Control of severe strictures after circumferential endoscopic submucosal dissection for esophageal carcinoma: oral steroid therapy with balloon dilation or balloon dilation alone

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Background: Recent technological advances have allowed superficially spreading intramucosal carcinomas of the esophagus to be successfully resected by circumferential endoscopic submucosal dissection (cESD). After this procedure, esophageal strictures develop in most patients and are mainly treated by endoscopic balloon dilation (EBD).

Objective: To compare oral steroids plus EBD with EBD alone for the management of benign esophageal strictures after cESD.

Design: Retrospective cohort study.

Setting: Tertiary-care referral center.

Patients: We studied 23 consecutive patients who underwent complete cESD for superficial esophageal carcinoma (22 squamous cell carcinomas and 1 adenocarcinoma associated with Barrett's esophagus).

Intervention: After cESD, patients were managed with EBD alone (EBD, n = 13) or with EBD and oral prednisolone (steroid + EBD, n = 10), 30 mg daily, started 2 days after cESD and gradually tapered and discontinued after 8 weeks.

Main Outcome Measurements: Total number of EBD sessions and total EBD period (months).

Results: Steroid + EBD patients required fewer sessions (13.8 ± 6.9 vs 33.5 ± 22.9; $P < .001$) and a shorter management period (4.8 ± 2.3 vs 14.2 ± 17.5 months, $P = .005$) compared with the EBD group. An additional 3 patients received oral steroids a mean interval of 158 days after cESD. These patients required more EBD sessions (46.3 ± 30.0; $P = .002$), and the EBD period was significantly longer (17.5 ± 13.0 months; $P = .005$) than in the early steroid + EBD group.

Limitations: Nonrandomized study; retrospective analysis.

Conclusion: After cESD, oral steroid therapy dramatically reduced the need for EBD. We conclude that oral steroid therapy after EBD is an effective strategy for the management of esophageal strictures after complete cESD. (Gastrointest Endosc 2013;78:250-7.)

The use of steroids to prevent the formation of benign esophageal strictures after circumferential endoscopic submucosal dissection (cESD) has been described; however, few studies have evaluated the effectiveness of this approach.[1-4] Although the underlying mechanism is poorly understood, corticosteroids are thought to locally

Abbreviations: cESD, circumferential endoscopic submucosal dissection; EBD, endoscopic balloon dilation; ESD, endoscopic submucosal dissection.

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inhibit the deposition and enhance the breakdown of collagen, reducing scar-tissue formation.[5] The two reported approaches, oral[1-3] and locally injected[4] steroids, have particular advantages and disadvantages. Oral steroids are easy to administer and achieve a continuous effect, produced by stable steroid concentrations in serum, at the expense of developing systemic adverse effects. By contrast, endoscopic injection of triamcinolone is locally effective and avoids the systemic effects and complications associated with oral steroid use, the potential for repeated injections is limited, and it is possible to localize injected steroid therapy when a stricture has already formed. The extensive nature of the resection involved in cESD suggests that the wider delivery of systemic steroids to the esophagus is preferable. Indeed, this approach has been used (albeit for another indication, when intralesional steroid therapy has failed).[6]

Ono et al[7] reported that stricture formation occurred in 90% of patients who underwent cESD. This high incidence is related to the extent of circumferential resection (more than three-fourths of the total circumferential area). Although previous studies have shown that either systemic or local corticosteroids can effectively decrease the need for endoscopic balloon dilation (EBD) after cESD,[1-4] these were conducted in small series of patients or involved a mix of cases (both complete circumferential and semi-cESD).

In our center, our initial approach was to perform EBD as required after cESD. From 2010 onward, prophylactic systemic steroids were used in addition to EBD to prevent esophageal stricture formation in patients undergoing cESD (alongside the reports of the value of this approach).[1-4] In this analysis, we compared the requirement for EBD after cESD in patients who had received steroids to those who had not. The total number of EBD sessions required and the total EBD period were compared. We also examined procedural complications of EBD and adverse events related to oral steroids, such as poor control of blood glucose levels or increased susceptibility to infection.

Take-home Message

- Oral steroids reduced the number of endoscopic balloon dilation sessions required and the total endoscopic balloon dilation period after circumferential endoscopic submucosal dissection of the esophagus.

METHODS

All patients with esophageal neoplasms treated by complete cESD at Northern Yokohama Hospital from April 2007 through March 2012 were included in this study. Tumor morphology was examined under white light endoscopy and classified according to the Paris Classification,[8] followed by magnifying endoscopy with narrow-band imaging to estimate tumor depth. Chromoendoscopy that used Lugol solution was done to clearly delineate the tumor margins (Fig. 1A). Patients identified to have lesions confined to the mucosa underwent cESD after CT scanning. Patients with more invasive lesions extending into the submucosa but not amenable to surgery also were studied. Informed consent for cESD was obtained from all patients.

Because this was a retrospective analysis of case notes, investigating the results of accepted practice, formal approval from the hospital's institutional review board was not sought (although generic approval to examine case notes was granted).

Complete cESD procedure

Esophageal cESD was performed in the operating suite, with patients under general anesthesia. Carbon dioxide insufflation was used throughout the procedure to mitigate mediastinal emphysema in the event of perforation. cESD was completed by the "tunneling technique" (Fig. 1B and C). First, a dual-knife (Olympus Co, Tokyo, Japan) was used to mark the borders of the lesion. A solution of glycerol (10% glycerol and 5% fructose) was then locally injected to lift and separate the mucosa and submucosa from the muscularis propria. An incision was made in the mucosa at the distal margin of the tumor and extended around the entire circumference of the esophagus. A proximal circumferential incision was then made in the mucosa. Three separate, longitudinal submucosal tunnels were created, connecting the proximal and distal margins. The remnant submucosa between the 3 tunnels was then dissected, and the circumferential lesion was removed en bloc. Throughout the entire cESD procedure, a high-frequency generator (VIO 300D; ERBE Elektromedizin GmbH, Tübingen, Germany) was used under the following conditions: to mark the mucosa, soft coagulation mode, 100 W, effect 4; mucosal incision, Endocut I mode, cut duration 3, cut interval 2, effect 2; and submucosal dissection, forced coagulation mode, 45 W, effect 4. A flush-knife (Fujifilm Co, Tokyo, Japan) was used throughout the procedure, except in difficult situations, in which a hook-knife (Olympus) was generally used.

Post-ESD management for stricture prevention

In our cohort, routine use of steroids after cESD was established only in mid-2010. Thus, two groups of patients emerged and were able to be compared. After cESD, patients received systemic steroids plus EBD (steroids + EBD group) or EBD alone (EBD group) (Fig. 1). Oral prednisolone was used and started 2 days after ESD (when patients are permitted oral intake) in a dose of 30 mg/day. The dose was then gradually tapered in decrements of 5 mg/day every 2 weeks for 1 month followed by decre-

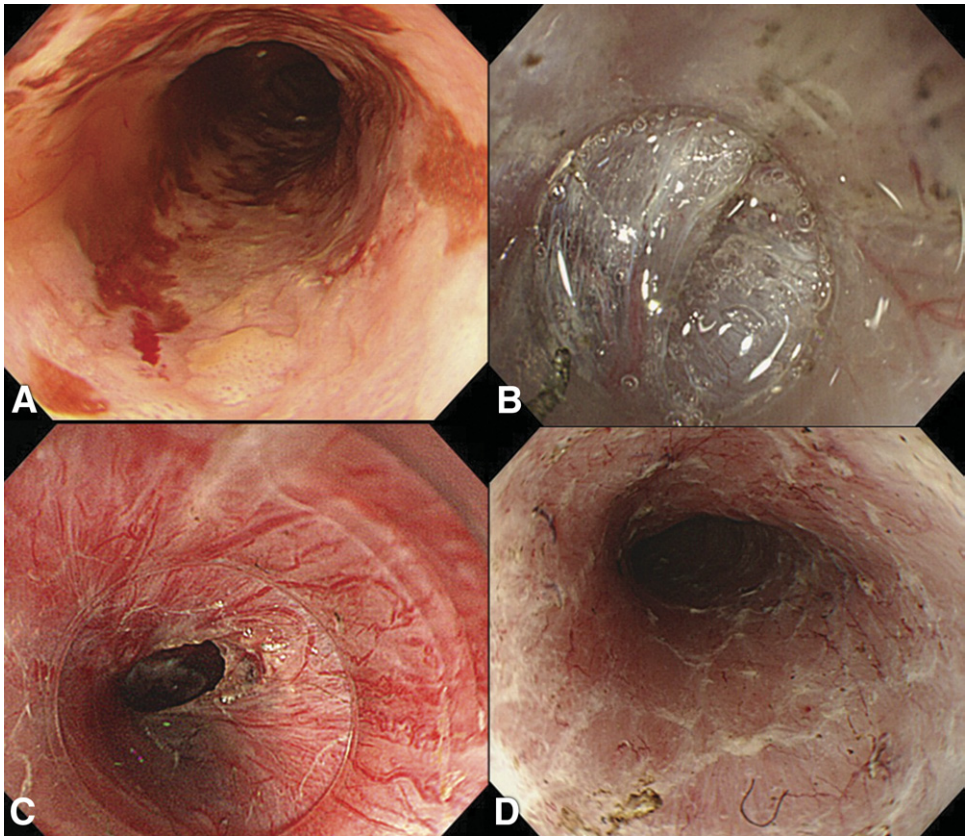

Figure 1. A, Chromoendoscopy with iodine staining showing a circumferential esophageal cancer in the middle thoracic esophagus. **B,** The submucosa is incised by using a hook-knife in the forced coagulation mode. **C,** A longitudinal submucosal tunnel is created, connecting the proximal and distal margins. B and C show the submucosal tunneling technique. **D,** Mucosal defect after circumferential endoscopic submucosal dissection.

ments of 5 mg/day every week for the next 4 weeks. Steroids were discontinued after 8 weeks.

Both groups underwent esophagoscopy 7 days after ESD. A 9.9-mm endoscope (Olympus GIF Q260J) was used to assess stricture development. An esophageal stricture was defined as the presence of resistance to passage of the endoscope, (type α) or failure to pass the endoscope through a stenosed segment (type β), regardless of the presence or absence of dysphagia.

EBD by using an esophageal balloon dilation catheter (CRE Fixed Wire 15 mm/16.5 mm/18 mm, Boston Scientific Co, Boston, Ma) (Fig. 2) was performed with patients under conscious sedation induced by intravenous injection of pethidine (25-50 mg) and diazepam (1-2 mg). The balloon was positioned in the stenosed segment and inflated in increments of 0.5 atmospheres until the balloon came into full contact with the esophageal wall. Dilation was performed up to a maximum pressure of 7 atmospheres (18 mm) or until a laceration or tear was seen on direct visualization.

Repeated endoscopy and EBD were performed according to the schedule shown in Figure 3. Surveillance esophagoscopy was terminated if the patient remained free from stricture for 9 weeks, after obtaining negative results on the last endoscopic examination.

Statistical analysis

Patient demographics and tumor characteristics were retrieved from a computer database. Continuous variables are expressed as means ± standard deviation. Statistical comparison was by t test and the Mann-Whitney U test for parametric and nonparametric data, respectively, with significance assumed at $P < .05$. Statistical analysis was performed by using SPSS, Version 20 (IBM SPSS Inc, Chicago, Ill).

RESULTS

A total of 269 esophageal neoplasms were treated by ESD in Northern Yokohama Hospital from April 2007 through March 2012. Twenty-three lesions (8.6%) satisfied the criteria for complete cESD for a diagnosis of superficial esophageal carcinoma (cESD: resection margins extending over three-fourths of esophageal circumference). There was no procedure-related bleeding or perforation. Patient and tumor characteristics are shown in Table 1. All lesions were resected en bloc and removed with tumor-free vertical and lateral margins (R0 = 100%).

Fourteen (60.9%) of the resected esophageal lesions were limited to the mucosa (m1, m2, m3). However, we also performed cESD for 9 lesions (39.1%) that were later found to have invaded the submucosa (Table 1), a relative

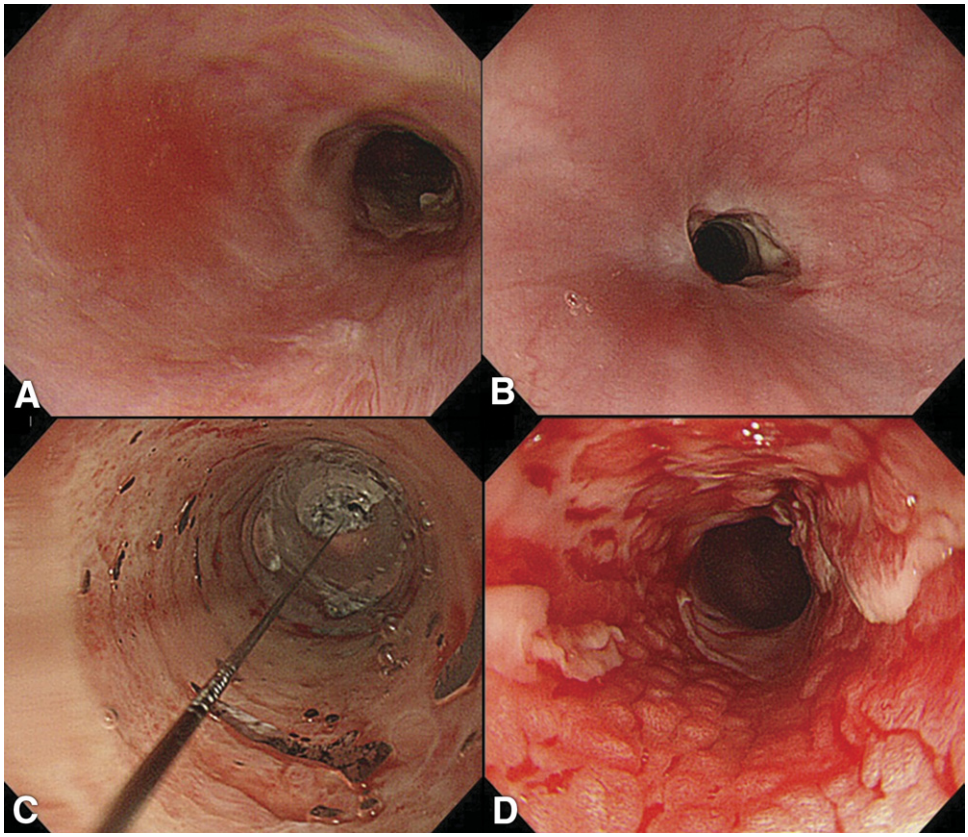

Figure 2. A, Follow-up endoscopy 2 weeks after endoscopic submucosal dissection, showing the mucosal defect still under re-epithelialization (resistance to endoscope passage was experienced in this patient) and a type α stricture. **B,** Endoscopic image of a type β stricture that could not be passed. **C,** Endoscopic balloon dilation (EBD) of esophageal stricture. **D,** Laceration is seen at the 1 o'clock position after EBD. *EBD,* endoscopic balloon dilation.

contraindication for the procedure. Although the potential for submucosal invasion was suspected before complete cESD (see Discussion) these patients still underwent the procedure because they either refused surgery or were high-risk candidates for surgery.

The total number of EBD sessions and the total EBD period (months) are shown in Table 2. Patients in the steroids + EBD group required significantly fewer EBD sessions than those in the EBD group (13.8 ± 6.9 v. 33.5 ± 22.9 sessions; $P < .001$). Moreover, the total EBD period required until the complete resolution of stricture was significantly shorter in the steroids + EBD group than in the EBD group (4.8 ± 2.3 vs 14.2 ± 15.7 months; $P = .005$). Treatment with oral prednisolone administration was not associated with any adverse events. There were no statistically significant differences for any of the parameters studied, when a subanalysis was performed for type α vs type β strictures (data not shown).

Three additional patients eventually received prednisolone after a mean interval of 158 days because they no longer responded to EBD therapy alone (patients were all male, mean age 76.0 years, with mean tumor length 59.7 cm). These patients underwent ESD before the routine practice of using steroids after the procedures was commenced in our unit but during the data collection period. Because steroids were used in these patients without our accepted protocol (on compassionate grounds), it was felt worthwhile to include a subgroup analysis to compare these 3 patients (termed the *late oral steroids group*) with the 10 patients in the steroids + EBD group (Table 3). The number of EBD sessions required was significantly fewer (13.8 ± 6.9 vs 46.3 ± 30.0; $P = .002$), and the total EBD period was significantly shorter (4.8 ± 2.3 vs 17.5 ± 13.0 months; $P = .005$) in the steroids + EBD group than in the 3 patients who received late oral steroids in the EBD group. There were no procedural complications associated with EBD or adverse events related to oral steroids.

DISCUSSION

Postoperative stricture formation remains a challenging complication of esophageal ESD.[9,10] Complete cESD for extensive esophageal cancers carries a particularly high risk of persistent strictures.[2] Several studies have assessed the therapeutic usefulness of steroids in patients with benign esophageal strictures,[5,11-15] although the underlying mechanism of action remains poorly understood. The use of steroids to prevent stenosis after esophageal ESD has been described.[1-4]

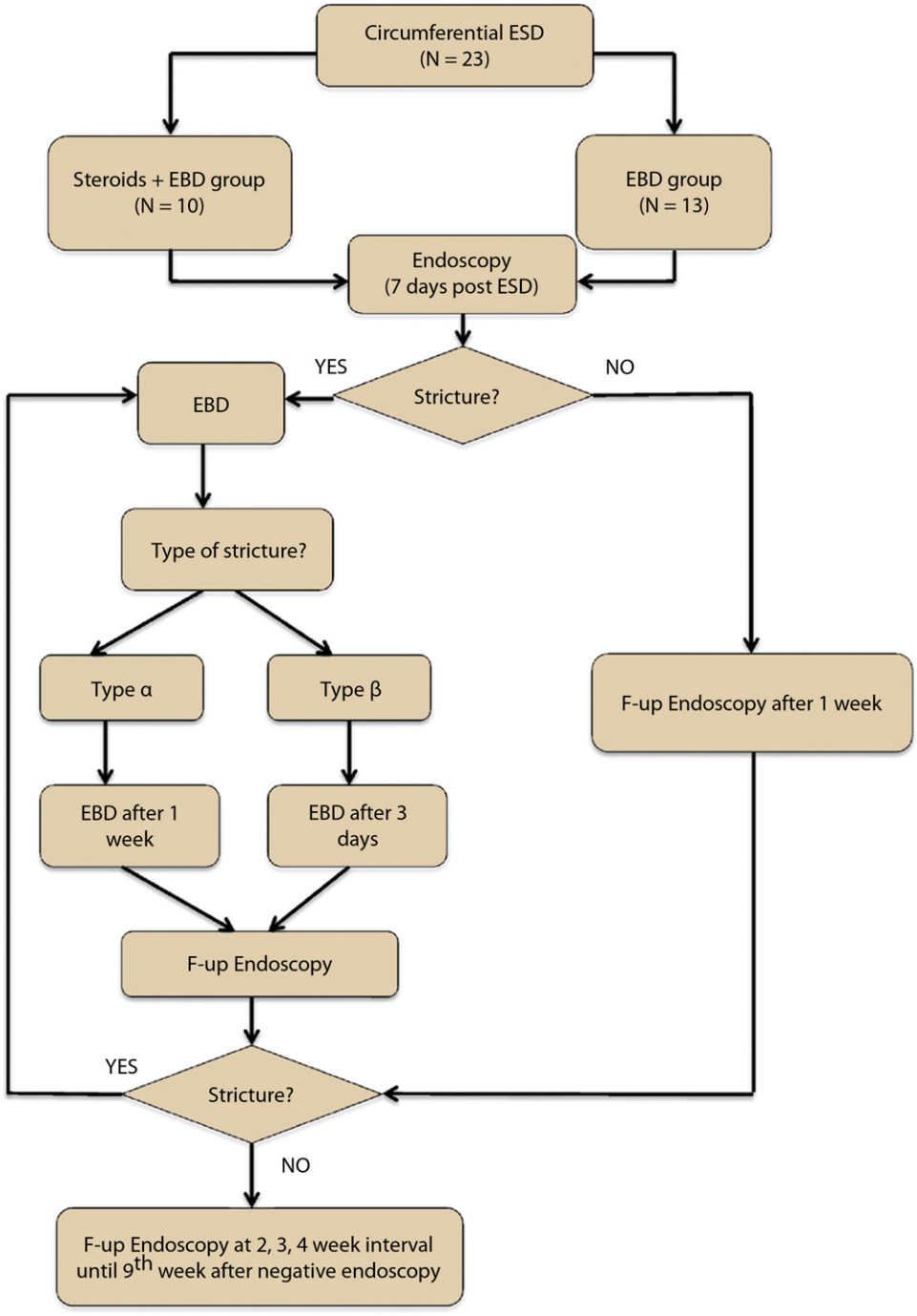

Figure 3. Treatment algorithm for patients who underwent circumferential endoscopic submucosal dissection. A close follow-up was carried out with at least weekly surveillance endoscopies. An esophageal stricture was defined as the presence of resistance to the passage of a 9.9-mm standard endoscope (type α) or failure of its passage (type β). Both types were balloon dilated (endoscopic balloon dilation) even if asymptomatic. Endoscopic balloon dilation was repeated after 3 days for type β and after 1 week for type α. If no stricture was identified, weekly surveillance endoscopies were terminated after 9 weeks. *ESD,* endoscopic submucosal dissection; *EBD,* endoscopic balloon dilation; *F-up,* follow-up.

Although this was a retrospective analysis, our data suggest that oral steroids plus EBD is a more effective approach than EBD alone for the management of strictures occurring after cESD. The concomitant use of steroids not only decreased the total number of EBD sessions required (13.8 vs 33.5; $P < .001$) but also reduced the total EBD period (4.8 vs 14.2 months; $P = .005$). In our cohort, all the patients received close endoscopic follow-up, and EBDs were performed by operators experienced with the technique in the context of cESD. We would always recommend that the follow-up endoscopic examinations and therapies be performed either by the original operator or

TABLE 1. Clinicopathologic profile of patients with esophageal carcinoma treated by complete circumferential endoscopic submucosal dissection (N = 23)

	Steroids + EBD (N = 10)	EBD alone (N = 13)	*P* value
Sex			
Male/female	9/1	12/1	NS
Age, mean (± SD), y	68.7 (± 8.7)	71.8 (± 6.1)	
Tumor location			NS
Upper	0	0	
Middle	8	12	
Lower	1	1	
Esophagogastric junction	1	0	
Tumor type			NS
Squamous cell cancer	9	13	
Adenocarcinoma	1	0	
Tumor depth*			NS
M1*	2	0	
M2*	3	1	
M3*	2	6	
SM1/SM2*	3	6	
Resection size, mean (± SD), mm			
Circumferential	67.0 ± 10.7	65.2 ± 12.7	NS
Length	60.1 ± 19.9	51.6 ± 20.5	NS
Tumor size, mean (± SD), mm			
Longitudinal	66.6 ± 12.4	60.5 ± 10.2	NS
Width	43.1 ±14.4	38.5 ± 15.2	NS

EBD, Endoscopic balloon dilation; *NS,* not significant.
*M1: Tumor limited to the epithelium; M2: Tumor invading the lamina propria; M3: Tumor invading the muscularis mucosa; SM1: superficial invasion (≤200 μm below the muscularis mucosa into the submucosa); SM>2/3: massive invasion (>200 μm into the submucosa).[19]

TABLE 2. Comparison of the steroids + EBD group (N = 10) with the EBD group (N = 13)

	Steroids + EBD	EBD alone	*P* value
Total EBD sessions	13.8 ± 6.9	33.5 ± 22.9	<.001
Total EBD period (mo)	4.8 ± 2.3	14.2 ± 15.7	.005

EBD, Endoscopic balloon dilation.

TABLE 3. Comparison of the 10 patients in the steroids + EBD group (early oral steroids) with the 3 patients in the EBD group who received late oral steroids

	Early oral steroids (N = 10)	Late oral steroids (N = 3)	*P* value
Total EBD sessions	13.8 ± 6.9	46.3 ± 30.0	.002
Total EBD period (mo)	4.8 ± 2.3	17.5 ± 13.0	.005

EBD, Endoscopic balloon dilation.

by similarly experienced colleagues, with appropriate time slots allocated. Such patients should not be offered follow-up on routine lists.

The rate of strictures after complete cESD was 100% in our series, similar to the results of Mizuta et al.[16] We are thus able to conclude only a therapeutic, rather than preventative, effect. Our results suggest that prospective studies examining whether steroids (perhaps in the perioperative period) prevent benign stricture formation after cESD

are warranted. The generic mechanism of action of corticosteroids (as anti-inflammatory agents or otherwise) is to affect gene expression after binding and cytoplasmic translocation by cell-surface receptors.[17] As such, the onset of a clinically significant effect may be delayed and could explain why the effect of steroids in our study was only mitigating, not preventative, for strictures.[18]

Our study has similarities to that of Yamaguchi et al.[2] However, in our study, the end point was extended until the patients became stricture-free because this was thought to be more clinically relevant. Furthermore, perhaps because of the larger size of resections in our study (approximately 2-fold), including only the circumferential lesions performed complete cESD, the stricture rate was 100%. The end point of rate of stricture used by Yamaguchi et al was therefore not felt to provide a useful comparison in our cohort.

It is important to recognize the histopathologic definition used in our analysis. The Japanese classification of esophageal carcinoma[19] categorizes neoplastic lesions confined within the epithelial layer as *carcinoma,* whereas this is defined as *high-grade dysplasia* in Western classification systems.[20] In other words, deeper invasion is not required for the definition of carcinoma. Nevertheless, in our group, 9 patients were found to have submucosal invasion after histologic examination of the resection specimens. In our practice, the evaluation of the depth of tumor invasion is made on endoscopy (by using an accepted classification when high-definition, magnification narrow-band imaging is used to examine the surface microvasculature)[21] and then confirmed or revised on histological specimen analysis. It is thus very important to achieve en bloc resection. If there is deep invasion, lymphovascular invasion, or positive resection margins on histopathologic examination, additional therapy, such as surgery, radiotherapy, chemotherapy, or a combination thereof, should be used. This is because, although the primary lesion has been removed, the risk of lymph node metastasis is high.[22-25] In our series, when deep invasion or lymphovascular invasion was found on careful histopathologic evaluation, the patients received adjuvant chemotherapy. Each decision was made after specialist multidisciplinary review and discussion with patients. Careful endoscopic and radiologic follow-up was opted for in these cases, with no reports of recurrence to date.

In our endoscopic practice, we can estimate the depth of the tumor invasion correctly before treatment. It is not difficult to distinguish tumors that have submucosal invasion and those having deep invasion by examining the surface microvasculature. Although it is not technically possible to differentiate between SM2 and SM3 without a full-thickness specimen, the deep invasion in our series was not classified beyond SM2, because the level of invasion was not deep.

If adjuvant radiotherapy or chemotherapy is required after ESD, it is highly desirable (and some may argue necessary) for patients to be stricture-free, especially because of the potential for radiation to either worsen existing strictures or induce new strictures. Given that this adjuvant approach is possible when required, it may then be argued that the indications of primary ESD could be extended to stage I (cT1bN0M0) circumferential esophageal cancer.

At present, only data on the beneficial effects of late steroid injection on benign esophageal stricture are available.[12,15] To our knowledge, this is the first study to compare the effects of early and late administration of systemic steroids on after-ESD strictures. Our results suggest that early administration of systemic steroids significantly reduces the number of EBD sessions and the total EBD period (as compared with late administration or no steroid therapy). The effectiveness of early steroid treatment may be attributed to the fact that collagen deposition and fibrosis do not occur until 3 to 7 days after injury.[26] Further studies comparing early and late systemic steroid administration in larger groups of patients are needed to confirm our results and clarify the underlying mechanism of action of steroids.

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