

Salvage endoscopic submucosal dissection for incompletely resected esophageal or gastric neoplasms (case series)



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ABSTRACT

Background and study aims Given that positive lateral margins indicate possible residual carcinoma, salvage endoscopic submucosal dissection (ESD) should be considered for curative therapy. Presence of submucosal fibrosis, however, makes the procedure difficult to perform. We present our case series to discuss the feasibility of salvage ESD and the timing of the procedure.

Introduction

Endoscopic submucosal dissection (ESD) is now performed all around the world. Advances in the procedure have enabled endoscopic en bloc resection of lesions regardless of their site or presence of ulcer scars [1]. To achieve curative resection, it is essential to accurately determine the margin of the neoplasm before performing the ESD. Magnifying image-enhanced endoscopy and chromoendoscopy are widely used to determine the appropriate tumor margin in advance of the procedure [2], but precise results can be difficult to obtain. Hence, positive lateral margins of a neoplasm can still occur after ESD. Salvage ESD should be considered in such cases, as positive lateral margins indicate possible residual carcinoma. The chief challenge in performing a salvage ESD is presence of fibrosis at the site where the submucosal layer has been eliminated by the previous ESD. No consensus has been reached on timing of sal-

vage ESD. We present our case series to discuss the feasibility of salvage ESD and the timing of the procedure.

Case reports

Patients

Six patients who underwent salvage ESD for residual tumors between January 2015 and October 2018 were enrolled in this study. Consecutive patients were identified from a computerized database listing all patients who underwent endoscopic procedures at Keio University Hospital and the National Hospital Organization Tokyo Medical Center. Four cases had early gastric cancer and two cases had superficial esophageal cancer. The salvage ESDs were performed after histological confirmation of positive lateral margins in the initial ESD specimens.

► **Table 1** Clinical characteristics of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	Male	Female	Male	Male	Male	Male
Age	77	82	65	67	78	68
Location	Esophagus	Stomach	Stomach	Esophagus	Stomach	Stomach
Days after first ESD	15	21	35	104	210	247
Histological type	Squamous cell carcinoma	Tubular adenocarcinoma	Tubular adenocarcinoma	Squamous cell carcinoma	Tubular adenocarcinoma	Tubular adenocarcinoma
Residual lesion size (mm)	5×3	1.5×1.5	30×23	0	15×12	19×5
Resection size (mm)	15×12	35×35	50×35	90×30	25×20	40×17
Procedure time (min)	45	52	136	70	65	65
En bloc resection	+	+	+	+	+	+ -
Fibrosis	F0	F1	F2	F2	F2	F2
Complication	-	-	-	-	-	-

ESD procedures

ESD procedures were performed using video endoscopy (GIF-Q260J or GIF-H260Z; Olympus Co, Tokyo, Japan). The border of a residual lesion was determined by magnifying image-enhanced endoscopy and chromoendoscopy. The safety margin was set as 3 mm or more. For ESD-induced ulcers in the scarring stage, the residual lesion was resected together with the scar. Open ESD-induced ulcers were not included in the resected area. The ESD was performed using a DualKnife (Olympus) and a transparent hood (Olympus) attached to the tip of the endoscope to obtain a good endoscopic view of the submucosal layer and facilitate dissection [3]. A mucosal incision was made after administering a submucosal injection of Glycerol (Chugai Pharmaceutical, Tokyo, Japan) with small amounts of indigo carmine and epinephrine added. More Glycerol was then injected into the submucosal layer to lift the lesion, and the thickened submucosal layer was dissected. A HookKnife (Olympus) was also used when fibrosis in the submucosal layer was severe. Hyaluronic acid solution also was injected into the submucosal layer when submucosal fibrosis impeded sufficient lifting. CO₂ insufflation was performed during all procedures. Patients undergoing gastric ESD were sedated with midazolam and pethidine; patients undergoing esophageal ESD were sedated with midazolam, pethidine, and dexmedetomidine. Salvage ESDs were performed by four experienced endoscopists, each of whom had performed more than 200 ESDs. The resected specimens were pathologically assessed by experienced pathologists. An R0 resection was defined as en bloc resection with no remaining lateral or vertical margins. Degree of submucosal fibrosis was classified into three groups based on findings observed at the time of submucosal local injection: F0, no fibrosis, which manifested as a transparent layer; F1, mild fibrosis, which appeared as a white, web-like structure in the submucosal layer; and F2, severe fibrosis, which appeared as a white muscular structure without a transparent layer in the submucosal layer

[4]. Procedure time was defined as time from incision until complete removal of the lesion.

All specimens were examined to determine tumor size, macroscopic type, histological type, depth of invasion, lateral resection margin, and vertical resection margin.

All six patients have undergone follow-up endoscopies once a year since the salvage ESDs.

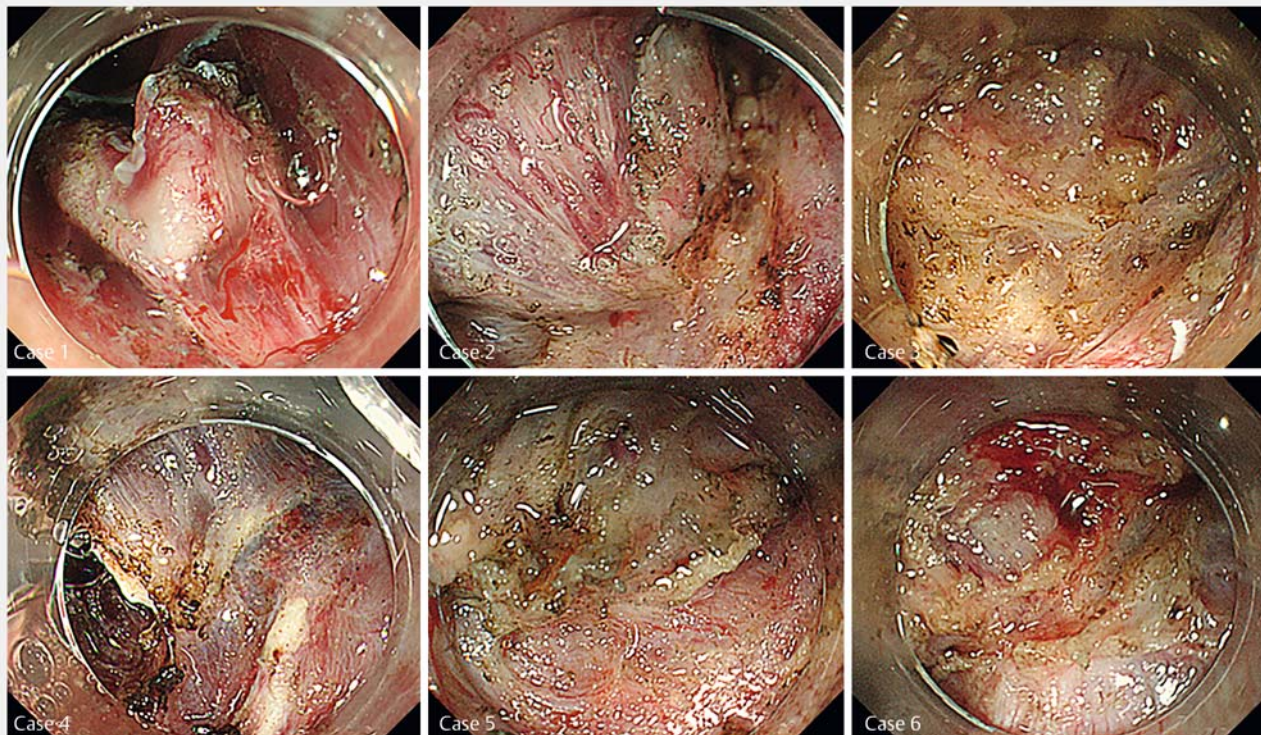
Patient characteristics

Characteristics of the six patients are shown in ► **Table 1**.

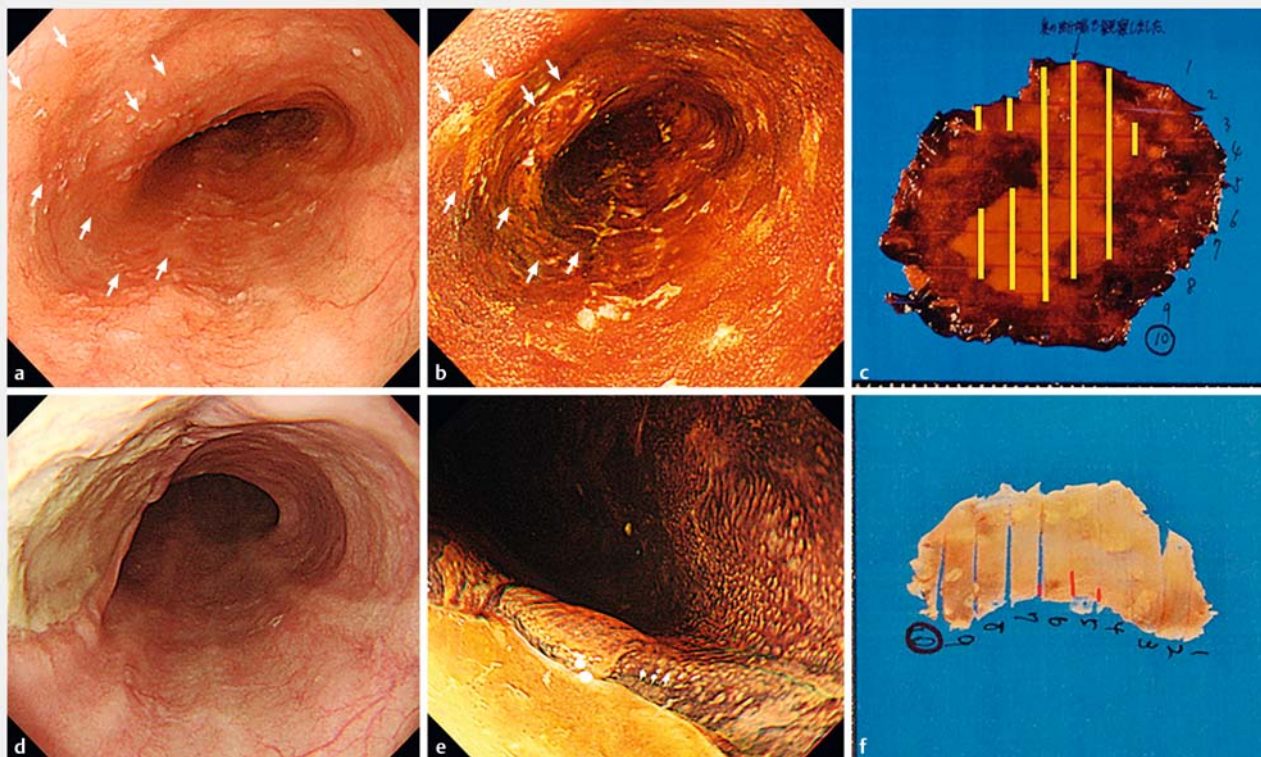
Days elapsed after the first ESD were 15, 21, 35, 104, 210 and 247, respectively. Degree of fibrosis during ESD was F0 (none) in Case 1, F1 (mild) in Case 2 and F2 (severe) in Cases 3 to 6 (► **Fig. 1**). En bloc resection was achieved in all cases, and no instances of postoperative bleeding or intraoperative perforation have occurred in any case. No local recurrence was observed after salvage ESD. Median follow-up time was 301 days (range 14–570 days).

Superficial esophageal cancer case

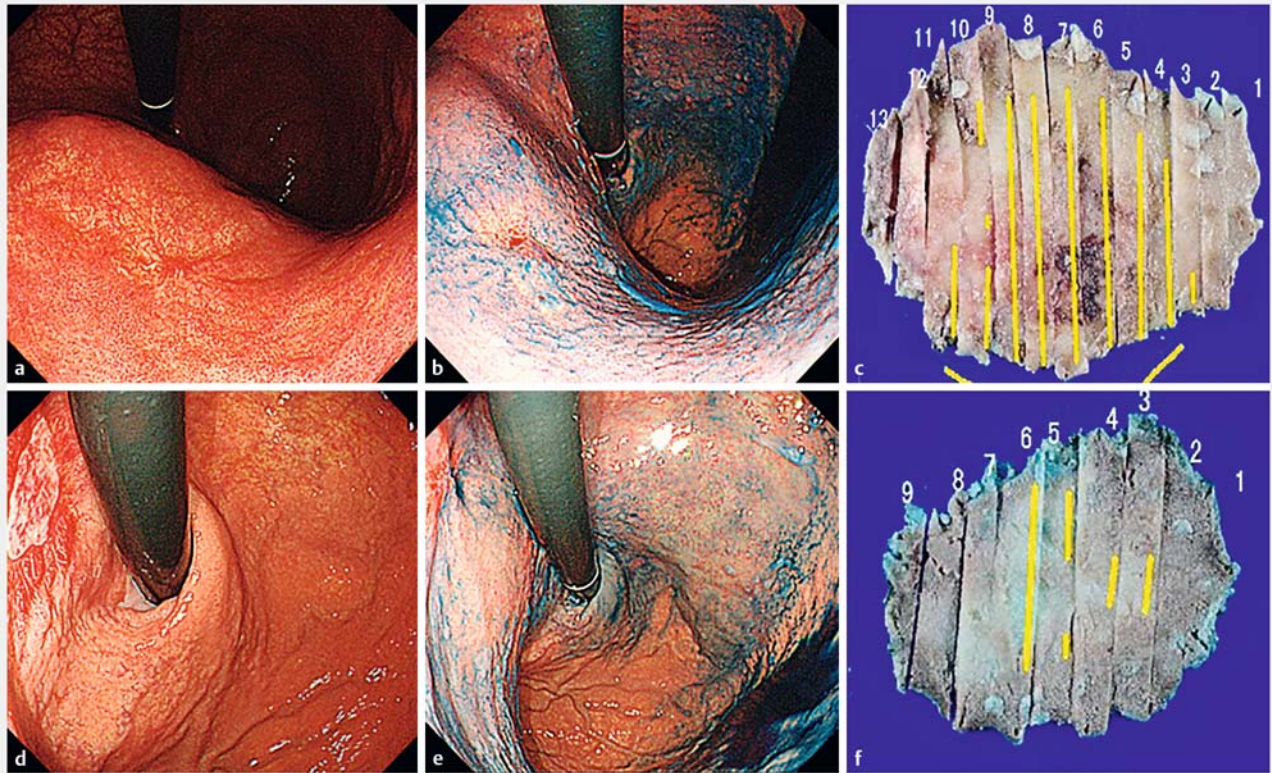
Case 1 was a 77-year-old male patient (► **Fig. 2**) in whom a superficial esophageal cancer, Type 0-II, measuring 12 mm in diameter, was found in the middle of the thoracic esophagus. ESD was performed after Lugol staining. Histological examination of the resected specimen revealed intramucosal squamous cell carcinoma without lymphatic or vascular involvement. The vertical margin was negative, but the horizontal margin was positive. Salvage ESD was performed 15 days later to remove any possible residual carcinoma. No fibrosis was observed in the submucosal layer during the 45-minute procedure (F0). Histological examination of the resected specimen revealed high-grade intraepithelial neoplasia without lymphatic or vascular involvement. The vertical and horizontal margins were both pathologically negative.



► **Fig. 1** Degree of fibrosis during ESD. Case 1, F0 (none); Case 2, F1 (mild); Cases 3–6, F2 (severe).



► **Fig. 2** Case 1: superficial esophageal cancer. **a** A type 0-IIc superficial esophageal cancer was observed in the middle of the thoracic esophagus. Arrows indicate the lesion. **b** Lugol staining. **c** Histological examination of the resected specimen revealed intraepithelial squamous cell carcinoma with a positive horizontal margin. **d** ESD-induced ulcer. **e** Lugol staining. **f** We performed salvage ESD after 15 days. Vertical and horizontal margins were both negative.



► **Fig. 3** Case 3: early gastric cancer. **a** A superficial elevated 24-mm lesion was observed in the lesser curvature of the upper stomach. **b** Acetic acid-indigo carmine chromoendoscopy. **c** Histological examination of the resected specimen revealed a well-differentiated mucosal adenocarcinoma with a positive horizontal margin. **d** ESD-induced ulcer. **e** Acetic acid-indigo carmine chromoendoscopy. **f** We performed salvage ESD after 35 days. Vertical and horizontal margins were both negative.

Early gastric cancer case

Case 3 was a 65-year-old female patient with early gastric cancer (► **Fig. 3**). A superficial elevated lesion 24 mm in diameter was observed in the lesser curvature of the upper stomach. Histological examination of the ESD resected specimen revealed a well-differentiated mucosal adenocarcinoma without lymphatic or vascular involvement. The vertical margin was negative but the horizontal margin was positive. A salvage ESD was performed 35 days later to remove any possible residual carcinoma. Severe fibrosis was observed in the submucosal layer (F2) of the 136-minute procedure. Histological examination of the resected specimen revealed a well-differentiated mucosal adenocarcinoma measuring 30 mm in diameter, with no lymphatic or vascular involvement. The vertical and horizontal margins were both negative.

Discussion

Precise determination of tumor margin is sometimes difficult, because the background mucosa can be influenced by inflammation. Lesions with a wide-spreading area have been reported to be a risk factor for residual tumor after ESD for superficial esophageal cancer [5]. Reported risk factors for positive lateral margins in early gastric cancer are lesions with a flat spreading

area, lesions with lateral submucosal cancer extension beneath non-cancerous mucosa, and lesions with unexpected nearby lesions [6]. Endoscopists should be wary of unexpected lateral extension and the appearance of multiple lesions at the same time.

Positive lateral margins indicate possible residual carcinoma. Sekiguchi et al. [7] demonstrated that a cancer-positive lateral margin length greater than 6 mm is a useful predictive factor for local recurrence after noncurative ESD with a positive lateral margin. An early salvage ESD may be technically more acceptable than ESD performed for a local recurrence at a later point of time.

Jeong et al. [8] have shown that submucosal fibrosis may be predictive of prolonged ESD. Sato et al. [9], meanwhile, have reported that presence of fibrosis is associated with difficult ESD procedures and low rates of complete resection. The perforation rate was significantly higher in cases with accompanying fibrosis than in cases without fibrosis [4]. Early salvage ESD before the appearance and spread of submucosal fibrosis therefore merits consideration.

Optimal timing between initial ESD and salvage ESD remains undefined. Han et al. demonstrated that EMR delayed by more than 21 days from the initial biopsy was a significant risk factor of submucosal fibrosis, which suggests that a longer interval

between diagnostic biopsies and EMR may lead to submucosal fibrosis [10]. Our study was similar to that by Han et al., and the two of our patients who underwent salvage ESD within 21 days were rated as F0 (no fibrosis) and F1 (mild fibrosis).

The retrospective design of this study was a limitation. Moreover, the number of cases was too small to support a recommendation of salvage ESD within 21 days. A further study with a large number of cases should be conducted to learn more about the clinical outcomes and define the golden time for salvage ESD after initial ESD.

Conclusion

Salvage ESD by experienced endoscopists seems feasible. Early timing might be a promising option when salvage ESD is performed.

Competing interests

None

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