatment if endoscopic resection was non-curative, type of additional treatment (surgery or CRT), presence of distant or lymph node recurrence, site of recurrence, overall survival (OS) period, recurrence-free period, outcome, causes of death, presence of malignancy in other organs throughout the course).

2.5. Pathological evaluation

Histopathological examination was performed by a skilled pathologist, and the diagnosis was based on the standard methods recommended by the Japanese Classification of Esophageal Cancer, 11th Edition. Intramucosal carcinoma (pT1a) was divided into epithelium/lamina propria mucosae/MM, and submucosal invasive carcinoma was classified as pT1b-SM1 if the invasion was up to 200 μm or pT1b-SM2 if it was over 200 μm. Endoscopically resected specimens were formalin-fixed and sectioned with a thickness of 2 to 3 mm. Tissue specimens were embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin and eosin. Additional immunostaining with D2-40 was performed, as required.

2.6. Follow-up policy after ER

The patient underwent endoscopy and cervical, chest, and abdominal computed tomography (CT) and tumor marker assessment every 6 months if the pathological diagnosis after ER was pT1a-MM LVI (-). If the patient diagnosed with pT1a-MM LVI (+) or deeper than T1b-SM1 was not in good general condition due to multiple comorbidities or did not wish to receive additional treatment after sufficient explanation, surveillance by endoscopy and CT was performed every 6 months as well.

2.7. Additional treatment methods

Surgical resection or chemoradiotherapy CRT have been performed as additional treatments to endoscopic treatment. The chemotherapy regimen comprised platinum-based and 5-fluorouracil based anticancer drugs based on Japanese guidelines. The dosage of radiotherapy was 50.4 Gy in 28 fractions over 6 weeks. Chemotherapy and radiotherapy were initiated simultaneously on day1.

2.8. Endpoints

The endpoints were defined as follows: OS, death or deterioration leading to transfer or home care best supportive care; recurrence, confirmed by endoscopy or CT; and recurrence-free survival (RFS), confirmation of either recurrence or death.

The start of follow-up was set at the date of the first post-discharge visit, and no patients were excluded thereafter. Patients were followed up until the event occurred, the final examination (i.e.,

last date the patient was confirmed alive for OS and final date of CT for recurrence), or the end of June 2021, whichever came first. For RFS, deaths after final confirmation of the absence of recurrence were included. Hence, patients were followed-up in accordance with OS, even after the recurrence confirmation date ended.

Metastatic recurrence was defined as the development of intraesophageal, lymph node, or distant metastasis after a series of treatments for esophageal cancer, including additional treatment, as needed. Metastatic recurrence was diagnosed using radiography, pathology, or endoscopy.

The causes of death were classified as follows: Causes of death that could be directly confirmed by checking the electronic medical records and; Causes that could be attributed to the patients' terminal phases if they were transferred to another hospital or home care.

2.9. Statistical analysis

Patient background characteristics are summarized separately for pT1a-MM and pT1b-SM1. Additionally, follow-up information was compared between; pT1a-MM versus pT1b-SM1; 2) LVI (+) versus LVI (-) within pT1a-MM and pT1b-SM1; and pT1a-MM, LVI (-) without additional treatment (Group A), pT1a-MM, LVI (+), and pT1b-SM1 with additional treatment according to the guidelines (Group B) versus pT1a-MM LVI (+) and pT1b-SM1 followed up without additional treatment (Group C). Continuous variables are expressed as means and standard deviations or medians and upper/lower quartiles. Categorical variables are summarized as numbers and proportions and compared using the chi-square test and Fisher's exact test.

According to the third classification (i.e., Groups A to C), the OS, recurrence, and RFS rates were estimated separately using the Kaplan–Meier method. To check the sensitivity to including/excluding early censored cases, we also obtained the Kaplan–Meier curves based on patients who were followed for more than 1 year.

The Cox proportional hazards models for OS, recurrence, and RFS were fitted with the following variables: lesion size, tumor depth of invasion, lymphatic invasion, venous invasion, lateral margin, vertical margin, and the presence of malignancy in other organs throughout the course.

All statistical analyses were performed using SAS version 9.4 (Cary, NC).

3. Results

3.1. Study group

There were 124 cases of pT1a-MM/ pT1b-SM1 during the observation period, and after excluding 20 cases that met the exclusion criteria, 104 ESCC cases were eligible for analysis in this study. Of the 104 patients, 81 were pT1a-MM (of which 24 were LVI + and 57 were LVI -), and 23 were pT1b-SM1 (of which 10 were LVI + and 13 were LVI-). A flowchart of the process is shown in Figure 1.

3.2. Patient background

The baseline characteristics of the enrolled patients are shown in Table 1. Patients with pT1b-SM1 ESCC showed smaller tumor size (20.2 ± 13.9 mm vs 29.4 ± 15.6 mm), higher rates of lymphatic invasion (34% vs 14 %) and positive vertical margins (13% vs 1%), and more common additional treatment (65% vs 21%) than pT1a-MM. Overall, ESD was performed in 95% (99/104) of patients, en bloc resection was achieved in 99% (103/104), and *R*0 resection was performed in 83% (86/104). The median observation period (upper to lower quartiles) was 46 (24–83) months.

3.3. Prognosis

A flowchart of the clinical course after ER according to the depth of invasion is shown in Figure 2. Of the 57 pT1a-MM LVI (-) ESCC patients, 48 patients were alive and 9 patients died (1 patient died of ESCC and 8 patients died of other causes). Of the 24 pT1a-MM LVI (+) ESCC patients, 20 patients were alive, and 4 patients died (1 patient died of ESCC and 3 patients died of other causes). Of the 23 pT1b-SM1 ESCC patients, 19 were alive, and 4 died of other causes.

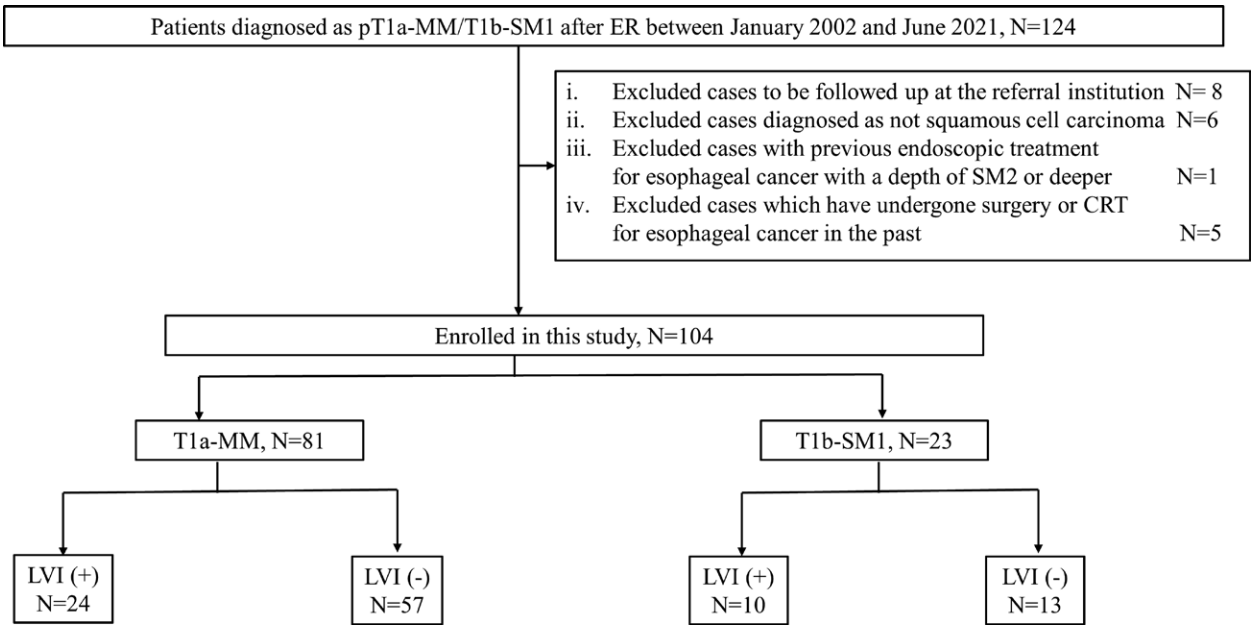


Figure 1. Flow chart of the enrolled patients. MM = muscularis mucosa, SM = submucosa, ER = endoscopic resection, LVI = lymphovascular invasion, CRT = chemoradiotherapy.

Table 1

Baseline characteristics and follow-up information.

	Total	MM	SM1	
N	104	81	23	*P* value
Age	68.3 ± 9.7	69.0 ± 9.8	66.2 ± 9.4	.21
Sex：male/female (%M)	92/12 (88.5)	73/8 (90.1)	19/4 (82.6)	.46
Resection size (mm)	40.2 ± 15.9	41.6 ± 16.1	35.0 ± 14.5	.13
Lesion size (mm)	27.4 ± 15.6	29.4 ± 15.6	20.2 ± 13.9	.01
Location (Ce/Ut/Mt/Lt/Ae)	6/10/74/13/1	5/7/56/12/1	1/3/18/1/0	
Lesion circumstance (<1/2)/ (>1/2)/ (>3/4)/ whole	67/16/16/4	53/11/13/4	14/5/3/0	
Defect circumstance (<1/2)/ (>1/2)/ (>3/4)/ whole	39/26/32/6	27/22/26/6	12/4/6/0	
ER： ESD/EMRC (%ESD)	99/5 (95.2)	80/1 (98.8)	19/4 (82.6)	.008
En bloc	103 (99.0)	81 (100)	22 (95.7)	.22
*R*0 resection	86 (82.7)	70 (86.4)	16 (69.6)	.11
v+ (%)	19 (18.3)	14 (17.3)	5 (21.7)	.76
ly+ (%)	19 (18.3)	11 (13.6)	8 (34.8)	.03
VM+ (%)	4 (3.8)	1 (1.2)	3 (13.0)	.03
LM+ (%)	14 (13.5)	10 (12.3)	4 (17.4)	.50
Additional treatment (%)	32 (30.8)	17 (21.0)	15 (65.2)	.0002
Ope (%)	23 (22.1)	11 (13.6)	12 (52.2)	
CRT (%)	9 (8.7)	6 (7.4)	3 (13.0)	
Metastatic recurrence (%)	8 (7.7)	7 (8.6)	1 (4.3)	.68
Other organ malignant tumor	45 (43.3)	39 (48.1)	6 (26.1)	.09
mortality (%)	17 (16.3)	13 (16.0)	4 (17.4)	1.00
Cancer specific mortality (%)	2 (1.9)	2 (2.5)	0	1.00
Follow-up period (mo), median (quartiles)	46 (24–83)	46 (23.6–81.1)	55 (28.6–83.3)	

Ae = abdominal esophagus, Ce = cervical, CRT = chemoradiotherapy, ER = endoscopic resection, ESD = endoscopic submucosal resections, Lt = lower thoracic, MM = muscularis mucosa, Mt = middle thoracic, SM = submucosa, Ut = upper thoracic.

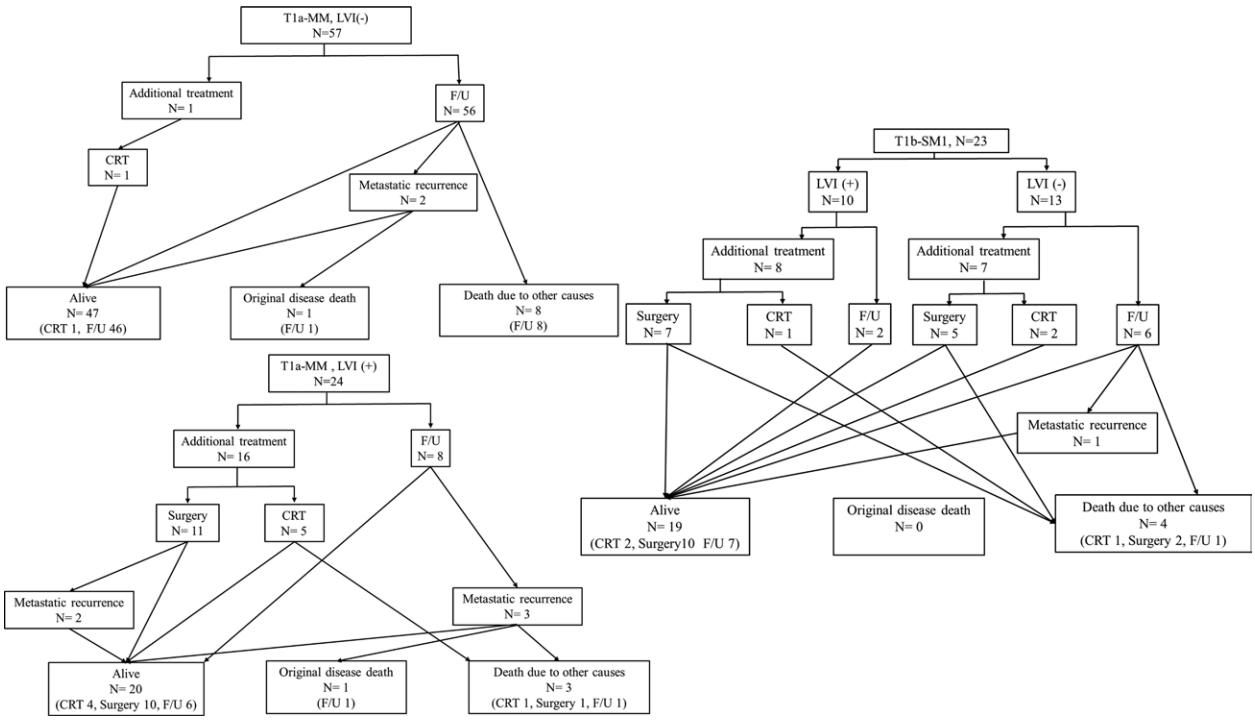


Figure 2. Flow chart of the clinical course after ER according to the depth of invasion. Patients with pT1a-MM were further divided into 2 groups according to the presence or absence of lymphovascular invasion. The median observation period (IQR) was 46 months (24–83). ESCC = esophagus squamous cell carcinoma, LVI = lymphovascular invasion, CRT = chemoradiotherapy, F/U = follow-up.

Metastatic recurrence was observed in 8 patients (7.7% of 104 patients), with no clear difference between pT1a-MM and pT1b-SM1. Overall, only 2 patients died of ESCC, but 17 all-cause deaths (16.3%) were observed. A total of 43.3% (45/104) of patients had malignant tumors in other organs throughout the course (Table 1).

Table 2 shows the prognosis classified according to the presence or absence of LVI in pT1a-MM and pT1b-SM1 ESCC.

Metastatic recurrence was observed in 20.8% of pT1a-MM and LVI (+) ESCC patients, while it was observed in 3.6% (2/57) of pT1a-MM and LVI (-) ESCC patients.

Table 3 shows the prognosis of groups A to C. There seemed to be no difference in the metastatic recurrence rate, overall mortality rate, or mortality rate from ESCC between Groups A and B, while the comparison between Groups A and C suggests a difference in metastatic recurrence rate.

The Kaplan–Meier curves for OS, RFS, and recurrence rates in each group are shown in Figure 3. Differences in OS between the 3 groups were unclear: the 5-year OS rates of each group were 0.848 (95% confidence interval [CI]: 0.687, 0.931) in Group A, 0.831 (95% CI: 0.605, 0.934) in Group B, and 0.679 (95% CI: 0.282, 0.888) in Group C. However, there was a significant difference in the metastatic recurrence rates: the 5-year metastatic recurrence rates were 0.061 (95% CI: 0.014, 0.240) in Group A, 0.103 (95% CI: 0.026, 0.360) in Group B, and 0.242 (95% CI: 0.083, 0.589) in Group C. The estimated Kaplan–Meier curves based on patients who were followed for more than 1 year are shown in Figure S1, Supplemental Digital Content, http://links.lww.com/MD/I46. By excluding cases with an observation period of less than 1 year, the number of eligible cases was 87. These curves remained essentially the same as the Kaplan–Meier curves without the exclusion period because no event occurred within the first year. The change in risk-set numbers during the period only slightly affected the estimates.

The characteristics of the patients with metastatic recurrence are shown in Supplemental Digital Content 1, http://links.lww.com/MD/I47. The median time to metastatic recurrence (quartiles) was 23 months (14.2–48.0). Eight patients had a metastatic recurrence, 3 of whom died (2 died of ESCC and 1 of lung cancer).

3.4. Clinical course of pt1a-MM, LVI (-) patients with metastatic recurrence

Patient 1 had lymph node and liver metastases after 217 days of observation. Chemotherapy was administered up to the third line (first line: 4 courses of 5-fluorouracil plus cisplatin; second line: 2 courses of docetaxel hydrate plus cisplatin plus 5-fluorouracil; and third line: 1 course of irinotecan hydrochloride hydrate plus tegafur/gimeracil/oteracil potassium). The patient eventually received best supportive care for 491 days. This case has already been reported.[20]

Patient 2 had right paratracheal lymph node metastasis and suspected tracheal invasion after 1519 days of observation. The patient requested radiation therapy, received it at another hospital, and was alive as of 1862 days of observation.

Table 2

Summary of follow-up information in the subgroups with and without LVI (in T1a-MM and T1b-SM1).

	MM			SM1		
	LVI (+)	LVI (-)		LVI (+)	LVI (-)	
N	24	57	*p* value	10	13	*p* value
v+ (%)	14 (58.3)	0	<.0001	5 (50.0)	0	.008
ly+ (%)	11 (45.8)	0	<.0001	8 (80.0)	0	<.0001
VM+ (%)	1 (4.2)	0	.30	1 (10.0)	2 (15.4)	1.00
LM+ (%)	4 (16.7)	6 (10.5)	.47	3 (30.0)	1 (7.7)	.28
Additional treatment (%)	16 (66.7)	1 (1.8)	<.0001	8 (80.0)	7 (53.8)	.38
Ope (%)	11 (45.8)	0		7 (70.0)	5 (38.5)	
CRT (%)	5 (20.8)	1 (1.8)		1 (10.0)	2 (15.4)	
Metastatic recurrence (%)	5 (20.8)	2 (3.6)	.02	0	1 (7.7)	1.00
Other organ malignant tumor	6 (25.0)	33 (57.9)	.008	2 (20.0)	4 (30.8)	.66
mortality (%)	4 (16.7)	9 (15.8)	1.00	2 (20.0)	2 (15.4)	1.00
Cancer specific mortality (%)	1 (4.2)	1 (1.8)	.51	0	0	

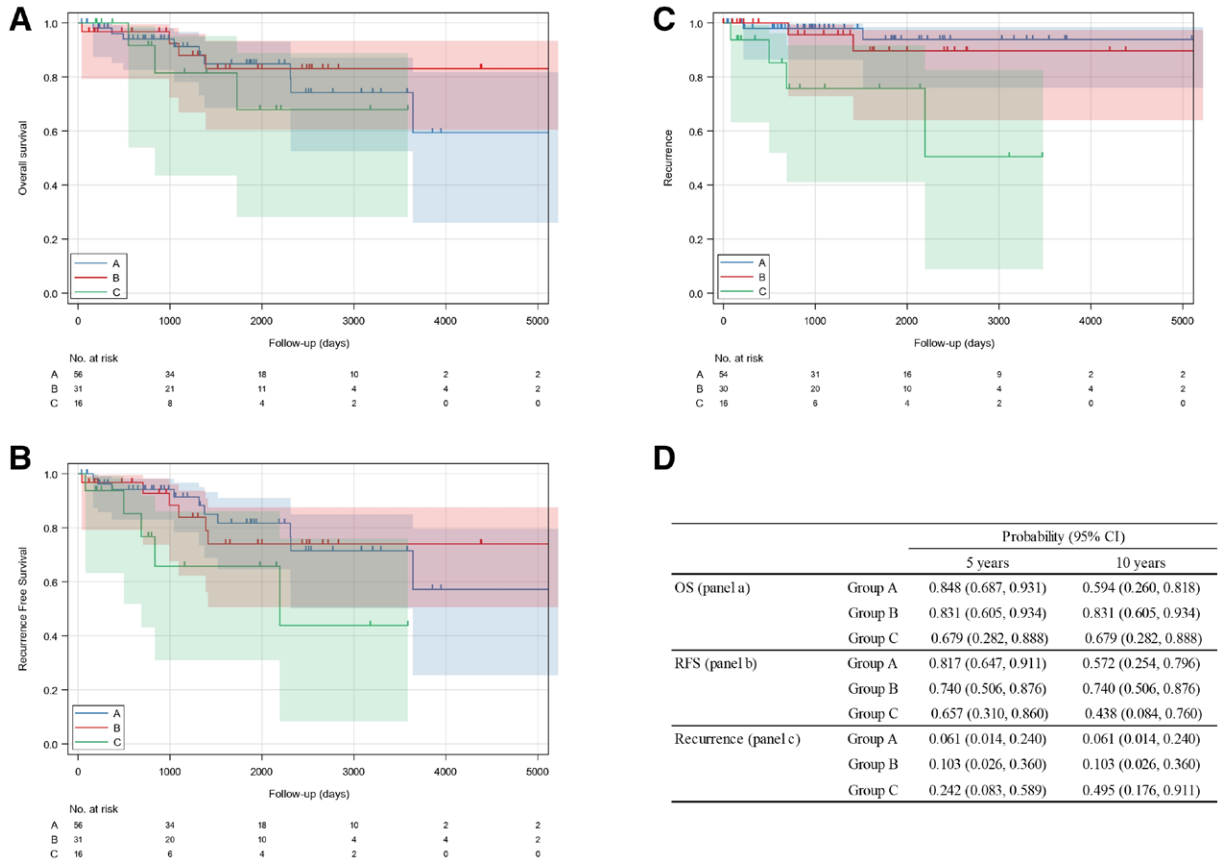
CRT = chemoradiotherapy, MM = muscularis mucosa, LVI = lymphovascular invasion, SM = submucosa.

Table 3

Summary of follow-up information in the subgroups defined based on the combination of pT1a-MM or pT1b-SM1, LVI, and additional treatment.

	Group A MM, LVI (-) follow-up	Group B MM, LVI (+) and SM1 additional treatment	A vs B	Group C MM, LVI (+) and SM1 follow-up	A vs C
N	56	31	*p* value	16	*p* value
V + (%)	0	16 (51.6)	<.0001	3 (18.8)	.01
Ly + (%)	0	12 (38.7)	<.0001	7 (43.8)	<.0001
VM + (%)	0	2 (6.5)	.12	2 (12.5)	.05
LM+ (%)	6 (10.8)	5 (16.1)	.51	3 (18.8)	.41
Additional treatment (%)	0	31 (100)	<.0001	0	
Ope (%)	0	23 (74.2)		0	
CRT (%)	0	8 (25.8)		0	
Recurrence (%)	2 (3.6)	2 (6.5)	.61	4 (25.0)	.02
Other organ malignant tumor	33 (58.9)	3 (9.7)	<.0001	9 (56.3)	1.00
mortality (%)	9 (16.1)	5 (16.1)	1.00	3 (18.8)	.72
Cancer specific mortality (%)	1 (1.8)	0	1.00	1 (6.3)	.40

CRT = chemoradiotherapy, MM = muscularis mucosa, LVI = lymphovascular invasion, SM = submucosa.



		Probability (95% CI)	
		5 years	10 years
OS (panel a)	Group A	0.848 (0.687, 0.931)	0.594 (0.260, 0.818)
	Group B	0.831 (0.605, 0.934)	0.831 (0.605, 0.934)
	Group C	0.679 (0.282, 0.888)	0.679 (0.282, 0.888)
RFS (panel b)	Group A	0.817 (0.647, 0.911)	0.572 (0.254, 0.796)
	Group B	0.740 (0.506, 0.876)	0.740 (0.506, 0.876)
	Group C	0.657 (0.310, 0.860)	0.438 (0.084, 0.760)
Recurrence (panel c)	Group A	0.061 (0.014, 0.240)	0.061 (0.014, 0.240)
	Group B	0.103 (0.026, 0.360)	0.103 (0.026, 0.360)
	Group C	0.242 (0.083, 0.589)	0.495 (0.176, 0.911)

Figure 3. The Kaplan–Meier estimates for OS, RFS, and recurrence rates. Group (A): the group that was followed-up with pT1a-MM and LVI (–). Group (B): the group that received additional treatment according to the guidelines for pT1a-MM, LVI (+), and pT1b-SM1. Group (C): the group that was followed-up with pT1a-MM LVI (+) and pT1b-SM1. (a): OS of each group. (b): Recurrence-free survival of each group. (c): Metastatic recurrence rate of each group. (d): Five-year and 10-year rates of each group for OS, RFS, and recurrence. MM = muscularis mucosa, LVI = lymphovascular invasion, OS = overall survival, RFS = recurrence-free survival, SM = submucosa.

3.5. Prognostic factors for metastatic recurrence

Univariable and multivariable Cox regression analyses were performed for OS, RFS, and metastatic recurrence (Table 4). In both univariable and multivariable analyses, only lymphatic invasion was strongly associated with metastatic recurrence (adjusted hazard ratio, 10.3; 95% CI: 2.01–53.3; P = .005).

4. Discussion

In this study, we investigated the long-term prognosis of pT1a-MM ESCC and T1b-SM1 ESCC patients. The mortality rate in ESCC in both pT1a-MM and pT1b-SM1 was 1.9% (2/104), and the prognosis was good, which is consistent with a previous report.[9–13]

At our hospital, we discussed how to treat pT1a-MM and LVI (-) with surgeons and radiologists and decided on a policy of careful follow-up, where CT and endoscopy were performed every 6 months. In this study, we found that 3.6% (2/56) of the patients in the pT1a-MM and LVI (-) groups had metastatic recurrence. Moreover, 8.6% (7/81) of all patients in the total pT1a-MM group, including LVI (+), had a prognosis similar to that previously reported.[14,17]

One of the patients who had metastatic recurrence of pT1a-MM, LVI (-) was treated with chemotherapy for recurrence but died. In other words, although the incidence of recurrence is low in pT1a-MM and LVI (-), there are cases of recurrence that may threaten the patient's prognosis. Therefore, careful consideration is required when deciding on policy.

A comparison of the survival time analysis of the pT1a-MM, LVI (-) ESCC follow-up group (Group A), pT1a-MM, LVI (+) and pT1b-SM1 ESCC additional treatment according to guidelines (Group B), and pT1a-MM, LVI (+), and pT1b-SM1 ESCC follow-up group (Group C) showed that the metastatic recurrence rate was significantly higher in Group C than in Groups A and B. There was no statistically significant difference in OS; however, the data suggested a difference between the 3 groups (Fig. 3). The results of this study suggest that ER in ESCC and additional treatment as needed could reduce the incidence of death from ESCC and metastatic recurrence. However, the same degree of death from other diseases was observed in all 3 groups, and the number of deaths from other diseases was higher than that from ESCC. This was attributed to the cause of death, and it was thought that there was no statistically significant difference in OS.

In this study, the proportion of deaths from other diseases was considerably higher (17/104, 16.3%) than that from ESCC. This may be related to the high complication rate of malignant tumors in other organs (43.3%,45/104) throughout the course. Common malignant tumors in other organs included gastric cancer (16 cases), pharyngeal cancer (15 cases), colorectal cancer (7 cases), lung cancer (5 cases), and other cancers (Supplemental Digital Content 2, http://links.lww.com/MD/I48). Additionally, 13 cases of multiple cancers were observed. In this study, 15 patients died of causes other than ESCC. The causes of death included 4 cases of pneumonia, 3 cases of pharyngeal cancer, and 1 case of other cancers (Supplemental Digital Content 3, http://links.lww.com/MD/I49).

Table 4

The estimates of univariable and multivariable Cox models for different outcomes.

	Univariable				Multivariable			
	HR	95% CI		P	HR	95% CI		P
Outcome: OS								
Lesion size ≥ 30 mm (vs <30 mm)	1.52	0.57	4.10	.405	1.44	0.51	4.09	.497
Tumor depth, SM1 (vs MM)	0.79	0.23	2.77	.711	0.77	0.18	3.29	.725
ly + (vs none)	0.73	0.16	3.20	.671	0.71	0.15	3.32	.660
v + (vs none)	0.92	0.26	3.25	.899	0.72	0.17	2.94	.641
LM + (vs none)	1.86	0.60	5.78	.284	2.01	0.58	7.00	.272
VM + (vs none)	1.13	0.15	8.62	.906	1.65	0.16	17.47	.679
Other organ malignant tumor (vs absence)	0.96	0.36	2.59	.941	0.85	0.29	2.47	.765
Outcome: Recurrence								
Lesion size ≥ 30 mm (vs <30 mm)	1.14	0.27	4.77	.862	0.67	0.13	3.36	.627
Tumor depth, SM1 (vs MM)	0.45	0.06	3.64	.451	0.13	0.01	1.39	.092
ly + (vs none)	5.93	1.47	23.91	.012	10.34	2.01	53.32	.005
v + (vs none)	1.48	0.30	7.35	.630	1.19	0.15	9.47	.873
LM + (vs none)	0.81	0.10	6.56	.840	1.25	0.10	16.23	.864
VM + (vs none)	2.24	0.27	18.44	.453	12.05	0.74	197.18	.081
Other organ malignant tumor (vs absence)	0.43	0.09	2.15	.305	0.57	0.10	3.19	.525
Outcome: RFS								
Lesion size ≥ 30 mm (vs <30 mm)	1.22	0.50	2.95	.661	0.94	0.37	2.40	.893
Tumor depth, SM1 (vs MM)	0.76	0.26	2.27	.626	0.43	0.12	1.58	.202
ly + (vs none)	1.81	0.66	4.97	.249	2.35	0.77	7.17	.134
v + (vs none)	1.02	0.34	3.05	.967	0.64	0.18	2.27	.491
LM + (vs none)	1.77	0.65	4.85	.266	2.43	0.78	7.55	.124
VM + (vs none)	1.72	0.40	7.43	.470	4.50	0.74	27.49	.103
Other organ malignant tumor (vs absence)	0.77	0.32	1.85	.552	0.76	0.30	1.97	.577

CI = confidence interval, HR = hazard ratio, MM = muscularis mucosa, OS = overall survival, RFS = recurrence-free survival, SM = submucosa.

It has been reported that lifestyle habits, such as smoking and alcohol consumption,[21] are also strongly associated with ESCC, and there is a high rate of complications from cancer in other organs.[22] Furthermore, it has been reported that the prognostic factor after ER of superficial ESCC is not esophageal cancer, but Eastern Cooperative Oncology Group performance status of ≥ 2 and a Charlson comorbidity index of ≥ 2 are significantly related.[23] Our study showed that many patients did not die from ESCC itself but from malignant tumors in other organs, pneumonia, and other diseases caused by deterioration of their general condition, which is consistent with the findings of these reports. Moreover, even in cases of non-curative resection at our hospital, some patients will eventually be followed up if the patient is old and has a poor general condition. Since there are reports that follow-up is acceptable even for non-curative resection in the elderly population,[18,19] it is necessary to carefully consider when deciding whether to provide additional treatment, especially in the elderly population.

Our study has some limitations. First, this was a single-center retrospective study with a small number of cases. In particular, there were as few as 23 cases of pT1b-SM1, so it is necessary to be careful when interpreting the results. Second, the median follow-up period for patients was 46 months, which may not be sufficient to evaluate the long-term results. However, 44 of 104 patients were followed up for more than 5 years. Third, in both pT1a-MM LVI (+) and pT1b-SM1 ESCC cases, there were patients with metastatic recurrence who were not treated at our hospital but were transferred to another hospital. These cases were censored at that time, but the corresponding patients may be dead because more than 5 years have passed since that time. Therefore, the number of deaths from ESCC is likely to increase if confirmed.

In conclusion, the prognosis of ER in pT1a-MM and LVI (-) ESCC is good. The follow-up examination policy for pT1a-MM and LVI (-) ESCC is acceptable, although it needs adequate explanation to patients because a few pT1a-MM LVI (-) cases resulted in death after relapse. It has also been suggested that superficial ESCC after ER often develops into malignant tumors in other organs, which can be a major prognostic factor.

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