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Original Article

Risk of metachronous recurrence after endoscopic submucosal dissection of esophageal squamous cell carcinoma

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SUMMARY. **Development of endoscopic submucosal dissection (ESD) improves the *en bloc* resection rate of superficial esophageal squamous cell carcinoma (SESCC). Although the background mucosa after ESD remains malignant potential, esophageal (sub)circumferential ESD, in cases where the mucosal defect is greater than three-fourths of the circumference, might induce refractory stricture, and it may disturb early detection of the recurrence. Therefore, we aimed to elucidate whether the patients treated by (sub)circumferential ESD for SESCC may remain at risk of metachronous recurrence. In a single-center retrospective study, we collected data from 154 consecutive patients who were treated with curative ESD for SESCC from 2002 to 2013 and followed by surveillance for longer than 12 months. Metachronous recurrence was defined as histologically proven SESCC at other site of the ESD scar or abnormal nodal swelling was detected later than 12 months after ESD. The primary endpoint was to identify the risk of metachronous recurrence using multivariate analyses. The secondary endpoint was to investigate difference in clinical pathological features between patients with and without the recurrence. The overall rate of metachronous recurrence was 14.9% during 40.5 median months after the initial ESD. 24.1% and 9.0% of overall metachronous recurrence were observed in patients treated with (sub)circumferential ESD and non-subcircumferential ESD, respectively, despite no significant difference in their observation duration. After the application of a stepwise regression model that included all variants, a Cox proportional hazards regression model identified (sub)circumferential ESD as the only risk for the recurrence (hazard ratio (HR): 1.48, 95% confidence intervals (CI): 1.04–2.08, $P = 0.028$). The cumulative recurrence rate revealed a significant difference between patients treated by (sub)circumferential ESD and those by nonsubcircumferential ESD (HR: 3.094, 95% CI: 1.33–7.52, $P = 0.009$), despite no significant difference in their cause-specific survival. Additionally, the session numbers of the follow-up endoscopy until the detection of metachronous recurrence after the non-subcircumferential ESD were significantly less than those after the (sub)circumferential ESD (7.8 ± 1.8 vs. 15.2 ± 1.5 $P = 0.005$), despite no significant difference in their cancer-free duration. In conclusion, we demonstrated that patients treated by curative (sub)circumferential ESD for SESCC might be high risk for metachronous recurrence. Therefore, we should establish a risk-stratified surveillance program after (sub)circumferential ESD and preventive strategies for post-ESD stricture.**

KEY WORDS: **endoscopic surgical procedure, esophageal squamous cell carcinoma, recurrence.**

ABBREVIATIONS: CI: confidence intervals; CRT: chemoradiation therapy; CT: computed tomography; EBD: endoscopic balloon dilation; ER: endoscopic resection; ESD: endoscopic submucosal dissection; EMR: conventional endoscopic mucosal resection; HGIN: high-grade intraepithelial neoplasms; HR: hazard ratios; IQR: interquartile range; LVL: Lugol-voiding lesion; MM: muscularis mucosae; NBI: narrow-band imaging; QOL: quality of life; SCC: squamous cell carcinoma; SESCC: superficial esophageal SCC; SM1: submucosal invasion up to 200 μm

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INTRODUCTION

Esophageal cancer ranks as the sixth leading cause of cancer mortality in the world, and the major histotype in Japan is squamous cell carcinoma (SCC).[1,2] As many studies demonstrated favorable outcomes of endoscopic resection (ER) with its minimal invasiveness, the indication for ER has expanded as a central

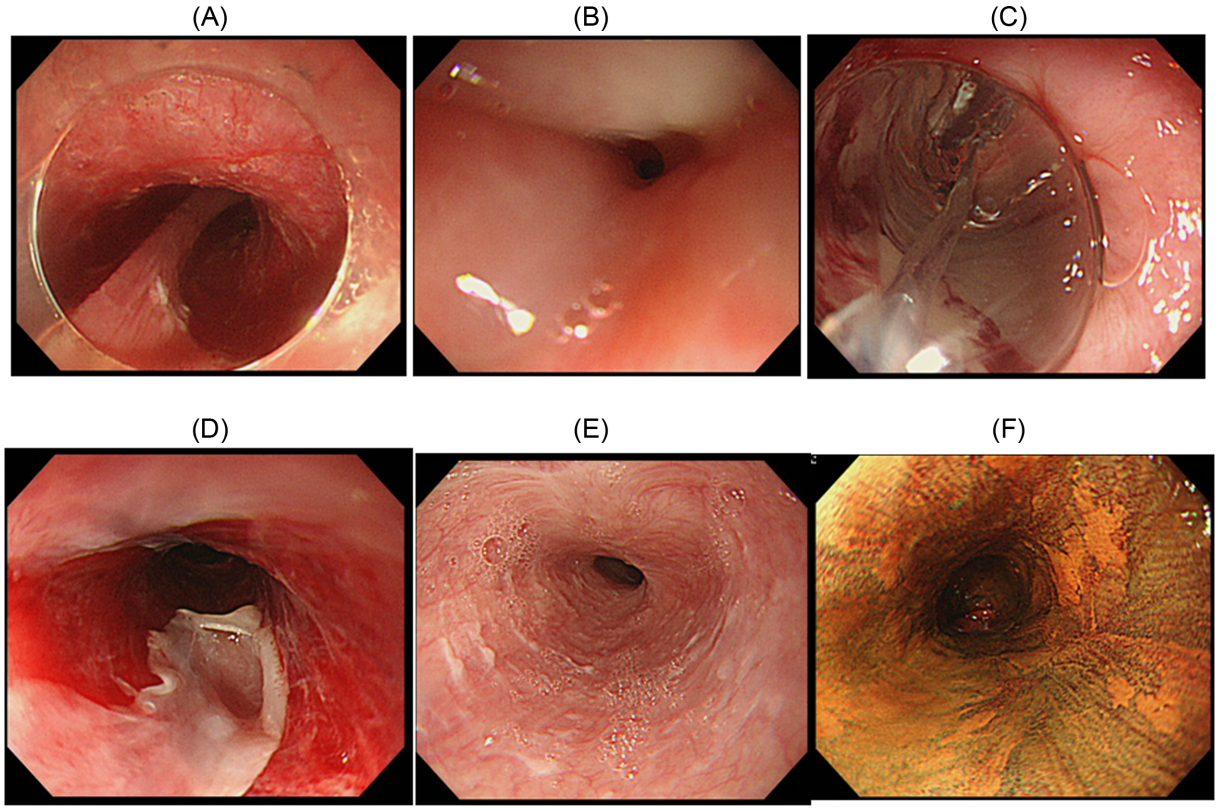


Fig. 1 Representative endoscopic images. (A) Endoscopic imaging after subcircumferential ESD for SESCC located within the middle esophagus. ESD was performed in 2009, and the pathological diagnosis was pT1a-MM, ly0, v0, HM0, VM0. (B) Two months after the ESD, severe stricture was observed. (C) EBD was performed by standardized 15/18-mm CRE balloon catheters (Microvasive). (D) The endoscopic view immediately after the EBD showed blinded spots of endoscopic inspection. (E) Five months after the ESD, mild stricture was observed, but he did not experience dysphagia. (F) A recurrent lesion was detected on the upper esophagus in 2011 and treated curatively by ESD.

strategy, rather than esophagectomy or chemoradiation therapy (CRT), to combat superficial esophageal SCC (SESCC).[3,4] Previous studies showed local recurrence rates from approximately 0% to 17% after ER and extremely low rates of lymph node metastasis.[5] Compared to endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) was reported to have higher rate of *en bloc* resection with lower rate of local recurrence, despite the tumor size.[6] As a result, the indication of ESD has been expanded for large-sized high-grade intraepithelial neoplasms (HGIN) or SESCC invaded up to the layer of muscularis mucosae (MM) or submucosa up to 200 μm (SM1), but there are limited data of metachronous recurrence after ESD.[7]

Recently, some light has been shed on possible incidence of severe stricture after esophageal ESD. As larger-sized SESCC became candidates for ESD, more patients began to suffer from post-ESD strictures.[8–10] Specifically, the rate of stricture formation after esophageal (sub)circumferential ESD, where the mucosal defects were greater than three-fourths of the circumference, was reported to be 88%–100%. This range was much higher than 1.6%–25%, 3.3%–40%, and 6.0%–18%, which were reported after esophagectomy, CRT, and EMR, respectively.[11] Furthermore, the strictures after (sub)circumferential ESD are reported to be so refractory that repeated dilation therapy is clinically needed, while other preventive strategies are still in the research and development stage. Instead, repeated dilation therapy may present the risks of bleeding and perforation, which result in a worsening quality of life (QOL) and potentially lethal complications, as well as interference with endoscopic inspection (Fig. 1). Due to these interference, severe strictures after (sub)circumferential ESD might mask the presence of recurrent lesions in malignant backgrounds. Therefore, we conducted a single-center retrospective study to elucidate whether patients who are treated by (sub)circumferential ESD of the esophagus might have a higher risk of metachronous recurrence of SESCC than those with smaller than subcircumferential ESD.

MATERIALS AND METHODS

Subjects

Using the existing records and databases, we retrospectively collected data from 263 consecutive patients who were treated with esophageal ESD in our division from April 2002 to December 2013. Among

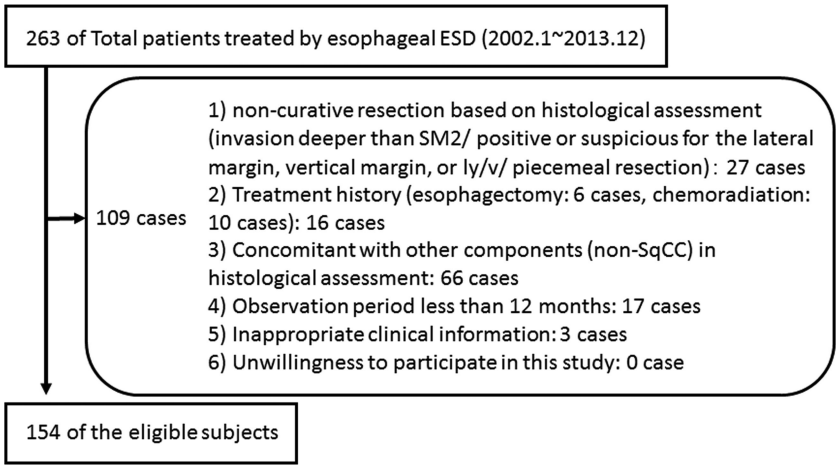


Fig. 2 Flow diagram of patient recruitment and clinical course.

them, patients with histologically proven SESCC that was treated by curative ESD and followed by regular surveillance for more than 12 months were enrolled. The following were excluded: (1) patients whose age was under 20 years or over 90 years, (2) patients with a history of esophagectomy or CRT, (3) patients with insufficient specimen for histological evaluation, (4) patients with a histological diagnosis of non-SCC (dysplasia, or other variants of carcinoma) based on ESD specimens, (5) patients who selected EMR or piecemeal resection, and (6) patients with a concomitant presence or history of invasive cancers of other organs (Fig. 2). This study was approved by the Tohoku University Hospital Ethics Committee (2014-1-815). All subjects provided written informed consent, and no complications were observed.

Endoscopic resection

The indication of ESD for SESCC was preoperatively determined by endoscopy with/without magnifying narrow-band imaging (NBI) (GIF-Q240, GIF-H260, GIF-H260Z, Olympus Medical Systems, Tokyo, Japan), endosonography, computed tomography (CT), or positron emission tomography (PET)–CT.[12] Within one month prior to the ESD, we typically did not perform Lugol chromoendoscopy, but rather we used NBI so as not to misread endoscopic diagnosis of the horizontal lateral margin; this is because Lugol spray is thought to exert deciduous effects on esophageal epithelium, which would result in an overlay of neosquamous epithelium on the target lesion. At the ESD session, we made a definitive diagnosis on the horizontal margin by chromoendoscopy with 1.5% iodine dye and performed *en bloc* ESD with a Hook knife (Olympus).[13]

We collected the data on the endoscopic findings of SESCC and the presence of synchronous lesions or Lugol-voiding lesions (LVLs), well-defined, and irregularly shaped lesions, in the whole esophageal mucosa. SESCCs whose horizontal extent was over or under three-fourths of the circumference were classified as the '(sub)circumferential group' or the 'non-subcircumferential group', respectively. The A/B/C/D classification based on the grade of LVLs was determined by an endoscopist who individually reviewed more than five stocked endoscopic photographs, as follows: A, no LVL; B, several small LVLs; C, many small LVLs; D, multiple LVLs.[14]

Histological evaluation and indication of additional treatment

The histological assessment of the resected specimens was performed according to the Japanese Classification of Esophageal Carcinoma by two expert pathologists.[15] The resection was considered curable when a tumor was resected *en bloc*, had an invasion depth up to SM1, no lymphovascular involvement, and had negative horizontal and vertical margins.

Follow-up

Regular follow-up endoscopy was performed after 1, 3, 6, and 12 months to verify the healing of artificial ulcers or the presence of residual/recurrent lesions. Moreover, additional endoscopic examination was occasionally performed after (sub)circumferential ESD to verify the presence of post-ESD strictures. When the patients complained of severe dysphagia, and/or when a standard endoscope could not pass through the site, we defined 'post-ESD stricture' as a condition that required endoscopic balloon dilation (EBD) treatment. The chromoendoscopy was performed after recovery of the ulceration or stricture. When biopsy specimens obtained from abnormal lesions or irregular LVLs greater than 5 mm were pathologically diagnosed as SCC or HGIN, they were determined to be recurrent lesions. Additionally, CT or endosonography was performed once a year to

Table 1 Demographics of the subjects

		Number
Age	(year old)	68.9 ± 8.4 (S.D.)
Gender	Male/female	138/16
BMI		22.0 ± 3.1 (S.D.)
MCV		96.9 ± 6.4 (S.D.)
Alcohol abuse		54/100
Smoking history		68/86
Current smoking		56/98
LVL	A/B/C/D	13/44/86/11
Hiatal hernia		119/35
Gastric atrophy	Open-type/-~closed-type	123/31
Primary Tumor		
Tumor location	Ce-Ut/Mt/Lt-Ae	8/97/49
Pathological T-staging	EP/LPM/MM/SM1/SM2-	22/93/34/5/0
Circumference of ESD	(sub)circumference/ non-subcircumference	54/100
EBD after primary ESD		109/45
Observation period	Months (median [IQR])	40.5 [28.8–69.5]
Recurrence		131/23

BMI, body mass index; EBD, endoscopic balloon dilation; IQR, interquartile range; LVL, Lugol-voiding lesions, MCV, mean corpuscular volume, SD, standard deviation.

detect nodal or distant metastases when the pathological stage was MM or SM1. We defined newly lesions detected before 12 months as synchronous lesions, whereas lesions that were detected after 12 months were defined as metachronous lesions. Finally, lesions that were detected at the site of the ESD scar were indicative of local recurrence.[14] The start date of the follow-up was defined as the date of ESD, while the end of the follow-up was either the date of the detection of metachronous recurrence/death or the end of December 2014.

Outcomes

We recorded the data, such as demographic information and medical history of the patient, clinical pathological features of the primary/recurrent lesions, and clinical course during the surveillance. 'Alcohol abuse' was defined as consumption of more than 75 mL per day.[7]

The primary endpoint was to identify risks of metachronous recurrence after esophageal ESD in multivariate analyses. The secondary endpoints were to investigate difference in the clinical pathological characteristics between patients with/without metachronous recurrence.

Statistical analysis

Parametric data are expressed as the mean ± standard deviation (SD) and nonparametric data are expressed as the median and interquartile range (IQR). Quantitative data were compared using the Student *t*-test. For categorical variables, Fisher's exact test was used. Univariate logistic regression analysis and hazard ratios (HR) with 95% confidence intervals (CI) were used to assess associations between each parameter and the risk of metachronous recurrence. To prevent possible effects of confounding factors, factors that were identified in a univariate analysis were analyzed in a stepwise manner, in which all covariates were included, followed by a Cox proportional hazards regression model and a Kaplan–Meier method for metachronous recurrence. A P value of <0.05 was considered significant. Analyses were performed using a JMP Pro 11 version statistical analysis software package (SAS Institute, Cary, NC, USA).

RESULTS

Demographics

In all, 263 patients were treated with ESD. 6 and 10 patients who were previously treated with esophagectomy and CRT, respectively, were excluded. Based on the histopathological assessment of the ESD specimens, 27 patients with noncurative resection and 66 patients with other histotypes (non-SCC) were excluded. Seventeen patients who were lost to follow-up within 12 months and 3 patients whose clinical records were insufficient were also excluded. Totally, 109 patients were excluded, and 154 patients with 184 lesions were enrolled (Fig. 2). The demographics are shown in Table 1.

Recurrence rate after esophageal ESD

The overall rate of metachronous recurrence was 14.9% (23/154) during 40.5 [28.8–69.5 IQR] months after the initial ESD. There is no significant difference in the recurrence days or the observation period between the (sub)circumferential group (37.5 [24–49 IQR] months or 41.5 [29.5–54.5 IQR] months, respectively) and the non-subcircumferential group

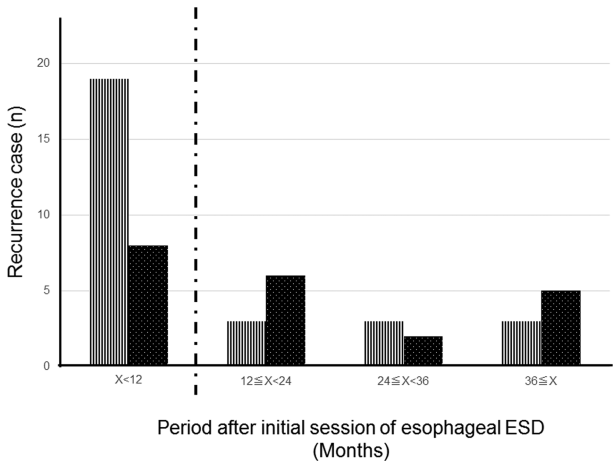


Fig. 3 Numbers of recurrent lesions after the initial ESD: 24.1% and 9.0% of over-all rate of metachronous recurrence were observed in the (sub) circumferential (■) and the non-subcircumferential group (▥), respectively, while 19.0% of synchronous tumors in the non-subcircumferential group were slightly higher than 14.8% observed in the (sub)circumferential group.

(39 [25.3–75.8 IQR] months or 40 [28.3–77 IQR] months, respectively).

Among 22 patients whose metachronous recurrence was detected in the esophageal mucosa, 24.1% (13/54) and 9.0% (9/100) were observed in the (sub)circumferential and non-subcircumferential group, respectively. The synchronous recurrence rate of 19.0% (19/100) observed in the non-subcircumferential group was slightly higher than the rate of 14.8% (8/54) observed in the (sub)circumferential group (Fig. 3). The session numbers of the follow-up endoscopy until the detection of the recurrence in the non-subcircumferential group were significantly less than those in the (sub)circumferential group (7.8 ± 1.8 vs. 15.2 ± 1.5, $P = 0.005$), despite no significant difference in their cancer-free duration.

In regards to the clinical pathological characteristics of metachronous recurrence, 68.2% (15/22) of them were located on the oral side of the ESD scar, while 95.5% (21/22) of them were less than 20 mm in size. All of them were endoscopically treated, and their pathological diagnosis showed that 17, 2, and 3 tumors had invaded the EP-LPM, MM-SM1, and beyond the SM2, respectively. All three patients with recurrent SM2 cancer were treated with additional CRT, but one patient with SM2 recurrence died 30 months after the initial ESD. Mediastinal nodal recurrence was detected in one patient by follow-up CT at 12 months after the initial subcircumferential ESD for MM-invading SESCC without lymphatic/vessel infiltration; this patient died 9 months after additional CRT.

Univariate and multivariate analysis of metachronous recurrence

The univariate analysis showed that patients who are current smokers, with a lower BMI, a history of smoking, synchronous SESCC, treatment history of (sub)circumferential ESD, or post-ESD stricture had a significantly higher rate of the recurrence than those without these factors (Table 2). After the application of a stepwise regression model that included all variants, a multivariate logistic regression model revealed that lower BMI, synchronous SESCC, and (sub)circumferential ESD for primary SESCC were independent risks. Finally, a Cox proportional hazards regression model demonstrated that a history of (sub)circumferential ESD was an independent risk factor (HR: 1.479 (95% CI 1.044–2.079), $P = 0.028$) (Table 3).

According to the Kaplan–Meier method, the cumulative recurrence rate at the 36 or 60 months after ESD

Table 2 Univariate analysis of the risks for metachronous recurrence after esophageal ESD

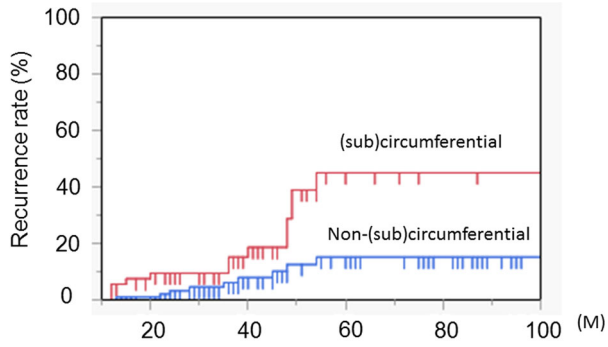
		Recurrence	Nonrecurrence	*P*-value
Age	Mean (SD)	66.6 (1.7)	69.4(8.5)	0.09
Gender	F/M	2/21	14/117	0.77
BMI	<21/≧21	15/8	45/86	0.005*
Smoking history		4/19	52/79	0.04*
Current smoking		8/15	78/53	0.002*
Alcohol abuse		17/6	83/48	0.33
MCV	Mean (SD)	98.4 (1.3)	96.7 (0.6)	0.11
Hiatal hernia		5/18	30/101	0.90
LVL	A/B/C/D	2/5/12/4	11/39/74/7	0.21
Gastric atrophy	Open/-~closed	18/5	105/26	0.84
Synchronous lesions		10/13	17/114	<0.001*
Tumor location	Ce-Ut/Mt/Lt-Ae	3/13/7	5/84/42	0.18
pT-staging	EP/LPM/MM/SM1	3/11/8/1	19/82/26/4	0.42
Size of ESD specimens	>50 mm/≦50 mm	12/11	46/85	0.12
(sub)circumference/non-subcircumference		14/9	40/91	0.02*
Post-ESD stricture		12/11	33/98	0.009*

*showed that there were significantly difference between two groups, $P < 0.01$.
BMI, body mass index; EBD, endoscopic balloon dilation, LVL, Lugol-voiding lesions; MCV, mean corpuscular volume, SD, standard deviation.

Table 3 Cox proportional hazard ratio

		HR	95% CI	*P*-value
(sub)circumference/ non-subcircumference		1.479	1.04–2.08	0.028*
BMI	<21/≧21	1.11	0.79–1.53	0.544
Synchronous multiple lesions		1.35	0.87–2.02	0.176

Co-variants were selected by a step-wise method.
*showed that there were significantly difference between two groups, $P < 0.05$.
CI, confidence intervals; HR, hazard ratio.



No. at risk	0	12	24	36	48	60	(M)
(sub)circumferential	54	54	42	32	16	7	
Non-subcircumferential	100	100	83	59	37	31	

Fig. 4 The cumulative metachronous recurrence rate after initial ESD. The Kaplan–Meier curve demonstrated that the cumulative recurrence rate at the 36 months after ESD in the (sub)circumferential group and the non-subcircumferential group was 15.2% and 6.2%, respectively. There were significant difference between them (Cox-hazard ratio: 3.094 (95% CI 1.331–7.521), $P = 0.0089$).

in the (sub)circumferential ESD group and the non-subcircumferential ESD group were 15.2% or 45.1% and 6.2% or 15.2%, respectively, and there were significant difference between the two groups (Cox-hazard ratio: 3.094 (95% CI 1.331–7.521), $P = 0.0089$, Fig. 4), despite no significant difference in their cause-specific survival.

DISCUSSION

We demonstrated that treatment history of (sub)circumferential ESD might be an independent risk of metachronous recurrence after curative ESD for SESCC in multivariate analyses. Surprisingly, 24.1% and 9.0% of overall rate of metachronous recurrence in the (sub)circumferential and non-subcircumferential group, respectively, were observed during a median of 3.4 years of follow-up period. As conventional EMR is performed for small lesions, our results were compatible with those of previous reports demonstrating that the development of metachronous recurrence after esophageal EMR occurred in 2%–14% of patients.[5,16] Considering that the size of ESD specimens was not significantly associated with the recurrence, these might emphasize high recurrence rate after (sub)circumferential ESD.

First, we discuss the possible origin of the recurrence. Indeed, most of them were small mucosal cancers, which were curatively treated by endoscopic treatment, despite no difference in tumor size and stage between the two groups. As the presence of carcinoma in situ was reported to be an independent predictor for recurrence after esophageal ER in a metaanalysis,[16] tiny synchronous neoplasia might be missed at the initial ESD and might develop into visible recurrence during the 3.4-year surveillance period. Actually, prior studies showed that biopsy-proven mild, moderate, and severe squamous dysplasia might develop into esophageal SCC in 5%, 27%, and 65% of patients, respectively, after 3.5 years of endoscopic surveillance.[17] Moreover, using a multivariate logistic regression model, we demonstrated that low BMI, as well as a treatment history of (sub)circumferential ESD and the presence of synchronous SESCC, were independent risks. In fact, previous epidemiological studies showed that poor diet, which leads to micronutrient deficiencies and malnutrition in patients with low BMI, might be a risk for primary SESCC, together with multiple LVLs, alcohol abuse, and smoking.[18] Therefore, tiny precancerous lesions might develop into recurrent tumors, which can be endoscopically detected at a later phase of post-ESD surveillance, although we did not identify exact factors associated with cancer development.

Next, we hypothesized that technological and technical difficulties in their early detection after (sub)circumferential ESD might cause high recurrence rate. As for the technological aspects, esophageal (sub)circumferential ESD is highly associated with the occurrence of severe strictures. Clinically, such refractory strictures are treated with repeated EBD but with risks of complications, which may interfere with endoscopic inspection. In fact, the session numbers of follow-up endoscopy until the detection of recurrence in the non-subcircumferential group were significantly less than those in the (sub)circumferential group, even though no significant difference was found in their cancer-free period and their observational period. Additionally, the numbers of recurrent lesions that were detected later than 12 months after the initial ESD were significantly larger than those that were detected before 12 months in the (sub)circumferential group. As previous studies reported that 0–4 of EBD sessions during 28.0–58.0 days or 13.8–46.3 of EBD sessions during 4.8–17.5 months was excessively required for recovery of the stricture after subcircumferential or circumferential ESD, respectively,[10] these delay required for recovery of the stricture might interfere with early detection

of recurrent lesions. As for the technical aspects, we practically devoted more attention to the main target at the (sub)circumferential ESD. Actually, such large SESCCs might be more important in deciding their treatment strategy, rather than concomitant tiny lesions, because the accuracy of preoperative staging of larger SESCC is lower than that of smaller SESCCs.[19] Although the background mucosa of both groups had analogous malignant potential, we typically used high-resolution endoscopy with NBI prior to ESD and Lugol chromoendoscopy only at the ESD session. After the ulceration or the stricture was healed, we comfortably performed the chromoendoscopy. Considering that the detection ability of NBI was reported to be significantly lower than that of chromoendoscopy,[20] it is reasonable to assume that the endoscopic detection of recurrence might be postponed by consequential delays in sufficient inspection by Lugol chromoendoscopy in the (sub)circumferential group.

Furthermore, mediastinal nodal metastasis was observed in one patient after subcircumferential ESD for MM-invading SESCC. Motoyama reported that nodal metastasis was pathologically confirmed in 29% of the specimens resected by additional esophagectomy after ESD for patients diagnosed with clinically confirmed mucosal and pathologically confirmed submucosal SESCC, nonetheless no nodal metastasis was detected preoperatively.[21] These indicated discrepancy in the detection rate of nodal metastasis between histology of surgically resected specimens and preoperative clinically available imaging. As the indication of ESD has expanded for clinically confirmed mucosal (sub)circumferential SESCC, in spite of the limited accuracy of preoperative staging, the numbers of clinically confirmed mucosal and pathologically confirmed submucosal SESCC will increase. Therefore, the development of new technologies for the detection of nodal metastasis will also be required with careful follow-up after ESD.

This study has several limitations. First, this was a single-center retrospective study, which might cause bias. The presence of synchronous esophageal neoplasia and the degree of LVLs were evaluated by the database, although the exact presence of occult (pre)malignant lesions at the initial ESD or their natural course during surveillance could not be investigated. Instead, there may be less variation in the instruments and the observation interval during surveillance. Furthermore, our careful review of the recorded database is reasonable in view of the distinction of ectopic recurrence and locoregional recurrence, as previous studies also showed that all patients with pathologically proven complete resection did not have local recurrence.[22] Second, the setting of this study, which featured a relatively high ratio of subjects in the (sub)circumferential group in an academic center, did not seem to be general. However, considering that the recurrence rate in the nonsubcircumfirential group was much lower than that in the (sub)circumferential group, the hypothetical increase in the subjects in the nonsubcircumferential group might not affect our conclusion. Further multicenter prospective studies will be needed.

In conclusion, we provided clinically important information that treatment history of (sub)circumferential ESD of the esophagus might be an independent risk for metachronous recurrence. Due to several issues of clinical management after (sub)circumference ESD, we should pay careful attention for choosing treatment strategy for such large SESCCs among surgery, CRT, or ESD. Further studies will be expected to establish management strategies for precursor lesions that occur concomitantly with primary SESCC as well as to develop preventive strategies for the stricture after esophageal (sub)circumferential ESD.

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