



Effectiveness and safety of endoscopic aspiration mucosectomy and endoscopic submucosal dissection in patients with superficial esophageal squamous-cell carcinoma

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Abstract

Background Endoscopic submucosal dissection (ESD) has been performed in a high proportion of patients with superficial esophageal squamous-cell carcinoma. Endoscopic aspiration mucosectomy (EAM) is a more straightforward technique that is easier to perform. We retrospectively evaluated the safety and efficacy of EAM and ESD to clarify the advantages and disadvantages of each procedure.

Methods A total of 374 patients (423 lesions) who underwent endoscopic resection were retrospectively studied. The following variables were evaluated (1) procedure time and adverse events as safety, and (2) en bloc complete resection rate, local recurrence rate, lymph node recurrence rate, overall survival rate, and cause-specific survival rate as efficacy.

Results EAM was performed in 134 patients (149 lesions), and ESD was performed in 240 patients (274 lesions). The procedure times of EAM and ESD were 31.0 ± 22.4 and 85.7 ± 46.5 min ($p < 0.001$), respectively. The perforation rates were 0 and 6.2% ($p = 0.002$), respectively. The en bloc complete resection rates were 48.3 and 91.6% ($p < 0.001$), respectively. The local recurrence rates were 5.5 and 0% ($p < 0.001$), respectively. For lesions measuring less than 15 mm in diameter, EAM had a relatively good en bloc complete resection rate (EAM, 76.1% vs. ESD, 100%) and a significantly short procedure time (EAM, 25.2 ± 15.2 min vs. ESD, 62.7 ± 35.2 min; $p < 0.001$).

Conclusions ESD has a higher en bloc complete resection rate and a better local control rate than EAM. For lesions measuring less than 15 mm in diameter, EAM may be a treatment option.

Keywords Esophageal squamous-cell carcinoma · Endoscopic aspiration mucosectomy · Endoscopic submucosal dissection · Safety · Efficacy

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been developed as minimally

invasive treatments for superficial esophageal cancer [1–9]. In our hospital, we have sequentially introduced 2-channel EMR, [3, 7] endoscopic aspiration mucosectomy (EAM), [5] and ESD [6]. Two-channel EMR and EAM are classified as procedures for EMR. EAM is performed with the use of an oblique aspiration mucosectomy device attached to the tip of a conventional endoscope (Top Co., Tokyo, Japan), which is used to aspirate and resect lesions with a snare [5].

Previous studies have reported that the size of tumors that can be resected en bloc by EMR is limited and that EMR tends to have a relatively high rate of local recurrence [10–13]. On the other hand, ESD is technically difficult to perform, but has a high en bloc complete resection rate [11–16]. However, few studies have compared the effectiveness and safety of EAM, a technique for EMR, with those

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of ESD. We therefore retrospectively evaluated the safety and efficacy of EAM and ESD to clarify the advantages and disadvantages of each procedure.

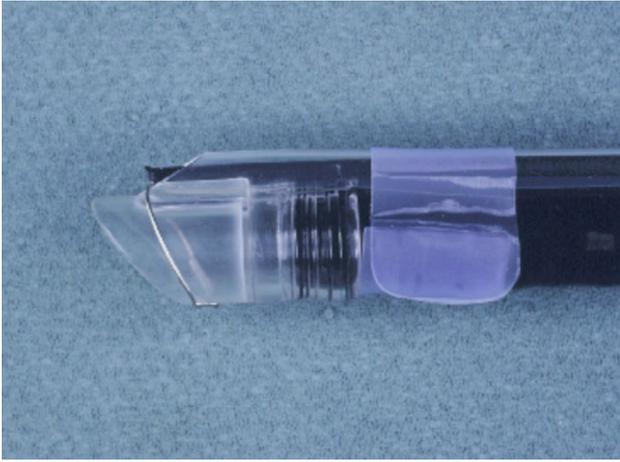


Fig. 1 Oblique aspiration mucosectomy device attached to the tip of a conventional endoscope

Materials and methods

Patients who underwent endoscopic resection in Kitasato University Hospital from November 1999 through August 2015 and met the following inclusion criteria were studied: (1) a histologically confirmed diagnosis of squamous-cell carcinoma, (2) initially treated lesions, and (3) treatment by EAM or ESD. To assess the safety and effectiveness of EAM and ESD, we retrospectively evaluated the following variables: (1) procedure time and adverse events as safety-related variables, and (2) en bloc complete resection rate, local recurrence rate, lymph node recurrence rate, overall survival rate, and cause-specific survival rate as effectiveness-related variables.

EAM was performed with the use of an oblique aspiration mucosectomy device attached to the tip of a conventional endoscope (Top Co., Tokyo, Japan). The lesion was aspirated and resected with a snare (Fig. 1) [5]. ESD was performed with an IT knife (Olympus, Tokyo, Japan), which was used to incise and dissect the lesions. From November 1999 through September 2008, all patients underwent EAM, in principle. From September 2008 onward, ESD was

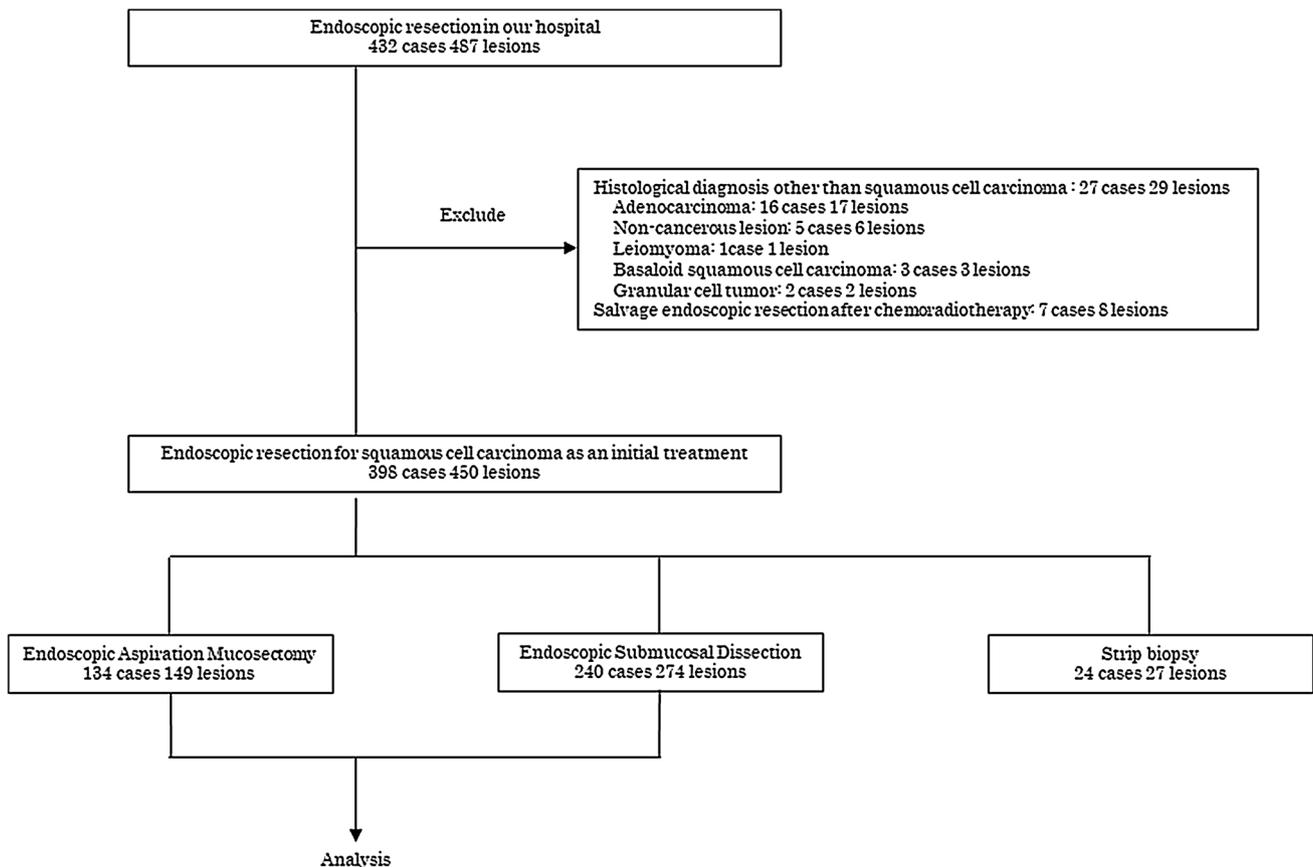


Fig. 2 Flow chart of the patients

Table 1 Clinicopathological characteristic of the patients

	EAM group	%	ESD group	%	<i>p</i> value
Patients	134		240		
Lesions	149		274		
Sex (male/female)	110/24		204/36		0.354
Age (year, mean ± SD)	67.6 ± 7.6		70.2 ± 7.2		0.001
Size (mm, mean ± SD)	16.5 ± 10.9		20.7 ± 12.4		0.001
Location	Ce/Ut/Mt/Lt		8/21/174/71		<0.001
Macroscopic type	Ip/Is/IIa/IIb/IIc/III		0/2/13/41/216/2		0.001
Depth of squamous-cell carcinoma	EP/LPM/MM/SM1/SM2 or deeper		69/31/26/10/13		0.021
Procedure time (min, mean ± SD)	31 ± 22.4		85.7 ± 46.5		<0.001
En bloc complete resection	72	48.3	251	91.6	<0.001
Additional treatment after EAM and ESD	14	10.4	36	15.1	0.135
	Chemoradiotherapy or irradiation	13	9.7	35	14.7
	Surgery	1	0.7	1	0.4
Local recurrence rate	8	6	0	0	<0.001
Lymph node recurrence	3	2.2	8	3.3	0.546
Complications	Major bleeding	0	0	0	NA
	Perforation	0	0	17	6.2
	Stenosis	14	9.4	20	7.3
Treatment-related death	0	0	0	0	NA

NA not applicable, SD standard deviation, EAM endoscopic aspiration mucosectomy, ESD endoscopic submucosal dissection, Ce cervical esophagus, Ut upper thoracic esophagus, Mt middle thoracic esophagus, Lt lower thoracic esophagus, EP epithelium, LPM lamina propria mucosae, MM muscularis mucosae, SM submucosa

Table 2 Average procedure times for EAM and ESD according to the tumor size

Size (mm)	EAM group (min)	ESD group (min)	<i>p</i> value
1–4	19.1 ± 6.2	41.9 ± 39.7	0.425
5–9	29 ± 9.6	57.3 ± 38.7	<0.001
10–14	31 ± 15.8	70.4 ± 29.9	<0.001
15–19	37.1 ± 20.7	76.1 ± 38	<0.001
≥ 20	41.8 ± 24.0	108.3 ± 47.4	<0.001
Total	31 ± 22.4	85.8 ± 46.6	<0.001

EAM endoscopic aspiration mucosectomy, ESD endoscopic submucosal dissection

performed in all patients, in principle. During these periods, the operators who performed EAM and ESD did not change.

All patients underwent upper gastrointestinal endoscopy at least once every 6 months after endoscopic resection [17]. In patients with histopathological evidence of tumor invasion of the muscularis mucosa or deeper layers, computed tomographic examinations of the neck, chest, abdomen, and pelvis were performed at least once every 6 months.

The development of a lesion on the scar remaining after endoscopic treatment was defined as local recurrence. However, the development of a lesion on a scar after en bloc resection of the primary lesion with negative lateral

Table 3 Complications of EAM and ESD according to the tumor size

Size (mm)	EAM group	<i>n</i> (%)	ESD group	<i>n</i> (%)	<i>p</i> value
Perforation					
1–4	0/7	0	0/11	0	NA
5–9	0/29	0	1/35	2.9	0.359
10–14	0/31	0	2/54	3.7	0.278
15–19	0/29	0	3/50	6	0.179
≥ 20	0/49	0	11/124	8.9	0.022
Total	0/145	0	17/274	6.2	0.002
Stenosis					
1–4	0/7	0	0/11	0	NA
5–9	3/29	10.3	0/35	0	0.051
10–14	2/31	6.5	1/54	1.9	0.269
15–19	2/29	6.9	0/50	0	0.06
≥ 20	7/49	18.4	19/124	15.3	0.87
Total	14/145	9.7	20/274	7.3	0.115

NA not applicable, EAM endoscopic aspiration mucosectomy, ESD endoscopic submucosal dissection

resection margins was defined as metachronous multiple cancer.

Bleeding that required blood transfusion was defined as major bleeding. Stenosis was defined as narrowing of the

Table 4 En bloc complete resection rates of EAM and ESD according to the tumor size

Size (mm)	EAM group	n (%)	ESD group	n (%)	p value
1–4	6/7	85.7	11/11	100	0.197
5–9	22/29	75.9	35/35	100	0.002
10–14	23/31	74.2	54/54	100	0.001
15–19	13/29	44.8	47/50	94	<0.001
≥20	7/49	14.3	105/124	84.7	<0.001
Total	71/145	49	252/274	92	<0.001

EAM endoscopic aspiration mucosectomy, ESD endoscopic submucosal dissection

Table 5 Local recurrence rates after EAM and ESD according to the tumor size

Size (mm)	EAM group	n (%)	ESD group	n (%)	p value
1–4	1/7	14.2	0/11	0	0.197
5–9	1/29	3.4	0/35	0	0.268
10–14	0/31	0	0/54	0	NA
15–19	1/29	3.4	0/50	0	0.186
≥20	5/49	10.2	0/124	0	0.002
Total	8/145	5.5	0/274	0	<0.001

EAM endoscopic aspiration mucosectomy, ESD endoscopic submucosal dissection, NA not applicable

esophagus that precluded the passage of an endoscope with a conventional diameter.

All statistical analyses were performed with the use of SPSS, version 22 (SPSS Japan Inc., Tokyo, Japan). The Chi-square test and the Mann–Whitney *U* test were used to compare groups. The overall survival rate and cause-specific survival rate were calculated according to the Kaplan–Meier method. *p* values of less than 0.05 were considered to indicate statistical significance. Our study was approved by the Ethics Committee of Kitasato University.

Table 6 Subgroup analysis for lesions less than 15 mm in diameter

	EAM group	n (%)	ESD group	n (%)	p value
Lesions	67		100		
En bloc complete resection	51	76.1	100	100	<0.001
Procedure time (min, mean ± SD)	25.2 ± 15.2		62.7 ± 35.2		<0.001
Perforation	0	0	3	3	0.153
Stenosis	5	7.5	1	1	0.028
Local recurrence rates	2	3	0	0	0.082

SD standard deviation, EAM endoscopic aspiration mucosectomy, ESD endoscopic submucosal dissection

Results

Endoscopic resection was performed in 432 patients (487 lesions). Twenty-seven of these patients (29 lesions) had a histological diagnosis other than squamous-cell carcinoma (SCC) and 7 patients (8 lesions) who underwent salvage endoscopic resection after chemoradiotherapy were excluded from the study. Endoscopic resection for SCC was performed as an initial treatment in 398 patients (450 lesions). After excluding the 24 patients (27 lesions) who underwent strip biopsy, 374 patients (423 lesions) were included in analysis. EAM was performed in 134 patients (149 lesions), and ESD was performed in 240 patients (274 lesions) (Fig. 2).

The maximum tumor diameter was 15.0 mm (2.0–72.0) in the EAM group and 18.0 mm (2.0–65.0) in the ESD group ($p=0.0016$). The procedure time was 31.0 min (12.0–100.0) in the EAM group and 85.0 min (22.0–240.0) in the ESD group ($p<0.001$). The rate of perforation was 0% in the EAM group and 6.2% in the ESD group ($p=0.002$). Perforation could be managed endoscopically in 16 (94.1%) of the 17 patients with perforation. The other patient required surgical treatment. There was no treatment-related death. The en bloc complete resection rate was 48.3% in the EAM group and 91.6% in the ESD group ($p<0.001$). The local recurrence rate was 5.5% in the EAM group and 0% in the ESD group ($p<0.001$) (Table 1).

The procedure time was studied according to the maximum tumor diameter. The EAM procedure time tended to be significantly shorter than that the ESD procedure time for lesions with a maximum diameter of 5–9 mm ($p<0.001$), 10–14 mm ($p<0.001$), 15–19 mm ($p<0.001$), or 20 mm or greater ($p<0.001$) (Table 2).

When the rates of perforation and stenosis were analyzed according to the maximum tumor diameter, ESD tended to be associated with a significantly higher perforation rate for lesions with a maximum tumor diameter of 20 mm or greater ($p=0.022$) (Table 3).

When the en bloc complete resection rate was analyzed according to the maximum tumor diameter, ESD was associated with a trend toward a significantly higher en bloc

complete resection rate for lesions with a maximum tumor diameter of 5–9 mm ($p=0.002$), 10–14 mm ($p=0.001$), 15–19 mm ($p<0.001$), or 20 mm or greater ($p<0.001$) (Table 4).

When the local recurrence rate was analyzed according to the maximum tumor diameter, EAM was significantly associated with a higher local recurrence rate for lesions with a maximum tumor diameter of 20 mm or greater ($p=0.002$) (Table 5).

The en bloc complete resection rate, procedure time, perforation rate, stenosis rate, and local recurrence rate were compared between EAM and ESD for lesions less than 15 mm in diameter. The en bloc complete resection rate was 76.1% in the EAM group and 100% in the ESD group ($p<0.001$). The procedure time was 25.2 ± 15.2 min in the EAM group and 62.7 ± 35.2 min in the ESD group ($p<0.001$). The perforation rate was 0% in the EAM group and 3% in the ESD group ($p=0.153$). The stenosis rate was 7.5% in the EAM group and 1% in the ESD group ($p=0.028$). The local recurrence rate was 3% in the EAM group and 0% in the ESD group ($p=0.082$) (Table 6).

Table 7 shows the clinical course of 8 patients (8 lesions) with local recurrence. All patients with local recurrence had undergone EAM. The median time to recurrence was 23.5 months (range 2–146). Local recurrence was treated by argon-plasma coagulation (APC) in 6 patients, surgery in 1 patient, and chemoradiotherapy in 1 patient. One patient with local recurrence died of a disease other than esophageal cancer, and the others are alive without disease.

Table 8 shows the clinical course of 11 patients with lymph node recurrence. Three of the patients had undergone EAM, and 8 patients had undergone ESD. Two patients additionally received chemoradiotherapy immediately after EAM and ESD. The histological depth of invasion was the muscularis mucosae (MM) in 6 patients, the submucosa to a depth of 200 μm or less from the muscularis mucosae (SM1)

in 1 patient, and the deeper (SM2) in 4 patients [18]. Lymphatic invasion was found in 5 patients, and venous invasion was found in 4 patients. Two patients had positive deep margins. The median time to recurrence was 46 months (range 9–101). Lymph node recurrence was treated by chemoradiotherapy in 8 patients, preoperative adjuvant chemotherapy plus surgery in 2 patients, and chemotherapy in 1 patient. Five patients with lymph node recurrence died of esophageal cancer, and the others are alive without disease.

The median follow-up period was 83.0 months (range 1–205) in the EAM group and 34.0 months (range 1–135) in the ESD group. The 3-year overall survival rate and the 3-year cause-specific survival rate were, respectively, 96.9% and 100% in the EAM group and 96.6% and 100% in the ESD group (Fig. 3).

Discussion

In our hospital, we started to perform EAM in November 1999. Since April 2005, we started to perform ESD in all patients [11–16]. We previously performed a phase II trial of ESD for superficial esophageal cancer (KDOG 0901) and reported that ESD is a useful treatment option for patients with esophageal SCC [6]. ESD had a high en bloc complete resection rate of 91.6%, with no evidence of local recurrence. However, ESD required a prolonged procedure time and had a perforation rate of 6.2%. On subgroup analysis according to tumor size, EAM had a relatively good en bloc complete resection rate of 76.1% for lesions less than 15 mm in diameter. The local recurrence rate was 3%, but all cases could be controlled by APC. The procedure time was significantly shorter in the EAM group (25.2 ± 15.2 min) than in the ESD group (62.7 ± 35.2 min, $p<0.001$). No patient in the EAM group had perforation (EAM vs. ESD, 0% vs. 3%; $p=0.153$). EAM can thus be safely performed within a short

Table 7 Clinical course of patients with local recurrence

Case no.	Sex	Age	Size (mm)	Location	Depth of primary lesion	Time to recurrence (months)	Procedure for primary lesion	Treatment for recurrence	Survival time (months)	Outcome
1	M	79	4	Lt	EP	3	EAM	APC	31	Survival
2	M	67	6	Mt	EP	40	EAM	APC	182	Survival
3	M	74	15	Lt	EP	36	EAM	APC	36	Survival
4	M	70	30	Mt	MM	24	EAM	APC	59	Death of other disease
5	M	68	32	Lt	MM	3	EAM	APC	19	Survival
6	F	59	35	Mt	EP	2	EAM	APC	189	Survival
7	M	62	48	Lt	EP	146	EAM	Surgery	161	Survival
8	M	67	72	Lt	LPM	23	EAM	Chemoradiotherapy	169	Survival

EAM endoscopic aspiration mucosectomy, APC argon-plasma coagulation

Table 8 Clinical course of patients with lymph node recurrence

Case no.	Sex	Age	Size (mm)	Location	Procedure for primary lesion	Depth of primary lesion [‡]	ly	v	VM	Additional treatment immediately after endoscopic resection	Time to recurrence	Lymph node site of recurrence [‡]	Treatment for recurrence	Survival time (months)	Outcome
1	M	53	NA	Mt	EAM	MM	-	-	-	-	101	#113	CT + Surgery	192	Death of esophageal cancer
2	M	52	19	Mt	ESD	MM	-	-	-	-	22	#106recR, #16	CRT	54	Survival
3	M	63	18	Lt	EAM	MM	+	-	-	-	52	#106	CRT	147	Survival
4	M	74	18	Mt	ESD	MM	-	-	-	-	24	#104R	CRT	30	Survival
5	M	73	30	Mt	ESD	MM	-	-	-	-	46	#107	CRT	60	Survival
6	M	74	20	Mt	ESD	MM	+	+	-	-	9	#106recL	CRT	29	Death of esophageal cancer
7	M	77	7	Lt	ESD	SM1	-	-	-	-	72	#105	CRT	98	Survival
8	M	69	44	Mt	ESD	SM2	+	+	+	-	15	#1	CT + surgery	26	Death of esophageal cancer
9	M	71	12	Ce	ESD	SM2	-	+	-	CRT	46	#101	CRT	47	Survival
10	M	61	20	Mt	EAM	SM2	+	-	-	CRT	47	#3	CT	71	Death of esophageal cancer
11	M	79	32	Mt	ESD	SM2	+	+	+	-	20	#3	CRT	31	Death of esophageal cancer

NA not applicable, [‡]Japanese Classification of Esophageal Cancer, 11th Edition, *ly* lymphatic invasion, *v* venous invasion, *VM* vertical margin, *EAM* endoscopic aspiration mucosectomy, *ESD* endoscopic submucosal dissection, *CT* chemotherapy, *CRT* Chemoradiotherapy

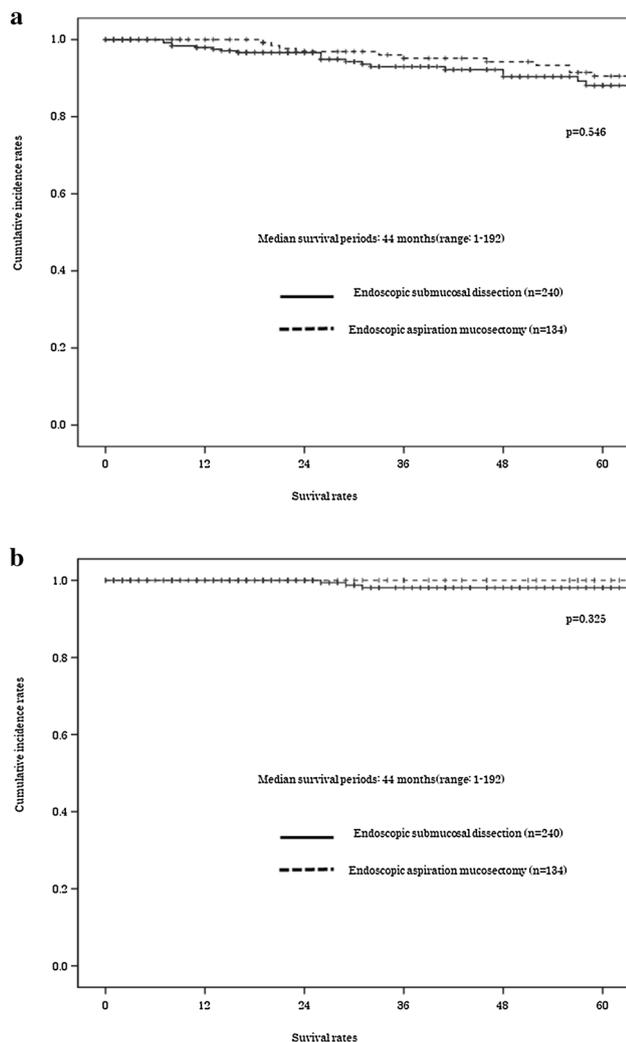


Fig. 3 Overall survival and cause-specific survival of the patients with esophageal squamous-cell carcinoma after endoscopic resection. **A** Overall survival, **B** cause-specific survival

time and with good local control for lesions measuring less than 15 mm in diameter, making it a viable treatment option.

In our study, EAM tended to be associated with a somewhat high rate of stenosis. During the era when EAM was commonly performed, prophylactic treatment with locally injected or oral steroids was not given to prevent stenosis. During the ESD era, prophylactic treatment with locally injected or oral steroids was given to prevent stenosis when three-fourths or more of the esophageal circumference was resected [19–21]. This factor might account for the slight difference in the rate of stenosis. Because it is difficult to finely adjust the area resected by EAM, lesions might have been excessively resected. Stenosis was associated with 5 (7.5%) of 67 lesions less than 15 mm in diameter that were resected by EAM. The indication of local injection or oral administration of steroids for the prevention of stenosis

should therefore be considered according to the resected circumference of the esophagus, even when lesions are less than 15 mm in diameter.

Recently, ESD has been widely disseminated, but is technically challenging [6, 14–16]. In contrast, EAM is a technically straightforward, simple procedure [3, 5, 12]. Because endoscopic resection of ESCC requires accurate pathological examinations of resected specimens to assess the need for additional treatment, en bloc complete resection is required. ESD is an excellent treatment technique with a high rate of en bloc complete resection and good local control. However, our study demonstrated that ESD requires a long procedure time and has the risk of perforation. ESD should therefore be performed by well-trained endoscopists who have mastered the technique. EAM has a lower risk of perforation and can be performed within a short procedure time. In patients who require short time or safe treatment, EAM can therefore be a treatment option in patients, particularly when the target lesions are less than 15 mm in diameter.

In our study, all patients with lymph node metastasis had primary lesions that histologically invaded the muscularis mucosa or deeper layers. All of these lesions carried the risk of lymph node metastasis [22, 23]. It was thus feasible to evaluate histopathological factors for lymph node metastasis, irrespective of the treatment procedure. Among the 5 patients who died of esophageal cancer, 3 patients underwent ESD (3/240, 1.3%), and 2 underwent EAM (2/134, 1.5%). Because the overall survival rate and cause-specific survival rate did not differ significantly, the treatment procedure may not have a direct effect on outcomes.

Our study was a retrospective study performed in a single center. In the future, a multicenter single-arm confirmatory study of EAM or a randomized controlled trial comparing EAM with ESD in patients with superficial esophageal cancer measuring less than 15 mm in diameter should be considered to validate the effectiveness and safety of EAM for the management of lesions less than 15 mm in diameter.

In conclusion, ESD was associated with a higher rate of en bloc complete resection than EAM and good local control, but required a long procedure time and had a high rate of perforation. EAM can be performed within a short procedure time and did not cause perforation, but had a low en bloc complete resection rate and a high local recurrence rate. EAM may be a treatment option that can be safely performed within a short procedure time especially for lesions measuring less than 15 mm in diameter, for which EAM has a relatively good en bloc complete resection rate.

Compliance with ethical standards

Disclosures Yasuaki Furue, Chikatoshi Katada, Satoshi Tanabe, Kenji Ishido, Yuki Kondo, Yo Kubota, Natuko Kawanishi, Sakiko Yamane,

Akinori Watanabe, Hiromitsu Moriya, Keishi Yamashita, Takuya Wada, Takafumi Yano, Mizutomo Azuma, and Wasaburo Koizumi have no conflicts of interest or financial ties to disclose.

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