

Management of strictures after endoscopic submucosal dissection for superficial esophageal cancer

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Abstract: Endoscopic resection of early esophageal cancer has a high therapeutic effect while being minimally invasive. Especially, the establishment of the endoscopic submucosal dissection (ESD) procedure has made it possible to resect large lesions in an en-bloc manner. As a result, accurate pathology evaluation became possible, and the risk of local recurrence was extremely low. On the other hand, esophageal strictures after endoscopic treatment of an extensive circumferential lesion are a potential problem. Previously, for the prevention and treatment of esophageal strictures, patients had to undergo painful endoscopic balloon dilation (EBD) many times. It is, however, associated with complications (perforation, bleeding, etc.). For this, oral intake and/or a local injection of steroids were given and EBD sessions were less frequently or even unnecessarily performed. Furthermore, oral mucosa epithelial cell sheet transplantation and biodegradable stents are applied for controlling post-ESD stricture. Nevertheless, EBD was still the treatment option for refractory cases of stenosis. Recently, endoscopic radial incision and cutting methods have been applied to esophageal post-procedural strictures and even for anastomotic strictures following surgery. Thus, it is now becoming possible to treat circumferential lesions with ESD and to control the resultant stenosis.

Keywords: Esophageal cancer; endoscopic submucosal dissection (ESD); esophageal stricture; steroid; sequential steroid therapy; endoscopic radial incision and cutting method (ERIC); epithelial sheet engraftment

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Introduction

The burden between endoscopic treatment [endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD)] and surgical therapy for esophageal cancer are greatly different (1), therefore it is extremely important to find an early lesion that is an indication for endoscopic resection. Advances in image enhancement endoscopy and magnified endoscopy have increased the number of cases of early esophageal cancer detection (2), and the correct diagnosis rate for pretreatment diagnosis has also increased (3). The ESD procedure, an application of conventional EMR, has been developed and established in

Japan (4). ESD has relatively high complication rates; the notification of perforation risk is essential especially in the esophagus (1,5). Bleeding during ESD can be managed by endoscopic hemostasis with soft coagulation by forceps. Even with these ESD-related incident risks taken into consideration, the merit that large lesions (i.e., superficial spreading carcinoma) can be resected en-bloc is more beneficial (6). And the number of lesions for endoscopic therapy including diagnostic treatment is increasing because of the invasiveness of surgery and chemo-radio therapy (CRT) (1). Furthermore, as the result of JCOG0508 (phase III) coming out in 2016, the relative adaptation of endoscopic therapy is expected to expand (described later).

Indication for EMR/ESD in superficial esophageal cancer

For early esophageal cancer involving the epithelium (EP) or the lamina propria (LPM), endoscopic treatment (EMR/ESD) is indicated, because of the almost nominal possibility of lymph node metastasis at that depth reaching these layers (7). For esophageal cancer invading the muscularis mucosa (MM), the lymph node metastasis rate is reported as 9%, and for cancer with shallow (<200 µm) submucosal (s-SM) invasion it increases to 19% (8). However, in these settings, there are reports that the frequency of metastasis is no less than 5% except for lesions of 50 mm or more, macroscopic type 0-I/0-III, or positive cases of vascular invasion (8), and it is regarded as a relative indication of there being lesions from EMR/ESD there (9). *Table 1* shows the risk factor of lymph node metastasis in MM/s-SM esophageal cancer. In submucosal cancer that invades deeper than SM 200 µm (d-SM), metastasis is seen in 30–50% (7,8), so there is originally no indication for endoscopic therapy. But the diagnostic accuracy of MM/s-SM cancer is not satisfactory enough (3), especially for so-called superficial spreading carcinoma, it is necessary to consider a diagnostic treatment for esophageal cancer with a high surgical-related mortality rate (2–3%) (1). Furthermore, as JCOG0508 (phase III) shows, non-surgical treatments combining endoscopic resection and CRT for esophageal cancer with a suspected SM invasion were examined and proved to be effective and safe (the results shown online in Japanese). In this situation, as above, the larger lesions were also endoscopically resected by the ESD technique. Accordingly, esophageal luminal stenosis after endoscopic treatment appeared as a problem and remains unresolved.

Risk and prevention of post-procedural stenosis

The risk of stenosis after esophageal ESD is primarily affected by the circumference of the resected area, and if the mucosal defect after resection exceeds 3/4 of the circumference, there is a possibility of a stricture that is clinically problematic (10). If it is resected in a complete circular (or semi-circumferential) manner, a post-procedural structure must occur. For this reason, in the 2007 edition of esophageal cancer diagnosis and treatment guidelines in Japan, an absolute indication for endoscopic therapy was described as having a circumference of less than 2/3. If larger than 2/3 the lesion is resected, and it may be necessary to dilate frequently for prevention

Table 1 Risk of lymph node metastasis of esophageal cancer with infiltration in MM, s-SM

Category	Risk factor
Macroscopic type	0-I, 0-III
Longitudinal diameter	50 mm
Infiltrative growth pattern	Inf b, c
Vascular invasion	Ly (+), v (+)
Pre-procedural diagnosis	SM deep

MM, muscularis mucosa; SM, submucosal.

of post-procedural stenosis. For prevention of esophageal strictures after ESD, endoscopic balloon dilation (EBD), starting from an early postoperative day, was effective, but the burden on the patients compromises their quality of life.

However, in recent years, it has been reported that the occurrence of stenosis after ESD and the frequency of required EBD sessions can be substantially decreased by local injection or oral administration of steroids (11–13), and such prophylactic ways have been widely spread in clinical practice. As a result, the limitation on the circumference of a lesion was deleted from the guidelines of esophageal cancer in the current version (9), and added on as the following comment: “*When the mucosal defect is over 3/4 of circumference, the occurrence of scar stricture after mucosal resection is predicted. Therefore, sufficient preoperative explanation and prevention of stenosis are necessary.*” And, it is now becoming possible to treat the whole circumference lesion via ESD and to control the stenosis (14).

Table 2 shows prevention methods of post-procedural strictures by steroids. Such treatment with steroids can be more effective than preventive EBD leading to less of a burden on patients. Currently, it is under examination by JCOG 1217 as a phase III study as to whether the steroid administration method is superior to local injections or oral administration (15). In turn, we propose that local steroid injections of triamcinolone on the day of ESD followed by oral intake of prednisolone a few days later would be “sequential steroid therapy” for post-procedural strictures against extensive excision of large esophageal cancer lesions, and is an emerging concept in single institutional preliminary trials which requires confirmation with larger prospective studies.

According to the method reported by Yamaguchi *et al.* (11), prednisolone 0.5 mg/kg/day (30 mg/day)

Table 2 Prevention methods of stenosis by steroids

Methods	Case No.	Success rate (%)
Oral administration of Prednisolone for 8 weeks (tapered gradually) vs. Preventive EBD*	19, 22	95, 68
Local injection of Triamcinolone for 3 times after ESD procedure vs. Preventive or Therapeutic EBD	21, 20	81, 25
Local injection of Triamcinolone at once immediately post-procedure vs. Preventive EBD	30, 29	90, 34

*, endoscopic balloon dilatation. ESD, endoscopic submucosal dissection; EBD, endoscopic balloon dilatation.

starts to gradually taper. Oral steroid intake is easier than the local injection method and it was reported that the prevention effect of stenosis was rather high. On the other hand, there are reports that it is difficult to use in cases of diabetes, osteoporosis and certain psychiatric disorders etc. and it can develop infectious diseases that can become lethal as a result of systemic administration (16). Characteristics of steroid refractory cases are shown in *Table 3* (17). *Figure 1* shows our case.

Hashimoto *et al.* for the first time reported a method of using a local injection of triamcinolone on days 3, 7, and 10 after ESD (12). However, it was technically difficult to locally inject steroids into the ulcer base after ESD, and there were risks such as perforation. Therefore, Hanaoka *et al.* reported about their results of locally pouring triamcinolone into the ulcer base for only one session immediately after ESD procedure (13), and this method is now mainstream. *Figure 2* shows our case.

Recently, oral mucosal epithelial cell sheet transplantation applying regenerative medicine technology (18,19), and the usefulness of biodegradable stents (20) have been reported and new clinical applications are expected. In cell sheet transplantation, expensive medical expenses are required to prepare cell sheets, and there are problems to be solved such as it taking no less than 2 weeks at Tokyo Women's Medical University Hospital. However, a clinical study of cell sheet transplantation accompanied by the transfer of a patient at Nagasaki University Hospital was conducted, and it was found to be clinically applicable to patients in remote areas and proved effective for the prevention of stenosis. The summarized results were briefly as follows. Ten patients who underwent complete circular or semicircular ESD for ESCC were transplanted with autologous oral epithelial cell sheets. The safety in every process throughout the cell sheet preparation, transport, and transplantation was confirmed. Using cell sheet transplantation, the luminal stenosis rate was 40%, while the median EBD session was 0. Median

Table 3 Characteristics of steroid refractory case

Resected circumference: 9/10 or more
Resected longitudinal diameter: 50 mm
Location of esophagus: cervical esophagus
History of chemo-radio therapy
A case with two or more factors is at high risk of refractory to oral administration of steroid.

post-ESD ulcer healing period was rather short at 36 days (21). In fact, Ohki *et al.* have already applied endoscopic transplantation of autologous oral mucosal epithelial cell sheets in 9 patients with superficial esophageal squamous carcinoma to prevent post-ESD stricture in Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Tokyo. Eight of the 9 patients had no experience of esophageal strictures and the procedure was safely performed without complications (19). Nevertheless, oral mucosal epithelial cell sheets transplantation has potential disadvantages. The fabrication of cell sheets is still technically and financially difficult in clinical practice even in most tertiary university hospital settings. To resolve this issue we would have to create ready-made oral mucosal epithelial cell sheets that can be transported from production facilities equipped with a cell culture facility (CCF) to a remote hospital that does not have CCFs to fabricate cell sheets, where they will be transplanted (*schematic Figure 3*). Then, this treatment can be performed in almost all hospitals everywhere in Japan without the necessity for the hospitals themselves to fabricate the cell sheets in their own CCF, promising regenerative medicine technology that offers a safe treatment option to prevent esophageal strictures after extensive ESD through faster healing until epithelialization. It has not yet been conclusively determined whether cell sheet transplantation is more effective for stenosis than steroid

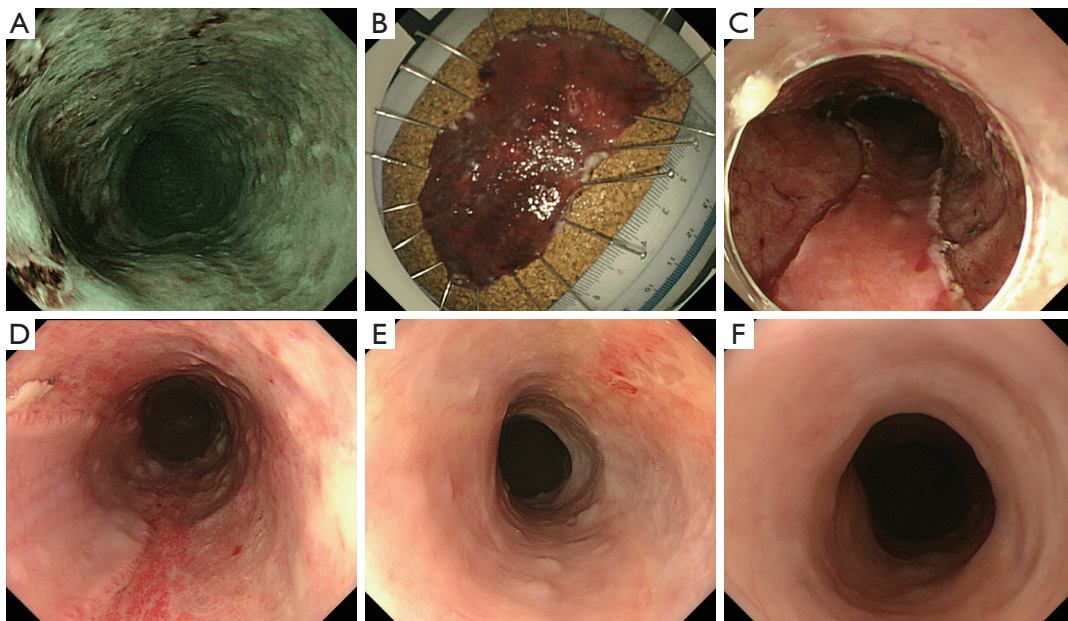


Figure 1 Case of 0-IIc type superficial esophageal cancer with submucosal (SM) infiltration in a small part resected en bloc via ESD. Judged by narrow band imaging (NBI). (A) The lesion size was 4/5 of circumference; (B) resected specimen size was 80×45 mm; (C) maximum esophageal mucosal defect was 5/6 of circumference and 12 cm of longitudinal diameter; (D) oral prednisolone was prescribed at an initial dose of 30 mg on the second day of ESD, then tapered gradually, and discontinued after 8 weeks. The ulcer healed without stenosis, 1 week, (E) 5 weeks, and (F) 3 months after ESD. ESD, endoscopic submucosal dissection.

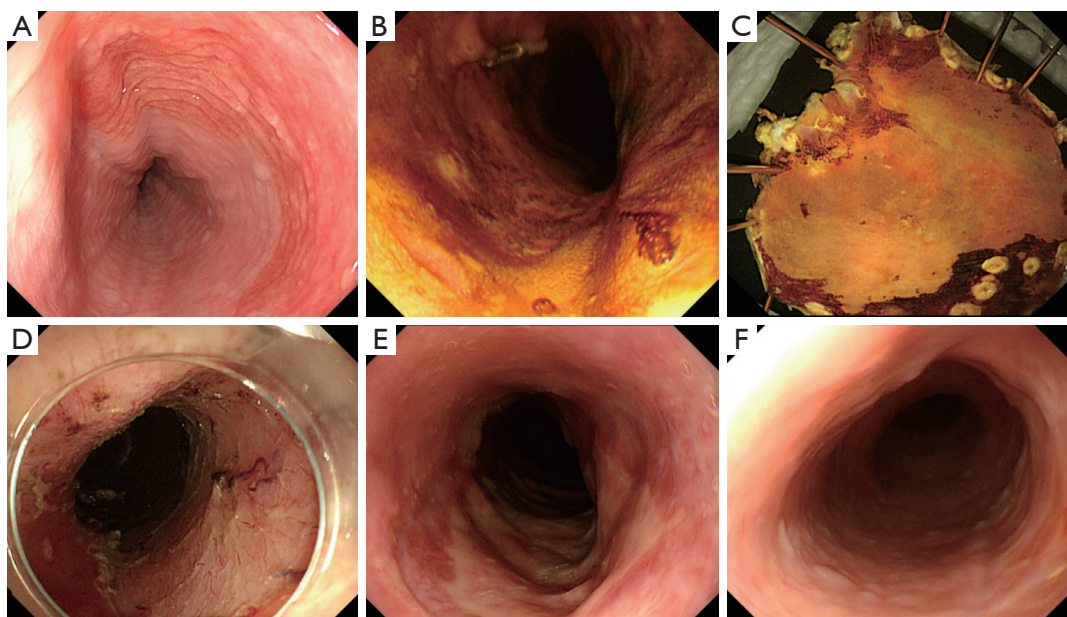


Figure 2 Case of 0-IIb type early esophageal cancer (EP) resected en-bloc via ESD. (A) The lesion size was about 2/3 of circumference; (B) this lesion included previous treatment scar; (C) resected specimen size was 55×45 mm; (D) maximum esophageal mucosal defect was 3/4 of circumference; triamcinolone was injected onto the artificial ulcer bed immediately post procedure. The ulcer healed without stenosis, (E) 2 week and (F) 5 weeks after ESD. ESD, endoscopic submucosal dissection.

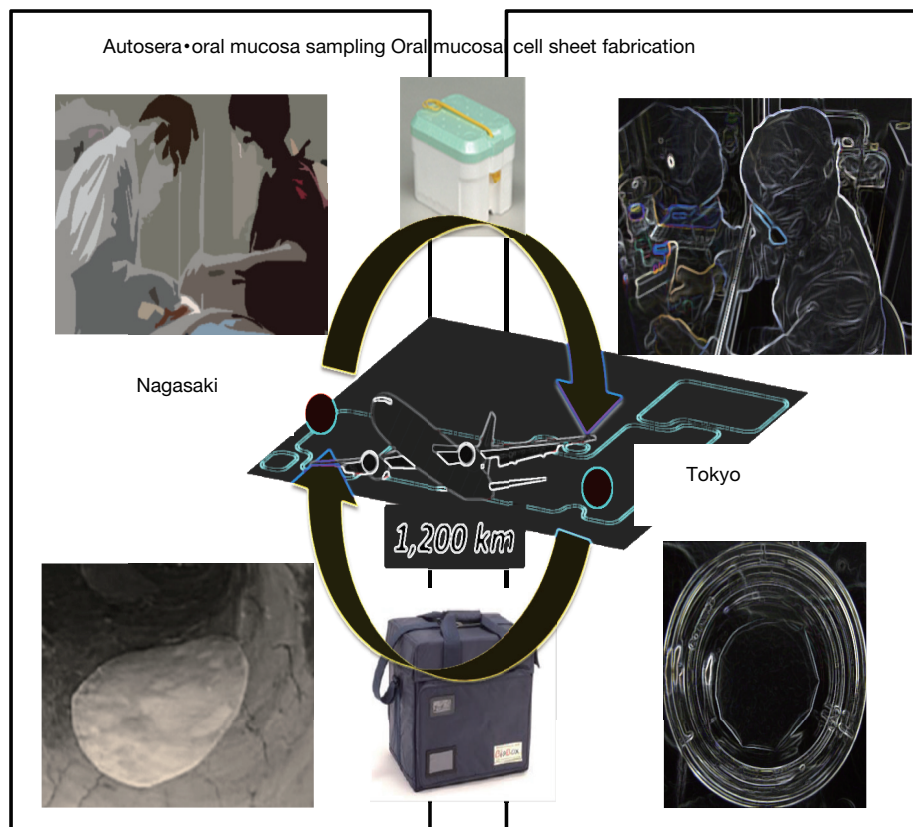


Figure 3 First, the patients' oral mucosa is taken in Nagasaki University Hospital. Then, along with autoserra it is transferred to Tokyo Women's Medical University Hospital where the oral mucosal cell sheets are manipulated. The cell sheets are to be transported again to Nagasaki University Hospital, and transplanted onto the post-ESD ulcer. ESD, endoscopic submucosal dissection.

administration, and further prospective studies are required.

Treatment of post-procedural stenosis

Even for cases in which stenosis had occurred, the main treatment was frequent EBD. However, there were cases where adequate effects were not obtained, and complications such as bleeding and perforation were reported, which above all else might cause a tremendous burden on patients.

In recent years, Muto *et al.* reported on the usefulness of endoscopic radial incision and cutting method (ERIC) (22). This method was carried out as follows: (I) the stricture area was incised radially by using an IT knife endoscopically; (II) the virtual line that connects the esophageal lumen on the oral side and the lumen on the anal side was assumed, and an incision was performed along this line; (III) the incision area was sliced off with an IT knife; and (IV) after RIC, preventive EBD was performed repeatedly at the

frequency of once per week, to maintain patency until the cutting surface became a scar. It can be expected there will be refractory stenosis after ESD, except for extremely hard scarring stenosis and long stenosis (23). *Figure 4* shows our case.

Conclusions

ESD against superficial esophageal cancer has been technically capable of resecting a large lesion including wholly circumference lesions, but it remains a major task for postoperative stenosis. Although problems remain in the risk of infection and the certainty of the effect, the steroid administration method is established and the problem is being overcome by spreading it. Facilities that can administer oral mucosal epithelial cell sheet transplantation at present are limited, but clinical trials among multi-centers for using transferring cell sheets are also planned.

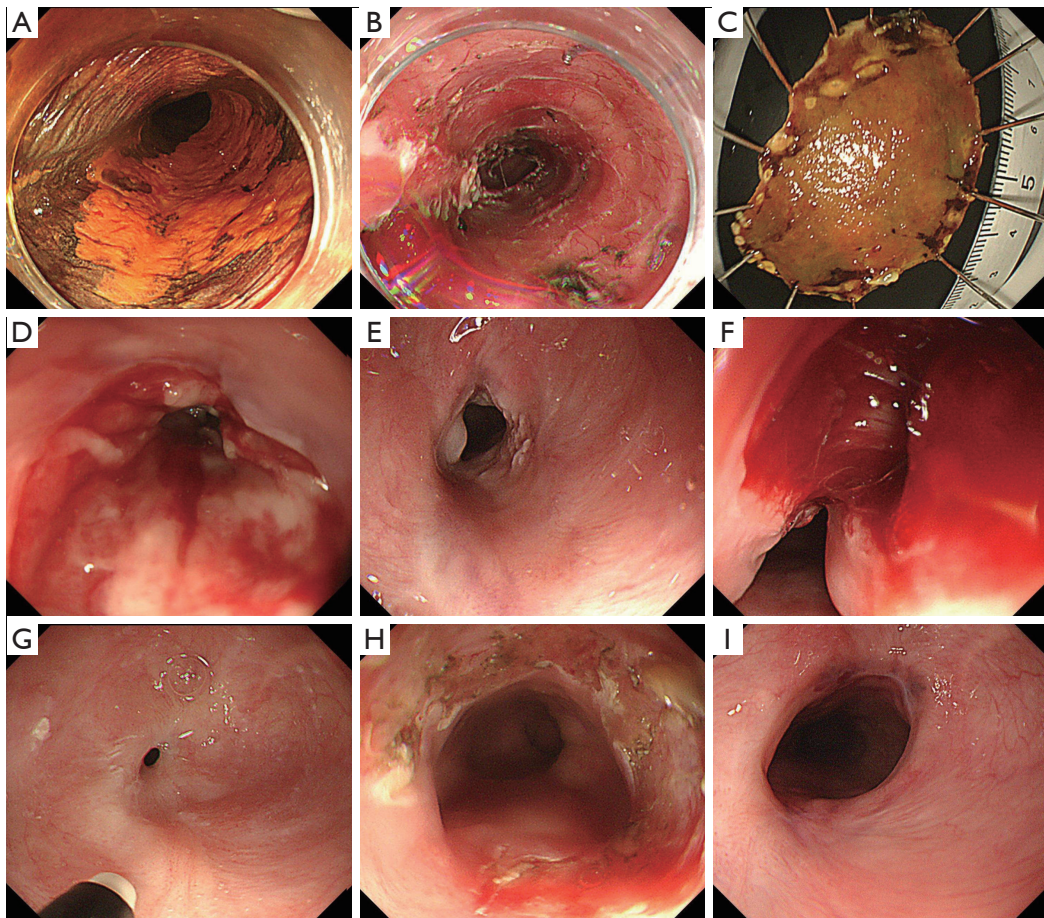


Figure 4 Case of 0-IIb type early esophageal cancer (MM) resected en-bloc via ESD. (A) This lesion was located beside the previous treatment scar on the anal side and occupied 4/5 of circumference or more; (B) maximum esophageal mucosal defect was 9/10 of circumference; (C) resected specimen size was 55×35 mm. Though 100 mg of triamcinolone was injected onto the ulcer bed immediately post-procedure, the patient experienced a post-procedural stricture, requiring 10 sessions of EBD. The ulcer healed with stenosis at 1 month (D) and 3 months (E) after ESD. It resulted in a very deep laceration that reached the muscularis propria (F) in the 11th session of EBD 3 months after ESD. Thus, the patients underwent ERIC for the severe stenosis at 5 months after ESD (G). After the procedure, the stricture improved immediately, and the patient could eat solid foods. The patient has maintained patency for 3 months after ERIC (I). ESD, endoscopic submucosal dissection; EBD, endoscopic balloon dilatation; ERIC, endoscopic radial incision and cutting method.

The usefulness of the ERIC method has also been reported for refractory stenosis cases. In the future, solving the problem of stenosis after esophagus ESD will lead to the expansion of esophageal ESD indication.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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