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DISEASES OF THE ESOPHAGUS

Original article

Predictive factors for esophageal stenosis after endoscopic submucosal dissection for superficial esophageal cancer

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SUMMARY. **Endoscopic submucosal dissection (ESD) has been utilized as an alternative treatment to endoscopic mucosal resection for superficial esophageal cancer. We aimed to evaluate the complications associated with esophageal ESD and elucidate predictive factors for post-ESD stenosis. The study enrolled a total of 42 lesions of superficial esophageal cancer in 33 consecutive patients who underwent ESD in our department. We retrospectively reviewed ESD-associated complications and comparatively analyzed regional and technical factors between cases with and without post-ESD stenosis. The regional factors included location, endoscopic appearance, longitudinal and circumferential tumor sizes, depth of invasion, and lymphatic and vessel invasion. The technical factors included longitudinal and circumferential sizes of mucosal defects, muscle disclosure and cleavage, perforation, and en bloc resection. Esophageal stenosis was defined when a standard endoscope (9.8 mm in diameter) failed to pass through the stenosis. The results showed no cases of delayed bleeding, three cases of insidious perforation (7.1%), two cases of endoscopically confirmed perforation followed by mediastinitis (4.8%), and seven cases of esophageal stenosis (16.7%). Monovalent analysis indicated that the longitudinal and circumferential sizes of the tumor and mucosal defect were significant predictive factors for post-ESD stenosis ($P < 0.005$). Receiver operating characteristic analysis showed the highest sensitivity and specificity for a circumferential mucosal defect size of more than 71% (100 and 97.1%, respectively), followed by a circumferential tumor size of more than 59% (85.7 and 97.1%, respectively). It is of note that the success rate of en bloc resection was 95.2%, and balloon dilatation was effective for clinical symptoms in all seven patients with post-ESD stenosis. In conclusion, the most frequent complication with ESD was esophageal stenosis, for which the sizes of the tumor and mucosal defect were significant predictive factors. Although ESD enables large en bloc resection of esophageal cancer, practically, in cases with a lesion more than half of the circumference, great care must be taken because of the high risk of post-ESD stenosis.**

KEY WORDS: **complication, endoscopic mucosal resection, endoscopic submucosal dissection, esophageal cancer, stenosis.**

INTRODUCTION

With the recent development of endoscopic diagnostic techniques with iodine staining and narrow band imaging,[1–4] the number of patients with superficial esophageal cancer indicative of local endoscopic treatments has markedly increased. Initially, endoscopic mucosal resection (EMR) had been utilized in endoscopic treatment for localized neoplasm as an alternative to esophagectomy, because the quality of life after EMR is much better than that after the surgical treatment. A number of retrospective studies involving histopathological analyses of surgically resected specimens of esophageal cancers showed that non-invasive epithelial carcinoma (EP, carcinoma *in situ*) and intra-mucosal invasive carcinoma limited to lamina propria mucosae (LPM) swithout vessel invasion had neither lymph node nor distant metastasis.[2,5–8] Based on these findings, the Japanese Esophagus Association proposed the indication criteria of EMR for early esophageal cancer: EMR should be restricted to the lesions of EP or LPM.[9] However, the specimen size resectable by a single procedure of EMR is often so small as to require additional EMRs, resulting in piecemeal resection in

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cases of large lesions. It is of clinical importance that the local recurrence rate in cases with piecemeal resection was significantly higher than that in cases with en bloc resection.[10] Further, it is difficult for the operators to precisely control the target area to be endoscopically resected, which might lead not only to incomplete removal of even small lesions but also to excessive mucosal resection. It was reported that mucosal defects over three-fourths of the esophageal circumference by EMR caused esophageal stenosis.[5,11]

Based on clinical issues arising from the esophageal EMR described earlier, endoscopic submucosal dissection (ESD) has been introduced as an alternative treatment to EMR for esophageal cancer.[5,6] ESD was originally developed for en bloc resection of large mucosal tumors in the stomach[12–14] and recently has also been applied to superficial lesions of the colorectum.[15–18] However, there has been no systematic study to evaluate risk factors for complications associated with ESD, especially esophageal stenosis. In this study, to elucidate the clinical factors causing esophageal stenosis, we retrospectively evaluated the regional and technical factors of ESD for esophageal cancer.

MATERIALS AND METHODS

Patients

This study enrolled a total of 42 lesions of superficial esophageal cancer in 33 consecutive patients who underwent ESD in our hospital from April 2003 to March 2008. Seven patients had more than two lesions independently located in the esophagus; five patients had two lesions and two patients had three lesions. The mean ± standard deviation of age in all 33 patients was 67.5 ± 9.9 years and the male–female ratio was 28 : 5. All 42 lesions were histologically diagnosed as being squamous cell carcinoma. It is of note that, to simplify the parameters to be analyzed, we excluded ESD cases in which histological study of resected tissue specimens showed adenocarcinoma arising from Barrett's esophagus. Further, we excluded patients who underwent additional treatments such as argon plasma coagulation therapy, chemotherapy, radiotherapy, and/or surgical treatment before or immediately after ESD.

ESD procedure

We performed ESD using a single-channel upper gastrointestinal endoscope (GIF Q260J; Olympus, Tokyo, Japan) and a high-frequency electric surgical unit (VIO; Erbe, Tubingen, Germany), with an IT knife (KD-610L, Olympus) and a FLEX knife (KD-630L, Olympus). The transparent attachment was fitted on the tip of the endoscope mainly to obtain a constant endoscopic view and to create tension on the connective tissue for ESD.[5,6]

Diagnosis of post-ESD complications

We routinely checked the vital signs of the patients after the ESD. On the first and third days after the ESD, the patients underwent peripheral blood cell counts and chest X-ray examinations. When the peripheral blood hemoglobin concentration significantly decreased, esophageal bleeding was assessed by upper gastrointestinal endoscopy. When the patients showed any clinical manifestations suggesting perforation and/or mediastinitis, such as chest pain, shortness of breath, pyrexia, or leukocytosis, we immediately performed chest computed tomography (CT). We defined major esophageal perforation when it was endoscopically confirmed during the ESD, and defined minor perforation when mediastinal emphysema or a small amount of free air was observed on chest CT without any endoscopical finding suggesting esophageal perforation. In addition to these major and minor perforations, when patients showed mediastinal effusion on chest CT with pyrexia and/or leukocytosis, we made the diagnosis of mediastinitis. All treated patients routinely underwent upper gastrointestinal endoscopy from 2 to 4 weeks after ESD. Esophageal stenosis was defined when a standard endoscope of 9.8 mm in diameter (GIF H260 and Q260J; Olympus) failed to pass through the stenosis.

Clinical factors

We comparatively analyzed a panel of regional and technical factors associated with ESD between patients with and without esophageal stenosis. The regional factors of esophageal cancer include location, endoscopic appearance, longitudinal and circumferential sizes, depth of invasion, and lymphatic and vessel invasion. The tumor location was classified into five groups according to the guidelines proposed by Japanese Society for Esophageal Disease:[9] cervical (Ce); upper thoracic (Ut); middle thoracic (Mt); lower thoracic (Lt); and abdominal (Ae) esophagus. The endoscopic appearance of the tumor lesion was subdivided into three types: (i) depressed; (ii) flat; and (iii) elevated.[9] The depth of tumor invasion was histologically classified into three groups on the resected specimens[6,19] EP–LPM, muscularis mucosae-submucosal layer 1 (MM-SM1), and submucosal layer 2-muscularis propria (SM2-MP). The technical factors include the longitudinal and circumferential sizes of the mucosal defect, the presence or absence of muscle disclosure, muscle cleavage and perforation, and en bloc or piecemeal resection. Muscle cleavage was defined as occurring when wounded muscularis propia was endoscopically observed. The circumferential sizes of the tumor and mucosal defect were

Table 1 Complications accompanying endoscopic submucosal dissection of superficial esophageal cancer

Complication type	*n* (%, total 42 lesions)
Delayed bleeding	0 (0)
Perforation (major)	2 (4.8)†
Perforation (minor)	3 (7.1)
Mediastinitis	2 (4.8)†
Stenosis	7 (16.7)†

†Major perforation and mediastinitis concomitantly occurred in two identical patients, one of whom was also complicated with stenosis.

expressed as a ratio (%) of their sizes to the whole circumference of the esophagus.

Statistical analysis

The Fisher exact test and a χ^2 test were used for comparison of categorical variables; Student's *t*-test was used for continuous variables, which were presented as means ± standard deviation. A *P*-value of <0.05 was considered significant. All analyses, including receiver operating characteristic (ROC) analysis, were performed using SPSS (SPSS Inc., Chicago, IL, USA).

RESULTS

Complications, treatment, and outcome

Several types of complications occurred with esophageal ESD other than delayed bleeding (Table 1). Major esophageal perforation during ESD in two lesions (one in each of two patients) was endoscopically observed during the procedure. These two patients were subsequently complicated with mediastinitis and one of them was also complicated with post-ESD stenosis. Minor esophageal perforation appeared with ESD in three lesions (7.1%; one in each of three patients) but was not accompanied with mediastinitis. Mediastinitis in two patients with major perforation subsided with conservative treatments including fasting and intravenous administrations of antibiotics for several days. Esophageal stenosis appeared after ESD in seven lesions (16.7%; one in each of the seven patients). These patients initially complained to varying degrees of dysphasia and thus were treated with endoscopic balloon dilatation once a week by using a wire-guided balloon dilatation catheter (Boston Scientific, Natick, MA, USA) according to the previously established method.[2,5,6] Dysphagia completely disappeared for 1 month in six patients without any complication by endoscopic balloon dilatation. In one patient, dysphagia was refractory against the treatment but was finally resolved 6 months after the ESD by consequential balloon dilatation at an outpatient clinic.

It is of note that a total of 13 patients with the lesions deeper than MM (see Table 2) have been observed without any additional treatment, because of a variety of clinical reasons such as advanced age and serious dysfunction of vital organs. Fortunately, no patient showed an apparent finding suggestive of the recurrent lesion on chest CT and ^{18}F-fluorodeoxyglucose positron emission tomography during a post-ESD observation period of 6–48 months.

Predictive factors for post-ESD esophageal stenosis

Because the most frequently observed complication in our patient series of ESD was esophageal stenosis, we further analyzed the predictive factors for this complication in a comparison between the stenosis group (n = 7) and the non-stenosis group (n = 35).

Table 2 Monovalent analysis of predictive factors causing esophageal stenosis after endoscopic submucosal dissection (n = 42)

Factor classification	Factors		Stenosis (+) (n = 7)	Stenosis (–) (n = 35)	*P*-value
Regional factors	Location;Ce/Ut/Mt/Lt/Ae†		2/1/3/1/0	1/2/17/15/0	0.172
	Endoscopic appearance; depressed/flat/elevated		0/4/3	10/19/6	0.081
	Tumor size	Circumferential (%)	69.2 ± 10.4	31.3 ± 12.1	<0.001
		Longitudinal (mm)	36.9 ± 20.8	20.7 ± 9.8	0.003
	Depth of invasion EP–LPM/MM–SM1/SM2–MP‡		3/3/1	26/6/3	0.270
	Lymphatic invasion (yes/no)		1/6	1/34	0.076
	Venous invasion (yes/no)		0/7	0/35	>0.999
Technical factors	Mucosal defect size	Circumferential (%)	80.4 ± 5.1	45.8 ± 15.7	<0.001
		Longitudinal (mm)	49.3 ± 23.4	28.9 ± 10.4	<0.001
	Muscle disclosure (yes/no)		5/2	15/20	0.438
	Muscle cleavage (yes/no)		4/3	6/29	0.104
	Perforation (yes/no)		2/5	2/33	0.167
	En bloc resection (yes/no)		6/1	34/1	0.194

†The tumor location was classified into five groups according to the guidelines proposed by the Japanese Society for Esophageal Disease[9] as follows: cervical esophagus (Ce), upper thoracic (Ut), middle thoracic (Mt), lower thoracic (Lt), and abdominal (Ae).
‡The depth of tumor invasion was histologically classified into three groups in the resected specimens.[6,9]
EP, carcinoma *in situ*; LPM, lamina propria mucosae; MM, muscularis mucosae; MP, muscularis propria; SM1, submucosal layer 1; SM2, submucosal layer 2.

Table 3 Cut-off values with specificity and sensitivity to predict esophageal stenosis after endoscopic submucosal dissection

Factors		Cut-off value	Sensitivity	Specificity	*P*-value
Tumor size	Circumferential (%)	59	85.7%	97.1%	<0.001
	Longitudinal (mm)	32	71.4%	94.3%	0.012
Mucosal defect size	Circumferential (%)	71	100%	97.1%	<0.001
	Longitudinal (mm)	33	85.7%	71.4%	0.002

Table 2 shows the results from a comparative analysis of a panel of regional and technical factors between the two groups.

Among the regional factors, there was no significant difference between the two groups in location, endoscopic appearance, depth of invasion, and lymphatic and venous invasion. It is notable that when the tumor location was subdivided into two groups, that is, upper esophagus (Ce and Ut) and lower esophagus (Mt, Lt, and Ae), the upper esophagus in the stenosis group (3/7, 42.9%) was significantly higher than that in the non-stenosis group (3/35, 8.6%; $P = 0.018$). A high statistical significance was observed in both circumferential and longitudinal tumor sizes between the two groups ($P < 0.001$ and 0.003, respectively). It is of note that the tumor sizes in the stenosis group (69.2 ± 10.4% and 36.9±20.8 mm) were almost twice as big as those in the non-stenosis group (31.3 ± 12.1% and 20.7 ± 9.8 mm).

Among technical factors, there were highly significant differences between the two groups in both circumferential and longitudinal mucosal defect sizes ($P < 0.001$ in each, Table 2) but not in other technical factors including muscle disclosure, muscle cleavage, perforation, and en bloc resection. The mucosal defect sizes in the stenosis group (80.4 ± 5.1% and 45.8 ± 15.7 mm) were almost twice as big as those in the non-stenosis group (49.3 ± 23.4% and 28.9 ± 10.4 mm) as were the tumor sizes. It is of note that we failed to complete en bloc resection in only two of 42 lesions, yielding a success rate of 95.2%.

The cut-off values for the factors with statistical significance as described earlier were obtained by using ROC curve analysis (Table 3). By using these cut-off values, the specificity and sensitivity of each factor for post-ESD esophageal stenosis were evaluated (Table 3). The highest sensitivity and specificity were observed in the circumferential mucosal defect size with a cut-off value of 71% ($P < 0.00$), followed by the circumferential tumor size with a cut-off value of 58.5% ($P < 0.001$). Data distributions of these two factors are shown in Figure 1, which demonstrates an apparent contrast in the cut-off values between the stenosis and non-stenosis groups.

DISCUSSION

Among the 42 lesions of superficial esophageal cancer treated by ESD in 33 consecutive patients, the most frequently observed complication was esophageal stenosis (16.7%). Complications associated with EMR for esophageal cancers have been well analyzed, including the risk factors for complications, especially post-EMR esophageal stenosis.[1] It was

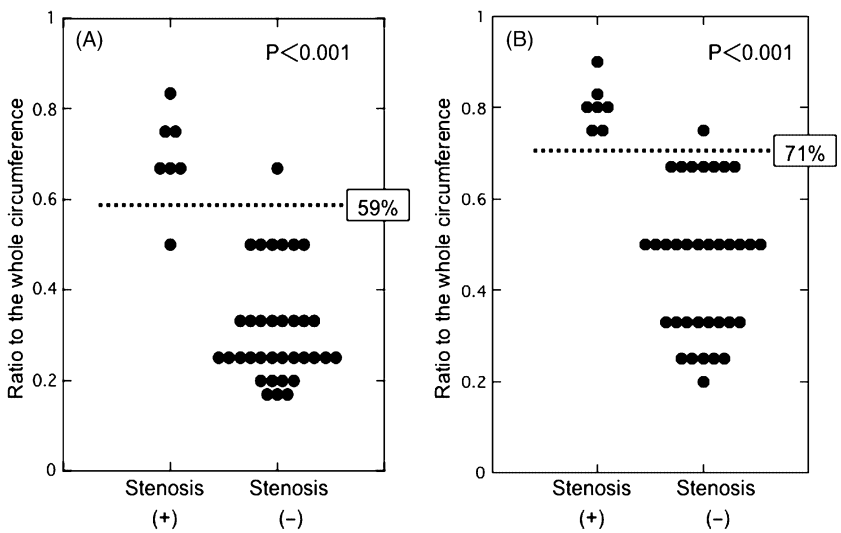

Fig. 1 Circumferential sizes of esophageal cancer and mucosal defect by endoscopic resection. The circumferential sizes of the tumor (A) and mucosal defect (B) are expressed as a ratio (%) of their sizes to the whole circumference of the esophagus (254 × 190 mm [72 × 72 DPI]).

reported that piecemeal resection by EMR increased the risk of esophageal perforation and stenosis.[19] However, this is not the case with ESD, as we successfully completed en bloc resection in 95.2% of esophageal cancer lesions.

This study showed the predictive factor of post-ESD esophageal stenosis, for the first time, as being a circumferential mucosal defect size, with a cut-off value of 71% yielding the highest sensitivity (100%) and specificity (97.1%). This is so strong factor that we fail to calculate odd ratios in multivalent analyses (data not shown). The finding is in agreement with previous studies involving esophageal EMR, which showed that esophageal stenosis may appear unless EMR is limited in extent to less than three-fourths of the esophageal circumference.[9] Because the circumferential mucosal defect size caused by EMR and ESD usually depends on the size of the esophageal cancer, it is not surprising that the circumferential tumor size with a cut-off value of 59% also showed high sensitivity (85.7%) and specificity (97.1%) as a predictive factor for post-ESD stenosis. Taken together, these findings suggest that in cases of tumor size more than half of the esophageal circumference, we should reconsider the indication of ESD. If ESD is utilized for the treatment of such lesions caused by – for instance – advanced age and serious dysfunction of vital organs, we should obtain informed consent from patients regarding the unavoidable risk of esophageal stenosis. In addition, we should routinely perform the second-look endoscopy at 2 or 3 weeks after the ESD, because esophageal stenosis may be evident a few weeks after ESD during the mucosal healing process.[11]

It is interesting that a half of the six patients with the cancer lesion in the upper esophagus were complicated with post-ESD stenosis. In contrast, only 11% of 36 patients with the lesion in the lower esophagus showed post-ESD esophageal stenosis. The most likely explanation for this interesting finding is the difference in a luminal diameter of the esophagus; the diameter of the upper esophagus is smaller than that of the lower esophagus.[20] It is not surprising that the smaller diameter induces the higher risk of post-ESD stenosis. As a patient number with the lesion in the upper esophagus was small in the present study, further study with an increased number of patients is required.

Although the quality of life after endoscopic treatment is much better than that after extended esophagectomy with dissection of regional lymph nodes, which is a standard surgical procedure for the treatment of esophageal cancer, esophageal stenosis after the endoscopic treatment is a clinical problem in some patients. In the present study, fortunately, post-ESD esophageal stenosis was successfully relieved in all seven patients by repeated balloon dilatation. Recently, it was reported that balloon dilatation for several days after ESD could prevent the esophageal stenosis.[5,6,21] Trial studies of the treatment of patients with esophageal stenosis using a biodegradable stent[22] and a self-expanding plastic stent[23] are currently underway. These additional treatments following ESD and the development of devices for treating esophageal stenosis will enable us to extend the indication of ESD for esophageal cancer in the near future.

The present study showed for the first time the predictive factors for post-ESD esophageal stenosis, namely a lesion size of more than 59% and a mucosal defect size of more than 71%; these factors showed very high sensitivity and specificity. Practically, in cases involving a tumor size more than half of the esophageal circumference, we should reconsider the ESD indication and take the necessary steps to cope with the esophageal stenosis. Meanwhile, in cases involving a tumor size less than half of the circumference, we should avoid to make mucosal defect more than two-thirds of the circumference by ESD.

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